

Defining Clinical Indications of Proton Beam Therapy at National Level in the Kingdom of Saudi Arabia

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ABSTRACT

يقوم المركز السعودي للعلاج بالجسيمات بتأسيس خدمات العلاج الإشعاعي بالبروتون في المملكة العربية السعودية لذلك فإنه في غاية الأهمية وضع الأدلة السريرية الوطنية لعلاج الأورام بتقنية البروتون حيث قام المركز السعودي للعلاج بالجسيمات بدعوة لجنة من الأطباء الاستشاريين الخبراء الممارسين داخل المملكة العربية السعودية في تخصص طب الأورام العلاجي الإشعاعي لصياغة الدليل السريري الوطني لعلاج الأورام بتقنية البروتون شاملاً الحالات المرضية التي تتطلب العلاج بالبروتون أو التي يمكن أن يكون العلاج بالبروتون خياراً جيداً وأدلة أهلية العلاج لتحويل الحالات للمركز وكذلك جرعة العلاج وعدد الجلسات لكل حالة. قام الفريق بتحديد الأسئلة السريرية الرئيسية كمثل إجراء بحث مستفيض من خلال PubMed وEMBASE ومحركات البحث المختلفة للاطلاع على الدراسات المقارنة والتجارب السريرية والحالات والتقارير المنشورة وقد تم وضع منهج مصنف للتوصيات والتقييم لصياغة التوصيات النهائية. أوصت لجنة الخبراء السعودية للعلاج بالجسيمات باستخدام العلاج بأشعة البروتون مطلقاً لعلاج أورام العين، قاع الجمجمة و أورام العمود الفقري، وسرطان الكبد، و أورام الأطفال وخصوصاً أورام الجهاز العصبي المركزي، والأورام الخبيثة الأنفية وأورام التجويف الأنفي وفي حالات تكرار العلاج بالأشعة كما قد يستخدم العلاج بالبروتون، في حالة عدم توفر خيار مواز آخر، أو عندما تتجاوز خطط العلاج بالفوتون (العلاج التقليدي) مستويات السلامة المقبولة للحفاظ على سلامة الأعضاء السليمة من أضرار الإشعاع ولم يوصَ فريق الخبراء باستخدام أشعة البروتون روتينياً للحالات غير المشمولة في الدليل إلا في نطاق التجارب السريرية ومن خلال مشاورات طبية مشتركة من استشاريي الأورام.

The Saudi Particle Therapy Centre (SPTC) is establishing proton beam therapy (PBT) services within Kingdom of Saudi Arabia (KSA). Thus, national guidelines for the pertinent draft, and recommendations of PBT for cancer patients are utmost important. Saudi Particle Therapy Centre invited a panel of expert radiation oncologists practicing within KSA to formulate national clinical practice guidelines for the referral, absolute and

relative indications and dose/fractionation for PBT. After identifying the key clinical questions, ample search through PubMed, EMBASE, and various search drives was accomplished for appropriate meta-analyses, clinical trials, case-control, and case series studies, and case reports. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was incorporated to formulate various recommendations. Saudi Particle Therapy Centre expert panel recommended PBT as utter modality for ocular tumors, base of skull/spine tumors, hepatocellular carcinoma, all pediatric central nervous system (CNS) malignancies, para-nasal sinuses/nasal cavity tumors and for re-irradiation of all sites aimed for cure. However, PBT may be contemplated, as a relative indication if no other parallel option is available, or when photon therapy plans exceed the dose constraints for critical structures. Further, panel did not recommend routine PBT for other sites beyond clinical trials. However, individual oncology patients can be considered for PBT after a multidisciplinary approach and expert's opinion.

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1. Introduction. The unequivocal evidence suggests that higher radiation doses to various tumors translate into high local control (LC) rates in oncology patients at the expanse of substantial normal tissue

complications, which have spurred radiation therapy metamorphosis to optimize the therapeutic gain by maximizing the tumor dose without increasing normal tissue toxicities.¹

Proton beam therapy (PBT) has gained special interest in cancer management in past few decades. With its unique dose-distribution and radiobiological properties, proton therapy has the prospects to improve the therapeutic balance of radiation therapy by allowing an escalation in tumor dose without a considerable increase in side effects.^{1,2} 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 contributed by the lack of functional PBT cancer centres worldwide.³ Thus, the main reference of PBT evidence including clinical indications, doses-fractionation schedules and toxicity profile relies on prospective or retrospective studies.³ Based on current available data, American Society of Radiation Oncology (ASTRO) have recently composed a policy model for the absolute and relative indications for PBT.⁴

As stated by Particle Therapy Co-Operative Group (PTCOG). Statistics report 2018, more than 2,20,000 patients have been treated worldwide with particle radiotherapy, about 190'000 with PBT.⁴

Currently, Kingdom of Saudi Arabia (KSA) lacks the facilities of PBT. Therefore, Saudi cancer patients travel abroad to access PBT at higher costs. The Saudi Particle Therapy Centre (SPTC) has recently launched PBT unit within King Fahad Medical City (KFMC), Riyadh, KSA.⁶

Current guidelines represent the evidence-based opinions designed by radiation oncology expert panel for the apt selection and referral of oncology patients for PBT, who are most likely to cure and with less harm.

2. Methods. 2.1. Formulation of Panel of Experts.

After formal approval by the Institutional Ethics Committee, a panel of radiation oncologists practicing

in the KSA based on their expert 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).⁶ 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.

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 PubMed, EMBASE, Cochrane Library and Google drives were foraged using MeSH key words: “protons”, or “proton radiotherapy”, “high energy”, or “particle beam therapy”, or “charged particle therapy”, and “neoplasms”, or “malignancy”. The search was restricted to studies published between the years 1990-2018. The relevant articles were retrieved. The studies with insufficient clinical data, or confined to dosimetric data only were excluded.

2.3 Level of Evidence. Grading of Recommendations, Assessment, Development and Evaluation approach was adopted to define various levels and grading of recommendations;⁷

Level I: Well conducted randomized, controlled trial, or good quality meta-analyses without heterogeneity

Level II: Clinical trials with potential bias, or meta-analyses with heterogeneity

Level III: Non-randomized trials

Level IV: Retrospective, or case-control studies

Level V: Case series or reports, or expert opinion

GRADE's recommendation were A (level I/II) = strongly recommended, B (level III) = generally recommended, C (level IV/V) = insufficient evidence D = generally not recommended, and E = never recommended.

3. Results. 3.1 Ocular Neoplasms: Uveal/

Choroidal Melanoma. Uveal melanoma is the most common primary intraocular tumor in adults, which leads to permanent blindness and distant metastases.⁸ Available treatment options for such tumors are enucleation, mould brachytherapy and photons. Proton beam therapy has shown not only a homogeneous doses within narrow and complex target volumes, but also maximum vision preservation.

The Nice Teaching Hospital, France published its 16 years' experience of PBT in uveal melanoma treatment.

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They found that among 886 patients, treated with dose of 60 cobalt Gray equivalent (CGE), eye preservation was achieved in 87.3% of patients at 10 years of follow up. The 10-year local control rate (LCR) was 92.1%. Similarly, 10-year metastasis-free survival rate (MFSR) was 76.4%.⁹

Choroidal Melanomas. Choroidal melanomas are managed surgically, which often results into photophobia and lens subluxation. At Clatterbridge Centre for Oncology (CCO), 349 patients with choroidal melanomas were treated with PBT between 1993 and 2003, with total doses of 53.1 CGE. The 5-year LCR was 96.5% in patients treated with PBT as compared to enucleation (90.6%).¹⁰

Thus, panel strongly recommended the use of PBT in ocular tumors as a sheer indication (Levels II & III).

3.2 Base of Skull and Spinal Tumors. *Chordomas/Chondrosarcomas.*

En bloc resection of chordomas and chondrosarcomas at the base of the skull (BOS) and spinal cord by surgical maneuverers is often gruelling, and is related to significant morbidity. While, conformal and intensity modulated photon therapy modalities confront dosimetric challenge in delivering curative doses to such sites due to their proximity to vital organs.¹¹ Center for proton therapy, Paul Scherrer Institute, Villigen, Switzerland treated 251 patients BOS chondrosarcomas, with PBT, with or without photons, with dose of 70.2 CGE. The 7-year LCR and MFSR were 95.2% and 98.4% with an estimated 7-year OS of 93%.¹² Munzenrider et al¹³ found the 10-year LCR of 94% and OS of 88% in 229 patients with BOS chondrosarcomas treated with PBT with a doses of 74.5 CGE. Likewise, a small series of 26 patients with spine chordomas was presented by Rutz et al,¹⁴ who were treated PBT with doses of 72 CGE. Authors found tumor volumes above 30 ml and previous surgeries were poor prognostic factors.¹⁴ Rotondo et al¹⁵ recently reviewed 126 spine chordomas/chondrosarcomas patients treated with PBT. With a median follow-up of 3.5 years; the 5-year OS were 81% and LCR were 62%. Local control rate was much better for primary chordomas (68%) as compared to recurrent chordomas (49%) ($p=0.058$). The panel strongly recommended the use of PBT in BOS/spinal chordomas and chondrosarcomas as an absolute indication (Levels II & III).

Meningiomas. A pilot study from Geneva University Hospital, Switzerland appraised the long-term clinical outcomes of PBT (dose 56 Gy) in 39 patients with atypical BOS meningiomas. Five-year LCR rates were 84.8% and OS were 81.8% without any late toxicity.¹⁶

McDonald et al¹⁷ published case series of 22 patients with atypical meningiomas treated with PBT (63 CGE). The 5-year- LCR rate was 71%, and only one patient experienced late radiation necrosis. Thus, panel utterly recommended the use of PBT in spine and BOS meningiomas (Levels II & III).

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

In the year 2009, a Japanese prospective trial reported the results of 51 patients with HCC, who were treated with PBT (dose 66 CGE). The 5 year-LCR was 87.8%, with 5-year OS rate of 38.7%.¹⁸

Similarly, about 266 HCC patients were treated by PBT at the University of Tsukuba between 2001 and 2007. Median survival was 4.2 years, and one and 3-year OS rates were 87%, and 61% respectively (median survival = 4.2 years). One year LCR was 98% and 3 years LCR was 87%.¹⁹

Toranomon Hospital, Tokyo, Japan recently published the treatment outcomes of 83 patients HCC who were treated with PBT (dose 72.6 CGE). The LCR of the target tumor at 2 years was 84.8%, with 2-year OS of 55%.²⁰

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

3.4 Pediatric Malignancies. 3.4.1

The logic for using PBT for pediatric central nervous system (CNS) tumors is captivating mainly due to a lower risk of secondary malignancies in childhood cancer survivors, since improved dose distribution and substantial sparing of brain parenchyma in PBT as compared to other radiation modalities.

Medulloblastoma. Given the immanent nature of craniospinal axis (CSA) radiotherapy for the medulloblastoma, and potential late side effects secondary to this therapy, PBT has been widely advocated. Craniospinal axis radiation therapy via photons can theoretically enhance the risks for long-term sequelae in growing children (growth stunting, cardiomyopathy, hypothyroidism, or risk of second tumors mainly due to the exit beam of photons). While alternative means like electrons have limited acquisition in the current standard of care.²¹

A pilot study at Massachusetts General Hospital (MGH) carried on standard risk medulloblastoma children receiving CSA radiotherapy followed by tumor bed boost using either PBT or photons. Authors inferred that PBT remained a statically significant predictor of

reduced risk of stunning growth, hypothyroidism, and hormone deficiencies.²²

A minuscule study by Brodin et al²³ on 10 pediatric patients with medulloblastoma evaluated treatment plans that incorporated CSA photons therapy (dose: 36 and 23.4 Gy) followed by a posterior fossa boost to 54 Gy that were delivered with either conformal therapy, rapid arc, or PBT. The calculated second solid malignancy risk was significantly low in PBT than for both photon techniques. Similarly, the risk of developing late complications, were also significantly lower with PBT than photons.²³

While PBT-CSA irradiation has the potential for reduced delayed-toxicity, it minimize the acute side effects as well. MD Anderson Cancer Center (MDACC) retrospectively inspected 40 medulloblastoma patients treated with either PBT or photon CSA therapy. Authors found that, PBT-CSA patients lost less weight than photon patients ($p=0.004$). In addition, photons-CSA was associated with significantly higher rates of grade 2 emesis, dysphagia, and myelo-suppression.²⁴

Not long ago, a phase 2 trial on 59 patients with pediatric medulloblastoma treated between 2003 to 2009 with PBT CSI: 39 with standard-risk disease, and 20 with high-risk disease. Patients had CSI of 18-36 CGE followed by a boost dose. At 5 years, the hearing toxicity score was either the same as at baseline or was improved by one point in 35% of cases. Similarly, intelligence quotient (IQ) was maintained at 5 years. Five-year progression free survival rates were 80% and OS were 83%.²⁵

3.4.2 Non-CNS Tumors. Pediatric Ependymomas.

Due to deep location of ependymomas, photons (conformal and RapidArc) enface severe problems achieving dose constraints to adjacent critical structures, which alarms the potential for late neurocognitive, and endocrine dysfunction. For such cases, use of PBT is advantageous. Mizumoto et al²⁶ anatomized the effect of PBT on normal brain tissue dose in 6 patients with ependymomas after comparing PBT dosimetric plans with conformal photons plans. Study found that, PBT resulted in a decrease of mean normal brain dose by 47% as those in photons plans. Further, PBT could minimize the IQ level by 50%.²⁶

MacDonald et al²⁷ have also outlined the clinical outcomes of seventy children with ependymomas treated with PBT (dose 54CGE). With a median follow up of 4 years, they discerned 3-year PFS and OS rates of 76%, and 95% respectively.

Pediatric Rhabdomyosarcoma (RMS). A European study on 83 children with RMS, who were treated between 2000 and 2014 with systemic chemotherapy

followed by PBT (54 CGE). The 5-year LCR was 78.5%, and the 5-year OS rate was approximately 80%, with minimal delayed toxicity.²⁸

Low Grade Glioma (LGG). With decreased dose bath to growing brain tissue, PBT has manifested excellent survival outcomes without any serious sequelae. Contemporary retrospective review of 174 children with LGG treated with PBT (54 CGE) during 2007 to 2017, has reported the 5-year LCR rates of 85%, PFS 84%, and OS, 92%. Approximately 96% of patients did not show any deleterious late toxicity.²⁹

The panel recommends that PBT should receive far-reaching reflection as the preferred modality for the treatment of pediatric medulloblastoma, ependymomas, RMS and LGG (Levels II & III).

3.5 Paranasal Sinuses (PNS) and Nasal Cavity Tumors.

Craniofacial surgery followed by postoperative radiotherapy is the gold standard in the management of PNS tumors and nasal cavity tumors. It is often difficult to perform surgery on T4 disease without significant physical and functional compromise. For such unresectable tumors, definitive RT in form 3DCRT and IMRT poses an immense risk of late toxicity.³⁰

A recent meta-analysis has been published on patients with advanced stage PNS tumors who were treated with PBT with equivalent doses of 60CGE. At the follow up of 4 years, the LCR at one year was 77%, with 3-year OS of 59%. Predominant acute toxicities were grade I and II dermatitis (33.3%), but no late toxicity.³¹

Fukumitsu et al documented the clinical sequelae of PBT in 17 recurrent, unresectable PNS tumors. The two-year-LCR and OS rates were was 35% and 47% respectively. Delayed severe toxicity (brain necrosis and ipsilateral blindness) was found in 2 patients.³²

MGH also recently delineated the clinical upshots of 20 patients with sphenoid sinus tumors treated with PBT (dose; 76 CGE). The two-year LCR was 86%, while two-year OS rate was 53%.³³

The panel strongly recommends that unresectable PNS and nasal cavity tumors should be opted for PBT (Level II and III).

3.6 Re-irradiation of All Sites for Curative Intent.

Loma Linda University detailed the consequences of PBT to re-irradiate 11 patients with recurrent nasopharyngeal cancers, who were previously treated with photons. The range of PBT doses was between 59.4–70.2 CGE. LCR was achieved in 45%, and the median survival was 3.6 years, with The five-year OS rate of 31%. Authors reported no severe complications.³⁴

A large retrospective study by Romesser PB et al. outlined the outcomes of 92 recurrent head and neck (H&N) oncology who were re-irradiated with PBT (dose: 60 CGE) between 2011 and 2014. At a follow-up of one year, less than 10% of patients experienced serious toxicity.³⁵

Boimel et al³⁶ described auspicious results for re-irradiation by PBT for locally recurrent pancreatic cancer. Proton beam therapy resulted in prolonged OS, local-regional progression-free, and DMFS, when compared to historical controls. However, authors recommended a caution on its use in patients with biliary stents.

The panel recommended that PBT is ideal treatment modality for patients with locally recurrent H&N cancer, and any other site which has been previously irradiated provided the intent of treatment is for cure (Levels III & IV).

3.8 Acoustic Neuromas (AN)/Vestibular Schwannomas (VS). Vernimmen et al,³⁷ retrospectively assessed the impact of hypofractionated PBT for 51 patients with ANs. Mean dose prescribed was 26 CGE in 3 fractions. At the follow-up of 6 years, the 5-year LCR was gained in 98% of patients, with a hearing preservation rate in 42%, cranial nerve VII preservation in 90% and cranial nerve V preservation in 93% of cases. Comparably, MGH described the 2- and 5-year LCR of 95.3% and 93.6% respectively in 88 patients with VS treated with PBT (dose; 12 CGE). The 5-year facial conservation rates were approximately 90%.³⁸

The panel recommended the use of PBT in acoustic neuroma and vestibular Schwannoma (Levels III & IV).

3.9 Adult Low-grade glioma (LGG). Similar to pediatric LGG, there is increasing interest to consider the probability of extended radiation-induced toxicity especially cognitive impairment in this adult LGG group.³⁹ A small prospective trial of 20 adults with LGG treated with PBT of doses 54 CGE outlined intact intellectual functioning, visuospatial ability, cognition and executive functioning at the 5 years of follow up.⁴⁰ A systematic review of 9 studies reported comparative dosimetric outcomes, toxicity profiles and neurocognitive impairment in PBT and IMRT. Prescribed dose of PBT ranged between 50.4-68 CGE. Proton beam therapy treatment plans were found significantly superior to IMRT-plans regarding doses to uninvolved neural tissue. Acute grade 3 toxicities were; fatigue (10-17%), local erythema (5%) and headache (5%). No neurocognitive impairment was noticed, with 5-year OS of 84% and 5-year PFS of 40%.⁴¹

The panel recommended the use of PBT as an absolute indication in adult LGG (Level II).

3.10 Non-small Cell Lung Carcinoma (NSCLC).

Proton beam therapy for the treatment of NSCLC is under active research. The unique radiobiological characteristics of PBT theoretically reduce the irradiated volume of normal organs.

Nakayama et al⁴² detailed the outcomes of PBT in 35 patients with inoperable stages II and III NSCLC who were treated with PBT with dose of 78.3 Gy. Local PFS for stages II-III patients was 93% at one year and 66% at 2 years. The PFS rate for stages II-III patients was 60% at first year and reduced to its half in second year. The OS rate of stages II-III patients was 59% at 2 years. No harmful event was documented. MD Anderson Cancer Center reported early effects of a small trial of PBT with concurrent chemotherapy in terms of toxicity profile and OS in 44 patients with locally advanced NSCLC. Median follow-up time was 1.7 years. No patient experienced grade IV PBT-related side effects. Local recurrence was documented in 20% cases, and 43% patients developed distant metastasis. The one year OS rates were 86% and PFS were 63%.

The panel recommended the use of PBT as a relative indication in inoperable stages II and III NSCLC if other treatment modality deemed infeasible (Level IV).

3.11 Locally Advanced Pancreatic and Ampullary Tumors.

University of Florida, Proton Center, USA reviewed the PBT toxicity profile for 22 patients with pancreatic and ampullary cancers treated during 2009 through 2012. Proton beam therapy doses were 50.4 to 59.4 CGE. Median follow-up period was one year. None of the patients experienced any grade III and above toxicity. Significant small bowel sparing was achieved in PBT treatment plans.⁴⁴

The panel recommended the use of PBT as a parallel demonstration in locally advanced pancreatic and ampullary cancers if other treatment options are unsuitable (Level IV).

3.12 Locally Advanced Esophageal Cancer.

Sugahara et al⁴⁵ circulated the results of PBT for the 46 patients with esophageal cancer, who were treated with PBT with or without photons (median dose of 76 CGE). The 5-year OS rates for each stage (T1, T2, & T3/T4) were 34%, 55%, and 13%. The 5-year LCR for patients with early stage esophageal cancers was 83% and. Ishikawa et al further investigated the outcomes of PBT (dose 60 CGE) combined with chemotherapy

for 40 patients with locally advanced esophageal cancer. At the follow-up period of 2 years, no heart or lung complications were noticed. The 2-year LCR was approximately 66%.⁴⁶

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

3.13 Locally Advanced Rectal Cancer. A small study from Sweden, comprising seven patients with locally advanced rectal cancers (sacrum or pelvic sidewall invasion) with IMRT and PBT (45 Gy to elective lymph nodes, 50 Gy to the primary tumor and 62.5 Gy to boost areas in 25 fractions). More than 70% of patients had significant sparing of dose to the small intestine with PBT.⁴⁷

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

3.14 Soft Tissue Sarcomas (STS). Massachusetts General Hospital conducted a phase 2 study of shrinking field PBT (70 CGE to microscopic disease and 77 CGE to gross disease) in 50 patients with non-metastatic, spine or paraspinal or retroperitoneal sarcomas. At the follow-up of 4 years, the 5-year LCR rates were 78% and OS were 87%. No myelopathy was observed.⁴⁸

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

3.15 Bulky Mediastinal Lymphomas (NHL and HL). MD Anderson Cancer Center examined the PBT for minimizing radiation doses to adjacent normal organs in 10 patients with mediastinal lymphomas by comparing PBT plans to conformal ones. PBT prescribed total dose was 30.6-50.4 CGE. Proton beam therapy achieved much lower mean doses to the lung (6 vs. 9 Gy), esophagus (9 vs. 22 Gy), and heart (9 vs. 18 Gy) as compared to conformal. Complete remission was obtained in 86% of patients treated with PBT.⁴⁹ Hoppe et al⁵⁰ stated the early clinical outcomes of a small trial of PBT as consolidation; a component of multi-modality approach in fifteen patients with stages I-III HL with mediastinal involvement. The total dose was 30.6 to 39.6 CGE. The 3-year PFS rate was 93%. Neither acute nor late grade III or IV non-hematologic toxicities were noticed.⁵⁰

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

4. Discussion. 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 as absolute and un-mitigated indications for PBT was seen in:

4.1 Absolute indications

Ocular Tumors

- Benign and malignant
- Optic nerve tumors

Spine

- Spinal cord: Benign and malignant
- Spinal meningioma
- Spinal Meninges: Benign and Malignant

Base of Skull

- Chondrosarcoma
- Chordoma
- Base of Skull Meningioma
- Other rare Neoplastic Histopathologies

Liver

- Hepatocellular carcinoma (Child Pugh-A)

Pediatric Patients

- CNS tumors
- Non- CNS tumors

Para-nasal sinuses and nasal cavity tumors

Re-irradiation of all sites for curative intent

4.2 Relative Indications:

Justification:

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 lymphomas (NHL and HL)

For remaining oncologic sites, PBT is not routinely recommended, due to 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. These guidelines will be updated at the time more evidence based literature is available.

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