Proton vs Carbon-Ion therapy: Which particle therapy is best in head and neck cancer treatment

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Abstract

We systematically reviewed PT vs CIRT for head and neck cancer across primary and reirradiation settings (62 studies; 4158 patients). In primary radiation, PT showed higher 2-year efficacy (OS 87.1% vs 82.7%; DFS 85.4% vs 70.5%) with similar local control (84.5% vs 86.5%). In reirradiation, CIRT yielded better 2-year OS (75.6% vs 52.1%) and comparable local control (59.2% vs 54.1%). CIRT had more grade ≥3 acute toxicity (29.2% vs 21.7%), whereas PT had more grade ≥3 late toxicity (43.7% vs 26.9%). Overall, PT appears more effective for primary treatment, while CIRT shows advantages in reirradiation, with distinct toxicity profiles.

Introduction

Particle therapies (protons and carbon ions) are increasingly used for head & neck cancers to improve tumor control while limiting normal-tissue dose. PT has a modestly elevated RBE (~1.1) with low–moderate LET; CIRT delivers high-LET dose with higher, less repairable DNA damage (clustered DSBs). This can improve tumor kill, especially in hypoxic, radioresistant tumors, but also risks greater normal-tissue injury if not tightly conformed. Both exploit Bragg peaks, but carbon ions exhibit sharper lateral penumbra and reduced scattering, enabling steeper dose gradients around complex skull-base/para-spinal targets. That can lower off-target dose (potentially fewer late effects) yet demands exquisite setup/robustness. Data comparing proton therapy and carbon ion radiotherapy remains limited and scattered.

Objectives

To rigorously compare the efficacy and safety of proton therapy (PT) versus carbon-ion radiotherapy (CIRT) for head and neck cancer across primary and reirradiation settings

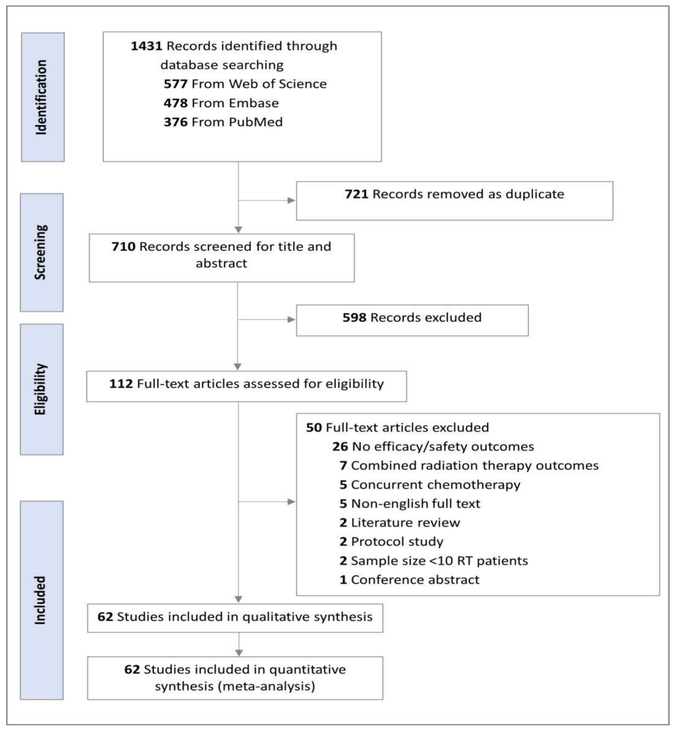
Methods and Materials

- Data Sources: A systematic search of PubMed, Web of Science, Embase, and ScienceDirect was conducted for studies published from 2001 to July 2025.
- Inclusion and exclusion criteria: Studies were eligible if they reported at least one efficacy endpoint, overall survival (OS), disease-free survival (DFS), or local control rate (LCR) at prespecified landmarks (e.g., 2 and/or 5 years), and/or toxicity graded with CTCAE (acute ≤90 days; late >90 days), including grade ≥3 events. Eligible designs were randomized/non-randomized trials, prospective/retrospective cohorts, and case series with ≥10 patients. We excluded non-English reports, reviews/editorials, case reports, dosimetric/planning-only papers, non-particle RT cohorts, mixed-modality studies without separable PT/CIRT data, and duplicate datasets.
- Data Extraction and Analysis: Three reviewers independently extracted data from the included studies; conflicts were resolved through discussion or adjudication by a fourth reviewer.
- Statistical Analysis: We pooled event rates for OS, DFS, LCR, and toxicity using random-effects models. Primary analyses were stratified by modality (PT vs CIRT) and setting (primary vs reirradiation). Heterogeneity was quantified with I^2 and τ^2; robustness was examined with leave-one-out sensitivity analyses.

Results

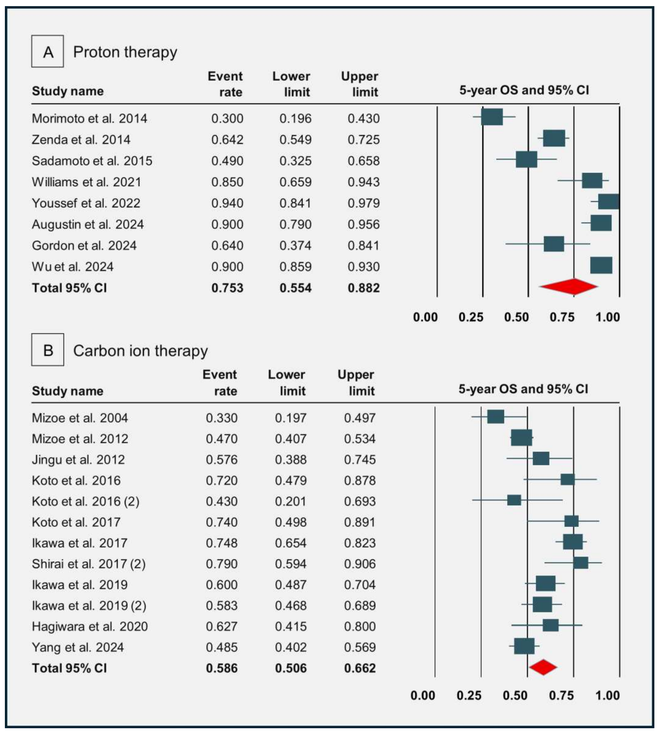
- From 1431 records, 710 titles/abstracts were screened. After full-text review of 112 studies, 62 met the inclusion criteria (Figure 1).

Figure 1. PRISMA Flowchart



- In total, 4,158 irradiated HNC patients were included (2,193 PT; 1,965 CIRT); mean age 56.1 years (SD=6.94).

Figure 2. Pooled 5-year Overall Survival After Primary Proton Therapy (A) and Carbon Ion Therapy (B) in HNC patients



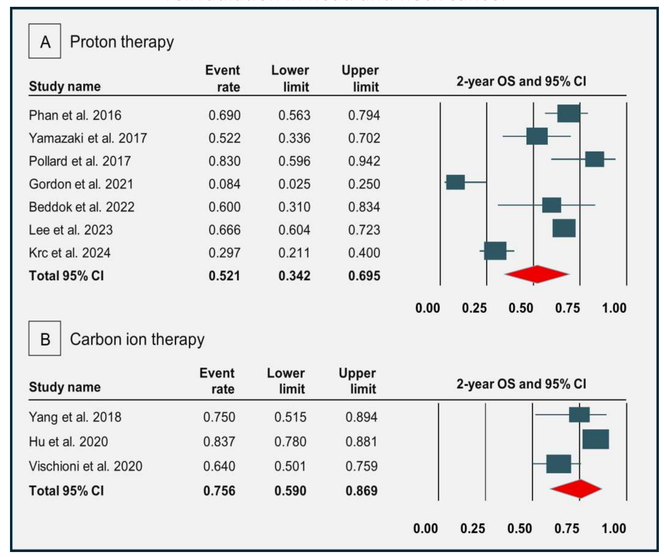
PRIMARY RADIATION:

- Overall survival: PT higher at 2 year (87.1% [81.2–91.4]) and 5 year (75.3% [55.8–88.1]) vs CIRT 2 year 82.7% (72.6–89.6), 5 y 55.6% (46.8–64.1) (Figure 2).
- Disease-free survival: PT higher at 2 year 85.4% (77.3–90.9) and 5 year 72.8% (56.1–84.8) vs CIRT 2 year 70.5% (62.9–77.2), 5 y 49.5% (39.0–59.9).
- Local control rate: CIRT has comparable 2 year LCR (86.5% [80.3–91.0] vs PT 84.5% [77.8–89.4]), and comparable 5 year LCR (CIRT 74.0% [66.5–80.4] vs PT 78.3% [34.6–96.1.

REIRRADIATION:

- Overall survival: CIRT had higher 2-year OS, 75.6% (59.0–86.9) vs PT 47.0% (28.8–66.0).
- 2-year LCR was comparable (CIRT 59.2% [53.0–65.0] vs PT 54.1% [39.0–68.6])

Figure 3. Pooled 2-year Overall Survival following proton (A) and carbon ion (B) reirradiation in head and neck cancer



- . For acute toxicity (AT), CIRT exhibited similar grade 1-2 AT events (91.2% vs. PT 87.5%) and a greater frequency of grade ≥3 AT (29.2% vs. PT 21.7%).
- Late toxicity rates for grade 1–2 were comparable (PT 79.7% [95% CI, 62.3–90.3%] vs CIRT 81.1% [95% CI, 72.6–87.5%]), whereas severe grade ≥3 LT occurred more often with PT (43.7% [95% CI, 22.9–66.9%]) than with CIRT (26.9% [95% CI, 17.8–38.6%]).

Discussion

- Evidence is constrained by predominantly retrospective designs, heterogeneous populations, planning techniques, dose/fractionation, and concurrent systemic therapy.
- Prospective (ideally randomized) head-to-head PT vs CIRT trials in primary and reirradiation settings

Conclusions

PT is favored for primary treatment, showing higher 5-year OS/DFS with broadly comparable local control to CIRT.In reirradiation, CIRT achieves higher 2-year OS with similar 2-year local control. CIRT has more grade ≥3 acute events, while PT has more grade ≥3 late events, supporting context-specific modality selection and motivating head-to-head trials.

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