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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 toxicity [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).

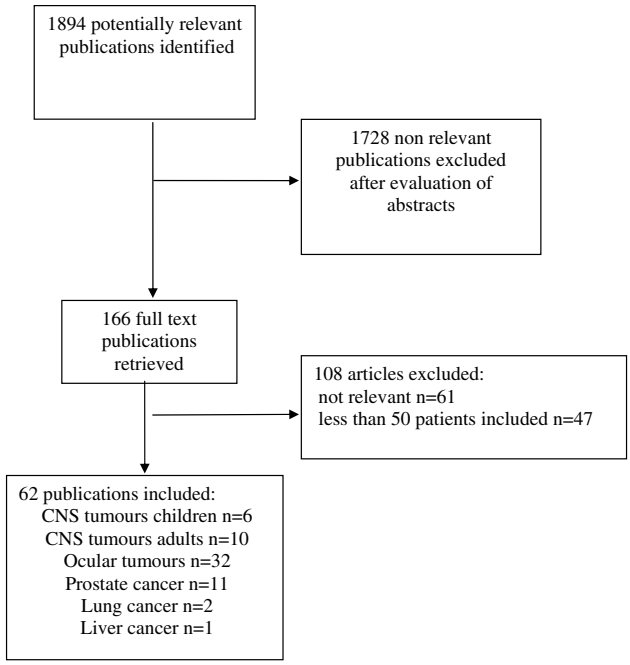

Fig. 1. Overview of the study selection procedure. Inclusion criteria were based on population, intervention, outcomes and study design.

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

Table 1
Studies on proton irradiation of paediatric cranial tumours

Centre	Diagnosis	Treatment	Period	Results	Quality assessment
MGH [11]	Chordomas	Proton + XRT (n = 18) 69 CGE	Na	5 yr overall survival 68% 5 yr disease-free survival 63% 5 yr local recurrence-free survival 78%	LoE: 3 Quality: +
MGH & Loma Linda [14]	Skull base tumours (malignant n = 20, benign n = 9)	Proton (n = 13) Proton + XRT (n = 16) Total dose 71 CGE for malignant, 60 CGE for benign tumours	1992–99	Overall survival: Malignant cases: 65% Benign cases: 100% Local control: Malignant cases: 75% Benign cases: 89% Complications: Pituitary: 27% Late severe effects: 7%	LoE: 3 Quality: +
Loma Linda [13]	Astro-cytomas	Proton (n = 26) 50.4–63 CGE Proton + XRT (n = 1)	1991–97	Overall survival: 82% Local control: 85%	LoE:3 Quality: +
Loma Linda [15]	Skull base tumours	Proton (n = 20) 40–70.2 CGE Proton + XRT (n = 8) 12.6–31.6 CGE + 18–45 Gy	1991–94	4 of 28 patients had treatment related morbidity. No evidence of tumour progression inr 9 out of 28 children	LoE:3 Quality: +
CPO [12,16]	CNS tumours	Proton + XRT (n = 17) 9–31 CGE + 24–54 Gy	1994–2000	1 yr survival 93 ± 6% 3 yr survival 83 ± 11% Local control 92 ± 8% Neuropsycological impairment: 3 of 17 children	LoE:3 Quality: +

XRT, conventional radiation therapy; MGH, Massachusetts General Hospital; CPO, Centre de Protonterapie d'Orsay; LoE, level of evidence; Na, not applicable.

outcomes after proton therapy in patients with such tumours (Table 2). Twenty-seven were case series from proton therapy facilities at Massachusetts General Hospital [17–30,71,72], Loma Linda Medical Center [31], Lousanne [32–35], Orsay [36–40] and Moscow [41]; four publications were from two cohort studies [42–45], and only one was a RCT [46].

The RCT included 186 patients with choroidal or ciliary body melanoma. The study aimed to assess clinical effects of a dose reduction from 70 to 50 CGE (Cobalt Gray Equivalent). The actual dose was 45 CGE [46] No difference was reported between the groups in 5 year recurrence rates, 5-year visual acuity, letters read, or rate of maculopathy and radiation induced papillopathy. The trial was underpowered to conclude whether a lower radiation dose provides comparable cancer control rates as a higher radiation dose.

One study (two publications) in patients with uveal melanomas compared cancer control rates following proton therapy versus enucleation [43,44]. Patients treated with proton therapy were younger, had smaller tumours and different locations compared with controls treated by surgery. Five year overall survival was 81% in the proton therapy group and 68% in the enucleation group. Cox regression analysis adjusted for prognostic variables found no difference in overall survival, RR 1.2 (95% CI 0.9–1.2), or disease free survival, RR 1.0 (95% CI 0.7–1.4).

One study analysed medical records for patients with choroidal melanoma treated with proton therapy or brachytherapy [42,45]. Local recurrence, mortality and visual acuity were analysed, but the model was not appropriately adjusted for possible confounders (only basal tumour diameter). Patients treated with proton therapy had a higher mortality rate (9.4%) compared to patients given brachytherapy (3.7% and 5.0% for ^{125}I or ^{106}Ru, respectively), but a lower rate of local recurrence (5.2%), compared with 4.2% and 10.7% for ^{125}I or ^{106}Ru, respectively.

Twenty-seven case-series reported outcomes following proton therapy treatment of ocular tumours. Several publications had overlapping data, and we therefore grouped them by treatment centre (Table 2). Reported 5 year survival rates ranged from 70% to 95%, reflecting the diversity in population, indication, and patient risk. Disease-free survival varied from 85% to 96% for 5 year follow up, 76% to 95% for 10 year follow up and 73% for 15 year follow up [28].

Table 2
Studies on proton irradiation of ocular tumours

Centre	Treatment	Period	N	Results	Quality score
MGH [46]	Proton 70 (n = 94) vs 45 CGE (n = 94)	1989—94	188	5 year outcomes: no difference in tumour regrowth, visual acuity, letters read or maculapathy	LoE: 1 Quality: +
MGH [43,44]	Proton (n = 556) vs surgery (n = 257)	1975—84	813	No difference in mortality (overall or cancer related) in adjusted Cox model	LoE: 2 Quality: +
St. Bart. [42,45]	Proton 60 CGE (n = 267) vs ^{125}I 100 CGE (n = 190) vs ^{106}Ru 100 CGE (n = 140)	1988—98	597	Local recurrence Proton: 5.2%, Ru: 10.7%, I: 4.2% RR 2.9 (95% CI 1.3—7-0) for proton vs Ru, but improper adjustment for confounders Complications: higher rates of later enucleation and vascular glaucoma for patients treated with protontherapy	LoE: 2 Quality: —
MGH [17—30,71,72]	Proton 70 CGE	1975—98	1922	Survival Overall: 5 yr 78—95%, 10 yr 63% Diseasefree: 5 yr 80—95% 10yr 76—79% 15 yr 73% Enucleation rates : 2 yr 5%, 5 yr 10% Visual acuity: 67% visual loss <20/100 5 yr radiation maculopathy: 64%	LoE: 3 Quality: +
Loma Linda [31]	Proton 70 CGE	1990—98	78	5 yr overall survival: 70 ± 7.8% 5 yr local control: 91 ± 3.7% 5 yr eye retention: 75 ± 6.3%	LoE: 3 Quality: +
Lousanne [32—35]	Proton 54.5 CGy (range 40—64 Gy)	1984—98	2432	5 yr survival: 83 ± 1% Local control: 5 yr 96% 10 yr 95% Visual acuity: improved in 22 of 31 patients Radiation induced complications reported in patients treated with highest doses	LoE:3 Quality: +
CPO [36—40]	Proton 60 CGE	1989—98	1272	5 yr overall survival: 78% 6 yr diseasefree survival: 77% Visual acuity: 67% reported reduction in visual acuity Eye retention: 88—96% Maculopathy: 35% Cataract: 23%	LoE: 3 Quality: +

MGH, Massachusetts General Hospital; CPO, Centre de Protonterapie d'Orsay; St. Bart., St Bartholomeus Hospital, London; LoE, level of evidence.

Chordomas and chondrosarcomas

Chordomas and chondrosarcomas in the head and neck region are usually treated with surgery and/or radiotherapy. Conventional radiotherapy with doses of 50—55 Gy do not provide sufficient cancer control, but higher doses may be offset by toxic effects on surrounding neurological tissues. Ten publications were included that reported clinical outcomes following proton therapy of chordomas and chondrosarcomas [47—56] (Table 3). One study randomized 96 patients with chordomas and chondrosarcomas of the skull base to receive 66.6 or 72 CGE with a combination of proton and photons [55]. The only publication identified from this study reported temporal lobe damage without analysing patents by initial allocation group, and was not able to relate temporal lobe damage to treatment strategy. Overall temporal lobe damage was 7.6% at 2 years and 13.2% after 5 years.

Nine case-series reported results for around 500 patients treated with proton therapy alone or as a supplement to conventional radiotherapy (Table 3). Proton therapy was given as part of primary treatment or for recurrence. Five and 10 year survival was 94% and 86%, respectively, for the whole population [49]. Two studies reported lower overall survival for chordomas compared with chondrosarcomas, at 3 year follow up 87—88% and 94—100%, respectively, [51,53]. Reported treatment related complications were grade 3 or 4 toxicity of 5—7.7%, hearing loss 3.4—18% [51,53]. In a multivariate analysis, risk of brain stem toxicity was increased with increasing volume of brainstem receiving over 60 CGE, RR 11.5 (p = 0.001) [49].

Table 3
Studies on proton irradiation of chordomas and chondrosarcomas

Centre	Treatment	Period	*N*	Results	Quality score
MGH [55]	Proton 67 vs 72 CGE	1984–93	96	Temporal lobe damage; 2 year 7.6% 5 year 13.2%	LoE:1 Quality: –
MGH [47–50,52]	Proton, proton +XRT	1974–95	367	Overall survival: All patients: 5 yr 94%, 10 yr 86% Chordoma: 5 yr 80% Chondrosarcoma: skull base 91%, cervical spine: 48% Disease free survival: All patients: 5 yr 76% Chordoma: 5 yr 69–73% Chondrosarcoma: skull base 98%, cervical spine 54%	LoE:3 Quality: +
Loma [51]	Proton, proton + XRT	1992–98	60	Overall survival: Chordoma: 5 yr 79% Chondrosarcoma: 100% Local control: Chordoma: 5 yr 59% Chondrosarcoma: 75% Grade 3 or 4 toxicities: 7%	LoE:3 Quality: +
CPO [53,54]	Proton + XRT 60–70 CGE	1995–2000	67	Overall survival: Chordoma: 3 yr 88% Chondrosarcoma: 94% Local control: Chordoma: 3 yr 71% Chondrosarcoma: 85% Grade 3 or 4 toxicities: 7.7%	LoE:3 Quality: +

MGH, Massachusetts General Hospital; CPO, Centre de Protonterapie d'Orsay; LoE, level of evidence.

Prostate cancer

There is a concern that conventional radiotherapy for prostate cancer at doses associated with acceptable adverse effects may not provide sufficient cancer control. Proton therapy may thus offer an option both for dose escalation and for better confinement of the treatment. We included eleven publications, two RCTs [57–59], eight comparative studies or case-series [60–67] (Table 4). Together these studies comprise almost 2000 patients.

One trial randomized 393 patients with early stage (TIB-TIIB) prostate cancer to a proton boost dose of 19.8 CGE or 28.8 CGE following photon irradiation to 50.4 Gy. There was no difference in 5-year survival (96 vs 97 %), but an improvement in 5-year biochemical local control rate from 61.4% for the low dose group to 80.4% for the high-dose group ($p < .001$), representing a 49% reduction in the risk of local failure. No difference in late and acute GI/U-toxicity was reported, nor was there any difference in late and acute GI-toxicity, grade III, between the groups. However, a moderate difference in acute grade II GI-toxicity (41% vs 57% for low and high dose group, respectively), and in late grade II GI-toxicity (8% vs 17% for low and high dose group, respectively) was seen in this study. In the other RCT, 202 patients with locally advanced (T3 or T4) prostate cancer were randomized to receive conventional radiation therapy to 50.4 Gy plus a proton boost of 25.2 CGE, or a photon boost of 16.8 Gy. No difference in overall survival was reported, but an improved local control in patients with poorly differentiated tumours was observed; 19% vs 85% local tumour control at 8 years in the low dose group and high dose group, respectively. The actuarial rectal bleeding rates at 8 years were significantly higher for the high radiation dose group (32%) than the conventional dose arm (12%). Eight publications reported results from low quality comparative studies or case-series [60–67], six with overlapping data (Table 4). In general patients treated with proton therapy had less advanced prostate cancer compared with conventional radiotherapy, and thus comparison regarding cancer control or complications may be confounded by underlying differences in severity.

Non-small cell lung cancer

We included two case series that addressed proton therapy for non-small cell lung cancer (NSCLC) in patients considered inoperable [68,69]. One study from Loma Linda included 68 patients with stage T1 or T2 NSCLC that were given proton irradiation to 51 or 60 CGE [68]. Overall survival at 3 year was 44%, disease specific survival was 72% and metastatic relapse rate was 31%. Overall survival was higher for patients in the high dose compared with the low dose group (55 vs 27%). The other study included 54 patients with stage I–IV NSCLC, that received proton irradiation of 49–93 CGE or conventional radiation therapy plus proton irradiation to 53–89 CGE. Further analysis and interpretation of

Table 4
Studies on proton irradiation of prostate cancer

Centre	Treatment	Period	Results	Quality score
MGH & Loma Linda [59]	XRT 50.4 Gy + proton 19.8 GyE (n = 197) vs XRT 50.4 Gy + proton 28.8 GyE (n = 196)	1996–99	5 year survival Low dose: 95% High dose: 97% 5 year local failure Low dose: 61% (95% CI: 54–68%) High dose: 80% (95% CI: 75–86%) Morbidities (low vs high dose) Acute GI grade II: 41% vs 57%, p = .004 Late GI grade II: 8 vs 17%, p = .005 Acute GU grade II: 42 vs 49%, p = ns Late GU grade II: 18 vs 20%, p = ns No difference in grade III or IV toxicities	LoE:1 Quality: ++
MGH [57,58]	XRT 50.5 Gy (n = 103) vs XRT + proton 50.4 Gy + 25.2 Gy (n = 99)	1982–92	No difference in overall or diseasefree survival Rectal bleeding grade I or II XRT + proton: 32 % p = .002 XRT: 12% Urethral stricture XRT + proton: 19% p = .007 XRT: 8%	LoE:1 Quality: +
MGH [60]	XRT 60–68 Gy (n = 116) vs XRT + Proton 70–76.5 Gy (n = 64)	1973–79	No difference in overall or disease free survival Rectal symptoms (proton boost vs XRT) 20% vs 16% Urinary symptoms 33% vs 34%	LoE:2 Quality: +
MGH [61]	Proton + XRT 50.4 Gy + 27 GyE (n = 39 of 167 patients)	1976–92	Grade II or higher GU morbidity 15 yr: 59% Grade II or higher GI morbidity 15 yr: 13%	LoE:3 Quality: +
Loma Linda [62–67]	Proton, proton + XRT 74–75 CGE (n = 909)	1991–95	Diseasefree survival Biochemical: 75–89% Clinical: 89–95% Morbidity 3 yr Rectal bleeding: 21% Grade II GI: 3.5% Grade II GU: 5.4%	LoE:3 Quality: +

MGH, Massachusetts General Hospital; LoE, level of evidence.

outcomes was hampered by selective censoring of patients from analysis, the heterogeneity of patient population and in treatment given.

Hepatocellular cancer

We included one case series on proton therapy for liver cancer [70]. 162 patients with hepatic tumours, mainly stage I and stage II, received proton irradiation to a median dose of 72 CGE, ranging from 50 to 88 Gy [70]. Overall survival at 5 years was 24% and local control was 87%. Acute effects like elevation of bilirubin and anemia were rare; late effects like bile duct stenosis and GI bleeding were also uncommon.

Discussion

This systematic review of clinical effectiveness of proton therapy demonstrates that although a large number of patients have been treated worldwide, few adequately controlled studies have been reported. We identified only 4 RCTs, comprising less than 700 patients, i.e., 1–2% of the entire population treated with proton therapy. The evidence of clinical efficacy of proton therapy is with a few exceptions at a rather low level, and the currently available information does not answer whether the outstanding dose distribution and conformality achieved with proton irradiation translates into improved clinical performance compared to conventional or intensity modulated radiotherapy. New randomized trials should thus be initiated to assess the clinical performance of proton therapy prior to a large scale routine clinical implementation.

Paediatric cranial tumours

All studies on proton irradiation of paediatric intracranial tumours were case series and offered no comparison to other treatment strategies. The studies comprised a limited number of patients and were heterogeneous with respect to diagnosis, stage and treatment. Local control rates reported

were high, but neuropsychological impairment, hypo-pituitarism and cataract were reported. A model study by Mu et al., shows that the risk of treatment-induced secondary malignancies can potentially be significantly reduced by proton irradiation instead of conventional photon irradiation of intensity modulated radiation therapy [8]. This conclusion is further supported by a theoretical study by Hall [7]. In the case series of paediatric intracranial tumours included in our review the evaluation of treatment-induced secondary malignancy was not possible due to numbers and short follow up time. Overall, the evidence level on clinical efficacy of proton therapy of these tumours is low.

Ocular tumours

The only randomized clinical trial identified addressing proton irradiation of ocular tumours aimed at assessing the clinical effects of a dose reduction and offered thus no evidence for the clinical effectiveness of proton treatment as such. Moreover, this trial was underpowered with respect to investigating cancer control rates. One non-randomized study compared local control for patients with uveal melanomas treated with proton therapy versus enucleation. The two groups were not comparable with respect to patient characteristics. However, adjusting for prognostic variables, Cox regression analysis revealed no difference in survival. Another non-randomized study analysed retrospectively the clinical effectiveness of proton irradiation of choroidal melanomas to intraocular brachytherapy. Again, the two groups were not comparable with respect to patient characteristics and the analyses were inconclusive. A number of case-series reported a wide range of survival rates, reflecting the diversity in patient population, indication, and tumour biology. Overall, the evidence level on clinical efficacy of proton therapy of these tumours is low.

Chordomas and chondrosarcomas

The only randomized clinical trial identified addressing proton irradiation of patients with chordomas and chondrosarcomas compared two different dose levels with respect to temporal lobe damage, and thus offered no evidence for the clinical effectiveness of proton treatment as such. No differences between the two groups were found. The several case series included in this review reporting on proton irradiation of chordomas and chondrosarcomas involve approximately 500 patients. They were treated with proton therapy alone or as a supplement to conventional radiotherapy, either for primary tumours or for recurrences. Five and 10 year survival was high in these studies and grade 3 or 4 toxicity limited. According to standard heath technology assessment criteria the evidence level on clinical efficacy of proton therapy of these tumours is low.

Prostate cancer

The studies on proton irradiation of prostate cancer comprise nearly 2000 patients, mostly from patient series. The two randomized clinical trials that were identified compared two different proton boost dose levels, following conventional photon irradiation to approximately 50 Gy. Both studies demonstrate an increase in 5-year biochemical local control, especially in poorly differentiated tumours, but now gain in survival. Toxicity reported was moderately increased in the high dose group as compared to the low dose group. A fraction of these patients were treated in the lithotomy position using a single 160-mV proton fixed beam, directed through the perineum. The Bragg-peak characteristic of the proton beam was thus not utilized for rectal shielding; the rectal shielding relies rather on the penumbra of the proton beam. A relevant question is of course whether the same degree of shielding could have been achieved by intensity modulated radiation therapy. In the comparative studies or case-series the patients treated with proton therapy had in general less advanced disease as compared to those given conventional radiotherapy, and thus largely inconclusive with respect to effectiveness of proton therapy of prostate cancer. Although the evidence level on clinical efficacy of proton therapy of prostate cancer is not high, clearly the two randomized clinical trials offer some evidence on the clinical implications of dose escalation using proton irradiation.

Non-small cell lung cancer and hepatocellular cancer

The two case series that addressed proton therapy for non-small cell lung cancer were hampered by selective exclusion criteria, heterogeneity of patient population and in the treatment given. Analysis and interpretation of outcomes were therefore difficult.

The one case series on proton therapy for liver cancer comprised 162 patients, mainly stage I and stage II, that received proton irradiation to 50–88 CGE [70]. Analysis of overall survival, local control and adverse effects was not possible due to the large variation in dose given, as well as heterogeneity in patient population.

According to standard heath technology assessment criteria the evidence level on clinical efficacy of proton therapy of these two groups of tumours is low.

Numerous treatment planning studies have clearly demonstrated that proton irradiation offers a superior conformality, and reduced dose to adjacent normal tissues and critical structures, as compared to conventional and other conformal irradiation techniques [7]. This alone is, however, not a sufficient argument for proven clinical effectiveness of proton therapy. Health technology assessment and evidence medicine require empirical data rather than arguments solely based on rationality. Since empirical arguments are scarce, more randomized clinical trials are required. Such studies are, however, only ethical if there is a true uncertainty with respect to the clinical performance of, in this case of, proton irradiation. Better clinical performance in the case of highly conformal radiation therapy would be enhanced therapeutic ratio; i.e. reduced late adverse radiation effects, increased local tumour control, or survival, or both. This concept of 'equipoise', or the 'uncertainty principle' of clinical medicine expresses the ethical basis of randomized clinical trials.

The crucial question is then whether there really is an uncertainty related to whether a lower dose to normal tissues and organs at risk as well as increased tumour dose actually is associated better clinical performance, irrespec-

tive of radiation delivery technology. There is solid clinical evidence that lowering doses to normal tissue structures will reduce late toxicity. Proton therapy may simply be regarded as a technology that allows for an extraordinary reduction in dose to healthy tissue, as compared to other treatment methods. It may therefore be questionable whether large randomized clinical trials investigating whether lowered doses to normal tissues by proton irradiation will reduce late toxicity, as compared to standard radiation therapy, are ethical. Also the evidence that increased tumour dose leads to better local tumour control is vast. On the other hand, there is an uncertainty with respect to what extent late adverse effects may be reduced by the extraordinary dose reduction achieved by proton therapy. The Helsinki declaration, article 6, provides support for conducting randomized clinical trials: ''Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality''. Randomized trials should in general be performed prior to introducing proton therapy as routine treatment. However, for rare malignancies, like paediatric intracranial tumours, the limited number of patients and the diversity in clinical presentation may not allow for randomized clinical trials to be conducted. Hence, a clinical decision on optimal treatment has to be taken even though the highest level of evidence may not be available.

The above discussion assumes that the sole difference between photon and proton irradiation is the physical dose distribution, and that the biological effect per dose is equivalent. In vitro experiments on cell survival indicate a substantial spread in relative biological effect (RBE) between diverse cell lines. The average RBE value at the Bragg-peak, and over a range of dose levels, is the order of 1.2 in vitro and 1.1 in vivo. However, an increased RBE for lower doses per fraction has been observed. This may be of particular importance to adjacent normal tissue structures where dose per fraction is low. Moreover, the possibility for secondary cancer close to the distal dose gradients of proton therapy due to an increased RBE of low-energy protons is of some concern [73]. However, most reports indicate that continued employment of a generic RBE value of 1.1 is reasonable [74]. The uncertainty with respect to the biological effect of proton irradiation calls for more extensive studies to further elucidate what factors influence the development of late toxicity and secondary tumours.

New technologies emerge rapidly in radiation oncology, as in many other fields of modern medicine. Health technology assessment is to some extent a tedious procedure, as it relies on randomized clinical trials, meta-analyses and systematic reviews of such. By the time the medical profession has established the required evidence on clinical performance, the technology has developed further and we are left with today's evidence on yesterday's technology. The technology implemented in modern proton facilities provides the flexibility required for clinical utilization. Appropriate assessment of the clinical performance of proton therapy can now be conducted. However, validation of the current technology can only be achieved within an acceptable time frame as a concerted effort between collaborating proton therapy centres world wide.

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