

Proton beam therapy indications in the Kingdom of Saudi Arabia

A SARO clinical practice guideline

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ABSTRACT

Objectives: To update the national guidelines for proton therapy to reflect the evolving literature. The Saudi Particle Therapy Centre is making efforts to establish proton therapy services in the Kingdom of Saudi Arabia.

Methods: The Saudi Particle Therapy Center collaborated with the Saudi Association of Radiation Oncology to formulate a panel of radiation oncologists with proton therapy experience to refine and update our previous publication. The recommendation level was based on the overall evidence using a 4-grade scale following the World Health Organization quality of evidence recommendations. These updates focus on summarizing the literature and the level of recommendation for each disease site. The Panel identified key clinical questions to ensure that the guidelines were evidence-based, followed by a comprehensive literature review of PubMed, EMBASE, and other academic databases.

Results: The Panel reported that the body of evidence favored proton therapy for specific indications, including ocular tumors, skull and spine tumors, oropharyngeal cancer, hepatocellular carcinoma, specific genetic syndromes and mutations, pediatric rhabdomyosarcoma, pediatric central nervous system malignancies, tumors of the paranasal sinuses/nasal cavity, and for re-irradiation of all sites when curative treatment was intended. In addition, proton therapy may be considered at other sites when photon therapy exceeds the acceptable dose constraints for critical structures.

Conclusion: The Panel did not recommend the routine use of proton therapy for all cancers. Each case should be assessed individually following a multidisciplinary review and expert consultation while accounting for financial, logistical, and patient-specific factors.

Keywords: proton therapy, practice guidelines as topic, clinical decision-making

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Proton beam therapy (PBT) has experienced exponential global growth over the past few years, with more than 100 proton centers established worldwide. The PBT benefits were first recognized by Wilson in 1946, with proton treatment starting as early as 1954 at the University of California, Berkeley, CA.^{1,2} The PBT therapeutic potential, compared to photon-based external beam radiation, lies in its unique dose deposition characteristics, which target specific areas while minimizing exposure to surrounding healthy tissues. The physical properties of protons, specifically the Bragg peak, allow for dose delivery over a narrow depth range in the body with no exit dose, unlike photon beams. This feature widens the therapeutic window,

allowing for dose escalation. Initially, the technology faced significant challenges, such as limitations in beam modulation and conformality, high costs, and a lack of expertise. However, recent advancements in PBT technology, such as pencil beam scanning, multi-leaf collimation, and compact single-room solutions, help offer highly conformal treatment plans with reduced footprints and lower costs.

Staying abreast of the growing literature and clinical evidence in PBT is essential to optimize patient selection and treatment outcomes. Despite its wider adoption, few randomized clinical trials have been published, with PBT being guided by prospective and retrospective studies. The American Society of Radiation Oncology has updated its policy model for PBT. Furthermore, the Saudi Association of Radiation Oncology (SARO) is a leading society in radiation oncology and is committed to enhancing patient clinical outcomes and quality of care. Central to this commitment is the development and distribution of updated guidelines for proton therapy.

The Saudi Particle Therapy Center recently launched its first proton facility in Riyadh, Saudi Arabia. With the growing interest in proton therapy and patient selection criteria among regional radiation oncologists, we aimed to compile an update to previously published guidelines. Given the high cost and potential limitations to the capacity of PBT, these guidelines will provide evidence-based recommendations for the selection of appropriate candidates for PBT, and may serve as a resource for healthcare professionals, patients, and healthcare funders to make informed decisions regarding advanced radiation therapy modalities.

Methods. Disclosure policy. The SARO guidelines were developed through evaluating evidence and classifying it in a systematic approach. Importantly, SARO created these guidelines without funding, relying on the efforts of its members. All members were asked to disclose their industry relationships and personal interests at least 6 months before their voluntary efforts.

History of development. The proton clinical practice guideline, first developed and published in 2018, was led by a panel of local experts. It was created under the World Health Organization (WHO) rules and grading recommendations and adopted by a newly formed task force under SARO.

Selection of task force members. The SARO selected its members from various practicing clinical institutions within Saudi Arabia. Members with clinical experience or training in proton therapy were preferred. Members with related interests who represented organizations or

professional societies were also invited.

Literature retrieval. The Panel pursued a comprehensive literature search covering multiple databases, including PubMed, EMBASE, Cochrane Library, MEDLINE, and Web of Science, for studies published between 1990 and 2024. Search terms included a combination of free-text keywords and Medical Subject Headings related to “protons,” “proton radiotherapy,” “particle beam therapy,” “charged particle therapy,” and “neoplasms” or “malignancy.” We included randomized controlled trials (RCTs), retrospective studies, case series, case reports, related systematic reviews, and meta-analyses published in peer-reviewed journals and available in English. Studies with insufficient clinical data were excluded. All included studies were reviewed by the Panel, and any disagreements were resolved by consensus.

Level of evidence. The level of evidence was defined using the Grading of Recommendations, Assessment, Development, and Evaluation working group, Level I: High-quality evidence, well-conducted RCTs, or good-quality meta-analyses without heterogeneity; Level II: Moderate-quality evidence, including clinical trials with potential bias or meta-analyses with heterogeneity; Level III: Low-quality evidence, including non-randomized trials; Level IV: Very low-quality evidence, including retrospective or case-control studies; and Level V: Expert opinion, including case series and reports. The Panel guideline recommendation level for proton therapy was based on the overall body of evidence using a 4-grade scale following the WHO quality of evidence recommendations: strong (A), body of evidence is strongly convincing; Moderate (B), the body of evidence is moderately convincing; Low (C), the body of evidence is partially convincing; and Very low (D), Body of evidence is not convincing.

Result. 1. General. 1.1 Benign or malignant tumors in children, adolescents, and young adults aged ≤39.

Radiation exposure is generally discouraged for healthy tissue in pediatric, adolescent, and young adult (AYA) populations. This is particularly true for infants and young children—especially those under 3 years of age—whose organs are undergoing critical developmental stages and are therefore highly sensitive to even low radiation doses. AYA individuals, typically defined as those between 15 and 39 years old, also face elevated risks of long-term radiation-related complications due to their longer post-treatment life expectancy. Documented late effects include the emergence of secondary cancers, neurocognitive impairments, hormonal insufficiencies, reproductive challenges,

cardiovascular issues, and functional deterioration of organs.

Currently, few randomized trials have directly assessed the comparative toxicity profiles of proton versus photon radiotherapy in the AYA demographic. In a study using the National Cancer Database (NCDB), Xiang et al³ investigated the incidence of secondary malignancies among pediatric and adult patients with various tumor types. Out of 450,373 patients, 33.5% underwent 3-dimensional conformal radiotherapy (3DCRT), 65.2% received intensity-modulated radiotherapy (IMRT), and 1.3% were treated with PBT. Over a median follow-up of 5.1 years, no significant difference in secondary cancer risk was found between IMRT and 3DCRT (adjusted odds ratio [OR]=1.00, $p=0.75$). However, patients treated with PBT demonstrated a significantly lower risk of developing secondary malignancies compared to those receiving IMRT (adjusted OR=0.31, $p<0.0001$), supporting the theoretical benefit of PBT in minimizing second cancer formation. Further evidence suggests that PBT may preserve cognitive function in central nervous system (CNS) tumor patients, with no observed decline in intelligence quotient (IQ), in contrast to a yearly reduction of 1.1 IQ points associated with photon therapy ($p=0.004$).⁴ Additional benefits of PBT include reduced rates of hypothyroidism (23% with PBT versus. [vs.] 69% with photons), sex hormone deficiencies (3% vs. 19%), and primary hypothyroidism (6% vs. 28%).⁵⁻⁷ Given these findings, the dosimetric superiority of PBT holds meaningful clinical relevance for young patients. Minimizing radiation exposure to vulnerable organs is key to lowering the probability of treatment-related toxicities. PBT is particularly well-suited for candidates such as children, AYAs requiring high-dose radiation for curative intent, those with tumors in anatomically sensitive regions, or tumors positioned near critical structures.

The Panel's review of the body of evidence is strongly convincing (Level A recommendation) for children and moderately convincing (Level B recommendation) for adolescents and young adults (<39 years).

1.2. Patients with genetic syndromes and mutations.

While various genetic pathways are known to influence adverse tissue reactions following radiation therapy, the precise molecular determinants of individual radiosensitivity are still not well defined. The propensity for radiation-induced toxicity is closely associated with patient-specific genetic characteristics, yet robust biomarkers for forecasting severe post-radiotherapy complications remain elusive. A prospective cohort study highlighted correlations between radiation

outcomes and genes such as ATM, CDKN1A, FDXR, SESN1, XPC, ZMAT3, and the BCL2/BAX ratio.⁸ Certain inherited DNA repair syndromes—including Ataxia-telangiectasia, xeroderma pigmentosum, Bloom syndrome, Fanconi anemia, and Li-Fraumeni syndrome—are strongly associated with significant morbidity and, in some cases, mortality after radiotherapy.⁹⁻¹¹ For individuals with these conditions, radiotherapy may need to be avoided altogether, or its parameters (dose, field size, and technique) should be adjusted with extreme care. Patients with TP53 mutations undergoing radiotherapy face a ~30% risk of secondary malignancies within the irradiated area, occurring 2 to 26 years post-treatment.¹² Although no absolute contraindications have been defined for other mutations, caution is advised in individuals with NF-1, MLH1 mutation, BRCA1/2, collagen vascular disease, and inflammatory bowel syndromes, due to heightened susceptibility to radiation-related side effects. The panel's review of the body of evidence is strongly convincing (Level A recommendation).¹³⁻¹⁶

1.3. Re-irradiation for curative intent treatment (all sites). The delivery of re-irradiation (reRT) is sometimes necessary for patients undergoing curative treatment. ReRT aims to enhance local control and achieve better clinical outcomes. However, this process is often complex and challenging, with many organs at risk of nearing their maximum radiation dose tolerance during delivery of the first course. PBT offers a clear advantage in reRT settings by minimizing the dose around the target without compromising the necessary target dose escalation.

Across different cancer types, proton therapy concurrently with chemotherapy reduces grade ≥ 3 toxicity and unplanned hospitalizations when compared to photons (11.5% vs. 27.6%, $p<0.01$).¹⁷ In a substantial retrospective analysis of cranial tumors, Atkins et al¹⁸ studied 815 metastases across 370 patients who underwent proton stereotactic radiosurgery (SRS), with approximately 55% having previously received whole-brain radiotherapy. Their results demonstrated a median survival of 12.4 months and a low incidence of pathologically verified radionecrosis (3.6%). Several extensive retrospective studies have examined reRT using PBT for recurrent head and neck cancers, with findings indicating that patients tend to have improved survival outcomes with intensive PBT reRT compared to photon-based approaches. Nonetheless, individuals who survive remain vulnerable to both early and delayed adverse effects.¹⁹⁻²¹ In another retrospective analysis, McDonald et al²² examined 16 individuals who underwent PBT re-irradiation for recurrent or

progressive skull base chordomas, receiving a median dose of 75.6 Gy relative biologic effectiveness (RBE). The reported 2-year estimated rates for local control (LC) and overall survival (OS) were 85% and 80%, respectively, with a chordoma-specific survival rate of 88%. Adverse events were rare: one patient experienced grade 4 radionecrosis affecting both temporal lobes, while another developed a cerebrospinal fluid (CSF) leak accompanied by meningitis, also classified as grade 4. In a prospective trial, Chao et al²³ evaluated 57 patients with recurrent non-small cell lung cancer who underwent proton beam re-irradiation. The majority (93%) completed the treatment course, with 39% experiencing grade ≥ 3 toxicities and 10% facing grade 5 events. The one-year OS rate was reported at 59%. While the study confirmed the feasibility of PBT, the authors emphasized the need for careful application, taking into account tumor size, anatomical location, and relevant dosimetric parameters.

A prospective, multi-center study²⁴ assessing proton re-irradiation for locoregionally recurrent esophageal cancer reported manageable levels of acute toxicity—23% of patients experienced grade ≥ 3 side effects, while 3% had grade 5 events. Disease control outcomes were also deemed acceptable, with 1-year LC, distant metastasis-free survival (DMFS), and OS rates of 67.1%, 83.4%, and 27%, respectively. In a separate study, Boimel et al²⁵ presented encouraging findings for PBT re-irradiation in cases of locally recurrent pancreatic cancer. Compared to historical data, PBT was associated with improved OS, better local–regional progression-free outcomes, and enhanced DMFS. Nonetheless, caution is advised when considering PBT in patients fitted with biliary stents.

Koroulakis et al²⁶ conducted a retrospective analysis on the use of a twice-daily (BID) proton regimen for re-irradiation in patients with recurrent rectal cancer. The study showed manageable acute toxicity levels, with grade ≥ 3 toxicities occurring in 10.7% of cases and grade 5 events in 3%. Reported 1-year outcomes included local progression at 33.7%, progression-free survival at 45%, and overall survival at 81.8%. In the context of breast cancer reRT, both PBT and volumetric modulated arc therapy (VMAT) were shown to deliver highly conformal radiation plans that minimize exposure to the brachial plexus. However, VMAT was associated with significantly greater loss in dose coverage to nearby at-risk target volumes compared to PBT.²⁷ Separately, Guttman et al²⁸ reported favorable outcomes using PBT re-irradiation for recurrent soft-tissue sarcomas, with no grade 4 or 5 toxicities observed and a 3-year local failure rate of 41%.

In summary, PBT continues to be the recommended modality for curative-intent reRT, especially when the critical structural accumulative dose exceeds tolerance. The Panel's review of the body of evidence is strongly convincing (Level A recommendations).

2. Central nervous system malignancies. 2.1. Ocular neoplasms. Uveal melanoma represents the most prevalent form of primary intraocular malignancy in adults, often resulting in irreversible vision loss and the potential for distant metastasis.²⁹ Treatment options for this condition include enucleation, photon-based radiotherapy, and mold brachytherapy. PBT offers the advantage of delivering a uniform radiation dose within narrow and anatomically complex target volumes while preserving the eye and visual function. The Nice Teaching Hospital in France reported 16 years of clinical experience with PBT for uveal melanoma, treating 886 patients with a dose of 60 cobalt gray equivalents (CGE). At a 10-year follow-up, 87.3% of patients retained their eyes, with a local control rate (LCR) of 92.1% and a metastasis-free survival rate (MFSR) of 76.4%.³⁰ Similarly, the Clatterbridge Centre for Oncology treated 349 individuals with choroidal melanoma between 1993 and 2003 using a total dose of 53.1 CGE. Their 5-year LCR was 96.5% for patients receiving PBT, compared to 90.6% for those who underwent enucleation.³¹ In the only randomized clinical trial comparing charged particle therapy with iodine-125 plaque brachytherapy, 12-year outcomes favored particle treatment, with local control rates of 98% versus 79%, especially for tumors located within 2 mm of the optic disc. Additionally, enucleation rates at 12 years were significantly lower with particle therapy (17%) compared to plaque therapy (37%).³² The Panel's review of the body of evidence is strongly convincing (Level A recommendations).

2.2. Base of skull and primary spinal tumors. Chordomas/Chondrosarcomas. Performing en bloc resections of chordomas and chondrosarcomas located at the Base of Skull (BOS) or near the spinal cord presents considerable surgical difficulty and often leads to high morbidity. Delivering curative radiation doses to these anatomically complex regions is also challenging with conventional photon therapy, due to the need for high-dose prescriptions and the proximity of critical structures.³³ At the Paul Scherrer Institute in Switzerland, a cohort of 251 patients with BOS chondrosarcomas was treated using a combined approach of proton beam and photon therapy, achieving a total dose of 70.2 cobalt CGE. Their results demonstrated excellent outcomes, with 7-year LC and MFSR of 95.2% and 98.4%, respectively, and an estimated 7-year OS rate of 93%.³⁴

They also reported outcomes for 77 chondrosarcoma patients treated with spot scanning, observing a local failure rate of 7.8%, with 8-year LC and OS rates of 89.7% and 93.5%, respectively.³⁵ Munzenrider et al³⁶ reported a 10-year local control rate (LCR) of 94% and OS of 88% in a cohort of 229 patients with BOS chondrosarcomas treated with PBT at a dose of 74.5 Gy (RBE). At the University of Florida Proton Therapy Institute, Deraniyagala et al³⁷ evaluated 33 patients with BOS chordomas, with a median follow-up of 21 months. They observed 2-year LC and OS rates of 86% and 92%, respectively. In a prospective study, Iannalfi et al³⁸ treated 70 patients with BOS chordomas using PBT, reporting a 5-year LC rate of 84% and OS of 83%. Rutz et al³⁹ examined a small series of 26 patients with spinal chordomas treated with PBT at 72 CGE. Their findings identified tumor volumes exceeding 30 cc and prior surgical interventions as adverse prognostic factors. Rotondo et al⁴⁰ reviewed 126 cases of spinal chordomas and chondrosarcomas treated with PBT. With a median follow-up of 3.5 years, the 5-year OS was 81%, and LC was 62%. Notably, primary chordomas showed a higher local control rate (68%) compared to recurrent cases (49%), approaching statistical significance ($p=0.058$). At the Paul Scherrer Institute (PSI), Staab et al⁴¹ evaluated 40 patients with spinal chordomas who underwent spot-scanning PBT. Following a median follow-up of 43 months, they found that patients who received spinal stabilization had a significantly lower LC rate of 30% compared to 100% in those without ($p = 0.0003$). In Japan, Mima et al⁴² reported on 23 patients with sacral chordomas treated with either PBT or carbon ion therapy (CIT). After a median follow-up of 38 months, the LC, OS, and PFS rates were 94%, 83%, and 68%, respectively. No significant differences in clinical outcomes were observed between the 2 treatment modalities. Finally, Chen et al⁴³ from Massachusetts General Hospital (MGH), presented data on 24 patients with spinal chordomas—mostly located at the S1-S2 level—who received high-dose definitive radiotherapy using a combination of protons and photons. After a median follow-up of 56 months, 3-year local PFS and OS were 90.4% and 91.7%, respectively. Tumor size was found to be a critical prognostic factor, with volumes exceeding 500 cm³ associated with poorer overall survival outcomes.

Meningiomas. Florijn et al⁴⁴ conducted a dosimetric comparison involving 20 patients with BOS meningiomas, analyzing treatment plans using intensity-modulated proton therapy (IMPT), IMRT, and non-coplanar VMAT. Their findings showed that IMPT significantly reduced radiation doses to the

bilateral hippocampi, total brain, and volumes receiving between 20 and 30 Gy. In a retrospective analysis from Geneva University Hospital in Switzerland⁴⁵ 39 patients with atypical BOS meningiomas were treated with PBT to a total dose of 56 Gy. The study reported favorable long-term outcomes, with a 5-year LCR of 84.8% and an OS rate of 81.8%, with no instances of late toxicity. Similarly, McDonald et al⁴⁶ presented a case series involving 22 patients with atypical meningiomas treated with PBT at a dose of 63 CGE. They observed a 5-year LCR of 71%, and only one patient developed late-onset radiation necrosis. The panel's review of the body of evidence is strongly convincing (Level A recommendation).

2.3. Primary adult CNS tumors that require craniospinal irradiation. Primary CNS cancers are localized tumors that tend to disseminate throughout the CSF. Medulloblastoma is the most common tumor type associated with dissemination. However, its incidence in adults is only 0.5 per million patients.⁴⁷ The treatment of these tumors usually includes craniospinal irradiation (CSI), which is associated with significant acute and late adverse events.⁴⁸ Dinh et al⁴⁹ compared plans for 10 patients requiring CSI using passive scattering proton therapy (PSPT) and multi-field optimized IMPT (MFO-IMPT) and reported that IMPT displayed superior sparing of the lens and cochleae. Brown et al⁵⁰ reported a retrospective review of 40 adult medulloblastoma patients treated with photon CSI ($n=21$) or proton CSI ($n=19$). Patients treated with proton CSI experienced less nausea, vomiting, weight loss, and esophagitis. The Panel's review of the body of evidence was moderately convincing (Level B recommendations).

2.4. Adult low-grade glioma (LGG). Growing attention is being given to the long-term risks of radiation-induced side effects, particularly cognitive decline.⁵¹ A systematic review of 9 studies compared PBT and IMRT, focusing on dosimetric outcomes, toxicity profiles, and neurocognitive effects. The PBT plans demonstrated clear advantages over IMRT, delivering significantly lower radiation doses to uninvolved brain tissues. The prescribed PBT doses ranged from 50.4 to 68.0 CGE. Acute grade 3 toxicities observed with PBT included fatigue (10–17%), localized skin erythema (5%), and headaches (5%). Importantly, no neurocognitive impairments were reported across the reviewed studies. Survival outcomes were also favorable, with 5-year OS and PFS rates of 84% and 40%, respectively.⁵² A small prospective study involving 20 adults with LGG treated with 54 CGE of PBT further supported these findings. At a 5-year follow-up,

patients maintained stable intellectual performance, visuospatial skills, cognitive abilities, and executive function.⁵³ Subsequent long-term analysis of this cohort confirmed the preservation of both neurocognitive and neuroendocrine functions.⁵⁴ The Panel's review of the body of evidence was moderately convincing (Level B recommendations).

2.5. Acoustic neuromas (AN) and vestibular schwannomas (VS). Vernimmen et al⁵⁵ conducted a retrospective analysis to evaluate the effectiveness of hypofractionated PBT in 51 patients diagnosed with AN. Patients received a mean dose of 26 CGE delivered over 3 fractions. At a median follow-up of 6 years, the study reported a 5-year LCR of 98%. Functional outcomes were also notable, with hearing preserved in 42% of cases, facial nerve (cranial nerve VII) function maintained in 90%, and trigeminal nerve (cranial nerve V) function preserved in 93% of patients. In a separate study from MGH, 88 patients with VS were treated with PBT at a dose of 12 CGE. The reported LC rates were 95.3% at 2 years and 93.6% at 5 years. Facial nerve preservation at 5 years was also high, approaching 90%.⁵⁶ The Panel's review of the body of evidence is partially convincing (Level C recommendations).

2.6. Leptomeningeal disease. Some patients with metastatic solid tumors in the CNS can have leptomeningeal dissemination, with limited treatment options and survival.^{57,58} Yang et al⁵⁹ conducted a prospective phase I clinical trial evaluating the use of proton CSI in 24 patients diagnosed with leptomeningeal metastases. The majority of participants had either non-small cell lung cancer (NSCLC, n=11) or breast cancer (n=7). The median PFS within the CNS was 7 months, while the median OS was 8 months. Notably, 4 patients remained free from CNS disease progression for more than 12 months, indicating a potential for durable response in select individuals. The Panel review of the body of evidence was not convincing (Level D recommendations).

3. Pediatric malignancies. 3.1 Pediatric CNS tumors.

Medulloblastoma. The PBT has become a preferred modality for treating pediatric medulloblastoma, primarily due to its ability to reduce both acute and long-term toxicities associated with CSI. In contrast, photon-based CSI has been linked to a higher risk of delayed adverse effects in children, including growth stunting, cardiomyopathy, hypothyroidism, and the development of secondary malignancies.⁶⁰ Several studies have reinforced the advantages of PBT in this setting. At MGH, a cohort of children with standard-risk medulloblastoma received CSI followed by a tumor bed boost using either PBT or photon therapy.

Results showed that PBT was a statistically significant predictor of reduced risks for growth suppression, hypothyroidism, and hormone deficiencies.⁵ Similarly, Brodin et al⁶¹ conducted a smaller planning study involving 10 pediatric medulloblastoma patients, comparing treatment plans that included photon CSI at doses of 23.4 Gy and 36 Gy followed by a posterior fossa boost to 54 Gy, delivered via conformal photons, VMAT, or PBT. The findings indicated that PBT significantly lowered the calculated risk of second solid malignancies and other long-term complications compared to photon-based techniques. Beyond long-term benefits, PBT also appears to minimize acute toxicities. A phase II trial involving 59 pediatric patients (39 with standard-risk and 20 with high-risk medulloblastoma) treated between 2003 and 2009 with PBT-based CSI (18–36 CGE) followed by a boost, reported encouraging outcomes. At 5 years, 35% of patients had hearing scores that either remained stable or improved by at least one point. Additionally, IQ was preserved throughout the follow-up period. The 5-year progression-free survival (PFS) and overall survival (OS) rates were 80% and 83%, respectively.⁶² In a multi-institutional comparative analysis, Liu et al⁶³ evaluated hematologic toxicity in 97 pediatric patients with medulloblastoma, including 60 who received proton CSI and 37 treated with photon CSI. The majority of patients (over 80%) had standard-risk disease. During weeks 3 to 6 of CSI treatment, patients in the proton group demonstrated significantly higher blood counts, suggesting reduced bone marrow suppression. However, there was no observed difference in OS between the 2 cohorts. Aldrich et al⁷ retrospectively assessed endocrine-related late effects in 118 medulloblastoma patients treated with either proton or photon CSI. Notably, the incidence of primary hypothyroidism was significantly higher in the photon-treated group (28%) compared to the proton group (6%) ($p=0.03$). No significant differences were found between the 2 groups in rates of central hypothyroidism, growth hormone deficiency (GHD), or adrenal insufficiency (AI). Neurocognitive outcomes were also examined by Kahalley et al⁶⁴ who analyzed 79 pediatric medulloblastoma patients—37 treated with proton CSI and 42 with photon CSI. The study found superior intellectual outcomes in the proton group, with stable cognitive scores across all domains except processing speed. In contrast, the photon group experienced notable declines in global IQ, working memory, and processing speed. The authors also reported significant differences in boost dose margins between the 2 cohorts ($p<0.001$), which may have contributed to the disparity in cognitive

outcomes.

One of the key concerns in pediatric CSI is the long-term risk of radiation-induced secondary malignancies. Baliga et al⁶⁵ investigated late toxicities in a cohort of 178 pediatric medulloblastoma survivors treated with proton therapy. With a median follow-up of 9.3 years, the 10-year cumulative incidence of brainstem injury was 2.1%, while the risk of developing a secondary malignancy was 5.6%. These results highlight the relatively low incidence of severe late effects following PBT. Similarly, Indelicato et al⁶⁶ conducted a large-scale analysis involving 1,713 consecutive pediatric patients treated with PBT at the University of Florida Proton Therapy Institute. Only 11 patients developed secondary tumors, resulting in 5- and 10-year cumulative incidence rates of 0.8% and 3.1%, respectively.

Pediatric ependymomas. The deep-seated location of ependymomas often presents a challenge for conventional photon-based techniques. This raises concerns over potential late effects, such as neurocognitive and endocrine dysfunction. PBT, with its superior dose distribution, offers a promising alternative. Mizumoto et al⁶⁷ demonstrated the dosimetric advantages of PBT in a comparative analysis involving 6 pediatric ependymoma cases. Their findings revealed a 47% reduction in the mean dose to normal brain tissue when using PBT over conformal photon therapy. Clinically, MacDonald et al⁶⁸ evaluated outcomes in 70 children treated with PBT (54 CGE), reporting 3-year PFS and OS rates of 76% and 95%, respectively, after a median follow-up of 4 years. Indelicato et al⁶⁹ presented long-term outcomes from 386 children with ependymoma treated at 2 major centers. At a median follow-up of 5 years, the 7-LC, PFS, and OS rates were 77%, 63.8%, and 82.2%, respectively. Importantly, subtotal resection was linked to poorer outcomes across all 3 measures. Additionally, a focused study by Amsbaugh et al⁷⁰ from MD Anderson Cancer Center reviewed 8 pediatric patients with spinal ependymomas treated using PBT. With a mean follow-up of 26 months, they observed 100% LC, event-free survival (EFS), and OS, with no patients experiencing grade 3 or higher toxicities.

Low-grade glioma. Reduced radiation dose to the surrounding growing brain tissue is especially valuable in the pediatric population with LGG. A retrospective analysis evaluated 174 children treated with PBT (54 CGE) between 2007 and 2017. The study reported excellent outcomes: a 5-year LC rate of 85%, PFS of 84%, and OS of 92%. Notably, approximately 96% of patients experienced no serious or lasting toxicities.⁷¹ These findings reinforce the rationale for

using PBT in pediatric LGG, as the therapy provides effective tumor control while significantly reducing the likelihood of long-term sequelae. The panel's review of the body of evidence is strongly convincing (Level A recommendations).

3.2. Pediatric rhabdomyosarcoma (RMS). A European analysis involving 83 pediatric patients diagnosed with RMS was conducted between 2000 and 2014. These children underwent systemic chemotherapy followed by PBT at a dose of 54 CGE. The majority of the cohort had embryonal histology (n=74), with parameningeal (PM) (n=46) and orbital involvement (n=17). The study reported a 5-year LC rate of 78.5% and an OS rate nearing 80%, with minimal long-term treatment-related side effects.⁷² In a separate investigation, Childs et al⁷³ at MGH evaluated 17 consecutive patients with PM-RMS and concluded that outcomes with PBT were comparable to historical cohorts. The 5-year failure-free survival was reported at 59% and OS rates was reported at 64%. Another study from the same institution examined 7 children with bladder or prostate RMS, comparing PBT planning with IMRT.⁷⁴ These proton-based plans demonstrated superior preservation of bony structures and reproductive organs. At a median follow-up of 27 months, 5 of the 7 patients remained disease-free with bladder function intact. PBT plans significantly lowered the average radiation dose delivered to the bladder, testes, femoral heads, growth plates, and pelvic bones compared to IMRT. Additionally, Indelicato et al⁷⁵ conducted a prospective trial involving 31 patients with pelvic RMS treated with PBT between 2007 and 2018. All participants had group III disease, excluding those with vaginal or cervical tumors. After a median follow-up period of 4.2 years, the study reported LC, PFS, and OS rates of 83%, 80%, and 84%, respectively. Notably, children under the age of 3 with embryonal histology demonstrated better clinical outcomes. The Panel's review of the body of evidence is strongly convincing (Level A recommendations).

4. Head and neck malignancies. 4.1. Nasopharynx, unresectable nasal cavity and paranasal sinuses (PNS) tumors. There is growing support for the application of PBT in treating locally advanced nasopharyngeal carcinoma (NPC), particularly in patients with T4 disease. In a phase II trial, Chan et al⁷⁶ assessed 23 individuals with advanced NPC who received a combination of photon and proton therapies. The outcomes showed a 2-year disease-free survival (DFS) rate of 90%, with both LC and OS reaching 100%. Among the reported grade ≥ 3 toxicities, 29% of patients experienced hearing loss and 38% had significant

weight loss; however, no cases of grade ≥ 3 xerostomia were observed.⁷⁷ In a separate retrospective study, McDonald et al⁷⁸ found that patients with NPC and paranasal sinus tumors treated with PBT demonstrated reduced dependence on feeding tubes and opioids. Despite these promising findings, further prospective research is necessary to validate the observed benefits and assess long-term toxicity profiles. Currently, several clinical trials are in progress to evaluate PBT's role in managing head and neck malignancies, including NPC.

For tumors of the nasal cavity and PNS, the standard approach involves craniofacial resection followed by adjuvant radiotherapy. However, surgical intervention in T4 cases is often technically challenging and may result in significant anatomical or functional impairment. In cases where resection is not feasible, definitive radiation therapy using 3DCRT or IMRT carries a substantial risk of long-term complications.⁷⁹ PBT offers the advantage of dose escalation while minimizing exposure to nearby critical structures such as the optic nerves and brainstem, potentially reducing toxicity. A meta-analysis of 41 observational studies concluded that PBT is associated with significantly improved 5-year OS and DFS compared to photon-based modalities, although the retrospective nature of these studies introduces certain limitations and potential biases.⁸⁰ In a multi-institutional analysis, Yu et al⁸¹ examined 69 patients with sinonasal tumors treated with PBT, reporting favorable 3-year outcomes: OS of 100%, DMFS of 84%, and LRC of 92.9%. Among patients undergoing re-irradiation, the 3-year OS was 76.2%, with a lower incidence of late adverse effects. Another retrospective review of 90 patients also demonstrated reduced rates of severe toxicity following PBT.⁸² Additionally, data from Memorial Sloan Kettering Cancer Center (MSKCC) involving 86 patients indicated better LC outcomes using IMPT compared to 3D conformal proton techniques.⁸³

The Panel's review of the body of evidence is moderately convincing (Level B recommendation) for locally advanced T4 nasopharyngeal cancer and strongly convincing (Level A recommendation) for unresectable nasal cavity and paranasal sinus tumors.

4.2. Oropharyngeal cancer. The PBT is gaining recognition as a promising treatment approach for reducing toxicity and enhancing quality of life (QoL) in patients with oropharyngeal carcinoma. In the first prospective PBT trial for this disease, Slater et al⁸⁴ evaluated 29 individuals with locally advanced oropharyngeal cancer. The treatment was well tolerated, achieving a 5-year LRC rate of 84%, with grade 3 toxicities reported in only 11% of patients. In a

separate analysis, Aljabab et al⁸⁵ examined 46 cases and observed 100% LRC, 93.5% PFS, and 95.7% OS at a median follow-up of 19.2 months. Blanchard et al⁸⁶ compared 50 patients treated with IMPT to 100 who received IMRT, finding similar 2-year OS and PFS rates between the 2 groups, but significantly lower rates of grade 3 weight loss and gastrostomy tube placement in the IMPT group. Likewise, Cao et al⁸⁷ reported that IMPT recipients experienced less moderate-to-severe xerostomia compared to IMRT patients at both 18–24 months (6% vs. 20%) and 24–36 months (6% vs. 20%).

Evidence from a randomized phase III trial further supports the benefits of PBT previously suggested by retrospective findings.⁸⁸ A total of 440 patients were randomized to IMRT (n=219) or IMPT (n=221) across 21 centers, with 95% being HPV/p16-positive. Median follow-up was 3.14 years. In the intention-to-treat analysis, the hazard ratio (HR) for disease progression or death at 3 years was 0.87 (95% confidence interval [CI]: 0.56–1.35; $p=0.006$), and for OS it was 0.63 (95% CI: 0.36–1.10), indicating a possible survival advantage with IMPT. Per-protocol analysis revealed reduced gastrostomy tube dependence with IMPT compared to IMRT (42% vs. 28%, $p=0.019$) and a higher proportion of IMPT patients maintaining nutritional status, as indicated by an end-of-treatment weight loss of less than 5% of baseline (24% vs. 14%, $p=0.037$). The Panel's review of the body of evidence is strongly convincing (Level A recommendations).

4.3. Head and neck cancers requiring ipsilateral radiation. In selected head and neck cancers where the risk of metastasis to the contralateral neck is low—such as certain salivary gland malignancies, oral cavity tumors, oropharyngeal cancers, and specific skin cancers—PBT can provide an advantage over IMRT by minimizing radiation exposure to the opposite side. Holliday et al⁸⁹ evaluated postoperative ipsilateral treatment with IMPT in 16 patients with adenoid cystic carcinoma, reporting a LCR rate of 93.8% and minimal severe toxicities after a median follow-up of 24.9 months. A randomized clinical trial currently in progress (NCT02923570) is comparing PBT with IMRT for unilateral head and neck irradiation, with the primary endpoint focused on acute toxicity reduction. Additionally, the phase II/III study RTOG 1008 (NCT01220583) has investigated radiotherapy, with or without concurrent chemotherapy, for resected malignant salivary gland tumors, incorporating PBT as one of the treatment modalities. The Panel's review of the body of evidence was moderately convincing (Level B recommendations).

5. Thoracic malignancies. 5.1. Primary mediastinal tumors. Limiting radiation exposure to mediastinal organs is advised to reduce the likelihood of long-term adverse effects. A review by the Proton Collaborative Group's multi-institutional prospective registry analyzed 70 individuals with thymic tumors who underwent PBT at 12 proton therapy centers between 2011 and 2021.⁹⁰ The median follow-up duration was 16 months. Thymoma accounted for 81.4% of cases, while thymic carcinoma represented 18.6%. Surgical removal was performed in 59 patients, whereas 11 received definitive PBT, 5 of whom also underwent concurrent chemotherapy. Overall, treatment was well tolerated, with only one incident of grade 4 pneumonitis. Findings indicated that PBT demonstrated favorable survival outcomes and local control, especially among those who had surgery before radiation. The Panel's review of the body of evidence is partially convincing (Level C recommendations).

5.2 Bulky mediastinal lymphomas. The mediastinum is frequently involved in lymphoma, placing nearby organs such as the heart, lungs, and breasts at risk for long-term radiotherapy-related complications, including cardiotoxicity and secondary cancers. Compared with conventional photon-based modalities like 3DCRT and IMRT, PBT provides notable advantages—particularly in cases with inferior mediastinal disease—by significantly lowering the mean doses to the heart, lungs, and breasts, thereby decreasing the likelihood of cardiac injury and radiation-induced malignancies. The use of pencil-beam scanning further refines dose distribution to the lungs and improves treatment robustness in mediastinal lymphoma, offering additional dosimetric benefits.⁹¹⁻⁹⁴ Furthermore, PBT has been associated with a more favorable adjusted odds ratio for secondary cancer development.³ Hoppe et al⁹⁵ evaluated 138 young individuals with Hodgkin's lymphoma who received chemotherapy followed by proton therapy—pediatric patients were given 15–36 Gy (RBE) and adults 20–45 Gy (RBE). The 3-year PFS was 96% in adults and 87% in pediatric patients, with no Grade 3 radiation-related toxicities reported. Similarly, Tseng et al⁹⁶ analyzed outcomes for 56 mediastinal lymphoma patients treated with PBT between 2012 and 2019, with a median age of 24 years (range, 12–88 years) and a female proportion of 55%. Nearly all participants (96%) met the International Lymphoma Radiation Oncology Group (ILROG) criteria: 95% presented with lower mediastinal disease, 46% were young women, and 9% had received extensive prior treatments. The lowest mean heart and lung doses were linked to cases with minimal mediastinal involvement.

ILROG guidelines specifically advocate PBT use in young females, heavily pretreated individuals, and patients with disease in the lower mediastinum to mitigate late toxicities.⁹¹ The Panel's review of the body of evidence was moderately convincing (Level B recommendations).

5.3 Malignant pleural mesothelioma (MPM). The MPM is an uncommon and highly aggressive malignancy, most frequently linked to asbestos exposure. Prognosis is generally poor, with a median OS of around one year. The disease is typically diagnosed at an advanced stage, and therapeutic options remain limited. PBT provides dosimetric benefits by delivering high radiation doses to the tumor while minimizing exposure to adjacent healthy structures. This is particularly advantageous for MPM due to the irregular geometry and anatomical position of its tumors. A Swiss study⁹⁷ evaluated 8 patients with MPM who had undergone extra-pleural pneumonectomy followed by IMRT and subsequently had their plans re-optimized with PBT. The PBT plans improved planning target volume (PTV) coverage and significantly lowered mean radiation doses to the spinal cord, both kidneys, the contralateral lung, the heart, and the liver. In particular, contralateral lung V5 Gy, V13 Gy, and V20 Gy were notably reduced. Another investigation from the University of Pennsylvania⁹⁸ involved 16 MPM patients treated with PBT, with a median treatment age of 69.8 years. All participants received chemotherapy either prior to or during proton therapy. PBT was delivered as adjuvant therapy post-surgery (n=8), for progressive disease (n=8), or as primary treatment (n=1), at a median dose of 51.75 Gy. At the time of analysis, the median OS had not yet been reached. No grade ≥3 toxicities were reported, and most adverse effects were mild (grade 2), including radiation dermatitis, dysphagia, esophagitis, anorexia, fatigue, cough, and one case of radiation pneumonitis. The Panel review of the body of evidence was not convincing (Level D recommendations).

5.4 Non-small cell lung cancer. Treating locally advanced NSCLC with radiation remains complex due to the proximity of vital structures such as the heart, esophagus, and lungs. PBT offers distinct benefits over conventional photon-based approaches by limiting unnecessary radiation to these critical organs, potentially enhancing survival outcomes, while decreasing toxicity and improving QoL. The standard treatment protocol for this condition continues to involve radiotherapy in combination with concurrent chemotherapy, followed by adjuvant immunotherapy.⁹⁹ Multiple retrospective analyses have shown that, after concurrent chemoradiation, PBT can reduce

pulmonary, esophageal, and hematologic toxicities compared to photon therapy, without compromising tumor control or overall survival.¹⁰⁰⁻¹⁰² In a phase 2 investigation 44 patients with locally advanced NSCLC received PBT with concurrent chemotherapy, and the results were evaluated for toxicity and OS.¹⁰³ The median follow-up was 1.7 years, with no cases of grade IV toxicities attributable to PBT. Local recurrence occurred in 20% of patients, while 43% experienced distant metastases. At one year, OS was 86% and PFS was 63%. The first randomized controlled trial comparing IMRT to passive scatter PBT (PS-PBT) in NSCLC showed no statistically significant differences in the primary endpoints—radiation pneumonitis and local failure—but reported more favorable heart dose-volume parameters with PS-PBT.¹⁰⁴ Secondary findings pointed to the influence of a learning curve on treatment outcomes and highlighted the importance of adaptive planning, particularly for larger tumors. Reducing cardiac dose via proton therapy could potentially translate into improved survival, a concept currently under investigation in the ongoing phase III RTOG 1308 trial (NCT01993810). The Panel's review of the body of evidence is partially convincing (Level C recommendations).

6. Breast cancer. 6.1 Breast cancer requiring nodal treatment, with specific conditions. Advanced radiotherapy techniques for the breast aim to improve target coverage while reducing toxicities such as heart disease, pneumonitis, dermatitis, lymphedema, and secondary malignancies. The risk of ischemic heart disease is associated with radiation-induced atherosclerotic lesions within the coronary arteries, particularly in the left anterior descending artery. Other heart-related morbidities include pericarditis and heart failure. Darby et al¹⁰⁵ reported a significant risk of cardiac morbidity beyond a mean cardiac dose of 5 Gy, with a 7% increase for each additional Gy. This study remains a medicolegal reference, despite methodological criticism. Advanced photon techniques, such as IMRT, VMAT, and TOMO, offer better nodal coverage than 3DCRT, especially for the internal mammary chain (IMC); however, this is at the cost of an increased mean heart dose.¹⁰⁶⁻¹⁰⁸ The advantage of PBT is that it improves nodal/IMC coverage and dose homogeneity while reducing the heart dose and morbidity. Radiation-induced secondary malignancies are another critical consideration, especially in young patients with long life expectancies. As previously discussed, a large National Cancer Database study reported lower secondary cancer risks with PBT than with IMRT and 3DCRT in patients with breast cancer.³ Currently,

there is no high-level evidence supporting the routine use of PBT for breast cancer. Available studies primarily consist of small prospective and retrospective studies. Macdonald et al¹⁰⁹ conducted a phase 1 prospective clinical trial that included 12 patients with breast cancer who received 50.4 Gy (RBE) to the chest wall and regional nodes. They reported maximum skin toxicity (CTCAE) of grade 2 and grade 3 fatigue. Jimenez et al¹¹⁰ conducted a phase 2 single-arm clinical trial that included 70 patients with nonmetastatic breast cancer who underwent postoperative PBT of the breast/chest wall and regional nodes. They reported 1 grade 2 (CTCAE) radiation pneumonitis event and no grade 4 toxicity. The study also revealed no significant changes in echocardiography or cardiac biomarker levels after proton therapy. The 5-year rate for OS and locoregional failure rates were 91% and 1.5%, respectively. Conventional fractionation of PBT in breast cancer cases with comprehensive nodal coverage remains standard practice. The COMPRO study is an ongoing non-inferiority phase 3 trial investigating conventional versus hypofractionation PBT.¹¹¹ RADCOMP/RTOG3510 is a large-scale, multicenter, randomized clinical study of proton versus photon radiotherapy in patients with nonmetastatic breast cancer requiring comprehensive nodal irradiation.¹¹² This study was recently completed and provided high-quality data. Other similarly anticipated international phase 3 clinical trials include the DBCG study in Denmark¹¹³ and the PARABLE study in the UK.¹¹⁴

In summary, PBT for breast cancer has low toxicity rates and similar rates of disease control to photons, with clear cardiac-sparing dosimetric advantages. However, its skin toxicity remains a major concern. Conditions in which PBT is best suited include bilateral breast cancer cases requiring nodal irradiation on one or both sides; locally advanced breast cancer requiring comprehensive nodal radiotherapy, including IMC; patients with breast cancer with an unfavorable anatomy (e.g., pectus excavatum) that would lead to the delivery of unacceptably high doses to at-risk organs; and patients requiring dose escalation to the involved or suspected IMC nodes. The Panel's review of the body of evidence was moderately convincing (Level B recommendations).

6.2 Early breast cancers and partial breast irradiation. Radiotherapy for early-stage breast cancer without nodal irradiation usually involves smaller radiation fields that benefit from advanced heart-sparing techniques, such as partial breast irradiation (PBI) and breath-hold techniques. Early phase II clinical trials reported disease control rates similar to those of photons, with no significant differences in

breast pain, fibrosis, or fat necrosis.^{115,116} However, significant acute and late cutaneous toxicities, such as telangiectasia and discoloration, result in lower rates of good-to-excellent cosmesis (60-70%). These poor results are attributed to the use of a single treatment field per fraction and a very high dose per fraction per day. The Boston group received 32 Gy in 8 fractions (4 Gy per fraction twice daily), whereas the Korean group received 30 Gy in 5 fractions (6 Gy per fraction daily). In addition, the Boston group used a 2–3-cm expansion in the surgical cavity to the PTV. More recent proton PBI clinical phase 2 trials used multiple fields (2–4) for every fraction and lower doses per fraction per day.^{117–119} The Loma Linda group received 40 Gy in 10 fractions (4 Gy per fraction daily), and the MD Anderson group received 34 Gy in 10 fractions (3.4 Gy per fraction twice daily). They used smaller PTV volumes with 0.5–1 cm expansions. These studies reported a high tumor control rate and no grade ≥ 3 acute skin toxicities, with high good/excellent cosmesis rates (80-90%). Currently, there is no substantial evidence supporting the use of PBT in early-stage breast cancer. Certain conditions may be worth considering, such as relatively large left-sided medial tumors near or overlying the heart where constraints with photons, photon/electron, or PBI using cardiac-sparing techniques are challenging to achieve; and patients with limited ipsilateral arm range of motion that require treatment in the arms-down position. The Panel review of the body of evidence was not convincing (Level D recommendations).

7. Gastrointestinal malignancies. 7.1. Locally advanced esophageal cancer. Retrospective analyses and dosimetric findings indicate possible advantages of PBT in the management of esophageal cancer. Nevertheless, translating these dosimetric benefits into tangible improvements in clinical outcomes remains uncertain due to the scarcity of robust clinical evidence. A retrospective review by Xi et al¹²⁰ involving 343 patients compared IMRT with PS-PBT delivered through 2-field posterior and left posterior-oblique approaches at a median total dose of 50.4 Gy in 28 fractions, combined with concurrent chemotherapy, without subsequent surgery. Results showed that PBT achieved a superior 5-year OS rate of 41.6% versus 31.6% for IMRT, with the survival advantage persisting in multivariate analysis. Furthermore, locoregional failure-free survival was significantly higher (HR=0.684; $p=0.041$), particularly among stage III cases, while adverse event rates were comparable between groups. Dosimetric evaluation revealed lower mean lung and heart doses with PBT (6.5 Gy and 11.6 Gy, respectively) compared to IMRT (10.0 Gy and 19.9 Gy; $p<0.001$).

Additionally, PBT patients exhibited significantly reduced lung V5 Gy (28% vs. 48%), V10 Gy (23% vs. 32%), and V20 Gy (11% vs. 18%), as well as a lower heart V30 Gy (19% vs. 24%; all $p<0.001$). Ishikawa et al¹²¹ examined PS-PBT with concurrent chemotherapy in 40 esophageal cancer patients, predominantly with squamous cell carcinoma. Treatment consisted of 60 Gy in 30 fractions with 5-fluorouracil and cisplatin. The study reported no grade 3 or higher cardiopulmonary toxicities, alongside a 2-year OS rate of 77% and a locoregional control (LRC) rate of 66%. Lin et al¹²² conducted a randomized phase IIB trial comparing PBT and IMRT in locally advanced disease, with primary endpoints of total toxicity burden (TTB) and PFS. Because treatment-related complications increase healthcare costs, a reduction in TTB could enhance the cost-effectiveness of PBT. The trial demonstrated that PBT yielded a mean TTB 2.3 times lower and a mean postoperative complication score 7.6 times lower than IMRT. However, 3-year PFS and OS rates were nearly identical between modalities (51.2% vs. 50.8% for PFS; 44.5% vs. 44.5% for OS). The group also initiated a randomized phase III trial (NRG GI-006) to compare PBT and IMRT in stage I–IVA esophageal cancer, with additional evaluation of symptom burden, functional capacity, and quality of life (QoL). The Panel's review of the body of evidence was moderately convincing (Level B recommendations).

7.2. Hepatocellular carcinoma (HCC). Radiosensitivity and the susceptibility of the liver to radiation-induced liver disease (RILD) are ongoing challenges in radiotherapy. Studies have reported a strong correlation between a normal liver volume receiving low doses of radiation (1–10 Gy) and hepatic toxicity.^{123,124} This challenge is exacerbated in cases of large HCC tumors or small normal liver volumes (<800 cc). Two retrospective studies compared PBT with photons in unresectable HCC and revealed an improvement in OS with PBT.^{125,126} The OS improvement was secondary to the lower rates of RILD in the PBT arm. Another challenge is that dose escalation is more difficult to achieve using photons than using PBT. NRG/RTOG 1112 was a randomized phase III study of sorafenib versus photon-based Stereotactic Body Radiation Therapy followed by sorafenib in HCC.¹²⁷ This study reported statistically significant improvements in OS, PFS, and time to progression. The study allowed doses of up to 50 Gy in 5 fractions; however, the median dose in the study was only 35 Gy because several patients required dose de-escalation to meet liver constraints. Conversely, several PBT studies have established that proton therapy has a low risk

of post-treatment Child–Pugh (CP) score elevation while allowing for dose escalation up to 66–72.6 Gy RBE.¹²⁸⁻¹³⁰ Regarding RCTs, Bush et al¹³¹ conducted a phase 3 study of trans-arterial chemoembolization (TACE) versus PBT 70.2 Gy RBE in 15 fractions. The 2-year OS rates were comparable between the PBT and TACE groups (68% and 65%, respectively; $p=0.80$). However, PBT significantly improved the median PFS and LC compared with TACE ($p=0.002$ and $p=0.003$, respectively). Post-treatment hospitalization duration was shorter for PBT at 24 days than compared to 166 days ($p<0.001$). Additionally, the total average cost per patient, including treatment and post-treatment care, demonstrated 28% cost savings with PBT. Similarly, Kim et al¹³² conducted a phase 3 study of radiofrequency ablation (RFA) versus PBT 66 Gy RBE in 10 fractions. The study included mainly small HCC tumors size <3 cm and number ≤ 2 , with most having a CP score of A. The 2- and 4-year OS rates were similar. However, the 2-year local PFS rate favored PBT, with a difference of 10.9% (94.8% vs. 83.9%; $p<0.001$). An ongoing phase 3 study (NRG GI-003) of photon therapy versus PBT for HCC will guide future clinical practice. The Panel's review of the body of evidence is strongly convincing (Level A recommendations).

7.3 Locally advanced pancreatic and ampullary tumors. Proton therapy has the potential to enhance the therapeutic ratio over traditional photon-based radiotherapy for pancreatic cancer. Multiple retrospective analyses have assessed the toxicity profile of PBT in this setting, with delivered doses typically ranging from 50.4 to 59.4 Gy (RBE). These studies demonstrated substantial sparing of the small bowel and reported no grade ≥ 3 non-hematologic toxicities.^{133,134} In a retrospective investigation, Hiroshima et al¹³⁵ evaluated the clinical outcomes of concurrent proton chemoradiotherapy in 42 patients with unresectable, locally advanced pancreatic carcinoma, administering doses up to 67.5 Gy (RBE). Nearly half of the patients (45%) experienced grade ≥ 3 toxicities, all of which were hematologic, with no late high-grade adverse events observed. The reported 2-year OS was 50.8%, with a median survival duration of 25.6 months. The 2-year LC rate reached 78.9%, and the median time to local recurrence exceeded 36 months. The authors concluded that concurrent chemoradiotherapy with proton beams improved survival compared to historical photon-based data, and that, in univariate analysis, the total radiation dose was the only significant predictor for prolonged OS and LC. The Panel's review of the body of evidence is partially convincing (Level C recommendations).

7.4 Locally advanced rectal and anal cancer.

Proton therapy may lower radiation exposure to organs at risk in patients with locally advanced rectal cancer. A systematic review and meta-analysis of eight retrospective studies found significantly reduced volumes of small bowel, bladder, and bone marrow receiving 40 Gy with PBT compared to photon therapy.¹³⁶ The Swedish PRORECT phase II randomized trial (NCT04525989) is the first ongoing study to assess PBT in primary rectal cancer. In anal cancer, clinical trials have aimed to minimize toxicity by limiting OAR radiation dose. Two multi-institutional investigations showed that while PBT reduced the volume of normal tissue exposed to low-dose radiation, it did not decrease high-dose exposure, resulting in no significant difference in grade ≥ 3 adverse events between PBT and photons.^{137,138} The Panel review of the body of evidence was not convincing (Level D recommendations).

8. Prostate cancer. Numerous retrospective studies have evaluated PBT versus photon therapy for prostate cancer, producing varied findings; the VA Evidence Synthesis Program recently reviewed these.¹³⁹ The largest retrospective study using the NCDB indicated better outcomes with PBT in patients with T1-3, N0, M0 prostate cancer.¹⁴⁰ More recently, results from the PARTIQoL randomized clinical trial comparing PBT and IMRT for prostate cancer were reported.¹⁴¹ In this trial, patients with low- or intermediate-risk disease, not receiving hormonal therapy, were randomly assigned to PBT or IMRT. Stratification factors included treatment center, patient age, use of rectal spacers, and radiation fractionation schedules (79.2 Gy in 44 fractions versus 70 Gy in 28 fractions). The primary outcome was the change from baseline in bowel QoL, while secondary endpoints evaluated urinary and sexual functions, toxicity profiles, and treatment efficacy. Findings revealed no significant differences between PBT and IMRT across any QoL measures or PFS, including within stratified subgroups. In the postoperative context, smaller studies have confirmed the practicality of prostate bed irradiation, with ongoing randomized trials exploring this indication further.^{142,143} The Panel review of the body of evidence was not convincing (Level D recommendations).

9. Gynecologic malignancies. A few published studies have shown the dosimetric benefits of PBT in gynecological cancers, including endometrial, cervical, and vaginal cancers.¹⁴⁴⁻¹⁴⁷ A retrospective study demonstrated that patients undergoing pelvic radiation for gynecologic cancers experienced significantly less acute grade 2 gastrointestinal toxicity with IMPT compared to VMAT.¹⁴⁸ A prospective single-arm phase

2 study investigating the safety of postoperative PBT for cervical or endometrial cancer reported low-grade acute and late toxicities.¹⁴⁹ A prospective phase II trial of PBT for cervical cancer is currently ongoing.¹⁵⁰ The Panel review of the body of evidence was not convincing (Level D recommendations).

10. Soft tissue sarcoma (STS).*10.1. Retroperitoneal sarcomas.* The PBT has gained attention as a promising approach for treating retroperitoneal STS, offering potential dosimetric and clinical benefits. Dosimetric analyses consistently show that PBT results in a lower integral radiation dose compared to IMRT and 3DCRT, thereby decreasing overall radiation exposure. This dose reduction results in significantly lower radiation being delivered to critical organs, particularly the bowels and kidneys. Swanson et al¹⁵¹ found that the volume of small bowel receiving 15 Gy was 16.4% with PBT, compared to 52.2% and 66.1% for IMRT and 3DCRT, respectively. Additionally, PBT achieved a contralateral kidney V5 of 0%, markedly less than 49.9% for IMRT and 99.7% for 3DCRT. Such precision is especially important in the retroperitoneal region, where critical organs lie in close proximity to the tumor. Although clinical evidence remains limited, early data appear promising. Chung et al¹⁵² reported a 3-year LCR of 90% in patients with primary retroperitoneal STS treated with PBT. These findings also indicate an acceptable toxicity profile, supporting the potential role of proton therapy in this setting. The Panel review of the body of evidence was not convincing (Level D recommendations).

10.2 Spinal and paraspinal sarcomas. Although data are limited, current evidence indicates a possible role for PBT in managing spinal and paraspinal STS. In a phase II trial involving 50 patients treated with high-dose photon and proton radiotherapy, doses of 70 CGE were delivered for microscopic disease and 77 CGE for gross tumor. Among these patients, 7 (14%) had soft tissue sarcomas, comprising individual cases of angiosarcoma, spindle and round cell sarcoma, myxoid liposarcoma, malignant peripheral nerve sheath tumor, osteosarcoma, Ewing's sarcoma, and giant cell tumor of bone. At a median follow-up of 4 years, the 5-year actuarial LC, recurrence-free survival, and OS rates for the cohort were 78%, 63%, and 87%, respectively.¹⁵³ The Panel's review of the body of evidence is partially convincing (Level C recommendations).

Discussion. The expert Panel reported that the body of evidence was strongly convincing in favor of PBT for specific indications, including ocular tumors,

tumors at the BOS or spine, oropharyngeal cancer, hepatocellular carcinoma, specific genetic syndromes and mutations, pediatric rhabdomyosarcoma, pediatric CNS malignancies, tumors of the paranasal sinuses/nasal cavity, and for re-irradiation of all sites when curative treatment was intended. In addition, PBT may be considered at other sites when photon therapy exceeds the dose constraints for critical structures. The body of evidence is not convincing for leptomeningeal disease, pleural mesothelioma, early-stage breast cancer, locally advanced rectal and anal cancer, prostate cancer, gynecologic malignancies, or retroperitoneal sarcoma. The Panel did not recommend the routine use of PBT for other cancer sites outside the context of a clinical trial. These guidelines will be updated as more evidence-based studies become available. **Table 1** outlines future studies, and **Table 2** summarizes the recommendations. The integration of PBT guidelines into clinical practice faces several barriers that may hinder widespread adoption. Limitations include limited accessibility and high treatment costs, which restrict patient access and contribute to disparities in treatment options. Additionally, many clinicians and institutions lack sufficient experience in proton treatment planning and delivery, leading to variability in clinical outcomes. To overcome some of these challenges, implementing multidisciplinary tumor boards, integrating decision-support tools, and engaging clinicians with proton experience may aid in facilitating appropriate patient selection and adherence to evidence-based guidelines.

The Panel updated the guidelines with the evolving literature to aid radiation oncologists in Saudi Arabia in determining proton therapy indications for their patients. These guidelines are not mandatory, and recommendations should be considered as part of the overall assessment plan. Individual cases should be assessed following a multidisciplinary review and expert consultation, while accounting for financial, logistical, and patient-specific factors.

In conclusion, the updated guidelines aim to align national practices with the evolving landscape of literature in the proton therapy space. Further randomized trials are necessary to refine the current guidelines. These guidelines provide a framework for radiation oncologists in Saudi Arabia to evaluate the indications for proton therapy and selectively refer patients for this treatment.

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Table 1 - Current proton versus photon clinical trials.

Site	Subsite	Study ID	Status	Phase
Central nervous system	High-grade glioma	NRG BN001	Closed 2023	Phase 2 RCT
Head and neck	Unilateral Radiation	MSK (NCT02923570)	Open	Phase 2 RCT
	Salivary Tumors	(NCT01220583)	Open	Phase 2/3 RCT
Thoracic	Lung cancer	RTOG 1308 (NCT01993810)	Closed 2023	Phase 3 RCT
Breast	Locally advanced	RADCOMP (US)	Closed 2024	RCT
	Locally advanced	PARABLE (UK)	Open	RCT
	Locally advanced	DBCG Skegan 2 (Denmark)	Open	RCT
	Hypofractionation	COMPRO	Open	RCT
Gastro-intestinal	Liver	NRG GI003	Open	Phase 3 RCT
	Esophageal	NRG GI006	Open	Phase 3 RCT
	Rectal	PRORECT	Open	Phase 2 RCT
Prostate	Prostate (standard and hypofractionation)	COMPPARE	Closed 2022	Prospective
	Prostate, post-prostatectomy	NRG GU008	Open	Phase 3 RCT
	Prostate, post-prostatectomy	PAROS	Open	Phase 3 RCT
	Prostate high-risk, allows protons	NRG GU009	Open	Phase 3 RCT
	Prostate intermediate-risk, allows protons	NRG GU010	Open	Phase 3 RCT
Gynecologic	Cervical cancer	PROTECT	Open	Phase 2

*RCT: Randomized controlled trial

Table 2 - Summary of Current Recommendations based on published evidence.

Disease site	No.	Description	Highest Level of Evidence	Recommendation level
1 General	1.1A	Benign/malignant tumors in children	IV	A
	1.1B	Benign or malignant tumors in patients (<39 years)	IV	B
	1.2	Tumors in patients with specific genetic syndromes and mutations	III	A
	1.3	Curative intent re-irradiation	III	A
2 Central nervous system (CNS)	2.1	Ocular tumors	II	A
	2.2	Base of skull and spinal tumors	III	A
	2.3	Primary adult CNS tumors that require craniospinal irradiation	IV	B
	2.4	Adult low-grade glioma	III	B
	2.5	Acoustic neuromas and vestibular schwannomas	IV	C
	2.6	Leptomeningeal disease requiring craniospinal irradiation	III	D
3 Pediatric malignancies	3.1	Pediatric CNS tumors	IV	A
	3.2	Pediatric Rhabdomyosarcoma	IV	A
4 Head and neck	4.1A	Locally advanced Nasopharynx	III	B
	4.1B	Unresectable nasal cavity and paranasal sinus cancers	III	A
	4.2	Advanced oropharyngeal cancer	I	A
	4.3	Head and neck cancers requiring ipsilateral radiation	III	B
5 Thoracic	5.1	Primary mediastinal tumors	IV	C
	5.2	Bulky mediastinal lymphomas	III	B
	5.3	Malignant pleural mesothelioma	IV	D
	5.4	Inoperable non-small cell lung cancer stages II & III	II	C
6 Breast	6.1	Breast cancers requiring nodal treatment, with specific conditions	III	B
	6.2	Early breast cancer	III	D
7 Gastrointestinal	7.1	Advanced esophageal cancer	II	B
	7.2	Hepatocellular carcinoma (Child-Pugh A)	I	A
	7.3	Locally advanced pancreatic & ampullary tumors	IV	C
	7.4	Advanced rectal/Anal cancer	III	D
8 Prostate	8.1	Prostate cancer	I	D
9 Gynecologic	9.1	Gynecologic malignancies	IV	D
10 Soft tissue sarcoma	10.1	Retroperitoneal sarcoma	IV	D
	10.2	Spinal and paraspinal sarcomas	III	C

References

- Wilson RR. Radiological use of fast protons. *Radiology* 1946; 47: 487-491.
- Tobias C, Lawrence J, Born J, McCombs R, Roberts J, Anger H, et al. Pituitary irradiation with high-energy proton beams a preliminary report. *Cancer research* 1958; 18 (2): 121-134.
- Xiang M, Chang DT, Pollom EL. Second cancer risk after primary cancer treatment with 3-dimensional conformal, intensity-modulated, or proton beam radiation therapy. *Cancer* 2020; 126: 3560-3568.
- Kahalley LS, Ris MD, Grosshans DR, Okcu MF, Paulino AC, Chintagumpala M, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. *J Clin Oncol* 2016; 34 (10): 1043-1049.
- Eaton BR, Esiashvili N, Kim S, Patterson B, Weyman EA, Thornton LT, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol* 2016; 18: 881-887.
- Vatner RE, Niemierko A, Misra M, Weyman EA, Goebel CP, Ebb DH, et al. Endocrine deficiency as a function of radiation dose to the hypothalamus and pituitary in pediatric and young adult patients with brain tumors. *J Clin Oncol* 2018; 36: 2854-2862.
- Aldrich KD, Horne VE, Bielamowicz K, Sonabend RY, Scheurer ME, Paulino AC, et al. Comparison of hypothyroidism, growth hormone deficiency, and adrenal insufficiency following proton and photon radiotherapy in children with medulloblastoma. *J Neurooncol* 2021; 155: 93-100.
- Palumbo E, Piotto C, Calura E, Fasanaro E, Groff E, Busato F, et al. Individual radiosensitivity in oncological patients: linking adverse normal tissue reactions and genetic features. *Front Oncol* 2019; 9: 987.
- Rogers PB, Plowman PN, Harris SJ, Arlett CF. 4 radiation hypersensitivity cases and their implications for clinical radiotherapy. *Radiother Oncol* 2000; 57: 143-154.
- Pollard JM, Gatti RA. Clinical radiation sensitivity with DNA repair disorders: an overview. *Int J Radiat Oncol Biol Phys* 2009; 74: 1323-1331.
- El-Nachef L, Al-Choboq J, Restier-Verlet J, Granzotto A, Berthel E, Sonzogni L, et al. Human radiosensitivity and radiosusceptibility: what are the differences? *Int J Mol Sci* 2021; 22: 7158.
- Bougeard G, Renaux-Petel M, Flaman J-M, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J Clin Oncol* 2015; 33: 2345-52.
- Sloan L, Terezakis S, Blakeley J, Slobogean B, Kleinberg L. Long-term outcomes of radiation therapy (RT) in the management of malignant peripheral nerve sheath tumors (MPNST) in patients with neurofibromatosis type 1 (NF1). *Int J Radiat Oncol Biol Phys* 2018 102: e474-e475.
- Morioka T, Miyoshi-Imamura T, Blyth BJ, Kaminishi M, Kokubo T, Nishimura M, et al. Ionizing radiation, inflammation, and their interactions in colon carcinogenesis in Mlh1-deficient mice. *Cancer Science* 2015; 106: 217-226.
- McGuire KP, Mamounas EP. Management of hereditary breast cancer: ASCO, ASTRO, and SSO Guideline. *Ann Surg Oncol* 2020; 27: 1721-1723.
- Lin D, Lehrer EJ, Rosenberg J, Trifiletti DM, Zaorsky NG. Toxicity after radiotherapy in patients with historically accepted contraindications to treatment (CONTRAD): An international systematic review and meta-analysis. *Radiother Oncol* 2019; 135: 147-152.
- Baumann BC, Mitra N, Harton JG, Xiao Y, Wojcieszynski AP, Gabriel PE, et al. Comparative effectiveness of proton vs photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer. *JAMA oncology* 2020; 6: 237-246.
- Atkins KM, Pashtan IM, Bussière MR, Kang KH, Niemierko A, Daly JE, et al. Proton stereotactic radiosurgery for brain metastases: a single-institution analysis of 370 patients. *Int J Radiat Oncol Biol Phys* 2018; 101: 820-829.
- Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. *Int J Radiat Oncol Biol Phys* 2016; 95: 386-395.
- Phan J, Sio TT, Nguyen TP, Takiar V, Gunn GB, Garden AS, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys* 2016; 96: 30-41.
- Lee A, Woods R, Mahfouz A, Kitpanit S, Cartano O, Mohamed N, et al. Evaluation of proton therapy reirradiation for patients with recurrent head and neck squamous cell carcinoma. *JAMA Netw Open* 2023; 6: e2250607.
- McDonald MW, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. *International J Radiat Oncol Biol Phys* 2013; 87: 1107-1114.
- Chao H-H, Berman AT, Simone II CB, Ciunci C, Gabriel P, Lin H, et al. Multi-institutional prospective study of reirradiation with proton beam radiotherapy for locoregionally recurrent non-small cell lung cancer. *J Thorac Oncol* 2017; 12: 281-292.
- Hotca A, Sindhu KK, Lehrer EJ, Hartsell WF, Vargas C, Tsai HK, et al. Reirradiation with proton therapy for recurrent malignancies of the esophagus and gastroesophageal junction: Results of the proton collaborative group multi-institutional prospective registry trial. *Adv Radiat Oncol* 2024; 9: 101459.
- Boimel PJ, Berman AT, Li J, Apisarnthanarax S, Both S, Lelionis K, et al. Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma. *J Gastrointest Oncol* 2017; 8: 665.
- Koroulakis A, Molitoris J, Kaiser A, Hanna N, Bafford A, Jiang Y, et al. Reirradiation for rectal cancer using pencil beam scanning proton therapy: A single institutional experience. *Adv Radiat Oncol* 2020; 6: 100595.
- Choi JI, McCormick B, Park P, Millar M, Walker K, Tung CC, et al. Comparative Evaluation of Proton Therapy and Volumetric Modulated Arc Therapy for Brachial Plexus Sparing in the Comprehensive Reirradiation of High-Risk Recurrent Breast Cancer. *Adv Radiat Oncol* 2023; 9: 101355.
- Guttmann DM, Frick MA, Carmona R, Deville Jr C, Levin WP, Berman AT, et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. *Radiother Oncol* 2017; 124: 271-276.
- Shields JA, Shields JA. Intraocular tumors: W.B. Saunders Company; 1992.
- Caujolle J-P, Mammar H, Chamorey E, Pinon F, Herault J, Gastaud P. Proton beam radiotherapy for uveal melanomas at nice teaching hospital: 16 years' experience. *Int J Radiat Oncol Biol Phys* 2010; 78: 98-103.
- Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD. Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience. *Int J Radiat Oncol Biol Phys* 2005; 62: 1405-1411.
- Mishra KK, Quivey JM, Daftari IK, Weinberg V, Cole TB, Patel K, et al. Long-term results of the UCSF-LBNL randomized trial: charged particle with helium ion versus iodine-125 plaque therapy for choroidal and ciliary body melanoma. *Int J Radiat Oncol Biol Phys* 2015; 92: 376-683.

33. Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 2000; 11: 627-638.
34. Weber DC, Murray F, Combesure C, Calugaru V, Alapetite C, Albertini F, et al. Long term outcome of skull-base chondrosarcoma patients treated with high-dose proton therapy with or without conventional radiation therapy. *Radiother Oncol* 2018; 129: 520-526.
35. Weber DC, Badiyan S, Malyapa R, Albertini F, Bolsi A, Lomax AJ, Schneider R. Long-term outcomes and prognostic factors of skull-base chondrosarcoma patients treated with pencil-beam scanning proton therapy at the Paul Scherrer Institute. *Neuro-oncology* 2015; 18: 236-243.
36. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol* 1999; 175: 57-63.
37. Deraniyagala RL, Yeung D, Mendenhall WM, Li Z, Morris CG, Mendenhall NP, et al. Proton therapy for skull base chordomas: an outcome study from the university of Florida proton therapy institute. *J Neurol Surg B Skull Base* 2014; 75: 53-57.
38. Iannalfi A, D'Ippolito E, Riva G, Molinelli S, Gandini S, Viselner G, et al. Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy. *Neuro Oncol* 2020; 22: 1348-13458.
39. Rutz HP, Weber DC, Sugahara S, Timmermann B, Lomax AJ, Bolsi A, et al. Extracranial chordoma: Outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. *Int J Radiat Oncol Biol Phys* 2007; 67: 512-520.
40. Rotondo RL, Folkert W, Liebsch NJ, Chen Y-LE, Pedlow FX, Schwab JH, et al. High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors. *J Neurosurg Spine* 2015; 23: 788-797.
41. Staab A, Rutz HP, Ares C, Timmermann B, Schneider R, Bolsi A, et al. Spot-scanning-based proton therapy for extracranial chordoma. *Int J Radiat Oncol Biol Phys* 2011; 81: e489-e96.
42. Mima M, Demizu Y, Jin D, Hashimoto N, Takagi M, Terashima K, et al. Particle therapy using carbon ions or protons as a definitive therapy for patients with primary sacral chordoma. *Br J Radiol* 2014; 87: 20130512.
43. Chen Y-L, Liebsch N, Kobayashi W, Goldberg S, Kirsch D, Calkins G, et al. Definitive high-dose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. *Spine (Phila Pa 1976)* 2013; 38: E930-E6.
44. Florijn MA, Sharfo AWM, Wiggendaad RG, van Santvoort JP, Petoukhova AL, Hoogeman MS, et al. Lower doses to hippocampi and other brain structures for skull-base meningiomas with intensity modulated proton therapy compared to photon therapy. *Radiother Oncol* 2020; 142: 147-53.
45. Weber DC, Schneider R, Goitein G, Koch T, Ares C, Geismar JH, et al. Spot Scanning-Based Proton Therapy for Intracranial Meningioma: Long-Term Results From the Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys* 2012; 83: 865-871.
46. McDonald MW, Plankenhorst DA, McMullen KP, Henderson MA, Dropcho EJ, Shah MV, Cohen-Gadol AA. Proton therapy for atypical meningiomas. *Journal of Neuro-Oncology* 2015; 123: 123-128.
47. Lai R. Survival of patients with adult medulloblastoma: a population-based study. *Cancer* 2008; 112: 1568-1574.
48. Chang EL, Allen P, Wu C, Ater J, Kuttresch J, Maor MH. Acute toxicity and treatment interruption related to electron and photon craniospinal irradiation in pediatric patients treated at the University of Texas MD Anderson Cancer Center. *Int J Radiat Oncol Biol Phys* 2002; 52: 1008-1016.
49. Dinh J, Stoker J, Georges RH, Sahoo N, Zhu XR, Rath S, et al. Comparison of proton therapy techniques for treatment of the whole brain as a component of craniospinal radiation. *Radiat Oncol* 2013; 8: 1-7.
50. Brown AP, Barney CL, Grosshans DR, McAleer MF, de Groot JF, Puduvalli VK, et al. Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2013; 86: 277-284.
51. Dennis ER, Bussi re MR, Niemierko A, Lu MW, Fullerton BC, Loeffler JS, Shih HA. A Comparison of Critical Structure Dose and Toxicity Risks in Patients with Low Grade Gliomas Treated with IMRT versus Proton Radiation Therapy. *Technol Cancer Res Treat* 2013; 12: 1-9.
52. Thurin E, Nystr m PW, Smits A, Werlenius K, B ck A, Liljegren A, et al. Proton therapy for low-grade gliomas in adults: A systematic review. *Clin Neurol Neurosurg* 2018; 174: 233-238.
53. Shih HA, Sherman JC, Nachtigall LB, Colvin MK, Fullerton BC, Daartz J, et al. Proton therapy for low-grade gliomas: Results from a prospective trial. *Cancer* 2015; 121: 1712-1719.
54. Tabrizi S, Yeap BY, Sherman JC, Nachtigall LB, Colvin MK, Dworkin M, et al. Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma. *Radiother Oncol* 2019; 137: 95-101.
55. Vernimmen FJAI, Mohamed Z, Slabbert JP, Wilson J. Long-term results of stereotactic proton beam radiotherapy for acoustic neuromas. *Radiotherapy and Oncology*. 2009; 90: 208-212.
56. Weber DC, Chan AW, Bussi re MR, Harsh GRI, Ancukiewicz M, Barker FGI, et al. Proton beam radiosurgery for vestibular schwannoma: Tumor control and cranial nerve toxicity. *Neurosurgery* 2003; 53: 577-588.
57. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* 1982; 49: 759-972.
58. Kaplan JG, DeSouza TG, Farkash A, Shafran B, Pack D, Rehman F, et al. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias. *J Neurooncol* 1990 ;9: 225-229.
59. Yang TJ, Wijetunga NA, Yamada J, Wolden S, Mehallow M, Goldman DA, et al. Clinical trial of proton craniospinal irradiation for leptomeningeal metastases. *Neuro Oncol* 2021; 23: 134-143.
60. Kopecky AS, Khan AJ, Pan W, Drachtman R, Parikh RR. Outcomes and patterns of care in a nationwide cohort of pediatric medulloblastoma: Factors affecting proton therapy utilization. *Adv Radiat Oncol* 2017; 2: 588-596.
61. Brodin NP, Rosensch ld PMAF, Aznar MC, Kiil-Berthelsen A, Vogelius IR, Nilsson P, et al. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. *Acta Oncologica* 2011; 50: 806-816.
62. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. *Lancet Oncol* 2016; 17: 287-298.

63. Liu KX, Ioakeim-Ioannidou M, Susko MS, Rao AD, Yeap BY, Snijders AM, et al. A multi-institutional comparative analysis of proton and photon therapy-induced hematologic toxicity in patients with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2021; 109: 726-735.
64. Kahalley LS, Peterson R, Ris MD, Janzen L, Okcu MF, Grosshans DR, et al. Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *J Clin Oncol* 2020; 38: 454-461.
65. Baliga S, Gallotto S, Bajaj B, Lewy J, Weyman E, Lawell MP, et al. Decade-long disease, secondary malignancy, and brainstem injury outcomes in pediatric and young adult medulloblastoma patients treated with proton radiotherapy. *Neuro Oncol* 2022; 24: 1010-1019.
66. Indelicato DJ, Bates JE, Mailhot Vega RB, Rotondo RL, Hoppe BS, Morris CG, et al. Second tumor risk in children treated with proton therapy. *Pediatr Blood Cancer* 2021; 68: e28941.
67. Mizumoto M, Oshiro Y, Takizawa D, Fukushima T, Fukushima H, Yamamoto T, et al. Proton beam therapy for pediatric ependymoma. *Pediatr Int* 2015;57: 567-571.
68. MacDonald SM, Sethi R, Lavally B, Yeap BY, Marcus KJ, Caruso P, et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. *Neuro Oncology* 2013; 15: 1552-1559.
69. Indelicato DJ, Ioakeim-Ioannidou M, Bradley JA, Mailhot-Vega RB, Morris CG, Tarbell NJ, et al. Proton therapy for pediatric ependymoma: mature results from a bicentric study. *Int J Radiat Oncol Biol Phys* 2021; 110: 815-820.
70. Amsbaugh MJ, Grosshans DR, McAleer MF, Zhu R, Wages C, Crawford CN, et al. Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes. *Int J Radiat Oncol Biol Phys* 2012; 83: 1419-1424.
71. Indelicato DJ, Rotondo RL, Uezono H, Sandler ES, Aldana PR, Ranalli NJ, et al. Outcomes following proton therapy for pediatric low-grade glioma. *Int J Radiat Oncol Biol Phys* 2019;104: 149-156.
72. Leiser D, Calaminus G, Malyapa R, Bojaxhiu B, Albertini F, Kliebsch U, et al. Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy. *Radiother Oncol* 2016; 120: 163-168.
73. Childs SK, Kozak KR, Friedmann AM, Yeap BY, Adams J, MacDonald SM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. *Int J Radiat Oncol Biol Phys* 2012; 82: 635-642.
74. Cotter SE, Herrup DA, Friedmann A, Macdonald SM, Pieretti RV, Robinson G, et al. Proton radiotherapy for pediatric bladder/prostate rhabdomyosarcoma: clinical outcomes and dosimetry compared to intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2011;81: 1367-173.
75. Indelicato DJ, Rotondo RL, Krasin MJ, Vega RBM, Uezono H, Bradfield S, et al. Outcomes following proton therapy for group III pelvic rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys* 2020; 106: 968-976.
76. Chan A, Adams J, Weyman E, Parambi R, Goldsmith T, Holman A, et al. A phase II trial of proton radiation therapy with chemotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2012; 84: S151-S152.
77. Chan A, Liebsch L, Deschler D, Adams J, Vrshali L, McIntyre J, et al. Proton radiotherapy for T4 nasopharyngeal carcinoma. *J Clin Oncol* 2004; 22: 5574.
78. McDonald MW, Liu Y, Moore MG, Johnstone PA. Acute toxicity in comprehensive head and neck radiation for nasopharynx and paranasal sinus cancers: cohort comparison of 3D conformal proton therapy and intensity modulated radiation therapy. *Radiat Oncol* 2016; 11: 1-10.
79. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001; 92: 3012-3029.
80. Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncol* 2014; 15: 1027-1038.
81. Nathan YY, Gamez ME, Hartsell WF, Tsai HK, Laramore GE, Larson GL, et al. A multi-institutional experience of proton beam therapy for sinonasal tumors. *Adv Radiat Oncol* 2019; 4: 689-698.
82. Zenda S, Kawashima M, Arahira S, Kohno R, Nishio T, Tahara M, et al. Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up. *Int J Clin Oncol* 2015;20: 447-454.
83. Fan M, Kang JJ, Lee A, Fan D, Wang H, Kitpanit S, et al. Outcomes and toxicities of definitive radiotherapy and reirradiation using 3-dimensional conformal or intensity-modulated (pencil beam) proton therapy for patients with nasal cavity and paranasal sinus malignancies. *Cancer* 2020; 126: 1905-1916.
84. Slater JD, Yonemoto LT, Mantik DW, Bush DA, Preston W, Grove RI, et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. *Int J Radiat Oncol Biol Phys* 2005; 62: 494-500.
85. Aljabab S, Liu A, Wong T, Liao JJ, Laramore GE, Parvathaneni U. Proton therapy for locally advanced oropharyngeal cancer: initial clinical experience at the University of Washington. *Int J Part Ther* 2019; 6: 1-12.
86. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer—a case matched analysis. *Radiother Oncol* 2016; 120: 48-55.
87. Cao J, Zhang X, Jiang B, Chen J, Wang X, Wang L, et al. Intensity-modulated proton therapy for oropharyngeal cancer reduces rates of late xerostomia. *Radiother Oncol* 2021;160:32-9.
88. Frank SJ, Busse P, Rosenthal DI, Hernandez M, Swanson DM, Garden AS, et al. Phase III randomized trial of intensity-modulated proton therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for the treatment of head and neck oropharyngeal carcinoma (OPC). *J Clin Oncol* 2024; 42.
89. Holliday E, Bhattasali O, Kies MS, Hanna E, Garden AS, Rosenthal DI, et al. Postoperative intensity-modulated proton therapy for head and neck adenoid cystic carcinoma. *Int J Part Ther* 2016; 2: 533-543.
90. Tian S, McCook A, Choi I, Simone C, Vargas C, Yu N, et al. Treatment of thymoma and thymic carcinoma with proton beam therapy: outcomes from the proton collaborative group prospective registry. *Int J Radiat Oncol Biol Phys* 2023; 117: e66.

91. Dabaja BS, Hoppe BS, Plastaras JP, Newhauser W, Rosolova K, Flampouri S, et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines. *Blood* 2018; 132: 1635-1646.
92. Ntentas G, Dedekova K, Andrik M, Aznar MC, George B, Kubeš J, et al. Clinical intensity modulated proton therapy for Hodgkin lymphoma: which patients benefit the most? *Pract Radiat Oncol* 2019; 9: 179-187.
93. Zeng C, Plastaras JP, James P, Tochner ZA, Hill-Kayser CE, Hahn SM, Both S. Proton pencil beam scanning for mediastinal lymphoma: treatment planning and robustness assessment. *Acta Oncol* 2016; 55: 1132-1138.
94. Tseng YD, Cutter DJ, Plastaras JP, Parikh RR, Cahlon O, Chuong MD, et al. Evidence-based review on the use of proton therapy in lymphoma from the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. *Int J Radiat Oncol Biol Phys* 2017; 99: 825-842.
95. Hoppe B, Hill-Kayser C, Tseng Y, Flampouri S, Elmongy H, Cahlon O, et al. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. *Annals of Oncology* 2017; 28: 2179-2184.
96. Tseng YD, Pankuch M, Mohindra P, McGee L, Rossi C, Flampouri S, et al. Selection of mediastinal lymphoma patients for proton therapy within the Proton Collaborative Group Registry: Concordance with the ILROG guidelines. *Am J Clin Oncol* 2021; 44: 269-274.
97. Krayenbuehl J, Hartmann M, Lomax AJ, Kloeck S, Hug EB, Ciernik IF. Proton therapy for malignant pleural mesothelioma after extrapleural pleuropneumectomy. *Int J Radiat Oncol Biol Phys* 2010; 78: 628-634.
98. Li YR, Alley EW, Friedberg J, Culligan M, Busch TM, Hahn S, et al. Prospective assessment of proton therapy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys* 2020; 108.
99. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018; 379: 2342-2350.
100. Nakayama H, Satoh H, Sugahara S, Kurishima K, Tsuboi K, Sakurai H, et al. Proton beam therapy of stage II and III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 81: 979-984.
101. Sejpal S, Komaki R, Tsao A, Chang JY, Liao Z, Wei X, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for non-small cell lung cancer. *Cancer* 2011; 117: 3004-3013.
102. Wang XS, Shi Q, Williams LA, Komaki R, Gomez DR, Lin SH, et al. Prospective study of patient-reported symptom burden in patients with non-small-cell lung cancer undergoing proton or photon chemoradiation therapy. *J Pain Symptom Manage* 2016; 51: 832-838.
103. Chang JY, Komaki R, Lu C, Wen HY, Allen PK, Tsao A, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III non-small cell lung cancer. *Cancer* 2011; 117: 4707-4713.
104. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. *J Clin Oncol* 2018; 36: 1813-1822.
105. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987-998.
106. Tyran M, Mailleux H, Tallet A, Fau P, Gonzague L, Minsat M, et al. Volumetric-modulated arc therapy for left-sided breast cancer and all regional nodes improves target volumes coverage and reduces treatment time and doses to the heart and left coronary artery, compared with a field-in-field technique. *J Radiat Res* 2015; 56: 927-937.
107. Yang J-F, Lee M-S, Lin C-S, Chao H-L, Chen C-M, Lo C-H, et al. Long-term breast cancer patient outcomes after adjuvant radiotherapy using intensity-modulated radiotherapy or conventional tangential radiotherapy. *Medicine (Baltimore)* 2016; 95: e3113.
108. Lauche O, Kirova YM, Fenoglio P, Costa E, Lemanski C, Bourgier C, et al. Helical tomotherapy and volumetric modulated arc therapy: new therapeutic arms in the breast cancer radiotherapy. *World J Radiol* 2016; 8: 735.
109. MacDonald SM, Patel SA, Hickey S, Specht M, Isakoff SJ, Gadd M, et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2013; 86: 484-490.
110. Jimenez RB, Hickey S, DePauw N, Yeap BY, Batin E, Gadd MA, et al. Phase II study of proton beam radiation therapy for patients with breast cancer requiring regional nodal irradiation. *J Clin Oncol* 2019; 37: 2778-2785.
111. Choi I, Dutta S, Pankuch M, Morris C, Panoff J, Bradley J, Wang P. PCG BRE009-23.
112. Bekelman JE, Lu H, Pugh S, Baker K, Berg CD, De Gonzalez AB, et al. Pragmatic randomised clinical trial of proton versus photon therapy for patients with non-metastatic breast cancer: the Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. *BMJ Open* 2019; 9: e025556.
113. Stick LB, Lorenzen EL, Yates ES, Anandadas C, Andersen K, Aristei C, et al. Selection criteria for early breast cancer patients in the DBCG proton trial—The randomised phase III trial strategy. *Clin Transl Radiat Oncol* 2021; 27: 126-131.
114. Kirby A, Haviland J, Mackenzie M, Fleming H, Anandadas C, Wickers S, et al. Proton beam therapy in breast cancer patients: The UK PARABLE trial is recruiting. *Clin Oncol (R Coll Radiol)* 2023; 35: 347-350.
115. Kozak KR, Smith BL, Adams J, Kornmehl E, Katz A, Gadd M, et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. *Int J Radiat Oncol Biol Phys* 2006; 66: 691-698.
116. Chang JH, Lee NK, Kim JY, Kim Y-J, Moon SH, Kim TH, et al. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol* 2013; 108: 209-214.
117. Bush DA, Slater JD, Garberoglio C, Do S, Lum S, Slater JM. Partial breast irradiation delivered with proton beam: results of a phase II trial. *Clin Breast Cancer* 2011; 11: 241-245.
118. Bush DA, Do S, Lum S, Garberoglio C, Mirshahidi H, Patyal B, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys* 2014; 90: 501-505.
119. Pasalic D, Strom EA, Allen PK, Williamson TD, Poenisch F, Amos RA, et al. Proton accelerated partial breast irradiation: Clinical outcomes at a planned interim analysis of a prospective phase 2 trial. *Int J Radiat Oncol Biol Phys* 2021; 109: 441-448.

120. Xi M, Xu C, Liao Z, Chang JY, Gomez DR, Jeter M, et al. Comparative outcomes after definitive chemoradiotherapy using proton beam therapy versus intensity modulated radiation therapy for esophageal cancer: a retrospective, single-institutional analysis. *Int J Radiat Oncol Biol Phys* 2017; 99: 667-676.
121. Ishikawa H, Hashimoto T, Moriwaki T, Hyodo I, Hisakura K, Terashima H, et al. Proton beam therapy combined with concurrent chemotherapy for esophageal cancer. *Anticancer Res* 2015; 35: 1757-1762.
122. Lin SH, Hobbs BP, Verma V, Tidwell RS, Smith GL, Lei X, et al. Randomized phase IIB trial of proton beam therapy versus intensity-modulated radiation therapy for locally advanced esophageal cancer. *J Clin Oncol* 2020; 38: 1569-15679.
123. Pursley J, El Naqa I, Sanford NN, Noe B, Wo JY, Eyler CE, et al. Dosimetric analysis and normal-tissue complication probability modeling of child-pugh score and albumin-bilirubin grade increase after hepatic irradiation. *Int J Radiat Oncol Biol Phys* 2020; 107: 986-995.
124. Hsieh C-E, Venkatesulu BP, Lee C-H, Hung S-P, Wong P-F, Aithala SP, et al. Predictors of radiation-induced liver disease in eastern and western patients with hepatocellular carcinoma undergoing proton beam therapy. *Int J Radiat Oncol Biol Phys* 2019; 105: 73-86.
125. Sanford NN, Pursley J, Noe B, Yeap BY, Goyal L, Clark JW, et al. Protons versus photons for unresectable hepatocellular carcinoma: liver decompensation and overall survival. *Int J Radiat Oncol Biol Phys* 2019; 105: 64-72.
126. Cheng J-Y, Liu C-M, Wang Y-M, Hsu H-C, Huang E-Y, Huang T-T, et al. Proton versus photon radiotherapy for primary hepatocellular carcinoma: a propensity-matched analysis. *Radiat Oncol* 2020; 15: 1-10.
127. Dawson L, Winter K, Knox J, Zhu A, Krishnan S, Guha C, et al. NRG/RTOG 1112: randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC)(NCT01730937). *Int J Radiat Oncol Biol Phys* 2022; 114: 1057.
128. Fukumitsu N, Sugahara S, Nakayama H, Fukuda K, Mizumoto M, Abei M, et al. A Prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2009; 74: 831-836.
129. Mizumoto M, Okumura T, Hashimoto T, Fukuda K, Oshiro Y, Fukumitsu N, et al. Proton Beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys* 2011; 81: 1039-1045.
130. Sugahara S, Oshiro Y, Nakayama H, Fukuda K, Mizumoto M, Abei M, et al. Proton beam therapy for large hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2010; 76: 460-466.
131. Bush DA, Volk M, Smith JC, Reeves ME, Sanghvi S, Slater JD, deVera M. Proton beam radiotherapy versus transarterial chemoembolization for hepatocellular carcinoma: Results of a randomized clinical trial. *Cancer* 2023; 129: 3554-3563.
132. Kim TH, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, Park J-W. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. *J Hepatol* 2021;74: 603-612.
133. Nichols Jr RC, George TJ, Zaiden Jr RA, Awad ZT, Asbun HJ, Huh S, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. *Acta Oncol* 2013; 52: 498-505.
134. Jethwa KR, Tryggestad EJ, Whitaker TJ, Giffey BT, Kazemba BD, Neben-Wittich MA, et al. Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes. *Adv Radiat Oncol* 2018; 3: 314-321.
135. Hiroshima Y, Fukumitsu N, Saito T, Numajiri H, Murofushi KN, Ohnishi K, et al. Concurrent chemoradiotherapy using proton beams for unresectable locally advanced pancreatic cancer. *Radiation Oncol* 2019; 136: 37-43.
136. Fok M, Toh S, Easow J, Fowler H, Clifford R, Parsons J, Vimalachandran D. Proton beam therapy in rectal cancer: A systematic review and meta-analysis. *Surgical Oncology* 2021; 38: 101638.
137. Mohiuddin JJ, Jethwa KR, Grandhi N, Breen WG, Wang X, Anvari A, et al. Multi-institutional comparison of intensity modulated photon versus proton radiation therapy in the management of squamous cell carcinoma of the anus. *Adv Radiat Oncol* 2021; 6: 100744.
138. Chuong M, Kozarek J, Rubens M, Kaiser A, Hartsell W, Larson G, et al. Reduced acute toxicity after proton versus photon chemoradiation for anal cancer: outcomes from the proton collaborative group REG001-09 trial. *Int J Radiat Oncol Biol Phys* 2019; 105: S158.
139. Hickam DH, Anderson JK, Rahman B, Ward RM, Parr NJ. Evidence Brief: Proton Beam Therapy for Treatment of Localized Prostate Cancer. Washington (DC): Department of Veterans Affairs (US); 2022 Aug.
140. Liu Y, Patel SA, Jani AB, Gillespie TW, Patel PR, Godette KD, et al. Overall survival after treatment of localized prostate cancer with proton beam therapy, external-beam photon therapy, or brachytherapy. *Clin Genitourin Cancer* 2021; 19: 255-66. e7.
141. Efsthathiou J, Yeap B, Michalski J, Horick N, Zietman A, Christodouleas J, et al. Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL): Phase III randomized clinical trial of proton therapy vs. IMRT for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2024; 120: S1.
142. Deville Jr C, Hwang W-T, Barsky AR, Both S, Christodouleas JP, Bekelman JE, et al. Initial clinical outcomes for prostate cancer patients undergoing adjuvant or salvage proton therapy after radical prostatectomy. *Acta Oncologica* 2020; 59: 1235-1239.
143. Körber SA, Katayama S, Sander A, Jäkel C, Häfner M, Debus J, Herfarth K. Prostate bed irradiation with alternative radio-oncological approaches (PAROS). *Radiat Oncol* 2019;1 4: 122.
144. Lin LL, Kirk M, Scholey J, Taku N, Kiely JB, White B, Both S. Initial report of pencil beam scanning proton therapy for posthysterectomy patients with gynecologic cancer. *Int J Radiat Oncol Biol Phys* 2016; 95: 181-189.
145. Xu MJ, Maity A, Vogel J, Kirk M, Zhai H, Both S, Lin LL. Proton therapy reduces normal tissue dose in extended-field pelvic radiation for endometrial cancer. *Int J Part Ther* 2017; 4: 1-11.
146. Shang H, Pu Y, Wang W, Dai Z, Jin F. Evaluation of plan quality and robustness of IMPT and helical IMRT for cervical cancer. *Radiat Oncol* 2020; 15: 1-11.
147. Li YR, Kirk M, Lin L. Proton therapy for vaginal reirradiation. *Int J Part Ther* 2016; 3: 320-326.

148. Brown M, Pollock A, Li E, Sun K, Risher H, Rao G, et al. A Retrospective Comparison of Acute Toxicities in Patients Receiving Pelvic Radiation for Newly Diagnosed Gynecologic Primaries with Intensity Modulated Proton Therapy and Volume Modulated Arc Therapy. *Int J Radiat Oncol Biol Phys* 2024; 120: S189-S90.
149. Arians N, Lindel K, Krisam J, Oelmann-Avendano JT, Meixner E, König L, et al. Treatment tolerability and toxicity of postoperative proton beam therapy for gynecologic malignancies: results of the prospective phase 2 APROVE trial. *Int J Radiat Oncol Biol Phys* 2023; 116: 825-836.
150. Corbeau A, Nout RA, Mens JWM, Horeweg N, Godart J, Kerkhof EM, et al. PROTECT: prospective phase-II-trial evaluating adaptive proton therapy for cervical cancer to reduce the impact on morbidity and the immune system. *Cancers* 2021; 13: 5179.
151. Swanson EL, Indelicato DJ, Louis D, Flampouri S, Li Z, Morris CG, et al. Comparison of three-dimensional (3D) conformal proton radiotherapy (RT), 3D conformal photon RT, and intensity-modulated RT for retroperitoneal and intra-abdominal sarcomas. *Int J Radiat Oncol Biol Phys* 2012;83(5):1549-57.
152. Chung C, Trofimov A, Adams J, Kung J, Kirsch DG, Yoon S, et al. Comparison of 3D conformal proton therapy, intensity-modulated proton therapy, and intensity-modulated photon therapy for retroperitoneal sarcoma. *Sarcoma* 2022; 2022: 5540615.
153. DeLaney TF, Liebsch NJ, Pedlow FX, Adams J, Dean S, Yeap BY, et al. Phase II study of high-dose photon/proton radiotherapy in the management of spine sarcomas. *Int J Radiat Oncol Biol Phys* 2009; 74: 732-739.