Proton Beam Therapy in Cancer Treatment: Evaluation of Its Safety, Efficacy, Effectiveness and Cost-Effectiveness vs Photon-Based Radiotherapy

HTA258

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/ INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality around the globe, including Spain. Photon-based radiotherapy (RTx) is one of the available treatment strategies, often combined with surgery and/or chemotherapy.

Proton beam therapy (PT) uses proton radiation to treat tumors and is a potential alternative to RTx. It might offer dosimetric advantages over RTx and hence reduce damage to healthy tissues. There are currently 2 private PT centers in Spain, and the incorporation of another 11 PT units in public centers is planned for the near future.

Commissioned by the Spanish Ministry of Health and under the umbrella of the Spanish Network of HTA Agencies (RedETS), the Agency for Health Quality and Assessment of Catalonia (AQuAS) has produced, since 2009, 3 HTA reports on the safety, efficacy, effectiveness and cost-effectiveness of PT for cancer treatment (1-3). In 2021, RedETS requested AQuAS a new HTA report to assess the new evidence published on the topic.

/ OBJECTIVE

To evaluate, via a systematic literature review, the safety, clinical efficacy/effectiveness and cost-effectiveness of PT compared to RTx in cancer treatment in both adults and children.

Sub-objective 1: Evaluation of the safety and efficacy/effectiveness of PT vs RTx.

Sub-objective 2: Evaluation of the cost-effectiveness of PT vs RTx.

Indications that are already approved for PT reimbursement in Spain (most of them in children) (4), as well as non-melanoma skin cancers, were out of the scope of the evaluation.

/ METHODS

- Evaluation team: HTA experts (AQuAS) + 3 clinical experts in radiation oncology + 1 in medical physics.
- Methodology systematic literature review of original studies: following the methodological standards of the Cochrane Collaboration, PRISMA and GRADE for evidence synthesis and assessment of the level of certainty (very low, low, moderate, and high) (5,6).
- Eligibility criteria: defined based on the PICO-DT framework.

Domain	Inclusion criteria
P: Population	Adults and in children with any cancer, except from those already approved for PT reimbursement in Spain (4).
I: Intervention	PT alone or combined with other forms of RT and/or radiation-free therapies.
C: Comparator	RTx alone or combined with other forms of RT and/or radiation-free therapies.
O: Outcomes	Sub-objective 1: Safety: serious and non-serious acute and chronic/late adverse events (AEs), radiation-induced secondary neoplasms; Efficacy/effectiveness: mortality/survival (overall survival, OS), disease progression (progression-free survival, PFS), quality of life, patient satisfaction/acceptability. Outcomes were classified as **primary** (OS, PFS; acute and chronic severe AEs) or **secondary**. Sub-objective 2: Cost-effectiveness, cost-utility, cost-benefit.
D: Design	Sub-objective 1: randomized controlled trials (RCTs) and non-RCTs comparative studies. Sub-objective 2: full economic evaluations.
T: Time	Studies published from 2012.

- Search date and searched databases: January (safety, efficacy/effectiveness) and February (cost-effectiveness) 2024, and in 4 and 6 databases, respectively.
- Data synthesis and conclusions: the availability of primary outcomes + the certainty of the evidence according to the GRADE framework were taken into account. To be able to suggest the use of PT over RTx (ideal scenario), PT should be equal or better than RTx in terms of clinical efficacy/effectiveness (OS, PFS) and safety (acute and chronic severe AEs), with low or higher level of certainty.

/ RESULTS

1. Results of the search

Safety and efficacy/effectiveness: 6,958 unique references were screened, from which 946 at full text. Finally, 77 studies were included for analysis. These encompassed 16 cancer types; 1 in children and 15 in adults.

Cost-effectiveness: 1,361 unique references were screened, from which 135 at full text. Finally, 16 studies were included for analysis. These encompassed 7 cancer types, all in adults.

	ADULT POPULATION			PEDIATRIC POPULATION		
	RCT	Non-RCT (OC)	Cost-effectiveness	RCT	Non-RCT (OC)	Cost-effectiveness
Head and Neck						
1 & 2. Oral cavity and pharyngeal cancer		9	4		1	
3. Nasal cavity and paranasal sinus cancer		5	2			
Central Nervous System						
4. Gliomas/Glioblastomas/Gliosarcomas	1	4				
5. Medulloblastoma		1				
6. Acoustic neuroma or vestibular schwannoma		1				
7. Leptomeningeal metàstasis	1					
Thorax						
8. Lung cancer	1	14	1			
Digestive System						
9. Esophageal cancer	1	9				
10. Pancreatic cancer		1	1			
11. Hepatocellular carcinoma		5	1			
12. Anal cancer		1				
Genitourinary System						
13. Prostate cancer	1	13	3			
14. Testicular cancer		1				
Breast and female reproductive System						
15. Breast cancer		5	4			
16. Uterine cancer		2				
TOTAL STUDIES INCLUDED	5	71	16	0	1	0

RCT: randomized controlled trial; OC: observational comparative

Ongoing studies identified:
27 ongoing RCTs and 11 ongoing non-RCTs (observational comparative; OC), addressing safety and/or clinical efficacy/effectiveness outcomes in adults. 4 ongoing cost-effectiveness studies.

2. Safety and clinical efficacy/effectiveness

The ideal scenario did not occur in any of the studied indications (scenario 1, bright green). In 6 indications, there was evidence of enough certainty (LOW or higher) according to GRADE to suggest that PT might be equivalent or better than RTx (scenarios 2 and 3, light green and light orange). These results have to be considered with caution.

Scenario 1: ideal	Scenario 2	Scenario 3	Scenario 4	Scenario 5: not assessable
PT is equal or better than RTx in terms of clinical efficacy/effectiveness (OS and PFS) and safety (acute and chronic severe toxicity). Level of certainty*: LOW or higher.	At a minimum: 1 primary safety and 1 primary efficacy/effectiveness outcome where the results point towards the possibility of using PT as an equivalent or better strategy than RTx. Level of certainty*: LOW or higher in at least 1 primary safety and 1 primary efficacy/ effectiveness outcome.	At a minimum: 1 primary safety and 1 primary efficacy/effectiveness outcome where the results point towards the possibility of using PT as an equivalent or better strategy than RTx. Level of certainty*: LOW or higher in only one domain (safety or efficacy/effectiveness).	At a minimum: 1 primary safety and 1 primary efficacy/effectiveness outcome where the results point towards the possibility of using PT as an equivalent or better strategy than RTx. Level of certainty*: VERY LOW in all primary outcomes.	No primary outcomes identified. Or primary outcomes identified in only one domain (safety or efficacy/effectiveness). Not possible to assess the benefit/risk balance of PT vs RTx.
This occurred in 0 out of 16 indications evaluated	This occurred in 3 our of 16 indications evaluated • Leptomeningeal metastasis • Lung cancer • Anal cancer	This occurred in 3 out of 16 indications evaluated • Gliomas/Glioblastomas/ Gliosarcomas • Oesophageal cancer • Prostate cancer	This occurred in 5 out of 16 indications evaluated • Oral cavity and pharyngeal cancer (adults) • Nasal cavity and paranasal sinus cancer • Pancreatic cancer • Hepatocellular carcinoma • Breast cancer	This occurred in 5 out of 16 indications evaluated • Testicular cancer • Oral cavity and pharyngeal cancer (children) • Medulloblastoma • Acoustic neuroma or vestibular schwannoma • Uterine cancer

*According to the GRADE framework

3. Cost-effectiveness

16 studies included: from USA (n=6), China (n=5), the Netherlands (n=2), Australia (n=1), Japan (n=1), Taiwan (n=1). None performed in Spain.

PT probably CE vs RTx for:	PT is probably not CE for:	PT CE depending on specific patient characteristics for:
• Nasal cavity and paranasal sinus cancer • Pancreatic cancer • Hepatocellular carcinoma	• Lung cancer	• Oral cavity and pharyngeal cancer (HPV-positive and younger patients) • Prostate cancer (younger patients without prior erectile dysfunction) • Breast cancer (patients with higher pre-existing cardiovascular risk, or those where normal tissue would receive significantly higher doses with RTx than with PT)

The evidence on the cost-effectiveness should be considered with caution because it is based on safety and efficacy/effectiveness data that may be questionable in terms of quality, quantity, and representativeness of current practices, and because the results of CE analyses largely depend on the assumptions made in each study.

/ CONCLUSIONS

In the studied indications, PT has not proved with enough certainty to be better than RTx in terms of safety, efficacy/effectiveness nor cost-effectiveness.

Until more evidence is generated, PT might be considered with caution in some scenarios.

/ RECOMMENDATIONS

- To establish a strategy to select patients who could benefit from PT.
- To create a registry of PT treatment outcomes and conduct studies using these real world data (RWD).
- To conduct studies in the indications with knowledge gaps.
- To perform studies on those indications with most knowledge gaps, using the highest quality study designs possible to ensure low risk of bias, preferably RCTs.
- To periodically update this HTA report to assess new published evidence.

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The full HTA report will be soon published here:

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