REVIEW

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A Systematic Review of the Economic Burden of Proton Therapy in Head and Neck Cancer

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Abstract

Background: Radiation therapy is used to treat head and neck cancer (HNC) patients. Proton beam therapy (PBT) is one of the newer treatment options. This systematic review will describe the cost and cost-effectiveness of PBT compared with other first-line treatment options based on available literature and provide a better understanding of its usage in HNC in the future. **Methods:** This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Systematic searches were conducted in PUBMED, EMBASE and SCOPUS till February 2022. Original pharmacoeconomic articles written in English that considered PBT for HNC were included; the title, abstract and full text of the search items were screened. The included studies were critically appraised using the Drummond Checklist followed by data extraction. **Results:** Eight of the ten included studies were of good quality; most were cost-effectiveness or cost comparison studies and used the Markov model and lifetime horizon. The dominant comparator was intensity-modulated radiotherapy. The willingness to pay threshold ranged from $30,828 to $150,000 per QALY. The incremental cost-effectiveness ratio (ICER) was between $4,436.1 and $695,000 per QALY. In HNC patients with human papillomavirus infection, the ICER was lower ($288,000/QALY) from the payer's perspective, but much higher ($390,000/QALY) from the societal perspective. **Conclusion:** Our systematic review showed that appropriate patient selection can make PBT cost-effective. HPV-associated tumors can be cost-effectively treated with PBT. From the payer's perspective, PBT is a cost-effective treatment option. In younger patients, PBT can result in lesser incidence of adverse effects, and hence, can reduce the subsequent need for long-term supportive care. Lower fractionation schedules can also make PBT a cost-effective treatment.

Keywords: Proton beam therapy- head and neck cancer- radiation therapy- cost effectiveness- economic evaluation

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Introduction

Head and neck cancer (HNC) is the seventh most common malignancy in the world with an annual incidence of 800,000 cases and 300,000 deaths (Kawakita et al., 2022). South and Southeast Asia have the highest malignancy rates (Argirion et al., 2019); India currently accounts for roughly 60% of all HNC cases worldwide., and this number is projected to double by 2030 (Prabhash et al., 2020). In the United States (US), 53,000 new cases of HNC and 10,860 fatalities were reported in 2019 (Siegel et al., 2019).

Currently, whether used as the main treatment or as an adjuvant after surgical resection, radiation helps around 75% of patients with HNC (Alfouzan 2021). However, developments in newer targeted therapies over the past two decades coupled with increasing experience in the use of radiation therapy have made more treatment options available for an individual patient and increased the complexity of decision-making. Radiation exposure to vital bodily structures is decreased by intensity-modulated radiation treatment (IMRT), which offers a precisely targeted dose distribution. It was demonstrated in a randomized trial that IMRT performed better than conventional therapy in improving xerostomia (Grutters et al., 2010; Nutting et al., 2011). Protons rather than photons are used to administer the dose in intensity-modulated proton therapy (IMPT), a more contemporary delivery method for proton beam treatment (PBT) (Lukens et al., 2015).

PBT was established for use in radiotherapy to target tumors with proximity to vital anatomical structures. This method enables the radiation energy to be accurately focused at a given depth, resulting in dosage reduction. It differs from external photon (x-ray) radiotherapy in that it allows the radiation dose delivered to the tumour area to be increased without a corresponding increase in exposure to the surrounding healthy tissues (Alfouzan 2021). In patients with nasal cavity, paranasal sinus, and nasopharyngeal cancer, dosimetric comparisons of

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IMPT with IMRT indicate better sparing of the parotid glands, oral cavity, oesophagus, and larynx (Holliday et al., 2016; Jeremic et al., 2021). Therefore, IMPT's dosimetric advantages can lessen the radiation toxicity, both acute and long-term, in patients with HNC (Moreno et al., 2019). PBT delivery, on the other hand, necessitates sophisticated equipment and is far more expensive than photon-based therapy.

Over the past decade, a large number of centres equipped to offer IMPT have been established, with more than 70 now in operation and another 40 in various stages of development globally (Jones et al., 2019). PBT is now more widely available, and as a result, more clinical evidence demonstrating its significance and efficacy has been produced (Verma et al., 2016). With the available resources and cost associated with proton therapy, information regarding cost and cost-effectiveness is potentially crucial for healthcare decision-makers The available evidence is limited and a thorough systematic review and assessment of available studies including studies based on modeling could potentially help to identify areas for further research. Though the benefits of proton therapy have been shown in the treatment of HNC, there is still doubt and debate over the potential eventual role of PBT in disease management given the paucity of level 1 evidence for PBT in HNC (Gunn et al., 2016; Mody et al., 2021). The debate appears to have centered on cost-effectiveness and cost-competitiveness in recent years. From the standpoint of global health, PBT's cost is not outrageous and shouldn't be used as an excuse to deny our patient's potentially curative and less toxic therapies (Lievens and Van den Bogaert 2005). Even though PBT is currently expensive, it may become far less expensive if the initial built-in cost recovery is not considered. The additional cost of PBT can be justified only if it provides a significant clinical benefit. This needs an understanding of the outcomes and dose distributions to specific cancer sites (Goitein and Jermann 2003). Extensive pharmacoeconomic evaluations on proton therapy were carried out for prioritized sites, basically pediatric tumors and base of skull cancers, but not for head and neck cancers which is one of the important sites (Ontario Health 2021; Austin et al., 2019). This systematic review is an attempt to describe the cost and cost-effectiveness of IMPT compared with other treatment modalities based on data from published studies in HNC.

Materials and Methods

The protocol was entered into PROSPERO under the registration number CRD42022306597 (Accessible from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022306597). We used a particular search strategy (https://sites.google.com/view/searchstragegypbt/home) to conduct systematic searches in PUBMED, EMBASE, and SCOPUS, three electronic bibliographic databases, from January 2011 to February 2022.

Original articles for cost studies that only consider PBT for HNC treatment, pharmacoeconomic studies (cost-effectiveness, cost-minimization, cost-benefit analyses and cost-utility), and cost comparison evaluations that take into account both proton therapy and comparators, regardless of the comparator or comparator(s), for HNC treatment were incorporated in the review. Articles published in the aforementioned time period in the English language from any nation were taken into consideration.

The following studies were excluded: editorials, commentaries and systematic reviews; preclinical and other research that did not fall under the aforementioned categories; studies whose objectives did not include economic evaluation cost comparison or economic evaluation, such as budget impact analyses, the burden of disease or cost of illness.

First, the article titles and abstracts were reviewed separately by two authors; any discrepancies in the screening were settled by the third author. The entire studies that were qualified were also analyzed for relevance. A Microsoft Excel sheet was used to define and record the coding for the inclusion criteria and the exclusion criteria for each step. Finally, references of all the shortlisted studies were screened for any additional studies that met the inclusion/exclusion criteria.

The Drummond Checklist was used by two authors to critically evaluate the included research impartially (Drummond 2005). The primary outcomes, including incremental cost-effectiveness ratios (ICERs), cost per treatment and cost/quality-adjusted life year (QALY), were extracted into a pre-piloted, standard format by two authors independently, and any discrepancies were settled by the third author. Additional outcomes like cost per treatment, methods/ source utilized to calculate the cost, efficacy/ effect of therapy, methods/ source used to estimate effectiveness, benefits, discount rate, time horizon; standard outcomes for cost-utility and cost-effectiveness analysis, analysis of sensitivity, willingness to pay (WTP) threshold or uncertainty measures, expected reported value of perfect value, the pharmacoeconomic evaluation type, analysis type and utilities were also obtained in a similar manner.

Results

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart is illustrated in Figure 1.

Characteristic features of pharmacoeconomic literature included in the systematic review

Characteristic features of the pharmacoeconomic literature are presented in table 1 and table 2. The included studies were hosted in the USA, the Netherlands, China and Sweden. All the studies used the Markov model as the study design except for two studies that used case control. Eight studies compared proton therapy (IMPT, PBT) with photon therapy (IMRT). One study compared PBTwith both photon and combined therapy and one study compared PBT with conventional radiation.

Four evaluations were conducted using the payer's perspective, two used the provider's perspective, two used the societal perspective and one used both the payer and the societal perspective. Two studies from USA done from a payer perspective showed comparable

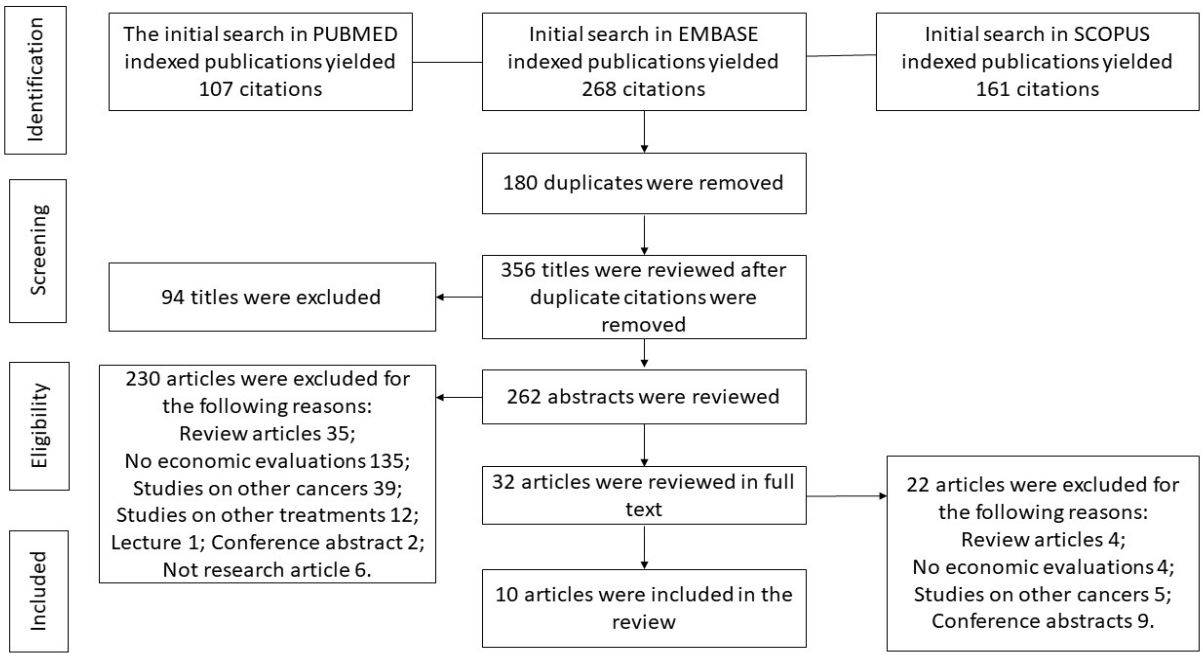

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart is Illustrated

ICER of $288,000–516,000/ QALY and $361,405/ QALY respectively. Two reports from China, conducted from different perspectives - payer and societal, also showed comparable ICER of $ 23,611.2 to 74,440.1/QALY and $4,436.1 to 102,684/QALY. When evaluated in the same study under two different perspectives, ICER was found to be reduced in both HPV positive and HPV negative status in the payer perspective ($ 288,000/QALY, $ 516,000/

Table 1. Features of Incorporated Pharmacoeconomic Evaluations

Author	Study design	Economic perspective	Population	Intervention (Number of patients)	Comparator (Number of patients)
Thaker et al., 2021	Retrospective case-control study	Payer	Adult patients (age range, 37-83) with OPC	IMPT (25)	IMRT (Cross matched 25)
Sher et al., 2018	Markov model	Payer (Medicare) and societal	65-year-old male with OPC T2 N2	35 fractions of bilateral chemoradiotherapy IMPT 70 Gy/7 wk, 5 fractions/ wk with bolus cisplatin (50,000 iteration trials)#	35 fractions of bilateral chemoradiotherapy IMRT 70 Gy/7 wk, 5 fractions/wk with bolus cisplatin (50,000 iteration trials)#
Ramaekers et al., 2013	Markov model	Health care	Stage III and stage IV HNC (pharyngeal, oral cavity and laryngeal cancer), ~ 61 years of age at the start of radiation therapy	IMPT (25)	IMRT (25)
Peeters et al., 2010	NA	Hospital	skull base chordoma, prostate, lung and HNC	1810 patients/year (based on assumptions, literature and expert opinion) for a combined facility	1618 patients/year for the proton-only facility, 2287 patients/year for the photon facility
Li et al., 2022	Markov model	Societal	Male patient aged 43 years with undifferentiated nonkeratinizing stage III (T2N2M0) nasopharyngeal carcinoma	IMPT (50000 iteration trials)#	IMRT (50000 iteration trials)#
Cheng et al., 2016	Markov model	NA	Head and neck cancer patients	IMPT (23)	IMRT (23)
Brodin et al., 2021	Normal tissue complication probability model	Payer*	Oropharyngeal cancer patients	IMPT 33 fractions (33)	IMRT 33 fractions (33)
Lunkdvist et al., 2009	Markov model	Societal *	Breast cancer (55-year female), prostate cancer (65-year male), HNC (65-year), medulloblastoma (5-year child)	Proton therapy (300 for each indication except 25 for medulloblastoma)	Conventional radiation (300 for each indication except 25 for medulloblastoma)
Ning et al., 2020	Case-control study	Payer	9 HNC, 8 prostate, 3 breast, 2 thoracic cancer	Proton therapy (17)	Photon therapy (17)
Li et al., 2020	Markov model	Payer*	47-year-old Tumor stage T3N1M0, Stage III nasal cavity cancer and paranasal sinus cancer	IMPT (50,000 iteration trials)#	IMRT (50,000 iteration trials)#

*Suggests that perspective was assumed by the author based on data from the selected article. # Over 50,000 iteration trials were performed in a probabilistic sensitivity analysis to estimate the 90% confidence interval for the model parameters. IMPT, Intensity-modulated proton therapy; IMRT, Intensity-modulated radiation therapy; HNC, Head and neck cancer; OPC, Oropharyngeal cancer; NA, Not applicable; T, Tumour; N, nodes; M, metastases

Table 2. Features of Incorporated Pharmacoeconomic Evaluations

Author	Source/Methods to estimate costs	Source/Methods to estimate effectiveness, benefits	Time Horizon, Discount rate and standard reporting outcomes for cost-effectiveness or cost-utility analysis	Willingness to Pay the Threshold	Performance of Probabilistic Sensitivity Analysis or other measures of uncertainty	Expected Value of Perfect Information if reported	Utilities
Thaker et al., 2021	IMPT- Prospectively collected database from 2011-2012. IMRT- Institutional database 2000-2009. Hourly compensation for personnel, direct and indirect costs based on hospital costing approach, depreciation cost were considered.	NA	From the first consultation to 30 days after RT is terminated.	NA	TDABC expenses were modified according to FY2019 inflation. The need for gastrostomy tubes was considered.	NA	NA
Sher et al., 2018	Costs/ patient (Medicare payment 2016 schedule) Monthly costs post-recurrence (previous literature)	Literatures	Lifetime horizon used. 3 % annual discount rate for QALY and Cost. cycle length was 1 month. QALY, ICER measured.	$100,000 per QALY and $150,000per QALY	Assumed symmetric triangular distributions (from 0% - 50%) 25% mode for I-year reduction dysgeusia, PEG, and xerostomia. The impressive improvement (50%) in this distribution was considered a "best-case scenario," to intentionally favor the more expensive therapy.	For 65-year-old patients, the mean net monetary benefit of perfect information was $0 in both perspectives at a societal WTP of $100,000/QALY. Over a 30-year period, at a societal WTP of $150,000/ QALY, the total value of information was $247,000 from the payer perspective and $0 dollars from the societal perspective.	CRT (first 3 mo), Base NED (after 3 mo), Base NED with PEG (first 2 y), Base NED with PEG, (after 2 y), Dysgeusia disutility, Xerostomia disutility, DM, Dead
Ramaekers et al., 2013	Price/ unit and use of resources depended on guidelines, the cross-sectional survey, or expert opinions. IMPT treatment cost was calculated by multiplying IMRT treatment cost with a 2.1 cost ratio. To consider IMPT-if efficient, IMRT and IMPT plans were compared for each dose distribution and decide upon the most efficient treatment per patient. Therefore, the costs of an extra treatment plan (€88) were added for this strategy. A half-cycle correction was applied for QALYs and costs.	The occurrence of xerostomia and/or dysphagia was estimated according to 2 available NTCP models. The proportion of patients who had both xerostomia and dysphagia was calculated using conditional toxicity probabilities from a cross-sectional survey. Scoring for the utility was sourced from cross-sectional research (with n = 396) by using a Dutch Euroqol 5D questionnaire in HNC patients. Utility scoring were added with the life expectancy to derive QALY.	Lifetime horizon used. The future QALY and the costs were further discounted by 1.5 and 4.0 %, respectively. Costs were converted to 2010 money value. Expected mean costs, toxicity occurrence, disease and toxicity free life- years, QALYs, ICER.	€80,000/ QALY	Assigning distribution to the input parameters	The population EVPI was calculated by multiplying EVPI/ patient by the capable population in the next decade (expected lifetime of the technology) and at a 4% discount rate	Utility scoring ranged from 0 - death to 1 - full health
Peeters et al., 2010	Estimates for the input parameters based on literature, business plans Maastro Clinics, and report from Belgian on hadron therapy. Data on the staffing, workflow, and costs/ personnel according to the Netherlands. Construction and equipment expenses rely on pat projects by Townsend and Turner construction and management consultants.	NA	NA	NA	Sensitivity analysis done for costs and treatment utilization. Capital costs, operational costs, lifetime of the facilities, patient throughput, time per fraction, treatment hours per day, treatment room availability, treatment room utilization, energy costs, interest rate and patient mix.	NA	NA
Li et al., 2022	Literature, assumptions, calibration, institutional data	Literatures	Lifetime horizon, All the costs and the QALY were discounted at a 3% annual rate. ICER	$ 33558 per QALY, $ 50000 per QALY and $ 100000 per QALY	Probabilistic sensitivity analysis to assess the model's robustness in light of a joint uncertainty for this parameter (cost and utility) after running around 50000 repetitive trials	NA	State of health utilities for the states such as "no complication"; "dysphagia," "xerostomia," "hearing loss," and combinations thereof; "death" ranging from 0 to 1.

Table 2. Continued

Author	Source/Methods to estimate costs	Source/Methods to estimate effectiveness, benefits	Time Horizon, Discount rate and standard reporting outcomes for cost-effectiveness or cost-utility analysis	Willingness to Pay the Threshold	Performance of Probabilistic Sensitivity Analysis or other measures of uncertainty	Expected Value of Perfect Information if reported	Utilities
Cheng et al., 2016	Incorporated reported the Markov model to evaluate the cost of the therapy.	incorporated reported the Markov model to evaluate the QALY of the therapy.	NA	80,000€ per gained QALY	NA	NA	Pretreatment RTOG- 2nd grade (xerostomia and swallowing malfunction)
Brodin et al., 2021	The cost of therapy is determined from the 2017 CMS national Medicare average physician price structure reimbursement amounts. Prices for medical operations, emergency visits, and inpatient hospital stays were taken from the US national statistics or published publications. Drug treatment costs were taken from database (the US National Average Drug Acquisition Cost). Based on data from the 2018 Census Bureau, the cost of lost income is calculated using the US median per capita income.	NA	A standard discounting rate of 3 %/year. All the costs were standardized to the year 2018 timeframe. ICER	NA	One-way sensitivity analysis (proportion of chronic dysphagia, cost of proton therapy), Full sensitivity analysis (critical assumptions of QALY and cost-effectiveness calculation steps)	NA	1 represented perfect health and 0 represented death.
Lunkdvist et al., 2009	Assumption based on published literature	Swedish cancer registry between 1986 and 1995. Based on earlier data, a 24% mortality risk deduction of as presumed for proton therapy.	From diagnosis until death or till 100 years.	NA	Estimates based on the standard case, high and low proton radiation cost, 50%, 75% and 90% less favourable hazard rate, 25% and 50% more favorable hazard rate, No dentistry cost savings	NA	Quality weight (utility) with 0 signifying death and 1 full health.
Ning et al., 2020	Value-based analysis	NA	1-month pretreatment through 6 months posttreatment	NA	NA	NA	NA
Li et al., 2020	Based on local data	Literature	Lifetime horizon, Cost and QALY were all discounted at a 3% annual rate. Cost/ treatment, ICER and patient age	Societal WTP of China ($30,828/ QALY).	Transition probabilities-(IMPT eradicating cancer, IMRT eradicating cancer, “no cancer” - “alive with cancer”, “alive with cancer” - “death”)	NA	Cancer-free, living with cancer, and deceased

IMPT, Intensity,modulated proton therapy; IMRT, Intensity,modulated radiation therapy; WTP, willingness,to,pay threshold; QALYs, quality,adjusted life,years; ICER, Incremental cost,effectiveness ratio; NA, Not applicable; TDABC, Time Driven Activity Based Costing; PEG, percutaneous endoscopic gastrostomy; RTOG, Radiation Therapy Oncology Group; CRT, chemoradiotherapy; NED, no evidence of disease and DM, distant metastasis

Table 3. Quality of Incorporated Pharmacoeconomic Evaluations

Author	Was a well-defined question posed in answerable form? Yes / No / Can't tell	Was a comprehensive description of the competing alternatives stated (i.e. Could you identify who performed what to whom, how frequently and where)? Yes / No / Can't tell	Was the effectiveness of the programme or services established? Yes / No/ Can't tell	Were all the important and relevant costs and consequences for each alternative identified? Yes / No / Can't tell	Were costs and consequences measured accurately in appropriate physical units? Yes / No / Can't tell	Were costs and consequences valued credibly? Yes / No / Can't tell	Were costs and consequences adjusted for differential timing? Yes / No / Can't tell	Was an incremental analysis of costs and consequences of alternatives performed? Yes / No / Can't tell	Was allowance made for uncertainty in the estimates of costs and consequences? Yes / No / Can't tell	Did the presentation and discussion of study results include all issues of concern to users? Yes / No / Can't tell	Total score
Thaker et al., 2021	Yes	Yes	No	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	8
Sher et al., 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Ramaekers et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Peeters et al., 2010	Can’t tell (the aim was to determine the cost of treatment)	Can’t tell	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Li et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Cheng et al., 2016	Yes	No	Yes	Can't tell	Can't tell	can't tell	No	No	Yes	No	3
Brodin et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Lunkdvist et al., 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	8
Ning et al., 2020	Yes	Yes	No	Yes	No	Yes	No	No	No	No	4
Li et al., 2020	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8

Table 4. Principle Findings of Incorporated Pharmacoeconomic Evaluations

Author	Incremental cost-effectiveness ratios (ICERs)	Cost per treatment	Type of economic evaluation	Conclusion
Thaker et al., 2021	NA	TDABC range, mean ± SD for IMRT: 1.00–3.33, 1.65 ± 0.56; for IMPT: 1.88–4.32, 2.58 ± 0.39 (P, 0.05)	Partial economic evaluations assessing the cost	The main reason why IMPT is more expensive than IMRT on average is because of higher equipment expenses, although a subset of IMRT patients have expenditures that are comparable to IMPT patients because they require supportive care resources more frequently.
Sher et al., 2018	In terms of payer's and societal perspectives, the ICER for proton therapy in HPV-positive patients is $ 288,000/QALY and $ 390,000/ QALY, respectively. From the payer's and societal perspectives, HPV-negative patients ICER is $ 516,000/QALY and $ 695,000/QALY, respectively.	IMRT $23,137 (payer) and $27,192 (societal) IMPT $45,457 (payer) and $56,659 (societal)	CEA	IMPT is cost-effective only from Payer's perspective if it significantly reduces the long-term morbidity in the younger population; not cost-effective from the societal perspective
Ramaekerset al., 2013	When IMPT if efficient (expected to be cost-effective) was compared with IMRT for all the patients an ICER of € 60,278 / QALY was calculated. When IMPT for every patient was compared with the IMPT if found efficient, an ICER of € 127,946 / QALY was calculated.	IMRT for all patients € 41,038 (38,878–44,158); IMPT if efficient 43,650 (41,523–46,949); IMPT for all patients 50,989 (48,227–54,852)	CEA	IMPT is only cost-effective carefully chosen patients based on a reduction in complications.
Peeters et al., 2010	NA	Total costs per year for combined facility [carbon ion with a proton) €36.7 million, proton-only facility € 24.9 million, photon facility € 9.6 million; cost / fraction is €1128, €743 and €233, respectively.	Partial pharmacoeconomic evaluation assessing the cost	Particle treatments are more expensive than photon therapy.
Li et al., 2022	For the patients at a median age (43 years) possessing NTCP deduction of 10 %, 20 %, 30 %, 40 %, 50 %, and 60 %, the ICER/QALY of them were $102684.0, $43161.2, $24134.7, $13991.6, $8259.8, and $4436.1, respectively	NA	CEA	IMPT was cost effective in all the patients at a median age level if normal tissue complication probability reduction is ≥24%
Cheng et al., 2016	NA	NA	CEA	Proton therapy is cost effective at a WTP of € 80,000 / QALY in 35% patients.
Brodin et al., 2021	Considerable Patient-to-patient variation in the estimated ICERs, with a median of $361,405/QALY (IQR, $45,453-$1,556,948) for the whole cohort. Patients under 65 years old have a median ICER of $341,081/QALY as opposed to patients over 65, who have a median ICER of $399,533/QALY. According to the p16 status, the median ICER for patients with p16 negative tumors was $ 516,297 / QALY while the median ICER for those with p16 positive tumors was $ 234,201 / QALY.	$ 20,257 and $ 36,659, as the initial price of 33 IMRT and IMPT fractions respectively.	CEA	For the patients with p16 positive tumours, proton treatment had a higher likelihood of cost effective. The patients who are older than 65 have a median ICER that is $58,452/QALY lower than patients who are younger than 65.
Lunkdvist et al., 2009	€10 130 per QALY For combined population	€ 13 049 for proton therapy, € 5477 for conventional therapy	CEA	Proton therapy is cost-effective if the right risk categories are selected
Ning et al., 2020	NA	NA	Partial pharmacoeconomic evaluation assessing the cost	Access to proton therapy appropriately did neither lead to overuse nor significantly greater total employer costs.
Li et al., 2020	ICER of $23,611.2 / QALY. $ 14,999.4/QALY, $ 15,621.2/ QALY, $ 16,663.5/QALY, $ 18,195.8/QALY, $ 20,721.7/ QALY, $ 25,310.7/ QALY, $ 35,134.5/QALY, $ 74,440.1/ QALY for 0,10, 20, 30, 40, 50, 60, 70-year-old levels to evaluate.	NA	CEA	In paranasal and nasal cavity malignancies, the superiority of IMPT's tumor control over IMRT and the patient's age make IMPT cost-effective.

IMPT, Intensity,modulated proton therapy; IMRT, Intensity,modulated radiation therapy; WTP, willingness,to,pay threshold; QALYs, quality,adjusted life,years; ICER, Incremental cost,effectiveness ratio; NA, Not applicable; TDABC, Time Driven Activity Based Costing; PEG, percutaneous endoscopic gastrostomy; RTOG, Radiation Therapy Oncology Group; CRT, chemoradiotherapy; NED, no evidence of disease and DM, distant metastasis

QALY) when compared to both HPV positive and HPV negative status in societal perspective ($ 390,000/QALY, $ 695,000/QALY) where PBT was not found cost-effective. All other evaluations included suggested that a particular subset of patients is cost-effective. (refer to Table 1)

A lifetime horizon was used as a time horizon in majority of the studies. In one study, the time horizon was from the first hospital visit to 30 days post-radiation therapy; in another, the time horizon was considered from one month before to six months post-treatment. The sources of cost were literature, medicare payment schedule, institutional database, cross-sectional survey and value-based analysis. The populations in included studies were head and neck patients, oropharyngeal cancers patients, nasopharyngeal carcinoma patients and paranasal sinus and nasal cavity cancer patients.

Willing to pay (WTP) threshold is stated in five studies. Three studies mentioned the WTP threshold in US dollars ranging from 30,828 to 1,50,000 per QALY. Two studies mentioned the WTP threshold in euro currency as 80,000 per QALY.

Quality of pharmacoeconomic literature included in the systematic review

The study quality is illustrated in the 10-item Drummond's checklist in Table 3. Eight of the 10 included studies received a score ≥7. The items with low scores were regarding comparator, effect, cost and consequences credible valuation, incremental analysis and incomplete results.

Principal findings of pharmacoeconomic literature included in the systematic review

Full economic evaluation and cost-effectiveness analysis was conducted in all except three studies (refer to Table 4) where partial economic evaluation was carried on to primarily focus on the costs. This was done to analyze and compare the costs of two or more alternatives without taking into account the effects. All these studies which assessed only cost used specific analysis methods. Thaker et al. (2021) used time-driven activity-based costing (TDAB), a tool that helps providers study alternative payment models. Peeters et al. (2010) conducted a cost analysis comparing per fraction and per treatment costs. Ning et al. (2020) utilized value-based analysis that addressed both employer and payer's potential concerns.

The efficacy of the proton therapy and comparators in the studies were analyzed in the cost-effectiveness analysis. It includes QALY, survival rates, and tissue complications. Among the 7 studies that conducted cost-effectiveness analysis, only 5 calculated ICER; ICER ranged from $4436.1 to $695000. This wide variation in ICER can be explained based on the country where the study was conducted, HPV p16-status, the pharmacoeconomic perspective used, age of the patient, efficiency and reduction in complications. The upper limit of the ICER range in China ($102,684/QALY) is much less than the lower limit in the USA ($234,201/ QALY). The ICER upper limit in studies from the Netherlands (€127,946) is also lesser than that from the USA. These variations reflect the varied healthcare costs in each country. In the two studies conducted in the USA from payer perspective, HPV-positive / positive p-16 status showed an ICER of $288,000/QALY and $234,201/QALY, respectively, compared with an ICER of $ 516,000/QALY and $ 516,297/QALY, respectively, in those with HPV negative/ p16 negative status. In two studies, ICER was found to be less in younger patients compared with that in elderly patients. In the first study done in the USA, ICER was $341,081/QALY in those <65 years of age and $399,533/QALY in those ≥65 years. A study from China also showed an increase in ICER with age; ICER was $14,999.4, $15,621.2, $16,663.5, $18,195.8, $20,721.7, $25,310.7, $35,134.5, and $74,440.1 per QALY for 0, 10, 20, 30, 40, 50, 60, and 70-years-old patients, respectively. Proton therapy, if efficient, was found to reduce the ICER from €127,946/QALY to €60,278/QALY. Normal tissue complication probability (NTCP) reduction of 10%, 20%, 30%, 40%, 50%, and 60%, involving dysphagia, loss of sensory neural hearing, and xerostomia, was found to reduce ICER to $102,684.0, $43,161.2, $24,134.7, $13,991.6, $8,259.8, and $4,436.1 per QALY, respectively. The total cost of proton therapy and its comparator was estimated in 6 studies, while incremental cost difference was estimated in one study (Table 4).

Discussion

Our systematic review identified 10 studies conducted between 2009 to 2021. The study quality assessment based on 10-item Drummond's checklist showed that eight of the ten included studies received a score ≥7. The studies by Cheng et al., (2016) and Ning et al., (2020) scored 3 and 4, respectively; costs and consequences were not accurately measured in the right physical units in either of these studies, their values were not modified for differing timelines, no incremental analysis of alternatives was carried out, and neither the presentation nor the test results addressed all user-relevant concerns. The quality of the source research affects the internal validity of the synthesis produced by the systematic review. Cheng et al., (2016) suggest that proton therapy would be cost-effective in 35% of HNC patients at a WTP of €80,000/QALY without analyzing the ICER. Ning et al., (2020) suggest that though the direct costs of proton therapy are higher upfront, the patients can still obtain benefits from lesser medical costs over their lifetime. Since these costs were not measured in appropriate physical units, not adjusted for differential timing, and no allowance was made for uncertainties in cost estimation, the findings of these studies need to be considered with caution.

Except for two case-control studies, all other studies used the Markov model which simulates the development of chronic conditions, such as a tumour, through numerous cycles of operation, and therefore, is useful to assess the long-term cost-effectiveness of cancer therapy (Russell et al., 1996). Eight studies compared IMPT with IMRT. The head and neck area is an excellent target for IMRT, thereby making it the lead comparator (Lee et al., 2007). A horizon of a lifetime has been used in most studies even though there is a lack of long-term evidence following proton therapy. The premise is that there is

no substantial difference between the two therapies in terms of delayed recurrence risk or toxicity risk despite their potential improvements (Sher et al., 2018). This time horizon is used because delayed side effects of radiation, which generally manifest after six months, can adversely affect the quality of life during the entire life span. A shorter follow-up will account for only the acute side effects and will not reflect the actual QALY. While majority of published studies focused on all HNC subsites, three of them focused on oropharyngeal malignancies which have a high propensity for HPV positivity, with associated superior treatment response and survival. The cost-effectiveness threshold, which reflects society's WTP for an additional unit of benefit, is a significant issue connected to the generalizability of research results. Studies from the Netherlands displayed a highly uniform pattern with respect to the threshold, which was €80,000/QALY gained. Studies from the United States displayed an extended range of this threshold, from $100,000 to $150,000/QALY gained. However, the Chinese studies had a consistently lower threshold of $30,000/QALY gained. WTP for healthcare services is based on the thematic domains of sociodemographic traits; perceived barriers, benefits, and threats; study design and setting. This explains the variation across the nations (Steigenberger et al. 2022). This predetermined WTP is used to compare with ICER to determine what will constitute a cost-effective approach in that country (McDougall et al., 2020).

Cost-effectiveness analysis was conducted in seven included studies; only five of these determined ICER. The valuable measurement ICER is the ratio of the variation in costs of two medical procedures to the variations in their outcome. Hence, ICER represents extra costs per increased units of treatment outcome received by changing between one medical treatment and the other. Despite having certain drawbacks, ICER is one of the crucial measures required to assist and guide decisions about allocating limited resources among competing healthcare programs (Bambha and Kim, 2004). In the current review, ICER ranged from $4,436.1 to $695,000. HPV virus infection/ p16 status, the pharmacoeconomic perspective used, patient age, and incidence of adverse effects accounted for the variation in ICER.

Sher et al., (2018) concluded the cost-effective superiority of proton therapy in younger HPV-positive patients; ICERs for proton therapy were $288,000/QALY and $516,000/QALY in favorable HPV-positive and negative patients, respectively. Brodin et al., (2021) inferred that, when compared with p16 negative tumors ($516,297 per QALY), p16 positive tumors ($234,201 per QALY) were cost-effectively treated with the proton therapy. Both these studies which were done in the USA from the payer's perspective give us a comparable ICER for both HPV positive and negative status which makes this inference highly relevant. Contrasting with p16 negative tumors, ≥ 50% of p16 positive tumors were cost-effectively treated with proton therapy at $500,000 per QALY (Brodin et al., 2021). But it is worth to mention that a very high ICER is still observed in these tumors.

The various vantage points from which health costs and benefits might be evaluated are known as perspectives (Tonis et al., 2021). Societal perspective is the most thorough since it incorporates the perspectives of all healthcare stakeholders and aims to reflect the complete spectrum of societal opportunity costs related to various interventions. This specifically refers to productivity losses brought on by patients' incapability to work and modifications to these losses brought on by new technologies (McIntosh and Luengo-Fernandez, 2006). Patient mortality and morbidity as well as the total cost of providing and receiving medical care are considered from a societal perspective. Societal perspectives are more prevalent in nations with nationalized healthcare. When insurance firms and employers collaborate together to choose medical coverage for their employees, the payer perspective is used.

According to the current research, even with a proton facility that costs $25 million per gantry, there is no chance that PBT would indeed be cost-effective from the societal perspective under given favorable assumptions. However, the United States and other countries already have a large number of proton facilities. Compared to the up-front costs of building a proton center, the marginal cost for each patient is important from the payer's perspective. Payer's perspective in the pharmacoeconomic evaluation is of value only when PBT is cost-effective when compared to its remuneration. In the study done by Sher et al., (2018), the payer's perspective found IMPT to be cost-effective, while a societal perspective did not.

Current policy recommendations state that a clinically substantial decrease in toxicities (xerostomia, oral mucositis, dysphagia, and percutaneous endoscopic gastrostomy tube implantation) is necessary for patients to be cost-effective candidates for PBT (Health Care Insurance Board 2011; Sherry et al., 2021). Lunkdvist et al., (2005) indicated that, if the right risk categories are selected as proton therapy targets, proton therapy might be a cost-effective therapy and that a proton treatment facility investment could be better cost-effective relative to employing conventional radiation. Individuals who have an increased risk of adverse effects should be identified and treated with proton therapy in practice advantages of this treatment.

The study by Li et al., (2022) shows that, according to the present WTP in China ($33558 per QALY), NTCP of xerostomia, dysphagia and sensorineural hearing loss should be reduced by ≥17%, ≥19%, ≥20%, ≥24%, ≥28% and ≥39% in patients aged >10, >20, >30, >40, >50, and >60 years appropriately, for proton therapy to be cost-effective; proton therapy is not cost-effective for the ≥70-year-old patients as NTCP reduction of ≥90% needs to be achieved. According to Brodin et al., (2021), patients less than 65 years of age had a median ICER of $ 341,081 per QALY, whilst patients equal and greater than 65 years of age had a median ICER of $ 399,533 per QALY. As per the study by Li et al., (2020) of the cost-effectiveness of IMPT in patients with varying ages, the ICERs ranged from $14,999.4 per QALY at age 0 to $74,440.1 per QALY at 70 years, respectively. Therefore, utilizing the existing WTP threshold of China, IMPT was deemed to be cost-effective in all the patients with age ≤56

years. Hence, it can be inferred that head and neck proton therapy is cost-effective in patients of younger age groups who are at risk of treatment-related complications that warrant additional supportive care following treatment.

In three of the included studies, only partial economic evaluation was done to analyze and compare the costs of two or more alternatives without taking into account the outcomes (Thaker et al., 2021; Peeters et al., 2010; Ning et al., 2020). Thaker et al., (2021) determined that IMPT expenses are, on average, greater than IMRT because of the increased equipment expenditures. They identified that 28% of the total costs of IMRT and IMPT patients were overlapping. Higher expenses of IMRT resulted in part from a larger usage of supporting resources (such as emergency, gastroenterology, and inpatient care), which may not have been needed with IMPT because of its improved dosimetry. Ning et al., (2020) found that despite having greater direct costs, PBT may provide long-term indirect benefits in terms of productivity and disability. The overall cost of medical care did not increase in the setting of ancillary service. Both studies point out that PBT reduces the cost of treatment by reducing the need for supportive care. Peeters et al., (2010) suggested that it may be possible to administer particle treatment in the future using much lower fractions than now, thereby reducing the cost of particle treatment.

While most of the included studies estimated the total cost, Thaker et al., (2021) and Ning et al. (2020) estimated incremental cost differences in their study as they were unable to reveal absolute costs for each step in the workflow due to the sensitive nature of internal expenditures but instead offered an overview of relative costs. Lunkdvist et al., (2005) in their study indicated that investing in the proton setting might be deemed cost-effective based on the simulation's assumptions. It should be mentioned that the study findings were predicated on the idea that the proton facility exclusively treated patients with the four forms of cancer- medulloblastoma, breast cancer, prostate cancer and HNC. It won't be the case in practice, since identifying other patients who would be more cost-effective might potentially boost the cost-effectiveness of the proton therapy (Lunkdvist et al., 2005). Only articles published in English were included; so there is a chance that all the relevant articles were not included in this systematic review. The quantitative description cannot be done, since the cost per treatment and outcome was not measured using uniform criteria in the included evaluations. The majority of the studies have not taken into consideration the initial investment costs and machine throughput. Also, with increasing adoption of the technology, the cost of machinery is bound to reduce, and thereby increase cost-effectiveness; this has not been considered in the studies included in this systematic review.

To conclude, our systematic review found that proton therapy in HNC was cost-effective from the payer's perspective when compared to the societal perspective. There was a significant variation in WTP amongst the countries, with lower WTP countries demonstrating greater cost-effectiveness. Appropriate patient selection is required. The proton therapy will be cost-effective in HPV-associated tumors, in young patients due to lesser incidence of adverse effects by decreasing the need for supportive care and in patients with lower fractionation schedules.

Author Contribution Statement

MSA: Conceptualization; PBR, MSA, AK: Literature search; MSA, PBR: Data extraction; PBR, MSA, AK: Data interpretation; PBR: writing – original draft; MSA, AK: writing – review and editing. All the authors have read and approved the final version of the manuscript.

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Data availability statement

All the relevant data is presented in the manuscript and the sources have been cited.

Conflicts of interest

The authors declare no conflicts of interest.

References

Alfouzan AF (2021). Radiation therapy in head and neck cancer. *Saudi Med J*, **42**, 247-54.

Argirion I, Zarins KR, Defever K, et al (2019). Temporal Changes in Head and Neck Cancer Incidence in Thailand Suggest Changing Oropharyngeal Epidemiology in the Region. *J Glob Oncol*, **5**, 1-11.

Austin AM, Douglass MJJ, Nguyen GT, et al (2019). Cost-effectiveness of proton therapy in treating base of skull chordoma. *Australas Phys Eng Sci Med*, **42**, 1091-98.

Bambha K, Kim WR (2004). Cost-effectiveness analysis and incremental cost-effectiveness ratios: uses and pitfalls. *Eur J Gastroenterol Hepatol*, **16**, 519-26.

Brodin NP, Kabarriti R, Schechter CB, et al (2021). Individualized quality of life benefit and cost-effectiveness estimates of proton therapy for patients with oropharyngeal cancer. *Radiat Oncol*, **16**, 19.

Cheng Q, Roelofs E, Ramaekers BL, et al (2016). Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer - Comparison of dose, toxicity and cost-effectiveness. *Radiother Oncol*, **118**, 281-5.

Drummond MF (2005). Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press.

Goitein M, Jermann M (2003). The Relative Costs of Proton and X-ray Radiation Therapy. *Clin Oncol*, **15**, 37-50.

Grutters JP, Kessels AG, Pijls-Johannesma M, et al (2010). Comparison of the effectiveness of radiotherapy with

photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol*, **95**, 32–40.
Gunn GB, Blanchard P, Garden AS, et al (2016). Clinical Outcomes and Patterns of Disease Recurrence After Intensity Modulated Proton Therapy for Oropharyngeal Squamous Carcinoma. *Int J Radiat Oncol*, **95**, 360-7.
Health Care Insurance Board (2011). Indications for Proton Therapy (Part 2): Model-based Indications [In Dutch]. Diemen, The Netherlands.
Holliday EB, Kocak-Uzel E, Feng L, et al (2016). Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: A case-matched control analysis. *Med Dosim*, **41**, 189-94.
Jeremic B, Kiladze I, Ozyigit G, Filipovic N, Dubinsky P (2021). Novel technological aspects of radiation therapy in head and neck cancer. *Turk Onkoloji Dergisi*, **36**, 236-46.
Jones DA, Smith J, Mei XW, et al (2019). A systematic review of health economic evaluations of proton beam therapy for adult cancer: Appraising methodology and quality. *Clin Transl Radiat Oncol*, **20**, 19-26.
Kawakita D, Oze I, Iwasaki S, et al (2022). Trends in the incidence of head and neck cancer by subsite between 1993 and 2015 in Japan. *Cancer Med*, **11**, 1553-60.
Lee N, Puri DR, Blanco AI, Chao KS (2007). Intensity-modulated radiation therapy in head and neck cancers: an update. *Head Neck*, **29**, 387-400.
Li G, Qiu B, Huang YX, et al (2020). Cost-effectiveness analysis of proton beam therapy for treatment decision making in paranasal sinus and nasal cavity cancers in China. *BMC Cancer*, **20**, 599.
Li G, Xia YF, Huang YX, et al (2022). Intensity-modulated proton radiation therapy as a radical treatment modality for nasopharyngeal carcinoma in China: Cost-effectiveness analysis. *Head Neck*, **44**, 431-42.
Lievens Y, Van Den Bogaert W (2005). Proton Beam Therapy: Too Expensive to Become True?. *Radiother Oncol*, **75**, 131-3.
Lukens JN, Lin A, Hahn SM (2015). Proton therapy for head and neck cancer. *Curr Opin Oncol*, **27**, 165-71.
Lundkvist J, Ekman M, Ericsson SR, Jönsson B, Glimelius B (2005). Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol*, **44**, 850-61.
McDougall JA, Furnback WE, Wang BCM, Mahlich J (2020). Understanding the global measurement of willingness to pay in health. *J Mark Access Health Policy*, **8**, 1717030.
McIntosh E, Luengo-Fernandez R (2006). Economic evaluation. Part 1: Introduction to the concepts of economic evaluation in health care. *J Fam Plann Reprod Health Care*, **32**, 107-12.
Mody MD, Rocco JW, Yom SS, Haddad RI, Saba NF (2021). Head and Neck Cancer. *Lancet*, **398**, 2289-99.
Moreno AC, Frank SJ, Garden AS, et al (2019). Intensity modulated proton therapy (IMPT) - The future of IMRT for head and neck cancer. *Oral Oncol*, **88**, 66-74.
Ning MS, Palmer MB, Shah AK, et al (2020). Three-Year Results of a Prospective Statewide Insurance Coverage Pilot for Proton Therapy: Stakeholder Collaboration Improves Patient Access to Care. *JCO Oncol Pract*, **16**, e966-e976.
Nutting CM, Morden JP, Harrington KJ, et al (2011). Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. *Lancet Oncol*, **12**, 127-36.
Ontario Health (Quality) (2021). Proton Beam Therapy for Cancer in Children and Adults: A Health Technology Assessment. *Ont Health Technol Assess Ser*, **21**, 1-142.
Peeters A, Grutters JP, Pijls-Johannesma M, et al (2010). How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. *Radiother Oncol*, **95**, 45-53.
Prabhash K, Babu G, Chaturvedi P, et al (2020). Indian clinical practice consensus guidelines for the management of squamous cell carcinoma of head and neck. *Indian J Cancer*, **57**, 1-5.
Ramaekers BL, Grutters JP, Pijls-Johannesma M, et al (2013). Protons in head-and-neck cancer: bridging the gap of evidence. *Int J Radiat Oncol Biol Phys*, **85**, 1282-8.
Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC (1996). The role of costeffectiveness analysis in health and medicine. Panel on cost-effectiveness in health and medicine. *JAMA*, **276**, 1172–7.
Sher DJ, Tishler RB, Pham NL, Punglia RS (2018). Cost-Effectiveness Analysis of Intensity Modulated Radiation Therapy Versus Proton Therapy for Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys*, **101**, 875-82.
Sherry AD, Pasalic D, Gunn GB, et al (2021). Proton Beam Therapy for Head and Neck Carcinoma of Unknown Primary: Toxicity and Quality of Life. *Int J Part Ther*, **8**, 234-47.
Siegel RL, Miller KD, Jemal A (2019). Cancer statistics, 2019. *CA Cancer J Clin*, **69**, 7-34.
Steigenberger C, Flatscher-Thoeni M, Siebert U, Leiter AM (2022). Determinants of willingness to pay for health services: a systematic review of contingent valuation studies. *Eur J Health Econ*, **23**, 1455-82.
Thaker NG, Boyce-Fappiano D, Ning MS, et al (2021). Activity-Based Costing of Intensity-Modulated Proton versus Photon Therapy for Oropharyngeal Cancer. *Int J Part Ther*, **8**, 374-82.
Tonin FS, Aznar-Lou I, Pontinha VM, Pontarolo R, Fernandez-Llimos F (2021). Principles of pharmacoeconomic analysis: the case of pharmacist-led interventions. *Pharm Pract (Granada)*, **19**, 2302.
Verma V, Mishra MV, Mehta MP (2016). A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer*, **122**, 1483-501.