Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons


CRD summary
This review found improved survival with carbon-ion therapy in comparison with photon therapy for treatment of mucosal malignant melanomas. Except for paranasal and sinonasal cancer, tumour control and survival appeared similar for proton and photon therapies. Photon therapy had greater toxicity. Given potential limitations in the evidence and review methods, these conclusions should be interpreted with caution.

Authors' objectives
To compare the effectiveness of carbon-ion, proton and photon radiotherapy for treatment of head and neck cancers.

Searching
PubMed was searched from 1990 to February 2010 for studies published in English. Search terms were reported and a full search strategy was presented in an appendix. Further studies were sought through manual searches of reference lists and conference proceedings.

Study selection
Clinical studies that assessed carbon-ions, protons or photons for radical treatment of primary tumours of the head or neck were eligible for inclusion in the review. Studies needed to include at least 10 patients. Radical treatment was defined as treatment with intent to obtain locoregional disease control. Photon studies had to include intensity modulated radiotherapy (IMRT); where no such studies were available, studies that administered conventional photon therapy were considered. Photon studies had to report on tumour control and/or survival.

Included studies assessed patients with various types of head/neck cancer: nasopharyngeal, oropharyngeal, paranasal and sinonasal, mucosal malignant melanoma and adenoid cystic carcinoma. Numbers of patients with each stage of cancer varied between studies (further details were reported). Where reported, total treatment dose of radiotherapy ranged from 10.5 to 75.9 Gray-equivalent (GyE). The number of fractions ranged from 25 to 46 for patients with nasopharyngeal/oropharyngeal cancer. Mean/median age of included participants ranged from 41 to 71 years. The proportion of patients who received chemotherapy ranged from zero to 100%. Various adverse events were reported: xerostomia and dysphagia were considered in nasopharyngeal and oropharyngeal cancer, visual toxicity in paranasal and sinonasal cancer, visual, skin and mucosal toxicity in mucosal malignant melanomas and all reported toxicities in adenoid cystic carcinomas.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the percentage of patients for each outcome. Discrepancies were resolved through consensus. Survival was assessed at two and five years and toxicity data were extracted per type and grade independent of the classification system used. The difference between treatment groups (with 95% confidence intervals CIs) was calculated for each study. Where the required data were not reported, estimates were made from figures or other data where possible. Study authors provided additional data. Discrepancies were resolved by consensus between all the reviewers.

Methods of synthesis
Studies were grouped by outcome and intervention. Effect sizes (with 95% CIs) were pooled using a random-effects model. Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were performed for patients with
nasopharyngeal cancer, oropharyngeal cancer, paranasal and sinonasal cancer, mucosal malignant melanomas and adenoid cystic carcinomas. Meta-regression was performed to explore the effect of various covariates. Covariates that were found to be statistically significant were included in the final model. No statistical analyses were performed for in-silico (performed on a computer or via computer simulation) studies.

Results of the review
Eighty-six observational studies (74 photon, five carbon-ion and seven proton) and eight comparative in-silico studies were included in the review. Individual study sample sizes ranged from 10 to 323 participants (total 4,643).

Nasopharyngeal cancer (15 studies, 1,372 participants): No statistically significant differences were observed for any of the outcomes. Pooled analysis for three-year overall survival showed evidence of significant statistical heterogeneity ($I^2=67.5\%$).

Oropharyngeal cancer (11 studies, 606 participants): No statistically significant differences were observed for any of the outcomes. Pooled analysis for two-year disease-free survival showed evidence of significant statistical heterogeneity ($I^2=49.9\%$).

Paranasal and sinonasal cancer (five studies, 235 participants): Five-year local control after proton therapy was significantly higher compared to intensity modulated photon therapy (88% versus 66%, $p=0.035$, effect size 0.216, 95% CI 0.025 to 0.407, $I^2$ not reported).

Mucosal malignant melanomas (20 studies, 853 participants): Five-year overall survival was significantly higher after carbon-ion therapy compared to conventional photon therapy (44% versus 25%, $p=0.007$, effect size 0.185, 95% CI 0.058 to 0.313, $I^2=51.7\%$).

Adenoid cystic cancer (25 studies, 1,577 participants): No statistically significant differences were observed for any of the outcomes, but all of the pooled analyses showed evidence of significant statistical heterogeneity ($I^2=73.6\%$ to 93.7%).

Comparative in-silico studies (eight studies, number of participants not reported): One study compared carbon-ion therapy and photon therapy and seven studies compared proton therapy and photon therapy. One in-silico study suggested that for paranasal sinus tumours, carbon-ion therapy had the ability to statistically significantly decrease the dose to the contralateral optic nerve. One proton therapy study reported a lower dose to the optic nerves compared with IMRT. For patients with nasopharyngeal, oropharyngeal, hypopharyngeal and squamous cell carcinomas, six studies consistently showed a lower dose to the parotid glands for proton therapy than with IMRT.

Toxicity: Toxicity was generally poorly reported but tended to be less frequent in carbon-ion and proton studies than with studies of photon therapy. In-silico studies showed that the organs at risk were exposed to a lower treatment dose that was independent of the tumour site.

The review reported further covariate analyses.

Authors’ conclusions
Carbon-ion therapy appeared to be associated with an increase in survival for mucosal malignant melanomas in comparison with photon therapy. Tumour control and survival appeared to be similar for proton and photon therapies except for paranasal and sinonasal cancers. Carbon-ion and proton therapies tended to be associated with lower toxicity rates than with photon therapy.

CRD commentary
This review answered a clearly defined research question. Broad inclusion criteria were applied for participants and study designs. Searches for relevant studies were limited to one electronic source. Conference proceedings and reference lists of retrieved studies were screened for further studies. The review was at risk from language and publication biases as only published studies in English were included in the review. Risks of reviewer error and bias were unclear; two reviewers performed data extraction and this suggested that some attempt was made to reduce error and bias. Methodological quality of the studies was not assessed and this made the reliability of the findings unclear.
Inclusion of mostly small observational studies suggested that studies were likely to have methodological problems that may have affected the reliability of the data. The studies varied considerably in other respects that included the characteristics of patient populations and treatment regimens. In some cases, pooling was judged to be inappropriate by the authors. Some attempts were made to investigate the effects of this variability and the presence of co-variables through further analyses. The authors reported that their analyses did not stratify data according to the presence/type of accompanying chemotherapy and/or surgery and also that the reporting of covariates within the included studies was poor. The authors’ description of the analysis methods and also the summary figures of data also lacked clarity in some places. Survival analyses and the reporting of hazard ratios for time to event data such as overall survival were lacking.

This review had a number of potential limitations and the conclusions were based on a relatively small amount of generally poor quality evidence (acknowledged by the authors) which suggest that the findings should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors stated that particle therapy seemed at least as effective as photon therapy with respect to tumour control and may have advantages in sparing organs at risk. Whether there was a beneficial effect in terms of cost was unclear.

Research: The authors stated that an international particle therapy register should be set up to facilitate a definitive comparison of carbon-ion, proton and photon therapies for head and neck cancers with respect to survival and treatment toxicity.

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