

Proton Beam Radiation Therapy

Effective Date: July 2019



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^{1,2}. To date, there are no 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. Published reports focus mainly on toxicity, and include pediatric, adolescent, and adult patients treated with proton beam radiotherapy primarily for ocular cancers, spine or skull base chordomas and chondrosarcomas, spinal and paraspinal bone and soft tissue sarcomas, head and neck cancers, and brain tumours. In addition, there is some literature reporting the use of proton beam radiotherapy for patients with lymphoma, non-small cell lung cancer, prostate cancer, and some gastrointestinal cancers.

By December 2017, 170,556 patients worldwide had been treated with proton beam radiotherapy³. 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. Between 2004 and 2014, the number of facilities in the United States alone grew to 13 from 2 and from 13 to 32 between 2014 and 2017³. Compact single-room cyclotron centres have drastically reduced the capital cost and account for 10 of the 22 facilities under construction worldwide³. 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, 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 go through the out of country Health Services Committee.

Guideline Questions

1. What is the evidence for the use of proton beam radiation therapy 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 proton beam radiation therapy?
3. What are the steps involved in referring a patient for out of country proton beam radiation therapy?

Development

The Cancer Care Alberta Proton Therapy Guideline Advisory Group took the following steps in producing this guideline:

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.

Search Strategy

Medical journals were searched using the MEDLINE, EMBASE, PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials; the references and bibliographies of studies identified through these searches were scanned for additional sources. The search terms were: Protons (MeSH term) AND Radiotherapy (MeSH term), proton therapy (MeSH term), proton beam (keyword), particle beam therapy (keyword), and charged particle therapy (keyword). The search was limited to studies published in the English language between the years 2000 and 2014. There were no limitations by study design. A search for new or updated guidelines, health technology assessments, and medical policies was conducted by accessing the websites of guideline developers and the National Guidelines Clearinghouse database, and by searching the grey literature using online search engines. A search for ongoing trials at <http://www.clinicaltrials.gov> was performed in May 2014 and identified 218 trials involving proton beam radiotherapy; of the 20 randomized controlled trials identified, 6 are comparing proton beam radiotherapy with photon radiotherapy. The latest update searched PubMed, MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews (2014- March 2019) and retrieved 286 articles. A total of 28 relevant articles were identified. In addition, eight clinical practice guidelines were identified from AIM Specialty Health, American Society for Radiation Oncology (ASTRO), American College of Radiology (ACR)-ASTRO, The Canadian Association of Drugs and Technology of Health (CADTH), The National Institute of Excellence in Health and Social Services (INESSS), National Association for Proton Therapy and the National Health Service.

Target Population

The recommendations in this guideline are for pediatric, adolescent, young adult and adult patients who are residents of Alberta and may qualify to receive proton beam radiotherapy at a facility outside of Canada for treatment of their cancer.

Summary of Recommendations

1. Factors other than diagnosis should be taken into account in assessing whether proton beam radiotherapy will confer a significant advantage for the patient over photon therapies available in Alberta such as photon intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy, and brachytherapy.
2. Pediatric and adolescent tumour sites that may be considered for referral for out of country proton beam radiotherapy include:
 - a. those requiring craniospinal irradiation
 - b. the following central nervous system tumours or lesions: arteriovenous malformations, ependymomas, craniopharyngiomas, CNS germ cell tumours, primitive neuroectodermal tumours, and low grade gliomas

- c. the following non-central nervous system tumours: chordoma and chondrosarcoma, pelvic sarcomas, rhabdomyosarcoma, Ewing's sarcoma, pituitary and pineal tumours (excluding pineoblastomas), and mediastinal lymphoma.
3. Adult tumour sites that may be considered for referral for out of country proton beam radiotherapy include:
 - a. the following central nervous system tumours or lesions in patients under the age of 40 years: arteriovenous malformations, benign meningioma, neuromas, craniopharyngioma, CNS germ cell tumours, and low grade gliomas
 - b. the following non-central nervous system tumours: sarcoma including chordoma and chondrosarcoma, lymphoma in patients under the age of 30 years, paranasal sinus and nasal cavity tumours, and intraocular melanomas that are not suitable for plaque brachytherapy.
4. Members of the working group do not currently recommend that patients with other head/neck, breast, lung, gastrointestinal tract, and pelvic cancers including prostate cancer, be referred for proton beam radiotherapy, due to an insufficient evidence base. However, individual patient cases should be discussed by the Proton Therapy Referral Rounds.
5. For all cases, the referral for proton beam radiotherapy 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 recommend Proton Beam Therapy, and that recommendation is approved by the Senior Medical Director of Cancer Care Alberta.
6. Additional and over-riding principles for approval and funding include:
 - a. the treatment should be given with curative intent
 - b. the patient should have a good performance status (0-2)
 - c. the expected survival of the patient should be greater than 5 years
 - d. the patient must be able and willing to travel.

Discussion

I. Indications and Evidence for Proton Beam Therapy

Pediatric Tumours

Radiation therapy has played an important role in the treatment and cure of children diagnosed with malignant tumours over the past 30 years; given that approximately 70% of children with malignancies can now expect to be cured, the late effects of treatment have now become a major focus⁴. Proton beam therapy is associated with a reduction in acute and long-term toxicities, as well as lower rates of radiation-induced second malignancies, and potentially less acute and long-term damage to developing organs in pediatric and adolescent patients with cancer⁴⁻⁶; therefore, the benefits of proton beam radiotherapy are potentially the greatest in this population. Although limited, published reports of pediatric and adolescent patients treated with proton beam radiotherapy have mostly addressed tumours arising on or near critical structures, as well as tumours where organs in the exit path of photon radiotherapy present significant secondary malignancy risk or risk of impaired

development and function; such tumours include medulloblastomas, gliomas, ependymomas, retinoblastomas, rhabdomyosarcomas, and pelvic sarcomas^{4,7}.

In one of the larger pediatric series published to date, MacDonald and colleagues reported the results of 17 pediatric patients with WHO grade II or III intracranial ependymomas treated with 3-dimensional conformal proton beam radiotherapy⁸. At a median follow-up of 26 months, the rates of local control, progression free survival, and overall survival rates were 86%, 80%, and 89%, respectively. Similarly, Amsbaugh and colleagues published the results of a prospective case series of eight pediatric patients with WHO grade I or II spinal ependymomas treated with proton beam radiotherapy⁹. Five patients were treated with proton beam radiotherapy as part of their primary management, while three were treated for recurrence of their disease. The entire vertebral body was treated in all but two patients, with a mean dose of 51.1 cobalt grey equivalents (CGE). The rates of local control, event-free survival, and overall survival were all 100% at a mean follow-up of 26 months, and the investigators reported minimal acute side effects.

In a case series of three pediatric patients with medulloblastoma, Yuh and colleagues reported minimal acute side effects, excellent sparing of surrounding critical structures, and no treatment disruptions when the patients were treated with 36 CGE to the craniospinal axis and 18 CGE to the posterior fossa¹⁰. Similarly, St. Clair and colleagues compared treatment plans from standard photon therapy to intensity modulated radiotherapy (IMRT) and proton beam radiotherapy for craniospinal axis irradiation and posterior fossa boost in a pediatric patient with medulloblastoma. They reported substantial normal-tissue dose sparing with IMRT and proton treatment of the posterior fossa and spinal column, and also that protons were superior to IMRT in this case¹¹. In another case series, six pediatric medulloblastoma patients were treated with vertebral-body-sparing proton craniospinal irradiation after maximal safe resection¹². These patients received a dose of 23.4 Gy or 36 Gy to the craniospinal axis followed by a boost to the posterior fossa and any metastatic lesions. After a median follow-up of 13.6 years, the overall survival and disease-free survival were 83%, treatment did not increase spinal abnormalities compared with historical data, and it allowed for vertebral body growth outside of radiation field and bone marrow sparing. In a modeling study evaluating the consequences of radiotherapy in five year old patients with medulloblastoma, Lundkvist and colleagues reported that proton radiation therapy was cost-effective and was associated with an additional 0.68 quality-adjusted life-years per patient compared with conventional photon radiotherapy¹³. Reductions in IQ loss and growth hormone deficiency contributed most to the cost savings and were the most important parameters for cost-effectiveness. This analysis suggests that proton beam radiotherapy may be cost saving in comparison to photon radiotherapy for pediatric patients with medulloblastoma due to the reduction of late side-effects. A reduction in side-effects for pediatric patients with medulloblastoma treated with proton beam radiotherapy was also demonstrated in a prospective study of 23 pediatric patients who were followed for high-grade ototoxicity¹⁴, although a cost-benefit analysis was not reported for this trial.

Young Adult Tumours

Adolescent and young adult patients (age range 19-40) can be particularly vulnerable to complications from radiotherapy. With increased survival, the long term complications of treatment can have a major impact on growth, fertility, and emotional well-being¹⁵. Particularly the risk of radiation-induced secondary cancer is of concern in these patients. Zhang and colleagues reported on 17 medulloblastoma patients treated with passively scattered proton or field-in-field photon craniospinal irradiation (CSI)¹⁶. They found that proton CSI reduced the predicted risks of radiogenic second cancer incidence and cardiac mortality by six times compared with photon CSI. Yoon *et al.* retrospectively review 10 randomly selected cancer patients treated with either photon or proton radiotherapy¹⁷. The secondary cancer risks to lungs, stomach, liver and pancreas were at least five fold higher in patients treated with photon therapy compared to proton beam therapy. Another retrospective review studied 86 patients with retinoblastoma treated with proton or photon radiotherapy¹⁸. The 10-year cumulative incidence of radiation-induced or in-field second malignancies was 0% for patients treated with proton beam therapy versus 14% for patients treated with photon therapy (p=0.015). The 10-years cumulative incidence of all second malignancies was 5 % after proton therapy and 14% after photon therapy (p=0.120). Chung and colleagues performed a retrospective cohort study where they matched 558 proton patients with 558 photon patients¹⁹. Secondary malignancies occurred in 42 (7.5%) photon patients versus only 29 (5.2%) proton patients. They found that proton therapy was not associated with an increased risk of secondary cancer with an adjusted hazard ratio of 0.52 [95% confidence interval, 0.32-0.85]; p=0.009.

Central Nervous System Tumours

Similar to pediatric patients with favourable prognoses, adult patients with benign lesions and indolent malignant tumours also benefit from proton beam radiotherapy due to a decreased risk of late neurologic toxicities.

Meningiomas. Meningiomas are the second most common intracranial tumour reported in adults, accounting for 13 to 26% of all primary brain tumours in this population^{20,21}. 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 tumour²². In the [Meningiomas](#) clinical practice guideline, the Alberta Provincial CNS Tumour Team members recommend surgery as the primary treatment for patients who are not candidates for management by watch-and-wait. This guideline also states that 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. Boskos and colleagues reported on 24 patients with either atypical or metastatic meningioma treated at the Centre Protonthérapie d'Orsay with a postoperative combination of proton and photon radiotherapy²³. The mean local relapse-free survival was 28.3 months (range 10-50) for atypical meningioma and 23 months (range 13-33) for malignant meningioma; ten tumours recurred locally. Overall survival rates were 100% at one year, 80.4% ± 8.8% at three years, 53.2% ± 11.6% at five years, and 42.6% ± 13%

at eight years. Noël *et al.* also reported on the outcomes of 51 patients treated for base of skull meningiomas with a combination of proton and photon radiotherapy²⁴. The four-year local control rate was 98%, and the four-year overall survival rate was 100%. The investigators reported tumour stabilization in 38 patients (72%), volume reduction in ten patients (20%), and intra-tumour necrosis in three patients; grade three side effects were observed in two patients. Similarly, Wenkel *et al.* reported on 46 patients with partially resected, biopsied, or recurrent meningiomas who were treated with combined proton and photon radiotherapy at the Massachusetts General Hospital and the Harvard Cyclotron Laboratory²⁵. Five- and ten-year overall survival rates were 93% and 77%, respectively, and the five- and ten-year recurrence-free rates were 100% and 88%, respectively. Survival without severe toxicity was 80% at both five and ten years. The use of stereotactic and hypofractionated stereotactic proton beam radiotherapy were reported by Vernimmen and colleagues in a study of 27 patients with large or complex intracranial meningiomas²⁶. Of the 18 patients treated with hypofractionated stereotactic proton beam radiotherapy, 16 remained clinically stable or improved. Of the five patients treated with stereotactic proton beam radiotherapy, two showed clinical improvement and three remained clinically stable. The radiologic control rate was 88% for the patients treated with hypofractionation, and 100% for patients treated without hypofractionation. In a study investigating the use of spot-scanning proton beam radiotherapy, Weber and colleagues reported on 13 patients treated postoperatively for incomplete resection or recurrence and three patients treated radically after presumptive diagnosis based on imaging²⁷. The cumulative three-year local control, progression-free survival and overall survival rates were 91.7%, 91.7%, and 92.7%, respectively, and no patient died from recurrent disease. The cumulative three-year toxicity-free survival rate was 76.2%; radiation-induced side effects included grade III optic neuropathy, grade II retinopathy, and grade IV brain necrosis. El Shafie *et al.* reported on 110 patients with meningiomas of the skull base treated with particle radiotherapy (proton: 95%, carbon ion: 5%)²⁸. Progression-free survival was 100% after 36 months and 96.6% after 60 months. The overall survival was 96.2% after 60 months and 92% after 72 months.

Arteriovenous malformations. 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 deficits²⁹. Standard interventions for brain AVMs include resection for surgically accessible lesions and embolization; stereotactic radiosurgery 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 stereotactic radiosurgery, Seifert *et al.* reported symptoms control in 85.7% in patients with Spetzler-Martin grades I and II AVMs, 54.2% of patients with grade III AVMs, and 24% of patients with grade IV AVMs³⁰. Vernimmen and colleagues followed 64 patients with predominantly large AVMs who were treated with hypofractionated stereotactic proton radiosurgery, and reported obliteration rates of 67% for patients with AVM volumes less than 14cc and 43% for AVM volumes greater than 14cc³¹. Grade IV acute complications were observed in 3% of patients, and transient delayed effects were seen in 23% of patients. A recent review of 248 patients with 254 cerebral AVMs (23% in deep locations) treated with single-fraction proton stereotactic radiosurgery reported a 31 month median time to total obliteration,

with 70% and 90% respective five- and ten-year cumulative incidences of total obliteration³². Similarly, in 59 patients with high-risk cerebral AVMs treated with two-fraction proton stereotactic radiosurgery because of large tumour size or eloquent brain location, the median time to total obliteration was 62 months and the five-year actuarial total obliteration rate was 33%³³. Complications associated with radiosurgery include radiation necrosis, seizures, and new neurologic deficits, therefore the efficacy of radiosurgery must be weighed against the potential toxicities of treatment³⁴.

Acoustic neuromas. 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 adults³⁵. Options for treatment depend on tumour size, tumour growth rate, symptoms, health status, and patient preference, and may include observation, single-session stereotactic radiosurgery, fractionated conventional radiotherapy, fractionated stereotactic radiotherapy, proton beam radiotherapy, or surgery^{36,37}. Although a distinct advantage of proton therapy over photon therapy for acoustic neuromas has not been demonstrated to date, larger tumours may benefit from proton beam radiotherapy because of the reduction of exit dose to the non-targeted brain and surrounding normal tissues³⁴. In a review of 88 patients treated with proton beam radiotherapy at the Harvard Cyclotron Laboratory, Weber and colleagues reported two- and five-year actuarial control rates of 95.3% and 93.6% respectively in patients treated with stereotactic proton beam radiotherapy³⁸. Facial and trigeminal nerve function was preserved in 91% and 89% of patients, respectively, and the five-year cumulative radiologic response rate was 94.7%. Salvage therapy was required in five patients post-radiotherapy. In a trial of 30 patients with acoustic neuromas treated with fractionated proton beam radiotherapy at the Loma Linda Medical Center, Bush *et al.* reported no disease progression at a mean follow-up of 34 months, and radiographic regression in 11 patients³⁹. The rate of hearing preservation was 31%, however only 13 patients had useful hearing prior to radiotherapy. No transient or permanent treatment-related trigeminal or facial nerve dysfunction was observed.

Spinal and Skull Base Chordomas and Chondrosarcomas

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 sphenoccipital region^{40,41}. Chordomas are rare in both adults and children, accounting for only three to four percent of all primary bone tumours⁴¹. 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 fossae⁴². The clinical features of chordomas and chondrosarcomas are quite similar, as is the optimal treatment strategy, which involves maximal surgical resection⁴¹⁻⁴³. Adjuvant postoperative radiotherapy is commonly used for patients with chordomas, and high doses have been associated with lower rates of local recurrence or treatment failure^{44,45}. Postoperative radiotherapy has also been reported for the management of patients with chondrosarcomas. 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 proton beam radiotherapy. Despite the relative rarity of these tumours, the results of over 1,700 patients with spinal and skull base chordomas and chondrosarcomas treated with proton beam radiotherapy have been reported worldwide since the early 1970's³⁴. Ares and colleagues recently reported the results of a long-term follow-up study of 64 patients with skull base chordomas or chondrosarcomas treated with spot-scanning proton beam radiotherapy at the Paul Scherrer Institute⁴⁶. The five-year overall survival rate was 91% for patients with chondrosarcomas, and 62% for patients with chordomas; the five-year local control rate was 94% for patients with chondrosarcoma, and 81% for patients with chordomas. Adverse events included grade III (N=1) and grade IV (N=1) unilateral optic neuropathy, grade III temporal lobe parenchyma (N=2) and grade I leukoencephalopathy (N=5). In the largest series published to date, Munzenrider and Liebsch retrospectively reviewed 621 patients with spinal and skull base chordomas or chondrosarcomas treated between 1975 and 1998 at the Harvard Cyclotron Laboratory⁴⁷. Treatment involved combined proton and photon irradiation, with a dose range of 66 to 83 CGE. For patients with skull base tumours, the five-year overall survival rates were 91% for chondrosarcomas and 80% for chordomas ($p=0.010$), and the ten-year overall survival rates were 88% for chondrosarcomas and 54% for chordomas ($p<0.0001$). Local recurrence rates were also better for chondrosarcomas versus chordomas at five years (98% versus 73%, $p<0.0001$) and ten years (94% versus 54%, $p<0.0001$). For patients with cervical spine tumours, the five-year overall survival rates were 48% for chondrosarcomas and 80% for chordomas ($p=0.008$), and the ten-year overall survival rates were 48% for chondrosarcomas and 33% for chordomas ($p=0.109$). Local recurrence rates for chondrosarcomas and chordomas were 54% and 69% at five years, and 54% and 48% at ten years, with no significant differences between the two groups of patients. In a systematic review of seven studies involving 416 adult and pediatric patients with inoperable or incompletely resected chordomas of the skull who were treated with proton beam radiotherapy, Amichetti *et al.* reported an average five-year overall survival rate of 79.8% (range 66.7-80.5%) and an average five-year local control rate of 69.2% (range 46-73%)⁴¹. Late toxicity was reported in the range of 5-17%, with some grade III and IV toxicities reported. Similarly, in another systematic review of four studies involving 254 patients with chondrosarcomas of the skull base treated post-operatively with proton beam radiotherapy, Amichetti and colleagues reported a five-year overall survival rate of 99-100% and a five-year local control rate of 75-99%⁴².

The use of proton beam radiotherapy has also been described for soft tissue sarcomas of the spine. DeLaney and colleagues reported the results of a prospective phase II trial involving 50 patients mostly with spinal and paraspinal chordomas and chondrosarcomas, but patients with liposarcoma, osteosarcoma, Ewing's sarcoma, giant cell tumour, angiosarcoma, malignant schwannoma, and spindle cell sarcoma were also included⁴. Patients were treated post-operatively with high-dose proton-photon radiotherapy at a median dose of 76.6 CGE and select patients with high-grade tumours also received chemotherapy. Thirty-six patients were treated for primary tumours, and 14 for recurrent disease. With 7.3-year median follow-up, the respective five- and eight-year actuarial local control rates were 94% and 85% for primary tumours and 81% and 74% for the entire group. Local recurrence was less common for primary tumours, compared to recurrent tumours, (11% vs. 50%,

p=0.002). The eight-year actuarial risk of grade 3-4 late RT morbidity was 13%⁴⁸. Guttmann and colleagues studied 23 recurrent soft tissue sarcoma patients treated with proton reirradiation, prospectively⁴⁹. All sarcomas were in a previously irradiated field. The three-year progression-free survival was found to be 43% (95% CI 21-62%) and the three-year overall survival was 64% (95% CI 39-81%). Weber *et al.* retrospectively reviewed 38 Ewing sarcoma patients treated with pencil beam scanning proton therapy⁵⁰. The five- year actuarial rate of local control, distant metastasis-free survival and overall survival were 81.5%, 76.4% and 83.0% respectively. This treatment was associated with a low rate of high –grade late toxicity. Demizu and colleagues retrospectively reviewed 91 patients with unresectable or incompletely resected bone and soft tissue sarcomas, treated with 70.4 GyRBE proton or carbon ion particle therapy in 16 or 32 fractions⁵¹. They found that particle therapy was effective with a 3- year overall survival of 83%, a 3- year progression free survival of 72% and a 3- year local control of 92%. The 16 fractions protocol was associated with significantly (p<0.001) more late grade ≥ 3 toxicities.

Ocular Melanoma

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^{52,53}. 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 proton beam radiation therapy for larger tumours has been reported extensively in the literature, with five recent comparative studies and numerous non-comparative studies showing high rates of local control and minimal adverse effects⁵⁴⁻⁶⁸. However, a publication based on data from the SEER database in the United States reported that survival rates for patients with uveal melanoma have not improved from 1973 to 2008, despite a shift toward more conservative treatments such as proton beam radiotherapy during this time period⁶⁹.

Head and Neck Tumours

Tumours of the paranasal sinuses and nasal cavity are rare, accounting for 2-3% of all head and neck tumours⁷⁰. Optimal treatment involves surgical resection and postoperative radiotherapy; chemotherapy, either alone or in combination with radiotherapy and/or surgery, is also an option for patients who are at high risk of recurrence or for patients with inoperable tumours^{71,72}. For patients with paranasal sinus and nasal cavity tumours who are good candidates, proton beam radiotherapy is the ideal form of radiotherapy, 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 brain³⁴. Resto *et al.* retrospectively reviewed the outcomes of 102 patients with locally advanced sinonasal tumours of varying histologies treated at the Harvard Cyclotron Laboratory, the Francis Burr Proton Center, or the Massachusetts General Hospital between 1991 and 2002⁷³. Combined photon and proton beam radiotherapy was given as definitive treatment in 32 patients, as adjuvant treatment after partial resection in 50 patients, and as adjuvant treatment after complete resection in 20 patients. Five-year local control rates were 95% for patients

with a complete resection, 82% for patients with a partial resection, and 87% for patients with biopsy only. Five-year overall survival rates were 90% for patients with a complete resection, 53% for patients with a partial resection, and 49% for patients with a biopsy only. Also from the Massachusetts General Hospital, Truong and colleagues described 20 patients with primary sphenoid sinus tumours treated with proton beam radiotherapy at a median dose of 76 CGE⁷⁴. The two-year rates of local control, regional control, and freedom from distant metastasis were 86%, 86%, and 50%, respectively. The two-year disease-free and overall-survival rates were 31% and 53%, respectively. The investigators identified brain invasion and involvement of the oropharynx and anterior cranial fossa as important prognostic factors. In a systematic review and meta-analysis which included the Resto *et al.* study, Ramaekers and colleagues reported a significantly higher pooled estimated five-year local control rate for patients with paranasal and sinonasal tumours treated with proton beam radiotherapy compared to intensity modulated photon therapy (88% vs. 66%; $p=0.035$)⁷⁵. Tokuyue and colleagues reported the results of a retrospective review of 33 patients with head and neck tumours and no history of surgery who were treated with proton beam radiotherapy with or without photon beam radiotherapy at the University of Tsukuba Hospital in Japan⁷⁶. The five-year overall survival rate was 44%, and the five-year local control rate was 74%; acute toxicity greater than grade III was reported in one patient, and late toxicity greater than grade III was reported in six patients. Similarly, in a retrospective analysis of 39 adult patients with unresectable malignant tumours of the nasal cavity, paranasal sinus, or skull base who were treated with proton beam radiotherapy at a dose of 60 CGE or higher at the National Cancer Center Hospital East in Japan, Zenda and colleagues reported a one-year local control rate of 77%, and three-year progression-free and overall survival rates of 49.1% and 59.3%, respectively⁷⁷. Acute toxicity included grade II dermatitis; long-term grade III-IV toxicity was reported in five patients, and one treatment-related death was reported. Romesser and colleagues retrospectively reviewed 92 patients with recurrent head and neck cancer treated with proton beam therapy at a median dose of 60.6 GyRBE⁷⁸. The actuarial 12 month freedom-from-distance metastasis and overall survival rates were 84% and 65.2% respectively. Grade III or greater toxicities were noted in 10.8% of patients.

II. Potential Indications and Evidence for Proton Beam Therapy

Lymphoma

Cure rates of early Hodgkin lymphoma are high, and the avoidance of late complications and second malignancies has become increasingly important for these patients; proton beam radiotherapy may therefore offer an advantage over conventional methods for patients with lymphoma requiring radiotherapy. In a study of ten consecutive patients with mediastinal masses from lymphoma who were treated with three-dimensional proton beam radiotherapy, Li *et al.* reported a complete metabolic response rate of 86%⁷⁹. The patients ranged in age from 26 to 45 years of age; eight of these patients had nodular sclerosing stage II Hodgkin lymphoma, one had stage II diffuse large B cell lymphoma, and one had disseminated T-cell lymphoblastic lymphoma. At the time of referral for

proton beam radiotherapy, seven patients had either primary refractory disease or recurrent disease. When compared to conventional radiotherapy, proton beam radiotherapy resulted in mean lower doses to the lungs, esophagus, and heart, but not to the breasts⁷⁹. Hoppe and colleagues also recently reported the results of a phase II trial involving dosimetric comparisons of three-dimensional conformal radiotherapy, intensity modulated radiotherapy, and proton beam radiotherapy for ten patients with stage IA-III B Hodgkin lymphoma with mediastinal (bulky or nonbulky) involvement after chemotherapy⁸⁰. Proton beam radiotherapy resulted in the lowest mean dose to the heart, lungs, and breasts for all ten patients compared with both the three-dimensional and intensity modulated radiotherapy.

Prostate Cancer

Several studies have suggested that proton beam radiotherapy may be beneficial for patients with locally advanced prostate cancer, due to the low rate of radiation scattering to adjacent structures. The largest report to date comes from an analysis of 1255 patients treated with either proton beam radiotherapy alone or in combination with photons between 1991 and 1997 at Loma Linda University⁸¹. The authors reported minimal morbidity, and a 5-year overall biochemical disease-free survival rate of 73%, which is comparable to rates reported with other modalities in this population of patients. The long-term results of the only randomized trial examining proton beam radiotherapy comparing conventional and high-dose radiotherapy were recently published by Zietman and colleagues^{82,83}. Three hundred and ninety three patients with stage T1b through T2b prostate cancer and PSA levels less than or equal 15 ng/mL received photon beam radiotherapy at a fixed dose 50.4 Gy, and were then randomized to receive boost proton beam radiotherapy to a total dose of either 70.2 Gy (conventional dose) or 79.2 Gy (high dose). For patients with low-risk disease (N=228), the 10-year biochemical failure rate was significantly different between the two treatment groups (28.2% conventional dose versus 7.1% high dose, $p<0.0001$). There were no differences in the 10-year overall survival rates among the treatment arms (78.4% versus 83.4%; $p=0.41$). Treatment with higher-dose radiotherapy was not associated with an increase in acute or late patient-reported prostate cancer symptoms⁸⁴. Although these results are promising, this trial was not designed to test whether proton beam radiotherapy is more or less efficacious than other conformal techniques or brachytherapy for the treatment of patients with prostate cancer. In an analysis of data from the Surveillance, Epidemiology and End Results (SEER) database, patients treated for primary prostate cancer with IMRT (N=684) were compared to patients treated with proton beam radiotherapy (N=684)⁸⁵. Patients treated with IMRT had a lower rate of gastrointestinal morbidity (relative risk=0.66, 95% CI=0.55-0.79), but there were no significant differences in rates of other morbidities between IMRT and proton therapy. AIM Specialty Health published proton beam therapy clinical appropriateness guidelines in 2019⁸⁶. After reviewing the evidence, it was concluded that proton beam therapy is not medically necessary for the treatment of prostate cancer. The evidence quality is low and insufficient to determine how proton therapy and photon-based therapies differ.

Non-Small Cell Lung Cancer

A limited number of studies have reported an 80-90% rate of local control for patients with stage I non-small cell lung cancer (NSCLC) treated with hypofractionated proton beam radiotherapy⁸⁷⁻⁹⁰. However, in a meta-analysis comparing photon, proton, and carbon-ion radiotherapy for patients with inoperable stage I NSCLC, Grutters and colleagues concluded that proton beam radiotherapy did not offer a statistically significant improvement in overall survival when compared to photon-based stereotactic radiotherapy, although both modalities were significantly better than conventional photon radiotherapy⁹¹. Proton beam radiotherapy may offer an advantage for patients with advanced inoperable NSCLC, and may spare lung volumes from receiving low-dose irradiation from exiting photon beams. In a retrospective review by Nakayama *et al.*, the progression-free survival rate of 35 patients with stage II and III NSCLC was 59.6% at one year and 29.2% at two years, and the overall survival rate was 81.8% at one year and 58.9% at two years⁹². Similarly, in a retrospective review of 57 patients with inoperable stage IIIA-IIIB NSCLC, Oshiro and colleagues reported one- and two-year progression-free survival rates of 36.2% and 24.9% respectively, and one- and two-year overall survival rates of 65.5% and 39.4%, respectively⁹³. While these results are promising, it is important to note that proton beam radiotherapy planning is particularly challenging for lung tumours, owing to organ motion and changes to lung density during respiration⁹⁴.

Members of the working group do not currently recommend that patients with prostate cancer, non-small cell lung cancer, or most lymphomas be referred for proton beam radiotherapy, due to an insufficient evidence base. However, individual patient cases should be discussed by the multidisciplinary team during a Tumour Board meeting.

III. Referral and Funding Process for Out of Country Treatment

A standalone document outlining this process, in Alberta, is available on Insite on the Cancer Care Alberta resource page.

Patient Selection Criteria.

Health care providers must take into account a wide range of factors in assessing if proton beam radiotherapy will confer a significant advantage for the patient over standard radiotherapy – the diagnosis alone is often not sufficient⁹⁵. 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.

Table 1: Patient Selection Criteria for Proton Beam Therapy

Patient Criteria	Requirements
Age	<ul style="list-style-type: none">• pediatric age ranges = 0 to 20 years• young adult age ranges = 19- 40• adult age ranges = 41 to 65 years
Fitness	<ul style="list-style-type: none">• treatment given with curative intent• good performance status (0-2)• expected survival > 5 years• ability and willingness to travel
Approved diagnoses	<p>Pediatric Patients:</p> <ul style="list-style-type: none">• requiring craniospinal radiation• CNS cancers or lesions: arteriovenous malformations, ependymoma, craniopharyngioma, CNS germ cell tumours, primitive neuroectodermal tumours, low-grade gliomas• Non-CNS cancers: sarcoma including chordoma and chondrosarcoma, rhabdomyosarcoma, Ewing's sarcoma, pineal tumours, and lymphoma <p>Adult Patients:</p> <ul style="list-style-type: none">• CNS cancers or lesions: arteriovenous malformations, benign meningioma, acoustic neuroma, craniopharyngioma, CNS germ cell tumours, low-grade gliomas• Non-CNS cancers: sarcoma including chordoma and chondrosarcoma, lymphoma in patients under the age of 30, and paranasal sinus and nasal cavity tumours

Referral Process (Appendix A).

The Radiation Oncologist presents the patient case, which meets the criteria in Table 1, at the Proton Therapy Referral Rounds. A patient deemed borderline for meeting the criteria, requires the referring Radiation Oncologist to contact the Florida Proton Beam Program and request a comparative proton-photon plan. The borderline patient's case and comparative plan is then discussed by members of the Proton Therapy Referral Rounds.

The Proton Therapy Referral Rounds is a multidisciplinary tumour board meeting. At this meeting, all members can provide input on patient cases presented. The team also discusses possible additional treatments, travel arrangements and follow-up care. If a referral is recommended, a summary note of the meeting is generated (checklist in **Appendix B**), 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 Radiation Oncologist must make the request through the out of country Health Services Committee.

Once capacity is confirmed, the referring Radiation Oncologist completes the *Request for Approval Form* (available on Insite on the Cancer Care Alberta Resource page), which is then sent, along with all items on the Alberta Health Checklist (**Appendix C**), via FAX or mail to the Senior Medical Director

of Cancer Care Alberta. If approved, the Senior Medical Director's office sends the referral 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 expedited 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

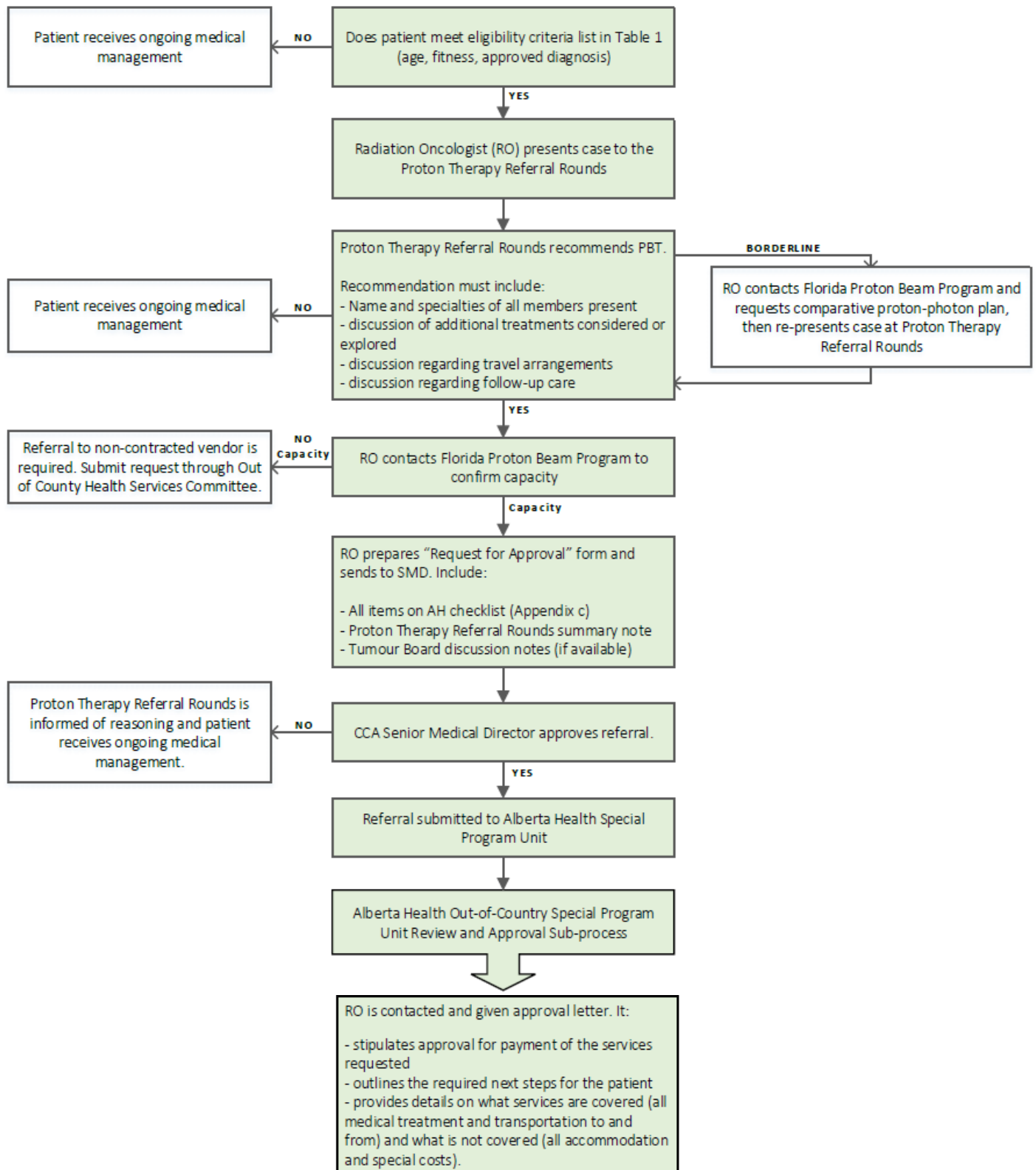
The Alberta Health Special Program Unit does not have access to any electronic medical records. All details on the case must be included in the referral letter. The application is considered complete when all the required information has been submitted, and the Alberta Health Special Program Unit Chair 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, they will direct them to the lead of the Proton Beam Therapy Referral Rounds.

Once decided, the Alberta Health Special Program Unit will contact the referring Radiation Oncologist. 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 must complete two release forms and return them 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: Cancer Care Alberta Proton Beam Therapy Selection and Approval Process



Appendix B: Proton Beam Referral Rounds Checklist

Age of Patient	
Diagnosis	
Curative Treatment	<input type="checkbox"/> yes <input type="checkbox"/> no
Performance Status	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4
Comorbidities	<input type="checkbox"/> yes <input type="checkbox"/> no
	<i>comorbidities</i>
Metastatic Disease	<input type="checkbox"/> yes <input type="checkbox"/> no
Referring Oncologist	
Proton Beam Therapy Referral Rounds	
Date of PBT referral rounds _____	
<input type="checkbox"/>	Name and specialties of all members present at PBT referral rounds documented
<input type="checkbox"/>	Discussion of additional treatments considered or explored
<input type="checkbox"/>	Discussion regarding travel arrangements
<input type="checkbox"/>	Discussion regarding follow-up care
Proton Beam Therapy Referral Form	
<input type="checkbox"/>	Application completed by referring radiation oncologist
<input type="checkbox"/>	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 C: Alberta Health Referral Checklist

Patient Name:	Date:
Requirements for Submission to Alberta Health for Funding of Proton Beam Radiation Therapy	
	<ul style="list-style-type: none"> • 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: <ol style="list-style-type: none"> 1. Alberta Health Services Tumour Board and CancerCare 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	
	<ul style="list-style-type: none"> • Referring Physician - Contact Information (Name, Specialty, Facility Address, Cell Phone, Email, Fax)
	<ul style="list-style-type: none"> • Patient Information (Name, Date of Birth, Address, Email, Phone, Patient AB Personal Health Card Number) • Pediatric requires parents'/guardians' contact information
	<ul style="list-style-type: none"> • Indicate approved diagnoses: Patient must have a confirmed diagnosis that is consistent with the indications established above
	<ul style="list-style-type: none"> • Notification of access to Proton Beam Therapy (standard process or expedited process and rationale)
	<ul style="list-style-type: none"> • Verification of capacity at the University of Florida Proton Beam Institute • Admission date of treatment
	<ul style="list-style-type: none"> • 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	
	<ul style="list-style-type: none"> • No other treatment options are available in Canada
	<ul style="list-style-type: none"> • Proposed treatment meets the Standard of Care in Alberta and Canada
	<ul style="list-style-type: none"> • Proposed treatment is not part or a portion therefore of a Clinical Trial/Experimental

References

1. Levin WP, Kooy H, Loeffler JS, DeLaney TF. Proton beam therapy. *Br J Cancer* 2005 Oct 17;93(8):849-854.
2. Trikalinos TA, Terasawa T, Ip S, Raman G, Lau J. Particle beam radiation therapies for cancer: technical brief no. 1(Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHS-290-07-10055). 2009; Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cancer-radiation_technical-brief.pdf. Accessed December 18, 2012.
3. Particle Therapy Co-Operative Group. Particle Therapy Facilities in Operation. Available at: <http://ptcog.web.psi.ch/>. Accessed December 18, 2012 and May 10, 2019.
4. 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 Jul 1;74(3):732-739.
5. Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys* 2002 Nov 1;54(3):824-829.
6. Newhauser WD, Fontenot JD, Mahajan A, Kornguth D, Stovall M, Zheng Y, et al. The risk of developing a second cancer after receiving craniospinal proton irradiation. *Phys Med Biol* 2009 Apr 21;54(8):2277-2291.
7. Merchant TE. Proton beam therapy in pediatric oncology. *Cancer J* 2009;15(4):298-305.
8. MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. *Int J Radiat Oncol Biol Phys* 2008 Jul 15;71(4):979-986.
9. 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 Aug 1;83(5):1419-1424.
10. Yuh GE, Loreda LN, Yonemoto LT, Bush DA, Shahnazi K, Preston W, et al. Reducing toxicity from craniospinal irradiation: using proton beams to treat medulloblastoma in young children. *Cancer J* 2004;10(6):386-390.
11. St Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004 Mar 1;58(3):727-734.
12. MacEwan I, Chou B, Moretz J, Loreda L, Bush D, Slater JD. Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma. *Adv Radiat Oncol* 2017 Mar 10;2(2):220-227.
13. Lundkvist J, Ekman M, Ericsson SR, Isacson U, Jonsson B, Glimelius B. Economic evaluation of proton radiation therapy in the treatment of breast cancer. *Radiother Oncol* 2005 May;75(2):179-185.
14. Moeller BJ, Chintagumpala M, Philip JJ, Grosshans DR, McAleer MF, Woo SY, et al. Low early ototoxicity rates for pediatric medulloblastoma patients treated with proton radiotherapy. *Radiat Oncol* 2011 Jun 2;6:58.
15. National Health Service England. Clinical Commissioning Policy: Proton Beam Radiotherapy (High Energy) for Teenage and Young Adult Cancer Treatment – NHS Overseas Programme. 2015; Available at: <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/b01-pc-prtn-bm-thrpy-teens-yng-oct15.pdf>. Accessed March 25, 2019.
16. Zhang R, Howell RM, Taddei PJ, Giebeler A, Mahajan A, Newhauser WD. A comparative study on the risks of radiogenic second cancers and cardiac mortality in a set of pediatric medulloblastoma patients treated with photon or proton craniospinal irradiation. *Radiother Oncol* 2014 Oct;113(1):84-88.
17. Yoon M, Shin DH, Kim J, Kim JW, Kim DW, Park SY, et al. Craniospinal irradiation techniques: a dosimetric comparison of proton beams with standard and advanced photon radiotherapy. *Int J Radiat Oncol Biol Phys* 2011 Nov 1;81(3):637-646.
18. Sethi RV, Shih HA, Yeap BY, Mouw KW, Petersen R, Kim DY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer* 2014;120(1):126-133.
19. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. *Int J Radiat Oncol Biol Phys* 2013 Sep 1;87(1):46-52.
20. Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM. Epidemiology of intracranial meningioma. *Neurosurgery* 2005 Dec;57(6):95.

21. Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: a review. *J Neurooncol* 1996 Sep;29(3):197-205.
22. Whittle IR, Smith C, Navoo P, Collie D. Meningiomas. *Lancet* 2004 May 8;363(9420):1535-1543.
23. Boskos C, Feuvret L, Noel G, Habrand JL, Pommier P, Alapetite C, et al. Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *Int J Radiat Oncol Biol Phys* 2009 Oct 1;75(2):399-406.
24. Noel G, Bollet MA, Calugaru V, Feuvret L, Haie-Meder C, Dhermain F, et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. *Int J Radiat Oncol Biol Phys* 2005 Aug 1;62(5):1412-1422.
25. Wenkel E, Thornton AF, Finkelstein D, Adams J, Lyons S, De La Monte S, et al. Benign meningioma: partially resected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. *Int J Radiat Oncol Biol Phys* 2000 Dec 1;48(5):1363-1370.
26. Vernimmen FJ, Harris JK, Wilson JA, Melvill R, Smit BJ, Slabbert JP. Stereotactic proton beam therapy of skull base meningiomas. *Int J Radiat Oncol Biol Phys* 2001 Jan 1;49(1):99-105.
27. Weber DC, Lomax AJ, Rutz HP, Stadelmann O, Egger E, Timmermann B, et al. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas. *Radiother Oncol* 2004 Jun;71(3):251-258.
28. El Shafie RA, Czech M, Kessel KA, Habermehl D, Weber D, Rieken S, et al. Clinical outcome after particle therapy for meningiomas of the skull base: toxicity and local control in patients treated with active rasterscanning. *Radiat Oncol* 2018 Mar 27;13(1):5.
29. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. *Brain* 2001 Oct;124(Pt 10):1900-1926.
30. Seifert V, Stolke D, Mehdorn HM, Hoffmann B. Clinical and radiological evaluation of long-term results of stereotactic proton beam radiosurgery in patients with cerebral arteriovenous malformations. *J Neurosurg* 1994 Nov;81(5):683-689.
31. Vernimmen FJ, Slabbert JP, Wilson JA, Fredericks S, Melvill R. Stereotactic proton beam therapy for intracranial arteriovenous malformations. *Int J Radiat Oncol Biol Phys* 2005 May 1;62(1):44-52.
32. Hattangadi-Gluth JA, Chapman PH, Kim D, Niemierko A, Bussiere MR, Stringham A, et al. Single-fraction proton beam stereotactic radiosurgery for cerebral arteriovenous malformations. *Int J Radiat Oncol Biol Phys* 2014 Jun 1;89(2):338-346.
33. Hattangadi JA, Chapman PH, Bussiere MR, Niemierko A, Ogilvy CS, Rowell A, et al. Planned two-fraction proton beam stereotactic radiosurgery for high-risk inoperable cerebral arteriovenous malformations. *Int J Radiat Oncol Biol Phys* 2012 Jun 1;83(2):533-541.
34. Shih HA, Chapman PH, Bussière MR, Chen CC, Loeffler JS editor. Central nervous system. 1st ed. Philadelphia: Lipincott Williams & Wilkins; 2008.
35. Propp JM, McCarthy BJ, Davis FG, Preston-Martin S. Descriptive epidemiology of vestibular schwannomas. *Neuro Oncol* 2006 Jan;8(1):1-11.
36. Arthurs BJ, Fairbanks RK, Demakas JJ, Lamoreaux WT, Giddings NA, Mackay AR, et al. A review of treatment modalities for vestibular schwannoma. *Neurosurg Rev* 2011 Jul;34(3):9.
37. Murphy ES, Suh JH. Radiotherapy for vestibular schwannomas: a critical review. *Int J Radiat Oncol Biol Phys* 2011 Mar 15;79(4):985-997.
38. Weber DC, Chan AW, Bussiere MR, Harsh GR,4th, Ancukiewicz M, Barker FG,2nd, et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. *Neurosurgery* 2003 Sep;53(3):8.
39. Bush DA, McAllister CJ, Loreda LN, Johnson WD, Slater JM, Slater JD. Fractionated proton beam radiotherapy for acoustic neuroma. *Neurosurgery* 2002 Feb;50(2):5.
40. Heffelfinger MJ, Dahlin DC, MacCarty CS, Beabout JW. Chordomas and cartilaginous tumors at the skull base. *Cancer* 1973 Aug;32(2):410-420.
41. Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev* 2009 Oct;32(4):403-416.
42. Amichetti M, Amelio D, Cianchetti M, Enrici RM, Minniti G. A systematic review of proton therapy in the treatment of chondrosarcoma of the skull base. *Neurosurg Rev* 2010 Apr;33(2):155-165.

43. Crockard HA, Steel T, Plowman N, Singh A, Crossman J, Revesz T, et al. A multidisciplinary team approach to skull base chordomas. *J Neurosurg* 2001 Aug;95(2):175-183.
44. Potluri S, Jefferies SJ, Jena R, Harris F, Burton KE, Prevost AT, et al. Residual postoperative tumour volume predicts outcome after high-dose radiotherapy for chordoma and chondrosarcoma of the skull base and spine. *Clin Oncol (R Coll Radiol)* 2011 Apr;23(3):199-208.
45. Foweraker KL, Burton KE, Maynard SE, Jena R, Jefferies SJ, Laing RJ, et al. High-dose radiotherapy in the management of chordoma and chondrosarcoma of the skull base and cervical spine: Part 1--Clinical outcomes. *Clin Oncol (R Coll Radiol)* 2007 Sep;19(7):509-516.
46. Ares C, Hug EB, Lomax AJ, Bolsi A, Timmermann B, Rutz HP, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys* 2009 Nov 15;75(4):1111-1118.
47. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol* 1999 Jun;175 Suppl 2:57-63.
48. DeLaney TF, Liebsch NJ, Pedlow FX, Adams J, Weyman EA, Yeap BY, et al. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. *J Surg Oncol* 2014 Aug;110(2):115-122.
49. Guttmann DM, Frick MA, Carmona R, Deville, Curtiland,, Jr, Levin WP, Berman AT, et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. *Radiother Oncol* 2017;124(2):271-276.
50. Weber DC, Murray FR, Correia D, Bolsi A, Frei-Welte M, Pica A, et al. Pencil beam scanned protons for the treatment of patients with Ewing sarcoma. *Pediatr Blood Cancer* 2017;64(12).
51. Demizu Y, Jin D, Sulaiman NS, Nagano F, Terashima K, Tokumaru S, et al. Particle Therapy Using Protons or Carbon Ions for Unresectable or Incompletely Resected Bone and Soft Tissue Sarcomas of the Pelvis. *Int J Radiat Oncol Biol Phys* 2017 Jun 1;98(2):367-374.
52. Sato T, Han F, Yamamoto A. The biology and management of uveal melanoma. *Curr Oncol Rep* 2008 Sep;10(5):431-438.
53. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. *Cancer Treat Rev* 2012 Aug;38(5):549-553.
54. Marucci L, Ancukiewicz M, Lane AM, Collier JM, Gragoudas ES, Munzenrider JE. Uveal melanoma recurrence after fractionated proton beam therapy: comparison of survival in patients treated with reirradiation or with enucleation. *Int J Radiat Oncol Biol Phys* 2011 Mar 1;79(3):842-846.
55. Vavvas D, Kim I, Lane AM, Chaglassian A, Mukai S, Gragoudas E. Posterior uveal melanoma in young patients treated with proton beam therapy. *Retina* 2010 Sep;30(8):1267-1271.
56. Bellmann C, Lumbroso-Le Rouic L, Levy C, Plancher C, Dendale R, Sastre-Garau X, et al. Uveal melanoma: management and outcome of patients with extraocular spread. *Br J Ophthalmol* 2010 May;94(5):569-574.
57. Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, Dendale R, Delacroix S, Nauraye C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res* 2006;38(5):255-260.
58. Gragoudas ES, Lane AM, Regan S, Li W, Judge HE, Munzenrider JE, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol* 2000 Jun;118(6):773-778.
59. Caujolle JP, 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 Sep 1;78(1):98-103.
60. Mosci C, Mosci S, Barla A, Squarcia S, Chauvel P, Iborra N. Proton beam radiotherapy of uveal melanoma: Italian patients treated in Nice, France. *Eur J Ophthalmol* 2009;19(4):654-660.
61. Levy-Gabriel C, Rouic LL, Plancher C, Dendale R, Delacroix S, Asselain B, et al. Long-term results of low-dose proton beam therapy for circumscribed choroidal hemangiomas. *Retina* 2009 Feb;29(2):170-175.
62. Rundle P, Singh AD, Rennie I. Proton beam therapy for iris melanoma: a review of 15 cases. *Eye (Lond)* 2007 Jan;21(1):79-82.
63. Lumbroso-Le Rouic L, Delacroix S, Dendale R, Levy-Gabriel C, Feuvret L, Noel G, et al. Proton beam therapy for iris melanomas. *Eye (Lond)* 2006 Nov;20(11):1300-1305.

64. Dendale R, Lumbroso-Le Rouic L, Noel G, Feuvret L, Levy C, Delacroix S, et al. Proton beam radiotherapy for uveal melanoma: results of Curie Institut-Orsay proton therapy center (ICPO). *Int J Radiat Oncol Biol Phys* 2006 Jul 1;65(3):780-787.
65. Hocht S, Bechrakis NE, Nausner M, Kreusel KM, Kluge H, Heese J, et al. Proton therapy of uveal melanomas in Berlin. 5 years of experience at the Hahn-Meitner Institute. *Strahlenther Onkol* 2004 Jul;180(7):419-424.
66. Kodjikian L, Roy P, Rouberol F, Garweg JG, Chauvel P, Manon L, et al. Survival after proton-beam irradiation of uveal melanomas. *Am J Ophthalmol* 2004 Jun;137(6):1002-1010.
67. Egger E, Zografos L, Schalenbourg A, Beati D, Bohringer T, Chamot L, et al. Eye retention after proton beam radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys* 2003 Mar 15;55(4):867-880.
68. Gragoudas ES, Lane AM, Munzenrider J, Egan KM, Li W. Long-term risk of local failure after proton therapy for choroidal/ciliary body melanoma. *Trans Am Ophthalmol Soc* 2002;100:9.
69. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology* 2011 Sep;118(9):1881-1885.
70. 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 Dec 15;92(12):3012-3029.
71. Hanna EY, Cardenas AD, DeMonte F, Roberts D, Kupferman M, Weber R, et al. Induction chemotherapy for advanced squamous cell carcinoma of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg* 2011 Jan;137(1):78-81.
72. Licitra L, Locati LD, Cavina R, Garassino I, Mattavelli F, Pizzi N, et al. Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. *Ann Oncol* 2003 Mar;14(3):367-372.
73. Resto VA, Chan AW, Deschler DG, Lin DT. Extent of surgery in the management of locally advanced sinonasal malignancies. *Head Neck* 2008 Feb;30(2):222-229.
74. Truong MT, Kamat UR, Liebsch NJ, Curry WT, Lin DT, Barker FG, 2nd, et al. Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors. *Head Neck* 2009 Oct;31(10):1297-1308.
75. Ramaekers BL, Pijls-Johannesma M, Joore MA, van den Ende P, Langendijk JA, Lambin P, et al. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons. *Cancer Treat Rev* 2011 May;37(3):185-201.
76. Tokuyue K, Akine Y, Kagei K, Hata M, Hashimoto T, Mizumoto T, et al. Proton therapy for head and neck malignancies at Tsukuba. *Strahlenther Onkol* 2004 Feb;180(2):96-101.
77. Zenda S, Kohno R, Kawashima M, Arahira S, Nishio T, Tahara M, et al. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys* 2011 Dec 1;81(5):1473-1478.
78. 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 May 1;95(1):386-395.
79. Li J, Dabaja B, Reed V, Allen PK, Cai H, Amin MV, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. *Int J Radiat Oncol Biol Phys* 2011 Sep 1;81(1):167-174.
80. Hoppe BS, Flampouri S, Su Z, Morris CG, Latif N, Dang NH, et al. Consolidative involved-node proton therapy for Stage IA-IIIB mediastinal Hodgkin lymphoma: preliminary dosimetric outcomes from a Phase II study. *Int J Radiat Oncol Biol Phys* 2012 May 1;83(1):260-267.
81. Slater JD, Rossi CJ, Jr, Yonemoto LT, Bush DA, Jabola BR, Levy RP, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. *Int J Radiat Oncol Biol Phys* 2004 Jun 1;59(2):348-352.
82. Zietman AL, DeSilvio ML, Slater JD, Rossi CJ, Jr, Miller DW, Adams JA, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005 Sep 14;294(10):1233-1239.
83. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010 Mar 1;28(7):1106-1111.
84. Talcott JA, Rossi C, Shipley WU, Clark JA, Slater JD, Niemierko A, et al. Patient-reported long-term outcomes after conventional and high-dose combined proton and photon radiation for early prostate cancer. *JAMA* 2010 Mar 17;303(11):1046-1053.

85. Sheets NC, Goldin GH, Meyer AM, Wu Y, Chang Y, Sturmer T, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* 2012 Apr 18;307(15):1611-1620.
86. AIM Specialty Health. Clinical Appropriateness Guidelines: Radiation Oncology; Proton Beam Therapy Guidelines. 2019; Available at: http://www.aimspecialtyhealth.com/PDF/Guidelines/2019/Mar09/AIM_Guidelines_ProtonBeam.pdf. Accessed Mar 29, 2019.
87. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for Stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006 May 1;65(1):107-111.
88. Hata M, Tokuyue K, Kagei K, Sugahara S, Nakayama H, Fukumitsu N, et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. *Int J Radiat Oncol Biol Phys* 2007 Jul 1;68(3):786-793.
89. Bush DA, Slater JD, Bonnet R, Cheek GA, Dunbar RD, Moyers M, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest* 1999 Nov;116(5):1313-1319.
90. Bush DA, Slater JD, Shin BB, Cheek G, Miller DW, Slater JM. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004 Oct;126(4):1198-1203.
91. Grutters JP, Kessels AG, Pijls-Johannesma M, De Ruyscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010 Apr;95(1):32-40.
92. 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 Nov 15;81(4):979-984.
93. Oshiro Y, Mizumoto M, Okumura T, Hashimoto T, Fukumitsu N, Ohkawa A, et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2012 Feb;7(2):370-375.
94. Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. *Radiother Oncol* 2012 Apr;103(1):8-11.
95. National Health Services. National Specialised Commissioning Team. Guidance for the referral of patients abroad for NHS proton treatment. Version 2.3. 2011; Available at: <http://www.specialisedservices.nhs.uk/service/proton-beam-therapy>. Accessed December 18, 2012.

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 2019.

Maintenance

A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AVM, arteriovenous malformation
CGE, cobalt grey equivalent
CI, confidence interval
CNS, central nervous system
Gy, grey
IMRT, intensity modulated radiotherapy
NSCLC, non-small cell lung cancer
OOCHSC, Out of Country Health Services Committee
WHO, World Health Organization

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.

Copyright © (2022) Alberta Health Services

This copyright work is licensed under the [Creative Commons Attribution-NonCommercial-NoDerivative 4.0 International license](#). You are free to copy and distribute the work including in other media and formats for non-commercial purposes, as long as you attribute the work to Alberta Health Services, do not adapt the work, and abide by the other license terms. To view a copy of this license, see <https://creativecommons.org/licenses/by-nc-nd/4.0/>. The license does not apply to AHS trademarks, logos or content for which Alberta Health Services is not the copyright owner.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).

Conflict of Interest Statements

Dr. Keith Aronyk has nothing to disclose

Dr. Salman Faruqi has nothing to disclose.

Dr. Gerald Lim has nothing to disclose.

Dr. Natalie Logie has nothing to disclose.

Dr. Samir Patel* reports reimbursement for travel expenses to the 'A Vision for Proton Therapy in Ontario' symposium, November 5-6, 2018, Toronto, Canada.

Rachel Vanderploeg has nothing to disclose.

*Guideline Lead and corresponding author