ScienceDirect

Critical Reviews in Oncology/Hematology

Volume 222, June 2026, 105276

Proton beam therapy versus photon therapy for multiple malignancies: An umbrella systematic review and meta-analysis

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Received 14 July 2025, Revised 7 March 2026, Accepted 10 March 2026, Available online 12 March 2026, Version of Record 17 March 2026.

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Highlights

- Comparative evidence between PBT and photon therapy is presented.
- Pooled evidence for comparing data across studies is at high risk of bias.
- Current results are not supported by high-quality evidence.

- High-quality prospective comparative studies are strongly encouraged.

Abstract

Background

Direct comparative evidence between proton beam therapy (PBT) and photon therapy for the treatment of malignant diseases is lacking.

Methods

Electronic databases were searched for meta-analyses of PBT *vs.* photon therapy for patients with malignancies from database inception up until March 13, 2025. The methodological quality of meta-analyses was assessed using AMSTAR 2. Where possible, the DerSimonian and Laird random-effects model was used to repeat each meta-analysis. For pooled evidence from two-arm studies, the certainty of the evidence was assessed using GRADE criteria.

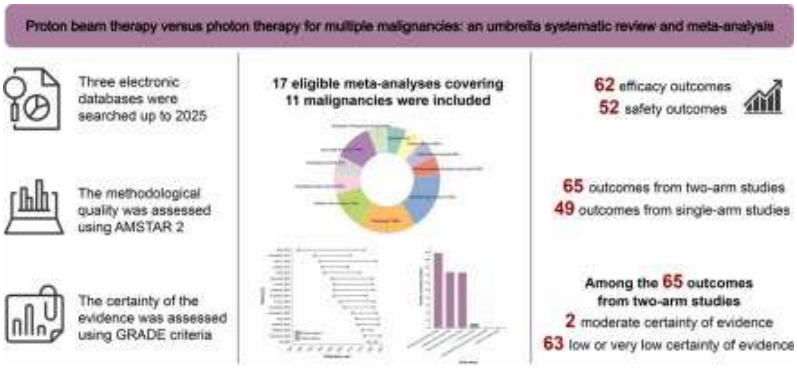
Results

Seventeen meta-analyses covering 11 cancers were included. Compared to photon therapy, PBT was associated with improved prognosis in glioma, head and neck cancer (for certain loci), esophageal cancer, intrahepatic cholangiocarcinoma, extrahepatic biliary tract cancer, renal cell carcinoma, and colorectal cancer with pelvic recurrence. Use of PBT also correlated with reduced toxic effects in head and neck cancer, pediatric CNS tumors, esophageal cancer, early-stage NSCLC, and prostate cancer. Within the 65 outcomes from two-arm studies, GRADE assessment found that only two outcomes were supported by moderate certainty of evidence, while 63 were supported by low or very low certainty of evidence.

Conclusions

Our findings indicate, that for several tumors, PBT is associated with improved survival outcomes and toxicities. In the absence of high-quality evidence, these findings need to be validated by more large-scale comparative studies and clinical trials.

Graphical Abstract



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Introduction

Over the past 30 years, a number of innovations on radiation therapy (RT) have been successfully implemented, including proton beam therapy (PBT) (Salem et al., 2024). Due to the comparatively large mass and consequently low linear energy transfer of protons, PBT focuses the maximum dose on the target organ area, leaving the surrounding organs with a relatively small radiation dose and thus reducing normal tissue toxicity (Sejpal et al., 2011, Wilson, 1946). This makes PBT particularly well suited to tumors situated in sensitive anatomical locations, whose position near critical organs at risk renders it difficult or even impossible to increase the dosage of conventional RT (Pollom et al., 2014, Liu et al., 2022, Baliga and Yock, 2019). The evidence demonstrating that the physical advantages translate into improved survival outcomes and quality of life for patients is essential for supporting the clinical application of PBT. A phase 3 study was the first to demonstrate the survival benefits of PBT in oropharyngeal cancer (Frank et al., 2026). At the same time, the PBT group also showed advantages in key toxicities and quality of life (Frank et al., 2026). However, the TORPEdO trial for oropharyngeal cancer indicated that there was no significant difference in quality of life between conventional RT and PBT (Thomson et al., 2023). These controversial findings have caused confusion in clinical decision-making and policy development.

Although some meta-analyses comparing PBT and photon therapy for treating malignant diseases have been published, many of these meta-analyses have only included single-arm trials, failing to directly compare treatment effects or provide relative efficacy and toxicity between these two therapies (Al-Lami et al., 2024, Ramaekers et al., 2011, Zhou et al., 2018, Saito et al., 2024). Moreover, of those meta-analyses that include two-arm studies, many do not assess the overall quality of the evidence (He et al., 2024, Kiss-Miki et al., 2025). Critical questions remain unanswered regarding which cancer types and patient subgroups derive clinically meaningful benefit from PBT, as well as the methodological rigor of the existing studies. Addressing these issues is essential for establishing an evidence-based hierarchical system that to guide treatment guidelines and health care policies.

To address these shortcomings, we decided to conduct this umbrella review. Umbrella reviews

are able to assess the available evidence from multiple meta-analyses done on the same research topic and grade the evidence using well-defined criteria (Silva et al., 2023, Fusar-Poli and Radua, 2018, Kim et al., 2019, Muka et al., 2020). This study, with standardized reanalysis, cross-study data comparison, and unified quality grading, synthesized existing meta-analyses comparing treatment outcomes with PBT and photon therapy for multiple malignancies and assessed the quality, biases, and validity of the evidence.

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Section snippets

Methods

We prospectively registered the protocol on October 3, 2024 in the International Prospective Register of Systematic Reviews (PROSPERO, No. CRD42024590409). This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a complete PRISMA checklist was provided in Supplementary Methods Tables S1 and S2. …

Study selection

Using the above method, we systematically screened the candidate literature. The complete screening process is presented in Fig. 1. We identified 1736 references from three electronic databases. After removing duplicates, 1562 references remained. 1468 references were excluded based on the title or the abstract, leaving just 94, which were assessed at the full text level. Ultimately, seventeen studies met our inclusion criteria and were retained (Al-Lami et al., 2024, Ramaekers et al., 2011, …

Discussion

PBT has been used in clinical practice since 1952 (Schreuder and Shamblin, 2020). As of December 2023, there were more than 113 operational PBT centers worldwide, with an additional 32 under construction (Isaksson et al., 2024). However, the evidence supporting the clinical application of PBT remains heterogeneous (Mohan and Grosshans, 2017). PBT theoretically possesses significant advantages over photon therapy. The physical property of rapid dose reduction beyond the target volume minimizes …

Conclusion

In conclusion, by comparing clinical outcomes documented in PBT studies with photon therapy studies, the present umbrella review indicates that, for certain tumors, PBT is associated with improved tumor control, survival outcomes, and toxic effects. This study provides a quantitative summary of currently published clinical results for multiple malignant diseases treated with proton *vs.* photon therapy. In the future, these findings should be validated by more large-scale comparative studies and …

Critical view

This study provided a comparative evidence set regarding PBT *vs.* photon therapy for multiple malignant tumors. Using the AMSTAR 2 and GRADE system, we found that although there was supportive evidence in certain tumors, the majority of the evidence was of low quality, with substantial heterogeneity and a lack of direct comparative evidence. Our critical contribution was in synthesizing current evidence gaps and proposing directions for conducting high-quality controlled trials and comparative …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgements

This work was supported by the following grants: National Natural Science Foundation of China (82272753), Shandong Provincial Natural Science Foundation (ZR2021LZL002), Bethune Cancer Radiotherapy Translational Medicine Research Fund (flzh202103), The Key Research and Development Program of Shandong (Major Science & Technology Innovation Project) (2021SFGC05012021). We sincerely thank Prof. Huiyong Yang, School of Medicine, Huaqiao University, for assistance in GRADE methodology for this study. …

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