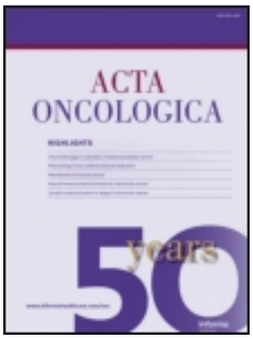

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ORIGINAL ARTICLE

The potential of proton beam radiation therapy in intracranial and ocular tumours

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Abstract
A group of oncologists and hospital physicists have estimated the number of patients in Sweden suitable for proton beam therapy. The estimations have been based on current statistics of tumour incidence, number of patients potentially eligible for radiation treatment, scientific support from clinical trials and model dose planning studies and knowledge of the dose-response relations of different tumours and normal tissues. In intracranial benign and malignant tumours, it is estimated that between 130 and 180 patients each year are candidates for proton beam therapy. Of these, between 50 and 75 patients have malignant glioma, 30–40 meningeoma, 20–25 arteriovenous malformations, 20–25 skull base tumours and 10–15 pituitary adenoma. In addition, 15 patients with ocular melanoma are candidates.

Tumours of the brain and of the nervous system in general are diagnosed in total of 1 300 Swedish cases annually. Some of these are histologically benign, but because of their location they have serious implications unless radically removed. Radiotherapy has an established role in the treatment of both malignant and benign CNS tumours.

Malignant glioma

External radiotherapy is widely used for cases of highly malignant glioma because it affects survival and improves the patient's symptoms [1–6]. On the other hand, irradiation for malignant glioma is unlikely to "cure" patients. Now that radiotherapy is being administered to the majority of patients with highly malignant glioma, a certain improvement has occurred in recent decades regarding time to progression, survival and improvement in the quality of life. The mean survival for material comprising unselected patients is usually between 7 and 10 months. Attempts at raising total dose above 60 Gy, administered in 1.8–2 Gy fractions of photons to treatment volumes corresponding to between half and whole brain have not prolonged survival [7,8]. Most recently, temozolomide given concomitantly to the radiotherapy prolonged survival from median survival from 12.1 months to 14.6 months [9] and two year survival rate was improved from 10.4% to 26.5%.

Studies with the aim to escalate the total radiation dose have been conducted for glioma of high grade malignancy, using implantation or injection of radioactive nuclides [10–13]. In selected cases, a survival was seen that could correspond to a prolongation 3 or 4 times the mean survival achieved with conventional radiotherapy. However, the results have not been confirmed in randomized trials.

In the case of patients with low grade malignant glioma, the size of the radiation dose (*sic*) and its timing in relation to date of diagnosis and surgery have not been shown to influence survival. Consensus is thus lacking with regard to proper time for and design of radiotherapy for patients with low grade malignancy glioma [14].

Clinical experience of proton beam therapy

Protons have been used in the treatment of malignant gliomas, in an attempt to improve the grim

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prognosis [15]. A study at Harvard Cyclotron Laboratory and Massachusettes General Hospital (HCL/MGH) in which the total proton dose was raised to 90 Gy with shrinking fields showed a mean survival of 20 months for 23 patients [16]. Helium ion therapy at the Bevalac multi-ion accelerator (Berkeley University, CA, USA) has not given better survival [17,18], nor does neutron treatment appear to prolong survival. The latter includes both high energy neutrons and epithermal neutrons, used in boron-neutron capture therapy [19,20]. In Uppsala, 80 patients have been treated hitherto, with results suggesting that survival can have been prolonged by 3–5 months compared with "conventional therapy" (Blomquist et al., unpublished data). In these patients proton therapy was used as a boost to external photon irradiation. Closer assessment of any survival prolongation is precluded, however, as the study was not randomized.

Model studies

The dose distributions which can be achieved with protons, scanned protons especially, mean a smaller dose load on the adjacent and apparently healthy brain [21]. This may reduce the acute and long-term effects of irradiation being of particular importance in paediatric tumours [22]. Due to the uncertainty of dose-response relations for irradiation of malignant glioma, it is impossible to judge whether the dose elevation attainable implies greater long-term survival. A complicating factor is the diffuse infiltration of tumour cells far away from the primary glioma.

Assessment of the number of cases for proton beam therapy

The SBU 12-week survey in the autumn of 2001 shows 288 radiotherapy treatments given to patients with brain tumours [23]. Ninety-eight of these were primary brain tumours. In addition, brain metastases were treated with radiotherapy on 179 occasions. On an annual basis, this means that about 400 patients were given radiotherapy for primary tumours of the brain and that just over half of them were suffering from malignant glioma (about 150 high-grade and 50 low-grade).

Given the severity of the prognosis for malignant gliomas, various new therapy concepts are called for. Proton beam therapy seems unlikely to bring about a radical improvement in treatment outcomes, but it is quite possible that survival and quality of life can be improved, which may be clinically meaningful, above all in younger patients and in more favourable histology, e.g. grade III astrocytoma.

Patients with low-grade malignant glioma are not front-line candidates for proton beam radiotherapy. A clear delimitation of the radiation dose, which is possible with proton therapy, would, however, reduce the long-term effect on cognitive functions, depending on the localization of the primary tumour. At a rough estimate, 100 or possibly 150 of the total of 350–400 new malignant glioma cases occurring annually could be eligible for inclusion in a clinical trial.

Research needed

Extensive research is needed in order to identify radically improved treatment of malignant gliomas. These studies will also have to include better possibilities of delimiting volumes containing tumour cells [24–27]. Prospective studies should be initiated when a facility is in clinical operation. In view of the great dependence on results on the selection of patients, the studies should be randomised. It seems less likely that of ion beam irradiation leads to any substantial improvement in treatment outcomes.

Proton beam therapy will probably have to be combined with other modalities such as chemotherapy and injection into the brain of substances with selectivity for certain receptors tagged with radioactive nuclides. High-grade malignant gliomas are highly heterogeneous, both within and between tumours in virtually all aspects studied. A combined approach using different treatment modalities might overcome this problem and create control both of the relatively solid primary tumour and the diffusely infiltrating disease.

It is doubtful whether ions present any therapeutic advantage. The limited radiation-sensitising effect of misonidazole, for example, argues against this [28].

Summary assessment

Between 50 and 75 is a reasonable estimate of the number of malignant glioma patients eligible for proton beam therapy in a clinical study. For a randomised study, the number of potentially includable patients is higher.

Meningeoma

Meningeoma accounts for roughly a quarter of all intracranial tumours, i.e. over 300 new cases are diagnosed in Sweden annually [29]. The majority are benign, WHO grade I. Surgery is nearly always the prime alternative for treatment [30–32]. In cases where the tumour recurs within a few years of the primary operation and the patient is re-operated, or

for technical reasons the surgeon is forced to leave residual tumour, radiotherapy is probably indicated [33–40]. Historical controls and phase II studies suggest that a large proportion of these patients can then avoid new surgery. The effect of radiotherapy is usually that the remnant of the meningeoma does not grow again for an observation period of many years. Controlled phase III studies are lacking, however.

Clinical experience of proton beam therapy

In Uppsala hitherto, 140 patients have been treated with residual WHO grade 1 skull-base meningeoma. The treatment was given with four fractions of 5 or 6 Gy in the course of one week. The results with a follow-up time of up to eight years show that 85–90% of the tumours do not progress after irradiation [41,42].

The results from Paul Scherrer Institute (PSI), Switzerland, using spot-scanning proton radiation therapy and radiosurgery, for 16 patients with untreated, recurrent or residual meningeomas were found to be effective with a three-year progression-free survival exceeding 90%, with predictable, dose-related toxicity [43].

Similar results have been reported for conventional photon radiotherapy and radiosurgery. The treatment time for protons is limited to one week, as against the 5–6 weeks required for conventional techniques. Proton beam therapy also means smaller treatment volumes. This is expected to result in decreased risk of complications, especially as regards long-term cognitive effects.

Model studies

Five cases of meningeoma were included in a comparative model study, revealing superiorly for protons above all other techniques including stereotactic radiotherapy [44].

Assessment of the number of cases eligible for proton beam therapy

No reliable statistics are available concerning the number of meningeoma patients receiving radiotherapy. We estimate that radiotherapy is indicated for 20–25% of patients, primary or relapsed, and that at least half of these are eligible for proton beam therapy. In the SBU survey, nine patients were irradiated to locally "adequate" doses (50–60 Gy), which on an annual basis in Sweden meant roughly 40 patients [23].

Research needed

Randomised studies are lacking in this field. No phase III study is known in which post-operative radiotherapy is compared with waiting. Any attempt at such a study in Sweden has been precluded previously by the fluctuation of interest in post-operative radiotherapy. EORTC is at present designing a new randomised protocol [45]. Further studies using PET technique are for target definition and follow-up. It will also be necessary to develop techniques for treating meningeomas of thin meningeal extent, "carpet-like growth". An approach with a scanning proton beam may solve the problem of treating such thin targets.

Summary assessment

In Sweden, between 30 and 40 patients annually with meningeoma may be eligible for proton treatment.

Arteriovenous malformations (AVM)

In Sweden, between 50 and 75 new cases of arteriovenous malformations (AVM) in the brain are diagnosed annually. A database on this subject is under construction.

Patients with AVM of the brain risk suffering cerebral haemorrhage which can cause lasting disability and at worst prove fatal [46,47]. This often affects relatively young or middle-aged patients. Diagnosis is best undertaken with the aid of angiography. Surgery for the removal of the malformation is usually the prime treatment option [48], but this is only feasible in between a quarter and one-third of the patients (preliminary database information). If surgery is not possible, an investigation is made to see whether the AVM can be embolised and/or obliterated with radiotherapy. Embolisation does not always result in complete obliteration. In some cases, for technical reasons, embolisation is not feasible, possibly because the vessels supplying the malformation are too small or have kinks which preclude catheterisation. Radiotherapy is frequently an option where these patients are concerned [49–53].

Experience using protons therapy

In cases where the radiation target measures less than 10 cm^3, Larsson's/Leksell's gamma knife is used on some patients [51,52] and a linear accelerator with stereotactic equipment on others [53]. Where bigger radiation targets are involved, these modalities do not always give the same obliteration frequency as proton beam therapy [54,55]. The time

from treatment to obliteration frequently is several years for AVMs between 10 and 30 cm^3 in volume. In Uppsala, the majority of the 80 patients treated hitherto have shown total or near-total regression after treatment [56]. Favourable results among 64 patients with predominantly large AVMs have also been reported from Tygerberg hospital, South Africa [57]. The current approach adopted by many centres, in inoperable patients, is to offer embolisation as the first treatment followed by irradiation for a possible remnant. The use of an increased number of comparably lower dose fractions to a higher total dose, e.g. five fractions of 7 Gy to a total dose of 35 Gy should be investigated. Adjuvant treatment with substances targeted to the angiogenesis may also be fruitful to explore.

Model studies

In a patient with a large, deep-seated AVM, clear dose distribution advantages were seen with protons [58].

Assessment of the number of cases for proton beam therapy

Twenty to 25 patients annually, especially patients with AVMs exceeding 10 cm^3. For smaller tumours, the same results can probably be achieved by other stereotactic irradiation methods.

Research needed

The interaction of embolisation and radiotherapy needs to be further investigated. Can further volume reduction with embolisation be achieved prior to irradiation? The relation between fraction dose, total dose and possibility of obliteration needs to be mapped in controlled studies [59,60].

Summary assessment

Arteriovenous malformations are highly suitable for proton beam therapy, especially those exceeding 10 cm^3. This corresponds to 20–25 patients per annum.

Skull-base chordoma and chondrosarcoma

The statistics for incidence are not wholly reliable, but in Sweden probably 20 or 30 patients annually develop chordoma or chondrosarcoma of the base of the skull. The literature gives the number of cases as 3–11% of the patients developing sarcoma from bone tissue.

Curative treatment is difficult, for three reasons:

1. Radical surgery to the base of the skull is almost impossible without permanent damage [61].
2. Relatively high radiation doses are needed for local control, especially of chordoma.
3. Proximity to the medulla oblongata and brainstem, which have lower radiation tolerance, limits the possibility of conventional radiotherapy in higher doses [62].

Clinical experience of proton beam therapy

Since proton beam therapy in a clearly defined area makes it possible to raise the total radiation dose compared with other external radiotherapy, from about 60 Gy to 70–76 CGE (Cobalt Gray Equivalents), proton beam therapy has come to be particularly used in the treatment of skull-base tumours [63–74]. Some experience has also been accumulated of carbon ion radiation of these patients (GSI Darmstadt) [75,76] and of helium ion radiation using the now defunct Berkeley University (Bevalac) [77,78].

A protocol for dose increase applied at the HCL, MGH has raised the number of patients with local control from 36% (conventional therapy) to 62% after five years of follow-up. The long-term results are better for chondrosarcoma than for chordoma [69].

In Uppsala, 18 patients for chordoma/chondrosarcoma of the base of the skull have been treated with a schedule modified in the light of experience from HCL/MGH. External radiotherapy has been given with 2 Gy fractions to 46–50 Gy followed by four proton fractions of 3–5 Gy, depending on extent and location. Our limited experience tallies with that reported from HCL/MGH, where the majority of patients achieve local tumour control and the treatments are also tolerated well in the long term.

Assessment of the number of cases for proton beam therapy

All patients, i.e. some 25 patients annually. These patients can also be treated with ion irradiation. Ions may possibly have a better anti-tumoral effect on chordoma, especially for those with large tumours (>30 mL), where the results for protons are not sufficient.

Research needed

The main need here is for clinical studies in which as many patients as possible can be uniformly treated, with prolonged follow-up. It is worthwhile studying proton beam therapy as a boost treatment, e.g. 40–50 Gy photons followed by proton beam therapy

with 2–5 Gy fractions, as well as proton beam therapy with conventional fractionation at total doses corresponding to 70–72 Gy. Examination with sophisticated MR and PET techniques for better radiation target definition for dosage planning is also desirable.

Summary assessment

Assuming all patients operated, or at least biopsied, can take part in a national protocol, treatment of 20–25 patients annually should be possible.

Pituitary adenoma

Pituitary tumours in most patients are benign adenomas. These constitute roughly 15% of all intracranial tumours. With modern immune staining techniques, the majority of adenomas are hormonally active. The hormonal effects resulting from increase hormone production can be manifold. They include hypertension, amenorrhoea, galactorrhoea, reduced libido, acral enlargement associated with acromegaly, change of body habitus accompanying Cushing's syndrome, and development of diabetes. Mass effect, i.e. direct pressure on surrounding brain tissue, can entail decline and elimination of visus and field of vision, i.e. blindness. This is often combined with severe headache.

The treatment is multidisciplinary, comprising both medical-endocrine treatment and surgery. Today radiotherapy is primarily recommended for patients who have already developed pituitary insufficiency [79–82]. Usually "conventional" radiotherapy is given with a three-field technique at doses between 45 and 50 Gy in 1.8–2.0 Gy fractions. The intention is to prevent further adenomal growth and to achieve a certain reduction of size in the long term. Control as regards excess production of growth hormone and ACTH cannot always be achieved. Higher doses increase the risk of complications regarding visual capacity, because the chiasma opticum is located only a few millimetres above the pituitary gland and in certain cases can be "elevated" by the pituitary adenoma. In cases of micro adenoma located within the sella turcica, stereotactic radiotherapy with Larsson's/Leksell's gamma knife can be successful as regards control of hormone production and prevention of growth [79,83].

Clinical experience of proton beam therapy for pituitary adenoma

The results described in the literature mainly stem from previous Harvard experience (R. Kjellberg, mostly unpublished data) [84]. Kjellberg generally used two opposing unmodified Bragg-peaks in his proton beam treatments. The long-term effects of these treatments are questionable and care should be taken in interpreting those data as relevant to cases with proper dose-planning before treatment. Earlier results have also been reported from Moscow [85]. Ions have also been used [86].

Model studies

In a comparative model study, including two pituitary adenomas and 10 other small intra cranial tumours, proton techniques (spot scanning and passive scattering) were superior in all relevant aspects to 3D-CRT, stereotactics arc therapy and IMRT [44].

Assessment of the number of cases for proton beam therapy

Patients with endocrine overproduction can be eligible for proton beam therapy. In view of the proximity to the chasma opticum, it is possible that protons, if they have to be delivered with high fractions, do not present any significant advantages over photons for supracellular growth. Patients with micro adenoma are probably best treated with Larsson's/Leksell's gamma knife [83].

Research needed

Little is known concerning the effect of fractionated treatment with a sharply delimited dose. The primary need is for controlled studies of patients with acromegaly and pituitary Cushing's syndrome where other treatment methods are inadequate. Post-treatment clinical evaluation may take several years.

Summary assessment

It is estimated that in Sweden each year between 10 and 15 patients with pituitary adenoma can be better treated with proton beams than any other technique, but this estimate is uncertain.

Intraocular melanoma

Between 70 and 75 patients annually in Sweden develop intraocular melanoma, which comprises both uveal melanoma and melanoma of the anterior uveal tract. The treatment methods used vary, depending on the size and location of the tumour:

1. Surgical excision, or possibly enucleation.
2. Laser photocoagulation of the fundus.

3. Plaque brachytherapy with a suitable nuclide (Rh-106 or I-125), with a template sutured to the base of the tumour for a few days.
4. Proton beam therapy.
5. Active waiting, with regular observation and recording of the pigmented lesion.

Clinical experience of proton beam therapy

There is widespread experience from many centres concerning proton beam treatment of eye melanoma, with at least 8 000 patients treated. The longest treatment series are from Boston (Harvard Cyclotron Laboratory, now the Northeastern Proton Therapy Center) and the Paul Scherrer Institut in Villigen, Switzerland. In Europe, proton beam therapy is also given in Berlin, Orsay, Nice and Clatterbridge [87–92].

The following doses have been applied: four fractions to 60 CGE (PSI); five fractions to 70 CGE (HCL/MGH). A local control of up to 99% can be achieved after five years' follow-up. The results also include patients surviving for 10 years after treatment, with eye retention in between 80 and 90% of cases.

Twenty intraocular melanoma patients were treated at TSL between 1989 and 1991 with a 72 MeV proton beam. These patients received four 13.5 Gy fractions to a total dose of 54 Gy. Ten patients with melanoma of the iris were treated between 2002 and June 2005.

Assessment of the number of cases for proton beam therapy

Protons are particularly indicated for patients with malignant melanoma located on or near the optic nerve and melanoma located in the iris. For these locations the results of brachytherapy are unsatisfactory [93]. This will probably mean about 15 patients annually. It is possible that ions can achieve similar treatment results, but since those results are excellent already, there is no real scope for further improvement.

Research needed

Studies are needed concerning the feasibility of reducing the total radiation dose or fractions, or of otherwise reducing side effects. A not uncommon phenomenon when treating ocular melanomas is neo-vascularization that may be associated with glaucoma. Substances that interact with that process are highly desirable.

Summary assessment

Each year about 15 patients with ocular melanoma are candidates for proton beam therapy.

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