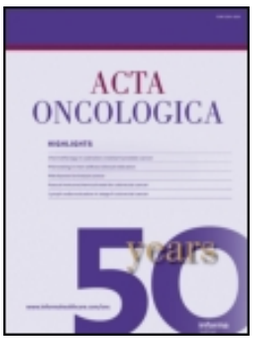

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ORIGINAL ARTICLE

Number of patients potentially eligible for proton therapy

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Abstract

A group of Swedish radiation oncologists and hospital physicists have estimated the number of patients in Sweden suitable for proton beam therapy in a facility where one of the principal aims is to facilitate randomized and other studies in which the advantage of protons can be shown and the magnitude of the differences compared with optimally administered conventional radiation treatment, also including intensity-modulated radiation therapy (IMRT) and brachytherapy, can be shown. The estimations have been based on current statistics of tumour incidence in Sweden, 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 together with information on normal tissue complication rates. In Sweden, it is assessed that between 2200 and 2500 patients annually are eligible for proton beam therapy, and that for these patients the potential therapeutic benefit is so great as to justify the additional expense of proton therapy. This constitutes between 14–15% of all irradiated patients annually.

Radiation therapy plays an important role in curative and palliative tumour treatments and projections show that it will in the future play an even increasingly important role [1–3]. It has continuously improved ever since radiation beams were detected more than a century ago, and this improvement is likely to continue. Radiation therapy research and development, however, also faces many challenges, some of them financial [2]. In spite of large investment costs, radiation therapy remains a comparatively low-cost curative treatment modality [4]. In radiation therapy, investment costs of equipment have to be borne by the hospitals/providers of health care, in contrast for example to medical oncology, where all investment costs are borne by the drug companies, in the hope of new drugs being paid for by hospitals for each individual patient as a result.

Protons have physical properties that will confer dose distribution advantages compared to the conventional rays, photons and electrons. These advantages will result in lower doses to surrounding, non-tumour-containing tissues with reduced acute and late toxicities, and/or higher doses to the tumour with increased probabilities of tumour control. The lower doses to normal tissues may also result in improved tolerance of chemotherapy or other drugs which are being increasingly given with radiation [5]. The distribution advantages may convince fellow radiation oncologists, and thus the experts, but a proven effect on patient-related outcomes must be shown to convince the non-experts [6–8]. Still, dose distribution advantages have generally been sufficient in the past to motivate new investments in high technology treatments. This is no longer the case, partly because of financial constraints, but mainly due to recognition of the importance of evidence-based medicine [6,9,10]. The dose distribution advantages using protons, seen in a number of comparative dose planning studies, must be explored in properly controlled clinical trials to prove

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a sufficiently increased clinical gain in increased tumour cure or improved tolerability.

In spite of almost 43 000 patients being treated with protons worldwide [11], there is an almost complete lack of controlled clinical trials. This is not to say that conclusions cannot be drawn regarding the value of proton therapy from this extensive clinical experience. The many thousand patients with uveal melanoma who have been treated have given 95% local tumour control after 15 years and a retained eye in 84% of cases [4,12]. These results are unlikely to be achieved with any other technique, at least not in cases of larger tumours and tumours located close to the optic nerve. Similarly, the results from the thousands of patients with skull base tumours who have received proton or ion beam treatment have shown clear advantages in the form of better tumour control with unchanged risk of complications compared with those attainable with conventional types of radiation [6,13,14]. Similar experience has been achieved in several studies in the treatment of solid tumours in children. Some improvements in oncology are so evident that randomized clinical trials are impossible to run, being actually unethical. However, patient selection is also important for outcome, and apparently marked improvements may frequently turn out to be absent or at best marginal when the properly controlled clinical trials are performed. This also applies to radiation therapy.

In order to provide better knowledge about the clinical value of proton therapy, prior to a decision to invest in a facility capable of running large clinical trials, i.e. to create better scientific evidence, a national group of experts evaluated the entire literature to estimate the potential number of patients for whom there are potentially sufficient clinical gains to motivate the higher investment costs. A report was originally written in Swedish (available at http://qp1.lul.se/QuickPlace/sptc/Main.nsf) and has now been partly translated and updated to June 2005.

Methods

Estimation of potential number of patients

The number of patients for a new therapy, in this case proton therapy, depends on the number of patients with diseases where the treatment in clinical trials has proved to be better than previous therapies. Since this investigation was made to provide support for an investment in a research facility capable of revealing improved treatment results in clinical trials, the estimations cannot be based upon strong evidence from clinical trials.

A systematic approach to the literature was used [10,15]. A computerized search of the literature was performed in Medline and in the Cochrane Library. These searches had to include mainly clinical trials providing limited scientific information (phase I and II trials) as well as model studies comparing dose distributions achieved with conventional techniques and protons. These model studies have, in one or a limited number of patients, compared the dose distributions achieved with different radiation techniques. They have generally evaluated the physical dose distributions but sometimes also used biological models, estimating the probability of tumour control (TCP) and the probability of normal tissue complications (NTCP).

The number of patients of different ages with a certain type of cancer is obtained from population statistics, and these are well developed in the Nordic countries (e.g. Cancer Incidence in Sweden). Evidence-based indications for radiotherapy in general [16] and in specific tumour types have been estimated in several studies [17–35], and this information was used by the group to get an estimate of the number of patients with the different cancer types in different stages treated with radiation therapy. The differences between these sources of radiotherapy utilization and evidence-base have been discussed [36]. The most relevant information, for this investigation, about the number of patients irradiated was obtained from the 12-week survey performed by the Swedish Council on Technology Assessment in Health Care (SBU) group [37].

Evaluation of the literature and evidence-base for the estimations

The literature for the various diagnoses of interest for radiation therapy was first evaluated by one member of the team. A preliminary draft with conclusions was prepared. This was then scrutinized by the rest of the group and a joint manuscript prepared. The manuscript was sent to all Swedish radiation therapy experts in the different diagnoses, and modifications were made. Finally, the writing was evaluated by invited specialists from the other Nordic countries and a joint decision was taken.

The scientific evidence for proton therapy is not very high according to generally held agreements [10]. In Table I, describing the potential number of patients eligible for proton therapy, the tumour types are ranked according to the clinical experience reported so far, albeit from phase I and II trials only, differences seen in the dose planning model studies, and knowledge about dose-response relationships. For those listed in the top there is very high or high support that protons will be used in

Table I. Estimate of the number of cases from Sweden eligible for proton beam therapy.

Tumour type[1)]	No. new cases in Sweden per annum	No. radiotherapy treatments in Sweden per annum[2)]	Suitable no. patients proton therapy
Intraocular melanoma	75	?	15
Skull-base chordoma/chondrosarcoma	30	?	20–25
Meningeoma	300	40	30–40
AVM	70	?	20–25
Medulloblastoma	30	30	20
Reirradiations		?	150–400
Paediatric cancer (not incl. medulloblastoma)	300	90–100	60–80
Pituitary adenoma	?	?	10–15
ENT cancer-nasopharynx/sinus	80	80	60
Sarcoma	375	175	40
ENT cancer-others	920	570	240
Oesophageal cancer	400	150	80
Rectal cancer	1800	830	150
Breast cancer	6300	3370	300
Thymoma	30	?	20
Lung cancer	2850	485	350
Gynaecological cancer	2700	650	50
Malignant gliomas	375	200	50–75
Cancer of the liver	400	70?	65+
Mesothelioma	100	?	20
Prostate cancer	7800	1420	300
Malignant lymphomas	2000	460	20
Urinary bladder cancer	2300	180	?
Pancreatic cancer	800	50	50?
Gastric cancer	1100	70?	?
Palliations			90
	31 050	7650[3)]	2220–2475+

[1)] The tumour types are listed according to the support in favour of these treatments being given with protons in routine medical care (at the top) or that there are very good (middle) and good prospects (bottom), respectively, of clinical studies showing clinically relevant, "cost-effective" benefits.
[2)] The number of patients, according to the SBU survey, receiving external radiotherapy with a curative purpose in the diagnoses evaluated.
[3)] 9100 treatments were given to 7650 patients.

routine health care, whereas for those listed in the middle and lower part of the table there are very good or good possibilities that randomized clinical trials could show clinically relevant and "cost-effective" gains.

Results

The number of patients potentially eligible for proton therapy each year in Sweden amounts to between 2200 and 2500 (Table I). This figure constitutes about 14–15% of the number of patients (n = 16 000 in the year 2001 according to the SBU-survey [37]), who each year receive radiation therapy in Sweden. A brief summary is given below for each of the diagnoses. A more complete description of the various diagnoses will be found in separate articles. The diagnosis articles also contain a description of the results seen in the model dose planning studies which, without exception, reveal potential advantages using proton beams in one or several aspects compared to the conventional beams. The identified model studies are listed in Table II, which also includes a brief description of the main results.

Intraocular melanoma

Proton irradiation is an established therapy for intraocular melanoma, mainly for large melanomas and melanomas located on or adjacent to the optic nerve and iris. Some 15 patients annually may be eligible.

Base of skull chordoma and chondrosarcoma

Better dose distribution means greater tumour control and less risk of long-term side-effects in the majority of these patients, i.e. 20–25 patients per annum. These tumours are routinely treated with protons wherever possible. Encouraging experiences have also been reported using ion therapy.

Meningeoma

Better dose distribution with less risk of long-term side-effects can imply clear advantages to 30 or 40

Table II. Comparative dose planning studies.

Reference	Year	Tumour type	Number of patients planned	Photons		Protons		Comments
				3D-CRT	IMXT	Regular	Scanned	
Suit et al. [59]	1988	Cervical cancer	1	X		X		Better dose distributions with improved local control, less toxicity
Brown et al. [60]	1989	Nasopharynx	2	X		X		Better dose distributions with improved local control, less toxicity
Urie+Gotein [61]	1989	Chordoma/ chondrosarcoma	12	X		X	X	Variably (intensity) modulated protons reduce dose to normal tissues (integral dose by 3–12%-units) compared to fixed (SOBP) protons, however, the largest difference was between protons and photons (2 patients)
Austin-Seymour et al. [62]	1990	Skull base	1	X		X		Less dose to OARs, e.g. the optic nerve
Austin-Seymour et al. [62]	1990	Prostate	1	X		X		Less dose to OARs
Tatsuzaki et al. [63]	1991	Rectum	1	X		X		Reduced dose to small bowel using protons
Archambeau et al. [64]	1992	Thalamic pediatric astrocytoma	1	X		X		Improved dose distribution, lower normal brain dose, higher tumour dose possible
Gademann & Wannenmacher [65]	1992	Pediatric retroperitoneal tumour	1	X		X		Better dose localization, less second cancers
Levin [66]	1992	Para-aortic nodes, cervical cancer	1	X		X		Higher doses could be reached using protons, improved tumour control by 10–20%
Miralbell et al. [67]	1992	Maxillary sinus	1	X		X		Less dose to OARs using a proton boost
Slater et al. [68]	1992	Tonsil	2	X		X		Superior dose distributions, higher tumour doses, less doses to OARs (chiefly mandible parotic glands)
Smit [69]	1992	Cervical cancer	1	X		X		Higher doses (by 20%) could be reached using protons, 40% increase in tumour control
Tatsuzaki et al. [70]	1992	Glioblastoma	1	X		X		Less dose to non-target brain using protons
Wambersie et al. [71]	1992	Pediatric brain tumours	3	X		X		Less dose to non-target brain using protons
Miralbell & Urie [72]	1993	Large AVM	1	X		X		Less dose to non-target brain, brain stem and optic chiasm using protons
Lee et al. [73]	1994	Prostate	12	X		X		Distinctly reduced rectal NTCP using protons in one-third of the cases, minimal gain in the remaining
Isacsson et al. [74]	1996	Rectum	6	X		X		At 5% NTCP in any organ, TCP is increased by 14%-units with protons
Isacsson et al. [75]	1997	Ewing/paraspinal	1	X		X		At 1% NTCP in spinal cord, TCP in increased by 5%-units
Miralbell et al. [76]	1997	Medulloblastoma-supratentorial target	1	X	X		X	Better sparing of normal tissues with protons and IMXT compared to conventional with less IQ-reduction
Miralbell et al. [77]	1997	Medulloblastoma-spina techa target	1	X	X		X	Decreased dose to all OARs using protons
Sandison et al. [78]	1997	Chest wall	1	X		X		Less lung dose using protons
Isacsson et al. [79]	1998	Oesophagus	5	X		X		At 5% NTCP in any organ TCP is increased by 20%-units (from 2 to 25%) with protons
Verhey et al. [80]	1998	CNS	5	X		X		Less dose to normal brain
Fuss et al. [81]	1999	Optic nerve, gliomas	7	X		X		CI 2.9 photons, 2.3 protons, larger differences in larger tumours

Table II (*Continued*)

Reference	Year	Tumour type	Number of patients planned	Photons		Protons		Comments
				3D-CRT	IMXT	Regular	Scanned	
Glimelius et al. [47]	1999	Sacral chordoma	1	X		X		Lower doses to rectum and urinary bladder using one proton beam compared to 3D-CRT photons
Lee et al. [82]	1999	Lung	13	X		X		More patients could be treated to higher tumour doses using protons compared to any photon technique
Lomax [83]	1999	Nasopharynx	1			X	X	Intensity modulation show advantages when few beams are used
Lomax et al. [84]	1999	Various	9	X	X		X	Reduced medium to low dose for protons compared to IMXT
Fuss et al. [85]	2000	Pediatric optic nerve glioma	7	X		X		Reduced NTCPs, likely clinically significant for cognitive impairment
Lin et al. [86]	2000	CNS, pediatric fossa	9	X		X		Protons result in increased normal tissue sparing, e.g. the cochlea (25% of dose compared to 75% of prescribed dose)
Miralbell et al. [87]	2000	Orbital and paraorbital	4		X		X	Similar PTV coverage, lower integral doses to OARs (x1.5–1.9), predicted NTCPs (severe late tox) similarly low
Oelfke+Bortfeld [88]	2000	–			X	X	X	IMPT advantages to SOBP protons and IMXT in a theoretical study, integral dose 30% lower using IMPT vs SOBP, a factor 2–3 vs IMXT
Paulino et al. [89]	2000	Medulloblastoma	5	X		X		Lower doses to all OARs
Smith et al. [90]	2000	Multiple sites	10+	X	X	X	X	Improved clinical outcomes at all sites, reduced NTCPs/higher TCPs
Zurlo et al. [91]	2000	Pancreas/biliary	4	X	X		X	Protons allowed delivery of planned dose in all patients, not or barely possible with photons
Baumert et al. [92]	2001	CNS	7	X			X	For complex PTV shapes and when PTV close to critical organs, protons yield better dose distributions than photons for SRT
Cella et al. [93]	2001	Prostate	1	X	X	X	X	Both IMXT and IMPT gave better dose distributions than non-IM plans and less NTCP in rectum, all proton plans improved PTV homogeneity and reduced medium-low dose in normal tissues compared to the photon plans
Cozzi et al. [94]	2001	Head and neck	5	X	X		X	Protons give improved dose homogeneity, higher EUD, better preserved organ function and quality of life
Johansson et al. [95]	2002	Breast	11	X	X	X		Lowest NTCP values for protons for the heart (0.5 vs 2.1%) and lung (0.6 vs 124.7%) compared with the best other plan
Miralbell et al. [96]	2002	Pedicatric rhabdomyosarcoma	1	X	X	X	X	Reduced risk of sec. malignancy by ≥ 2
Miralbell et al. [96]	2002	Medulloblastoma	1	X	X	X		Reduced risk of sec. malignancy by a factor of 8–15
Bolsi et al. [97]	2003	Small intracranial, different tumours	12	X	X	X	X	Improved CI, reduced OAR dose at all sites, less sec. cancer induction
Lomax et al. [98]	2003	Breast	1	X	X	X		Protons spare lungs and heart better than IMXT/standard treatment
Lomax et al. [99]	2003	Paranasal sinus	1		X		X	Critical structures could be spared best by protons at all dose levels
Suit et al. [14]	2003	Rectum	1		X	X		Improved dose distribution, less toxicity
Johansson et al. [100]	2004	Hypopharynx	5	X	X	X	X	Protons give lower non-target doses compared to 3D-CRT/IMXT. NTCP parotid glands 40–43% protons, 51–65% IMXT, 93+% 3D-CRT

Table II (*Continued*)

Reference	Year	Tumour type	Number of patients planned	Photons			Protons		Comments
				3D-CRT	IMXT	Regular	Scanned	
Mock et al. [101]	2004	Paranasal sinus	5	X	X	X		Similar CI but reduced doses to OAR (by 60%) and integral doses using protons
St Clair et al. [102]	2004	Medulloblastoma	1	X	X	X		Substantial normal tissue sparing, e.g. to the cochleas and the heart
Weber et al. [103]	2004	Paraspinal sarc	5		X		X	Similar conformity, reduced integral dose to OARs, dose escalation to 93 CGE possible with protons
Yoch+Tarbell [104]	2004	Pediatric, CNS	2	X	X	X		Better dose homogeneity and conformity
Krengli et al. [105]	2005	Retinoblastoma	3	X		X		Protons can achieve significant lens sparing and reduced risk of second malignancies
Mu et al. [106]	2005	Medulloblastoma	5	X	X		X	Risk second cancer conv RT 18%, IMXT 28%, IMPT 4%

Abbreviations: CI = conformity index; IMXT = intensity-modulated photon therapy; IMPT = intensity-modulated proton therapy; TCP = tumour control probability, NTCP = normal tissue complication probability; SRT = stereotactic radiotherapy; OAR = organ at risk; EUD = equivalent uniform dose; SOBP = spread-out Bragg peak.

patients annually. There is good experience of administering proton therapy for one week instead of the conventional five or so.

Arteriovenous malformations (AVMs)

For AVMs exceeding 10 cm^3 in size, protons afford a better possibility than any other technique of achieving complete obliteration. Some 20 or 25 patients annually are potentially eligible.

Medulloblastoma

Patients with medulloblastoma and related tumours, occurring mainly in children, derive benefit from the improved dose distribution of protons. There is a degree of uncertainty regarding the number of cases, but it is estimated that at least 20 patients per annum can be treated.

Reirradiation

It is estimated that about 150 patients in need of reirradiation are potentially eligible for proton therapy every year, since the volume of tissue irradiated has to be limited according to the radiation therapy administered previously. In this way the chances of local tumour control and, accordingly, cure should be increased, at the same time as adverse effects should be reduced.

Paediatric cancer (other than medulloblastoma)

Between about 60 and 80 of the 100 or so children irradiated annually for a malignancy of one kind or another (excluding medulloblastoma) are suitable for proton therapy, since the risk of serious late complications can be reduced. It is theoretically possible to raise the radiation dose for radioresistant paediatric tumours and achieve better tumour control.

Pituitary adenoma

Some 10 or 15 patients with endocrinologically active adenoma which, despite medical treatment, cannot be adequately controlled are suitable for proton therapy as routine treatment.

Cancer of the ear, nose and throat region

Some 30% or about 300 of the almost 1100 new cases of these cancers diagnosed annually in Sweden are judged to benefit from a higher radiation dose for better tumour control, at the same time as the radiation dose to critical organs can be reduced, and with it the risk of long-term side-effects, e.g.

xerostomia. Tumours growing in and near the base of the skull, e.g. nasopharyngeal cancer and paranasal sinus tumours are likely treated as a part of routine medical care, while other treatments should be given in studies where it is possible to show either greater tumour control or fewer long-term side-effects.

Sarcoma

Proton therapy for sarcoma is of great importance for tumours close to critical risk organs, e.g. tumours in the base of the skull, the orbit and the spine. Proton therapy may possibly also have advantages in advanced unresectable retroperitoneal sarcomas. The number of patients, however, is small, totalling about 40 per annum (skull base chordoma and chondrosarcoma are not included in this figure).

Oesophageal cancer

Increased radiation dose to the tumour simultaneously with the possibility of reducing the dose to adjacent sensitive structures may mean improved treatment outcomes. About 80 patients are judged eligible for inclusion in a clinical study.

Rectal cancer

It is estimated that primarily 150 patients annually with primarily unresectable rectal cancer growing onto adjacent organs may be eligible for proton therapy. If so, treatment of this kind can give greater tumour control, at the same time as the acute and long-term side-effects can be limited.

Breast cancer

It is estimated that primarily 300 patients in Sweden who are at risk of heart and lung adverse effects can be eligible for proton therapy, given the possibility. The risks of heart/lung complications and the risk of secondary malignancy should then be reduced to very low levels. The treatment should take place in a prospective study where the risk of complications with advanced 3D-CRT/IMRT can be quantified according to the dose to these organs, and in which the outcome for proton-treated patients can be observed after prolonged follow-up.

Thymoma

It is estimated that more than half the thymoma cases diagnosed in Sweden, corresponding to 20 patients, would be eligible for proton therapy within the framework of clinical studies, if treatment of this kind were available in Sweden. Potential benefits of such treatment mainly comprise reduction of acute and long-term side-effects prominently occurring in connection with the large treatment volumes of the thoracic cavity and the radiation doses used today.

Lung cancer

An estimated 350 lung cancer patients annually are eligible for proton therapy. Most of them should be included in clinical studies. Proton therapy is judged in the majority of cases to present advantages in the form of less radiation to surrounding risk organs and the possibility of dose escalation, which can mean better long-term survival.

Gynaecological cancer

Brachytherapy plays an important role in the treatment of gynaecological cancer, for the achievement of local tumour control. There is very great uncertainty concerning the value of protons, but their use is unlikely to become widespread. In cases where, for some reason, brachytherapy is not technically feasible, protons can offer a possibility of increased local control compared with conventional external radiotherapy. At the present state of knowledge, the number is of the order of 50.

Malignant glioma

There is great uncertainty regarding the value of protons in cases of malignant glioma. Better dose distribution with a lower dose administered to an adjacent and apparently normal brain, and a high dose to a visible tumour with a margin, can mean better quality of life and possibly prolonged survival for 20 or 25% of the patients. This applies above all to younger patients with astrocytoma grade III, among whom survival can sometimes be long. Between 50 and 75 patients annually may become eligible for treatment, all of them in prospective studies. The number of patients potentially includible in a randomized study comparing protons with photons is 100–150.

Liver cancer

It is estimated that primarily 65 Swedish patients annually with primary cancer of the liver can be eligible for proton therapy, given the possibility. The chances of local tumour control and, accordingly, survival prospects, might then increase. The treatments should take place in randomized studies. There is a future potential here for a much greater number of patients, above all patients with metastases from colorectal cancer, than stated above.

Mesothelioma

At present this is a grim disease with a grim prognosis and little possibility of treatment. Only about 20 patients annually can be judged eligible for proton therapy, which should make possible a higher dose without any additional risk of complications.

Prostate cancer

It is estimated that in the first instance some 300 patients in Sweden annually are eligible for proton therapy, given the possibility. This therapy can give increased probability of tumour control without increased side-effects compared with the present therapy. About 200 of the 300 patients are primarily at stage T3N0, and the remainders have undergone non-radical surgery. The larger the tumour is locally, the greater the role which protons are capable of playing, but in that case the risk of distant metastasis is also greater, and the impact on total survival is impossible to assess. Local tumour control, however, is a precondition of long-term survival.

Malignant lymphoma

An estimated 20 or so patients annually with Hodgkin's lymphoma (HL) can be treated with reduced risks of long-term complications. If, however, a proton facility is available, more patients can be considered, i.e. including also certain patients with non-Hodgkin lymphoma. Knowledge based on randomized studies will probably be unobtainable, since conclusive results concerning reduced long-term complications can only be expected after 10 or 20 years follow-up.

Cancer of the urinary bladder

It is estimated that between 100 and 150 bladder cancer patients in Sweden per annum undergo radiotherapy with a curative purpose. It is impossible to judge the fraction of these patients who may benefit from proton therapy. Ion therapy is hardly to be considered, since it is uncertain whether the bladder wall can tolerate the higher biological doses which are then administered against the primary tumour located in the bladder wall.

Pancreatic cancer

Potentially up to 240 patients annually may be eligible for a clinical study evaluating proton therapy. This figure is, however, probably too high in relation to the present state of knowledge and therapy tradition, but pancreatic cancer is a diagnosis for which a clinical facility in Sweden can mean the possibility of carrying out randomized studies to judge whether long-term survival can increase for one of the diagnoses having the worst prognosis of all cancers.

Gastric cancer

There is great uncertainty regarding the value of irradiation for gastric cancer, although a major American study has shown such a survival gain that post-operative radiation therapy in large volumes is routinely administered by many centres all over the world. Potentially, proton therapy (but not ion therapy) may prove better than any other radiation therapy, since with better tolerance the dose load can probably be reduced. Because of the great uncertainty prevailing, no attempt has been made to estimate the number of patients, and post-operative radiation therapy has yet to be accepted as routine treatment in Sweden.

Palliation

It is estimated that approximately 90 patients in need of palliation from an advanced malignant tumour should be offered symptom relief with proton therapy within the framework of clinical studies if such treatment was available in Sweden. The potential benefits of such treatment are a reduction of the acute side-effects and the possibility of improved quality of life.

Discussion

Since protons interact with tissues in much the same way as photons and electrons but with better dose distribution, it is arguable that they are virtually always at least as good as conventional radiation therapy. If the tissue surrounding the tumour is highly heterogeneous and is liable to vary, e.g. different quantities of air, there is some risk of protons giving a less certain and, consequently, inferior dose distribution in a few cases. Further, the skin-sparing effect of proton beams is less than that of photon beams, which may be of clinical importance in some instances for the cosmetic results. Since, on the other hand, protons are hardly ever inferior but can only be better, it is arguable that, if supply and cost were equal, protons would generally be used instead of photons and electrons. Thus the potential number of patients is the same as the majority of patients treated with external radiation therapy.

Since proton facility investments will always be higher and the cost of running the treatments probably also somewhat higher (it remains uncertain

by how much, especially as compared with IMRT), the cost in relation to the potential gains, i.e. cost-effectiveness, must always decide which patients protons are indicated for [38–41]. Because our knowledge of cost-effectiveness is limited, all estimates of the proportion of potentially eligible patients will be very tentative. There is no sound knowledge of what is cost-effective, and so all assessments are open to criticism. Our premises are based on the point at which we believe the medical profession will find the potential benefits great enough to justify the extra trouble and expenses entailed by "sending patients for proton therapy in a national facility".

Similar attempts to estimate the number of patients suitable for hadrons (protons and ions, generally not separated in the studies) therapy have likely been performed by several groups prior to decisions to proceed with the process towards realisation of a treatment facility. Three such investigations have been performed in other European countries and, at least partly, published.

The Centro Nazionale Adroterapia Oncologica (CNAO) separated patients for whom hadron therapy was indicated into two categories. Category A included all tumours in which the use of proton therapy had clearly demonstrated superiority and category B tumours where improved locoregional control, possible with protons, likely would result in more patients cured. The study was originally published in 1998 [42] and updated, based upon more recent statistics and knowledge, in 2004 [43]. According to the update, 830 patients, constituting 44% of the number of patients with these diagnoses in Italy per year were candidates for elective proton therapy (category A) and more than 15 000 patients (13% of the population) for therapy in clinical trials (category B). It was totally estimated that about 16% of the irradiated patients were candidates for proton therapy. The most common diagnoses in category A (corresponding to those listed in the upper part of Table I) were uveal melanomas, paranasal sinus tumours and meningeomas of the base of the skull. In category B (middle, lower part of Table I), prostate cancer constitutes the largest group (5600 patients, 25% of irradiated patients) followed by pancreatic cancer (1800, 20%), bladder carcinoma (1700, 10%), lung cancer (1550, 5%), liver cancer (1300, 10%) and head and neck tumours (1000, 15%). In the update, an estimate was also made for the number of Italian patients eligible for carbon ion therapy of those eligible for proton therapy. About 3700, or between 3000–4000 patients, were considered as such candidates, constituting 23% of those considered candidates for proton therapy (5% of all irradiated patients). Lung cancer (1550 patients) followed by prostate cancer (1100 patients) and liver cancer (500 patients) were the most common diagnoses.

The French ETOILE project made a "one day survey" at five university hospitals, identifying 77 patients, mainly head and neck cancers (n = 31), gliomas (n = 8), lung cancer (n = 6), uterus (n = 5), gastric (n = 5) and prostate (n = 3), being potential candidates for hadron therapy. This figure constituted 14.5% of the number of patients irradiated. Extrapolated to 160 000 irradiated patients per year in France, 23 000 were potential candidates for hadron (proton or carbon) therapy each year [44].

A nationwide Austrian survey (MedAustron) identified all new patients starting radiotherapy during a three months period. It was then estimated that about 2000 patients, representing 5.6% of all newly diagnosed cancer patients and 13.5% of all irradiated cancer patients, were candidates for hadron (proton and ions) therapy [45]. The most common diagnoses suitable were prostate cancer (470 patients, 29% of all irradiated), head and neck tumours (251, 25%) and lung cancer (239, 27%). Primary breast cancer was not considered a candidate.

Thus we find that this Swedish study and three separate other European investigations, having very different designs, reach the conclusion that between 13–16% of all irradiated patients are suitable for proton therapy. A proportion of these, not always accurately estimated, are also suitable for ion therapy. Ideally, any estimate of the potential number of patients for a new treatment should be made by a prospective assessment during a prolonged time period. Although the figures reached in such a recording can always be criticized, since there is no clear definitions of what criteria are set for an improvement (higher TCP and/or lower NTCP) of such a magnitude that the increased costs are motivated, this was done in the MedAustron project. In order to get a reasonable estimate also of uncommon tumour types, frequently suitable for proton therapy, the estimates must be made during a prolonged time period. In this respect, three months appears reasonable. The French investigation was also made after a prospective assessment, but only of one day's duration, which makes all estimations very unreliable. The SPTC estimate was based upon a recording of all irradiated patients within the SBU report [37], but the estimations of the number of patients eligible for proton therapy was made retrospectively, based upon a literature review. In the evaluations of the potential value of proton beams for improved tumour control, we considered the SBU-estimations of gains after dose escalation [46].

Given the lack of relevant clinical information for most tumour types, we also evaluated the results of

dose-planning model studies. Similar to the differences in scientific quality between clinical trials with different designs and performance, these model studies can also be conducted with varying quality [47]. The physical evaluations can only provide an idea of whether one technique confers dose distribution advantages over another, but cannot tell how much better one treatment can be. This is possible using biological models, but, since knowledge of the size of the coefficients in the different models still is limited, these estimations must be carefully interpreted [48,49]. Relative differences between different techniques are probably more robust than absolute differences. However, absolute differences are fundamental in order to evaluate the potential number of patients gaining sufficiently from a new treatment. Due to the variability between patients and tumours, it is then necessary to include and plan several patients in order to arrive at a reasonable estimate of the absolute differences. This has rarely been done (Table II). The body of evidence from the literature that proton beams confer physical dose distribution advantages is at present so extensive that further studies provide only limited new information. Rather, they must focus on the absolute gains from proton beams to aid in the decision of what clinical study designs should be used and in the dimension of the randomized trials.

Protons or ions?

The capacity of protons and ions for improving cancer treatment has been a topic of widespread discussions in Sweden and elsewhere in recent years. These discussions have also proceeded within the Swedish Proton Therapy Centre (SPTC) project. No further description of the arguments for and against one or the other kind of radiation will be presented here. Instead, we refer to the report published by the Swedish Cancer Society [49] and to the Proceedings of the heavy charged particles in Biology and Medicine (HCPBM) and ENLIGHT meetings in Baden and Lyon, published in a supplement of Radiotherapy and Oncology in December 2004 [50].

Our primary concern being to show in clinical studies whether particle radiation offers such great therapeutic advantages that it should be part of the routine care of cancer patients, protons are the natural choice. Proton therapy is already a practical clinical treatment for a number of tumour indications, and clinical experience of proton therapy greatly exceeds that of light ion therapy. We consider that the use of ions presently is clinically immature. Furthermore, a proton therapy facility is to a great extent based on proven technology and systematically co-ordinated individual main components. The great difference today between proton and light ion radiation is perhaps one of facility design and operational dependability. It is reasonable to assume that necessary clinical studies, prompted for example by the great explosion of knowledge in imaging techniques, cell-, tumour- and molecular biology, can be started and completed much faster with protons than with ions.

Ions, with their high LET (linear energy transfer) component, offer potential advantages in the treatment of hypoxic and slow-growing, radiation-resistant tumours [8]. The physical advantages of ions (sharper penumbras at greater depths) over protons are probably limited and are unlikely ever to be a sole reason for the choice of ions rather than protons [52]. The biological consequences of the high LET of light ions make it of scientific interest to explore, in greater depths, the possibilities of ions improving treatment outcomes. In the long term it is very interesting to carry out comparable clinical studies of protons and ions. This is also the focus of the facility under construction in Heidelberg, Germany [51].

Given our great uncertainties concerning the relative biological effect of different parts of the ion beam, as well as the other biological effects of the high LET component, it is very hard to judge the number of cases in which ions are potentially better than protons. Light ions are contraindicated for some tumour sites, for example, for virtually all pediatric tumours, for AVMs, and for sites where the tumour is intimately connected to sensitive tissues, like oesophagus and other parts of the gastrointestinal tract, pancreas, and urinary bladder, whose preservation is important. The three estimates performed in Austria, France and Italy have considered the use of both protons and ions, but with the exception of the Italian study [43], the published material has not been detailed enough to estimate what proportion would do sufficiently better with ions than with protons. The investigations have, however, resulted in decisions to invest in combined proton and ion facilities in Vienna, Austria (MedAustron) [53], Pavia, Italy (TERA/CNAO project) [54], and Lyon, France (ETOILE) [55] within the ENLIGHT project.

Development of methods of diagnosis and tumour characterisation

Adequate delineation of tumour extent is fundamental to all radiation therapy. The requirements in this respect do not differ essentially from those for other advanced (locally) curative radiation treatment. Since, however, protons (and ions) confer very good possibilities of saving adjacent normal

tissue; the diagnostic requirements must be very high and at least on a par with those indicated by the world's leading centres. The Cancer Society, in its report on radiation therapy research in Sweden, has referred to problems with tumour imaging in Sweden [56]. Regardless of whether a proton therapy facility is built in Sweden, local tumour diagnosis needs to be reviewed and necessary improvements made. A national proton therapy facility will provide a strong incentive for co-ordinating this on a national basis. Given the purpose of most patients being examined and their treatment fully planned at their (university) home clinic, all equipment and competence must in principle be universally available.

Future development of image-based adapted radiotherapy

The possibilities of PET for staging and target definition are currently under discussion [57,58], and it seems reasonable to suppose that PET is at least superior to other staging methods for several diagnoses. Although certain studies assert that targets can be drawn better, either smaller or larger, with PET in connection, for example, with ear, nose and throat tumours and lung cancer, it is still unclear whether this entails a better treatment outcome. The importance of PET and magnetic resonance imaging (MRI) for target drawing must be studied further, primarily in prospective studies. The potential of PET, MRI and other techniques for revealing areas of the tumour which require deviations from the usual mean dosage must be investigated more closely. There is a need here for more research in Sweden, research which the proton therapy initiative may serve to accelerate.

Clinical therapy research

One express purpose of the dedicated proton beam therapy facility is to show in clinical studies how great are the advantages of protons compared to conventional radiation. The aim is to treat the majority or at least 80% of Swedish patients in clinical prospective protocols. We have identified the need of clinical therapy research for each diagnosis separately and have also briefly described suitable study designs. In certain cases randomized studies are desirable and necessary in which proton therapy, partly or completely, is one experimental arm, compared with a control arm without protons. In other case randomization can take place between protons only or as a boost treatment, or alternatively with different proton dose levels etc. There are many cases where randomized studies are neither necessary nor possible. For these cases, prospective protocols are to be drawn up in which staging and the implementation and follow-up of therapy are defined and subjected to research-ethical review. Protocols of this kind are to be drawn up for the majority of clinical situations which can come into question for proton therapy. There will always be unusual cases where a clinical study is not feasible, e.g. extremely uncommon forms of tumour, reirradiations and special cases due to anatomical idiosyncrasy.

The Swedish Health Care system is well suited for this type of clinical trials as all citizens are fully covered by the national social security system. Patient selection will thus be based solely on clinical and scientific grounds. Efficient inclusion of patients and complete follow-up will further be secured by the planned infrastructure of the SPTC where all planning and full responsibility for the patient will remain with the regional university hospitals. Only the actual proton beam treatment will be performed at SPTC.

It is assumed that the studies will be worked out through discussions on a national (Nordic) basis, e.g. under the aegis of regional/national therapy programme groups or the planning groups supported by the Swedish Cancer Society. Mandators and peer assessors for the studies comprise those who are most interested in and suited to this function. It is hoped that responsibility for the studies and their implementation will be decentralised in Sweden, according to the research interest and competence existing.

Conclusions

After an extensive literature review, including clinical trials and model dose planning studies, it is estimated that in Sweden between 2200 and 2500 patients annually are eligible for proton beam therapy. For these patients, the potential therapeutic benefit appears to be so great as to justify the additional expense of proton beam therapy. The assessed number constitutes between 14–15% of all irradiated patients annually. Similar proportions have been reached in three other similar European investigations. Even if these four, very differently designed investigations, reached the same overall results (13–16%), major differences were found though, regarding which patient subgroups would benefit the most. These discrepancies can only be resolved in properly designed clinical trials.

A facility based on the SPTC-concept, with a distributed logistics and expert support, will offer a unique base for conclusive randomized clinical trials. Inclusion of patients in the trials will not depend on individual economical input. Further, general access

to this type of high precision therapy for all university hospitals will accelerate research in image-based individualisation of cancer therapy.

The present estimations of patients suitable for proton therapy are based on a large collection of calculations and clinical experience. Future research and development in a dedicated clinical proton facility will hopefully result in more individually adapted high precision therapy based on verified clinical evidence.

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