Establishing Proton Technology Equipment for Cancer treatment- Is this treatment cost-effective: A Rapid Health technology Assessment

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Research question

The Scope

Population	**Adult or pediatric population suffering from any type of cancer irrespective of stage**
Intervention	Proton beam therapy (PBT)
Current comparators	Current standard of care including conventional radiotherapy (CRT), Stereotactic body therapy (SBRT), Intensity Modulated Radiation therapy (IMRT), Carbonion therapy, Photon radiotherapy, Enucleation and plaque brachytherapy
Outcomes of Interest	Local recurrence - free survival, overall survival, toxicity, relapse - free survival including local recurrence, loco - regional recurrence, distant metastasis and death, quality of life and economic costs.

Key recommendation:

Based on current international clinical and cost-effectiveness evidence from peer reviewed studies and decision-making bodies, proton beam therapy in comparison to existing current clinical practice including conventional radiotherapy (CRT), Stereotactic body radiation therapy (SBRT), Intensity Modulated Radiation therapy (IMRT), Carbonion therapy, Photon radiotherapy, Enucleation and plaque brachytherapy is **recommended as cost-ineffective technology** for use in adults with different types of cancers including non-small cell lung cancer, localized prostate cancer, head and neck cancer, intraocular melanoma, breast cancer, advanced hepatocellular carcinoma, oropharyngeal squamous cell carcinoma. There is limited evidence to suggest that PBT is a clinically effective technology in comparison to current clinical practice. With randomized controlled trials to inform comparative effectiveness lacking, other approaches to estimate the effectiveness of PBT were employed for use in economic evaluations in the context of PBT. Single armed studies and observational data was used to derive efficacy estimates in 4 out of 7 economic evaluations. An alternative approach, applying risk stratification through predictive dose–response models derived from radiobiological and epidemiological studies of photon radiotherapy outcomes, was employed by two studies. Current indication for proton therapy in a few international clinical guidelines for PBT is only for a small number of cancers such as skull, spine, ocular soft tissue cancers and few pediatric cancers. No international agency has appraised the cost-effectiveness of PBT in comparison to conventional radiotherapy.

Evidence summary

- There is lack of evidence on comparative effectiveness of Proton Beam Therapy (PBT) among cancer patients.
- Less than half of published clinical studies of PBT are prospective.
- Only 10% of prospective studies of PBT are randomized. Most of the studies reporting clinical effectiveness of PBT are single armed observational studies.
- Toxicity is the most common primary endpoint in interventional studies.
- Overall, there is insufficient evidence on the efficacy, safety and feasibility of PBT as single armed observational studies cannot establish a cause-and-effect relationship between proton therapy and fewer side effects. Moreover, as most of the studies are single -centric so it is difficult to generalize the findings to a larger population.
- Multiple studies have assessed the cost-effectiveness of PBT against different modalities of radiotherapy in a high-income study context with most studies finding that PBT is a cost-ineffective alternative to photon therapy. PBT was found to be effective in certain type of cancer among subset of a population.
- Due to lack of impediment evidence on clinical effectiveness of PBT for cancer treatment, different methodological approaches are used in economic evaluations assessing the cost-effectiveness of PBT against current clinical practice i.e. photon therapy.
- One of the approaches used is deriving data from single-armed trials and observational data. The authors have meta-analyzed results from systematically identified single-armed studies to inform survival, disease progression, treatment-related death, and occurrence of grade 3–5 adverse events such as pneumonitis, oesophagitis, and irreversible dyspnoea for each of the compared interventions.
- Similarly, few studies ‘‘pooled” results of single-armed studies to inform disease progression after treatment to local recurrent and metastatic health states and to inform probability of long-term toxicities.
- Another approach used was applying risk stratification through predictive dose–response models derived from radiobiological and epidemiological studies of photon radiotherapy outcomes. This approach has been used by 2 out of 7 economic evaluations. For instance, Ramaekers et al 2012 estimated risk of suffering xerostomia and dysphagia after intensity

modulated radiotherapy (IMRT) and PBT at an individual patient level using dosimetry data from a comparative planning study of 25 patients (oropharyngeal (n = 21) and hypo-pharyngeal (n = 4)) linked to normal tissue complication probability (NTCP) models.

- Another study by Mailhot Vega et al 2015 used the similar approach and estimated bounds for cost-effective treatment depending again on dosimetry and baseline patient characteristics.
- Furthermore, approaches and sources used to estimate proton related treatment costs ranged across studies in relation to their jurisdiction and perspective.
- Two out of seven HTA studies have conducted their analyses from a health-care perspective, making use of a previous costing analysis. Capital and operational costs of constructing and running a proton facility were incorporated as well as various other assumptions on rate of use and case-mix. A similar costing approach was used in another two studies by Mailhot Vega et al 2015 and Sher et al 2018 from a US societal perspective.
- Sher et al 2018 and Parthan et al 2012 also used medicare reimbursement rates to estimate cost per treatment from a payer perspective. The latter also incorporated an estimate of the age-specific opportunity cost of lost time due to radiotherapy into a societal analysis. Medicare reimbursement rates were also used by Moriaty et al 2015 who then applied an adjustment to account for discrepancies between billed charges and actual resource use for a provider perspective. Finally, Leung et al. simply used insurance reimbursement package for PBT.
- Current indication for proton therapy in various international clinical guidelines for PBT is only for a small number of cancers such as skull, spine, ocular soft tissue cancers and few pediatric cancers.
- No international agency has appraised the cost-effectiveness of PBT in comparison to conventional radiotherapy.
- There are significant concerns on whether cost-effectiveness findings of PBT from a high-income context can be transferred to India considering resource use and economic costs will be significantly different across private and public providers in different states of India.

Disclaimer - all recommendations are based on current evidence in the public domain.

Background

There is growing interest in the use of proton beam therapy (PBT) for the treatment of cancer. Unlike traditional photon based radiotherapy, protons release most of their dose at the end of their range, limiting proximal and distal irradiation. PBT therefore has the potential to reduce unwanted irradiation of normal tissues, enabling higher treatment dose for better tumor control or greater normal tissue sparing to reduce treatment-related toxicities. **T**he costs of delivering PBT are significant, with up-front capital expenditure far greater than that of a photon unit. Although there has been steady growth in the number of centres over the past decade, with more than 70 now operational world-wide and another 40 under construction, the availability of treatment remains limited.

Given the limited capacity and higher costs, decisions on which radiation therapy should be used to treat cancer patients should be based on comparisons of proton therapy against current best practice. This is typically performed through health economic evaluation (HEE). Reliable evidence of the relative cost-effectiveness of both modalities can only come from the results of randomized clinical trials. Since comparative effectiveness research is often scarcely available for innovative radiation therapy techniques, which makes it challenging to examine cost-effectiveness. Therefore, we have attempted a review of existing literature on clinical effectiveness of PBT relative to other available modalities for radiation therapy. Furthermore, existing literature on health economic evidence and recommendations of various international guidelines was being reviewed using methods for rapid health technology assessment.

Evidence

Systematic Reviews & Meta-Analysis: Clinical effectiveness

	Systematic Review – Ofuya et al, 2019	**Systematic review and meta-analysis - Grutters et al, 2009**
Indication	Adult or pediatric population suffering from any type of cancer irrespective of cancer stage.	Adult or pediatric population suffering from non-small cell lung cancer
Link to source	https://www.ctro.science/article/S2405-6308(19)30085-0/fulltext	https://sci-hub.mksa.top/10.1016/j.radonc.2009.08.003
Intervention	Proton beam therapy (standard dose of 70 Cobalt Gray equivalents (CGE). Few studies have also assessed the effect of a reduction in PBT dose from standard 70 to 50 CGE on treatment outcomes.	Particle therapy (proton and carbon ion therapy)
Comparator	Photon therapy, Chemotherapy, Carbon ion therapy, Trans-arterial chemo-embolization, Trans-pupillary thermotherapy	Conventional radiotherapy and Stereotactic body radiation therapy
Primary Outcome	There were three types of primary outcomes reported in the studies namely toxicity-related endpoints-acute and late toxicity, efficacy related such as progression free survival, overall survival and local failure, and composite or co-primary endpoints namely toxicity and feasibility of treatment delivery, toxicity and local recurrence/disease control and disease-free and overall survival.	Primary outcomes were 2- and 5-year overall and disease-specific survival rates
Secondary Outcomes	Patient reported outcome measures	Secondary outcomes included occurrence of grade 3/4 pneumonitis, grade 3/4 oesophagitis, grade 3/4 irreversible dyspnoea and grade 5 adverse events (treatment-related death).
Study Contexts	Includes low income countries (LICs), lower-middle income countries (LMICs), Upper-middle income (UMICs)and High-income countries (HICs)	Includes low income countries (LICs), lower-middle income countries (LMICs), Upper-middle income (UMICs)and High-income countries (HICs)
Reference period	1979-2018	1994-2008

No of studies	219 studies included in the review. These include 130 retrospective (medical records=117, cancer database/registry=8, past prospective study data=2, no source stated=2) and 89 prospective studies (43 interventional and 46 observational). Among 43 interventional studies, 8 randomized controlled trials (phase II-5 and Phase III-3) were included.	Search on CRT and SBRT found 22 articles (11 each). The particle therapy review resulted in 5 studies on proton therapy and 3 studies on carbon ion therapy. There was non-randomized controlled trial included in the review. All studies were single armed except one non-randomized trial by Bush et al wherein the patients were assigned to treatment arm based on cardiopulmonary function and results were presented for total group only.
Follow up duration	Follow-up period was mentioned in 79 out of total 89 prospective studies. Follow-up period ranged from 4 days to 191 months. This includes observational: 4 days-191 months; phase I/feasibility/pilot:2-97 months; phase I/II: 2-104 months; phase II-2-150 months; phase III-3-139 months. In 38% studies, authors recommended an increase in length of follow-up in patients treated with PBT.	Median follow up ranged between 12-91 months in different studies
Recurrence (local or distant)	Only one study by Liao et al 2018 compared Intensity Modulated Radiotherapy (IMRT) versus Passive scattering proton therapy (PSPT) among non-small cell lung cancer (NSCLC) adult patients aged 33-85 years. The primary endpoints were grade≥ 3 radiation pneumonitis (RP) and local failure (LF). No statistically significant difference in the primary endpoints after IMRT or PSPT for patients with locally advanced NSCLC. No benefit in grade≥ 3 RP or LF after PSPT was found as PSPT was not associated with improved lung dose-volume indices. However, PSPT was found to be associated with significant reduction in heart exposure in terms of both radiation dose and heart volume. The influence on cardiac toxicity and OS is under active investigation in various phase II and III trials. The magnitude of improvement in RP for patients enrolled after study midpoint was greater (13.1% rate) and statistically more significant in the PSPT	No information

	arm as compared to IMRT(18.2% incident rate).	
Survival (cancer-specific or overall)	The median overall survival time was 29.5 months for patients in the IMRT group and 26.1 months for patients in the PSPT group (p value 0.297). The posterior probability of IMRT being better than PSPT was 0.54. No significant difference in breast cancer-specific survival (n = 3 studies with 673 breast cancer deaths in 5685 women): Hazard Ratio 0.91 (95% CI 0.78 to 1.06).	The corrected 2-year disease-specific survival estimates were 67% (95% CI: 59–76%) for CRT, 83% (95% CI: 75–92%) for SBRT, 74% (95% CI: 61–87%) for proton therapy and 82% (95% CI: 70–93%) for carbon-ion therapy. The corrected pooled estimates for 5-year overall survival were 19% (95%CI: 15–24%) for CRT, 42% (95% CI: 34–50%) for SBRT, 40% (95% CI: 24–55%) for proton therapy and 42% (95% CI: 32–52%) for carbon-ion therapy.
Safety	No significant differences were observed in toxicity rates between PSPT and IMRT.	The SBRT studies also reported more adverse events than the proton and carbon-ion studies, which is only partly attributable to the lower number of patients at risk in the particle therapy studies. Particle therapy resulted in no grade 3/4 oesophagitis, dyspnoea or treatment-related deaths, while only 4 out of 336 patients with stage I NSCLC treated with particle therapy had grade 3/4 pneumonitis.
Resource Use or Costs	No data was found with respect to costs.	No data was found with respect to costs.
Health Related Quality of Life	Sio et al 2016 compared patient reported outcome measures among oropharynx cancer treated with IMPT Vs IMRT. No difference in two groups in acute phase. Improved PROs in IMPT group with taste and appetite (P < .05) in subacute phase. Improved PROs in IMPT group with appetite (P= .04) in chronic phase. Average of highest 5 parameters statistically non-significant between groups in acute or chronic phases, statistically significantly improved with IMPT (P=.01). Less moderate-severe taste and mucus in IMPT group during subacute phase. Wang et al 2016 compared PROs among non-small cell lung cancer patients on PBT, 3-DCRT, IMRT. They reported that symptomatic PROs during and after higher for PBT treated patients over IMRT and 3DCRT.	

Conclusion	This review indicates that there is limited randomized evidence on benefits of PBT over existing standard clinical practice. Few ongoing trials assessing clinical effectiveness of PBT against photon therapy will be critical for addressing the gaps in the literature and provide additional evidence on efficacy of PBT relative to photons	The results of this meta-analysis of observational studies reported that particle therapy results in higher survival rates than CRT in stage I inoperable NSCLC patients. However, the survival rates of particle therapy are almost equal to those of SBRT in these patients. Based on the currently available data, although preliminary results show a trend towards less adverse events with particle therapy than with photon therapy, no firm conclusions can be drawn on the reduction of side effects after particle therapy. Particle therapy may be more beneficial in stage III NSCLC, where 2-year survival is only 26–36% with concurrent chemoradiation with photons, and severe adverse events occur more frequently. However, more evidence is needed on whether particle therapy is actually beneficial in advanced stage NSCLC.

Clinical Guidelines

	NICE Interventional Procedures	International Lymphoma Radiation Oncology Group (ILROG)	National Comprehensive Cancer Network	American Society of Clinical Oncology and American Society for Radiation Oncology	European Society for Medical Oncology
Title	Proton beam therapy for the treatment of malignant brain tumors and prostate cancer is currently being monitored (1047/1 and 1231/1)	The use of proton therapy in adults with mediastinal lymphomas and for young women is recommended. In young adult women, proton therapy delivers reduced breast dose, thus reducing the risk for secondary breast cancer. The ILROG also recommends proton therapy in heavily pretreated patients who are at elevated risk for radiation-related toxicity to the heart, lungs, and/or bone marrow.	NCCN GUIDELINES ON PROTON THERAPY	ASTRO Model Policies-Proton Beam Therapy	No recommendation on PBT due to lack of clear evidence on benefits associated with PBT
Link	https://www.nice.org.uk/guidance/ng101/chapter/Recommendations#radiotherapy	https://pubmed.ncbi.nlm.nih.gov/30898780/	http://tncancerpatient.org/wp-content/uploads/2018/05/NCCN-Guidelines-on-Proton-Therapy-042318-PV.pdf	https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf	https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2819%2931287-6
Is Proton Beam therapy recommended within the clinical guideline?	No	Yes	Yes	Yes	No

Description of the intervention in the clinical guideline.			NCCN Panel recommends for chondosarcomas of the skull base and axial skeleton, cancer of the nasopharynx, nasal cavity, or paranasal sinuses, cranio-spinal irradiation. No significant differences between charged particle therapy and SBRT were found in hepatocellular carcinoma patients for PFS, loco-regional control and OS. The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray based regimens at	On the basis of the published clinical data, PBT is recommended for following disease sites: • Ocular tumors, including intraocular melanomas • Tumors that approach or are located at the base of skull, including but not limited to: • Chordoma •Chondrosarcomas • Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated • Hepatocellular cancer • Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply	NA

			clinics with appropriate technology, physics, and clinical expertise. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.		

Health Economic Evidence

- No international agency has appraised the cost-effectiveness of proton beam therapy in comparison to photon therapy.
- Current indication for proton therapy in various international clinical guidelines for PBT is only for a small number of cancers such as skull, spine, ocular soft tissue cancers and few pediatric cancers.
- Majority of the economic evaluations have reported PBT as a cost-ineffective technology among various types of cancers. Few studies suggested PBT to be cost-effective in a population sub-group. For instance- a study by Sher et al 2018 found that IMRT was the cost-effective modality. However, it also found that IMPT has the potential to be cost-effective for younger patients with a favorable prognosis if its actual quality-of-life benefits are at the extreme ends of superiority over IMRT.
- There are significant concerns on whether cost-effectiveness findings of PBT from a high-income context can be transferred to India considering lack of randomized controlled trial data on comparative effectiveness of proton and photon therapies. Furthermore, the cost-effectiveness analyses have compared proton therapy only among a particular type of cancer patients. The effectiveness of proton therapy varies significantly across different cancer sites based on data from observational studies.
- The transferability of HTA can occur only in case we are looking at specific type of cancer which has also been under focus in previous health technology assessment across the world.
- Furthermore, resource use and economic costs will be significantly different across different countries. The infrastructure cost of proton therapy unit depends on various factors and hence it may not correct to do HTA transfer.
- Further research on the costs, clinical efficacy and safety of PBT and cost-effectiveness of PBT compared to conventional radiotherapy should be explored by researchers in India.

Health Economic evidence: Summary of economic evaluations

Study and year	Country	Cancer type	Interventions assessed	Stated Perspective	Reported main result
Grutters et al 2010	The Netherlands	Inoperable stage I non small cell lung cancer	PBT, carbon ion therapy, CRT, and SBRT	Dutch health Care perspective	CRT dominated by carbon-ion therapy and SBRT ICER for carbon-ion versus SBRT: €67,257
Parthan et al 2012	USA	Localized prostate cancer	PBT, IMRT, and SBRT	Health care payer and societal	PBT and IMRT dominated by SBRT in both perspectives
Ramaekers et al 2013 Dutch	The Netherlands	Locally advanced (stage 3–4) head and neck cancer	PBT for all patient, IMRT for all patients, and PBT if efficient	health Care perspective	ICER for PBT if efficient versus IMRT for all: €60,278 ICER for PBT for all versus IMPT if efficient: €127,946
Moriaty et al 2015 ICER for PBT	USA	Intraocular melanoma	PBT, enucleation, and plaque brachytherapy	Provider perspective	ICER for PBT versus enucleation: $106,100 ICER for plaque brachytherapy versus enucleation: $77,500 ICER for PBT versus plaque brachytherapy not reported
Mailhot Vega et al 2016.	USA	Breast cancer	PBT and photon radiotherapy	Societal perspective	In base case analysis with $50,000 threshold: Women with no CRFs: PBT not cost effective for all ages and for all photon MHD tested (up to 10 Gy) Women with CRFs: PBT cost-effective for 50- and 60-year-old women with MHD of 9 Gy and 10 Gy respectively In base case analysis with $100,000 threshold: Women with no CRFs: PBT cost-effective for 40- and 50-year-old women with MHD of 10 Gy and 9 Gy respectively Women with

					CRFs: PBT cost-effective for 40-, 50- and 60-year-old women with MHD of 6 Gy, 5 Gy and 6 Gy respectively
Leung et al 2017	Taiwan	Inoperable advanced hepatocellular carcinoma (large tumours)	PBT and SBRT	Single payer healthcare system	ICER for PBT versus SBRT: NT$ 213,354 (equivalent to US $14,180 in 2016 prices)
Sher et al 2018	USA	Oropharyngeal squamous cell carcinoma	PBT and IMRT	Payer perspective and societal perspective	HPV-positive patients: ICERs for PBT versus IMRT: $288,000 and $390,000 in the payer and societal perspectives respectively HPV-negative patients: ICERs for PBT versus IMRT: $516,000 and $695,000 in the payer and societal perspectives respectively

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