Pan-Canadian Consensus Recommendations for Proton Beam Therapy Access in Canada

FINAL CAPCA Board Endorsed 21 June 2021

Executive Summary

The Canadian Association of Provincial Cancer Agencies (CAPCA) developed the *Pan-Canadian Consensus Recommendations for Proton Beam Therapy Access in Canada* to improve coordination and harmonization of proton beam therapy (PBT) planning and delivery.

Intended for clinical leaders, program staff and health care funders, this document is divided into three sections: patient eligibility requirements, program level requirements and system level requirements.

PBT is a useful treatment option for select cancer patients; however, several clinical and health system challenges impede consistent access to PBT for patients in Canada including:

- While PBT evidence is available in select paediatric and adult cancers, ongoing advances to PBT and photon technologies require more study to confirm its clinical benefit for specific indications in both populations;
- Cancer patients are sent out of country for treatment because there is no active proton facility for clinical use in Canada. Referral criteria vary widely across the country due to limitations in evidence, the need for process harmonization and competing provincial system priorities; and
- Cost effective data in the Canadian context is limited and long term follow up using real world evidence is needed.

This suite of recommendations will support application of consistent clinical criteria to inform treatment options, treatment planning and referrals, and serve as a companion to existing provincial and national clinical practice guidelines, legislation, and professional practice standards. These recommendations will also help cancer programs with health human resource training and facility set-up, should a jurisdiction move forward with establishing a proton facility.

The consensus-based recommendations were developed with input from clinical experts in PBT, provincial cancer and system partners, as well as feedback from a targeted community consultation. CAPCA and its member organizations endorsed the recommendations in June 2021. As evidence continues to evolve, these recommendations will be reviewed annually to reflect best practices, emerging evidence and status of PBT delivery in Canada.

Table of Contents

Purpose

The Canadian Association of Provincial Cancer Agencies (CAPCA) developed a set of evidence-based consensus recommendations for PBT access. Recognizing there are widening inequities across populations, with people who are part of underserviced populations being disproportionately affected by cancer, these recommendations will help coordinate consistent and equitable access to planning and delivery of proton beam therapy (PBT) for patients either in Canada or out of country. This document will also provide consistent clinical criteria to inform treatment options, treatment planning and referrals. This initiative falls under CAPCA's strategic plan (2020-2023) under Pillar 1: Enhancing Quality and Priority 4: Prioritizing and implementing pan-Canadian standards.

The PBT recommendations have been created for cancer program staff, including decision makers responsible for developing PBT policies and practice, clinical radiation oncologists, radiation therapists, medical physicists and health care funders. This document was informed by a current-state analysis of existing traditional and grey literature and a modified-Delphi consensus process. The working group reviewed, revised and achieved consensus for each recommendation, and a targeted community consultation process was subsequently conducted.

Proton Beam Therapy Consensus Working Group

A Proton Beam Therapy Consensus Working Group (PBT CWG) was assembled to develop consensus-based recommendations that are evidence-based, feasible and practical for provincial cancer programs and ministries of health to implement. The PBT CWG was comprised of provincial radiation oncology leadership, clinical experts, radiation oncology partners and representatives from organizations involved in pan-Canadian health technology assessment.

Table 1: Working Group Members

Name	Organization	Role
Tim Craig	University Health Network, Toronto Ontario	Clinical expert
Annie Ebacher	Université de Sherbrooke, Sherbrooke Québec	Clinical expert
Sophie Foxcroft	Ontario Health, Toronto Ontario	Clinical administrator
Karen Goddard	BC Cancer, Vancouver British Columbia	Clinical expert
Jonathan Greenland	Eastern Health, St. John's Newfoundland	Clinical administrator
Rashmi Koul	CancerCare Manitoba, Winnipeg Manitoba	Clinical administrator
Natalie Logie	Alberta Health Services, Calgary Alberta	Clinical expert
Boyd McCurdy	CancerCare Manitoba, Winnipeg Manitoba	Clinical administrator
Mike Milosevic	Canadian Partnership for Quality Radiotherapy, Toronto Ontario	CAPCA partner

Table 1: Working Group Members (continued)

Name	Organization	Role
Mélanie Morneau	Ministère de la santé et des services sociaux, Québec City, Québec	Clinical administrator
Andra Morrison	Canadian Agency for Drugs and Technologies in Health, Ottawa Ontario	CAPCA partner
Larry Pan	PEI Cancer Treatment Centre, Charlottetown Prince Edward Island	Clinical administrator
Jason Pantarotto	Ontario Health, Ottawa Ontario	Clinical administrator
Samir Patel	Alberta Health Services, Edmonton Alberta	Clinical expert
Jean-Philippe Pignol	Nova Scotia Health, Halifax Nova Scotia	Clinical expert
Robert Rutledge	Nova Scotia Health, Halifax Nova Scotia	Clinical administrator
Jonathan Sussman	Program for Evidence Based Care, Hamilton Ontario	CAPCA partner
Robert Thompson	Horizon Health Network, Saint John New Brunswick	Clinical administrator
Derek Tsang	University Health Network, Toronto Ontario	Clinical expert
Scott Tyldesley	BC Cancer, Vancouver British Columbia	Clinical administrator
Padraig Warde	Ontario Health, Toronto Ontario	Clinical administrator
Philip Wright	Saskatchewan Cancer Agency, Regina Saskatchewan	Clinical administrator

Abbreviations and Definitions

Table 2: Abbreviations

AAPM	American Association of Physicists in Medicine
ACR-AAPM	American College of Radiology-American Association of Physicists in Medicine
ACR-ASTRO	American College of Radiology-American Society for Radiation Oncology
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPCA	Canadian Association for Provincial Cancer Agencies
CPQR	Canadian Partnership for Quality Radiotherapy
ECOG	Eastern Cooperative Oncology Group
IMRT	Intensity-modulated radiation therapy
PBT	Proton beam therapy
PBT CWG	Proton beam therapy Consensus Working Group
TG	Task Group
VMAT	Volumetric modulated arc therapy

Table 3: Definitions

AAPM TG-185	AAPM Task Group on the Clinical commissioning of intensity-modulated proton therapy systems.[5]
AAPM TG-224	AAPM Task Group on Comprehensive proton therapy machine quality assurance.[3]
Delphi process	Accepted group communication method for gathering data from respondents within their domain of expertise.
Proton beam therapy	Radiation therapy that uses a beam of protons, a type of charged particle, to treat malignant tumours or other conditions while minimizing dose to surrounding normal tissues compared to photon radiation therapy.[34]

Background

PBT complements widely available photon technologies. It works by delivering high doses of radiation conformally to target volumes while providing superior sparing of radiation dose to surrounding normal tissues and organs relative to photon technologies.[23] Improved normal tissue sparing properties of this treatment may provide short and long-term clinical benefits of reduced toxicity for many tumours in close proximity to sensitive tissue and organs, particularly with large field sizes. It is worth highlighting that the normal tissue sparing superiority of PBT over photon radiotherapy has been narrowing over time with improvement in photon radiotherapy planning, immobilization and delivery, such as volumetric modulated arc therapy (VMAT) and stereotactic ablative radiotherapy (SABR). Moreover, there may be a potential for bias in published literature; therefore, caution should be made when interpreting older comparisons of PBT versus photon therapy, and reassessment over time may be necessary.

In 1995, TRIUMF, a particle accelerator centre in Vancouver, dedicated one of its proton beamlines to the clinical treatment of ocular melanoma. While more than 200 patients were treated at the facility, the clinical component of the program was terminated in 2018.[12] While the MEVION S250 proton beam therapy technology was approved for use in Canada in 2015,[23] there are currently no facilities providing clinical treatments in Canada and patient eligibility criteria vary across provinces. In some provinces, eligible patients are being sent out of country at the discretion of provincial ministries of health. It is expected that PBT could be available in Canada in select provinces in the future. Regardless, if a patient is treated in Canada or referred out of country, cost considerations include operational, treatment and patient- related.

This set of consensus recommendations will serve as a companion to existing provincial and national clinical practice guidelines and legislation, regulation and professional practice standards and are intended to supplement mandatory legislative requirements. In the event of inconsistency or conflict between the statements in this document, and any mandatory requirements, the latter shall prevail.

As an expensive technology, implementation of PBT in Canadian practice presents clinical challenges including long term effectiveness and variability of clinical course for both adult and pediatric populations. Health system planning challenges also exist. Cost effectiveness has been evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH), but Canadian costing data and long-term follow-up are limited at this time.[14]

It is recommended that oncology programs refer to the latest publications related to clinical eligibility criteria to ensure that patient access protocols are aligned with those most recently published and commonly adhered to international standards. CAPCA also plans to conduct an annual review of this document to ensure that new evidence is evaluated, and if appropriate, used to update the recommendations.

Methodology and Current-State Analysis

CAPCA board members nominated jurisdictional and national clinical and administrative experts to the PBT CWG. PBT guidance documents and related reference materials from Canada, Europe, and the United States were collected. Working group members supplemented these documents with others where available.

A framework for the current-state analysis was drafted by the CAPCA staff and reviewed by the PBT CWG members to serve as the outline for this document. Consensus recommendations were then developed and refined using a modified-Delphi consensus approach.[25] Any aspect of the current-state analysis framework receiving less than 70% agreement was brought back to the PBT CWG for discussion.

The PBT CWG was divided into three sub-groups based on self-selected expertise. Data was extracted using pre-defined categories for the data to be included. The overarching categories for current-state analysis data extraction were patient eligibility requirements, program level requirements and system level requirements. The degree of detail, categorized as minor or considerable within each category, was also captured and consensus recommendations were drafted. Four rounds of discussions occurred through surveys and meetings to arrive at a final set of statements.

Source documents included in the current-state analysis were used to inform the development of the consensus recommendations. These are listed, together with other references included in the document's supporting narrative and have been included in the Bibliography section.

To ensure the recommendations have value for health system partners, radiation oncology and PBT providers and experts, CAPCA sought input on the draft recommendations through a targeted consultation process. The draft document was emailed directly to 118 individuals and organizations identified by the PBT CWG. Feedback was considered and addressed by the PBT CWG and incorporated into the final document.

Consensus Recommendations

In June 2021, this recommendation document was endorsed by CAPCA and its member organizations. This document is intended to facilitate consistent and equitable access to PBT for appropriate patients in Canada, using consistent clinical criteria.

Patient Eligibility Requirements

As of the writing of this document in 2021, patients being considered for PBT are referred out of country for treatment. To promote access for clinically appropriate cancers in patients, consistent evidence-based patient eligibility criteria should be applied when prioritizing patients based on the greatest need and expected benefit. Moreover, it is recognized that pediatric patients may experience a greater absolute benefit due to an expected reduction in late effects risk with proton beam therapy as compared with photon therapy.[26, 28, 29] Based on the existing evidence and expert consensus, there are specific clinical indications that support the use of PBT as a preferred option for a selected patients.[2, 26, 28, 29, 38, 49] However, challenges remain with trying to evaluate the published clinical and treatment planning evidence in a field that is continually improving its PBT and photon technologies. A paucity of high-quality evidence regarding PBT exists, and this field of study is evolving. Long-term monitoring of the benefits of PBT should be considered to enhance the understanding of the role that this therapy may play in oncology care.

ANATOMICAL SITE	
1	Clinical evidence should be considered when evaluating the appropriateness of proton beam therapy, and anatomical sites with the best available clinical evidence should be prioritized for access. There may be instances where case-by-case consideration is required as described in Statements 4 and 5. Jurisdictions should monitor evolving evidence.
2	Adults with the following diagnoses should be considered for proton beam therapy when the potential reduction in risks and anticipated clinical outcomes seem to justify the costs: • Uveal melanoma cancer unsuitable for plaque brachytherapy. • Select central nervous system or head and neck tumours for which clear dosimetric, safety and clinical benefits are expected.[29] • Base of skull or spinal tumours, including chordoma and chondrosarcomas, as post-operative therapy in patients who have had a biopsy or resection, without evidence of metastatic disease.[38] • Young adults up to the age of 40 with diagnoses fitting within paediatric guidelines.[2]
3	Paediatric patients with the following diagnoses[26, 28] should be considered for proton beam therapy: • Central nervous system tumours. • Chordomas and chondrosarcomas. • Sarcomas in patients for whom dosimetric, safety and clinical benefits are expected.

	• Young adults up to the age of 40 with paediatric-type tumours.
4	Paediatric patients[8] with genetic syndromes predisposing them to secondary malignancies and who have an expected median overall survival of at least 5 years should be considered for proton beam therapy since it has lower integral radiotherapy dose and may reduce the risk of late effects and secondary malignancies.[49]
PATIENT CHARACTERISTICS	
5	Proton beam therapy treatment may be considered on a case-by-case basis for re-irradiation cases, where proton beam therapy provides a dosimetric benefit compared to other radiation treatment options, and a potential for long-term survival is considered likely.[9, 36, 47]
6	For both adult and paediatric patients, proton beam therapy should be offered as curative-intent treatment, with an expected median overall survival of at least 5 years.[35]
7	Patients who need to travel outside of their local region for proton beam therapy should, at the time of travel, have an ECOG Performance Status of between 0 and 2 to safely travel.[35] Patients' willingness to travel should be considered in decision making.
CLINICAL EFFICACY	
8	Assessing the benefit of proton beam therapy for individual cases should be undertaken by an interdisciplinary team (including a radiation oncologist) with experience in IMRT/VMAT dosimetry and proton beam dosimetry. They should consider the proximity to critical normal tissue structures and resulting toxicities from radiation exposure that may be reduced or avoided with proton beam therapy as compared to photon therapy.
9	For cases where the benefit of proton beam therapy remains unclear, a comparison of treatment plans of proton beam therapy and photon therapy or use of a model-based approach[37, 42] to estimate differences in toxicity expected with proton and photon therapy should be undertaken to aid clinical decision making where possible. The exception is when this process may result in unacceptable delays in initiating radiation therapy. For comparative plans, objectives should be stated upfront and incorporate any planning and equipment limitations that the requesting centre may require to ensure that a realistic comparative plan is generated.

Program Level Requirements

Given the complexity and specialized skills required for PBT planning and delivery, any Canadian or international radiation treatment programs involved in the planning and delivery of PBT should have appropriate accreditations and licences, be staffed by an interdisciplinary team with specific training in PBT, have an active peer-review program, and be active participants in national and international research groups. Where appropriate, consideration should also be given to additional medical services that may be required on-site or at a local facility. For example,

anesthesiology and neurosurgery for patients with brain tumours or pediatric oncology/medical oncology if concurrent chemotherapy is required.

Staff involved in PBT should have appropriate training, credentials and licences to ensure patients are accessing quality care reflective of current best practice. There are well developed models of care that address equipment and technologies requirements together with quality assurance protocols. When followed, they are expected to ensure safe and high-quality delivery of PBT.

Equipment involved in the planning and delivery of proton beam therapy should adhere to all relevant technical standards as described in the consensus recommendations below. Proton beam therapy treatments should use appropriate proton-specific equipment.

REGULATORY AND STAFF REQUIREMENTS	
10	Proton beam therapy should be delivered by a qualified and experienced interdisciplinary team including radiation oncology, medical physics, and radiation therapy.
11	Proton beam therapy treatments delivered in Canada should be overseen by a licenced radiation oncologist certified by the Royal College of Physicians and Surgeons of Canada or the Collège des Médecins du Québec who has specific training in proton beam therapy. Other staff involved in the delivery of proton beam therapy should be licensed or certified by their national certification bodies such as the Canadian College of Physicists in Medicine for medical physicists and the provincial regulatory body for radiation therapists. Treatments being delivered out-of-country should be undertaken by staff with equivalent national licenses or certifications.[16]
12	Staff involved in proton beam therapy should be trained in proton beam therapy following the recommendations of ACR-ASTRO, ACR-AAPM, AAPM task group 185[5] or equivalent.
13	Whenever possible, patients enrolled in a clinical trial should be referred to an academic facility where the clinical trial has been activated to ensure continuity of care. Arrangements should be made prior to referral between the referring and treating institutions regarding submission of data required by the study protocol.
14	The proton beam therapy facility should maintain appropriate accreditations based on its jurisdiction. To enable referral and treatment of patients enrolled within cooperative group clinical trials, the proton beam therapy facility should be a member of the National Cancer Institute National Clinical Trials Network or equivalent. Facilities providing proton beam therapy to paediatric patients should be members in good standing of the Children's Oncology Group or equivalent.
EQUIPMENT AND TECHNOLOGIES	
15	Patients should be treated at a proton beam therapy facility co-located, or closely located to a tertiary care centre that has appropriate diagnostic imaging and supporting medical services.

16	Institutions delivering eye treatments require special accommodation. Ocular tumours may require only limited medical support during treatment, and treatment outside tertiary care centres may be appropriate.
17	Paediatric patients should only receive proton beam therapy at institutions with access to, and expertise in, paediatric anaesthesia and intensive care in treatment rooms that can accommodate anaesthesia equipment. In the case of an emergency, paediatric surgery and intensive care services should be available when required.
18	Proton beam therapy treatment equipment, commissioning and quality control should follow the recommendations of ACR-AAPM technical standards and AAPM task groups 185[5] and 224[3] or equivalent.
QUALITY ASSURANCE	
19	Proton beam therapy should be delivered at a facility that adheres to programmatic quality assurance guidelines such as those set forth by the Canadian Partnership for Quality Radiotherapy[16] or equivalent.

System Level Requirements

The Canadian Association of Provincial Cancer Agencies and its members are committed to facilitating standardized implementation and equitable access of PBT across the country.[23] System level initiatives should include a focus on quality of patient care including the referral process and communication between providers if the patient is referred out-of-country, continuity of follow-up care after PBT, monitoring of wait-times for PBT, and budget impact. Considerations such as provincial readiness, capacity and inter-provincial and international access agreements are necessary to support this commitment.

Recognizing the costs associated with the creation of PBT infrastructure and ongoing treatment delivery, provincial cancer programs and ministries of health should organize a coordinated approach to procurement to ensure best value for public investment.

According to model estimates, 48.5% of people with cancer will require radiotherapy at some point after diagnosis.[20] Approximately 80% of these indications arise in the first year after diagnosis. The model estimates for the number of patients requiring PBT is evolving as the capability for treatment with other forms of radiotherapy continues to improve and primary economic evaluation data is minimal due to the uncertainty in the clinical evidence.[19, 21] Moreover, a recent health technology assessment released by Ontario Health suggests that existing clinical evidence may not reflect treatment with the latest advancements in PBT, which could provide some improvement in clinical outcomes. Therefore, the cost-effectiveness of PBT in Canada is unknown.[34]

REFERRAL PROCESS	
20	All patients considered for out of country proton beam therapy should be seen by a qualified radiation oncologist in Canada and be assessed against approved provincial

	clinical indications to determine the suitability of proton beam therapy in the overall course of treatment.
21	Written or electronic referral and approval processes for out of country proton beam therapy should be streamlined provincially to minimize delays and optimize timely and accurate communication between referring teams and approving administrators.
22	A standardized provincial referral process of approved diagnoses will reduce the likelihood of delays in commencing urgent therapy out-of-country.
23	When proton beam therapy is offered in Canada, inter-provincial agreements between provincial health ministries and cancer agencies have the potential to support equitable and timely access for all eligible patients in Canada and should be considered where appropriate.[15, 40]
24	Routine follow-up care after proton beam therapy should be the responsibility of the referring Canadian physician.
COSTING, BUDGET IMPACT AND QUALITY ADJUSTED LIFE YEAR (QALY)	
25	Funding to cover the direct costs of out of country referral including proton beam therapy, concurrent therapy such as chemotherapy and anaesthesia, and treatment of acute complications during therapy, should be considered whenever possible.[35] Coverage of reasonable incidental costs (i.e., meals, travel, and accommodation for the patient, and one companion for paediatric patients age <18 or those requiring such support for other reasons) should be considered by provincial insurance.
26	Programs should refer to the Canadian Agency of Drugs and Technologies in Health review of clinical effectiveness and cost effectiveness[12] when considering patient eligibility.
ELIGIBLE PATIENT ESTIMATES	
27	Eligible patient estimates should reflect both the need and unmet need for proton beam therapy in the region/jurisdiction. New clinical trial evidence should be reassessed regularly.

Implementation and Relevance

It is recognized that provinces will have variable timelines and priorities for introducing PBT locally, and for supporting inter-provincial patient access agreements. The Canadian Association of Provincial Cancer Agencies and its members support a coordinated approach to the implementation of the consensus recommendations included in this document, and to the introduction of PBT in Canada. The Canadian Association of Provincial Cancer Agencies has agreed to review, on an annual basis these consensus recommendations to ensure continued relevancy and currency within this rapidly changing landscape.

Conclusions

Since PBT evidence continues to evolve, variation in clinical eligibility and access criteria for patients requiring PBT is a reality in Canada. The long-term risks and outcomes associated with the technology remain unclear and there is value to collecting more information through clinical trials to better understand the potential benefits and risks.

CAPCA has developed evidence-informed pan-Canadian consensus recommendations to support harmonization of access to this therapy out of country or within Canada if a facility is created.

This consensus guidance document was developed in collaboration with provincial cancer programs, clinical experts in proton beam therapy, system partners and a targeted community consultation. It describes clinical criteria, program requirements and systems level processes necessary to support planning and delivery of PBT in Canada. These guidelines demonstrate a commitment by CAPCA, and its members, to support consistency in access to important cancer therapies for patients in Canada.

In reality, the ability to implement PBT in Canada will be tempered by many factors including facility capacity and clinical evidence. Consensus recommendations such as these, when coupled with existing provincial and national clinical practice guidelines, legislation and professional practice standards, can help the oncology system respond to and implement technological innovations such as PBT.

Bibliography

1. AIM Specialty Health. (2019). *Clinical appropriateness guidelines: radiation oncology – proton beam therapy guidelines.* https://aimspecialtyhealth.com/guidelines/PDFs/2019/Nov10/AIM_Guidelines_ProtonBeam.pdf

2. Alberta Provincial Cancer Control, Alberta Proton Therapy Guideline Working Group & Guideline Advisory Group Tumour Team. (2019). *Proton beam radiation therapy*. https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-rt002-proton-beam-RT.pdf

3. American Association of Physicists in Medicine. (2019). *Comprehensive proton therapy machine quality assurance: report of AAPM task group 224.* https://www.aapm.org/pubs/reports/detail.asp?docid=187

4. American Association of Physicists in Medicine. (2019). *The relative biological effectiveness of proton beams in radiation therapy: report of AAPM task group 256*. https://www.aapm.org/pubs/reports/detail.asp?docid=182

5. American Association of Physicists in Medicine. (2020). *Clinical commissioning of intensity-modulated proton therapy systems: report of AAPM task group 185*. https://www.aapm.org/pubs/reports/detail.asp?docid=208

6. American Association of Physicists in Medicine. (2020). *Physical uncertainties in the planning and delivery of light ion beam treatments: report of AAPM task group 202*. https://www.aapm.org/pubs/reports/RPT_202.pdf

7. American Medical Association. (2017). *ASTRO model policies: proton beam therapy*. https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf

8. Armenian, S. H. & Robinson, L. L. (2013). Childhood cancer survivorship: an update on evolving paradigms for understanding pathogenesis and screening for therapy-related late effects. *National Centre for Biotechnology Information, 25*(1), 16-22. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3771864/

9. Bismarck, O., Frandsen, J. E., Boothe, D., Ermoian, R. P., & Poppe, M. M. (2016). Patterns of care in proton radiation therapy for pediatric central nervous system malignancies. *International Journal of Radiation Oncology, 97*(1), 60-63. https://doi.org/10.1016/j.ijrobp.2016.09.011

10. Brenner, D. R., Weir, H. K., Demers, A. A., Ellison, L. F., Louzado, C., Shaw, A., Turner, D., Woods, R. R., & Smith, L. M. (2020). Projected estimates of cancer in Canada in 2020. *CMAJ, 192*(9), E199-E205. https://doi.org/10.1503/cmaj.191292

11. CADTH. (2016). *Proton beam therapy for the treatment of locally advanced adenoid cystic carcinoma: clinical effectiveness, cost-effectiveness, and guidelines.* https://www.cadth.ca/sites/default/files/pdf/htis/apr-2016/RB0980%20Proton%20Beam%20Cancer%20Therapy%20Final.pdf

12. CADTH. (2016). *Proton beam therapy versus photon radiotherapy for adult and pediatric oncology patients: a review of the clinical and cost-effectiveness.* https://www.cadth.ca/sites/default/files/pdf/htis/may-2016/RC0779%20Proton%20Beam%20Therapy%20Final.pdf

13. CADTH. (2017). *The use of proton beam therapy in Canada, the United Kingdom, and Australia: an environmental scan of funding, referrals, and future planning*. https://cadth.ca/sites/default/files/pdf/ES0305_PBT_Use_in_Canada.pdf

14. CADTH. (2017). *Proton beam therapy for the treatment of cancer in children and adults: A health technology assessment*. https://cadth.ca/sites/default/files/pdf/HT0017_PBT_Report.pdf

15. Canada Health Act, C-6, s.11 (1985). https://laws-lois.justice.gc.ca/eng/acts/c-6/page-1.html

16. Canadian Partnership for Quality Radiotherapy. (2019). *Quality Assurance Guidelines for Canadian Radiation Treatment Programs.* http://www.cpqr.ca/wp-content/uploads/2020/03/QRT2019-12-04.pdf

17. Cancer Care Ontario. (2019). *Proton beam therapy in Ontario: a feasibility assessment to build a proton beam therapy facility in Ontario compared with out of country referrals* [Unpublished report].

18. Chang, J. Y., Zhang, X., Knopf, A., Li, H., Mori, S., Dong, L., Lu, H-M., Liu, W., Badiyan, S. N., Both, S., Meijers, A., Lin, L., Flampouri, S., Li, Z., Umegaki, K., Simone II, C. B., & Zhu, X. R. (2017). Consensus guidelines for implementing pencil-beam scanning proton therapy for thoracic malignancies on behalf of the PTCOG thoracic and lymphoma subcommittee. *International Journal of Radiation Oncology, 99*(1), 41-50. https://doi.org/10.1016/j.ijrobp.2017.05.014

19. Contreras, J., Zhao, T., Perkins, S. Baozhou, S., Sreekrishna, G., Mutic, S., Bottani, B., Endicott, S., Michalski, J., Robinson, C., Tsien, C., Huang, J., Fisher-Valuck, B. W., Hallahan, D., Klein, E., & Bradley, J. (2017) *National Center for Biotechnology Information, 7*(1), 71-76. https://pubmed.ncbi.nlm.nih.gov/27637138/

20. Delaney, G.P. & Barton, M.B. (2015). Evidence-based estimates of the demand for radiotherapy. *Clinical Oncology, 27*(2), 70-76. https://doi.org/10.1016/j.clon.2014.10.005

21. Glimelius, B., Ask, A., Bjelkengren, G., Björk-Eriksson, T., Blomquist, E., Johansson, B., Karlsson, M., & Zackrisson. (2005). Number of patients potentially eligible for proton therapy. *Acta Oncologica, 44*(8), 836-849. https://doi.org/10.1080/02841860500361049

22. Hall, E. J. (2006). Intensity-modulated radiation therapy, protons, and the risk of second cancers. *International Journal of Radiation Oncology*, 65(1), 1-7. https://doi.org/10.1016/j.ijrobp.2006.01.027

23. Health Canada. (2020). *Summary basis of decision – Mevion S250 proton beam radiation therapy system.* https://hpr-rps.hres.ca/reg-content/summary-basis-decision-medical-device-detailThree.php?lang=en&linkID=SBD00401

24. Hijal, T., Freeman, C. R., & Seuntjens, J. (2019). Proton beam therapy should remain in the public domain. *CMAJ, 191*(46), 1284. https://doi.org/10.1503/cmaj.73445

25. Hsu, C.-C., & Sandford, B. A. (2007). The Delphi technique: making sense of consensus. *Practical Assessment, Research, and Evaluation*, *12*(10). https://doi.org/10.7275/pdz9-th90

26. Indelicato, D. J., Merchant, T., Laperriere, N., Lassen, Y., Vennarini, S., Wolden, S., Hartsell, W., Pankuch, M., Brandal, P., Law, C-C. K., Taylor, R., Laskar, S., Okcu, M. F., Bouffet, E., Mandeville, H., Björk-Eriksson, T., Nilsson, K., Nyström, H., Constine, L. S., ... Kortmann, R-D. (2016). *Consensus report from the Stockholm pediatric proton therapy conference. International Journal of Radiation Oncology, 96*(2), 387-392. https://doi.org/10.1016/j.ijrobp.2016.06.2446

27. Institute for Clinical and Economic Review. (2014). *Health technology assessment: final appraisal document: proton beam therapy*. http://icerorg.wpengine.com/wp-content/uploads/2020/10/pbt_final_report_040114.pdf

28. Kahalley, L. S., Peterson, R., Ris, M. D., Janzen, L., Okcu, M. F., Grosshans, D. R., Ramaswamy, V., Paulino, A. C., Hodgson, D., Mahajan, A., Tsang, D. S., Laperierre, N., Whitehead, W. E., Dauser, R. C., Taylor, M. D., Conklin, H. M., Chintagumpala, M., Bouffet, E., & Mabbott, D. (2020). Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. *Journal of Clinical Oncology, 38*(5), 454-461. https://ascopubs.org/doi/full/10.1200/JCO.19.01706

29. Leeman, J. E., Romesser, P. B., Zhou, Y., McBride, S., Riaz, N., Sherman, E., Cohen, M. A., Cahlon, O., & Lee, N (2017). Proton therapy for head and neck cancer: expanding the therapeutic window. *Lancet Oncol*., 18(5), e254-e265. https://doi.org/10.1016/S1470-2045(17)30179-1

30. Ligtenberg, G., Staal, P.C., & S. Kleijnen. (2010). *Indications for proton therapy (part 1).* (287). https://english.zorginstituutnederland.nl

31. Mercado, C.E., Holtzman, A. L., Rotondo, R., Rutenberg, M. S., & Mendenhall, W. M. (2019). Proton therapy for skull base tumors: A review of clinical outcomes for chordomas and chondrosarcomas. *Head Neck*, 41(2), 536-541. https://doi.org/10.1002/hed.25479

32. Mombo, N. N. (2017). *Indications of proton beam therapy in oncology, updated*. INESSS. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/INESSS_Proton_radiation_therapy_EnglishSummary.pdf

33. NHS England Specialised Services Clinical Reference Group for Radiotherapy. (2020). *Clinical commissioning policy: proton beam therapy for children, teenagers and young adults in the treatment of malignant and non-malignant tumours*. https://www.england.nhs.uk/wp-content/uploads/2020/10/proton-beam-therapy-clinical-commissioning-policy.pdf

34. Ontario Health. (2021). *Proton beam therapy for cancer in children and adults: a health technology assessment.* https://www.hqontario.ca/Portals/0/Documents/evidence/open-comment/hta-proton-beam-therapy-for-cancer-in-children-and-adults-draft-2102.pdf

35. Patel, S., Kostaras, X., Parliament, M., Olivotto, I. A., Nordal, R., Aronyk, K., & Hagen, N. (2014). Recommendations for the referral of patients for proton-beam therapy, an Alberta health services report: a model for Canada?. *Current Oncology, 21*(5), 251-262. https://doi.org/10.3747/co.21.2207

36. Roos, L., Benahmed, N., Hulstaert, F., Van Damme, N., & De Ruysscher, D. (2015). Proton therapy in children: a systematic review of clinical effectiveness in 15 pediatric cancers. *International Journal of Radiation Oncology, 95*(1), 267-278. https://doi.org/10.1016/j.ijrobp.2015.10.025

37. Rwigema, J-C. M., Langendijk, J. A., van der Laan, H. P., Lukens, J. N., Swisher-McClure, S. D., & Lin, A. (2019). A model-based approach to predict short-term toxicity benefits with proton therapy for oropharyngeal cancer. *International Journal of Radiation Oncology, 104*(3), 553-562. https://doi.org/10.1016/j.ijrobp.2018.12.055

38. Sahgal, A., Chan, M. W., Atenafu, E. G., Masson-Cote, L., Bahl, G., Yu, E., Millar, B-A., Chung, C. Catton, C., O'Sullivan, B., Irish, J. C., Gilbert, R., Zadeh, G., Cusimano, M., Gentili, F., & Laperriere, N. J. (2015). Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. *Neuro-oncology*, *17*(6), 889-894. https://doi.org/10.1093/neuonc/nou347

39. Shih, H. A., Rengan, R., Apisarnthanarax, S., Cheng, C-W., Daartz, J., DeLaney, T. F., Hartsell, W. F., Indelicato, D. J., Keole, S. R., Rosenthal, S., & Hartford, A. C. (2020). ACR-ASTRO Practice parameter for the performance proton beam radiation therapy. *American Journal of Clinical Oncology, 43*(3), 149-159. https://doi.org/10.1097/coc.0000000000000672

40. Smith, W. L., Smith, C. D., Patel, S., et al. (2018) What Conditions Make Proton Beam Therapy Financially Viable in Western Canada? *Cureus, 10*(11), E3644. https://doi.org/10.7759/cureus.3644

41. Society of Radiographers. (2018). *Proton beam therapy – guidance*. https://www.sor.org/learning/document-library/proton-beam-therapy-guidance

42. Tambas, M., Steenbakkers, R. J. H. M., van der Laan, H. P., Wolters, A. M., Kierkels, R. G. J., Scandurra, D., Korevaar, E. W., Oldenhinkel, E., van Zon-Meijer, T. W. H., Both, S., van den Hoek, J. G. M., & Langendijk , J. A. (2020). First experience with model-based selection of head and neck cancer patients for proton therapy. *Radiation & Oncology, 151*, 206-213. https://doi.org/10.1016/j.radonc.2020.07.056

43. Tsang, D.S., Patel, S. (2019). Proton beam therapy for cancer. *CMAJ, 191*(24), E664-E666. https://www.cmaj.ca/content/191/24/E664

44. UHN Princess Margaret Cancer Centre. (2020). *Proton Therapy Consultation Service*. https://www.uhn.ca/PrincessMargaret/Health_Professionals/Programs_Departments/RMP/Pages/proton_therapy.aspx

45. Vega, R.M., Kim, J., Bussiere, M., Hattangadi, J., Hollander, A., Michalski, J., Tarbell, N. J., Yock, T., & MacDonald, S. M. (2013). Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *American Cancer Society Journals, 119*(24), 4299-4307. https://doi.org/10.1002/cncr.28322

46. Vega, R. M., Kim, J., Hollander, A., Hattangadi-Gluth, J., Michalski, J., Tarbell, N. J., Yock, T. I., Bussiere, M., & MacDonald, S. M. (2015). Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. *American Cancer Society Journals, 121*(10), 1694-1702. https://doi.org/10.1002/cncr.29209

47. Waddle, M. R., Sio, T. T., Van Houten, H. K., Foote, R. L., Keole, S. R., Schild, S. E., Laack, N., Daniels, T. B., Crown, W., Shah, N. D., & Miller, R. C. (2017). Photon and proton radiation therapy utilization in a population of mora than 100 million commercially insured patients. *International Journal of Radiation Oncology, 99*(5), 1078-1082. https://doi.org/10.1016/j.ijrobp.2017.07.042

48. Washington State Health Care Authority. (2019). *Proton beam therapy—re-review. Final evidence report.* https://www.hca.wa.gov/assets/program/proton-beam-therapy-rr-final-report-20190418.pdf

49. Xiang, M., Chang, D. T., & Pollom, E. L. (2020). Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy. *Cancer*, 126(15), 3560-3568. https://doi.org/10.1002/cncr.32938