EXECUTIVE SUMMARY
(Adapted from the report by LEE SIT WAI)

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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

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

Methods

Search from databases 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.

Results and conclusion:

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.

Safety and effectiveness

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 oesophageal cancer, head and neck cancer, and prostate cancer. However, the quality level of the evidence is low to very low.

Organisational issues

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.

Economic implication

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.