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TECHNOLOGY REVIEW (MINI-HTA)

PROTON BEAM THERAPY FOR THE TREATMENT OF CANCER – AN UPDATE

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
013/2021

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EXECUTIVE SUMMARY

Background

X-rays have been used to treat cancer since 1895. Advances in x-ray therapy over the years include development of linear accelerators that produce high-energy x-rays for deeper penetration. The likelihood of tumour control through radiation therapy is related to the dose delivered to the tumour, and the likelihood of severe organ injury is related to the dose to the organ and volume of the organ exposed to radiation. The challenge in using high-energy x-rays to treat cancer is that the x-rays pass through the thickness of the body, depositing an entrance and an exit dose to healthy organs. The dose to healthy organs limits the dose that can be safely administered to the tumour. Radiation oncologists constantly find the optimal balance between a high-enough dose to prevent cancer recurrence and a low-enough dose to avoid injury to healthy organs.

Proton beam therapy (PBT) offer an option for obtaining that balance. Protons are positively charged subatomic particle. The biologic effects of protons and x-rays on cells are similar since both are sparsely ionising with a relatively small linear energy transfer. However, the way protons interact with matter provides advantages compared with x-rays. As protons enter the body, they deposit a very low entrance dose. The depth of proton penetration is dependent on kinetic energy and, hence, the higher the energy, the deeper is the penetration. When the proton arrives at its target, it delivers the dose and stops, thereby eliminating an exit dose. This physical advantage serves to lower the dose to healthy organs both superficial and deep to the tumour, thus reducing the risk of injury to the cell. It also allows administration of a higher dose to the tumour, having the possibility in reducing the recurrence rate without increasing the complication rate and leading to better organ function and quality of life. This result can lead to an avoidance of costs associated with treating recurrent tumours and damaged organs. This effect is particularly important in young children with a high likelihood of cure who are strongly susceptible to the long-term effects of x-ray therapy and in patients with cancers located adjacent to critical healthy organs, such as the eye, brain, brainstem, spinal cord, lung, heart, liver, bowel and kidneys.

A technology review report by Malaysian Health Technology Assessment Section (MaHTAS) in 2006 concluded that there was good evidence to support the use of PBT in ocular (uveal) melanoma. There was fair evidence to support the use of PBT in skull base chordomas and chondrosarcomas, in intracranial tumours, particularly benign meningioma and pituitary adenoma, in lung cancer, particularly the small non-cell carcinoma, in prostate cancer and in acoustic neuroma. There was poor evidence to support the use of PBT for liver cancer, gastrointestinal cancers and paediatric malignancies.

An updated review report in 2017 found that there was no new high level of evidence retrieved to determine the effectiveness and safety of proton beam therapy for cancer

treatment. Most of the studies were cohort or case-series with methodological limitations, yielding a low level of clinical evidence for the outcomes. Only limited RCTs were conducted in certain cancer. However, no significant differences were noticed from the studies. In terms of effectiveness, in paediatric cancer, insufficient clinical evidence to support or to refute the use of proton beam therapy. Limited evidences were found on breast cancer, ocular tumour, chordomas & chondrosarcomas, non small cell lung cancer, liver cancer and prostate cancer. In terms of safety, no mortality and severe adverse events reported. Skin toxicities, oesophageal toxicities and other acute toxicities like fatigue, chest wall pain, lymphoedema were reported in breast cancer patients. Hearing loss and brain stem toxicities with increased volume of proton beam were reported in chordomas and chondrosarcomas. In terms of cost-effectiveness, the ICER varies from $4,254 per QALY in head and neck cancer to $80,596 per QALY in breast cancer. Therefore, it is highly unlikely PBT will be the most economic option for all cancers. Rather, more research that involved cost-effectiveness studies can be used to decide for whom PBT is most cost effective.

This technical review was requested by the Director of National Cancer Institute to assess the safety and effectiveness of PBT service following a request to offer the service in Malaysia.

Objective/ aim

The objective of this systematic review was to update the evidence on safety, effectiveness, cost, cost-effectiveness and organisational issues of PBT for treatment of cancer.

Results and conclusions:

A total of 169 records were identified through the Ovid interface and PubMed. After removal of 154 irrelevant or duplicates, 15 records were screened. Three full text articles were included, and 12 full text articles were excluded due to the study was already included in systematic review. One HTA, one systematic review and one systematic review and meta analysis articles were included in this report.

There was no new high level of evidence retrieved to determine the safety and effectiveness of proton beam therapy for cancer treatment. No significant differences were noticed from the outcome of the studies.

Compared with photon therapy, proton beam therapy may result in fewer adverse event but similar overall survival and progression-free survival in children with brain tumours, adults with esophageal cancer, head and neck cancer, and prostate cancer. However, the quality level of the evidence is low to very low.

Organisational

The setting of proton therapy centre faced many challenges and obstacles. Development of technology is in slow pace and very high cost involved in establishing and operating of proton therapy facilities. The minimum setting for the facility including the building, a proton accelerator and a multi-ion accelerator. Mohan and Grosshans stated that current proton

therapy facilities with three to four treatment rooms cost well over a $100 million. A single room facility costs of the order of $30 million. These costs are an order of magnitude higher than the cost of a high-end photon treatment unit.

Methods

Electronic databases were searched through Ovid interface:

- EBM Reviews - Health Technology Assessment 2nd Quarter 2021
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 5, 2021
- EBM Reviews - Cochrane Central Register of Controlled Trials October 2021
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1948 to November 15, 2021

Other databases:

- Pubmed

Search was limited to studies published from 2017 to November 2021. Google was used to search for additional web-based materials and information. The search was limited only to human studies. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 15 November 2021.

TABLE OF CONTENTS

ABBREVIATION

AEs	Adverse events or adverse effects
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
MaHTAS	Malaysian Health Technology Assessment Section
MD	Mean difference
MOH	Ministry of Health
NHS	National Health Service
OR	Odds ratio
PBT	Proton Beam Therapy
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Risk ratio
SMD	Standardized mean difference
US FDA	United States Food and Drug Administration
WMD	Weighted mean difference

1.0 BACKGROUND

X-rays have been used to treat cancer since 1895. Advances in x-ray therapy over the years include development of linear accelerators that produce high-energy x-rays for deeper penetration. The likelihood of tumour control through radiation therapy is related to the dose delivered to the tumour, and the likelihood of severe organ injury is related to the dose to the organ and volume of the organ exposed to radiation. The challenge in using high-energy x-rays to treat cancer is that the x-rays pass through the thickness of the body, depositing an entrance and an exit dose to healthy organs. The dose to healthy organs limits the dose that can be safely administered to the tumour. Radiation oncologists constantly need to find the optimal balance between a high-enough dose to prevent cancer recurrence and a low-enough dose to avoid injury to healthy organs.[1]

Proton beam therapy (PBT) offer an option for obtaining that balance. Protons are positively charged subatomic particle. The biologic effects of protons and x-rays on cells are similar since both are sparsely ionising with a relatively small linear energy transfer. However, the way protons interact with matter provides advantages compared with x-rays. As protons enter the body, they deposit a very low entrance dose. The depth of proton penetration is dependent on kinetic energy and, hence, the higher the energy, the deeper is the penetration. When the proton arrives at its target, it delivers the dose and stops, thereby eliminating an exit dose. This physical advantage serves to lower the dose to healthy organs both superficial and deep to the tumour, thus reducing the risk of injury to the cell. It also allows administration of a higher dose to the tumour, having the possibility in reducing the recurrence rate without increasing the complication rate and leading to better organ function and quality of life. This result can lead to an avoidance of costs associated with treating recurrent tumours and damaged organs. This effect is particularly important in young children with a high likelihood of cure who are strongly susceptible to the long-term effects of x-ray therapy and in patients with cancers located adjacent to critical healthy organs, such as the eye, brain, brainstem, spinal cord, lung, heart, liver, bowel and kidneys.

A technology review report by Malaysian Health Technology Assessment Section (MaHTAS) in 2006 concluded that there was good evidence to support the use of PBT in ocular (uveal) melanoma. There was fair evidence to support the use of PBT in skull base chordomas and chondrosarcomas, in intracranial tumours, particularly benign meningioma and pituitary adenoma, in lung cancer, particularly the small non-cell carcinoma, in prostate cancer and in acoustic neuroma. There was poor evidence to support the use of PBT for liver cancer, gastrointestinal cancers and paediatric malignancies.[2]

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treatment. Most of the studies were cohort or case-series with methodological limitations, yielding a low level of clinical evidence for the outcomes. Only limited RCTs were conducted in certain cancer. However, no significant differences were noticed from the studies. In terms of effectiveness, in paediatric cancer, insufficient clinical evidence to support or to refute the use of proton beam therapy. Limited evidences were found on breast cancer, ocular tumour, chordomas & chondrosarcomas, non-small cell lung cancer, liver cancer and prostate cancer. In terms of safety, no mortality and severe adverse events were reported. Skin toxicities, oesophageal toxicities and other acute toxicities like fatigue, chest wall pain, lymphoedema were reported in breast cancer patients. Hearing loss and brain stem toxicities with increased volume of proton beam were reported in chordomas and chondrosarcomas. In terms of cost-effectiveness, the ICER varies from $4,254 per QALY in head and neck cancer to $80,596 per QALY in breast cancer. Therefore, it is highly unlikely PBT will be the most economic option for all cancers. Rather, more research that involved cost-effectiveness studies can be used to decide for whom PBT is most cost effective [3]

This technical review was requested by the Director of National Cancer Institute to assess the safety and effectiveness of PBT service following a request to offer the service in Malaysia.

2.0 OBJECTIVE / AIM

The objective of this systematic review was to update evidence synthesis on safety, effectiveness, cost, cost-effectiveness and organisational issues of PBT for treatment of cancer.

3.0 TECHNICAL FEATURE

The therapeutic potential of protons was first recognised in a report by Robert Wilson in 1946.[4] He theorised how proton beams could be used for treating localised cancers. Proton Beam Therapy (PBT) uses protons, which deposit less energy before and after the tumour, hence delivering the greatest dose to the exact tumour location.

Most of the current practice of clinical radiotherapy utilizes photon beams of energies ranging from 4 to 18 megavolt (MV). Less than 1% of the patients world-wide are treated with protons and heavier ions, though the number is increasing as new facilities are established. In contrast to photons, when protons of a given energy (typically in the range of 70 to 250MeV) penetrate matter, they slow down continuously as a function of depth. The rate of their energy loss (called “linear energy transfer” or LET) increases with decreasing velocity. This continues until their entire energy is depleted and then they come to an abrupt stop. This

process of dose (energy deposited per unit mass) deposition produces a characteristic depth-dose curve ("Bragg curve") for a broad monoenergetic beam of protons.[4]

Most commonly, protons for therapeutic applications are accelerated using cyclotron or a synchrotron; each has its advantages and disadvantages. Cyclotrons produce a continuous stream of protons. In theory, cyclotrons are more compact and have higher beam intensity. Protons are accelerated to the maximum of the energy of the cyclotron (e.g., 230 MeV), and the required lower energies are achieved by electromechanically inserting energy degraders in the path of protons between the accelerator and the treatment room.

Synchrotrons, on the other hand, accelerate batches (pulses) of protons to the desired energy. Once a batch has reached the required energy, it is extracted and transmitted via the "beam line" to the treatment room. The extraction may occur over a variable period of time from 0.5 to 4.5s, depending on the application. The duration of the pulse, i.e., the cycle time, is 1 to 2s longer to allow for resetting of the acceleration system between pulses. Each cycle can produce protons of a different energy. Generally, the advantage of synchrotrons is that they have greater energy flexibility, smaller energy spread, and lower power consumption.

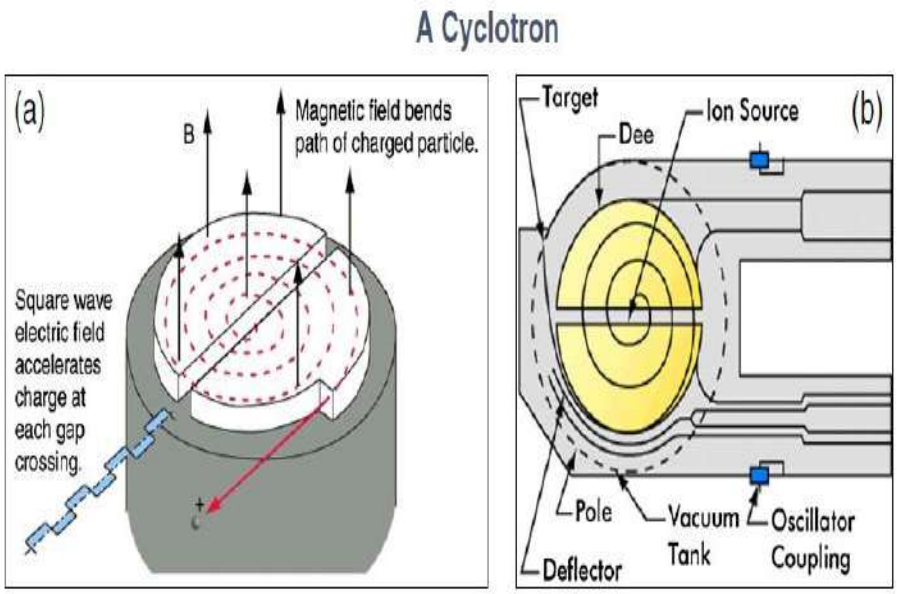

Fig. 2. Acceleration of protons in a cyclotron. A fixed magnetic field bends the path of protons, and they are accelerated by a square wave electric field applied between gaps of two D-shaped regions (known as "Dees"). As energy increases, the radius of the proton path increases until the designated maximum is reached and protons are extracted. Panel on the right shows key components of the cyclotrons.
(Adapted from [16].).

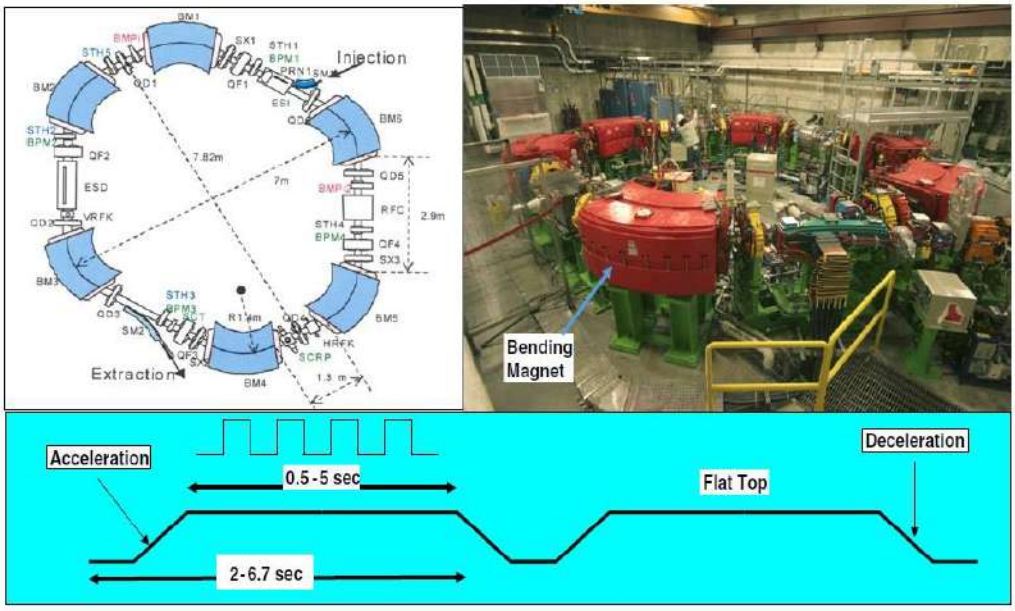

Fig. 3. The synchrotron at MD Anderson Proton Therapy Center. A batch of protons is initially accelerated by a linear accelerator to a low energy (7 MeV) and injected into the synchrotron. Protons, as they are accelerated by the successive application of an alternating electric field, are constrained to move in a fixed circular path by increasing the magnetic field. When the batch of protons has reached the specified energy, it is extracted and transmitted to one of the treatment rooms.

Figure 1: Photos adapted from “Proton therapy-Present and future” by Mohan and Grosshans. 2017 Advanced Drug Delivery Reviews 109(2017):26-44

Regardless of the type of accelerator, the extracted narrow monoenergetic beam is magnetically guided through the beam line to the nozzle mounted, in most cases, on a rotating gantry in the treatment room. The gantry is used to aim the beam to the target in the patient lying on a treatment couch. The couch can also be rotated and shifted to achieve optimum beam directions to avoid as much normal tissue as possible.

A typical proton accelerator serves multiple rooms. The beam is switched automatically from one room to the next based on the order of request and priority. Although PBT has now become a clinical reality with US Food and Drug Administration approval granted in 1988, appropriate utilisation has become a polarising issue within the oncology community.[5]

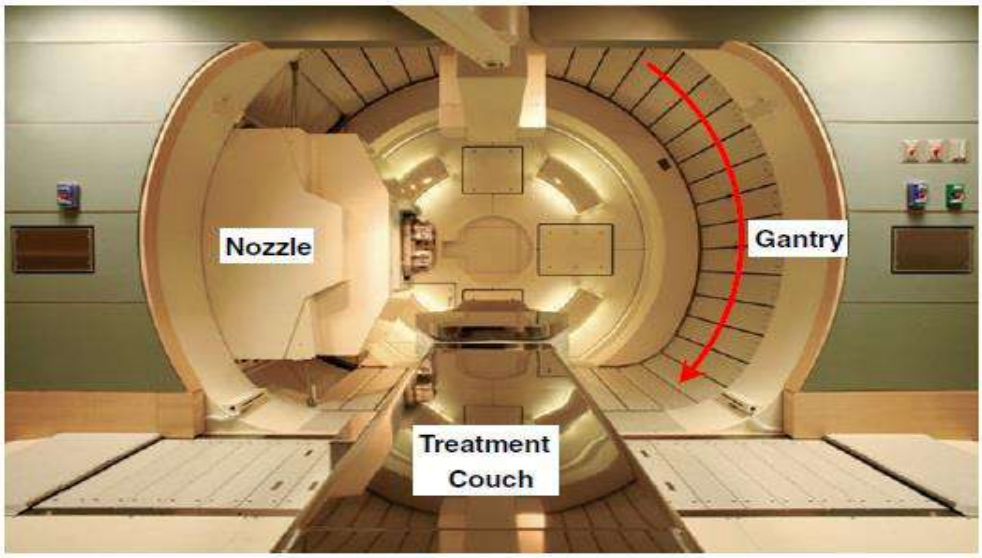

Fig. 4. Nozzle (treatment head) mounted on a rotating gantry to direct the beam to the tumor in the patient lying on the treatment couch.

Figure 2: Photos adapted from "Proton therapy-Present and future" by Mohan and Grosshans. 2017 Advanced Drug Delivery Reviews 109(2017):26-44

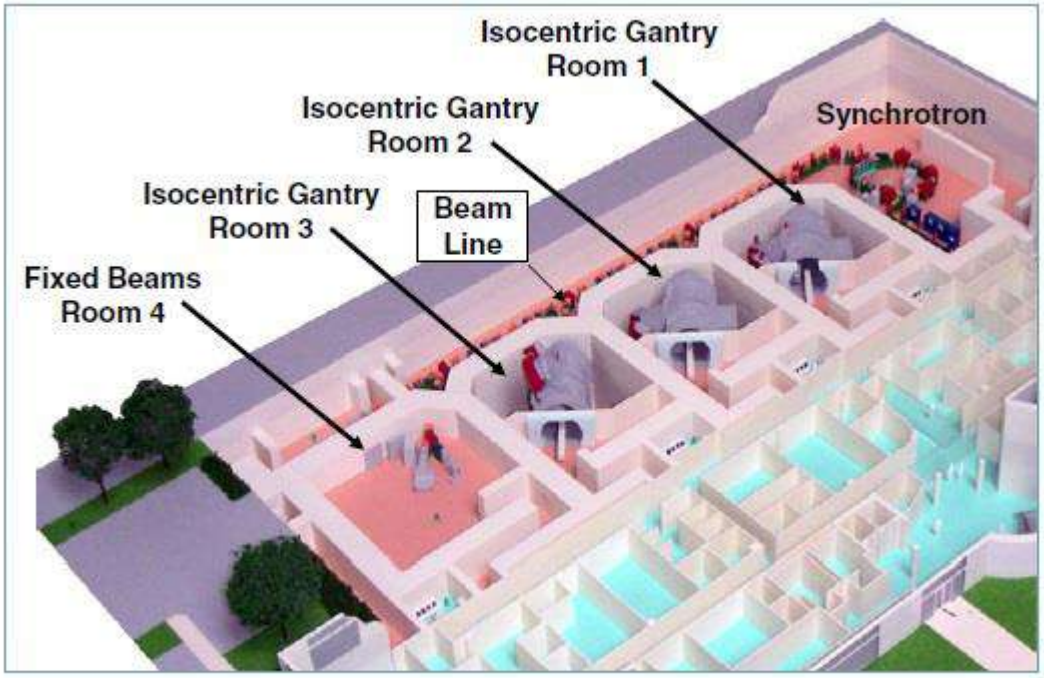

Fig. 5. Layout of the treatment floor of MD Anderson's Proton Therapy Center.

Figure 3: Photos adapted from "Proton therapy-Present and future" by Mohan and Grosshans. 2017 Advanced Drug Delivery Reviews 109(2017):26-44

4.0 METHODS

A systematic review was conducted. Review protocol and search strategy was developed by the main author and *Information Specialist*.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface: **MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) 1946 to November 2021.**

Other databases:

- PubMed
- Other websites: US FDA, INAHTA.

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 15th November 2021.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *Critical Appraisal Skills Programme (CASP) checklist* and Cochrane risk of bias tool for randomised trials (RoB 2). Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). Data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Patients with cancer
b.	**Intervention**	Proton beam therapy
c.	**Comparator**	Conventional radiotherapy
d.	**Outcomes**	One or more of the following outcome measures were assessed: • Efficacy/effectiveness such as: a. Reduction in progression of cancer b. Survival rate • Safety (adverse events and complications) • Cost/cost-effectiveness/cost-analysis
e.	**Study design**	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, case-control, case series, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case report, animal study, laboratory study, narrative review
b.	Non English full text articles	

5.0 RESULTS

Search results

A total of 169 records were identified through the Ovid interface and PubMed. After removal of 154 irrelevant or duplicates, 15 records were screened. Three full text articles were included, and 12 full text articles were excluded due to the study was already included in systematic review. One HTA, one systematic review and one systematic review and meta-analysis articles were included in this report.

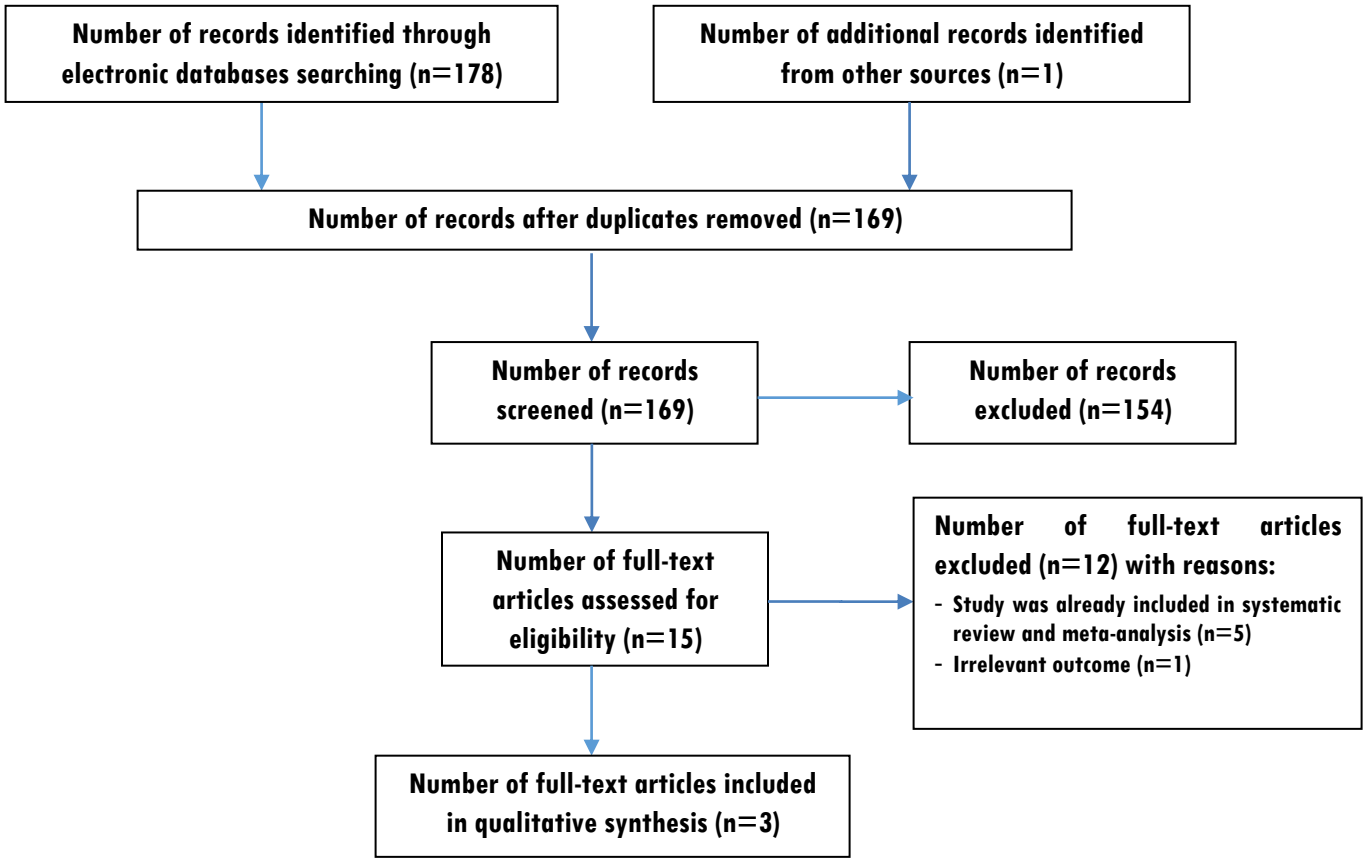

Figure 4: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

All the studies included in this review were systematic review. The tool used to assess the quality of the systematic review was the Critical Appraisal Skills Programme (CASP) checklist. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement:

+	**Indicates YES (low risk of bias)**
?	**indicates UNKNOWN risk of bias**
-	**Indicates NO (high risk of bias)**

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Ontario HTA.[6, level I]	+	+	+	**Not Relevant**
Paul et al.[7 level I]	+	+	+	**Not Relevant**
Meixuan Li et al.[8, level I]	+	+	+	**Not Relevant**

Figure 2: Systematic Review Assessment using CASP checklist

For the assessment of quality of included studies, Ontario HTA included the risk of bias in Systematic Reviews (ROBIS) tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. Paul et al. did not conduct Risk of Bias assessment. It may be due to the limited evidence available for the Population and Intervention selected. Meixuan Li et al. assessed the risk of bias of randomised controlled trials (RCT) studies using Cochrane Handbook v.5.1.0 and the ROB of cohort studies using Newcastle Ottawa Scale (NOS).

5.1 SAFETY AND EFFICACY/EFFECTIVENESS

Ontario Health Technology Assessment (HTA) reported proton beam therapy, compared with photon therapy, for children and adults with cancer requiring radiotherapy. [6, level I] One systematic review of the clinical evidence reporting on 215 publications on proton beam therapy in children and adults across 19 tumour categories/conditions was included in HTA. Compared with photon therapy, proton beam therapy may result in fewer adverse events but similar overall survival and progression-free survival in children with brain tumours (GRADE: Low), adults with oesophageal cancer (GRADE: Low to Very low), head and neck cancer (GRADE: Low to Very low), and prostate cancer (GRADE: Low). Proton beam therapy may result in similar adverse events, overall survival, and progression-free survival in adults with brain tumours (GRADE: Low), breast cancer (GRADE: Low), gastrointestinal cancer (GRADE: Very low), liver cancer (GRADE: Moderate to Very low), lung cancer (GRADE: Moderate to Very low), and ocular tumours (GRADE: Low). There was insufficient evidence to evaluate the effectiveness and safety of proton beam therapy in other pediatric tumours, as well as bladder cancer, bone cancer, lymphoma, and benign tumours in adults.

Paul et al conducted a systematic review [7, level I] on proton therapy for the treatment of intracranial benign tumours in adults. Twenty-four studies were included but all the studies were not randomised. Nine studies were on low grade meningiomas, four studies on neurinoma, five studies on pituitary adenoma, five studies on paraganglioma and one study on craniopharyngioma. Most of the studies included were case series. Despite the different indication, long term local control was systematically higher than 90% and equivalent to series with conventional radiotherapy. One study on pituitary adenoma reported seven patients developed minor visual deficits and two patients developed major visual deficits that consisted of de novo quadranopsia and bilateral optic nerve atrophy. The authors concluded the proton therapy for treatment of adult benign intracranial and cervical tumours is safe. Randomised or prospective cohorts with long term cognitive evaluations are needed to assess the real place of proton therapy in the treatment of adult benign head and neck tumours.

Meixuan Li et al in a systematic review and meta-analysis [8, level I] for the prostate cancer patients included twenty proton beam related studies published from 2010 to 2020. Seven studies analysed overall survival (OS) of PBT for prostate cancer. A random-effect meta-analysis indicated that the 3-, 4-, 5-year OS was 97% (95% CI, 96–98%), 87% (85–89%), 92% (95% CI, 87–97%), respectively. The results of a randomised controlled trial showed that the incidence of grade 2 Acute Gastro Intestinal (AGI) toxicity of proton and heavy-ion radiotherapy was 8.7% and 2.2%, respectively. A random-effects model single-arm meta analyses showed that the Grade 2 or higher AGI and late gastrointestinal (LGI) of PBT for

prostate cancer was 1% (95% CI, 0–2%) and 4% (95% CI, 2–5%). It can be seen that the incidence of GI toxicity of CIRT and PBT was lower than that of conventional photon radiotherapy and hypo fractionated photon radiotherapy. Twelve studies reported acute genitourinary (AGU) of PBT for prostate cancer, and 15 studies focused on more serious late genitourinary toxicity (LGU) of PBT for prostate cancer. The random effects model single-arm meta analyses showed that the grade 2 or higher AGU and LGU of PBT was 13% (95%CI, 9–17%) and 5% (95% CI, 4–7%). The incidence of GU toxicity of CIRT and PBT was lower than that of conventional photon radiotherapy and hypo fractionated photon radiotherapy. Author concluded that the current available evidence demonstrated that the efficacy and safety of PBT for prostate cancer were similar for carbon ion radiotherapy (CIRT) and PBT, and they may significantly improve the OS and reduce the incidence of GU and GI toxicity compared with photon radiotherapy. However, the quantity and quality of the available evidence are insufficient. More high-quality controlled studies are needed in the future.

5.2 ORGANISATIONAL ISSUES

As mentioned earlier in the previous report, the setting of proton therapy centre facing many challenges and obstacles. Development of technology is in slow pace and very high cost involved in establishing and operating of proton therapy facilities. The minimum setting for the facility including the building, a proton accelerator and a multi-ion accelerator. Mohan and Grosshans stated that current proton therapy facilities with three to four treatment rooms cost well over a $100 million. A single room facility costs of the order of $30 million. These costs are an order of magnitude higher than the cost of a high-end photon treatment unit. [4]

5.3 COST/COST-EFFECTIVENESS

Ontario Health Technology Assessment (HTA) in the report identified 16 studies with different methodologies evaluating the cost-effectiveness of proton beam therapy for various indication of cancer. [6, level I] Five economic evaluation studies explored the cost-effectiveness of proton beam therapy compared with conventional radiation therapy in children with medulloblastoma, using a societal and health system perspective in Sweden, the United States, and Brazil. The ICERs ranged from proton beam therapy being the dominant strategy (more effective and less costly than the comparator treatment) to costing $28,883 CAD per quality-adjusted life-year (QALY) gained ($21,716 USD/QALY gained). Four studies found that proton beam therapy is likely to be cost-effective, mainly due to reduction in adverse events such as hearing loss, reductions in intelligence quotient scores, hypothyroidism, and growth hormone deficiency. One study found that proton beam therapy was only likely to be cost-effective if more than 150 children are treated annually. As for adult indications, findings were inconsistent or did not show cost-effectiveness. Overall, the available studies had limited relevance to the Ontario context.

5.4 LIMITATIONS

We acknowledge some limitations in our review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers.

6.0 CONCLUSION

There was no new high level of evidence retrieved to determine the safety and effectiveness of proton beam therapy for cancer treatment. There were no significant differences in the outcome of the studies.

Compared with photon therapy, proton beam therapy may result in fewer adverse event but similar overall survival and progression-free survival in children with brain tumours, adults with oesophageal cancer, head and neck cancer, and prostate cancer. However, the quality level of the evidence is low to very low.

8.0 REFERENCES

1. Foote RL, Stafford SL, Petersen IA, Pulido JS, Clarke MJ, Schild SEet al. The Clinical Case for Proton Beam Therapy. Radiation oncology (London, England). 2012 Oct 22;7:174.
2. Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia. Technology Review. Proton therapy for cancer treatment. 2006.
3 Malaysian Health Technology Assessment Section, Medical Development Division, Ministry of Health Malaysia. Technology Review. Proton therapy for cancer treatment - An update. 2017.
4. Wilson RR. Radiological Use of Fast Protons. Radiology. 1946;47(5):487-491.
5. Radhe Mohan DG. Proton Therapy-Present and Future. Advanced Drug Delivery Reviews. 2017(109):26-44.
6. Ontario Health. Proton beam therapy for cancer in children and adults: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2021 May;21(1):1–142. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-andrecommendations/proton-beam-therapy-for-cancer-in-children-and-adults
7. Paul L, Valentin C, Catherine N et al. Proton therapy for treatment of intracranial benign tumors in adults: a systematic review.2019.Cancer Treatment Review 72:56-64
8. Meixuan L, Xiuxia L, Liang Y et al. Clinical efficacy and safety of proton and carbon ion radiotherapy for prostate cancer: a systematic review and meta-analysis.2021. Frontier in Oncology (11)

9.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1	NEOPLASMS/
2	(benign adj1 neoplasm*).tw.
3	cancer*.tw.
4	malignanc*.tw.
5	neoplasm*.tw.
6	tumor*.tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	PROTON THERAPY/
9	(beam therap* adj1 proton).tw.
10	(proton beam adj1 therap*).tw.
11	(proton adj1 therap*).tw.
12	8 or 9 or 10 or 11
13	7 and 12
14	limit 14 to (yr="2017 -Current" and humans)

Other Databases

PubMed
INAHTA
US FDA

} Same MeSH and keywords as per MEDLINE search

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

Evidence Table : Safety and efficacy/effectiveness

Question: Is proton beam therapy safe and effectiveness to be used in cancer patients?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up	Outcome measures/ Effect size	General comments
1. Ontario Health. Proton beam therapy for cancer in children and adults: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2021 May;21(1):1–142. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-andrecommendations/proton-beam-therapy-for-cancer-in-children-and-adults	Health Technology Assessment **Inclusion Criteria** • English-language full-text Publications • Studies published from database inception until July 24, 2019 • Systematic reviews, meta-analyses, and health technology assessments that included a systematic review of any study designs. • Studies that matched the research question and populations, interventions, comparators, and outcomes (see Participants, Interventions, Comparators, and Outcomes [PICO] below) **Exclusion Criteria** • Animal and in vitro studies • Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries	I	Childen and adults with cancer requiring radiotherapy. One Systematic Review or the clinical evidence reporting on 215 publications on proton beam therapy in children dan adults across 19 tumour categories/conditions.	Proton beam therapy (alone or in combination with other treatment modalities)	Photon therapy (alone or in combination with other treatment modalities), including image-guided intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques, other external beam therapies, or brachytherapy	The reviews were published between 2007 and 2019.	Ultimately selected HTA by Washington State Health Care Authority published in 2019 (search end date Dec 2018) because it included a comprehensive literature search of all cancer types in children and adults, and it provided detailed information on the included study designs, outcomes, and risk of bias assessment. Compared with photon therapy, proton beam therapy may result in fewer adverse events but similar overall survival and progression-free survival in children with brain tumours (Low), adults with oesophageal cancer (GRADE: Low to Very low), head and neck cancer (GRADE: Low to Very low), and prostate cancer (GRADE: Low). Proton beam therapy may result in similar adverse events, overall survival, and	

							progression-free survival in adults with brain tumours (GRADE: Low), breast cancer (GRADE: Low), gastrointestinal cancer (GRADE: Very low), liver cancer (GRADE: Moderate to Very low), lung cancer (GRADE: Moderate to Very low), and ocular tumours (GRADE: Low). There was insufficient evidence to evaluate the effectiveness and safety of proton beam therapy in other paediatric tumours, as well as bladder cancer, bone cancer, lymphoma, and benign tumours in adults. The economic evidence suggests that proton beam therapy may be cost-effective in paediatric populations with medulloblastoma; however, studies were based on limited clinical evidence. In other indications, the cost-effectiveness of proton beam therapy is unclear.	

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2. Paul Leseur, Valentin C, Catherine N et al. Proton therapy for treatment of intracanial benign tumors in adults: a systematic review. 2019. Cancer Treatment Reviews 72:56-64	Bibliographical investigation according to PRISMA guidelines was conducted. All retrospective or prospective clinical studies related with the use proton therapy in benign tumors in adults such as: low grade meningioma, paraganglioma, neurinoma, pituitary adenoma, benign craniopharyngioma, and pleiomorphic adenoma were included. PubMed database was investigated without any limiting dates or interval, based on following keywords: (Proton therapy OR Proton irradiation OR Proton beam) AND (Meningioma OR pituitary adenoma OR neuroma OR craniopharyngioma OR pleomorphic adenoma OR paraganglioma). ASTRO and ESTRO congress proceedings and international journal of particle therapy, which were not indexed in Pubmed Database were ordered. The literature search was limited to “human” and “English” language. Studies with combined proton and photon therapy were excluded. These schedules were mostly favored by first generation proton therapy facilities with limited time slots access in a basic physics environment. Furthermore, papers including reports of heterogenous particle treatment or heterogenous primaries, from which it was	I	Twenty four clinical articles were included. Most studies dealt with low grade meningiomas (n=9) neurinomas (n=4), pituitary adenomas (n=5), paragangliomas (n=5) and craniopharyngioma(n=1) respectively. No study was found for pleomorphic adenomas. For nine of the 24 studies recorded, proton irradiation was delivered using active pencil beam scanning (or rasterscanning). The other studies used passive scattering (PS) technical. For each selected article, local progression free survival rate and toxicity outcomes were extracted when possible.	Proton Therapy or proton irradiation	No comparator mentioned	The reviews were published between 2007 and 2019.	<u>Low Grade Meningiomas (n=9)</u> Meningiomas are extra-axial, slow-growing tumors that arise from the arachnoid cap cells of the central nervous system. Fractionated proton therapy led to five years excellent local control rates ranging from 88% to 100%. <u>Neurinoma (n=4)</u> Neurinomas, also called schwannomas, are benign tumors that arise from Schwann cells lining the nerves. The 5-year local control rate was comprised between 87 and 98%. <u>Pituitary adenomas (n=5)</u> Ronson and Wattson reported high radiological control rates, between 98% and 100% after a 4 years follow up, whatever the proton therapy fractionation. Petit reported the overall response rate was 95% Aghi reported 58% cured. After a long term visual follow up, in Ronson series, 7 patients developed minor visual deficits and 2 patients developed major visual deficits that consisted of	

	impossible to extract precise data were excluded. Doses were reported in Gy(RBE) considering a relative biological effectiveness of proton equal to 1.1						de novo quadranopsia and bilateral optic nerve atrophy. <u>Paragangliomas (n=5)</u> Paraganglioma is a rare disease with an estimated occurrence of 2–5 patients per million per year. The largest retrospective series reported 41 patients treated with fractionated proton therapy. <u>Craniopharyngioma (n=1)</u> Only one study from Ajithkumar et al., reported a series of 16 craniopharyngioma treated with protontherapy in which 3 patients were adults. After 54 Gy(RBE) delivered and a follow up of 25 months, the 3 patients exhibited a complete radiological response.	

Evidence Table : Safety and efficacy/effectiveness
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3. Meixuan L et al. 2021.Clinical efficacy and safety of proton and carbon ion radiotherapy for prostate cancer: a systematic review and meta-analysis	Databases was searched until July 2021. Two independent reviewers assessed the quality of included studies using different tools according to different types of study design and used the GRADE approach to rate the quality of evidence. R 4.0.2 software was used to conduct the meta-analysis. A meta-regression test was performed based on the study design and tumour stage of each study. Types of Study Design: All types of primary studies.	I	Studies involved 48,765 patients with a median mean age of 66 years old. Median follow-up across all studies was 43.4 months (range 6 – 85.2 months). Including men (⩾18 years of age) diagnosed with prostate cancer (any stage) or mixed cancers were eligible if separate data for men with prostate cancer were available.	CIBT or PBT alone or combined with other therapies.	Control group intervention was photon radiotherapy including conventional RT, two- or three dimensional conformal RT, IMRT, and so on.		Overall survival (OS), local control rate (LCR), biochemical relapse-free rate (BRF), gastrointestinal (GI), and genitourinary (GU) toxicity. A total of 33 studies including 13 CIRT- and 20 PBT-related publications, involving 54,101, participants were included. The quality of the included studies was found to be either low or moderate quality. Random model single-arm meta-analysis showed that both the CIRT and PBT have favorable efficacy and safety, with similar 5-year overall survival (OS) (94 vs 92%). Incidence of grade 2 or greater acute genitourinary (AGU) toxicity (5 vs 13%), late genitourinary (LGU) toxicity (4 vs 5%), acute	

							gastrointestinal (AGI) toxicity (1 vs 1%), and late gastrointestinal (LGI) toxicity (2 vs 4%). Compared with CIRT and PBT, photon radiotherapy was associated with lower 5-year OS (72–73%) and a higher incidence of grade 2 or greater AGU (28–29%), LGU (13–14%), AGI (14–19%), and LGI toxicity (8–10%). The meta-analysis showed the 3-, 4-, and 5-year local control rate (LCR) of CIRT for prostate cancer was 98, 97, and 99%; the 3-, 4-, 5-, and 8-year biochemical relapse-free rate (BRF) was 92, 91, 89, and 79%. GRADE assessment results indicated that the certainty of the evidence was very low.	

Evidence Table : Cost/Cost-effectiveness
Question: Is proton beam therapy cost-effectiveness to be used in cancer patients?

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1. Ontario Health. Proton beam therapy for cancer in children and adults: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2021 May;21(1):1–142. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-andrecommendations/proton-beam-therapy-for-cancer-in-children-and-adults	An economic literature search was performed on July 25, 2019 to retrieve studies published from database inception until the search date. To retrieve relevant studies, a search was developed using the clinical search strategy with an economic and costing filter applied.	I	Childen and adults with cancer requiring radiotherapy. One Systematic Review or the clinical evidence reporting on 215 publications on proton beam therapy in children dan adults across 19 tumour categories/conditions.	Proton beam therapy (alone or in combination with other treatment modalities)	Photon therapy (alone or in combination with other treatment modalities), including image-guided intensity-modulated radiation therapy (IMRT), stereotactic radiation techniques, other external beam therapies, or brachytherapy	The reviews were published between 2007 and 2019.	16 studies included <u>Pediatric Tumours</u> Medulloblastoma Five economic evaluations explored the cost-effectiveness of proton beam therapy compared with conventional radiation therapy in children with medulloblastoma, using a societal and health system perspective in Sweden, the United States, and Brazil.42-46 The ICERs ranged from proton beam therapy being the dominant strategy (more effective and less costly than the comparator treatment) to costing $28,883 CAD per quality-adjusted life-year (QALY) gained ($21,716 USD/QALY gained). Four studies found that proton beam therapy is likely to be cost-effective, mainly due to reduction in adverse events such as hearing loss, reductions in intelligence quotient scores, hypothyroidism, and growth hormone deficiency.42-45 One study found that proton beam therapy was only likely to be cost-effective if more than 150 children are treated annually <u>Adult cancers</u> Head and Neck Cancer Two studies evaluated the cost-effectiveness of proton beam therapy compared with IMRT in adults with head and neck cancer, and a third study compared the cost-effectiveness of proton beam therapy with IMRT alongside chemotherapy. In each study, proton beam therapy was more effective but more costly. The ICERs ranged from approximately $5,500 CAD per QALY gained (€3,811 EUR/QALY gained) to $924,300 CAD per QALY gained ($695,000 USD/QALY gained).	

							These studies differed in terms of their study populations (type of head and neck cancer), and proton beam therapy was only found to be likely cost-effective when modelled in a population of patients aged 65 years old with head and neck cancers of all stages with an assumed risk reduction in adverse events. Lung Cancer One study evaluating the cost-effectiveness of stereotactic body radiation therapy (SBRT) compared with proton beam therapy, conventional radiation therapy, and carbon iontherapy (another alternative to photon therapy) in patients with inoperable and operable stage I non–small cell lung cancer. Proton beam therapy was dominated by SBRT: for inoperable non–small cell lung cancer, proton beam therapy was found to be both more expensive and less effective than either carbon ion or SBRT. <u>Breast Cancer</u> Three studies evaluated the cost-effectiveness of proton beam therapy in treating breast cancer. The ICERs ranged from approximately $50,000 CAD per QALY gained (€34,290 EUR/QALY) to over $191,152 CAD per QALY gained ($147,093 USD/QALY gained). Two evaluations found proton beam therapy was not cost-effective compared with conventional radiation therapy in breast cancer patients.51,52 In the studies where proton beam therapy was deemed cost-effective (in the high risk population in the third study48 and in sensitivity analyses of the other two studies51,52), the study populations were either younger or had a risk of cardiovascular disease. Lundkvist et al assessed the cost-effectiveness of proton beam therapy versus conventional radiation therapy in 55-year-old women with left-sided breast cancer over a lifetime horizon. In this study, proton beam therapy was much more costly and generated an ICER of approximately $97,200	

							CAD per QALY gained (€66,608/QALY gained). An additional study by Lundkvist et al assessed the cost-effectiveness of proton beam therapy versus photon therapy in women with left-sided breast cancer, but the target population was focused on women at high risk of cardiac disease, which yielded an ICER of approximately $50,000 CAD per QALY gained (€34,290/QALY gained). Liver Cancer One study evaluated the cost-effectiveness of proton beam therapy compared with SBRT in patients with inoperable, advanced, large hepatocellular carcinoma, over a 5-year time horizon. Proton beam therapy was found to be more costly than SBRT but led to an additional 2.61 QALYs and an ICER of $9,300 CAD per QALY gained ($213,354 New Taiwan dollar [NT]/QALY gained) and was therefore deemed cost-effective. 97% cost-effective at a willingness-to-pay threshold of $2,157,024 (NT), or approximately $100,000 CAD per QALY gained. Intraocular Melanoma One study evaluated the cost-effectiveness of proton beam therapy versus enucleation (surgery to remove the eye) and plaque brachytherapy (radiation delivered via an implant) in 59-year-old patients with intraocular melanoma, over a 5-year time horizon. Base-case results showed that both proton beam therapy and brachytherapy were more costly than enucleation. The ICER for proton beam therapy versus enucleation was reported as approximately $141,000 CAD per QALY gained ($106,100 USD/QALY gained). The ICER for plaque brachytherapy was $103,000 CAD per QALY gained ($77,500 USD/QALY gained). Base of Skull Cancer (Chordoma) One economic evaluation comparing proton beam therapy and photon therapy in seven people with base of the skull cancers. The	

							mean ICER in this study was approximately $1,700 CAD per QALY gained ($1,990/QALY gained, ranging from −$19,840 to $20,170/QALY gained in Australian dollars [AUD]). The study authors did not conduct a probabilistic sensitivity analysis to test for uncertainty in their cost-effectiveness estimates.	

PROTON BEAM THERAPY FOR THE TREATMENT OF CANCER-UPDATE

CAWANGAN PENILAIAN TEKNOLOGI KESIHATAN (MAHTAS)