



CLINICAL GUIDELINES

Radiation Therapy

Effective September 2, 2016

CareCore National, LLC d/b/a eviCore healthcare (eviCore)





Please note the following:

CPT Copyright 2016 American Medical Association. All rights reserved.
CPT is a registered trademark of the American Medical Association.



Please note the following:

All information provided by the NCCN is “Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) © 2015/2016 National Comprehensive Cancer Network. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.”



Dear Provider,

This document provides detailed descriptions of eviCore's basic criteria (also known as clinical guidelines) for radiation therapy arranged by diagnosis. They have been carefully researched and are continually updated in order to be consistent with the most current evidence-based guidelines and recommendations for the provision of radiation therapy from national medical societies and evidence-based medicine research centers. In addition, the criteria are supplemented by information published in peer-reviewed literature.

Our health plan clients review the development and application of these criteria. Every eviCore health plan client develops a unique list of CPT codes or diagnoses that are part of their radiation therapy utilization management programs. Health Plan medical policy supersedes the eviCore criteria when there is conflict with the eviCore criteria and the health plan medical policy. If you are unsure of whether or not a specific health plan has made modifications to these basic criteria in their medical policy for Radiation Therapy please contact the plan or access the plan's website for additional information.

While eviCore encourages participation in clinical trials when consistent with each health plan's policies, we want to clarify our position on the use of such standard arms outside of the research setting. The use of a control arm or standard arm in a Phase III clinical trial does not necessarily mean that other standard treatment techniques are not equally effective. Examples of multiple "standard" arms can easily be found in the treatment of prostate cancer where Intensity-Modulated Radiation Therapy (IMRT), 3-Dimensional (3-D), low dose implant or High Dose Rate (HDR) can be equally effective or breast cancer

where standard whole breast fractionation or hypo-fractionation can be used. Indeed, national criteria such as National Comprehensive Cancer Network (NCCN) and American College of Radiology (ACR) Appropriateness Criteria often suggest more than one radiation technique.

It is eviCore's process to apply evidence-based criteria to the particular clinical characteristics in evaluating a case, and to certify the most appropriate regimen/modality. This regimen/modality may match one that is used as a "standard arm" in a federally funded clinical trial, or it may be one that is considered an "alternate standard". The alternate standard will be one supported by nationally published guidelines such as the NCCN, ACR Appropriateness Guidelines, or American Society for Radiation Oncology (ASTRO) Evidence-Based Guidelines, or supported by other acceptable peer-reviewed publications.

As such, eviCore will not automatically certify a case based solely on the fact that it matches the standard (control) arm of a clinical trial. This concept applies also to regimens/modalities listed by the NCCN or ACR as "acceptable" treatments for specific disease sites. Rather, we commit to working with the providing Radiation Oncologist to certify the most appropriate regimen/modality for a particular case.

eviCore healthcare works hard to make your clinical review experience a pleasant one. For that reason, we have peer reviewers available to assist you should you have specific questions about a procedure.

For your convenience, eviCore's Customer Service support is available from 7 a.m. to 7 p.m. Our toll free number is (800) 918-8924.

Gregg P. Allen, M.D. FAAFP
EVP and Chief Medical Officer

TABLE OF CONTENTS

Treatment	Page
Brachytherapy of the Coronary Arteries	7
Hyperthermia.....	16
Image-Guided Radiation Therapy (IGRT)	20
Neutron Beam Radiotherapy in Cancer Treatment	27
Proton Beam Radiation Therapy	29
Radiation Therapy of the Skin: Basal Cell, Squamous Cell, and Malignant Melanoma Cancers of the Skin	42
Radiation Treatment for Hodgkin's Lymphoma	47
Radiation Treatment for Non-Hodgkin's Lymphoma	51
Radiation Treatment of Bladder Cancer	56
Radiation Treatment of Bone Metastases	59
Radiation Treatment of Brain Metastases	65
Radiation Treatment of Breast Carcinoma	73
Radiation Treatment of Carcinoma of Esophagus and Gastroesophageal Junction (GEJ) Cancer.....	83
Radiation Treatment of Cervical Cancer	89
Radiation Treatment of Endometrial Cancer	96
Radiation Treatment of Extra-cranial Oligometastases	103
Radiation Treatment of Gastric Adenocarcinoma.....	110
Radiation Treatment of Head and Neck Cancer.....	115
Radiation Treatment of Hepatobiliary Cancer (primary liver, intrahepatic bile duct, extrahepatic bile duct, gallbladder)	120
Radiation Treatment of Kidney and Adrenal Cancer	128
Radiation Treatment of Lung Cancer	130
Radiation Treatment of Non-malignant Disease.....	141
Radiation Treatment of Pancreas Adenocarcinoma.....	147
Radiation Treatment of Primary Cranial and Spinal Tumors and Neurologic Conditions.....	153
Radiation Treatment of Prostate Cancer	162
Radiation Treatment of Rectal and Anal Canal Cancer	171
Radiation Treatment of Soft Tissue Sarcomas.....	175
Radiation Treatment of Testicular Cancer.....	182
Radiation Treatment of Urethral Cancer and Upper Genitourinary Tract Tumors	185
Radioactive Yttrium-90 Microspheres.....	187
Radioimmunotherapy (RIT) – Zevalin®	194

Brachytherapy of the Coronary Arteries

POLICY

I. Coronary artery brachytherapy

- A. Is medically necessary when used as an adjunct to percutaneous coronary intervention (PCI) for treatment of in-stent restenosis in a native coronary artery bare-metal stent or saphenous vein graft (SVG)
- B. All other indications, including use in drug-eluting stents (DES) are not covered because it is considered experimental, investigational, or unproven (EIU)

Key Clinical Points

Revascularization of obstructed arteries due to coronary artery disease (CAD) may be accomplished by PCI with balloon angioplasty, a minimally-invasive procedure in which a catheter with an inflatable balloon at the tip is inserted into the lumen of the artery and inflated, dilating the area of blockage. Coronary stents are implanted in most patients during PCI, resulting in lower rates of restenosis compared to balloon angioplasty alone. Several DES have been developed to minimize the incidence of restenosis, and represent approximately 70 to 90% of stent implantations. The choice of stent (bare metal vs. drug-eluting) depends on various factors, including lesion location and morphology, patient characteristics, and the patient's ability to adhere to the extended period of dual antiplatelet therapy required for drug-eluting stents. In-stent restenosis continues to be a significant problem with bare metal stents, and is thought to be caused by neointimal hyperplasia within the stent. Several mechanical treatments of in-stent restenosis were attempted, including balloon re-dilation, removal of in-stent hyperplasia by atherectomy, and repeated bare metal stenting. Brachytherapy was introduced as a method to treat in-stent restenosis by the delivery of gamma or beta radiotherapy via a catheter-based system. Brachytherapy affects the proliferation of smooth muscle cells that are responsible for restenosis, and may be used to treat in-stent restenosis of native coronary arteries and SVGs. The role of brachytherapy has diminished, however, and drug-eluting stents have emerged as the preferred method of treatment for in-stent restenosis. Brachytherapy may play a role in treatment of selected patients, however.

Three brachytherapy devices received U.S. Food and Drug Administration (FDA) premarket approval (PMA). The Novoste™ Beta-Cath™ System (Novoste Corp., Norcross, GA) and the GALILEO™ Intravascular Radiotherapy System (Guidant Corp., Houston, TX) deliver beta radiation, while the Cordis Checkmate™ System (Cordis Corp., Miami, FL) delivers gamma radiation. Each operates in a similar fashion. A

delivery catheter is placed in the coronary artery at the site of in-stent restenosis and a transfer device is connected to the catheter, delivering the radioactive seeds to administer radiation to the artery. After a specified period of time, the radioactive seeds are returned to the transfer device and removed. Although significant data was collected through the use of all of these devices, both the Checkmate™ and GALILEO™ systems have been discontinued by their respective manufacturers (2007) as DES are now most frequently used. The Beta-Cath™ System is now distributed by Best Vascular, Inc.

Literature Review

I. In-stent restenosis of native coronary arteries and SVGs

- A. Several early multicenter trials of brachytherapy demonstrated the treatment benefits of intracoronary radiation for the treatment of in-stent restenosis:
 1. **IN**itial **H**yperplasia **I**nhibition with **B**eta **I**n-stent **T**rial [**INHIBIT**], Waksman et al. (2002)
 2. **ST**ents **A**nd **R**adiation **T**herapy [**START**], Popma et al. (2002)
 3. GAMMA-1 trial, Leon, et al. (2001)
 4. Coronary Radiation to Inhibit Proliferation Post Stenting [**SCRIPPS**], Teirstein, et al. (1997)
 5. **W**ashington **R**adiation for **I**n-**S**tent **R**estenosis **T**rial [**WRIST**], Ajani et al. (2002)
- B. Ellis et al., for the TAXUS V ISR Investigators (2008), conducted a randomized study to evaluate two-year outcomes of treatment with a paclitaxel-eluting stent (PES) (n = 195) or brachytherapy (n = 201) in patients referred for PCI for bare metal stent in-stent restenosis. Between 9 and 24 months, ischemia-driven target lesion revascularization (TLR) tended to be required less in the PES group compared to the brachytherapy group (5.3. vs. 10.3%, p = .07). At 24 months, ischemia-driven TLR and ischemia-driven target vessel revascularization (TVR) were significantly reduced in the PES group compared to the brachytherapy group (10.1 vs. 21.6%, p = 0.003, and 18.1 vs. 27.5%, p = .03, respectively). There were no significant differences between the two groups in death, myocardial infarction, or target vessel thrombosis between 12 and 24 months, or cumulative to 24 months.
- C. Holmes et al., for the SISR Investigators (2008) conducted a randomized trial to evaluate the safety and efficacy of sirolimus-eluting stents (SES) (n = 259) compared to vascular brachytherapy (VBT) (n = 125) for treatment of in-stent restenosis in a bare metal stent. At three years, survival free from TLR or TVR was significantly improved with SES; freedom from TLR was 81.0% for SES vs. 71.6% for brachytherapy, p = 0.018; TVR was 78.2% for SES vs. 68.8% for brachytherapy, p = 0.022. Target vessel failure and major adverse cardiac events (MACE) were improved with SES but did not reach statistical significance. There was no statistically significant difference in definite or probable stent thrombosis between the two groups. Five-year follow-up of the SISR trial was published by Alli et al. in 2012. There were no differences in

- safety or efficacy outcomes for treatment of BMS restenosis with SES vs. VBT. There were no significant differences in survival free from TLR, TVR, or major adverse cardiac events between the two groups.
- D. Drug-eluting stents were compared to beta-radiation for the treatment of in-stent restenosis in a case series conducted by Zavalloni et al. (2006). The first 68 patients (group I) were treated with brachytherapy using the Novoste Beta-Cath system. The latter 73 patients (group II) were treated with a Cypher™ sirolimus-eluting stent or a Taxus™ paclitaxel-eluting stent. Nine months following treatment, restenosis rates were 37.8% (28/74) for patients in group I and 14.9% (11/74) for patients in group II ($p = .0028$). A diffuse pattern of recurrence was more frequently seen after brachytherapy (20/74 vs. 6/74, $p = .005$). The “edge effect” following brachytherapy was associated with worse outcomes and accounted for most failures. Recurrence within the original restenotic stent was similar in both groups (12.9% vs. 14.9%, $p = .8$). Patients treated with drug-eluting stents for diffuse in-stent restenosis experienced more favorable clinical and angiographic outcomes compared to a similar cohort of patients treated with beta-brachytherapy.
- E. The three devices described above received FDA approval for in-stent restenosis in native coronary arteries, and most published studies have focused on this indication. Brachytherapy has also been used to successfully treat in-stent restenosis in SVGs. The SVG-WRIST trial (Waksman, et al., 2002), a randomized, double-blind, placebo-controlled trial, evaluated the effect of intravascular gamma radiation in 120 patients with in-stent restenosis in saphenous vein grafts. Patients underwent balloon angioplasty, atherectomy, additional stenting or a combination of these procedures. If the intervention was successful, patients were randomly assigned in a double-blind fashion to intravascular treatment with a ribbon containing iridium-192 ($n = 60$) or nonradioactive seeds ($n = 60$). Revascularization and radiation therapy were successful in all patients. At six months, the restenosis rate was lower in the iridium-192 group (21%) than in the placebo group (44%). At 12 months, revascularization of the target lesion was lower in the iridium-192 group (17%) than in the placebo group (57%). The rate of major cardiac events at 12 months was also lower in the iridium-192 group (32%) than the placebo group (63%).
- F. Rha et al. (2005) published a follow-up to the SVG-WRIST trial to determine whether the safety and efficacy of brachytherapy is durable. At 36 months, target lesion revascularization (TLR), repeat percutaneous transluminal coronary angioplasty (PTCA) and TLR-major adverse cardiac events (MACE) remained significantly lower in the irradiated group, although TVR and TVR-MACE did not. The beneficial effect and efficacy of irradiation declined with time and manifested with late recurrences. The authors stated that saphenous vein grafts are known to degenerate over time, and when PCI is

required, the clinical outcome of these patients is markedly impaired. The outcomes of patients in the SVG-WRIST trial are driven, therefore, by the restenotic process, with a high likelihood that graft failure was a result of progression of degenerative disease within the graft or within the native coronary arteries distal to the graft. The authors concluded that patients in the SVG-WRIST trial treated with brachytherapy had a marked reduction in the need for repeat TLR at 36 months, with sustained clinical benefit at three years despite late recurrences, which were more pronounced in the irradiated group.

II. Meta-analyses

- A. A meta-analysis by Lu et al. (2012) was conducted to determine whether DES implantation remains favorable in large sample size and long-term follow-up when compared to intracoronary brachytherapy (ICBT) in patients with in-stent restenosis. The analysis included 1942 patients in twelve controlled trials (four randomized controlled and eight nonrandomized controlled trials). DES were significantly more effective in reducing TVR ($p = 0.009$) and binary restenosis ($p < 0.00001$) compared to ICBT at a midterm follow-up of six to twelve months. There were no significant differences in cardiac death, MI, and late stent thrombosis at midterm follow-up. At a follow-up of 24 to 36 months, there continued to be no significant difference in cardiac death ($p = 0.59$) or MI ($p = 0.65$), although a statistically significant difference was found in TVR ($p = 0.005$) in favor of DES.
- B. Oliver et al. (2008) conducted a meta-analysis of randomized trials assessing the outcome of brachytherapy or drug-eluting stents for the treatment of in-stent restenosis. The analysis included 14 studies/3103 patients. Neither treatment had any effect on mortality or rate of myocardial infarction. At intermediate follow-up, brachytherapy reduced the rate of revascularization, binary restenosis, and late loss compared to balloon angioplasty and selective bare metal stents alone. MACE rates were lower in patients treated with brachytherapy at both intermediate and long-term follow-up. Drug-eluting stents reduced the rate of revascularization, MACE, and binary restenosis compared to brachytherapy, but follow-up was limited to nine months. The authors concluded that vascular brachytherapy improves the long-term outcome of angioplasty compared with bare metal stents alone in the treatment of in-stent restenosis, and drug-eluting stents appear to provide similar results during short-term follow-up.
- C. Uchida et al. (2006) conducted a meta-analysis of randomized controlled trials comparing intracoronary gamma- and beta-radiation therapy to placebo for in-stent restenosis. The authors assessed the effectiveness of brachytherapy and of the two radiation sources, and also evaluated the performance of the procedure in native coronary arteries and SVG. Five randomized controlled trials that compared brachytherapy to placebo in 1310 patients were reviewed. There was considerable between-study variance, and

diabetes was found to be a significant factor in this variance. In multivariate meta-regression analyses adjusted for diabetes and lesion length, neither gamma radiation source nor SVG was a significant factor for the between-study variance ($p = 0.675$ and 0.433 , respectively). Neither procedure in SVG (gamma radiation) nor difference in radiation source (beta or gamma) in native coronary arteries was a significant factor in brachytherapy effectiveness compared to placebo. Intracoronary brachytherapy was effective compared to placebo at mid-term follow-up.

D. Additional proposed indications include:

1. Intracoronary brachytherapy has been proposed as a treatment for new stenosis of native coronary arteries and SVG, as well as restenosis of native coronary arteries and SVG at the unstented site of a previous PCI
2. Brachytherapy has also been evaluated as a method of primary prevention of restenosis after stent implantation for de novo lesions

E. In the BetAce randomized trial, Ribichini et al. (2006) evaluated brachytherapy for prevention of in-stent restenosis after angioplasty of de novo lesions in patients with high plasma angiotensin converting enzyme (ACE). Elevated plasma ACE levels have been proposed to increase the risk of in-stent restenosis. Thirty-one patients (33 stenoses) were randomized to stent implantation (control group), and 30 patients (31 stenoses) were randomized to brachytherapy and stented angioplasty. Following angioplasty, in-stent minimal lumen diameter (MLD) was similar in both groups. At 6 months, MLD had decreased in the control group to 1.74 ± 0.8 mm, compared to 2.25 ± 1.05 mm in the brachytherapy group. The mean in-stent diameter was 2.3 ± 0.8 in the control group vs. 2.9 ± 1.05 in the brachytherapy group, and the restenosis rate was 37.5% in the control group vs. 17.9% in the brachytherapy group. At six months, a higher need for TVR was seen in the control group (35.5%) than in the brachytherapy group (13.3%). The authors concluded that this study confirms that patients with high plasma ACE levels are exposed to an increased risk for in-stent restenosis and that the preventive use of brachytherapy in these patients reduced neointimal formation and increased MLD.

F. Ferrero et al. (2007) reported five-year follow-up of the BetAce trial, analyzing the incidence of death, myocardial infarction (MI), and ischemia-driven target vessel revascularization (TVR). The incidence of stent thrombosis was slightly higher in the brachytherapy group (10%) than in the control group (6.5%). This difference was not statistically significant. Although there was a significantly higher need for TVR in the control group at six months, the difference lost its significance at 12 months and five years because of a late catch-up phenomenon in the brachytherapy group, with a higher incidence of edge stenosis and stent occlusion. Five-year event-free survival rank for death, MI and TVR was 43% in the brachytherapy group compared to 45% in the control group ($p = .95$). The occurrence of additional ischemic events in

both groups equalized the long-term clinical outcomes. The authors stated that intracoronary beta radiation at the time of stent implantation only transiently prevents excessive neointimal proliferation that leads to stenosis recurrence in the first year after treatment. The late catch-up phenomenon, along with the natural progression of the atherosclerotic disease in other segments, is responsible for the loss of the clinical benefit of brachytherapy in the long term.

- G. Syeda et al. (2006) conducted a double-blind, randomized trial of beta brachytherapy for prevention of restenosis after stent implantation in native coronary de novo lesions. Eighty-nine diabetic patients (106 lesions) were randomly assigned to treatment with beta radiation or placebo treatment. Angiographic analysis at nine months demonstrated a late lumen loss of 0.7 ± 0.9 mm in the brachytherapy group vs. 1.2 ± 0.8 mm in the control group at the injured segment, 0.9 ± 1.0 vs. 1.3 ± 0.7 mm at the radiated segment, and 0.9 ± 1.0 vs. 1.3 ± 0.7 mm at the target segment. Binary restenosis rates were significantly lower in the brachytherapy group in all subsegments. TVR for restenosis was necessary in nine lesions (17.6%) in the brachytherapy group vs. 18 (34%) in the placebo group. Late thrombosis occurred in four brachytherapy patients after premature discontinuation of antiplatelet therapy, resulting in a MACE rate of 37.2%, compared to 38.6% in the placebo group. The authors concluded that, in diabetic patients with de novo coronary lesions, intracoronary radiation after stent implantation significantly reduced restenosis. This clinical benefit was reduced, however, by the frequent occurrence of new thrombosis.

III. Professional societies/organizations

- A. A guideline update for PCI published by the American College of Cardiology (ACC), American Heart Association (AHA) and the Society for Cardiovascular Angiography and Interventions (SCAI) (Smith et al., 2005) states that vascular brachytherapy has been successful in treating restenosis occurring within stents, while other adjunctive therapies, such as the cutting balloon, rotary ablation, excimer laser and restenting have shown mixed results. The ACC/AHA/SCAI guideline states that brachytherapy can be useful as a safe and effective treatment for in stent restenosis (Class IIa recommendation). A Class IIa recommendation indicates that there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment but that the weight of evidence is in favor of usefulness/efficacy. No changes to this recommendation were made in focused updates to the PCI guideline published in 2007 and 2009.
- B. A 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) PCI guideline (Wijns et al.) does not include recommendations for brachytherapy. The background of the guideline references studies demonstrating superiority of DES over brachytherapy.

- C. Guidelines for PCI issued by the European Society of Cardiology (ESC) state that brachytherapy proved to be the only evidence-based nonsurgical treatment for in-stent restenosis. The guideline also states that a prolonged intake of clopidogrel for one year after radiation is necessary. The ESC guideline recommends brachytherapy for the treatment of in-stent restenosis in native coronary arteries as a Class 1A recommendation. Brachytherapy for treatment of in-stent restenosis of a saphenous vein bypass graft is considered as a Class 1B recommendation. Class I indicates evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective. Level of evidence A indicates that data is derived from multiple randomized clinical trials or meta-analyses, while level of evidence B indicates data is derived from a single randomized clinical trial or large non-randomized studies (Silber et al., 2005).
- D. Guidelines on Myocardial Revascularization developed by The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) state that currently, intracoronary brachytherapy is of very limited use: restenosis rates have declined and in-stent restenoses after BMS are treated by DES or CABG.

IV. Summary

Prior to the widespread use of drug-eluting stents, in-stent restenosis following percutaneous coronary intervention (PCI) was a significant clinical problem, frequently resulting in the need for repeat revascularization procedures. Intracoronary brachytherapy was shown to be an effective treatment for in-stent restenosis of native coronary arteries or saphenous vein grafts. Brachytherapy procedures have decreased in frequency, however, and drug-eluting stents have emerged as the treatment of choice in the majority of cases. Brachytherapy may still play a role in the treatment of in-stent restenosis in selected patients, however.

There is insufficient evidence in the published medical literature to demonstrate the safety and efficacy of brachytherapy for expanded indications, including treatment for new stenosis of native coronary arteries and SVGs; restenosis of native coronary arteries and SVGs at the unstented site of a previous PCI; or as primary prevention of restenosis after stent implantation for de novo lesions. The use of brachytherapy for treatment of restenosis in a DES also remains investigational, as medical efficacy has not yet been demonstrated.

References

1. Ajani AE, Waksman R, Sharma AK et al. Three-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. Original WRIST. Washington Radiation for In-Stent Restenosis Trial. *Cardiovasc Radiat Med*. 2001 Oct-Dec; 2(4):200-204. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S1522186502001051>
2. Alli OO, Teirstein PS, Satler L et al. Five-year follow-up of the sirolimus-eluting stents vs vascular brachytherapy for bare metal in-stent restenosis (SISR) trial. *Am Heart J*. 2012 Mar; 163(3):438-445. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0002870311008775>
3. Bonow RO, Mann DL, Zipes DP, et al ed. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th Edition. Saunders, an imprint of Elsevier; 2011.
4. Brenner DJ, Miller RC. Long-term efficacy of intracoronary irradiation in inhibiting in-stent restenosis. *Circulation*. 2001 Mar 6; 103(9):1330-1332. Accessed June 22, 2016. <http://circ.ahajournals.org/content/103/9/1330.full>
5. Castagna MT, Mintz GS, Waksman R, et al. Comparative efficacy of γ -irradiation for treatment of in-stent restenosis in saphenous vein graft versus native coronary artery in-stent restenosis: an intravascular ultrasound study. *Circulation*. 2001 Dec 18; 104(25):3020-3022. Accessed June 22, 2016. <http://circ.ahajournals.org/content/104/25/3020.full>
6. Castagna MT, Mintz GS, Weissman NJ, et al. Intravascular ultrasound analysis of the impact of gamma radiation therapy on the treatment of saphenous vein graft in-stent restenosis. *Am J Cardiol*. 2002 Dec 15; 90(12):1378-1381. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0002914902028771>
7. Ellis SG, O'Shaughnessy CD, Martin SL, et al. Two-year clinical outcomes after paclitaxel-eluting stent or brachytherapy treatment for bare metal stent restenosis: the TAXUS V ISR trial. *Eur Heart J*. 2008 Jul; 29(13):1625-1634. Accessed June 22, 2016. <http://eurheartj.oxfordjournals.org/content/29/13/1625.full>
8. Ferrero V, Ribichini F, Heyndrickx GR, et al. Angiographic and three-dimensional intravascular ultrasound analysis of combined intracoronary beta radiation and self-expanding stent implantation in human coronary arteries. *Am J Cardiol*. 2004 Nov 15; 94(10):1237-1242. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0002914904012202>
9. Ferrero V, Ribichini F, Piessens M, et al. Intracoronary β -irradiation for the treatment of de novo lesions: 5-year clinical follow-up of the BetAce randomized trial. *Am Heart J*. 2007 Mar; 153(3):398-402. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0002870306010404>
10. Geiger MH, Ludwig J, Burckhard R, et al. High-dose intracoronary irradiation after de novo stent implantation. *Strahlenther Onkol*. 2006 Jan; 182(1):9-15. Accessed June 22, 2016. <http://link.springer.com/article/10.1007/s00066-006-1434-y>
11. Grise MA, Massullo V, Jani S, et al. Five-year clinical follow-up after intracoronary radiation: results of a randomized clinical trial. *Circulation*. 2002 Jun 11; 105(23):2737-2740. Accessed June 22, 2016. <http://circ.ahajournals.org/content/105/23/2737.full>
12. Holmes DR Jr, Teirstein PS, Satler L, et al. 3-year follow-up of the SISR (Sirolimus Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial. *JACC Cardiovasc Interv*. 2008 Aug; 1(4):439-448. Accessed June 22, 2016. http://ac.els-cdn.com/S1936879808002719/1-s2.0-S1936879808002719-main.pdf?_tid=ebd48668-7414-11e4-918e-00000aach361&acdnat=1416859573_0a1b5e04bbabd75e2e8ea79501af3814
13. Kolh P, Wijns W, Danchin N, et al. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association for Percutaneous Cardiovascular Interventions (EAPCI), Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg*. 2010 Sep; 38 Suppl:S1-S52. Accessed June 22, 2016. http://ejcts.oxfordjournals.org/content/38/Supplement_1/S1.full.pdf+html
14. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med*. 2001 Jan 25; 344(4):250-256. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM200101253440402>
15. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2012 Feb 15; 79(3):453-495. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/ccd.23438/abstract>
16. Lu YG, Chen YM, Li L, et al. Drug-eluting stents vs. intracoronary brachytherapy for in-stent restenosis: a meta-analysis. *Clin Cardiol*. 2011 Jun; 34(6):344-351. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/clc.20900/full>
17. Oliver LN, Buttner PG, Hobson H, et al. A meta-analysis of randomised controlled trials assessing drug-eluting stents and vascular brachytherapy in the treatment of coronary artery in-stent restenosis. *Int J Cardiol*. 2008 May 23; 126(2):216-223. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0167527307008042>

18. Popma JJ, Suntharalingam M, Lansky AJ, et al. Randomized trial of $^{90}\text{Sr}/^{90}\text{Y}$ β -radiation versus placebo control for treatment of in-stent restenosis. *Circulation*. 2002 Aug 27; 106(9):1090-1096. Accessed June 22, 2016. <http://circ.ahajournals.org/content/106/9/1090.full>
19. Rha SW, Kuchulakanti P, Ajani AE, et al. Three-year follow-up after intravascular γ -radiation for in-stent restenosis in saphenous vein grafts. *Catheter Cardiovasc Interv*. 2005 Jun; 65(2):257-262. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/ccd.20372/abstract>
20. Ribichini F, Ferrero V, Piessens M, et al. Intracoronary β -irradiation prevents excessive in-stent neointimal proliferation in de novo lesions of patients with high plasma ACE levels. The BetAce randomized trial. *Cardiovasc Revasc Med*. 2005 Jan-Mar; 6(1):7-13. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S155383890500031X>
21. Schiele TM, Pollinger B, Kantlehner R, et al. Evolution of angiographic restenosis rate and late lumen loss after intracoronary beta radiation for in-stent restenotic lesions. *Am J Cardiol*. 2004 Apr 1; 93(7):836-842. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S000291490301748X>
22. Serruys PW, Wijns W, Sianos G, et al. Direct stenting versus direct stenting followed by centered beta-radiation with intravascular ultrasound-guided dosimetry and long-term anti-platelet treatment: results of a randomized trial: Beta-Radiation Investigation with Direct Stenting and Galileo in Europe (BRIDGE). *J Am Coll Cardiol*. 2004 Aug 4; 44(3):528-537. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0735109704009544>
23. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J*. 2005 Apr; 26(8):804-847. Accessed June 22, 2016. <http://eurheartj.oxfordjournals.org/content/26/8/804.full>
24. Silber S, Popma JJ, Suntharalingam M et al., START Investigators. Two-year clinical follow-up of $^{90}\text{Sr}/^{90}\text{Y}$ β -radiation versus placebo control for the treatment of in-stent restenosis. *Am Heart J*. 2005 Apr; 149(4):689-694. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0002870304006143>
25. Syeda B, Schukro C, Kirisits C, et al. Randomized blinded clinical trial of intracoronary brachytherapy with $^{90}\text{Sr}/^{90}\text{Y}$ beta-radiation for the prevention of restenosis after stent implantation in native coronary arteries in diabetic patients. *Radiother Oncol*. 2006 Jan; 78(1):60-66. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814005004743>
26. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med*. 1997 Jun 12; 336(24):1697-1703. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199706123362402>
27. Uchida T, Bakhai A, Almonacid A, et al. A meta-analysis of randomized controlled trials of intracoronary gamma- and beta-radiation therapy for in-stent restenosis. *Heart Vessels*. 2006 Nov; 21(6):368-374. Accessed June 22, 2016. <http://link.springer.com/article/10.1007/s00380-006-0919-z>
28. U.S. Food and Drug Administration. Center for Devices and Radiological Health. PMA-Premarket Approval database. Accessed June 22, 2016. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>
29. Van Belle E, Bauters C, Bertrand ME. The biology of restenosis. Topol EJ, ed. *Textbook of cardiovascular medicine*. Philadelphia: Lippincott Williams & Wilkins a Wolters Kluwer business 2007.
30. Verin V, Popowski Y, de Bruyne B, et al. Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group. *N Engl J Med*. 2001 Jan 25; 344(4):243-249. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM200101253440401>
31. Waksman R, Ajani AE, White RL, et al. Intravascular gamma radiation for in-stent restenosis in saphenous-vein bypass grafts. *N Engl J Med*. 2002 Apr 18; 346(16):1194-1199. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa012579>
32. Waksman R, Ajani AE, White RL, et al. Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. *Circulation*. 2004 Jan 27; 109(3):340-344. Accessed June 22, 2016. <http://circ.ahajournals.org/content/109/3/340.full>
33. Waksman R, Raizner AE, Yeung AC, et al. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet*. 2002 Feb 16; 359(9306):551-557. Accessed June 22, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(02\)07741-3/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)07741-3/fulltext) Erratum in: *Lancet* 2002 Jun 1; 359(9321):1950. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(02\)08760-3/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(02)08760-3/fulltext)
34. Zavalloni D, Bello G, Rossi ML, et al. Comparison between drug-eluting stents and beta-radiation for the treatment of diffuse in-stent restenosis: clinical and angiographic outcomes. *Am Heart J*. 2006 Nov; 152(5):908.e1-908.e7. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0002870306000664>

Brachytherapy of the Coronary Arteries

[Return to Table of Contents](#)

Hyperthermia

POLICY

I. The use of hyperthermia and concurrent radiation therapy treatment is medically necessary for any of the following:

- A. Superficially recurrent melanoma
- B. Chest wall recurrence of breast cancer
- C. Recurrent cervical lymph nodes from head and neck cancer

Treatment of the above conditions will be approved in the absence of both of the following:

- D. Metastatic disease for which chemotherapy or hormonal therapy is being given concurrently or planned
- E. Evidence of tumor recurrence exceeding 4 cm in depth

When hyperthermia is indicated, no more than 10 hyperthermia treatments delivered twice weekly at 72-hour intervals should be utilized.

II. The use of intraluminal, endocavitary, interstitial, regional deep tissue hyperthermia exceeding 4 cm in depth, and whole body hyperthermia is considered experimental, investigational, or unproven (EIU)

Key Clinical Points

After initial enthusiasm for the use of hyperthermia in the late 1970s, interest waned with the publication of studies showing little or no benefit in the mid-1980s. Later review of the negative findings disclosed that the critical temperature necessary for hyperthermic cell death, 42 to 43 degrees centigrade (C), was either poorly measured or poorly maintained in these studies. Point measurements rather than volume mapping of thermal gradients were relied upon in planning these hyperthermia studies.

Renewed interest in the use of hyperthermia began to emerge in both Europe and the United States (US) in the 1990s. Research from Duke University, Northwestern University, University of Southern California, Stanford University, Washington University, as well as centers in Holland, Germany, Norway, Austria, Italy, and Switzerland have contributed substantially to the emergence of hyperthermia as a useful treatment modality when combined with radiation therapy.

Currently, in the US, the Food and Drug Administration (FDA) has approved hyperthermia for use in the treatment of cancer when combined with radiation therapy for the "...palliative management of certain solid surface and subsurface malignant tumors (i.e. melanoma, squamous or basal cell tumors, adenocarcinoma, or sarcoma) that are progressive or recurrent despite conventional therapy." The National Cancer Center Network (NCCN) recommends "...that the use of hyperthermia be limited to treatment centers with appropriate training, expertise and equipment..." The NCCN Panel on Breast Cancer concluded that it was a controversial Category 3 recommendation in the treatment of local or regional recurrent breast cancer.

Following FDA approval, Medicare approved coverage for local hyperthermia when used together with radiation therapy. A National Coverage Determination (NCD 110.1) was issued by Medicare (CMS) in December 1984 and remains unchanged. It states, "Local hyperthermia is covered under Medicare when used in conjunction with radiation therapy for the treatment of primary or metastatic cutaneous or subcutaneous superficial malignancies. It is not covered when used alone or in connection with chemotherapy." Coding for this treatment is recognized and published in the current 2010 ACR/ASTRO guide.

Although research into hyperthermic treatments at depths greater than 4 cm is ongoing in the US, it is currently recognized only as investigational as are intraluminal, endocavitary, and interstitial applications.

On May 15, 2009, the FDA granted humanitarian use device (HUD) status to the BSD-2000 and on November 18, 2011, the FDA granted humanitarian device exemption (HDE) to the BSD-2000 for the treatment of cervical cancer patients ineligible for chemotherapy (treatment population less than 4,000). This is the only approval for deep heating, and only actual costs incurred in the research may be billed. Other applications for deep heating are pending for both BSD and Medifocus devices.

In the US, only the BSD-500 has FDA commercial clearance for superficial heating (less than a 4 cm depth). This is currently the only device approved for reimbursement. It operates at the microwave range of 915 MHz with different applicators and power setting ranging from 20 to 250 watts. The standard recommended treatment regimen for use with radiation therapy is a "...total of 10 hyperthermia treatments delivered two times per week at 72-hour intervals, with each heat treatment preceded or followed by a standard prescribed dose of ionizing radiation within 30 minutes of the heat treatment." A sustained intratumoral temperature of 42.5 degrees C for 60 minutes is recommended.

The FDA granted per-market approval for the Sonotherm® 1000 Ultrasound Therapy System on September 29, 1989. This approval was for hyperthermia to treat tumors at a depth of 8 cm. Although FDA approval was granted, the device remains in clinical study and is designated EIU.

ExAblate® 2000/2100 is a Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) system designed to treat pain from metastatic bone tumors that have recurred or progressed despite attempts with conventional radiation treatment. This device, although FDA approved remains the object of clinical study and is designated EIU. There is a clinical trial (NCT00981578) investigating its use underway.

There are three clinical sites in which randomized studies have documented the benefit of hyperthermia given in conjunction with radiotherapy.

1. Melanoma – 134 metastatic or recurrent lesions of malignant melanoma in 70 patients were randomly assigned to receive radiation therapy (three fractions of 8 or 9 Gy over 8 days) alone or followed by hyperthermia (43 degrees C for 60 minutes). Beneficial local effect was 28% for radiation alone, and 46% for combined treatment. Toxicity was not higher with hyperthermia (Overgaard, 1995)
2. Breast – Five randomized trials were combined to report the benefit of combined treatment for superficial localized breast cancer. The control rate for radiation therapy alone was 41%, while that for combined treatment was 59%. The greatest effect was observed in patients with recurrent lesions in previously irradiated lesions where further irradiation was limited to low doses (Vernon, 1996)
3. Head and neck metastatic lymph nodes – a randomized study of 44 nodes in 41 patients confirmed the improved five-year actuarial nodal control of the combined treatment arm. In addition, the study reports a statistically significant in survival at five years, and no increased toxicity from combined modality therapy (Valdagni, 1994)

1. American College of Radiology (ACR)/American Society of Radiation Therapy (ASTRO) Coding Guide. Accessed June 24, 2016. <https://www.astro.org/Practice-Management/Radiation-Oncology-Coding/Index.aspx>
2. BSD-2000 Brochure. Accessed June 24, 2016. http://hyperthermia.pyrexar.com/acton/attachment/15060/f-0001/1/-/f-0001/f-0001:4a/BSD-2000_brochure.pdf
3. BSD-500 Brochure. Accessed June 24, 2016. http://hyperthermia.pyrexar.com/acton/attachment/15060/f-0002/1/-/f-0001/f-0001:4a/BSD-500_brochure.pdf
4. ExAblate Conformal Bone System Treatment of Metastatic Bone Tumors for the Palliation of Pain. Last verified November 2015. Accessed June 24, 2016. <https://clinicaltrials.gov/ct2/show/NCT00981578>
5. ExAblate Model 2000/2100 – P110039. Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) system. Accessed June 24, 2016. <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm327521.htm>
6. HUD and HDE for BSD-2000. Accessed June 24, 2016. http://www.accessdata.fda.gov/cdrh_docs/pdf9/H090002a.pdf
7. Hyperthermia for Treatment of Cancer. National Coverage Determination (NCD) 110.1. Accessed June 24, 2016. <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=66&ncdver=1&DocID=110.1&SearchType=Advanced&bc=IAAAAAGAAAAAA%3d%3d&>
8. National Comprehensive Cancer Network (NCCN) Guidelines. Version 2.2016. Breast Cancer. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Breast Cancer Version 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
9. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. Lancet. 1995 Mar 4; 345(8949):540-543. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0140673695904638>
10. PMA for BSD-500. Accessed June 24, 2016. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P820088> and supplement <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P820088S017>
11. Sonotherm® 1000 Ultrasound Therapy System. Accessed June 24, 2016. <http://www.labthermics.com/sono.html>
12. Valdagni R, Amichetti M. Report of long-term follow up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int. J. Radiat. Oncol. Biol. Phys. 1994 Jan 1; 28(1):163–169. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/0360301694901546>
13. Vernon CC, Hand JW, Field SB et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys. 1996 Jul 1; 35(4):731-44. Accessed June 24, 2016. [http://www.redjournal.org/article/0360-3016\(96\)00154-X/abstract](http://www.redjournal.org/article/0360-3016(96)00154-X/abstract)

Page 19 of 206
www.eviCore.com

Image-Guided Radiation Therapy (IGRT)

POLICY

IGRT is a method by which image guidance is applied to place the isocenter for the upcoming treatment appropriately. This technology typically is applied for an individual undergoing Intensity-Modulated Radiation Therapy (IMRT). However, in some cases in which the isocenter is the main concern, occasionally it could be seen with three-dimensional (3D) conformal radiation therapy (CRT). It is not appropriate to apply IGRT to non-IMRT or non-3DCRT. The American Society for Radiation Oncology (ASTRO) has published general guidelines and safety issues regarding IGRT, as well as a coding guide. There are also publications regarding risks associated with daily radiation exposure from IGRT (Lisbona et al., 2012).

Historical methodology of using port films to confirm patient set-up and block placement has not been replaced by IGRT. Outside of treatment procedures requiring only isocenter placement, port films and/or verification simulations are still the appropriate modalities. If the isocenter placement is the primary concern, i.e. for IMRT, then IGRT is typically the method utilized. This does, however, imply the target can be localized with the specific IGRT modality requested, i.e., stereoscopic imaging for target localization, computed tomography (CT) guidance for field placement or ultrasound (US) guidance for field placement (Weiss et al., 2011). In the event no target is localized, blocking and patient set-up is accomplished through typical alignment of bony structures using portal imaging; appropriate coding for port films would apply.

I. IGRT techniques

- A. Effective 1/1/2015, IGRT techniques are covered under two different coding systems. CPT[®] code 77387 is for billing in the Hospital Outpatient Prospective Payment System (HOPPS) and for those non-Medicare health plans that accept this definition. It may be necessary to check with the individual health plan directly before billing this code for this purpose. Also, the new IMRT treatment delivery CPT[®] codes (77385 and 77386) include IGRT guidance and tracking, when performed. The technical component of IGRT (77387-TC) is packaged into the IMRT service with which it is performed and is not reported separately. In the Medicare Physician Fee Schedule (MPFS) setting, as well as the Healthcare Common Procedure Coding System (HCPCS) setting, the G-Code system has replaced CPT[®] codes. G6001 replaces CPT[®] code 76950, G6002 replaces CPT[®] code 77421, and G6017 replaces CPT[®] code 0197T. In contrast to the HOPPS reporting, IGRT is not bundled into IMRT for MPFS and HCPCS and is reported separately.

The descriptions of the commonly used IGRT techniques are listed here:

A. US guidance

Ultrasound is authorized only for use in the definitive treatment of prostate cancer using IMRT. This method requires the utilization of US to place the field appropriately prior to each treatment.

B. 3-Dimensional Computed Tomography (3DCT) guidance/MV/kV

This method requires the utilization of CT to place the field appropriately prior to each treatment. Cone-beam CT (CBCT) or tomotherapy are the approved devices.

C. Stereoscopic xray guidance

There are several kilovoltage (kV) and megavoltage (MV) technologies in general use for stereoscopic xray guidance. This method requires the direct visualization of the designated target or localization through visualization of implanted fiducial markers. If the target volume is well visualized, implanted fiducials may not be necessary clinically. Matching to surgical clips in the treatment volume for post-operative cases is allowed in selected cases. It is appropriate to bill one IGRT unit when IGRT is used to treat two separate anatomical areas. Use of stereoscopic IGRT technique requires direct physician supervision to bill for the professional and technical component of the work performed. The use of orthogonal portal imaging to locate fiducial markers in and of itself would not fulfill the required criteria to use the IGRT code. The stereoscopic images have to be fused and registered with the pretreatment digitally reconstructed radiographs and the required shifts calculated. A radiation oncologist, or a medical physicist or trained therapist under the direct supervision of the radiation oncologist, reviews the automated image fusion and makes manual or automatic adjustments as necessary.

D. Continuous localization systems

These non-ionizing technologies, which are designed to localize the tumor, patient, or surrogate continuously, include the electromagnetic guidance system Calypso[®], as well as the camera systems RadioCameras[™] and AlignRT[®].

Respiratory motion management may be clinically appropriate for treating some cancers, including lung cancer and some cases of breast cancer (deep breath inspiration hold [DBIH]). Respiratory tracking by continuous localization systems or four-dimensional CT (4D-CT) are now included in CPT[®] code 77387. This code is for billing in the HOPPS and for those non-Medicare health plans that accept this definition. It may be necessary to check with the individual health plan directly before billing this code for this purpose. In the MPFS setting as well as the HCPCS setting, the G-Code

G6017 has replaced CPT® code 0197T. In the hospital-outpatient setting, G6017 is considered image guidance and is packaged into the primary service payment. For all other purposes, this code is considered carrier-priced and may be accepted or refused by different health plans and Medicare contractors.

In IGRT-approved cases, only one method or technique of IGRT is allowed daily.

CPT® codes 77370 and 77470 should not be billed based on the use of IGRT.

II. eviCore IGRT policy

IGRT is approved for most cases where IMRT has been approved. See below for details. IGRT is approved less frequently in conjunction with 3DCRT. For exceptions, see below. For Stereotactic Body Radiation Therapy (SBRT), the IGRT codes may not be billed separately because by American Medical Association (AMA) definition they are bundled and included in the daily treatment codes. In addition, the IGRT codes may not be billed separately with Stereotactic Radiosurgery (SRS) as stated in the ASTRO coding guide. Because of the concern of radiation exposure that can result from kV or MV imaging and CBCT to normal tissues both within and outside of the treatment field, IGRT should be used only when clinically necessary, and techniques that minimize radiation exposure should be adhered to.

III. IGRT documentation

The medical record should contain documentation of the medical necessity for the procedure, describing the medical appropriateness, the target delineation methodology, the type and frequency of imaging, acceptable parameters for shifts and information on the fusion algorithm. The images and shifts are to be reviewed and approved by the radiation oncologist prior to the member's next treatment. Appropriate documentation could be a note to the individual's chart and/or a physician's electronic signature on the shifts/images. A unique daily note is not required.

IV. IGRT for approved IMRT cases

The use of IMRT requires extraordinary accuracy due to the numerous beamlets and gantry angles required in this very sophisticated form of radiation therapy. When the use of IMRT has been approved, IGRT may be used to visualize and ensure proper localization of the target volume.

Indications:

- A. Prostate cancer
 - 1. US guidance may be used daily for treatment of prostate cancer. It is not to be used with other IGRT modalities
 - 2. Daily CT guidance may be used as a sole modality
 - 3. Daily kV or MV imaging is permissible when treating the intact prostate only if fiducial markers have been placed in the prostate
 - 4. In post-prostatectomy cases, when bony landmarks are being used to align the patient, IGRT is not medically necessary
- B. Head and neck cancer
 - 1. Daily MV or kV imaging may be used when bone and soft tissue structures or surgical clips in the treatment volume can be successfully fused. When clinically indicated, daily CBCT will be authorized
- C. Breast cancer
 - 1. For partial breast accelerated IMRT with fiducial markers or fusable surgical clips, IGRT is appropriate.
- D. Anal cancer
 - 1. CBCT is authorized daily
- E. Pancreatic cancer
 - 1. CBCT is authorized daily when IMRT is approved in the curative setting
 - 2. kV/MV imaging may be used in the curative setting when fiducial markers or surgical clips in the treatment volume are present
- F. Lung cancer
 - 1. CBCT is authorized daily when IMRT is approved
 - 2. Daily kV/MV imaging is authorized when fiducial markers or surgical clips in the treatment volume are present or when the tumor can be visualized and fused successfully on xray
- G. Postoperative endometrial and cervical cancers
 - 1. IGRT should not be necessary for daily treatment to the whole pelvis to total doses of 45 to 50 Gy. IGRT will be authorized when there is concern about toxicity to the small bowel, and CBCT will be utilized to verify avoidance of hotspots. kV/MV imaging using fiducial markers or surgical clips in the treatment volume may also be used in approved cases
- H. All other IMRT approved sites
 - 1. For preoperative, definitive, postoperative cases with fiducials or surgical clips in the treatment volume in place, stereoscopic imaging may be used daily
 - 2. For preoperative, definitive, postoperative cases without fiducials or surgical clips in the treatment volume in place, stereoscopic imaging would not be considered helpful if the target volume could not be seen on kV/MV imaging. In this situation, CT guidance may be more appropriate

V. IGRT for 3D cases

IGRT frequently is considered not medically necessary in conjunction with 3DCRT. There is a long history of accurate treatment set-up with attention to immobilization, tattoo marking, simulation verification, and weekly MV portal

imaging. In most sites, the images obtained from standard portal imaging are acceptable in terms of isocenter determination and block verification. IGRT generally is not medically necessary in the palliative setting.

Exceptions to this policy will be made on a case-by-case basis based on the following circumstances:

- A. Close proximity to a previously treated region – IGRT may be indicated on a daily basis when fiducial markers or surgical clips in the treatment volume are present or when the spine needs to be accurately visualized and other landmark structures, such as bony anatomy or the airway, are not present within the portal image
- B. Small treatment volume within the chest or abdomen when the target volume is not in close proximity to a landmark structure such as bone or airway, making accurate set-up difficult with MV image only
- C. As per the 2016 ASTRO Radiation Oncology Coding Resource example of an “...extremely obese patient.”: It is presumed that MV imaging may not be helpful, and IGRT imaging techniques may offer better definition of landmark structures including bone and soft tissue structures
- D. For curative 3DCRT for prostate cancer for those fractions in which whole pelvis treatment is not being delivered CBCT may be beneficial
- E. All cases of lung cancer
- F. Any case including the spine where MV imaging is poor and acceptable landmarks cannot be identified. Please notify eviCore when this occurs to ensure that claims will not be denied. It is anticipated that this will not be necessary in most cases
- G. Cases of esophageal and gastroesophageal junction cancers
- H. Pelvic cancers treated in the prone position with the use of a belly board
- I. In the adjuvant treatment of breast cancer only during the boost to the surgical or lumpectomy bed when using photons
- J. In cases of photon-based external beam-based accelerated partial breast irradiation
- K. In cases where DIBH technique is being used to treat left-sided breast cancer
- L. In the preoperative or postoperative treatment of sarcoma

VI. IGRT for brachytherapy cases

In brachytherapy cases, imaging is medically necessary to verify source position in all but the simplest of cases. The images may also be used to perform dosimetry calculations. Use of applicable simulation and/or field verification codes is appropriate, such as CPT[®] Code 77280. Unique circumstances may require the use of IGRT with brachytherapy, such as gynecologic or breast cancers and will be reviewed on a case-by-case basis.

References

1. ASTRO coding FAQs and tips. Accessed June 22, 2016 <https://www.astro.org/Daily-Practice/Coding/Coding-Guidance/FAQ-IGRT/>
2. ASTRO Radiation Oncology Coding Resource. Available on-line for purchase. Accessed June 22, 2016. <https://www.astro.org/MyASTRO/Products/FindProduct.aspx>
3. Chadha M, Young A, Geraghty C, et al. Image guidance using 3D-ultrasound (3D-US) for daily positioning of lumpectomy cavity for boost irradiation. *Radiat Oncol*. 2011 May 9; 6:45. Accessed June 22, 2016. <http://www.royjournal.com/content/6/1/45>
4. Chen Y-J, Suh S, Nelson RA, et al. Setup variations in radiotherapy of anal cancer: advantages of target volume reduction using image-guided radiation treatment (IGRT). *Int J Radiat Oncol Biol Phys*. 2012 Sep 1; 84(1):289-295. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03476-6/abstract](http://www.redjournal.org/article/S0360-3016(11)03476-6/abstract)
5. Eldredge HB, Studenski M, Keith S, et al. IGRT after prostatectomy: evaluation of corrective shifts and toxicity using online conebeam CT vs. weekly port films for target localization. *Int J Radiat Oncol Biol Phys*. 2010 Nov 1; 78(3 Suppl):S380. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01870-5/fulltext](http://www.redjournal.org/article/S0360-3016(10)01870-5/fulltext)
6. Graff P, Hu W, Yom SS, et al. Does IGRT ensure target dose coverage of head and neck IMRT patients? *Radiother Oncol*. 2012 Jul; 104(1):83-90. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814011006062>
7. Hyer DE, Serago CF, Kim S, et al. An organ and effective dose study of XVI and OBI cone-beam CT systems. *J Appl Clin Med Phys*. 2010 Apr 17; 11(2):3183. Accessed June 22, 2016. <http://www.jacmp.org/index.php/jacmp/article/view/3183/1879>
8. Jaffray D, Langen KM, Mageras G, et al. Safety considerations for IGRT: executive summary. *Practical Radiation Oncology*. 2013 Jul-Sep; 3(3):167-170. Accessed June 22, 2016. [http://www.practicalradonc.org/article/S1879-8500\(13\)00007-6/fulltext](http://www.practicalradonc.org/article/S1879-8500(13)00007-6/fulltext)
9. Kan MW, Leung LHT, Wong W, et al. Radiation dose from cone beam computed tomography for image-guided radiation therapy. *Int J Radiat Oncol Biol Phys*. 2008 Jan 1; 70(1):272-279. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)04081-3/abstract](http://www.redjournal.org/article/S0360-3016(07)04081-3/abstract)
10. Leonard CE, Tallhamer M, Johnson T, et al. Clinical experience with image-guided radiotherapy in an accelerated partial breast intensity-modulated radiotherapy protocol. *Int J Radiat Oncol Biol Phys*. 2010 Feb 1; 76(2):528-534. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00185-0/abstract](http://www.redjournal.org/article/S0360-3016(09)00185-0/abstract)
11. Lisbona A, Averbek D, Supiot S, et al. IMRT combined to IGRT: increase of the irradiated volume consequences? *Cancer Radiother*. 2010 Oct; 14(6-7):563-570. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S1278321810003598>
12. Mohammed N, Kestin L, Grills I, et al. Comparison of IGRT registration strategies for optimal coverage of primary lung tumors and involved nodes based on multiple four-dimensional CT scans obtained throughout the radiotherapy course. *Int J Radiat Oncol Biol Phys*. 2012 Mar 15; 82(4):1541-1548. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)00546-3/abstract](http://www.redjournal.org/article/S0360-3016(11)00546-3/abstract)
13. Ottosson W, Baker M, Hedman M, et al. Evaluation of setup accuracy for NSCLC patients; studying the impact of different types of cone-beam CT matches based on whole thorax, columna vertebralis, and GTV. *Acta Oncol*. 2010 Oct; 49(7):1184-1191. Accessed June 22, 2016. <http://informahealthcare.com/doi/full/10.3109/0284186X.2010.500303>
14. Park CK, Pritz J, Zhang GG, et al. Validating fiducial markers for image-guided radiation therapy for accelerated partial breast irradiation in early-stage breast cancer. *Int J Radiat Oncol Biol Phys*. 2012 Mar 1; 82(3):e425-e431. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03097-5/abstract](http://www.redjournal.org/article/S0360-3016(11)03097-5/abstract)
15. Potters L, Gaspar LE, Kavanagh B, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT). *Int J Radiat Oncol Biol Phys*. 2010 Feb 1; 76(2):319-325. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03303-3/abstract](http://www.redjournal.org/article/S0360-3016(09)03303-3/abstract)
16. Sangalli G, Passoni P, Cattaneo GM, et al. Planning design of locally advanced pancreatic carcinoma using 4DCT and IMRT/IGRT technologies. *Acta Oncol*. 2011 Jan; 50(1):72-80. Accessed June 22, 2016. <http://informahealthcare.com/doi/full/10.3109/0284186X.2010.484425>
17. Shah A, Aird E, Shekhdar J. Contribution to normal tissue dose from concomitant radiation for two common kV-CBCT systems and one MVCT system used in radiotherapy. *Radiother Oncol*. 2012 Oct; 105(1):139-144. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814012002216>
18. Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: results of Radiation Therapy Oncology Group RTOG-0630 trial. *J Clin Oncol*. 2015 Feb 9. Published online before print. Accessed June 22, 2016. <http://jco.ascopubs.org/content/early/2015/02/03/JCO.2014.58.5828.full>
19. Weiss, K. IGRT, are you applying it correctly? Revenue Cycle. *Radiation Oncology News*. January 2011. Accessed June 22, 2016. <https://www.revenuecycleinc.com/medical-radiation-oncology-news/2842>

20. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys. 2012 Sep 1; 84(1):125-129. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03604-2/abstract](http://www.redjournal.org/article/S0360-3016(11)03604-2/abstract)

Image-Guided Radiation Therapy (IGRT)

[Return to Table of Contents](#)

Neutron Beam Radiotherapy in Cancer Treatment

POLICY

- I. **Neutron beam radiotherapy is medically necessary for salivary gland cancers that are inoperable, recurrent, or are resected with gross residual disease or positive margins.**
- II. **All other indications are not covered because neutron beam radiotherapy is experimental, investigational, or unproven (EIU).**

Key Clinical Points

Neutron beam radiotherapy differs from other forms of radiation particle treatment such as protons or electrons as neutrons have no electrical charge. The treatment effects are the results of the neutron mass producing dense radiation energy distributions. This effect is high energy linear transfer (LET) and may offset the negative effects of low oxygen tension in tumors, leading to increased rate of control in hypoxic tumors.

Currently, the number and location of neutron facilities in the United States is quite small. This has limited research and has resulted in a lack of substantial information on its clinical effectiveness, although it has been tried in soft tissue sarcoma, prostate cancer, pancreas, colon, and lung cancers amongst others. The lack of data and comparative trials limits its designation to EIU, with the exception of salivary gland cancers. The most recent advance in neutron treatment has been the development of Intensity Modulated Neutron Therapy (IMNRT) at the Wayne State Facility which may permit biologic dose escalation compared to IMRT while maintaining reasonable toxicity rates. The use of this technique is highly experimental at this time.

The effectiveness of neutrons as treatment of choice in the treatment of salivary gland tumors was most recently confirmed by Stannard et al. (2013) with the treatment of 335 patients at IThimba Labs. The patients were either unresectable or had gross macroscopic residual disease. Localregional control was 60.6% at 5 years and 39.1% at 10 years. Disease specific survival was 66.8% at 5 years and 53.7% at 10 years.

References:

1. Aihara T, Morita N, Kamitani N, et al. Boron neutron capture therapy for advanced salivary gland carcinoma in head and neck. In J Clin Oncol. 2014 Jun; 19(3):437-444. Accessed June 22, 2016. <http://link.springer.com/article/10.1007/s10147-013-0580-3>
2. American Society of Radiation Therapy (ASTRO Coding (2016). Accessed June 22, 2016. <https://www.astro.org/Coding.aspx>
3. Burmeister J, Spink R, Liang L, et al. Commissioning of intensity modulated neutron therapy (IMNRT). Med Phys 2013 Feb; 40(2):021718. Accessed June 22, 2016. <http://scitation.aip.org/content/aapm/journal/medphys/40/2/10.1118/1.4766878>
4. Douglas JG, Laramore GE, Austin-Seymour M, et al. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. Int J of Radiat Oncol Biol Phys. 2000 Feb 1; 46(3):551-557. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(99\)00445-9/abstract](http://www.redjournal.org/article/S0360-3016(99)00445-9/abstract)
5. Huber PE, Debus J, Latz D, et al. Radiotherapy for advanced adenoid cystic carcinoma: neutrons, photons or mixed beam? Radiotherapy and Oncology. 2001 May 1; 59(2):161-167. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814000002735>
6. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016 Head and Neck Cancers. Accessed June 22, 2016. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Head and Neck Cancers 1.2016. ©2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
7. Prott FJ, Micke O, Haverkamp U et al. Results of fast neutron therapy of adenoid cystic carcinoma of the salivary glands. Anticancer Research 2000 Sep-Oct; 20(5C):3743-9. Accessed June 22, 2016. <http://www.ncbi.nlm.nih.gov/pubmed/11268448>
8. Stannard C, Vernimmen E, Carrara H, et al. Malignant salivary gland tumors: can fast neutron therapy results point the way to carbon ion therapy? Radiother Oncol. 2013 Nov; 109(2):262-268. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S016781401300399X>

Neutron Beam Radiotherapy in Cancer Treatment

[Return to Table of Contents](#)

Proton Beam Radiation Therapy

POLICY

Proton Beam Therapy (PBT) is medically necessary for the treatment of the following tumors:

- I. Chordomas and chondrosarcomas of the base of the skull, localized and in the postoperative setting**
- II. Uveal melanoma, when PBT is considered preferential compared to brachytherapy**
- III. Localized unresectable hepatocellular carcinoma, when considered preferential to Stereotactic Body Radiation Therapy (SBRT) or radiofrequency ablation**
- IV. Stage IIA seminoma**

Prostate Cancer

- I. For prostate cancer where no prostatectomy was performed, PBT is not medically necessary**
- II. For adjuvant or salvage treatment of prostate cancer where prostatectomy was performed, PBT is experimental, investigational, and/or unproven (EIU)**

PBT is experimental, investigational and/or unproven (EIU) for all other tumors.

PBT in combination with photon therapy for any tumor is experimental, investigational and/or unproven (EIU).

Key Clinical Points

PBT is a form of external beam radiation therapy (EBRT) also known as charged particle therapy. Proton beam therapy provides the opportunity of achieving dose escalation and decreasing toxicity by delivering physical dose to a narrowly defined region, while avoiding normal tissue. The potential benefit is to improve local control, improve survival, and decrease toxicity.

While PBT has been used in individuals in the United States since the mid-1950s, and although it has been shown to be effective in some malignancies, there is no published

data clearly demonstrating superiority over conventional forms of radiation therapy (external photon beam therapy, electron beam therapy, or brachytherapy) (Brada et al., 2009).

In addition to the excellent American Society for Radiation Oncology (ASTRO) evidence-based review of PBT, there are other systematic reviews of PBT which also conclude that rationale for PBT is often associated with a low level of evidence according to standard health technology assessment and evidence-based medicine criteria (Brada et al., 2007; Olsen et al., 2007).

I. Central nervous system (CNS)

A. Chordomas and chondrosarcomas of the skull base

These rare primary malignant tumors of the skull base are treated primarily by surgery and postoperative radiotherapy. There is extensive data on the use of PBT for the treatment of these tumors postoperatively, although there are no randomized trials and no evidence of the superiority of PBT over conventional therapy in these tumors. A recent systematic review of all published cases of chordoma (416 patients) treated with proton radiotherapy revealed a local control of 69% and 5 year overall survival (OS) of 80% (Amichetti et al., 2009). While comparison to older historical data of conformal photon radiotherapy may imply some benefit to PBT, more current Stereotactic Radiosurgery (SRS) outcomes compare more favorably with PBT results. However, based on the rare nature of these tumors, their location adjacent to critical CNS structures, and the documented efficacy of PBT, treatment of these tumors with PBT is medically necessary.

B. Gliomas

Clinical published studies are limited, and the results are mixed with one study showing no significant benefit to PBT over conventional treatment while another small study showed a slightly longer median survival of 20 months, compared to standard photon therapy (Fitzek et al., 1999; Fitzek et al., 2001). At this time there is no data showing significant clinical benefit to PBT in the treatment of gliomas, and this treatment is deemed not medically necessary.

C. Benign CNS tumors

Meningiomas have been treated with PBT with good outcomes, but there is no evidence that this treatment is superior to conventional therapy (Boskos et al., 2009). Pituitary adenomas, craniopharyngiomas, arteriovenous malformations, and acoustic neuromas have also been treated with PBT; but conventional techniques and relatively safe doses of radiation also yield excellent results. (Barker et al., 2003; Bush et al., 2002; Luu et al., 2006;

Murphy et al., 2011; Ronson et al., 2006; Rowe et al., 2007; Weber et al., 2003). There is no definitive clinical evidence in this setting that PBT is associated with superior control rates or a decrease in secondary malignancies compared to treatment with conventional fractionated radiation therapy or radiosurgery techniques. The ASTRO emerging technology committee report on proton therapy specifically states “...more clinical data (published clinical trials) are needed to fully establish the role of PBT in CNS tumors.” Therefore, PBT is not medically necessary in the treatment of benign CNS tumors.

Of note, a recent retrospective analysis compared outcomes in pediatric patients who underwent proton therapy and IMRT for ependymoma and found increased rates of post-radiation magnetic resonance imaging (MRI) changes, and neurologic deficits from brainstem necrosis in those who underwent proton therapy vs. IMRT. These findings demonstrate the need for further comparative research examining clinical differences between proton and photon therapy.

II. Ocular tumors

A. Uveal Melanomas

PBT is effective in the treatment of these tumors with local control rates of over 95%, 85% cause-specific survival, and eye preservation rate of 90% with reasonable vision retained in approximately 50% of individuals. Intermediate tumors are treated just as effectively with brachytherapy, and the superiority of PBT in these tumors has not been demonstrated. For large uveal melanomas, PBT has been associated with a lower rate of secondary enucleation. Based on the extensive and excellent data on the use of protons in uveal melanomas, PBT is medically necessary, particularly in an individual who is not an optimal candidate for brachytherapy (Char et al., 2002; Conway et al., 2006; Desjardins et al., 2006; Egger et al., 2003; Lumbroso-Le Rouic et al., 2006).

III. Prostate cancer

- A. IMRT is the most commonly used technique of EBRT for the treatment of prostate cancer. Currently, the evidence does not support any definitive benefit to PBT over IMRT in the treatment of prostate cancer (Efsthathiou et al., 2009). There are no published patient-reported outcomes for prostate cancer patients treated with IMRT versus PBT.

Since IMRT and/or brachytherapy are considered the standard of care, any discussion on PBT must be compared to these modalities. The table below shows recent outcome data in prostate cancer using standard modalities.

Table 1

Trial	Boost Modality	Planning Technique	High Dose Arm	5-Year Control	10-year Control	Gastrointestinal Toxicity	
						≥ G2	≥ G3
PROG 95-09 (Zietman et al., 2010)	protons	3D	79.2 Gy	91%	83%	17%	1%
ACR phase 2 03-12 (Coen et al., 2011)	protons	3D	82 Gy	Not reported yet	Not reported yet	26%	7%
Single institution MSK (Spratt et al., 2013)	xrays	IMRT	86.4 Gy		98.8% (7 year)*	4.4%	0.70%
MSK LDR – seeds (Kollmeier et al., 2013)	seeds	Brachytherapy	>100 Gy		97% (8 year)**	3%	
MSK HDR brachytherapy (Kotecha et al., 2013)	Ir-192	IMRT	>100 Gy		95% (7 year)***	1%	0.40%

*control at 7 years is 100%, 97.7%, 85.6% and 67.9% for very low risk, low risk, intermediate risk and high risk patients

**control for low risk is 97% and for intermediate risk is 94%

*** 7-year prostate specific antigen (PSA) relapse-free survival (RFS) for low risk, intermediate risk and high risk is 95%, 90% and 57%

While not meant to make an exact comparison, the point of the table is to show the very high local control rates and low toxicity rates against which PBT will ultimately need to be compared in order for PBT to be considered a standard therapy for early prostate cancer.

A Surveillance, Epidemiology and End Results (SEER)-Medicare analysis evaluated the comparative effectiveness of IMRT, proton therapy, and conformal radiation therapy for prostate cancer. In the comparison between IMRT and proton therapy, IMRT patients had a lower rate of gastrointestinal morbidity. There were no other significant differences regarding toxicities between IMRT and proton therapy (Sheets et al., 2012). Another analysis of early toxicity compared 421 patients treated for prostate cancer with proton therapy and 842 matched case controls treated with IMRT within the SEER-Medicare database. There was a statistically significant decrease in genitourinary toxicity at 6 months with proton therapy, however this difference disappeared by one year. There were no other significant differences in toxicity between the two techniques. Costs were approximately 75% higher with proton therapy (Yu et al., 2013).

Three prospective single arm studies at the University of Florida found a five-year rate of biochemical freedom from progression at 99%, 99%, and 76%, respectively, in patients with low, intermediate, and high risk disease (Mendenhall et al., 2014). A prospective study performed by the University of Florida examined quality of life data in patients treated with proton therapy and IMRT for prostate cancer and found no significant differences in quality of life (QOL) summary score between the two modalities (Hoppe, 2014).

In 2013 ASTRO stated, “At the present time, ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear.” The National Comprehensive Cancer Network (NCCN) Guidelines include ASTRO’s current model policy statement, “Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry.” The ASTRO Choosing Wisely® Campaign also states that “...there is no clear evidence that proton beam therapy for prostate cancer offers any clinical advantage over other forms of definitive radiation therapy”. As such, for prostate cancer where no prostatectomy was performed PBT is not medically necessary. For adjuvant or salvage treatment of prostate cancer where prostatectomy was performed, PBT is EIU.

IV. Lung cancer

Radiation therapy is used as a sole modality in the treatment of medically inoperable stage I non-small cell lung cancer (NSCLC). In stage III NSCLC lung cancer radiation therapy is used in conjunction with chemotherapy with or without surgery as definitive treatment. It is also used in limited stage small cell lung cancer (SCLC) with chemotherapy and in palliative settings. There is limited data on the use of PBT in lung cancer and the very significant concern of accurately delivering the high dose Bragg Peak region of protons directly into the target when there is organ motion.

Eight PBT case series were identified in the assessment that included a total of 340 patients. No comparative studies, randomized or nonrandomized, were found. In stage I lung cancer, recent results of SBRT has yielded excellent control rates of over 90%, with low toxicity in peripheral lesions. While there have been several single institution PBT series, the results are similar to that of SBRT. A recent indirect meta-analysis reviewed in the assessment found a non-significant difference of nine percentage points between pooled two-year overall survival estimates favoring SBRT over PBT (Grutters et al., 2010). The non-

significant difference of 2.4 percentage points at 5 years also favored SBRT over PBT. Based on separate groups of single-arm studies on SBRT and PBT, it is unclear if this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT. The assessment noted that adverse events reported after PBT generally fell into the following categories: rib fracture, cardiac, esophageal, pulmonary, skin, and soft tissue. Adverse events data in PBT studies are difficult to interpret due to lack of consistent reporting across studies, lack of detail about observation periods and lack of information about rating criteria and grades. The report concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC.

All PBT studies examining lung cancer are case series; there are no completed studies directly comparing PBT and SBRT. Analyses of these studies included several quality issues such as, failure to use an independent assessor of patient-reported adverse events and were lacking in details on several aspects of the PBT treatment regimens. The PBT studies were similar in patient age, but there was great variability in percent within stage IA, sex ratio, and percent medically inoperable. There is a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning volume, total dose, number of fractions, and number of beams. In the absence of randomized controlled trials, the comparative effectiveness of PBT and SBRT is uncertain.

In stage III lung cancer, there are also theoretic advantages to PBT, especially in terms of decreasing toxicity. At this time, there are only three published clinical trials (phase I and II) on PBT for locally advanced NSCLC. This is insufficient to consider PBT standard therapy for lung cancer (Chang et al., 2011; Hoppe et al., 2012; Jiang et al., 2012). A phase III trial comparing proton beam radiation therapy vs. photon beam radiotherapy is currently accruing patients (RTOG 1308). Therefore, at this time, PBT is not medically necessary in the treatment of lung cancer.

V. Gastrointestinal malignancies

Hepatocellular, esophageal, and pancreatic cancers are treated definitively with radiation therapy, and in these cancers, higher doses to the target sparing normal tissue is important. Theoretically, PBT may be useful in these cancers; however, in esophageal and pancreatic tumors, there is minimal data on the clinical use of PBT, and therefore PBT remains not medically necessary in these tumors.

In hepatocellular cancer, radiation therapy plays a role in unresectable cancers and in those not amenable to radiofrequency ablation. SBRT has been used as well as PBT. The larger PBT series are from Japan suggesting excellent local control rates and modest 2 to 5 year survival rates. Four retrospective (360 patients) and two prospective studies (64 patients) of hypofractionated PBT in patients with hepatocellular cancer show results similar to those achieved with SBRT. In patients with unresectable hepatocellular cancers who are not optimally treated with radiofrequency ablation or SBRT, PBT is medically necessary (Fukumitsu et al., 2009; Hashimoto et al., 2006; Hata et al., 2005; Hata et al., 2006; Hsiung-Stripp et al., 2001; Koyama et al., 2003; Kozak et al., 2007; Macdonald et al., 2001; Sugahara et al., 2005; Sugahara et al., 2010; Zhang et al., 2008; Zurlo et al., 2000).

VI. Head and neck cancers

IMRT is the conventional form of photon radiation therapy in the treatment of head and neck cancers.

The ASTRO emerging technology committee reported there was insufficient evidence to support the use of PBT in head and neck cancer. A recent review of PBT in head and neck cancer noted that there are very few ongoing randomized studies comparing proton therapy with standard IMRT (Holliday et al., 2014). The lack of evidence comparing proton beam therapy to IMRT in head and neck cancer makes it difficult to draw any definitive conclusions, and therefore, at this time, PBT for head and neck cancer is not medically necessary.

VII. Seminoma

Per NCCN Guidelines for Testicular Cancer, radiation therapy is the preferred treatment modality for individuals who present with stage IIA seminoma. Previous research in longer-term survivors of para-aortic and pelvic radiation therapy for seminoma has revealed this group to be at increased risks for developing secondary cancers in the abdomino-pelvic region with an incidence ratio of 1.6 compared to the general populations (Horwich, 2014). Previous planning studies have revealed a significant potential reduction in the volume of irradiated tissue in patients treated with proton therapy compared to standard photon techniques (Hoppe, 2013). Therefore, PBT will be considered in this group of typically young adult individuals who are highly prone to develop secondary malignancies.

VIII. Toxicities and risk of second malignancies

There has been a suggestion that there may be a lower risk of second malignancies with PBT compared to IMRT. A larger volume of normal tissue is

exposed low dose radiation with IMRT, and this higher integral dose theoretically could cause a higher rate of second malignancies. There is a large body of data discussing the theoretic risks and benefits of PBT with respect to second malignancies, based on modeling (Athar et al., 2009; Brenner et al., 2008; Moteabbed et al., 2012; Shih et al., 2010; Zacharatou et al., 2008). Both sides of the argument can be supported based on this data. It is best summed up by a comprehensive review from the NIH published in June 2013. The publication concluded that "...to date, no observational studies have directly assessed the second cancer risks after IMRT or proton therapy. Until sufficient follow-up is available to conduct such studies, assessment of the risks relies on risk projection studies or theoretical models." (Berrington de Gonzales et al., 2013)

There is also a publication from the Massachusetts General Hospital (MGH) proton facility that looks at the risk of second malignancies in their patient population (Chung et al., 2013). The authors admit to several significant limitations of their study, including having lost 26% of the patients to follow-up. While their data shows a lower risk of second malignancies in the proton group (5.2%) compared to a National Cancer Institute SEER database matched with a photon control group (7.5%) at a median follow-up of 6.7 years, their conclusion of the study is that "...these findings are reassuring that the risk of second tumors was at least not increased when using protons compared with photons..." and that "...given the limitations of the study, the reduced second tumor rate in the proton cohort that we observed should be viewed as hypothesis generating." There is also debate about the reliability of the SEER database matched cohort in determining the risk of second malignancies from photon therapy. An editorial by Bekelman et al. (2013), accompanying this publication concludes that in light of the absence of a clear difference in subsequent malignancy rates in the critical longer-term period after treatment and the early differences suggesting study design limitations, hypotheses about the relative benefits or harms of PBT remain questionably two-sided. PBT may be associated with increased or decreased subsequent malignancies compared with photon therapy. A publication by Zelefsky et al. (2013) from Memorial Sloan-Kettering Cancer Center on the rate of second malignancies after treatment of prostate cancer with radical prostatectomy, brachytherapy and external beam radiotherapy yielded a different outcome related the conventional radiotherapy. Two thousand six hundred fifty-eight (2658) patients treated over 3 years were followed over 10 years. The study found that, when adjusted for age and smoking history, the incidence of second malignancies after radiotherapy was not significantly different from that after radical prostatectomy. Regarding the risk of second malignancy after cranial irradiation with SRS, a study with 5000 patients showed no increased risk

(Kollmeier et al., 2013). The authors conclude, “Pragmatically, in advising patients, the risks of malignancy would seem small, particularly if such risks are considered in the context of the other risks faced by patients with intracranial pathologies requiring radiosurgical treatments.”

Whether PBT increases or reduces the risk of second malignancies is very much an unanswered issue, and this argument cannot currently play a role in determining the appropriate or inappropriate use of PBT for any individual.

Furthermore, proton therapy dose calculations are based on a proton relative biological effectiveness (RBE) relative to photons of 1.1. However, emerging data suggests that this assumption may not be accurate and the RBE may not be constant for the whole radiation field which would lead to differential normal tissue toxicities between protons and photons. For example, a recent retrospective analysis compared outcomes in pediatric patients who underwent proton therapy and IMRT for ependymoma and found increased rates of post-radiation MRI changes, and neurologic deficits from brainstem necrosis in those who underwent proton therapy vs. IMRT. These findings demonstrate the need for further comparative research examining clinical differences between proton and photon therapy.

References:

1. Athar BS, Paganetti H. Neutron equivalent doses and associated lifetime cancer incidence risks for head & neck and spinal proton therapy. *Phys Med Biol*. 2009 Aug 21; 54(16):4907-4926. Accessed June 22, 2016. <http://iopscience.iop.org/article/10.1088/0031-9155/54/16/005>
2. Allen AM, Pawlicki T, Dong L, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. *Radiother Oncol*. 2012 Apr; 103(1):8-11. Accessed June 22, 2016 [http://www.thegreenjournal.com/article/S0167-8140\(12\)00058-8/fulltext](http://www.thegreenjournal.com/article/S0167-8140(12)00058-8/fulltext)
3. American Society for Radiation Oncology Model Policies. Proton Beam Therapy (PBT). 2014 May 20. Accessed June 22, 2016. https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ASTRO%20PBT%20Model%20Policy%20FINAL.pdf
4. Amichetti M, Amelio D, Cianchetti M, et al. A systematic review of proton therapy in the treatment of chondrosarcoma of the skull base. *Neurosurg Rev*. 2010 Apr; 33(2):155-165. Accessed June 22, 2016. <http://link.springer.com/article/10.1007/s10143-009-0235-z>
5. Amichetti M, Cianchetti M, Amelio D et al. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev*. 2009 Oct; 32(4):403-16. Accessed June 22, 2016. <http://link.springer.com/article/10.1007%2Fs10143-009-0194-4>
6. ASTRO release list of five radiation oncology treatments to question as part of national Choosing Wisely® campaign. 2013 Sep 13. Accessed June 22, 2016. <http://www.choosingwisely.org/astro-releases-list-of-five-radiation-oncology-treatments-to-question-as-part-of-national-choosing-wisely-campaign>
7. Barker FG 2nd, Butler WE, Lyons S, et al. Dose-volume prediction of radiation-related complications after proton beam radiosurgery for cerebral arteriovenous malformations. *J Neurosurg*. 2003 Aug; 99(2):254-263. Accessed June 22, 2016. <http://thejns.org/doi/abs/10.3171/jns.2003.99.2.0254>
8. Bekelman JE, Schultheiss T, Berrington De Gonzalez A. Subsequent malignancies after photon versus proton radiation therapy. *Int J Radiat Oncol Biol Phys*. 2013 Sep 1; 87(1):10-12. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)00548-8/fulltext](http://www.redjournal.org/article/S0360-3016(13)00548-8/fulltext)

9. Berrington de Gonzalez A, Gilbert E, Curtis R, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. *Int J Radiat Oncol Biol Phys*. 2013 Jun 1; 86(2):224-233. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)03512-2/fulltext](http://www.redjournal.org/article/S0360-3016(12)03512-2/fulltext)
10. Boskos C, Feuvret L, Noel G, et al. Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *Int J Radiat Oncol Biol Phys*. 2009 Oct 1; 75(2): 399-406. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)03728-0/abstract](http://www.redjournal.org/article/S0360-3016(08)03728-0/abstract)
11. Brada M, Pijls-Johannesma M, De Ruyscher D. Current clinical evidence for proton therapy. *Cancer J*. 2009 Jul-Aug; 15(4):319-324. Accessed June 22, 2016. http://journals.lww.com/journalppo/Abstract/2009/08000/Current_Clinical_Evidence_for_Proton_Therapy.9.aspx
12. Brada M, Pijls-Johannesma M, De Ruyscher D. Proton therapy in clinical practice: current clinical evidence. *J Clin Oncol*. 2007 Mar 10; 25(8):965-970. Accessed June 22, 2016. <http://jco.ascopubs.org/content/25/8/965.full>
13. Brenner DJ, Hall EJ. Secondary neutrons in clinical proton radiotherapy: a charged issue. *Radiother Oncol*. 2008 Feb; 86(2):165-70. Accessed June 22, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(07\)00655-X/abstract](http://www.thegreenjournal.com/article/S0167-8140(07)00655-X/abstract)
14. Bush DA, McAllister CJ, Loreda LN et al. Fractionated proton beam radiotherapy for acoustic neuroma. *Neurosurgery*. 2002 Feb; 50(2): 270-275. Accessed June 22, 2016. http://journals.lww.com/neurosurgery/Abstract/2002/02000/Fractionated_Proton_Beam_Radiotherapy_for_Acoustic.7.aspx
15. Chan AW, Liebsch NJ. Proton radiation therapy for head and neck cancer. *J Surg Oncol*. 2008 Jun 15; 97(8):697-700. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/jso.21013/abstract>
16. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer*. 2011 Oct 15; 117(20):4707-4713. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.26080/full>
17. Char DH, Kroll S, Phillips TL, et al. Late radiation failures after iodine 125 brachytherapy for uveal melanoma compared with charged-particle (proton or helium ion) therapy. *Ophthalmology*. 2002 Oct; 109(10):1850-1854. Accessed June 22, 2016. [http://www.aaojournal.org/article/S0161-6420\(02\)01174-0/abstract](http://www.aaojournal.org/article/S0161-6420(02)01174-0/abstract)
18. Chung CS, Yock TI, Nelson K, et al. Incidence of second malignancies among patients treated with proton versus photon radiation. *Int J Radiat Oncol Biol Phys*. 2013 Sep 1; 87(1):46-52. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)00459-8/abstract](http://www.redjournal.org/article/S0360-3016(13)00459-8/abstract)
19. Coen JJ, Bae K, Zietman AL, et al. Acute and late toxicity after dose escalation to 82 GyE using conformal proton radiation for localized prostate cancer: initial report of American College of Radiology Phase II study 03-12. *Int J Radiat Oncol Biol Phys*. 2011 Nov 15; 81(4):1005-1009. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)00900-4/abstract](http://www.redjournal.org/article/S0360-3016(10)00900-4/abstract)
20. Conway RM, Poothulil AM, Daftari IK, et al. Estimates of ocular and visual retention following treatment of extra-large uveal melanomas by proton beam radiotherapy. *Arch Ophthalmol*. 2006 Jun; 124(6):838-843. Accessed June 22, 2016. <http://archophth.jamanetwork.com/article.aspx?articleid=417712>
21. Debus J, Schulz-Ertner D, Schad L, et al. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. *Int J Radiat Oncol Biol Phys*. 2000 Jun 1; 47(3):591-596. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(00\)00464-8/abstract](http://www.redjournal.org/article/S0360-3016(00)00464-8/abstract)
22. Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res*. 2006; 38(5):255-260. Accessed June 22, 2016. <http://www.karger.com/Article/FullText/94834>
23. Efsthathiou JA, Trofimov AV, Zietman AL. Life, liberty, and the pursuit of protons: an evidence-base review of the role of particle therapy in the treatment of prostate cancer. *The Cancer J*. 2009 Jul-Aug; 15(4):312-318. Accessed June 22, 2016. http://journals.lww.com/journalppo/Abstract/2009/08000/Life_Liberty_and_the_Pursuit_of_Protons_An.8.aspx
24. Egger E, Zografos L, Schalenbourg A, et al. Eye retention after proton beam radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys*. 2003 Mar 15; 55(4):867-880. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(02\)04200-1/abstract](http://www.redjournal.org/article/S0360-3016(02)04200-1/abstract)
25. Fitzek MM, Thornton AF, Harsh GT, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial. *Int J Radiat Oncol Biol Phys*. 2001 Sep 1; 51(1):131-137. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(01\)01589-9/abstract](http://www.redjournal.org/article/S0360-3016(01)01589-9/abstract)
26. Fitzek MM, Thornton AF, Rabinov JD, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. *J Neurosurg*. 1999 Aug; 91(2):251-260. Accessed June 22, 2016. <http://thejns.org/doi/abs/10.3171/jns.1999.91.2.0251>
27. Fukumitsu N, Sugahara S, Nakayama H, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2009 Jul 1; 74(3):831-836. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)03862-5/abstract](http://www.redjournal.org/article/S0360-3016(08)03862-5/abstract)
28. Grutters JPC, Kessels AGH, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol*. 2010 Apr; 95(1):32-40. Accessed June 22, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(09\)00436-8/abstract](http://www.thegreenjournal.com/article/S0167-8140(09)00436-8/abstract)

29. Gunther JR, Sato M, Chintagumpala M, et al. Imaging changes in pediatric intracranial ependymoma patients treated with proton beam radiation therapy compared to intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. Published online: 2015 May 16. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(15\)00528-3/abstract](http://www.redjournal.org/article/S0360-3016(15)00528-3/abstract)
30. Hasegawa T, Ishii D, Kida Y, et al. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg*. 2007 Oct; 107(4):752-757. Accessed June 22, 2016. <http://thejns.org/doi/abs/10.3171/JNS-07/10/0752>
31. Hashimoto T, Tokuyue K, Fukumitsu N, et al. Repeated proton beam therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2006 May 1; 65(1):196-202. Accessed June 22, 2016 [http://www.redjournal.org/article/S0360-3016\(05\)03090-7/abstract](http://www.redjournal.org/article/S0360-3016(05)03090-7/abstract)
32. Hata M, Tokuyue K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis. *Strahlenther Onkol* 2006 Dec; 182(12):713-720. Accessed June 22, 2016. <http://link.springer.com/article/10.1007/s00066-006-1564-2/fulltext.html>
33. Hata M, Tokuyue K, Sugahara S et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. *Cancer* 2005 Aug 15; 104(4):794-801. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.21237/full>
34. Holliday EB, Frank SJ. Proton radiation therapy for head and neck cancer: a review of the clinical experience to date. *Int J Radiat Oncol Biol Phys*. 2014 Jun 1; 89(2):292-302. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(14\)00241-7/abstract](http://www.redjournal.org/article/S0360-3016(14)00241-7/abstract)
35. Hoppe BS, Flampouri S, Henderson RH, et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. *Clin Lung Cancer*. 2012 Sep; 13(5):352-358. Accessed June 22, 2016. [http://www.clinical-lung-cancer.com/article/S1525-7304\(11\)00299-3/abstract](http://www.clinical-lung-cancer.com/article/S1525-7304(11)00299-3/abstract)
36. Hoppe BS, Mamalui-Hunter M, Mendenhall NP, et al. Improving the therapeutic ratio by using proton therapy in patients with stage I or stage II seminoma. *Am J Clin Oncol*. 2013 Feb; 36(1):31-37. Accessed June 22, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2013/02000/Improving_the_Therapeutic_Ratio_by_Using_Proton.6.aspx
37. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer*. 2014 Apr 1; 120(7):1076-1085. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.28536/abstract>
38. Horwich A, Fossa SD, Huddart R, et al. Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. *Brit J Cancer*. 2014 Jan; 110 (1): 256-263. Accessed June 22, 2016. <http://www.nature.com/bjc/journal/v110/n1/full/bjc2013551a.html>
39. Hsiung-Stripp DC, McDonough J, Masters HM, et al. Comparative treatment planning between proton and xray therapy in pancreatic cancer. *Med Dosim*. 2001 Autumn; 26(3):255-259. Accessed June 22, 2016. [http://www.meddos.org/article/S0958-3947\(01\)00072-3/abstract](http://www.meddos.org/article/S0958-3947(01)00072-3/abstract)
40. Jiang ZQ, Yang K, Komaki R, et al. Long-term clinical outcome of intensity-modulated radiotherapy for inoperable non-small cell lung cancer: The MD Anderson experience. *Int J Radiat Oncol Biol Phys*. 2012 May 1; 83(1):332-339. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)02835-5/abstract](http://www.redjournal.org/article/S0360-3016(11)02835-5/abstract)
41. Kollmeier MA, Fidaleo A, Pei X, et al. Favourable long-term outcomes with brachytherapy-based regimens in men ≤60 years with clinically localized prostate cancer. *BJU Int*. 2013 Jun; 111(8):1231-1236. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11663.x/abstract>
42. Kotecha R, Yamada Y, Pei X, et al. Clinical outcomes of high-dose-rate brachytherapy and external beam radiotherapy in the management of clinically localized prostate cancer. *Brachytherapy*. 2013 Jan-Feb; 12(1):44-49. Accessed June 22, 2016. [http://www.brachyjournal.com/article/S1538-4721\(12\)00166-3/fulltext](http://www.brachyjournal.com/article/S1538-4721(12)00166-3/fulltext)
43. Koyama S, Tsujii H. Proton beam therapy with high-dose irradiation for superficial and advanced esophageal carcinomas. *Clin Cancer Res*. 2003 Sep 1; 9(10 Pt 1):3571-3577. Accessed June 22, 2016. <http://clincancerres.aacrjournals.org/content/9/10/3571.full>
44. Kozak KR, Kachnic LA, Adams J, et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. *Int J Radiat Oncol Biol Phys*. 2007 Aug 1; 68(5):1557-1566. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)00548-2/abstract](http://www.redjournal.org/article/S0360-3016(07)00548-2/abstract)
45. Lumbroso-Le Rouic L, Delacroix S, Dendale R, et al. Proton beam therapy for iris melanomas. *Eye*. 2006; 20(12):1300-1305. Accessed June 22, 2016. <http://www.nature.com/eye/journal/v20/n11/full/6702102a.html#close>
46. Luu QT, Loredon LN, Archambeau JO, et al. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. *Cancer J*. 2006 Mar-Apr; 12(2):155-159. Accessed June 22, 2016. http://journals.lww.com/journalppo/Abstract/2006/03000/Fractionated_Proton_Radiation_Treatment_for.12.aspx
47. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001 Sep 6; 345(10):725-730. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa010187>
48. Mendenhall NP, Hoppe BS, Nichols RC, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014 Mar; 88(3):596-602. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)03310-5/abstract](http://www.redjournal.org/article/S0360-3016(13)03310-5/abstract)

49. Moteabbed M, Geyer A, Drenkhahn R, et al. Comparison of whole-body phantom designs to estimate organ equivalent neutron doses for secondary cancer risk assessment in proton therapy. *Phys Med Biol*. 2012 Jan 21; 57(2):499-515. Accessed June 22, 2016. <http://iopscience.iop.org/article/10.1088/0031-9155/57/2/499/meta>
50. Murphy ES, Suh JH. Radiotherapy for vestibular schwannomas: a critical review. *Int J Radiat Oncol Biol Phys*. 2011 Mar 15; 79(4):985-997. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)03428-0/abstract](http://www.redjournal.org/article/S0360-3016(10)03428-0/abstract)
51. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2016. Prostate Cancer. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Prostate Cancer 3.2016. ©2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
52. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016. Testicular Cancer. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Testicular Cancer 2.2016. ©2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
53. Noël G, Feuvret L, Calugaru V et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol*. 2005; 44(7):700–708. Accessed June 22, 2016. <http://informahealthcare.com/doi/abs/10.1080/02841860500326257>
54. Olsen DR, Bruland ØS, Frykholm G, et al. Proton therapy – a systematic review of clinical effectiveness. *Radiother Oncol*. 2007 May; 83(2):123–132. Accessed June 22, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(07\)00093-X/abstract](http://www.thegreenjournal.com/article/S0167-8140(07)00093-X/abstract)
55. Radiation Therapy Oncology Group (RTOG). RTOG 1308 Protocol Information. Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIb NSCLC. Accessed June 22, 2016. <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1308>
56. Ronson BB, Schulte RW, Han KP, et al. Fractionated proton beam irradiation of pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 2006 Feb 1; 64(2):425-434. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)02364-3/abstract](http://www.redjournal.org/article/S0360-3016(05)02364-3/abstract)
57. Rowe J, Grainger A, Walton L et al. Risk of malignancy after gamma knife stereotactic radiosurgery. *Neurosurgery*. 2007 Jan; 60(1):60-65. Accessed June 22, 2016. http://journals.lww.com/neurosurgery/Abstract/2007/01000/RISK_OF_MALIGNANCY_AFTER_GAMMA_KNIFE_STEREOTACTIC.6.aspx
58. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA*. 2012 Apr 18; 307(15):1611-1620. Accessed June 22, 2016. <http://jama.jamanetwork.com/article.aspx?articleid=1148148>
59. Shih HA, Arvold ND, Niemierko A, et al. Second tumor risk and projected late effects after proton vs. intensity modulated photon radiotherapy for benign meningioma: a dosimetric comparison. *Int J Radiat Oncol Biol Phys*. 2010 Nov 1; 78(3): S272. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01622-6/fulltext](http://www.redjournal.org/article/S0360-3016(10)01622-6/fulltext)
60. Spratt DE, Pei X, Yamada J, et al. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2013 Mar 1; 85(3):686-92. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)00679-7/abstract](http://www.redjournal.org/article/S0360-3016(12)00679-7/abstract)
61. Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. *Radiother Oncol*. 2006 Aug; 80(2):263-267. Accessed June 22, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814006003045>
62. Sugahara S, Oshiro Y, Nakayama H, et al. Proton beam therapy for large hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2010 Feb 1; 76(2):460-466. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00312-5/abstract](http://www.redjournal.org/article/S0360-3016(09)00312-5/abstract)
63. Sugahara S, Tokuyue K, Okumura T, et al. Clinical results of proton beam therapy for cancer of the esophagus. *Int J Radiat Oncol Biol Phys*. 2005 Jan 1; 61(1):76-84. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(04\)00606-6/abstract](http://www.redjournal.org/article/S0360-3016(04)00606-6/abstract)
64. Tommasino F, Durante M. Proton radiobiology. *Cancers*. 2015 Feb 12; 7(1):353-381. Accessed June 22, 2016. <http://www.mdpi.com/2072-6694/7/1/353>
65. Weber DC, Chan AW, Bussiere MR, et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. *Neurosurgery*. 2003 Sep; 53(3):577-588. Accessed June 22, 2016. http://journals.lww.com/neurosurgery/Abstract/2003/09000/Proton_Beam_Radiosurgery_for_Vestibular.6.aspx
66. Yu JB, Soulos PR, Herrin J et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. *J Natl Cancer Inst*. 2013 Jan 2; 105(1):25-32. Accessed June 22, 2016. <http://jnci.oxfordjournals.org/content/105/1/25.full>

67. Zacharatou Jarlskog C, Paganetti H. Risk of developing second cancer from neutron dose in proton therapy as function of field characteristics, organ, and patient age. *Int J Radiat Oncol Biol Phys*. 2008 Sep 1; 72(1):228-235. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)00815-8/abstract](http://www.redjournal.org/article/S0360-3016(08)00815-8/abstract)
68. Zelefsky MJ, Pei X, Teslova T, et al. Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention. *BJU Int*. 2012 Dec; 110(11):1696-701. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2012.11385.x/abstract>
69. Zhang X, Zhao KL, Guerrero TM, et al. Four-dimensional computed tomography-based treatment planning for intensity-modulated radiation therapy and proton therapy for distal esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2008 Sep 1; 72(1):278-287. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)00828-6/abstract](http://www.redjournal.org/article/S0360-3016(08)00828-6/abstract)
70. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol*. 2010 Mar 1; 28(7):1106-1111. Accessed June 22, 2016. <http://jco.ascopubs.org/content/28/7/1106.full>
71. Zorlu F, Gurkaynak M, Yildiz F et al. Conventional external radiotherapy in the management of clivus chordomas with overt residual disease. *Neurol Sci*. 2000 Aug; 21(4):203–207. Accessed June 22, 2016. <http://link.springer.com/article/10.1007%2Fs100720070077>
72. Zurlo A, Lomax A, Hoess A, et al. The role of proton therapy in the treatment of large irradiation volumes: a comparative planning study of pancreatic and biliary tumors. *Int J Radiat Oncol Biol Phys*. 2000 Aug 1; 48(1):277-288. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(00\)00522-8/abstract](http://www.redjournal.org/article/S0360-3016(00)00522-8/abstract)

Proton Beam Radiation Therapy

[Return to Table of Contents](#)

Radiation Therapy of the Skin: Basal Cell, Squamous Cell, and Malignant Melanoma Cancers of the Skin

POLICY

I. Basal Cell and Squamous Cell Skin Cancers

A. Photon and/or electron beam techniques

1. The goal of management of non-melanomatous skin cancers is to achieve cure of the cancer while preserving maximum cosmetic and functional outcome. Surgical resection is the treatment of choice in the majority of non-melanomatous skin cancers. Photon and/or electron beam techniques are medically necessary for the treatment of basal cell and squamous cell cancers of the skin for any of the following:
 - a. Definitive treatment for a cancer in a cosmetically significant location in which surgery would be disfiguring
 - b. Adequate surgical margins have not been achieved and further resection is not possible
 - c. Definitive management of large cancers as an alternative to major resection requiring significant plastic repair
 - d. Definitive management of large cancers that are considered inoperable
 - e. Definitive, preoperative, or postoperative adjuvant therapy for a cancers at risk for local or regional recurrence due to perineural, lymphovascular invasion, and/or metastatic adenopathy
 - f. Definitive management for non-surgical candidates
2. Contraindications to the use of photon and/or electron beam techniques:
 - a. Radiation therapy should not be used in genetic conditions which predispose to skin cancer, such as xeroderma pigmentosum or basal cell nevus syndrome.
 - b. Radiation treatments should be avoided or only used with great caution in cases of connective tissue disorders

B. Brachytherapy (low dose rate [LDR], high dose rate [HDR], surface, or interstitial technique) is medically necessary when both of the following are contraindicated:

1. Surgical resection
2. Photon and/or electron beam techniques

C. All brachytherapy requests require medical review and discussion with an eviCore radiation oncologist prior to certification.

D. Electronic brachytherapy is experimental, investigational, or unproven (EIU) for the treatment of basal cell and squamous cell skin cancers

II. Cutaneous Malignant Melanoma

- A. Photon and/or electron beam techniques may be medically necessary in the treatment of malignant melanoma at the primary site of the skin in these situations:
 - 1. Adjuvant treatment after resection of a primary deep desmoplastic melanoma with close margins
 - 2. Adjuvant treatment after resection of the primary tumor and the specimen shows evidence of extensive neurotropism
 - 3. Locally recurrent disease after resection
- B. Photon and/or electron beam techniques may be medically necessary in the treatment of regional malignant melanoma in these situations:
 - 1. Upon resection of clinically appreciable lymph nodes when
 - a. The lactate dehydrogenase (LDH) level is less than 1.5 times the upper limit of normal **and**
 - b. Extranodal extension of tumor is present in the resected nodes **and/or**
 - i. One or more involved **parotid** lymph nodes of any size
 - ii. Two or more involved **cervical** lymph nodes and/or tumor within a node is 3 cm or larger
 - iii. Two or more involved **axillary** lymph nodes and/or tumor within a node is 4 cm or larger
 - iv. Three or more involved **inguinal** lymph nodes and/or tumor within a node is 4 cm or larger
- C. Photon and/or electron beam techniques may be medically necessary to palliate unresectable nodal, satellite, or in-transit disease
- D. Photon and/or electron beam techniques are medically necessary in the treatment of metastatic malignant melanoma in these situations:
 - 1. Symptomatic or potentially symptomatic soft tissue metastases
 - 2. Symptomatic or potentially symptomatic bone metastases (also see the section of the criteria entitled, Radiation Treatment of Bone Metastases)
 - 3. Symptomatic or potentially symptomatic visceral metastases
 - 4. Metastases to the brain (also see the section of the criteria entitled, Radiation Treatment of Brain Metastases)

The policy for radiation therapy for scar revision (keloids) and other non-malignant conditions is now located in the section of the criteria entitled, Radiation Treatment of Non-Malignant Disease.

Key Clinical Points

Radiation treatments are to be appropriately matched to the clinical circumstance and include a variety of techniques:

I. Photon and/or electron beam techniques

- A. Superficial or kilovoltage (kV) xray treatments with low energy (up to 250 kV) external beam devices are generally used for thinner lesions. The beam

energy and hardness (filtration) dictate the thickness of a lesion that may be treated with this technique.

- B. Higher-energy external electron beam teletherapy (4 megaelectron volt [MeV] and greater) is most commonly utilized to treat the majority of localized lesions. The use of appropriate energy and thickness of build-up bolus material is required, along with proper sizing of the treatment field to account for the electron beam penumbra. Photon external beam teletherapy is required in circumstances in which other beams of lower energy are inadequate to reach the target depth.

In the great majority of cases, simple appositional Complex technique is required, accompanied by lead, cerrobend, or other beam-shaping cutouts applied in the path of the beam and/or on the skin surface to match the shape of the target lesion. In complicated cases, such as when regional adenopathy or perineural invasion is present, more complicated techniques may be medically necessary. Intensity-Modulated Radiation Therapy (IMRT) will be approved when comparative three-dimensional (3D) and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN). Unless clinically evident, dose comparison plans will be required.

- C. Treatment schedules with photons and/or electrons should be matched to the clinical circumstance, including size and depth of the lesion, histology, cosmetic goal, and risk of damage to underlying structures. These schedules can range from a single fraction to a course of 33 fractions. Radiation doses typically range from 35 Gy in fractions of 7 Gy over 5 days, to 66 Gy in 33 fractions of 2 Gy over six and one-half weeks. The margin around tumor is typically different for basal and squamous histologies and for technique used (electrons, photons, superficial radiation).
- D. The radiation prescription is to be made by a qualified radiation oncologist who is familiar with the nuances of the dose deposition that accompany the physical characteristics of the radiation beams and techniques. Dose prescription for electrons is at the 90% isodose line, and for superficial or orthovoltage radiation at the Dmax. When sophisticated Complex photon, 3D, or IMRT treatments are used, attention is to be paid to the skin dose, and may require the use of bolus.

When regional nodes are to be treated, the dose range is 54 Gy to 66 Gy at 2 Gy per fraction.

- E. When treating malignant melanoma, the dose schedules may include hypofractionated regimens with large fraction size that take advantage of

theoretical radiobiological characteristics. Schedules such as 5 fractions of 6 Gy have been reported as having acceptable acute toxicity and increased response rates, but may be at the expense of long term side effects. Requests to use highly conformal techniques such as Stereotactic Body Radiation Therapy (SBRT), require individual review and must also satisfy criteria set forth in the Radiation Treatment of Extra-cranial Oligometastasis section of the criteria.

II. Brachytherapy

Brachytherapy technique employs the use of radioisotopes placed either at, above, or deep to the tumor surface using permanent or temporary placement of sources, in single or multiple sessions. There are devices on the market that substitute a non-isotopic means of supplying the radiation, collectively known as electronic brachytherapy. The use of electronic brachytherapy is currently considered to be EIU.

HDR brachytherapy with afterloading devices has been used to treat significant lesions based on size of lesion or complicated geometry of the target (e.g. total scalp) in which the radiation dose distribution is found to be superior to conventional or highly conformal external beam technique. HDR brachytherapy has also been used to treat relatively simple lesions by placing isotope sources at or slightly above the surface of the lesion (contact therapy and plesiotherapy). When utilized, HDR brachytherapy is performed over several sessions.

LDR therapy has been employed using surface moulds or permanent seed implants, with the advantage of delivering a course of radiation over a short period of time that is equivalent to a lengthy course of daily external beam treatments. A permanent seed implant requires one session. Surface mould applications typically require one lengthy session of several days, or two to three shorter sessions.

HDR and LDR brachytherapy with isotopes are subject to additional rules and regulations of federal and state agencies.

References

1. Agrawal S, Kane III JM, Guadagnolo BA, et al. The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. *Cancer*. 2009 Dec 15; 115(24):5836-5844. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.24627/>
2. Alam M, Nanda S, Mittal BB, et al. The use of brachytherapy in the treatment of nonmelanoma skin cancer: a review. *J Am Acad Dermatol*. 2011 Aug; 65(2):377-388. Accessed June 22, 2016. [http://www.jaad.org/article/S0190-9622\(10\)00381-6/abstract](http://www.jaad.org/article/S0190-9622(10)00381-6/abstract)
3. American Cancer Society: Skin cancer: Basal and Squamous Cell Skin Cancer. Accessed June 22, 2016. <http://www.cancer.org/cancer/skincancer/index>

4. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol*. 2012 Jun; 13(6):589-597. Accessed June 22, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(12\)70138-9/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70138-9/fulltext)
5. Chang DT, Amdur RJ, Morris CG, et al. Adjuvant radiotherapy for cutaneous melanoma: comparing hypofractionation to conventional fractionation. *Int J Radiat Oncol Biol Phys*. 2006 Nov 15; 66(4):1051-1055. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)00972-2/abstract](http://www.redjournal.org/article/S0360-3016(06)00972-2/abstract)
6. Guadagnolo BA, Prieto V, Weber R, et al. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. *Cancer*. 2014 May 1; 120(9):1361-1368. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/enhanced/doi/10.1002/cncr.28415/>
7. Lee RJ, Gibbs JF, Proulx GM, et al. Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000 Jan 15; 46(2):467-474. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(99\)00431-9/abstract](http://www.redjournal.org/article/S0360-3016(99)00431-9/abstract)
8. Olivier KR, Schild SE, Morris CG, et al. A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma. *Cancer*. 2007 Oct 15; 110(8):1791-1795. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/enhanced/doi/10.1002/cncr.22988/>
9. Mendenhall WM, Mancuso AA, Kiorwan JM et al. Skin: principles and practice of radiation oncology in Halperin EC, Wazer DE, Perez CA, and Brady LW, ed. *Perez and Brady's Principles and Practice of Radiation Oncology*. 6th Edition. Philadelphia, PA: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2013:626-637.
10. National Comprehensive Cancer Network (NCCN) Guidelines. Version 2.2016. Basal Cell Skin Cancer. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Basal Cell Skin Cancer Version 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
11. National Comprehensive Cancer Network (NCCN) Guidelines. Version 1.2016. Squamous Cell Skin Cancer. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Squamous Cell Skin Cancer Version 1.2016®. 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
12. National Comprehensive Cancer Network (NCCN) Guidelines. Version 2.2016. Melanoma. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Melanoma Version 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
13. Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *Int J Radiat Oncol Biol Phys*. 1991 Mar; 20(3):429-432. Accessed June 22, 2016. [http://www.redjournal.org/article/0360-3016\(91\)90053-7/abstract](http://www.redjournal.org/article/0360-3016(91)90053-7/abstract)
14. Seegenschmiedt MH, Tepper JE, Gunderson LI. Benign Diseases (chapter 65) in: Gunderson L, Tepper J, editors. *Clinical Radiation Oncology*. 3rd edition. Philadelphia, PA: Churchill Livingstone; 2012:1400.
15. Strom T, Caudell JJ, Han D, et al. Radiotherapy influences local control in patients with desmoplastic melanoma. 2014 May 1; 120(9):1369-1378. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/enhanced/doi/10.1002/cncr.28412/>

Radiation Therapy of the Skin: Basal Cell, Squamous Cell, and Malignant Melanoma Cancers of the Skin

[Return to Table of Contents](#)

Radiation Treatment for Hodgkin's Lymphoma

POLICY

I. Definitive radiation therapy

- A. Definitive radiation therapy as sole therapy is medically necessary for selected cases of stage I-IIA lymphocyte predominant Hodgkin's lymphoma
 - 1. Doses ranging from 30 to 36 Gy in a single phase may be required
 - 2. Complex, three dimensional (3D) Conformal Radiation Therapy (3DCRT) or Intensity-Modulated Radiation Therapy (IMRT) techniques may be used

II. Adjuvant radiation therapy (combined modality treatment) after chemotherapy

- A. Radiation treatment regimens following chemotherapy depend on clinical stage, presence or absence of bulky disease, the chemotherapy regimen used (ABVD or Stanford V), as well as the response to treatment (Positron Emission Tomography [PET] scan Deauville 3-4)
 - 1. Doses ranging from 20 to 45 Gy with conventional fractionation may be required
 - 2. Complex, 3DCRT, or IMRT techniques are medically necessary
- B. Combined modality treatment after chemotherapy is medically necessary in some cases of individuals with stage III-IV disease to areas of initial bulky involvement or to areas of less than a complete response (CR)
 - 1. Doses ranging from 20 to 45 Gy with conventional fractionation may be required
 - 2. Complex, 3DCRT, or IMRT techniques are medically necessary, directed at up to 4 separate sites in up to 2 phases apiece
- C. Concurrent chemotherapy carries a high toxicity burden, requires substantial supportive care, and the expertise of an experienced multidisciplinary team

III. Salvage radiation therapy

- A. Salvage radiation therapy is medically necessary after chemotherapy to areas of relapsed bulky involvement
 - 1. Doses ranging from 20 to 45 Gy with conventional fractionation may be required
 - 2. Complex, 3DCRT, or IMRT techniques are medically necessary, directed at up to 4 separate sites in up to 2 phases apiece
- B. Salvage radiation therapy may be medically necessary in an individual who relapses after solo chemotherapy for initial stage I/IIA disease
 - 1. Definitive radiation doses ranging from 30 to 45 Gy using conventional fractionation may be required

2. Depending on the extent of the disease, Complex, 3DCRT or IMRT techniques may be necessary
 - a. Treatment of up to 3 sites may be required with up to 2 phases per site
 - b. Complex, 3DCRT, or IMRT techniques may be used

IV. Palliative radiation therapy

- A. In an individual with advanced or recurrent disease that is felt not to be curative and who has symptomatic local disease, photon and/or electron techniques are indicated for symptom control
 1. Up to 10 fractions are medically necessary in 1 phase
 2. Complex, 3DCRT, or IMRT techniques may be used

V. Radiation therapy, photon and/or electron techniques

- A. Complex, 3DCRT, and IMRT techniques are medically necessary
- B. Respiratory gating techniques and image guidance techniques may be appropriate to minimize the amount of critical tissue (such as lung) that is exposed to the full dose of radiation. IGRT may be approved for 3D treatment in the thorax or for small volume fields elsewhere
- C. The use of photon beam and/or electron beam radiation therapy may be medically necessary

Key Clinical Points

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines (American College of Radiology [ACR]/American Society for Radiation Oncology [ASTRO], National Comprehensive Cancer Network [NCCN]), radiation therapy is considered an integral component in the multidisciplinary management of Hodgkin's lymphoma (HD). Proper management of the disease requires the cooperation of a complex multi-disciplinary team that includes experts in diagnostic imaging, pathology, radiation oncology and medical oncology. HD treatment is based on initial stage of disease as well as the medical condition of the individual, and treatment is dynamically modified based on the speed and extent of response to initial therapy. At diagnosis, areas of involvement may be supra-diaphragmatic only, sub-diaphragmatic only, or a combination of the two in the more advanced stages. The stage determines decisions made about the proper extent of radiation. The varied pathologic subtypes, for the most part at present, do not materially affect the dose or field decisions to be made in this disease.

Treatment decisions are preceded by workup and staging and planned in conjunction with the appropriate members of the multi-disciplinary team. Participation in a national clinical trial is encouraged.

Initial management will usually require chemotherapy (in a variety of different acceptable regimens), followed by assessment of response, leading to an appropriate choice of doses and fields of radiation therapy. Chemotherapy alone may be appropriate for early stage non-bulky disease, with radiation therapy reserved for

relapse. As mentioned in the Policy section, treatment is individualized depending on the initial clinical stage, presence or absence of bulky disease, chemotherapy regimen used, and response to chemotherapy as evaluated by repeat staging including a PET scan with results incorporating the Deauville criteria.

References

1. Abuzetun JY, Loberiza F, Vose J, et al. The Stanford V regimen is effective in patients with good risk Hodgkin lymphoma but radiotherapy is a necessary component. *Br J Haematol*. 2009 Feb;144(4):531- 537. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2008.07500.x/full>
2. Aleman BMP, Raemaekers JMM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *N Engl J Med*. 2003 Jun 12; 348(24):2396-2406. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa022628>
3. Aleman BM, Raemaekers JMM, Tomišić R, et al. Involved-field radiotherapy for patients in partial remission after chemotherapy for advanced Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys*. 2007 Jan 1; 67(1):19-30. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)02813-6/abstract](http://www.redjournal.org/article/S0360-3016(06)02813-6/abstract)
4. Aversa SM, Salvagno L, Soraru M, et al. Stanford V regimen plus consolidative radiotherapy is an effective therapeutic program for bulky or advanced-stage Hodgkin's disease. *Acta Haematol*. 2004 August; 112(3):141-147. Accessed June 22, 2016. <http://www.karger.com/Article/Abstract/79725>
5. Behar RA, Horning SJ, Hoppe RT. Hodgkin's disease with bulky mediastinal involvement: effective management with combined modality therapy. *Int J Radiat Oncol Biol Phys* 1993 Apr 2; 25(5):771-776. Accessed June 22, 2016. [http://www.redjournal.org/article/0360-3016\(93\)90304-E/abstract](http://www.redjournal.org/article/0360-3016(93)90304-E/abstract)
6. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*. 2004 Jul 15; 22(14):2835-2841. Accessed June 22, 2016. <http://jco.ascopubs.org/content/22/14/2835.full>
7. Canellos GP, Abramson JS, Fisher DC, et al. Treatment of favorable, limited-stage Hodgkin's lymphoma with chemotherapy without consolidation by radiation therapy. *J Clin Oncol*. 2010 Mar 20; 28(9):1611-1615. Accessed June 22, 2016. <http://jco.ascopubs.org/content/28/9/1611.full>
8. Cella L, Liuzzi R, Conson M, et al. Multivariate normal tissue complication probability modeling of heart valve dysfunction in Hodgkin lymphoma survivors. *Int J Radiat Oncol Biol Phys*. 2013 Oct 1; 87(2):304-310. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)00647-0/abstract](http://www.redjournal.org/article/S0360-3016(13)00647-0/abstract)
9. de Vathaire F, El-Fayech C, Ayed FFB, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study. *Lancet Oncol*. 2012 Oct; 13(10):1002-1010. Accessed June 22, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(12\)70323-6/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70323-6/fulltext)
10. Domínguez AR, Marquez A, Gumá J, et al. Treatment of stage I and II Hodgkin's lymphoma with ABVD chemotherapy: results after 7 years of a prospective study. *Ann Oncol*. 2004 Dec; 15(12):1798-1804. Accessed June 22, 2016. <http://annonc.oxfordjournals.org/content/15/12/1798.full>
11. Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol*. 2010 Mar; 21(3):574-581. Accessed June 22, 2016. <http://annonc.oxfordjournals.org/content/21/3/574.full>
12. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *J Clin Oncol*. 2007 Aug 10; 25(23):3495-3502. Accessed June 22, 2016. <http://jco.ascopubs.org/content/25/23/3495.full>
13. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol*. 2003 Oct 1; 21(19):3601-3608. Accessed June 22, 2016. <http://jco.ascopubs.org/content/21/19/3601.abstract>
14. Fabian CJ, Mansfield CM, Dahlberg S, et al. Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. *Ann Intern Med* 1994 Jun 1; 120(11):903-912. Accessed June 22, 2016. <http://annals.org/article.aspx?articleid=707421>
15. Fermé C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. 2007 Nov 8;357(19):1916-1927. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa064601>
16. Fox AM, Dosoretz AP, Mauch PM, et al. Predictive factors for radiation pneumonitis in Hodgkin lymphoma patients receiving combined-modality therapy. *Int J Radiat Oncol Biol Phys*. 2012 May 1; 83(1):277-282. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)02829-X/abstract](http://www.redjournal.org/article/S0360-3016(11)02829-X/abstract)
17. Gobbi PG, Levis A, Chisesi T, et al. ABVD versus modified Stanford V versus MOPPEBVCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. *J Clin Oncol*. 2005 Dec 20; 23(38):9198-9207. Accessed June 22, 2016. <http://jco.ascopubs.org/content/23/36/9198.full>

18. Hoppe RT. Hodgkin's lymphoma: the role of radiation in the modern combined strategies of treatment. Hematol Oncol Clin North Am. 2007; 21(5):915-927. Accessed June 22, 2016. [http://www.hemonc.theclinics.com/article/S0889-8588\(07\)00082-2/abstract](http://www.hemonc.theclinics.com/article/S0889-8588(07)00082-2/abstract)
19. Horning SJ, Hoppe RT, Breslin S, et al. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol. 2002 Feb 1; 20(3):630-637. Accessed June 22, 2016. <http://jco.ascopubs.org/content/20/3/630.abstract>
20. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009 Nov 10; 27(32):5390-5396. Accessed June 22, 2016. <http://jco.ascopubs.org/content/27/32/5390.full>
21. Jacobson CA, Longo DL. Management of early-stage Hodgkin's lymphoma. PPO Updates. Principles & Practice of Oncology. 2011. 25(2).
22. Johnson PWM, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 Randomized Controlled Trial (ISRCTN97144519). J Clin Oncol. 2010 Jul 10; 28(20):3352-3359. Accessed June 22, 2016. <http://jco.ascopubs.org/content/28/20/3352.full>
23. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need? J Clin Oncol. 2004 Jan 1; 22(1):62-68. Accessed June 22, 2016. <http://jco.ascopubs.org/content/22/1/62.full>
24. Longo D, Glatstein E, Duffey P, et al. Radiation therapy versus combination chemotherapy in the treatment of early-stage Hodgkin's disease: seven-year results of a prospective randomized trial. J Clin Oncol. 1991 Jun 1; 9(6):906-917. Accessed June 22, 2016. <http://jco.ascopubs.org/content/9/6/906.abstract>
25. Longo DL, Russo A, Duffey PL, et al. Treatment of advanced- stage massive mediastinal Hodgkin's disease: the case for combined modality treatment. J Clin Oncol. 1991; 9(2):227-235. Accessed June 22, 2016. <http://jco.ascopubs.org/content/9/2/227.abstract>
26. Macdonald DA, Connors JM. New strategies for the treatment of early stages of Hodgkin's lymphoma. Hematol Oncol Clin North Am. 2007; 21(5):871-880. Accessed June 22, 2016. [http://www.hemonc.theclinics.com/article/S0889-8588\(07\)00081-0/abstract](http://www.hemonc.theclinics.com/article/S0889-8588(07)00081-0/abstract)
27. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. J Clin Oncol. 2005 Jul 20; 23(21):4634-4642. Accessed June 22, 2016. <http://jco.ascopubs.org/content/23/21/4634.full>
28. National Comprehensive Cancer Network (NCCN) Guidelines. Version 3.2016. Hodgkin Lymphoma. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Hodgkin Lymphoma Version 3.2016©. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
29. Press OW, LeBlanc M, Lichter AS, et al. Phase III randomized intergroup trial of subtotal lymphoid irradiation versus doxorubicin, vinblastine, and subtotal lymphoid irradiation for stage IA to IIA Hodgkin's disease. J Clin Oncol. 2001 Nov 15; 19(22):4238-4244. Accessed June 22, 2016. <http://jco.ascopubs.org/content/19/22/4238.full>
30. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol. 1987 Jan; 5(1):27-37. Accessed June 22, 2016. <http://jco.ascopubs.org/content/5/1/27.abstract>
31. Solanki AA, LeMieux, MH, Chiu BC-H, et al. Long-term outcomes in patients with early stage nodular lymphocyte-predominant Hodgkin's lymphoma treated with radiotherapy. PLOS ONE. 2013 Sep; 8(9):1-6. Accessed June 22, 2016. <http://www.plosone.org/article/doi/10.1371/journal.pone.0075336&representation=PDF>
32. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. 2014 Jul 15; 89(4):854-862. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)00534-8/abstract](http://www.redjournal.org/article/S0360-3016(13)00534-8/abstract)
33. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. Blood. 2004 Dec 1; 104(12):3483-3489. Accessed June 22, 2016. <http://www.bloodjournal.org/content/104/12/3483>

Radiation Treatment for Hodgkin's Lymphoma

[Return to Table of Contents](#)

Radiation Treatment for Non-Hodgkin's Lymphoma

POLICY

I. **Photon and/or electron techniques for the treatment of non-Hodgkin's lymphoma (NHL) are medically necessary, generally using involved-site radiation therapy (ISRT)**

- A. Complex and three-dimensional conformal radiation therapy (3DCRT) techniques
- B. Intensity-Modulated Radiation Therapy (IMRT) for an individual with disease located above the diaphragm. Respiratory gating techniques and image guidance techniques may be appropriate to minimize the amount of critical tissue (such as lung) that is exposed to the full doses of radiation
- C. In sub-diaphragmatic presentations, IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN)
- D. Photon and/or electron beam radiation therapy
- E. The treatment of lymphomas with radiation is generally done using relatively low doses in the range of 15 to 36 Gy at standard fractionation, sometimes with doses as low as 4 Gy in 2 fractions
- F. IMRT is not medically necessary for the treatment of an individual with low dose radiation, i.e., 2 Gy in 2 fractions

II. **Definitive radiation therapy**

- A. As sole therapy is medically necessary for an individual with stage I-IIA low grade NHL
 - 1. Doses up to 36 Gy, directed at a single site in a single phase
 - 2. Using Complex or 3D techniques with image guidance
 - 3. IMRT for an individual with supra-diaphragmatic presentation. A request for IMRT for an individual with sub-diaphragmatic presentation will require a case-by-case discussion to document that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by RTOG/NCCN
- B. Mucosa-associated lymphoid tissue (MALT) lymphomas of gastric or non-gastric origin, that are confined to the organs of involvement
 - 1. Doses of 36 Gy directed at a single site in a single phase
 - 2. Complex or 3D techniques with image guidance
 - 3. IMRT will be considered on a case-by-case basis for gastric involvement, as it is a sub-diaphragmatic presentation

- C. Extranodal NK/T-cell lymphoma, nasal lymphoma
 - 1. Doses of 54 Gy
 - 2. 3D or IMRT techniques
 - 3. 30 fractions in 2 phases
- D. Consolidative radiotherapy after initial chemotherapy
 - 1. Doses of 36 Gy to the original extent of disease for the following histologies:
 - a. Mantle cell lymphoma
 - b. Diffuse large cell B-cell lymphoma (DLBCL)
 - c. Burkitt's lymphoma
 - d. Lymphoblastic lymphoma
 - e. Primary cutaneous B-cell lymphoma
 - f. Peripheral T-cell lymphoma

III. Radioimmunotherapy

- A. Please refer to the separate Radioimmunotherapy -- RIT with Zevalin® criteria

IV. Adjuvant radiation after chemotherapy

- A. Areas of initial involvement
 - 1. Adjuvant radiation therapy after chemotherapy in an individual with stage I-II B disease to areas of initial involvement
 - a. Doses of up to 36 Gy
 - b. Up to 20 fractions with a conventional schedule
 - 2. Supra-diaphragmatic presentations
 - a. Complex, 3DCRT, or IMRT techniques, with image guidance, directed at a single site in 1 phase
 - 3. Sub-diaphragmatic presentations
 - a. Complex or 3DCRT techniques
 - b. IMRT will be considered on a case-by-case basis
- B. Areas of less than a complete response (CR)
 - 1. Adjuvant radiation after chemotherapy in an individual with stage III-IV disease, to areas of less than a CR
 - a. Doses of up to 36 Gy
 - b. Up to 20 fractions with conventional schedule
 - 2. Supra-diaphragmatic presentations
 - a. Complex, 3DCRT, or IMRT techniques, with image guidance, directed at up to 4 separate sites in 1 phase apiece
 - 3. Sub-diaphragmatic presentations
 - a. Complex or 3DCRT techniques
 - b. IMRT will be considered on a case-by-case basis
- C. Sequential chemotherapy carries a high toxicity burden and requires substantial supportive care and the expertise of an experienced multidisciplinary team

V. Radiation therapy, palliative

- A. In an individual with advanced or recurrent disease that is felt not to be curative and who is experiencing symptomatic local disease, photon and/or electron techniques are indicated for symptom control
 - 1. Supra-diaphragmatic presentations
 - a. Complex, 3D, or IMRT techniques
 - b. Up to 10 fractions in 1 phase
 - 2. Sub-diaphragmatic presentations
 - a. Complex or 3D techniques
 - b. IMRT will be considered on a case-by-case basis
 - c. Up to 10 fractions in 1 phase

Key Clinical Points

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines (American College of Radiology [ACR]/American Society of Radiation Oncologists [ASTRO], NCCN), radiation therapy is considered an integral component in the multidisciplinary management of NHL. Proper management of the disease requires the cooperation of a complex multi-disciplinary team that includes experts in diagnostic imaging, pathology, radiation oncology and medical oncology. NHL treatment is based on the pathologic subtype of the disease, initial stage of disease as well as the medical condition of the individual. Pathology and stage have a critical role in the planning process.

Treatment decisions are preceded by workup and staging and planned in conjunction with the appropriate members of the multi-disciplinary team. Participation in a national clinical trial is encouraged.

Initial management requires chemotherapy as the cornerstone of therapy (in a variety of different acceptable regimens), followed by assessment of response leading to an appropriate choice of radiation therapy technique, dose, and use of radioimmunotherapy as clinically indicated.

I. Radiation treatment schedules

- A. Radiation therapy treatment schedules published in peer-reviewed consensus documents such as NCCN Practice Guidelines in Oncology include regimens that encompass a relatively limited range of doses and fields that may be influenced by the histology, initial stage, bulk of the disease at each site, the choice of chemotherapy regimens, and the response to initial chemotherapy. Using current combined modality approaches, the fields covered are usually confined to the initial areas of documented involvement, ISRT.
- B. Histology specific recommendations
 - 1. Chronic lymphocytic leukemia (CLL)
 - a. Will not require radiation routinely

2. Follicular low-grade lymphoma, stage I-II
 - a. Radiation alone may be considered adequate therapy, or
 - b. Radiation treatment may be given after initial chemotherapy to the original extent of disease
 - i. Omitting sites that had no clear involvement in an effort to minimize toxicity
 - ii. To doses that range from 20 to 36 Gy
 - iii. Generally encompassable in a single site setup, requiring the use of Complex or 3D techniques, with image guidance
 - iv. Under some circumstances, IMRT may be appropriate
 - v. Radioimmunotherapy may be appropriate
3. Follicular lymphoma, stage III-IV
 - a. Systemic chemotherapy is the standard of care
 - b. Radiation may be considered for an individual with a sub-optimal response to therapy
4. Transformed lymphoma, i.e., an individual with an original diagnosis of follicular lymphoma that has transformed to a more malignant subtype
 - a. Systemic chemotherapy is the mainstay of therapy
 - b. Radiation may be considered as an adjunct for locally uncontrolled disease
 - c. Radioimmunotherapy may be considered for the management of this disease
5. MALT-lymphoma (gastric or non-gastric)
 - a. Radiation may be appropriate as curative therapy
 - b. Doses of up to 36 Gy
6. Extranodal natural killer (NK)/T-cell lymphoma, nasal lymphoma
 - a. Definitive radiation therapy to a dose of 54 Gy
7. Consolidative radiation therapy after initial chemotherapy, to a dose of 36 Gy, to the original extent of disease for the following histologies:
 - a. Mantle cell lymphoma
 - b. DLBCL
 - c. Burkitt's lymphoma
 - d. Lymphoblastic lymphoma
 - e. Primary cutaneous B-cell lymphoma
 - f. Peripheral T-cell lymphoma

References

1. Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. *Cancer*. 2010; 116(16):3797-3806. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.25117/full>
2. Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy *Cancer*. 2010; 116(16):3815-3824. Accessed June 22, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.25226/full>
3. Haas RLM, Poortmans PH, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. *J Clin Oncol*. 2003 Jul 1; 21(13):2474-2480. Accessed June 22, 2016. <http://jco.ascopubs.org/content/21/13/2474.abstract>
4. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group Study 1484. *J Clin Oncol*. 2004 Jun 21; 22(15):3032-3038. Accessed June 22, 2016. <http://jco.ascopubs.org/content/22/15/3032.full>
5. Illidge t, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma—target definition and dosing guidelines from the International Lymphoma Radiation Oncology Group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014 May 1; 89(1):49-58. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(14\)00064-9/fulltext](http://www.redjournal.org/article/S0360-3016(14)00064-9/fulltext)
6. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1998 Jul 2; 339(1):21-26. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199807023390104>
7. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008 Nov 10; 26(32):5156-5164. Accessed June 22, 2016. <http://jco.ascopubs.org/content/26/32/5156.abstract>
8. National Comprehensive Cancer Network (NCCN) Guidelines. Version 3.2016. Non-Hodgkin's Lymphomas. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Non-Hodgkin's Lymphomas Version 3.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
9. Phan J, Mazloom A, Medeiros LJ, et al. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *J Clin Oncol*. 2010 Sep 20; 28(27):4170-4176. Accessed June 22, 2016. <http://jco.ascopubs.org/content/28/27/4170.full>
10. Witzig TE, Gordon LI, Cabanillas F, et al: Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002 May 15; 20(10):2453-2463. Accessed June 22, 2016. <http://jco.ascopubs.org/content/20/10/2453.abstract>

Radiation Treatment for Non-Hodgkin's Lymphoma

[Return to Table of Contents](#)

Radiation Treatment of Bladder Cancer

POLICY

External beam photon radiation therapy (EBRT) is medically necessary for the following:

- I. Definitively in an individual undergoing bladder preservation with T2-T4, node positive or recurrent disease**
- II. Postoperatively in an individual with T3-T4 disease, node positive, or positive surgical margins**
- III. Palliation**

Fractionation

- I. In the definitive setting up to 37 fractions is medically necessary**
- II. In the adjuvant setting up 30 fractions is medically necessary**
- III. In the palliative setting up to 20 fractions is medically necessary**

Techniques

- I. EBRT with three-dimensional conformal radiation therapy (3DCRT) is medically necessary in the treatment of bladder cancer. Treatment prescriptions include the bladder with or without pelvic lymph nodes to 40 to 45 Gy followed by a boost to 66 Gy in 2 phases of treatment.**
- II. In the curative setting, intensity modulated radiation therapy (IMRT) may be indicated when dose to critical organs is of concern. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the acceptable normal tissue constraints using standard radiation therapy**

criteria from the Radiation Therapy Oncology Group (RTOG) or National Comprehensive Cancer Network (NCCN).

III. When irradiating the bladder alone or delivering a boost to the bladder tumor during definitive therapy, image guidance is medically necessary.

Key Clinical Points

Treatment of non-muscle invasive bladder is performed with a transurethral resection of the bladder tumor (TURBT) followed by intravesical therapy (Babjuk, 2013). For an individual with muscle-invasive bladder cancer, treatment options include cystectomy or definitive chemoradiation as part of a bladder preserving approach (Gakis, 2013).

Bladder preservation is an option for an individual who is medically inoperable or who wants an alternative to cystectomy. An ideal candidate for bladder preservation includes one with tumors < 5 cm, a visibly complete TURBT, absence of associated carcinoma in situ, and no evidence of ureteral obstruction (Milosevic, 2007). Radiotherapy with concurrent cisplatin is the most common bladder sparing approach used to treat muscle-invasive bladder cancer. Following TURBT, 40 to 45 Gy is given to the whole pelvis using 3DCRT. Afterwards, repeat endoscopy is performed to examine the tumor response. If residual disease is seen, then a cystectomy is recommended. If a complete response is noted, then an additional 20 to 25 Gy is delivered with cisplatin. This approach demonstrated a 5-year survival of 49% when examined prospectively in RTOG 89-03 (Shipley, 1998). In a phase III randomized trial, concurrent chemoradiation improved 5-year disease-free survival (DFS) from 54% to 67% ($p = 0.01$) (James, 2012). Furthermore, approximately 80% of long-term survivors will maintain an intact bladder with this approach (Mak, 2014; Rodel, 2002). While several phase II prospective studies have examined alternative radiation fractionation schemes, none has demonstrated a clinically meaningful benefit compared to standard once a day fractionation schedules (Hagan, 2003; Kaufman, 2000). Definitive radiotherapy alone is considered for an individual with no evidence of metastatic disease who cannot undergo a cystectomy or concurrent chemoradiation.

There is a lack of strong clinical evidence demonstrating the benefit of adjuvant radiation therapy for bladder cancer following cystectomy. Due to retrospective series demonstrating a higher local recurrence rates noted in T3-T4 disease, node positive, or positive surgical margins (30 to 60%) radiation therapy is medically necessary in these individuals, up to 30 fractions (Herr, 2004).

In an individual with evidence of metastatic disease, palliative radiation is medically necessary, up to 20 fractions using 3D techniques.

References:

1. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013 Oct; 64(4):639-653. Accessed June 22, 2016. [http://www.europeanurology.com/article/S0302-2838\(13\)00601-5/fulltext/eau-guidelines-on-non-muscle-invasive-urothelial-carcinoma-of-the-bladder-update-2013](http://www.europeanurology.com/article/S0302-2838(13)00601-5/fulltext/eau-guidelines-on-non-muscle-invasive-urothelial-carcinoma-of-the-bladder-update-2013)
2. Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. Euro Urol. 2013. 2013 Nov; 64(5):823-830. Accessed June 22, 2016. [http://www.europeanurology.com/article/S0302-2838\(13\)00298-4/fulltext/eau-guidelines-on-primary-urethral-carcinoma](http://www.europeanurology.com/article/S0302-2838(13)00298-4/fulltext/eau-guidelines-on-primary-urethral-carcinoma)
3. Hagan MP, Winter KA, Kaufman DS, et al. RTOG 97-06: Initial report of a Phase I–II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. Int J Radiat Oncol Biol Phys. 2003 Nov 1; 57(3):665-672. Accessed June 22, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)00718-1/abstract](http://www.redjournal.org/article/S0360-3016(03)00718-1/abstract)
4. Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol. 2004 Jul 15; 22(14):2781-2789. Accessed June 22, 2016. <http://jco.ascopubs.org/content/22/14/2781.full>
5. James ND, Hussain SA, Hall, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. NEJM. 2012 Apr 19; 366(16):1477-1488. Accessed June 22, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa1106106>
6. Kaufman DS, Winter KA, Shipley WU, et al. The initial results in muscle-invasive bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist. 2000 Dec; 5(6):471-476. Accessed June 22, 2016. <http://theoncologist.alphamedpress.org/content/5/6/471.full>
7. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol. 2014 Dec 1; 32(34):3801-3809. Accessed June 22, 2016. <http://jco.ascopubs.org/content/32/34/3801.full>
8. Milosevic M, Gospodarowicz M, Zietman A, et al. Radiotherapy for bladder cancer. Urology. 2007 Jan; 69(1 Suppl):80-92. Accessed June 22, 2016. [http://www.goldjournal.net/article/S0090-4295\(06\)02058-9/fulltext](http://www.goldjournal.net/article/S0090-4295(06)02058-9/fulltext)
9. Rödel C, Gragenbauer, GG, Kühn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. J Clin Oncol. 2002 Jul 15; 20(14):3061-3071. Accessed June 22, 2016. <http://jco.ascopubs.org/content/20/14/3061.abstract>
10. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Bladder Cancer. Accessed June 22, 2016. http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Bladder Cancer 1.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
11. Shipley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. Accessed June 22, 2016. <http://jco.ascopubs.org/content/16/11/3576.abstract>

Radiation Treatment of Bladder Cancer

[Return to Table of Contents](#)

Radiation Treatment of Bone Metastases

POLICY

I. Conventional photon treatments utilizing Complex techniques are considered medically necessary as palliative treatment for bone metastasis for any of the following:

- A. Pain related to the bone metastasis
- B. High risk of impending fracture
- C. Post-operative pain from repair of a pathological fracture
- D. Symptomatic spinal cord compression

II. Fractionation

- A. Bedridden more than 50% of the time
 - 1. Up to 5 fractions; 1 fraction of 8 Gy recommended
- B. Bedridden less than or equal to 50% of the time
 - 1. Up to 10 fractions; 1 fraction of 8 Gy recommended

III. Techniques

- A. Complex: These planning techniques are medically necessary for the majority of individuals requiring palliative treatment for bone metastases. One or 2 gantry angles can usually produce the appropriate dose distribution. More than 1 phase (i.e. a conedown) is rarely medically necessary. In rare circumstances where there exists significant extraosseous component or where higher doses are justified, up to 3 gantry angles and use of complex blocking may be medically necessary.
- B. Three-dimensional (3D) Conformal Radiation Therapy (3DCRT) and Intensity-Modulated Radiation Therapy (IMRT): Use of conformal radiation therapy techniques including 3DCRT and IMRT generally are not medically necessary for the treatment of bone metastasis. 3DCRT will be considered when there is a significant complex extraosseous component to the target volume. IMRT will be considered only in cases where overlap with previous radiotherapy fields is likely to cause complications. For other presentations, IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN).

- C. Stereotactic Body Radiosurgery (SBRT): SBRT is not standard of care and is not medically necessary. SBRT will be considered in cases that require treatment to a portion of the spine that has been previously irradiated. Consideration for the use of SBRT will also be given in cases of radio-resistant tumors (sarcoma, melanoma and renal cell carcinoma) that have metastasized to the spine. Discussion with an eviCore healthcare radiation oncologist will be required for authorization of cases outside of eviCore standard policy.

IV. Radium-223 (Xofigo®) is medically necessary for the treatment of castration-resistant prostate cancer for an individual with all of the following:

- A. Skeletal (bone) metastases
- B. No evidence of past or current lymph nodes or visceral metastases on imaging performed within the past 30 days
- C. Who has received and exhausted all medical- or surgical-ablative hormonal treatments. The individual may be kept on his ablative hormonal treatment to maintain a castrate level in accordance with NCCN® guidelines.
- D. Medically- or surgically-castration resistant prostate cancer, as defined by
 - 1. A serum testosterone level of less than < 50 ng/dL **and either**
 - a. Sequential rise of prostate specific antigen (PSA) levels **or**
 - b. Worsening of existing bone metastases or development of new bone metastases on a bone scan performed within the past 60 days despite androgen-deprivation treatment

Xofigo® is administered intravenously once a month for 6 months.

Concurrent chemotherapy with Xofigo® is considered experimental, investigational, or unproven (EIU).

Key Clinical Points

Bone is a common site of metastatic cancer. Photon techniques are the mainstay of treatment for symptomatic bone metastases. Local field radiotherapy is highly effective in relieving pain and preventing fractures and is typically associated with minimal side effects. Eighteen trials assessing fractionation and dose of radiotherapy for painful bone metastases have been published (Hartsell et al., 2003; Wu et al., 2003). Randomized trials comparing single fraction of 8 Gy with multiple fraction radiotherapy regimens (20 to 30 Gy in 5 to 10 fractions) reveal similar overall response rates. Pain relief is typically achieved 1 to 4 weeks after treatment and the duration of response is 12 to 24 weeks. In a pooled analysis of patients with bone metastases, approximately one-third of patients will have complete pain relief and an additional one-third of patients will have partial relief of pain, irrespective of the dose-fractionation used. ROTG trial 9714 included 949 patients who were randomly assigned between 8 Gy in a single dose or 30 Gy in 10 fractions. Pain response rates were similar with 8 Gy in 1 fraction compared

with 30 Gy in 10 fractions (66% in each group). A British trial (Yarnold et al., 1999) randomized 765 patients with painful bony metastases to 8 Gy as a single fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions. There were no differences in pain endpoints among the groups. A Dutch trial (van der Linden et al., 2004) randomized 1171 patients with bone metastases to 8 Gy in 1 fraction or 24 Gy in 6 fractions and found no difference in pain relief or toxicity. While retreatment was higher with patients treated with a single fraction (18% vs. 9%), a reanalysis revealed this was because physicians were only more willing to treat after a single fraction. The study concluded that with or without the effect of retreatment, single fraction and multi-fraction radiation provided equal palliation.

The American Society for Radiation Oncology (ASTRO) Choosing Wisely® campaign has recommended not to use extended fractionation schemes (> 10 fractions) for palliation of bone metastases. It also states that, "...strong consideration should be given to a single 8 Gy fraction for patients with limited prognosis or with transportation difficulties." The NCCN guidelines for prostate non-vertebral metastases also state that, "...8 Gy as a single dose should be used instead of 30 Gy in 10 fractions."

Photon techniques as sole therapy have been used most commonly for the treatment of spinal cord compression. Corticosteroids are initiated immediately prior to radiation. A total dose of up to 30 Gy in 10 fractions may be appropriate in an individual predicted to have more extended life span, although shorter dose schedules including single and 5-fraction treatment have been employed with similar outcome. One trial (Maranzano et al., 2005) randomized patients with cord compression with a short life expectancy to 8 Gy x 2 (16 Gy total dose) or 5 Gy x 3 followed by 3 Gy x 5 (30 Gy total dose). It found no significant difference in outcomes between the two schedules.

Surgery may be appropriate to establish a diagnosis, if uncertain, in an individual with acceptable performance status where bony retropulsion is likely to be the primary cause of neurologic deficit, in one with rapid deterioration of neurologic function or with high grade cervical cord compression, and can be considered more generally based on the results of a randomized trial comparing surgery and post-operative radiotherapy versus radiotherapy alone. Vertebral body resection and radical decompressive surgery with postoperative radiotherapy was found to be superior to radiotherapy alone in the only randomized trial of spinal cord compression conducted to date (Regine et al., 2003). Patients with a single site of cord compression and a minimum three-month life expectancy were enrolled. The trial was stopped early after 101 patients were enrolled. Patients who received surgery plus conventional radiation therapy retained the ability to walk significantly longer (126 days vs. 35 days with conventional radiation therapy alone). In a total of 32 patients who could not walk at the time of enrollment, 56% of

those who received surgery and conventional radiation therapy recovered the ability to walk versus 19% who received conventional radiation therapy alone. Functional scores, maintenance of continence, and use of steroids and narcotics were all improved in patients undergoing decompressive surgery versus radiotherapy alone. Survival was slightly better in patients undergoing surgery (median 4.2 months vs. 3.3 months, $p = 0.08$). An individual with neurologic deficit and life expectancy of at least 3 months should be considered for surgery based on the results of this phase III study.

The ASTRO Task Force on radiotherapy for bone metastases published its guidelines in 2011. The task force clearly states that dosing and target volume have yet to be fully defined for SBRT and that SBRT should be considered investigational. Further, the task force states that SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression. For recurrent painful lesions, the task force recommends that SBRT should be limited to clinical trials. The summary of the task force is that SBRT "...holds theoretical promise in the treatment of new or recurrent spine lesions... [and that]...its use be limited to highly selected patients and preferably within a prospective trial."

I. Radiation Fractionation and Technique

The ACR Appropriateness Criteria[®] panel recommends fractionation schedules ranging from a single 8 Gy fraction to 30 Gy in 10 fractions for the palliation of long bone involvement, whereas 35 Gy in 14 or 15 fractions and 40 Gy in 20 fractions is considered less appropriate due to the protracted length of therapy. A shorter course of radiation offers equivalent palliation and increased convenience for the individual and caregivers. CT simulation, to include accurately the involved vertebrae and account for body habitus in conventional radiation therapy dose calculation is most desirable. Fluoroscopic simulation is regarded as a reasonable alternative. An individual with spinal involvement may be considered for treatment using 20 Gy in 5 fractions or 30 Gy in 10 fractions. An individual who requires more than 10 fractions for the treatment of bone metastases will require discussion with an eviCore radiation oncologist for authorization.

Complex techniques are medically necessary for the majority of individuals requiring palliative treatment for bone metastasis. According to ACR Appropriateness Criteria[®], conformal radiotherapy techniques, including IMRT and protons, generally are not medically necessary for the treatment of bone metastases. Furthermore, Complex simulation, planning, and treatment charges do not apply in most cases. One study (Pope et al., 2013) found no clinical benefit among patients who underwent Complex or 3D planning for bone metastases. Therefore, 1 or 2 gantry angles can usually produce the appropriate

dose distribution. Due to the palliative nature of the treatment, and the dose fractionations utilized, construction of a dose volume histograms of normal structures or of gross tumor volumes is not medically necessary and unlikely to significantly affect the treatment delivered. More than 1 phase (i.e. a conedown) is rarely medically necessary. In rare circumstances where there exists a significant extraosseous component or where higher doses are justified, up to 3 gantry angles and use of complex blocking may be medically necessary.

In cases of reirradiation of painful bone metastases, a phase III study (Chow, et al., 2014) randomized 425 patients between receiving 8 Gy vs. 20 Gy in multiple fractions. It found no difference in pain response to treatment, and that a single fraction of radiation was associated with less toxicity. Based on these results, reirradiation can be delivered safely with Complex techniques, and the use of SBRT in this setting to non-vertebral lesions is not medically necessary.

II. Management of Oligometastases

Please refer to the separate Radiation Treatment of Extra-cranial Oligometastases policy.

III. Radiopharmaceutical Therapy

Radium-223 (Xofigo®) is an alpha emitter that targets areas of increased bone turnover in osteoblastic or sclerotic metastases. A phase III study examined patients with castration resistant prostate cancer with two or more bone metastases and no visceral metastases and randomized them to Radium-223 or matching placebo. It found improved overall survival (OS) for patients who received Radium-223 with a survival 14.9 months vs. 11.3 months ($p < .001$) in those who received best standard of care. The targeted nature of Radium-223 with alpha particles of short range minimizes myelosuppression and has limited effects on the normal tissue. Based on these results, Radium-223 is medically necessary for the treatment of castration resistant prostate cancer with bone metastases but no visceral metastases and is administered intravenously once a month for 6 months.

References

1. ASTRO release list of five radiation oncology treatments to question as part of national Choosing Wisely® campaign. 2013 Sep 23. Accessed June 23, 2016. <http://www.choosingwisely.org/astro-releases-list-of-five-radiation-oncology-treatments-to-question-as-part-of-national-choosing-wisely-campaign>
2. Chander SS, Sarin R. Single fraction radiotherapy for bone metastases: are all questions answered? Radiother Oncol 1999 Aug 1; 52(2):191-193. Accessed June 23, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(98\)00105-4/abstract](http://www.thegreenjournal.com/article/S0167-8140(98)00105-4/abstract)
3. Chow E, van der Linden YM, Roos D et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol. 2014 Feb; 15(2):164-71. Accessed June 23, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(13\)70556-4/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70556-4/fulltext)

4. Hartsell WF, Scott C, Bruner DW et al. Phase III randomized trial of 8 Gy in 1 fraction vs. 30 Gy in 10 fractions for palliation of painful bone metastases: preliminary results of RTOG 97-14. *Int J Radiat Oncol Biol Phys* 2003; 57(2 Suppl):S124. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)00823-X/abstract](http://www.redjournal.org/article/S0360-3016(03)00823-X/abstract)
5. Hartsell WF, Scott CB, Bruner DW et al. Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005 Jun 1; 97(11):798–804. Accessed June 23, 2016. <http://jnci.oxfordjournals.org/content/97/11/798.full.pdf+html>
6. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomized, double-blind, phase 3 ALSYMPCA trial. *Lancet Oncol*. 2014 Nov; 15(12):1397-1406. Accessed June 23, 2016. <http://www.sciencedirect.com/science/article/pii/S1470204514704747>
7. Hoskin PJ, Grover A, Bhana R. Metastatic spinal cord compression: radiotherapy outcome and dose fractionation. *Radiother Oncol* 2003 Aug; 68(2):175-189. Accessed June 23, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(03\)00191-9/abstract](http://www.thegreenjournal.com/article/S0167-8140(03)00191-9/abstract)
8. Kim EY, Chapman TR, Ryu S et al. Expert panel on radiation oncology. ACR Appropriateness Criteria® Non-Spinal Bone Metastases. *J Palliat Med*. 2012 May; 15(5): 521-526. Published at ACR website. Date of Origin: 1996. Last review date: 2014. Accessed June 23, 2016. <https://acsearch.acr.org/docs/69354/Narrative/>
9. Lo SS, Lutz ST, Chang EL et al. Expert panel on radiation oncology. ACR Appropriateness Criteria® Spinal Bone Metastases *J Palliat Med*. 2013 Jan; 16(1):9-19. Published at ACR website. Date of Origin: 1996. Last review date: 2012. Accessed June 23, 2016. <https://acsearch.acr.org/docs/71097/Narrative/>
10. Lutz S, Berk L, Chang E et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys*. 2011; 79(4): 965-976. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)03577-7/pdf](http://www.redjournal.org/article/S0360-3016(10)03577-7/pdf)
11. Maranzano E, Bellavita R, Rossi R et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. *J Clin Oncol*. 2005 May 20; 23(15):3358-65. Accessed June 23, 2016. <http://jco.ascopubs.org/content/23/15/3358.full.pdf+html>
12. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2016. Prostate Cancer. Accessed June 23, 2016. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Prostate Cancer 3.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
13. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013 Jul 18; 369(3):213-223. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa1213755>
14. Pope K, Fitzpatrick D, Potter A et al. Dosimetric and clinical impact of 3D vs. 2D planning in palliative radiotherapy for bone metastases. *Support Care Cancer*. 2013 Aug; 21(8):2229-35. Accessed June 23, 2016. <http://link.springer.com/article/10.1007/s00520-013-1777-8>
15. Regine WF, Tibbs PA, Young A et al. Metastatic spinal cord compression: a randomized trial of direct decompressive surgical resection plus radiotherapy vs. radiotherapy alone. *Int J Radiat Oncol Biol Phys* 2003 Oct 1; 57(2 suppl):S125. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)00825-3/abstract](http://www.redjournal.org/article/S0360-3016(03)00825-3/abstract)
16. Sahgal A, Bilsky M, Chang EL et al. Stereotactic body radiotherapy for spinal metastases: current status, with a focus on its application in the postoperative patient. *J Neurosurg Spine*. 2011 Feb; 14(2):151–166. Accessed June 23, 2016. <http://thejns.org/doi/pdf/10.3171/2010.9.SPINE091005>
17. van der Linden YM, Lok JJ, Steenland E et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys*. 2004 Jun 1; 59(2):528-37. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)02110-2/abstract](http://www.redjournal.org/article/S0360-3016(03)02110-2/abstract)
18. Vapiwala N, Glatstein E. Fighting prostate cancer with Radium-223—not your madame's isotope. *N Engl J Med*. 2013 Jul 18; 369(3):276-278. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMe1304041>
19. Wu JS, Wong R, Johnston M et al. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys*. 2003 Mar 1; 55(3):594-605. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(02\)04147-0/abstract](http://www.redjournal.org/article/S0360-3016(02)04147-0/abstract)
20. Yarnold JR. on behalf of the Bone Pain Trial Working Party. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. *Radiother Oncol*. 1999 Aug ; 52(2):111-21. Accessed June 23, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(99\)00097-3/abstract](http://www.thegreenjournal.com/article/S0167-8140(99)00097-3/abstract)

Radiation Treatment of Bone Metastases

[Return to Table of Contents](#)

Radiation Treatment of Brain Metastases

POLICY

I. In considering optimal treatment for an individual with brain metastases, several prognostic factors must be considered.

Risk factors for early death include:

- A. More than 3 brain metastases
- B. Not fully ambulatory
- C. Diagnosis other than breast cancer
- D. Presence of visceral disease
- E. Progression of systemic disease after at least one prior chemotherapy regimen for metastatic disease

II. Whole brain radiotherapy (WBRT)

- A. For an individual with most of the risk factors listed above, up to 10 fractions of WBRT is medically necessary. For an individual with a better prognosis, up to 15 fractions of WBRT is medically necessary. WBRT is limited to 2 fields planned using a complex isodose technique (77307), 3-Dimensional (3D) conformal planning or intensity-modulated radiation therapy (IMRT) are not medically necessary. A boost of up to 10 fractions is medically necessary following WBRT.

III. Partial brain radiotherapy with stereotactic radiosurgery (SRS)

- A. Initial treatment
 - 1. Any number of lesions to be treated with SRS at initial presentation is medically necessary when no lesion is greater than 3 cm, the individual has a good performance status, systemic disease is limited and under control (or good options for systemic treatment are available), and all lesions can be encompassed in a single treatment plan. In addition, the total volume of treated lesions should be considered safe to deliver SRS
 - 2. An SRS boost is medically necessary in an individual with a single lesion when WBRT is being delivered
- B. Previously treated individual
 - 1. If previous WBRT has been delivered, SRS may be medically necessary if the individual's performance status is good and systemic disease is under control
 - 2. If no previous WBRT was delivered, and recurrence has > 3 lesions, WBRT is medically necessary and SRS is not medically necessary
 - 3. If no previous WBRT was delivered, and recurrence is 1-3 lesions, previous RT was more than 6 months ago, performance status is good, and systemic disease is controlled, SRS is medically necessary

IV. Partial brain radiotherapy with external beam radiation therapy (EBRT)

A. Partial brain radiotherapy may be delivered with EBRT, usually 3D conformal treatment (3DCRT) or intensity-modulated radiation therapy (IMRT)

1. IMRT or 3DCRT as the sole treatment of partial brain therapy is medically necessary in an individual with a good prognosis, for up to 20 fractions

Key Clinical Points

I. WBRT

The median survival following the diagnosis of metastatic disease involving the brain is generally four to six months. Many patients develop brain metastases late in the course of their disease when progressive extracranial disease dictates survival. The majority of symptomatic patients will have clinical response with WBRT. The clinical response rate, degree of response, and duration of response depend on the extent of tumor and the severity of initial neurologic deficits. The most common WBRT fractionation is 30 Gy in 10 fractions over two weeks. In two randomized Radiation Therapy Oncology Group (RTOG) trials of over 1800 patients, fractionation schedules of 20 Gy in 1 week, 30 Gy in 2 weeks, 30 Gy in 3 weeks, 40 Gy in 3 weeks, and 40 Gy in 4 weeks were tested (Borgelt et al., 1980). No significant differences between the fractionation regimens were seen. Overall improvement in neurologic function was seen in approximately half of patients and maintained in over three-fourths of these patients. Normal functionality was achieved in one-third of patients that were partly bedridden. Brain metastasis was the cause of death in 40% of patients. Additional randomized trials from the RTOG have shown no significant differences in outcome based on dose-fractionation schemes, including 30 Gy in 2 weeks versus 50 Gy in 4 weeks (Kurtz et al., 1981) or versus a hyperfractionated regimen of 54.4 Gy at 1.6 Gy bid (Murray et al., 1997). All regimens were associated with response of neurologic symptoms in the majority of patients and a median survival of approximately 4 months. Recursive partitioning analysis of patients treated with a variety of dose-fractionation regimens suggests that factors unrelated to radiotherapy treatment parameters best predict survival: patients with a KPS of at least 70, controlled primary tumor, brain as the only site of metastases, and age less than 65 years were found to have the longest median survival, however even with all of these factors, the median survival was only 7.1 months (Gaspar et al., 1997). Shorter course regimens are appropriate for patients at increased risk of early death, such as those with more than 3 brain metastases, poor performance status, non-breast cancer histology, presence of visceral metastases, and progressive extracranial metastases despite prior chemotherapy. In patients with many of these factors present, treatment regimens longer than 30 Gy in 10 fractions is inappropriate, and shorter

hypofractionated regimens should be considered. In patients with few of these factors present, consideration could be given to more protracted and aggressive regimens, such as 37.5 Gy in 15 fractions.

In patients who have undergone resection, the need for whole brain radiation has been studied. The majority of patients will have further failure in the brain, at both the site of resection and at remote sites in the brain. For example, in a randomized study of 95 patients who underwent MRI-defined complete resection of a solitary brain metastasis, 70% of patients had recurrence in the brain either at the index lesion or elsewhere. Post-operative WBRT was associated with a three-fourths relative risk reduction in recurrence (absolute risk reduction 18%) and was associated with decreased risk of death from neurologic causes (Patchell et al., 1998). Therefore, postoperative whole brain radiotherapy is generally recommended for patients who undergo resection of a solitary metastasis and who have controlled extracranial disease. In a patient who has had a solitary metastasis completely resected, there is no established role for partial brain radiotherapy.

Whole brain radiotherapy involves the use of two lateral opposed fields, with or without the use of custom blocking. Often, simple simulation without blocking suffices. RTOG 0933 was a phase II study that looked at the role of hippocampal sparing and neurocognitive decline after WBRT. Compared to historical data, the study concluded that sparing the hippocampal region might lead to fewer neurocognitive complications associated with WBRT. At this time, use of 3D conformal techniques or IMRT for the purpose of sparing the hippocampal region is still considered investigational. Conedown phase (e.g. boost) is inappropriate in patients undergoing whole brain radiotherapy after complete gross resection of the tumor. Similarly, there is no evidence of benefit from partial brain radiotherapy techniques (see below) after gross total resection of brain metastasis.

II. Partial brain radiotherapy (PBRT)

The survival outcome with WBRT alone for brain metastases is poor, and up to half of patients will develop progressive disease with the use of WBRT alone. WBRT increasingly is being supplemented by more aggressive treatment directed at known sites of brain metastases, using surgical resection or partial brain radiotherapy techniques such as stereotactic single fraction radiotherapy (“radiosurgery”), stereotactic multi-fraction radiotherapy, 3D-CRT, IMRT.

The value of more aggressive treatment in selected patients is exhibited by two of the three randomized trials of surgical resection of solitary metastasis plus WBRT versus WBRT alone. Patchell et al. (1990) found improved local control

(20% brain failure versus 52%) and median survival (40 weeks versus 15 weeks) with the addition of surgery. In another trial, surgery improved median survival from 6 months to 10 months (Noordijk et al., 1994). A more recently published multicenter randomized trial of 84 patients did not reveal any advantage to surgical resection (Mintz et al., 1996). This may be due to the selection of patients with worse performance status, more extracranial disease, failure to achieve complete resection in some patients, and crossover of one-fourth of patients receiving WBRT to surgery. Stereotactic radiosurgery (SRS) offers an alternative means for focal treatment. SRS is described by the American Society of Therapeutic Radiology and Oncology (ASTRO) as follows: "...SRS is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate a defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist." The adjective "stereotactic" describes a procedure during which a target lesion is localized relative to a fixed three-dimensional reference system, such as a rigid head frame affixed to a patient, fixed bony landmarks, a system of implanted fiducial markers, or other similar system. This type of localization procedure allows physicians to perform image-guided procedures with a high degree of anatomic accuracy and precision. Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system. If dose to each lesion is fractionated, SRS can be performed in a limited number of sessions, up to a maximum of five. Selection criteria for radiosurgery are similar to those for surgical resection, i.e. patients with solitary metastases, good performance status, and limited or responsive extracranial disease. In a study of 248 patients with 421 brain lesions from a variety of primary cancers, there was only 11% progression within the radiosurgery volume(s) at a median follow-up of 26 months. Surgery was required for 6% of patients for mass effect or steroid dependency secondary to radiation necrosis (Alexander et al., 1995). Mehta and colleagues (1998) reviewed more than 2100 lesions treated with radiosurgery to a median dose of 18 Gy and found 86% of lesions were stable or responded. A retrospective study of 122 patients who were eligible for surgical resection combined 37.5 Gy WBRT followed by a median radiosurgery boost of 17 Gy. An 86% brain tumor control rate was obtained and the median survival was greater than one year, which compares favorably with results of trials of surgical resection and WBRT (Auchter et al., 1996). RTOG 95-08 randomized patients with 1 to 3 brain metastases to WBRT followed by radiosurgery boost versus WBRT alone (37.5 Gy in 15 fractions). There was improved survival in

only the subset of patients with a solitary metastasis (median of 4.9 months in the WBRT arm versus 6.5 months in the WBRT plus radiosurgery arm). Therefore, there is likely to be little benefit for radiosurgery in most patients with more than one brain metastasis.

WBRT has been recommended before or after radiosurgery. In a multi-institutional retrospective study of stereotactic radiosurgery in the treatment of single brain metastasis, of 71 patients who had newly diagnosed brain metastases, the brain control rate at one year was 53% with radiosurgery and WBRT as compared with 18% for radiosurgery alone (Flickinger et al., 1994). However, salvage therapy with WBRT is possible after radiosurgery and survival appears uncompromised with a deferred treatment strategy (Sneed et al., 2002; Aoyama et al., 2006). Because survival is not compromised, ASTRO's most recent "Choosing Wisely" recommendation is that adjuvant whole brain radiation therapy should not be routinely added to SRS for limited brain metastases. The reference article quoted of an EORTC study refers to a maximum of 3 lesions treated with SRS (Soffietta et al., 2013). Patients with metastasis larger than 3 cm are best treated with WBRT as initial treatment as tumor control may be inferior with radiosurgery alone. Patients who respond to WBRT can be considered for radiosurgery. Alternative methods to treat larger solitary brain metastases include partial brain 3D CRT and IMRT.

ASTRO has published its 2012 guidelines on radiotherapeutic and surgical management for newly diagnosed brain metastasis(es). There is no convincing evidence of a survival advantage using SRS alone versus WBRT with SRS boost, versus WBRT alone. Randomized trials which have examined the use of radiosurgery, included selected patients with up to 4 brain metastases, while retrospective reports document use of radiosurgery that exceed 4 brain metastases (Bhatnagar et al., 2006; Serizawa et al., 2010). The optimal number of brain lesions that can be safely treated without using WBRT is unknown, although several studies treating multiple lesions as part of an initial course of brain metastases therapy have documented the safety of this treatment when largest size of any lesion and total volume of all treated regions are taken into account (Hunter et al., 2012). While some have postulated that the use of WBRT leads to a more rapid decline in neurocognitive function, the ASTRO guideline states that it remains to be reported whether neurocognitive outcomes differ using SRS versus SRS and WBRT. Of more concern, is that the brain tumor recurrence rate is significantly higher when WBRT is omitted (Tsao et al., 2012), and that there can be a shorter duration to neurocognitive decline attributable to the increased risk of recurrence in patients treated with SRS alone. This

increased risk of recurrence in patients receiving SRS alone may be associated with symptomatic recurrence, which may not fully recover despite salvage treatment (Aoyama et al., 2006).

A systematic review of SRS for brain metastases published in June 2014 (Nieder et al.) concluded that “SRS results in a high probability of treated-lesion control and, when adhering to typical dose/volume recommendations, a low normal tissue complication probability. However, SRS as sole first-line treatment carries a risk of failure in non-treated brain regions. SRS might also be prescribed as salvage treatment in patients relapsing despite previous SRS and/or WBRT. An optimal balance between intracranial control and side effects requires continued research efforts.”

As per the NCCN Guideline of brain metastases, low disease volume is a better selection criterion for SRS than number of metastatic lesions. Other clinical factors discussed which make patients a better candidate for SRS include favorable histology, radio-resistant histologies, and controlled primary tumors. Predictors of longer survival include younger age and good performance status.

If a patient is deemed a candidate for partial brain IMRT as sole treatment, the dose conformity that is achievable generally obviates the need to utilize protracted courses of treatment (i.e. greater than 20 fractions). Additionally, when appropriate, as a boost in conjunction with whole brain radiotherapy, no more than 10 IMRT fractions should be necessary. IMRT with simultaneous integrated boost may also be considered medically necessary when given in 10 fractions (Liang et al., 2013).

References

1. Alexander E III, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *J Natl Cancer Inst*. 1995; 87(1): 34-40. Accessed June 23, 2016. <http://jnci.oxfordjournals.org/content/87/1/34.abstract>
2. American Society for Radiation Oncology (ASTRO) Stereotactic Radiosurgery (SRS) Model Coverage Policy. Final Approval: 1-14-11. Updated 7-25-11. Accessed June 23, 2016. https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/SRSMPJuly2011.pdf
3. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of RTOG 9508 randomized trial. *Lancet*. 2004 May 22; 363(9422):1665-1672. Accessed June 23, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(04\)16250-8/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(04)16250-8/fulltext)
4. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases. A randomized controlled trial. *JAMA*. 2006 Jun 7; 295(21):2483-2491. Accessed June 23, 2016. <http://jama.jamanetwork.com/article.aspx?articleid=202954>
5. ASTRO 2014 Choosing Wisely List. Accessed June 23, 2016. <https://www.astro.org/Patient-Care/Patient-Education/2014-Choosing-Wisely-List/>
6. Auchter RM, Lamond JP, Alexander E III, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. *Int J Radiat Oncol Biol Phys*. 1996 Apr 1; 35(1):27-35. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(96\)85008-5/abstract](http://www.redjournal.org/article/S0360-3016(96)85008-5/abstract)
7. Bhatnagar AK, Flickinger JC, Kondziolka D, et al. Stereotactic radiosurgery for four or more intracranial metastases. *Int J Radiat Oncol Biol Phys*. 2006 Mar 1; 64(3):898-903. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)02580-0/abstract](http://www.redjournal.org/article/S0360-3016(05)02580-0/abstract)
8. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1980 Jan; 6(1):1-9. Accessed June 23, 2016. [http://www.redjournal.org/article/0360-3016\(80\)90195-9/abstract](http://www.redjournal.org/article/0360-3016(80)90195-9/abstract)
9. Flickinger JC, Kondziolka D, Lunsford LD, et al. A multiinstitutional experience with stereotactic radiosurgery for solitary brain metastasis. *Int J Radiat Oncol Biol Phys*. 1994 Mar 1; 28(4):797-802. Accessed June 23, 2016. [http://www.redjournal.org/article/0360-3016\(94\)90098-1/abstract](http://www.redjournal.org/article/0360-3016(94)90098-1/abstract)
10. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997 Mar 1; 37(4):745-751. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(96\)00619-0/abstract](http://www.redjournal.org/article/S0360-3016(96)00619-0/abstract)
11. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014 Oct 27. Published online before print. Accessed June 23, 2016. <http://jco.ascpubs.org/content/early/2014/10/21/JCO.2014.57.2909.abstract>
12. Hunter GK, Suh JH, Reuther AM, et al. Treatment of five or more brain metastases with stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012 Aug 1; 83(5): 1394-1398. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03388-8/abstract](http://www.redjournal.org/article/S0360-3016(11)03388-8/abstract)
13. Kurtz JM, Gelber R, Brady LW, et al. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981 Jul; 7(7):891-895. Accessed June 23, 2016. [http://www.redjournal.org/article/0360-3016\(81\)90005-5/abstract](http://www.redjournal.org/article/0360-3016(81)90005-5/abstract)
14. Liang X, Ni L, Hu W, et al. A planning study of simultaneous integrated boost with forward IMRT for multiple brain metastases. *Med Dosim*. 2013 Summer; 38(2):115-116. Accessed June 23, 2016. <http://www.sciencedirect.com/science/article/pii/S0958394712001434>
15. Mehta MP, Boyd TS, Sinha P. The status of stereotactic radiosurgery for cerebral metastases in 1998. *J Radiosurg*. 1998; 1(1):17-30. Accessed June 23, 2016. <http://link.springer.com/article/10.1023/B%3AJORA.0000010873.43368.21>
16. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996 Oct 1; 78(7):1470-1476. Accessed June 23, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/\(SICI\)1097-0142\(19961001\)78:7%3C1470::AID-CNCR14%3E3.0.CO;2-X/abstract](http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0142(19961001)78:7%3C1470::AID-CNCR14%3E3.0.CO;2-X/abstract)
17. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation vs. standard treatment in patients with unresected brain metastases. A report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys*. 1997 Oct; 39(3):571-574. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(97\)00341-6/abstract](http://www.redjournal.org/article/S0360-3016(97)00341-6/abstract)

18. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2015. Central Nervous System Cancers. Accessed June 23, 2016 http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Central Nervous System Cancers 1.2015®. 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
19. Nieder C, Grosu AL, Gaspar LE. Stereotactic radiosurgery (SRS) for brain metastases: a systematic review. Radiat Oncol. 2014 Jul 12; 9: 155. Accessed June 23, 2016. <http://www.ro-journal.com/content/9/1/155>
20. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. Int J Radiat Oncol Biol Phys. 1994 Jul 1; 29(4):711-717. Accessed June 23, 2016. [http://www.redjournal.org/article/0360-3016\(94\)90558-4/abstract](http://www.redjournal.org/article/0360-3016(94)90558-4/abstract)
21. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998; 280(17):1485-1489. Accessed June 23, 2016. <http://jama.jamanetwork.com/article.aspx?articleid=188127>
22. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990 Feb 22; 322(8):494-500. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199002223220802>
23. Serizawa T, Hirai T, Nagano O, et al. Gamma knife radiosurgery for 1-10 brain metastases without prophylactic whole-brain radiation therapy: analysis of cases meeting the Japanese prospective multi-institute study (JLG0901) inclusion criteria. J Neuro Oncol. 2010 Jun; 98(2):163-167. Accessed June 23, 2016. <http://link.springer.com/article/10.1007/s11060-010-0169-x>
24. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000 May 1; 47(2):291-298. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(99\)00507-6/abstract](http://www.redjournal.org/article/S0360-3016(99)00507-6/abstract)
25. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys. 2002 Jul 1; 53(3): 519-526. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(02\)02770-0/abstract](http://www.redjournal.org/article/S0360-3016(02)02770-0/abstract)
26. Soffietta R, Kocher M, Abacioqlu UM, et al. A European Organisation for research and treatment of cancer phase III trial of adjuvant whole brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol. 2013 Jan 1; 31(1):65-72. Accessed June 23, 2016. <http://jco.ascopubs.org/content/31/1/65.full>
27. Tsao M, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis/es: An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol. 2012 Jul-Sep; 2(3):210-225. Accessed June 23, 2016. [http://www.practicalradonc.org/article/S1879-8500\(11\)00380-8/abstract](http://www.practicalradonc.org/article/S1879-8500(11)00380-8/abstract)

Radiation Treatment of Brain Metastases

[Return to Table of Contents](#)

Radiation Treatment of Breast Carcinoma

POLICY

I. Breast cancer

- A. For an individual who undergoes mastectomy, post-mastectomy radiation therapy is medically necessary when any of the following are present:
 - 1. Positive axillary lymph node(s)
 - 2. Primary tumor > 5 cm
 - 3. Positive or narrow (< 1 mm) margins
- B. For an individual who undergoes local excision (lumpectomy, breast conservation surgery) adjuvant partial or whole breast radiotherapy is medically necessary

Up to 38 fractions, including the boost, is medically necessary. Three-dimensional (3D) conformal technique which includes forward-planned Intensity-Modulated Radiation Therapy (IMRT) (field-in-field segments) is medically necessary. Inverse-planned IMRT is not medically necessary for either whole-breast irradiation (WBI) (with or without nodal irradiation) or the boost. Exceptions will be made on a case-by-case basis after discussion with an eviCore radiation oncologist in those unusual clinical situations where inverse-planned IMRT dosimetry yields clinically meaningful and significant dosimetric improvement over forward-planned dosimetry. IMRT may be certified for whole breast radiation therapy when the internal mammary lymph nodes are being treated or the mid-tangent separation exceeds 25.5 cm. IMRT will also be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN).

A boost may be clinically indicated and is medically necessary. Medically necessary boost techniques include electron and photon energies. A photon boost with multiple fields is medically necessary (these photon boosts are often planned using a complex isodose technique [77307]). Inverse-planned IMRT is not medically necessary for a photon boost. A brachytherapy boost is not medically necessary.

Daily image-guided radiation therapy (IGRT) is allowed for a photon boost but not for WBI or an electron boost.

When delivering WBI a dose of 45 to 50 Gy in 1.8 to 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. All dose schedules are given 5 days per week.

Partial breast radiotherapy is medically necessary in those individuals with clinical criteria conforming to published guidelines of one of the major societies (e.g., NCCN, American Society for Radiation Oncology [ASTRO], American College of Radiology [ACR], American Brachytherapy Society [ABS]). Acceptable techniques include 3D conformal radiation therapy (3DCRT), inverse-planned IMRT, and intracavitary high-dose rate (HDR) brachytherapy (Ir-192 or kilovolt [kV] energy), up to a total of 10 fractions. Single-fraction adjuvant intraoperative radiotherapy is investigational. The AccuBoost® technique is investigational.

II. Metastatic breast cancer

A. Symptomatic breast or chest wall disease

1. The same techniques used in the treatment of early stage breast cancer with up to 25 fractions, if a boost is utilized, are medically necessary

Key Clinical Points

Early stage breast cancer is typically treated with mastectomy with or without radiotherapy to the chest wall, or breast local excision followed by radiotherapy. Indications for post-mastectomy radiotherapy are controversial but include the presence of multiple positive axillary lymph nodes, positive or narrow margins (< 1 mm), or large primary tumor size (> 5 cm). Radiotherapy is indicated for most women after local excision of ductal carcinoma in situ (DCIS) or invasive carcinoma. In some women over the age of 70 who have been diagnosed with invasive breast cancer, radiation therapy may be safely omitted, especially if they have comorbidities.

Primary therapy for women with metastatic breast cancer (M1 stage) is systemic therapy. However, if there is symptomatic breast or chest wall disease, a short course of radiotherapy may alleviate symptoms. In most cases, short course hypofractionated (HF) treatment (i.e., 10 fractions) is appropriate. It is not appropriate to deliver more than 20 fractions in that setting (or 25 fractions if a boost is included). Evidence is limited with regard to the role of locoregional radiotherapy for M1 stage disease in the absence of symptomatic locoregional disease. Locoregional radiation therapy may be appropriate for women who initially present with metastatic disease but after surgery and/or chemotherapy are found to have no clinical evidence of disease.

Most women with early stage breast cancer are treated with a five- to seven-week course of radiation therapy. Use of simple devices for positioning (e.g., angle board) is usually adequate. The five- to seven-week course of treatment is based on dose-fractionation considerations that might decrease long-term side effects and provide

optimal local control of disease. More than 30 fractions (or 38 fractions when a boost is utilized) are not medically necessary.

Several randomized trials have demonstrated that, for treatment of node-negative breast cancer patients, a shorter course of radiation given in just over 3 weeks has been proven to be as effective and was associated with no greater toxicity than 5 weeks of treatment. Based on the study described by Whelan et al. (2010) and trials in the United Kingdom, an American Society of Radiation Oncology (ASTRO) task force on WBI fractionation recently concluded that patients aged 50 years or older, who have disease Stage pT1-2 pN0, do not receive chemotherapy, and are treated with a radiation dose homogeneity within +/- 7% in the central axis plane experience equivalent outcomes with either HF or conventionally-fractionated WBI. The task force also recommended that the heart should be excluded from the primary treatment fields (when HF-WBI is used) due to lingering uncertainty regarding late effects of HF-WBI on cardiac function. Patients not meeting these criteria were relatively underrepresented in the trials, and few of the trials reported subgroup analyses. Therefore, the task force could not agree for or against the use of HF-WBI in other individuals, which nevertheless should not be interpreted as a contraindication to its use. The appropriateness of HF-WBI has also been recognized in the most recent NCCN guidelines.

Boost radiotherapy has been shown to improve local control, particularly in younger women. A boost to the tumor bed is recommended in individuals at higher risk for local failure (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). Electron beam or photon fields are most commonly used. Typical boost regimens after conventionally-fractionated WBI give total doses of 10 to 16 Gy at 2 Gy per fraction. It is appropriate to give up to an additional 4 or 5 fractions for a boost after HF-WBI when a boost is felt to be indicated.

An electron field is the simplest and most available technique used for delivering the boost. Women with deep-seated tumor beds or very large breasts often require treatment with photon boosts, which may consist of two or more fields.

Interstitial brachytherapy was commonly used for performing the boost during the development of breast-conserving therapy. While the use of brachytherapy in giving the boost is recognized in the NCCN guidelines, it does not improve tumor control compared to external-beam boosts and results in worse cosmesis. Other brachytherapy techniques (such as the MammoSite® balloon brachytherapy system) and intraoperative radiotherapy (IORT) have also been used to perform the boost, but again they have not been shown to be superior to external-beam boosts, and they may have added toxicities. One prospective trial (Wong et al., 2014) of 52 patients treated at the Mayo Clinic with an intraoperative electron boost found difficulty in wound healing in 2 patients

who had additional surgery later and 1 patient who developed significant fibrosis after aspiration of a symptomatic seroma. Therefore, the use of interstitial or intracavitary brachytherapy or IORT as a boost is not medically necessary and generally will not be reimbursed. For chest wall and regional nodal irradiation, the NCCN Guidelines® state that the appropriate dose is 50 Gy, given as 1.8 to 2 Gy fraction size, with or without the addition of a scar boost of 10 Gy given at 2 Gy per fraction, for a total dose of approximately 60 Gy. All dose schedules are given 5 days per week.

The acute side effects of radiation and the cosmetic result can be affected by inhomogeneities of dose within the breast, which, if the simplest methods are applied, can be significant given the irregular shape of the breast. Therefore, many methods can be applied to “compensate” for the shape of the breast and improve dose homogeneity by altering the fluence of radiation as it exits the treatment machine. A Complex planning method utilizes tungsten wedges, which are devices placed in the head of the machine to increase the fluence at the base of the breast and decrease the fluence anteriorly, where the tissue is thinner. However, this technique takes into account only the shape of the breast in one plane, and not the entire breast, and has been shown to be associated with more temporary acute skin reactions as compared to more sophisticated 3D techniques.

3D methods include real-time modulation of the beam to improve the dose distribution, including forward-planned 3DCRT with segments to modulate the fluence (also referred to as “step-and-shoot”), forward-planned electronic compensation method, and inverse-planned IMRT. Inverse planning requires dedicated software for IMRT planning in order to calculate and optimize the fluence to the outlined target and spare surrounding organs, which are also outlined. This approach requires trained personnel, individual-specific treatment delivery verification (i.e., comparison of calculated and measured doses in a solid-water phantom), and specific delivery equipment. Forward-planned 3D radiotherapy with segments can be performed with a 3D planning system. The treatment plan consists of several fields with different weights at the same gantry position (called segments). One study (Cardinale et al., 2007) compared the dose inhomogeneity within the breast and dose to heart and lung with inverse-planned IMRT and 3D segments (typically up to 5 fields total and 2 gantry angles) and found no significant differences. A recent study found no difference in normal tissue exposure from forward-planned 3D radiotherapy and IMRT plans. A study of 358 patients (Pignol et al., 2008) found no differences in acute toxicity whether the forward-planning technique was used as compared with inverse planning ($p = 0.31$).

There are several advantages of forward-planned 3D compensation using a limited number of segments compared to inverse-planned IMRT. Forward planning requires

less beam-on time, so that scatter to non-target tissues is minimized, which is especially important in young women or smokers, who may have a small increased risk of contralateral breast cancer or lung cancer years after radiotherapy, respectively. Forward-planned 3D radiotherapy is widely available. Facilities that perform inverse-planned IMRT would have the equipment and personnel to perform forward-planned 3D radiotherapy, although the converse is not necessarily true. The forward-planning techniques are an extension of 3DCRT. Inverse-planning IMRT for breast cancer thus has no documented advantage over the forward planning step-and-shoot technique and as mentioned above, results in less beam-on time. Therefore, although IMRT is an acceptable method of breast irradiation, IMRT treatment planning is not medically necessary. In lieu of IMRT, the appropriate 3D radiotherapy will be considered medically necessary. An exception will be made when a physician requests the use of multiple-gantry angle IMRT in an individual with left-sided breast cancer in whom forward-planned tangential fields result in excessive dose to the heart. The requesting physician will need to state that plans and dose-volume histograms comparing the IMRT and forward-planned treatment plans have documented a superior result. (The treating physician should be encouraged to use deep inspiration breath hold techniques or prone positioning if available, as these usually give greater sparing of the heart than multiple-gantry angle IMRT. However, not all centers have such capabilities, and these approaches cannot be used for all individuals because of the need to treat regional nodes, individual ability to follow commands for breath holding, etc.). IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the RTOG/NCCN.

Accelerated Partial Breast Irradiation (APBI) is an emerging technique in which the target of the radiation is only a portion of the breast with the greatest likelihood of harboring residual cancer cells after lumpectomy. The technique is called "accelerated" because it is given twice daily for five days, sparing the patient the inconvenience of daily radiation therapy for up to 7 weeks. Treatment is given in a "hypofractionated" fashion, with higher doses per fraction, which can be associated with greater delayed toxicity. This is considered medically necessary, because a smaller volume of breast tissue is being treated. However, brisk skin reactions can occur soon after the course of treatment and late skin changes and soft tissue fibrosis could potentially affect the cosmetic result or make the interpretation of future mammography more difficult.

There are several techniques of APBI:

1. Interstitial technique in which multiple needles are placed percutaneously and catheters are threaded into the breast (Brachytherapy)

2. Intracavitary single catheter balloon catheter, in which a device is placed into the surgical cavity (Brachytherapy)
3. Intracavitary multiple catheter device – single device with multiple catheter channels inserted into surgical cavity (Brachytherapy)
4. Multiple coplanar or non-coplanar field photon technique
5. Single fraction IORT using electrons or photons

Several single-institution, non-randomized studies using the multicatheter technique have shown low local recurrence rates that are comparable to standard photon technique. Data on newer techniques are not yet as mature but show comparable results at shorter follow-up.

There is no consensus on exactly which individuals are appropriate candidates for APBI. An ASTRO task force on this subject encouraged individuals to participate in clinical trials. If not eligible for trials, it is recommended that individuals who may be suitable for APBI are women 60 years and older who are not carriers of a BRCA1/2 mutation treated with primary surgery for a unifocal T1N0 estrogen receptor- (ER) positive cancer. Histology should be infiltrating ductal or a favorable ductal subtype, not be associated with extensive intraductal component (EIC) or lobular carcinoma in situ (LCIS), and margins should be negative. This was adopted for the most recent NCCN guidelines. However, other groups such as the ABS and the American Society of Breast Surgeons (ASBrS) have promulgated more liberal guidelines in the past (age 45 years old or greater, invasive ductal carcinoma (IDC) or DCIS, total tumor size (IDC and DCIS) 3 cm or smaller, negative microscopic excision margins, and pathologically-negative axillary lymph nodes). Further, many experts have contested the correctness of the ASTRO guidelines, with an increasing number of studies showing low failure rates in patients who do not meet these criteria, comparable to that of similar patients treated with WBI (e.g., from the William Beaumont Hospital group). Therefore, selection criteria for an individual for the use of APBI have not been established. Until there is firmer consensus in the community, it is reasonable to allow reimbursement for APBI when an individual is treated within the guidelines of any of the major professional groups.

The ASTRO and NCCN Guidelines[®] state that appropriate schemes for APBI are 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day. Other fractionation schemes are currently under investigation. Therefore up to 10 fractions (whether photon or brachytherapy) for APBI is considered medically necessary.

The Axxent[®] electronic brachytherapy (Xoft Inc, Fremont, CA) is a novel way of

delivering APBI. Electronic brachytherapy delivers HDR radiation without radioactive isotopes. In lieu of radioactive isotopes, the electronic brachytherapy system uses a miniature 50 kV xray tube, measuring 2.2 mm in diameter as a radiation source. The xray source can be turned off and on as necessary. The low energy of the xray source allows delivery in minimally shielded settings.

For treatment, the surgeon inserts a balloon applicator into the lumpectomy cavity. The balloon is inflated with saline. The catheter is connected to a robotic controller. At the time of treatment, a protective xray shield is placed over the breast. The miniature xray source travels into the catheter into the inflated balloon. The xray tube is encased in a sheath. Water is pumped through the xray sheath to cool the source. After the delivery of the treatment, the xray source is turned off and withdrawn through the catheter. Treatments are typically delivered in 10 fractions, twice daily. The dose-distribution is very similar to that achieved by HDR brachytherapy.

A study by Mehta et al. (2010) included 44 women treated with Axxent[®] electronic brachytherapy. Eligibility included age > 49, completely resected IDC (< 2 cm) or DCIS (< 2 cm), lymph node negative, with negative margins of at least 1 mm. The prescribed dose was 3.4 Gy, prescribed to 1 cm beyond the balloon surface. Follow up was 6 months in 43 patients. Four grade 3 toxicities were reported, including pain, blistering and moist desquamation. The study demonstrated that the Axxent[®] system delivered the planned dose of radiation successfully and was well tolerated.

The ASTRO emerging technology committee report on electronic brachytherapy (EBT) (Park et al., 2010) stated that, "...advantages of electronic brachytherapy over existing technologies are as yet unproven in terms of efficacy or patient outcomes...EBT is currently an unregulated treatment delivery modality for cancer therapy, with minimal clinical data available from small single institution studies, none with any significant follow-up."

Although the clinical data on this technology is limited, it appears very likely that it will result in results equivalent to those using HDR brachytherapy for APBI, which is reimbursed. Therefore, electronic brachytherapy will be approved for use.

AccuBoost[®] Non-Invasive Image-Guided Breast Brachytherapy (NIIGBB) (Advanced Radiation Therapy, Inc., Billerica, MA) is a method of IGRT that incorporates a real-time image guidance mammography-based system to deliver noninvasive brachytherapy. The breast is immobilized using moderate compression. Digital mammography provides localization of the target volume. Custom applicators, ranging from 4 to 8 cm in diameter, are designed to deliver a highly collimated beam, which are used with an

HDR remote afterloading system. The applicators are mounted on mammography paddles, centered on the target to deliver HDR IR-192 along two intersecting orthogonal axes sequentially. To use AccuBoost®, the tumor bed must be visible on mammogram, the planning target volume (PTV) must be less than or equal to 8 cm, and the breast must be compressible to a plate separation less than or equal to 7 cm.

Sioshansi et al. (2011) conducted a study of dose modeling of NIIGBB, compared with electron beam and 3DCRT partial breast radiation. This study modeled the NIIGBB dose distributions as a point source. Dose volume comparisons were evaluated in eight patients and compared to 3DCRT and electron boost simulations. Patient eligibility required a clearly defined target cavity identified on CT, ≥ 5 mm distance between the posterior aspect of the cavity and the chest wall, and a breast that could be compressed in ≤ 8 cm. The authors reported that the NIIGBB PTVs were significantly less than those of the 3DCRT and electron boost, allowing for more normal tissue sparing. Because NIIGBB directs radiation parallel to the chest wall, there is negligible dose delivered to the chest wall and lung. NIIGBB, compared to electrons and 3DCRT, resulted in lower maximum dose to the skin (60% and 10% respectively), and chest wall/lung (70 to 90%).

There is, as yet, little clinical information available on the long-term results in patients treated with this technique. A multi-institutional study showed acceptable rates of acute skin toxicity and a high rate of excellent or good cosmetic results at 6 months. In a study from Tufts Medical Center (Leonard et al., 2012), the cosmetic results and skin and subcutaneous toxicities were similar in 18 matched pairs of patients with more than 6 months follow-up treated with either AccuBoost® or a conventional electron boost. This device has also been used for APBI, again with very limited follow-up of small numbers of patients. Given the paucity of data regarding the use of NIIGBB, particularly on local control, additional research is necessary prior to widespread approval of NIIGBB outside of a clinical trial. NIIGBB is considered investigational.

Although there are now adequate data to support the use of multiple-fraction APBI for selected individuals, there are still few data on the use of single-dose IORT as the sole treatment for individuals with early-stage breast cancer. The TARGIT-A trial compared this approach to conventional WBI. The first full publication of this trial showed comparable 4-year local failure rates between the arms (1.2% and 0.95%, respectively), but the median follow-up was only slightly more than 2 years, and fewer than 20% of patients were followed beyond 4 years. The most recent update of this trial, in which 35% still have 5-year follow up, showed that the 5-year cumulative incidence of local recurrence in the IORT arm was 3.3%, compared to 1.3% in the control arm. The ELIOT trial performed at the European Institute of Oncology in Milan compared IORT using electrons to whole-breast irradiation in 1305 patients with early-stage cancer. With a

median follow-up of 5.8 years, the 5-year local recurrence rate in the IORT patients was 4.4%, compared to 0.4% in the control arm ($p < 0.0001$). NCCN Guidelines® do not discuss whether IORT is an acceptable treatment approach. Therefore, IORT as a treatment modality is considered investigational until mature data are available showing equivalent long-term outcome to conventional WBI or other APBI approaches.

References:

1. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med*. 2001 Nov 8; 345(19):1378-1387. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa010874>
2. Cardinale RM, Steele J, Fein DA, Mao L, Chon BH. The minimal dosimetric benefit of breast IMRT as compared to using a small number of forward planned MLC segments does not justify the cost. *Int J Rad Oncol Biol Phys* 2007 Nov 1; 69(3) Suppl. S553-S554. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)03090-8/fulltext](http://www.redjournal.org/article/S0360-3016(07)03090-8/fulltext)
3. Caudell JJ, De Los Santos JF, Keene KS, et al. A dosimetric comparison of electronic compensation, conventional intensity modulated radiotherapy, and tomotherapy in patients with early-stage carcinoma of the left breast. *Int J Radiat Oncol Biol Phys*. 2007 Aug 1; 68(5):1505-11. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)00696-7/abstract](http://www.redjournal.org/article/S0360-3016(07)00696-7/abstract)
4. Collette S, Collette L, Budiharto T, et al. Predictors of the risk of fibrosis at 10 years after breast conserving therapy for early breast cancer: a study based on the EORTC Trial 22881-10882 'boost versus no boost. *Eur J Cancer*. 2008 Nov 44(17); 44:2587-99. Accessed June 23, 2016. [http://www.ejancer.com/article/S0959-8049\(08\)00580-7/abstract](http://www.ejancer.com/article/S0959-8049(08)00580-7/abstract)
5. Hamid S, Rocchio K, Arthur D, et al. A multi-institutional study of feasibility, implementation, and early clinical results with noninvasive breast brachytherapy for tumor bed boost. *Int J Radiat Oncol Biol Phys*. 2012 Aug 1; 83(5):1374-80. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03378-5/abstract](http://www.redjournal.org/article/S0360-3016(11)03378-5/abstract)
6. Hepel JT, Hiatt JR, Sha S, et al. The rationale, technique, and feasibility of partial breast irradiation using noninvasive image-guided breast brachytherapy. *Brachytherapy*. 2014 Sept-Oct; 13(5):493-501. Accessed June 23, 2016. [http://www.brachyjournal.com/article/S1538-4721\(14\)00541-8/abstract](http://www.brachyjournal.com/article/S1538-4721(14)00541-8/abstract)
7. Horst KC, Haffty BG, Harris EE, et al. ACR Appropriateness Criteria® Postmastectomy Radiotherapy. American College of Radiology (ACR). Date of origin: 1996. Last review date: 2012. Accessed June 23, 2016. <https://acsearch.acr.org/docs/69347/Narrative/>
8. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med*. 2004 Sep 2; 351(10):971-977. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa040587>
9. Leonard KL, Wazer DE, Styczynski JR, et al. Breast boost using noninvasive image-guided breast brachytherapy versus en face electrons: a matched pair analysis. *Int J Radiat Oncol Biol Phys* 2012;84(3S suppl):S226 (abstract 2023). Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)01532-5/fulltext](http://www.redjournal.org/article/S0360-3016(12)01532-5/fulltext)
10. Mehta VK, Algan O, Griem KL, et al. Experience with an electronic brachytherapy technique for intracavitary accelerated partial breast irradiation. *Am J Clin Oncol*. 2010 Aug; 33(4):327-335. Accessed June 23, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2010/08000/Experience_With_an_Electronic_Brachytherapy_2.aspx
11. Moran MS, Truong PT. Intraoperative accelerated partial breast irradiation: caution still warranted. *Int J Radiat Oncol Biol Phys*. 2014 Jul 1; 89(3):496-498. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(14\)00109-6/abstract](http://www.redjournal.org/article/S0360-3016(14)00109-6/abstract)
12. National Comprehensive Cancer Network (NCCN) Guidelines. Breast Cancer Version 2.2016. Accessed June 23, 2016. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Breast Cancer Version 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
13. Park CC, Yom SS, Podgorsak MB, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) Emerging Technology Committee report on electronic brachytherapy. *Int J Radiat Oncol Biol Phys*. 2010 Mar 15; 76(4):963-972. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03553-6/fulltext](http://www.redjournal.org/article/S0360-3016(09)03553-6/fulltext)
14. Pignol JP, Olivetto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol*. 2008 May 1; 26(13):2085-2092. Accessed June 23, 2016. <http://jco.ascopubs.org/content/26/13/2085.full>

15. Roof KR, Marks LB. Breast intensity modulated radiation therapy versus tissue compensation: what's in a name? *Pract Radiat Oncol* 2014 Jan-Feb; 4(1):3-5. Accessed June 23, 2016. [http://www.practicalradonc.org/article/S1879-8500\(13\)00132-X/abstract](http://www.practicalradonc.org/article/S1879-8500(13)00132-X/abstract)
16. Shah C, Vincini F, Wazer, DE, et al. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy*. 2013 Jul-Aug; 12(4):267-277. Accessed June 23, 2016. [http://www.brachyjournal.com/article/S1538-4721\(13\)00226-2/fulltext](http://www.brachyjournal.com/article/S1538-4721(13)00226-2/fulltext)
17. Sioshansi S, Rivard MJ, Hiatt JR, et al. Dose modeling of noninvasive image- guided breast brachytherapy in comparison to electron beam boost and three-dimensional conformal accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2011 Jun 1; 80(2):410-416. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)00221-X/abstract](http://www.redjournal.org/article/S0360-3016(10)00221-X/abstract)
18. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys*. 2009 Jul 15; 74(4):987-1001. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00313-7/fulltext](http://www.redjournal.org/article/S0360-3016(09)00313-7/fulltext)
19. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys*. 2011 Sep 1; 81(1):59-68. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)00631-0/fulltext](http://www.redjournal.org/article/S0360-3016(10)00631-0/fulltext)
20. Taunk NK, Prosnitz RG. Planning comparison of intensity modulated radiation therapy delivered with 2 tangential fields versus 3-dimensional conformal radiotherapy for cardiac sparing in women with left-sided breast cancer. *Pract Radiat Oncol*. 2012 October-December; 2(4):248-256. Accessed June 23, 2016. [http://www.practicalradonc.org/article/S1879-8500\(11\)00321-3/abstract](http://www.practicalradonc.org/article/S1879-8500(11)00321-3/abstract)
21. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority trial. *Lancet*. 2010 Jul 10; 376(9735):91-102. Accessed June 23, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(10\)60837-9/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60837-9/fulltext)
22. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15; 383(9917):603-613. Accessed June 23, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(13\)61950-9/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61950-9/fulltext)
23. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec; 14(13):1269-1277. Accessed June 23, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(13\)70497-2/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70497-2/fulltext)
24. Vicini FA, Arthur D, Wazer D, et al. Limitations of the American Society of Therapeutic Radiology and Oncology consensus panel guidelines on the use of accelerated partial breast irradiation. *Int J Radiat Oncol Biol Phys*. 2011 Mar 15; 79(4):977-984. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03728-6/abstract](http://www.redjournal.org/article/S0360-3016(09)03728-6/abstract)
25. Wazer DE. Technological Updates on Targeting Partial Breast Dose via Non-Invasive Brachytherapy. *AccuBoost Webinar*. 2013 Apr 23. Accessed June 23, 2016. <https://varian.force.com/apex/CpWebSummary?id=a0OE000000NqoOiMAJ>
26. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010 Feb 11; 362(6):513-20. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa0906260>
27. Wong WW, Pockaj BA, Vora SA, et al. Six-year outcome of a prospective study evaluating tumor bed boost with intra-operative electron irradiation followed by whole-breast irradiation for early-stage breast cancer. *Breast J*. 2014 Mar-Apr; 20(2):125-130. Accessed June 23, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/tbj.12235/abstract>
28. Xoft Website. Accessed June 23, 2016. <http://www.xoftinc.com/>

Radiation Treatment of Breast Carcinoma

[Return to Table of Contents](#)

Radiation Treatment of Carcinoma of Esophagus and Gastroesophageal Junction (GEJ) Cancer

POLICY

External beam photon radiation therapy is medically necessary in any of the following situations:

I. Neoadjuvant treatment

- A. Stage T1b node-positive or any T2-T4a

II. Adjuvant treatment (if no preoperative or prior irradiation given)

- A. For squamous cell carcinoma and adenocarcinoma, if the clinical and/or pathologic features warrant

III. Definitive treatment

- A. Inoperable and/or stage T4b
- B. Consider definitive treatment for tumors located in the cervical esophagus

IV. Local recurrence or palliation

- A. Up to 15 fractions using three dimensional conformal radiation therapy (3DCRT)
- B. Brachytherapy, up to 3 fractions

V. Radiation technique

- A. Dose
 - 1. In the preoperative setting, a dose of 45 to 50.4 Gy (in 25 to 28 fractions) is typically employed. A dose as low as 41.4 Gy may be considered when large fields are necessary and/or when constraints for critical structures cannot be met
 - 2. In the postoperative setting, a dose of 45 to 50.4 Gy (in 25 to 28 fractions) is typically employed
 - 3. In definitive treatment, a dose of 50 to 50.4 Gy (in 25 to 28 fractions) is typically employed. For tumors located in the cervical esophagus, a dose of up to 70.2 Gy can be employed
- B. Planning technique
 - 1. Cervical esophagus
 - a. 3DCRT
 - b. Intensity-Modulated Radiation Therapy (IMRT)
 - 2. Thoracic esophagus and GEJ
 - a. 3DCRT
 - b. IMRT can be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet normal tissue constraints using standard metrics published by the Radiation Therapy Oncology

Group (RTOG)/National Comprehensive Cancer Network (NCCN)

- c. It is recommended that when using IMRT, attention be paid to the low dose region within the lung (integral dose), particularly in patients in whom surgery is planned. It is also recommended that respiratory motion and variations in gastric filling be accounted for
- C. Image Guided Radiation Therapy (IGRT)
 - 1. IGRT can be used when delivering 3DCRT or IMRT

Key Clinical Points

I. Neoadjuvant (preoperative) chemoradiotherapy (CRT)

Historically, surgery alone has been associated with relatively high rates of recurrence and dismal rates of survival. Among the treatments investigated to improve upon these results is the use of preoperative chemoradiotherapy.

One of the largest randomized controlled trials to investigate preoperative CRT was the CROSS trial. In this trial, 368 patients with resectable clinical stage T1N1 or T2-3N0-1M0 squamous cell carcinoma, adenocarcinoma or large-cell undifferentiated carcinoma of the esophagus and GEJ were randomized to preoperative CRT (carbo/taxol with 41.4 Gy) followed by surgery or to surgery alone. At a median follow up of 45.4 months, the median overall survival (OS) was 24.0 months (CRT) vs. 4.94 months (surgery alone). The OS at 1, 2, 3, and 5 years was 82% vs. 70%, 67% vs. 50%, 58% vs. 44% and 47% vs. 34%, respectively for preoperative CRT vs. surgery alone. Other benefits to preoperative CRT included a significantly higher R0 resection (92% vs. 69%), higher incidence of a pathological complete response (pCR) (29% vs. 23%), a lower incidence of node positivity (31% vs. 75%) and no difference in occurrence of postoperative complications.

A recent analysis of CROSS I and II trials revealed a reduced rate of local-regional recurrence (LRR) with preoperative CRT (34.7% vs. 57.1%). Furthermore, the majority of these recurrences had a component of distant recurrence whereas the rate of an isolated LRR was (3.3% vs. 9.3%).

Finally, a large meta-analysis revealed a significant reduction in all-cause mortality with preoperative CRT (hazard ratio [HR] 0.78) compared with surgery alone, translating into an absolute survival benefit of 8.7% at 2 years (Sjoquist et al., 2011).

II. Adjuvant chemoradiotherapy (CRT)

A. Squamous cell carcinoma

There is no definitive evidence of a benefit with postoperative CRT. For

example, a randomized control trial of 45 patients found no significant improvement with postoperative CRT vs. postoperative chemotherapy (Tachibana et al., 2003). It is also noted that NCCN recommends adjuvant treatment only in the setting of a R1 or R2 resection.

B. Adenocarcinoma

Postoperative CRT is indicated for an individual with stage IB-IV (M0) based on the INT 0116 study. In INT 0116, 559 patients with stage IB-IV adenocarcinoma of the stomach or GEJ (20% of patients) following R0 resection were randomized to CRT (5-FU/leucovorin before, during and concurrent with radiation to 45 Gy) or to no further treatment. In the most recent update with a 10-year median follow up, CRT continues to show a significant improvement in OS (HR 1.32) and for relapse-free survival (RFS) (HR 1.51). This benefit extended to all T stages, N stages as well as location in the GEJ.

III. Definitive chemoradiotherapy (CRT)

In an individual who is not medically operable or who refuses surgery, definitive CRT remains the standard treatment. This is primarily based on data from RTOG 8501 (Herskovic et al., 1992). In this randomized stratified phase III trial, patients with T1-3, N0-1, M0 squamous cell carcinoma or adenocarcinoma (90% were squamous cell carcinoma) of the esophagus, including GEJ, were randomized to radiation alone (to 64 Gy) or CRT (50 Gy + 5-FU/cisplatin). In the most recent update, 5-year survival was 26% vs. 0% and persistence of disease was 37% vs. 25%.

In an attempt to improve upon these results, INT 0123 evaluated radiation dose escalation in combination with chemotherapy (Minsky et al., 2002). Two hundred and thirty-six (236) patients with T1-4, N0-1 squamous cell carcinoma or adenocarcinoma were randomized to 50.4 Gy + 5-FU/cisplatin or 64.8 Gy + 5-FU/cisplatin. It is noted "...because of the concern that the stomach could not safely tolerate 64.8 Gy, eligibility was limited to patients whose tumors did not extend to within 2 cm of the GEJ." This trial was stopped early due to an increase in death in the high-dose arm. Specifically, 11 deaths occurred in the high-dose arm vs. 2 in the standard-dose arm. Of these 11 deaths, 7 occurred at or below a dose of 50.4 Gy. As such, the standard-dose arm was associated with a non-significant improvement in median survival (18.1 months vs. 13 months) and 2-year survival (40% vs. 31%). On the other hand, the high-dose arm was associated with a non-significant reduction in local-regional persistence or failure (50% vs. 55%) and in distant failure (9% vs. 16%). As a result of these findings, the authors conclude, "...the standard radiation dose is 50.4 Gy."

In a quality of life (QOL) analysis (Kachnic et al., 2011), the high-dose arm had a significantly lower total QOL at the end of CRT ($p=0.02$). At 8 and 12 months, the high-dose arm had a lower total QOL as compared to the standard arm, though this was not statistically significant. These results support that the high-dose arm does not improve patient QOL. The authors state, "...these results lend further weight to our previous conclusion that radiotherapy to 50.4 Gy should remain the standard of care in patients treated with definitive CRT for esophageal cancer."

IV. Treatment technique

Recently published data from RTOG 0617 suggests that, on multivariate analysis cardiac volume of lung (V), V5 and V30 predict patient survival. Though there is no indication that similar findings will be borne out of INT 0123, it underscores the importance of cardiac dose. For example, in the treatment of esophageal carcinoma, several studies have confirmed an association between cardiac dose and toxicity.

Konski et al. (2012) found that symptomatic cardiac toxicity correlated with the whole heart V20, V30 and V40. Symptomatic toxicity was not observed if the whole heart V20, V30 and V40 was kept below 70%, 65% or 60%, respectively. In addition, Tait et al. (2013) also found a correlation of cardiac V20, V30 and V40 with toxicity whereby patients with a V20 above 71%, a V30 above 64.5% and V40 above 57% had increased odds of developing cardiac toxicity.

In attempt to reduce dose to nearby critical structures, several studies have evaluated the use of IMRT.

For example, Kole et al. (2012) revealed that in the treatment of 19 patients with carcinoma of the distal esophagus, IMRT significantly reduced heart dose, spared more of right coronary artery and improved target conformity.

Using a fitted multivariate inverse probability weighted-adjusted Cox model, Lin et al. (2012) found that patients treated with 3DCRT had significantly greater risk of dying (72.6% vs. 52.9%) and of local regional recurrence. In addition, and increased cumulative incidence of cardiac death was also seen.

IMRT should be considered with caution, however, due to the integral dose within the lungs. For example, Kumar et al. (2012) found that IMRT, compared to 3DCRT, increased the lung V20 and that a V20 of > 15% increased the risk of chronic pneumonitis.

Other studies have also shown the effect of low-dose radiation within the lung. For example, Gergel et al. (2002) found that, in the 3D treatment of esophageal cancer in 20 patients, the percent of absolute lung volume that received a total dose between 7 and 10 Gy may be significantly correlated with the percent decline of carbon monoxide diffusing capacity, total lung capacity and vital capacity.

Lee et al. (2003) also found an increase in postoperative pulmonary complications when the pulmonary V10 was greater than 40% and when the V15 was greater than 30%. In an update of this study, Wang et al. (2006) revealed that the pulmonary V5 correlated with postoperative pulmonary complications.

Given the available data, the use of IMRT in the treatment of esophageal cancer will be considered when documentation is provided that 3D conformal planning is unable to meet dose constraints for organs at risk.

References

1. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomized, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015 Feb; 16(2):187-199. Accessed June 23, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(14\)71207-0/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)71207-0/fulltext)
2. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA*. 1999 May 5; 281(17):1623-1627. Accessed June 23, 2016. <http://jama.jamanetwork.com/article.aspx?articleid=189737>
3. Gergel TJ, Leichman L, Nava HR, et al. Effect of concurrent radiation therapy and chemotherapy on pulmonary function in patients with esophageal cancer: dose-volume histogram analysis. *Cancer J*. 2002 Nov-Dec; 8(6):451-460. Accessed June 23, 2016. http://journals.lww.com/journalppo/Abstract/2002/11000/Effect_of_Concurrent_Radiation_Therapy_and.9.aspx
4. Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med*. 1992 Jun 11; 326(24):1593-1598. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199206113262403>
5. Kachnic LA, Winter K, Wasserman T, et al. Longitudinal quality-of-life analysis of RTOG 94-05 (Int 0123): A phase III trial of definitive chemoradiotherapy for esophageal cancer. *Gastrointest Cancer Res*. 2011 Mar-Apr; 4(2):45-52. Accessed June 23, 2016. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3109887/pdf/gcr45.pdf>
6. Kole TP, Aghayere O, Kwah J, et al. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. *Int J Radiation Oncol Biol Phys*. 2012 Aug 1; 83(5):1580-1586. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03461-4/abstract](http://www.redjournal.org/article/S0360-3016(11)03461-4/abstract)
7. Konski A, Li T, Christensen M, et al. Symptomatic cardiac toxicity is predicted by dosimetric and patient factors rather than changes in ¹⁸F-FDG PET determination of myocardial activity after chemoradiotherapy for esophageal cancer. *Radiotherapy and Oncology*. 2012 Jul; 104(1):72-77. Accessed June 23, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(12\)00219-8/abstract](http://www.thegreenjournal.com/article/S0167-8140(12)00219-8/abstract)
8. Kumar G, Rawat S, Puri A, et al. Analysis of dose-volume parameters predicting radiation pneumonitis in patients with esophageal cancer treated with 3D-conformal radiation or IMRT. *Jpn J Radiol*. 2012; 30(1):18-24. Accessed June 23, 2016. <http://link.springer.com/article/10.1007/s11604-011-0002-2>
9. Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. *Int J Radiation Oncol Biol Phys*. 2003 Dec 1; 57(5):1317-1322. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)01373-7/abstract](http://www.redjournal.org/article/S0360-3016(03)01373-7/abstract)

10. Lin SH, Wang L, Myles B, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy for esophageal cancer. *Int J Radiation Oncol Biol Phys*. 2012 Dec 1; 84(5):1078-1085. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)00227-1/abstract](http://www.redjournal.org/article/S0360-3016(12)00227-1/abstract)
11. MacDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001 Sep 6; 345(10):725-730. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa010187>
12. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: High-dose versus standard-dose radiation therapy. *J Clin Oncol*. 2002 Mar 1; 20(5):1167-1174. Accessed June 23, 2016. <http://jco.ascopubs.org/content/20/5/1167.abstract>
13. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Esophageal and Esophagogastric Junction Cancers. Accessed June 23, 2016. http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Esophageal and Esophagogastric Junction Cancers. 1.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
14. Opendijk V, van der Gaast A, van Lanschot JJB, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol*. 2014 Feb 10; 32(5):385-391. Accessed June 23, 2016. <http://jco.ascopubs.org/content/32/5/385.full>
15. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol*. 2011 Jul; 12(7):681-692. Accessed June 23, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(11\)70142-5/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70142-5/fulltext)
16. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed Intergroup Study 0116: A phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol*. 2012 Jul 1; 30(19):2327-2333. Accessed June 23, 2016. <http://jco.ascopubs.org/content/30/19/2327.full>
17. Tachibana M, Yoshimura H, Kinugasa S, et al. Postoperative chemotherapy vs. chemoradiotherapy for thoracic esophageal cancer: a prospective randomized clinical trial. *EJSO*. 2003 Sep; 29(7):580-587. Accessed June 23, 2016. [http://www.ejso.com/article/S0748-7983\(03\)00111-2/abstract](http://www.ejso.com/article/S0748-7983(03)00111-2/abstract)
18. Tait LM, Meyer JE, McSpadden E, et al. Women at increased risk for cardiac toxicity following chemoradiation therapy for esophageal carcinoma. *Practical Radiation Oncology*. 2013 Oct-Dec; 3(4):e149-155. Accessed June 23, 2016. [http://www.practicalradonc.org/article/S1879-8500\(13\)00123-9/abstract](http://www.practicalradonc.org/article/S1879-8500(13)00123-9/abstract)
19. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012 May 31; 366(22):2074-2084. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa1112088>
20. Wang S, Liao Z, Vaporciyan A, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. *Int J Radiation Oncol Biol Phys* 2006 Mar 1; 64(3):692-699. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)02231-5/abstract](http://www.redjournal.org/article/S0360-3016(05)02231-5/abstract)

Radiation Treatment of Carcinoma of Esophagus and Gastroesophageal Junction (GEJ) Cancer

[**Return to Table of Contents**](#)

Radiation Treatment of Cervical Cancer

POLICY

- I. Brachytherapy alone, for stages 0 or 1A, is medically necessary for any of the following:**
 - A. Medically inoperable
 - B. Surgical refusal
 - C. Invasive carcinoma diagnosed by microscopy; microscopic lesions with stromal invasion 3.0 mm or less in depth without lymphatic or vascular space involvement. Visualized lesions are not included in this category even with superficial invasion

- II. Pelvic radiation alone for stages IB or IIA is medically necessary for any of the following:**
 - A. External beam photon radiation therapy
 1. Preoperative
 2. Definitive treatment when additional brachytherapy cannot be performed and the individual is inoperable
 3. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement
 - B. Intensity-Modulated Radiation Therapy (IMRT)
 1. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement

- III. Pelvic radiation and brachytherapy for stages IB, IIA, IIB, IIIA, IIIB or IVA are medically necessary for any of the following:**
 - A. External beam photon radiation therapy with brachytherapy
 1. Microscopic lesions with stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread with lymphovascular space invasion
 2. All microscopic lesions with stromal invasion more than 3.0 mm
 3. All clinically visible lesions confined to the cervix with or without extension to the parametria, pelvic sidewall(s), lower third of vagina, or causing hydronephrosis or nonfunctioning kidney
 4. Tumor invading the mucosa of the bladder or rectum, and/or extends beyond the true pelvis
 5. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement.
 - B. IMRT
 1. As postoperative treatment for positive surgical margins, positive pelvic

nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement

IV. External beam photon radiation therapy, IMRT, and brachytherapy are medically necessary for palliative therapy in an individual with or without evidence of distant metastases

A. In the non-curative setting and where symptoms are present, palliative external beam photon radiation therapy may be medically necessary. In this scenario, treatment is typically delivered with Complex or 3D conformal radiation therapy (3DCRT), up to 4 gantry angles, 1 phase, and up to 15 fractions. IMRT may be medically necessary when previous external beam photon radiation therapy or brachytherapy has been given.

V. External beam photon radiation therapy, IMRT, and brachytherapy are medically necessary for the treatment of loco-regional recurrence in an individual without evidence of distant metastases

A. When salvage radiotherapy is attempted, treatment is typically 3DCRT, up to 4 gantry angles, and up to 30 fractions. Two phases may be medically necessary, with or without brachytherapy. IMRT may be considered based on clinical presentation and anatomic location.

Key Clinical Points

Within the United States in 2015, 12,900 new cases of cervical cancer are projected resulting in approximately 4,100 deaths. The prognosis of individuals with cervical cancer is markedly affected by the extent of disease at the time of diagnoses.

I. Brachytherapy (internal radiation)

Brachytherapy is an important component of the radiation therapy regimen in the curative treatment of cervical cancer. Brachytherapy may be given by either Low Dose Rate (LDR) or High Dose Rate (HDR) techniques. Dose recommendations are available in the literature of the American Brachytherapy Society. It is recognized that disease presentations and anatomic deformity may result in less than optimal dosimetry using conventional radiation applicators, and that supplementary interstitial brachytherapy may be required on an individual basis to achieve optimal therapeutic effect.

The type of implant may include tandem and ovoids, tandem alone, ovoids only, interstitial, or vaginal cylinder only. For LDR therapy, up to 2 interstitial or intracavitary applications are considered medically appropriate. For HDR interstitial therapy, when 1 application is used, up to 5 fractions may be appropriate. When 2 applications are used, up to 3 fractions may be appropriate.

For HDR tandem and ovoids, up to 6 applications may be appropriate. For HDR vaginal cylinder, up to 3 applications may be medically necessary.

Electronic/kilovoltage brachytherapy is considered experimental, investigational, or unproven (EIU) for the treatment of cervical cancer.

II. Postoperative external beam photon radiation therapy / IMRT

The use of postoperative radiation treatment in this setting will depend on the type of surgery performed (simple or radical hysterectomy) and the surgical findings. Surgical findings of clinical relevance include the size of the primary tumor, depth of stromal invasion, and presence of lymphovascular invasion. Positive pelvic and/or para-aortic nodes, surgical margins, and involvement of the parametrium are also important. Chemotherapy generally is given concurrently in these situations as well. When indicated, postoperative radiation therapy typically is delivered using up to 30 fractions. Either IMRT or 3DCRT may be used as postoperative treatment for positive surgical margins, positive pelvic nodes, surgical margins less than 0.5 cm, extensive lymphovascular or capillary involvement. An intracavitary boost may be clinically appropriate in the setting of positive surgical findings. IMRT may also be used for pelvic and/or para-aortic radiation treatment when surgical lymph node sampling or dissection is positive for metastatic disease.

III. Management of the para-aortic nodes

The treatment of para-aortic nodal regions may be indicated in the following clinical situations:

- A. Positive para-aortic lymph nodes on surgical staging if lymph nodes are less than 2 cm and are below L3
- B. Positive para-aortic lymph nodes on surgical staging and all macroscopic para-aortic nodes are removed
- C. Recurrent disease without evidence of distant metastases
- D. Positive pelvic and/or para-aortic lymph nodes on Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scan. Pathologic confirmation is recommended if technically feasible.

When treatment of the para-aortic nodes is indicated, treatment may be concurrent or sequential. External beam photon radiation therapy, IMRT, and brachytherapy, are considered medically appropriate. For concurrent treatment, up to 6 gantry angles are approved, and a conedown (additional phase) may be appropriate. For sequential treatment, up to 6 gantry angles, 1 conedown, and up to 28 additional fractions may be appropriate. If judged clinically necessary by the radiation oncologist and supported by dosimetry analysis, IMRT may be used in

lieu of 3DCRT to reduce doses to critical organs including the kidneys, small bowel, liver and spinal cord. IMRT may also be used concurrently or sequentially for this treatment.

IV. IMRT

The use of IMRT routinely is not appropriate for the definitive treatment of cancer of the intact cervix, as studies have demonstrated difficulty in daily reproducibility and dosimetry. The cervix has been shown to move as much as 2 cm on a daily basis (Lim et al., 2009; Lim et al., 2011; National Comprehensive Cancer Network [NCCN] Guidelines Version 2.2015 Cervical Cancer; Small et al., 2008; Welsh et al., 2007). Devices for the immobilization of the cervix are considered experimental at this time. Significant and rapid tumor shrinkage seen in cervical cancer can also affect IMRT distributions. Thus, as recommended by NCCN, certification of IMRT treatment involving the intact cervix is restricted to individuals participating in IRB protocols. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/NCCN. There is solid evidence that the risk of severe small bowel injury after conventional radiotherapy for postoperative patients with gynecologic cancer is 5 to 15% (Corn et al., 1994; Gallagher et al., 1986). IMRT is considered medically necessary when doses to critical organs can be meaningfully reduced compared to 3DCRT. RTOG 0418 showed that postoperative pelvic IMRT for endometrial cancer is feasible across multiple institutions with use of a detailed protocol and centralized quality assurance. A similar result for cervical cancer is expected from this trial. Multiple dosimetric studies and smaller clinical studies have demonstrated that dose to the small bowel can be decreased using IMRT and should impact on the risk of small bowel injury (Jhingran et al., 2012; Klopp et al., 2010; Salama et al., 2006). The major concern at RTOG was the ability of multiple institutions to safely implement IMRT programs for pelvic RT in gynecologic patients. The conclusion of RTOG 0418 is that this can be done. Preliminary data from RTOG 0418 in 40 cervical cancer patients receiving postoperative IMRT and chemotherapy was reported by Klopp et al. in abstract form and showed 0% grade 4 hematologic toxicity with IMRT compared to 18% with conventional treatment, $p = 0.002$ with a median of 32 months, 2-year disease-free survival (DFS) and overall survival (OS) were 86.9% and 94.6%, comparing favorably to an intergroup postoperative study of concurrent chemoradiation with conventional RT in high risk early stage cervical cancer patients reported by Peters et al. (2000) where 3-year progression-free survival (PFS) and OS was 84% and 88%. Recently a report on 34 patients from Memorial Sloane-Kettering Cancer Center (MSKCC) in

intermediate and high-risk cervical cancer receiving postoperative chemotherapy and concurrent IMRT showed a 3- and 5-year OS of 91% and PFS of 91.2% with a 44-month median follow up. There were only 2 locoregional failures, 1 vaginal and 1 pelvic (Folkert et al., 2013). These data suggest that with the tighter margins of IMRT local control can be maintained with a decrease in toxicity. Additionally, the use of IMRT may be considered when co-morbid medical conditions and/or surgical history may significantly increase risk to critical organs. It is recommended that all IMRT treatments be accomplished with photon beams not exceeding 10 MV to reduce integral neutron dose in this highly curable population.

V. Palliative therapy

In the non-curative setting and where symptoms are present, palliative external beam photon radiation therapy may be medically necessary. In this scenario, treatment is typically delivered with Complex or 3DCRT, up to 4 gantry angles, 1 phase, and up to 15 fractions. IMRT may be medically necessary when previous external beam photon radiation therapy or brachytherapy has been given. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

VI. Loco-regional recurrence

When salvage radiotherapy is attempted, treatment is typically 3DCRT, up to 4 gantry angles, and up to 30 fractions. Two phases may be medically necessary, with or without brachytherapy. IMRT may be considered based on clinical presentation and anatomic location. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

VII. Chemotherapy

Five randomized phase III trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy, while one trial examining this regimen demonstrated no benefit. The patient populations in these studies included women with FIGO stages 1B-2 to IVA cervical cancer treated with primary radiation therapy and women with FIGO stages I to IIA disease found to have poor prognostic factors (metastatic disease in pelvic lymph nodes, parametrial disease, or positive surgical margins) at primary surgery, who then go on to receive adjuvant chemoradiation. Although the positive trials vary in terms of the stage of disease, dose of radiation, and schedule of cisplatin and

radiation; the trials demonstrate significant survival benefit for this combined approach. Based on these results strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for the treatment of cervical cancer (Albuquerque et al., 2011; Chen et al., 2008; Folkert et al., 2013; Hall et al., 2003; Kloppe et al., 2010; Peters 3rd et al., 2000; Portelance et al., 2011; Rose et al., 2007).

References

1. The AJCC Cancer Staging Handbook. 7th Ed. 2010: Cervix Uteri, 473-479.
2. Albuquerque K, Giangreco D, Morrison C, et al. Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT. *Int J Radiat Oncol Biol Phys*. 2011 Mar 15; 79(4):1043-1047. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03690-6/abstract](http://www.redjournal.org/article/S0360-3016(09)03690-6/abstract)
3. American Cancer Society: Cancer Facts and Figures 2015. Atlanta, Ga.:American Cancer Society, 2015. Last medical review: 9/19/14. Last revised 2/26/15. Accessed June 23, 2016. <http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-key-statistics>
4. ASTRO 2014 Choosing Wisely® List. Accessed June 23, 2016. <https://www.astro.org/Patient-Care/Patient-Education/2014-Choosing-Wisely-List/>
5. Benowitz, S, Saenz, C, Mundt, AJ et al. Cervix moves significantly more than previously thought during radiation for cancer. UC San Diego News Center. 2009 Feb 10. Accessed June 23, 2016. <http://ucsdnews.ucsd.edu/archive/newsrel/health/02-09CervixCancer.asp>
6. Chen MF, Tseng CJ, Tseng CC, et al. Adjuvant concurrent chemoradiotherapy with intensity-modulated pelvic radiotherapy after surgery for high-risk, early stage cervical cancer patients. *Cancer J*. 2008 May-Jun; 14(3):200-206. Accessed June 23, 2016. http://journals.lww.com/journalppo/Abstract/2008/05000/Adjuvant_Concurrent_Chemoradiotherapy_With.12.aspx
7. Corn BW, Lanciano RM, Greven KM, et al. Impact of improved irradiation technique, age, and lymph node sampling on the severe complication rate of surgically staged endometrial cancer patients: a multivariate analysis. *J Clin Oncol*. 1994; 12(3):510–515. Accessed June 23, 2016. <http://jco.ascopubs.org/content/12/3/510.abstract>
8. Esthappan J, Chaudhari S, Santanam L, et al. Prospective clinical trial of positron emission tomography/computed tomography image-guided intensity-modulated radiation therapy for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys*. 2008 Nov 15; 72(4):1134-1139. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)00413-6/abstract](http://www.redjournal.org/article/S0360-3016(08)00413-6/abstract)
9. Esthappan J, Mutic S, Malyapa RS, et al. Treatment planning guidelines regarding the use of CT/PET-guided IMRT for cervical carcinoma with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys*. 2004 Mar 15; 58(4):1289-1297. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)02017-0/abstract](http://www.redjournal.org/article/S0360-3016(03)02017-0/abstract)
10. Folkert MR, Shih KK, Abu-Rustum NR, et al. Postoperative pelvic intensity-modulated radiotherapy and concurrent chemotherapy in intermediate- and high-risk cervical cancer. *Gynecol Oncol*. 2013 Feb; 128(2):288-293. Accessed June 23, 2016. <http://www.sciencedirect.com/science/article/pii/S0090825812008785>
11. Gallagher MJ, Brereton HD, Rostock RA, et al. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys*. 1986; 12(9):1565–1573. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(86\)90279-8/abstract](http://www.redjournal.org/article/S0360-3016(86)90279-8/abstract)
12. Hall EJ, Wu C-S. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys*. 2003 May 1; 56(1):83-88. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)00073-7/abstract](http://www.redjournal.org/article/S0360-3016(03)00073-7/abstract)
13. Jhingran A, Winter K, Portelance L, et al. A phase II study of intensity modulated radiation therapy to the pelvis for postoperative patients with endometrial carcinoma: Radiation Therapy Oncology Group Trial 0418. *Int J Radiat Oncol Biol Phys*. 2012 Sep 1; 84(1):e23-e8. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)00310-0/abstract](http://www.redjournal.org/article/S0360-3016(12)00310-0/abstract)
14. Kidd EA, Siegel BA, Dehdashti F, et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2010 Jul 15; 77(4):1085-1091. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00954-7/abstract](http://www.redjournal.org/article/S0360-3016(09)00954-7/abstract)

15. Klopp, AH, Moughan, J, Portelance, L, et al. Hematologic toxicity on RTOG 0418: a phase II study of post-operative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys*. 2010 Nov 1; 78(3 Supp):S121. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01281-2/abstract](http://www.redjournal.org/article/S0360-3016(10)01281-2/abstract)
16. Lim K, Small Jr W, Portelance L, et al. on behalf of Gyn IMRT Consortium. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys*. 2011 Feb 1; 79(2):348-355. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03587-1/abstract](http://www.redjournal.org/article/S0360-3016(09)03587-1/abstract)
17. Lorenz E, Strickert T, Hagen B. Cervical carcinoma: postoperative radiotherapy: fifteen-year experience in a Norwegian health region. *Int J Gynecol Cancer*. 2009 Dec; 19(9):1595-1599. Accessed June 23, 2016. http://journals.lww.com/ijgc/Abstract/2009/12000/Cervical_Carcinoma_Postoperative_Radiotherapy_.27.aspx
18. Lim K, Kelly V, Stewart J, et al. Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver? *Int J Radiat Oncol Biol Phys*. 2009 May 1; 74(1):304-312. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00019-4/abstract](http://www.redjournal.org/article/S0360-3016(09)00019-4/abstract)
19. Macdonald DM, Lin LL, Biehl K, et al. Combined intensity-modulated radiation therapy and brachytherapy in the treatment of cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008 Jun 1; 71(2):618-624. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)00291-5/abstract](http://www.redjournal.org/article/S0360-3016(08)00291-5/abstract)
20. National Comprehensive Cancer Network (NCCN) Guidelines. Version 1.2016. Cervical Cancer. Accessed June 23, 2016. http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Cervical Cancer Version 1.2016®. 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
21. Peters 3rd, WA, Liu, PY, Barrett 2nd RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*. 2000 Apr 1; 18(8):1606–1613. Accessed June 23, 2016. <http://jco.ascopubs.org/content/18/8/1606.full>
22. Portelance L, Moughan J, Jhingran A, et al. A phase II multi-institutional study of postoperative pelvic intensity modulated radiation therapy (IMRT) with weekly cisplatin in patients with cervical carcinoma: two year efficacy results of the RTOG 0418 *Int J Radiat Oncol Biol Phys*. 2011 Oct 1; 81(2 Suppl):3. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)00828-5/abstract](http://www.redjournal.org/article/S0360-3016(11)00828-5/abstract)
23. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007 Jul 1; 25(19):2804-2810. Accessed June 23, 2016. <http://jco.ascopubs.org/content/25/19/2804.full>
24. Salama JK, Mundt AJ, Roeske J, et al. Preliminary outcome and toxicity report of extended-field, intensity modulated radiation therapy for gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2006 Jul 15; 65(4):1170-1176. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)00370-1/abstract](http://www.redjournal.org/article/S0360-3016(06)00370-1/abstract)
25. Small W Jr, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008 Jun 1; 71(2):428-434. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)04253-8/abstract](http://www.redjournal.org/article/S0360-3016(07)04253-8/abstract)
26. Viswanathan AN, Thomadsen B. American Brachytherapy Society Cervical Cancer Brachytherapy Task Group. Accessed June 23, 2016. http://www.americanbrachytherapy.org/guidelines/cervical_cancer_taskgroup.pdf
27. Welsh JS, Mackie TR, Limmer JP. High-energy photons in IMRT: uncertainties and risks for questionable gain. *Technol Cancer Res Treat*. 2007 Apr; 6(2):147-149. Accessed June 23, 2016. <http://tct.sagepub.com/content/6/2/147.full.pdf+html>
28. Zwahlen DR, Ruben JD, Jones P, et al. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys*. 2009 Jun 1; 74(2):539-545. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00231-4/abstract](http://www.redjournal.org/article/S0360-3016(09)00231-4/abstract)

Radiation Treatment of Cervical Cancer

[Return to Table of Contents](#)

Radiation Treatment of Endometrial Cancer

POLICY

Treatment options for a fully surgically staged individual:

- I. Postoperative brachytherapy (alone) is medically necessary for any of the following:**
 - A. Stage IA with adverse risk factors (G1, G2, G3)
 - B. Stage IA without adverse risk factors (G2, G3)
 - C. Stage IB (G1, G2, G3)
 - D. Stage II (G1, G2)

- II. Pelvic external beam photon radiation therapy (alone) is medically necessary for either of the following:**
 - A. Medically inoperable
 - B. Postoperative for any of the following:
 1. Stage IA (G2, G3) with adverse risk factors
 2. Stage IB (G3) without adverse risk factors
 3. Stage IB (G1, G2, G3) with adverse risk factors
 4. Stage II (G1, G2)
 5. Stage IIIA and Stage IIIB vaginal or parametrial involvement (combination with brachytherapy preferred)
 6. Stage IIIC1 with positive pelvic nodes and negative para-aortic nodes (G1, G2, G3)

- III. Postoperative pelvic external beam photon radiation therapy and brachytherapy are medically necessary for any of the following:**
 - A. Stage IA with adverse risk factors (G2, G3)
 - B. Stage IB without adverse risk factors (G3)
 - C. Stage IB with adverse risk factors (G1, G2, G3)
 - D. Stage II (G1, G2, G3)
 - E. Stage IIIA (G1, G2, G3)
 - F. Stage IIIB
 - G. Stage IIIC1 positive pelvic but negative para-aortic nodes

- IV. Para-aortic lymph node radiation treatment with pelvic external beam photon radiation therapy with or without brachytherapy is medically necessary for either of the following:**
 - A. Stage IIIC1 (involvement of only pelvic nodes)
 - B. Stage IIIC2 (involvement of para-aortic lymph nodes with or without pelvic nodes) documented at surgery or by image-guided biopsy

V. Tumor directed radiation therapy is medically necessary for any of the following:

- A. Stage IVA (tumor invading bladder and/or bowel mucosa) or Stage IVB (distant metastases including inguinal nodes, intra-peritoneal disease, lung, liver or bone metastases) following a debulking surgical procedure with no evidence of gross residual disease or microscopic abdominal disease
- B. Recurrence
- C. Palliation including primary and/or metastatic disease sites

VI. Electronic/kilovoltage brachytherapy is considered experimental, investigational or unproven for the treatment of endometrial cancer.

Key Clinical Points

Within the United States in 2015, 54,870 new cases of uterine malignancy are projected resulting in projected 10,170 deaths. Uterine cancers represent the most common female genital tract malignancy. Endometrioid (tumors resembling the lining of the uterus; adenocarcinomas) are the most prevalent subtype. Serous papillary carcinoma is not covered under this criteria.

The staging definitions used in the creation of the treatment criteria may be found in the 7th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. The treatment options for treatment of cancer of the endometrium are defined by stage of disease, grade of the cancer, completeness of surgical staging and the presence of adverse risk factors. Complete surgical staging is defined as total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO), peritoneal lavage for cytology, dissection of pelvic and para-aortic lymph nodes and careful inspection and palpation of abdominal organs including but not limited to diaphragm, liver, peritoneal surfaces of the abdomen, pelvis, bowel and omentum. Adverse risk factors include advancing age, lymphovascular extension, tumor size, lower uterine involvement classified as cervical glandular involvement (newly classified as Stage I). For cases that are not completely surgically staged, radiologic imaging plays an important role in selecting a treatment strategy.

For Stage IA G1-2 without evidence of myometrial invasion, the individual may be safely observed per current NCCN Guidelines®. Vaginal brachytherapy may be considered in Stage IA G2-3. Combined treatment with both external beam photon radiation therapy and brachytherapy may be considered in Stage IA G3 with negative imaging. With more advanced clinical state and/or radiological presentations, more extended external beam photon radiation fields with or without brachytherapy may be medically necessary.

In advanced disease, the increased utilization of adjuvant chemotherapy has called into question the magnitude of the added benefit of adjuvant radiation therapy. We are awaiting the results of some recent trials that may help to answer some of these questions. Gynecologic Oncology Group (GOG) trial 249 randomized high risk early-stage patients to pelvic external beam photon radiation therapy or intravaginal external beam photon radiation therapy and chemotherapy. GOG 258 is comparing surgical Stage III or IVA patients to concurrent tumor directed external beam photon beam radiation therapy/chemotherapy to chemotherapy alone and PORTEC-3 is comparing concurrent pelvic external beam photon radiation therapy/chemotherapy to pelvic external beam photon beam radiation therapy alone in high risk surgical Stage IB-III patients.

For all other stages and those with positive radiologic imaging, surgical restaging or pathologic confirmation of more advanced disease is recommended (image directed biopsy). Patients then enter the fully surgically staged treatment recommendations with their newly assigned stage.

Palliation/Recurrence: Either brachytherapy or pelvic external beam photon radiation therapy alone or combined treatment may be considered based on the clinical presentation. In the non-curative setting and where symptoms are present, palliative external beam photon radiation therapy may be appropriate. In this scenario, treatment is typically delivered with Complex or three-dimensional conformal therapy (3DCRT), up to 4 gantry angles, 1 phase, and up to 15 fractions. When salvage radiotherapy is attempted for recurrence, treatment is typically 3DCRT, up to 4 gantry angles, and up to 35 fractions. Two phases may be appropriate, and the use of brachytherapy may be appropriate. Intensity-Modulated Radiation Therapy (IMRT) may be considered based on clinical presentation and anatomic location.

Treatment Discussion

I. Brachytherapy

Current guidelines for the use of brachytherapy in the treatment of endometrial cancer with High Dose Rate (HDR) from the American Brachytherapy Society may be found in the International Journal of Radiation Oncology Biology & Physics (Nag et al., 2000). Additional information is available from the American Brachytherapy Society Survey (Small et al., 2005).

Consistent with published guidelines including NCCN, appropriate medically necessary treatments are:

- A. Preoperative Stage II with gross disease:
 - 1. External beam photon radiation therapy and intrauterine brachytherapy
 - 2. Up to a total dose of 75 to 80 Gy Low Dose Rate (LDR) equivalent

B. Postoperative:

1. Brachytherapy should be initiated as soon as the vaginal cuff has healed or no later than 12 weeks following surgery
 - a. Following the performance of a hysterectomy, brachytherapy using a vaginal cylinder is generally limited to the upper vagina with the dose prescribed at the vaginal surface or to a depth of 0.5 cm
 - b. HDR vaginal cylinder regimens of 4 to 6 Gy for 2 to 3 fractions to the vaginal mucosa are common in conjunction with external beam photon radiation treatment
2. As definitive treatment alone without external beam photon radiation therapy
 - a. HDR regimens using a vaginal cylinder include 7 Gy for 3 fractions prescribed to a depth of 0.5 cm from the vaginal surface or 6 Gy for 5 fractions prescribed to the vaginal surface

II. External beam photon radiation therapy doses to the pelvis and tumor volume for microscopic disease

- A. Doses range from 45 to 50 Gy usually in 1.8 Gy daily fractions
- B. Computed tomography (CT)-planned 3D techniques are generally used
- C. For treatment of the postoperative pelvis with planned external beam photon radiation therapy boosts to positive lymph nodes or positive surgical margins, IMRT may be considered medically necessary to reduce doses to critical organs
- D. IMRT may also be considered for postoperative pelvic radiation as part of a sequential or concurrent treatment plan incorporating the para-aortic lymph node treatment. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/NCCN

III. External beam photon radiation therapy doses to the para-aortic region

- A. When treatment of the para-aortic nodes is indicated, treatment may be concurrent or sequential. Both regimens are considered medically appropriate
- B. For concurrent treatment, up to 6 gantry angles are approved, and a conedown (additional phase) may be appropriate
- C. For sequential treatment, up to 6 gantry angles, one conedown, and up to 28 additional fractions may be appropriate
- D. If judged clinically necessary by the radiation oncologist and supported by dosimetry analysis, IMRT may be used in lieu of 3DCRT to reduce doses to

critical organs including the kidneys, small bowel, liver and spinal cord. IMRT may also be considered for postoperative para-aortic radiation as part of a sequential or concurrent treatment plan in which IMRT is being administered to the postoperative pelvis with planned external beam photon radiation therapy boosts to positive lymph nodes or positive surgical margins

IV. IMRT

- A. The use of IMRT is not routinely appropriate for the treatment of cancer of the uterus as studies have demonstrated difficulty in daily reproducibility and dosimetry
- B. IMRT is medically necessary in the postoperative setting when doses to critical organs can be meaningfully reduced compared to 3DCRT
- C. There is solid evidence that the risk of severe small bowel injury after conventional radiotherapy for postoperative patients with gynecologic cancer is 5 to 15% (Corn et al., 1994; Gallagher et al., 1986). RTOG 0418 showed that postoperative pelvic IMRT for endometrial cancer is feasible across multiple institutions with use of a detailed protocol and centralized quality assurance. Multiple dosimetric studies and smaller clinical studies have demonstrated that dose to the small bowel can be decreased using IMRT and should impact on the risk of small bowel injury. The major concern at RTOG was the ability of multiple institutions to safely implement IMRT programs for pelvic RT in gynecologic patients. The conclusion of RTOG 0418 is that this can be done. More mature data on the use of postoperative IMRT in endometrial cancer has now been reported. With a median follow up of 52 months, Shih et al. (2013) at Memorial Sloan-Kettering Cancer Center (MSKCC), reported on 46 high risk patients. Thirty also received concurrent chemotherapy. There were only 2% grade III gastrointestinal and 11% hematologic toxicities. The 5-year disease-free survival (DFS) and overall survival (OS) rates were 87% and 97%. There was only 1 vaginal failure (2%) and no pelvic failures. IMRT was not used.
- D. It is recommended that all IMRT treatments be accomplished with photon beams not exceeding 10 MV to reduce integral neutron dose in this highly curable population of individuals

V. Chemotherapy

- A. The use of chemotherapy and radiation treatment in the management of endometrial cancer either concurrently or sequentially remains for the most part the object of clinical study and investigation
- B. Combined modality treatment may be considered for an individual with high risk of recurrence, recurrent, or metastatic disease
- C. For a completely surgically staged individual, current disease presentations

considered for chemotherapy and radiation include but are not limited to Stage IB G3; Stage II G3; Stages III A, B, and C; Stages IVA and IVB

- D. An incompletely surgically staged individual with Stage IA G3, and all Stage IB and Stage II disease should be treated with external beam photon radiation therapy and brachytherapy.
- E. An individual with Stage IB or Stage II with G3 cancer should be considered for chemotherapy as well
- F. An individual with positive imaging studies is treated according to further surgical and/or biopsy results

References:

1. American Cancer Society: Cancer Facts and Figures 2015. Atlanta, Ga.:American Cancer Society, 2014. Last medical review: 2/9/15. Last revised 3/25/15. Accessed April 20, 2016. <http://www.cancer.org/cancer/endometrialcancer/overviewguide/endometrial--uterine--cancer-overview-key-statistics>
2. The AJCC Cancer Staging Handbook 7th Ed. 2010: Corpus Uteri, 481-491.
3. ASTRO 2014 Choosing Wisely® List. Accessed April 20, 2016. <https://www.astro.org/Patient-Care/Patient-Education/2014-Choosing-Wisely-List/>
4. Carboplatin and paclitaxel with or without cisplatin and radiation therapy in treating patients with stage I, stage II, stage III, or stage IVA endometrial cancer. Gynecologic Oncology Group and National Cancer Institute. Last verified December 2014. Accessed April 20, 2016. <http://clinicaltrials.gov/show/NCT00942357> (GOG 258).
5. Corn BW, Lanciano RM, Greven KM, et al. Impact of improved irradiation technique, age, and lymph node sampling on the severe complication rate of surgically staged endometrial cancer patients: a multivariate analysis. *J Clin Oncol*. 1994; 12(3):510–515. Accessed April 20, 2016. <http://jco.ascopubs.org/content/12/3/510.abstract>
6. Cozad SC. Stage II adenocarcinoma of the endometrium: adjuvant radiotherapy and recurrence patterns. *Int J Radiat Oncol Biol Phys*. 2008 May 1; 71(1): 205-212. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)04245-9/abstract](http://www.redjournal.org/article/S0360-3016(07)04245-9/abstract)
7. Creutzberg CL, van Putten WLJ, Wárlám-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with Stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial. *J. Clinical Oncology*. 2004 Apr 1; 22(7): 1234-1241. Accessed April 20, 2016. <http://jco.ascopubs.org/content/22/7/1234.full>
8. Gallagher MJ, Brereton HD, Rostock RA, et al. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys*. 1986; 12(9):1565–1573. Accessed April 20, 2016. [http://www.redjournal.org/article/0360-3016\(86\)90279-8/abstract](http://www.redjournal.org/article/0360-3016(86)90279-8/abstract)
9. Jhingran A, Winter K, Portelance L, et al. A phase II study of intensity modulated radiation therapy to the pelvis for postoperative patients with endometrial carcinoma: Radiation Therapy Oncology Group Trial 0418. *Int J Radiat Oncol Biol Phys*. 2012 Sep 1; 84(1):e23-e8. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)00310-0/abstract](http://www.redjournal.org/article/S0360-3016(12)00310-0/abstract)
10. Lin LL, Grigsby PW, Powell MA, et al. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. *Int J Radiat Oncol Biol Phys* 2005 Oct 1; 63(2): 500-504. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00290-7/abstract](http://www.redjournal.org/article/S0360-3016(05)00290-7/abstract)
11. Nag S, Erickson B, Parikh S, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys*. 2000 Oct 1; 48(3):779-790. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(00\)00689-1/abstract](http://www.redjournal.org/article/S0360-3016(00)00689-1/abstract)
12. Nakayama K, Nagai Y, Ishikawa M, et al. Concomitant postoperative radiation and chemotherapy following surgery was associated with improved overall survival in patients with FIGO Stages III and IV endometrial cancer. *Int J Clin Oncol*. 2010 Oct; 15(5): 440-446. Accessed April 20, 2016. <http://link.springer.com/article/10.1007/s10147-010-0081-6>

13. National Comprehensive Cancer Network (NCCN) Guidelines. Version 2.2016. Uterine Neoplasms. Accessed April 20, 2016. http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Uterine Neoplasms. Version 2.2016®. 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
14. Pelvic radiation therapy or vaginal implant radiation therapy, paclitaxel, and carboplatin in treating patients with high-risk stage I or Stage II endometrial cancer. Gynecologic Oncology Group and National Cancer Institute. Last verified February 2012. Accessed April 20, 2016. <http://clinicaltrials.gov/show/NCT00807768> (GOG 249)
15. Randomized Trial of Radiation Therapy With or Without Chemotherapy for Endometrial Cancer Leiden University Medical Center. Last verified August 2014. Accessed April 20, 2016. <http://clinicaltrials.gov/ct2/show/NCT00411138> (PORTEC-3)
16. Scholten AN, van Putten WLJ, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005 Nov 1; 63(3) 834-838. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00419-0/abstract](http://www.redjournal.org/article/S0360-3016(05)00419-0/abstract)
17. Shih KK, Milgrom SA, Abu-Rustum NR, et al. Postoperative pelvic intensity-modulated radiotherapy in high risk endometrial cancer Gynecol Oncol. 2013 Mar; 128(3):535-539. Accessed April 20, 2016. <http://www.sciencedirect.com/science/article/pii/S0090825812008864>
18. Siddiqui F, Ibrahim DR, Aref I, et al. Clinical outcome of pathologic Stage IIA endometrial adenocarcinoma after intravaginal brachytherapy alone. Brachytherapy. 2009 Oct-Dec; 8(4): 396-400. Accessed April 20, 2016. [http://www.brachyjournal.com/article/S1538-4721\(09\)00246-3/abstract](http://www.brachyjournal.com/article/S1538-4721(09)00246-3/abstract)
19. Small Jr. W, Erickson B, Kwakwa F. American Brachytherapy Society survey regarding practice patterns of postoperative irradiation for endometrial cancer: current status of vaginal brachytherapy. Int J Radiat Oncol Biol Phys. 2005 Dec 1; 63(5):1502-1507. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00805-9/abstract](http://www.redjournal.org/article/S0360-3016(05)00805-9/abstract)
20. Solhjem NC, Petersen IA, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. Int J Radiat Oncol Biol Phys. 2005 August 1; 62(5): 1379-1384. Accessed April 20, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00144-6/abstract](http://www.redjournal.org/article/S0360-3016(05)00144-6/abstract)

Radiation Treatment of Endometrial Cancer

[Return to Table of Contents](#)

Radiation Treatment of Extra-cranial Oligometastases

POLICY

I. Stereotactic Body Radiotherapy (SBRT) for extra-cranial oligometastases is medically necessary in the following clinical situations:

- A. For an individual with non-small cell lung cancer who:
 - 1. Has had or who will undergo curative treatment of the primary tumor (based on T and N stage) and
 - 2. Has 1 to 3 metastases in the synchronous setting
- B. For an individual with colorectal cancer who:
 - 1. Has had or who will undergo curative treatment of the primary tumor and
 - 2. Presents with 1 to 3 metastases in the lung or liver in the synchronous setting and
 - 3. For whom surgical resection is not possible
- C. For an individual with:
 - 1. A clinical presentation of one 1 to 3 adrenal gland, lung, liver or bone metastases in the metachronous setting when all the following criteria are met:
 - a. Histology is non-small cell lung, colon, breast, sarcoma, renal cell, or melanoma
 - b. Disease free interval of > 1 year from the initial diagnosis
 - c. Primary tumor received curative therapy and is controlled
 - d. No prior evidence of metastatic disease (cranial or extracranial)

All cases will require review by an eviCore radiation oncologist of the consultation note and the most recent positron emission tomography (PET) scan (demonstrating no evidence of widespread metastatic disease).

Key Clinical Points

I. Definitions

- A. Oligometastatic
 - 1. A malignancy that has progressed to 1 to 3 hematogenous metastatic sites
- B. Synchronous Oligometastasis
 - 1. Oligometastatic disease found at the time of the diagnosis of the primary tumor
- C. Metachronous Oligometastasis
 - 1. Oligometastatic disease found after treatment of the primary tumor
- D. Oligoprogression
 - 1. Progression of a limited number of metastatic sites while other metastatic

disease sites remain controlled. SBRT is not routinely medically necessary in an individual with oligoprogressive disease.

II. Discussion

Oligometastases is described as an intermediate state in the spread of cancer between early-stage localized disease and widespread metastases. Specifically, it is a malignancy that has progressed to a limited number of hematogenous metastatic sites, defined in most studies as 1 to 3 sites. Chemotherapy remains the standard of care for patients with metastatic cancer, however this is rarely curative. The concept of oligometastasis has important implications for cancer treatment because it is believed that patients with limited numbers of metastasis previously thought by some clinicians to be incurable may be cured with local treatments such as radiotherapy.

The data supporting the treatment of extracranial oligometastases is limited to single institution or registry studies demonstrating improved survival outcomes compared to historical controls. There is no level one phase III evidence demonstrating a clear benefit. The data with the longest follow-up is the surgical literature examining the resection of non-small cell lung and hepatic metastases. The International Registry of Lung Metastases examined 5,206 patients between 1945 and 1995 at 18 institutions and found 36% survival at 5 years (Pastorino et al., 1997). Patients with the best prognosis were those with a single resectable metastases with a disease free interval > 3 years. In metastatic colorectal cancer to the liver, hepatic resection has resulted in a 5-year survival of 28% in a well-selected population (Nordlinger et al., 1996). Similar outcomes have been demonstrated in adrenal metastectomy for non-small cell lung cancer and pulmonary metastatectomy for osteosarcoma in children (Kager et al., 2003; Tanvetyanon, et al., 2008).

Recently, SBRT or Stereotactic Ablative Radiotherapy (SABR) has been investigated as an alternative to surgical resection in the treatment of oligometastatic disease. SBRT offers greater precision to a limited target volume than previous radiation delivery technologies. There have been several phase I/II studies which have demonstrated the technical feasibility of delivering SBRT for patients with non-small cell lung, liver and spine metastases (Lee et al., 2009; Milano et al., 2012; Rusthoven, et al., 2009; Salama et al., 2012; Wang et al., 2012). Furthermore, there have been several reports documenting the efficacy of SBRT or hypofractionated radiation in various different histologies including non-small cell lung, breast, colon, renal, melanoma, and sarcoma (Hasselle, et al., 2012; Hoyer, et al., 2006; Milano, et al., 2009; Ranck et al., 2013). These studies

have used anywhere from 3 to 10 fractions across a range of total doses. All have demonstrated local control of the treated lesions from 70 to 90%.

The major limitation of these studies is that they are single arm, non-controlled, with small patient numbers and often limited to single institutions. Furthermore, they are subject to “immortal” time bias that artificially inflates the survival of patients who underwent metastatectomy compared to those who did not. Therefore, none of these reports offers definitive clinical evidence that overall outcomes are improved with metastases directed SBRT compared to best standard therapies. Selection of an appropriate individual is imperative when deciding who is eligible to receive SBRT in the oligometastatic setting. One study revealed a 40% progression rate within 3 months of SBRT for 1 to 5 metastases and 80% progression at 2 years, which emphasizes the fact that the vast majority of patients have micro-metastatic disease at time of treatment (Milano, et al., 2012). Furthermore, disease free survival (DFS) after SBRT is associated with time to recurrence. One analysis found 3-year survival after SBRT was 53% for patients with a disease free interval of more than 12 months vs. 19% for patients with a disease free interval of less than 12 months (Inoue, et al., 2010). Another analysis found a disease free interval of more than 12 months was also associated with improved outcomes following treatment with SBRT for oligometastatic disease (Zhang, et al., 2011).

A. Non-small cell lung

There is a population of individuals with non-small cell lung cancer presenting with oligometastatic disease that will benefit from metastases-directed ablative procedures. A recent retrospective analysis of patients with oligometastatic non-small cell lung cancer who underwent metastasis directed treatment (intra and extra cranial) found a 2-year survival of 38% (Griffioen, et al., 2013). A recent review of the literature found that while the majority of patient's progress within 12 months, there is a subset of long-term survivors (Ashworth et al., 2013).

SBRT is considered medically necessary in an individual with non-small cell lung cancer who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease, and good performance status, assuming SBRT can be delivered safely to the involved sites.

Recent evidence has suggested that patient with actionable mutations in non-small cell lung cancer may derive a greater benefit from receiving SBRT or hypofractionated radiotherapy for oligoprogressive disease (Gan, et al., 2014; Iyengar, et al., 2014). Due to the limited number of patients included in these

analyses, it is difficult to make definitive conclusions regarding the benefit of SBRT for oligoprogressive disease for patients with actionable mutations. Therefore, SBRT is not considered medically necessary for an individual with oligoprogressive non-small cell lung disease.

B. Colon

Surgical series have shown that selected patients with colorectal cancer undergoing resection of hepatic and/or pulmonary metastases results in a cure for a proportion of patients with a 5-year survival of 38% (Kanas et al., 2012). The European Organisation for Research and Treatment of Cancer (EORTC) conducted the only randomized phase II study in the oligometastatic setting where patients with liver metastases from colon cancer were randomized to radiofrequency ablation plus chemotherapy or chemotherapy alone (Ruers et al., 2012). The 30 month survival was 61% in the radiofrequency ablation arm and 56% in the control arm ($p = 0.22$), demonstrating the excellent survival of patients with oligometastatic disease who do not receive local therapy.

SBRT is considered medically necessary in an individual with colorectal cancer who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease limited to the lung or liver, and good performance status, assuming surgical resection is not feasible.

C. Breast

An analysis of breast cancer patients who underwent treatment with SBRT for oligometastatic disease compared outcomes to other histologies. Patients who underwent SBRT for oligometastatic breast cancer had a progression free survival (PFS) at 2 years of 36% vs. 13% for non-breast histology, and overall survival (OS) at 6 years was 47% vs. 9% for non-breast histology.

SBRT is considered medically necessary in an individual with breast cancer who presents in the metachronous setting; has 1 to 3 sites of disease limited to the lung, liver, or bone, has a disease free interval of > 1 year; and received curative therapy to the primary tumor.

D. Sarcoma, Renal, Melanoma

A retrospective analysis examining pulmonary metastases from sarcoma found those who received local ablative treatment to have improved and improved median survival of 45 months vs. 12 months for those who had no local therapy to the metastases (Falk, et al., 2015). Previous retrospective literature has demonstrated a survival benefit for patients with metastatic

sarcoma who underwent a pulmonary metastasectomy (van Geel, et al., 1996). Pulmonary resection for renal cell cancer is associated with a 5-year survival of 20% (Murthy, et al., 2006). In the setting of melanoma there have also been retrospective studies demonstrating a benefit to lung resection of metastases. An analysis of melanoma in the international registry of lung metastasis found a 5-year survival of 22% after complete metastasectomy.

Based on this data, SBRT is considered medically necessary in an individual with sarcoma, renal, or melanoma metastases who meets the following criteria: disease free interval of > 1 year from the initial diagnosis, primary tumor received curative therapy and is controlled, and no prior evidence of metastatic disease.

E. Treatment of > 3 sites or nonhematogenous sites

The toxicity of using SBRT for treating multiple metastases (> 3 metastases) can be potentially significant. In light of this, the Radiation Therapy Oncology Group (RTOG) is currently conducting a phase I study examining the safety of SBRT for the treatment of multiple metastases. Furthermore, there is an ongoing international randomized phase II study examining SBRT for up to 5 metastases vs. standard of care without SBRT. Based on these ongoing studies, SBRT to > 3 sites is considered experimental/investigational. Furthermore, the current medical literature has primarily only examined the use of SBRT in patients with hematogenous spread (lung, liver, bone). Therefore, the use of SBRT to non-hematogenous sites of spread such as lymphatic regions is considered experimental/investigational.

References

1. Ashworth A, Rodrigues G, Boldt G, et al. Is there an oligometastatic state in non-small cell lung cancer? a systematic review of the literature. *Lung Cancer*. 2013 Nov; 82(2):197-203. Accessed June 23, 2016. [http://www.lungcancerjournal.info/article/S0169-5002\(13\)00379-6/abstract](http://www.lungcancerjournal.info/article/S0169-5002(13)00379-6/abstract)
2. Corbin KS, Hellman S, Weichselbaum RR. Extracranial oligometastases: a subset of metastases curable with stereotactic radiotherapy. *J Clin Oncol*. 2013 Apr 10; 31(11):1384-1390. Accessed June 23, 2016. <http://jco.ascopubs.org/content/31/11/1384.full>
3. Falk AT, Moureau-Zabotto L, Ouali M, et al. Effect on survival of local ablative treatment of metastases from sarcomas: a study of the French sarcoma group. *Clin Oncol (R Coll Radiol)*. 2015 Jan; 27(1):48-55. Accessed June 23, 2016. [http://www.clinicaloncologyonline.net/article/S0936-6555\(14\)00343-4/abstract](http://www.clinicaloncologyonline.net/article/S0936-6555(14)00343-4/abstract)
4. Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys*. 2014 Mar 15; 88(4):892-898. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)03313-0/abstract](http://www.redjournal.org/article/S0360-3016(13)03313-0/abstract)
5. Griffioen GHMJ, Toguri D, Dahele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. *Lung Cancer*. 2013 Oct; 82(1):95-102. Accessed June 23, 2016. [http://www.lungcancerjournal.info/article/S0169-5002\(13\)00332-2/abstract](http://www.lungcancerjournal.info/article/S0169-5002(13)00332-2/abstract)
6. Hasselle MD, Haraf DJ, Rusthoven KE, et al. Hypofractionated image-guided radiation therapy for patients with limited volume metastatic non-small cell lung cancer. *J Thorac Oncol*. 2012 Feb; 7(2):376-381. Accessed June 23, 2016. [http://www.jto.org/article/S1556-0864\(15\)33241-X/fulltext](http://www.jto.org/article/S1556-0864(15)33241-X/fulltext)
7. Hoyer M, Roed H, Hansen AT, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol*. 2006; 45(7):823-830. Accessed June 23, 2016. <http://informahealthcare.com/doi/full/10.1080/02841860600904854>
8. Inoue T, Katoh N, Aoyama H, et al. Clinical outcomes of stereotactic brain and/or body radiotherapy for patients with oligometastatic lesions. *Jpn J Clin Oncol*. 2010 Aug; 40(8):788-794. Accessed June 23, 2016. <http://jco.oxfordjournals.org/content/40/8/788.full>
9. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol*. 2014 Dec 1; 32(34):3824-3830. Accessed June 23, 2016. <http://jco.ascopubs.org/content/32/34/3824.abstract>
10. Kager L, Zoubek A, Pötschger U, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol*. 2003 May 15; 21(10):2011-2018. Accessed June 23, 2016. <http://jco.ascopubs.org/content/21/10/2011.abstract>
11. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol*. 2012 Nov; 4(1):283-301. Accessed June 23, 2016. <http://www.dovepress.com/survival-after-liver-resection-in-metastatic-colorectal-cancer-review-peer-reviewed-article-CLEP>
12. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol*. 2009 Apr 1; 27(10):1585-1591. Accessed June 23, 2016. <http://jco.ascopubs.org/content/27/10/1585.full>
13. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys*. 2012 Jul 1; 83(3):878-886. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03197-X/abstract](http://www.redjournal.org/article/S0360-3016(11)03197-X/abstract)
14. Milano MT, Zhang H, Metcalfe SK, et al. Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat*. 2009 Jun; 115(3):601-608. Accessed June 23, 2016. <http://link.springer.com/article/10.1007/s10549-008-0157-4>
15. Murthy SC, Kim K, Rice TW, et al. Can we predict long-term survival after pulmonary metastasectomy for renal cell carcinoma? *Ann Thorac Surg*. 2005 Mar; 79(3):996-1003. Accessed June 23, 2016. [http://www.annalsthoracicsurgery.org/article/S0003-4975\(04\)01782-5/fulltext](http://www.annalsthoracicsurgery.org/article/S0003-4975(04)01782-5/fulltext)
16. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. a prognostic scoring system to improve case selection, based on 1568 patients. *Association Francaise de Chirurgie. Cancer*. 1996 Apr 1; 77(7):1254-1262. Accessed June 23, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/\(SICI\)1097-0142\(19960401\)77:7%3C1254::AID-CNCR5%3E3.0.CO;2-I/epdf](http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0142(19960401)77:7%3C1254::AID-CNCR5%3E3.0.CO;2-I/epdf)
17. Palma DA, Salama JK, Lo SS, et al. The oligometastatic state - separating truth from wishful thinking. *Nat Rev Clin Oncol*. 2014 Sep; 11(9):549-557. Accessed June 23, 2016. <http://www.nature.com/nrclinonc/journal/v11/n9/abs/nrclinonc.2014.96.html>
18. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg*. 1997 Jan; 113(1):37-49. Accessed June 23, 2016. <http://www.sciencedirect.com/science/article/pii/S0022522397703970>

19. Ranck MC, Golden DW, Corbin KS, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. *Am J Clin Oncol*. 2013 Dec; 36(6):589-595. Accessed June 23, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2013/12000/Stereotactic_Body_Radiotherapy_for_the_Treatment.10.aspx
20. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol*. 2012 Oct; 23(10):2619-2626. Accessed June 23, 2016. <http://annonc.oxfordjournals.org/content/23/10/2619.full>
21. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol*. 2009 Mar 2; 27(10):1579-1584. Accessed June 23, 2016. <http://jco.ascopubs.org/content/27/10/1579.full>
22. Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer*. 2012 Jun 1; 118(11):2962-2970. Accessed June 23, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.26611/full>
23. Tanvetyanon T, Robinson LA, Schell MJ, et al. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. *J Clin Oncol*. 2008 Mar 1; 26(7):1142-1147. Accessed June 23, 2016. <http://jco.ascopubs.org/content/26/7/1142.abstract>
24. van Geel AN, Pastorino U, Jauch KW, et al. Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. *Cancer*. 1996 Feb 15; 77(4):675-682. Accessed June 23, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/\(SICI\)1097-0142\(19960215\)77:4<3C675::AID-CNCR13%3E3.0.CO;2-Y/epdf](http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0142(19960215)77:4<3C675::AID-CNCR13%3E3.0.CO;2-Y/epdf)
25. Wang XS, Rhines LD, Shiu AS, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1-2 trial. *Lancet Oncol*. 2012 Apr; 13(4):395-402. Accessed June 23, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(11\)70384-9/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70384-9/fulltext)
26. Zhang Y, Xiao JP, Zhang HZ, et al. Stereotactic body radiation therapy favors long-term overall survival in patients with lung metastases: five-year experience of a single-institution. *Chin Med J (Engl)*. 2011; 124(24):4132-4137. Accessed June 23, 2016. http://124.205.33.103:81/ch/reader/view_abstract.aspx?file_no=2011121939260730&flag=1

Radiation Treatment of Extra-cranial Oligometastases

[Return to Table of Contents](#)

Radiation Treatment of Gastric Adenocarcinoma

POLICY

External beam photon radiation therapy with three-dimensional conformal radiation therapy (3DCRT) is medically necessary for any of the following:

I. Preoperatively (neoadjuvant)

- A. Tumor stage T2, T3 or T4
- B. Any N stage

II. Postoperatively (adjuvant) if any of the following is present:

- A. Tumor stage T2, T3 or T4
- B. Positive lymph nodes
- C. Microscopic residual disease
- D. Macroscopic residual disease
- E. High risk features such as poor differentiation, lymphovascular invasion, neural invasion, and age less than 50

III. Medically inoperable (due to co-morbidity)

IV. Palliation

- A. For a symptomatic individual with local recurrence not amenable to surgical salvage, or in the palliative setting, a brief course of radiotherapy using Complex or 3D techniques, multiple radiation fields, and up to 15 fractions may be indicated.

Radiation treatment planning

I. Definitive radiation treatment

- A. Multiple radiation fields
- B. Up to 28 fractions with doses of 45 to 50.4 Gy (1.8 Gy/day)
 - 1. Higher doses (as a boost) may be indicated in select cases with positive surgical margins
- C. Customized blocking
- D. CT simulation
- E. 3DCRT
- F. IMRT may be indicated when dose to critical organs, such as the small bowel, liver, heart, lung, kidneys, and spinal cord is of concern IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group

(RTOG)/National Comprehensive Cancer Network (NCCN)

- G. Radiation treatment fields are different depending on the portion of the esophagus and stomach being treated. NCCN Guidelines[®] and radiation treatment planning atlases may be of benefit in planning preoperative or postoperative treatment to the following primary regions:
1. Proximal one-third/cardia/esophagogastric (EG) junction
 2. Middle one-third/body
 3. Distal one-third/antrum/pylorus

Key Clinical Points

The Intergroup 0116 Gastric Surgical Adjuvant Trial randomized high-risk (T3, T4 and/or node positive), completely resected gastric or gastroesophageal adenocarcinomas to receive either observation alone or radiochemotherapy. Radiochemotherapy produced significant improvements in relapse-free and overall survival (OS). External beam photon radiation therapy was given to a dose of 45 Gy in 25 fractions, usually via AP-PA fields. Thirty-five percent of initially submitted radiotherapy plans in the Gastric Surgical Adjuvant Trial had major or minor treatment errors at initial review, demonstrating the difficulty many clinicians had in implementing the complex radiotherapy field. Toxicity was significant, with 49% of patients experiencing National Cancer Institute (NCI) Common Toxicity Criteria Grade 3 or worse.

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial (MAGIC) (Cunningham et al., 2006) proved that patients with operable adenocarcinoma of the stomach derived benefits in terms of decreased tumor size and stage, as well as improved progression-free survival (PFS) and OS from a perioperative regimen of chemotherapy (epirubicin, cisplatin and fluorouracil). The use of radiation therapy was omitted.

In terms of historical progression of treatment planning techniques; after the Intergroup 0116 trial, which used AP-PA field arrangement, in 2007 Soyfer et al. published data concluding that non-coplanar 3D conformal approach yielded better results than AP-PA plans. In 2008 this same group compared IMRT to 3D conformal techniques for adjuvant management of gastric cancer, concluded that IMRT confers only marginal benefit, and should be used "...only in the small subset of patients with risk factors for kidney disease or those with preexisting nephropathy."

In 2010, the group at Stanford (Minn et al.) published on sequential groups of patients treated in the adjuvant setting, initially 3DCRT (26 patients), and after 2002 with IMRT (33 patients). The 2-year OS for the 3DCRT and IMRT groups was 51% and 65%, respectively ($p = 0.5$). The 2-year disease-free survival (DFS) for the 3DCRT and IMRT groups was 60% and 54%, respectively ($p = 0.8$). The two-year local control rate for the 3DCRT and IMRT groups was 83% and 81%, respectively ($p = 0.9$). The Stanford group

interpreted this data to show that IMRT could be delivered effectively without compromising outcome. In terms of toxicity, 3 patients required a treatment break of a median duration of 7 days due to toxicity in the 3DCRT group (range, 4 to 10 days), whereas no patient in the IMRT group required a treatment break. Grade 2 or higher acute GI toxicity was noted in 61.5% and 61.2% of patients in the 3DCRT and IMRT groups, respectively. Regarding late toxicity, among the 3DCRT patients, 1 patient died of small bowel perforation requiring surgical intervention (grade 5). Grade 3 late toxicity was experienced by 3 patients who developed small bowel obstruction. Two patients developed grade 2 late toxicity (jaundice and esophagitis). In the IMRT group, grade 3 late toxicity was experienced by 1 patient who had a stricture requiring surgery. Grade 2 late toxicity was experienced by 3 patients: 1 with gastritis, 1 with esophagitis, and 1 with an ulcer. The conclusion of this paper was "...although locoregional control is good with adjuvant chemoradiotherapy, overall outcomes for gastric cancer remain poor. Improvements in both local and systemic therapy are required. Adjuvant chemoradiotherapy was well tolerated with either 3DCRT or IMRT, with similar acute and late toxicities reported. Despite higher doses used, IMRT provides sparing to the liver and possibly the kidneys."

A study from China (Li et al., 2012) documents successful implementation of IMRT for postoperative gastric cancer at a single institution.

MD Anderson (Chakravarty et al., 2012) has used IMRT in the preoperative setting for gastric cancer.

A 2012 publication from Memorial Sloan Kettering (Kole et al.) documents that a lower dose to the heart and coronary arteries can be achieved with IMRT compared to 3DCRT in the treatment of distal esophageal cancer. It is not clear what the clinical significance of this is.

NCCN Guidelines[®] describe the use of 3DCRT approach as appropriate, with a dose of 45 to 50.4 Gy. The Guideline states that IMRT may be appropriate in selected cases to reduce dose to the normal structures including heart, lung, kidneys, and liver. Surgery alone is an insufficient treatment for most individuals according to NCCN Guidelines[®], except in stage 0 or stage IA presentations. Based on the results of the MAGIC trial, perioperative chemotherapy or chemoradiation may be considered for individuals with more advanced disease (T2 or higher, and any N stage). Based on the results of the Intergroup 0116 trial, postoperative chemoradiation is recommended for selected individuals.

Summary

While the Intergroup 0116 trial documented the benefit of adjuvant chemoradiotherapy and the MAGIC trial documented the benefit of chemotherapy in the perioperative setting, there is a completed European trial (CRITICS) to specifically study the contribution radiotherapy in the adjuvant setting in patients with resectable gastric cancer (Dikken et al, 2011). eviCore supports the use of adjuvant radiotherapy in resectable high-risk gastric cancer as medically necessary. 3DCRT is appropriate, and IMRT will be considered in those cases in which clinically meaningful reduction in doses to critical organs can only be achieved with IMRT.

References:

1. Alani S, Soyfer V, Strauss N, et al. Limited advantages of intensity-modulated radiotherapy over 3D conformal radiation therapy in the adjuvant management of gastric cancer. *Int J Radiat Oncol Biol Phys*. 2009 Jun 1; 74(2):562-566. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)00195-3/abstract](http://www.redjournal.org/article/S0360-3016(09)00195-3/abstract)
2. Chakravarty T, Crane CH, Ajani JA, et al. Intensity-modulated radiation therapy with concurrent chemotherapy as preoperative treatment for localized gastric adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2012 Jun 1; 83(2):581-586. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03106-3/abstract](http://www.redjournal.org/article/S0360-3016(11)03106-3/abstract)
3. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006 Jul 6; 355(1):11–20. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa055531>
4. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. BMC Cancer. 2011 Aug 2; 11:329. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). Accessed June 23, 2016. <http://www.biomedcentral.com/1471-2407/11/329>
5. Kole TP, Aghayere O, Kwah J, et al. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. *Int J Radiat Oncol Biol Phys*. 2012 Aug 1; 83(5):1580-1586. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)03461-4/abstract](http://www.redjournal.org/article/S0360-3016(11)03461-4/abstract)
6. Li P, Sheng LM, Deng QH, et al. Treatment of high-risk gastric cancer postoperatively using intensity-modulated radiotherapy; a single-institution experience. *Hepatogastroenterology*. 2012 Jan-Feb; 59 (113):159-163. Accessed June 23, 2016. http://www.researchgate.net/publication/221762402_Treatment_of_high-risk_gastric_cancer_postoperatively_using_intensity-modulated_radiotherapy_a_single-institution_experience
7. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001 Sep 6; 345(10):725-730. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa010187>
8. Minn AY, Hsu A, La T, et al. Comparison of intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy as adjuvant therapy for gastric cancer. *Cancer*. 2010 Aug 15; 116(16):3943-3952. Accessed June 23, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.25246/full>
9. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Gastric Cancer. Accessed June 23, 2016. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Gastric Cancer 1.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
10. Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. *Int J Radiat Oncol Biol Phys*. 2002 Feb 1; 52(2):283-293. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(01\)02646-3/abstract](http://www.redjournal.org/article/S0360-3016(01)02646-3/abstract)
11. Soyfer V, Corn BW, Melamud A, et al. Three-dimensional non-coplanar conformal radiotherapy yields better results than traditional beam arrangements for adjuvant treatment of gastric cancer. *Int J Radiat Oncol Biol Phys*. 2007 Oct 1; 69(2):364-369. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)00512-3/abstract](http://www.redjournal.org/article/S0360-3016(07)00512-3/abstract)
12. Yu C, Yu R, Zhu W, et al. Intensity-modulated radiotherapy combined with chemotherapy for the treatment of gastric cancer patients after standard D1/D2 surgery. *J Cancer Res Clin Oncol*. 2012 Feb; 138(2):255-259. Accessed June 23, 2016. <http://link.springer.com/article/10.1007/s00432-011-1085-y>

Radiation Treatment of Gastric Adenocarcinoma

[**Return to Table of Contents**](#)

Radiation Treatment of Head and Neck Cancer

POLICY

I. Radiation therapy techniques

- A. Three-dimensional conformal radiation therapy (3DCRT) and Intensity-Modulated Radiation Therapy (IMRT) techniques are medically necessary when the extent of disease allows preferential sparing of organs not needing radiation without compromising the dose delivered to tumor. In certain situations in which the extent of disease precludes better sparing of organs at risk by IMRT, an IMRT technique may not be medically necessary. In certain situations of limited disease, IMRT is not medically necessary
- B. Adaptive therapy is medically necessary with re-planning, upon significant alteration of tumor status or neck contour due to weight change
- C. The use of photon beam and electron beam radiation therapy is medically necessary
- D. The use of neutron beam therapy is medically necessary in select cases of salivary gland tumors (See Neutron Beam Radiotherapy in Cancer Treatment policy)
- E. Preoperative radiation therapy is medically necessary in select cases
 - 1. May be given in up to 35 fractions in 3 phases
 - 2. May use Complex, 3DCRT, or IMRT techniques

II. Radiation therapy treatment intent/timing

- A. Definitive radiation therapy
 - 1. Is medically necessary for selected T1-2, N0 cases as monotherapy
 - 2. May employ up to 42 fractions in a maximum of 2 phases
 - 3. Depending on the simplicity or complexity of the case, Complex, 3DCRT, or IMRT techniques may be necessary
- B. Definitive radiation therapy as monotherapy
 - 1. Is medically necessary for selected T1N1 and T2N0-1 cases
 - 2. Radiation may be given utilizing any of several schedules including conventional daily fractionation, concomitant boost accelerated fractionation, and hyperfractionation (twice-daily radiation)
 - 3. Up to 68 fractions may be medically necessary, in 2 phases
- C. Definitive concurrent chemoradiation
 - 1. Is medically necessary in unresected T2-4a, N0-3 cases utilizing up to 42 fractions with conventional schedule
 - 2. 3DCRT or IMRT techniques are medically necessary, in up to 4 phases
 - 3. Concurrent chemotherapy carries a high toxicity burden and requires substantial supportive care and the expertise of an experienced multidisciplinary team

D. Postoperative radiation therapy

1. Is medically necessary for cases that have any of the following high risk factors:
 - a. PT3 or pT4 primary tumors
 - b. N2 or N3 nodal disease
 - c. Positive nodes in levels IV or V
 - d. Perineural invasion
 - e. Vascular tumor embolism
 - f. Positive surgical margins or residual gross disease
2. 35 fractions are medically necessary
3. 3DCRT or IMRT techniques are medically necessary, in up to 3 phases
4. Chemotherapy may be added concurrently with postoperative radiation and is medically necessary in cases with positive margins or extracapsular nodal extension
5. Concurrent chemotherapy also may be considered in cases with the other high risk factors mentioned above, in which up to 40 fractions in 2 phases are medically necessary
6. Concurrent chemotherapy carries a high toxicity burden and requires substantial supportive care and the expertise of an experienced multidisciplinary team

III. Radiation therapy, brachytherapy

- A. Low Dose Rate (LDR) or High Dose Rate (HDR) brachytherapy is medically necessary in select cases of epithelial tumors of the head and neck region. In appropriate early cases, it is medically necessary as monotherapy. In more advanced cases, it may be substituted for one phase of 3DCRT or IMRT
- B. Brachytherapy for head and neck malignancies should be performed only by those radiation oncologists specifically trained in its use

IV. Radiation therapy, palliative

- A. In a previously un-irradiated individual with symptomatic local disease, Complex, 3DCRT or IMRT techniques are indicated for symptom control
- B. Up to 15 fractions are medically necessary, in 1 phase

V. Re-treatment for salvage after prior radiation

- A. Re-irradiation may be indicated in cases of recurrent or persistent disease, or for in-field new primary tumors, in cases in which there are no known distant metastases.
- B. Reirradiation carries increased risk. Per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Head and Neck Cancers Version 1.2016, "In general, the reirradiated population of head and neck cancer patients as described in the current literature represents a diverse but highly selected group of patients treated in centers where there is a high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment

is curative and surgery is not an option, reirradiation strategies can be considered for patients who: develop locoregional failures or second primaries at ≥ 6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully and analyzed through review of dose volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy."

- C. Enrollment in a clinical trial is preferred
- D. Stereotactic Body Radiation Therapy (SBRT) may be medically necessary for retreatment in patients who have no evidence of metastatic disease

Key Clinical Points

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines (American College of Radiology [ACR]/American Society for Radiation Oncology [ASTRO], NCCN), radiation therapy is considered an integral component in the multidisciplinary management of malignancies of the head and neck region. Primary anatomic sites included in this category include paranasal sinuses (ethmoid and maxillary), salivary glands, the lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, nasopharynx, and occult/unknown head and neck primary sites. The preponderance of literature addresses tumors of epithelial origin. Non-epithelial malignancies of the head and neck region (e.g. tumors arising in bone, cartilage, soft tissues, and lymphomas) are not covered by this policy.

Utilization of radiation therapy should be preceded by workup and staging and planned in conjunction with the appropriate members of a multi-disciplinary team that also includes: diagnostic imaging, pathology, medical oncology; otorhinological, oral, plastic and reconstructive, neuro- and ophthalmologic surgeons; psychiatry; addiction services; audiology and speech therapy; rehabilitation and nutritional medicine; pain management, dentists, prosthodontists, xerostomia management, smoking and alcohol cessation, tracheostomy and wound management, social workers and case management. Participation in a national clinical trial is encouraged.

Initial management may require surgery, chemotherapy, and radiation therapy in various combinations and sequences.

I. Radiation treatment schedules

Radiation therapy treatment schedules published in peer-reviewed consensus documents such as NCCN Guidelines® include the following regimens that encompass a broad range of doses that must be customized to an individual's

circumstance. These schedules are based on the extent of the primary and nodal disease as well as the treatment intent, such as definitive, preoperative or postoperative. The use of additional therapeutic strategies such as concurrent chemotherapy or brachytherapy is described in the NCCN Guidelines®.

A. Primary site and lymph nodes

1. Conventional schedule, high risk
 - a. 50 to 74 Gy at 2 Gy/daily fraction, with or without brachytherapy
 - b. For doses greater than 70 Gy, the use of daily doses less than 2 Gy may be considered for all or a portion of the radiation therapy to minimize toxicity
2. Conventional schedule, low to intermediate risk (possible sub-clinical spread)
 - a. 44 to 50 Gy at 2 Gy per fraction to 54 to 63 Gy at 1.6 to 1.8 Gy per fraction
3. Accelerated fractionation schedule
 - a. 66 to 74 Gy in 30 fractions, 6 fractions per week
4. Concomitant boost accelerated schedule
 - a. 72 Gy in six 6 weeks, with twice-daily treatments on each of the final 12 treatment days
5. Hyperfractionation schedule
 - a. 81.6 Gy in 68 fractions at 1.2 Gy twice daily

B. Postoperative

1. High risk adverse features such as positive margins
 - a. 60 to 66 Gy at 2 Gy/daily fraction
2. Low to intermediate risk sites with suspected sub-clinical spread
 - a. 44 to 50 Gy at 2 Gy per fraction to 54 to 63 Gy at 1.6 to 1.8 Gy per fraction

References

1. ACR-ASTRO Practice Parameter for the Performance of Low-Dose-Rate Brachytherapy. Revised 2015. Accessed June 23, 2016. http://www.acr.org/-/media/ACR/Documents/PGTS/guidelines/Low_Dose_Rate_Brachytherapy.pdf
2. ACR-ASTRO Practice Parameter for the Performance of High-Dose-Rate Brachytherapy. Revised 2015. Accessed June 23, 2016. http://www.acr.org/-/media/ACR/Documents/PGTS/guidelines/High_Dose_Rate_Brachy.pdf
3. Bernier J, Dumenige C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004 May 6; 350(19):1945-1952. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa032641>
4. Bernier J, Cooper JS, Pajuk TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck*. 2005 Oct; 27(10):843-850. Accessed June 23, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/hed.20279/abstract>
5. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. *N Engl J Med*. 2004 May 6; 350:1937-1944. Accessed June 23, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa032646>
6. Dogan N, King S, Emami B, et al. Assessment of different IMRT boost delivery methods on target coverage and normal-tissue sparing. *Int J Radiat Oncol Biol Phys*. 2003 Dec 1; 57(5):1480-1491. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)01569-4/abstract](http://www.redjournal.org/article/S0360-3016(03)01569-4/abstract)
7. Eisbruch A, Foote R, Beitler J, et al. Intensity-modulated radiation therapy for head and neck cancer: emphasis on the selection and delineation of targets. *Seminars in Radiation Oncology*. 2002 Jul; 12(3):238-49. Accessed June 23, 2016. [http://www.semradonc.com/article/S1053-4296\(02\)80064-9/abstract](http://www.semradonc.com/article/S1053-4296(02)80064-9/abstract)

8. Lee NY, de Arruda FF, Puri DR, et al. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2006 Nov; 66(4):966-974. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)01127-8/abstract](http://www.redjournal.org/article/S0360-3016(06)01127-8/abstract)
9. Lee NY, O'Meara w, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. *Int J Radiat Oncol Biol Phys*. 2007 Oct 1; 69(2):459-468. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)00508-1/abstract](http://www.redjournal.org/article/S0360-3016(07)00508-1/abstract)
10. Mohan R, Wu Q, Morris M, et al. "Simultaneous Integrated Boost" (SIB) IMRT of advanced head and neck squamous cell carcinomas-dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2001 Nov 1; 51(3):180-181. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(01\)02151-4/abstract](http://www.redjournal.org/article/S0360-3016(01)02151-4/abstract)
11. National Comprehensive Cancer Network (NCCN) Guidelines. Head and Neck Cancers Version 1.2016. Accessed June 23, 2016. http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Head and Neck Cancers Version 1.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
12. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol*. 2013 Feb 10; 31:543-550. Accessed June 23, 2016. <http://jco.ascopubs.org/content/31/5/543.full>
13. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous cell carcinoma of head and neck: DAHANCA 6 and 7 randomised control trial. *Lancet*. 2003; 362(9388):933-940. Accessed June 23, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(03\)14361-9/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(03)14361-9/fulltext)
14. Schoenfeld GO, Amdur RJ, Morris CG, et al. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2008 Jun 1; 71(2):377-385. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)04423-9/abstract](http://www.redjournal.org/article/S0360-3016(07)04423-9/abstract)
15. Wolden SL, Chen WC, Pfister DG, et al. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys* 2006 Jan 1; 64(1):57-62. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00592-4/abstract](http://www.redjournal.org/article/S0360-3016(05)00592-4/abstract)
16. Wu Q, Manning M, Schmidt-Ullrich, Mohan R. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. *Int J Radiat Oncol Biol Phys*. 2000 Jan 1; 46(1):195-205. Accessed June 23, 2016. [http://www.redjournal.org/article/S0360-3016\(99\)00304-1/abstract](http://www.redjournal.org/article/S0360-3016(99)00304-1/abstract)

Radiation Treatment of Head and Neck Cancer

[**Return to Table of Contents**](#)

Radiation Treatment of Hepatobiliary Cancer (primary liver, intrahepatic bile duct, extrahepatic bile duct, gallbladder)

POLICY – Primary Liver Cancer (Hepatocellular Carcinoma [HCC])

External beam photon radiation therapy (EBRT) is medically necessary for the following:

- I. Definitive management of medically or technically unresectable localized HCC in an individual with adequate hepatic reserve**
- II. Palliative management of localized disease or local disease with minimal extrahepatic disease**

Fractionation

- I. Stereotactic Body Radiation Therapy (SBRT): 3 to 5 fractions in the definitive setting to treat concurrently one or more tumors is medically necessary when there is evidence of the ability to protect an adequate volume of uninvolved liver. Most commonly 5 fractions are given, and a sliding scale dose is dictated by the size of the lesion and satisfaction of constraints**
- II. EBRT: 25 to 39 fractions in the definitive setting is medically necessary**
- III. EBRT: Up to 20 fractions in the palliative setting is medically necessary**

Techniques

- I. EBRT: 3-dimensional Conformal Radiation Therapy (3DCRT) and IMRT is medically necessary in the definitive setting**
- II. EBRT: 3DCRT is medically necessary in the palliative setting**

III. Proton Beam Therapy: see Proton Beam Radiation Therapy guideline

IV. Selective Internal Radiation Therapy (SIRT): see Radioactive Yttrium-90 Microspheres guideline

POLICY – Intrahepatic Bile Duct Cancer (Cholangiocarcinoma)

EBRT is medically necessary for the following:

- I. Definitive management of unresectable localized intrahepatic bile duct cancer**
- II. Adjuvant postoperative management of resected intrahepatic bile duct cancer with positive margins and/or positive regional lymph nodes**
- III. Palliative treatment of unresectable localized intrahepatic bile duct cancer**

Fractionation

- I. EBRT: 25 to 33 fractions in the definitive setting is medically necessary**
- II. EBRT: up to 20 fractions in the palliative setting is medically necessary**
- III. SBRT: up to 5 fractions in the definitive setting is medically necessary**

Techniques

- I. EBRT: 3-dimensional Conformal Radiation Therapy (3DCRT) and IMRT is medically necessary in the definitive setting**
- II. EBRT: 3DCRT is medically necessary in the palliative setting**
- III. SBRT: Is medically necessary in the definitive setting**

IV. Proton Beam Therapy: see Proton Beam Radiation Therapy guideline

POLICY – Extrahepatic Bile Duct Cancer (Cholangiocarcinoma)

EBRT is medically necessary for the following:

- I. Definitive management of unresectable localized extrahepatic bile duct cancer**
- II. Adjuvant postoperative management of resected extrahepatic bile duct cancer**
- III. Palliative treatment of unresectable localized extrahepatic bile duct cancer**

Fractionation

- I. EBRT: 25 to 33 fractions in the definitive setting is medically necessary**
- II. EBRT: 6 to 20 fractions in the palliative setting is medically necessary**

Techniques

- I. EBRT: 3DCRT is medically necessary in the definitive setting**
- II. EBRT: IMRT is medically necessary in the definitive setting when 3DCRT technique is unable to satisfy constraints to protect normal OAR**
- III. EBRT: 3DCRT is medically necessary in the palliative setting**
- IV. SBRT: Is considered not medically necessary**
- V. Proton Beam Therapy: see Proton Beam Radiation Therapy guideline**

POLICY – Gallbladder Cancer

EBRT is medically necessary for the following:

- I. Definitive management of unresectable localized gallbladder cancer**
- II. Adjuvant postoperative management of resected gallbladder cancer with positive margins and/or positive regional lymph nodes**
- III. Palliative treatment of unresectable localized gallbladder cancer**

Fractionation

- I. EBRT: 25 to 33 fractions in the definitive setting is medically necessary**
- II. EBRT: up to 20 fractions in the palliative setting is medically necessary**

Techniques

- I. EBRT: 3DCRT is medically necessary in the definitive setting**
- II. EBRT: IMRT is medically necessary in the definitive setting when 3DCRT technique is unable to satisfy constraints to protect normal organs at risk (OAR)**
- III. EBRT: 3DCRT is medically necessary in the palliative setting**
- IV. SBRT: Is considered not medically necessary**
- V. Proton Beam Therapy: see Proton Beam Radiation Therapy guideline**

Key Clinical Points**I. Primary Liver Cancer (HCC)**

The incidence of HCC is increasing in the United States, most notably in the population infected with hepatitis C virus that have developed cirrhosis. Cirrhosis from other causes, such as genetic hemochromatosis, also carries a high risk of developing HCC. Because of the underlying cirrhosis, the healthy liver reserve is often decreased. Screening of populations known to be at high risk for HCC has led to an increased rate of detection of HCC and often at an earlier stage amenable to local treatment.

Prior to treatment, an assessment of liver health is necessary and is traditionally quantitated using the Child-Pugh classification system. The Child-Pugh score is based on laboratory and clinical measures and assigns a patient with cirrhosis into compensated (class A) or uncompensated (class B or C) status. Additional measures of liver health include factors of portal hypertension and the presence of varices. The Model for End-stage Liver Disease (MELD) includes a numerical scale that often is applied when there is consideration of liver transplantation.

There are three types of HCC based on morphology: nodular (most commonly associated with cirrhosis), massive (most commonly in a non-cirrhotic liver), and diffuse (numerous nodules throughout the liver).

Numerous staging systems have been devised for HCC; each often having its own specific applicability, such as prognosis, suitability for a given intervention, or based on HCC etiology. National Comprehensive Cancer Network (NCCN) categories include potentially resectable or transplantable based on performance status or comorbidities, unresectable, inoperable based on performance status or comorbidities with local disease only, and metastatic disease.

Management of HCC depends on etiology and the underlying health of uninvolved liver. Partial hepatectomy, liver transplantation, bridge therapy while awaiting transplantation, downstaging strategies, and locoregional therapies are potentially available. Locoregional therapies include ablation (chemical, thermal, cryo) with criteria regarding tumor number, size, location, and general liver health often dictating the ideal approach. Locoregional therapy may be performed by laparoscopic, percutaneous, or open approach. Arterially directed therapy involves the selective catheter-based infusion of material that causes embolization of tumors using bland, chemotherapy-impregnated, or radioactive products.

EBRT is suitable for certain cases of HCC not amenable to other measures, and can be delivered using one of several available highly-conformal techniques such as 3DCRT, IMRT and SBRT. Proton Beam Radiation Therapy (PBT) generally is not medically necessary but may be considered in unique clinical settings. (See Proton Beam Radiation Therapy guideline) For each technique, there must be sufficient uninvolved liver such that the technique is capable of respecting the tolerance of normal liver tissue. While the intent of aggressive locoregional therapy is local control, EBRT may also play a role of palliation of symptoms in the liver, or distantly in cases of metastatic disease.

Combinations of several locoregional therapies may be required. Locoregional management may serve as a bridge to liver transplant.

For the many cases of HCC that are advanced at the time of presentation and not amenable to locoregional therapies with intent to cure, systemic therapy has been employed. Systemic therapies include cytotoxic chemotherapy drugs and the

multikinase angiogenesis inhibitor sorafenib. These are most commonly utilized in Child-Pugh class A patients, where data demonstrating a benefit in overall survival and better tolerance have been reported.

II. Intrahepatic Bile Duct Cancer (Cholangiocarcinoma)

The junction of the right and left hepatic ducts serves as the dividing location. Cholangiocarcinomas that occur on the hepatic side of the junction of the right and left hepatic ducts within the hepatic parenchyma are also known as intrahepatic bile duct cancers, or "peripheral cholangiocarcinomas". Early stage cancers in this location are less likely to present with biliary obstruction than their extrahepatic counterparts. Symptoms may be nonspecific, and detection may be incidental. They are typically adenocarcinomas. Surgical resection has the highest potential for cure, though surgery is often not possible due to local extent of disease or metastases.

The role of radiation therapy is not firmly established, but is included in guidelines as an option for adjuvant management in the post-resection R1 and R2 situations, and/or when nodes are positive, for definitive management of unresectable tumors, and for palliation. Numerous other methods of locoregional treatment, such as radiofrequency ablation, transarterial chemoembolization and photodynamic therapy are available. The use of intraluminal brachytherapy (low dose rate [LDR] or high dose rate [HDR]) has been described and may be useful in unique situations.

The selection of radiation technique and the use of concurrent chemotherapy are best made in the context of a multidisciplinary approach. When radiation therapy is used, the preservation of normal liver function and respect for constraints of nearby other normal organs must be maintained. When SBRT has been employed for larger lesions, doses ≥ 80.5 Gy biologically equivalent dose (BED) have been found to be effective. When SBRT type technique is used for more than 5 fractions, it is to be reported as 3D or IMRT.

III. Extrahepatic Bile Duct Cancer (Cholangiocarcinoma)

The junction of the right and left hepatic ducts serves as the dividing location of intra- and extrahepatic bile duct cancers. Those extrahepatic cholangiocarcinomas that arise near the right and left hepatic duct junction are known as hilar or Klatskin tumors. Those more distal may occur anywhere along the common bile duct down to near the ampulla of Vater. They are typically adenocarcinomas, and are more likely to present with bile duct obstruction than their intrahepatic counterpart. Surgical resection is the only potentially curative treatment.

As the incidence is low, there is no firmly established role of radiation therapy, though its use is included in guidelines of management in postoperative cases of R0, R1, R2 margins and/or positive nodes. When radiation therapy is used, the preservation of normal liver function and respect for constraints of nearby other normal organs must be maintained, especially the small bowel, stomach, and kidneys.

The selection of radiation technique and the use of concurrent chemotherapy are best

made in the context of a multidisciplinary approach. Because of the proximity to hollow viscus structures, daily doses in excess of 2.2 Gy are avoided.

IV. Gallbladder Cancer

Gallbladder cancers are the most common of the biliary tract cancers, tend to be very aggressive, and most commonly are adenocarcinomas. They tend to invade locally and cause both nodal and distant metastases. It is not unusual for gallbladder cancer to be diagnosed at the time of cholecystectomy for what was preoperatively thought to be cholecystitis. Complete resection provides the only realistic chance for cure, the likelihood of which decreases as the extent of surgery needs to increase to achieve clear margins.

The use of adjuvant radiation therapy after resection appears to be most beneficial in patients with T2 and higher primary tumor status, or if nodes are positive, and is most commonly given concurrent with capecitabine or gemcitabine. T1a and T1b, N0 cases have not been shown to benefit from adjuvant radiation, which may be omitted. Because of the proximity to hollow viscus structures, daily doses in excess of 2.2 Gy are avoided.

Radiation therapy with fluoropyrimidine-based chemotherapy is listed in guidelines as an option for patients with unresectable gallbladder cancer.

References:

1. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol. 2013 Oct; 64(4):639-653. Accessed June 24, 2016. [http://www.europeanurology.com/article/S0302-2838\(13\)00601-5/fulltext/eau-guidelines-on-non-muscle-invasive-urothelial-carcinoma-of-the-bladder-update-2013](http://www.europeanurology.com/article/S0302-2838(13)00601-5/fulltext/eau-guidelines-on-non-muscle-invasive-urothelial-carcinoma-of-the-bladder-update-2013)
2. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. Accessed June 24, 2016. <http://jco.ascopubs.org/content/33/24/2617.abstract>
3. Carr, BI (editor). New perspectives in hepatocellular cancer. Seminars in Oncology. 2012 Aug; 39(4):p367-522, e9-e22. Accessed June 24, 2016. [http://www.seminoncol.org/article/S0093-7754\(12\)00119-4/fulltext](http://www.seminoncol.org/article/S0093-7754(12)00119-4/fulltext)
4. Mazloom A, Hezel AF, Katz AW. Stereotactic body radiation therapy as a bridge to transplantation and for recurrent disease in transplanted liver of a patient with hepatocellular carcinoma. Case Rep Oncol. 2014 Jan-Apr; 7(1):18-22. Accessed June 24, 2016. <https://www.karger.com/Article/FullText/357801>
5. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Hepatobiliary Cancers. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Hepatobiliary Cancers 1.2016. ©2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
6. O'Connor JK, Trotter, J, Davis GL, et al. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl. 2012 Aug; 18(8):949-954. Accessed June 24, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/lt.23439/full>
7. Radiation Therapy Oncology Group Protocol 1112: Randomized Phase III Study of Sorafenib versus Stereotactic Body radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma. Accessed June 24, 2016. <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1112>
8. Tao, R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol. 2016 Jan 20; 34(3):219-226. Accessed June 24, 2016. http://jco.ascopubs.org/content/34/3/219.abstract?ijkey=f863a408a8afd9426722a1818988392f84385b4b&keytyp e2=tf_ipsecsha
9. Wahl DR, Stenmark MH, Tao Y. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol. 2016 Feb 10; 34(5):42-459. Accessed June 24, 2016. <http://jco.ascopubs.org/content/34/5/452.abstract>
10. Wang SJ, Fuller CD, Jong-Sung K, et al. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. J Clin Oncol. 2008 May 1; 26(13):2112-2117. Accessed June 24, 2016. <http://jco.ascopubs.org/content/26/13/2112.full>
11. Want SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. J Clin Oncol. 2011 Dec 10; 29(35):4627-4632. Accessed June 24, 2016. <http://jco.ascopubs.org/content/29/35/4627.full>
12. Welling TH, Feng M, Wan S, et al. Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. Liver Transpl. 2014 Jan; 20(1):81-88. Accessed June 24, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/lt.23757/full>

Radiation Treatment of Hepatobiliary Cancer (primary liver, intrahepatic bile duct, extrahepatic bile duct, gallbladder)

[Return to Table of Contents](#)

Radiation Treatment of Kidney and Adrenal Cancer

POLICY

External beam photon radiation therapy is medically necessary for the following:

- I. In the adjuvant setting for a high risk individual with adrenal cancer**
- II. Palliation**
- III. Radiation is not medically necessary in the definitive or adjuvant treatment of renal cancer**

Fractionation

- I. In the adjuvant setting for adrenal cancer, up to 30 fractions is medically necessary**
- II. In the palliative setting, up to 20 fractions is medically necessary**

Techniques

- I. 3D conformal technique is medically necessary in the adjuvant or palliative setting**
- II. In the adjuvant setting, intensity modulated radiation therapy (IMRT) may be indicated when dose to critical organs is of concern. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the acceptable normal tissue constraints using standard radiation therapy criteria from the Radiation Therapy Oncology Group (RTOG) or National Comprehensive Cancer Network (NCCN).**

Key Clinical Points

Standard of care for localized renal cell cancer is surgical resection. A partial nephrectomy can be used in the treatment of early stage renal cell cancer while an

open radical nephrectomy is used with locally advanced disease. There is no benefit with radiotherapy in the adjuvant or neo-adjuvant setting in the treatment of renal cell cancer (Escudier, 2014). In an individual with unresectable disease or recurrent disease, radiation can be utilized to improve local control (Mourad, 2014). There are preliminary reports examining the use of stereotactic body radiotherapy (SBRT) in the treatment of early stage inoperable renal cancer. However, there are no prospective studies examining this issue, and current standard of care for patients with inoperable localized renal cell cancer include radio frequency or cryo-ablative therapies (Mourad, 2014).

Adrenal cancers include adrenocortical carcinoma and malignant pheochromocytoma. Surgical resection of adrenal tumors remains the standard of care. For nonmetastatic adrenocortical cancer, adjuvant radiation can be considered for an individual with high risk of recurrence including one with positive margins, ruptured capsule, large size (> 7 cm), or high grade (Sabolch, 2015). Adjuvant mitotane can also be considered in this setting (Terzolo, 2007).

References:

1. Escudier B, Eisen T, Porta C, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct; 23(suppl 7):vii65-vii71. Accessed June 24, 2016. http://annonc.oxfordjournals.org/content/23/suppl_7/vii65.full
2. Mourad WF, Dutcher J, Ennis RD. State-of-the-art management of renal cell carcinoma. Am J Clin Oncol. 2014 Oct; 37(5):498-505. Accessed June 24, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2014/10000/State_of_the_Art_Management_of_Renal_Cell.14.aspx
3. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2016. Bladder Cancer. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Bladder Cancer 3.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
4. Sabolch A, Else T, Griffith KA, et al. Adjuvant radiation therapy improves local control after surgical resection in patients with localized adrenocortical carcinoma. Int J Radiat Oncol Biol Phys. 2015 Jun 1; 92(2):242-259. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(15\)00026-7/abstract](http://www.redjournal.org/article/S0360-3016(15)00026-7/abstract)
5. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. NEJM. 2007 Jun 7; 356(23):2372-2380. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa063360#t=abstract>

Radiation Treatment of Kidney and Adrenal Cancer

[Return to Table of Contents](#)

Radiation Treatment of Lung Cancer

I. Non Small Cell Lung Cancer (NSCLC) POLICY

- A. Definitive external beam photon radiation therapy is medically necessary for an individual with either:
 - 1. Stage III
 - 2. Stage I or Stage II
 - a. Surgery refused or
 - b. Medically inoperable
- B. Preoperative (neoadjuvant) external beam photon radiation therapy is medically necessary for an individual with either:
 - 1. N2 disease clinically or by mediastinoscopy with planned lobectomy
 - 2. T3 or T4 primary lesion
 - 3. Superior sulcus tumors
- C. Postoperative external beam photon radiation therapy is medically necessary for an individual with one or more of the following:
 - 1. Any mediastinal nodes positive for tumor
 - 2. No surgical sampling of mediastinal nodes
 - 3. Margins of the resected specimen are positive or close
- D. Palliative external beam photon radiation therapy is medically necessary in an individual with:
 - 1. Stage IV disease and at least one of the following symptoms:
 - a. Airway obstruction
 - b. Hemoptysis
 - c. Pain
 - d. Cough
 - e. Endobronchial obstruction
 - f. Superior vena cava obstruction or syndrome

II. Small Cell Lung Cancer (SCLC) POLICY

- A. Definitive external beam photon radiation therapy is medically necessary for an individual with:
 - 1. Limited stage disease, defined as disease which is limited to the thorax and that can be entirely encompassed in a radiation field
 - 2. Extensive stage disease in which all systemic disease (metastases) has complete or near-complete resolution with chemotherapy
- B. Prophylactic cranial irradiation (PCI) is medically necessary in a responding individual (local disease and extensive disease) with good performance status.
- C. Palliative radiation therapy is medically necessary for an individual with:
 - 1. Extensive stage SCLC

2. Airway obstruction
3. Hemoptysis
4. Pain
5. Cough
6. Endobronchial obstruction
7. Superior vena cava obstruction or syndrome

III. Technique

- A. Three-dimensional Conformal Radiation Therapy (3DCRT) is medically necessary
- B. Intensity-Modulated Radiation Therapy (IMRT) is not medically necessary
 1. Exceptions to the IMRT rule will be made on a case-by-case basis, especially in situations:
 - a. Where there is disease in the bilateral mediastinum or bilateral hilar regions
 - b. Where there is disease in the para-spinal region
 - c. For superior sulcus tumors
 - d. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN)
- C. Stereotactic Body Radiation Therapy (SBRT) (with 3D or IMRT planning) is medically necessary for an individual with medically inoperable Stage I or II NCSLC
- D. In the palliative treatment of lung cancer, the use of 3DCRT or radiation planned using a complex isodose technique is medically necessary
- E. Image-Guided Radiation Therapy (IGRT). Please refer to separate IGRT policy

Key Clinical Points

I. Treatment of Stage III non-small cell lung carcinoma

Approximately one-third of individuals with non-small cell lung carcinoma present with locally advanced disease that is considered unresectable due to clinically apparent involvement of mediastinal lymph nodes or T4 disease. Until the mid-1990s such individuals were treated with radiation therapy alone. RTOG 73-01 (Perez et al., 1987) was designed to assess the optimal dose of radiotherapy for patients with locally advanced disease, including those with poor performance status and/or significant weight loss. Local control and 2-year survival were better with 60 Gy in 6 weeks compared with lower doses. The seminal study of Dillman et al. from the Cancer and Leukemia Group B (CALGB) was published in 1996 and was the first study to demonstrate a survival benefit with the use of induction chemotherapy followed by external beam photon radiation therapy for patients with good performance status and weight loss of less than 5%. Cisplatin-

vinblastine for two cycles followed by thoracic external beam photon radiation therapy to a dose of 60 Gy in 6 weeks was compared with the same external beam photon radiation therapy alone in 155 randomized patients. Induction chemotherapy improved median survival, and 3- and 7-year overall survival (OS). These results were confirmed in RTOG 88-08 (Sause et al., 2000), a study of 458 patients with Stage III NSCLC randomized to the positive arm of the CALGB trial (induction vinblastine-cisplatin followed by external beam photon radiation therapy) versus hyperfractionated external beam photon radiation therapy to 69.6 Gy versus standard fractionation external beam photon radiation therapy of 60 Gy in 6 weeks. These and other trials established the use of induction chemotherapy followed by standard fractionation of external beam photon radiation therapy as superior to external beam photon radiation therapy alone, and such therapy became the standard of care in the early 1990's for inoperable patients with Stage III disease and good performance status. Use of concurrent chemo-radiotherapy was also evaluated. RTOG 9410 is the largest trial assessing the value of concurrent versus sequential chemo-radiotherapy. In this trial, 610 patients with Stage III disease were randomized to three arms: the positive arm of the CALGB trial reported by Dillman et al. (induction cisplatin-vinblastine for two cycles followed by external beam photon radiation therapy to 63 Gy) versus the same chemotherapy given concurrently versus a third arm of oral etoposide and weekly cisplatin given concurrently with 69.6 Gy hyperfractionated external beam photon radiation therapy (HART). Local control was better with concurrent HART, however, the best survival was seen with concurrent cisplatin-vinblastine and standard fractionated external beam photon radiation therapy. The use of concurrent external beam photon radiation therapy was associated with a significantly increased acute esophagitis as compared to sequential therapy, and concurrent HART was associated with even more frequent severe esophagitis.

The use of 3DCRT techniques, which are now standard, has made possible a decrease in normal tissues receiving high doses. 3DCRT techniques allow the development of complex multiple field radiotherapy plans that decrease the amount of normal tissue exposed to high doses. Better delineation of the target volume can be achieved with F-fluorodeoxyglucose-Positive Emission Tomography (FDG-PET). If FDG-PET has not been done for prior staging purposes, use of FDG-PET for staging and radiation planning is appropriate. Incorporating the information from PET/Computed Tomography (CT) can change the target volume in a significant proportion of patients as compared with CT alone. The radiotherapy target volume can decrease (due to the ability of PET to differentiate atelectatic lung from tumor) or increase (due to FDG uptake at

mediastinal lymph nodes that were not positive by CT size criteria alone). In the increasingly common situation today when elective nodal irradiation is avoided, more accurate definition of involved sites of disease with PET decreases the likelihood that tumor-bearing nodes will not be encompassed in the target volume.

The use of techniques that account for mobility of the tumor with respiration takes on greater importance when 3DCRT treatment planning is utilized. By accounting for tumor motion on an individualized basis, smaller margins can be utilized thereby decreasing exposure to normal lung tissue. One approach to this problem is the use of respiratory gating or breath-hold technique. Gating the treatment with the respiratory cycle or treating with breath hold can help to reduce the planning target volume or avoid marginal miss. Another method incorporates so-called four-dimensional (4D) imaging. Use of rapid spiral CT scanning and acquisition of multiple images during breathing allows for better definition of the target volume, so that changes in the shape and location of the tumor during the breathing cycle can be taken into account in radiation delivery. With this technique temporal changes in tumor position and anatomy are incorporated into the treatment planning process. External beam photon radiation therapy delivery that adjusts in real-time to changes in tumor and normal anatomy holds further promise to decrease the necessary tumor margin and exposure to uninvolved lung.

Use of IMRT is also being studied. With this technique, the intensity of the beam is spatially varied in real time and delivery is accomplished using multiple fields at different angles or with rotational arc therapy. The primary disadvantage is that a greater volume of normal tissue gets low doses. Since the normal lung has low tolerance to even small doses, this technique is not appropriate in the majority of cases of locally advanced non-small cell carcinoma. IMRT may offer advantages in the treatment of an individual with bilateral mediastinal nodal involvement or in the treatment of an individual with definitive radiotherapy (without surgery) for superior sulcus tumors or para-spinal tumors. Recent attempts (Harris et al., 2014) to support the use of IMRT concluded that IMRT is “as effective as” but is “not better than” 3D. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

Dose and fractionation regimens are evolving in the definitive treatment of locally advanced NSCLC, but no randomized trial has shown a benefit to doses higher than 60 Gy. The results of RTOG 0617, in which patients with stage IIIA or IIIB

non-small-cell-lung cancer were randomized to standard-dose external beam chemoradiation (60 Gy) or high-dose chemoradiation (74 Gy) revealed that OS was 28.7 months in the standard-dose population vs. 20.3 months in those receiving high-dose radiation therapy. There was a trend towards increased treatment-related deaths in the high-dose population (8 vs. 3), and severe esophagitis was significantly increased in the high dose population 21% (43/207) vs. the standard-dose population (7% (16/217)). The authors concluded that high-dose radiation for individuals with stage IIIA or stage IIIB non-small-cell-lung cancer was not better and might actually be harmful.

II. Preoperative and postoperative therapy

An individual with Stage IIIA disease on the basis of ipsilateral mediastinal nodal involvement has traditionally been considered unresectable, as outcome with surgery has generally been poor when there has been clinically apparent mediastinal involvement, particularly when multiple station N2 disease is present. However, with improvements in modern staging and more generalized use of multimodality therapy, there may be subsets of individuals with clinical N2 disease who might benefit from surgery. Attempts have been made to “downstage” individuals with preoperative chemoradiotherapy. The dose of radiation in the preoperative setting is generally 45 Gy in 25 fractions of external beam photon radiation therapy. 3DCRT techniques may be helpful, even at these lower doses, to reduce the dose to normal lung. Similarly, respiratory gating techniques may also be helpful, particularly for lower lobe primary tumors.

Postoperative radiotherapy (PORT) with external beam photon radiation therapy improves locoregional control as demonstrated by an early trial conducted by the Lung Cancer Study Group; however, this did not translate into an overall survival benefit. Enthusiasm for postoperative external beam photon radiation therapy diminished after the publication of the PORT meta-analysis, which included 2,128 patients with stage I to III non-small cell lung carcinoma enrolled on 9 randomized trials from 1966 to 1994. In the entire group of patients, there was a 7% absolute reduction in survival for patients who received external beam photon radiation therapy. The trials included in the meta-analysis have a variety of serious pitfalls, including the inclusion of ineligible patients, inadequate staging work-up, inclusion of node negative patients, and techniques that today would be expected to produce deleterious outcomes. Most of the trials used higher total dose (> 50 Gy) or high dose per fraction (e.g. 2.5 Gy per fraction). In many of the trials, opposed off-cord lateral fields were used, which exposes a significant volume of normal lung to intolerable radiation volume, dose per fraction and total doses. Additionally, systemic therapy was not used, and improved local control is

more likely to translate into a survival benefit if effective systemic therapy is available. An individual with N2 disease is likely to achieve a significant local control benefit from postoperative external beam photon radiation therapy, and with modern techniques the individual may accrue a survival benefit. An American Intergroup trial and a European Organisation for Research and Treatment of Cancer (EORTC) trial are presently underway to re-evaluate the role of external beam photon radiation therapy for patients with N2 disease.

III. PCI for NSCLC

Twenty to 50% of individuals with clinical Stage III non-small cell lung carcinoma will develop brain metastases during the course of the disease and in individuals who have responded to prior multimodality therapy; a significant proportion experience relapse in the brain as the first or isolated site of failure. Early trials of PCI (Russell et al., 1991) showed greater than 50% relative risk reduction in the incidence of brain metastases with PCI, however, this did not translate into a survival benefit in any of the trials. Concerns of neurocognitive morbidity from PCI are largely related to the early experience with the use of PCI for small cell carcinoma, which is associated with a significant proportion of patients having neurocognitive dysfunction prior to radiation. More modern trials (Gregor et al., 1997) that employ lower dose per fraction and avoid concurrent chemotherapy have not found any impact of PCI on neurocognitive function. The RTOG conducted a study (Gore et al., 2009) of patients with Stage III non-small cell carcinoma who did not have progressive disease to evaluate the potential benefit of PCI. Patients were randomized to 30 Gy in 15 fractions versus observation after definitive local therapy. The primary endpoint was survival, and secondary endpoints were the rate of CNS metastasis, quality of life, and neurocognitive effects. The trial was negative for survival, but decreased local failure. Results of effects on neuropsychological function and quality of life are not yet available. Outside of a clinical trial, PCI for NSCLC is not appropriate.

IV. Early Stage NSCLC

External beam photon radiation therapy is appropriate for curative intent treatment of an individual with Stage I and II NSCLC who is medically inoperable. An individual with hilar nodal involvement should be treated with standard fractionation (e.g. 60 Gy in 6 weeks) and 3DCRT techniques are preferred. For node negative Stage IA and IB non-small cell lung cancer in an individual who is medically inoperable or who refuse surgery, SBRT is an appropriate option. SBRT is a technique that uses multiple intersecting beams of radiation to deliver a very high radiation dose to a precisely defined area, while minimizing radiation to surrounding areas. Precise immobilization techniques are required to deliver SBRT. Treatment is generally delivered in 3 to 5 fractions. A linear accelerator

can be used to deliver SBRT. The CyberKnife™ is a robotic version that can be used to treat any part of the body. SBRT is an appropriate technique for patients with node negative peripheral lung cancers less than 5 cm in maximum dimension. Patients with central tumors can experience excessive toxicity when higher fraction sizes and fewer fractions (e.g. 3) are utilized. Use of mediastinoscopy is appropriate for staging of clinical stage T2N0 patients prior to definitive SBRT. IGRT may also improve the therapeutic ratio. Accurate set-up of the individual with the use of radiopaque markers placed in the tumor or use of daily CT scan imaging can essentially eliminate any additional margin that might otherwise be needed for daily individual set-up variability.

V. Palliative treatment

An individual with localized disease but with significant co-morbidities, poor performance status, or significant weight loss may be appropriate for external beam photon radiation therapy as definitive treatment with a hypofractionated schedule, use of split-course treatment, or use of more conventional fractionation alone (e.g. 60 Gy in 6 weeks). In addition, external beam photon radiation therapy is effective in the palliation of symptoms due to local tumor, such as hemoptysis, cough, or imminent endobronchial obstruction. Approximately 40% of individuals with NSCLC present with Stage IV disease. One multi-institutional phase III randomized study (Simpson et al., 1985) examined a variety of fractionation schemes including 40 Gy split course, 30 Gy in 10 fractions, and 40 Gy in 20 fractions. There was no difference between arms, and 60% of patients achieved symptom relief. Bezjak et al. (2002) reported a phase III trial of 231 patients randomized to 20 Gy in 5 fractions versus 10 Gy in 1 fraction. Similar palliation was seen in both arms, although patients in the 20 Gy arm had longer median survival. The Medical Research Council compared 17 Gy in 2 fractions (one per week) with 30 Gy in 10 fractions over 2 weeks. There was no difference in survival or palliation of symptoms. Hemoptysis was relieved in 86% of patients, cough in approximately 60% of patients, and pain in approximately 50% of patients. Therefore, data supports the use of short hypofractionated regimens, and there is generally no general role for more protracted schemes beyond 10 or 15 fractions. Endobronchial (EBB) radiation has also been found in retrospective studies to be effective in the palliation of symptoms due to intraluminal tumor, including obstruction, dyspnea, and cough. The procedure requires bronchoscopic guidance of the brachytherapy catheter. There is no proven role for more than 3 applications. EBB will be considered medically necessary after a failed course of external beam photon radiation therapy. American Society for Radiation Oncology (ASTRO) has published an evidence-based guideline for palliative lung cancer that reviews the various dose and

fractionation regimens and the role of EBB. The ASTRO guideline specifically states that there is no benefit to adding concurrent chemotherapy to external beam photon radiation therapy in the palliative setting.

VI. Small Cell Carcinoma

There is little role for surgery in the management of an individual with SCLC. In the few cases of clinical stage T1-T2N0 disease, surgery establishes the diagnosis and effectively removes the primary tumor. Such individuals should also be staged with mediastinoscopy, and if mediastinal lymph nodes are negative, chemotherapy alone can be entertained. External beam photon radiation therapy improves survival of an individual with limited stage SCLC. Concurrent chemoradiotherapy leads to improved survival as compared with sequential therapy. Standard external beam photon radiation therapy fractionation consists of either 45 Gy given at 1.5 Gy bid (hyper-fractionation/accelerated) or at 1.8 to 2 Gy per day to 54 to 70 Gy. Local thoracic external beam photon radiation therapy for individuals with extensive stage disease is not an established approach, however, in selected individuals it may be considered, such as those with clinically apparent disease only at the primary site and complete response elsewhere.

More than 50% of individuals with SCLC will experience brain metastases during the course of disease. Prophylactic cranial radiotherapy reduces this risk by approximately 50% in relative terms, and improves overall survival in an individual with chemo-responsive limited stage SCLC and extensive stage SCLC. Concerns regarding neurocognitive defects are obviated by avoiding high dose per fraction treatment and concurrent chemotherapy. PCI is not appropriate for an individual with severe co-morbidities, one who is bedridden most of the time, or one with severely impaired cognitive functioning. The recommended doses/fractionation for PCI are 25 Gy in 10 daily fractions, 30 Gy in 10 to 15 daily fractions, or 24 Gy in 8 daily fractions. In selected individuals with extensive disease, a shorter course, such as 20 Gy in 5 fractions may be appropriate. Higher doses have not proved beneficial and are associated with more neurocognitive deficits.

References:

1. Aupérin A, Arriagada R, Pignon JP, et al. for the Prophylactic Cranial Irradiation Overview Collaborative Group. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med*. 1999 Aug 12; 341(7):476-484. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199908123410703#t=abstract>
2. Bezjak A, Dixon P, Brundage M, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). *Int J Radiat Oncol Biol Phys*. 2002 Nov 1; 54(3):719-728. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(02\)02989-9/abstract](http://www.redjournal.org/article/S0360-3016(02)02989-9/abstract)
3. Bogart JA, Herndon II JE, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys*. 2004 Jun 1; 59(2): 460-468. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)02217-X/abstract](http://www.redjournal.org/article/S0360-3016(03)02217-X/abstract)
4. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell-lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol*. 2015 Feb; 16(2):187-199. Accessed June 24, 2016. Accessed June 24, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(14\)71207-0/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)71207-0/fulltext)
5. Bradley JD, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer. *J Clin Oncol* 2013 May 20; 31(15) (suppl; abstr 7501). Accessed June 24, 2016. http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7501?sid=31c5f710-9f21-469f-8051-decc7138d440
6. Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *J Clin Oncol*. 2011 Jun 10; 29(17):2305-2311. Accessed June 24, 2016. <http://jco.ascopubs.org/content/29/17/2305.full>
7. Curran WJ, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs. concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol* 2003; 22:621a. Abstract 2499.
8. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996 Sep 4; 88(17):1210–1215. Accessed June 24, 2016. <http://jnci.oxfordjournals.org/content/88/17/1210.full.pdf+html>
9. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small cell lung cancer. *J Clin Oncol*. 2004 Dec 1; 22(23):4837-4845. Accessed June 24, 2016. <http://jco.ascopubs.org/content/22/23/4837.abstract> Erratum in *J Clin Oncol*. 2005 Jan 1; 23(1):248. Accessed June 24, 2016. <http://jco.ascopubs.org/content/23/1/248.full>
10. Gore EM, Bae K, Wong S, et al. A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer: Initial analysis of Radiation Therapy Oncology Group 0214. *J Clin Oncol*. 27(15); 2009 May 20 (suppl; abstr 7506). Accessed June 24, 2016. <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/7506?sid=f92f9325-5a21-462a-b557-b1f6aab15643>
11. Gregor A, Cull A, Stephens RJ, et al. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. *Eur J Cancer*. 1997 Oct; 33(11):1752–1758. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0959804997001354>
12. Harris JP, Murphy JD, Hanlon AL, et al. A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2014 Mar 15; 88(4):872-884. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)03666-3/abstract](http://www.redjournal.org/article/S0360-3016(13)03666-3/abstract)
13. Lagerwaard FJ, Haasbeek CJA, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2008 Mar 1; 70(3): 685-692. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)04468-9/fulltext](http://www.redjournal.org/article/S0360-3016(07)04468-9/fulltext)
14. Lavrenkov K, Partridge M, Cook G, et al. Positron emission tomography for target volume definition in the treatment of non-small cell lung cancer. *Radiother Oncol*. 2005 Oct; 77(1):1–4. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814005004251>
15. Le Péchoux C, Hatton M, Halton M, Kobierska A, et al. Randomized trial of standard dose to a higher dose prophylactic cranial irradiation (PCI) in limited-stage small cell cancer (SCLC) complete responders (CR): primary endpoint analysis (PCI99-01, IFCT 99-01, EORTC 22003-08004, RTOG 0212) . *J Clin Oncol*. 26(15S); 2008 May 20 (suppl; abstr LBA7514). Accessed June 24, 2016. http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/LBA7514?sid=2444c12a-5422-4acb-8273-e4bb27cb0839

16. Le Péchoux C, Laplanche A, Faivre-Finn C, et al. on behalf of the Prophylactic Cranial Irradiation (PCI) Collaborative Group. Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). *Ann Oncol*. 2011 May; 22(5):1154-1163. Accessed June 24, 2016. <http://annonc.oxfordjournals.org/content/22/5/1154.full>
17. Mamon HJ, Yeap BY, Jänne, Pasi A, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol*. 2005 Mar 1; 23(7):1530–1537. Accessed June 24, 2016. <http://jco.ascopubs.org/content/23/7/1530.full>
18. National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2016. Non-Small Cell Lung Cancer. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Non-Small Cell Lung Cancer 4.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
19. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Small Cell Lung Cancer. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/scl.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Small Cell Lung Cancer 1.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
20. Nestle U, Kremp S, Grosu AL. Practical integration of [18F]-FDG-PET and PET-CT in the planning of radiotherapy for non-small cell lung cancer (NSCLC): the technical basis, ICRU-target volumes, problems, perspectives. *Radiother Oncol*. 2006 Nov; 81(2):209–225. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814006004889>
21. Perez CA, Pajak TF, Rubin P, et al. Report by the Radiation Therapy Oncology Group. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. *Cancer* 1987 Jun 1; 59(11):1874–1881. Accessed June 24, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(19870601\)59:11%3C1874::AID-CNCR2820591106%3E3.0.CO;2-Z/pdf](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19870601)59:11%3C1874::AID-CNCR2820591106%3E3.0.CO;2-Z/pdf)
22. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992 Dec 3; 327(23):1618-1624. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199212033272302>
23. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet*. 1998 Jul 25; 352(9124):257-263. Accessed June 24, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(98\)06341-7/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)06341-7/fulltext)
24. Report to the Medical Research Council by its Lung Cancer Working Party. Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomised trial of palliative radiotherapy with two fractions or ten fractions. *Br J Cancer* 1991 Feb; 63(2):265-270. Accessed June 24, 2016. <http://www.nature.com/bjc/journal/v63/n2/pdf/bjc199162a.pdf>
25. Rodrigues G, Videtic GMM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol*. 2011 Apr-Jun; 1(2):60-71. Accessed June 24, 2016. [http://www.practicalradonc.org/article/S1879-8500\(11\)00091-9/fulltext](http://www.practicalradonc.org/article/S1879-8500(11)00091-9/fulltext)
26. Russell AH, Pajak TE, Selim HM, et al. Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. 1991 Aug; 21(3):637–643. Accessed June 24, 2016. [http://www.redjournal.org/article/0360-3016\(91\)90681-S/abstract](http://www.redjournal.org/article/0360-3016(91)90681-S/abstract)
27. Sause W, Kolesar P, Taylor IV S, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000 Feb; 117(2):358–364. Accessed June 24, 2016. <http://journal.publications.chestnet.org/article.aspx?articleID=1078606>
28. Simpson JR, Francis ME, Perez-Tamayo R, et al. Palliative radiotherapy for inoperable carcinoma of the lung: final report of a RTOG multi-institutional trial. *Int J Radiat Oncol Biol Phys*. 1985 Apr; 11(4): 751-758. Accessed June 24, 2016. [http://www.redjournal.org/article/0360-3016\(85\)90307-4/abstract](http://www.redjournal.org/article/0360-3016(85)90307-4/abstract)
29. Slotman B, Faivre-Finn C, Kramer G, et al. for the EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007 Aug 16; 357(7):664-672. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa071780>
30. The Lung Cancer Study Group. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med*. 1986 Nov 27; 315(22):1377-1381. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM198611273152202>

31. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006 Oct 20; 24(30): 4833-4839. Accessed June 24, 2016. <http://jco.ascopubs.org/content/24/30/4833.full>
32. Turrisi AT, Kim K, Blum R, et al. Twice daily compared to once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999 Jan 28; 340(4): 265-271. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199901283400403>
33. Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment related pneumonitis (TRP) in patients with non-small cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys. 2006 Dec 1; 66(5):1399-1407. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)02575-2/abstract](http://www.redjournal.org/article/S0360-3016(06)02575-2/abstract)

Radiation Treatment of Lung Cancer

[Return to Table of Contents](#)

Radiation Treatment of Non-malignant Disease

POLICY

Non-malignant disorders for which radiation therapy is medically necessary can be grouped into the following categories:

I. Central nervous system (CNS) benign tumors

- A. Acoustic neuroma (vestibular schwannoma)
- B. Arteriovenous malformation (AVM)
- C. Cavernous malformation
- D. Chordoma
- E. Craniopharyngioma
- F. Langerhans cell histiocytosis
- G. Meningioma
- H. Pituitary adenoma
- I. Other benign CNS tumor

II. CNS functional disorders

- A. Epilepsy
- B. Parkinson's disease
- C. Trigeminal neuralgia

III. Skin disorders

- A. Keloid scar
- B. Psoriasis
- C. Other benign skin disorder

IV. Non-skin, non-CNS disorders

- A. Bursitis
- B. Carotid body tumor (see chemodectoma)
- C. Castleman Disease (giant lymph node hyperplasia)
- D. Chemodectoma (aortic, carotid, glomus jugulare)
- E. Choroidal hemangioma
- F. Desmoid tumor
- G. Dupuytren's contracture
- H. Glomus jugulare
- I. Glomus tympanicum
- J. Glomus vagale
- K. Gorham-Stout syndrome (disappearing bone syndrome)
- L. Graves ophthalmopathy
- M. Gynecomastia
- N. Hypertrophic ossification (before or after surgery)
- O. Langerhans cell histiocytosis

- P. Macular degeneration (wet)
- Q. Orbital myositis
- R. Orbital pseudotumor
- S. Osteoarthritis
- T. Paraganglioma
- U. Peyronie disease
- V. Pigmented villonodular synovitis
- W. Plantar fasciitis
- X. Pterygium
- Y. Rosai-Dorfman disease
- Z. Rotator cuff syndrome
- AA. Splenomegaly
- BB. Tendonitis
- CC. Tennis elbow
- DD. Thymoma
- EE. Vertebral hemangioma
- FF. Other non-skin, non-CNS benign condition

This policy summarizes those non-malignant conditions for which there is support of the medical necessity of radiation treatments, either by scientifically valid study or by consensus, in the American and world literature. **The necessity of its use assumes that competing modalities have been exhausted, are less effective, are of greater risk, or are not available.** Those disorders for which there is either sufficient evidence-based proof of efficacy or there is sufficient consensus in the literature may be considered for radiation treatment.

Key Clinical Points

In the evolution of the use of radiation treatment of disease, both malignant and non-malignant disorders have been subjected to ionizing radiation. Historically, the empiric use of radiation therapy progressed quickly in situations in which it was found to be effective, often without the formal proof of efficacy that the modern era requires. Its use in the treatment of malignancies progressed rapidly because of several factors, not the least of which was the unavailability of other effective measures and the often fatal consequence of an untreated cancer. Only upon the development of competing medical and surgical alternatives to treat malignancies have the merits of radiation therapy been subjected to analysis that is more stringent and its role more evidence based.

In contrast, the use of ionizing radiation in the treatment of many non-malignant conditions is largely on a legacy basis without the rigor of evidence-based study. An analysis of the use of ionizing radiation for the treatment of benign diseases was published in 1977 by the National Academy of Sciences (NAS) at the request of the Bureau of Radiological Health (BRH) of the Food and Drug Administration (FDA). The

next major compendium of similar information, authored by Order and Donaldson, was published as a textbook, *Radiation Therapy of Benign Diseases: a Clinical Guide* (2003). In recent years, there has been a mild renaissance such that the topic is now included in reputable textbooks of radiation oncology, such as those edited by Gunderson and Tepper and those edited by Halperin, Perez, and Brady, with many entities studied using the same rigor as when studying the treatment of malignancies.

Table 1 summarizes disorders for which radiation treatment may be considered and the recommended treatment schedule. Any disorder or treatment schedule not listed will require medical review. Please note that some of these disorders, particularly those involving the CNS, are also listed in the Radiation Treatment of Craniospinal Tumors – Primary Tumors and Neurologic Conditions section of this document.

Table 1

Benign Conditions List	Typical XRT	Typical XRT	Typical XRT
CNS Tumors	Treatment 1	Treatment 2	Treatment 3
Acoustic neuroma (vestibular schwannoma)	SRS $\leq$ 5 Fx	IMRT 30 Fx	
Arteriovenous malformation (AVM)	SRS $\leq$ 5 Fx		
Cavernous malformation	SRS $\leq$ 5 Fx		
Chordoma	3D $\leq$ 34 Fx	IMRT 34 Fx	Protons require medical review
Craniopharyngioma	3D $\leq$ 30 Fx	IMRT 30 Fx	SRS x 5
Langerhans cell histiocytosis	3D $\leq$ 28 Fx		
Meningioma	SRS $\leq$ 5 Fx	IMRT 30 Fx	3D $\leq$ 30 Fx
Pituitary adenoma	3D $\leq$ 30 Fx	IMRT 30 Fx	SRS x 5
Other benign CNS tumor	requires medical review		
CNS functional disorders			
Epilepsy	requires medical review		
Parkinson's disease	requires medical review		
Trigeminal neuralgia	SRS $\leq$ 5 Fx		
Skin disorders			
Keloid scar	electrons $\leq$ 4 Fx	superficial $\leq$ 4 Fx	Complex $\leq$ 4 Fx
Psoriasis	Complex $\leq$ 5 Fx	electrons $\leq$ 5 Fx	superficial $\leq$ 5 Fx

Benign Conditions List	Typical XRT	Typical XRT	Typical XRT
Skin disorders			
Other benign skin disorder	requires medical review		
Non-skin, non-CNS conditions			
Bursitis	Complex <= 5 Fx		
Carotid body tumor (see chemodectoma)	Complex, 3D <= 31 Fx	IMRT 31 Fx	SRS x 5
Castleman disease (giant lymph node hyperplasia)	Complex, 3D <= 25 Fx		
Chemodectoma (aortic, carotid, glomus jugulare)	Complex, 3D <= 31 Fx	IMRT 30 Fx	SRS x 5
Choroidal hemangioma	Complex, 3D <= 10 Fx	LDR plaque	protons require medical review
Desmoid tumor	3D <=28 Fx		
Dupuytren's contracture	Complex <=10 Fx		
Glomus jugulare	Complex, 3D <= 31 Fx	IMRT 31 Fx	SRS x 5
Glomus tympanicum	Complex, 3D <= 31 Fx	IMRT 31 Fx	SRS x 5
Glomus vagale	Complex, 3D <= 31 Fx	IMRT 31 Fx	SRS x 5
Gorham-Stout syndrome (disappearing bone syndrome)	3D <= 25 Fx		
Graves ophthalmopathy	Complex, 3D <= 10 Fx		
Gynecomastia	electrons <= 5 Fx	Orthovoltage <= 5 Fx	
Hypertrophic ossification (before or after surgery)	Complex, 3D single Fx	Complex, 3D 5 Fx	
Langerhans cell histiocytosis	3D <= 28 Fx		
Macular degeneration	SRS <=5 Fx	LDR x 1 per eye	
Orbital myositis	Complex, 3D <= 15 Fx		
Orbital pseudotumor	Complex, 3D <= 10 Fx		
Osteoarthritis	Complex <= 5 Fx		
Paraganglioma	Complex, 3D <=31Fx	IMRT <=31Fx	

Benign Conditions List	Typical XRT	Typical XRT	Typical XRT
Non-skin, non-CNS conditions cont'd			
Peyronie disease	Complex <=5 Fx		
Pigmented villonodular synovitis	Complex, 3D <= 28 Fx		
Plantar fasciitis	Complex <= 8 Fx	Electrons <= 8 Fx	
Pterygium	surface HDR x 3		
Rosai-Dorfman disease	Complex, 3D <= 22 Fx		
Rotator cuff syndrome	Complex <= 5 Fx		
Splenomegaly	Complex, 3D <=10 Fx		
Tendonitis	Complex <= 5 Fx		
Tennis elbow	Complex <= 5 Fx		
Thymoma	Complex, 3D <=30 Fx	IMRT <=30 Fx	
Vertebral hemangioma	Complex, 3D <= 30 Fx	IMRT 30 Fx	
Other non-skin, non-CNS benign condition	requires medical review		

Abbreviations: SRS=stereotactic radiosurgery; Fx = fractions; IMRT = Intensity modified radiation therapy; 3D = three dimensional conformal radiation therapy; LDR = low dose rate brachytherapy; HDR = high dose rate brachytherapy.

References

1. Assembly of Life Sciences (U.S.). Committee to Review the Use of Ionizing Radiation for the Treatment of Benign Diseases. Bureau of Radiological Health. National Academies. 1977.
2. Borok TL, Bray M, Sinclair I, et al. Role of ionizing irradiation for 393 keloids. *Int J Radiat Oncol Biol Phys*. 1998 Oct; 15(4):865-870. Accessed June 27, 2016. [http://www.redjournal.org/article/0360-3016\(88\)90119-8/abstract](http://www.redjournal.org/article/0360-3016(88)90119-8/abstract)
3. Chao KS, Perez, CA, Brady LW, eds. *Radiation Oncology: Management Decisions*. Philadelphia, PA: Lippincott-Raven, 1999.
4. Dewing SB. Radiotherapy of Benign Diseases: Overview by Dr. Dewing. (Chapter 36) in Gofman JW, O'Connor E, ed. *Preventing Breast Cancer: The Story of a Major, Proven, Preventable Cause of This Disease*. 2nd Edition. San Francisco, CA: Committee for Nuclear Responsibility, Inc. Book Division; 1996: 243-254.
5. Eng TY, Boersma MK, Fuller CD, et al. The role of radiation therapy in benign diseases. *Hematol Oncol Clin North Am*. 2006 Apr; 20(2):523-527. Accessed June 27, 2016. [http://www.hemonc.theclinics.com/article/S0889-8588\(06\)00024-4/abstract](http://www.hemonc.theclinics.com/article/S0889-8588(06)00024-4/abstract)
6. Micke O, Seegenschmiedt MH. The German Working Group on Radiotherapy of Benign Disease. Consensus guidelines for radiation therapy of benign diseases: a multicenter approach in Germany. *Int J Radiat Oncol Biol Phys*. 2002 Feb; 52(2):496-513. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(01\)01814-4/abstract](http://www.redjournal.org/article/S0360-3016(01)01814-4/abstract)
7. Order SE, Donaldson SS. *Radiation Therapy of Benign Diseases: A Clinical Guide (Medical Radiology)*. Berlin, (Heidelberg): Springer-Verlag, 2003.
8. Seegenschmiedt MH. Nonmalignant Disease (Chapter 63) in Gunderson L, Tepper J, ed. *Clinical Radiation Oncology*. 2nd Edition. Philadelphia, PA: Elsevier Churchill Livingstone; 2007: 1551-1568.
9. Winkfield KM, Bazan JG, Gibbs IC, et al. Nonmalignant Diseases (Chapter 91) in Halperin EC, Wazer DE, Perez CA, and Brady LW, ed. *Perez and Brady's Principles and Practice of Radiation Oncology*. 6th Edition. Philadelphia, PA: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2013: 1729-1752.

Radiation Treatment of Non-malignant Disease

[**Return to Table of Contents**](#)

Radiation Treatment of Pancreas Adenocarcinoma

POLICY

I. Indications for radiation therapy

- A. Preoperatively (neoadjuvant) resectable
- B. Preoperatively (neoadjuvant) borderline resectable
- C. Locally advanced/unresectable
- D. Postoperatively (adjuvant) resectable
- E. Palliation

II. Radiation treatment techniques

- A. Three-Dimensional Conformal Radiation Therapy (3DCRT) is medically necessary for most presentations of pancreatic cancer
- B. Intensity-Modulated Radiation Therapy (IMRT) may be considered medically necessary on a case-by-case basis when acceptable doses to critical organs, such as the kidney, spinal cord, small bowel, stomach, or liver cannot be achieved with 3D planning. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN)
- C. Motion management techniques should be employed when respiration significantly impacts on stability of the target volume
- D. Stereotactic Body Radiation Therapy (SBRT) using up to 5 radiation treatment fractions will be considered on a case-by-case basis for:
 - 1. Preoperative (neoadjuvant resectable or borderline resectable) cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression
 - 2. Definitive treatment for medically inoperable or locally advanced cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression and the disease volume can be entirely encompassed in the radiation treatment volume
 - 3. Postoperative (adjuvant) cases in which there is residual gross disease or positive microscopic margins that can be entirely encompassed in the radiation treatment volume
- E. For palliative situations, up to 15 fractions in 1 phase of Complex or 3D external beam photon radiation therapy is considered medically necessary. IMRT and SBRT are not considered medically necessary

Key Clinical Points

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. Surgical resection is integral to the curative management of pancreatic cancer. Unfortunately only twenty percent of individuals present with resectable disease. Resectability is typically defined by a lack of encasement of the superior mesenteric vein and portal veins and clear fat planes around the celiac artery, superior mesenteric artery and hepatic artery. Borderline resectability generally includes involvement of superior mesenteric vein or portal vein, but lack of encasement of the adjacent arteries. Patel et al. (2011) have reported on the use of neoadjuvant chemotherapy and IMRT to improve the likelihood of successful complete resection. In their study, 8 of 17 borderline resectable patients achieved negative margin resection after neoadjuvant therapy.

The underpowered but landmark Gastrointestinal Tumor Study Group (GITSG) study established the role of postoperative chemoradiation by demonstrating a survival benefit with this treatment strategy. The GITSG study included 43 patients, randomized to surgery alone or surgery followed by chemoradiation. This trial used a 40 Gy split course regimen that is rarely used today. Though underpowered, there was a 5-year improvement in overall survival (OS). Studies from the Mayo Clinic and Johns Hopkins have supported the use of chemoradiation following resection. The Mayo Clinic study retrospectively reviewed 472 patients. The Johns Hopkins study included 616 patients. Both studies demonstrated improved 5-year overall survivals in the cohorts receiving chemoradiation. A Johns Hopkins-Mayo Clinic Collaborative Study analyzed patients receiving adjuvant chemoradiation compared with surgery alone. In a retrospective review of 1,045 patients with resected pancreatic cancer, 530 patients received chemoradiation. Median and overall survivals were significantly improved in the chemoradiation group. In contrast, the heavily criticized European Organization for Research and Treatment of Cancer (EORTC) and European Study Group for Pancreatic Cancer (ESPAC) studies have not supported the use of adjuvant chemoradiation. These studies were heavily criticized for trial design, inclusion of more favorable histologies, lack of quality assurance, and use of split course radiation.

Following surgical resection, chemotherapy alone or chemoradiation may be the appropriate course of action. In an individual with borderline resectable pancreatic cancer, radiation is often utilized in the neoadjuvant setting in conjunction with chemotherapy. In an individual with unresectable pancreatic cancer, external beam photon radiation therapy is generally used as definitive treatment usually in conjunction with chemotherapy. A GITSG study of 194 patients with unresectable pancreatic cancer, randomized patients to 60 Gy of radiation alone, split course 40 Gy with concurrent fluorouracil (5-FU), and split course 60 Gy with concurrent 5-FU. Survival was improved in the chemoradiation arms with 1-year survival rates of 38% and 36%.

3D techniques are critical to respect the radiation tolerance of the surrounding critical structures, notably the kidneys, liver, small bowel and spinal cord. Dose prescription is typically 50.4 to 60 Gy and generally involves a conedown following 45 Gy. Dose escalation studies are under investigation. IMRT has increasingly been employed to decrease radiation dose to surrounding critical structures, in particular, the kidneys, liver, small bowel and spinal cord, and dosimetric studies have confirmed significantly lower doses to these structures with IMRT compared to 3D techniques. IMRT is associated with a statistically significant decrease in acute upper and lower GI toxicity among individuals treated with chemoradiotherapy for pancreatic/ampullary cancers. Based on these studies, IMRT is considered medically necessary in the treatment of pancreatic cancer in the definitive and adjuvant settings, when dose constraints to organs at risk cannot be met with 3DCRT techniques. When using IMRT in the upper abdominal region, the uncertainty inherent due to organ motion underscores the utility of image guidance. Respiratory gating techniques are often used with both 3DCRT and IMRT.

The benefits of dose escalation with both 3DCRT and IMRT techniques are under investigation and thus far inconclusive. The aforementioned landmark GITSG study did not demonstrate a meaningful improvement in survival for the cohort receiving 60 Gy split-course with concurrent 5-FU compared with 40 Gy split-course with concurrent 5-FU. A phase III trial of locally advanced unresectable pancreatic cancer, compared intensive induction chemoradiotherapy consisting of 60 Gy, 5-FU and cisplatin followed by maintenance gemcitabine, to gemcitabine alone. Survival was improved in the gemcitabine alone arm. One year OS was 32% in the chemoradiotherapy cohort vs. 53% in the gemcitabine alone arm. There was greater grade 3 and 4 toxicity in the chemoradiotherapy arm. A phase II study from the Netherlands analyzed the feasibility of dose escalation in locally advanced unresectable pancreatic cancer, treated with radiation alone. Forty-one patients were treated with 3DCRT in doses of 70 to 72 Gy. The median survival was 11 months with acceptable toxicity. RTOG 8801 was a phase I/II trial of localized unresectable pancreatic cancer. Treatment consisted of 61.2 Gy with continuous infusion (CI) 5-FU, prophylactic hepatic irradiation, followed by 6 months of 5-FU. Seventy-nine patients were evaluable with a minimum follow up of 8.2 months. Thirty-one patients had severe grade 3 toxicity. Persistent or progressive pancreatic cancer was noted in 73%. Median survival was 8.4 months.

There is no clear consensus regarding the appropriate maximum dose when utilizing IMRT. Fuss et al. (2007) retrospectively reviewed 41 patients undergoing ultrasound-based image guided IMRT for pancreatic cancer. The mean total dose was 55 Gy (range 45 to 64 Gy). Grade 3 toxicity was 7.3%. Actuarial one- and two-year survival were 38% and 25%, respectively, comparable to published survival data. Brown et al.

(2006) reviewed dose escalation in unresectable pancreatic cancer comparing 3DCRT, sequential IMRT boost and integrated IMRT boosts techniques. In 15 patients, treatment plans were generated and dosimetric analysis performed at doses of 54 Gy, 59.4 Gy and 64.8 Gy. Doses to the kidney, small bowel, liver and spinal cord were analyzed as well as target coverage. The authors concluded that the integrated boost IMRT technique allowed dose escalation to 64.8 Gy with acceptable normal tissue doses. Cost, as well as increased effectiveness of IMRT, has been questioned. Continued investigation of radiation dose escalation in the setting of clinical trials is warranted.

While data on the use of SBRT in cancer of the pancreas continues to emerge, there is a growing consensus on its use following 2 to 3 cycles of chemotherapy. Mellon EA et al. (2015) reported on 159 patients with borderline resectable and locally advanced disease. Patients received chemotherapy for 2 to 3 months followed by a total of 30 Gy to tumor and 40 Gy dose painted to tumor-vessel interfaces administered with 5 SBRT daily treatments. The resection and negative margin rate for borderline resectable patients who completed treatment was 51% and 96% respectively. Median survival was 34.2 months for surgically resected patients and 14.0 months for unresected patients. Locally advanced pancreas cases that received FOLFIRINOX (leucovorin calcium [folinic acid], fluorouracil, irinotecan hydrochloride, oxaliplatin) and SBRT underwent a negative margin (R0) resection with a trend towards improved survival. Grade 3 or higher possible radiation toxicity was 7%. A phase II multi-institution trial evaluating gemcitabine and SBRT in locally advanced unresectable patients by Herman JM et al. (2015) reported a median survival of 13.9 months and freedom from disease progression at one year of 78%. Of the 49 patients entered, 4 patients (8%) underwent negative margin and negative lymph node resections. Both early and late gastrointestinal toxicity was reported as minimal. A single institution review of 88 patients by Moningi S et al. (2015) had similar findings. Of the 19 patients who underwent surgery, 79% had locally advanced disease and 84% had margin negative resections. SBRT in resected pancreatic adenocarcinoma with close or positive margins combined with post-radiation chemotherapy (Rwigema JC et al., 2012) achieved freedom from local progression at 6 months, 1, and 2 years of 94.7%, 66% and 44% in a series of 24 patients. Overall median survival was 26.7 months and the 1- and 2-year statistics were 80.4% and 57.2% respectively. Gastrointestinal toxicities were minor with no patients having a grade 3 or 4 toxicity. Given these encouraging findings, requests for the use of SBRT will be considered on a case-by-case basis as described above in section II, which outlines treatment techniques and indications.

Dose escalation studies investigating intraoperative radiation therapy (IORT), SBRT, brachytherapy as well as IMRT are ongoing in an attempt to improve the therapeutic ratio and disease outcome.

References

1. Brown MW, Ning H, Arora B, et al. A dosimetric analysis of dose escalation using two intensity-modulated radiation therapy techniques in locally advanced pancreatic carcinoma. *Int J Radiat Oncol Biol Phys*. 2006 May 1; 65(1):274-283. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)00117-9/abstract](http://www.redjournal.org/article/S0360-3016(06)00117-9/abstract)
2. Brunner TB, Nestle U, Grosu AL, et al. SBRT in pancreatic cancer: what is the therapeutic window? *Radiother Oncol*. 2015 Jan; 114(1):109-116. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814014004654>
3. Ceha HM, van Tienhoven G, Couma DJ, et al. Feasibility and efficacy of high dose conformal radiotherapy for patients with locally advanced pancreatic carcinoma. *Cancer*. 2000 Dec 1; 89(11):2222-2229. Accessed June 24, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(20001201\)89:11%3C2222::AID-CNCR10%3E3.0.CO;2-V/full](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(20001201)89:11%3C2222::AID-CNCR10%3E3.0.CO;2-V/full)
4. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol*. 2008 Sep; 19(9):1592-1599. Accessed June 24, 2016. <http://annonc.oxfordjournals.org/content/19/9/1592.full>
5. Clinicaltrials.gov. Search for SBRT and pancreas. Accessed June 24, 2016. <https://www.clinicaltrials.gov/ct2/results?term=SBRT+and+Pancreas&Search=Search>
6. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). *J Clin Oncol*. 2008 Jul 20; 26(21):3511-3516. Accessed June 24, 2016. <http://jco.ascopubs.org/content/26/21/3511.full>
7. Fuss M, Wong A, Fuller CD, et al. Image-guided intensity-modulated radiotherapy for pancreatic carcinoma. *Gastrointest Cancer Res*. 2007 Jan-Feb; 1(1):2-11. Accessed June 24, 2016. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632515/>
8. Gastrointestinal Tumor Study Group (GITS). Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer*. 1987 Jun 15; 59(12):2006-2010. Accessed June 24, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(19870615\)59:12%3C2006::AID-CNCR2820591206%3E3.0.CO;2-B/pdf](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19870615)59:12%3C2006::AID-CNCR2820591206%3E3.0.CO;2-B/pdf)
9. Goyal K, Einstein D, Ibarra RA, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *J Surg Res*. 2012 May 15; 174(2): 319-325. Accessed June 24, 2016. [http://www.journalofsurgicalresearch.com/article/S0022-4804\(11\)00674-3/abstract](http://www.journalofsurgicalresearch.com/article/S0022-4804(11)00674-3/abstract)
10. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer*. 2015 Apr 1; 121(7):1128-1137. Accessed June 24, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.29161/abstract>
11. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol*. 2008 Jul 20; 26(21):3503-3510. Accessed June 24, 2016. <http://jco.ascopubs.org/content/26/21/3503.full>
12. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol*. 2010 Apr; 17(4):981-990. Accessed June 24, 2016. <http://link.springer.com/article/10.1245/s10434-009-0743-7/fulltext.html>
13. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999 Dec; 230(6):776-782. Accessed June 24, 2016. http://journals.lww.com/annalsofsurgery/Abstract/1999/12000/Adjuvant_Radiotherapy_and_5_Fluorouracil_After.6.aspx
14. Komaki R, Wadler S, Peters T, et al. High-dose local irradiation plus prophylactic hepatic irradiation and chemotherapy for inoperable adenocarcinoma of the pancreas. A preliminary report of a multi-institutional trial (Radiation Therapy Oncology Group Protocol 8801). *Cancer*. 1992 Jun 1; 69(11):2807-2812. Accessed June 24, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(19920601\)69:11%3C2807::AID-CNCR2820691128%3E3.0.CO;2-O/pdf](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19920601)69:11%3C2807::AID-CNCR2820691128%3E3.0.CO;2-O/pdf)
15. Koong AC, Christofferson E, Le QT et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2005 Oct; 63(2):320-323. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)01153-3/abstract](http://www.redjournal.org/article/S0360-3016(05)01153-3/abstract)

16. Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2004 Mar 15; 58(4):1017-1021. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)02294-6/abstract](http://www.redjournal.org/article/S0360-3016(03)02294-6/abstract)
17. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys*. 2011 Nov 15; 81(4):e615-e622. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)00566-9/abstract](http://www.redjournal.org/article/S0360-3016(11)00566-9/abstract)
18. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Acta Oncol*. 2015 Jul; 54(7):979-985. Accessed June 24, 2016. <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1004367>
19. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer*. 1981 Oct 15; 48(8):1705-10. Accessed June 24, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(19811015\)48:8%3C1705::AID-CNCR2820480803%3E3.0.CO;2-4/pdf](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19811015)48:8%3C1705::AID-CNCR2820480803%3E3.0.CO;2-4/pdf)
20. Moningi S, Dholakia AS, Raman SP, et al. The role of stereotactic body radiation therapy for pancreatic cancer: a single-institution experience. *Ann Surg Oncol*. 2015 Jul; 22(7):2352-2358. Accessed June 24, 2016. <http://link.springer.com/article/10.1245%2Fs10434-014-4274-5>
21. Murphy JD, Chang DT, Abelson J, et al. Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer. *Cancer*. 2012 Feb 15; 118(4):1119-1129. Accessed June 24, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.26365/full>
22. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Pancreatic Adenocarcinoma. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Pancreatic Adenocarcinoma 1.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
23. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001 Nov 10; 358(9293): 1576-1585. Accessed June 24, 2016. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(01\)06651-X/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(01)06651-X/fulltext)
24. Patel M, Hoffe S, Malafa M, et al. Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer. *J Surg Oncol*. 2011 Aug 1; 104(2):155-161. Accessed June 24, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/jso.21954/full>
25. Pollom EL, Alagappan M, von Eyben R, et al. Single- versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: outcomes and toxicity. *Int J Radiat Oncol Biol Phys*. 2014 Nov 15; 90(4):918-925. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(14\)03457-9/abstract](http://www.redjournal.org/article/S0360-3016(14)03457-9/abstract)
26. Poppe M, Narra V, Yue NJ, et al. A comparison of helical intensity-modulated radiotherapy, intensity-modulated radiotherapy, and 3D-conformal radiation therapy for pancreatic cancer. *Med Dosim*. 2011 Winter; 36(4):351-7. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0958394710001305>
27. Rwigema JC, Heron DE, Parikh SD, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer*. 2012 Mar; 43(1):70-76. Accessed June 24, 2016. <http://link.springer.com/article/10.1007/s12029-010-9203-7>
28. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2008 Nov 1; 72(3):678-686. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)00227-7/abstract](http://www.redjournal.org/article/S0360-3016(08)00227-7/abstract)
29. Trakul N, Koong AC, Chang DT. Stereotactic body radiotherapy in the treatment of pancreatic cancer. *Semin Radiat Oncol*. 2014 Apr; 24(2):140-147. Accessed June 24, 2016. [http://www.semradonc.com/article/S1053-4296\(13\)00102-1/abstract](http://www.semradonc.com/article/S1053-4296(13)00102-1/abstract)
30. Yang W, Fraass BA, Reznik R, et al. Adequacy of inhale/exhale breathhold CT based ITV margins and image-guided registration for free-breathing pancreas and liver SBRT. *Radiat Oncol*. 2014 Jan 9; 9(1):11. Accessed June 24, 2016. <http://www.ro-journal.com/content/9/1/11>
31. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys*. 2011 Jan; 79(1): 158-162. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03510-X/abstract](http://www.redjournal.org/article/S0360-3016(09)03510-X/abstract)

Radiation Treatment of Pancreas Adenocarcinoma

[Return to Table of Contents](#)

Radiation Treatment of Primary Cranial and Spinal Tumors and Neurologic Conditions

POLICY

I. Complex, three-dimensional conformal radiation therapy (3DCRT), or Intensity-Modulated Radiation Therapy (IMRT) techniques are medically necessary for:

- A. The treatment of primary malignant gliomas of the brain in any of the following cases:
 - 1. Diagnosed by biopsy or resection
 - a. Low grade tumors (WHO grade I-II)
 - i. Up to 30 fractions
 - ii. 3DCRT/IMRT
 - iii. Procarbazine, lomustine (CCNU) and vincristine (PCV) should be considered upon the completion of radiation therapy
 - b. High grade tumors (WHO grade III-IV)
 - i. Up to 33 fractions
 - ii. 3DCRT/IMRT
 - iii. Radiation therapy combined with temozolomide is the current standard of care
 - c. In a poorly performing or elderly individual, a hypofractionated-accelerated course may be effective. Typical fraction schedules are 34 Gy/10, 40.05 Gy/15 or 50 Gy/20
- B. Recurrent disease with good prognostic factors including an Eastern Cooperative Oncology Group (ECOG) status of 0, 1, or 2
- C. Proton beam therapy – please refer to the policy on Proton Beam
- D. Craniospinal irradiation (CSI) in ependymoma, adult medulloblastoma and primitive neuroectodermal tumors (PNET)
 - 1. Up to 20 fractions depending on risk of recurrence and use of concurrent chemotherapy and a boost – up to a combined total of 33 fractions including CSI

II. Recurrent inoperable malignant gliomas that have received prior radiation treatment will be considered for stereotactic radiosurgery (SRS) on a case-by-case basis

III. Brachytherapy is considered experimental, investigational, or unproven (EIU) for the treatment of a malignant glioma brain tumor

IV. Complex, 3DCRT, or IMRT techniques are medically necessary for the treatment of a primary central nervous system (PCNS) lymphoma for any of the following:

- A. A young adult with good performance status and good response to chemotherapy
- B. Poor response to chemotherapy
- C. Without chemotherapy in an individual with a poor performance status, or who is severely immunocompromised
- D. Presence of ocular disease
- E. Recurrent disease

V. 3DCRT, IMRT, or SRS is considered medically necessary for the treatment of the following benign conditions:

- A. Arteriovenous (AV) malformations (only SRS)
- B. Benign brain tumors including any of the following:
 - 1. Acoustic neuroma
 - 2. Craniopharyngioma
 - 3. Glomus tumor
 - 4. Hemangioblastoma
 - 5. Meningioma
 - 6. Pineocytoma
 - 7. Pituitary adenoma
 - 8. Schwannoma
- C. Cavernous malformations
 - 1. Please note that a maximum of 5 fractions is authorized for SRS. For an individual prescribed more than 5 fractions, 3DCRT or IMRT technique should be specified as appropriate.

VI. SRS is medically necessary for any of the following diseases that are refractory to medical treatment and/or invasive neurosurgical treatment:

- A. Epilepsy
- B. Parkinson's disease
- C. Essential tremor
- D. Familial tremor classifications with major systemic disease
- E. Trigeminal neuralgia.
- F. Authorization for this class of diseases will only be granted once all standard treatments have proven to be ineffective. Discussion with an eviCore radiation oncologist will be required.

VII. 3DCRT, IMRT, or SRS is medically necessary for the treatment of an inoperable primary spinal tumor with compression or intractable pain

Key Clinical Points

Surgical removal is recommended for most types of brain tumors in most locations, and their removal should be as complete as possible within the constraints of preservation of neurologic function. Treatment with photons has a major role in the treatment of patients with most tumor types, as evidenced in the European Organization for Research and Treatment of Cancer [EORTC-22845](#) and Medical Research Council [MRC-BR04](#) trials, and can increase the cure rate or prolong disease-free survival. IMRT may yield better dosimetry with sparing of normal brain tissue, especially in dose-escalated protocols.

I. High-grade gliomas

Since the development of the Radiation Therapy Oncology Group-Recurse Partitioning Analysis (RTOG-RPA) risk classes for high-grade glioma, radiation therapy in combination with temozolomide (TMZ) has become standard care. While this combination has improved survival, the prognosis remains poor in the majority of individuals. In a phase III randomized study (Keime-Guibert, et al., 2007) of glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA) in the New England Journal of Medicine (NEJM), post-operative external beam photon radiation therapy in the elderly statistically significantly improved the median survival compared to observation. Another phase III randomized study (Stupp et al., 2005) of high-grade gliomas revealed temozolomide plus external beam photon radiation therapy statistically significantly increased the survival rate compared to external beam photon radiation therapy alone. For high-grade brain tumors (WHO grade III-IV), typically 33 fractions of external beam photon radiation therapy are administered post-operatively with up to five coplanar or non-coplanar beams using 3DCRT or IMRT.

II. Low-grade gliomas (LGG)

For low-grade brain tumors (WHO grade I-II), the role of postoperative radiotherapy (PORT) remains controversial. Cerebral low-grade gliomas (LGG) in adults are mostly composed of astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. An analysis using data from the EORTC 22844/22845 studies concluded that several factors portend a poor prognosis: age ≥ 40 years, astrocytoma histology, tumor size ≥ 6 cm, tumor crossing midline, and preoperative neurologic deficits. PORT may benefit patients with high-risk features. The EORTC trial 22844 did not reveal the presence of radiotherapeutic dose-response for patients with LGG for the two dose levels investigated with this conventional setup. A phase III prospective randomized trial (Shaw et al., 2002) of low- versus high-dose radiation therapy for adults with supratentorial low-grade astrocytoma, oligodendroglioma, and oligoastrocytoma found somewhat lower survival and slightly higher incidence of radiation necrosis

in the high-dose RT arm. The most important prognostic factors for survival are histologic subtype, tumor size, and age. Recently updated results of RTOG 9802 showed significant improvement in progression-free survival (PFS) when patients also received chemotherapy with procarbazine/CCNU/vincristine (PCV). Median, 5-year, and 10-year PFS improved dramatically with the combined approach from 4.0 years to 10.4 years, from 44.1% to 61.2%, and from 20.9% to 50.5% respectively. For those patients who receive PORT, typically 30 fractions of external beam photon radiation therapy are administered with up to 5 coplanar or non-coplanar beams 3DCRT or IMRT.

III. Recurrent disease

Currently the following options for salvage may be considered: re-resection, re-irradiation with either conventionally-fractionated doses, Stereotactic Radiation Therapy (SRT), Stereotactic Radiosurgery (SRS), interstitial brachytherapy, or single/poly-chemotherapy schedules including new dose-intensified or alternative treatment protocols employing targeted drugs. A recent review publication (Niyazi et al., 2011) concluded that these have only modest efficacy. The relative value of each approach compared to other options is unknown as well as it remains open which sequence of modalities should be chosen. Some individuals with recurrent disease may benefit from retreatment with radiotherapy, depending on prognostic factors including grade of tumor, age, and performance status. Other factors such as corticosteroid use may be important. A study (Wong et al., 1999) of several hundred patients retreated for recurrent gliomas at MD Anderson showed that 34 (9%) had complete or partial response, whereas 80 (21%) were alive and progression-free at 6 months (APF6). The median PFS was 10 weeks and median overall survival (OS) was 30 weeks. Histology was a robust prognostic factor across all outcomes. GBM patients had significantly poorer outcomes than AA patients did. The APF6 proportion was 15% for GBM and 31% for AA, whereas the median PFS was 9 weeks for GBM and 13 weeks for AA. Results were also significantly poorer for patients with more than two prior surgeries or chemotherapy regimens.

IV. Primary CNS lymphoma

The incidence of primary CNS lymphoma dramatically increased in the last several decades, in part related to human immunodeficiency virus (HIV) infection. Primary CNS lymphoma (PCNSL) now accounts for 2 to 5% of CNS tumors. PCNSL occurs in the brain, leptomeninges, eye and spinal cord. Untreated PCNSL portends a dismal prognosis. Treatment is dependent on age, performance status, extent of disease, and HIV status. Surgery plays little role in the management of PCNSL. Continued investigation is underway to develop the optimal treatment strategy. Recommendations for individuals with good

performance status include a high dose methotrexate regimen. For younger individuals, this is usually followed by radiation (24 to 45 Gy in standard fractionation). The timing of radiation is controversial; despite high response rates with a combination of the two modalities, increased neurotoxicity has been observed. Therefore, the recommendation for older (non-immune-suppressed) individuals is chemotherapy alone. For individuals with poor performance status single modality treatment is used, either radiation therapy or chemotherapy. Radiation is also indicated when there has been an incomplete or limited response to chemotherapy and in the setting of ocular or recurrent disease. For individuals with acquired immunodeficiency syndrome (AIDS) with low CD4 counts, treatment is usually palliative radiotherapy alone, 30 Gy in 10 fractions.

V. SRS

A. Malignant tumors

In 2005, the American Society for Radiation Oncology (ASTRO) published an evidenced-based review on the use of SRS for malignant glioma. ASTRO concluded that for individuals with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam photon radiation therapy and bis-chlorethyl nitrosourea (BCNU) does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam photon radiation therapy and BCNU. The use of radiosurgery boost is associated with increased toxicity. For an individual with malignant glioma, there is insufficient evidence regarding the benefits/harms of using SRS at the time progression or recurrence. There is also insufficient evidence regarding the benefits/harms in the use of stereotactic fractionated radiation therapy for individuals with newly diagnosed or progressive/recurrent malignant glioma. More recent publications have not provided evidence that would change these conclusions. While small, well-defined, unresectable low-grade gliomas are attractive targets for stereotactic irradiation, and fractionated stereotactic irradiation of these targets has the theoretical benefit of increased normal tissue sparing beyond that provided by the physical characteristics of SRS, no study has demonstrated its benefit compared to standard techniques. Published results from McGill (Roberge et al., 2006) which includes those of 241 patients treated in nine other institutional series conclude that data regarding the use of SRS is limited and, in their opinion, insufficient to claim a clear therapeutic advantage to SRS in the initial management of low-grade glioma (2006). Several small single institution retrospective studies of higher-grade malignancies have been published between 2007 and 2012, and while they claim efficacy, there is no convincing evidence that these are better than standard therapies (Cuneo et al., 2012; Ernst-Stecken et al., 2007; Fields et al., 2012).

B. Benign conditions

The success and excellent safety margin of SRS in many other clinical situations has led to exploration of its use in benign tumors and neurologic conditions which are refractory to medical treatment and would otherwise require surgical procedures with significant morbidity and possible mortality. The condition to be treated must be causing severe symptoms or pose a serious threat to function or life expectancy and have an expected benefit of stabilizing or improving the clinical state. An individual with limited life expectancy and/or generally poor performance status (ECOG > 2) which are not expected to improve significantly with treatment should not be considered for SRS.

The delivery of SRS may take 1 to 5 treatment sessions. By definition the performance of SRS must include:

1. Patient immobilization with or without a frame
2. Radiographic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) or other radiologic modalities to localize precisely the target area
3. The use of computerized image guidance to insure precise treatment delivery. As per American Medical Association (AMA) coding guidelines, Image-Guided Radiation Therapy (IGRT) is included in the daily treatment delivery code and may not be billed separately.
4. Dedicated treatment planning and precise calculation with verification of setup and accuracy of all treatment parameters including but not limited to multiple isocenters, arcs, angles, number of beams (size and weight), isodose plans and calculations.
5. Accurate simulation and reproducibility of all treatment angles or arcs

References

Malignant tumors

1. Buckner JC, Pugh SL, Shaw EG et al. Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG. J Clin Oncol. 2014 May 20; 32(15 suppl). Abstract 2000. Accessed June 24, 2016. <http://meetinglibrary.asco.org/content/127483-144>
2. Carson KA, Grossman SA, Fisher JD, et al. Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. J Clin Oncol. 2007 Jun 20; 25(18):2601-2606. Accessed June 24, 2016. <http://jco.ascopubs.org/content/25/18/2601.full>
3. Cuneo KC, Vredenburg JJ, Sampson JH, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2012 Apr 1; 82(5):2018-2024. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)00226-4/abstract](http://www.redjournal.org/article/S0360-3016(11)00226-4/abstract)
4. Ernst-Stecken A, Ganslandt O, Lambrecht U, et al. Survival and quality of life after hypofractionated stereotactic radiotherapy for recurrent malignant glioma. J Neurooncol. 2007 Feb; 81(3):287-294 Accessed June 24, 2016. <http://link.springer.com/article/10.1007/s11060-006-9231-0>
5. Fields EC, Damek D, Gaspar LE, et al. Phase I dose escalation trial of vandetanib with fractionated radiosurgery in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2012 Jan 1; 82(1):51-57. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)03247-5/pdf](http://www.redjournal.org/article/S0360-3016(10)03247-5/pdf)
6. Karim ABMF, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) study 22844. Int J Radiat Oncol Biol Phys. 1996 Oct 1; 36(3):549-556. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(96\)00352-5/abstract](http://www.redjournal.org/article/S0360-3016(96)00352-5/abstract)
7. Keime-Guibert F, Chinot O, Taillandier L, et al. for the Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. N Engl J Med. 2007 Apr 12; 356(15):1527-1535. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa065901>
8. Li J, Wang M, Won M, et al. Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys. 2011 Nov 1; 81(3):623-630. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)00861-8/abstract](http://www.redjournal.org/article/S0360-3016(10)00861-8/abstract)
9. Limentani SA, Asher A, Heafner M, et al. A phase I trial of surgery, Gliadel wafer implantation, and immediate postoperative carboplatin in combination with radiation therapy for primary anaplastic astrocytoma or glioblastoma multiforme. J Neurooncol. 2005 May; 72(3):241-244. Accessed June 24, 2016. <http://link.springer.com/article/10.1007/s11060-004-2339-1>
10. MacDonald SM, Ahmad S, Kachris S, et al. Intensity modulated radiation therapy (IMRT) versus three-dimensional conformal radiation therapy (3DCRT) for the treatment of high grade glioma: a dosimetric comparison. J Appl Clin Med Phys. 2007 Apr 19; 8(2):47-60. Accessed June 24, 2016. <http://jacmp.org/index.php/jacmp/article/view/2423/1258>
11. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2015 Central Nervous System Cancers. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Central Nervous System Cancers. 1.2015. ©2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
12. Niyazi M, Siefert A, Schwarz SB et al. Therapeutic options for recurrent malignant glioma. Radiother Oncol. 2011 Jan; 98(1):1-14. Accessed June 24, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(10\)00709-7/pdf](http://www.thegreenjournal.com/article/S0167-8140(10)00709-7/pdf)
13. Roberge D, Souhami L, Olivier A, et al. Hypofractionated stereotactic radiotherapy for low grade glioma at McGill University: long-term follow-up. Technol Cancer Res Treat. 2006 Feb; 5(1):1-8. Accessed June 24, 2016. http://www.unboundmedicine.com/medline/citation/16417396/Hypofractionated_stereotactic_radiotherapy_for_low_grade_glioma_at_McGill_University_long-term_follow-up
14. Ruden E, Reardon DA, Coan AD, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. J Clin Oncol. 2011 Jul 20; 29(21):2918-2923. Accessed June 24, 2016. <http://jco.ascopubs.org/content/29/21/2918.abstract>
- Shaw E, Arusell R, Scheithauer B, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol. 2002 May 1; 20(9):2267-76. Accessed June 24, 2016. <http://jco.ascopubs.org/content/20/9/2267.abstract>
15. Stupp R, Mason WP, van den Bent MJ, et al. for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10; 352(10):987-996. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa043330>

16. Suneja G, Alonso-Basanta M, Lustig R, et al. Postoperative radiation therapy for low-grade glioma: patterns of care between 1998 and 2006. *Cancer*. 2012 Aug 1; 118(15):3735-3742. Accessed June 24, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.26693/full>
17. Tsao MN, Mehta MP, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for malignant glioma. *Int J Radiat Oncol Biol Phys*. 2005 Sep 1; 63(1):47-55. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00888-6/abstract](http://www.redjournal.org/article/S0360-3016(05)00888-6/abstract)
18. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol*. 1999 Aug; 17(8):2572-2578. Accessed June 24, 2016. <http://jco.ascopubs.org/content/17/8/2572.abstract>
19. Wu W, Lamborn KR, Buckner JC, et al. Joint NCCTG and NABTC prognostic factors analysis for high-grade recurrent glioma. *Neuro Oncol*. 2010 Feb; 12(2):164-172. Accessed June 24, 2016. <http://neuro-oncology.oxfordjournals.org/content/12/2/164.full>

Benign conditions

20. Andrews DW, Suarez O, Goldman HW, et al. Stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of acoustic schwannomas: comparative observations of 125 patients treated at one institution. *Int J Radiat Oncol Biol Phys*. 2001 August 1; 50(5):1265-1278. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(01\)01559-0/abstract](http://www.redjournal.org/article/S0360-3016(01)01559-0/abstract)
21. Bledsoe JM, Link MJ, Stafford SL, Park PJ, Pollock BE. Radiosurgery for large-volume (> 10 cm³) benign meningiomas. *J Neurosurg*. 2010 May; 112(5):951-6. Accessed June 24, 2016. <http://thejns.org/doi/abs/10.3171/2009.8.JNS09703>
22. Castinetti F, Brue T. Gamma Knife radiosurgery in pituitary adenomas: Why, who, and how to treat? *Discov Med*. 2010 Aug; 10(51):107-111. Accessed June 24, 2016. <http://www.discoverymedicine.com/Frederic-Castinetti/2010/08/04/gamma-knife-radiosurgery-in-pituitary-adenomas-why-who-and-how-to-treat/>
23. Chang SD, Gibbs IC, Sakamoto GT, et al. Staged stereotactic irradiation for acoustic neuroma. *Neurosurgery* 2005; 56(6):1254-1263. Accessed June 24, 2016. http://journals.lww.com/neurosurgery/Abstract/2005/06000/Staged_Stereotactic_Irradiation_for_Acoustic.10.aspx
24. De Braganca KC, Packer RJ. Treatment options for medulloblastoma and CNS primitive neuroectodermal tumor (PNET). *Curr Treat Options Neurol*. 2013 Oct; 15(5):593-606. Accessed June 24, 2016. <http://link.springer.com/article/10.1007/s11940-013-0255-4>
25. Elaimy AL, Arthurs BJ, Lamoreaux WT, et al. Gamma knife radiosurgery for movement disorders: a concise review of the literature. *World J Surg Oncol*. 2010 Jul 21; 8:61. Accessed June 24, 2016. <http://www.wjso.com/content/pdf/1477-7819-8-61.pdf>
26. Elaimy AL, Demakas JJ, Arthurs BJ, et al. Gamma knife radiosurgery for essential tremor: a case report and review of the literature. *World J Surg Oncol*. 2010 Mar 22; 8:20. Accessed June 24, 2016. <http://www.wjso.com/content/pdf/1477-7819-8-20.pdf>
27. Engenhart R, Kimmig B, Höver KH, et al. Stereotactic single high dose radiation therapy for benign tumors of the brain. *Int J Radiat Oncol Biol Phys*. 1989; 17(S1):95. Accessed June 24, 2016. [http://www.redjournal.org/article/0360-3016\(89\)90783-9/abstract](http://www.redjournal.org/article/0360-3016(89)90783-9/abstract)
28. Flickinger JC, Niranjan A. Stereotactic radiosurgery and radiotherapy in Halperin EC, Wazer DE, Perez CA, and Brady LW, ed. *Perez and Brady's Principles and Practice of Radiation Oncology*. 6th Edition. Philadelphia:Lippincott Williams & Wilkins, a Wolters Kluwer business, 2013:351-361.
29. Hasagawa T, McNerney J, Kondziolka D, et al. Long-term results after stereotactic radiosurgery for patients with cavernous malformations. *Neurosurgery* 2002; 50(6):1190-1198. Accessed June 24, 2016. http://journals.lww.com/neurosurgery/Abstract/2002/06000/Long_term_Results_after_Stereotactic_Radiosurgery.3.aspx
30. Henson, CF, Goldman HW, Rosenwasser RH, et al. Glycerol rhizotomy versus gamma knife radiosurgery for the treatment of trigeminal neuralgia: An analysis of patients treated at one institution *Int J Radiat Oncol Biol Phys*. 2005 Sep 1; 63(1):82-90. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(05\)00150-1/abstract](http://www.redjournal.org/article/S0360-3016(05)00150-1/abstract)
31. Kondziolka D. Gamma Knife thalamotomy for disabling tremor. *Arch Neurol*. 2002 Oct; 59(10):1660. Accessed June 24, 2016. <http://archneur.jamanetwork.com/article.aspx?articleid=782834>
32. Kondziolka D, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for the treatment of trigeminal neuralgia. *Clin J Pain*. 2002 Jan-Feb; 18(1):42-47. Accessed June 24, 2016. http://journals.lww.com/clinicalpain/Abstract/2002/01000/Stereotactic_Radiosurgery_for_the_Treatment_of.7.aspx
33. Kondziolka D, Nathoo N, Flickinger JC, et al. Long-term results after radiosurgery for benign intracranial tumors. *Neurosurgery*. 2003 Oct; 53(4):815-822. Accessed June 24, 2016. http://journals.lww.com/neurosurgery/Abstract/2003/10000/Long_term_Results_after_Radiosurgery_for_Benign.5.aspx

34. MacNally SP, Rutherford SA, Ramsden RT, et al. Trigeminal schwannomas. Br J Neurosurg. 2008 Dec; 22(6):729-38. Accessed June 24, 2016. <http://informahealthcare.com/doi/abs/10.1080/02688690802272172>
35. Malmstrom A, Gronberg BH, Marosi C, et al. Temozolomide versus 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol. 2012 Sep; 13(9): 916-920. Accessed June 24, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(12\)70265-6/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70265-6/fulltext)
36. Onodera S, Aoyama H, Katoh N, et al. Long-term outcomes of fractionated stereotactic radiotherapy for intracranial skull base benign meningiomas in single institution. Jpn J Clin Oncol. 2011 Apr; 41(4):462-468. Accessed June 24, 2016. <http://jco.oxfordjournals.org/content/41/4/462.full.pdf+html>
37. Portnow LH, Scott M, Morris CG, et al. Fractionated radiotherapy in the management of benign vascular tumors. Am J Clin Oncol. 2012 Dec; 35(6):557-561. Accessed June 24, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2012/12000/Fractionated_Radiotherapy_in_the_Management_of.9.aspx
38. Roa W, Brasher PMA, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Onc. 2004 May 1; 22(9):1583-1588. Accessed June 24, 2016. <http://jco.ascopubs.org/content/22/9/1583.full>
39. Saraceni C, Ashman JB, Harrop JS. Extracranial radiosurgery--applications in the management of benign intradural spinal neoplasms. Neurosurg Rev. 2009 Apr; 32(2):133-141. Accessed June 24, 2016. <http://link.springer.com/article/10.1007/s10143-008-0183-z>
40. Yap L, Kouyialis A, Varma TR. Stereotactic neurosurgery for disabling tremor in multiple sclerosis: thalamotomy or deep brain stimulation? Brit J Neurosurg. 2007 Aug; 21(4):349-54. Accessed June 24, 2016. <http://informahealthcare.com/doi/abs/10.1080/02688690701544002>
41. Young RF, Jacques S, Mark R, et al. Gamma knife thalamotomy for treatment of tremor: long-term results. J Neurosurg. 2000 Dec; 93(Suppl 3):128-35. Accessed June 24, 2016. <http://thejns.org/doi/abs/10.3171/jns.2000.93.supplement%203.0128>

Radiation Treatment of Primary Cranial and Spinal Tumors and Neurologic Conditions

[**Return to Table of Contents**](#)

Radiation Treatment of Prostate Cancer

POLICY*

Low-risk prostate cancer is defined as having all of the following:

1. Stage T1 to T2a
2. Gleason score (GS) ≤ 6
3. Prostate specific antigen (PSA) < 10 ng/mL

Intermediate-risk prostate cancer is defined as having any of the following:

1. Stage T2b to T2c
2. Gleason score (GS) is 7
3. PSA 10 to 20 ng/mL

High-risk prostate cancer is defined as having any of the following:

1. Stage $\geq T3a$
2. Gleason score (GS) ≥ 8
3. PSA > 20 ng/mL

Bone scans are recommended only for an individual with the following presentations:

1. T1 and PSA > 20
2. T2 and PSA > 10
3. GS > 8
4. T3, T4
5. Symptomatic

Radiation therapy for prostate cancer is medically necessary in the following situations:

- I. Monotherapy with three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), radioactive seed implant, or high dose rate (HDR) brachytherapy when the individual meets both of the following:**
 - A. Low- and intermediate-risk prostate cancer
 - B. Negative bone scan within the last 6 months, where applicable
- II. External beam photon radiation therapy (3DCRT or IMRT) alone or combined with brachytherapy (HDR or radioactive seed implant)**
 - A. Intermediate-risk and high-risk prostate cancer
 - B. Negative bone scan within the past 6 months, where applicable

III. Stereotactic body radiation therapy (SBRT) alone

- A. Low-, intermediate-, and high-risk prostate cancer
- B. Negative bone scan within the last 6 months, where applicable

IV. External beam photon radiation therapy (3DCRT or IMRT) in the postoperative setting for at least one of the following:

- A. Positive surgical margins
- B. Extracapsular extension
- C. Seminal vesicle involvement
- D. Positive lymph nodes
- E. Detectable or rising postoperative PSA level

*For proton beam treatment of prostate cancer, please see separate Proton Beam Therapy policy.

Key Clinical Points**I. Brachytherapy**

Brachytherapy is one type of radiation therapy used to treat prostate cancer. Unlike 3DCRT or IMRT photon techniques, in which high-energy xray beams generated by a machine are directed at the tumor from outside the body, brachytherapy involves placing radioactive material directly inside the prostate. This can be accomplished by performing a permanent seed implant by injecting radioactive seeds directly into the prostate gland, and typically using either Iodine or Palladium seeds. As part of the post-implant evaluation of the adequacy for the implant, a single computed tomography (CT) scan of the prostate is performed approximately one month after the implant to determine the dosimetric quality of the implant, so that decisions about the potential need for additional therapy can be made. HDR brachytherapy, as opposed to permanent low dose seed implants, uses temporary radioactive sources. Needles are placed into the prostate gland. A high activity radioactive seed (Iridium-192) is directed to pre-determined positions in these needles for precalculated dwell times via a remote after-loading system, and after the appropriate dose is delivered the needles are removed, usually within 24 hours.

Brachytherapy, either as monotherapy or combined with external beam photon radiation therapy (3DCRT or IMRT), may be appropriate depending on the clinical situation. The resurgence of interest in prostate brachytherapy is principally due to the evolution of transrectal ultrasonography, the development of a closed transperineal approach, and sophisticated treatment planning software. These imaging and planning advances dramatically improved the accuracy of seed placement. Brachytherapy as monotherapy is well established for low-risk prostate cancer. Permanent prostate brachytherapy is a highly efficacious treatment for clinically localized prostate cancer with biochemical outcomes and morbidity profiles that compare favorably with those of competing local modalities. HDR monotherapy is also appropriate in cases of low-risk

disease, and either form of brachytherapy may be appropriate in selected low and intermediate-risk cases. Both the National Comprehensive Cancer Network (NCCN) Guidelines® and the American Brachytherapy Position Paper on HDR back these approaches despite lack of prospective randomized data. The American College of Radiology (ACR) Appropriateness Criteria® published in Brachytherapy in 2014 is clear that data for HDR monotherapy is still emerging.

A modest amount of data has been published from single institutions and in small prospective studies on the strategy of combining external beam photon radiation therapy (3DCRT or IMRT) with either a low dose rate (LDR) or HDR brachytherapy boost for patients with intermediate- to high-risk prostate cancer, and is considered appropriate. However, such combination therapy is generally inappropriate for an individual with low risk disease.

II. Complex

Complex photon technique is a method for delivering a beam of high-energy x-rays to the location of the individual's tumor. The beam is generated outside the individual, usually by a linear accelerator and is targeted at the tumor site. With careful planning the tumor cells are destroyed and the surrounding tissue is spared from the harmful effects of the radiation. No sources are placed inside the individual's body. Complex technique refers to a treatment planning method wherein the prostate and other target tissues are identified by surrounding anatomy such as bony landmarks and contrast enhanced viscera. Complex technique (plain films are used) is generally not considered appropriate for the definitive treatment of prostate cancer especially in cases of locally advanced or high-risk prostate cancer where higher doses of radiation are usually delivered.

III. 3DCRT

3DCRT is an advanced form of external beam photon radiation therapy that uses CT and computers to create a 3D picture of the tumor so that multiple radiation beams can be shaped exactly to the contour of the treatment area.

IV. IMRT

IMRT employs a very sophisticated computerized 3D treatment-planning system that accurately delivers a high dose of photon radiation to tumors of varying shapes with even more accurate sparing of surrounding tissue than can be accomplished with 3DCRT. IMRT evolved out of the inability of 3DCRT to irradiate tumors that are concave, surrounded by normal tissue, or in very close proximity to sensitive normal tissue, without causing excessive radiation exposure of adjacent normal tissue. IMRT incorporates two distinct features over 3DCRT: 1) inverse treatment planning and 2) computer-controlled intensity modulation of the photon radiation beam. IMRT is high precision treatment that

utilizes computer-controlled linear accelerators to deliver precise radiation doses with photons to the 3D shape of the tumor. This results in sparing surrounding normal tissue and ultimately limiting side effects.

Radiation therapy directed to the prostate is generally not appropriate in men with distant metastatic (stage M1) disease. IMRT with photons is medically necessary for an individual with non-metastatic prostate cancer when there is a reasonable concern about damage to the surrounding normal tissue with the use of Complex or 3DCRT external beam photon radiation therapy. Guidelines on prostate cancer from the NCCN state that 3DCRT and IMRT techniques using photons should be employed in preference to conventional techniques in the treatment of prostate cancer. Doses of 75.6 to 79.2 Gy to the prostate (+/- seminal vesicles for part of the therapy) typically are appropriate for an individual with low-risk cancer. For an individual with intermediate- or high-risk disease, doses of 81 Gy improved PSA-assessed disease control.

In order to ensure that disease is localized prior to delivering high dose radiotherapy, a bone scan must be obtained within the 6 months leading up to radiotherapy in an individual with advanced disease. This includes an individual with stage T3a, T3b, or T4, GS eight (8) to 10, or PSA > 20 ng/ml. An individual being considered for postoperative radiotherapy must also have a bone scan.

Standard 3DCRT and IMRT courses with photons span up to 9.5 weeks (maximum 48 fractions). There may be radiobiologic benefits to using larger doses per fraction and hypofractionated courses. A phase is defined as a distinct change in the target volume, and phases are delivered sequentially. An individual with low-risk disease is treated with 1 or 2 phases (one directed to the prostate and seminal vesicles and another to the prostate alone). In selected intermediate- or high-risk cases, another phase encompassing the pelvic lymph nodes may be appropriate. When external beam photon radiation therapy (IMRT or 3DCRT) is delivered using multiple gantry angles, use of more than 9 gantry angles per treatment phase/target volume is unlikely to provide clinically meaningful improvements in dose distribution and can create greater inhomogeneity within the target. There is also concern over the longer treatment time.

V. Proton beam therapy (PBT)

PBT has been used in a number of institutions to deliver standard doses of radiation to the prostate either as solo therapy or as a boost after conventional therapy directed at the pelvic lymph nodes, building upon the hypothesis that the unique dose deposition characteristics of the proton beam may allow for a

reduction in the acute and late toxicity of definitive radiation for early stage prostate cancer. Prospective randomized studies are underway to determine the risks and benefits of this approach compared to IMRT. In the interim, the reader is directed to the specific Proton Beam Therapy policy section of the eviCore clinical guidelines.

VI. SBRT

The American Society for Radiation Oncology (ASTRO) consensus panel statement from April 2010 on the use of stereotactic body radiotherapy approaches (5 fractions or less) states, "...results, primarily available only in abstract form and consisting of reports of clinical experiences from single institutions, show that SBRT for the prostate is technically feasible, with little reported acute morbidity. Very early results, of limited statistical power, suggest that treatment will induce an initial PSA response of a magnitude equivalent to that seen with conventionally fractionated radiotherapy." Since the publication of the ASTRO consensus panel, there have been many more publications on the outcome and toxicity of SBRT for prostate cancer. The data confirms that PSA relapse-free survival and acute and chronic toxicity are equivalent with those of conventional EBRT or permanent brachytherapy, in publications now with medium follow up beyond 5 years. Although late outcome and toxicity data beyond 10 years are not yet available, SBRT for low- and intermediate-risk prostate cancer, in a selected and well-informed individual, is considered a medically necessary first line of treatment. ASTRO has published an updated model policy on SBRT that now confirms that SBRT is "...an appropriate alternative for select patients with low- to intermediate-risk disease".

The use of SBRT in the treatment of high-risk patients continues to evolve. For example, in a prospective trial of 97 patients with high-risk prostate cancer, the actuarial 6-year biochemical disease-free survival (bDFS) was 69% at a median follow up of 5 years. The incidence of late genitourinary (GU) toxicity was low. The incidence of late grade 2 gastrointestinal (GI) toxicity was found to have been higher (13.3%) in those patients who received SBRT following pelvic radiation vs. 0% in those patients receiving SBRT alone. In a subsequent publication, at a median follow up of 6 years, the actuarial 7-year freedom from biochemical failure was 68.5% for high-risk patients with low rates of late toxicity. In a study of 41 high- or very high-risk patients, whole pelvic radiation followed by SBRT resulted in an estimated 4-year biochemical failure-free survival of 91.9%. Finally, in a pooled analysis of prospective phase II clinical trials, the biochemical relapse free survival was 81% for high-risk patients. With long-term data emerging to support the efficacy and safety of SBRT for treatment of high-risk prostate cancer, SBRT can be considered medically necessary. It should be

noted that SBRT is defined as an entire treatment course consisting of five or fewer fractions. Thus, SBRT cannot be billed as a boost.

VII. Postoperative radiation therapy

In the setting of postoperative prostate cancer, external beam photon radiation therapy may be beneficial in the setting of positive margins, extracapsular extension, seminal vesicle involvement, lymph node involvement, or prostate cut-through. In addition, an individual with a detectable or rising postoperative PSA level may benefit from postoperative radiotherapy. In the postoperative setting, the treatment course generally does not exceed 8 weeks (maximum of 42 fractions).

References:

1. Abdel-Wahab M, Mahmoud O, Merrick G, et al. ACR Appropriateness Criteria®. External beam radiation treatment planning for clinically localized prostate cancer. Date of origin: 1996. Last review date: 2011. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69396/Narrative/>
2. Agazaryan N, Tenn S, Chow P, et al. Volumetric modulated arc therapy treatment protocol for hypo-fractionated stereotactic body radiotherapy for localized prostate cancer. *Int J Clin Oncol Biol Phys*. 2010 Nov 1; 78(3):S844. Abstract 3431. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)02927-5/fulltext](http://www.redjournal.org/article/S0360-3016(10)02927-5/fulltext)
3. Aluwini S, van Rooji P, Hoogeman M, et al. CyberKnife® stereotactic radiotherapy as monotherapy for low- to intermediate-stage prostate cancer: early experience, feasibility, and tolerance. *J Endourol*. 2010 May 17; 24(5):865-869. Accessed June 27, 2016. <http://online.liebertpub.com/doi/abs/10.1089/end.2009.0438>
4. ASTRO Model Policies – Stereotactic Body Radiation Therapy (SBRT) Approved 8-2-10. Updated 4-17-13. Accessed June 27, 2016. https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/2013HPCoding%20guidelines_SBRT_Final.pdf
5. Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol*. 2011 May 20; 29(15):2020-2026. Accessed June 27, 2016. <http://jco.ascopubs.org/content/29/15/2020.full>
6. Bolzicco G, Favretto MS, Scremin E, et al. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results. *Technol Cancer Res Treat*. 2010 Oct; 9(5):473-477. Accessed June 27, 2016. <http://tct.sagepub.com/content/9/5/473.abstract>
7. Buyyounski MK, Price RA, Harris EER, et al. Stereotactic body radiotherapy for primary management of early stage, low- to intermediate-risk prostate cancer: Report of the ASTRO Emerging Technology Committee. *Int J Radiat Oncol Biol Phys*. 2010 Apr; 76(5):1297-1304. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03543-3/fulltext](http://www.redjournal.org/article/S0360-3016(09)03543-3/fulltext)
8. Ciezki JP, Merrick G, Hsu ICJ, et al. ACR Appropriateness Criteria®. Locally advanced (high-risk) prostate cancer. Date of origin: 1996. Last review date: 2011. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69397/Narrative/>
9. Copp H, Bissonette EA, Theodorescu D. Tumor control outcomes of patients treated with trimodality therapy for locally advanced prostate cancer. *Urology*. 2005 Jun; 65(6):1146-1151. Accessed June 27, 2016. [http://www.goldjournal.net/article/S0090-4295\(04\)01474-8/abstract](http://www.goldjournal.net/article/S0090-4295(04)01474-8/abstract)
10. D'Amico AV, Cote K, Loffredo M, et al. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer *J Clin Oncol*. 2002, 20(23):4567-4573. Accessed June 27, 2016. <http://jco.ascopubs.org/content/20/23/4567.abstract>
11. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998 Sep 16; 280(11):969-974. Accessed June 27, 2016. <http://jama.jamanetwork.com/article.aspx?articleid=187980>
12. Demanes DJ, Rodriguez RR, Schour L, et al. High-dose- rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys*. 2005 Apr 1; 61(5):1306-1316. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(04\)02264-3/abstract](http://www.redjournal.org/article/S0360-3016(04)02264-3/abstract)
13. Eberhardt SC, Carter S, Casalino DD, et al. ACR Appropriateness Criteria®. Prostate cancer—pretreatment detection, staging, and surveillance. Date of origin: 1995. Last review date: 2012. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69371/Narrative/>
14. Frank SJ, Arterbery VE, Merrick G, et al. ACR Appropriateness Criteria®. Permanent source brachytherapy for prostate cancer. Date of origin: 1996. Last review date: 2010. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69399/Narrative/>
15. Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. *Radiation Oncology* 2011 Jan 10; 6(3). Accessed June 27, 2016. <http://www.ro-journal.com/content/6/1/3>
16. Friedland JL, Freeman DE, Masterson-McGary ME, et al. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat*. 2009 Oct; 8(5):387-392. Accessed June 27, 2016. <http://tct.sagepub.com/content/8/5/387.abstract>
17. Fuller DB, Mardirossian G, Wong D, et al. Prospective evaluation of stereotactic body radiotherapy for low- and intermediate-risk prostate cancer: emulating high-dose-rate brachytherapy dose distribution. *Int J Radiat Oncol Biol Phys*. 2012 Nov 1; 84(3):S149. Abstract 368. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)01328-4/fulltext](http://www.redjournal.org/article/S0360-3016(12)01328-4/fulltext)
18. Galalae RM, Martinez A, Mate T, et al. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2004 Mar 15; 58(4):1048-1055. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(03\)01746-2/abstract](http://www.redjournal.org/article/S0360-3016(03)01746-2/abstract)

19. Gustafson GS, Nguyen PL, Assimos DG, et al. ACR Appropriateness Criteria®. Prostatectomy irradiation in prostate cancer. Date of origin: 1996. Last review date: 2014. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69400/Narrative/>
20. Hossain S, Xia P, Huang K, et al. Dose gradient near target–normal structure interface for nonisocentric CyberKnife® and isocentric intensity-modulated body radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2010 Sep 1; 78(1):58-63. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)02947-2/abstract](http://www.redjournal.org/article/S0360-3016(09)02947-2/abstract)
21. Hsu ICJ, Yamada Y, Assimos DG, et al. ACR Appropriateness Criteria®. High-dose-rate brachytherapy for prostate cancer. Date of origin: 2013. Accessed June 27, 2016. <https://acsearch.acr.org/docs/3082863/Narrative/>
22. Jabbari S, Weinberg VK, Kaprealian T, et al. Stereotactic body radiotherapy as monotherapy or post-external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. *Int J Radiat Oncol Biol Phys.* 2012 Jan 1; 82(1):228-234. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)03447-4/fulltext](http://www.redjournal.org/article/S0360-3016(10)03447-4/fulltext)
23. Kang JK, Cho CK, Choi CW, et al. Image-guided stereotactic body radiation therapy for localized prostate cancer. *Tumori.* 2011; 97(1):43-48. Accessed June 27, 2016. <http://www.tumorjournal.com/article/image-guided-stereotactic-body-radiation-therapy-for-localized-prostate-cancer>
24. Katz AJ. CyberKnife® Radiosurgery for Prostate Cancer. *Technol Cancer Res Treat.* 2010 Oct; 9(5):463-472. Accessed June 27, 2016. <http://tct.sagepub.com/content/9/5/463.abstract>
25. Katz AJ and Kang J. Quality of life and toxicity after SBRT for organ-confined prostate, a 7-year study. *Front Oncol.* 2014 Oct 28; 4(31):1-6. Accessed June 27, 2016. <http://journal.frontiersin.org/article/10.3389/fonc.2014.00301/full>
26. Katz AJ and Kang J. Stereotactic body radiotherapy with or without external beam radiation as treatment for organ confined high-risk prostate carcinoma: a six year study. *Radiation Oncol.* 2014 Jan 1; 9(1):1-10. Accessed June 27, 2016. <http://ro-journal.biomedcentral.com/articles/10.1186/1748-717X-9-1>
27. Katz AJ, Santoro M. Quality of life and efficacy for stereotactic body radiotherapy for treatment of organ confined prostate cancer. *Int J Radiat Oncol Biol Phys.* 2010 Nov 1; 78(3):S58. Abstract 123. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01143-0/fulltext](http://www.redjournal.org/article/S0360-3016(10)01143-0/fulltext)
28. Katz AJ, Santoro M, Ashley R, et al. Stereotactic body radiotherapy for organ-confined prostate cancer. *BMC Urology* 2010; 10:1. Accessed June 27, 2016. <http://www.biomedcentral.com/1471-2490/10/1>
29. King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012 Feb 1; 82(2):877-882. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)03677-1/abstract](http://www.redjournal.org/article/S0360-3016(10)03677-1/abstract)
30. King CR, Brooks JD, Gill H, et al. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys.* 2009 Mar 15; 73:1043-1048. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(08\)02459-0/abstract](http://www.redjournal.org/article/S0360-3016(08)02459-0/abstract)
31. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiation Oncol.* 2013 Nov; 109(2):217-221. Accessed June 27, 2016. [http://www.thegreenjournal.com/article/S0167-8140\(13\)00430-1/fulltext](http://www.thegreenjournal.com/article/S0167-8140(13)00430-1/fulltext)
32. Lin Y-W, Lin L-C, and Lin K-L. The early result of whole pelvis radiotherapy and stereotactic body radiotherapy boost for high-risk localized prostate cancer. *Front Oncol.* 2014 Oct; 4(278):1-8. Accessed June 27, 2016. <http://journal.frontiersin.org/article/10.3389/fonc.2014.00278/full>
33. Michalski J, Pisansky TM, Lawton CA, et al. Prostate cancer (chapter 51) In: Gunderson L, Tepper J, editors. *Clinical Radiation Oncology*. 3. Philadelphia, PA: Churchill Livingstone; 2012. 1037-1097.
34. Mantz CA, Fernandez E, Zucker I, et al. A phase II trial of real-time target tracking SBRT for low-risk prostate cancer utilizing the Calypso 4D localization system: patient reported health-related quality of life and toxicity outcomes. *Int J Radiat Oncol Biol Phys.* 2010 Nov 1; 78(3):S57-S58. Abstract 121. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01141-7/fulltext](http://www.redjournal.org/article/S0360-3016(10)01141-7/fulltext)
35. Martinez AA, Gustafson G, Gonzalez J, et al. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. *Int J Radiat Oncol Biol Phys.* 2002 Jun 1; 53(2):316-327. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(02\)02733-5/abstract](http://www.redjournal.org/article/S0360-3016(02)02733-5/abstract)
36. Martinez A, Gonzalez J, Spencer W, et al. Conformal high dose rate brachytherapy improves biochemical control and cause specific survival in patients with prostate cancer and poor prognostic factors. *J Urol.* 2003 Mar; 169(3):974-979. Accessed June 27, 2016. [http://www.jurology.com/article/S0022-5347\(05\)63867-0/abstract](http://www.jurology.com/article/S0022-5347(05)63867-0/abstract)
37. Meier R, Beckman A, Kaplan I, et al. Stereotactic radiotherapy for organ-confined prostate cancer: early toxicity and quality of life outcomes from a multi-institutional trial. *Int J Radiat Oncol Biol Phys.* 2010 Nov 1; 78(3):S57. Abstract # 120. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01140-5/fulltext](http://www.redjournal.org/article/S0360-3016(10)01140-5/fulltext)
38. Meier R, Mark R, St. Royal L, et al. Postoperative radiation therapy after radical prostatectomy for prostate carcinoma. *Cancer.* 1992 Oct 1; 70(7):1960-1966. Accessed June 27, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/1097-0142\(19921001\)70:7%3C1960::AID-CNCR2820700725%3E3.0.CO;2-W/pdf](http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(19921001)70:7%3C1960::AID-CNCR2820700725%3E3.0.CO;2-W/pdf)

39. Merrick GS, Wallner KE, Butler WM. Permanent interstitial brachytherapy in the management of carcinoma of the prostate gland. J Urol. 2003 May; 169(5):1643-1652. Accessed June 27, 2016. <http://www.sciencedirect.com/science/article/pii/S0022534705636397>
40. Merrick GS, Wallner KE, Butler WM. Minimizing prostate brachytherapy-related morbidity. Urology. 2003 November; 62(5):786-792. Accessed June 27, 2016. [http://www.goldjournal.net/article/S0090-4295\(03\)00558-2/abstract](http://www.goldjournal.net/article/S0090-4295(03)00558-2/abstract)
41. Mroz P, Martin JM, DiPetrillo TA, et al. Analysis of potential cost benefits using reported hypofractionated radiation therapy regimens in prostate cancer in the United States. Int J Radiat Oncol Biol Phys. 2010 Nov 1; 78(3):S341-S342. Abstract 2309. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01783-9/fulltext](http://www.redjournal.org/article/S0360-3016(10)01783-9/fulltext)
42. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2016. Prostate Cancer. Accessed June 27, 2016. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Prostate Cancer 3.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
43. Nguyen P, Aizer A, Davis BJ, et al. ACR Appropriateness Criteria® Definitive external-beam irradiation in state T1 and T2 prostate cancer. Date of origin: 1996. Last review date: 2013. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69350/Narrative/>
44. Pham HT, Song G, Badiozamani K, et al. Five-year outcome of stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP) for patients with low-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2010 Nov 1; 78(3):S58. Abstract 122. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)01142-9/fulltext](http://www.redjournal.org/article/S0360-3016(10)01142-9/fulltext)
45. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol. 2005 Feb 20; 23(6):1192-1199. Accessed June 27, 2016. <http://jco.ascopubs.org/content/23/6/1192.full>
46. Stock RG, Cahlon O, Cesaretti JA, et al. Combined modality treatment in the management of high-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2004 Aug 1; 59(5):1352-1359. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(04\)00125-7/abstract](http://www.redjournal.org/article/S0360-3016(04)00125-7/abstract)
47. Townsend NC, Huth BJ, Ding W, et al. Acute toxicity after Cyberknife-delivered hypofractionated radiotherapy for treatment of prostate cancer. Am J Clin Oncol. 2011 Feb; 34(1):6-10. Accessed June 27, 2016. http://journals.lww.com/amjclinicaloncology/Fulltext/2011/02000/Acute_Toxicity_After_CyberKnife_Delivered.3.aspx
48. Trabulsi EJ, Valicenti RK, Hanlon AL, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for PT3/4N0 prostate cancer. Urol. 2008 Dec; 72(6):1298-1302. Accessed June 27, 2016. [http://www.goldjournal.net/article/S0090-4295\(08\)00770-X/abstract](http://www.goldjournal.net/article/S0090-4295(08)00770-X/abstract)
49. Van der Kwast TH, Bolla M, Poppel HV, et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy EORTC 22911. J Clin Oncol. 2007 Sep 20; 25(27):4178-4186. Accessed June 27, 2016. <http://jco.ascopubs.org/content/25/27/4178.full>
50. Wiegner EA, King CR. Sexual function after stereotactic body radiotherapy for prostate cancer: results of a prospective clinical trial. Int J Radiat Oncol Biol Phys. 2010 Oct 1; 78(2):442-448. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)02950-2/abstract](http://www.redjournal.org/article/S0360-3016(09)02950-2/abstract)
51. Yu JB, Soulos PR, Herrin J et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst. 2013 Jan 2; 105(1):25-32. Accessed June 27, 2016. <http://jnci.oxfordjournals.org/content/105/1/25.full>

Radiation Therapy of Prostate Cancer

[Return to Table of Contents](#)

Radiation Treatment of Rectal and Anal Canal Cancer

POLICY – Rectum

External beam photon radiation therapy using three-dimensional conformal radiation therapy (3DCRT) is medically necessary for the treatment of rectal cancer in any of the following clinical situations:

I. Surgical candidate

- A. Preoperative (neoadjuvant)
- B. Postoperative (adjuvant)

II. Medically inoperable

- A. As definitive radiation therapy

III. Local recurrence or salvage therapy in an individual with isolated pelvic / anastomotic recurrence when either of the following criteria is met:

- A. Resectable cases for either of the following:
 - 1. Preoperative chemotherapy and radiation therapy
 - 2. Postoperative followed by chemotherapy and radiation therapy
- B. Unresectable cases in conjunction with chemotherapy

IV. Palliative treatment in a previously un-irradiated individual who meets both of the following criteria:

- A. Has reasonable life expectancy
- B. Has unresectable metastatic disease and symptomatic local disease or near-obstructing primary tumors

POLICY – Anal Canal

External beam photon radiation therapy using 3DCRT or Intensity-Modulated Radiation Therapy (IMRT) is medically necessary for the definitive treatment of anal canal cancer

Key Clinical Points

Colorectal cancer is the third most commonly diagnosed cancer in the United States. Surgical resection plays a key role in treatment. The surgical approach depends on the extent and stage of disease. Transanal excisions are used for early stage lesions. Other transabdominal approaches include low anterior resections, total mesorectal excisions, and abdominal perineal resections. The Swedish Rectal Cancer Trial demonstrated an overall survival advantage to preoperative radiation. The German Rectal Cancer Study Group investigated preoperative chemoradiation compared with postoperative therapy.

Preoperative chemoradiation showed decreased local recurrence rates and improved sphincter function.

External beam photon radiation therapy is utilized in the neoadjuvant, adjuvant, palliative and medically inoperable settings.

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines American College of Radiology/American Society for Radiation Oncologists (ACR/ASTRO), National Comprehensive Cancer Network (NCCN) external beam photon radiation therapy is considered an integral component in the multidisciplinary management of rectal cancer. The rectum extends from the transitional zone of the dentate line to the sigmoid colon. Tumors extending below the peritoneal reflection are considered rectal, while more proximal tumors are considered colonic.

I. Treatment of rectal cancer

- A. Treatment of rectal cancer requires interdisciplinary interaction between the radiologist, gastroenterologist, colorectal surgeon, radiation oncologist, and medical oncologist. Surgical treatment can range from polypectomy for selected T1 tumors, transanal local excision for selected individuals with low risk T1/T2 tumors in the absence of positive margins, lymphovascular invasion (LVI), or high grade. For individuals who have T2 primary and negative margins, postoperative chemoradiation is appropriate after transanal excision. For individuals with T3 primary or positive nodes total mesorectal excision (TME) either by low anterior resection (LAR) or abdominoperineal resection (APR), depending on the proximity of the tumor to the anal verge.

Based on earlier randomized trial data, the National Institutes of Health (NIH) Consensus Conference of 1990 recommended postoperative chemoradiotherapy for individuals with T3 and/or node positive disease. More recent trials of preoperative chemoradiation have established that as the preferred approach. Preoperative therapy affords the opportunity for downstaging of the tumor, improved resectability, greater likelihood of sphincter preservation, and improved local control. Individuals who present with synchronous limited metastatic disease amenable to R0 resection may also be candidates for definitive post-operative chemoradiation. Individuals with isolated pelvic or anastomotic recurrence who have not received prior radiation may be appropriately treated with preoperative or postoperative chemoradiation with or without intraoperative external beam photon radiation therapy or with primary chemoradiation if deemed unresectable.

II. External beam photon radiation therapy treatment techniques and schedules for the treatment of rectal cancer

- A. External beam photon radiation therapy, preoperative and postoperative
Treatment technique typically involves the use of multiple fields to encompass the regional lymph nodes and primary tumor site. Customized blocking is utilized. 3DCRT is appropriate. IMRT is not medically necessary (see below). A dose of 45 to 54 Gy in 25 to 30 fractions over 5 to 6 weeks is commonly used.

Various treatment techniques may be used to decrease complications, such as prone positioning, customized immobilization (e.g. belly boards), and the use of multiple fields and incorporation of 3D treatment planning.

IMRT with photons is not medically necessary except in rare extenuating circumstances where higher doses are required (e.g. unresectable cases or those with positive margins) and normal tissues such as small bowel cannot be adequately spared. IMRT with photons in the pre- and postoperative settings should only be used in the setting of an institutional review board (IRB)-approved clinical trial. Consideration may be given to the use of IMRT with photons in select cases of locally and regionally advanced cancer when higher doses of radiation may be necessary.

For unresectable cancers or individuals who are medically inoperable, doses higher than 54 Gy may be appropriate. In the preoperative setting a dose of 50.4 Gy in 28 fractions is appropriate. A dose of 25 Gy in 5 fractions can also be considered in select individuals. In the postoperative setting with negative margins, 54 Gy in 30 fractions may be appropriate. Individuals with positive margins may require doses higher than 54 Gy.

- B. External beam photon radiation therapy, palliative
In previously un-irradiated individuals with unresectable metastatic disease and symptomatic local disease or near obstructing primaries who have reasonable life expectancy, external beam photon radiation therapy may be appropriate. Up to 20 fractions in 1 phase using 3DCRT or radiation planned using a complex isodose technique with photons is medically necessary. IMRT with photons is not medically necessary.

III. Treatment of anal canal cancer

- A. The role of radiation therapy in the treatment of anal canal cancer continues to evolve and is the subject of ongoing study. The current combination of chemotherapy and external beam photon radiation therapy is being explored,

as are the optimal doses and techniques. Dose escalation regimens, beyond those mentioned below, have not been established firmly as improving either local control or survival rates.

IV. External beam photon radiation therapy treatment techniques and schedules for the treatment of anal canal cancer

- A. External beam photon radiation therapy using 3DCRT or IMRT is medically necessary for the definitive treatment of anal canal cancer
- B. A dose of 45 Gy to 59.4 Gy in 25 to 33 fractions over 5 to 7 weeks is commonly used

References

1. Jones III WB Thomas Jr CR, Suh WW, et al. ACR Appropriateness Criteria® Resectable Rectal Cancer. Date of origin: 1998. Last review date: 2012. Accessed June 24, 2016. <https://acsearch.acr.org/docs/69381/Narrative/>
2. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016. Anal Carcinoma. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Anal Carcinoma 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
3. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016. Rectal Cancer. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Rectal Cancer 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
4. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA. 1990; 264(11):1444-50. Accessed June 24, 2016. <http://jama.jamanetwork.com/article.aspx?articleid=383259>
5. Sauer R, Becker H, Hohenberger W. et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004 Oct 21; 351(17):1731-1740. Accessed June 24, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa040694>

Radiation Treatment of Rectal and Anal Canal Cancer

[**Return to Table of Contents**](#)

Radiation Treatment of Soft Tissue Sarcomas

POLICY

This policy applies to sarcomas of soft tissues in the adult population. Soft tissue sarcomas are grouped in the following categories:

- Extremity, trunk, head and neck
- Retroperitoneal, intra-abdominal
- Gastrointestinal stromal tumor (GIST)
- Desmoid tumor (aggressive fibromatoses)
- Rhabdomyosarcoma

I. Extremity, trunk, head and neck sites

A. Preoperative radiation therapy with photons and/or electrons

Radiation therapy with photons and/or electrons is medically necessary when delivered prior to resection or attempted resection of a soft tissue sarcoma of an extremity, the trunk, or a head and neck site. At the time of surgery, the surgeon is encouraged to place clips both to identify the periphery of the surgical field and also to identify any potential sites of microscopic or gross residual disease that may be in need of higher amounts of radiation.

The medically necessary preoperative dose is 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day followed by a postoperative boost that depends on the extent of any disease remaining after resection.

Indications and doses medically necessary for a boost due to positive margins are the following:

1. External beam radiation therapy with photons and/or electrons
 - a. For microscopic residual disease (R1 resection) 16 Gy to 18 Gy
 - b. For gross residual disease (R2 resection) 20 Gy to 26 Gy
2. Brachytherapy - low dose rate (LDR)
 - a. For microscopic residual disease (R1 resection) 16 Gy to 18 Gy
 - b. For gross residual disease (R2 resection) 20 Gy to 26 Gy
3. Brachytherapy - high dose rate (HDR)
 - a. For microscopic residual disease (R1 resection) 3 Gy to 4 Gy given twice daily for a total of 14 Gy to 16 Gy
 - b. For gross residual disease (R2 resection) 3 Gy to 4 Gy given twice daily for a total of 18 Gy to 24 Gy
4. Intra-operative radiation therapy (IORT) with photons and/or electrons
 - a. For microscopic residual disease (R1 resection) 10 Gy to 12.5 Gy
 - b. For gross residual disease (R2 resection) 15 Gy

- B. Postoperative radiation therapy with photons and/or electrons (all radiation treatments planned to be given during and/or after resection)
- C. Radiation therapy is medically necessary when delivered at the time of or subsequent to resection or attempted resection of a soft tissue sarcoma of an extremity, the trunk, or a head and neck site. It is expected that the surgeon will have placed clips both to identify the periphery of the surgical field and also to identify any potential sites of microscopic or gross residual disease that may be in need of higher amounts of radiation, if anything other than an R0 (negative margins) was anticipated.

Indications and doses medically necessary for postoperative radiation therapy are the following:

1. External beam radiation therapy with photons and/or electrons - 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day followed by a boost:
 - a. For microscopically positive margins 16 Gy to 18 Gy
 - b. For gross residual disease 20 Gy to 26 Gy
2. LDR Brachytherapy
 - a. For positive surgical margins 16 Gy to 20 Gy followed by 50 Gy external beam radiation therapy using photons and/or electrons with conventional fractionation of 1.8 Gy to 2 Gy per day
 - b. For negative margins 45 Gy. No boost is medically necessary.
3. HDR Brachytherapy
 - a. For positive surgical margins 3 Gy to 4 Gy given twice daily for a total of 14 Gy to 16 Gy followed by 50 Gy external beam radiation therapy using photons and/or electrons using conventional fractionation of 1.8 Gy to 2 Gy per day
 - b. For negative margins 36 Gy given in 10 fractions on a twice-daily basis, 3.6 Gy per fraction. No boost is medically necessary.
4. IORT with photons and/or electrons - 10 Gy to 16 Gy followed by 50 Gy external beam radiation therapy using photons and/or electrons with conventional fractionation of 1.8 Gy to 2 Gy per day

II. Retroperitoneal and intra-abdominal sites (excluding desmoid tumors):

- A. Preoperative radiation therapy with photons
With the exception of desmoid tumors, radiation therapy with photons is medically necessary when delivered prior to resection or attempted resection of a soft tissue sarcoma of a retroperitoneal or intra-abdominal location. At the time of subsequent surgery, the surgeon is encouraged to place clips both to identify the periphery of the surgical field and any potential sites of microscopic or gross residual disease that may be in need of higher amounts of radiation.

Two dose schedules/techniques are medically necessary:

1. The preoperative dose is 50 Gy using conventional fractionation with photons of 1.8 Gy to 2 Gy per day, followed by a postoperative boost of photons that depends on the extent of any disease remaining after resection.
2. A preoperative dose-painting technique with photons is medically necessary to deliver the following:
 - a. Coverage of the entire clinical target volume (CTV) to a dose of 45 Gy to 50 Gy in 25 to 28 once-daily fractions
 - b. Simultaneous integrated boost to anticipated high risk margins to a dose of 57.5 Gy
- B. Intraoperative radiation therapy with photons and/or electrons
 1. IORT with photons and/or electrons: 10 Gy to 16 Gy followed by external beam radiation with photons and/or electrons of 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day
 - a. IORT with photons and/or electrons
 - i. For microscopically positive margins: 10 Gy to 12.5 Gy
 - ii. For gross residual disease: 15 Gy
- C. Postoperative radiation therapy with photons
Radiation therapy with photons is medically necessary when delivered subsequent to resection or attempted resection of a soft tissue sarcoma of a retroperitoneal or intra-abdominal location. It is expected that the surgeon will have placed clips both to identify the periphery of the surgical field and to help define potential sites of microscopic or gross residual disease that may benefit from additional radiation.

Indications and doses medically necessary for postoperative radiation therapy with photons are the following:

1. External beam radiation therapy with photons of 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day, followed by a boost:
 - a. For selected cases with negative margins (R0): 10 Gy with photons
 - b. For microscopically positive margins (R1): 16 Gy to 18 Gy with photons
 - c. For gross residual disease (R2 and re-resection not possible): 20 Gy to 26 Gy with photons

III. Treatment of primary or metastatic sites for salvage or palliation

Palliation of recurrent or metastatic sites of soft tissue sarcoma may be medically necessary when other alternatives are less appropriate. The use of radiation in such circumstances must balance between expedience, the need and ability to relieve symptoms, the high doses that are required to achieve a response, and the potential normal tissue damage that can be inflicted. All requests for the palliative use of radiation with photons that involve Intensity-Modulated Radiation Therapy (IMRT), Stereotactic Body Radiation Therapy (SBRT), or more than 15 fractions require medical review. Palliative treatment with electrons is done with

Complex Radiation Therapy technique and should not exceed 15 fractions as well.

IV. Radiation techniques

A. Complex

Complex technique with photons and/or electrons is medically necessary most commonly in the palliative setting in which a simple, expeditious approach is required to relieve symptoms.

B. Three-dimensional conformal radiation therapy (3DCRT)

3DCRT with photons is medically necessary in all cases of curative intent in order to limit the radiation dose to normal nearby organs at risk (OARs). 3DCRT is also medically necessary in the palliative treatment of soft tissue sarcomas.

C. IMRT

IMRT is considered medically necessary when 3DCRT is unable to protect adequately the nearby OARs from doses of radiation that exceed published constraints. This is commonly the situation in cases of curative intent where the clinical circumstance requires doses in excess of 50 Gy. IMRT is medically necessary when a dose-painting technique is appropriate to deliver a simultaneous integrated boost. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN).

D. IORT

IORT is medically necessary when given in conjunction with external beam radiation therapy with photons and/or electrons and is not regarded as medically necessary as a sole means of delivering radiation therapy to a soft tissue sarcoma. IORT requires special technology in that it is delivered in a single fraction to the tumor or tumor bed during the surgical procedure being performed to resect the sarcoma.

E. Brachytherapy

Brachytherapy may be given using an HDR approach or an LDR approach and is medically necessary in cases in which a boost is required or as the sole means of delivering radiation for tumors that have been completely resected with clear margins.

When HDR is utilized, afterloading catheters are placed at the time of surgery, and the radioactive sources are briefly placed within them multiple times, most commonly twice daily, for several days. One placement of HDR afterloading catheters is medically necessary, as is up to six loadings of the radioactive sources into them.

When utilized, LDR brachytherapy is performed by placing radioactive material permanently into the region of the tumor. As the radioisotope decays fully, the radiation dose is delivered; the material becomes non-radioactive and can be left in place. One LDR insertion is medically necessary.

F. SBRT

SBRT with photons is medically necessary to treat a locally recurrent soft tissue sarcoma that is within or immediately adjacent to an area that has received radiation treatments as part of the primary management.

For SBRT treatment of metastases, please refer to the separate Radiation Treatment of Extra-Cranial Oligometastases clinical guideline.

G. Image-Guided Radiation Therapy (IGRT)

Please refer to the separate IGRT criteria.

Key Clinical Points

Radiation therapy with photons and/or electrons is medically necessary in all potentially curable cases of soft tissue sarcoma of the extremity, trunk, head and neck, retroperitoneal and intra-abdominal sites, with the exceptions of retroperitoneal or intra-abdominal desmoid tumors, and of low grade, stage I sarcomas that have been resected and oncologically appropriate margins have been achieved.

Radiation therapy with photons and/or electrons is medically necessary in palliative cases of soft tissue sarcoma of the extremity, trunk, head and neck, retroperitoneal and intra-abdominal sites when other simpler methods of palliation are inadequate, ineffective, or not available.

Radiation therapy is not medically necessary in the initial management of GIST but does have a role in management of refractory or unresectable cases.

Radiation therapy with photons and/or electrons may play a role in the management of desmoid tumors but is generally limited to sites other than retroperitoneal or intra-abdominal.

Of the rhabdomyosarcomas, management of the pleomorphic variety is similar to that of other soft tissue sarcomas. The non-pleomorphic variety often occurs in the pediatric population, and its management is less well defined.

Treatment is to be given in a multi-disciplinary environment in which the radiation oncologist is consulted prior to a resection attempt.

Medically necessary radiation therapy with photons and/or electrons employs the use of highly sophisticated treatment planning and the use of highly conformal delivery techniques to achieve a suitable therapeutic ratio of target coverage versus protection

of normal tissues. Radiation dose is to be influenced by normal tissue tolerance, i.e. doses listed herein may require modification based on normal tissue constraints.

Radiation therapy is not a substitute for completeness of resection. Re-resection may be indicated in some cases. However, further resection may not be feasible for medical or technical reasons and this may serve as an indication for additional radiation (boost) in selected cases. Examples include extremely large tumors, high-grade lesions, or the morbidity of further surgery. The risk and feasibility of administering additional radiation must be weighed against that of additional surgery. Means to mitigate radiation to nearby structures, such as tissue displacement using omentum, biologic or synthetic material, may be incorporated into the resection procedure when additional postoperative radiation is contemplated.

References

1. Al Yami A, Griffin AM, Ferguson PC, et al. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? *Int J Radiat Oncol Biol Phys*. 2010 Jul 15; 77(4):1191-1197. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)02771-0/abstract](http://www.redjournal.org/article/S0360-3016(09)02771-0/abstract)
2. Alektiar KM, Brennan MF, Healey JH, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol*. 2008 Jul 10; 26(20):3440-3444. Accessed June 24, 2016. <http://jco.ascopubs.org/content/26/20/3440.full>
3. Baldini EH. Soft Tissue Sarcoma (Excluding Retroperitoneum) in Halperin EC, Wazer DE, Perez CA, et al., ed. *Perez and Brady's Principles and Practice of Radiation Oncology*. 6th Edition. Philadelphia, PA: Lippincott Williams & Wilkins, a Wolters Kluwer business, 2013: Chapter 83:1617-1631.
4. Catton C, Davis A, Bell R, et al. Soft tissue sarcoma of the extremity. Limb salvage after failure of combined conservative therapy. *Radiother Oncol*. 1996 Dec; 41(3):209-214. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S0167814096018567>
5. Chung CS, Trofimov A, Adams J, et al. A comparison of 3D conformal radiation therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas, *Int J Radiat Oncol Biol Phys* 2006; 66(3S):S116. Abstract 207. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)01476-3/fulltext](http://www.redjournal.org/article/S0360-3016(06)01476-3/fulltext)
6. Edge S, Byrd DR, Compton CC et al., ed. *AJCC Cancer Staging Handbook from the AJCC Cancer Staging Manual*, 7th edition. Chicago, IL: Springer, 2010: Chapter 28:345-355.
7. Folkert MR, Singer S, Brennan MF, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol*. 2014 Oct 10; 32(29):3236-3241. Accessed June 24, 2016. <http://jco.ascopubs.org/content/32/29/3236.abstract>
8. Haas RML, DeLaney TF, O'Sullivan B, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol Phys*. 2012 Nov 1; 84(3):572-580. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(12\)00135-6/abstract](http://www.redjournal.org/article/S0360-3016(12)00135-6/abstract)
9. Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol*. 2006 Feb 1; 24(4):619-625. Accessed June 24, 2016. <http://jco.ascopubs.org/content/24/4/619.full>
10. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys*. 2010 Mar 1; 76(3S):S10-S19. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(09\)03288-X/abstract](http://www.redjournal.org/article/S0360-3016(09)03288-X/abstract)
11. Musat E, Kantor G, Caron J, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional conformal radiotherapy for postoperative retroperitoneal sarcoma [original article published in French]. *Cancer Radiother*. 2004 Aug; 8(4):255-261. Accessed June 24, 2016. <http://www.sciencedirect.com/science/article/pii/S127832180400071X>
12. Nag S, Shasha D, Janjan N, et al. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 2001 Mar 15; 49(4):1033-1041. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(00\)01534-0/abstract](http://www.redjournal.org/article/S0360-3016(00)01534-0/abstract)
13. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016. Soft Tissue Sarcoma. Accessed June 24, 2016. http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Soft Tissue Sarcoma Version 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
14. Torres MA, Ballo MT, Butler CE, et al. Management of locally recurrent soft-tissue sarcoma after prior surgery and radiation therapy. *Int J Radiat Oncol Biol Phys*. 2007 Mar 15; 67(4):1124-1129. Accessed June 24, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)03375-X/abstract](http://www.redjournal.org/article/S0360-3016(06)03375-X/abstract)
15. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2014, *J Natl Compr Canc Netw*. 2014 Apr; 12(4):473-483. Accessed June 24, 2016. <http://www.jnccn.org/content/12/4/473.full>

Radiation Therapy of Soft Tissue Sarcomas

[Return to Table of Contents](#)

Radiation Treatment of Testicular Cancer

POLICY

External beam photon radiation therapy is medically necessary for the following:

- I. Stage IA, IB, IIA, and IIB testicular seminoma**

Fractionation

- I. For seminoma stages IA-IB in the adjuvant setting, up to 10 fractions is medically necessary**
- II. For seminoma stages IIA-IIB in the adjuvant setting, up to 18 fractions is medically necessary**

Technique

- I. External beam photon radiation therapy with three-dimensional conformal radiation therapy (3DCRT) is medically necessary in the treatment of seminoma**

In stages IA-IB, the treatment prescription is to the para-aortic nodes to a dose of 20 Gy in 10 fractions delivered with an AP-PA field arrangement.

In stages IIA-IIB, the initial treatment prescription is to a modified dog-leg field to 20 Gy in 10 fractions followed by a boost of 10 to 16 Gy in 5 to 8 fractions with an AP-PA field arrangement, in two phases.

Key Clinical Points

I. Seminoma

In an individual with stage I seminoma, radical orchiectomy serves as the initial treatment for testicular malignancies (Groll et al, 2007). Following orchiectomy, the management of the individual is dependent on the histologic type and whether residual disease is present.

Treatment options for those who have a pure seminoma with no sign of residual disease (stage I) include active surveillance, radiation therapy to the para-aortic lymph nodes or single agent carboplatin (Bernard et al., 2015). Cure rates with orchiectomy alone

approach 85% (Mortensen, et al., 2014). Furthermore, salvage therapies for seminoma are very effective and administered with curative intent. Therefore, active surveillance is the recommended treatment option in an individual with stage I seminoma because it avoids unnecessary treatment and the treatment-related side effects that are associated with radiation and chemotherapy (Kollmannsberger et al., 2015).

For an individual who refuses active surveillance, chemotherapy or radiation therapy is a treatment option. A phase III trial studied both treatment approaches in 1,477 patients with stage I seminoma and found similar relapse free rates with one cycle of carboplatin vs. radiation (94.7% vs. 96%, respectively) (Oliver et al., 2011). Radiation therapy may be associated with worse long term complications including an increased risk of secondary malignancies and increased risk for cardiovascular disease. In an individual who refuses active surveillance and chemotherapy, radiation can be administered to a dose of 20 Gy to the para-aortic lymph nodes (Jones et al., 2005).

For an individual with stage II seminoma, radiation therapy can be effective in the treatment of stage IIA and non-bulky IIB disease (nodes < 3cm) (Classen et al., 2003). Chemotherapy is recommended for an individual with bulky nodal disease. Studies in patients with IIA and non-bulky IIB seminoma show 5-year disease free results of greater than 90%. Treatment with radiation consists of 20 Gy in 10 fractions to the para-aortic and superior ipsilateral pelvis followed by a boost of 10 to 16 Gy in 5 to 8 fractions to the involved nodal areas, in two phases (Schmoll et al., 2004).

An individual receiving radiation therapy for seminoma should be treated with a scrotal shield and with an AP-PA technique to limit dose the kidneys, liver and small bowel. Intensity modulated radiation therapy is not medically necessary because it increases the amount of tissue receiving a low dose of radiation which may increase the risk of second cancers relative to an AP-PA beam arrangement.

II. Nonseminoma

Nonseminomatous germ cell tumors are primarily managed with surgery and chemotherapy (Kollmannsberger et al., 2010). Men at low risk of relapse can be managed with an orchiectomy alone. Those with a higher risk of relapse are managed with chemotherapy. In general, there is no established role for the routine use of radiation therapy in the management of nonseminomatous germ cell tumors.

References

1. Bernard B, Sweeney CJ. Diagnosis and treatment of testicular cancer: a clinician's perspective. Surg Pathol Clin. 2015 Dec; 8(4):717-723. Accessed June 24, 2016. [http://www.surgpath.theclinics.com/article/S1875-9181\(15\)00090-2/fulltext](http://www.surgpath.theclinics.com/article/S1875-9181(15)00090-2/fulltext)
2. Classen J, Schmidberger H, Meisner C, et al. Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol. 2003 Mar 15; 21(6):1101-1106. Accessed June 24, 2016. <http://jco.ascopubs.org/content/21/6/1101.full>
3. Groll RJ, Warde P, Jewett MAS. A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol. 2007 Dec; 64(3):182-197. Accessed June 24, 2016. [http://www.croh-online.com/article/S1040-8428\(07\)00109-6/fulltext](http://www.croh-online.com/article/S1040-8428(07)00109-6/fulltext)
4. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on medical research council trial TE18, european organisation for the research and treatment of cancer trial 30942 (ISRCTN18525328). J Clin Oncol. 2005 Feb 20; 23(6):1200-1208. Accessed June 24, 2016. <http://jco.ascopubs.org/content/23/6/1200.full>
5. Kollmannsberger C, Moore C, Chi KN, et al. Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. Ann Oncol. 2010 Jun; 21(6):1296-1301. Accessed June 24, 2016. <http://annonc.oxfordjournals.org/content/21/6/1296.full>
6. Kollmannsberger C, Tandstad T, Bedard PL, et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. J Clin Oncol. 2015 Jan 1; 33(1):51-57. Accessed June 24, 2016. <http://jco.ascopubs.org/content/33/1/51.full>
7. Mortensen MS, Lauritsen J, Gundgaard MG, et al. A nationwide cohort study of stage I seminoma patients followed on a surveillance program. Eur Urol. 2014 Dec; 66(6):1172-1178. Accessed June 24, 2016. [http://www.europeanurology.com/article/S0302-2838\(14\)00629-0/abstract/a-nationwide-cohort-study-of-stage-i-seminoma-patients-followed-on-a-surveillance-program](http://www.europeanurology.com/article/S0302-2838(14)00629-0/abstract/a-nationwide-cohort-study-of-stage-i-seminoma-patients-followed-on-a-surveillance-program)
8. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016 Testicular Cancer. Accessed June 24, 2016. https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Testicular Cancer. 2.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
9. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol. 2011 Mar 10; 29(8):957-962. Accessed June 24, 2016. <http://jco.ascopubs.org/content/29/8/957.full>
10. Schmoll HJ, Souchon R, Krege S, et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the european germ cell cancer consensus group (EGCCCG). Ann Oncol. 2004 Sep; 15(9):1377-1399. Accessed June 24, 2016. <http://annonc.oxfordjournals.org/content/15/9/1377.full>

Radiation Treatment of Testicular Cancer[**Return to Table of Contents**](#)

Radiation Treatment of Urethral Cancer and Upper Genitourinary Tract Tumors

POLICY

External beam photon radiation therapy (EBRT) is medically necessary for the following:

- I. Definitively in urethral cancer in an individual with T2-T4 disease or node positive**
- II. Postoperatively in urethral cancer in an individual with T3-T4 disease, node positive, or positive surgical margins**
- III. Palliation**
- IV. Radiation therapy is not considered medically necessary in the definitive treatment of cancers of the ureter or renal pelvis**

Fractionation

- I. In the definitive setting up to 39 fractions is medically necessary**
- II. In the adjuvant setting in an individual with no high risk features, up 30 fractions is medically necessary**
- III. In the adjuvant setting in an individual with positive margins or extra-nodal extension, up to 39 fractions is medically necessary**
- IV. In the palliative setting up to 20 fractions is medically necessary**

Techniques

- I. EBRT with three-dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT) is medically necessary in the definitive treatment of urethral cancer. Treatment prescriptions include the pelvic and inguinal**

lymph nodes to 40 to 45 Gy followed by a boost to 70 Gy to areas of gross disease in 2 to 3 phases of treatment

II. 3DCRT is medically necessary in the palliative setting

Key Clinical Points

Treatment for urethral cancer is dependent on gender, tumor location and tumor size (Dayyani, 2014). In males, surgical options include a distal urethrectomy, partial penectomy, or a urethrectomy with a cystoprostatectomy in males. In females, surgical options include a urethrectomy with or without a cystectomy.

Adjuvant radiation can be delivered for an individual with a high risk of recurrence including one with positive nodes, positive margins or T3-T4 disease.

In an individual who refuses surgery or one with advanced disease, concurrent chemoradiation can be used (Gakis, 2013; Grivas, 2012). Often the draining lymphatics will include the pelvic and inguinal lymph nodes and appropriate techniques include 3DCRT or IMRT. Brachytherapy can also be utilized and will be considered on a case-by-case basis.

References:

1. Dayyani F, Hoffman K, Eifel P, et al. Management of advanced primary urethral cancer. BJU Int. 2014 Jul; 114(1):25-31. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/bju.12630/full>
2. Gakis G, Witjes JA, Comp  rat E, et al. EAU guidelines on primary urethral carcinoma. Euro Urol. 2013. 2013 Nov; 64(5):823-830. Accessed June 27, 2016. [http://www.europeanurology.com/article/S0302-2838\(13\)00298-4/fulltext/eau-guidelines-on-primary-urethral-carcinoma](http://www.europeanurology.com/article/S0302-2838(13)00298-4/fulltext/eau-guidelines-on-primary-urethral-carcinoma)
3. Grivas PD, Daignault MS, Tagawa ST, et al. Double-blind, randomized, phase 2 trial of maintenance sunitinib versus placebo after response to chemotherapy in patients with advanced urothelial carcinoma. Cancer. 2014 Mar 1; 120(5):692-701. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.28477/abstract>
4. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016. Bladder Cancer. Accessed June 27, 2016. http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN GuidelinesTM) for Bladder Cancer 2.2016[ ]. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN GuidelinesTM and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Radiation Treatment of Urethral Cancer and Upper Genitourinary Tract Tumors

[Return to Table of Contents](#)

Radioactive Yttrium-90 Microspheres

Overview

Selective internal radiation therapy (SIRT), also known as radioembolization with microsphere brachytherapy device (RMBD) and transarterial radioembolization (TARE), is a form of arterially directed therapy for primary and secondary liver cancer. The treatment involves catheter-based injection of radioactive Yttrium-90 (^{90}Y) microspheres, in either glass or resin form, through the arterial branch feeding the affected portion of the liver. Although radioembolization with Yttrium-90 (^{90}Y) microspheres involves some level of particle-induced vascular occlusion, it has been proposed that such occlusion is more likely to be microvascular than macrovascular, and that the resulting tumor necrosis is more likely to be induced by radiation rather than ischemia.

POLICY

I. Indications

Selective internal radiation therapy (SIRT), using radioactive Yttrium-90 (^{90}Y) microspheres, is indicated in an individual with:

- A. Unresectable and/or medically inoperable primary or metastatic liver malignancies
 - 1. Unresectable liver only or liver dominant metastases from neuroendocrine tumors (e.g., carcinoids, pancreatic islet cell tumors, endocrine tumor)
 - 2. Unresectable primary hepatocellular carcinoma (HCC)
 - 3. Unresectable metastatic liver tumors from primary colorectal cancer
 - 4. Requests for the treatment of liver metastases from other primary malignancies, including breast carcinoma, ocular melanoma, cutaneous melanoma, and intrahepatic cholangiocarcinoma, will be considered on a case-by-case basis. These requests should be based on the lack of any known systemic or liver-directed treatment options for this individual in an effort to relieve symptoms and/or possibly extend life expectancy
- B. The tumor burden should be liver dominant, not necessarily exclusive to the liver
- C. Eastern Cooperative Oncology Group (ECOG) performance status should be 0 or 1 or Karnofsky Performance Status (KPS) of 70 or more
- D. Life expectancy should be at least 3 months
- E. Radioactive Yttrium-90 (^{90}Y) microspheres treatment is allowed only in the outpatient setting unless the documentation supports the medical necessity of inpatient treatment

Repeat radioembolization may be used for new or progressive primary or metastatic liver cancers when:

- A. The individual has had a previous satisfactory response to an initial radioembolization treatment as evidenced on results of a computed tomography (CT) scan or positron emission tomography (PET)-CT scan performed 3 months following the previous procedure. Response should be graded according to the revised RECIST guideline (Version 1.1)
- B. The disease still must be liver dominant
- C. Life expectancy of at least 3 months
- D. ECOG performance status no greater than 2 or KPS of 70 or more
- E. There are no other effective systemic or liver-directed treatment options
- F. The individual has compensated liver function tests (LFTs)
- G. Estimated lung dose and combined lung dose from previous embolizations are within acceptable dose volume constraints. Exclude an individual with lung shunting in which the lung radiation dose is greater than 35 to 30 Gy per treatment or greater than 50 Gy cumulatively for all treatments
- H. Treatment should be given to a targeted tumor volume
- I. Repeat whole liver irradiation is considered experimental, investigational, or unproven (EIU) and will not be certified
- J. Requests for a third radioembolization will not be certified
- K. All requests for repeat radioembolization are subject to medical review and will be judged on a case-by-case basis

Key Clinical Points

Radioembolization with Yttrium-90 microspheres has proven safe and effective in palliation of symptoms as well as possible increase in survival in selected cancer patients. Given this proven effect, consideration is now being given to repeating the procedure in an individual who has responded well previously, has good performance status, and has liver dominant disease without other treatment options. In their series of 148 patients diagnosed with neuroendocrine tumor metastases to the liver treated with Yttrium-90 microspheres, Vyleta et al. (2011) noted a subgroup of 33 patients who were retreated to the same liver lobe with very low toxicity and no evidence of radiation-induced liver disease (RILD). They also commented on other published studies in which a few patients even received a third treatment. In their analysis, increased duration of tumor responses was noted and most deaths were attributed to progression of extrahepatic disease. Similarly, Lewandowski et al. (2006) noted further palliation and prolongation of survival in individuals retreated for viable residual or recurrent liver metastases. Favorable prognostic indicators for longer survival in their entire series of 82 initial and retreated patients included a lower pretreatment level of alpha-fetoprotein (AFP) and a higher tumor to baseline uptake ratio.

Lam et al. (2013) attempted to correlate the occurrence of RILD in a population of 247 patients treated to a targeted area with Yttrium-90 microspheres within univariate

analyses of multiple variables. This population included 8 patients who were retreated. Two of these patients received a second treatment to the whole liver and died shortly after the second treatment with signs and symptoms of RILD. Cumulative doses of 3.08 and 2.66 GBq were noted respectively. The remaining 6 patients experienced minor side effects with cumulative doses of 2.41 to 3.88 GBq. Objective responses were noted in all patients. Risk factor analysis disclosed repeat radioactive remobilization, serum total bilirubin and baseline serum aspartate aminotransferase as significant factors in the development of RILD but only repeat radioembolization proved to be an independent indicator. The authors noted objective tumor responses but commented on the need for improved safety limits, which will require better dosimetric measurement.

At this time, requests for a second radioembolization treatment will be considered on a case-by-case basis. Third treatment requests will not be certified nor will requests for a second radioembolization procedure to the whole liver.

I. Absolute contraindications

- A. Inability to catheterize the hepatic artery
- B. Fulminant liver failure (Childs-Pugh status late B or C)
- C. ^{99m}Tc-Albumin Macroaggregates (^{99m}Tc-MAA) hepatic arterial perfusion scintigraphy demonstrating significant reflux or non-target deposition to the gastrointestinal organs that cannot be corrected by angiographic techniques. It is important that liver injection of ^{99m}Tc-MAA is delivered with flow rates and catheter position that mimic the anticipated ⁹⁰Y infusion rate catheter position
- D. ^{99m}Tc-MAA hepatic arterial perfusion scintigraphy demonstrating the potential > 30 Gy radiation exposure to the lung

II. Relative contraindications

- A. Excessive tumor burden in the liver with greater than 70% of the parenchyma replaced by tumor
- B. Prior extensive liver resection
- C. Total bilirubin greater than 2 mg/dL in the absence of reversible cause (e.g. obstruction), which indicates severe liver function impairment. Nonobstructive bilirubin elevations generally indicate that liver metastases have caused liver impairment to a degree at which risks outweigh benefits for this therapy. In contrast, patients with hepatocellular carcinoma (HCC) and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed
- D. Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the authorized user required). Based on a study by Lam et al. (2013) the fraction of liver exposed to ≥ 30 Gy (V30) is the strongest predictor of hepatotoxicity. All patients with V30 > 13% experienced hepatotoxicity

- E. Concurrent or prior capecitabine chemotherapy (within the previous two months)
- F. If the patient is known to be pregnant, the potential radiation risks to the fetus and clinical benefits of the procedure required before, during, and after RMBD, and any scatter radiation from the hepatic implant should be considered before proceeding with treatment
- G. Portal vein thrombosis (PVT): Tsi et al. suggests ^{90}Y microspheres are tolerated in patients with HCC and major PVT. Kulik et al. (2008) reported more grade 3/4 adverse events in patients with main portal vein thrombosis. Schwartz et al. (2010) states ^{90}Y is a safe microembolization treatment that can be used as an alternative to TACE in patients in case of PVT

III. Chemotherapy (adjuvant or concurrent) for case-by-case requests

- A. Requests submitted on a case-by-case basis for the use of SIRT as a debulking agent will not be certified. There are currently no national guidelines, such as those of the National Comprehensive Cancer Network (NCCN), for the use of SIRT in this manner. As both the clinical effectiveness and toxicity of combined treatment is not known, treatment in this setting is considered experimental, investigational, or unproven (EIU)

IV. Treatment target planning

- A. Treating multiple tumors within the entire liver in a single treatment session is termed whole liver delivery. Treating the entire liver by first treating one lobe and then the other in separate sessions is termed sequential delivery; both are described in the literature. Treatment to a single lobe only is termed lobar delivery. In the sequential treatment, a 30 to 45 day interval is the generally accepted practice
- B. Treatment to additional lobes may be done if a positive response of the first is achieved as evidenced by any of the following:
 - 1. Stability in tumor size
 - 2. Tumor shrinkage
 - 3. Necrosis within the tumor with or without shrinkage
 - 4. Improvement in liver function test results
 - 5. Improvement in performance status or pain

Repeat treatment of a lobe/segment may be necessary in a previously treated vascular bed (lobe), such as recurrent disease or incompletely treated disease. A 90-day interval before retreatment of the PTV is recommended for adequate hepatic healing.

References:

1. ACR-SIR practice parameter for radioembolization with microsphere brachytherapy device (RMBD) for treatment of liver malignancies. Revised 2014. Accessed June 27, 2016. <http://www.acr.org/-/media/ACR/Documents/PGTS/guidelines/RMBD.pdf>
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. American Association for Study of Liver Disease (AASLD) Practice Guideline. Hepatology. 2011 Mar; 53(3):1020-1022. Accessed June 27, 2016. <http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf>
3. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo-controlled trial. Lancet Oncol. 2009 Jan; 10(1):25-34. Accessed June 27, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(08\)70285-7/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(08)70285-7/fulltext)
4. Chua TC, Bester L, Saxena A et al. Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases. J Cancer Res Clin Oncol. 2011 May; 137(5):865-873. Accessed June 27, 2016. <http://link.springer.com/article/10.1007/s00432-010-0948-y>
5. ClinicalTrials.gov Searched for Radioembolization on June 27, 2016. <http://www.clinicaltrials.gov/ct2/results?term=RADIOEMBOLIZATION+&Search=Search>
6. Coldwell D, Sangro B, Salem R, et al. Radioembolization in the treatment of unresectable liver tumors: experience across a range of primary cancers. Am J Clin Oncol. 2012 Apr; 35(2):167-77. Accessed June 27, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2012/04000/Radioembolization_in_the_Treatment_of_Unresectable.15.aspx
7. Deleporte A, Flamen P, Hendlitz A. State of the art: radiolabeled microspheres treatment for liver malignancies. Expert Opin Pharmacother. 2010 Mar; 11(4):579-86. Accessed June 27, 2016. <http://informahealthcare.com/doi/abs/10.1517/14656560903520916?journalCode=eop>
8. Gray B, Van Hazel G, Hope M, et al. Randomized trial of SIR-Spheres[®] plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001; 12(12):1711-1720. Accessed June 27, 2016. <http://annonc.oxfordjournals.org/content/12/12/1711.full.pdf+html>
9. Hendlitz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with Yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010 Aug 10; 28(23):3687-3694. Accessed June 27, 2016. <http://jco.ascopubs.org/content/28/23/3687>
10. Kennedy AS, DeZam WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol. 2008 Jun; 31(3):271-279. Accessed June 27, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2008/06000/Radioembolization_for_Unresectable_Neuroendocrine.12.aspx
11. Kennedy A, Nag S., Salem R. et al. Recommendations for radioembolization of hepatic malignancies using Yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007 May 1; 68(1):13-23. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(07\)00097-1/abstract](http://www.redjournal.org/article/S0360-3016(07)00097-1/abstract)
12. King J, Quinn R, Glenn DM, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer. 2008 Sep 1; 113(5):921-929. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.23685/full>
13. Kouri BE, Funaki BS, Ray Jr CE. Expert Panel on Interventional Radiology. ACR Appropriateness Criteria[®] radiologic management of hepatic malignancy. Date of origin 2007. Last review date 2011. Accessed June 27, 2016. <https://acsearch.acr.org/docs/69379/Narrative/>
14. Kulik LM, Atassi B, van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere[®]) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol. 2006 Dec 1; 94(7):572-586. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/jso.20609/abstract>
15. Kulick LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of ⁹⁰Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008 Jan; 47(1):71-81. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/hep.21980/full>
16. Lam MGEH, Abdelmaksoud MH, Chang DT, et al. Safety of ⁹⁰Y radioembolization in patients who have undergone previous external beam radiation therapy. Int J Radiat Oncol Biol Phys. 2013 Oct 1; 87(2):323-329. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(13\)00634-2/abstract](http://www.redjournal.org/article/S0360-3016(13)00634-2/abstract)
17. Lau WY, Kennedy AS, Kim YH, et al. Patient selection and activity planning guide for selective internal radiotherapy with Yttrium-90 resin microspheres. Int. J Radiat Oncol Biol Phys 2012 Jan 1; 82(1):401-407. Accessed June 27, 2016. <http://www.sciencedirect.com/science/article/pii/S0360301610030610>

18. Lau WY, Lai ECH, Leung TWT. Current role of selective internal irradiation with Yttrium-90 microspheres in the management of hepatocellular carcinoma: a systematic review. *Int. J. Radiat Oncol Biol Phys.* 2011 Oct 1; 81(2):460-467. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(10\)00819-9/abstract](http://www.redjournal.org/article/S0360-3016(10)00819-9/abstract)
19. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant.* 2009 Aug 9; 9(8):1920–1928. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2009.02695.x/full>
20. Llovet JM, Di Bisceglie AM, Bruix J, et al., Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008 May 21; 100(10):698-711. Accessed June 27, 2016. <http://jnci.oxfordjournals.org/content/100/10/698.full.pdf+html>
21. Llovet JM, Ricci S, Mazzaferro V, et al., Sorafenib in advanced hepatocellular carcinoma *N Engl J Med.* 2008 Jul 24; 359(4):378-390. Accessed June 27, 2016. <http://www.nejm.org/doi/full/10.1056/NEJMoa0708857>
22. Mazzaferro V, Regalia E, Doci R, et al., Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996 Mar 14; 334(11):693-700. Accessed June 27, 2016. <http://www.nejm.org/doi/full/10.1056/NEJM199603143341104#t=abstract>
23. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2016. Hepatobiliary Cancers. Accessed June 27, 2016. http://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Hepatobiliary Cancers 1.2016. © 2015 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.
24. Nichols EM, Grabowski S, Hanlon A et al. Performance status (PS), number of lesions and interval from metastatic diagnosis treatment (IMDTT) predict for overall survival (OS) in patients treated with hepatic transarterial radioembolization (TARE) with Yttrium-90 (Y⁹⁰) microspheres. *Int J Radiat Oncol Biol Phys.* 2011 Oct 1; 81(2 Suppl):S346–S347. Abstract 2281. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(11\)02650-2/pdf](http://www.redjournal.org/article/S0360-3016(11)02650-2/pdf)
25. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010 Jan; 138(1):52-64. Accessed June 27, 2016. <http://www.sciencedirect.com/science/article/pii/S0016508509015741>
26. Salem R., Thurston KG. Radioembolization with ⁹⁰Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodological considerations. *J Vasc Interv Radiol.* 2006 Aug; 17(8):1251-1278. Accessed June 27, 2016. [http://www.jvir.org/article/S1051-0443\(07\)60901-4/abstract](http://www.jvir.org/article/S1051-0443(07)60901-4/abstract)
27. Salem R., Thurston KG. Radioembolization with ⁹⁰Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. *J Vasc Interv Radiol.* 2006 Sep; 17(9):1425-1439. Accessed June 27, 2016. [http://www.jvir.org/article/S1051-0443\(07\)60924-5/abstract](http://www.jvir.org/article/S1051-0443(07)60924-5/abstract)
28. Sangro B, Bilbao JI, Boan J, et al., Radioembolization using 90Y-resin microspheres for patients with advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2006 Nov 1; 66(3):792-800. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(06\)00958-8/abstract](http://www.redjournal.org/article/S0360-3016(06)00958-8/abstract)
29. Saxena A, Bester L, Shan L, et al. A systematic review on the safety and efficacy of Yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. *J Cancer Res Clin Oncol.* 2014 Apr; 140(4):537-547. Accessed June 27, 2016. <http://link.springer.com/article/10.1007/s00432-013-1564-4>
30. Schwarz RE, Abou-Alfa GK, Ghassan K., et al., Nonoperative therapies for combined modality treatment of hepatocellular cancer: expert consensus statement. *HPB (Oxford)* 2010 Jun, 12(5):313–320. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1111/j.1477-2574.2010.00183.x/abstract>
31. SIR-Spheres® Microspheres Bibliography: September 2013. Accessed June 27, 2016. http://foxfireglobal.sirtex.com/sites/foxfireglobal.sirtex.com/files/user/sir-spheres_publications_774-u-1013.pdf
32. SIR-Spheres® microspheres (Yttrium-90 Microspheres). Package insert. Sirtex Medical Inc. Wilmington MA. U.S. Food and Drug Administration (FDA). Updated January 23, 2003. Accessed June 27, 2016. http://www.accessdata.fda.gov/cdrh_docs/pdf/P990065c.pdf
33. TheraSphere® Yttrium-90 Glass Microspheres). Package insert. BTG International Group. U.S. Food and Drug Administration (FDA). Humanitarian Device Exemptions. Updated January 4, 2000. Accessed June 27, 2016. http://www.accessdata.fda.gov/cdrh_docs/pdf/H980006c.pdf
34. Tsai AL, Burke CT, Kennedy AS, et al. Use of yttrium-90 microspheres in patients with advanced hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol.* 2010 Sep; 21(9):1377-1384.. Accessed June 27, 2016. [http://www.jvir.org/article/S1051-0443\(10\)00508-7/abstract](http://www.jvir.org/article/S1051-0443(10)00508-7/abstract)
35. U. S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH). Medical Device Reporting. Searched SIR-Spheres® MAUDE in All of FDA on June 27, 2016. [Maude SIR-Sphere](#)
36. U. S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH). Medical Device Reporting. Searched TheraSphere® MAUDE in All of FDA on June 27, 2016. [Maude TheraSphere](#)

37. U.S. Food and Drug Administration (FDA). Summary and Effectiveness Data, Radioactive Implant (Yttrium-90 microspheres). SIR-Spheres® Issued March 5, 2002. Accessed June 27, 2016.
http://www.accessdata.fda.gov/cdrh_docs/pdf/p990065b.pdf
38. U.S. Food and Drug Administration (FDA). Summary of Safety and Probably Benefit, Yttrium-90 Glass Microsphere, TheraSphere® Issued December 10, 1999. Accessed June 27, 2016.
http://www.accessdata.fda.gov/cdrh_docs/pdf/H980006b.pdf
39. Van Hazel G, Blackwell A, Anderson J, et al. Randomized phase 2 trial of SIR-Spheres® plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. J Surg Oncol. 2004 Nov 1; 88(2):78-85. Accessed June 27, 2016.
<http://onlinelibrary.wiley.com/doi/10.1002/jso.20141/abstract>

Radioactive Yttrium-90 Microspheres

[Return to Table of Contents](#)

Radioimmunotherapy (RIT) – Zevalin®

POLICY

I. Indications

- A. RIT with Zevalin® is medically necessary for an individual with any of the following:
 - 1. Relapsed low grade B-cell CD20-positive follicular Non-Hodgkin's lymphomas (NHLs)
 - 2. Refractory low grade B-cell CD20-positive follicular NHLs
 - 3. Newly diagnosed (consolidation after chemotherapy) low grade B-cell CD20-positive NHLs after at least a partial response (PR) to therapy
 - 4. Newly diagnosed (initial treatment) low grade B-cell CD20-positive follicular NHLs for the elderly or infirm when no other option is expected to be tolerated
 - 5. Transformed B-cell follicular NHLs that are CD20-positive (off-label for Zevalin®, recommended in National Comprehensive Cancer Network [NCCN] Guidelines®)
- B. NCCN Guidelines® consider RIT an option:
 - 1. In primary cutaneous diffuse large B-cell Lymphoma, LEG type (T3, generalized disease only with either PR or relapse after R-CHOP +/- local RT)
 - 2. For stage III/IV non-gastric MALT lymphoma with extranodal disease and multiple nodal sites as well as post RT recurrent gastric MALT lymphoma [through follicular lymphoma (FL) pathway]
 - 3. For progressive splenic marginal zone lymphoma (through FL pathway)
 - 4. In an individual with transformed B-cell FLs who has received multiple prior therapies, and
 - 5. In an individual with minimal or no prior chemotherapy with progression of disease, no response, or partial response to chemotherapy +/- rituximab +/- radiation therapy.

II. Contraindications

- A. Poor bone marrow reserve (platelet count < 100,000/microL, absolute neutrophil count < 1,500/microL, bone marrow cellularity < 15%)
- B. High tumor burden in the bone marrow (lymphoma bone marrow involvement > 25%). Bilateral cores are recommended and the pathologist should provide the percent of cellular elements involved in the marrow. Cytogenetics +/- fluorescence in situ hybridization (FISH) for known Myelodysplastic syndrome (MDS) markers. A trend towards an increased risk of MDS with RIT has been suggested
- C. Previous radiation to > 25% of active marrow sites

- D. In an individual with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended.
- E. An individual who is pregnant

III. Investigational

- A. Newly diagnosed (consolidation after chemoimmunotherapy)
 - 1. It is not known whether the addition of RIT improves the outcome of an individual receiving chemoimmunotherapy. The role in the frontline setting is under investigation. NCCN Guidelines® on FL (grade 1-2) consider radioimmunotherapy after induction with chemotherapy or chemoimmunotherapy a category 1 recommendation but adds the following footnotes:
 - a. “f First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied.”
 - b. “g The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.”
- B. RIT as single-agent (initial therapy/previously untreated disease)
- C. Preparative regimens for hematopoietic cell transplantation (HCT)
- D. Any type of NHL other than mentioned above
- E. Solid tumors

Key Clinical Points

I. Agent

Currently, there is one Food and Drug Association (FDA) approved RIT agent in the United States (US), ^{90}Y ibritumomab tiuxetan (Zevalin®). Iositemomab (Bexxar™) was withdrawn permanently from the US market in February 2014. Zevalin® has FDA approval for relapsed or refractory CD20 positive follicular NHL and as a frontline adjuvant agent for CD20 positive follicular NHL achieving a complete response (CR) or partial response (PR) to induction chemotherapy (consolidation after chemotherapy). It contains murine Immunoglobulin-G (IgG) monoclonal antibodies (mAbs) that target the CD20 surface antigen on CD20 positive follicular NHL.

Zevalin® utilizes ^{90}Y , a pure β -particle emitter with a physical half-life of 2.7 days. The β -particle has an energy of 2.3 megaelectronvolts (MeV) and a maximum tissue penetration of approximately 12.0 mm ($R_{90} = 5.2$ mm). As such, physical contact with loved ones after administration is not limited except that sexual intercourse and kissing should be avoided in the first 24 hours. Tiuxetan is a DTPA-type chelate that attaches ^{90}Y to the mAb, ibritumomab. Because there is no gamma emission in the spectrum of this isotope, it is not visualized by gamma camera scans. As a result, a biodistribution assessment cannot be performed.

Therefore, a surrogate imaging radionuclide that emits gamma radiation (^{111}In) is required.

The treatment is delivered over 1 to 2 weeks. On day 1, an infusion of nonradioactive (cold) rituximab is delivered. This is designed to saturate the CD20 antigen sink (depletion of peripheral B-cells and the binding of nonspecific sites in the liver and spleen) and provide antibody mass, which improves biodistribution and tumor targeting.

The administered activity for Zevalin® is based on weight (0.4 mCi/kg for a platelet count $\geq 150,000$; 0.3 mCi/kg for a platelet count of 100,000 to 149,000; maximum of 32 mCi). A single gamma scan (^{111}In ibritumomab tiuxetan) is used to confirm a normal biodistribution on days 3 to 4. A review of the Zevalin® imaging registry reveals that only 0.6% of scans exhibited an altered biodistribution. An eligible individual is also required to have an absolute neutrophil count (ANC) $\geq 1,500$ and a bone marrow biopsy that reveals $< 25\%$ involvement with lymphoma.

II. Discussion of indications

A. Relapsed or refractory setting

There is no standard therapy for an individual with relapsed or refractory FL, and practice varies widely; as such, an individual should be encouraged to participate in clinical trials whenever possible.

The main treatment options for an individual with relapsed or refractory FL include:

1. Clinical trials of new agents or new combinations of existing agents
2. Immunotherapy either with single agent rituximab or rituximab plus chemotherapy
3. RIT with radiolabeled antibodies
4. Re-challenge of original therapy
5. High dose chemotherapy with autologous hematopoietic cell transplantation (HCT) rescue
6. Allogeneic HCT

RIT has demonstrated response rates of approximately 60% to 80%. However, RIT is not recommended for an individual with poor bone marrow reserve or high tumor burden in the bone marrow and requires coordination with physicians trained in the safe use of radionuclides.

Prospective trials of RIT demonstrate response rates of 60% to 80% in previously treated disease (Bucheegger et al., 2006; Davies et al., 2004; Davis et al., 2004; Fisher et al., 2005; Horning et al., 2005; Leahy et al., 2006; Vose et al., 2000; Wiseman et al., 2002). Median progression-free survival (PFS) is less than 1 year, but an individual who achieves a complete response has a median time to progression of close to 4 years (Gordon et al., 2004; Witzig et al., 2007).

A phase III study comparing Zevalin® versus rituximab for patients with relapsed or refractory low-grade follicular B-cell NHL or transformed NHL was performed (Witzig, et al., 2002). Patients were randomized to either a single intravenous (IV) dose of Zevalin® 0.4 mCi/kg (n = 73) or IV rituximab 375 mg/m² weekly for 4 doses (n = 70). The RIT group was pre-treated with 2 rituximab doses (250 mg/m²) to improve biodistribution and tumor targeting. After the first rituximab dose on day 1, ¹¹¹In ibritumomab tiuxetan was administered to assess biodistribution and to aide in dosimetry. No patients received the therapeutic dose of Zevalin® if > 20 Gy or 3 Gy was calculated to any non-tumor organ or the red marrow, respectively. Zevalin® was administered after the second rituximab dose approximately 1 week (days 7 to 9) after the first dose of rituximab and ¹¹¹In ibritumomab tiuxetan. The administered activity of Zevalin® was capped at 32 mCi. Patients in both arms of the study received 2 prior chemotherapy regimens. The overall response rate (ORR) was 80% for Zevalin® and 56% for rituximab (p = 0.002). The CR rates were 30% and 16% (p = 0.04), respectively, in the Zevalin® and rituximab group. Durable responses 6 months were 64% versus 47% (p = 0.030) for Zevalin® versus rituximab. The conclusion of the study was that RIT with Zevalin® was well tolerated and resulted in statistically significant and clinically significant higher ORRs and CRs than rituximab alone.

In a pivotal, nonrandomized, phase III multicenter trial (Kaminski et al., 2001), patients with relapsed, refractory, or transformed follicular B-cell NHL were treated with Bexxar™ (n = 60). A single dose resulted in an overall response rate of 65% (20% CR). Eligible patients were required to have been treated with at least two prior protocol-specific chemotherapy regimens (median of four regimens in the study) and to either have not responded or progressed within 6 months of therapy. A PR or CR was observed in 39 patients (65%) after Bexxar™ compared to 17 patients (28%) after last qualifying chemotherapy (LQC) (p < 0.001). The median duration of response was 6.5 months for Bexxar™ and 3.5 months for the LQC group (p < 0.001). The CR rate was 20% for Bexxar™ and 3% for the LQC group (p < 0.001). The conclusion of the study was that a single dose of Bexxar™ was significantly

more efficacious than the LQC received by heavily pre-treated patients with relapse or refractory follicular B-cell NHL.

Early evidence suggests that an individual relapsing following treatment with RIT may tolerate other treatment approaches including chemotherapy, external beam radiation therapy (EBRT) with photons and/or electrons, and autologous HCT.

B. Frontline therapy

Seventy to 85 percent of individuals present with advanced stage disease. Individuals with advanced stage disease are usually not cured with conventional treatment. While remissions can be attained, repeated relapses are common. Treatment focuses on the alleviation of symptoms, reversal of cytopenias, and improvement of quality of life. The disease course is variable with some individuals demonstrating stable disease for years and others progressing more rapidly. Rarely, individuals may have spontaneous remissions lasting longer than one year.

Considering the concerns about RIT for treating large bulky tumors (tumor penetration, overall required dose, non-uniform dose distribution), it would appear that bringing RIT into a frontline therapeutic setting after induction chemotherapy and maximum cyto-reduction would be the next logical direction.

A phase III first-line indolent trial (FIT) of consolidation with Zevalin® compared to no additional therapy after first remission was reported for follicular B-cell NHL (Morschhauser et al., 2013; Morschhauser et al., 2008).

Patients with CD20+ stage III/IV follicular B-cell NHL who achieved a PR or CR to induction chemotherapy were randomized to Zevalin® (n = 208) or to the control arm, representing no further treatment (n = 206). After a median follow-up of 7.3 years, consolidation with Zevalin® resulted in an estimated 8-year PFS advantage of 41% versus 22% in the control arm (p < 0.0001). The median PFS was 4.1 years vs. 1.1 years, respectively (p < 0.001). No significant difference in overall survival (84% vs. 81%) was observed between treatment arms. The incidence of secondary malignancies was higher in the RIT arm but the difference was not statistically significant (13% vs. 7%). Incidence of MDS/AML was significantly higher in RIT arm with an actuarial 8-year incidence rate of 4.2% vs. 0.6% (p < 0.042). Only 14% of patients in this study received rituximab in combination with chemotherapy as induction. The estimated eight-year PFS advantage was 56% versus 45% in the control

arm. The median PFS was 7.9 years vs. 4.9 years, respectively. The difference in PFS outcomes was not significant in this subgroup; however, the trial was not statistically powered to detect differences in subgroups based on induction therapies. Since only a small portion of patients enrolled in the FIT trial received rituximab-containing induction therapy, the effects of RIT consolidation following rituximab-containing regimens cannot be fully evaluated.

The phase III randomized intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation following R-CHOP. In this study, 554 patients with newly diagnosed FL were randomly assigned to chemoimmunotherapy alone (RCHOP for 6 cycles) or to chemotherapy plus a radioimmunoconjugate (CHOP for 6 cycles followed by ¹³¹I. When compared with R-CHOP, CHOP plus Bexxar™ resulted in similar rates of overall (84% each) and complete (45% vs. 40%) remissions. Severe (grade 3/4) thrombocytopenia was greater (18% vs. 2%) among those who received a radioimmunoconjugate. At a median follow-up of 4.9 years, chemoimmunotherapy alone resulted in similar rates of PFS (76% vs. 80%) and OS (97% vs. 93%) at 2 years.

These trials suggest that consolidation with a radioimmunoconjugate may be able to improve the quality of remission by converting PRs into CRs. Indication of RIT in relapsed or refractory disease as well as consolidation in frontline therapy when chemotherapy alone has been used for induction is well supported in literature. However, it is not known whether the addition of an anti-CD20 radioimmunoconjugate improves outcomes of patients already receiving chemoimmunotherapy. The role in the frontline setting is under investigation.

NCCN Guidelines® (Follicular Lymphoma [grade 1-2], FOLL-B 1 of 3, First-line Consolidation or Extended Dosing [optional]) consider RIT after induction with chemotherapy or chemoimmunotherapy a category 1 recommendation but adds the following footnotes:

- “f First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied.”
- “g The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.”

In frontline setting, RIT is also indicated for the elderly or infirm when no other option is expected to be tolerated.

C. Off-label use of radioimmunoconjugates as single-agent therapy for the management of previously untreated disease

Nonrandomized trials support use of radioimmunoconjugates as single-agent therapy for the management of previously untreated disease. While initial reports suggest good response rates and tolerability, long-term follow-up of such an approach is limited. The following describes the largest phase II trials evaluating RIT for initial management of advanced stage FL.

In an international phase II trial (Scholz et al., 2013) of 59 older patients (> 50) with stage II to IV FL, Zevalin® was used as first line therapy and resulted in an ORR of 87% at 6 months with 56% of patients achieving a CR. After a median follow-up of 31 months, the median PFS was 26 months and the median overall survival had not been reached. Rates of PFS at 1 and 2 years were 77% and 54%, respectively. Severe (grade 3/4) thrombocytopenia, leukopenia, neutropenia, and lymphopenia were seen in approximately 48%, 34%, 32%, and 20%. Non-hematologic toxicities were mostly mild to moderate and included infections (20%) and gastrointestinal toxicities (10%).

In an international phase II trial (Illidge et al., 2014), 74 patients with previously untreated FL (78% advanced stage) received two cycles of Zevalin®. Patients with > 20% bone marrow infiltration were pretreated with four cycles of rituximab. The overall response rate was 94% (CR/complete response unconfirmed [CRu] 58%). At a median follow-up of 3 years, the estimated rates of PFS and OS at 3 years were 58% and 95%, respectively. Median PFS was 40 months. Toxicity was mild with the most common side effects being lethargy and gastrointestinal side effects.

In another phase II trial evaluating Bexxar™ (Kaminski et al., 2005) in 76 patients with stage III or IV FL requiring therapy, the ORR was 95% with 75% CRs. The median PFS was 6 years and the 10-year PFS rate was 40%. One patient developed MDS 8 years after treatment.

D. Histologic transformation of follicular lymphoma

The most commonly employed treatment regimens for an individual with histologic transformation (HT) include conventional chemotherapy with immunotherapy (e.g., R-CHOP), RIT, and high-dose therapy followed by autologous HCT. An individual who is not a candidate for HCT may be considered for RIT.

An individual with HT of FL who is resistant to initial therapy or who relapses following initial therapy, is expected to do poorly. Available treatment options include enrollment in a clinical trial, use of chemotherapy regimens similar to

that employed in relapsed/resistant diffuse large B cell lymphoma (DLBCL), or RIT. An individual with disease that responds to treatment may be a candidate for autologous or allogeneic HCT.

There are no prospective trials evaluating the use of RIT as consolidation in individuals with chemotherapy sensitive HT or DLBCL. Some clinicians offer the off-label use of RIT as consolidation in individuals with chemotherapy sensitive HT who have received extensive prior therapy and who are not candidates for autologous HCT. Given the paucity of data regarding this approach, RIT should be used in the context of a clinical trial.

NCCN Guidelines® consider RIT an option for an individual with multiple prior therapies and for an individual with minimal or no prior chemotherapy with progression of disease, no response, or partial response to chemotherapy +/- rituximab +/- radiation therapy.

- E. Preparative regimens for HCT – (Experimental/Investigative/Unproven [EIU])
The maximally tolerated dose of total body irradiation (TBI) is approximately 15 Gy. A randomized trial comparing 12 and 16 Gy found that the higher dose was associated with a lower relapse rate (12% vs. 35% at three years in patients with acute myeloid leukemia) (Clift, et al., 1991). One approach to achieving this goal has been the administration of mAbs radiolabeled with high energy emitting radioisotope. This would permit targeting of the radiation dose to the tumor cells and marrow with potential reduction in dose to other organs, such as the liver, lungs and kidneys.

RIT has been added to standard preparative regimens in the autologous setting for the treatment of patients with B cell NHL, with encouraging preliminary results and tolerable toxicity profiles (Gopal et al., 2007, Gopal et al., 2011; Krishnan et al., 2008). A randomized trial comparing Bexxar™-BEAM with BEAM has been conducted by the Bone Marrow Transplantation Clinical Trials Network (BMT-CTN 0401). Patient accrual has been completed but results have not yet been released.

III. Toxicities

The most profound side effects of RIT are potentially prolonged and significant cytopenias with cell count nadirs ranging from four to nine weeks post-therapy with recovery one to four weeks post-nadir. The most common cytopenias are leucopenia and thrombocytopenia, which are easily managed in the majority of individuals. RIT causes a transient depletion of B cells for approximately 6 to 9 months but has not been associated with significant increases in severe

infections or hospitalizations. RIT can be associated with an infusion reaction similar to that seen with other monoclonal antibodies.

Although initial reports suggested a possible risk of treatment-related MDS (t-MDS) and acute myeloid leukemia (t-AML), the rate of t-MDS and t-AML does not appear to be increased. An evaluation of 746 patients treated for NHL with Zevalin® found that the rates of t-MDS and t-AML were not increased compared with historic rates in those who had received multiple chemotherapeutic regimes (Czuczman et al., 2007).

A bilateral bone marrow biopsy is required prior to the initiation of RIT to assess bone marrow involvement. RIT is not recommended in an individual with inadequate marrow reserve (i.e., platelet count < 100,000/microL, absolute neutrophil count < 1,500/microL, bone marrow cellularity < 15%), lymphoma bone marrow involvement > 25%, or previous radiation to > 25% of active marrow sites. Due to the risk of delayed hematologic toxicity, an individual should have blood count monitoring at least weekly following treatment until hematologic recovery.

References:

1. ACR–ASTRO practice parameter for the performance of therapy with unsealed radiopharmaceutical sources. Revised 2015. Accessed June 27, 2016. <http://www.acr.org/~media/99393be60e964af6830b57c3e52e2339.pdf>
2. Akabani G, Reardon DA, Coleman RE, et al. Dosimetry and radiographic analysis of 131I-labeled anti-tenascin 81C6 murine monoclonal antibody in newly diagnosed patients with malignant gliomas: a phase II study. J Nucl Med. 2005 Jun 1; 46(6):1042-1051. Accessed June 27, 2016. <http://jnm.snmjournals.org/content/46/6/1042.full>
3. Bexxar™ (Tositumomab and Iodine I 131 Tositumomab) Discontinued. Accessed June 27, 2016. [http://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Tositumomab_and_Iodine_I_131_Tositumomab_\(Bexxar\)&st=d](http://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Tositumomab_and_Iodine_I_131_Tositumomab_(Bexxar)&st=d)
4. Brady LW, Markoe AM, Woo DV, et al. Iodine-125-labeled anti-epidermal growth factor receptor-425 in the treatment of glioblastoma multiforme: a pilot study. Front Radiat Ther Oncol. 1990; 24:151-165. Accessed June 27, 2016. <http://www.karger.com/Article/Abstract/417780>
5. Buchegger F, Antonescu C, Delaloye AB, et al. Long-term complete responses after ¹³¹I-tositumomab therapy for relapsed or refractory indolent non-Hodgkin's lymphoma. Br J Cancer. 2006 Jun 19; 94(12):1770-1776. Accessed June 27, 2016. <http://www.nature.com/bjc/journal/v94/n12/full/6603166a.html>
6. Burdick M, Mackkil RM. Radioimmunotherapy for non-Hodgkin's lymphoma: a clinical update in Speer TW, ed. Targeted radionuclide therapy. Philadelphia, PA:Lippincott William & Wilkins. 2011:426-440. Accessed June 27, 2016. <http://www.worldcat.org/title/targeted-radionuclide-therapy/oclc/650953409#relatedsubjects>
7. Chatal JF, Campion L, Kraeber-Bodéré F, et al. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group. J Clin Oncol. 2006 Apr 10; 24(11):1705-1711. Accessed June 27, 2016. <http://jco.ascopubs.org/content/24/11/1705.full>
8. Chen S, Yu L, Jiang C, et al. Pivotal study of iodine-131-labeled chimeric tumor necrosis treatment radioimmunotherapy in patients with advanced lung cancer. J Clin Oncol. 2005 Mar 1; 23(7):1538-1547. Accessed June 27, 2016. <http://jco.ascopubs.org/content/23/7/1538.full>
9. Cheson BD. Radioimmunotherapy of non-Hodgkin lymphomas. Blood. 2003 Jan 15; 101(2):391-398. Accessed June 27, 2016. <http://www.bloodjournal.org/content/101/2/391>
10. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase: a randomized trial of two irradiation regimens. Blood. 1991; 77(8):1660-1665. Accessed June 27, 2016. <http://www.bloodjournal.org/content/77/8/1660>

11. Cokgor I, Akabani G, Kuan CT, et al. Phase I trial results of iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with newly diagnosed malignant gliomas. *J Clin Oncol*. 2000 Nov 15; 18(22):3862-3867. Accessed June 27, 2016. <http://jco.ascopubs.org/content/18/22/3862.abstract>
12. Czuczman MS, Emmanouilides C, Darif M, et al. Treatment-related myelodysplastic syndrome and acute myelogenous leukemia in patients treated with ibritumomab tiuxetan radioimmunotherapy. *J Clin Oncol*. 2007 Sep 20; 25(27):4285-92. Accessed June 27, 2016. <http://jco.ascopubs.org/content/25/27/4285.full>
13. Davies AJ, Rohatiner AZ, Howell S, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2004 Apr 15; 22(8):1469-1479. Accessed June 27, 2016. <http://jco.ascopubs.org/content/22/8/1469.full>
14. Davis TA, Kaminski MS, Leonard JP, et al. The radioisotope contributes significantly to the activity of radioimmunotherapy. *Clin Cancer Res*. 2004 Dec 1; 10(23):7792-7798. Accessed June 27, 2016. <http://clincancerres.aacrjournals.org/content/10/23/7792.full>
15. Devizzi L, Guidetti A, Seregini E, et al. Long-term results of autologous hematopoietic stem-cell transplantation after high-dose ⁹⁰Y-ibritumomab tiuxetan for patients with poor-risk non-Hodgkin lymphoma not eligible for high-dose BEAM. *J Clin Oncol*. 2013 Aug 10; 31(23):2974-2976. Accessed June 27, 2016. <http://jco.ascopubs.org/content/31/23/2974.full>
16. Dillman RO. Radiolabeled anti-CD20 monoclonal antibodies for the treatment of B-cell lymphoma. *J Clin Oncol*. 2002 Aug 15; 20(16):3545-3557. Accessed June 27, 2016. <http://jco.ascopubs.org/content/20/16/3545.full.pdf+html>
17. Emrich JG, Brady LW, Quang TS, et al. Radioiodinated (I-125) monoclonal antibody 425 in the treatment of high grade glioma patients: ten-year synopsis of a novel treatment. *Am J Clin Oncol*. 2002 Dec; 25(6):541-546. Accessed June 27, 2016. http://journals.lww.com/amjclinicaloncology/Abstract/2002/12000/Radioiodinated_I_125_Monoclonal_Antibody_425_in.1.aspx
18. Epenetos AA, Hird V, Lambert H, et al. Long term survival of patients with advanced ovarian cancer treated with intraperitoneal radioimmunotherapy. *Int J Gynecol Cancer*. 2000 Jan/Feb; 10(S1):44-46. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1046/j.1525-1438.2000.99510.x/abstract>
19. Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol*. 2005 Oct 20; 23(30):7565-7573. Accessed June 27, 2016. <http://jco.ascopubs.org/content/23/30/7565.full>
20. Forero A, Weiden PL, Vose JM, et al. Phase 1 trial of a novel anti-CD20 fusion protein in pretargeted radioimmunotherapy for B-cell non-Hodgkin lymphoma. *Blood*. 2004 Jul 1; 104(1):227-236. Accessed June 27, 2016. <http://www.bloodjournal.org/content/104/1/227>
21. Gopal AK, Guthrie KA, Rajendran J, et al. ⁹⁰Y-ibritumomab tiuxetan, fludarabine, and TBI-based nonmyeloablative allogeneic transplantation conditioning for patients with persistent high-risk B-cell lymphoma. *Blood*. 2011 Jul 29; 118(4):1132-1139. Accessed June 27, 2016. <http://www.bloodjournal.org/content/118/4/1132>
22. Gopal AK, Rajendran JG, Gooley TA, et al. High-dose [¹³¹I]tositumomab (anti-CD20) radioimmunotherapy and autologous hematopoietic stem-cell transplantation for adults ≥ 60 years old with relapsed or refractory B-cell lymphoma. *J Clin Oncol*. 2007 Feb 20; 25(11):1396-1402. Accessed June 27, 2016. <http://jco.ascopubs.org/content/25/11/1396.full>
23. Gordon LI, Molina A, Witzig T, et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20⁺ B-cell lymphoma: long-term follow-up of a phase 1/2 study. *Blood*. 2004 Jun 15; 103(12):4429-4431. Accessed June 27, 2016. <http://www.bloodjournal.org/content/103/12/4429>
24. Hainsworth JD, Spigel DR, Markus TM, et al. Rituximab plus short-duration chemotherapy followed by yttrium-90 ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. *Clin Lymphoma Myeloma*. 2009 Jun; 9(3):223-228. Accessed June 27, 2016. [http://www.clinical-lymphoma-myeloma-leukemia.com/article/S1557-9190\(11\)70196-2/abstract](http://www.clinical-lymphoma-myeloma-leukemia.com/article/S1557-9190(11)70196-2/abstract)
25. Hernandez MC, Knox SJ. Radiobiology of radioimmunotherapy: targeting CD20 B-cell antigen in non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys*. 2004 Aug 1; 59(5):1274-87. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(04\)00597-8/abstract](http://www.redjournal.org/article/S0360-3016(04)00597-8/abstract)
26. Hopkins K, Chandler C, Bullimore J, et al. A pilot study of the treatment of patients with recurrent malignant gliomas with intratumoral yttrium-90 radioimmunoconjugates. *Radiother Oncol*. 1995; 34(2):121-131. Accessed June 27, 2016. [http://www.thegreenjournal.com/article/0167-8140\(95\)01514-H/abstract](http://www.thegreenjournal.com/article/0167-8140(95)01514-H/abstract)
27. Hopkins K, Chandler C, Eatough J, et al. Direct injection of ⁹⁰Y MoAbs into glioma tumor resection cavities leads to limited diffusion of the radioimmunoconjugates into normal brain parenchyma: a model to estimate absorbed radiation dose. *Int J Radiat Oncol Biol Phys*. 1998 Mar 1; 40(4):835-844. Accessed June 27, 2016. [http://www.redjournal.org/article/S0360-3016\(97\)00915-2/abstract](http://www.redjournal.org/article/S0360-3016(97)00915-2/abstract)

28. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. *J Clin Oncol*. 2005 Feb 1; 23(4):712-719. Accessed June 27, 2016. <http://jco.ascopubs.org/content/23/4/712.full>
29. Illidge TM, Mayes S, Pettengell R, et al. Fractionated ⁹⁰Y-ibritumomab tiuxetan radioimmunotherapy as an initial therapy of follicular lymphoma: an international phase II study in patients requiring treatment according to GELF/BNLI criteria. *J Clin Oncol*. 2014 Jan 20;32(3):212-218. Accessed June 27, 2016. <http://jco.ascopubs.org/content/32/3/212.abstract>
30. Jacobs SA, Swerdlow SH, Kant J, et al. Phase II trial of short-course CHOP-R followed by ⁹⁰Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. *Clin Cancer Res*. 2008 Nov 1; 14(21):7088-7094. Accessed June 27, 2016. <http://clincancerres.aacrjournals.org/content/14/21/7088.full>
31. Kalofonos HP, Pawlikowska TR, Hemingway A, et al. Antibody guided diagnosis and therapy of brain gliomas using radiolabeled monoclonal antibodies against epidermal growth factor receptor and placental alkaline phosphatase. *J Nucl Med*. 1989 Oct 1; 30(10):1636-1645. Accessed June 27, 2016. <http://jnm.snmjournals.org/content/30/10/1636>
32. Kaminski MS, Tuck M, Estes J, et al. ¹³¹I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med*. 2005 Feb 3; 352(5):441-449. Accessed June 27, 2016. <http://www.nejm.org/doi/pdf/10.1056/NEJMoa041511>
33. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*. 2001 Oct 1; 19(19):3918-3928. Accessed June 27, 2016. <http://jco.ascopubs.org/content/19/19/3918.abstract>
34. Kraeber-Bodéré F, Rousseau C, Bodet-Milin C, et al. Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and ¹³¹I-labeled bivalent hapten in a phase I optimization clinical trial. *J Nucl Med*. 2006 Feb; 47(2):247-255. Accessed June 27, 2016. http://jnm.snmjournals.org/content/47/2/247.abstract?ikey=e0bbf7c1df8838140fd56d57e8cec301ea604933&keytype2=tf_ipsecsha
35. Krishnan A, Nademanee A, Fung HC, et al. Phase II trial of a transplantation regimen of yttrium-90 ibritumomab tiuxetan and high-dose chemotherapy in patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 2008 Jan 1; 26(1):90-95. Accessed June 27, 2016. <http://jco.ascopubs.org/content/26/1/90.full>
36. Leahy MF, Seymour JF, Hicks RJ, et al. Multicenter phase II clinical study of iodine-131-rituximab radioimmunotherapy in relapsed or refractory indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2006 Sep 20; 24(27):4418-4425. Accessed June 27, 2016. <http://jco.ascopubs.org/content/24/27/4418.full>
37. Leahy MF, Turner JH. Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. *Blood*. 2011 Jan 6; 117(1):45-52. Accessed June 27, 2016. <http://www.bloodjournal.org/content/117/1/45>
38. Leonard JP, Siegel JA, Goldsmith SJ. Comparative physical and pharmacologic characteristics of iodine-131 and yttrium-90: implications for radioimmunotherapy for patients with non-Hodgkin's lymphoma. *Cancer Invest*. 2003 Apr; 21(2):241-252. Accessed June 27, 2016. http://www.unboundmedicine.com/medline/citation/12743990/Comparative_physical_and_pharmacologic_characteristics_of_iodine-131_and_yttrium-90_implications_for_radioimmunotherapy_for_patients_with_non-Hodgkin
39. Mamelak AN, Rosenfeld S, Bucholz R, et al. Phase I single-dose study of intracavitary-administered iodine-131-TM-601 in adults with recurrent high-grade glioma. *J Clin Oncol*. 2006 Aug 1; 24(22):3644-3650. Accessed June 27, 2016. <http://jco.ascopubs.org/content/24/22/3644.full>
40. McLendon RE, Akabani G, Friedman HS, et al. Tumor resection cavity administered iodine-131-labeled antitenascin 81C6 radioimmunotherapy in patients with malignant glioma: neuropathology aspects. *Nucl Med and Biol*. 2007 May; 34(4):405-413. Accessed June 27, 2016. [http://www.nucmedbio.com/article/S0969-8051\(07\)00036-4/abstract](http://www.nucmedbio.com/article/S0969-8051(07)00036-4/abstract)
41. Morschhauser F, Radford J, Van Hoof A, et al. ⁹⁰Yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 7.3 years from the international, randomized, phase III first-line indolent trial. *J Clin Oncol*. 2013 Jun 1; 31(16):1977-1983. Accessed June 27, 2016. <http://jco.ascopubs.org/content/31/16/1977.full>
42. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008 Nov 10; 26(32):5156-64. Accessed June 27, 2016. <http://jco.ascopubs.org/content/26/32/5156.abstract>
43. National Comprehensive Cancer Network (NCCN) Guidelines. Version 3.2016. Non-Hodgkin's Lymphomas. Accessed June 27, 2016. http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Non-Hodgkin's Lymphomas Version 3.2016®. 2016 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

44. Oei AL, Verheijen RH, Seiden MV, et al. Decreased intraperitoneal disease recurrence in epithelial ovarian cancer patients receiving intraperitoneal consolidation treatment with yttrium-90-labeled murine HMFG1 without improvement in overall survival. *Int J Cancer*. 2007 Jun 15; 120(12):2710-2714. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/ijc.22663/full>
45. Order SE, Pajak T, Leib S, et al. A randomized prospective trial comparing full dose chemotherapy to ¹³¹I antiferritin: an RTOG study. *Int J Rad Oncol Biol Phys*. 1998 May 1; 20(5):953-963. Accessed June 27, 2016. [http://www.redjournal.org/article/0360-3016\(91\)90191-6/abstract](http://www.redjournal.org/article/0360-3016(91)90191-6/abstract)
46. Pandit-Taskar N, O'Donoghue JA, Morris MJ, et al. Antibody mass escalation study in patients with castration-resistant prostate cancer using ¹¹¹In-J591: lesion detectability and dosimetric projection for ⁹⁰Y radioimmunotherapy. *J Nucl Med* 2008 Jul; 49(7):1066-1074. Accessed June 27, 2016. <http://jnm.snmjournals.org/content/49/7/1066.full>
47. Papanastassiou V, Pizer BL, Coakham HB, et al. Treatment of recurrent and cystic malignant gliomas by a single intracavity injection of ¹³¹I monoclonal antibody: feasibility pharmacokinetics and dosimetry. *Br J Cancer*. 1993; 67(1):144-151. Accessed June 27, 2016. <http://www.nature.com/bjc/journal/v67/n1/pdf/bjc199325a.pdf>
48. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus ¹³¹I-iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. *J Clin Oncol*. 2013 Jan 20; 31(3):314-320. Accessed June 27, 2016. <http://jco.ascopubs.org/content/31/3/314.full>
49. Reardon DA, Akabani G, Coleman RE, et al. Salvage radioimmunotherapy with murine iodine-131-labeled antitenascin monoclonal antibody 81C6 for patients with recurrent primary and metastatic malignant brain tumors: phase II study results. *J Clin Oncol*. 2006 Jan 1; 24(1):115-122. Accessed June 27, 2016. <http://jco.ascopubs.org/content/24/1/115.full>
50. Reardon DA, Akabani G, Coleman RE, et al. Phase II trial of murine ¹³¹I-labeled antitenascin monoclonal antibody 81C6 administered into surgically created resection cavities of patients with newly diagnosed malignant gliomas. *J Clin Oncol*. 2002 Mar 1; 20(5):1389-1397. Accessed June 27, 2016. <http://jco.ascopubs.org/content/20/5/1389.abstract>
51. Reardon DA, Zalutsky MR, Akabani G, et al. A pilot study: ¹³¹I-antitenascin monoclonal antibody 81C6 to deliver a 44-Gy resection cavity boost. *Neuro Oncol*. 2008 Apr; 10(2):182-189. Accessed June 27, 2016. <http://neuro-oncology.oxfordjournals.org/content/10/2/182.full>
52. Riva P, Franceschi G, Arista A, et al. Local application of radiolabeled monoclonal antibodies in the treatment of high grade malignant gliomas: a six-year clinical experience. *Cancer*. 1997 Dec; 80(12):2733-2742. Accessed June 27, 2016. [http://onlinelibrary.wiley.com/doi/10.1002/\(SICI\)1097-0142\(19971215\)80:12%2B%3C2733::AID-CNCR53%3E3.0.CO;2-9/full](http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0142(19971215)80:12%2B%3C2733::AID-CNCR53%3E3.0.CO;2-9/full)
53. Scholz CW, Pinto A, Linkesch W, et al. ⁹⁰Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. *J Clin Oncol*. 2013 Jan 20; (31)3:208-313. Accessed June 27, 2016. <http://jco.ascopubs.org/content/31/3/308.full>
54. Sharkey RM, Karacay H, Goldenberg DM. Improving the treatment of non-Hodgkin lymphoma with antibody-targeted radionuclides. *Cancer*. 2010 Feb 15; 116(4 Suppl):1134-1145. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.24802/full>
55. Speer, TW. Radioimmunotherapy and Unsealed Radionuclide Therapy and Unsealed Radionuclide Therapy; Conjugated Therapy p. 530, Solid Tumor Trials and Approved Therapeutics p. 532; Malignant Glioma; Radioimmunotherapy p. 662 in Halperin EC, Wazer DE, Perez CA, and Brady LW, ed. *Perez and Brady's Principles and Practice of Radiation Oncology*. 6th Edition. Philadelphia:Lippincott Williams & Wilkins, a Wolters Kluwer business, 2013. Accessed June 27, 2016. <http://www.worldcat.org/title/perez-and-bradys-principles-and-practice-of-radiation-oncology/oclc/904142769?ht=edition&referer=br>
56. Speer TW, Limmer JP, Henrich D, et al. Evolution of radiotherapy toward a more targeted approach for CNS malignancies in Speer TW, ed. *Targeted radionuclide therapy*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011:356–376. Accessed June 27, 2016. <http://www.worldcat.org/title/targeted-radionuclide-therapy/oclc/650953409>
57. Tennvall J, Fischer M, Delaloye AB, et al. EANM procedure guideline for radio-immunotherapy for B-cell lymphoma with ⁹⁰Y-radiolabelled ibritumomab tiuxetan (Zevalin). *Eur J Nucl Med Mol Imaging*. 2007 Apr; 34(4):616-622. Accessed June 27, 2016. <http://link.springer.com/article/10.1007/s00259-007-0372-y>
58. Thurber GM. Kinetics of antibody penetration into tumors in Speer TW, ed. *Targeted radionuclide therapy*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011:168-181. Accessed June 27, 2016. <http://www.worldcat.org/title/targeted-radionuclide-therapy/oclc/650953409>
59. Verheijen RH, Massuger LF, Benigno BB, et al. Phase III trial of intraperitoneal therapy with yttrium-90-labeled HMFG1 murine monoclonal antibody in patients with epithelial ovarian cancer after a surgically defined complete remission. *J Clin Oncol*. 2006 Feb 1; 24(4):571-578. Accessed June 27, 2016. <http://jco.ascopubs.org/content/24/4/571.full>
60. Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*. 2000 Mar 13; 18(6):1316-1323. Accessed June 27, 2016. <http://jco.ascopubs.org/content/18/6/1316.abstract>

61. Wang H, Cao C, Li B, et al. Immunogenicity of iodine 131 chimeric tumor necrosis therapy monoclonal antibody in advanced lung cancer patients. *Cancer Immunol Immunother* 2008 May; 57(5):677-684. Accessed June 27, 2016. <http://link.springer.com/article/10.1007/s00262-007-0406-0>
62. Weigert O, Illidge T, Hiddemann W, et al. Recommendations for the use of yttrium-90 ibritumomab tiuxetan in malignant lymphoma. *Cancer*. 2006 Aug 15; 107(4):686-95. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.22066/full>
63. Wiseman GA, Gordon LI, Multani PS, et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial. *Blood*. 2002 Jun 15; 99(12):4336-4342. Accessed June 27, 2016. <http://www.bloodjournal.org/content/99/12/4336>
64. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002 May 15; 20(10):2453-2463. Accessed June 27, 2016. <http://jco.ascopubs.org/content/20/10/2453.abstract>
65. Witzig TE, Molina A, Gordon LI, et al. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. *Cancer*. 2007 May 1; 109(9):1804-10. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/cncr.22617/full>
66. Witzig TE, White CA, Gordon LI, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin's lymphoma. *J Clin Oncol*. 2003 Apr 1; 21(7):1263-1270. Accessed June 27, 2016. <http://jco.ascopubs.org/content/21/7/1263.abstract>
67. Wygoda Z, Kula D, Bierzyńska-Macyszyn G, et al. Use of monoclonal anti-EGFR antibody in the radioimmunotherapy of malignant gliomas in the context of EGFR expression in grade III and IV tumors. *Hybridoma (Larchmt)*. 2006 Jun; 25(3):125-32. Accessed June 27, 2016. <http://www.ncbi.nlm.nih.gov/pubmed/16796458>
68. Xu J, Shen Z-Y, Chen X-G, et al. A randomized controlled trial of licartin for preventing hepatoma recurrence after liver transplantation. *Hepatology*. 2007 Feb; 45(2):269-276. Accessed June 27, 2016. <http://onlinelibrary.wiley.com/doi/10.1002/hep.21465/full>
69. Yu L, Ju DW, Chen W, et al. ¹³¹I-chTNT radioimmunotherapy of 43 patients with advanced lung cancer. *Cancer Biother Radiopharm*. 2006 Feb; 21(1):5-14. Accessed June 27, 2016. <http://online.liebertpub.com/doi/abs/10.1089/cbr.2006.21.5>
70. Zalutsky MR, Reardon DA, Akabani G, et al. Clinical experience with α -particle-emitting ²¹¹At: treatment of recurrent brain tumor patients with ²¹¹At-labeled chimeric antitenascin monoclonal antibody 81C6. *J Nucl Med*. 2008 Jan; 49(1):30-38. Accessed June 27, 2016. <http://jnm.snmjournals.org/content/49/1/30.full>
71. Zelenetz A, Saleh M, Vose J, Younes A, Kaminski M. Patients with transformed low grade lymphoma attain durable responses following out-patient radioimmunotherapy with tositumomab and iodine I 131 tositumomab (Bexxar). *Blood*. 2002; 100:357a, abstract 1384.
72. Zevalin® (ibritumomab tiuxetan) FDA Label Accessed June 27, 2016. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125019s0156.pdf
73. Zevalin® FDA Supplement Approval Accessed June 27, 2016. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/125019s0156ltr.pdf
74. Zinzani PL, Tani M, Pulsoni A, et al. Fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in previously untreated patients with follicular non-Hodgkin lymphoma trial: a phase II non-randomised trial (FLUMIZ). *Lancet Oncol*. 2008 Apr; 9(4):352-358. Accessed June 27, 2016. [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(08\)70039-1/fulltext](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(08)70039-1/fulltext)

Radioimmunotherapy
[Return to Table of Contents](#)