CLINICAL GUIDELINES

Radiation Therapy

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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.

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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. Intravascular brachytherapy (VBT) is considered medically necessary for recurrent drug-eluting stent in-stent restenosis
   C. All other indications are not covered because they are 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 drug-eluting stents (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 DES. 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 DES 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. Initial Hyperplasia Inhibition with Beta In-stent Trial [INHIBIT], Waksman et al. (2002)
2. STents And Radiation Therapy [START], Popma et al. (2002)
3. GAMMA-1 trial, Leon, et al. (2001)
5. Washington Radiation for In-Stent Restenosis Trial [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 = 0.07). 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 = 0.03, 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 = 0.0028). A diffuse pattern of recurrence was more frequently seen after brachytherapy (20/74 vs. 6/74, p = 0.005). 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, 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 DES 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. DES 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 DES 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 comparative effectiveness of brachytherapy and the two radiation sources. They 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 gamma radiation in SVG 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.

3. VBT may be used for recurrent DES in-stent restenosis. Recent studies have shown that VBT is safe with low recurrence rates at one year post procedure. It is considered to be a safe short-term method of restoring patency although repeat intervention will be eventually medically necessary. In a study of 186 patients with 283 lesions, Negi et al (2016), unstable angina was treated with balloon angioplasty followed by VBT. In 99% of cases treatment was delivered without adverse effects. Similarly, Ohri et al. (2016), reported on 134 patients with 141 treated lesions as well as a control group of 37 patients. This study confirmed the safety and usefulness of the procedure in a high risk population. Additional investigation was recommended.

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 mm in the control group vs. 2.9 ± 1.05 mm 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, MI, and ischemia-driven 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 = 0.95). 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 $0.7 \pm 0.9$ mm in the brachytherapy group vs. $1.2 \pm 0.8$ mm in the control group at the injured segment, $0.9 \pm 1.0$ vs. $1.3 \pm 0.7$ mm at the radiated segment, and $0.9 \pm 1.0$ vs. $1.3 \pm 0.7$ 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 restenosis after BMS are treated by DES or Coronary Artery Bypass Graft (CABG).

IV. Summary

Prior to the widespread use of drug-eluting stents, in-stent restenosis following 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.
References


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 2018 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 pre-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.

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 improvement in survival at five years and no increased toxicity from combined modality therapy (Valdagni, 1994)

References:
Image-Guided Radiation Therapy (IGRT)

POLICY

I. IGRT during IMRT
   IGRT is considered medically necessary when IMRT has been approved and is being utilized.

II. IGRT during 3DCRT
   IGRT in conjunction with 3DCRT is medically necessary in the following circumstances:
   A. When the planning target volume (PTV) is in close proximity to a previously irradiated area
   B. Treatment of the hepatobiliary tract
   C. Treatment of head and neck cancer
   D. Treatment of Hodgkin’s and Non-Hodgkin’s Lymphoma
   E. Treatment of lung cancer
   F. Treatment of prostate cancer
   G. Treatment of esophageal cancer
   H. Treatment of gastric cancer
   I. Treatment of pancreatic cancer
   J. Treatment of pelvic cancers (i.e. rectal cancer) when the individual is in the prone position on a belly board
   K. During breast boost when using photons
   L. During external beam-based accelerated partial breast irradiation (APBI)
   M. During treatment of breast cancer when a DIBH technique is being used
   N. Treatment of breast cancer when the individual is in the prone position
   O. During the boost to the bladder
   P. Preoperative or postoperative treatment of sarcomas
III. IGRT during SRS/SBRT

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.

IV. IGRT and brachytherapy

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.

V. IGRT and superficial radiation therapy or electron beam therapy

The use of IGRT with either superficial radiation therapy or electron beam therapy is considered not medically necessary.

Key Clinical Points

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, IGRT occasionally can be used with three-dimensional (3D) conformal radiation therapy (3DCRT). The American Society for Radiation Oncology (ASTRO) together with the American College of Radiology (ACR) have published practice parameters (Loo et al, 2014) and technical standards (Cheng et al, 2014) regarding IGRT. In addition, in their 2018 Radiation Oncology Coding Resource, ASTRO has addressed IGRT in detail.

Historical methodology of using port films to confirm patient set-up and block placement has not been replaced by IGRT. For example, the Coding Resource states “…guidance and tracking are not indicated…” when "...replacing ‘port check’ imaging when target localization is not medically necessary." 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.

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.
Radiation Therapy Criteria

V2.0.2019

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.

Respiratory motion management may be clinically appropriate for treating some cancers, including lung cancer and some cases of breast cancer (deep inspiration breath hold [DIBH]). 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.

References
Neutron Beam Therapy

POLICY

I. Neutron beam radiotherapy is considered 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 considered 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.

There is limited research, resulting 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 use of this technique is highly experimental at this time. Currently, the University of Washington Medical Cyclotron Facility in Seattle is the only clinical neutron facility in the United States.

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 IThemba Labs. The patients had either unresectable tumors or had gross macroscopic residual disease. Local regional 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. A recent publication by Davis, et al. (2016) reported a 6 year overall survival of 58% in 140 patients, with the most common subtype being adenoid cystic carcinoma and the submandibular gland being the most common site. The current standard neutron dose was reported as 1.15 neutron Gray (nGy) 4 times per week for 4 weeks (total 18.4 nGy) equivalent to 60 to 70 Gy over 6 to 7 weeks with conventional photon radiation.

Neutrons do have limitations, especially at the skull base, which can result in an increased complication rate. Recent studies at the University of Washington (Douglas et. al, 2008; Rockhill and Laramore, 2016) have focused on reducing the neutron contribution at the superior portion of the tumor in skull-based tumors using SRS, Gamma Knife, as a boost. The 40 month actuarial control rate was 82% compared to a historical control rate of 39% with neutrons alone.
References:
Proton Beam Therapy

Prior Authorization Requirements:
For Proton Beam Therapy, please refer to Aetna Clinical Policy Bulletin 0270.
Radiation Therapy for Anal Canal Cancer

POLICY

I. Definitive Treatment

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

A dose of 45 Gy to 59.4 Gy in 25 to 33 fractions delivered in up to 3 phases is considered medically necessary.

Palliation

Up to 10 fractions of 3DCRT is considered medically necessary.

Key Clinical Points

Anal canal cancer is a rare cancer with an annual incidence of approximately 8,500 new cases (American Cancer Society, 2018). However, the incidence of new cases has been increasing over the last 3 decades (American Cancer Society, 2018). Historically, surgery with an abdominoperineal resection (APR) was the mainstay of treatment for patients with anal cancer but was associated with a 40 to 70% 5-year overall survival (OS) rate (Ghosn et al, 2015). In 1974, Nigro and colleagues from Wayne State reported their experience of 3 patients with anal carcinoma who received neoadjuvant chemoradiation therapy and were found to have a complete response at the time of surgery. Following this initial data, multiple studies have demonstrated the effectiveness of chemoradiation therapy in anal cancer with local response rates of 80 to 90% (Glynne-Jones et al., 2014). While there is no prospective randomized data comparing chemoradiation versus APR, chemoradiation therapy is considered the standard of care for initial definitive treatment of anal cancer (Glynne-Jones et al., 2014).

Several studies have evaluated various treatment regimens for the definitive care of patients with nonmetastatic squamous cell anal cancer. Randomized trials have reported on radiation therapy alone versus combined chemoradiation therapy for treatment of patients with anal cancer (Bartelink et al, 1997; Northover et al, 2010). These studies typically utilized doses of 45 Gy to the pelvis followed by a 15 to 20 Gy boost. The data from the UKCCR ACT I trial and the EORTC trial demonstrated improved locoregional control and decreased risk of requiring a colostomy with combined chemoradiation therapy compared to radiation therapy alone (Bartelink et al, 1997; Northover et al, 2010). Locoregional control with radiation therapy alone ranged from 40 to 50% vs. 60 to 70% with chemotherapy and radiation therapy (Bartelink et al, 1997; Northover et al, 2010).
In RTOG 0529, Kachnic and colleagues (2013) performed a Phase II prospective trial to evaluate IMRT as definitive therapy for patients with anal cancer treated with radiation therapy and chemotherapy with 5-FU and mitomycin-C. The radiation therapy dose ranged from 50.4 Gy in 28 fractions to 54 Gy in 30 fractions, depending on tumor or nodal stage. The primary endpoint of this study was to evaluate if IMRT is able to reduce the rate of gastrointestinal (GI) and genitourinary (GU) acute toxicity of chemoradiation by 15% in a multiinstitutional cooperative group setting, when compared to anal cancer patients treated with conventional radiation techniques in RTOG 9811. When the rate of acute GI/GU toxicity was analyzed, the primary endpoint was not met. The rate of grade 2+ GI/GU acute adverse was exactly equivalent in RTOG 9811 and RTOG 0529 (77% vs. 77%, p = 0.5). They found that IMRT was associated with a significant reduction in Grade 2 hematologic toxicity and Grade 3 dermatologic and GI toxicity. An additional primary endpoint of this trial was to determine if dose-painting IMRT is feasible to be performed in accordance with prescribed radiation planning guidelines. In an analysis of radiation planning quality, 81% of submitted cases required revision of planning following the initial submission secondary to incorrect contouring, noncompliance of normal tissue constraints, or incorrect target dosing. Forty-six percent of cases required multiple plan revisions and re-submissions. This trial did not meet the primary endpoint of a reduction in Grade 2 GI/GU toxicity, and there was a high rate of required treatment planning revisions. The authors concluded that dose-painting IMRT is associated with a significant decrease in Grade 2 hematologic, grade 3 gastrointestinal, and grade III dermatologic toxicity.

There is limited data on radiation therapy in the palliative treatment of anal cancer. Anal cancer is a radiosensitive tumor with studies of radiation alone associated with 60 to 90% local control rates depending on the size of the tumor (Newman G et al, 1992; Touboul et al, 1994). The initial studies demonstrating the effectiveness of chemoradiation employed doses of 30 Gy in 15 fractions with concurrent chemotherapy and demonstrated greater than 80 to 90% response rates. NCCN Guidelines™ recommend 20 to 25 Gy in 5 fractions to 30 Gy in 10 fractions in the clinical setting of palliation of disease symptoms. Therefore, up to 10 fractions is recommended in the palliative treatment of anal cancer.

References
Radiation Therapy for Bladder Cancer

**POLICY**

I. Non-muscle invasive bladder carcinoma (stages Ta, Tis, T1)
   A. In the treatment of newly diagnosed non-muscle invasive bladder carcinoma, the use of radiation therapy is considered not medically necessary

II. Muscle-invasive bladder carcinoma (stages T2-T4)
   A. In an individual undergoing bladder preservation, the use of up to 37 fractions of 3D conformal radiation (3DCRT) is considered medically necessary.
   B. In the preoperative setting (i.e. prior to planned cystectomy), the use of radiation therapy is considered medically necessary
   C. In the postoperative setting (i.e. following cystectomy), the use of up to 33 fractions of 3DCRT is considered medically necessary in those who have pT3-T4 disease, positive lymph nodes and/or positive surgical margins

III. Palliation
   A. In the palliative treatment of bladder carcinoma, the use of up to 20 fractions of 3DCRT is considered medically necessary

**Key Clinical Points**

For non-muscle invasive (stages Ta, Tis, T1) bladder carcinoma (NMIBC), treatment includes transurethral resection of bladder tumor (TURBT) often followed by intravesical therapy (Babjuk, 2013; Brausi 2011). In patients with high-risk non-muscle invasive bladder cancer, radiation has been evaluated. However, its use in this group of patients is not well defined. For example, in a retrospective study of 141 patients with high-risk T1 bladder cancer, radiation alone or combined with chemotherapy was found to be a “…reasonable alternative to intravesical treatment or early cystectomy...” (Weiss, 2006). On the other hand, in a randomized control trial of 210 patients with pT1G3 bladder cancer, radiation therapy was found to be equivalent to more conservative treatment (Harland, 2007). Further, NCCN currently does not endorse the use of radiation therapy for non-muscle invasive bladder cancer (NCCN v3.2018). As such, the use of radiation is considered not medically necessary for the treatment of non-muscle invasive bladder cancer.

For an individual with muscle-invasive bladder cancer, treatment options include cystectomy or definitive chemoradiation as part of a bladder-preserving approach (Gakis, 2013). 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). NCCN also indicates that “…concurrent chemoradiotherapy or radiation therapy alone is most successful for patients with hydronephrosis and without extensive carcinoma in situ…”
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). Recently, anti-PD-L1 immunotherapy with agents such as atezolizumab (Tecentriq) was approved for the treatment of advanced bladder cancer for patients who are unable to receive cisplatin. However, the use of radiation therapy with these agents is considered investigational, experimental, and unproven (EIU) at this time. Definitive radiotherapy alone is considered for an individual with no evidence of metastatic disease who cannot undergo a cystectomy or concurrent chemoradiation.

In the preoperative setting, there remains insufficient data to determine the benefit of radiation therapy. For example, in an intergroup trial of 140 patients with invasive bladder cancer or recurrent superficial high-grade cancer, preoperative radiation (20 Gy in 5 fractions) was not associated with a survival advantage at five years (Smith, 1997). On the other hand, several publications have suggested a benefit to preoperative radiation in patients with high stage disease (Parsons, 1988; Cole, 1995). Further, recent NCCN Guidelines™ state, “…for invasive tumors, consider low-dose preoperative radiation therapy prior to segmental cystectomy…” though this is a category 2B recommendation.

In the postoperative setting, the role of radiation is more defined. Data from a retrospective series demonstrate higher local recurrence rates in patients with T3-T4 disease, positive nodes or positive surgical margins (Herr, 2004). The benefit of postoperative radiation and reducing local recurrence and improving disease-free survival has been shown in several studies (Bayoumi, 2014; Zaghoul, 1992; Nasr 2015). Further, recent NCCN Guidelines™ recommend consideration of postoperative pelvic radiation for patients with pT3/pT4 pN0-2 disease. As a result, the use of radiation in the postoperative setting is considered medically necessary for an individual with pT3-T4 disease, positive lymph nodes and/or positive surgical margins.

In an individual with evidence of metastatic disease, palliative radiation is medically necessary, up to 20 fractions using 3D techniques.
References:
Radiation Therapy for Bone Metastases

POLICY

I. Up to 10 fractions of radiation planned using a complex isodose technique is considered medically necessary in the palliative treatment of bone metastases.

II. Techniques

A. Complex isodose technique: According to the 2018 Radiation Oncology Coding Resource published by the American Society for Radiation Oncology (ASTRO), “…a teletherapy isodose plan (CPT® code 77306 and CPT® code 77307) determines the radiation dose within the target and surrounding normal tissues.” CPT® code 77306 describes a simple teletherapy isodose plan (using 1 or 2 unmodified ports), while CPT® code 77307 describes a complex teletherapy isodose plan. The latter code may be used when the ports (or beams) are modified. An ‘example clinical scenario’ for CPT® code 77306 described in this Resource is “…a 65 year-old man with advanced lung cancer (who) presents with a painful metastasis to the lumbar spine. Following simulation, a teletherapy isodose plan and monitor unit calculation is performed.” As the ports (beams) used to target and treat the metastasis are often modified, a complex teletherapy isodose plan (CPT® code 77307) is considered medically necessary for the treatment of bone metastasis.

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. 3DCRT and IMRT will be considered in cases where overlap with previous radiotherapy fields is likely to cause complications.

C. Stereotactic Body Radiosurgery (SBRT): For oligometastatic disease, please refer to the eviCore Radiation Therapy for Oligometastases Clinical Guideline. For all other scenarios, SBRT will be considered in cases that require treatment to a portion of the spine that has been previously irradiated. SBRT will also be considered for treatment of sarcoma, melanoma, and renal cell carcinoma that have metastasized to the spine.
III. 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 visceral metastases or bulky regional lymph nodes greater than 3 cm 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).

**Please be aware that a new warning and precaution was identified by the company. Specifically, “Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials...At the primary analysis (of the phase 3 ERA-223 study that evaluated concurrent initiation of Xofigo in combination with abiraterone acetate plus prednisone/prednisolone in 806 asymptomatic or mildly symptomatic mCRPC patients,) an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone. Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established.” (Bayer, 2018).
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.”

The American College of Radiology (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.

Surgery may be appropriate to establish a diagnosis, if uncertain, in an individual with acceptable performance status. In individuals where bony retropulsion is likely to be the primary cause of neurologic deficit or those with rapid deterioration of neurologic function or with high grade cervical cord compression, surgery can be considered based on the results of a randomized trial comparing surgery and postoperative 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.”

**Management of oligometastases**

Please refer to the eviCore Radiation Therapy for Oligometastases Clinical Guideline.

**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 < 0.001) 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.
Persons who have treated me are:

Radiation Therapy for Brain Metastases

POLICY
I. Whole brain radiotherapy (WBRT)
   A. Up to 15 fractions of WBRT using radiation planned with complex isodose technique is considered medically necessary
   B. For an individual identified as possibly having a poorer survival using methods such as the Graded Prognostic Assessment (GPA) or based on the presence of poor prognostic factors, a shorter course of up to 10 fractions of WBRT is considered medically necessary
   C. Three-dimensional (3D) conformal planning, intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT) are not medically necessary

II. Stereotactic radiosurgery (SRS)
   A. Determination of medical necessity
      1. SRS is medically necessary for individuals
         a. Who have a Karnofsky Performance Score (KPS) > 70 and
         b. Whose systemic disease is under control or good options for systemic treatment are available and
         c. Who do not have leptomeningeal disease and
         d. Whose primary histology is not germ cell, small cell, or lymphoma
   B. Treatment and retreatment
      1. Initial treatment with SRS for brain metastases is medically necessary when all of the following conditions are met:
         a. No lesion is greater than 5 cm and all lesions can be treated in a single treatment plan in a single fraction (for SRS) or 2 to 5 fractions (for fractionated SRS)
         b. Note that all lesions present on imaging must be targeted as a single episode of care. If in order to accomplish this, more than 5 fractions are needed, each fraction must be billed as 3D conformal or IMRT, depending on the planning technique, as the definition of fractionated SRS is not met.
2. In an individual who has received prior SRS, retreatment with SRS is medically necessary when all of the following conditions are met:
   a. No lesion is greater than 5 cm and all lesions can be treated in a single treatment plan in a single fraction (for SRS) or 2 to 5 fractions (for fractionated SRS).
   b. The individual has not been treated with more than two episodes of SRS in the past 9 months
   c. Note that all lesions present on imaging must be targeted as a single episode of care. If in order to accomplish this, more than 5 fractions are needed, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met
   d. Life expectancy > 6 months
   e. Submission of recent consultation note and recent restaging studies

3. In an individual who has received prior WBRT, SRS is medically necessary if the individual's life expectancy is > 3 months

4. Postoperative SRS is considered medically necessary for treatment of:
   a. A combination of up to 4 resected and unresected lesions that are individually < 4 cm in size

**Key Clinical Points**

I. Whole brain radiation therapy (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 clinical response rate, degree of response, and duration of response depend on the extent of tumor and the severity of initial neurologic deficits.

The use of alternative fractionation schedules during WBRT has been studied in patients with brain metastases and in those undergoing prophylactic cranial radiation (Borgelt et al., 1980, Le Péchoux et al, 2009; Murray et al., 1997; Wolfson et al., 2011). These studies have not shown any improvement in neurocognitive outcomes with alternative schedules. Shorter course regimens are appropriate for patients at increased risk of early death, such as those with a poor performance status and progressive systemic disease. Whole brain radiation using 30 Gy in 10 fractions is considered medically necessary in the treatment of brain metastases. For patients with an improved prognosis and few risk factors for early death, 37.5 Gy in 15 fractions can be considered medically necessary. In patients with a poor performance status, a shorter course of radiation using 20 Gy in 5 fractions should be utilized.

The use of whole brain radiation for individuals who are eligible for treatment with SRS to all brain metastases has changed. A meta-analysis in 2014 analyzed 5 randomized studies and found the addition of whole brain radiation with SRS vs. SRS or surgery alone decreased the risk of intra-cranial progression by 53% but did not improve overall survival (Soon, 2014). A recent large randomized study conducted by the
Alliance group came to similar conclusions. This study randomized patients to SRS with whole brain radiation or SRS alone and found higher rates of cognitive deterioration in patients who received whole brain radiation (92% vs. 64%). Similarly, it found improved intracranial tumor rates (85% vs. 50% at one year) but no improvement in overall survival with whole brain radiation (HR 1.02, 95% CI 0.75-1.38) (Brown, 2016). Furthermore, in 2014, ASTRO released its second Choosing Wisely® recommendations, which stated “Don’t routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases. (www.choosingwisely.org/astro-releases-second-list)”. Therefore, in individuals who can undergo routine surveillance, WBRT is not considered medically necessary as adjunctive therapy following treatment with SRS.

In patients who have undergone surgical resection, postoperative 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 can be recommended for individuals who undergo resection of a solitary metastasis and who have controlled extracranial disease.

Whole brain radiotherapy involves the use of two lateral opposed fields, with or without the use of custom blocking. Radiation planned using a complex isodose technique is considered medically necessary for the majority of patients requiring whole brain radiation therapy. Due to the palliative nature of the treatment, and dose delivered construction of a dose volume histogram is not medically necessary. In cases where the patient has received prior radiation 3D planning techniques will be considered.

One strategy to reduce the neurocognitive decline following whole brain radiation is the use of memantine. A single randomized study found a decrease in cognitive decline in patients who were started on memantine compared to observation, (hazard ratio 0.78, 95% CI 0.62 to 0.99).

Hippocampal avoidance whole brain IMRT has been studied as a strategy to decrease neurocognitive decline associated with whole brain radiation therapy. A phase II study RTOG 0933 examined whether hippocampal avoidance whole brain IMRT was associated with a decrease in neurocognitive decline. It found a mean decline in the Hopkins Verbal Learning Test of 7% at four months which compared favorably to historical comparison value of 30%. Overall survival was 6.8 months. There are limitations when comparing the results of this study to historical controls. For instance, the improved survival seen on 0933 could explain the improvement in neurocognitive decline. Furthermore, the delivery of hippocampal radiation is technically challenging as shown in an analysis that found 24% of cases submitted to RTOG 0933 had unacceptable deviations when the contours were submitted for pretreatment review (Gondi, 2015).

Gondi (2018) presented preliminary results of NRG oncology CC001 trial: Memantine Hydrochloride and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Reducing Neurocognitive Decline in Patients with Brain Metastases. NRG CC001 was a randomized phase III trial of 518 patients with brain metastases 5 mm outside of the hippocampus and KPS>70 who were randomized to whole brain
radiation therapy (WBRT) to 30 Gy with memantine hydrochloride or to hippocampal avoidance whole-brain radiotherapy (HA-WBRT) to 30 Gy with memantine hydrochloride. Patients were stratified by recursive partitioning analysis class and prior therapy. The primary endpoint was time to neurocognitive failure. The study found a statistically significant difference in the cognitive function failure rate at 6 months (HA-WBRT 58.0% vs. WBRT 69.1%, p=0.012). There was no difference in intracranial progression free survival or overall survival. While not statistically significant, the overall survival and intracranial progression free survival curves separate and appear to have better outcomes at 12 months in the WBRT patients compared to the HA-WBRT patients. The authors conclude that on preliminary analysis hippocampal avoidance WBRT using IMRT preserves cognitive function in patients with brain metastases. An analysis of preliminary data suggests that the benefit of HA-WBRT is patients who have an expected survival of greater than 4 months. The data from this trial has not been published in peer reviewed literature. Therefore, policy regarding the necessity of hippocampal avoidance will be reexamined upon publication.

II. Stereotactic radiosurgery (SRS)

Selection criteria for radiosurgery are similar to those for surgical resection, i.e. individuals with solitary metastases, tumor size, tumor location, good performance status, and limited or responsive extracranial disease (Andrews, 2004; Kocher, 2011; Soon, 2014; Yamamoto, 2014). In tumors, up to 3 cm in size, radiosurgery is associated with a local control of approximately 70% at one year (Kocher, 2011). A recent prospective nonrandomized study revealed radiosurgery could be utilized in the treatment of up to 10 brain metastases with similar efficacy and no increase in toxicity as long as the cumulative volume < 15 mL.

Given the available data, radiosurgery is considered medically necessary in the initial management of individuals with brain metastases who meet the following conditions: 1) no lesion is greater than 5 cm, 2) the individual has a KPS ≥ 70, 3) systemic disease is under control or good options for systemic treatment are available, 4) there is no leptomeningeal disease, 5) primary histology is not germ cell, small cell, or lymphoma, and 6) all lesions can be treated in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS).

According to guidance published by ASTRO, CPT instructions for CPT® 77373 “Stereotactic body radiation therapy (SBRT), treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions...” and include the possibility of treating multiple sites of disease in one treatment course. Further, “…for single fraction cranial lesion(s), see CPT® 77371 and CPT® 77372.” Therefore, if the sum of the treatment days for all of the sites treated during a single course of therapy exceeds five, it is not appropriate to charge CPT® 77373 for SBRT delivery.

Following radiosurgery alone, approximately 25 to 50% of patients will develop new metastases within the first year (Ayala-Peacock, 2014; Gorovets, 2017). Treatment options for new metastases include further radiosurgery or whole brain radiation therapy. Factors predicting for recurrences within the brain include age, histology, increasing number of brain metastases, and increasing extracranial disease burden.
(Gorovets, 2017). The primary drawback with the use of radiosurgery upfront is the increased risk of distant failure in the brain (Kotecha, 2017). Individuals who present with early and extensive distant failure in the brain and those with limited survival are better treated with whole brain radiation therapy. About 40% of individuals will require whole brain radiation within 6 months of initial treatment with radiosurgery. In individuals who do experience further recurrence in the brain following radiosurgery it is critical to risk stratify this cohort to determine who will benefit from further radiosurgery vs. whole brain radiation (Gorovets, 2017).

Therefore, further treatment with radiosurgery, in a previously treated individual will be considered medically necessary in those who meet the following conditions: 1) new lesions (no lesion is greater than 5 cm) are present, 2) life expectancy is > 6 months, 3) the individual has a KPS ≥ 70, 4) systemic disease is under control or good options for systemic treatment are available, 5) there is no leptomeningeal disease, 6) primary histology is not germ cell, small cell, or lymphoma, 7) all lesions can be treated in a single treatment plan with a single fraction (for SRS) or up to 5 fractions (for fractionated SRS), and 8) the individual has not been treated with more than two episodes of radiosurgery in the past 9 months.

In addition, submission of the consultation note and recent restaging studies will be required for review to verify that the individual’s systemic disease is controlled, life expectancy, history of previous treatments, and performance status.

A. Postoperative SRS

1. MD Anderson Cancer Center (MDACC)

Mahajan et al. (2017) reported a phase III randomized trial (NCT00950001) of 132 patients with 1 to 3 completely resected brain metastases treated with postoperative SRS or observation. Patients were excluded if the tumor cavity was greater than 4 cm, the unresected brain metastases were no greater than 3 cm, there was prior history of brain radiation, presence of leptomeningeal disease, a prior history of resection of any brain metastases, incomplete resection, poor performance status (KPS < 70), and small cell lung malignancies (1 vs. 2 to 3), histology (melanoma vs. other), and preoperative tumor size (< 3 cm vs. > 3 cm).

At 12 months, the use of SRS was associated with improved freedom from local recurrence (73% vs. 43% in observation, p = 0.015) with no statistically significant increase in distant brain metastases or time to whole brain radiation. Median overall survival (OS) was similar (17 months for the SRS group vs. 18 months for the observation group). In a post-hoc analysis, patients with an initial tumor diameter of 2.5 cm or less was associated with a 91% 12-month freedom from local recurrence rate, whereas those with a tumor > 2.5 cm had a local control rate of 40 to 46%. In multivariate analysis, predictors for time to local recurrence were SRS and metastases size. For overall survival, only stable disease (compared to progressive disease) was a significant predictor.
2. N107C/CEC.3

Brown et al. (2017) reported on a phase III trial randomizing patients to SRS or WBRT to the resection cavity after resection (total or subtotal) of brain metastases. Patients eligible included those with one resected brain metastasis (with a resection cavity under 5 cm) with up to an additional 3 unresected metastases (each under 3 cm). It is noted that in both groups, SRS was given to the unresected metastases. Patients were excluded if there was prior cranial radiation; leptomeningeal metastases; lesions within 5 mm of the optic chiasm or within the brain stem; or germ cell, small-cell, or lymphoma histologies. Patients were stratified according to age, duration of extracranial disease control, number of brain metastases, histology, and diameter of resection cavity and treatment center. The primary endpoints were cognitive deterioration free survival (CDFS) and OS.

One hundred ninety-four (194) patients were included in the study with a median follow up of 11.1 months. It is noted that of the 98 patients assigned to SRS, 5 did not receive treatment, 1 did not have baseline testing done, 11 died prior to 3 months, 20 did not complete cognitive assessment at 3 months, 13 died between 3 and 6 months, 1 was lost to follow up between 3 and 6 months, and 16 did not complete cognitive assessment at 6 months.

The authors reported that the median CDFS was longer following SRS than WBRT (3.7 months vs. 3.0 months, p < 0.0001). When they conducted a stratified analysis, the median CDFS was longer following SRS than WBRT (3.7 months vs. 3.1 months, p < 0.0001).

Cognitive deterioration at 6 months was lower in the SRS group vs. WBRT (52% vs. 85%). However, about half of the patients enrolled (54 [SRS] and 48 [WBRT]) were available for analysis at this time.

Median OS was not statistically different between the two groups (12.2 months for SRS vs. 11.6 months for WBRT). It is noted, however, that brain metastases was the cause of death in 87% of SRS patients vs. 73.1% in those receiving WBRT (p value not provided).

Local control and distant brain control were worse in the SRS group. For example, surgical bed control was significantly worse with SRS at 6- and 12-months (80.4% and 60.5% vs. 87.1% and 80.6% respectively). Local control was significantly worse with SRS at 3-, 6-, and 12-months (84.7%, 69.4%, and 61.8% vs. 96.7%, 92.5%, and 87.1% respectively). Distant brain control was significantly worse with SRS at 6- and 12-months (72.1% and 64.7% vs. 94.6% and 89.2% respectively). SRS was associated with a shorter time to intracranial progression as compared to WBRT (6.4 months vs. 27.5 months, p < 0.0001). Twenty percent (20%) of patients in the SRS group received WBRT as salvage therapy.
With respect to quality of life measurements, a clinically significant improvement was noted more frequently in the SRS group as compared to the WBRT group for physical well-being at 6 months. On the other hand, there was no difference in functional independence change from baseline at 6 months. The authors conclude that "SRS in the postoperative setting is a viable treatment option...and should be considered one of the standards of care as a less toxic alternative to WBRT."

References
4. ASTRO releases second list of five radiation oncology treatments to question, as part of national Choosing Wisely® campaign.
5. ASTRO 2014 Choosing Wisely List.
23. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2018 – March 20, 2018. Central Nervous System Cancers. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Central Nervous System Cancers 1.2018© 2018 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.
Radiation Therapy for Breast Cancer

POLICY

I. Whole breast irradiation following breast-conserving surgery
   A. For an individual receiving radiation treatment to the whole breast with or without treatment to the low axilla, the use of a hypofractionated regimen is preferred (see Key Clinical Points below). This includes the use of up to 16 fractions of three-dimensional conformal radiation therapy (3DCRT) followed by up to 8 fractions of electrons or photons as a boost to the surgical bed
   B. For individuals not eligible for a hypofractionated regimen, the use of up to 28 fractions of 3DCRT followed by up to 8 fractions of electrons or photons as a boost to the surgical bed is considered medically necessary
   C. Note that the boost to the surgical bed is planned using either electrons (CPT® 77321) or if using photons, a complex isodose technique (CPT® 77307). A brachytherapy boost is considered not medically necessary. The use of AccuBoost® is considered experimental, investigational and/or unproven (EIU).
   D. The use of Intensity Modulated Radiation Therapy (IMRT) for treatment of the whole breast is considered not medically necessary

II. Partial breast irradiation following breast-conserving surgery
   A. Accelerated partial breast irradiation using 10 fractions delivered twice daily with 3DCRT, IMRT or high dose rate (HDR) brachytherapy (intracavitary or interstitial) is considered medically necessary.
   B. Partial breast irradiation using 15 or 16 fractions delivered once daily with 3DCRT is considered medically necessary
   C. The use of electronic brachytherapy or AccuBoost® is considered EIU.

III. Intraoperative radiation therapy (IORT)
   A. For single fraction IORT at the time of breast conserving surgery in a node-negative individual 50 years of age or older with invasive cancer and negative surgical margins, the use of electron-beam IORT and low-energy x-ray IORT using the INTRABEAM® device are considered medically necessary
   B. In an individual who is found to have adverse pathologic features, supplemental radiation using up to 28 fractions of 3DCRT is considered medically necessary
   C. IORT not done at the time of lumpectomy (i.e. as a boost after whole breast irradiation) is considered not medically necessary
   D. The use of other forms of intraoperative brachytherapy, including but not limited to electronic brachytherapy, is considered EIU.
IV. Post-mastectomy radiation is considered medically necessary in an individual with positive axillary lymph node(s), a primary tumor greater than 5 cm or positive or close (< 1 mm) surgical margins

A. The use of up to 28 fractions of 3DCRT to the chest wall and, if needed, to regional nodes followed by up to 8 fractions of an electron boost is considered medically necessary

B. The use of IMRT is considered not medically necessary

V. Palliation

A. The use of up to 25 fractions of 3DCRT is considered medically necessary

Key Clinical Points

Early stage breast cancer is typically treated with mastectomy with or without radiotherapy to the chest wall, or lumpectomy followed by radiotherapy. Indications for post-mastectomy radiotherapy include the presence of multiple positive axillary lymph nodes, positive or narrow margins (< 1 mm), or large primary tumor size (> 5 cm). In breast-conserving therapy, 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.

Hypofractionated Whole Breast Irradiation (HF-WBI)

Several randomized trials have confirmed the efficacy of a hypofractionated regimen in the adjuvant treatment of breast cancer. In the Ontario trial, Whelan et al. (2010) randomized 1234 women with invasive carcinoma, negative axillary nodes and negative margins to 50 Gy in 25 fractions or to 42.5 Gy in 16 fractions to the whole breast. At 10 years, the hypofractionated regimen was not inferior to standard fractionation with respect to recurrence, survival or toxicity.

The START-B trial enrolled, 2215 women with stage pT1-3a, pN0-1 invasive carcinoma were randomized to 50 Gy in 25 fractions or to 40 Gy in 15 fractions. At a median follow up of 6 years, there was no statistical difference in the rate of locoregional recurrence (LRR) between the groups (Yarnold et al., 2008). At a median follow up of 9.9 years, there remained no difference in LRR. The hypofractionated regimen was associated with higher rates of disease-free survival (DFS) and overall survival (OS) as well as reduced rates of breast shrinkage, telangiectasia and breast edema.

The recently updated evidence-based guideline on radiation therapy for the whole breast has expanded upon the original 2011 recommendations (Smith et al., 2018). The guideline now recommends a hypofractionated regimen for all age groups and all stages as long as additional fields are not used to encompass regional lymph nodes. DCIS may be included for hypofractionated regimens. The tangent fields may encompass the low axilla, as clinically necessary. Recommended dose regimens are 4000 cGy in 15 fractions or 4250 cGy in 16 fractions. 3DCRT with field-in-field technique is recommended. The
volume of breast tissue receiving greater than 105% of the dose should be kept to a minimum. The contoured tumor bed should receive a minimum of 95% of the prescribed dose. Breast size and mid-plane separation should not be determining factors as long as dosimetric homogeneity guidelines are met. There is no longer a contraindication to the use of chemotherapy prior to radiation or the use of concurrent treatment with hormonal or trastuzumab.

**Radiation Planning Techniques**

**Whole Breast**

The updated guideline referenced above also provided guidelines around treatment technique and planning for women receiving whole breast irradiation. The authors state that “…3-dimensional conformal treatment planning with a ‘field-in-field’ technique is recommended as the initial treatment planning approach.” Further, “(d)epth inspiration breath hold, prone positioning, and/or heart blocks are recommended to minimize heart dose.” They also state that “(f)or patients with significant daily positioning variations, daily imaging may be used.”

As a participant in the Choosing Wisely® campaign, ASTRO recommended not to “…routinely use intensity modulated radiotherapy (IMRT) to deliver whole breast radiotherapy as part of breast conservation therapy.” They further state that “…the term ‘IMRT’ has generally been applied to describe methods that are more accurately defined as field-in-field 3-D conformal radiotherapy.” And “…while IMRT may be of benefit in select cases where the anatomy is unusual, its routine use has not been demonstrated to provide a significant clinical advantage.”

Therefore, in treatment of the whole breast, the use of 3DCRT without IGRT is considered medically necessary. The use of IMRT is considered not medically necessary, though an exception will be considered if an optimized 3D conformal plan fails to meet tolerances of nearby organs at risk (OARs).

**Boost**

The guideline also discusses recommendations concerning a boost. Specifically, “…a tumor bed boost is recommended for patients with invasive breast cancer who meet any of the following criteria: age < 50 years with any grade, age 51 to 70 years with high grade, or a positive margin.” They also state that “…omitting a tumor boost is suggested in patients…age >70 with hormone receptor-positive tumors of low or intermediate grade resected with widely negative (>2 mm) margins.”

The dose recommended “(i)n the absence of strong risk factors for local recurrence (is)...1000 cGy in 4 to 5 fractions...(i)n the presence of strong risk factor(s) for local recurrence…a higher radiation boost dose of 1400 to 1600 cGy in 5 fractions may also be used.”

With respect to timing and technique, the guideline states that a “…sequential boost is currently recommended” and that “…external beam treatment is recommended…” Given this, the use of a photon or electron boost is considered medically necessary. The use of brachytherapy, including but not limited to interstitial, intracavitary, or intraoperative, for a boost is considered not medically necessary.
Partial Breast Irradiation
The IMPORT LOW trial is a multicenter, randomized phase 3 trial which demonstrated non-inferiority for partial breast radiation therapy using standard external beam radiation therapy techniques (Coles et al., 2017). Between May 2007 and October 2010, 2018 women with low risk, early stage breast cancer who underwent breast conserving surgery were randomized to whole breast radiation therapy versus partial breast radiation. Patients were randomized to receive 40 Gy in 15 fractions to the whole breast, 36 Gy in 15 fractions to the whole breast, or 40 Gy in 15 fractions to the partial breast. The study required that all patients receive 3D conformal radiation therapy using forward-planned, field in field radiation techniques. The treatment was delivered with medial and lateral tangential beams to minimize dose to surrounding lung and heart and to ensure that the beams exit within the breasts. At a median follow-up of 72.2 months, there was no difference in the 5 year local relapse rate (whole breast 1.1% vs partial breast 0.5%, p=0.42). The estimated 5-year absolute differences in local relapse compared with the control group were -0.38% (-0.84 to 0.90) for the partial breast group and -0.73% (-0.99 to 0.22) for the reduced-dose group. The patients in the partial breast group reported statistically significant fewer adverse cosmetic events (change in breast appearance, p=0.007 and breast harder or firmer, p=0.002) compared to the whole breast group. As this study used the same dose fractionation scheme for the whole breast and the partial breast group, this study concluded that partial breast radiation using standard external beam radiation therapy techniques is non-inferior to standard dose whole breast radiation therapy in terms of local relapse and resulted in a lower rate of adverse late tissue effects.

Accelerated Partial Breast Irradiation (APBI) is a 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, with each fraction delivering a relatively higher dose.

Correa et al. (2017) recently published an update of an ASTRO evidence-based consensus statement for APBI. In this update, a “Suitable Group” was defined as eligible for APBI. The “Suitable Group” included those with stage T1s or T1, age 50 or greater, and with negative margins by at least 2 mm. The DCIS group now considered “Suitable” must include all of the following: screen-detected, low to intermediate nuclear grade, no more than 2.5 cm, and have a resection margin of at least 3 mm. Definition of both the “Cautionary” and “Unsuitable” Groups are defined in the updated ASTRO consensus statement. These updates were accepted by the National Comprehensive Cancer Network (NCCN) which further recommends 10 fractions twice daily using brachytherapy or external beam photon therapy. Typical doses cited in the NCCN Guidelines™ are 34 Gy in 10 fractions with twice daily treatment using brachytherapy. External beam treatment is recommended with 38.5 Gy in 10 fractions with twice daily treatment. They also indicate that “…other fractionation schemes are currently under investigation.” Therefore, up to 10 fractions (whether photon or brachytherapy) for APBI is considered medically necessary.

The American Brachytherapy Society issued their consensus statement for APBI in early 2018. They reviewed guidelines and consensus statements from ASTRO, GEC-ESTRO, the American Society of Breast Surgeons as well as their own previous guidelines. Seven randomized trials of APBI and two trials evaluating intraoperative radiation, the TARGIT-
A and ELIOT clinical trials were reviewed. The new consensus statement criteria include age 45 years or older; size 3 cm or less; all invasive subtypes and DCIS; positive or negative ER status; negative surgical margins with no tumor on ink for invasive cancers and at least a 2 mm margin for DCIS; no evidence of lymphovascular space invasion and negative lymph node status. Recommendations on treatment technique with strong or moderate evidence include multicatheter interstitial brachytherapy; external beam techniques of IMRT and 3DCRT; and applicator brachytherapy. Participation in clinical trials and protocols was recommended for proton beam, intraoperative radiation therapy, and electronic brachytherapy. In considering electronic brachytherapy as an APBI technique and intraoperative technique, the review centered on the reports of 702 patients and a group of 146 DCIS patients and concluded that electronic brachytherapy should not be used outside of a clinical trial.

Most recently, data from NSABP B39/RTOG 0413 was presented at the 2018 SABCS conference. In this trial, 4216 patients with DCIS or stage I-II (≤ 3cm and 0-3 positive axillary nodes) invasive adenocarcinoma were randomized to whole breast irradiation (WBI) or APBI (using MammoSite® or 3D conformal external beam radiotherapy) after lumpectomy. The primary endpoint was rate of ipsilateral breast tumor recurrence (IBTR) while secondary endpoints included relapse free survival (RFI), distant disease free survival (DDFI) and overall survival (OS). At 10 years, 95.2% of APBI patients were IBTR-free vs. 95.9% of WBI patients. Though this was not statistically significantly different, the “hazard ratio did not meet the statistical criteria for treatment equivalance.” Further, the 10-year RFI was statistically improved with WBI as compared to APBI (93.4% vs. 91.9%). There was no difference, however, in DDFI, DFS or OS. Given the small differences in IBTR and RFI, “PBI may be an acceptable alternative to WBI for a proportion of women who undergo breast-conserving surgery.”

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. Hepel et al presented the results of the patient registry for APBI at the 2018 ASTRO meeting and concluded longer follow up follow up is needed to confirm late end points. Given the paucity of data regarding the use of NIIGBB, particularly on local control, additional research is necessary prior to widespread approval of NIIGBB. Therefore, NIIGBB is considered investigational.

**IORT**
The use of IORT for the treatment of breast cancer has been evaluated in two prospective randomized clinical trials, TARGIT-A which utilized low-energy xrays (using INTRABEAM®) and ELIOT, which utilized electrons.

**TARGIT-A**
In the TARGIT-A trial, patients 45 years or older with unifocal invasive ductal carcinoma (preferably less than 3.5 cm) were randomized to receive IORT (to the lumpectomy bed) or external beam radiation therapy (EBRT) to the whole breast (with or without a boost). Those receiving IORT were stratified by timing of the IORT (pre-pathology versus post-pathology) and by facility. For pre-pathology patients randomized to IORT, supplemental EBRT to the whole breast (without a boost) was given when pathology from the lumpectomy revealed either invasive lobular carcinoma, extensive intraductal component or another adverse criterion (i.e. high-grade, lymphovascular invasion, nodal involvement). In this setting, IORT was considered the boost. The primary outcome evaluated was local control in the conserved breast.

Initial results were published in 2010 at which time data was presented on 2232 patients, 862 who had a median follow up of 4 years and 1514 who had a median follow up of 3 years. Of the 1113 patients randomized to IORT, 996 received the allocated treatment. Of the 1119 patients randomized to EBRT, 1025 received the allocated treatment. At four years, there was no significant difference in the estimate of local recurrence between IORT and EBRT (1.2% versus 0.95%, p = 0.41). It is noted that in the pre-pathology IORT group, 14.2% of patients received supplemental EBRT.

In a more recent update published in 2014, a total of 3451 patients randomized to IORT and 1730 patients randomized to EBRT were evaluated. Within the IORT group, 2298 were randomized prior to the lumpectomy (pre-pathology strata) and 1153 were randomized after lumpectomy (post-pathology strata). Median follow-up of the 3451 patients who had received IORT was two years and five months. 2020 patients had a median follow up of four years and 1222 patients had a median follow up of five years (note that only 611 patients [18%] had 5-year follow up). At five years, the risk for local
recurrence with IORT was significantly higher as compared to EBRT (3.3% versus 1.3%, p = 0.042). When considering the pre-pathology strata, the risk of local recurrence was 2.1% with IORT versus 1.1% (p = 0.31). This contrasts with the post-pathology strata where the recurrence was 5.4% with IORT versus 1.7% with EBRT (p = 0.069). Based on this data, the authors conclude that “TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative external beam breast radiotherapy.”

In response to this publication, several authors have criticized the statistical analysis. For example, Cuzick (2014) states “…there are several major deficiencies in the analysis…” including “…the misuse of the non-inferiority criterion…” which “…clearly fails…” as the “…Kaplan-Meier estimates… establish a 2% superiority of external beam radiotherapy (p = 0.04) and a CI extending beyond 2.5%.” Cuzick further states the “…protocol clearly states that the primary analysis population includes all randomized patients. However, the report concentrates on the prepathology group.”

Haviland et al. (2014) stated that “…assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point. This analysis, including the non-inferiority test statistic, is therefore unreliable.” The authors conclude that “…the TARGIT-A trial remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.”

Finally, Silverstein et al. (2014) indicated that “…the results of the TARGIT-A trial, with a median follow-up (FU) of 29 months, is still well below the median time when breast recurrences can be expected, especially since more than 90% of TARGIT-A women were estrogen receptor positive, and at least 65% received adjuvant hormonal therapy, a treatment well-known to delay recurrences in ER+ women.” In addition, they note that “…overall breast recurrence rates in the TARGIT group also exceeded rates in the EBRT group, a difference at borderline statistical significance (p = 0.053).” They conclude that “…with 29 months of median follow-up, the TARGIT data are still immature and risk-adapted IORT with 50-kV X-rays is still too early in follow-up to select the subset of women whose local control will be within their noninferiority criteria margin of 2.5%. Until the data are more mature, 50-kV patients should be treated under strict institutional protocols.”

ELIOT

In the ELIOT trial, 1305 patients 48 years or older with tumors 2.5 cm or smaller were randomized to receive IORT with electrons or EBRT. Patients were stratified by tumor size (<1.0 cm vs. 1.0 to 1.4 cm vs. ≥1.5 cm). The primary endpoint was the occurrence of ipsilateral breast tumor recurrences (IBTR), which included true local relapse plus new ipsilateral breast tumor. Median follow up for all patients was 5.8 years.

Results revealed that there was a significantly greater occurrence of IBTR in the IORT group compared to the EBRT group at five years (4.4% versus 0.4%, p = 0.0001). The five-year rate of true local recurrence (occurring in the index quadrant) was also significantly higher in the IORT group compared to the EBRT group (2.5% versus 0.4%, p = 0.0003). The rate of new ipsilateral breast carcinoma was also significantly higher in
the IORT group compared to the EBRT group (1.9% versus 0%, \( p = 0.0001 \)). Finally, it was noted that the IORT group developed a significantly higher rate of axillary or other regional lymph node metastases (1% versus 0.3%, \( p = 0.03 \)). At five years, overall survival did not differ between the two groups.

In a multivariate analysis of the IORT group, tumor size greater than 2 cm, presence of four or more positive lymph nodes, a poorly differentiated tumor and triple negative subtype was associated with nearly twice the risk of IBTR. The risk of IBTR at five years was 11.3% if any one of these unfavorable characteristics was present versus 1.5% in those without these features (\( p < 0.0001 \)). It is noted that this group of patients with a low risk of IBTR is similar to that of the “suitable” APBI group as defined by ASTRO.

**ASTRO CONSENSUS STATEMENT**

ASTRO recently released an Evidence-Based Consensus Statement for APBI. In this statement, the authors recommend that patients “…be counseled that in 2 clinical trials the risk of IBTR was higher with IORT.”

With respect to IORT using electrons, the authors state that “ELIOT has a median of 5.8 years follow up (\( n = 1305 \)). However, ELIOT patients with invasive cancer fitting the ‘suitability’ criteria had a very low rate of IBTR. Among these patients, the 5-year occurrence of IBTR was approximately 1.5%, pointing out the importance of patient selection.” Hence the recommendation that “…electron beam IORT should be restricted to women with invasive cancer considered “suitable” for PBI.”

With respect to IORT using low-energy x-rays, the authors recommend that “…low-energy x-ray IORT for PBI should be used within the context of a prospective registry or clinical trial, per ASTRO Coverage with Evidence Development (CED) statement. When used, it should be restricted to women with invasive cancer considered ‘suitable’ for partial breast irradiation based on the data at the time of this review.”

When further detailing their recommendations, the authors note that “…the five-year IBTR risk is based on the overall short follow up of the TARGIT trial, which limits precision of the five-year risk estimates. Although there was no statistically significant difference in IBTR risk for patients treated with IORT versus WBI in the TARGIT prepathology subgroup, the task force thought greater weight should be placed on evaluation of the efficacy of IORT in the prespecified primary analysis population that included all patients.” Given this and the concern of “…misuse of the noninferiority criterion…,” the authors “…felt low-energy x-ray IORT should continue to be used within the context of a prospective registry or clinical trial to ensure long-term local control and toxicity outcomes are prospectively monitored.” In addition, “…given the increased risk of IBTR, the task force advised that low-energy x-ray IORT, when used, be confined to patients with the lowest risk of IBTR, specifically those in the ‘suitable’ group.”

In response to the Consensus Statement, Small et al. reiterated that the “TARGIT-A trial specified stratification between pre- and post-pathology before randomization…” and that “…the panel’s recommendations regarding IORT should have acknowledged the results for the pre-specified analysis for the primary end-point of IORT treatment in the whole trial (\( n = 3451 \), a difference of 2 % \( p = 0.04 \)), as well the pre-pathology stratum (\( n = 2298 \), a difference of 1% \( p = 0.31 \)).
Conclusion
When considering all published data and editorials, electron beam and low-energy x-ray (INTRABEAM®) IORT are considered medically necessary for a node-negative individual with invasive cancer when used in accordance with the updated ASTRO Evidence-Based Consensus Statement for APBI.

Electronic Brachytherapy
The updated American Brachytherapy Society Consensus Statement recommends patients treated with electronic brachytherapy should not be offered...outside of clinical trial. Therefore, until such evidence is available, electronic brachytherapy for APBI or IORT is considered EIU.

Palliation
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 (i.e. 10 fractions). 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 considered for women who initially present with metastatic disease but after surgery and/or chemotherapy are found to have no clinical evidence of disease. In such a scenario, the use of up to 25 fractions is considered medically necessary.

References:
1. AASTRO releases list of five radiation oncology treatments to question as part of national Choosing Wisely® campaign. 2013 Sep 13.


Radiation Therapy for Cervical Cancer

POLICY

I. Brachytherapy alone, for IA1, is considered medically necessary for any of the following:
   A. Medically inoperable
   B. Surgical refusal
   C. Invasive carcinoma diagnosed only by microscopy without evidence of a gross lesion; microscopic lesions with stromal invasion 3.0 mm or less in depth and a horizontal spread of 7.0 mm or less without lymphatic or vascular space involvement.

II. Pelvic radiation alone for stages IB or IIA is considered 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 IA1 with lymphovascular space invasion (LVSI), IA2, IB, IIA, IIB, IIIA, IIIB or IVA are considered 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 extending 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 considered 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 considered medically necessary for the treatment of locoregional recurrence in an individual without evidence of distant metastases

A. When salvage radiotherapy is attempted to an isolated local/regional recurrence without evidence of distant metastatic disease, 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. Stereotactic Body Radiation Therapy (SBRT) may be considered based on a history of previous radiation to the same or abutting region and inability to deliver therapeutic doses of radiation with other techniques.

Key Clinical Points

Within the United States in 2018, 13,240 new cases of cervical cancer are projected resulting in approximately 4,170 deaths. The prognosis of an individual with cervical cancer is markedly affected by the extent of disease at the time of diagnosis.

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 will be approved for a vaginal cylinder. Electronic/kilovoltage brachytherapy for other gynecologic devices, such as a tandem and colopostats 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 1.2019 – August 9, 2018 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. Locoregional 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

Randomized 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 that benefit include FIGO stages 1B1 to IVA cervical cancer treated with primary radiation therapy and FIGO stages I to IIA disease with 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 and incorporate varying radiation treatment regimens with chemotherapy schedules of cisplatin alone or combined with fluorouracil, the trials demonstrate significant survival benefit for this combined approach. Based on these results, strong consideration should be given to the incorporation of concurrent chemotherapy with radiation therapy in women who require radiation therapy for the treatment of cervical cancer.
References

Radiation Therapy for Endometrial Cancer

POLICY

Treatment options for a fully surgically staged individual:

I. Postoperative brachytherapy (alone) is considered 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 considered 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, G3)
      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 considered 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 considered medically necessary for either of the following:
   A. Stage III C1 (involvement of only pelvic nodes)
   B. Stage III C2 (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 considered medically necessary for any of the following:
   A. Stage IVA (tumor invading bladder and/or bowel mucosa)
   B. Local only recurrence with no evidence of metastatic disease
   C. Palliative treatment of symptoms such as pain or bleeding from the endometrial tumor

VI. Electronic/kilovoltage brachytherapy
   A. Electronic/kilovoltage brachytherapy is considered medically necessary when utilizing a vaginal cylinder
   B. Electronic/kilovoltage brachytherapy for other gynecologic devices, such as a tandem and colopstats is considered experimental, investigational, or unproven (EIU) for the treatment of endometrial cancer

Key Clinical Points

Within the United States in 2018, 63,230 new cases of uterine malignancy are projected, resulting in projected 11,350 deaths. Uterine cancers represent the most common female genital tract malignancy. Endometriod (tumors resembling the lining of the uterus; adenocarcinomas) are the most prevalent subtype. Serous papillary carcinoma is not covered under this guideline.

The staging definitions used in the creation of the treatment criteria may be found in the 8th 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 surgically staged Stage IA with or without adverse risk factors, all individuals regardless of pathologic grading may be observed as per NCCN Guidelines™.
Observation may also be employed for individuals with Stage IB G1, G2, and G3 disease without risk factors as well as individuals with G1 and G2 Stage IB disease with risk factors. Should treatment rather than observation be decided upon for these same groups, radiation techniques are stratified in the preceding guideline statements. 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. The early-stage endometrial cancer study by Aalders et al. (1980) updated by Onsrud, et al. (2013) of 568 patients with a median follow up of 20.5 years suggested no statistical difference in overall survival (OS) between women treated with vaginal brachytherapy alone versus those treated with vaginal brachytherapy and external beam radiation. Patients younger than age 60 who received external beam treatment did not have a survival benefit but did suffer an increased risk of secondary cancers with subsequent increased mortality.

For all other stages and those with positive radiologic imaging, surgical restaging or pathologic confirmation of more advanced disease is recommended (image directed biopsy). Individuals 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 radiation 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 to 2.0 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 considered 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 OS rates were 87% and 97%. There was only 1 vaginal failure (2%) and no pelvic failures. Intravaginal radiation therapy (IVRT) 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.

An incompletely surgically staged individual with no risk factors and a tumor less than 2 cm with Stage IA G1-G2 disease may be observed. All other individuals with Stage IA, IB, and II incompletely staged disease should undergo either imaging or surgical restaging. If imaging results are negative, they should be treated according to their assigned stage. If positive or suspicious, however, an attempt should be made to either restage surgically or document the presence of metastatic disease. Individuals who have been surgically restaged should be treated according to their appropriate new Stage and findings. It should be noted that immediate surgical restaging without the benefit of imaging is a Category 3 NCCN recommendation.

D. An individual with Stage IB or Stage II with G3 cancer should be considered for chemotherapy as well.

References


Radiation Therapy Criteria

Radiation Therapy for Esophageal Cancer

POLICY

I. Neoadjuvant treatment
   A. For an individual with stage T1b node-positive or T2-T4a disease, the use of 23 to 28 fractions of three-dimensional conformal radiation (3DCRT) is considered medically necessary.

II. Adjuvant treatment (if no preoperative or prior irradiation given)
   A. For an individual with squamous cell carcinoma when there are positive margins or adenocarcinoma with at least pT2 or node-positive disease, the use of 25 to 28 fractions of 3DCRT is considered medically necessary.

III. Definitive treatment
   A. For an individual with T1b node-positive or T2-T4a disease, the use of 25 to 28 fractions of 3DCRT is considered medically necessary.
   B. For tumors located in the cervical esophagus, up to 39 fractions of 3DCRT or IMRT is considered medically necessary.

IV. Palliation
   A. The use of 15 fractions of 3DCRT is considered medically necessary.

Key Clinical Points

I. Neoadjuvant 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 gastroesophageal junction (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 (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.

NCCN Guidelines™ indicate that IMRT “…is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is required that cannot be achieved by 3D techniques.” Given this and the available data, the use of IMRT will be considered on a case-by-case.

References


Radiation Therapy for Gastric Cancer

POLICY

I. Neoadjuvant treatment
   A. For an individual with stage T2-T4 or node-positive disease, the use of up to 28 fractions of 3D conformal radiation (3DCRT) is considered medically necessary.

II. Adjuvant treatment (if no preoperative or prior irradiation given)
   A. For an individual with at least pT2 or node-positive disease, microscopic or macroscopic residual disease or high-risk features such poor differentiation, lymphovascular invasion, neural invasion, and age less than 50, the use of up to 28 fractions of 3DCRT is considered medically necessary.

III. Definitive treatment
   A. For an individual who is inoperable (i.e. due to co-morbidity), the use of up to 28 fractions of 3DCRT is considered medically necessary.

IV. Palliation
   A. The use of 15 fractions of 3DCRT is considered medically necessary.

Key Clinical Points

According to Eighth Edition of the AJCC Cancer Staging Manual, “...if a tumor involves the esophagogastric junction (EGJ) and its epicenter is ≤ 2 cm into the proximal stomach (i.e., ≤ 2 cm distal to the EGJ)...” it is classified as esophageal cancer. “Tumors involving the EGJ with their epicenter > 2 cm into the proximal stomach (i.e., > 2 cm distal to the EGJ)...” are classified as gastric cancer.

In the postoperative treatment of gastric carcinoma, chemoradiation 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 chemoradiotherapy (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 overall survival (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.
In terms of historical progression of treatment planning techniques; after the Intergroup 0116 trial, which used AP-PA field arrangement, Soyfer et al (2007) published data concluding that a 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 two-year OS for the 3DCRT and IMRT groups was 51% and 65%, respectively ($p = 0.5$). The two-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.”

Additional publications have failed to show a definitive benefit to IMRT. Further, NCCN Guidelines™ state that IMRT “…may be used in clinical settings where reduction in dose to organs at risk (eg, heart, lungs, liver, kidneys, small bowel) is required, which cannot be achieve by 3-D techniques.” Further, variations in gastric filling and respiratory motion should be accounted for when delivering IMRT. Given this and as data remains mixed with respect to the benefit of IMRT, the use of IMRT is considered not medically necessary.
References:
Radiation Therapy Criteria

Radiation Therapy for 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.
   B. The use of neutron beam therapy is medically necessary in select cases of salivary gland tumors (See Neutron Beam Therapy guideline)
   C. 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 20 fractions are medically necessary, in 1 phase

V. Re-treatment for salvage after prior radiation  
A. Reirradiation 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, “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. 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 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™.
References
Radiation Therapy for Hepatobiliary Cancer

For treatment using Proton Beam Therapy, please refer to the Proton Beam Therapy guideline.

For treatment using Selective Internal Radiation Therapy (SIRT), please see Selective Internal Radiation Therapy (SIRT) guideline.

POLICY

I. Primary hepatocellular carcinoma (HCC)
   A. Definitive treatment
      1. In the treatment of medically or technically unresectable localized HCC in an individual with adequate hepatic reserve
         a. The use of 25 to 39 fractions of three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) is considered medically necessary
         b. The use of 3 to 5 fractions of stereotactic body radiation therapy (SBRT) is considered medically necessary to treat concurrently one or more tumors when there is evidence of the ability to protect an adequate volume of uninvolved liver
   B. Palliative treatment
      1. In an individual with localized disease or local disease with minimal extrahepatic disease, up to 20 fractions of 3DCRT is considered medically necessary

II. Intrahepatic bile duct cancer (cholangiocarcinoma)
   A. Definitive treatment
      1. In the management of unresectable localized intrahepatic bile duct cancer
         a. The use of 25 to 33 fractions of 3DCRT or IMRT is considered medically necessary
         b. The use of up to 5 fractions of SBRT is considered medically necessary
   B. Adjuvant (postoperative) treatment
      1. In the management of resected intrahepatic bile duct cancer with positive margins and/or positive regional lymph nodes
         a. The use of 25 to 33 fractions of 3DCRT or IMRT is considered medically necessary
C. Palliative treatment
   1. In an individual with unresectable localized intrahepatic bile duct cancer, up to 20 fractions of 3DCRT is considered medically necessary

III. Extrahepatic Bile Duct Cancer (cholangiocarcinoma)
   A. Definitive treatment
      1. In the management of unresectable localized extrahepatic bile duct cancer
         a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
         b. The use of SBRT is considered not medically necessary
   B. Adjuvant (postoperative) treatment
      1. In the management of resected extrahepatic bile duct cancer
         a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
         b. The use of SBRT is considered not medically necessary
   C. Palliative treatment
      1. In an individual with unresectable localized extrahepatic bile duct cancer, up to 20 fractions of 3DCRT is considered medically necessary

IV. Gallbladder Cancer
   A. Definitive treatment
      1. In the management of unresectable localized gallbladder cancer
         a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
         b. The use of SBRT is considered not medically necessary
   B. Adjuvant (postoperative) treatment
      1. In the management of resected gallbladder cancer with positive margins and/or positive regional lymph nodes
         a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
         b. The use of SBRT is considered not medically necessary
   C. Palliative treatment
      1. In an individual with unresectable localized gallbladder cancer, up to 20 fractions of 3DCRT is considered medically necessary
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.

External Beam Radiation Therapy (EBRT) is a treatment option for certain cases of HCC not amenable to resection for technical or medical reasons, and can be delivered using one of several available highly-conformal techniques such as 3DCRT, IMRT and SBRT. Proton Beam Therapy (PBT) generally is not medically necessary but may be considered in unique clinical settings. (See Proton Beam 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. Several radiation schedules are available, including hypofractionation, SBRT (1 to 5 fractions), and conventional fractionation. Safety data are limited for treating other than Child-Pugh class A cases. A dose modification is needed when treating Child-Pugh class B. Radiation therapy
is generally not given for Child-Pugh class C cases. 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. While the intent of 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.

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". Those cancers that occur at or near the junction of the right and left hepatic ducts are known as Klatskin tumors and are considered extrahepatic. 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. Highest surgical cure rates are seen if there is only one lesion, vascular invasion is not present, and lymph nodes are not involved.

The role of adjuvant radiation therapy after resection is not firmly established, but is considered 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. Data are limited; the optimal approach is not established.

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 $\geq 80.5$ 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 3DCRT 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 an accepted option 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. Data to support specific regimens are limited.

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. A common presentation of gallbladder cancer is 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, unless the target is within the hepatic parenchyma.

Definitive radiation therapy along with fluoropyrimidine-based chemotherapy is an option for patients with unresectable gallbladder cancer that has not spread beyond a locoregional state. Such an approach often becomes a palliative exercise, and should be weighed against other means of palliation that includes biliary decompression followed by chemotherapy.
References


Radiation Therapy 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 a piece
   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 a piece
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 multidisciplinary 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 multidisciplinary team.

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


Radiation Therapy for 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. In the palliative setting

III. Radiation is not medically necessary in the definitive or adjuvant treatment of renal cell cancer

Fractionation

I. In the adjuvant setting for adrenal cancer, up to 30 fractions is medically necessary
   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
   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 radiofrequency 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:
Radiation Therapy for Multiple Myeloma and Solitary Plasmacytomas

POLICY

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

I. Solitary osseous plasmacytoma or solitary extraosseous plasmacytoma
II. As palliative treatment for multiple myeloma

Fractionation

I. Plasmacytoma
   A. 40 to 50 Gy in 1.8 to 2.0 Gy fractions to involved field with or without surgery

II. Multiple myeloma
   A. 10 to 30 Gy in 2.0 to 3.0 Gy fractions for pain, impending fracture, and/or impending spinal cord compression
   B. 8 Gy in a single fraction can be considered

Techniques

I. Three-dimensional conformal radiation therapy (3DCRT) is considered medically necessary for the definitive treatment of solitary osseous or solitary extraosseous plasmacytoma

II. Intensity-modulated radiation therapy (IMRT) is considered medically necessary for the definitive treatment of a solitary plasmacytoma presenting in the head and neck region

III. Radiation planned using a Complex isodose technique (CPT® 77307) is considered medically necessary for the palliative treatment for multiple myeloma
Key Clinical Points

I. Solitary Plasmacytoma

These lesions are diagnosed by a complete multiple myeloma evaluation to rule out the presence of other lesions or systemic disease. Solitary plasmacytomas of the bone generally involve the axial skeleton and account for almost seventy percent of clinical presentations. The remaining are extramedullary lesions generally presenting in the upper aerodigestive tract.

The optimal radiation dose for the treatment of these lesions is not well known, with doses ranging from 30 Gy to 60 Gy in the published literature. The largest series, with 258 patients, reported is the European Multicenter Rare Cancer Network study (Ozsahin et al., 2006) which included 206 patients with solitary plasmacytoma of bone and 52 patients with extramedullary plasmacytoma. Two hundred and fifteen patients were treated only with radiation therapy. Thirty-three were treated with a combination of radiation therapy and chemotherapy. Eight patients were treated only with surgery. One was treated with chemotherapy alone. One died before radiation therapy. The median dose of radiation administered was 40 Gy with a range of 20 to 66 Gy. At median follow up of 56 months, 14% developed a local recurrence. Sixty percent of the patients who did not receive radiation therapy relapsed locally, while only 12% of the radiation therapy group experienced local relapse. Overall survival (OS) was 74% with disease free survival (DFS) of 50%. A 10-year probability of disease progression to multiple myeloma was 36% for extramedullary plasmacytoma and 72% for solitary plasmacytoma of bone.

Considerable care must be taken in the workup of a suspected solitary plasmacytoma to ensure that other lesions and hence, a diagnosis of multiple myeloma, are not present. Following a positive biopsy of the lesion, a full multiple myeloma evaluation should be performed. CBC, peripheral smear, serum BUN, creatinine, electrolytes, albumin, calcium, uric acid, LDH and Beta2 microglobulin are part of the basic blood workup. Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis should be ordered as well as a serum free light chain assay. Urine for creatinine clearance and a 24-hour urine for total protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE) should be performed. Bone marrow aspirate and biopsy are mandatory to document the lack of clonal cells for a diagnosis of solitary plasmacytoma. A variant of solitary plasmacytoma, when there are fewer than 10% of clonal plasma cells is termed solitary plasmacytoma with minimal bone marrow involvement.
In addition to the previous workup, diagnostic imaging plays an important role in securing the diagnosis. Skeletal survey or whole body low-dose Computed Tomography (CT) scan may reveal other lesions. If abnormal, Magnetic Resonance Imaging (MRI) of the spine or whole body MRI can be utilized as the clinical presentation dictates. Positron Emission Tomography (PET)/CT may be needed to distinguish between smoldering and active myeloma. It has proven helpful in finding additional lesions in approximately 30% of cases diagnosed by MRI as solitary plasmacytoma.

Following confirmation of the diagnosis, surgery may play a role in certain definitive clinical presentations or is performed for clinical presentations requiring neurologic decompression or stabilization of a weight-bearing bone prior to the performance of radiation therapy. The optimal radiation dose for a solitary plasmacytoma of bone (SBP) is not known due to the lack of phase III studies with differing recommendations from the NCCN and ILROG (International Lymphoma Radiation Oncology Group). While the NCCN has a dose range of 40 to 50 Gy that is independent of tumor size, ILROG recommends 35 Gy to 40 Gy for a SBP < 5 cm. Tumors ≥ 5 cm have a dose range of 40 to 50 Gy. For Solitary Extramedullary Plasmacytoma (SEP), ILROG recommends a dose range of 40 to 50 Gy. Lesions excised with positive margins or small, well-defined lesions may be treated with 40 Gy.

Anatomic location, tumor size, surgical resection, older age at diagnosis and persistence of myeloma protein for one year post radiation treatment have all been postulated to be of prognostic significance but none have been definitely proven due to contrasting studies. Monoclonal protein has been noted to disappear in up to 50% of cases. The reappearance of the protein herald recurrence.

II. Multiple Myeloma

The role of radiation therapy in multiple myeloma is largely palliative with use of radiation dose regimens as listed in the Policy section of this guideline. Total Body Irradiation (TBI) can be performed prior to autologous stem cell transplant, but is no longer commonly used as it has a higher toxicity profile compared to melphalan alone. Helical tomographic total marrow irradiation is currently investigational.
References:
Radiation Therapy 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. Complex or 3D techniques with image guidance

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

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 guideline, Radioimmunotherapy with Zevalin®

IV. Adjuvant radiation after chemotherapy
   A. Areas of initial involvement
      1. In an individual with stage I-IIB 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
         b. Directed at a single site in 1 phase
      3. Sub-diaphragmatic presentations
         a. Complex or 3DCRT techniques
   B. Areas of less than a complete response (CR)
      1. 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
         b. Directed at up to 4 separate sites in 1 phase a piece
      3. Sub-diaphragmatic presentations
         a. Complex or 3DCRT techniques
   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. 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 multidisciplinary 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 multidisciplinary team.

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
Radiation Therapy for Non-malignant Disorders

POLICY

I. Radiation therapy is considered medically necessary for the following non-malignant disorders:
   A. Choroidal hemangioma
   B. Desmoid tumor
   C. Dupuytren’s contracture (fibromatosis)
   D. Extramammary Paget’s disease (adenocarcinoma of the skin)
   E. Extramedullary hematopoiesis (hypersplenism)
   F. Giant cell tumor of bone (osteoclastoma)
   G. Gorham-Stout syndrome (disappearing bone syndrome)
   H. Graves’ ophthalmopathy
   I. Gynecomastia
   J. Hemangiomas
   K. Heterotopic ossification
   L. Hypersalivation of amyotropic lateral sclerosis (ALS)
   M. Hyperthyroidism
   N. Keloid scar
   O. Langerhans cell histiocytosis (eosinophilic granuloma)
   P. Lethal midline granuloma (Stewards disease)
   Q. Paraganglioma (chromaffin positive)
   R. Parotid adenoma
   S. Peyronie’s disease (morbus peronie, induratio penis plastica)
   T. Pigmented villonodular synovitis (tenosynovial giant cell tumor)
   U. Pinealoma (pineal parenchymal tumors)
   V. Precancerous melanosis
   W. Pterygium
   X. Splenomegaly
   Y. Steward’s disease (lethal midline granuloma)
   Z. Total body irradiation used as preparation of patients for bone marrow or stem cell transplant
II. Radiation Therapy is medically necessary for the following non-malignant disorders when there is failure, intolerance, or contraindication to established medical therapy and surgical treatments:

A. Aneurysmal bone cyst  
B. Angiofibroma of nasopharynx (juvenile nasopharyngeal angiofibroma) with extension into the orbital apex or base of skull  
C. Angiomatosis retinae (von Hippel Lindau syndrome)  
D. Bowen’s disease (squamous cell carcinoma *in situ*)  
E. Carcinoid tumor  
F. Castleman’s disease (giant lymph node hyperplasia)  
G. Choroid plexus papilloma  
H. Degenerative skeletal and joint disorders  
I. Erythroplasia of Queyrat  
J. Inverted papilloma  
K. Lymphangiomas (capillary, cavernous, cystic hydromas, lymphangial hemangiomas)  
L. Neurofibromas (benign, von Recklinhausen)  
M. Orbital myositis  
N. Orbital pseudotumor  
O. Psoriasis  
P. Rosai-Dorfman disease  
Q. Neurosarcoidosis  
R. Tolosa-Hunt syndrome (episodic orbital pain)  
S. Total lymphoid irradiation in situations of chronic rejection  
T. Warts

III. Radiation therapy is considered experimental, investigational, or unproven (EIU) for the following non-malignant disorders:

A. Abortion  
B. Acne  
C. Adamantinoma (ameloblastoma)  
D. Amyloidosis  
E. Ankylosing spondylitis  
F. Anovulation
G. Arachnoiditis
H. Castration
I. Corneal vascularization
J. Corneal xanthogranuloma
K. Fibrosclerosis (sclerosing disorders)
L. Fungal infections
M. Gas gangrene
N. Herpes zoster
O. Infections (bacterial)
P. Infections (fungal and parasitic)
Q. Inflammatory (acute/chronic) disorders not responsive to antibiotics (furuncles, carbuncles, sweat gland abscesses)
R. Juvenile xanthogranuloma
S. Keratitis (bullous and filamentary)
T. Macular degeneration
U. Ocular trichiasis (epilation)
V. Osteoid osteoma (osteoblastoma, giant osteoid osteoma)
W. Otitis media
X. Pancreatitis
Y. Parotitis
Z. Peptic ulcer disease
AA. Perifolliculitis (scalp)
BB. Persistent lymphatic fistula
CC. Plasma cell granuloma (benign)
DD. Pregnancy
EE. Psychiatric disorders
FF. Pyogenic granuloma
GG. Rheumatoid arthritis
HH. Sinusitis
II. Thyroiditis
JJ. Tonsillitis
KK. Tuberculosis lymphadenitis
LL. Vernal catarrh
Key Clinical Points

It was not long after the discovery of x-rays in 1895 that radiation was used for therapeutic purposes. Since benign disorders do not always follow a benign course, radiation was employed for many conditions for which there was no suitable therapeutic alternative. As improvements in competing therapies have been developed, such as antibiotics, antifungals, antivirals, chemotherapies, improved surgical techniques, and immunological therapy, radiation therapy is no longer appropriate for many disorders, yet has become the preferred therapy for others. New indications have evolved over time. Where applicable, comments regarding changed indications are included in the brief discussion that follows of disorders for which radiation may have been used in the past or is presently in use. Each of the disorders listed is addressed in at least one of the references and, therefore, included in this policy.

Disorders treatable with radiation fall into the general categories of inflammatory, degenerative, hyperproliferative, functional, or "other" in nature.

Acceptance of the appropriateness of using radiation has developed using several means. Historically a trial and error approach prevailed, not different from the empiric use of pharmacological agents and surgical procedures that satisfied logic but lacked validation by now-customary rigor of prospective trials. Current indications may be based on experience-based consensus or on higher-level evidence that has resulted from formal study. Over the past five decades, consensus has been measured by polling practitioners on what is considered the appropriate uses of radiation. Such surveys in the United States, Germany and the United Kingdom supplement peer-reviewed journal publications and chapters in major radiation oncology texts, the latter reporting more evidence-based guidance that is the result of clinical studies. Both necessarily serve as the foundation for this policy.

As should be the case with all therapies, a decision whether to use radiation to treat a non-cancerous disorder should be based on safety, efficacy, and availability as measured against competing modalities, including the natural history of the disorder if left untreated, and must be subjected to informed consent. Consistent with that end, disorders have been grouped into categories for which radiation is considered: generally accepted; accepted if more customary therapy is unavailable, refused or has failed, or appropriate only as a last resort; or inappropriate under any circumstance. When utilized, radiation should be delivered using a technique that is not unnecessarily complex, and to the lowest dose that is sufficiently likely to achieve the desired result.

The earlier (more than 50 years ago) history of the use of radiation therapy to treat non-cancerous conditions is also very rich, but precedes the overview below. For a review of pre-1965 thoughts, the review by Dr. Stephen Dewing is recommended. Additional information regarding specific disorders may also be obtained from subscription services such as the Cochrane Review and UpToDate.
I. Condition

A. Abortion

It is known that radiation at sufficient dose can cause an abortion. There is no support for its use in any of the references cited.

B. Acne

Historically, superficial xray therapy was used to treat acne by 41.8% of dermatologists in the U.S. Department of Health, Education, and Welfare survey report of 1977. No subsequent modern era radiation oncology review supports the use of ionizing radiation in the treatment of acne. Improved alternative treatments and the risk of radiation-induced cancer render its use obsolete for the treatment of acne.

C. Adamantinoma (ameloblastoma)

D. These rare, locally aggressive but usually histologically benign tumors are of epithelial origin and are most commonly of jaw or tibial location. The etiology of epithelial tissue in an unusual location is the subject of debate. These tumors tend to recur and require aggressive surgery. Being rare, experience is very limited. Most references agree surgery is the treatment of choice. The use of radiation is reported historically as beneficial, but with little evidence. The 2002 text by Order and Donaldson supplies several references, each with few cases to report, and mainly of mandible or maxillary origin.

E. Amyloidosis

F. There is only an occasional case report of the use of ionizing radiation therapy in the treatment of amyloidosis. There is no support for its use in the modern era. **Policy: Not indicated and considered EIU.**

G. Aneurysmal bone cyst

These are relatively rare and benign osteolytic lesions of bone usually occurring in children or young adults. They are not true neoplasms, rather are a hyperplasia filled with blood-filled channels. Initial management is surgical. Interventional radiology procedures are also available. Because of the availability of alternative therapy and the typically young age of patients, the use of ionizing radiation is a last resort.

H. Angiofibroma of nasopharynx (juvenile nasopharyngeal angiofibroma)

While optimum management is controversial, there is general agreement that surgery is preferred if considered safe, as in cases when there is no extension into the orbital apex or base of skull. Since the typical patient is young, regard for the long-term hazard of radiation is important. When radiation is used, the radiation dose is lower than in malignant tumors of the same location. Response to treatment tends to be slow and may take several years to be evident.
I. Angiomatosis retinæ (von Hippel Lindau syndrome)

Capillary hemangiomas associated with von Hippel Lindau syndrome may be single or multiple, and can severely affect vision. They may be associated with hemangiomas in the cerebellum and brainstem. Multiple therapies exist including thermal and laser photocoagulation, cryotherapy, vitreoretinal surgery, beta plaque radiation therapy, and external beam radiation therapy (EBRT). Reports have described the successful use of EBRT for salvage.

J. Ankylosing spondylitis

The use of radiation therapy in the treatment of ankylosing spondylitis is of historical interest. The risk of radiation-induced cancer and other morbidity contraindicates its use and is often cited as a common example of radiation carcinogenesis in radiobiological studies.

K. Anovulation

The use of radiation therapy in the treatment of anovulation is of historical interest only and is occasionally discussed in the treatment of functional pituitary adenomas.

L. Arachnoiditis

In the pre-antibiotic era the beneficial use of radiation for the treatment of arachnoiditis was described. This is obsolete in the modern era.

M. Bowen's disease (squamous cell carcinoma in situ)

This entity is considered pre-malignant and may progress into invasive cancer. The term "Bowen's disease" refers to the specific anatomic locations of the shaft of the penis or the hairy skin of the inguinal or suprapubic regions. It can be mistaken for other disorders because of the features it shares with psoriasis and eczema. Earlier references include superficial radiation as a means of treatment. Evidence consists only of case reports and modest consensus in older literature. The use of superficial radiation should be limited to situations in which typical alternatives (surgery, electrodessication and curettage, topical 5FU), are not possible.

N. Carcinoid tumors

These may be secretory or non-secretory. Surgical resection is the indicated initial treatment if removal is possible. For those unresectable non-secretory lesions causing symptoms such as pain, radiation may be beneficial. For secreting tumors, radiation therapy is limited to those causing symptoms that are not controllable by medical means.

O. Castleman's disease (giant lymph node hyperplasia)

This disorder is characterized by angiofollicular lymphoid hyperplasia and can occur in any location in the body, commonly in the orbit (orbital pseudotumor) and Waldeyer's ring. The relationship to subsequent malignant lymphoma is unclear, with malignant lymphoma reported in as many as 30% of cases. Synonyms include giant follicular lymph node hyperplasia, follicular lymphoreticuloma, angiomatous
lymphoid hamartoma, and giant benign lymphoma. As described by Castleman, it is a benign condition. True lymphoma should be ruled out by biopsy to prove a polyclonal nature. Steroids are indicated as initial management. Low dose radiation therapy has been reported as effective in refractory or relapsed cases if further use of steroids is contraindicated.

P. Castration

There is evidence that with sufficient dose radiation can effectively and permanently cease gamete production and hormone production in the testes and ovaries. The indications for doing so are very limited. Surveys reported by Order and Donaldson (1998) indicated 75% of surveyed radiation oncologists would use radiation for this purpose with the appropriate indication. The U.S. Department of Health, Education, and Welfare survey report of 1977 included castration as an acceptable indication. The availability of drugs which achieve the same result has largely rendered this as obsolete.

Q. Choroid plexus papilloma

Choroid plexus papillomas range from the very benign (WHO grade 1) to the invasive carcinomas (WHO grade III). They are more common in very young children. Surgery is the treatment of choice. Adjuvant radiation is not indicated unless there is progression that cannot be dealt with surgically.

R. Choroidal hemangioma

These are rare vascular tumors and may be circumscribed or diffuse, the latter associated with Sturge-Weber syndrome. Non-radiation treatments are available (photodynamic, laser, thermotherapy.) Radiation therapy is preferable for diffuse lesions, especially if near the macula or papilla, and for those not responding to other therapeutic maneuvers. Typically, radiation therapy is given using complex or three dimensional conformal external photon beam technique, or using low dose rate brachytherapy plaque.

S. Corneal vascularization

Radiation therapy is not indicated in the treatment of corneal neovascularization. The entity is not to be confused with pterygium.

T. Corneal xanthogranuloma

Corneal xanthogranulomas may develop in association with generalized juvenile xanthogranuloma and generalized histiocytosis. Reports in old literature of the treatment by contact radiation or photons do not establish any definite benefit. They commonly regress spontaneously. First line therapy, when observation is not selected, is steroid therapy or surgery.

U. Degenerative skeletal disorders

Radiation therapy may be used for symptomatic degenerative skeletal and joint disorders (i.e. plantar fasciitis, trochanteric bursitis) that are refractory to conventional methods. For plantar fasciitis, for example, 1 Gy per week for 6 weeks was associated with a response rate approaching 80% and durable at 48
weeks. Using complex radiation planning, up to 8 fractions is considered appropriate.

V. Desmoid tumor

Also known as aggressive fibromatosis or deep musculoaponeurotic fibromatosis, a desmoid tumor is a histologically benign connective tissue tumor with a high recurrence rate after resection. Most common sites are trunk, extremity, abdominal wall, and intra-abdominal sites, including bowel and mesentery. If stable, observation is appropriate. Surgical resection with negative surgical microscopic margins in the treatment of choice for most. Radiation therapy is indicated for inoperable cases, and may be used in conjunction with surgery and chemotherapy. Typical treatment is with 3DCRT in 28 or fewer fractions. Fractionated radiation therapy in excess of 50 Gy is needed for control, which may preclude its use in those of intra-abdominal location.

W. Dupuytren’s contracture (fibromatosis)

This may develop in the hand (Morbus Dupuytren) or foot (Morbus Ledderhose) and is a connective tissue disorder of the palmar or plantar fascia. Radiation therapy is useful, especially in the earlier stages of development, and has been demonstrated in prospective clinical trials. Typical treatment is with photon beam therapy using, at most, Complex treatment planning, or with electron beam therapy in 10 or fewer fractions.

X. Erythroplasia of Queyrat

This in situ form of epidermoid carcinoma involves the mucosal or mucoepidermoid areas of the prepuce or glans penis. An invasive component is not infrequent. Sometimes it is referred to as Bowen's disease of the penis. Erythroplasia of Queyrat involves the mucosal or mucoepidermoid areas of the prepuce or glans penis, whereas the term Bowen's disease refers to squamous cell carcinoma in situ involving the shaft of the penis or the hairy skin of the inguinal or suprapubic region. While radiation treatments were used in the past, as Erythroplasia of Queyrat is non-invasive, its treatment can be managed with a non-radiotherapeutic approach using topical agents.

Y. Extramammary Paget’s disease (adenocarcinoma of the skin)

When it occurs, adenocarcinoma of the skin usually arises in areas of abundant apocrine glands. Most commonly, treatment is surgical. Radiation therapy is indicated when resection is inappropriate or incomplete. The entity is discussed this Guideline due to historical references to its being a benign condition.

Z. Extramedullary hematopoiesis (hypersplenism)

This is a myeloproliferative syndrome that most commonly involves the spleen, but can occur in the liver, lymph nodes, lungs, kidneys, GI tract, and central nervous system. Chemotherapeutic management is the initial treatment of choice. Radiation therapy is considered necessary in those cases in which medical management is ineffective or otherwise contraindicated.
AA. Fibrosclerosis (sclerosing disorders)

Unifocal and multifocal episodes of sclerosis have been treated in the past using radiation therapy. Sites reported include retroperitoneum, mediastinum, bile ducts, thyroid, meninges, orbits, and others. While anecdotal reports of improvement have been reported, generally radiation therapy is regarded as ineffective and should not be used.

BB. Fungal infections (see Infections, fungal)

In the 1940s and 1950s xrays were used, not infrequently, to treat tinea capitis and other skin fungal infections. In the modern era of available pharmacologic agents for the treatment of fungal infections, the benefit of use of radiation therapy is outweighed by the risk of carcinogenesis.

CC. Gas gangrene

Before the discovery of antibiotics, radiation therapy was used to treat open wounds to prevent infections, and reports exist that this was of benefit. There is no benefit of the use of radiation in the era of antibiotics.

DD. Giant cell tumor of bone (osteoclastoma)

Once thought to be a benign disorder, these tumors are best regarded as malignant with a potential for metastasis. Surgery is the initial treatment of choice, but many osteoclastomas arise in bones (spine and pelvis) in which surgical resection would be unnecessarily debilitating. Local control with radiation is reported in the 75% to 85% range and can be administered safely using modern era equipment.

EE. Gorham-Stout Syndrome (disappearing bone syndrome)

Also known as phantom bone, this entity is characterized by a destructive proliferation of endothelial-lined sinusoidal or capillary proliferation that may or may not be progressive, causing bone destruction most commonly in the pelvis or shoulder girdle that results in a functional deformity. Surgery is an alternative to radiation. Typical treatment is with 3DCRT in 25 or fewer fractions.

FF. Graves' ophthalmopathy

This is an autoimmune disorder associated with hyperthyroidism that affects the eye musculature and retrobulbar tissues causing proptosis and visual impairment. It may be unilateral or bilateral. Carefully selected cases that do not respond to medical measures may be improved with the use of carefully administered conformal radiation. Typical treatment is with complex or three dimensional conformal radiation therapy (3DCRT) in 10 fractions.

GG. Gynecomastia

In the older era of orchietomy or the use of diethylstilbestrol for the treatment of metastatic or locally advanced prostate cancer, it was commonplace to irradiate the breasts on a prophylactic basis to prevent uncomfortable gynecomastia. In the modern era of chemical androgen deprivation for the treatment of prostate cancer, the use of modest doses of radiation to the breasts may arrest or prevent the
resultant gynecomastia and is medically appropriate. Typically the radiation is given with electron beam therapy in 5 or fewer fractions.

**HH. Hemangiomas**

Though benign by histology, these vascular tumors that may arise in the brain, spinal cord, subglottis, glottis, liver, GI tract, urinary tract, joints and orbit may be disastrous. The use of radiation therapy is a suitable alternative to surgical or medical management. It is especially important to explore alternative therapy in pediatric cases. Depending on circumstances, the technique employed may range from simple to IMRT, and is usually delivered in 30 or fewer fractions.

**II. Herpes zoster**

Presented here only for historical perspective, the use of radiation to treat the nerve roots associated with cutaneous eruption of zoster was once employed, and even said to be sometimes acceptable in the 1977 survey of the U.S. Department of Health, Education and Welfare. More recent surveys and study have shown no benefit. The subsequent development and use of antiviral drugs is appropriate.

**JJ. Heterotopic ossification (before or after surgery)**

Radiation is known to prevent the heterotopic bone formation often seen in association with trauma or joint replacement in high risk patients. The radiation is most effective if given shortly (within four hours) prior to surgery, or within three or four days after surgery. A radiation dose of 7 Gy to 8 Gy in a single fraction of Complex planned therapy is typical.

**KK. Hypersalivation of amyotrophic lateral sclerosis (ALS)**

It is well known that radiation will decrease saliva production as a consequence of treating head and neck cancer. This phenomenon has occasionally been exploited in cases of excess saliva production in patients with ALS. While literature is scant, surveys indicate general acceptance of the use of radiation in this situation when other means of management are ineffective or impractical.

**LL. Hyperthyroidism**

The use of systemic 131-I is an accepted alternative to surgery and/or medical management.

**MM. Infections (bacterial)**

In the antibiotic era, there is no recognized indication for the use of radiation therapy in the treatment of bacterial infections.

**NN. Infections (fungal and parasitic)**

The experimental use of radiation to treat unusual and rare fungal and parasitic disorders, such as ocular histoplasmosis and cerebral cisticercosis, has been reported in the literature. This is regarded as investigational.
OO. Inflammatory (acute/chronic) disorders not responsive to antibiotics (furuncles, carbuncles, sweat gland abscesses).

Variations exist worldwide as to the appropriateness of using ionizing radiation for these disorders. The German review of 2002 lists them as potential indications, however elsewhere this opinion is not supported. The U.K. policy states that for a refractory case with no other alternative, low dose radiation therapy "might be worth considering".

PP. Inverted papilloma

The treatment of choice is surgical resection of these usually benign lesions of the nasal cavity and paranasal sinuses. However, a malignant component is found in a small percentage of cases, and radiation therapy is then indicated. In cases of incomplete resection or suspected malignant component, radiation therapy is considered medically necessary.

QQ. Keloid scar

Data is abundant that a few fractions of a relatively small amount of radiation will reduce the chance of recurrence after a keloid is resected. This is medically necessary when other means are less appropriate or have proven ineffective. Typical radiation treatment utilizes superficial x-ray, electron beam, or Complex photon beam therapy in 4 or fewer fractions.

RR. Keratitis (bullous and filamentary)

Bullous and filamentary keratitis were listed in the 1977 U.S. Department of Health, Education and Welfare as entities for which radiation therapy was sometimes appropriate. They are not included in the more recent German and U. K. reviews. Current literature does not support the use of radiation for either form of keratitis.

SS. Langerhans cell histiocytosis

The literature has consistently supported the use of radiation therapy for treatment of this disorder over the time period studied. Involvement can be focal or systemic, and behavior variable. The etiology is unknown, and it may prove to be a non-benign entity. Chemotherapy is commonly utilized when treatment is necessary, with radiation more commonly used to treat localized growths. Typical treatment is with 3DCRT in 28 or fewer fractions.

TT. Lymphangiomas

There are four types: capillary; cavernous; cystic hygromas; and lymphangiomatous hemangiomas. Surgery is the treatment of choice. In rare instances, radiation therapy may be appropriate for refractory lesions with repeated recurrence after resection. These may cause a chylous effusion if there is pleural involvement, in which case radiation therapy may be useful in managing chylothorax. A specific presentation of lymphangioma may be Gorham-Stout syndrome (see above).
UU. Lethal midline granuloma

This is a progressive, destructive process which involves the mid-facial structures. It has many synonyms depending on its anatomic presentation. It has been considered a benign entity, may mimic other lymphoproliferative processes, requires caution in diagnosis, and may be a malignant T-cell disorder. Alternative therapy may be more appropriate, but radiation therapy is considered appropriate for management of localized presentations or in conjunction with systemic therapy.

VV. Macular degeneration

There was great optimism that age related wet macular degeneration could be controlled by the use of radiation therapy to arrest the progression of choroidal neovascularization. Radiation was a preferred method of treatment in the USA in the 1990s and early 2000s. Subsequent multi-centered randomized trials have not proven benefit. The use of intraocular injections of anti-VEGF drugs has emerged as the first line of management. Newer approaches to the use of radiation therapy, such as epimacular brachytherapy and SRS are being investigated as alternatives or as complementary methods so as to reduce the frequency of intraocular injections. Until the results of these studies are known, the appropriateness of using radiation is unproven.

WW. Neurofibromas (benign, von Recklinghausen)

Benign neurofibromas most commonly develop in association with von Recklinhausen disease, and may occur in central nervous system (CNS) and non-CNS locations. Symptomatic lesions may benefit from treatment with relatively high doses of radiation if not amenable to resection.

XX. Ocular trichiasis (epilation)

Of historical interest, on occasion, to cause epilation of eyelashes, radiation has been used in dermatology or ophthalmology practices to aid in the clearance of trachoma or ocular pemphigoid. Radiation is not medically necessary for this in the modern era.

YY. Orbital myositis

This entity is an idiopathic inflammatory condition of the extraocular muscles and may be of autoimmune etiology. It can mimic other similar-appearing orbital inflammatory disorders. Management without radiation, usually with steroids, is first line. Failing conservative measures, radiation is given typically using 3DCRT or Complex planning in 15 or fewer fractions.

ZZ. Orbital Pseudotumor (lymphoid hyperplasia)

The indications for the use of radiation therapy are for those lesions which recur after surgery, or become refractory to steroids and are not amenable to other management. Typical treatment is with Complex or 3DCRT in 10 fractions.
AAA. Osteoid osteoma (osteoblastoma, giant osteoid osteoma)

Osteoid osteoma, osteoblastoma, giant osteoid osteoma are synonyms. Old literature reports included anecdotes of the use of radiation to treat this entity, for which surgery is the treatment of choice.

BBB. Otitis media

Bilateral otitis media caused by swollen lymphoid tissue in the nasopharynx was in the past sometimes treated by placement of radioactive material in the nasopharynx to reopen the eustachian tubes. The carcinogenic effect of this makes this treatment inappropriate.

CCC. Pancreatitis

Radiation therapy has been used in the past for its anti-inflammatory effect in the treatment of pancreatitis. There is no role for its use for this purpose in the modern era.

DDD. Paraganglioma (chromaffin positive)

As with their chromaffin negative counterparts, radiation therapy is indicated in those cases which are inaccessible by surgery, for salvage if recurrent, or as adjuvant therapy if incompletely removed. Typical treatment is with 3DCRT, SRS, or IMRT.

EEE. Parotid adenoma

Pleomorphic adenomas of the parotid gland more commonly occur in younger persons and the use of radiation must be approached judiciously. There are indications for radiation therapy such as size > 4 cm. positive margin status, and multinodularity.

FFF. Parotitis

Although historically appropriate in the pre-antibiotic era because of a high mortality rate for post-operative suppurative parotitis, radiation is not indicated in the present era.

GGG. Peptic ulcer disease

Subsequent to the availability of H2 blockers, radiation therapy is not indicated in the management of peptic ulcer disease despite prior evidence of its efficacy. The increased risk of carcinogenesis of the pancreas, colon, and stomach is a strong contraindication.

HHH. Perifolliculitis (scalp)

The use of radiation to cause hair loss and allow the infection of this disease to then clear has been described in older literature. The availability of topical agents and of laser treatment has rendered obsolete the use of radiation for this purpose.
III. Persistent lymphatic fistula

Lymphatic leaking, most commonly after arterial reconstruction surgery in the groin, is usually treated with additional surgery (ligation, flap construction), direct pressure, application of hemostatic healing agents, and the use of negative pressure. It is listed in the German literature as an indication for the use of radiation therapy, without reference.

JJJ. Peyronie’s disease (Morbus Peronie, Induratio penis plastica)

There is sufficient (older and current) literature support to justify the use of low doses of radiation in the treatment of this disease of the penis. Simple, complex-planned photon beam radiation, orthovoltage, or electron beam radiation in five or fewer fractions is typical.

KKK. Pigmented villonodular synovitis (tenosynovial giant cell tumor)

Surgical resection and synovectomy or joint replacement is the treatment of choice. However if recurrent after resection, or diffuse or bulky disease causing bone destruction is present, the use of radiation is justified. Radiation treatment with photon beam therapy using complex treatment planning or three dimensional conformal radiation therapy (3DCRT) planning in twenty-eight or fewer sessions is typical.

LLL. Pinealoma (Pineal parenchymal tumors)

Pinealoma refers to tumors that arise in the pineal gland. For the tumors at the benign end of the spectrum of such tumors, surgical resection is preferred. Postoperative radiation is appropriate for those that cannot be removed completely. For higher grades of tumor, refer to the separate Guideline, Radiation Treatment of Primary Cranial and Spinal Tumors and Neurologic Conditions.

MMM. Pituitary Adenoma

Surgical removal is the treatment of choice, with radiation therapy indicated for medically inoperable cases, recurrence after surgery, incomplete resection, or persistence of elevated hormones after resection of functional adenomas. Typical treatment is with 3DCRT, SRS, or IMRT.

NNN. Plasma cell granuloma (benign)

Treatment of a true benign plasma cell granuloma is surgical resection.

OOO. Precancerous melanosis

Precancerous melanosis may also be called Lentigo Maligna, Hutchinson's melanotic freckle, or circumscribed precancerous melanosis of Dubreuilh, and has lentigo maligna melanoma as an invasive counterpart. About one third of these will transform into the malignant version if left untreated. Radiation therapy is indicated for those which recur or for more extensive lesions.
PPP. Pregnancy

Radiation therapy has been used in the past for both an attempt at improving fertility (see anovulation) and for the termination of intrauterine or tubal pregnancy (see abortion). Presently, neither indication is medically appropriate.

QQQ. Psoriasis

Both the German and the U.K. reviews include psoriasis as an indication for the use of low dose radiation in the treatment of some cases. Generally radiation is a treatment of last resort and is reserved for inaccessible locations such as the nail beds. Typical radiation treatment utilizes superficial x-ray, electron beam, or complex photon beam therapy in four or fewer fractions.

RRR. Psychiatric Disorders

Radiation therapy has been used to treat some psychiatric disorders in mimicry of surgical procedures with the same intent, such as SRS to achieve a ventral capsulotomy in the treatment of obsessive compulsive disorder. The use of radiation for this purpose is considered investigational and unproven.

SSS. Pterygium

The use of radiation to treat a pterygium is supported in the clinical references reviewed. It is usually performed with contact beta brachytherapy in 3 fractions.

TTT. Pyogenic granuloma

Despite one case report in the literature of successful treatment of a pyogenic granuloma of the middle ear with radiation, treatment of a pyogenic granuloma is surgical. There is no current support in the American or European literature.

UUU. Rheumatoid arthritis

Attempts at treating rheumatoid arthritis with radiation have included single joint external beam radiation, intra-articular infusions of radioactive isotopes, and total lymphoid irradiation for immunosuppression. None is standard of care.

VVV. Rosai-Dorfman disease

Rosai-Dorfman disease is a rare disorder characterized by a benign histiocyte proliferation. It can produce massive adenopathy. Treatments used have included surgery, chemotherapy, and steroids. In lesions involving the airway not responding to more conservative measures, radiation therapy has been used with success. When utilized, radiation planning using Complex or 3DCRT and delivered in up to 22 sessions is typical.

WWW. Sinusitis

Sinusitis caused by infection does not have literature support for treatment by radiation therapy.
XXX. Splenomegaly

Splenomegaly treated by radiation therapy is most commonly caused by leukemic or myeloproliferative diseases, and to a lesser extent by metastases from solid tumors. The policy for the use of radiation therapy in these malignant conditions is not covered in this Guideline. However, the use of radiation therapy for the treatment of hypersplenism or splenomegaly caused by a "benign" or pre-malignant myelodysplastic syndrome also has a basis in the literature. Very low doses of radiation on a less than daily schedule are usually advised. Typically radiation is delivered in 10 or fewer fractions, planned using Complex or 3DCRT.

YYY. Thyroiditis

Presently there is no indication for the use of radiation therapy for the treatment of thyroiditis.

ZZZ. Tolosa-hunt syndrome (episodic orbital pain)

This is caused by nonspecific inflammation of the cavernous sinus or superior orbital fissure. Steroids commonly are used first. For refractory cases, drugs such as methotrexate may be used. The successful use of low dose radiation has been reported and may be used as a last resort.

AAAA. Tonsillitis

In the modern era of antibiotics, the use of radiation to treat inflamed or infected tonsils is obsolete.

BBBB. Total body irradiation

For the preparation of patients for bone marrow or stem cell transplant for malignant disorders, see the Guideline for the primary disease. For non-malignant, pre-malignant and quasi-benign marrow disorders such as aplastic anemia or myelodysplastic disorders, total body irradiation prior to transplant may be appropriate if chemotherapeutic preparation is not possible. The use of total body irradiation for immunosuppression as treatment of totally non-malignant disorders, such as auto-immune diseases is not medically appropriate.

CCCC. Total lymphoid irradiation

Total lymphoid irradiation has been used for the purpose of immunosuppression in the treatment of immune-mediated disorders (e.g. autoimmune disorders) and for the purpose of prevention of rejection of transplanted organs, where it has been found useful in the short term, but with decreased subsequent efficacy and the development of myelodysplasia. Further research is needed to establish its role, but it remains an option in situations of chronic rejection in which conventional anti-rejection treatment is no longer viable.
DDDD. Tuberculosis lymphadenitis

Prior to the availability of antibiotics for tuberculosis, lymphadenitis caused by this disease responded to therapeutic radiation. Available antibiotics obviates this disorder as an indication for radiation.

EEEE. Vernal catarrh

This disorder is characterized by inflammation of the conjunctiva associated with infiltration by eosinophils, lymphocytes, plasma cells and histiocytes. The resultant hyperplasia of the conjunctival epithelium may respond to ionizing radiation, but alternative therapy is readily available, and the use of radiation is no longer supported in any literature.

FFFF. Warts

Older literature describes an 80% response rate in treating warts with a relatively low dose of radiation and it is described in at least one modern text (Gunderson). With the availability of alternative therapy, the use of radiation should be reserved for those cases requiring treatment for which alternative, simpler therapy has been unsuccessful.

References
7. Medicare Fee, Payment and Reimbursement Guideline, CPT, ICD, Denial.
Radiation Therapy for Non-Small Cell Lung Cancer

I. POLICY

A. Definitive external beam radiation therapy to a dose of 60-70 Gy in 30-35 fractions using a 3D conformal technique is medically necessary.

B. For inoperable node-negative stage I or II disease, up to 5 fractions of Stereotactic Body Radiation Therapy (SBRT) is medically necessary. When 6-10 fractions are being delivered (i.e. for central tumors), per coding guidelines, the request should be for 3D conformal or IMRT depending on the underlying planning method.

1. For a non-biopsied pulmonary nodule, evidence of progressive growth and a positive Positron Emission Tomography (PET)/CT with written documentation from a Tumor Board recommending proceeding with Radiation Therapy (RT) is required.

C. Preoperative external beam radiation therapy to a dose of 45-54 Gy in 25-30 fractions using a 3D conformal technique 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

D. Postoperative external beam radiation therapy using a 3D conformal technique 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
4. Depending on the extent of residual disease, a dose of 50-54 Gy in 25-28 fractions (negative margins) to 60-70 Gy in 30-35 fractions (gross residual disease) is recommended.

E. Palliative treatment

1. The use of up to 15 fractions of a 3D conformal techniques medically necessary

II. Technique

A. The Use of IMRT is considered medically necessary in the following situations:

1. Where there is disease in the bilateral mediastinum or bilateral hilar regions
2. Where there is disease in the paraspinal region
3. For superior sulcus tumors
4. Documentation that a 3D plan does not meet the normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN). This documentation must describe the specific OARs (organs at risk) whose tolerance has been exceeded. DVHs (dose volume histograms) are insufficient documentation.

**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 chemoradiotherapy was also evaluated. RTOG 9410 is the largest trial assessing the value of concurrent versus sequential chemoradiotherapy. In this trial, 610 patients with Stage III disease were randomized to three arms: the positive arm of the CALBG 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 paraspinal 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.

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. Following
publication of the official results of 0617, several additional analyses of the data
emerged which have provoked controversy in the literature.

The study does not include in its primary or secondary objectives a comparison of
randomized IMRT and 3DCRT treatment techniques. Indeed in the Treatment
Planning section, the study states: “IMRT is allowed as long as the participating
institution is credentialed by the RTOG for intra-thoracic IMRT Treatments.” Hence,
there is no formal randomization.

Chun et al. (2017a) published a secondary analysis of 0617 in which they compared
IMRT to 3DCRT. With a follow-up time period of two years, they noted no difference
in overall survival (OS), progression free survival (PFS), local failure, and distant
metastasis-free survival between the two techniques. They did conclude however that
IMRT produced statistically significant lower heart doses than 3DCRT and that the
volume of the heart receiving 40 Gy was also statistically significant in affecting OS.
They recommended continued follow-up of the IMRT cardiac effects as the time period
might be too short to measure them accurately. In their evaluation of pulmonary
toxicity, the authors stated no difference in survival. They noted however that IMRT
patients generally had larger tumor volumes, more advanced stage, and worse socio-
economic status. IMRT was associated with statistically significant fewer cases of
grade 3 pneumonitis though it is noted that the lung V20 was not different between
the IMRT and 3D groups. Grade 3 esophagitis, dysphagia, weight loss and
cardiovascular toxicity were not different. The lung V5 was significantly larger in the
IMRT cases but was not associated with grade 3 toxicity. The article concluded that
IMRT should be used routinely to treat locally advanced NSCLC.

Eaton et al. (2016) published a review of 0617 based on institutional accrual. They
noted that patients treated at High Volume Centers (HVCs) were more often treated
with IMRT than 3DCRT (54.0% vs. 39.5%) with lower mean esophageal and cardiac
doses. HVCs had a more statistically significant acceptability rating on Protocol review than Low Volume Centers (LVCs) as well. In acknowledging the importance of reduced cardiac dose with IMRT, the authors noted that the volume of heart receiving 50 Gy or more was an independent predictor of adverse events. In summarizing their review the authors stated: “The differences in treatment technique, however, cannot solely account for the statistically significant longer OS demonstrated at HVCs as IMRT itself was not found to be associated with clinical outcome. Although a greater proportion of patients treated at HVCs were randomly assigned to the 60 Gy dose level, treatment at an HVC was associated with longer OS even among the subsets of patients randomly assigned to 60 Gy.” They concluded that institutional accrual volume should be considered in future clinical trials.

In correspondence to the Journal of Clinical Oncology, Ball et al. (2017) pointed out that there were only two grade 5 toxicities due to pneumonitis in 0617. In their editorial, they questioned whether the 0617 analysis was a true planned secondary evaluation and noted that interstitial lung disease, as well as other risk factors, were not taken into account. They noted institutional settings might have played a role in the determinations. For some patients and in less experienced centers the authors felt that 3DCRT might actually result better and safer treatment. Their editorial concluded that it was premature to recommend IMRT routinely for all patients based on the 0617 paper. In their reply to Ball et al, Chun (2017b) agreed that the secondary analysis did not provide the same level of evidence as a properly randomized Phase III study intentioned to address the different techniques. They stated that RTOG 0617 “…used stratified blocked randomization, with radiation technique as one of the stratification factors…”and that it has “…long been the intent to perform a secondary analysis.” They pointed out that IMRT has been adopted for other cancers without randomized studies and that the evidence provided in 0617 was sufficient to recommend the routine use of IMRT in locally advanced NSCLC.

The described literature does indeed raise important questions. In the formally-stated objectives of 0617, the stratification and endpoints to not necessarily support the concept of a sub-analysis, especially since IMRT was “permitted.” Given the difference in plan acceptability between HVCs and LVCs and the better survival of patients regardless of technique at an HVC, there may indeed be an overall difference and possible unintentional bias not only in treatment but also in the supportive care and treatment of side effects. Kong and Wang (2015) reviewed the non-dosimetric risk factors for radiation-induced pulmonary toxicity. Age, sex, smoking status, pre-existing lung disease, pulmonary function, tumor location, volume stage, and biologic and genetic factors may also play a strong role in radiation treatment toxicity and possible outcomes. The 0617 study does not include all of these risk factors. Similarly, in assessing cardiac effects, current cardiac status and potential cardiac risk factors should be taken into account in trial design. As such, until additional evidence is available from properly designed studies, 3DCRT remains the usual and customary
treatment for locally advanced lung cancer. It is recognized, however that in individual cases, IMRT may be medically necessary.

II. Preoperative and postoperative therapy

An individual with Stage IIIA disease based on 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 in 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 considered not medically necessary.

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 I and Stage II non-small cell lung cancer in an individual who is medically inoperable or who refuses surgery, SBRT is an appropriate option. Treatment is generally delivered in 3 to 5 fractions. 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. Oligometastatic presentations/genetic variants

Lung cancer may present in an intermediate phase where cancer may be limited to the primary region with three or fewer metastatic sites that are also amenable to definitive treatment. Requests for definitive radiation treatment to the primary site will be considered on a case-by-case basis. Please see the Radiation Therapy for Oligometastases clinical guideline.

Similarly, a small subset of patients may present with Alk+; ROS1+ or EGFR+ mutations (exon 21, exon19) that have longer durable responses to targeted agents despite a significant metastatic disease burden. Alk+ tumors with CNS metastases may have survival in excess of 40 months. As such, circumstances may present where a more protracted radiation therapy regimen may benefit these patients rather than a short-term palliative regimen when substantial benefit has been gained from systemic therapy. These requests will also be reviewed individually. In the case of EGFR+ mutations it should be noted that exon 20 mutations are not associated with this benefit.

Additionally, the use of anti-PD-1 and PDL-1 agents such as Pembrolizumab are now being used as first line therapy in both metastatic squamous and adenocarcinomas which have a positive test of 50% or greater for PDL-1. The use of radiation therapy in this setting will also be reviewed on a case-by-case basis.

Please see the current NCCN Non-Small Cell Lung Cancer Guidelines® for additional discussion.

VI. 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.

References


Radiation Therapy for Oligometastases

POLICY

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

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)

II. SBRT used to stimulate the abscopal effect is considered EIU
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 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 largely limited to single institution studies, registry studies or limited phase II randomized studies. Some of the retrospective studies have demonstrated improved outcomes compared to historical controls. There is no level one phase III evidence demonstrating a clear benefit to treatment of extracranial oligometastases. 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 metastasis 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).

SBRT offers ablative doses delivered with 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 previous studies is that they have been 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. Patients included in these studies are highly selected, based on good performance status and slow pace of tumor progression. Therefore, the long-term survival achieved in these studies of treatment of oligometastases may be the result of the selection of fit patients with very slow-growing tumors rather than the result of treatment intervention. Also, the endpoints chosen or reported in these studies, such as progression free survival, interval until next systemic therapy, or local control of metastases, may not prove to be clinically relevant long term benefits. Therefore, none of these reports offers definitive clinical evidence that overall outcomes are improved with metastases directed SBRT compared to best standard therapies.

The SABR-COMET (Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors) trial results were presented in October 2018 at the American Society for Radiation Oncology (ASTRO) Annual Meeting (Palma et al., 2018). This randomized phase II trial included patients with controlled primary site and up to 5 sites of hematogenous metastasis. Inclusion criteria required histologically confirmed malignancy (of the primary or metastatic site), ECOG status 0-1, at least 3 month interval since definitive treatment of primary without recurrence, maximum of 3 metastases in any one organ system, not a candidate for surgical resection at all sites, and no concurrent chemotherapy. Some important exclusions were patients with brain only disease and 1-3 lesions, prior radiation to a treatment site, spinal cord compression or disease within 3 mm of the spinal cord. Patients with previously treated or resected metastases were eligible if there was no evidence of recurrence at that site on imaging. This trial was designed as a randomized phase II “screening” trial to determine possible evidence of efficacy. Additionally, this trial was designed to allow for more modest patient accrual numbers and to provide an initial, non-definitive comparison between the two arms. Therefore, the study used 0.20 as the two-sided p value for significance as opposed to the traditional p value of 0.05. Ninety-nine patients were accrued to the study, 66 in the SABR arm. The study was interpreted as positive with median survival in the SABR arm of 41 months compared to 28 months for the control arm (p=0.09).
Although the results of the SABR-COMET trial add significantly to the knowledge base for this clinical setting, there are several important limitations and observations about the study. The study has not yet been published in a peer reviewed journal. The chosen alpha for significance of 0.20 is not the traditionally accepted level of a statistically significant difference (0.05). It is important to note that the study investigators qualify the results of this screening study as initial and non-definitive. Furthermore, the study included patients from a broad spectrum of histologies including but not limited to metastatic breast, lung, colorectal, and prostate cancer. Diagnosis specific randomized control trials are needed to provide strong evidence of the benefit of SABR. Prostate cancer comprised 21% of the SABR arm but only 6% of the control arm patients which may skew results considering the long natural history and hormone-sensitivity of prostate cancer. Only 18 patients enrolled in the trial had lung cancer. Additionally, there were only 7 patients with 4-5 metastatic sites and no control arm patients with 5 sites, so data in that group is very limited and unreliable. It should be noted that Grade >2 toxicity was significantly higher in the SABR arm (29% vs. 9%, p=.03), and there were 3 deaths in the SABR arm attributed to treatment (4.5%) with none in the control arm. At the time of progression, patients in the SABR arm were eligible for further SABR treatment, while patients in the control arm were eligible only for palliative dose radiation. Considering the limitations of this early report, SBRT for treatment of patients with >3 metastases is not supported at this time and is not medically necessary. Ongoing prospective, randomized trials disease specific trials are needed to define the benefit of SBRT in this population.

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 after initial diagnosis. 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). Ashworth and colleagues (2013) performed a systematic review of 49 studies including 2,176
patients with one to five metastases from NSCLC who underwent surgery or radiation. 82% of patients had controlled primary disease, and 60% of studies were limited to intracranial metastasis. Median survival was 14.8 months, median time to progression was 12 months, and median 5-year overall survival (OS) was 23.3%. Control of primary disease, N stage, and disease-free interval of at least 6 to 12 months prior to diagnosis of oligometastasis were found to be prognostic on multivariable analysis.

Iyengar et al (2018) reported early results of a single institution phase II randomized study of SBRT for patients with biopsy-proven metastatic non-small cell lung cancer with stable or responsive disease after initial chemotherapy in 29 patients (14 treated with SBRT). Patient were randomized to chemotherapy alone for the control arm or to receive SBRT to up to 5 metastatic lesions plus the lung primary followed by maintenance chemotherapy. The study showed significant (p=0.01) reduction in progression free survival for the SBRT arm, with most progressive disease in areas of original disease in the control arm while progression in untreated areas was the only site of progression in the SBRT arm. A statistically significant OS benefit was not noted. Use of progression free survival as a primary endpoint has been criticized and improved PFS may not translate into meaningful survival benefit in such patients.

Gomez et al (2018) have reported a trial of treatment for 3 or fewer metastases that had not progressed on first line chemotherapy for lung cancer. Patients (n=49) were randomized to local therapy (surgery, SBRT or hypofractionated radiation, some with concurrent chemotherapy) or maintenance chemotherapy/observation. The updated results of the trial were presented in abstract form at ASTRO annual meeting in October 2018. The results showed a median survival of 17 months with maintenance/observation compared to 41 months for the treated arm (p=.017). Potential confounding issues included that patients in either arm could get SBRT/surgery at the time of progression so there was crossover permitted. Subgroup analysis showed that the only group with significant survival advantage were those with 0-1 metastases after initial chemotherapy, and those with 2-3 metastases had no improvement in survival.

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.

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., 2017). The 5 year overall survival was 43% in the radiofrequency ablation arm and 30% in the control arm \( p = 0.01 \), with median follow up of 9.7 years.

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. A review of literature by Kucharczyk et al (2017) identified 41 studies of treatment for oligometastasis from breast primary. All studies were observational cohort studies (level 2B or 4 evidence). The authors concluded that existing evidence does not provide meaningful direction on which metastatic breast cancer patients should have ablation of their residual disease due to heterogeneous reporting of disease factors, patient factors, and outcomes.

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 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: 1-3 metastases, 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. Prostate Cancer

There is limited comparative data regarding the use of SBRT for prostate cancer metastases. In the STOMP trial, Ost et al reported a trial of 62 patients randomized in a phase II study to SBRT to metastatic sites of recurrence after prior definitive treatment to the primary. Patients were diagnosed when there was PSA recurrence and choline PET scan showed ≤3 lesions. The primary endpoint was androgen deprivation therapy (ADT) free survival. The study found that there was prolongation of ADT initiation in the SBRT arm. However, this endpoint has been criticized as a measure of efficacy. Additionally, progression of untreated metastases before the treated metastases would be expected, which led to earlier initiation of ADT. This is not clearly a clinically meaningful benefit and is not equivalent to a survival benefit. Another criticism is that the control arm was observation but standard treatment for metastatic disease is ADT, which was initially withheld from both cohorts.

Due to the long natural history of prostate cancer progression, the sensitivity of prostate cancer to androgen deprivation therapy and other endocrine treatments, and lack of high quality evidence to suggest that ablative therapies for metastatic disease improve survival, SBRT for treatment of metastases from prostate cancer is not medically necessary.

F. Treatment of > 3 sites or nonhematogenous sites

There is limited data on the survival benefit of treating multiple metastases (> 3 metastases). Surgical studies have suggested that tumor burden is predictive of overall survival. In the surgical literature, the number and size of metastatic lesions (> 3 hepatic metastases, hepatic metastases ≥ 5 cm, > 1 lung metastasis), extrahepatic spread, poorly differentiated disease, positive resection margins, and a short disease free interval (< 36 months) have been independent predictors for poor survival. Salama et al. (2012) reported a longer progression free survival (PFS) in patients with 1–3 metastatic sites versus those with 4–5 metastases receiving escalating SBRT doses to all sites of disease. The toxicity of using SBRT for treating multiple metastases (> 3 metastases) can be potentially significant. As demonstrated in the SABR-COMET trial, Grade > 2 toxicity was significantly higher in the SABR arm (29% vs 9%, p=.03), and there were 3 deaths in the SABR arm attributed to treatment (4.5%) with none in the control arm. 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, SABR-COMET 10 is an ongoing randomized Phase III trial evaluating SBRT in the treatment of 4 -10 metastases.

Based on these ongoing studies, the limitation in the number of metastases treated in most reports, and the lack of evidence of a clinically significant benefit for treatment of larger number of metastases in the limited randomized literature, SBRT to > 3 sites is considered not medically necessary. 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 not medically necessary.

G. Oligoprogression is the clinical scenario where there is progression of a limited number of metastatic sites while other metastatic disease sites remain controlled. The other metastatic sites remain stable or are responding to systemic therapy while a few areas of metastatic disease progress (Cheung, 2016). There is limited published data on oligoprogression and most of the data on oligoprogression is focused on patients with nonsmall cell lung cancer while on targeted therapy (Cheung, 2016). Some studies have 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. There are ongoing trials to evaluate the use of SBRT for this population, such as the HALT trial in the UK and STOP-NSCLC in Canada (Cheung, 2016). Therefore, as there is limited information on the use of SBRT in patients with oligoprogression, SBRT is considered not medically necessary for an individual with oligoprogressive disease.

H. Summary

There is intense interest in the potential use of focal ablative radiation, and there are several ongoing or planned randomized trials to evaluate such treatment. At this time, the results of large well-designed randomized trials with mature follow up data are not available. Further information from such trials will assist with determining the proper place for such therapy in the future. Based on the current available data, the use of SBRT outside of the parameters of this policy is considered not medically necessary. Current ongoing randomized trials include: NRG LU002, NRG BR002, SABR-COMET-10, ORIOLE (Prostate) and trials for oligoprogression: STOP (NCT02756793), HALT (NCT03256981).
References


Radiation Therapy for Other Cancers

POLICY

Though the majority of requests for radiation therapy are addressed by individual eviCore clinical guidelines, it is recognized that there may be requests that are not. For such requests, adjudication will be conducted on a case-by-case basis utilizing, as appropriate and applicable:

I. Evidence-based guidelines including, but not limited to:
   A. National Comprehensive Cancer Network (NCCN) Guidelines™
   B. American Society for Radiation Oncology (ASTRO) (i.e. Evidence-Based Guidelines; Evidence-Based Consensus Statement)
   C. American College of Radiology (ACR) (i.e. ACR Appropriateness Criteria®)
   D. American Society of Clinical Oncology (ASCO)
   E. Radiation Oncology Coding Resource

II. Peer-reviewed literature

References
1. National Comprehensive Cancer Network (NCCN) Guidelines. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). 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. Accessed October 2, 2018
Radiation Therapy for Pancreatic Cancer

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 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 for:
   E. Definitive treatment for medically or surgically 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
      1. Postoperative (adjuvant) cases in which there is residual gross disease or positive microscopic margins that can be entirely encompassed in the radiation treatment volume
      2. The use of SBRT as planned neoadjuvant treatment is considered to be the subject of ongoing investigation at this time.
   F. 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 margin 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.

Recently, preliminary results from PREOPANC-1 were released at ASCO 2018. This was a multicenter trial that randomized 246 operable patients to immediate surgery followed by gemcitabine (127 patients) or neoadjuvant chemotherapy with radiation therapy followed by surgery and additional chemotherapy (119 patients). Neoadjuvant patients received 15 radiation therapy treatments of 2.4 Gy radiation combined with gemcitabine on days 1, 8, and 15. The treatment was both preceded and followed by 1 cycle of gemcitabine. Preliminary results based on the analysis of 142 events were presented. Seventy-two percent (72%) of the immediate surgical group underwent surgery while 60% of the neoadjuvant group underwent surgery. The rate of negative surgical margins (R0 resections) was doubled in the neoadjuvant arm 63% vs. 31% in the surgery only arm (p < 0.001). Only 50% of the neoadjuvant group experienced disease progression in contrast to 80% of the surgery only group. (p = 0.002). The death rate comparison, however, was 65% in the surgery alone group vs. 55% in the neoadjuvant group (p = 0.74). Lead author
of this Amsterdam-led study, Dr. Van Tienhoven, commented that while 10% of the patients in the neoadjuvant group died before surgery, the improved R0 rate indicated that treatment did indeed have a beneficial effect. The 2 year OS rate of the neoadjuvant group was 42% vs. 30% from a similar population that received surgery and adjuvant chemotherapy. Median disease-free survival (DFS) was 9.9 months with neoadjuvant vs. 7.9 months with surgery alone (p = 0.023). A median distant metastasis evaluation favored the neoadjuvant group at 18.4 months vs. 10.6 months in the surgery group (p = 0.013). Neoadjuvant therapy also favored the local recurrence rate with the median not reached vs. 11.8 months in the surgery alone group. (p = 0.002). An updated analysis of the study is expected as more events take place.

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 consisted 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. Increasingly, IMRT has 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 boost 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 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 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 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 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


Radiation Therapy for Primary Craniospinal Tumors and Neurologic Conditions

POLICY

I. Complex, three-dimensional conformal radiation therapy (3DCRT), or Intensity-Modulated Radiation Therapy (IMRT) techniques are considered 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 fractions, 40.05 Gy/15 fractions, or 50 Gy/20 fractions

B. Recurrent disease with good prognostic factors including an Eastern Cooperative Oncology Group (ECOG) status of 0, 1, or 2

C. 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 for up to a combined total of 33 fractions including CSI

II. Stereotactic Radiosurgery (SRS) or Fractionated Stereotactic Radiotherapy (FSRT) is considered medically necessary for reirradiation of recurrent inoperable malignant gliomas in individuals who maintain a good performance status
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
      Please note that a maximum of 5 fractions is authorized for SRS. For an individual being treated with more than 5 fractions, 3DCRT or IMRT technique should be requested.

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 group 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

VIII. Proton Beam Therapy – please refer to the Proton Beam Therapy clinical guideline

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-Recursive 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 5 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 revealed 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-chlorethylnitrosourea (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. 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**


Benign conditions


Radiation Therapy for Prostate Cancer

POLICY

I. Low-risk prostate cancer
   A. 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
   B. The following treatments are considered medically necessary for treatment of low-risk prostate cancer
      1. Conventional fractionation – when delivering 1.8 to 2.0 Gy/fraction, 36 to 45 fractions of three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT)
      2. Hypofractionation – up to 28 fractions of 3DCRT or IMRT
      3. Up to 5 fractions of Stereotactic body radiation therapy (SBRT) alone (i.e. not as a boost)
      4. Low dose rate (LDR) brachytherapy (i.e. seed implant) alone
      5. High dose rate (HDR) brachytherapy alone

II. Intermediate-risk prostate cancer
   A. Intermediate-risk prostate cancer is defined as having any of the following:
      1. Stage T2b to T2c
      2. GS is 7
      3. PSA 10 to 20 ng/mL
   B. The following treatments are considered medically necessary for treatment of intermediate-risk prostate cancer
      1. Conventional fractionation – when delivering 1.8 to 2.0 Gy/fraction, 36 to 45 fractions of three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT)
      2. Hypofractionation – up to 28 fractions of 3DCRT or IMRT
      3. Up to 5 fractions of Stereotactic body radiation therapy (SBRT) alone (i.e. not as a boost)
      4. Low dose rate (LDR) brachytherapy (i.e. seed implant) alone (for favorable intermediate risk disease) or in combination with 25 to 28 fractions of 3DCRT or IMRT (for unfavorable intermediate risk disease)
5. High dose rate (HDR) brachytherapy alone (for favorable intermediate risk disease) or in combination with 25 to 28 fractions of 3DCRT or IMRT (for unfavorable intermediate risk disease)

III. High-risk prostate cancer

A. High-risk prostate cancer is defined as having any of the following:
   1. Stage ≥ T3a
   2. GS ≥ 8
   3. PSA > 20 ng/mL

B. The following treatments are considered medically necessary for treatment of high-risk prostate cancer:
   1. Conventional fractionation – when delivering 1.8 to 2.0 Gy/fraction, 36 to 45 fractions of three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT)
   2. Hypofractionation – up to 28 fractions of 3DCRT or IMRT
   3. Low dose rate (LDR) brachytherapy (i.e. seed implant) in combination with 25 to 28 fractions of 3DCRT or IMRT
   4. High dose rate (HDR) brachytherapy in combination with 25 to 28 fractions of 3DCRT or IMRT

IV. Adjuvant (postoperative) or salvage radiation therapy in the setting of

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

A dose of 32 to 40 fractions of 3DCRT or IMRT is considered medically necessary

V. Palliative

A. For treatment of obstructive symptoms or hematuria due to tumor, a dose of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions is considered medically necessary

VI. Proton beam therapy

A. Please refer to the separate Proton Beam Therapy Clinical Guideline
Key Clinical Points

I. External beam radiation therapy and brachytherapy

For low-, intermediate-, and high-risk disease, guidelines on prostate cancer from the NCCN indicate that for a conventionally-fractionated regimen, doses of 72 to 80 Gy (at 2 Gy per fraction) or 75.6 to 81 Gy (at 1.8 Gy per fraction) are recommended. Hence, up to 45 fractions will be considered medically necessary. Hypofractionated regimens such as 60 Gy in 20 fractions should also be considered.

For individuals with intermediate- or high-risk disease, combination external beam combined with brachytherapy is considered medically necessary. Combination therapy is considered not medically necessary for individuals with low-risk disease. Guidelines on prostate cancer from the NCCN indicate that an external beam dose of up to 50.4 Gy is recommended. Therefore, up to 28 fractions will be considered medically necessary.

Recently, the American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), and the American Urological Association (AUA) published an evidence-based guideline for the performance of hypofractionated radiation therapy. Moderate hypofractionation was defined as a radiation fraction size between 240 cGy and 340 cGy. Ultrahypofractionation was defined as a radiation fraction size greater or equal to 500 cGy. For an individual with localized prostate cancer who declines active surveillance, an individual with intermediate-risk prostate cancer, or an individual with high-risk prostate cancer in whom the pelvic lymph nodes are not being treated, hypofractionation radiation therapy received a strong recommendation based on high quality evidence. The recommendation was made regardless of whether the seminal vesicles are included in the treatment field, patient age, comorbidities, anatomy, and/or urinary function. These recommendations were based on reviews of large multi-center clinical trials, including the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy (CHHiP) trial, Prostate Fractionated Irradiation Trial (PROFIT), Radiation Therapy Oncology Group (RTOG) 0415 trial, and the Dutch Hypofractionated versus Conventionally Fractionated Radiotherapy for Patients with Prostate Cancer (HYPRO) trial. Regimens of 6000 cGy in 20 radiation treatment fractions and 7000 cGy in 28 radiation treatment fractions are suggested by the guideline based on their review of the largest database. This recommendation has a consensus of 100%, but the quality of evidence was noted as moderate, and the recommendation strength was noted as conditional. The panel stated that most of the published fractionation schedules have not been studied in comparative clinical trials, thus, an optimal regimen has not yet been determined.
II. SBRT

In addition to the recommendations noted for hypofractionation, the new guideline reviewed SBRT, also called ultrahypofractionation. In men with low-risk prostate cancer who declined active surveillance, ultrahypofractionation was suggested as an alternative to conventional fractionation with a conditional recommendation based on a moderate quality of evidence. For an individual with intermediate-risk prostate cancer, the consensus also suggested that ultrahypofractionation could be used as an alternative to conventional fraction but strongly encouraged that these individuals be treated as part of a clinical trial or a multi-institutional registry. The strength of the recommendation was conditional and was based on a low quality of evidence. For an individual with high-risk prostate cancer, it was suggested that ultrahypofractionation not be offered outside of a clinical trial or a multi-institutional registry as data was lacking on a comparative basis. The quality of evidence was felt to be low for this conditional recommendation. On the basis of this consensus guideline, SBRT is considered medically necessary for low- and intermediate-risk prostate cancer. It is not considered medically necessary for high-risk prostate cancer. It should be noted that SBRT (ultrahypofractionation) is defined as an entire treatment course consisting of five or fewer fractions. Thus, SBRT cannot be billed as a boost.

III. 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, a dose of 64 to 72 Gy (i.e. up to 40 fractions) is recommended by the NCCN.

IV. Palliative radiation therapy

Per the NCCN Guidelines®, a dose of 30 Gy in 10 fraction or 37.5 Gy in 15 fractions is recommended for “…treatment of the primary site in men with metastatic disease…to palliate obstructive symptoms due to tumor.”

V. Metastatic Prostate Cancer and Radiation Therapy

In castration-naïve metastatic prostate cancer, the current stand of care is systemic therapy with androgen deprivation therapy (ADT) usually in combination with docetaxel or abiraterone with prednisone (Morris et al, 2018). There has been debate in the scientific literature on the role of local therapy to the prostate gland in the setting of metastatic disease with some studies suggesting a benefit while other studies have not found a similar benefit (Rusthoven et al, 2016; Steuber et al, 2017). There is particular interest in the role of local therapy in patients with low metastatic burden. Recent randomized trials have been published evaluating the role of local treatment to the prostate in the setting of metastatic disease.
In 2018, Bouve and colleagues (2018) reported the results of the HORRAD trial which is a multi-institution randomized controlled trial evaluating the role of definitive radiation therapy to the prostate in combination with androgen deprivation therapy for patients with metastatic prostate cancer. Four hundred thirty-two men with newly diagnosed, previously untreated prostate cancer with bone metastases were randomized to ADT alone or ADT with radiation therapy. Participants received 70 Gy in 35 fractions or 57.76 Gy in 19 fractions to the prostate with or without the seminal vesicles. There was no statistically significant difference in median overall survival between the ADT alone arm (43 months) vs. the ADT with radiation therapy arm (45 months) p=0.4. There was no significant difference in overall survival when stratified by number of bone metastases: < 5 bone metastases (HR 0.68; 95% CI: 0.42–1.10) vs. > 5 bone metastases (HR 1.06; 95% CI: 0.80–1.39). As this trial did not demonstrate an overall survival benefit to adding radiation therapy to the prostate gland to androgen deprivation therapy, the authors conclude that local therapy to the prostate gland in patients with metastatic prostate cancer at diagnosis should not be performed outside of a clinical trial.

The STAMPEDE trial, a multi-institutional randomized phase III trial, randomized 2061 men with newly diagnosed metastatic prostate cancer with no previous treatment to standard of care (androgen deprivation therapy with or without docetaxel) or standard of care and radiotherapy between January 2013 and September 2016 (Parker et al, 2018). Radiation therapy was delivered to the prostate gland as 36 Gy in 6 fractions weekly or 55 Gy of 20 fractions daily. In May 2018, the authors decided to do a prespecified subgroup analysis for survival by metastatic burden. Low metastatic burden was defined as 3 or fewer bone metastases. High metastatic burden was defined as four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both. While there was a difference in failure free survival, there was no difference in overall survival with the addition of radiation therapy. When analyzing the data by metastatic burden, the authors found an improvement overall survival in patients with a low metastatic burden (HR 0.68, 95% CI 0.52–0.90; p=0.007; 3-year survival 73% with control vs. 81% with radiotherapy). There was an improvement in failure free survival with the addition of radiation therapy for patients with low metastatic burden (HR 0.76, 95% CI 0.68–0.84; p<0.0001). The authors concluded that while radiation therapy to the prostate did not improve overall survival to unselected patients with newly diagnosed prostate cancer there was an improvement in overall survival in patients with low metastatic burden in a prespecified subgroup analysis.

Taken together, the HORRAD trial and the STAMPEDE trial both demonstrate that there is no overall survival advantage to the addition of radiation therapy to hormonal therapy in newly diagnosed prostate cancer which was the primary endpoint to both trials. These trials raise the question of a role for radiation therapy to the prostate in selected patients with a limited number of bone metastases. It is important to note that the HORRAD trial did not find a benefit in the low metastatic setting and the
STAMPEDE trial only found a benefit in a subgroup analysis that was prespecified in May 2018. As this endpoint was not initially defined, the authors had to ascertain metastatic burden by retrospectively collecting baseline data. Therefore, as the survival benefit was only seen on subgroup analysis, this finding must be interpreted with caution (Boeri et al, 2018). Furthermore, as noted by the authors in the STAMPEDE trial, the systemic therapy regimens used in treatment of metastatic prostate cancer have evolved. Currently, most patients with metastatic prostate cancer are usually treated upfront with androgen deprivation therapy (ADT) in combination with docetaxel or in combination with abiraterone with prednisone. Most patients in the STAMPEDE trial received upfront treatment with androgen deprivation therapy alone. Only 18% of patients received androgen deprivation therapy and docetaxel. The value of radiation therapy to the prostate in men with metastatic prostate cancer receiving abiraterone is unknown. Therefore, the benefit of local radiation therapy in the setting of more modern systemic therapy regimens is unknown and is being evaluated in the PEACE1 trial (NCT01957436). The PEACE1 trial (NCT01957436) is an ongoing multi-center phase III study evaluating the clinical benefit of androgen deprivation therapy (+ docetaxel) with or without local radiotherapy with or without abiraterone acetate and prednisone in patients with metastatic hormone-naïve prostate cancer. Additionally, the radiation dose used in the STAMPEDE trial (36 Gy in 6 fractions or 55 Gy in 20 fractions) is a dose lower than the > 70 Gy that is commonly used in current practice and 6 Gy/fraction each week is not a tumoricidal dose. This further calls into question the results of the subgroup analysis. Taken together, the data demonstrate that local treatment in the setting of metastatic prostate cancer either with low or high metastatic burden remains investigational and warrants continued evaluation in the setting of prospective, randomized trials.

References


47. National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2018 – August 15, 2018. Prostate Cancer. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Prostate Cancer 4.2018©. 2018 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.


Radiation Therapy for Rectal Cancer

**POLICY**

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

**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 postoperative 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 or electron 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. Intensity-Modulated Radiation Therapy (IMRT) is not
Radiation Therapy Criteria V2.0.2019

médicamente nécessaire (voir ci-dessous). Une dose de 45 à 54 Gy en 25 à 30 fractions sur 5 à 6 semaines est généralement utilisée.

Différentes techniques de traitement peuvent être utilisées pour réduire les complications, telles que la position ventrale, l'immobilisation personnalisée (par exemple, des planches de ventre), et l'utilisation de plusieurs champs et incorporation de la planification 3D de traitement.

L'IMRT avec des photons n'est généralement pas médicamente nécessaire à moins qu'il n'y ait des circonstances exceptionnelles où des doses plus élevées sont nécessaires (par exemple, des cas non résectables ou ceux avec des marges positives) et où les tissus normaux tels que le petit intestin ne peuvent pas être adéquatement préservés. L'IMRT avec des photons dans les contextes préopératoires et postopératoires devrait être utilisé uniquement dans le cadre d'une évaluation de la revue par un comité d'éthique de recherche (IRB)-approuvé. L'utilisation de l'IMRT avec des photons dans certains cas de cancer localement et régionalement avancés peut être nécessaire lorsque des doses plus élevées de rayonnement peuvent être nécessaires.

Pour les cancers non résectables ou les individus qui ne sont pas en mesure de subir une intervention, des doses plus élevées que 54 Gy peuvent être appropriées. Dans le contexte préopératoire, une dose de 50.4 Gy en 28 fractions est appropriée. Une dose de 25 Gy en 5 fractions peut également être considérée dans certains cas. Dans le contexte postopératoire avec des marges négatives, 54 Gy en 30 fractions peuvent être appropriées. Les individus avec des marges positives peuvent nécessiter des doses plus élevées que 54 Gy.

B. External beam photon radiation therapy, palliative

Dans les individus non irradiés antérieurement avec des cancers métastatiques non résectables avec des symptômes locaux ou des primaires proches d'obstruction qui ont une espérance de vie raisonnable, le rayonnement photon externe peut être approprié. Jusqu'à 20 fractions en 1 phase utilisant 3DCRT ou rayonnement planifié en utilisant une technique isodose complexe avec des photons est médicalement nécessaire. L'IMRT avec des photons n'est pas médicalement nécessaire.

References

Radiation Therapy for Skin Cancer

POLICY

I. Basal cell and squamous cell skin cancers

A. Overview

In the United States, the incidence of skin cancers outweighs all other cancers combined, and basal cell cancers are twice as common as squamous cell skin cancers. While the two types share many characteristics, risk factors for local recurrence and for regional or distant metastases differ somewhat. Both types tend to occur in skin exposed to sunlight, and share the head and neck region as the area having the greatest risk for recurrence. Both occur more frequently and be more aggressive in immunocompromised transplant patients. In general, it is the squamous cell cancers that tend to be more aggressive, with a greater propensity to metastasize or to recur locoregionally. A squamous cell cancer is more likely to possess one or more high risk factors.

Anatomic location plays a role in risk stratification and is broken down into: "L" areas (trunk and extremities, excluding pretibia, hands, feet, nail units, ankles); "M" areas (cheeks, forehead, scalp, neck, pretibial); "H" areas (mask areas of face, including central face, eyelids, eyebrows, periorbital skin, lips, chin, overlying mandible, preauricular and postauricular skin, temple, ears, genitalia, hands, feet). Factors identified as placing the patient at increased risk for recurrence for basal and squamous cell skin cancers are included in Table 1.

<table>
<thead>
<tr>
<th>Basal Cell Skin Cancer High Risk Factors</th>
<th>Squamous Cell Skin Cancer High Risk Factors</th>
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<tr>
<td>• &quot;L&quot; area diameter greater than 20 mm</td>
<td>• &quot;L&quot; area diameter greater than 20 mm</td>
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<td>• &quot;M&quot; area diameter greater than 10 mm</td>
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<td>• Recurrent presentation</td>
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<td>• Presence of immunosuppression</td>
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<td>• In a site of prior radiation therapy</td>
<td>• In a site of prior radiation therapy</td>
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<tr>
<td>• Aggressive growth pattern (morphoeform, basosquamous, sclerosing, micronodular features)</td>
<td>• Rapidly growing lesion</td>
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<tr>
<td>• Presence of perineural involvement</td>
<td>• Neurologic symptoms</td>
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<td></td>
<td>• Poorly differentiated</td>
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<td></td>
<td>• Unfavorable histology (adenoid, adenosquamous, desmoplastic, metaplastic)</td>
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<td></td>
<td>• ≥ 2mm depth, or Clark level IV or V</td>
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<tr>
<td></td>
<td>• Perineural, lymphatic, or vascular</td>
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</table>
B. Management

Treatment should be customized, taking into account specific factors and also patient preferences. The primary goal is to completely remove the tumor and to maximize functional and cosmetic preservation. Surgery is usually the most efficient and effective means to achieve these goals. Radiation therapy may be selected when cosmetic or functional outcome with surgery is expected to be inferior. In very low risk, superficial cancers, topical agents may be sufficient and cautiously used. When surgery is utilized, margin assessment using Mohs micrographic technique should include examining vertical sections of the specimen to assess deep margin and stage/depth of invasion. When radiation therapy is utilized, the following are applicable:

1. 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
   g. Contraindications to the use of photon and/or electron beam techniques:
      i. Radiation therapy should not be used in genetic conditions which predispose to skin cancer, such as xeroderma pigmentosum or basal cell nevus syndrome.
      ii. Radiation treatments should be avoided or only used with great caution in cases of connective tissue disorders

2. Brachytherapy (low dose rate [LDR], high dose rate [HDR], or electronic brachytherapy technique) is medically necessary when both a and b are contraindicated:
   a. Surgical resection
   b. Photon and/or electron beam techniques

3. When brachytherapy is required for treatment of skin cancers, up to ten (10) sessions is considered medically necessary.
4. 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 maximum thickness of a lesion that may be treated with this technique.

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.

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). 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.

When multiple skin cancers are present and to be treated with radiation therapy, they should be treated concurrently rather than sequentially. Medical review will be required for those cases in which sequential treatment is requested, or if a new request is received for treatment of additional skin cancers within 90 days of previous requests.
II. Malignant melanoma

A. Overview

Malignant melanoma is increasing in incidence in the United States at a rate more rapidly for men than any other malignancy, and more rapidly for women for all malignancies except lung cancer. There are over 75,000 new cases of melanoma in the USA annually, and it accounts for over 10,000 deaths each year. The incidence may be even higher, skewed by under-reporting of superficial and in situ cases. Like the non-melanoma skin cancers, excess sun exposure poses an increased risk of developing it, along with skin type, positive personal or family history, and environmental factors. Yet it can also occur in persons without substantial sun exposure and in any ethnic group or any color of skin. Survival is strongly inversely correlated with degree/depth of invasion, and decreases 50% with lymph node involvement. Some cases of melanoma take an indolent course while others are biologically much more aggressive.

Melanoma can arise outside of the skin, wherever melanocytes exist. Mucosal melanoma represents a spectrum of clinical entities depending on site of origin, and most commonly arises in the head and neck sinuses, the oral cavity, the anorectum, vagina, and mucosa of the GI and GU tracts. There are specific genetic alterations in distinct clinical subtypes of melanoma, often correlated with degree of sun damage. BRAF mutation is seen in roughly half of the non-CSD (non-chronic sun damaged) skin melanomas, whereas KIT gene aberrations are rare in that group. Non-mucosal, non-cutaneous melanomas also occur, such as in the uveal tract, and represent distinct presentations. Non-cutaneous melanoma cases (i.e. mucosal melanomas and those of the eye) are addressed in other sections of this clinical guideline, such as the Radiation Therapy for Head and Neck clinical guideline for melanomas of the sinuses, or the Radiation Therapy for Proton Beam Therapy clinical guideline on proton beam therapy for uveal melanomas.

The natural history of cutaneous melanoma is one of local invasion, lymphatic metastases, and hematologic dissemination. The risk of all three may be greater than that of a non-melanoma skin cancer in the same location. Surgery is the primary therapy for cutaneous melanoma. A preoperative evaluation should include a careful physical examination of the primary site, the regional lymphatics, and the entire skin surface. Equivocal findings on physical examination of the regional lymphatics may trigger an ultrasound exam of the area. If symptomatic, cross-sectional imaging is indicated, otherwise not routinely to be performed for early stage (0, I, II) cases. Sentinel lymph node evaluation is recommended for thicker lesions, but rarely needed with lesions less than 0.75 mm thick. As stage advances higher, baseline imaging is appropriate, or if there is clinical evidence of adenopathy or symptoms are present that suggest nerve or bone invasion. Clinically positive nodes should be confirmed with fine needle aspiration (FNA) or core biopsy. If there is clinical or radiographic evidence of distant metastases, confirmation by FNA or core biopsy is recommended, as is imaging of the brain. Patients with minimal signs or symptoms of CNS involvement should undergo a brain magnetic resonance imaging (MRI) scan due to the high risk of brain...
metastases.

The optimal degree of clear margin necessary to minimize the risk of local is
dependent on tumor thickness. For thin (<2 mm) lesions it appears a margin of
1 cm is adequate. For thicker lesions, a 2 cm margin is currently recommended.
Lentigo maligna and melanoma in situ present unique features because of possible
lateral subclinical extension, for which imiquimod is an option. Radiation therapy
has been also used in such cases, with complete clearance rates in the 85% to
90% range. For a melanoma that has undergone adequate wide local excision and
there is no adenopathy on clinical and/or sentinel node examination, adjuvant
radiation therapy is rarely indicated, the possible exception being desmoplastic
neurotropic melanoma. If regional adenopathy is clinically present, a complete
therapeutic node dissection should be included with wide excision of the primary
tumor. If melanoma is found in sentinel nodes but was not clinically suspicious,
current recommendations include offering a complete node dissection, though its
impact on disease control and survival is not well established and is the focus of
current study. Following wide excision and nodal dissection, radiation therapy to
the nodal basin is to be considered in high risk cases, based on location, size, and
number of positive nodes, and the presence or absence of extranodal extension
of melanoma.

Radiation therapy is one option for the treatment of in-transit disease (metastases
within lymphatics or satellite locations without metastatic nodes) for which
resection is not feasible. Alternatives include intralesional injections, local ablation
therapy, and topical imiquimod.

Radiation therapy for brain metastases has been delivered using either whole brain
radiation therapy (WBRT) or stereotactic radiosurgery (SRS), or both. While most
studies have been retrospective and reported on few patients with melanoma,
WBRT was generally associated with fewer intracranial recurrences but not
necessarily a survival advantage. Because of the benefit of emerging more
effective systemic therapies such as the immune checkpoint inhibitor Ipilimumab,
there is a trend towards increased use of SRS rather than WBRT because of the
increased survival with systemic therapy and the possibility of the cognitive
impairment late effect of whole brain radiation.

B. Management

1. Photon and/or electron beam techniques are considered medically necessary
in the treatment of malignant melanoma at the primary site of the skin in these
situations:
   a. Adjuvant treatment after resection of a primary deep desmoplastic
      melanoma with close margins
   b. Adjuvant treatment after resection of the primary tumor and the specimen
      shows evidence of extensive neurotropism
   c. Locally recurrent disease after resection
2. Photon and/or electron beam techniques are considered medically necessary in the treatment of regional (i.e. those with nodal involvement) malignant melanoma in these situations:
   a. Upon resection of clinically appreciable lymph nodes when:
      i. The lactate dehydrogenase (LDH) level is less than 1.5 times the upper limit of normal and
      ii. Extranodal extension of tumor is present in the resected nodes and/or one or more of the following:
         01. One or more involved parotid lymph nodes of any size
         02. Two or more involved cervical lymph nodes and/or tumor within a node is 3 cm or larger
         03. Two or more involved axillary lymph nodes and/or tumor within a node is 4 cm or larger
         04. Three or more involved inguinal lymph nodes and/or tumor within a node is 4 cm or larger
   3. Photon and/or electron beam techniques are considered medically necessary to palliate unresectable nodal, satellite, or in-transit disease
   4. Photon and/or electron beam techniques are medically necessary in the treatment of metastatic malignant melanoma in these situations:
      a. Symptomatic or potentially symptomatic soft tissue metastases
      b. Symptomatic or potentially symptomatic bone metastases (also see the Radiation Therapy for Bone Metastases clinical guideline)
      c. Symptomatic or potentially symptomatic visceral metastases
      d. Metastases to the brain (also see the Radiation Therapy for Brain Metastases clinical guideline)

C. Technique and dose considerations
   1. Superficial or kilovoltage (kV) x-ray 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.
   2. 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 electron beams 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, more conformal 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 NRG Oncology/National Comprehensive Cancer Network (NCCN). Unless clinically evident, dose comparison plans will be required.

3. 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. The radiation dose schedules used with non-melanoma skin cancers are commonly employed. However, 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 (two fractions per week) have been reported as having acceptable acute toxicity and increased response rates, but may be at the expense of long term side effects.

4. Requests to use highly conformal techniques such as Stereotactic Body Radiation Therapy (SBRT) to treat melanoma metastases require individual review and must also satisfy criteria set forth in the Radiation Therapy for Oligometastases clinical guideline.

5. 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.

References


Radiation Therapy for Small Cell Lung Cancer

I. POLICY

A. Definitive external beam 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
   3. A dose of 60-70 Gy in 30-35 fractions or 45 Gy delivered twice daily is recommended.

B. Prophylactic cranial irradiation (PCI) using a dose of 25 Gy in 10 fractions is medically necessary in a responding individual (local disease and extensive disease) with good performance status.

C. Palliative treatment
   1. The use of up to 15 fractions of a 3D conformal technique is medically necessary.

II. Technique

A. The use of IMRT is considered medically necessary in the following situations:
   1. Where there is disease in the bilateral mediastinum or bilateral hilar regions
   2. Where there is disease in the paraspinal region
   3. For superior sulcus tumors
   4. Documentation that a 3D plan does not meet the normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN). This documentation must describe the specific OARs (organs at risk) whose tolerance has been exceeded. DVHs (dose volume histograms) are insufficient documentation.

Key Clinical Points

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 twice daily (hyperfractionation/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 chemoresponsive 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 regimen for PCI is 25 Gy in 10 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
Radiation Therapy for 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, clips should be placed to both 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. Intraoperative 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. At the time of surgery, clips should be placed to both 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
   a. 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, clips should be placed to both 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. IORT 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. At the time of surgery, clips should be placed to both 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.

IV. Radiation techniques

A. 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.

B. IMRT

IMRT is considered medically necessary in the treatment of retroperitoneal sarcomas. 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.

C. 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.

D. 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 Therapy for Oligometastases clinical guideline.

E. Image-Guided Radiation Therapy (IGRT)

Please refer to the separate Image-Guided Radiation Therapy (IGRT) clinical guideline.

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 multidisciplinary 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
Radiation Therapy for 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, regimens of 20 Gy in 10 fractions or 25.5 Gy in 17 fractions are 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 < 3 cm) (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


Radiation Therapy for Thymoma and Thymic Cancer

POLICY

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

I. Stage I thymoma following resection with microscopic positive margins or gross residual disease

II. Stage I thymic carcinoma

III. Stage II to IVA thymoma or thymic carcinoma

IV. Unresectable or medically inoperable thymoma or thymic carcinoma

V. Isolated local recurrence in the setting of no additional sites of distant metastatic disease

VI. Palliation

Fractionation

I. Resectable disease with thymic histology or microscopic positive margins
   A. Up to 27 fractions is considered medically necessary

II. Unresectable or gross residual disease
   A. 30 to 35 fractions are considered medically necessary

III. Isolated local recurrence felt to be curative
   A. 30 to 35 fractions are considered medically necessary

IV. Palliation
   A. Up to 15 fractions is considered medically necessary

Techniques

I. External beam photon radiation therapy with three-dimensional conformal radiation therapy (3DCRT) is considered medically necessary

II. Intensity-Modulated Radiation Therapy is considered not medically necessary
Key Clinical Points

For individuals with thymic malignancies, surgery with total thymectomy with en bloc removal of contiguous and noncontiguous disease is the treatment of choice. The use of radiation therapy following surgical resection is guided by the stage and degree of resection. The radiation treatment volume includes the tumor or the tumor bed plus a margin (Komaki and Gomez, 2013). As the rate of lymph node involvement is low, elective nodal irradiation is not routinely utilized (Komaki and Gomez, 2013).

For individuals with Stage I disease who undergo a complete resection, adjuvant radiation therapy is not recommended (Komaki and Gomez, 2013; Zhang et al., 1999). A randomized trial evaluating the use of postoperative radiation therapy in patients with Stage I thymoma found no significant difference in survival for those who received surgery alone versus surgery and radiation therapy (Zhang et al., 1999). The 10 year survival rate with surgery alone was > 90% (Zhang et al., 1999).

The role of postoperative radiation therapy in the management of thymoma is controversial. There are studies indicating a benefit to postoperative radiation therapy while other studies have not shown a clear advantage. In an analysis of 2001 patients from the National Cancer Database, Jackson and colleagues (2017) found that postoperative radiation therapy was associated with improved overall survival in patients with Masaoka-Koga Stage IIB thymoma, Stage III thymoma, and positive margins. A SEER analysis of 1334 patients with thymic malignancies found adjuvant radiation therapy did not improve overall survival (OS) for patients with Stage I or IIA disease but was associated with increased survival for those with Stage III or IV disease (Fernandes et al., 2010). In an analysis of 1263 Stage II and III thymoma patients from the International Thymic Malignancy Interest Group database who underwent complete resection, postoperative radiation therapy was associated with improved 10 year overall survival compared with surgery alone (86% vs. 79%, p = 0.002) (Rimner et al., 2016). A retrospective review of 146 patients with Stage I-IVA thymic carcinoma or Stage III or IV thymoma found that patients with Stage III disease had improved OS with radiation therapy combined with surgical resection and chemotherapy compared to single modality therapy (Modh et al., 2016). In contrast, Ruffini et al. (1997) observed decreased survival in Stage III thymoma patients who received postoperative radiation therapy following complete resection.

Neoadjuvant chemoradiation has been evaluated in locally advanced thymoma. In a single arm prospective trial of 22 patients with locally advanced thymoma or thymic carcinoma, 77% of patients were able to undergo a complete resection after receiving neoadjuvant chemoradiation therapy (Korst et al., 2014). This prospective study was able to demonstrate that neoadjuvant chemoradiation therapy is feasible with acceptable toxicity for patients with locally advanced thymic tumors (Korst et al., 2014).
Radiation therapy combined with chemotherapy is recommended for patients with unresectable or medically inoperable thymic malignancies. Wang and colleagues (2016) conducted a retrospective review of 42 patients with thymoma with unresectable Stage III or Stage IV (limited to an adjacent pleural implant or lymph node) disease. The median dose of radiation was 60 Gy (34 to 70 Gy). This study found combined chemoradiation therapy resulted in a higher overall response rate (ORR) (87.5% vs. 43.8%, p = 0.009) and an increased 5 year OS (61.9% vs. 30%, p = 0.01) compared to radiation therapy alone.

There is no published literature that describes a definitive clinical benefit to IMRT in thymic malignancies compared to 3DCRT. The available literature is primarily retrospective reviews which tend to combine 3DCRT and IMRT together. For example, Fan and colleagues (2013) found a non-statistically significant trend towards improved survival with 3DCRT or IMRT when compared with conventional radiation therapy techniques (100% vs. 86.9%, p = 0.12).

There is no clear dose-response relationship in the treatment of thymoma. Kundel and colleagues (2007) found improved OS when doses of 45 Gy or higher were utilized for patients with thymoma who received adjuvant radiation therapy. When Fan et al. (2013) examined the outcomes for patients who received ≤50 Gy vs. > 50 Gy, there was no difference in difference in 5 year or 10 year OS with higher doses of radiation (65% vs. 58.2%, p = 0.7). Similarly, in 128 thymoma patients who received radiation therapy, the 5 year local control rate was comparable in patients who received ≤ 50 Gy and those who received > 50 Gy (Zhu et al, 2004).

As patients with thymoma have a long life expectancy, it is important to evaluate potential long term sequelae of treatment. The available literature has not demonstrated an increased rate of cardiac morbidity or an increased incidence of secondary malignancies in thymoma patients who receive radiation therapy. Fernandes and colleagues (2010) utilized the SEER database to analyze long term outcomes and complications for 1334 patients with thymoma who received radiation therapy. There was no difference in the 24 year rate of cardiac mortality for those patients who received surgery alone when compared to those who received surgery and radiation therapy (11.8% vs. 17.4%, p = 0.83). There was no difference in the incidence of all secondary malignancies (11.7% vs. 12.4%, p = 0.70) and thoracic secondary malignancies (3.4% vs. 4.3%, p = 0.31) for patients treated with surgery alone versus those who received radiation.
References:

Radiation Therapy for Urethral Cancer and Upper Genitourinary Tract Tumors

POLICY

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

I. Definitive treatment of urethral cancer in an individual with T2-T4 disease or node positive

II. Postoperative treatment of in urethral cancer in an individual with T3-T4 disease, node positive, or positive surgical margins

III. Postoperative radiation therapy is considered medically necessary in the definitive treatment of cancers of the ureter or renal pelvis for advanced T3-T4 disease, positive lymph nodes, or positive surgical margins

IV. Palliative treatment for urethral and upper genitourinary tract disease

Fractionation

I. Urethral cancer
   A. In the definitive setting up to 39 fractions is considered medically necessary
   B. In the adjuvant setting in an individual with no high risk features, up 30 fractions is considered medically necessary
   C. In the adjuvant setting in individual with positive margins or extra-nodal extension, up to 39 fractions is considered medically necessary
   D. In the palliative setting up to 20 fractions is considered medically necessary

II. Upper genitourinary tract
   A. Preoperative or neoadjuvant treatment is considered medically necessary when combined with chemotherapy in an effort to improve resectability. Usual doses are 30 to 45 Gy.
   B. In the postoperative adjuvant setting up to 30 fractions is considered medically necessary
   C. In the palliative setting up to 20 fractions is considered medically necessary
Techniques

I. EBRT with three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) is considered 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 considered 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.

Although the literature is relatively scant on the use of radiation therapy for the treatment of upper genitourinary tract tumors, there are some studies that suggest a survival advantage in an individual with T3-T4 disease of the renal pelvis or ureter receiving postoperative treatment with a median dose of 50 Gy to the tumor bed. Treatment may be considered for an individual with positive surgical margins, positive lymph nodes, or high grade tumors following nephroureterectomy. There is no data, however, to suggest that radiation therapy alone is helpful in the preoperative setting. As these tumors are responsive to chemotherapy, drug combinations currently employing platinum analogues have been found to be helpful in the treatment of this disease and may be used in combination with radiation therapy in an effort to downsize the disease and improve resectability.

References

Radiation Treatment with Azedra® (iobenguane I-131)

POLICY

I. Indications

Azedra® is considered medically necessary for the treatment of an individual aged 12 years and older with iobenguane scan positivity who has inoperable locally advanced or metastatic pheochromocytoma or paraganglioma requiring systemic treatment.

II. Submission Requirements

A. Official pathology report documenting pheochromocytoma or paraganglioma
B. Official radiology report of positive iobenguane scan
C. In the absence of metastatic disease, a surgical or medical consult documenting the reason for inoperability

III. Contraindications

A. Creatinine clearance ≥ 30 ml/minute
B. Platelet count < 80,000
C. Absolute neutrophil count < 1,200/mcL
D. Liver dysfunction with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.5 times the upper limit of normal or total bilirubin > 1.5 times the upper limit of normal
E. History of hepatitis or chronic alcohol abuse
F. History of external beam radiation to > 25% of the bone marrow
G. History of systemic radiotherapy resulting in myelosuppression within 3 months of proposed Azedra® administration

IV. Precautions and Warnings

A. The official manufacturer’s prescribing information, precautions and radiation safety instructions packaged with the medication should be fully reviewed and understood before using Azedra®
B. This radiopharmaceutical should be used by or under the supervision of physicians with specific training in the use of radiopharmaceuticals who have been authorized and approved by the appropriate governmental agency
C. Concerns about the use of this radiopharmaceutical include but are not limited to:

1. Radiation safety in handling the preparation
2. Pregnancy, lactation and precautions for both women and men of reproductive potential on appropriate contraception methods including embryo-fetal toxicity and risks of infertility
3. Risk from radiation exposure
4. Myelosuppression
5. Leukemia and Secondary Myelodysplastic Syndrome
6. Renal toxicity including use with renal impairment
7. Hepatic toxicity including use with hepatic impairment
8. Hypothyroidism
9. Pneumonitis
10. Hypertension
11. Pediatric and geriatric use

V. Usage

A. Users should read the manufacturer’s insert for all specific instructions as they could change as more experience is gained in the patient population

1. The current recommended dose of Azedra® is dependent on body weight. The drug is administered as a dosimetric dose followed by two therapeutic doses administered 90 days apart
2. Users should familiarize themselves with the therapeutic dose adjustments that may be necessary based on the dosimetry results and reactions to treatment
3. Particular attention should be given to the manufacturer’s instructions on the use of drugs that reduce catecholamine uptake or deplete catecholamine stores, mandatory thyroid blockade prior to treatment, as well as antiemetic and hydration requirements
Key Clinical Points

Recently, the Food and Drug Administration (FDA) announced approval of Azedra® for adults and pediatric patients 12 years and older with iobenguane scan positivity who have inoperable locally advanced or metastatic pheochromocytoma or paraganglioma requiring systemic treatment. The approval is based on Study IB12B open-label, single arm multicenter trial (NCT00874614). The required dosimetric dose was administered to 74 patients. Sixty-eight (68) patients subsequently received at least one therapeutic dose. Of this group, 50 patients received two therapeutic doses 90 days apart. Thirty-five (35) of the 68 patients had prior surgery and systemic therapy (I-131 MIBG and/or chemotherapy) for pheochromocytoma or paraganglioma. Fifty percent (50%) had previous external beam radiation therapy. Lung and/or liver metastases were present at baseline in 32 of 64 evaluable patients. Sixty-one percent (61%) had bone metastases. The primary endpoint specified in the study was the proportion of patients with at least 50% reduction of all anti-hypertensive medications for a minimum of 6 months during the efficacy period of 1 year. Overall tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST). After one (1) year, patients entered four (4) additional years of planned follow-up. The primary endpoint was met by 25% (95% CI 16% to 37%) of those receiving one therapeutic dose and 32% (95% CI 21% to 46%) of patients who received two (2) therapeutic doses, achieving pre-specified success criteria. For objective tumor response, 23% of one dose and 30% of two dose patients’ populations achieved partial response (PR). The 12-month overall survival (OS) was 91% in one dose patients. Median OS was 36.7 months (95% CI 29.9 to 49.1), and median survival appeared similar in patients with and without lung/liver metastasis at baseline (42.6 and 41.1 months, respectively). The most common (≥ 50%) treatment-emergent adverse events were myelosuppression, nausea, and fatigue. No acute drug-related hypertensive events were observed. On the basis of this data, FDA approval was given for the indications listed.

References
Radiation Treatment with Lutathera (Lutetium; Lu 177 dotatate)

POLICY

I. Indications

Lutetrium 177 dotatate is considered medically necessary in the treatment of select patients with low-, intermediate- or well-differentiated high-grade neuroendocrine tumors who have progressed on somastatin-anlaogs (SSA) in the following setting:

A. Inoperable or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) of the pancreas, foregut, midgut and hindgut in adults

B. Inoperable or metastatic somatostatin receptor positive bronchopulmonary or thymic tumors in adults

Lutetium 177 dotatate is considered experimental, investigational, or unproven (EIU) in the treatment of all other neuroendocrine tumors

II. Requirements

A. For neuroendocrine tumors pathology report documenting aKi67 index < 20%

B. Positive somatostatin receptor scintigraphy with correlative Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) imaging of metastatic measurable disease or 68-Ga-Dotatate Positron Emission Tomography (PET) scan positive for metastatic disease

C. In the absence of metastatic disease, a surgical or medical consult documenting the reason for inoperability

III. Contraindications

A. Serum creatinine: ≥ 1.7 mg per deciliter or creatinine clearance of ≤ 50 ml/minute

B. Hgb: ≤ 8.0 g/dl; WBC < 2000/mm3; platelets < 75,000 mm

IV. Precautions and Warnings

A. The official manufacturer’s prescribing information, precautions and radiation safety instructions packaged with the medication should be fully reviewed and understood before using Lutetium-177

B. This radiopharmaceutical should be used by or under the supervision of physicians with specific training in the use of radiopharmaceuticals who have been authorized and approved by the appropriate governmental agency
C. Concerns about the use of this radiopharmaceutical include but are not limited to:

1. Radiation safety in handling the preparation
2. Pregnancy, lactation and precautions for both women and men of reproductive potential on appropriate contraception methods including embryo-fetal toxicity and risks of infertility
3. Risk from radiation exposure
4. Myelosuppression
5. Leukemia and Secondary Myelodysplastic Syndrome
6. Renal toxicity including use with renal impairment
7. Hepatic Toxicity including use with hepatic impairment
9. Pediatric and geriatric use

V. Usage

A. Users should read the manufacturer’s insert for all specific instructions as they could change as more experience is gained in the patient population.

1. The current recommended dose of Lutathera is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses.
2. Users should familiarize themselves with the restrictions and usage of long and short acting octreotide agents before, during, and after Lutathera treatment as well as the manufacturer’s recommended use of anti-emetics and a specialized amino acid solution.
3. Users should be aware of detailed manufacturer’s instructions on dosing or withholding of treatment for circumstances including, but not limited to, thrombocytopenia, anemia, neutropenia, renal toxicity, hepatotoxicity, and possible other non-hematologic toxicities.
Key Clinical Points

Neuroendocrine tumors are relatively rare but appear to be rising in the U.S. with an incidence reported from 5.25 to 7.0 per 100,000 people. It is unclear as to whether this is a true increase or a better recognition of the entity or combination of these factors. They are classified by site of origin, stage, grade, and histologic classification. There appears to be a correlation between mitotic count and Ki67 proliferation. Additionally, these tumors may be classified as being functional or non-functional depending on their ability to secrete hormones or other peptides which are responsible for hypertension, flushing, diarrhea as documented in the carcinoid syndrome, or hyperinsulinemia and other associated syndromes.

Gastrointestinal Tumors: Over 60% of carcinoid tumors arise in gastrointestinal tract sites such as the stomach, small intestine, appendix and rectum which secrete serotonin, histamine and other substances. The portal circulation and its hepatic enzymes however rapidly metabolize most of these products. As such, only up to 25% of these tumors are responsible for the classic carcinoid and related syndromes, with the symptoms most likely due to liver metastases entering the circulatory system via the hepatic veins or other remote disease. Other common sites of metastases include the mesentery and peritoneum. Patients with non-secreting tumors usually are discovered at surgery after presenting with symptoms secondary to the presence of a mass lesion. Systemic treatment for metastatic disease has been with a somatostatin medication for control of tumor growth and hormonal secretion. Non-functioning tumors have few systemic options such as everolimus or trials of chemotherapy.

Pancreatic Neuroendocrine Tumors: There is an annual incidence of 1.8 per million in women and 2.6 per million in men. Approximately 60% are functioning tumors. Most pancreatic neuroendocrine tumors are sporadic. They are reported in several familial syndromes including, but not limited to, MEN1, MEN2, VHL, neurofibromatosis type 1, tuberous sclerosis, and Carney Complex. Pancreatic tumors occurring in MEN1 often have multiple tumors and require different management. Surgery is the mainstay for local and regional treatment. Debulking surgery has proven helpful in the management of more advanced disease. Systemic treatment options are similar to those mentioned above for gastrointestinal neuroendocrine disease. Systemic syndrome management and evaluation and treatment of inherited syndromes are best guided under current NCCN Guidelines™.

Recently, the FDA announced approval of Lutathera for treatment of neuroendocrine tumors arising from the foregut, midgut, hindgut and pancreas. The approval for this agent was based on two published studies NETTER 1 and the Erasmus Study.

In addition to the contraindications and precautions listed above, the use of Lutathera requires that long acting somatostatin analogs such as octreotide be discontinued for at least 4 weeks prior to the commencement of Lutathera treatment. Short-acting octreotide may be administered as needed but must be discontinued at least 24 hours before each Lutathera treatment. Currently, the prescribing information states that following Lutathera treatment long-acting octreotide 30 mg intramuscularly should be given every 4 weeks until disease progression or for up to 18 months following the commencement of Lutathera. The treating physician should be familiar with the prescribing information...
accompanying the Lutathera medication as information is subject to change by the manufacturer.

Additional prescribing information includes pre-medication with antiemetics and the use of a specialized amino acid infusion to significantly reduce the dose of radiation to the kidneys. Details of the time and method of administration, components, volume, and osmolarity may be found in the manufacturer’s prescribing information. The manufacturer has cautioned that this infusion should not be changed if the dose of Lutathera is reduced.

The FDA approval for the use of Lutathera is based on the results of two published studies. NETTER 1 compared treatment with Lutathera to octreotide in patients with inoperable, progressive somatostatin receptor-positive midgut carcinoid tumors. Eligibility included a Ki67 index of 20% or lower, OctreoScan uptake greater than or equal to that of the normal liver, creatinine clearance of 50 mL/min or greater, no prior treatment with Peptide Receptor Radionuclide Therapy (PRRT), and no prior external radiation therapy to more than 25% of the bone marrow. The primary outcome was progression free survival (PFS). A total of 229 patients were randomized to Lutathera 200 mCi for four infusions every 8 weeks concurrently with long-acting octreotide (30 mg) or high-dose octreotide alone (60 mg). Baseline characteristics were balanced between the groups. It was noted that 74% of patients had an ileal primary and 96% had metastatic disease in the liver.

At the data-cutoff date for the primary analysis, PFS at 20 months was 65.2% in the 177-Lu arm vs. 10.8% in the control group. The response rate was 18% in the 177-Lu group vs. 3% in the control group. In an updated analysis, progressive disease was seen in 23% of the 177-Lu group and 69% of the control group. Median PFS was not reached for the experimental group and was 8.5 months for the control group. Median overall survival (OS) was also not reached in the experimental group and was 27.4 months in the control arm.

The ERASMUS study included 1214 patients who received Lutathera, 610 of whom were treated with a cumulative dose of at least 100 mCi for safety analysis. Another subgroup of 443 Dutch patients were treated with a cumulative dose of at least 600 mCi. The objective response rate (ORR) of the combined group was 39%. Stable disease was seen in 43%. PFS was 29 months. OS was 63 months. The group included not only gastrointestinal tumors but also pancreatic and bronchial neuroendocrine tumors. Toxicity included acute leukemia in 0.7% and myelodysplastic syndrome in 1.5%.
References
Radioimmunotherapy with Zevalin®

POLICY

I. Indications

A. Radioimmunotherapy (RIT) with Zevalin® is considered 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

Key Clinical Points

I. Agent

Currently, there is one Food and Drug Association (FDA) approved RIT agent in the United States (US), ⁹⁰Y ibritumomab tiuxetan (Zevalin®). Tositumomab (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 ⁹⁰Y, a pure β-particle emitter with a physical half-life of 2.7 days. The β-particle has an energy of 2.3 mega electronvolts (MeV) and a maximum tissue penetration of approximately 12.0 mm (R₉₀ = 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 ⁹⁰Y 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 (¹¹¹In) 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 ≥ 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) ≥ 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 ([Buchegger 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 one 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/m\(^2\) weekly for 4 doses (n = 70). The RIT group was pre-treated with 2 rituximab doses (250 mg/m\(^2\)) to improve biodistribution and tumor targeting. After the first rituximab dose on day 1, \(^{111}\)In 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
tears, 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 8-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 an individual already receiving
chemoimmunotherapy. The role in the frontline setting is under investigation.

National Comprehensive Cancer Guidelines (NCCN) Guidelines® (Follicular
Lymphoma [grade 1-2], FOLL-B 1of 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 radioimmunoconjunctives as single-agent therapy for the management of previously untreated disease

Nonrandomized trials support use of radioimmunoconjunctives 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 2 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 three 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) includes conventional chemotherapy with immunotherapy (e.g.-CHOP), RIT, and high-dose therapy followed by autologous HCT. An individual who is not candidates 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 +/- RT.

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 radionuclide. 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.

F. 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.

G. 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 +/- RT

III. 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

IV. Investigational
A. Newly diagnosed (consolidation after chemoimmunotherapy)
   1. It is not known whether the addition of RIT improves outcome of 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

References:
3. Tositumomab and Iodine I 131 Tositumomab (Bexxar™) Discontinuation.


44. Practice Guidelines in Oncology (NCCN Guidelines™) for Non-Hodgkin's Lymphomas Version 1.2019. 2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations


72. Zevalin® (ibritumomab tiuxetan) FDA Label

73. Zevalin® FDA Supplement Approval

Selective Internal Radiation Therapy (SIRT)

POLICY

I. Indications

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 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 is considered medically necessary 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 25 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.

Key Clinical Points

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.

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. \(^{99m}\text{Tc}\)-Technetium-Albumin Macroaggregates (\(^{99m}\text{Tc}\)-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 \(^{99m}\text{Tc}\)-MAA is delivered with flow rates and catheter position that mimic the anticipated \(^{90}\text{Y}\) infusion rate catheter position
   D. \(^{99m}\text{Tc}\)-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 used 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): Tsai et al. (2010) 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 EIU. Results from the Phase III SIRFLOX trial (van Hazel, 2016) showed no difference in PFS. A prolonged liver response was demonstrated in the FOLFOX/Y-90 arm 20.5 months vs. 12.6 months for chemotherapy alone. As data fail to show an impact on survival, current NCCN Guidelines™ recommend SIRT as an option in carefully selected chemotherapy-resistant or refractory disease in patients with predominant liver metastases.

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 between sessions 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:


