



Systematic review

Charged particle therapy versus photon therapy for patients with hepatocellular carcinoma: A systematic review and meta-analysis

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ABSTRACT

Purpose: To perform a systematic review and meta-analysis to compare the clinical outcomes and toxicity of hepatocellular carcinoma (HCC) patients treated with charged particle therapy (CPT) with those of individuals receiving photon therapy.

Methods: We identified relevant clinical studies through searching databases. Primary outcomes of interest were overall survival (OS) at 1, 3, 5 years, progression-free survival (PFS), and locoregional control (LC) at longest follow-up.

Results: 73 cohorts from 70 non-comparative observational studies were included. Pooled OS was significantly higher at 1, 3, 5 years for CPT than for conventional radiotherapy (CRT) [relative risk (RR) 1.68, 95% CI 1.22–2.31; $p < 0.001$; RR 3.46, 95% CI: 1.72–3.51, $p < 0.001$; RR 25.9, 95% CI: 1.64–408.5, $p = 0.02$; respectively]. PFS and LC at longest follow-up was also significantly higher for CPT than for CRT ($p = 0.013$ and $p < 0.001$, respectively), while comparable efficacy was found between CPT and SBRT in terms of OS, PFS and LC at longest follow-up. Additionally, high-grade acute and late toxicity associated with CPT was lower than that of CRT and SBRT.

Conclusion: Survival rates for CPT are higher than those for CRT, but similar to SBRT in patients with HCC. Toxicity tends to be lower for CPT compared to photon radiotherapy.

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Hepatocellular carcinoma (HCC), accounting for 80–90% of primary liver cancer, is the fifth most common solid tumor and the third leading cause of cancer-related death worldwide, which leads to a 500,000 deaths per year [1,2]. Currently, several treatment modalities are available for HCC, including surgical interventions (tumor resection and liver transplantation) [3], percutaneous (ethanol injection, radiofrequency thermal ablation) [4,5] and transarterial (embolization, chemoperfusion, or chemoembolization) interventions [6], systemic chemotherapy [7], small molecular multi-kinase inhibitor [8,9], and radiation. Although HCC is currently known as a radiosensitive tumor, the use of radiotherapy is limited because of the poor radiation tolerance of normal liver to local control doses, and complexity of tumor localization.

However, modern advances in treatment design and delivery have renewed enthusiasm for radiation as an effective local-regional treatment modality for HCC. Modern three-dimensional radiotherapy techniques have allowed clinicians to increase dose conformity while escalating dose to the tumor while sparing more normal liver, thus, largely avoiding radiation-induced liver disease

(RILD). Several reports have shown that high-dose irradiation to a portion of the liver could be delivered safely with reasonable treatment efficacy [10,11]. More recently, the development of stereotactic body radiotherapy (SBRT), a technique minimizing RT dose to adjacent normal tissues by delivering high doses of RT in a single treatment or in a small number of fractions with high precision, has generated further promise for liver-directed RT [12]. Moreover, the role of charged particle-based RT in the treatment of HCC is also an area of active investigation [13,14]. The unique physical properties of charged particle therapy (protons and carbon ions)—with rapid fall-off of dose beyond the Bragg peak (a sharp deposition of dose at a specific depth in tissue)—and its greater relative biological effectiveness compared with photon therapy might further augment treatment outcomes, not only by reducing the incidence and severity of complications but also by allowing an escalation in radiation dose to improve tumor control and survival, which cannot be achieved with photon therapy. However, to our best knowledge, there is no head-to-head comparison data available for charged particle therapy versus photon therapy in the treatment of HCC. Therefore, we perform a systematic review and meta-analysis of published work to compare treatment outcomes with charged particle therapy and photon therapy for the management of patients with HCC.

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Method and materials

Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [15].

Procedures

To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of four databases, including Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to August, 2014. The search included the following terms: ('hepatocellular carcinoma' or 'HCC') and ('hepatocellular neoplasm/radiotherapy' [MESH terms] or 'Carcinoma, hepatocellular/radiotherapy' [MESH terms]) and 'survival' (see search strategy [Appendix 1](#)). Additional references were searched through manual searches of the reference lists and specialist journals.

To be eligible for inclusion in our systematic review and meta-analysis, study populations (referred to hereafter as cohorts) had to meet all the following criteria: (1) patients with hepatocellular carcinoma; (2) treatment with photon therapy, charged particle therapy, or combined photon therapy and charged particle therapy; (3) reported outcomes of interest (ie, tumor control, survival, and complications); and (4) from an original study (ie, randomized controlled trial, non-randomized clinical trial, observational studies, or case series). We defined charged particle therapy as radiation therapy using beams of protons, carbon ions, helium ions, or other charged particles. Photon therapy included three-dimensional radiation therapy (3DRT), image-guide radiation therapy (IGRT), intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT) techniques. We classed patients who received both photon therapy and charged particle therapy as a charged particle therapy cohort.

We excluded studies of photon therapy published before 1990 to ensure we included work incorporating modern radiation therapy techniques. We did not limit by time for charged particle therapy studies. We did not restrict our search to language, country, patients' characteristics, or underlying disease status (ie, primary disease, recurrent disease, primary charged particle therapy or photon therapy, or adjuvant charged particle therapy or photon therapy). We excluded case reports with fewer than five patients, reviews, notes, letters, errata, commentaries, and studies published only as abstracts.

Two investigators (W.X.Q. and S.F.) screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap.

The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: author, study design, study period, patients' characteristics (sex, age, tumor size, Child Push class, and patients with tumor vascular thrombosis), interventions (radiation dose and fractionation schedule), sample size, length of follow-up, and outcomes of interest. We defined outcomes of interest as overall survival, progression-free survival, locoregional control, toxic effects, functional status, and quality of life. We assessed survival outcomes at 1, 3, and

5 years, while we assess progression-free survival and locoregional control at the longest duration of complete follow-up.

To assess quality, since we included non-comparative (uncontrolled) studies in our systematic review and meta-analysis, we used the Newcastle-Ottawa quality assessment scale [16]. This scale is an eight-item instrument that allows for assessment of patient population and selection, study comparability, follow-up and outcome of interest ([Appendix 2](#)). We selected items that focused on representativeness of study patients, demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, and adequacy of follow-up.

Statistical analysis

We prespecified the analysis plan in the protocol. We analyzed all patients who started photon therapy or charged particle therapy, regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for both charged particle therapy and photon therapy. We pooled log-transformed event rates with DerSimonian and Laird random-effect models and assessed heterogeneity using the Mantel-Haenszel test [17]. We used the test of interaction proposed by Altman and Bland to compare log-transformed rates of outcomes between charged particle therapy and photon therapy [18]. When the difference between treatments was significant, we calculated the number needed to treat (NNT) from the absolute difference of the pooled estimates between the two groups. A statistical test with a p -value less than 0.05 was considered significant. To account for the potential effect of publication bias, we used the Duval and Tweedie non-parametric trim-and-fill method [19]. To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with I^2 greater than 50% indicating high heterogeneity. We assessed potential publication bias by visual inspection of the symmetry of funnel plots and with the Egger regression asymmetry test. We did all statistical analyses with Stata version 12.1 (Stata-Corp, College Station, TX, USA) and comprehensive meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA).

Results

636 studies were identified from the database search, of which 166 reports were retrieved for full-text evaluation. 70 non-comparative observational studies met the inclusion criteria and were included in this systematic review ([Appendix 3](#)). We did not find randomized controlled trials or controlled studies that compared charged particle therapy with photon therapy directly. [Appendix 4](#) shows the characteristics of the included studies. From the 70 studies, 73 cohorts were identified. 53 cohorts were treated with photon therapy [11,20–70] (3577 patients) whereas 20 received charged particle therapy [71–88] (1627 patients; [Table 2](#)). Overall, 5204 patients were included, with a median age of 67 years (range: 55–81) for the charged particle therapy (CPT) cohorts, 62.4 years (range: 53–74) for SBRT cohorts and 59.0 years (range: 51–68) for the conventional radiation therapy (CRT) cohorts. The median radiation dose and follow-up duration was higher in CPT cohorts than SBRT and CRT cohorts, while the median rate of patients with child-pugh A class was higher in CRT cohorts than CPT and SBRT cohorts ([Table 1](#)). Additionally, median tumor size, rate of male, rate of patients with ECOG PS 0–1, or median HCC patients with tumor vascular thrombosis did not significantly differ between groups.

Methodological quality of the included studies was fair; most studies provided adequate outcome ascertainment, enrolled a

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