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Systematic review

Proton therapy – A systematic review of clinical effectiveness

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Abstract

***Background and purpose*: Proton therapy is an emerging treatment modality for cancer that may have distinct advantages over conventional radiotherapy. This relates to its ability to confine the high-dose treatment area to the tumour volume and thus minimizing radiation dose to surrounding normal tissue. Several proton facilities are currently operating or under planning world-wide – in the United States, Asia and Europe. Until now no systematic review assessing the clinical effectiveness of this treatment modality has been published.**

***Materials and methods*: A systematic review of published studies that investigated clinical efficacy of proton therapy of cancer.**

***Results*: We included 54 publications: 4 randomized controlled trials (RCTs) reported in 5 publications, 5 comparative studies and 44 case series. Two RCTs addressed proton irradiation as a boost following conventional radiation therapy for prostate cancer, where one demonstrated improved biochemical local control for the highest dose group without increased serious complication rates. Proton therapy has been used to treat a large number of patients with ocular tumours, but except for one low quality RCT, no proper comparison with other treatment alternatives has been undertaken. Proton therapy offers the option to deliver higher radiation doses and/or better confinement of the treatment of intracranial tumours in children and adults, but reported studies are heterogeneous in design and do not allow for strict conclusions.**

***Conclusion*: The evidence on clinical efficacy of proton therapy relies to a large extent on non-controlled studies, and thus is associated with low level of evidence according to standard heath technology assessment and evidence based medicine criteria.**

Keywords: Systematic review; Proton therapy; Clinical effectiveness

Already in the mid 1940s Robert Wilson hypothesized that highly localized deposition of energy from proton beams could be utilized in increasing the radiation doses to tumours while minimizing radiation to adjacent normal tissues. Shortly thereafter, scientists at the Lawrence Berkeley Laboratory initiated the first studies on proton irradiation to confirm this hypothesis [1].

The depth dose distribution of proton beams differs significantly from that of photon beams. Protons show an increasing energy deposition with penetration distance leading to a maximum, named the Bragg-peak, near the end of the range of the proton beam. In front of the Bragg-peak, the dose level is modest as compared to photon beams; beyond the Bragg-peak the dose falls practically to zero. By choosing appropriate proton beam energies, the depth of the Bragg-peak can be adjusted according to the depth and extent of the target volume. Hence, excellent conformality can be achieved compared to conventional or intensity modulated radiotherapy.

A number of treatment plan comparison studies have demonstrated that proton irradiation offers a far better conformality as compared to conventional and other conformal irradiation techniques [2–6] Potentially, proton therapy may therefore lead to either reduction of adverse effects, and/or increased local tumour control, without an accompanying increase in late normal tissue/organ toxicitity [6]. Secondary malignancies are of particular concern in long-term survivors of paediatric cancers following conventional radiotherapy [7]. Results from dose-planning proton therapy studies have raised the question as to whether the improved dose confinement in proton therapy may reduce the risk of secondary malignancies. In contrast to photon intensity-modulated-radiation-therapy (IMRT), where large volumes of healthy tissue are irradiated, proton irradiation is associated with smaller irradiated volumes of normal tissues [2–8].

More than 40,000 patients have so far been treated with proton therapy worldwide. Approximately 20 proton facili-

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ties are in operation, and more are currently under construction or planning. Thus, the number of patients treated with proton therapy may rise considerably in the coming years. An important question is whether the outstanding dose distribution and conformality achieved with proton irradiation translates into improved clinical outcome with respect to increased tumour control and/or reduced treatment-associated complications. The aim of this study was to address these questions through a systematic literature review of clinical effects, using standard criteria for health technology assessment (HTA) [9].

Materials and methods

The review was conducted according to standard methods for health technology assessment [9].

A literature search was carried out in Medline and Embase up to March 2006 with the search profile: ''proton* and therapy and (cancer or carcinoma or malign* or meningeoma* or benign) not helicobacter'' The latter term was necessary to exclude studies on the use of proton pump inhibitors in the eradication of Helicobacter pylori.

Identified articles were assessed for relevance according to predefined inclusion criteria: *Population:* patients with malign or benign tumour, *Intervention:* proton irradiation alone or in combination with surgery or external beam irradiation, *Outcomes:* overall survival, cancer free survival, local control, acute and late adverse effects, functional measures, quality of life and biochemical markers and endocrine status. *Study design:* randomized controlled trials, cohort and case-control studies, patient series and cross sectional studies. Except for studies in children, papers involving <50 patients were excluded.

All studies were scored in accordance with the SIGN system for quality grading [10]. Studies were grouped according to level of evidence: 1 for randomized controlled trials (RCTs), 2 for controlled trials, cohort or case-control studies and 3 for patient series and cross sectional studies. For quality assessment, a checklist was used that considered the randomization process for RCTs, whether groups were comparable with respect to age, disease severity, intervention and co-interventions, co-morbidity, and the time and the actual number of patients that were followed. The validity score used was very good (++), good (+) or poor (−). Only very good or good studies were considered in the final summary of the evidence, though all relevant studies are described in text. Publications with overlapping patient populations were grouped according to treatment institution, and in large considered as one study.

All abstracts and articles were independently assessed by at least two reviewers, and disagreements resolved by consensus or a third reviewer.

Results

The literature search identified 1894 potentially relevant references, and 166 publications were assessed in full text (Fig. 1).

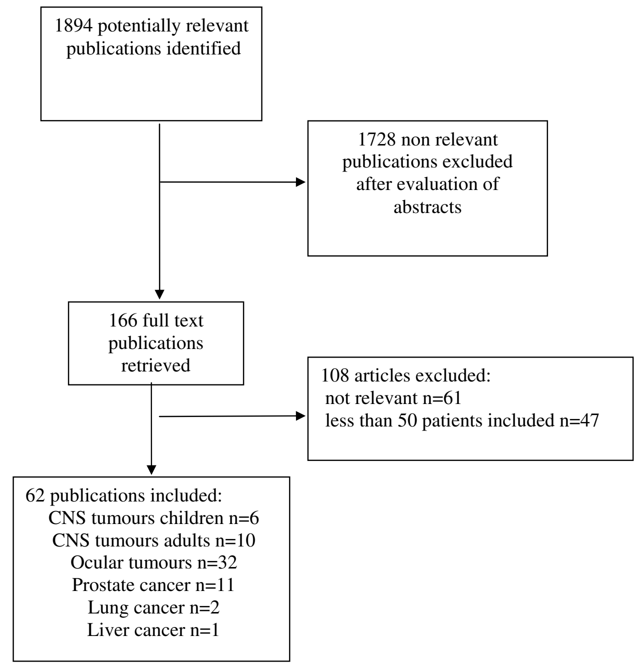

Fig. 1. Overview of the study selection procedure. Inclusion criteria were based on population, intervention, outcomes and study design.

Sixty publications fulfilled our inclusion criteria and were included in the review. Reasons for exclusion were selection bias resulting in incomparable groups, lack of information about important prognostic factors or incomplete follow-up. Four RCTs (five publications), 5 comparative studies and 44 case series were included that reported outcomes following proton therapy. Several publications had overlapping populations as presented below for each indication.

Paediatric intracranial tumours

Six case series were included reporting clinical results following proton irradiation of paediatric intracranial tumours (Table 1). All studies were case series with a limited number of patients included (<30) [11—16]. These studies were heterogeneous with respect to diagnosis, stage and treatment. One study evaluated proton therapy in malignant or benign paediatric intracranial tumours [14], five studies evaluated proton therapy in the treatment of malignant intracranial tumours (Table 1). Proton therapy was given as part of a primary treatment, or as treatment for recurrence. In most studies an aggressive treatment had been administered, and local control rates were high. Complications reported were neuropsychological impairment, hypo-pituitarism and cataract (Table 1). Importantly, only one study assessed quality of life following proton therapy [13]. Follow-up time was too short to evaluate treatment-induced secondary malignancy following proton irradiation.

Ocular tumours

Proton therapy has emerged as an alternative to enucleation or ocular brachytherapy in the treatment of ocular tumours. We included 32 publications that addressed clinical