A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer
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CRD summary
This review compared the efficacy and cost-effectiveness of hadron therapy and photon therapy. The authors concluded that no definitive conclusions can be drawn for most of the tumour sites, while proton therapy seems to offer some benefits for ocular tumours and base of skull chordomas. The authors’ cautious conclusions reflect the strength of the evidence presented and are likely to be reliable.

Authors’ objectives
To assess the efficacy of hadron therapy (HT), concentrating on external beam therapies, for cancer disease.

Searching
MEDLINE (1966 to 2007), EMBASE (1980 to 2007), the Cochrane Library (Issue 1, 2007), Biological Abstracts (1993 to 2006), CINAHL (1982 to 2007), HTA, ISI Proceedings (Science and Technical), NHS EED, HEED and SIGLE were searched; the search terms were reported. No language restrictions were applied. Experts in the field were contacted for additional unpublished studies.

Study selection

Study designs of evaluations included in the review
The authors did not state any inclusion criteria relating to the study design; it appears that randomised controlled trials, retrospective and prospective studies, and case series were included in the review. Studies were required to have a minimum of 20 patients and a follow-up of at least 2 years.

Specific interventions included in the review
Studies evaluating the efficacy of HT were eligible for inclusion. HT was defined as including neutron, proton and light or heavy ion therapy in the treatment of localised tumours. In the included studies, HT included proton and light or heavy ion therapy. In the control studies, the comparator of interest was photon therapy, which some studies provided together with HT.

Participants included in the review
No a priori inclusion criteria were reported. Studies of patients with tumours of the head and neck, prostate cancer, ocular tumours, gastrointestinal cancer, lung cancer, central nervous system tumours, pelvic cancers, or sarcomas were included in the review.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not explicitly stated. The outcomes extracted were local tumour control, overall survival, cause-specific survival and median survival.

How were decisions on the relevance of primary studies made?
At least two reviewers selected the studies, but the authors did not state how any disagreements were resolved.

Assessment of study quality
At least two reviewers assessed quality according to the criteria of the Cochrane Handbook, the Newcastle-Ottawa Scales for non-randomised studies and the British Medical Journal checklist for economic evaluations.

Data extraction
At least two reviewers extracted the data, but the authors did not state how any disagreements were resolved.

Methods of synthesis
How were the studies combined?
When the tumour site and pathology were similar, weighted means per outcome were calculated. Where this was not possible, the studies were combined in a narrative, grouped by type of intervention and tumour site.

How were differences between studies investigated?
Differences in study participants, design, outcomes and interventions were described in the text and presented in a table.

Results of the review
Seventy-five studies were included in the review: 40 studies on proton therapy (n=11,314), 22 studies on ion therapy (n=2,534) and 13 economic studies.

Head and neck cancer: proton and ion therapy carried similar local tumour control rates and overall survival to photon therapy. Ion therapy seemed to achieve a better 5-year local tumour control than photon therapy for adenoid cystic carcinomas (1 study).

Prostate cancer: the rates of local tumour control, 5-year overall survival, and late gastrointestinal and genitourinary toxicity were 74%, 89%, 15% and 7%, respectively, with proton therapy, 100%, 89%, 6% and <5%, with ion therapy, and 83%, 66%, 29% and 28% with high-dose photon therapy.

Ocular cancer: local tumour control at 5 years was 97% with both photon and proton therapy and 96% with ion therapy. The rate of neovascular glaucoma seemed lower with proton (12%) and higher with ion therapy (36%) in comparison with photon therapy (16%).

Gastrointestinal cancer: compared with historical controls treated with photon therapy, protons seemed to achieve better local tumour control and overall survival of oesophageal cancer. For hepatic cancers, the local tumour control and the 5-year overall survival were 87% and 61%, respectively, with protons, 81% and 50% with ions, and 80% and 43% with photons. For pancreatic cancer, one study suggested slightly higher rates of local control for patients treated with ions (10%) than for patients treated with photons (5%).

Lung cancer: the 3- to 5-year local control rate and the 5-year overall survival were 68% and 23%, respectively, with protons, 77% and 42% with ions, and 87% and 44% with photons. The incidence of pneumonia grade 2 or higher occurred more often with proton therapy (10%) than with ions (1%) or photons (4%).

Intracranial cancer: protons or C-ions appeared to achieve a higher local tumour control of skull base chordoma than photons. The local tumour control rate and 5-year overall survival for chordomas of the skull base were 63% and 81%, respectively, with protons, 72% and 83% with ions, and 25% and 44% with photons. For chondrosarcomas of the skull base, proton therapy achieved a 5-year tumour control rate of 95%, ion therapy achieved a rate of 86%, and photon therapy a rate of 100%.

Pelvic cancer.

Cervix cancer: local tumour control was obtained in 75% of cases with proton therapy and between 56% and 59% with ion therapy. Where reported, toxicity of at least grade 2 occurred in 30% of patients treated with protons, 6.5% of those treated with ions and 3% of those treated with photons.

Bladder cancer: local tumour control and 5-year overall survival were 59% and 16%, respectively, with protons and 69% and 54% with photons. A higher bladder preservation rate was reported by proton therapy (68% up to 96%) compared with photons (63%).

The authors stated that preliminary data on the effects of HT on sarcomas were promising.

Cost information
The authors stated that there was little evidence on the relative cost-effectiveness of HTs when compared with each other, with photon therapy, or with other cancer treatments.

**Authors' conclusions**

Overall, the introduction or extension of HT as a major treatment modality into standard clinical care is not supported by the current evidence base. However, the efficacy of proton therapy appears superior to that of photon therapy for some ocular and skull base tumours. For prostate cancer, the efficacy seems comparable to photon therapy. No definitive conclusions can be drawn for the other cancer types.

**CRD commentary**

This review addressed a well-defined question in terms of the study intervention, while it adopted a broad definition of study design. Several databases and trial registers were searched and efforts were made to find additional published and unpublished studies. No language restrictions were applied, thus limiting the potential for language bias. The potential for publication bias was not assessed in the report. The authors attempted to limit bias and error by conducting critical phases of the review process in duplicate. A formal quality assessment was planned but not reported in the review. Where the studies were quantitatively combined, summary estimates were given without confidence intervals and statistical heterogeneity was not formally evaluated. Few head-to-head studies were included in the review and direct comparison with photon therapy is therefore limited. The authors’ cautious conclusions seem to reflect the strength of the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that proton therapy emerges as the treatment of choice for some ocular and skull base tumours.

**Research:** The authors stated that further studies evaluating the clinical and cost-effectiveness of HT compared with conventional therapy are needed.

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