Saudi Arabia National Clinical Proton Beam Therapy (PBT) Guidelines

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Defining Clinical Indications of Proton Beam Therapy (PBT) at National level in the Kingdom of Saudi Arabia

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Abstract:

Background: The Saudi Particle Therapy Centre (SPTC) has recently established Proton Beam Therapy (PBT) services within Kingdom of Saudi Arabia. Thus, national guidelines for the appropriate selection and referral of patients, who are most likely to benefit from PBT are needed.

Methods: SPTC invited a panel of expert radiation oncologists practicing in Saudi Arabia to design national clinical practice guidelines on the referral, absolute and relative indications and dose/fractionation for PBT. After the panel identified key clinical questions, the PubMed/MEDLINE, CANCERLIT, EMBASE, and Cochrane Library databases were searched for relevant randomized clinical trials (RCT), retrospective studies, case series, case reports, systematic reviews, and meta-analyses. Recommendations were based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

Results: SPTC expert panel recommends PBT as absolute indication for ocular tumors, base of skull and spine tumours, hepatocellular carcinoma (Child-Pugh A), all pediatric malignancies, para-nasal sinuses/nasal cavity tumors and for re-irradiation of all sites for curative intent. Relative use of PBT may be considered if no other local alternative therapy is available, or when photon therapy plans are not meeting safe dose tolerance for critical organs at risk (low grade glioma, intracranial Meningioma, locally advanced Head and Neck, esophageal, pancreatic non-small cell lung, rectal cancer, retroperitoneal or spinal/parapsinal soft tissue sarcoma and Carcinoma, bulky mediastinal Lymphomas.

Conclusion: Apart from absolute and relative indications, panel did not recommend routine PBT for other sites. However, individual cancer patients can be considered for PBT after a multidisciplinary approach and expert's opinion.

Key words: Proton Beam therapy, Saudi Arabia, National level guidelines, absolute and relative indications, dose and fractionation.

1. INTRODUCTION:

The unequivocal evidence suggests that higher radiation doses to various tumors translate to higher local control rates (LC) in cancer patients at the expanse of substantial normal tissue complications; which have spurred technical innovations (conformal and intensity modulated radiation therapy techniques) in the field of radiation oncology to optimize the therapeutic gain by maximizing the tumor dose without increasing normal tissue toxicities.[1,2]

Recently, interest in the use of proton beam therapy (PBT) for the treatment of various tumors is sprouting. With its unique dose-distribution and radiobiological properties (characteristic Bragg-peak), proton therapy has the prospects to improve the therapeutic balance of radiation therapy by allowing for an escalation in tumor dose without a considerable increase in side effects.[3,4] While much evidence supports this perception in the context to many tumor sites; only a few randomized clinical trials of PBT have been conducted so far, mainly due to the lack of functional PBT cancer centers worldwide.[5] Thus, the main reference of PBT evidence including clinical indications, cumulative doses, fractionation schedules and toxicity profile relies on prospective or retrospective case series and cohort studies.[6,7,8,9] Based on the current available data, American Society of Radiation Oncology (ASTRO) have recently formulated the model policies for the absolute and relative indications for PBT.[10] According to Particle Therapy Co-Operative Group (PTOG) statistics suggest that nearly 111,088 cancer patients have been treated with PBT by 2013 worldwide.[11]

Currently, Kingdom of Saudi Arabia lacks the facilities of PBT. Therefore, Saudi cancer patients travel abroad to access PBT at higher costs. The Saudi Particle Therapy Center (SPTC) has recently established PBT unit within King Fahad Medical City (KFMC), Riyadh, Saudi Arabia.[12] Current guidelines represent the evidence-based opinions reached by experts for the selection and referral of patients most likely to benefit from PBT.

2. PATIENTS AND METHODS:

2.1. Formulation of Panel of Experts

After formal approval by institutional Ethics Committee, a panel of expert radiation oncologists practicing in Saudi Arabia based on their knowledge and clinical experience in the field PBT was coined. Potential conflicts of interest among all the panel members were managed according to the rules of the World Health Organization (WHO).[13] The panel reinforced crucial questions to be answered by these guidelines. Those essential questions tackled the following main domains:

1. The absolute indications for PBT.
2. The relative indications for PBT.
3. Proton radiation dose and fractionation schedules.

2.2. Literature Search Strategy

The search criteria included the randomized clinical trials (RCT), retrospective studies, case series, case reports, related systemic reviews, and meta-analyses. The abstracts with full details were also included. The PubMed/MEDLINE, CANCERLIT, EMBASE, and Cochrane Library databases were searched using terms: Protons (MeSH term) or proton radiotherapy, High Energy (MeSH term) or particle beam therapy or charged particle therapy and neoplasms (MeSH term) or malignancy (MeSH term). The search was limited to studies published in the English language between the years 1990-2016. The relevant articles were retrieved. The studies with insufficient clinical and dosimetric data were excluded.

2.3. Level of evidence

The levels of evidence and grades of recommendation were based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach, and were adapted from the Infectious Diseases Society of American-United States Public Health Services Grading System;[14]

Level I: One large randomised, controlled trial of good methodological quality or meta-analyses of well-conducted randomised trials without heterogeneity.

Level II: Small randomised trials or large randomised trials with potential bias or meta-analyses of such trials or of trials demonstrated heterogeneity.

Level III: Prospective cohort studies.

Level IV: Retrospective cohort studies or case-control studies.

Level V: Studies without control group, case reports, expert opinions.

Grades of recommendation were as A = strongly recommended, B = generally recommended, C = insufficient evidence D = generally not recommended and E = never recommended.

3. RESULTS:

3.1. Ocular neoplasms:

Uveal / Choroidal Melanoma

Uveal melanomas is the most common primary intraocular tumor in adults. Untreated tumors lead to permanent blindness and distant metastases.[15] Available treatment options for such tumors are enucleation, mould brachytherapy and photons. Recent data supports the use of PBT for uveal melanomas for accurate and homogeneous dose distribution within the target volume, with maximum preservation of vision.

The Nice Teaching Hospital, France published its 16 years' experience of PBT in 886 patients with uveal melanoma. PBT was administered on 4 consecutive days, delivering

a total dose of 60 cobalt Gray equivalent (CGE). Excellent eye preservation rates were reported; 91.1% and 87.3% at 5 and 10 years respectively. The tumor control rates were 93.9% at 5 years and 92.1% at 10 years and metastasis-free survival rates were 88.3 % and 76.4 % at 5 and 10 respectively. The ocular conservation rates were 91.1% at 5 years and 87.3% at 10 years.[16]

In similar fashion, primary treatment for choroidal melanoma is surgery, which tends to cause photophobia and lens subluxation. Damato B et al. reported an extensive series of 349 patients with choroidal melanoma treated with PBT at Clatterbridge Centre for Oncology (CCO) between 1993 and 2003. Four daily fractions of PBT were delivered, with a total dose of 53.1 CGE. At the 5 years of follow-up, excellent local control rates were achieved by PBT (96.5%) as compared to enucleation (90.6%) with eye preservation in 79.1% of patients.[17]

Recently, a retrospective German data reported the outcomes of PBT in 54 patients with diffuse and unresectable iris melanoma treated during 1998 and 2012. At a median follow-up of 62.7 months, local tumor was achieved in 96.3% of the patients with minimal toxicity. Only three patients underwent salvage enucleation (eye preservation = 87%).[18]

Recently, a Korean study reported the oucomes of 24 patients with choroidal melonimas treated with PBT with doses of 60-70CGE. At 3 years, local control, distant metastasis-free survival, and overall survival (OS) rates were 95.8%, 95.8%, and 100%, respectively.[19]

The panel strongly recommended the use of PBT in ocular tumors (Level II, III, and IV).

3.2. Base of skull and spinal tumors

Chordomas / chondrosarcomas

Complete resection of the tumors especially chordomas and sarcomas at the base of the skull (BOS) and spinal cord by surgical approaches is quite tricky and is associated with high morbidity. On the other hand, even modern photon therapy techniques (3DCRT and IMRT) face a fundamental challenge in providing a curative dose to such tumors due to their proximity to critical structures of the skull base and spine (brain stem, optic nerves, spinal cord).[20]

Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland reported the survival outcomes of 251 patients BOS chondrosarcoma, who were treated with protons with (n = 135) or without photons (n = 116). Median delivered dose was 70.2 CGE. At a median follow-up of 88 months, local and distant failures were observed 4.8% and 1.6% patients, respectively. The estimated 7-year OS was 93.6%.[21]

Munzenrider et al. reported the 10 years results of 229 patients with chondrosarcomas of the skull base treated with PBT with a dose ranging from 66 to 83 CGE. The 10-year actuarial local tumor control was seen in 94% of patients with the 10-year OS rate of 88%.[22]

Another pilot study by Austin-Seymour M et al. reported the 5-year tumor control rates of 82% and disease-free survival of 76% in 68 patients with chordoma or low- grade

chondrosarcomas of skull base treated with fractionated high-dose postoperative radiation delivered with a 160-MeV PBT with median tumor dose of 69 CGE.[23]

A case series by Hug et al. at the MGH/Harvard Cyclotron Laboratory on six patients with spine chondrosarcomas and 14 patients with spine chordomas treated with PBT alone or combined with surgery (dose 54-82 CGE) showed the 5-year local control rates for chordomas and chondrosarcomas were 53% and 100%, respectively. The 5-year OS rates were 50% for the chordomas and 100% for the chondrosarcomas.[24]

Rutz et al. reported on a cohort of 26 patients with spine chordomas treated at the Paul Scherrer Institute with PBT. The median dosed delivered was 72 CGE. At a median follow-up time of 35 months, the 3-year tumor control was 86% with 3-year actuarial OS of 84%.[25] Furthermore, subgroup analysis of this study revealed that patients with tumors >30ml and with surgical spine stabilization implants had the worst clinical outcomes.[25]

Rotondo et al. recently reported a review of 126 spine chordomas/chondrosarcomas patients treated with PBT. With a median follow-up of 41 months, the 5-year OS, and tumor control rates were 81%, and 62% respectively. Control rate was higher for primary chordomas (68%) as compared to recurrent chordomas (49%) P = 0.058.[26]

Meningiomas

Geneva University Hospital, Geneva, Switzerland assessed the long-term clinical results of PBT in the treatment of 39 patients with atypical skull base meningioma. The median administered dose was 56.0 Gy (range, 52.2-66.6). The 5-year tumor control and OS rates were 84.8% and 81.8% respectively without any severe toxicity.[27]

McDonald MW, et al., published case series of clinical outcomes of PBT in 22 patients with atypical meningioma treated with a median dose of 63 CGE. At a median follow up of 39 months (7-104), all patients remained alive with 5-year local tumor control rate of 71.1%. Radiation necrosis was observed in only in one patient who had a history of prior cranial irradiation.[28]

The panel strongly recommended the use of PBT in spine and skull base tumors and meningioma (Level II and III).

3.3. Hepatocellular carcinoma (Child Pugh-A) (HCC)

In the year 2009, Fukumitsu et al. reported the results of a prospective study of patients with HCC (Child Pugh-A) treated with hypofractionated PBT. Fifty-one patients were treated with 66 CGE in ten fractions. Local tumor control rates at the 3 and 5 years were exceptional; 94.5% and 87.8% respectively with 3 and 5 year OS rates of 49.2% and 38.7% respectively.[29]

Recently in a phase II trial, 76 HCC patients were treated at Loma Linda University with PBT with a median dose of 63 CGE in fifteen fractions. Median survival of 36 months was achieved, and among those 18 patients who eventually went on to a liver transplant. The 3 year OS rate was 70%.[30]

Three PBT protocols (A = 66 CGE in 10 fractions; B = 72.6 CGE in 22 fractions; and C = 77 CGE in 35 fractions) were compared in one prospective trial to avoid late side effects,

such as gastrointestinal ulceration and bile duct stenosis. 266 patients with HCC were treated by PBT at the University of Tsukuba between 2001 and 2007. The survival rates after 1, 3 and 5 years were 87%, 61%, and 48% respectively (median survival = 4.2 years). The local tumor control rates after 1, 3, and 5 years were 98%, 87%, and 81%, respectively.[31]

Sugahara S et al. investigated the clinical outcomes of PBT in 22 patients with large HCC (size > 10 cm). The median total dose delivered was 72.6 CGE in 22 fractions. The median follow-up period was 13.4 months. Tumor control rate at 2 years was 87%. Two-year OS and progression-free survival rates were 36% and 24%, respectively. The dominant tumor progression pattern was new hepatic tumor development outside the irradiated field. No late treatment-related toxicity of Grade 3 or higher was observed.[32]

Toranomon Hospital, Tokyo, Japan recently published the treatment outcomes of 83 patients HCC who were treated with PBT; median radiation dose was 72.6 CGE (50-74). The rates of local control of the target tumor at 6 months, 1 year, and 2 years were 91.9, 86.3, and 84.8%, respectively. The overall survival rates at 1, 2, and 3 years were 83.0, 65.6, and 55.1%, respectively.[33]

The panel strongly recommended the absolute use of PBT in HCC with Child-Pugh A and large size HCC > 10 cm who are not candidates for a liver transplant (Level II and III).

3.4. Pediatric malignancies

The rationale for using PBT for pediatric central nervous system (CNS) tumors lesions is captivating mainly due to a lower risk of secondary malignancies in childhood cancer survivors, because of improved dose distribution and substantial sparing of healthy tissue as compared to other radiation modalities.[34]

Medulloblastomas:

Given the constitutive nature of craniospinal irradiation (CSI) for the treatment of medulloblastoma, and potential late side effects secondary to this therapy, PBT has been considered for CSI delivery. CSI delivery with photon therapy can raise the potential risk of various long-term sequelae in children (growth retardation secondary to vertebral body irradiation, cardiac dysfunction, primary hypothyroidism, or increased risk of second malignancies due to the exit beam of photon therapy that results in low dose being delivered to non-target sites. While alternative means (electrons and hyperfractionated radiotherapy) have limited their adoption to the current standard of care.[35]

PBT, therefore, has emerged as an enticing alternative therapeutic modality to reduce dose to normal tissues. Massachusetts General Hospital (MGH) closely followed a well-matched cohort of standard risk medulloblastoma patients receiving CSI with posterior fossa/tumor bed boost using either proton or photon therapy for incidence of hypothyroidism, growth hormone deficiency, adrenal insufficiency, sex hormone deficiency, precocious puberty, need for endocrine replacement therapy and height and body mass index standard deviation score (SDS). Authors concluded that PBT remained a statically significant predictor of reduced risk of hypothyroidism, sex hormone deficiency, and need for endocrine therapy. Additionally, it was associated with greater height SDS in comparison to photon therapy in both multivariate and propensity-matched analysis.[36]

Similarly, Brodin et al. studied ten pediatric patients with medulloblastoma evaluating treatment plans that incorporated CSI doses of 36 and 23.4 Gy followed by a posterior fossa boost to 54 Gy that were delivered with 3D-CRT, Rapid Arc IMRT, or PBT; mean target doses were normalized to have the same value as the 3D-CRT plan to allow appropriate comparison of these techniques. The estimate of solid second cancer risk was significantly lesser in PBT than for both photon techniques for 23.4 and 36 Gy prescribed CSI doses. The risk of developing late normal tissue complications, such as long-term pneumonitis, heart failure, xerostomia, blindness and ototoxicity risks were also significantly lower with PRT than photons.[37]

While PBT-CSI has the potential for reduced delayed-toxicity, it too has the ability to reduce acute side effects. MD Anderson Cancer Center (MDACC) retrospectively analyzed 40 medulloblastoma patients treated with either proton or photon CSI therapy. In a well-matched cohort, they found that proton CSI patients lost less weight than photon patients (median percent weight change of -1.2% and -5.8%, respectively, P=0.004). Fewer patients treated with PBT suffered weight loss of >5% from baseline as compared to those received photon therapy (P=0.004). Additionally, photon CSI was associated with significantly higher rates of grade 2 nausea/ vomiting, esophagitis management and bone marrow suppression.[38]

Recently a phase II trial on 59 patients with pediatric medulloblastoma treated between 2003 and 2009 with PBT CSI: 39 with standard-risk disease, six with intermediate-risk disease, and 14 with high-risk disease. Patients had craniospinal irradiation of 18-36 CGE followed by a boost dose. Pediatric Oncology Group (POG) hearing ototoxicity score at a follow-up of 5·0 years (IQR 2·9 - 6·4) was the same as at baseline or improved by 1 point in 35% of cases. Full-Scale Intelligence Quotient (IQ) decreased by 1·5 points (95% CI 0·9-2·1) per year after median follow-up up of 5·2 years (IQR 2·6-6·4), driven by decrements in processing speed and verbal comprehension index. Perceptual reasoning index and working memory did not change significantly. 5-year r progression-free survival was 80%, and 5-year OS was 83%.[39]

Pediatric ependymomas:

Due to deep location of ependymomas, in spite of increasing conformity of radiation delivery, radiation doses exceed the adjacent normal organs at risk (brainstem, hypothalamus, pituitary, cochlea, hippocampi and normal brain parenchyma) which alarms the potential for long-term cognitive, neurological and endocrine dysfunction as a result of this increased dose bath. PBT has particular benefit in reducing dose to these structures. Mizumoto et al. analyzed the potential reduction of normal brain parenchyma irradiation in six patients with intracranial ependymoma who were treated with PBT by completing a dosimetric comparison to 3D-CRT for these patients' plans. Their study revealed that utilization of PBT resulted in a median decrease of mean normal brain dose by 47%. Further, authors predicted that using proton beam could reduce the IQ decrease by approximately half of what is predicted for photon therapy.[40]

MacDonald et al. have also reported one of the most extensive series of pediatric ependymomas patients treated with PBT. In their series, 70 patients underwent involved field PBT with most patients receiving 54 CGE. With a median follow up of 46 months, they reported a 3-year progression free survival 76% and 3 year OS rate of 95%.[41]

The panel recommends that PBT should receive serious consideration as the preferred technique for the treatment of pediatric tumors. (Level II and III).

3.5. Paranasal sinuses (PNS) and nasal cavity tumors

PNS tumors and nasal cavity tumors are curatively treated by craniofacial surgery and postoperative radiotherapy. However, surgical approaches are often complicated by severe functional deformity in T4 tumors, and adequate surgical clearance is usually challenging to obtain. Definitive RT in form 3DCRT and IMRT is usually opted for these cases, but aggressive irradiation of the intracranial component poses an immense risk of late toxicity.[42]

Zenda S et al., reviewed 39 patients with unresectable PNS and nasal cavity tumors who were treated with PBT with doses of 60 CGE during 1999 and 2006. With a median follow-up of 45.4 months, the tumor control rates at 6 months and 1 year were 84.6% and 77.0%, respectively. The 3-year progression-free survival and OS rates were 49.1% and 59.3%, respectively. The most common acute toxicities were Grade ½ dermatitis (33.3%), but no grade 3/4 toxicity was observed.[43]

Hojo H et al. demonstrated the clinical usefulness of PBT in 65 patients with PNS and nasal cavity tumors treated during 1998-2008. The median follow-up period was 51.6 months. Radiological complete response (CR) within 6 months was seen in 15% of the patients with the 3-year progression-free survival of 49.2%.[44]

Fukumitsu N et al. reported the clinical outcomes of PBT in 17 recurrent, unresectable PNS and nasal cavity tumors. The survival rate was 47.1% at 2 years and 15.7% at 5 years, with local control of 35.0% at 2 years and 17.5% at 5 years. Delayed toxicity of more than Grade 3 (brain necrosis and ipsilateral blindness) was found only in 2 patients.[45]

MGH also recently reported the clinical outcomes of 20 patients with primary sphenoid sinus malignancy treated with proton beam therapy to a median dose of 76 CGE. With a median follow-up of 27 months, the 2-year local, regional, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively. The disease- free and OS rates at 2 years were 31% and 53%, respectively.[46]

The panel recommends that PBT should receive serious consideration in unresectable PNS and nasal cavity tumors (Level II and III).

3.6. Re-irradiation of all sites for curative intent

Recurrent Nasopharyngeal carcinoma

Loma Linda University reported the outcomes of PBT to re-irradiate eleven patients with recurrent nasopharyngeal cancers who were previously treated with photons. The range of PBT doses was between 59.4–70.2 CGE. Local tumor control was achieved in 45%, and median survival was 42 months. 3 year OS rates were 59%, and 5 year OS rates were 31%. Authors reported no severe complications.[47]

Romesser PB et al. reported a retrospective review of 92 recurrent head and neck cancer patients who were re-irradiated with PBT between 2011 and 2014. The median PBT dose

was 60.6 Gy. Median follow-up among surviving patients was 13.3 months and among all patients was 10.4 months. Acute grade 3 and 4 toxicities were seen in less than 10% of patients. Two patients died of tumor-related bleeding.[48]

Buchsbaum J et al reported that re irradiation with PBT for recurrent gliomas at Indiana University was generally well tolerated and associated with favorable long-term survival in patients with WHO 1-3 gliomas. The 10% crude rate of radiation necrosis is modest give the high cumulative dose is these patients.[49]

Boimel PJ et al reported promising result for re-irradiation by Proton for Locally Recurrent Pancreatic Adenocarcinoma. It was well-tolerated and resulted in prolonged overall survival, local-regional progression-free, and distant metastasis-free survival, when compared to historical controls of locally recurrent pancreatic cancer. However, caution should be exercised when combining re-irradiation with stents.[50]

Thorpe C et al recently reviewed the use of Proton Beam Therapy Re-irradiation for Recurrent Breast Cancer, the 1-year local recurrence free survival was 93%, and 1-year OS was 97%. PBT was well tolerated with favorable local control with acceptable toxicity.[51]

The panel recommended that PBT should be considered for patients with recurrent HNC who have previously undergone head and neck irradiation (Level III, IV).

3.7. Acoustic neuromas and vestibular schwannomas (VS)

Vernimmen FJ et al., retrospectively evaluated the role of hypofractionated stereotactic PBT for 51 patients with acoustic neuromas. Mean dose prescribed to ICRU reference point was 26 CGE in 3 fractions. With a mean follow-up of 72 months, the 5-year local control was achieved in 98% of patients, with a hearing preservation rate in 42%, facial nerve preservation in 90.5% and trigeminal nerve preservation in 93% of cases.[52]

Similarly, MGH reported the actuarial 2- and 5-year local control rates of 95.3% and 93.6% respectively in 88 patients with vestibular schwannomas treated with PBT stereotactic radiosurgery. A median dose of 12 CGE was prescribed. The median follow-up period was 38.7 months. Actuarial 5-year facial and trigeminal nerve function preservation rates were 91.1% and 89.4% respectively.[53]

At Loma Linda University Medical Center, 31 patients with VS, with a mean tumor volume of 4.3 cm3, were treated with fractionated PBT. According to the hearing status of patients, the prescribed dose was 54 CGE in 30 fractions and 60 CGE in 30–33 fractions for patients with functional and non-functional hearing, respectively. Both dose groups had excellent results, with a 100% tumor control rates and without trigeminal and facial cranial nerve palsies.[54]

The panel recommended the use of PBT in acoustic neuroma and vestibular schwannoma (Level III, IV).

3.8. Adult Low-grade glioma (LGG)

With more aggressive combined treatment (surgery, radiotherapy and chemotherapy), an increasing proportion of patients with high risk LGG are considered to be long-term

survivors. It has therefore become increasingly important to consider the risk of long-term treatment-induced side effects especially cognitive impairment in this patient group.[55] Recently, a systematic review of nine studies reported dosimetric comparison and toxicity profile of PBT with IMRT. Prescribed dose of PBT ranged between 50.4 CGE to 68 Gy.

Most common acute grade 3 toxifies were Fatigue (10-17%), local erythema (5%) and headache (5%). One study reported no significant long-term cognitive impairments. One study reported a 5-year overall survival of 84% and 5-year progression-free survival of 40%.[56]

3.9. Non-small cell lung cancer (NSCLC)

PBT for the treatment of NSCLC is under active research. The unique radiobiological characteristics of PBT theoretically reduce the irradiated volume of normal tissues (heart, normal lungs, esophagus, and spinal cord). Higgens KA, et al analyzed the outcomes and predictors associated with PBT for NSCLC the National Cancer Database. A total of 243,822 patients (photon radiation therapy: 243,474; PBT: 348) were included in this analysis. On multivariate analysis of all patients, non-proton therapy was associated with significantly worse survival compared with PBT (hazard ratio 1.21 [95% CI 1.06-1.39]; P<.01). On propensity matched analysis, PBT was associated with better 5-year OS compared with non-proton radiation therapy, 22% versus 16% (P=.025). For stage II and III patients, non-proton radiation therapy was associated with worse survival compared with PBT (hazard ratio 1.35 [95% CI 1.10-1.64], P<.01).[57]

Nakayama H et al. reported the outcomes of PBT in 35 patients with inoperable stage II and III NSCLC who were treated with PBT between 2001 and 2008. The median proton dose given was 78.3 Gy. Local PFS for Stage II-III patients was 93.3% at 1 year and 65.9% at 2 years during a median follow-up period of 16.9 months. The PFS rate for Stage II-III patients was 59.6% at 1 year and 29.2% at 2 years. The OS rate of Stage II-III patients was 81.8% at 1 year and 58.9% at 2 years. No grade 3 or higher toxicity was observed.[58]

Recently, MDACC hey reported early results of a phase 2 trial of high-dose PBT with concurrent chemotherapy in terms of toxicity profile and survival outcomes in 44 patients with stage III NSCLC. Median follow-up time was 19.7 months. No patient experienced grade 4 PBT-related toxicity. The most common non-hematologic grade 3 toxicities were dermatitis, esophagitis, and pneumonitis. Local recurrence was documented in 20.5% cases, and 43.2% patients developed distant metastasis. The OS and PFS rates were 86% and 63% at 1 year.[59]

The panel recommended the use of PBT as a relative indication in inoperable stage II and III NSCLC (Level IV).

3.10. Locally advanced pancreatic and ampullary tumors

University of Florida Proton Therapy Institute, USA reviewed the PBT toxicity profile for 22 patients with pancreatic and ampullary cancers treated during 2009 through 2012. PBT doses were 50.40 -59.40 CGE. Median follow-up period was 11 (5-36) months. None of the patients demonstrated any grade 3 toxicity during treatment or during the follow-up. Significant bowel sparing was observed in PBT treatment plans.[60]

The panel recommended the use of PBT as a relative indication in locally advanced pancreatic and ampullary cancers (Level IV).

3.11. Locally Advanced Esophageal Carcinoma

Sugahara S et al. presented the results of PBT for the 46 patients with esophageal cancer, who were treated between 1985 and 1998 using proton beams with or without X-rays. Forty patients were treated with combined photons and PBT with a median dose of 76.0 CGE. The remaining 6 patients received only PBT (median, 82.0 Gy). The 5-year actuarial OS rates for T1, T2, and T3-T4 were 34%, 55%, and 13%, respectively. The 5-year disease-specific survival rates according to T stage (T1, T2, and T3-T4) were 67%, 95%, and 33%, respectively. The 5-year local control rates for patients with T1 and T2-T4 lesions was 83% and 29%, respectively.[61]

Ishikawa H et al. further investigated the outcomes of PBT combined with chemotherapy (cisplatin and 5-fluorouracil) for 40 patients with locally advance esophageal cancer. A total dose of 60 CGE in 30 fractions was delivered, and an additional boost of 4-10 CGE was given when residual tumors were suspected. The median follow-up time was 24 months. No cardiopulmonary toxicities of grade 3 or higher were observed. Recurrences were found in 16 patients, and the 2-year rates of disease-specific survival and locoregional control were 77% and 66%, respectively.[62]

Proton Medical Research Center, University of Tsukuba, Japan evaluated the efficacy and safety of hyperfractionated concomitant boost PBT for the 19 patients with locally advanced esophageal cancer. The median total dose was 78 CGE. The 1- and 5-year actuarial OS rates for all patients were 79.0% and 42.8%, respectively, and the median survival time was 31.5 months. Only 1 patient had late esophageal toxicity of Grade 3 at 6 months after hyperfractionated PBT.[63]

The panel recommended the use of PBT as a relative indication in locally advanced esophageal cancers (Level IV).

3.12. Locally Advanced Rectal Cancer

A small pilot Swedish study treated 7 patients with locally advanced rectal cancers (sacrum or pelvic sidewall invasion) with Intensity modulated photon and pencil beam scanning proton plans with simultaneously integrated boosts (45 Gy to elective lymph nodes, 50 Gy to the tumor and 62.5 Gy to boost area in 25 fractions). 5/7 patients (71.4%) had significant sparing of dose to the small intestine with PBT.[64]

The panel recommended the use of PBT as a relative indication in locally advanced rectal cancers (Level IV).

3.13. Soft tissue sarcomas (STS)

Paul Scherrer Institute, Switzerland assessed the clinical outcomes of PBT in the curative treatment of STS in 13 adult patients, who were treated between 1998 and 2005. The median prescribed dose was 69.4 CGE. Pre-PBT anthracycline-based chemotherapy was given to three patients only. Median follow-up period was 48.1 months. The 4-year local control and metastasis-free survival rates were 74.1% and 84.6%, respectively. Late grade ≥2 toxicity was observed only in two patients.[65]

MGH conducted a phase II trial of PBT in 50 patients with non-metastatic, thoracic, lumbar, and/or sacral spine/paraspinal sarcomas. Shrinking fields delivered 50.4 CGE to subclinical disease, 70.2 Gy CGE to microscopic disease in the tumor bed, and 77.4 Gy CGE to gross disease. With 48-month median follow-up, 5-year actuarial local control rates DFS, and OS rates were noticed as; 78%, 63%, and 87% respectively. No myelopathy was observed. However, three sacral neuropathies appeared after 77.12 to 77.4 Gy CGE.[66]

The panel recommended the use of PBT as a relative indication in spinal and paraspinal STS (Level II, III).

3.14. Bulky Mediastinal Lyphomas (NHL and HL)

University of Florida Proton Therapy Institute analyzed the dosimetric impact of PBT on various cardiac subunits in 13 patients with Hodgkin lymphoma (HL) as compared to 3DCRT and IMRT. The mean heart doses were 21 Gy, 12 Gy, and 8 Gy (RBE) with 3DCRT, IMRT, and PBT, respectively. Compared with 3DCRT and IMRT, PBT reduced the mean doses to the left and right atria; the left and right ventricles; the aortic, mitral, and tricuspid valves; and the left anterior descending, left circumflex, and right circumflex coronary arteries.[67]

MDACC evaluated the PBT for reducing doses to normal structures in 10 patients with mediastinal lymphomas compared with 3DCRT. PBT prescribed total dose was 30.6-50.4 CGE. PBT achieved lower mean doses to the lung (6.2 vs. 9.5 Gy), esophagus (9.5 vs. 22.3 Gy), and heart (8.8 vs. 17.7 Gy) than did conventional RT. Of the 7 patients who had residual disease on positron emission tomography before PBT, 6 (86%) showed a complete metabolic response.[68]

Hoppe BS et al. described the early clinical outcomes of a phase II trial of consolidative involved-node proton therapy (INPT) as a component of multi-modality approach in 15 patients with stages I to III HL with mediastinal involvement. The total dose was 30.6 to 39.6 CGE of INPT. At the median follow-up of 37 months, 2 events occurred during follow-up: 1 relapse (inside and outside the targeted field) and 1 transformation into a primary mediastinal large B cell lymphoma. The 3-year progression-free survival was 93%, and the 3-year event-free survival rate was 87%. No acute or late grade 3 non-hematologic toxicities were observed.[69]

The panel recommended the use of PBT as an indication in mediastinal NHL and HL with bulky mediastinal disease (Level II, III, and IV).

4. CONCLUSION:

This evidence-based and expert radiation oncologists' opinions recommendations apply to our pediatric and adult cancer patients for treatment with PBT. Grade A and grade B recommendations in cancer patients for absolute indications for PBT was seen in;

4.1. Absolute Indications:

Ocular Tumors:
- Eye: Benign and Malignant
- Carcinoma In situ of the Eye
- Optic nerve tumor

Spinal and Skull Base Tumors:
Spine:
- Spinal Cord: Benign, Malignant & uncertain behavior
- Spinal Meningioma
- Spinal Meninges: Benign, Malignant & uncertain behavior

Base of Skull:
- Chondrosarcoma
- Chordoma
- Base of Skull Meningioma
- Other rare Neoplastic Histopathologies (Schwannoma, Paraganglioma, Neuroblastoma, Adenoma)

Liver:
- Hepatocellular Carcinoma (Child Pugh-A) (HCC)

Pediatric Patients:
- CNS Tumors
- Non-CNS Solid Tumors

Para-Nasal Sinuses and Nasal Cavity Tumors

Re-irradiation of all sites for curative intent

4.2. Relative Indications:

Justifications:
1. No other local alternative therapy is available.
2. When photon therapy plan is not meeting safe dose tolerance for critical organs at risk.

- CNS Low Grade Glioma
- Intracranial Meningioma (Base of Skull Meningioma is an absolute indication)
- Locally Advanced Head and Neck Carcinoma
- Locally Advanced Esophageal Carcinoma

- Locally Advanced Pancreatic Carcinoma
- Locally Advanced Lung Carcinoma
- Locally Advanced Un-Resectable Rectal Cancer
- Retro-Peritoneal Sarcoma
- Spinal and Paraspinal Soft Tissue Sarcoma
- Bulky Mediastinal Lymphoma (NHL and HL)

For other oncologic sites, PBT was not recommended in routine practice because of non-availability of evidence-based literature or consensus of experts. However, individual cases of any malignancy can be considered for PBT after a multidisciplinary approach and expert's opinion.

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