Guideline Resource Unit
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Proton Beam Radiation Therapy

Effective Date: October 2023

Cancer Care Alberta

Background

Charged particle radiotherapy uses beams of protons or other particles such as helium or carbon instead of photons. In contrast to conventional photon radiotherapy, in which the greatest energy release is at the surface of the tissue and decreases exponentially the deeper the radiation travels, the energy of a proton beam is released near the end of its path, resulting in a sharp and localized dose peak, referred to as the Bragg peak. This allows for better dose distribution when compared to photon beam radiotherapy, thereby decreasing the dose to normal surrounding tissues, and reducing the risk of both acute and long-term side effects[1]. To date, there are few published controlled comparative studies describing outcomes from patients treated with proton beam radiotherapy versus other therapies; thus, the advantage of protons over conventional photon therapy is based on the dosimetric advantage of protons over photons for tumours that are in immediate proximity to critical structures. Most of the published literature is in the form of prospective or retrospective case series and cohort studies; there is also significant variation in the types and stages of cancer for which treatment with proton beam radiotherapy has been reported, as well as the reported doses and fractionation schedules.

As of the end of 2021, 280 000 patients worldwide had been treated with proton beam radiotherapy[2]. Historically, the high capital cost of proton facilities equipped with rotational gantries has limited the number of facilities in operation; however, that number is now increasing rapidly. As of May 2023, there are 101 proton facilities worldwide, with another 34 facilities under construction[3]. Gantry-equipped facilities capable of treating a broad range of tumour sites are not currently available in Canada.

In early 2012, the Cancer Care Alberta Proton Therapy Guideline Working Group and Guideline Advisory Group met to evaluate the most current evidence for the use of proton beam radiotherapy in pediatric and adult patients with cancer, and to develop a *de novo* guideline with recommendations based on an expert review of the available literature. The resulting evidence review, guideline document, and accompanying documents were presented to the Out of Country Health Services Committee, which operates at arm's length from Alberta Health, to establish a process to identify which patients are appropriate candidates to receive out-of-country treatment with proton beam radiation therapy. In 2019 and 2023 the evidence was reviewed, and this guideline was updated. In 2021, the Alberta Health working group set up a special program unit to review proton beam radiation therapy requests, which means the requests no longer routinely reviewed by the Out-of-Country Health Services Committee.

Guideline Questions

1. What is the evidence for the use of proton beam therapy (PBT) for the management of patients with cancer?
2. What are the published recommendations for the selection of patients most likely to benefit from treatment with PBT?

3. What are the steps involved in referring a patient for out-of-country PBT?

Development

The Cancer Care Alberta Proton Therapy Guideline Advisory Group guideline development process is available in Appendix A.

Search Strategy

Medical journals were searched using the PubMed database; the references and bibliographies of studies identified through these searches were scanned for additional sources. The search strategy is described in Appendix B.

Target Population

The recommendations in this guideline are for pediatric and adult patients who are residents of Alberta and may qualify to receive PBT at a facility outside of Canada for treatment.

Summary of Recommendations

1. Required eligibility criteria for approval and funding for PBT include:
    a. the treatment should be given with curative intent
    b. the patient should be well enough for outpatient treatment at time of out-of-country travel
    c. the expected survival of the patient should be greater than five years
    d. the patient must be able and willing to travel.

2. Pediatric and adolescent patients may be considered for referral for PBT if required eligibility criteria are met, regardless of diagnoses. Benign conditions including arteriovenous malformations qualify for referral for PBT.

3. Adult patients that may be considered for referral for PBT if required eligibility criteria are met with the listed diagnoses. For any case where the benefit of PBT appears unclear, comparative proton-photon dosimetric or model-based analysis to estimate the expected clinical benefit may be considered to aid decision-making. Physicians will consider individual factors in deciding on a referral.
    a. Ocular tumours
    b. Central nervous system diagnoses, including (but not limited to) arteriovenous malformations, benign meningioma, neuromas, craniopharyngioma, germ cell tumours, and low-grade gliomas
    c. Skull-based tumors
    d. Primary spinal tumours
    e. Advanced and/or unresectable head and neck cancers

f. Paranasal sinus, other accessory sinus, nasal cavity tumour and salivary gland tumours
g. Mediastinal lymphomas
h. Hepatocellular carcinoma
i. Sarcomas, including (but not limited to) non-metastatic retroperitoneal sarcomas
j. Patients with genetic syndromes including NF-1 and retinoblastoma, which requires that all possible efforts to reduce the irradiated/scatter volume of radiation therapy to be minimized
k. Re-irradiation cases, where cumulative critical structure tolerance dose is exceeded with photon therapy modalities available in Alberta

4. Highly selected adult patients with other diagnoses (i.e., not listed above) may be considered for referral for PBT if required eligibility criteria are met. Comparative proton-photon dosimetric or model-based analysis to document an expected clinical benefit may be required for other diagnoses unless this process is expected to result in an unacceptable delay in the PBT start date.
    a. Other diagnoses may include (but are not limited to) non-advanced and resectable head and neck tumours including nasopharyngeal cancers, left-sided breast cancers with mean heart dose >5 Gy despite use of best available photon therapy modalities, and non-metastatic tumours of the thorax, abdomen, and pelvis.
    b. Members of the working group note that this recommendation is consistent with practice in Ontario and supports equitable access of PBT in Canada. This recommendation is expected to yield an approximate rate of 6% of all patients treated in Alberta with radiation therapy (RT) of curative intent (including diagnoses listed in recommendations 2, 3 and 4) to be eligible for PBT[4].

5. Factors other than diagnosis should be considered in assessing whether PBT may confer a significant benefit for the patient over photon therapy modalities available in Alberta such as intensity-modulated radiation therapy (IMRT), volumetric arc modulated therapy (VMAT), stereotactic radiosurgery (SRS), and brachytherapy.

6. For all cases, the referral for PBT must come from the consultant Radiation Oncologist who has seen and assessed the patient. The referral can only be made if the Proton Therapy Referral Rounds recommends PBT, and that recommendation is approved by the Senior Medical Director of Cancer Care Alberta.

7. We recommend that PBT be delivered, when feasible, at an accredited facility credentialled by the Imaging and Radiation Oncology Core (IROC) that is co-located or closely located to a tertiary cancer centre with appropriate diagnostic imaging and supportive medical services (for example, delivery of concurrent chemotherapy in children). Proton beam therapy should be

delivered by an experienced, interdisciplinary team including radiation oncologists and medical physicists with training specific to PBT.

Table 1. Patient selection criteria for proton beam therapy

Patient criteria	Requirements
Age ranges	a. pediatric range: 0 to 21 years at initiation of RT b. adult range: > 21 years at initiation of RT
Fitness	a. the treatment should be given with curative intent b. the patient should be well enough for outpatient treatment at time of out-of-country travel c. the expected survival of the patient should be greater than five years d. the patient must be able and willing to travel.
Approved Diagnoses	See Summary of Recommendations section.
Comparative Proton-Photon Planning	Required for referral of non-routine diagnoses. See Summary of recommendations: recommendation 4.

Discussion

I. Indications for Proton Beam Therapy

A. Pediatric Tumours (0 to 21 years):

Radiation therapy has played an important role in the treatment and cure of pediatric patients diagnosed with malignant tumours over the past 30 years. As of 2020, approximately 86% of these patients with malignancies can now expect to be cured, and consequently the late effects of treatment have now become a major focus[5]. With increased survival, the long term complications of treatment can have a major impact on growth, fertility, and emotional well-being[6]. The benefits of PBT are potentially the greatest in this population. PBT is associated with a reduction in acute and long-term toxicities[7-12], lower rates of radiation-induced second malignancies[13-20], less acute and long-term damage to developing organs[21-25], and decreased neurocognitive decline[26-32] in pediatric and adolescent patients with cancer.

B. Adult Tumours (>21 years):

Adult patients may be considered for referral for PBT if the required eligibility criteria are met with the listed diagnoses. For any case where the benefit of PBT appears unclear, comparative proton-photon dosimetric or model-based analysis to estimate expected clinical benefit may be considered to aid decision-making.

Ocular tumours[33-50].

Uveal melanoma, which includes tumours in the iris, ciliary body, and choroid, is the most common type of primary ocular tumour in adults, accounting for 95% of all cases[51, 52]. Depending on the size and location of the tumour, treatment can range from local ablative treatments to complete removal of the eye. The use of PBT for tumours has been reported in the literature[35, 37-45]. A recent in silico study demonstrated a significantly improved beam penumbra, better dose homogeneity, shorter delivery time, and reduced mean dose to critical structures compared to other external beam radiation modalities[50]. A recent health technology assessment found similar survival, progression-free survival, and toxicity for patients with ocular tumours treated with photon and proton therapy[4]. Proton beam therapy may spare important and sensitive eye structures, leading to better visual acuity and eye retention[53]. Proton therapy is an option for ocular tumour, but the optimal choice of modality should be decided by a multidisciplinary team of radiation oncologist and ocular oncologist and medical physicists with experience in treating ocular malignancies[33].

Central nervous system diagnoses[54-60].

These diagnoses include (but are not limited to) arteriovenous malformations, benign meningioma, schwannoma, craniopharyngioma, germ cell tumours, and low-grade gliomas. Adult patients with benign lesions and indolent malignant tumours benefit from PBT due to a decreased risk of late neurologic toxicities. It has been observed that patients with central nervous system diagnoses who undergo PBT, do not have an increased risk of developing out-of-field secondary malignancies[20].

Meningiomas are the second most common intracranial tumour reported in adults, accounting for 13 to 26% of all primary brain tumours in this population[61, 62]. The management of a patient with a meningioma depends on the signs and symptoms produced by the tumour, the age of the patient, and the location and size of the tumour[63]. Radiotherapy offers reasonable control for patients who are not candidates for surgery, patients whose tumour location or shape is not amenable to surgery (such as a cavernous sinus meningioma), patients who have symptomatic residual disease, or for the treatment of recurrence. A recent study found meningioma patients treated with PBT had similar survival outcomes compared to photon therapy (76.0% vs 81.3% at 2 years; p=0.66). Poel and colleagues found PBT had a steeper dose falloff outside the target and allowed a lower integral dose compared to VMAT in patients with recurrent meningiomas[60].

Arteriovenous malformations (AVMs) are benign brain lesions that occur in approximately 0.1% of the population, and can cause intracerebral hemorrhage, seizures, and focal neurological deficits[64]. Standard interventions for brain AVMs include resection for surgically accessible lesions and embolization; SRS with either photons or protons can be used for patients with unresectable lesions, or those who are poor candidates or refuse surgery. In a review of 68 patients with cerebral AVMs treated with proton-beam SRS, Seifert *et al.* reported symptom control in 85.7% of patients with Spetzler-Martin grades I and II AVMs, 54.2% of patients with grade III AVMs, and 24% of patients with grade IV AVMs[65].

Acoustic neuromas, also known as vestibular schwannomas, are benign slow-growing tumours that commonly arise from the vestibular portion of the eighth cranial nerve and account for approximately 8% of intracranial tumours in adults[66]. Options for treatment depend on tumour size, tumour growth rate, symptoms, health status, and patient preference, and may include observation, single-session SRS, fractionated conventional RT, fractionated stereotactic RT, PBT, or surgery[67, 68]. In a trial of 30 patients with acoustic neuromas treated with fractionated proton beam radiotherapy, Bush *et al.* reported no disease progression at a mean follow-up of 34 months, and radiographic regression in 11 patients[69]. The rate of hearing preservation was 31%, however only 13 patients had useful hearing prior to RT. No transient or permanent treatment-related trigeminal or facial nerve dysfunction was observed.

Skull-based tumors[70] and primary spinal tumours[71, 72].

Chordomas are slow growing, locally aggressive bone tumours arising from the remnants of the notochord and most frequently occurring in the sacrococcygeal region or at the base of the skull near the spheno-occipital region[73, 74]. Chordomas are rare in both adults and children, accounting for only three to four percent of all primary bone tumours[74]. Chondrosarcomas are malignant cartilaginous tumours that can occur anywhere in the skeletal system, and most commonly in the long bones and pelvis; in the skull base, chondrosarcomas account for six percent of all tumours, and most commonly occur in the middle, posterior, or anterior fossae[75]. As a result of their proximity to critical neural structures, however, chordomas and chondrosarcomas of the skull base and spine are difficult to manage with conventional radiotherapy techniques, therefore making these tumours one of the main applications for PBT. Palm and colleagues observed better overall survival at five years in both chordoma and chondrosarcoma patients receiving PBT versus photon therapy (chordoma 100% versus 34.1% p=0.031; chondrosarcoma 75.0% versus 13.7% p=0.046). Florijn and colleagues found using PBT to treat skull base meningiomas allowed for a dose reduction in the hippocampi, normal brain and other organs at risk compared to VMAT[70].

Advanced and/or unresectable head and neck cancers[76-86].

In 2021, there were 7400 new cases of head and neck cancer in Canada[87]. These tumours are often in proximity to critical structures. PBT allows these patients to receive high total doses of target radiation while minimizing the dose to nearby structures such as eyes, mouth, and brain. This allows patients to retain important functions like swallowing, vision, smell, and taste after PBT is complete[88]. Sheikh and colleagues studied patients with locally advanced head and neck tumours and found that the mean doses to all organs at risk were significantly reduced in PBT plans compared to VMAT[25]. Nguyen *et al.* found similar results in a planning study. Intensity-modulated proton therapy (IMPT) plans had lower doses to the brain stem, spinal cord, optic structures, cochlea, larynx, contralateral parotid and oral cavity compared to IMRT plans[81]. PBT has also been reported to lower the risk of head and neck cancer patients developing a secondary cancer[20, 89], as well as reducing toxicities[90].

Paranasal sinus, other accessory sinus, nasal cavity tumour and salivary gland tumours[91].
Tumours of the paranasal sinuses and nasal cavity are rare, accounting for 2-3% of all head and neck tumours[92]. For patients with paranasal sinus and nasal cavity tumours who are good candidates, PBT is the ideal form of RT, owing to: the irregular shape of many of these tumours, the relative radioresistance of some of these tumours requiring high physical and biologically effective doses, the high risk of recurrence associated with these tumours, and the proximity to critical normal tissues in the ocular globes, optic nerves, and brain. Jean *et al.* reported patients with tonsil and salivary gland cancer undergoing IMPT had significantly lower mean radiation doses to organs at risk, compared to patients undergoing VMAT[91]. These patients also reported less deterioration following PBT. In a systematic review and meta-analysis, Ramaekers and colleagues reported a significantly higher pooled estimated five-year local control rate for patients with paranasal and sinonasal tumours treated with PBT compared to IMRT (88% vs. 66%;p=0.035)[93].

Mediastinal lymphomas[16, 17, 94-98].
Cure rates of early Hodgkin lymphoma are high, and the avoidance of late complications and second malignancies has become increasingly important for these patients. PBT may therefore offer an advantage over conventional methods for patients with lymphoma requiring RT. Ntentas and colleagues reported that lymphoma patients with mediastinal disease, treated with PBT, has decreased radiation doses to the heart by 1.0-3.2 Gy, to the left ventricle by 2.7-5.6 Gy, and to the heart valves by 3.6-5.1 Gy compared to photon replanning[96]. Everett *et al.* found similar results. PBT plans for lower mediastinal lymphoma patients reduced the dose to the lungs, heart, esophagus and nontarget body, reducing the risk of late complications, compared to photon plans[94]. Comparable results were observed by Tseng, who found PBT plans had better sparing of the lung and breast compared to photons[95]. Rosenbrock studied female Hodgkin lymphoma patients and compared the effect of radiation on fertility. The risk of ovarian failure for patients treated with PBT was 4.8-3.0 fertility years loss compared to 12.0-5.7 fertility years loss for patients treated with photon therapy[97].

Hepatocellular carcinoma[99-103].

The first-line treatment for hepatocellular cancer (HCC) is surgery, though only a few patients meet the requirements for radical resection[104]. Unresectable HCC treatments include chemotherapy and radiation: radiofrequency ablation, microwave ablation therapy, stereotactic ablative radiotherapy, and particle radiotherapy, including proton therapy. PBT to the cancerous part of the liver, allows the healthy part of the liver to remain unimpacted. HCC patients who undergo PBT have decreased non-classic radiation-induced liver disease (11.8% compared to 36% in photon treated patients; p=0.004[101]), and longer overall survival (median 31 months compared to 14 months in patients treated with photons[102]). Proton beam therapy also allows for the sparing of nearby critical structures such as the bowel, stomach, lung and heart[103].

Other Sarcomas[105-107].

Many sarcomas are in parts of the body that are difficult to treat. PBT, delivered to these hard-to-treat areas decreases the radiation dose to the surrounding tissues. In retroperitoneal sarcoma, it reduces the dose to the bowel and kidneys; in pelvis sarcoma, it reduces the dose to the ovaries; in bladder/ prostate sarcoma, it reduces the dose to the bladder, testes, femoral heads, growth plates and pelvic bones[107]. Morfouace and colleagues studied head and neck rhabdomyosarcoma patients treated with protons, photons, ablative surgery, or the paris method. They reported that patients' face appearance scores, and psychological function scores were highest in the group of patients treated with proton therapy[106]. Mizuno *et al.* investigated patients with angiosarcoma of the scalp treated with helical tomotherapy, VMAT or IMPT. Patients treated with IMPT had lower doses to the organs at risk: spinal cord, brain, hippocampus, brainstem, optic pathway, eyes, lens, parotid glands, and inner ears[105].

Patients with genetic syndromes including neurofibromatosis type 1 (NF-1) and retinoblastoma.

Patients with specific genetic syndromes such as NF-1 develop tumours, both benign and malignant, at increased rates compared to the general population[108]. In these patients, it is very important to minimize the total volume of radiation due to their increased radiosensitivity. They are at an increased risk for side effects and secondary tumour induction[109-112].

Breast Cancer[113-123]

Left-sided breast cancer patients with mean heart dose >5 Gy, despite use of best available photon therapy modalities, are eligible for PBT. There are many studies on the effectiveness of PBT in breast cancer patients. These studies demonstrate that PBT significantly lowers the mean doses to cardiac substructures compared to VMAT[113, 115, 120] and helical tomotherapy[118]. Dose to the lungs and the contralateral breast have also been shown to be reduced compared to IMRT[120, 122] and helical tomotherapy[118]. The dose to the organs at risk are reduced while maintaining excellent target coverage. Pencil beam scanning PBT has been found to be associated with a significant reduction in secondary cancer risk compared to patients treated with photon RT[121]. PBT reduces the lifetime attributable risk of ipsilateral lung[122], contralateral lung and contralateral breast developing a secondary cancer[123].

Lung Cancer[124-133].

Compared with photon therapy, PBT results in similar overall survival, progression free survival and toxicity events in lung cancer patients[4]. The dose escalation and hypofractionation can minimize doses to normal structures while improving local control and survival[134]. When photon-based plans cannot meet prescribed constraints or has too high a risk of toxicity, PBT should be used. This reduces radiation to the contralateral lung as well as other organs: the heart, liver, and kidneys[124, 135]. Yang and colleagues demonstrated that non-small-cell lung cancer patients with leptomeningeal metastasis who underwent PBT had improved central nervous system progression free survival and overall survival with no increase in serious treatment related adverse events compared to patients

treated with photons[133]. Yu *et al.* found similar results in non small cell lung cancer patients treated with definitive chemoradiation using protons. These patients had better overall survival, improved freedom from distant metastases and local recurrence, reduced pneumonitis, and reduced cardiac events compared to patients treated with definitive chemoradiation using photons[124].

Rectal[136, 137] and Anal Canal[138, 139] Cancer.

Radiation in these patients result in a significant dose to genitals, reproductive organs, bowels and bone marrow[140, 141]. PBT reduces toxicity to the organs at risk and increases treatment tolerance. A recent systematic review and meta-analysis of rectal cancer patients undergoing proton or photon-based RT found PBT delivered a lower dose to organs at risk compared to photon RT[136]. Similarly, Pedone *et al.* demonstrated significantly lower doses to the bladder, pelvic bones and bowel bag in rectal cancer patient treated with PBT compared to VMAT[137]. Nelson and colleagues reported decreased bone marrow dose in anal cancer patients treated with chemoradiation using protons compared to photons[138]. A feasibility study by Wo and colleagues investigated if PBT in combination with 5-flueoracil and mitomycin C, reduced grade 3+ dermatologic toxicity below previously reported percentages after photon treatment[139]. The results showed that proton therapy resulted in a 24% grade 3+ radiation dermatitis rate compared to a previously reported 48% with photon therapy.

Prostate Cancer[142-149].

Several studies have suggested that PBT may be beneficial for patients with locally advanced prostate cancer, due to the low rate of radiation scattering to adjacent structures. PBT is safe and effective in the management of prostate cancer. However, evidence dictates that PBT yields similar long-term outcomes as photon therapy[142]. Liu *et al.* reports significantly better overall survival in patients undergoing PBT compared to external beam radiation, but similar results compared to brachytherapy[143]. No difference was observed in toxicity of patients between moderately hypofractionated PBT compared to IMRT[145, 148, 149]. Several studies do report that PBT reduces radiation to nearby healthy tissue[144, 147]. After reviewing the evidence, it was concluded that PBT is not medically necessary for the treatment of prostate cancer. The evidence quality is low and insufficient to determine how PBT and photon-based therapies differ.

Cervix[150, 151] and endometrial cancers.

Pelvic radiation in patients with cervical cancer can cause damage to the ovaries that results in premature menopause. Qin and colleagues reported target coverage to be similar between PBT, bone marrow sparing PBT, IMRT, and bone marrow sparing IMRT. Bone marrow sparing PBT was the most protective on the bone marrow, decreasing the D_{mean} by 44.5%[150]. Shang *et al.* found that PBT plans for cervical cancer patients had lower toxicities of the rectum and sigmoid compared to IMRT[151]. The phase II APPROVE trial reported no gastrointestinal or genitourinary toxicity ≥grade 3, and 100% treatment tolerability in cervical and endometrial cancer patients who underwent PBT[152]. In endometrial cancer patients, it was observed that PBT was associated with significantly lower toxicity to the bowels compared with IMRT and vaginal cuff brachytherapy[153, 154].

C. Second Cancers:

Cancer survivors have a risk of developing a new malignancy 14% higher than the general population[155]. The surveillance, epidemiology and end results (SEER) program estimates the excess absolute risk (EAR) among all cancer patients combined was 21 excess subsequent cancer cases per 10,000 person-years[155]. Half of all cancer patients will undergo RT at some point in their treatment journey[156]. RT increases the risk of developing a second cancer. This increase can be as high as 6 to10-fold in pediatric patients and 1.2 to 3-fold in adult patients[89]. There are many different RT types, that have different dose distributions. A retrospective cohort study using data from the national cancer database, compared the risks of secondary cancer after primary treatment with three types of radiation modalities: three-dimensional conformal radiation (3DCRT), IMRT or PBT[89]. The crude absolute incidence of second cancer per 100 patient-years was 1.55 overall (95% CI, 1.53-1.57), 1.60 after 3DCRT (95% CI, 1.57-1.62), 1.55 after IMRT (95% CI, 1.53-1.57), and 0.44 after PBT (95% CI, 0.37-0.52). The use of PBT significantly decreased the incidence of secondary cancer compared to the two photon RT modalities studied.

II. Referral and Funding Process for Out-of-Country Treatment

A standalone document outlining this process, in Alberta, is available through the AHS internal website here.

Patient Selection Criteria:

A wide range of factors must be taken into account in assessing if proton beam radiotherapy will confer a significant advantage for the patient over standard radiotherapy – the diagnosis alone is often not sufficient[95]. Based on the data published to date, combined with the expert clinical experiences of the working group members, we recommend proton beam radiotherapy be considered for pediatric, adolescent, young adult and adult patients who are residents of Alberta, are covered by the Alberta Health Care Insurance Plan (AHCIP), and meet the criteria outlined in the table below.

Referral Process (Appendix C):

The Radiation Oncologist presents the patient case, that meets the criteria in **Table 1**, at the Proton Therapy Referral Rounds. If a patient is deemed borderline for meeting the criteria, the referring Radiation Oncologist contacts the Florida Proton Beam Program and requests a comparative proton-photon plan. Once the comparative plan is received, the patient's case is discussed at the Proton Therapy Referral Rounds.

The Proton Therapy Referral Rounds is a multidisciplinary tumour board meeting. At this meeting, the patient's case is presented, and all members can provide input on the case. The team also discusses additional treatments that can be considered, travel arrangements and follow-up care. If a referral is recommended, a summary note of the meeting is generated (checklist in **Appendix D**), and the

Radiation Oncologist contacts the Florida Proton Beam Program to confirm if they have capacity. If the Florida Proton Beam Program does not have capacity, a referral to a non-contracted vendor is required. The request must be made through the Out-of-Country Health Services Committee.

Once capacity is confirmed, the referring Radiation Oncologist completes the *Request for Approval* Form (available via AHS internal website here), which is then sent, along with all items on the Alberta Health Checklist (**Appendix E**), via FAX or mail to the Senior Medical Director of Cancer Care Alberta. If approved by the Senior Medical Director, the referral is sent by the Senior Medical Director's office via FAX or mail to the Alberta Health Special Program Unit. The referral letter must include the following:

- Referring physician's contact information: name, specialty, facility address, cell phone, email, fax
- Patient information: name, date of birth, address, email, phone, Alberta personal health card number, and if the patient is pediatric- parent's/guardians contact information
- Approved diagnosis
- Proton Therapy Referral Rounds date, summary note and treatment recommendation
- Notification of access to Proton Beam Therapy- standard process or expediated process and the rationale behind the choice
- Verification of capacity at the University of Florida Proton Beam Institute
- Admission date of treatment
- All medically necessary prerequisite investigations/assessments required to receive Proton Therapy have been completed in Alberta
- Evidence that:
    - no other treatment options are available in Canada
    - proposed treatment meets the Standard of Care in Alberta and Canada
    - proposed treatment is not part of a portion of a Clinical Trial/Experimental

The Alberta Health Special Program Unit does not have access to any electronic medical records. All details on the case must be included in the referral letter. The application is considered complete when all the required information has been submitted, and the Alberta Health Special Program Unit Chair notifies the referring Radiation Oncologist, in writing, that the application has been scheduled for review at an upcoming meeting. The Alberta Health Special Program Unit will assess the application and decide within 30 days. If the Alberta Health Special Program Unit has any additional questions regarding the referral, these will be directed to the lead of the Proton Beam Therapy Referral Rounds.

The referring Radiation Oncologist will be contacted once the Alberta Health Special Program Unit has decided. The approval letter will:

1. Stipulate approval for payment of the services requested
2. Outline the required next steps for the patient

3. Provide details on what services are covered (all medical treatment and transportation to and from) and what is not covered (all accommodation and special costs).

The patient will also be requested to complete two release forms that are to be returned to the manager of the Alberta Health Special Program Unit. These releases allow the medical management company to assist both the patient and the referring physician with the details of the approved medical treatment. The referral letter to the proton beam radiotherapy centre should clearly state that the patient has been approved by the Alberta Health Special Program Unit.

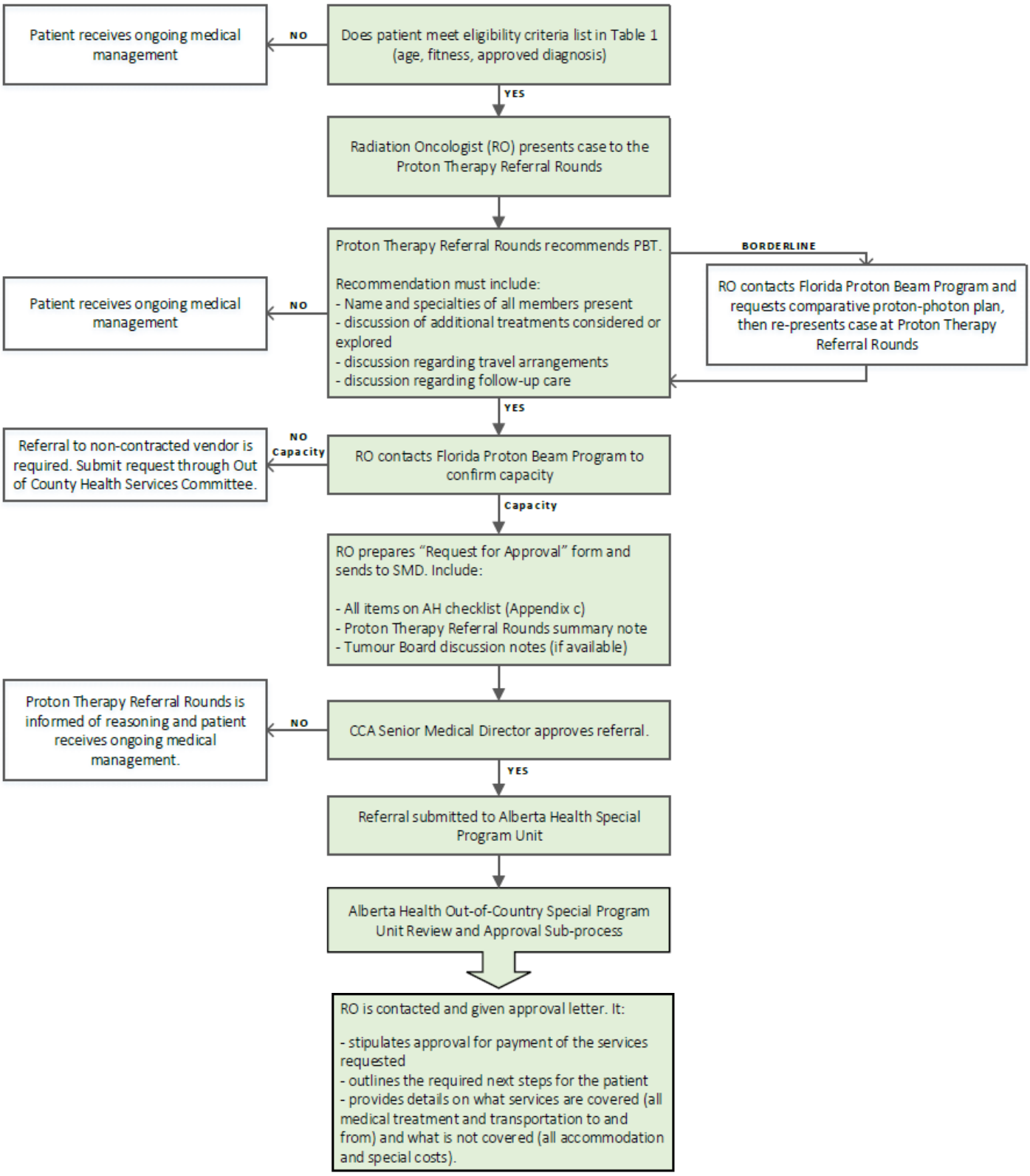
Appendix A: Guideline Development

1. The Guideline Advisory Group members individually reviewed the results of an environmental scan and literature review conducted by a Knowledge Management Specialist from the Guideline Resource Unit. Members of this group include representatives from Alberta Health, as well as the departments of medical oncology, radiation oncology, and pediatric neurosurgery at the two tertiary cancer centres in Alberta. For a detailed description of the methodology followed during the guideline development process, please refer to the Guideline Resource Unit Handbook.
2. Based on this review, the Guideline Advisory Group gave support to the Guideline Working Group to draft a guideline containing the recommendations and supporting evidence about the selection of patients most likely to benefit from treatment with proton beam radiation therapy.
3. The Guideline Working Group then distributed the draft document via an anonymous electronic survey to 17 healthcare professionals from various disciplines within the province for review and comment. The response rate was 59%.
4. The comments from the external review were incorporated into the guideline draft by the Guideline Working Group.
5. The final guideline was reviewed and endorsed in February 2013 by the Cancer Care Alberta Proton Therapy Guideline Advisory Group and Guideline Working Group and was posted on the external website in March 2013.
6. The updated guideline was reviewed and endorsed in 2019 by members of the Guideline Working Group and Guideline Advisory Group.
7. The out of country process was updated in 2022 by the Alberta Health working group.
8. The updated guideline was reviewed and endorsed in October 2023 by members of the Guideline Working Group and Guideline Advisory Group.

Appendix B: Search Strategy

Database	Date	Search Strategy	Limits	Results
PubMed	March 16, 2023	(((proton) AND (photon)) AND ((cancer) OR (oncology))) AND (proton therapy[MeSH Terms])	English, Humans, Full Text, Publication date 2019-present,	170
PubMed	March 27, 2023	((((secondary) AND ((maligna*) OR (cancer))) AND (proton)) AND (photon)) AND (proton therapy[MeSH Terms])	English, Humans, Full Text, Publication date 2019-present,	44
PubMed	March 31, 2023	((proton) AND (breast) AND ((cancer) OR (oncology)) AND (proton therapy[MeSH Terms]))	English, Humans, Full Text, Publication date 2019-present,	95
PubMed	April 5, 2023	((proton) AND ((gastrointestinal) OR (GI)) AND ((cancer) OR (oncology)) AND (proton therapy[MeSH Terms]))	English, Humans, Full Text, Publication date 2019-present,	57
PubMed	April 12, 2023	("proton therapy"[All Fields] OR ("proton"[All Fields] AND ("gy"[All Fields] OR "radiation"[All Fields] OR "radiotherapy"[All Fields])))	English, Humans, Full Text, Publication date 2019-present	2845

Appendix C: Cancer Care Alberta Proton Beam Therapy Selection and Approval Process



Appendix D: Proton Beam Referral Rounds Checklist

Age of Patient	
Diagnosis	
Curative Treatment	☐ yes ☐ no
Performance Status	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
Comorbidities	☐ yes ☐ no _____ *comorbidities*
Metastatic Disease	☐ yes ☐ no
Referring Oncologist	

Proton Beam Therapy Referral Rounds	
	Date of PBT referral rounds_____
☐	Name and specialties of all members present at PBT referral rounds documented
☐	Discussion of additional treatments considered or explored
☐	Discussion regarding travel arrangements
☐	Discussion regarding follow-up care
Proton Beam Therapy Referral Form	
☐	Application completed by referring radiation oncologist
☐	All items on Alberta Health checklist, PBT summary note, referral round notes (if available)
	Date application sent to CCA Senior Medical Director_____
	Date application sent to the Alberta Health Special Program Unit _____

Appendix E: Alberta Health Referral Checklist

Patient Name:	**Date:**
Requirements for Submission to Alberta Health for Funding of Proton Beam Radiation Therapy	
	• **Clinical Criteria:** The patient must be recommended by the Tumour Board to receive OOC proton beam therapy and demonstrate that the Patient has met all the requirements and is compliant with the most current version of the Clinical Practice Guidelines • **Include written submission from:** **1. Alberta Health Services Tumour Board and Cancer Care Alberta/AHS senior medical leaders that supports the treatment plan for the patient, and;** **2. Supporting current consultation and clinical notes outlining the current consultation and clinical notes outlining the current treatment and recommendations.**
Information required for Referral Letter	
	• Referring Physician - Contact Information (Name, Specialty, Facility Address, Cell Phone, Email, Fax)
	• Patient Information (Name, Date of Birth, Address, Email, Phone, Patient AB Personal Health Card Number) • Pediatric requires parents'/guardians' contact information
	• Indicate approved diagnoses: Patient must have a confirmed diagnosis that is consistent with the indications established above
	• Notification of access to Proton Beam Therapy (standard process or expedited process and rationale)
	• Verification of capacity at the University of Florida Proton Beam Institute • Admission date of treatment
	• All medically necessary prerequisite investigations/assessments required to receive Proton Therapy have been completed in Alberta
Evidence the Funding Request Follows the Clinical Practice Guidelines. Verify	
	• No other treatment options are available in Canada
	• Proposed treatment meets the Standard of Care in Alberta and Canada
	• Proposed treatment is not part or a portion therefore of a Clinical Trial/Experimental

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Development and Revision History

This guideline was reviewed and endorsed by the Cancer Care Alberta Proton Therapy Guideline Advisory Group. Members of the Cancer Care Alberta Proton Therapy Guideline Advisory Group include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2012.

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

3DCRT, three-dimensional conformal radiation; AVMs, arteriovenous malformations; EAR excess absolute risk; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; IROC, Imaging and Radiation Oncology Core; NF-1, neurofibromatosis type 1; PBT, proton beam therapy; RT, radiation therapy; SEER, surveillance, epidemiology and end results; SRS, stereotactic radiosurgery; VMAT, volumetric arc modulated therapy,

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Palliative Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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