

Evidence Discussion (RO.RTS.106.A)

In 2017, the American Society for Radiation Oncology (ASTRO) updated the “Proton Beam Therapy Model Policy.” The model policy update was developed by ASTRO’s Payer Relations Subcommittee and states that the model policies were developed to “...communicate what ASTRO believes to be correct coverage policies for radiation oncology services.” It also states that the ASTRO model policies “...do not serve as clinical guidelines...” and are “...recommendations for medical insurance coverage.” These recommendations together with a review of the published evidence and guidelines were used to develop coverage criteria.

Group 1

I. Chordomas and chondrosarcomas of the skull base

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

II. Uveal melanoma

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

Nag et al (2003) published The American Brachytherapy Society recommendations for the use of brachytherapy in individuals with uveal melanomas. The American Brachytherapy Society recommends that individuals with very small uveal melanomas (< 2.5 mm height and < 10 mm in largest basal dimension) undergo observation and treatment be reserved for tumor growth. Brachytherapy is suitable for individuals with medium size choroidal melanoma (between 2.5 and 10 mm in height and < 16 mm basal diameter). Individuals with gross extrascleral extension, ring melanoma, and tumor involvement of more than half of the ciliary body are considered not suitable for plaque brachytherapy.

III. Sinus Tumors

National Comprehensive Cancer Network (NCCN®) Guidelines® recommends either IMRT or proton therapy for maxillary sinus or paranasal/ethmoid sinus tumors.

IV. Hepatocellular carcinoma (HCC)

In HCC, proton beam treatment plays a role in unresectable cancers. PBT for HCC is a technology which, according to the National Comprehensive Cancer Network (NCCN®) Guidelines®, may have a role in certain clinical circumstances. The unique dosimetric advantages of heavy charged particle radiation (Bragg Peak) offer significant potential advantages in sparing hepatic parenchyma compared to traditional photon techniques. This theoretical advantage is still the object of on-going studies in this country. A multi-institutional phase II study (Hong et al, 2016) demonstrated a 2-year HCC local control rate of 94.8%. Treatment was given with a hypofractionated regimen of 67.5 Gy equivalent in 15 fractions to a patient population that included previously treated patients and those with tumor vascular thrombosis. On-going phase III studies are in progress. However, a meta-analysis of 70 studies demonstrated a decided advantage of charged particle treatment as compared to traditional radiation but found no difference when comparing charged particle treatment to stereotactic body radiation therapy (SBRT).

The larger PBT series are from Japan suggesting excellent local control rates and modest 2- to 5-year survival rates. Four retrospective (360 patients) and 2 prospective studies (64 patients) of hypofractionated PBT in patients with hepatocellular cancer show results similar to those achieved with SBRT. (Fukumitsu et al, 2009; Hashimoto et al, 2006; Hata et al, 2005; Hata et al, 2006; Hsiung-Stripp et al, 2001; Koyama et al, 2003; Kozak et al, 2007; Macdonald et al, 2001; Sugahara et al, 2005; Sugahara et al, 2010; Zhang et al, 2008; Zurlo et al, 2000).

In HCC, proton beam treatment may play a role in unresectable cancers that are not amenable to other forms of treatment including:

A. Ablative techniques (radiofrequency, cryosurgery, alcohol injection, microwave)

Several ablative techniques have been used both in the operable and definitive setting. For select lesions, generally under 3 cm in size that are well localized, definitive treatment may be considered. Contraindications to ablation include lack of anatomic accessibility, size, number, and location near abdominal organs, major ducts, and blood vessels. A complication reported with ablation is the development of tumor rupture with lesions located on the hepatic capsule or tumor seeding along the track with subcapsular and poorly differentiated lesions. Local control rates in the range of 90% at 2 years have been reported for ablative techniques.

B. Arterial treatments (selective internal radiation therapy [SIRT], also known as transarterial radioembolization [TARE]; transarterial chemoembolization [TACE]; or transarterial embolization [TAE])

These techniques require selective catheterization of the hepatic arterial supply to the tumor-involved liver segments. As HCC is a hypervascular tumor, there is preferential blood flow as compared to the normal hepatic parenchyma. Indications for these procedures include multiple tumors, generally 4 or more in number, lesions greater than 3 to 5 cm, lesions without vascular invasion or extra-hepatic spread. Absolute contraindications include decompensated cirrhosis, jaundice, clinical encephalopathy, refractory ascites, hepatorenal syndrome, extensive tumor replacement of both lobes, portal vein occlusion or severely reduced flow, hepatofugal flow and renal insufficiency. Relative contraindications include tumor size greater than 10 cm, severe cardiovascular or pulmonary disease, varices at high

risk of bleeding or bile duct occlusion. In clinical trials TACE appears superior to TAE. SIRT/TARE provide high doses of radiation to tumor capillary beds. Yttrium-90 beta radiation, delivered by SIR-Spheres®-or TheraSphere®- labeled microspheres, delivers preferential high doses of radiation and tends to spare normal hepatic tissues. Full discussion of the indications and contraindications to SIRT/TARE may be found in the Selective Internal Radiation Therapy (SIRT) clinical guideline.

In addition to the contraindications listed above, all arterial therapies must take into account their effect on liver function as embolic-, chemo-, or radiation-liver disease or dysfunction can result in severe morbidity or death. Bilirubin greater than 3 mg/dl for TACE/TAE and 2 mg/dl for SIRT/TARE are considered strong relative contraindications unless segmental treatment is being performed.

C. External beam radiation therapy (EBRT) (intensity-modulated radiation- therapy [IMRT], three-dimensional conformal radiation therapy [3DCRT], and SBRT)

Conformal radiation techniques such as 3DCRT generally have played a palliative role in the treatment of HCC. Yet, HCC is a radiosensitive tumor and highly conformal external beam techniques such as IMRT or 3DCRT should be considered in a definitive manner in inoperable tumors not amenable to other treatments. Great care must be given in considering the individual's liver function, Hepatitis B carrier status, prior transarterial or other treatments, portal vein thrombosis, and Childs-Pugh score. A dose volume constraint to be considered is for the mean liver dose (liver minus gross tumor volume) to be less or equal to 28 Gy in 2 Gy fractions. The University of Michigan has demonstrated that tumoricidal doses from 40 Gy to 90 Gy delivered in 1.5 Gy twice daily treatments along with hepatic-infused chemotherapy could result in a 1-year local control rate of 81% and survival rate of 57% in an individual who was unresectable and without portal vein thrombosis. Studies for conformal RT and TACE have also been done in Asia showing improved survival for the combination.

SBRT is considered the mainstay of the radiation effort to control inoperable HCC. Current indications for the use of SBRT include 3 or fewer tumors without evidence of vascular or organ invasion and away from hollow organs, such as the bowel or stomach, as perforation and hemorrhage are significant complications. Sufficient hepatic reserve as evidenced by a Childs-Pugh A score is extremely important as safety data are considered limited in Childs- Pugh B or those with poor liver reserve. Some controversy has existed over the size of eligible lesions with initial restriction to lesions of up to 5 cm now being expanded to larger lesions. RTOG 1112 eligibility criteria include up to 5 lesions with no 1 lesion exceeding 15 cm, with a total maximum sum of all lesions not exceeding 20 cm. Current optimal dose recommendations are 50 Gy in 5 treatment fractions with a mean liver dose of 13.0 Gy and an additional organ constraint of liver $V_{eff} < 25\%$. If these constraints are not met, dose reductions from this optimal dose down to 30 Gy for a mean lung dose (MLD) of 16 Gy are recommended. Optimal and acceptable dose volume constraints to critical organs may be found in the NRG Oncology GI003: A Phase III Randomized Trial of Protons Versus Photons for Hepatocellular Carcinoma.

SBRT has proven itself both as effective bridge therapy 1) for an individual with HCC and cirrhosis prior to transplant and 2) in an individual who is inoperable, both as an initial treatment and for an individual who is ineligible or incompletely treated by other methods. Excellent local control rates at 1- to 2- years ranging from 70 to 90% have been reported on initially treated patients and a 61% 2-year survival rate has been

reported in patients previously treated with TACE.

D. PBT

PBT for HCC is an emerging technology which, according to the NCCN Guidelines®, may have a role in certain clinical circumstances. The unique dosimetric advantages of heavy charged particle radiation (Bragg Peak) offer significant potential advantages in sparing hepatic parenchyma compared to traditional photon techniques. This theoretical advantage is still the object of on-going studies in this country. A multi-institutional phase II study (Hong et al, 2016) demonstrated a 2-year HCC local control rate of 94.8%. Treatment was given with a hypofractionated regimen of 67.5 Gy equivalent in 15 fractions to a patient population that included previously treated patients and those with tumor vascular thrombosis. On-going phase III studies are in progress. However, a meta-analysis of 70 studies demonstrated a decided advantage of charged particle treatment as compared to traditional radiation but found no difference when comparing charged particle treatment to SBRT.

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NRG Oncology GI003: A Phase III Randomized Trial of Protons Versus Photons for Hepatocellular Carcinoma provided radiographic size criteria that allow for use of photon based therapy (3DCRT, IMRT, or SBRT) and proton beam therapy for treatment of hepatocellular carcinoma. Per the protocol, for individuals with a single lesion, the lesion can be 15 cm or less in greatest dimension. For individuals with two lesions, no lesion can be greater than 10 cm in greatest dimension. For individuals with three lesions, no lesion can be greater than 6 cm in greatest dimension. Portal vein involvement or thrombosis combined with a single lesion that is ≥ 1 cm and ≤ 15 cm in greatest dimension is allowed. In an individual with HCC who is not acceptably treated with 3DCRT, IMRT, ablative, transarterial or SBRT techniques in the curative setting, PBT is considered medically necessary.

V. Seminoma

The risks of radiation-induced second malignancy in seminoma are well documented. The current NCCN Guidelines® continue to mention the increased risk of second cancers arising in the stomach, kidney, liver, and bowels in patients treated with radiation therapy. They caution against the use of IMRT in the treatment of seminoma as the radiation doses to these organs (integral dose) is increased compared to 3DCRT fields used in anterior and posterior fashion. However, it must be recognized that use of anterior/posterior fields whether 2D or 3D are the very technique which has been the subject of these reports. IMRT might theoretically make it worse.

A brief review of the literature outlines the risk. Lewinshtein et al (2012) used Surveillance, Epidemiology, and End Results Program (SEER) data between 1973 and 2000. They found a 19% increase in secondary primary malignancies in

seminoma patients exposed to radiation therapy as compared to the general population including pancreas, non-bladder urothelial, bladder, thyroid, and others. The risk lasted 15 years from the time of initial diagnosis. An accompanying editorial in the journal noted an increased incidence of seminoma during the last 4 decades with improved survival, which makes the issue of radiation-induced malignancies of increasing concern. Indeed, the NCCN® noted that the routine use of adjuvant therapy for stage I seminoma is not warranted as the risk of recurrence is low compared to the potential harms of adjuvant therapy.

Travis et al, reported twice on this issue- in 1997 and 2005. They identified risks of lung, bladder, pancreas, stomach, and other organs, noting that secondary primary cancers are a leading cause of death in men with a history of testicular cancer. The risk may extend as long as 35 years. Patients treated with radiation therapy had the highest risk of developing cancer especially when treated at a young age. Among organs treated in a radiation field, the stomach, large bowel, pancreas, and bladder stood out for the development of a later cancer.

Given these findings, radiation is no longer used in early seminoma, but there remains a population of patients with more advanced disease that may benefit. Although this population of patients is relatively small as 80% of seminoma, totaling approximately 8600 cases a year, is diagnosed in stage I, the relative doses of radiation and increased field sizes pose a problem. Dose modeling by Mazonakis et al, published in 2015, showed that medically necessary abdominopelvic irradiation increased the risk for induction of secondary malignancies by as much as 3.9%.

The use of protons brings a distinct advantage in lowering radiation dose to the population at risk. Simone II, et al, writing in the International Journal of Radiation Oncology Biology Physics in 2012, showed that proton plans could reduce mean doses to the stomach to 119 cGy vs. 768 cGy for photons as well as having meaningful reductions in doses to bladder and pancreas with a subsequent theoretical expected decrease in cancers.

Based on the above information documenting a higher risk of secondary malignancy unique to seminoma, the use of PBT is considered medically necessary.

Group 2

I. High-grade gliomas

Mizumoto et al (2015) published their results of using PBT in the treatment of a glioblastoma multiforme (GBM). In this study, 23 patients were treated postoperatively with standard photons to a dose of 50.4 Gy with a concurrent boost of 46.2 GyE using PBT. The 1- and 2-year survival was 78% and 43% respectively. Median survival was 21 months. It is noted that 6 patients developed radiation necrosis (who all survived at least 4 years without evidence of recurrence, but in whom the performance status had declined by 10% to 30%). The authors conclude that the studied regimen "...has a high potential to improve survival in GBM patients..." and that "...although radiation necrosis is inevitable in the treated area, it may be controllable with necrotomy and bevacizumab administration." At the present time, the results of this study cannot be used to support PBT as the dose used is significantly higher than what is considered a standard of care (ie, 66 Gy), and the rate of symptomatic brain necrosis is higher than with customary doses and techniques. Further, this study utilized both photons and protons.

In a retrospective dosimetric study of 12 patients with high-grade gliomas (HGGs) treated with intensity-modulated proton therapy (IMPT) and compared to volumetric-

modulated arc therapy (VMAT) and 3D conformal radiotherapy (3DCRT), Adeberg et al (2016) found that "...target coverage was comparable for all three modalities..." with the use of PBT resulting in "...significant reductions...in mean dose to the whole brain;...supratentorial...and infratentorial regions; brainstem;... pituitary gland;...contralateral hippocampus; and contralateral subventricular zone." The authors further state that "...this can potentially reduce the dose- and volume-related side effects of treatment..." However, no evidence of reduction in side effects has been demonstrated.

In an abstract, Ramakrishna et al (2016) developed passive scatter proton beam therapy plans for 19 patients recently treated with IMRT. The authors demonstrated similar target coverage using protons compared to IMRT and not unexpectedly, a lower mean V5, V10, V12 and V20 for uninvolved brain. Further, PBT resulted in lower mean hippocampal V5 and V10 relative to IMRT. The authors, however, conclude that "The overall potential clinical benefit of these dosimetric advantages in glioblastoma patients remains to be determined."

While studies have demonstrated that PBT is an acceptable form of treatment for GBM, analysis of the effectiveness of PBT compared to IMRT is needed. Additional information is awaited from ongoing studies such as the randomized phase II trial, NCT01854554, Glioblastoma Multiforme (GBM) Proton vs. Intensity Modulated Radiotherapy (IMRT) as well as NRG BN001.

II. Low-grade gliomas

There are a limited number of dosimetric studies that demonstrate the different dose distributions and doses to normal tissue structures with protons compared to 3DCRT or IMRT. Dosimetric results have predictably shown a dose reduction to nearby organs at risk (OARs), particularly those farther away from the target, primarily in the lower dose ranges. Dennis et al (2013) estimated doses in 11 patients and found that the equivalent uniform dose was 10 to 20 Gy lower with protons, but the estimated risk of toxicity using normal tissue complication probability modeling showed only negligible differences, with low risk of toxicity with both modalities. Harrabi et al (2016) evaluated doses with protons compared to 3DCRT (and not the more conformal technique, IMRT) in 74 patients and found expected reduction in mean dose to other structures and integral dose. They concluded that the dose distribution of PBT is significantly superior when compared to conventional radiotherapy, but also stated that to what extent this will have a clinical impact remains to be proven by long-term observations. The reduction in the volume of tissue receiving low doses of radiation has not clearly been associated with improved clinical outcomes.

Studies showing the clinical outcomes with PBT for low-grade glioma are mostly single institution series with relatively small numbers of patients. For example, Shih et al (2015) reported outcomes in 20 patients treated with 54 Gy of PBT for low-grade glioma. There was no evidence of decline in neurocognitive function or quality of life (QOL), but 30% of patients had endocrine dysfunction. With median follow-up of 5.1 years, the 3 year progression free survival (PFS) was 85% and 5 year PFS was only 40%. This study had notable limitations, including a relatively heterogeneous cohort comprised of both primary (n = 8) and recurrent (n = 12) LGGs, as well as patients with prior symptomatology leading to PBT initiation (thus, a potentially altered baseline). Patients that progressed were also removed from the study, and QOL for those patients was not included.

Other studies reporting clinical outcomes are difficult to interpret due to heterogeneous patient groups, often including a mixture of pediatric and adult patients, low- and high-

grade glioma, and both initial treatment and re-treatment patients. Greenberger et al (2014) published clinical outcomes for 32 pediatric patients and reported no significant declines in Full-Scale Intelligence Quotient and an 82.8% 8 year PFS rate. The applicability of this experience to adult patients is uncertain.

Hauswald et al (2012) published results from 19 patients, with progression after prior biopsy, resection or chemotherapy, delivering a median dose of 54 GyE. With 5-month median follow-up, 12 patients had stable disease, 2 had partial or complete remission, 1 had progression and 2 had “pseudo-progression”. This study had limitations of a heterogeneous patient group and short follow-up.

Wilkinson et al (2016) reported, in abstract form only, the largest study to date, a retrospective analysis of 58 patients from the Proton Collaborative Group registry, and illustrated no grade ≥ 3 toxicities when treated with up to 54 Gy relative biological effectiveness (RBE) (this abstract did not report other clinical outcomes).

Current NCCN Guidelines® for Central Nervous System Cancers do not mention or recommend use of PBT for treatment of low-grade glioma.

While dosimetric studies suggest the potential for a benefit of proton beam therapy in the treatment of low-grade glioma, the published studies of PBT in low-grade glioma do not offer comparisons of clinical outcomes compared to customary photon based treatment. Studies to evaluate any benefit of proton beam therapy are ongoing, including a phase II trial, NCT01358058, Proton Radiation Therapy for Gliomas, and another phase II trial NCT01024907, Proton Beam Radiation Therapy in Treating Patients with Low Grade Gliomas.

III. Esophageal cancer

There have been several dosimetric studies comparing dose distributions in a limited number of patients, using PBT or customary photon based techniques (Isacsson et al, 1998; Makishima et al, 2015; Zhang et al, 2008). These have shown reduction in low dose radiation distribution to some structures, such as heart and lung, and increased radiation dose to other structures, such as spinal cord and skin (Funk et al, 2015). Such studies suffer from the biases and talents of the investigators who plan and create computer models of dose deposition for one therapy or the other, and also do not present any clinical outcome data to show outcomes with PBT or to compare outcomes to customary photon-based techniques.

Reported clinical experiences for PBT have generally been limited to single- institution studies. Ishikawa et al (2015) treated 40 patients with 60 to 64 Gy equivalent and concurrent chemotherapy. There were no grade 3 or greater toxicities and 2 year disease-free survival (DFS) was 77% and 3 year overall survival (OS) was 70%. Lin et al (2012) reported outcomes for 62 patients with esophageal adenocarcinoma, treated with 50.4 Gy equivalent and surgery in almost half of the patients. Grade 3 toxicity was noted in $< 10\%$ of patients and there was pathologic complete response (CR) in 28% of patients having surgery. The 3-year overall, relapse-free, distant metastasis-free, and locoregional-free survival rates were 51.7%, 40.5%, 66.7%, and 56.5%, respectively. Prayongrat et al (2017) describe 19 patients with esophageal cancer treated with intensity- modulated proton therapy (IMPT) to 50.4 GyE between 2011 and 2016. The initial cohort was 32 patients with mostly unresectable cancer treated with definitive chemoradiation, but 13 were excluded for multiple reasons. The median follow-up was 17 months. Seven of the 19 had disease failure (3 locoregional). Acute toxicities included grade 3 esophagitis, nausea and vomiting, fatigue and

anorexia, and hematologic. Late toxicity included 1 each of grade 3 pleural effusion and an esophageal stricture. Late toxicities could not be fully evaluated because of short follow-up.

In a single institution, randomized phase IIB trial of proton beam therapy (PBT) versus Intensity Modulated Radiation Therapy (IMRT) for locally advanced esophageal cancer, Lin et al (2020) randomly assigned patients with stage II-III esophageal cancer eligible for chemoradiation therapy to PBT (73 patients assigned, but 46 evaluable) or IMRT (74 patients assigned, but 61 evaluable) to 50.4 Gy. The prespecified endpoints were total toxicity burden (TTB) and progression free survival (PFS) between these modalities. TTB encompassed multiple adverse events including asymptomatic pleural effusion, atrial fibrillation, and symptomatic pleural effusion. The trial was closed when there was a significant difference in the TTB between the 2 arms. The posterior mean TTB was 2.3 times higher for IMRT than PBT. When evaluating the surgical population, the mean post op complication (POC) score was 7.6 times higher for IMRT. The 3 year progression free survival rate (50.8% vs 51.2%) and 3 year overall survival rates (44.5% vs 44.5%) were similar. There was no significant difference in the quality of life (QOL) evaluation between the arms during or after the RT, or after adjusting for age/comorbidities and receipt of surgery and no difference in the degree of QOL decline from baseline. The authors conclude that PBT reduced the risk and severity of adverse events compared with IMRT. However, TTB is not a validated endpoint. Additionally, the study is further limited by its small sample sizes and by being a single institution experience which requires validation in a larger cooperative group.

A. Neoadjuvant treatment

Wang et al (2013) reported a retrospective review of patients treated with different radiation techniques prior to surgery for esophageal cancer, either 3DCRT, IMRT or PBT in 444 patients over 13 years. Protons were used in 72 patients. It should be noted that this was not a randomized study and treatment eras as well as clinical factors were not the same for the different groups. They found that 3D technique was associated with a statistically significant increase in risk of pulmonary toxicity compared to IMRT or protons. There was a non-significant trend towards higher pulmonary toxicity risk with IMRT compared to protons.

Lin et al (2017) retrospectively reviewed 580 esophageal cancer patients treated between 2007 and 2013 using 3DCRT, IMRT, or PBT modalities at 3 academic institutions (all proton beam was apparently done at MD Anderson Cancer Center). All patients had initially non-metastatic cancer treated with neoadjuvant concurrent chemoradiotherapy and surgical resection. Total radiation dose was 50.4 Gy. Lower post-operative complications were noted with protons compared to IMRT in terms of pulmonary and wound complications. Average length of stay was lower for protons as was 90 day mortality (0.9% with PBT vs. 4.2% with 3D and 4.3% with IMRT). The conclusion of the study was that the "...data provide meaningful new evidence that supports the potential clinical benefit of PBT in the treatment of esophageal cancer." This study was not a randomized comparison, and there is potential for important differences between the treatment groups.

This data suggests that for resectable esophageal cancers, patients treated with neoadjuvant chemoradiation are likely to do as well treated with proton beam as they would with IMRT. The authors suggest that proton beam may decrease acute toxicities and improve survival, but admit that additional studies including the

ongoing randomized trial (NCT01512589) are needed to confirm this.

B. Definitive treatment

Xi et al (2017) stated in their recent publication that "...the long-term clinical outcome of PBT over IMRT has never been well addressed, especially for the subset of patients receiving definitive CRT." In this retrospective review, Xi et al (2017) report on 343 patients who received either IMRT or PBT as part of definitive chemoradiation. In a dosimetric analysis of 308 of these patients, the use of PBT resulted in lower average doses to the heart and lung as well as significantly lower pulmonary V5, V10 and V20. PBT also led to a significant reduction in cardiac V30 but no improvement in the V40. These dosimetric differences did not translate into reduction in toxicity. In terms of grade 3, 4 and 5 toxicity, there were no significant differences between the 2 modalities.

At a median follow-up of 65.1 months for the IMRT group and 44.8 months for the PBT group, PBT was associated with a significantly lower distant recurrence rate whereas the locoregional recurrence rate was not statistically improved. At 5 years, PBT was associated with a significantly higher overall survival rate (41.6% vs. 31.6%). The authors note that "...more patients in the IMRT group developed early distant recurrence before surgery than in the PBT group (25.2% vs. 18.2%), which may have resulted in biased survival results." Thus, additional analyses were conducted including 1 by stage of disease. This revealed that for stage I-II disease, there was no benefit to PBT. However, for stage III disease, PBT was associated with a significantly higher 5-year OS and progression free survival (PFS).

Why proton beam therapy improved survival in the locally advanced stages is not clear. The primary advantage of PBT over IMRT is the ability to reduce the integral dose to nearby structures. The dose delivered to the target is equivalent and therefore should result in equivalent control rates. The authors acknowledge that "...it is difficult to fully account for all possible reasons why the PBT had more favorable survival...". Though "PBT might have contributed to the reduction in cardiopulmonary mortality in the PBT group, we do not have direct proof that this is in fact true because many of the deaths are due to unknown causes." Other considerations were made but ultimately the authors conclude that the "...results from the present study suggest that the theoretical advantage of PBT over IMRT might convert into survival benefit. Prospective controlled studies will better establish the role of PBT in EC."

C. Other considerations

The dose distribution using PBT is affected to a much greater extent by changes in tissue density than photon radiation therapy. As a result, there is concern about using PBT in the presence of significant target motion. This especially pertains to targets in the thorax and upper abdomen, including the distal esophagus that move as a result of diaphragmatic excursion (Mori and Chen, 2008; Mori et al, 2008). Because the diaphragm moves during respiration, this results in changes to the tissues in the beam path, which can cause significant interplay effects and dose uncertainty. This could result in unanticipated overdose of normal tissues or under dose of target volumes. Therefore, direct comparative studies will be helpful to determine the relative safety and efficacy of protons relative to customary photon radiation.

The results from the previously mentioned single-institution experiences of

esophageal PBT suggest the potential for improved clinical outcomes compared to customary photon treatments. Prospective trials comparing PBT with standard photon technologies like 3DCRT or IMRT will be necessary to provide high-quality evidence demonstrating the value of PBT. There are currently active clinical trials in the United States evaluating the role of PBT for esophageal cancer including an accruing randomized trial from MD Anderson Cancer Center that began in the spring of 2012 (NCT01512589) ("Phase IIB Randomized Trial of PBT versus IMRT for the Treatment of Esophageal Cancer").

IV. Breast cancer

To determine "...the feasibility of using proton radiation for the treatment of invasive breast cancer after mastectomy," MacDonald et al (2013) reported the toxicity outcomes of 12 patients, 5 of which had permanent implants in place. Eleven of the patients were also treated to the internal mammary lymph nodes (IMNs). Skin toxicity, fatigue and radiation pneumonitis were evaluated during radiation and at 4 and 8 weeks after completing radiation. The authors found that "...proton treatment was well tolerated..." with "...skin reactions (that) were mostly superficial and often with moderate to severe erythema and moderate to large areas of dry superficial desquamation." This is not uncommon as "...the entrance dose is higher for proton radiation, leading to some concern regarding skin tolerance." However, "...cosmesis at 4 and 8 weeks was favorable, inasmuch as most patients had only mild erythema or hyperpigmentation..." The authors conclude that "...proton radiation for PMRT is feasible, with acceptable early toxicity. Additional follow up is needed to assess late complications and outcomes of proton RT."

Cuaron et al (2015) retrospectively reported toxicity outcomes of 30 patients treated with proton beam therapy in the postmastectomy and postlumpectomy setting from 2013 to 2014. It is noted that the internal mammary nodes were treated in 28 patients. The authors found that 20 patients experienced grade 2 dermatitis with 8 experiencing moist desquamation which "...compares favorably to rates seen with both IMRT photons and conventional electrons..." Seven patients experienced skin pain and 8 developed grade 2 esophagitis. There were no cases of lung toxicity or cardiac toxicity. Lastly, 1 patient developed a grade 3 complication of the implant requiring removal. The authors note that "...with uniform scanning proton therapy there is 100% dose at the skin..." which "... warrants further study, because there are also long-term concerns associated with high surface doses to patients with implants." In addition, the esophagitis rate of "...33% in the current series is presumed to be higher than what would be expected with conventional techniques." The authors conclude that "...further study is needed to accurately select which patients stand to benefit from proton therapy for breast cancer."

In a prospective clinical study, Bradley et al (2016) reported on 18 women receiving proton beam therapy between 2012 and 2014. It is noted that radiation included treatment to the IMNs. The authors found that proton beam "... consistently resulted in decreased heart and lung dose for all patients..." With a median follow-up of 20 months, 22% of patients developed grade 3 dermatitis with the remaining patients experiencing grade 2 dermatitis which the authors state "... is not unexpected given the higher skin dose with a proton beam compared with a photon beam." In addition, 5 patients developed grade 2 esophagitis. The authors conclude that proton beam therapy is "...tolerated without excessive acute toxicity."

Verma et al (2017) recently published their results of acute toxicity in 91 patients treated with adjuvant proton beam therapy between 2011 and 2016. Treatment was

directed to the breast or chest wall as well as the regional lymph nodes including the IMNs. The authors reported grade 2 and 3 acute dermatitis in 72% and 5% respectively with 21% requiring opioids for pain control and 8% requiring a treatment break. Seven patients developed a skin infection requiring antibiotics, 1 of which resulted in nonlethal sepsis. Another patient developed a non-healing wound requiring closure with a latissimus flap. The authors state that the skin toxicity is comparable to prior data though they add that “US (Uniform Scanning) technique does not allow for any skin-sparing with radiation dose and also results in relatively more heterogeneity (i.e., larger-sized hotspots of higher magnitude) than what is typically accepted with photon plans.” Additional results also revealed that 33% of patients developed grade 2 esophagitis with 31% experiencing grade 1 esophagitis. Finally, at a median follow-up of 15.5 months, 4 patients developed locoregional relapse. The authors conclude that protons “...appears to have appropriate toxicity...” though “...further data with longer follow-up are greatly needed.”

To this end, the ASTRO Model Policy on Proton Beam Therapy states that “... there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT for various disease sites” including breast cancer.

Studies to evaluate any benefit of proton beam therapy are ongoing. For example, a phase III trial (NCT0260334 Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer Receiving Comprehensive Nodal Radiation: A Radiotherapy Comparative Effectiveness [RADCOMP] Trial) is currently recruiting patients. This study will help determine the benefit of proton beam therapy in the treatment of breast cancer in patients receiving comprehensive nodal radiation.

V. Prostate cancer

Comparative effectiveness studies have been published comparing toxicity and oncologic outcomes between proton and photon therapies and have reported similar early toxicity rates.

For example, Yu et al (2013) reviewed Medicare data for patients treated with protons or IMRT (> 27,000 patients in each group) and found that although proton radiation therapy (PRT) “...was associated with a statistically significant reduction in genitourinary toxicity at 6 months compared with IMRT (5.9% vs. 9.5%; odds ratio [OR] = 0.60, 95% confidence interval [CI] = 0.38 to 0.96, $p = .03$), at 12 months post-treatment there was no difference in genitourinary toxicity (18.8% vs. 17.5%; OR = 1.08, 95% CI = 0.76 to 1.54, $p = .66$). There was no statistically significant difference in gastrointestinal or other toxicity at 6 months or 12 months post-treatment.” They concluded that when comparing protons to IMRT “...there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment.”

Hoppe et al (2014) reported a prospective quality-of-life (QOL) comparison of patient-reported outcomes between IMRT (204 patients) and proton therapy (1234 patients). This was not a randomized study, but a single institution series compared to a population of patients from a different multi-institutional study using IMRT, with potentially significant differences in the compared groups (different treatment eras, uncontrolled use of androgen deprivation therapy, larger prostate volumes for IMRT patients, older age for IMRT patients, and superior baseline function in proton group). Even though some of these differences, such as older patients, more androgen deprivation and larger prostate volumes for IMRT patients, would be expected to result

in higher rates of adverse symptoms for the IMRT group, "...no differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts..." after up to 2 years of follow-up. The conclusion of this study states "The findings from this study provide evidence of excellent and comparable QOL outcomes for prostate cancer patients treated with either contemporary IMRT or PT."

A similar comparison of patient-reported outcomes between a single institution series of 95 patients treated with PBT with 153 IMRT patients in a multi-institutional study and 123 patients treated with 3D techniques was reported by Gray et al (2013). In the immediate post-treatment period, patients in the IMRT cohort reported clinically meaningful decrements in QOL in the urinary irritation/obstruction and urinary incontinence domains that were not observed in the other 2 cohorts. At 12 months, only patients in the PBT cohort reported clinically meaningful score decrements in the urinary irritation/obstruction domain. At 24 months, clinically meaningful changes in urinary QOL were not observed in any of the cohorts. The authors concluded that PBT resulted in patient-reported outcome declines similar to those with photon-based modalities.

Fang et al (2015) published a study of case-matched patients treated with protons (n = 181) or IMRT (n = 213), and reported "...the risks of acute and late GI/GU toxicities did not differ significantly after adjustment for confounders and predictive factors."

A review of Medicare data by Kim et al (2011) for 337 patients treated with protons and 4645 patients treated with IMRT evaluated the rate of GI toxicities requiring interventional procedures occurring at least 6 months after cancer diagnosis. This was 20.1 events per 1000-person years for the proton group, compared to 8.9 events for IMRT and 2.1 events for patients who did not receive radiation.

The largest retrospective comparative effectiveness analysis to date comparing IMRT to proton therapy was performed using SEER-Medicare claims data for the following long-term endpoints: gastrointestinal morbidity, urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, and hip fractures (Sheets et al, 2012). With follow-up as mature as 80 months, the authors concluded that men receiving IMRT therapy had statistically significantly lower gastrointestinal morbidity than patients receiving proton therapy, whereas rates of urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, hip fractures, and additional cancer therapies were statistically indistinguishable between the cohorts.

Considered as a whole, these studies do not show any significant benefit of proton beam therapy over IMRT for either treatment efficacy or long-term toxicity. A comprehensive review of 8 studies of PBT for prostate cancer with patient-reported outcomes (PRO) by Verma et al (2018) concluded "Prostate cancer is currently the focus of the greatest amount of QOL/PRO data; results for PBT analyzed here in are consistent with findings of retrospectively and prospectively collected data displaying no differences in toxicities between PBT and IMRT." There is no compelling evidence that clinical outcomes are superior for proton beam therapy and, therefore, no evidence that PBT is considered medically necessary for treatment of prostate cancer.

The primary dosimetric advantage of protons compared to IMRT is delivery of low or moderate doses of radiation to smaller volumes of tissue around the prostate, such as muscle, bone, vessels and fat that is not immediately adjacent to the prostate. These tissues do not routinely contribute to the morbidity of prostate radiation, are relatively resilient to radiation injury, and so the benefit of decreased dose to these

types of normal non-critical tissues has not been apparent. By contrast, the high dose region encompassing the prostate target and immediately adjacent tissues does not receive any less radiation using PBT and, in fact, may receive higher doses to a larger volume with protons due to the range and RBE uncertainty of protons and the need for a larger treatment volume to compensate for this uncertainty. Toxicity associated with prostate radiation is more closely associated with high dose exposure of normal tissues, > 50 Gy. Trofimov et al (2007) compared proton treatment plans using 2 opposed lateral beams to IMRT plans using 7 coplanar beams in 10 patients with early-stage prostate cancer. For a prescription dose of 79.2 Gy to the prostate, IMRT irradiated substantially greater volumes of normal tissue in the < 30 Gy RBE range, including both the bladder and the rectum. However, patients treated with PBT had significantly larger normal tissue exposure in the 50 to 75 Gy RBE range. The volume of bladder receiving 50 and 60 GyE was significantly higher with the proton plans, but no difference in rectal volume was noted at these doses. This may be one reason that the perceived dosimetric advantages of proton beam radiation have not translated into differences in toxicity or patient outcomes.

The NCCN® panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity.

The American Society of Radiation Oncology (ASTRO) has taken a clear position towards use of proton beam in the treatment of prostate cancer:

- A. ASTRO Model Medical Policy on Proton Beam Therapy (2017) evaluated proton therapy and created a model policy to support the society's position on payment coverage for proton therapy. ASTRO has stated in their Proton Beam Therapy Model Policy that "...in the treatment of prostate cancer, the use of PBT is evolving as the comparative efficacy evidence is still being developed. In order for an informed consensus on the role of PBT for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry."
- B. ASTRO Choosing Wisely (2013): "Don't routinely recommend proton beam therapy for prostate cancer outside of a prospective clinical trial or registry. There is no clear evidence that proton beam therapy for prostate cancer offers any clinical advantage over other forms of definitive radiation therapy. Clinical trials are necessary to establish a possible advantage of this expensive therapy."
- C. ASTRO Proton Beam Therapy for Prostate Cancer Position Statement (2013): At the present time, ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear. While proton beam therapy is not a new technology, its use in the treatment of prostate cancer is evolving. ASTRO strongly supports allowing for coverage with evidence development for patients treated on clinical trials or within prospective registries. ASTRO believes that collecting data in these settings is essential to informing consensus on the role of proton therapy for prostate cancer, especially insofar as it is important to understand how the effectiveness of proton therapy compares to other radiation therapy modalities such as IMRT and brachytherapy. An ongoing

prospective randomized trial is accruing patients to compare prostate proton therapy and prostate IMRT (PARTIQoL Trial/NCT01617161). Patients with low- and intermediate-risk prostate cancer are eligible. The primary measure of the study is to compare reduction in mean Expanded Prostate Cancer Index Composite (EPIC) bowel scores for PBT vs. IMRT treated patients at 24 months post radiation.

In addition to the above trial, there are at least 8 ongoing phase II-III trials investigating proton beam therapy in the treatment of prostate cancer:

- A. NCT01352429 A Phase II Trial of Proton Radiation Therapy or Intensity-Modulated Radiation Therapy Using Mild Hypofractionation for Low- and Intermediate-Risk Adenocarcinoma of the Prostate
- B. NCT02040610 A Phase II Study of Hypofractionated Image Guided Proton Therapy for Low and Intermediate Risk Prostate Cancer
- C. NCT01230866 A Phase III Prospective Randomized Trial of Standard-fractionation vs. Hypo-fractionation With Proton Radiation Therapy for Low Risk Adenocarcinoma of the Prostate
- D. NCT00831623 Phase I-II Trial of Hypofractionated Conformal Proton Beam Radiation Therapy for Favorable-risk Prostate Cancer
- E. NCT01950351 Phase II Trial of Hypofractionated Proton Beam Therapy in Men with Localized Prostate Adenocarcinoma
- F. NCT01045226 A Phase II Trial of Proton Radiation Therapy of Using Standard Fractionation for Low- and Low-Intermediate Risk Adenocarcinoma of the Prostate
- G. NCT01492972 Hypo-fractionated Radiation Therapy With or Without Androgen Suppression for Intermediate Risk Adenocarcinoma of the Prostate
- H. NCT02874014 Prospective Evaluation of Hypofractionation Proton Beam Therapy With Concurrent Treatment of the Prostate and Pelvic Nodes for Clinically Localized, High Risk or Unfavorable Intermediate Risk Prostate Cancer

VI. Head and neck cancers

A. Sinonasal and nasopharynx

Russo et al (2016) reported on 54 patients with newly diagnosed stage III-IV squamous cell carcinoma of the paranasal sinus or nasal cavity who were treated with proton beam therapy (passive scatter technique) between 1991 and 2008. Of the 54 patients, 37 (68.5%) had undergone surgical resection prior to receiving PBT, 18 of whom achieved a gross total resection (GTR). For patients achieving a GTR or partial resection, a median dose of 70.0 Gy relative biological effectiveness (RBE) was given (range of 59.4 to 79.4). For those undergoing a biopsy only, a median dose of 76 Gy RBE was delivered (range of 70 to 78.1). Forty patients also received elective nodal irradiation (utilizing photons for the low neck) to a median dose of 45 Gy RBE. Chemotherapy was given in 24 (44.4%) patients. The authors reported an 80% 2- and 5-year local control; an 89% and 83% regional control at 2- and 5-years respectively; and a 76% and 73% 2- and 5-year locoregional control (LRC). Freedom from distant metastases at 2- and 5-years was 78%. Disease-free survival (DFS) was 57% and 48% at 2- and 5-years respectively while OS was 67% and 47% at 2- and 5-years respectively. The authors indicate that the rates of LRC and OS were comparable to those previously published for sinonasal SCC and that

the toxicity profile "...was acceptable, with 8 grade 3, 6 grade 4, and no grade 5 toxicities."

McDonald et al (2016) conducted a retrospective review of patients with a primary cancer of the nasopharynx, nasal cavity or paranasal sinus; 12 patients treated with IMRT, 14 patients treated with protons to primary site and concurrent matched photons to lymph nodes; and 14 patients treated with protons alone to the head and neck. It is noted that all 12 patients treated with IMRT empirically had placement of a gastrostomy tube (G-tube) prior to treatment whereas those receiving PBT had these placed electively (ultimately no patients required it). In a dosimetric comparison, PBT delivered significantly lower mean dose to the oral cavity, larynx and esophagus and resulted in improved parotid sparing. On multivariate analysis, PBT was significantly associated with lower G-tube dependence at 3 months after completion of radiotherapy and lower opioid pain requirement (equivalent morphine dose; EMD) at completion of radiotherapy. At 1 and 3 months after completion, however, the significant association with EMD was lost as the majority of patients returned to baseline EMD by 3 months. The authors conclude that the initial results "...may serve in hypothesis formation for further investigation" and "...merit further evaluation in a larger study with more uniform patient and treatment characteristics..."

Holliday et al (2015) conducted a retrospective case-control study on 30 patients with nasopharyngeal cancer treated with IMRT and IMPT. In this study, 10 patients treated with IMRT on a prospective observational study were matched, in a 2:1 ratio, by 20 patients treated with IMPT. There were no significant differences between the groups with each group receiving 70 Gy. Dosimetric analysis revealed that patients receiving PBT had significantly lower mean doses to the oral cavity, brainstem, whole brain, and mandible. In addition, patients receiving PBT had a significantly lower rate of G-tube placement by the end of treatment (20% vs. 65%, $p = 0.02$). On bivariable analysis, increased mean oral cavity dose was associated with a higher rate of G-tube placement; no patient required a G-tube if the mean oral cavity dose was < 26 Gy whereas all patients with a mean dose of > 41.8 Gy did. On multivariate analysis, mean dose to the oral cavity remained significantly associated with G-tube placement (OR 1.31, $p = 0.003$); interestingly however treatment type (IMPT vs. IMRT) was not. Though there were no grade 4 or 5 acute toxicities, patients receiving IMPT experienced significantly fewer grade 3 acute toxicities ($p = 0.015$). There was no difference in rates of chronic toxicity between the groups.

Patel et al (2014) conducted a meta-analysis of charged particle therapy (protons, carbon ions, helium ions) vs. photon therapy (2D, 3D, and IMRT published after 1990) for cancers of the paranasal sinus and nasal cavity. In this analysis, 43 cohorts were identified; 30 treated with photons (1186 patients) and 13 with charged particles (286 patients). There were no statistically significant differences between the 2 groups. When comparing charged particle therapy to photons, the authors found charged particle therapy was associated with a significantly higher rate of OS at the longest duration of follow-up and at 5 years; significantly higher LRC at the longest duration of follow-up; and significantly higher 5-year DFS. When restricting the analysis to treatment-naïve patients, charged particle therapy was associated with a significantly higher OS, LRC and 5-year DFS. When comparing PBT to IMRT, PBT was associated with a significantly higher 5-year DFS and LRC at longest follow-up. In an analysis of toxicity, charged particle therapy was found to be

significantly associated with more neurological toxic effects ($p = 0.0002$). The authors indicate that this could be related to reporting bias (significantly higher proportion of charged particle therapy studies reported toxic effects ($p = 0.03$); referral bias (greater proportion of anatomically challenging cases were referred for charged particle therapy); and/or the greater RBE and higher physical dose associated with charged particle therapy.

B. Oropharynx

Sio et al (2016) reported on patient-reported outcomes (PROs) in patients with oropharyngeal cancer treated with chemotherapy and IMPT (35) vs. chemotherapy and IMRT (46). PROs were obtained using the MD Anderson Symptom Inventory (MDASI) for Head and Neck Cancers during the acute (during treatment), subacute (within 3 months after treatment) and chronic phases. At baseline, it was noted that the MDASI scores were equivalent between the 2 groups except that the IMRT group had higher scores for difficulty with swallowing/chewing. At a median follow-up of 7.7 months (IMPT) and 2.7 months (IMRT), there was no difference in the MDASI scores during the acute phase. In the subacute phase, IMPT was associated with significantly lower symptom burden related to taste and appetite. In the chronic phase, IMPT was associated with significantly lower symptom burden related to appetite. When limiting the analysis to moderate to severe symptoms, IMPT was only significantly associated with a lower symptom burden related to taste and mucus in the subacute phase. The authors state “Significant proportions of patients in both groups still experienced moderate to severe symptoms during the chronic phase (i.e., > 3 months after completion of treatment).” The authors conclude that “In this small cohort, we were unable to substantiate an improvement in quality of life from using IMPT...(which was) unexpected” and may be related to “...the small sample size in this retrospective cohort, the sensitivity of the PRO instrument, or the lack of a true difference in patient-reported quality of life between IMPT and IMRT.”

In a dosimetric analysis of IMPT vs. IMRT in the treatment of oropharyngeal cancer (OPC), Holliday et al (Autumn 2016) compared doses to various OARs in 2 different cohorts; the first included 25 patients who received IMPT for which IMRT plans were generated and the second included 25 patients treated with IMRT matched to those 25 patients treated with IMPT. In the first cohort, the authors found significant reductions in the mean doses to the anterior oral cavity, posterior oral cavity, esophagus, structures involved in dysphasia and CNS structures involved in the nausea-vomiting response using IMPT. In the second cohort, similar results were seen with IMPT except that the mean doses to the esophagus and structures involved in dysphagia were not significantly different. The authors state that “This discrepancy underscores the reality that, no matter how diligently one generates an excellent comparison IMRT plan, more care may be taken when generating a plan intended to actually treat a patient.” No difference was seen in the mean doses to the parotid or submandibular glands in either group. In discussing the improvements in the mean doses delivered to the CNS structures, the authors state “...it is difficult to gauge whether this statistical significance is clinically significant, as many of the CNS structures evaluated do not have well-established dose constraints.” The authors conclude that “Prospective trials enrolling patients with OPC will provide further information on oncologic control and toxicity end points for IMPT versus IMRT.”

Gunn et al (2016) reported on their experience with 50 patients treated with IMPT for a diagnosis of OPC between March 2011 and July 2014. A simultaneous integrated boost technique was used to deliver 66 Gy RBE for small-volume disease and 70 Gy RBE for more advanced disease. At a median follow-up of 29 months, the 2-year OS was 94.5% and 2-year PFS was 88.6%. Acute side effects included grade 3 dermatitis, mucositis, and dysphagia which occurred in 23, 29 and 12 patients respectively. Sixteen patients (32%) required evaluation in an emergency room during treatment with 10 subsequently requiring hospitalization primarily due to dehydration and pain from mucositis. Eleven patients had a G-tube placed during treatment which the authors state compare favorably with data in IMRT series. The median tube duration was 82 days after completing radiation therapy. There were 8 patients with grade 3 late toxicity, primarily dysphagia. The authors conclude that "...our findings demonstrate the feasibility and proof of principle of advanced proton therapy techniques delivering simultaneous integrated boost plans...thus laying the ground work for a direct head-to-head comparison study."

Blanchard et al (2016) conducted a 2:1 case-matched analysis of 50 patients treated with IMPT for a diagnosis of OPC to 100 patients treated with IMRT. At a median follow-up of 32 months (entire cohort), there was no difference in OS or PFS between IMPT and IMRT. In a multivariate analysis, insertion of a G-tube at the acute phase was the only significant variable associated with OS with a hazard ratio (HR) of 4.96 ($p = 0.04$) whereas this and advanced age were associated with PFS. It was noted that patients receiving a G-tube during radiotherapy had significantly longer history of smoking, greater comorbidity, more advanced disease, greater need for bilateral treatment, higher use of induction chemotherapy and concurrent chemotherapy, and a longer duration of treatment. With regards to toxicity, there were no differences in acute toxicity by technique. At 3 months post treatment, IMPT was significantly associated with less xerostomia and G-tube presence or weight loss greater than 20%. Only the latter remained significant at 1-year post radiation. The authors conclude "...that IMPT provides similar tumor control and lower rates of subacute and late swallowing-related morbidity than IMRT..." and that "...it is essential that our findings be replicated through prospective multicenter trials... and incorporate cost-effectiveness analysis as well as patient-reported outcomes."

C. Salivary gland

Romesser et al (2016) conducted a retrospective review of 41 patients diagnosed with major salivary gland cancer or cutaneous squamous cell carcinoma metastasis to a major salivary gland. These patients underwent unilateral irradiation with IMRT or uniform scanning proton beam therapy. In a dosimetric analysis, patients receiving PBT had a significantly lower brainstem maximum dose, spinal maximum dose, oral cavity mean dose, contralateral parotid gland mean dose and contralateral submandibular maximum dose. PBT was also associated with a significantly lower rate of grade 2 or greater acute mucositis and dysgeusia but resulted in a higher rate of grade 2 or greater dermatitis.

D. Adenoid cystic carcinoma

Bhattasali et al (2016) reported on 9 patients with unresectable adenoid cystic carcinoma (ACC) treated with definitive PBT and concurrent cisplatin. Sites of treatment included the larynx (1), nasopharynx (5), paranasal sinus

(2) and oropharynx (1). Treatment was to 70 Gy using either passive scatter protons (laryngeal ACC) or IMPT with cisplatin given concurrently. At a median follow-up of 27 months, 4 patients (44%) achieved a complete response, 4 achieved a partial response without disease progression and 1 developed local progression. With respect to toxicity, 4 patients experienced grade 3 acute toxicities and 1 developed a grade 4 toxicity (blindness in the treated eye).

In a retrospective analysis, Linton et al (2015) reported on 26 patients with head and neck ACC treated with PBT. This heterogeneous group of patients included 19 receiving treatment at initial diagnosis and 7 receiving treatment at recurrence (6 of whom had prior radiation and 3 of whom had pulmonary metastases). Twenty were treated after surgery with 18 of these exhibiting positive margins or gross residual disease. Six were treated after biopsy alone. It is noted that 2 patients also received IMRT as part of their PBT. The dose planned was 75.6 Gy for gross residual disease, 70.2 to 72 Gy for positive margins and 66 to 70.2 Gy for negative margins. At a median follow-up of 25 months, the 2-year estimate of OS was 82%, of LC was 92% and of development of distant metastases (DM) was 25%. One patient developed an acute grade 3 toxicity. Grade 3, 4 and 5 late toxicity was seen in 2, 1 and 1 patients respectively. The authors conclude "...high-dose proton therapy provides encouraging preliminary LC. Longer follow-up is needed to gauge the durability of disease control and to monitor for late toxicities of therapy."

Holliday et al (Spring 2016) reported on 16 patients who received postoperative PBT for a diagnosis of head and neck ACC. Sites of treatment included lacrimal gland or sac (5), paranasal sinus (4), parotid gland (4), submandibular gland (2) and buccal mucosa (1). Median dose delivered was 60 Gy with 12 patients receiving concurrent chemotherapy. At a median follow-up of 24.9 months, 15 patients (94%) were without evidence of disease. Four patients developed acute grade 3 toxicity and 1 patient experienced a grade 4 toxicity (blindness). An additional patient developed asymptomatic frontal lobe necrosis 18 months after treatment completion with near resolution at 24 months. The authors conclude that "Intensity-modulated proton therapy demonstrated comparable efficacy and safety when compared to other radiation modalities including other proton therapy delivery techniques."

E. Lacrimal gland

Esmaeli et al (2016) reported on 11 patients with lacrimal gland carcinoma who underwent globe sparing surgical reduction followed by radiation therapy from 2007 to 2014. This included 3 patients treated with IMRT and 7 with IMPT at initial diagnosis with a dose delivered ranging from 52 Gy to 64 CGE. One additional patient refused radiation and chemotherapy after surgery but received stereotactic radiosurgery at the time of recurrence. Patients had stage T1N0 (1), T2N0 (6), T3N0 (1) or T4N0 (3), all without metastases. Seven patients had ACC, 6 of whom received concurrent chemotherapy. At a median follow-up of 33 months, all 11 patients remained disease free. All 11 patients experienced grade I ocular toxicity with 1 patient, treated with IMRT, experiencing grade IV toxicity. The authors conclude that "...globe-sparing surgery followed by adjuvant radiotherapy or concurrent chemoradiotherapy is associated with acceptable short-term locoregional control..."

Holliday et al (2016 May 1) also reported on a similar cohort consisting of 20 patients receiving PBT following orbit-sparing surgery for cancers of the orbit and

ocular adnexa. Primary sites included the lacrimal gland (7), lacrimal sac/nasolacrimal duct (10) or eyelid (3). Seven patients had SCC and 7 had ACC. Median dose delivered was 60 Gy RBE with 11 patients receiving concurrent chemotherapy. At a median follow-up of 27.1 months, 1 patient with SCC of the eyelid developed parotid recurrence and 1 patient with sebaceous carcinoma of the nasolacrimal duct developed metastases while the remaining patients remained without recurrence. Seven patients experienced acute grade 3 while 9 patients developed chronic grade 3 ocular or eyelid function toxicity. Bivariate analysis revealed that a dose of 36 Gy or less to the ipsilateral cornea was associated with grade 3 chronic ocular toxicity ($p = 0.032$). The authors conclude that these findings "...suggest that adjuvant proton therapy can be delivered successfully after orbit-sparing surgery for epithelial tumors of the orbit and ocular adnexa."

F. Reirradiation

McDonald et al (2016 Nov 15) reported on 61 patients with head and neck cancer receiving curative proton beam reirradiation. It is noted that PBT was utilized "...when the dosimetric gains of proton therapy were believed advantageous because photon-based reirradiation could not adequately cover the reirradiation target without exceeding the critical normal tissue constraints, or would result in excessive risk of toxicity." Hence, 55 of the 61 patients had "...primary or recurrent disease involving skull base sites." The median dose of reirradiation was 66 Gy RBE for microscopic disease and 70.2 Gy RBE for gross disease. At a median follow-up of 15.2 months, median survival was 16.5 months and the 2-year OS was 32.7%. The 2-year risk of locoregional failure was 23% while 38.3% developed distant metastases. Grade 3 acute toxicity was seen in 13.1% while 1 patient (1.6%) experienced a grade 5 acute toxicity. Grade 3 late toxicity was seen in 15.1%, grade 4 late toxicity in 5.7% and grade 5 late toxicity in 3.8%. The authors conclude "Reirradiation with proton therapy, with or without chemotherapy, provided reasonable locoregional disease control, toxicity profiles, and survival outcomes for an advanced-stage and heavily pretreated population. Additional data are needed to identify which patients are most likely to benefit from aggressive efforts to achieve local disease control and to evaluate the potential benefit of proton therapy relative to other modalities of reirradiation."

In a study of 60 patients receiving proton beam therapy for reirradiation, Phan et al (2016) reported on 60 patients receiving proton beam reirradiation. At a median follow-up of 13.6 months, there was a 1-year locoregional failure-free survival of 68.4% and OS of 83.8%. Thirty percent experienced grade 3 acute toxicity while 16.7% experienced late grade 3 toxicity at 1 year. The authors concluded that proton "...reirradiation for patients with recurrent or secondary primary H&N cancer offers 2-year rates of LRC and survival compatible with those in modern IMRT series... Larger prospective studies with longer follow-up times are needed to evaluate the efficacy, tolerability, and cost-effectiveness of proton therapy compared with other conformal RT approaches such as IMRT, VMAT, and SBRT for H&N reirradiation."

VII. Non-small cell lung cancer

The data on proton beam therapy in the treatment of lung cancers is limited. Numerous dosimetric studies showing the potential for radiation dose reduction have been reported. Chang et al (2006) from MD Anderson compared the dose to the normal

tissue comparing proton radiotherapy with 3DCRT or IMRT in stage I or stage III non-small cell lung cancer. Twenty-five patients with medically inoperable stage I or inoperable stage IIIA/B (NCT01883810) non-small cell lung cancer (NSCLC) were studied. For stage III, the lung V5, V10, and V20 were 54.1%, 46.9%, and 34.8%, respectively, for photon 3DCRT with 63 Gy, whereas they were 39.7%, 36.6%, and 31.6%, respectively, for proton with dose escalation to 74 CGE ($p = 0.002$). In all cases, the doses to lung, spinal cord, heart, esophagus, and integral dose were lower with proton therapy compared with IMRT. No clinical outcomes were reported, and no evidence that these dose differences resulted in clinically meaningful improvement in results is presented. The authors acknowledged that proton radiotherapy in lung cancer raises many important issues among the most challenging of which is tumor motion during treatment resulting from the patient's breathing.

The result of a phase II study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III NSCLC was reported by Chang et al (2017). Sixty-five patients were treated with 74 Gy RBE proton therapy with weekly carboplatin and paclitaxel. Disease was staged with positron emission tomography (PET)/computed tomography (CT), protons were delivered as passively scattered beams, and adaptive re-planning was performed in 25% of patients. Patients all had Karnofsky Performance Status (KPS) ≥ 70 (median 90) and $< 10\%$ weight loss, which are more favorable prognostic features. At a median follow-up time of 27.3 months, the median overall survival time was 26.5 months. The total local failure rate was 20.5%. No patient experienced grade 5 toxicity. The most common grade 3 adverse effects related to proton therapy were dermatitis and esophagitis, each experienced by 5 patients (11.4%); 1 patient (2.3%) developed grade 3 pneumonitis, and 1 patient had a pulmonary/pleural fistula.

Early findings on toxicity of proton beam therapy with concurrent chemotherapy for NSCLC were reported by Sejpal et al (2011), at MD Anderson Cancer Center. They compared the toxicity of proton therapy + concurrent chemotherapy in 62 patients with NSCLC (treatment period 2006 to 2008) with toxicity for patients with similar disease given 3DCRT + chemotherapy ($n = 74$; treatment period 2001 to 2003) or IMRT+ chemotherapy ($n = 66$; treatment period 2003 to 2005). Proton therapy to the gross tumor volume was given with weekly intravenous paclitaxel and carboplatin. This report focuses only on acute and subacute toxicity, because the follow-up duration is too short to evaluate tumor control and survival. Median follow-up times were 15.2 months (proton), 17.9 months (3DCRT), and 17.4 months (IMRT). Rates of severe (grade > 3) pneumonitis and esophagitis in the proton group (2% and 5%) were lower despite the higher radiation dose (3DCRT, 30% and 18%; IMRT, 9% and 44%; $p < .001$ for all). Median overall survival times were 17.7 months for the 3DCRT group, 17.6 months for the IMRT group, and 24.4 months for the proton therapy group (log-rank $p = 0.1061$). The authors acknowledged several shortcomings of their study including the use of retrospective data for comparison, including substantial differences in pretreatment assessments (especially imaging) and treatment-planning capabilities over the periods of study and the heterogeneity of the patient populations. The proton therapy group was itself somewhat heterogeneous because of the inclusion of 25 patients with any stage (including recurrent) disease. Therefore differences in outcomes in this study are not clearly related to treatment modality.

Hoppe et al (2012) published the result of a retrospective study on proton therapy with concurrent chemotherapy for 19 patients with NSCLC (18 stage III, 1 stage IIB) either with or without induction chemotherapy. Non-hematologic and hematologic acute grade 3 toxicity (90 days) developed in 1 and 4 patients, respectively. Two of 16

patients assessable for late toxicity (90 days) developed a significant grade 3 non-hematologic late toxicity, whereas 1 patient developed a grade 3 hematologic late toxicity. Local progression was the site of first relapse in 1 patient. The median progression-free survival (PFS) and median overall survival (OS) were 14 and 18 months, respectively. Seven patients are currently alive without evidence of disease, and 7 other patients died from disease progression, including 6 with distant metastases as their first site of relapse and 1 with local progression as their first site of relapse. The authors concluded proton therapy for stage III lung cancer is a promising treatment approach. Larger prospective studies are needed to confirm these findings, define the critical dosimetric points that may be unique to proton therapy, and investigate the potential of proton therapy to facilitate radiation dose escalation and/or combined modality therapy.

Liao et al (2018) reported rates of local failure (LF) or radiation pneumonitis (RP) in a Bayesian randomized trial of intensity-modulated radiotherapy (IMRT) vs. 3D proton therapy (3DPT), both with concurrent chemotherapy, for locally advanced non-small cell lung cancer. Pairs of IMRT and 3DPT plans were created for each patient. Patients were eligible for randomization only if both plans satisfied normal tissue constraints at the same radiation dose. Of 255 enrolled patients, 149 were randomly allocated to IMRT ($n = 92$) or 3DPT ($n = 57$). The rate of grade 3 RP was 6.5% with IMRT and 10.5% with protons. LF rates were 10.9% with IMRT and 10.5% with protons. The conclusion was that proton treatment did not improve dose-volume indices for lung but did for heart. No benefit was noted in RP or LF after proton beam treatment. Similarly, Niedzielski et al (2017) reported esophageal toxicity results from this same patient cohort and concluded that there was no significant difference in esophageal toxicity from either proton- or photon- based radiation therapy as quantified by esophagitis grade or the esophageal expansion imaging biomarker.

Wang et al (2016) reported comparisons of patient-reported symptoms after treatment in a total of only 82 patients, treated with either 3D technique, IMRT or proton beam therapy. They found that pain, as a major esophagitis-related symptom, increased more during therapy ($p = 0.019$) and decreased more after ($p = 0.013$) therapy in the 3DCRT and IMRT groups than in the PBT group. Compared with the PBT group, the 3DCRT and IMRT groups reported greater decrease in systemic symptoms (fatigue, drowsiness, lack of appetite, disturbed sleep) after therapy ($p = 0.016$). They concluded that patients receiving PBT reported significantly less severe symptoms than did patients receiving IMRT or 3DCRT. These results should be confirmed in a randomized study with comparable tumor burden among therapies.

Considered together, these early reports of proton beam radiation for lung cancer are mostly single institution retrospective studies which do not demonstrate clearly superior outcomes compared to customary photon radiation techniques. The limited randomized study information from Liao et al (2017) and Niedzielski et al (2017) do not show evidence of improved outcomes with protons.

The American Society of Radiation Oncology (ASTRO) has taken a clear position towards the use of proton beam in the treatment of lung cancer. ASTRO Model Medical Policy on Proton Beam Therapy listed lung cancer in Group 2; Coverage with Evidence Development (CED). For the cancers in group 2, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other radiation therapy modalities. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of these cancers, including

locally-advanced lung cancer, should only be performed within the context of a prospective clinical trial or registry. This is consistent with the investigational and unproven nature of proton beam radiation therapy for treatment of lung cancer.

Currently there are multiple clinical trials recruiting patients to study the role of proton beam radiation therapy in stage II-III non-small cell lung cancer. These include RTOG 1308 (NCT01993810), A Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Chemoradiation Therapy for Inoperable Stage II-IIIB NSCLC. This randomized study aims to provide information on a clinically meaningful QOL benefit from proton therapy over photon therapy. The study will focus on 2 key toxicities:

- A. The primary QOL outcome: Pulmonary toxicity (ie, clinical pneumonitis and lung fibrosis), a chronic effect of treatment that can have long term negative effects on QOL
- B. The secondary QOL outcome: Esophageal toxicity (esophagitis), an acute/subacute effect which is largely transient

In addition, the following studies are active:

- A. NCT01770418 A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer
- B. NCT01629498 Phase I/II Trial of Image-Guided, Intensity-Modulated Photon (IMRT) or Scanning Beam Proton Therapy (IMPT) Both with Simultaneous Integrated Boost (SIB) Dose Escalation to the Gross Tumor Volume (GTV) with Concurrent Chemotherapy for Stage II/III Non-Small Cell Lung Cancer (NSCLC)
- C. NCT02731001 Proton Therapy to Reduce Acute Normal Tissue Toxicity in Locally Advanced Non-small-cell Lung Cancer (PRONTOX)
- D. NCT01076231 Feasibility and Phase I/II Trial of Preoperative Proton Beam Radiotherapy with Concurrent Chemotherapy for Resectable Stage IIIA or Superior Sulcus NSCLC

VIII. Pancreatic Cancer

There have been several dosimetric studies comparing dose distributions in a limited number of patients using PBT or customary photon-based techniques. In a dosimetric study of unresectable pancreatic cancers treated to 59.4 Gy, Hsiung- Stripp et al (2001) suggested the proton plans significantly reduced dose to the spinal cord ($p = 0.003$), left kidney ($p = 0.025$), right kidney ($p = 0.059$), and to the liver ($p = 0.061$).

Nichols et al (2012) reported on a comparison of retrospectively generated three-dimensional conformal proton plans with IMRT treatment planning on 8 consecutive patients with resected pancreatic head cancers from the same institution receiving 50.4 CGE. The proton plans offered significantly reduced normal-tissue exposure over the IMRT plans with respect to the median small bowel V20 Gy (15.4% versus 47.0% $p = 0.0156$); median gastric V20 Gy (2.3% versus 20.0% $p = 0.0313$); and median right kidney V18 Gy (27.3% versus 50.5% $p = 0.0156$).

Lee et al (2013) reported the outcomes of 12 consecutive patients who received neoadjuvant treatment for localized pancreatic cancers. They included high-risk nodal stations and delivered 50.4 CGE. In spite of the enlargement of the PTV, normal tissue exposures were well within tolerance limits and only minimally increased relative to exposures seen when only the gross tumor target was treated.

Thompson et al (2014) reported a dosimetric comparison of proton and photon therapy

in unresectable cancers of the head of pancreas. In this study, the authors investigated the potential use of double scattering (DS) and pencil beam scanning (PBS) proton therapy in limiting dose to critical organs at risk. All plans were calculated to 55 Gy in 25 fractions with equivalent constraints and normalized to prescription dose. Both DS and PBS decreased stomach, duodenum, and small bowel dose in low-dose regions compared to IMRT ($p < 0.01$). However, protons yielded increased doses in the mid to high dose regions (eg, 23.6 to 53.8 and 34.9 to 52.4 Gy for duodenum using DS and PBS, respectively; $p < 0.05$). Protons also increased generalized equivalent uniform dose to duodenum and stomach, however these differences were small ($< 5\%$ and 10% , respectively; $p < 0.01$). Doses to other organs at risk were within institutional constraints and placed no obvious limitations on treatment planning. The authors concluded that protons are able to reduce the treated volume receiving low-intermediate doses, however the clinical significance of this remains to be determined. Proton therapy does not appear to reduce OAR volumes receiving high dose.

Bouchard et al (2009) from M.D. Anderson Cancer Center compared 3DCRT, IMRT, or protons to define which unresectable pancreatic tumor locations are safe for dose escalation (72 Gy). They concluded that IMRT allows a more conformal dose distribution in the high-dose regions, while proton therapy reduces low-dose bath irradiation to the body. They suggested uncertainty margins needed for proton planning precluded its full potential for higher-dose areas, and IMPT might be a solution.

There is limited clinical data demonstrating outcomes for patients with pancreas cancer treated with PBT. Reported clinical experiences for PBT have generally been limited to single-institution studies. Nichols et al (2013) presented outcomes of 22 patients treated with proton therapy and concomitant capecitabine (1000 mg by mouth twice a day) for resected ($n = 5$), marginally resectable ($n = 5$), and unresectable/inoperable ($n = 12$) biopsy-proven pancreatic and ampullary adenocarcinoma. Proton doses ranged from 50.4 Gy RBE to 59.4 Gy RBE. No patient demonstrated any grade 3 toxicity during treatment or during follow-up. Three patients experienced grade 2 gastrointestinal toxicity. Chemotherapy was well-tolerated with a median of 99% of the prescribed doses delivered.

Sachsman et al (2014) published information on 11 patients with unresectable pancreatic cancer, evaluating whether the serious adverse event rate could be reduced from 15% (expected) to $< 5\%$. The prescribed dose was 59.4 CGE with concomitant oral capecitabine. Median follow-up was 14 months for all patients and 23 months for surviving patients. No patient experienced a grade 3 or greater toxicity during treatment or follow-up. Grade 2 toxicity was limited to a single patient experiencing grade 2 fatigue. Median weight loss over the course of treatment was 1.7 kg (range, loss of 5.7 to gain of 4.9 kg). The median survival was 18.4 months and at 2 years the freedom from local progression was 69%.

University of Pennsylvania (Lukens et al, 2013) investigated whether lower normal tissue exposure by proton therapy translated into lower rates of acute gastrointestinal (GI) toxicity compared to photon chemoradiation. They enrolled 13 patients with pancreatic adenocarcinoma in a prospective feasibility study of proton therapy with concurrent continuous infusion 5-FU or capecitabine CRT. Median total RT dose was 54 Gy (50.4 to 59.4). A concurrent cohort of 17 patients was treated with photon beam. In the proton group, the rate of grade 3 acute GI toxicity was 8%, and 10 patients (77%) had grade > 2 acute non-hematologic toxicity. In the photon group, 4 patients (24%) developed acute grade 3 GI toxicity.

Hong et al (2014) published a series of patients with resectable pancreatic cancer treated with hypofractionated preoperative radiation, 25 Gy RBE in 5 fractions. Patients had to have resectable disease, good performance status (ECOG = 0 to 1) and all had negative laparoscopy prior to treatment. Twelve point three percent (12.3%) of patients were excluded due to positive findings at the time of laparoscopy, even after appearing to have localized disease on CT imaging. Of the remaining 50 patients, only 78% had surgery, with 16% found to be unresectable, 4% diagnosed with metastases prior to surgery, and 2% diagnosed with cholangiocarcinoma instead of pancreatic cancer. The median PFS was 10.4 months, and median OS was 17.3 months. Median follow-up for analysis was 38 months among the 12 patients still alive. The OS rate at 2 years was 42% (95% CI: 28% to 55%). For the 37 eligible resected patients, median PFS was 14.5 months (95% CI: 10.2 to 21.8 months), and median OS was 27.0 months (95% CI: 16.2 to 32.3 months). Six of 37 eligible resected patients (16%) experienced locoregional recurrence, while 73% developed distant metastases. The authors concluded that short-course proton-based chemoradiation is well tolerated and is associated with favorable local control in resectable pancreatic cancer (although 16% local failure after surgery and radiation, particularly with such limited follow-up and early deaths, is not particularly favorable).

Takatori et al (2014) reported an analysis of the upper gastrointestinal complications associated with gemcitabine concurrent proton radiation therapy for patients with inoperable pancreatic cancer. The study demonstrated a 49.4% rate of gastric/duodenal ulceration in the treated patients. Advanced immobilization techniques, such as the use of breath hold gating or targeting with implanted fiducial markers, were not used in this series, and the dose of 67.5 Gy RBE was higher than customary preoperative doses. Of note, the initial report (Terashima, 2012) of this series, with 12.5 month median follow-up, concluded that this regimen was feasible and effective with only 12% grade 3 toxicity, 1 year local control of 82% and survival of 77%, emphasizing the need for an adequate follow-up period to assess outcomes.

Maemura et al (2017) published a comparison of protons and photons, with the photon group treated with hyperfractionated accelerated radiotherapy (HART). Moderate hematological toxicities were observed only in the HART group, whereas 2 patients in the PBRT group developed duodenal ulcers. All patients underwent scheduled radiotherapy, with overall disease control rates of 93% and 80% in the HART and PBRT groups, respectively. Local progression was observed in 60% and 40% of patients in the HART and PBRT groups, respectively. However, there was no statistical significance between the 2 groups regarding the median time to progression (15.4 months in both) and the median overall survival (23.4 vs. 22.3 months).

Jethwa et al reported on their initial experience with IMPT (intensity modulated proton therapy) for 13 patients with localized pancreatic cancer. Patients were treated to a dose of 50 Gy with chemotherapy. A VMAT plan was also generated for dosimetric comparison. At a median follow-up of 16 months, "low rates of acute GI AEs and favorable PROs."

Kim et al also reported low rates of toxicity in 37 patients treated with proton beam therapy using a simultaneous integrated boost in 10 total fractions. No grade 3 or higher toxicity was seen while maintaining a median overall survival of 19.3 months.

Other considerations

The dose distribution using PBT is affected to a much greater extent by changes in

tissue density than photon radiation therapy. As a result, there is concern about using PBT in the presence of significant target motion. This especially pertains to targets in the thorax and upper abdomen, including the pancreas, which move as a result of diaphragmatic excursion (Mori and Chen, 2008; Mori et al, 2008). Because the diaphragm moves during respiration, this results in changes to the tissues in the beam path, which can cause significant interplay effects and dose uncertainty. This could result in unanticipated overdose of normal tissues or under dose of target volumes.

Houweling et al (2017) compared the dosimetric impact of interfractional anatomical changes for photon and proton plans for pancreatic cancer patients based on daily cone beam CT images, and found that photon plans were highly robust against interfractional anatomical changes. However, the near-minimum CTV dose for protons was reduced 8%, and in proton therapy, such changes can severely reduce the dose coverage of the target. Therefore, direct comparative studies will be helpful to determine the relative safety and efficacy of protons relative to customary photon radiation.

The results from the previously mentioned single-institution experiences of pancreatic PBT do not demonstrate improved patient outcomes with PBT compared to customary photon treatments. Dosimetric studies suggest some possible benefits for PBT in the low/moderate dose ranges which could theoretically reduce toxicity, but there remain insufficient clinical publications documenting the benefits, risks, or efficacy of proton beam therapy. In addition, there are concerns about proton beam dose distributions in the setting of organ and respiratory motion and tissue differences and interfaces, as are seen in this location. Therefore, prospective trials comparing PBT with standard photon technologies like 3DCRT or IMRT will be necessary to provide high-quality evidence demonstrating the value of PBT. There are currently active clinical trials in the United States evaluating the role of PBT for pancreatic cancer, including NCT02598349, A Phase II Trial of Escalated Dose Proton Radiotherapy With Elective Nodal Irradiation and Concomitant Chemotherapy for Patients With Unresectable, Borderline Resectable or Medically Inoperable Pancreatic Adenocarcinoma, and NCT01683422, A Phase II Trial of Gemcitabine and Erlotinib (GE) Plus Proton-chemotherapy (PCT) and Capox for Locally Advanced Pancreatic Cancer (LAPC).

IX. Thymoma

The role of proton beam radiation for thymoma is primarily limited to small dosimetric studies mostly from single institutions. While these studies demonstrate a dosimetric advantage, there is no evidence presented as to how these dose differences translate into improved outcomes. For instance, Zhu et al (2018) report on 6 patients with stage II and III thymic malignancies who received treatment with proton beam therapy. Comparative photon based intensity modulated radiation therapy (IMRT) plans were also generated. This study reported an improvement in dosimetric outcomes with proton beam therapy. There was a significant reduction in heart, lung, and esophagus dose with proton beam therapy compared to IMRT planning. Clinically, 2 of the 6 patients developed recurrence. Similarly, Parikh et al (2016) presented a study of 4 patients with thymoma who underwent resection followed by adjuvant proton beam therapy. They also showed a dosimetric analysis comparing proton beam therapy and IMRT. The authors noted a significant reduction in mean lung dose (4.6 Gy vs. 8.1 Gy, $p = .02$), mean esophagus dose (5.4 Gy vs 20.6 Gy, $p = .003$), and mean heart dose (6.0 Gy vs. 10.4 Gy, $p = .007$). Three of the 4 patients reported grade 1 dermatitis. As noted by the authors, “prospective evaluation and longer follow-up is needed to assess

clinical outcomes and late toxicities.” These studies have demonstrated that proton beam therapy is well tolerated. Additional studies will be necessary to demonstrate the efficacy for proton beam therapy relative to photon based therapy in thymoma and thymic carcinoma.

X. Lymphoma

There is considerable interest in use of PBT for treatment of Hodgkin and Non-Hodgkin Lymphoma. These individuals often have relatively good prognoses, with 10-year survival rate of Hodgkin Lymphoma (HL) of approximately 90% and somewhat lower rates for Non-Hodgkin Lymphoma (NHL). Therefore, there is concern that this patient population has a longer duration of survival, allowing sufficient time for very late side effects of radiation for curative treatment to emerge and affect quality of life. However, the doses of radiation that are typically delivered for lymphoma are low or moderate compared to most solid tumors, and these doses often do not approach the established tolerance doses for organs at risk in the treated volume. The dosimetric advantage to PBT is primarily in the volume of tissue receiving low doses of radiation relative to the prescribed dose, and since the prescribed dose is already low in this setting, it is not clear that the reduction in the volume of organs at risk exposed to these relatively low doses is clinically meaningful.

There are several studies of dosimetric comparisons between PBT and photon therapy, most of which demonstrate modest reductions in radiation dose to organs at risk, primarily in the low-dose range. For example, Hoppe et al (2014, Aug 1) reported dose differences using 3DCRT, IMRT, or PBT for 15 patients with HL, and mean dose to organs at risk in the chest (eg, heart, lung, breast, thyroid, esophagus) was lower with protons. The mean reduction in heart dose with proton therapy compared with 3DCRT was 7.6 Gy, and the mean reduction in heart dose with proton therapy compared with IMRT was 3.4 Gy. Jørgensen et al (2013) reported on esophageal doses for 46 patients with mediastinal HL, and the mean dose with PBT was 1.7 Gy lower with protons than with 3D or IMRT techniques. Maraldo et al (2013) evaluated dose to heart, lungs, and breast with mantle technique, 3DCRT, IMRT, or PBT. They concluded that in early-stage, mediastinal HL, modern radiotherapy provides superior results compared with mantle fields. However, there is no single best radiotherapy technique for HL; the decision should be made at the individual patient level. Numerous other dosimetric studies (Cella et al, 2013; Chera et al, 2009; Horn et al, 2016; Maraldo et al, 2014; Sachsman et al, 2015; Toltz et al, 2015) have similarly demonstrated that lower doses to heart, breast tissue, and lung can be achieved using PBT. A review of studies by Tseng et al (2017) reported that weighted average difference in dose to different organs using PBT or modern radiation therapy (photon) techniques was 0 to 3.28 Gy. None of these studies has demonstrated a difference in clinical outcomes related to this dosimetric reduction.

In contrast to the large number of dosimetric studies comparing dose distributions, there are relatively few studies of patients treated with PBT that report patient outcomes. Much of the experience has been in the pediatric population, and whether extrapolation of this to adult patients is appropriate is not clear. Hoppe et al (2014 Aug 1) reported on 15 patients treated with involved nodal radiation for HL (5 children, 10 adults), with 37 month median follow-up. Three year relapse free survival was 93% and no late grade 3 or higher nonhematologic toxicities were noted. They concluded that PBT following chemotherapy in patients with HL is well-tolerated, and disease outcomes were similar to those of conventional photon therapy.

A registry study reported by Hoppe et al (2016) included 50 patients from a multi-

center study, 10 were excluded, leaving 40 patients (14 pediatric) treated with involved site PBT after chemotherapy. With median follow-up of only 21 months, the 2 year relapse-free survival was 85%, and there were no grade 3 or higher toxicities.

Winkfield et al (2015) published, in abstract form only, results of 46 patients with HL and NHL, 13 of whom were treated for salvage after prior relapse. With 50.5 month follow-up, the 5 year progression free survival was 80%. Nine of 46 patients developed late toxicities, though no grades of toxicity were reported.

Sachsman et al (2015) reported on 11 patients treated with PBT for NHL. With a 38-month median follow-up, the 2-year local control rate was 91%, with an in-field recurrence developing at the completion of proton therapy in 1 patient with natural killer/T-cell lymphoma, while no grade 3 toxicities were observed within the rest of the cohort. They concluded that PBT is a feasible and effective treatment for NHL. Early outcomes are favorable. Longer follow-up and more patients are needed to confirm these findings.

Plastaras et al (2016) published an abstract with 12 adults treated for mediastinal lymphoma (10 HL, 2 NHL). There were no grade 3 toxicities, and no recurrences noted with only 7 months median follow-up.

An abstract from the Proton Therapy Center of Prague (Dědečková et al, 2016) reported their experience with mediastinal lymphoma. Among 35 patients treated thus far with a median follow-up period of 10 months, no grade 3 toxicities or grade 2 pneumonitis have been observed. Furthermore, only 2 patients had disease relapse and both of these occurred outside of the proton field.

Group 3:

I. Anal canal cancer

There is limited data on the role of proton beam therapy in the treatment of anal cancer. The data is primarily limited to dosimetric studies comparing photon therapy and proton beam therapy (Anand et al, 2015; Ojerholm et al, 2015). Wo et al (2018) reported preliminary data on NCT01858025 which was a pilot study of 25 patients examining the feasibility of pencil beam scanning proton beam therapy in anal cancer. The study found proton beam therapy to be feasible. The authors note that “while felt to be unrelated to the study, the two Grade 5 adverse events on this small study highlights potentially treatment related risks of this effective yet toxic regimen.” As the data is limited and the 1 clinical study was associated with 2 grade 5 adverse events, the use of proton beam therapy in the treatment of anal cancer is unproven.

II. Bladder cancer

There is limited data on the role of proton beam therapy in the management of bladder cancer. Hata and colleagues report on 25 patients with transitional cell carcinoma of the urinary bladder who received photon based pelvic radiation combined with intra-arterial chemotherapy with methotrexate and cisplatin, transurethral resection biopsy of the bladder, followed by proton beam radiation boost. The authors found that radiation with photons followed by a proton boost was feasible. Similarly, Takaoka et al (2017) presented outcomes of 70 patients with bladder cancer treated with transurethral resection of the bladder tumor, photon based pelvic radiation, followed by proton boost. The authors found that bladder conservation therapy with photons followed by a proton boost is feasible. As these clinical studies were of photon therapy followed by proton therapy, there is limited data on the efficacy of proton beam therapy in bladder cancer. Therefore, proton beam therapy in the treatment of bladder cancer is unproven.

III. Cervical and endometrial cancer

There is limited data on the role of proton beam therapy in the treatment of cervical cancer. The data is primarily limited to dosimetric studies comparing photon therapy and proton beam therapy (de Boer P, 2018; Marnitz S et al, 2015; van de Schoot AJ et al, 2016). For instance, Clivio et al (2013) describe a dosimetric study of 11 patients with cervical cancer who receive 50.4 Gy followed by an intensity modulated proton therapy (IMPT) boost instead of brachytherapy. In this dosimetric study, the authors were able to achieve good target coverage and superior DVH coverage with photons followed by a proton boost. These studies describe a dosimetric benefit; however, it is unclear if this translates into a clinical benefit. There are limited clinical data on proton beam therapy and cervical cancer. Lin et al (2015) describe their single institution experience of treating 11 patients with posthysterectomy gynecologic cancers including endometrial cancer and cervical cancer with proton beam therapy. The authors report that their preliminary results demonstrate that treatment with proton beam therapy is feasible and there were dosimetric advantages with proton therapy compared to an IMRT plan. As there is limited clinical data on the efficacy of proton beam therapy in cervical and endometrial cancer, proton beam therapy in the treatment of cervical cancer or endometrial cancer is unproven.

IV. Gastric cancer

In gastric cancer, there is 1 study describing a potential dosimetric advantage of proton beam therapy (Dionisi et al, 2014). There are no published clinical studies. As treatment with protons is dependent on tissue density and changes in patterns of gas, treatment of gastric cancer with proton beam therapy presents challenges (Raldow and Hong, 2018). Therefore, the use of proton beam therapy in the treatment of gastric cancer is unproven.

V. Rectal cancer

The available published literature on proton beam therapy and rectal cancer is limited to dosimetric studies (Blanco et al, 2016; Colaco et al, 2014; Wolff et al, 2012). There is no readily available published data on clinical studies of proton beam therapy and rectal cancer. Therefore, the use of proton beam therapy in the treatment of rectal cancer is unproven.

VI. Sarcoma

Studies of proton beam therapy in soft tissue sarcoma are limited. With the exception of retroperitoneal sarcomas, there is limited clinical data on proton beam therapy in soft tissue sarcoma (Delaney et al, 2014). The studies of proton beam therapy in soft tissue sarcoma are primarily dosimetric comparisons. For example, in a dosimetric analysis of 5 patients with paraspinal sarcoma, Weber and colleagues (2007) found that intensity modulated photon therapy and intensity modulated proton plans produced equally homogeneous levels of tumor coverage. There was a reduction in the integral dose to the organs at risk with the intensity modulated radiation therapy plan. As there is limited clinical data on the efficacy of proton beam therapy in soft tissue sarcoma, proton beam therapy in the treatment of soft tissue sarcoma is unproven.

Additional considerations

I. Secondary malignancies

In a review of SEER registries, Berrington de Gonzales et al (2011) concluded from that “five excess cancers per 1000 treated with radiotherapy by 15 years after diagnosis.” A common argument by advocates for use of PBT is the potential to

reduce the risk of secondary malignancies further. A larger volume of normal tissue is exposed to low-dose radiation with IMRT, and this higher integral dose theoretically could cause a higher rate of second malignancies. There is a large body of data discussing the theoretic risks and benefits of PBT with respect to second malignancies, based on modeling (Arvola et al, 2012; Athar et al, 2009; Brenner et al, 2008; Moteabbed et al, 2012; Zacharatou et al, 2008). A commonly referenced study is one reported by Chung et al (2013) from Massachusetts General Hospital (MGH). While their data shows a lower risk of second malignancies in the proton group (5.2%) compared to a National Cancer Institute SEER database matched with a photon control group (7.5%) at a median follow-up of 6.7 years, their conclusion of the study is that "...these findings are reassuring that the risk of second tumors was at least not increased when using protons compared with photons..." and that "...given the limitations of the study, the reduced second tumor rate in the proton cohort that we observed should be viewed as hypothesis generating." The authors admit to several significant limitations of their study, including having lost 26% of the patients to follow-up. There is also debate about the reliability of the SEER database matched cohort in determining the risk of second malignancies from photon therapy. In a response to this publication, Bekelman et al (2013) noted that "...most of the excess of second cancers in the photon therapy cohort occurred in the first 5 years after treatment..." and that "...for the key period of interest for radiation-related solid malignancies, 5 or more years after treatment, the incidence rate was nearly identical..." between photons and proton beam therapy. It is best summed up by a comprehensive review from the NIH published in June 2013. The publication concluded that "...to date, no observational studies have directly assessed the second cancer risks after IMRT or proton therapy. Until sufficient follow-up is available to conduct such studies, assessment of the risks relies on risk projection studies or theoretical models." (Berrington de Gonzales et al, 2013). A publication by Zelefsky et al (2013) from Memorial Sloan-Kettering Cancer Center (MSKCC) on the rate of second malignancies after treatment of prostate cancer with radical prostatectomy, brachytherapy, and external beam radiotherapy yielded a different outcome related the conventional radiotherapy. Two thousand six hundred fifty-eight (2658) patients treated over 3 years were followed over 10 years. The study found that, when adjusted for age and smoking history, the incidence of second malignancies after radiotherapy was not significantly different from that after radical prostatectomy.

Regarding the risk of second malignancy after cranial irradiation with SRS, a study with 5000 patients showed no increased risk (Rowe et al, 2007). The authors conclude, "Pragmatically, in advising patients, the risks of malignancy would seem small, particularly if such risks are considered in the context of the other risks faced by patients with intracranial pathologies requiring radiosurgical treatments."

Whether PBT increases or reduces the risk of second malignancies is very much an unanswered issue, and as a result of the available published data, the use of proton beam is considered not medically necessary solely to reduce the risk of a secondary malignancy.

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