Curr Oncol, Vol. 21, pp. 251-262; doi: http://dx.doi.org/10.3747/co.21.2207

PRACTICE GUIDELINE

Recommendations for the referral of patients for proton-beam therapy, an Alberta Health Services report: a model for Canada?

S. Patel MD,* *X. Kostaras* MSc,† *M. Parliament* MD,* *I.A. Olivotto* MD,‡ *R. Nordal* MD,‡ *K. Aronyk* MD,§ *and N. Hagen* MD†

ABSTRACT

Background

Compared with photon therapy, proton-beam therapy (PBT) offers compelling advantages in physical dose distribution. Worldwide, gantry-based proton facilities are increasing in number, but no such facilities exist in Canada. To access PBT, Canadian patients must travel abroad for treatment at high cost. In the face of limited access, this report seeks to provide recommendations for the selection of patients most likely to benefit from PBT and suggests an out-of-country referral process.

Methods

The MEDLINE, EMBASE, PubMed, and Cochrane databases were systematically searched for studies published between January 1990 and May 2014 that evaluated clinical outcomes after PBT. A draft report developed through a review of evidence was externally reviewed and then approved by the Alberta Health Services Cancer Care Proton Therapy Guidelines steering committee.

Results

Proton therapy is often used to treat tumours close to radiosensitive tissues and to treat children at risk of developing significant late effects of radiation therapy (RT). In uncontrolled and retrospective studies, local control rates with PBT appear similar to, or in some cases higher than, photon RT. Randomized trials comparing equivalent doses of PBT and photon RT are not available.

Summary

Referral for PBT is recommended for patients who are being treated with curative intent and with an expectation for long-term survival, and who are able and willing to travel abroad to a proton facility. Commonly accepted indications for referral include chordoma and chondrosarcoma, intraocular melanoma, and solid tumours in children and adolescents who have the greatest risk for long-term sequelae. Current data do not provide sufficient evidence to recommend routine referral of patients with most head-and-neck, breast, lung, gastrointestinal tract, and pelvic cancers, including prostate cancer. It is recommended that all referrals be considered by a multidisciplinary team to select appropriate cases.

KEY WORDS

Proton-beam therapy, radiation therapy, review, recommendations

1. INTRODUCTION

In proton-beam therapy (PBT), high-energy protons enter the body, depositing less radiation dose at the body surface and most at the end of their range, deep in tissue (called the Bragg peak). The result is a minimal dose deep to the target, sharply contrasting with the exponential attenuation of dose along the beam path of photons (X-rays). The result is that PBT can spare radiation dose to healthy uninvolved tissues outside the target, potentially reducing the risk of radiation injury[1].

By December 2013, 111,088 patients worldwide had been treated with PBT[2]. Historically, the high capital cost of proton facilities equipped with rotational gantries (exceeding US$160 million)[3] has limited the number of facilities in operation; however, that number is now increasing rapidly (see Table I). In the 10 years up to 2014, the number of facilities in the United States alone grew to thirteen from two[3]. Compact single-room cyclotron centres have drastically reduced the capital cost (estimated at less than US$50 million) and account for 10 of the 22 facilities under construction worldwide[2]. In Canada, the TRIUMF Proton Treatment Facility in Vancouver, British

Columbia, makes a fixed beam suitable for the treatment of intraocular melanomas available episodically through the year[4]. Gantry-equipped facilities capable of treating a broad range of tumour sites are not currently available in Canada.

Patients with diagnoses other than intraocular melanoma must travel outside Canada to access PBT. In most cases, decisions to fund referrals are made case-by-case by the provincial ministries of health. The mean cost per referral is estimated at $200,000 for treatment including daily anesthesia, concurrent chemotherapy, and hospitalization when required. Additional costs, including those for travel, accommodation, and meals, can be incurred by patients.

The present report reviews the latest clinical evidence on the efficacy of PBT, provides recommendations for the selection of patients most likely to benefit from referral, and proposes an out-of-country referral process for Canadian patients.

2. METHODS

2.1 Literature Search

The MEDLINE, EMBASE, PubMed, and Cochrane Library databases were systematically searched for studies published in the English language between January 1, 1990, and May 25, 2014. Search terms were "protons" (MESH) and "radiotherapy" (MESH), "proton therapy" (MESH), "proton beam" (key word), "particle beam therapy" (key word), or "charged particle therapy" (key word). Two reviewers (XK, SP) screened citations for studies evaluating clinical outcomes after PBT (Figure 1). Reference lists of publications and personal files were searched for additional citations.

A search for ongoing trials at http://clinicaltrials.gov/, performed May 25, 2014, identified 218 trials involving PBT, including 20 randomized controlled trials (RCTS), of which only 6 are comparing PBT with photon radiation therapy (RT).

TABLE I Proton-beam facilities equipped with rotational gantries at March 24, 2014[2]

Country	*Facilities (*n*)*		
	In operation	*Under construction*[a]	*Planned*
United States	13	9	1
Japan	8	4	
Germany	3	1	
France	1	1	
South Korea	1	1	
China	1		1
Switzerland	1		1
Czech Republic	1		
Austria		1	
Italy		1	
Poland		1	
Saudi Arabia		1	
Sweden		1	
Taiwan		1	
Netherlands			4
England			2
TOTAL	29	22	9

[a] First patient to be treated during or before 2016.

2.2 Recommendation Development

The present report was produced by the Alberta Health Services (AHS) Cancer Care Proton Therapy Guidelines working group through review and interpretation of evidence. The working group was tasked with drafting guidelines and clinical pathways for the care of patients who could potentially be candidates for PBT. The draft report was distributed by electronic survey to 17 Alberta physicians (59% response rate) from across tumour groups for external review. Feedback was incorporated into the draft, which was then approved by the steering committee and posted on the external AHS Web site in March 2013 (updated in June 2014).

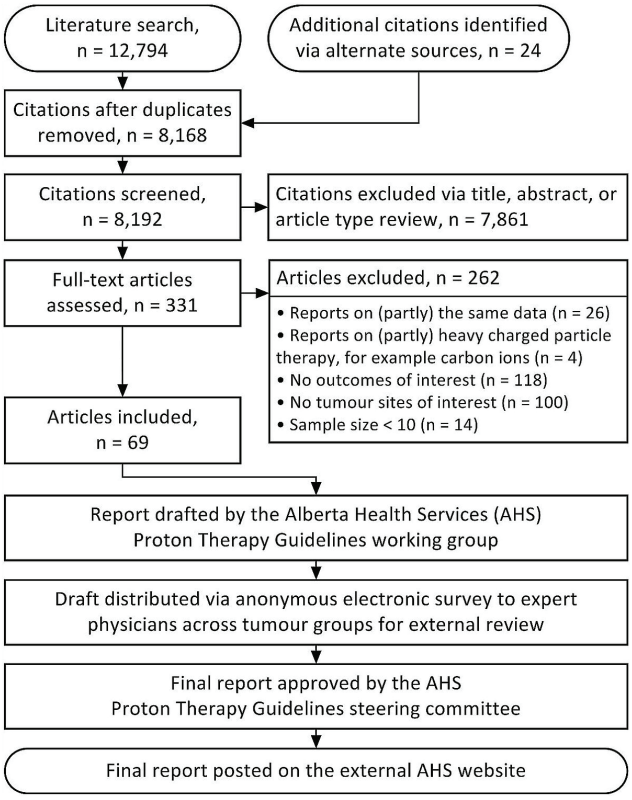

FIGURE 1 *Literature search, draft preparation, and validation process.*

The report was developed as part of the mandate of the AHS Proton Therapy Referral Committee to provide advice to the Out-of-Country Health Services Committee that considers funding for patients referred for medical care to facilities outside Canada.

3. RESULTS

3.1 Pediatrics

Childhood cancer survivors who undergo RT are at high risk of deleterious effects on growth and development and of tissue late effects, including secondary malignancies[5]. Models strongly suggest a lower risk of secondary malignancies in children treated with PBT because of improved dose distribution and a lower volume of normal tissue exposed to radiation[6,7]. Preliminary data from a review of 86 children with retinoblastoma demonstrated a lower 10-year cumulative incidence of RT-associated or in-field secondary malignancies with PBT than with photon RT (0% vs. 14%, $p = 0.015$)[8]. A review of 558 patients treated at the (then) Harvard Cyclotron Laboratory, matched to 558 patients from the Surveillance, Epidemiology, and End Results database who received photon RT, demonstrated fewer subsequent cancer events after PBT (4.2% vs. 7.5%; adjusted hazard ratio: 0.52; $p = 0.009$)[9]. However, limitations in epidemiologic data prevent conclusions being drawn[10].

The rational for using PBT for central nervous system (CNS) lesions is compelling. Compared with photon intensity-modulated RT (IMRT), PBT can achieve substantial sparing of normal tissue during craniospinal irradiation in medulloblastoma (including the cochlea and heart[11]) and during boost therapy (hippocampus[12] and subventricular zone[13]). In Monte Carlo simulations comparing PBT with photon RT for predicted reductions in ototoxicity, endocrine deficiencies, cardiac disease, and secondary malignancies in medulloblastoma survivors, PBT was found to be cost-effective and to be associated with greater quality-adjusted life years[14]. In 96% of simulations, PBT outperformed photon RT. The significant intellectual and academic decline that follow cranial RT[15] were not modelled because of a lack of cost data for productivity loss secondary to cognitive decline. Despite concerns that linear energy transfer variations in proton beams can alter patterns of failure, a review of 109 children with medulloblastoma treated with PBT suggested that the patterns of failure were similar to those with photon RT[16].

For craniopharyngiomas, planning studies show that, compared with IMRT, PBT delivers a lower integral dose to the hippocampus, dentate gyrus, and subventricular zone[17] and a lower dose to the optic chiasm, cochlea, brain, and scanned body[18]. In 5 children and 10 adults treated with combined proton–photon RT, Fitzek *et al.*[19] reported actuarial 5- and 10-year local control rates of 93% and 85% respectively.

Young age, proximity to critical structures, and expectation for a high tumour control rate make PBT an ideal modality for children with ependymoma[20]. A review of 70 children with intracranial ependymoma treated with PBT reported high rates of 3-year local control and overall survival (83% and 95% respectively) at a median follow-up of 46 months[20]. Few children treated with PBT developed growth hormone deficiency ($n = 2$), central hypothyroidism ($n = 1$), or hearing loss ($n = 2$). Amsbaugh *et al.*[21] reported local control and overall survival rates of 100% at a mean follow-up of 26 months in 8 children with spinal ependymoma treated with PBT. No patients experienced grade 3 or greater adverse events.

Studies of tumours outside the CNS—including skull base chordoma and chondrosarcoma[22,23], uveal melanoma[23,24], germ-cell tumours[25], high-risk neuroblastoma[26,27], parameningeal rhabdomyosarcoma[28], bladder and prostate rhabdomyosarcoma[29], other soft tissue sarcomas[30], Ewing sarcoma[31], and mediastinal Hodgkin lymphoma[32]—uniformly showed that PBT is well tolerated, with local control rates similar to or higher than those achieved with photon RT. Although planning studies and early clinical results are promising, long-term data supporting a clear advantage of PBT over photon RT are not yet available. Increased enrollment into clinical trials, including multicentre and registry trials with appropriate statistical designs and long-term follow-up, is needed[33].

3.2 Chordoma and Chondrosarcoma

Chordoma and chondrosarcoma often occur in close proximity to critical neural tissues such as the optic pathway, brainstem, or sacral plexus, posing challenges in the delivery of curative doses of RT. Historical series of photon RT demonstrated 5-year local control rates in the 20% range[34,35], which improved in small series of stereotactic[36] and image-guided RT[37] (published only in abstract form) to 50% and 77% respectively for skull base chordoma and to 100% and 93% respectively for skull base chondrosarcomas. A review of 621 patients treated with combined proton–photon RT at the Harvard Cyclotron Laboratory reported 5-year local relapse-free and overall survival rates of 73% and 80% respectively for skull base chordoma and 98% and 91% respectively for skull base chondrosarcomas[38]. Similar results from the Paul Scherrer Institute were reported with spot-scanned intensity-modulated proton therapy, including 94% freedom from grade 3 or 4 toxicity at 5 years[39]. Full-dose re-irradiation for recurrent or progressive chordoma, with or without salvage surgery, demonstrated encouraging 2-year rates of local control (85%) and overall survival (80%), with late grade 3 or 4 toxicity occurring in 3 of 16 cases[40].

Delaney *et al.* reported long-term results of a phase II study of combined proton–photon RT for spinal chordoma, chondrosarcoma, and other sarcomas. The

8-year actuarial local control was 85% for primary tumours[41]. Randomized data comparing proton with photon RT are not available. Differences in outcome for those RT modalities are confounded by extent of resection, dose escalation, and patient selection biases.

3.3 Intraocular Melanoma

Management of intraocular melanoma aims to preserve the eye and functional vision while achieving a high rate of tumour control. Protons are useful in treating larger tumours or tumours close to the fovea or optic disc that are not suitable for plaque brachytherapy. Local control and eye preservation rates exceed 90% at 5 years[42–46]. In 59 patients treated with PBT at TRIUMF in Vancouver, the 5-year actuarial local control rate was 91% (97% in patients treated with 60 GyE), with an overall eye conservation rate of 80%[46]. The 5-year actuarial rate of neovascular glaucoma was 31% at a median follow-up of 63 months. Radiation retinopathy (74%) and optic neuropathy (64%) were common in-field adverse events. Those results compare favourably with results from series using stereotactic photon RT, which spares the patient from surgical insertion of localization clips[47,48]. However, in the Canadian series, Krema *et al.*[47] reported higher actuarial rates of neovascular glaucoma (42% after a short median follow-up of 37 months) than were reported with proton RT[46].

A single-centre review of 2069 patients treated with PBT demonstrated a 15-year actuarial local control rate of 95%[49]. The cumulative rate of enucleation was 16%, most frequently because of neovascular glaucoma, blindness with ocular discomfort, or local recurrence. In an effort to reduce toxicity, Gragoudas *et al.*[50] randomized 188 patients to standard or reduced-dose PBT and observed less visual field loss, with maintenance of local control and metastatic death rates, in those receiving the lower dose. In a review of 597 patients, Wilson and Hungerford[51] reported similar local control rates with PBT and ^{125}I plaque brachytherapy. A review of 73 patients with recurrence after PBT suggested that, compared with enucleation, re-irradiation with PBT does not compromise overall survival[52].

3.4 Central Nervous System

The dosimetric advantages of PBT compared with photon RT include the former's ability to deliver high doses with steeper gradients to nearby critical structures. Whether those advantages result in a reduction in late effects such as neurocognitive function, vascular events, and second malignancies requires evaluation. For high-grade glioma, PBT has resulted in survival times typical for highly selected patients[53], but PBT is likely more useful in the treatment of benign tumours such as arteriovenous malformations (AVMs), meningiomas, acoustic neuromas, and pituitary adenomas, where long-term survivors are at risk of significant late effects, including secondary malignancies.

Among 248 patients with 254 cerebral AVMs (23% in deep locations) treated with single-fraction proton stereotactic radiosurgery (PSRS), the median time to total obliteration was 31 months, and the 5- and 10-year cumulative incidences of total obliteration were 70% and 91% respectively, comparing favourably with obliteration rates reported using photon radiosurgery, including Gamma Knife (Elekta, Stockholm, Sweden)[54]. In 59 patients with high-risk cerebral AVMs treated with two-fraction PSRS because of large size or eloquent brain location, median time to total obliteration was long at 62 months, with a low 5-year actuarial total obliteration rate of 33%[55]. Median time to obliteration was similar (49 months) in 44 children with high-risk cerebral AVMs treated with PSRS[56]. Those data suggest that AVMs can be safely treated with PSRS; however, no randomized comparisons between proton and photon RT have been published.

Studies of benign meningiomas treated with PBT show local control rates that are comparable to those achieved with photon RT[57–60]. In an older study, the use of PBT without modern spot-scanning and image-guidance appeared to be associated with worse morbidity than was seen with contemporaneous photon RT[60]. For acoustic neuromas, 100% local control at a mean follow-up of 34 months was observed in 30 patients with poor hearing treated with PBT[61]. Among 88 patients treated with single-fraction PSRS, the 5-year actuarial local control was 94%[62]. The 5-year actuarial rates for preservation of normal facial and trigeminal nerve function were 91% and 89% respectively and appeared to be higher than those seen with low-dose photon radiosurgery[63], but the differences could have been a result of patient selection.

Proton craniospinal irradiation has been proposed to spare dose to vertebral bodies and to reduce acute gastrointestinal and hematologic toxicity in adults[64]. In 40 adults with medulloblastoma, less nausea and vomiting, weight loss, and hematologic toxicity was associated with proton craniospinal irradiation than with photon RT, with 2-year overall survival being similar[65].

3.5 Head and Neck

Multiple *in silico* studies have demonstrated dosimetric advantages for PBT in head-and-neck cancers, but clinical data are limited[1]. Data for sinonasal tumours are particularly encouraging[66–69]. Resto *et al.*[66] reviewed 102 patients with locally advanced sinonasal tumours of varying histologies treated with PBT alone or combined with photons. The 5-year rates of local control and overall survival were, respectively, 95% and 90% with complete resection, 82% and 53% with partial resection, and 87% and 49% with biopsy alone. Truong *et al.*[69] reported 2-year local control and overall survival rates of 86% and 53%

respectively in 20 patients with primary sphenoid sinus tumours treated with PBT. A meta-analysis of 86 observational and 8 *in silico* studies demonstrated that, in paranasal and sinonasal cancer, 5-year local control rates were significantly higher for treatment with PBT than for treatment with IMRT (88% vs. 66%, $p = 0.035$)[70]. In other head-and-neck cancers, limited data indicate that toxicity tends to be lower with PBT and that rates of local control and survival are similar to those achieved with photon RT[70].

3.6 Prostate

More than 2000 men with prostate cancer treated with PBT have been reported, and many patients travel considerable distances for PBT[71]. Three RCTs to test the efficacy of dose escalation using PBT have compared combined proton–photon RT with photon RT[72,73]. Shipley *et al.*[72] treated 202 advanced-stage patients with 4-field photon RT (50.4 Gy), then either proton (25.2 GyE) or photon (16.8 Gy) boost RT. An increase in local control with higher dose was noted for subjects with high-grade disease. In the PROG-9509 study, 393 patients with clinically localized prostate cancer received PBT boosts of either 19.6 GyE or 28.8 GyE, and 4-field photon RT (50.4 Gy)[73]. Higher RT reduced the 10-year biochemical failure rate (7.1% vs. 28.2%, $p < 0.0001$) without increasing grade 3 or greater late urinary or rectal morbidity. A case-match analysis of the 196 men on the high-dose arm of that trial and 203 similar men treated with brachytherapy revealed similar 8-year biochemical failure rates[74]. Kim *et al.*[75] randomized 88 T1–3 prostate cancer patients to 5 hypofractionated arms that showed similar biochemical control rates and low rates of grade 3 or greater toxicity (2%); however, a control arm of standard fractionation was not included.

The University of Florida reported 5-year patient-reported outcomes from three prospective trials of image-guided proton-only therapy[76]. Prospectively collected quality-of-life scores during the first 2 years were similar in 1243 men after PBT and 204 men after IMRT[77]. Gray *et al.*[78] reported that PBT, conformal photon RT, and IMRT all result in similar clinically meaningful reductions in bowel (but not urinary) quality-of-life scores at 24 months.

Retrospective data from the Surveillance, Epidemiology, and End Results database comparing PBT with IMRT are controversial[79,80]. A review of 27,647 Medicare beneficiaries demonstrated no reductions in toxicity at 12 months after treatment and substantially higher cost for PBT compared with IMRT[71]. Dosimetric studies suggest that the greatest benefit of using PBT is lower mean integral dose, potentially reducing the risk of secondary malignancies[81], but clinical data are lacking. Currently, PBT appears to hold no clear benefit over IMRT for the management of patients with prostate cancer.

3.7 Other Sites

Other sites—including breast and lung cancers, gastrointestinal tract malignancies, and lymphoma—are reviewed in the full report available on the external Web site http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-rt002-proton-beam-rt.pdf. For those disease sites, PBT demonstrates no clear advantages over photon RT.

4. DISCUSSION

Adoption of new technologies in situations of uncertain clinical benefit is hotly debated[82–84]. Many innovations, including cobalt-60 units, linear accelerators, electron beams, IMRT, and image-guided RT, have entered into clinical practice without phase III RCT evidence[82]. The guiding principle for those advances was to deliver doses "as low as reasonably achievable" (ALARA principle). The current situation with respect to PBT is similar, with numerous dosimetric studies demonstrating potential advantages with PBT[85]. It has been argued that randomization between proton and photon RT would be unethical because normal tissues would be exposed to extra dose without any anticipated gain in the tumour control achieved with photons[82]. Fully informed patients aware that the risk of radiation injury increases with dose and volume irradiated might, appropriately, be unwilling to enrol in RCTs. Goitein and Cox[83] have questioned whether equipoise, a state of genuine uncertainty about the superiority of one arm or the other that ethically justifies a trial between two treatments[86], can be met in this situation, but others disagree[84]. Uncertainties about the range of protons in tissue (arising from patient set-up and motion, beam delivery, and dose calculation), especially in the spot-scanning of moving targets, could limit the physical benefits of PBT[87].

Despite the controversies, efforts to generate high-level evidence are under way, including six RCTs comparing proton and photon RT. The multicentre PARTIQOL RCT in patients with low-risk and low-to-intermediate–risk prostate cancer is comparing bowel quality-of-life as the primary endpoint (http://clinicaltrials.gov/show/NCT01617161). The Radiation Therapy Oncology Group is comparing overall survival in patients with inoperable non-small-cell lung cancer (http://clinicaltrials.gov/show/NCT01993810). These studies include cost effectiveness and quality-of-life as secondary endpoints. Enrollment at the MD Anderson Cancer Centre into four RCTs of intensity-modulated proton therapy compared with IMRT for glioblastoma (http://clinicaltrials.gov/show/NCT01854554), head-and-neck cancer (http://clinicaltrials.gov/show/NCT01893307), and esophageal cancer (http://clinicaltrials.gov/show/NCT01512589), and stereotactic body proton versus photon RT for non-small-cell lung cancer (http://clinicaltrials.gov/show/NCT01511081) include late effects as a primary

endpoint. Large registry studies collecting quality-of-life data in pediatric (http://clinicaltrials.gov/show/NCT01115777) and adult patients (http://clinicaltrials.gov/show/NCT01255748) have proceeded. *In silico* trials, such as those from the ROCOCO consortium[88], could help to guide clinical trial development.

The lack of RCTs comparing proton with photon RT required our working group, like other authors[1,89–97], to make recommendations based on prospective cohort and retrospective data. Loeffler *et al.*[1] suggested that patients with the highest priority for charged-particle therapy include those with chordomas or chondrosarcomas of the skull base, large uveal and mucosal melanomas, large unresectable sarcomas, renal cell carcinoma, pancreatic and liver cancers, and most pediatric patients. In 2012, the emerging technology committee of the American Society for Radiation Oncology reported on the benefits of PBT for large ocular melanomas and chordomas and the dosimetric benefits for craniospinal irradiation in pediatric patients[89]. That report suggested the superiority of proton over photon RT for pediatric CNS tumours; however, the data were insufficient to support a firm recommendation. The authors suggested that evidence was also insufficient to recommend PBT outside of clinical trials in head-and-neck, lung, gastrointestinal, and non-CNS pediatric cancers. Three systematic reviews published in 2007 reported insufficient evidence to recommend PBT for most disease sites[90–92]; however, one concluded that the evidence was sufficient to support PBT in chordomas and large ocular tumours, while not reviewing pediatric indications[92].

In June 2014, the American Society for Radiation Oncology released a model policy to address coverage for PBT[93]. Their policy considers PBT reasonable when clinical benefit can be expected from the sparing of surrounding normal tissue that cannot be adequately achieved using photon RT—for example, when the target volume is close to one or more critical structures and a steep dose gradient outside the target must be achieved, when a decrease in dose inhomogeneity is needed to avoid an excessive dose hotspot, when a photon technique would increase the risk of clinically meaningful normal-tissue toxicity, or when the same or an immediately adjacent area has previously been irradiated. England, Denmark, and the Netherlands have released national guidelines for PBT referral (Table II).

Factors other than diagnosis should be taken into account when deciding whether PBT confers a reasonable expectation of benefit over photon RT. The working group recommends that, to ensure that referred patients will have sufficient risk of late effects that could be reduced with PBT, the treatment intent should be curative and the patient's expected survival should be 5 years or more. In Alberta, criteria do not specifically exclude patients with metastatic disease or cases involving re-irradiation (which are excluded in the English guidelines[94]). Not all patients will be able and willing to relocate to a foreign city, often for 6–8 weeks, for PBT treatment planning and delivery. The psychosocial, occupational, and financial consequences patients endure while away from home cannot be overstated[85]. Fully informed patients should be told of the lack of high-level evidence supporting PBT. Patients or parents of pediatric patients who cannot travel for PBT for whatever reason could potentially be left with lifelong guilt that they did not undergo "optimal" treatment[85]. The working group recommends that every referral be discussed by a multidisciplinary team to provide transparency and accountability in the selection process. In Alberta, that team requests generation of proton and photon RT treatment plans for an assessment of the magnitude of the potential benefit of PBT in cases in which the dosimetric benefit of PBT is unclear.

Proton-beam technology is an evolving field. Passive scattering to produce a proton field is used in most facilities currently in operation[98,99]. Most published clinical studies are of patients treated with such fields. Faster energy changes between neighboring layers and overall dose delivery are advantages of passive scattering, but the need for patient-specific collimators (apertures) to laterally shape the beam reduces clinical efficiency[100]. In uniform scanning, a proton pencil beam is magnetically scanned in lateral directions to produce a large field[101,102]. Because no scattering material is in the beam path, the maximum range of such beams is slightly higher, but as in passive scattering, patient-specific collimators are needed for uniform scanning[100]. In spot scanning, a proton pencil beam is scanned over the target without the need for an aperture or compensator[103]. This technology, available in a limited number of facilities, allows for the delivery of intensity-modulated proton therapy. Relative to IMRT, neutron contamination from passively-scattered proton beams potentially increases the risk of secondary malignancies[5], but spot-scanning drastically reduces neutron production[104]. An evaluation of whether young children should be referred only to spot-scanning facilities is required.

The economics of referral will become increasingly important as patient volumes increase. In Alberta, the number of referrals more than doubled in the year after recommendations were posted on the external Web site (Table III). The working group recommends that patients with intraocular melanomas be sent to the TRIUMF facility in Vancouver to minimize out-of-country costs. Cost savings for other diagnoses could potentially be achieved by negotiation of provincial contracts with one or more preferred PBT providers. Referral to a single facility could also potentially promote communication and research collaboration[105]. Pediatric referrals should be made to a facility with a multidisciplinary pediatric oncology team. A national contract with a

preferred provider incorporating provincial cancer agencies and ministries of health could be negotiated, but would depend on the support of all stakeholders. If the 2013 Alberta rates of PBT utilization and health expenditure (11 referrals at a mean cost per referral of approximately $200,000) are extrapolated to Canada (based on 2013 population estimates[106]), the nationwide cost for an estimated

TABLE II Recommended indications for proton-beam therapy from other nations

Nation	*Recommendations*	
United States (ASTRO)[a,93]	Group 1: • Ocular tumours, including intraocular melanomas • Skull base tumours, including chordoma and chondrosarcoma • Primary or metastatic spinal tumours[b] • Primary or benign solid tumours in children, including occasional palliative treatments • Patients with genetic syndromes such as neurofibromatosis type 1and retinoblastoma • Hepatocellular cancer with hypofractionated regimens	Group 2: All other indications are suitable when the patient is enrolled in a clinical trial or patient registry.
England[c,94]	All ages: • Skull base chordoma or chondrosarcoma, spinal chordoma • Spine and paraspinal bone and soft-tissue sarcomas (non-Ewing)	Pediatric (<16 years of age): • Ependymoma • Selected low-grade gliomas • Craniopharyngioma • Pineal parenchymal tumours (not pineoblastoma) • Rhabdomyosarcoma • Ewing sarcoma • Pelvic sarcoma • Retinoblastoma • Esthesioneuroblastoma
Denmark[a,95]	Adults: • Chordoma and chondrosarcoma, other skull base sarcomas • Ependymoma • Primitive neuroectodermal tumour • Pituitary adenoma and sphenoidal meningioma • Acoustic neuroma • Arteriovenous malformation • Germinoma (brain, thorax, and abdomen) • Eye and orbital tumours • Lymphoma • Selected sarcomas • Nasopharyngeal cancer recurrences	Children and young adolescents: • Medulloblastoma • Ependymoma • Craniopharyngioma • Germinoma • Optic pathway glioma • Retinoblastoma • Nephroblastoma • Osteosarcoma or Ewing sarcoma • Other sarcomas
Netherlands[a,96]	Standard indications: • Skull base or spinal chordoma and chondrosarcoma • Other intracranial, spinal, and paraspinal tumours, including meningioma • Pediatric tumours, including bone tumours, soft-tissue sarcoma, low-grade glioma, meningioma, medulloblastoma, ependymoma, and neuroblastoma	Potential indications: • Re-irradiation (intracranial tumours, head and neck cancer) • Paranasal sinus tumours • Nasopharyngeal carcinoma • Retroperitoneal sarcoma

[a] Indications for proton therapy within a clinical trial or patient registry are not listed.
[b] Where the spinal cord would exceed the tolerance with photon therapy or has previously been irradiated.
[c] Additional requirements: curative intent, good performance status (World Health Organization 0–1), no other coincident diagnoses likely to limit 5-year survival or to make a prolonged period abroad difficult to manage, no metastatic disease, no re-treatment cases, weight 150 kg or less. Rhabdomyosarcoma includes orbital, parameningeal, head and neck, and pelvic sites only.

ASTRO = American Society for Radiation Oncology

TABLE III Patients referred out-of-country for proton-beam therapy from Alberta, 2009–2013

Fiscal year[a]	*Referrals*		
	Funding applications	*Cases denied*	*Cases funded*
2009	5	1	4
2010	4	0	4
2011	7	2	5
2012	4	0	4
2013[b]	11	0	11

[a] Each fiscal year starts April 1 and ends March 31 of the following year.

[b] Recommendations for referral were posted on the external Web site in March 2013.

96 referrals would be $19.2 million annually and growing. Referral patterns and actual costs across Canada have not yet been studied.

5. SUMMARY

Evidence from a literature review, consensus of expert opinion, feedback obtained through a review process, and final approval given by the steering committee form the basis of these recommendations, which were completed in March 2013 and updated in June 2014.

5.1 Target Population

These recommendations apply to pediatric and adult patients being considered for treatment with RT.

5.2 Recommendations

1. Factors other than diagnosis should be taken into account in assessing whether PBT confers a reasonable expectation of clinical benefit over photon therapy such as IMRT, stereotactic RT, and brachytherapy.
2. These general requirements for referral and approval of funding must all be met:
   - The treatment is being delivered with curative intent.
   - There is a reasonable expectation that overall survival will reach or exceed 5 years.
   - The patient's Eastern Cooperative Oncology Group performance status is 0–2.
   - The patient is able and willing to travel.
3. Commonly accepted indications for referral include
   - chordoma and chondrosarcoma;
   - intraocular melanomas that are not suitable for plaque brachytherapy; and
   - tumours of children and adolescents, including those requiring craniospinal irradiation, low-grade glioma, ependymoma, craniopharyngioma, germ-cell tumours, pituitary and pineal tumours (not pineoblastomas), rhabdomyosarcoma, Ewing sarcoma, pelvic sarcomas, and mediastinal lymphoma.
4. Indications in adults with possible benefit from referral include
   - benign tumours of the CNS, including AVM, benign meningioma, acoustic neuroma, pituitary and pineal tumours (not pineoblastomas), and craniopharyngioma; and
   - paranasal sinus and nasal cavity tumours.
5. Patients with other head-and-neck, breast, lung, gastrointestinal tract, and pelvic cancers, including prostate cancer, are not recommended for routine referral because of an insufficient evidence base. However, individual cases of any diagnosis can be considered in a multidisciplinary setting.
6. All referred cases should be discussed by a multidisciplinary team that includes a radiation oncologist. After that discussion, approval of funding is required by most provincial ministries of health. Once approved, responsibility for the referral, ongoing communication with the PBT facility, and post-treatment follow-up remains with the referring oncologist (Figure 2).
7. Patients with intraocular melanomas should be referred to the TRIUMF Proton Treatment Facility in Vancouver. Other patients will require referral to a proton facility outside Canada. A current list of facilities in operation is available on the Particle Therapy Co-Operative Group Web site[2].

5.3 Qualifying Statement

Funding for referral for PBT is generally considered on a case-by-case basis by the Ministry of Health in each province. In Alberta, the Out-of-Country Health Services Committee, a regulated committee operating at arm's length from the Ministry of Health and Alberta Health Services, reviews applications for hospital and physician services that are not available in Canada. Applications for PBT referral require documentation of case review at the AHS Proton Therapy Referral Committee multidisciplinary rounds, where discussion follows the recommendations reported here.

6. ACKNOWLEDGMENTS

The AHS Proton Therapy Referral Committee thanks the members of the AHS Provincial Tumour Programs and the Out-of-Country Health Services Committee, particularly Stella Hoeksema and Dr. Raymond Howard, for their support and feedback on draft versions of the recommendations.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

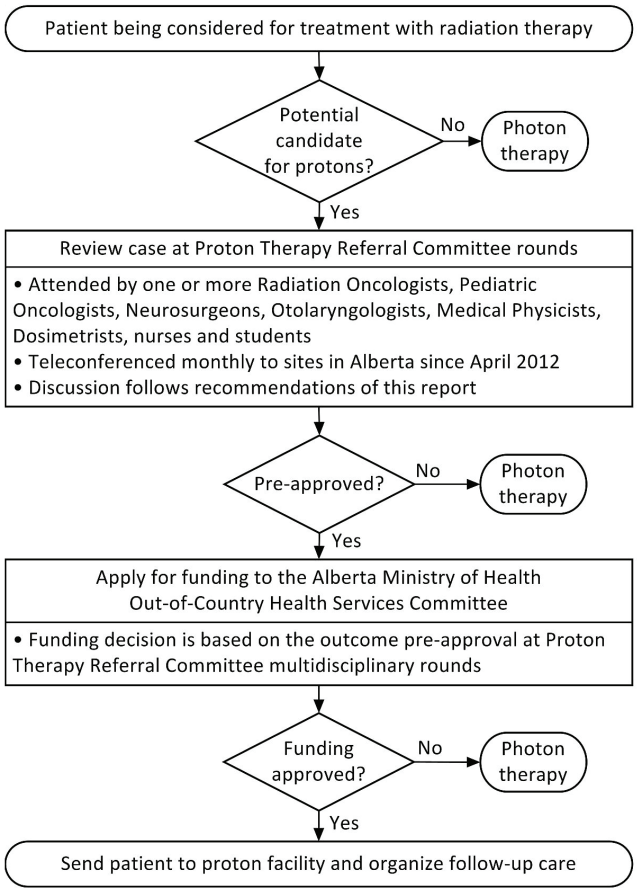

FIGURE 2 Clinical care pathway resulting from implementation of the recommendations in Alberta.

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Correspondence to: Samir Patel, Department of Radiation Oncology, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta T6G 1Z2.
E-mail: samir.patel2@albertahealthservices.ca

* Department of Radiation Oncology, Cross Cancer Institute, and Department of Oncology, University of Alberta, Edmonton, AB.
† Guideline Utilization Resource Unit, Alberta Health Services, Calgary, AB.
‡ Division of Radiation Oncology, Tom Baker Cancer Centre, and University of Calgary, Calgary, AB.
§ Division of Neurosurgery, University of Alberta, Edmonton, AB.