Potential Gains Using High-Energy Protons for Therapy of Malignant Tumours

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High-energy protons have physical properties that virtually always will result in geometrically better dose distributions than can be achieved using photons or electrons. The clinical gains in terms of the probability of higher tumour control and/or the reduced probability of normal tissue complications are, however, not completely known. Comparative model dose planning studies using real patients offer the possibility of estimating the potential gains using a new technique. Several recently completed model studies, including clinically relevant endpoints, indicate that protons may have advantages, even when compared with the conventional treatment that is likely to be introduced at the most advanced hospitals world-wide within the next decade. These advantages can be seen not only in well-demarcated targets close to risk organs, but also when irradiating extended irregular tissue volumes at risk of containing tumour cells.

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Ever since its start a few months after detection of the x-rays (1), radiation treatment of malignant tumours has steadily improved towards its ultimate goal, namely to deliver a sufficiently high radiation dose to the tissue volumes containing the tumour cells and as low a dose as possible to tissues not at risk of containing tumour cells. The dose to the tumour-bearing volumes should ideally also be adjusted according to tumour cell density so that all the tumour cells could be eradicated and radiation-induced damage, also to the organs affected, minimized. The improvements have involved all the steps in the radiotherapy process from the diagnosing and delineation of tumour cell localization to the delivery of the last radiation dose and the follow-up of the patients. All improvements have depended upon a number of technical developments related to the different aspects of the radiotherapy process. The development has, besides improving the treatment results, in principle also made radiotherapy more expensive due to both higher investment costs and higher running costs. Despite this, all technical improvements have continuously been introduced into clinical routines based upon theoretical and practical advantages. The advantages in terms of higher tumour control probabilities (TCPs) and/or lower normal tissue complication probabilities (NTCPs) have been shown afterwards, usually through clinical experience, but sometimes also in randomized controlled clinical trials (2). Owing to the improvements in the outcomes, the treatment may have become more cost-effective despite the higher costs, but this has rarely been investigated (3).

Protons have physical properties (see below) that will virtually always result in geometrically better dose distributions than can be reached by the conventional rays for treatment, photons and electrons, and thus, improved treatment results. Consequently, protons for therapy could be regarded as a next logical step in the radiotherapy development. However, protons require high-cost investments in accelerators, beam transport systems and gantries, and it is thus not yet fully known whether the clinical gains using protons rather than x-rays are sufficiently large to be cost-effective in relation to other improvements in the radiotherapy process, or in healthcare overall.

The improvements that can be achieved with protons for therapy are not fundamentally different from other improvements introduced into clinical routines during in recent decades. Owing to the relative stagnation in the general economic development, and that the requirements to prove superiority and cost-effectiveness are thus higher than only a couple of years ago, it is possible that proton therapy is not, after all, the next logical step in a continuous development. It is likely that the step in investment

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costs is greater going from a linear accelerator to a proton accelerator, but cost-effectiveness, i.e. the incremental gain in relation to the incremental cost, may not be fundamentally different compared with investing in, for example, a 3D dose planning system, multileaf collimators or higher electron energies.

HOW TO IMPROVE THE KNOWLEDGE ABOUT THE POTENTIAL GAINS BY A TECHNICAL IMPROVEMENT LIKE PROTONS?

The ultimate proof of superiority of one treatment modality over another requires prospective clinical trials. Since the differences between the modalities are usually limited, although they may be clinically highly relevant, most trials then need to be properly controlled, i.e. randomized. Since this ultimate proof requires that the investment is already made, other evidence is needed before any decisions about the investments are taken. Simulated model studies using real patients then offer the possibility of estimating the potential gains using a new technique. The model studies need to be as realistic and as comprehensive as possible, and include relevant endpoints, i.e. also long term clinical effects and costs. The studies should not only show whether a new treatment technique is likely to be superior, but ideally also how large the gain potentially can be. This latter knowledge could not only influence decisions about whether or not the investments should be made but also directs future clinical research, including the need for patient numbers in the trials.

These models aimed at improving the knowledge about potential gains with proton therapy, must comply with a series of requirements, each posing both theoretical and practical difficulties. In principle, the demands should follow what is summarized as 'Good Clinical Practice' for clinical trials.

1. The patients should be representative of the clinical problem. This may, however, not necessarily be particularly common. Several patients should be included in order adequately to reflect variations in body shape, organ and tumour location, and also to ascertain potential differences with statistical certainty.
2. In order to be of relevance prior to decisions about future investments, comparisons must be made with treatments that can be expected to be used at the most developed centres world-wide within the next 5 to 10 years. This poses several problems since it is difficult to foresee progress and since the tools for planning future treatments may not yet be available, at least not in dose planning systems that can properly handle computed tomography (CT) studies from patients.
3. Optimized dose plans must be produced, i.e. ideally, the plans using conventional rays and protons should be produced by independent groups each having the responsibility to produce the most optimized plan. The evaluations of the clinical results may then proceed jointly.
4. The evaluations should include not only physical and geometrical comparisons but also clinically relevant endpoints, such as TCPs and NTCPs. Several models that can translate dose distributions, usually in the shape of reduced dose volume histograms (DVHs) (4) to TCPs and NTCPs are available (5–7), but their relevance is far from proven, and universal acceptance does not exist. Sensitivity analyses, i.e. varying the size of the coefficients in the models within reasonable limits, may partly deal with this problem or at least provide an estimate of the robustness of a detected difference.
5. Based upon the estimated TCPs at a specified and acceptable NTCP in the comparisons, costs should be estimated as accurately as possible and appropriate cost-effectiveness analyses performed (3).

Physical and biological properties of proton beams

A clinical high-energy proton beam is characterized by the following properties:

(a) A definite range, beyond which the dose for all practical purposes is zero.
(b) A dose distribution where the dose increases with depth.
(c) A lateral penumbra which is similar to that achieved with high-energy photon beams.

The range of the protons is determined by their energy, so by choosing a suitable energy, the dose beyond the target can be made zero. Furthermore, by adding together protons of different energies, a region of constant dose can be formed at the end of the range, as shown in Fig. 1A (this region of constant dose is conventionally called the 'spread out Bragg peak', SOBP). A depth dose distribution of high-energy photons is also depicted in Fig. 1 for comparison. As can be seen, the proton dose is lower than the photon dose at all points outside the target except possibly for the first few millimetres, where the build-up of the photon beams makes the photon dose lower. Fig. 1A and C show dose distributions for 2 and 4 photon or proton beams, respectively. It can be seen that the proton dose is still lower outside the target, although to a lesser degree as the number of beams increases.

The beam from a high energy proton accelerator usually has a lateral extension of a few mm. To cover a typical treatment volume the beam must be made wider. Two principles can be used:

(a) Passive scattering by a system of metal foils (8), and
(b) Dynamic magnetic deflection of the beam (9, 10).

When using passive scattering the energy spectrum of the beam is constant over the field, so that the SOBP has

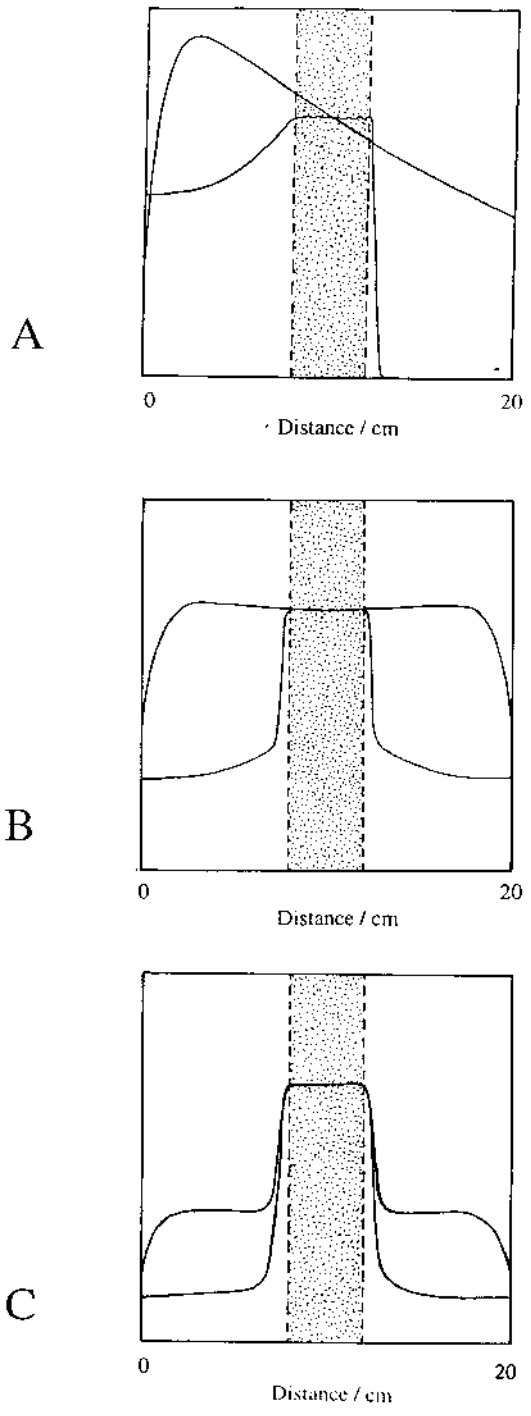

Fig. 1. By varying the energy of the proton beam, a constant dose, the 'spread out Bragg peak' (SOBP) can cover the target extension (shaded in the figure), while delivering a reduced dose anterior to the target and almost no dose to tissues beyond the target. Using a single high-energy x-ray beam (A), the dose to tissues outside the targets is much higher. If two (B) or four (C) beams are used instead, the x-rays still result in a higher dose to tissues outside the target. The dose distributions were calculated along a line coincident with one or two of the beam axes in a simple patient-like phantom.

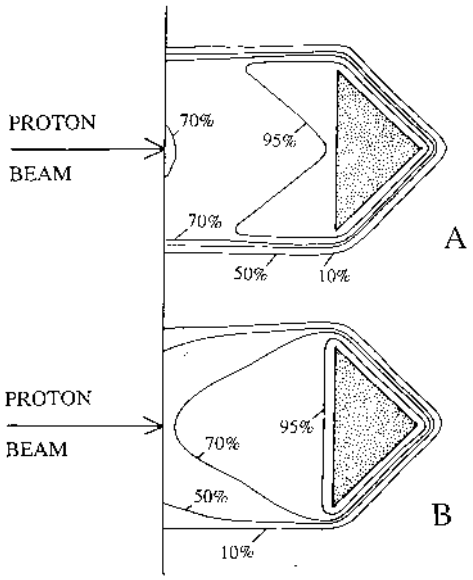

Fig. 2. Using magnetically or otherwise scanned beams (B) it is possible to reduce the dose to tissues anterior to a target (shaded areas) than using passively scattered beams (A). The figure shows the case of a simple target with triangular cross-section.

the same depth extension at all points, as shown in Fig. 2A. In contrast, when using a magnetic scanning system, it is possible to vary the energy distribution, so that the SOBP at each point only covers the target, which can be of varying extension (Fig. 2B). It is seen that this results in a lower dose in the entrance region. This offers a further lowering of the dose outside the target (9).

Because protons have a rest mass of approximately 1 836 times the rest mass of the electron, they are correspondingly more difficult to deflect by a magnetic field. Therefore a proton gantry is necessarily much larger and heavier than a gantry for a treatment machine using x-rays or electrons (11). However, a proton gantry using magnetic scanning can be made considerably more compact than a gantry using passive scattering. Another aspect of a magnetic scanning system is that it gives the possibility of creating inhomogeneous fluence distributions, which may be of some clinical value (12).

The first installation of a magnetic scanning system mounted in a rotating gantry, and used with a clinical proton beam, was made at the Paul Scherrer Institute (PSI), Villigen, Switzerland, where the first patient was treated in December 1996.

The comparative studies described below have with few exceptions used passively scattered proton beams.

The biological effect per unit dose of high-energy protons is virtually equal to that of high-energy photons and electrons so that the coefficient of relative biological effect (RBE) is close to unity. Clinically, an RBE of 1.1 has often been used for protons in a SOBP (10, 13). Protons of low

energy, in the region of a few tens of MeV, are more densely ionizing so that the linear energy transfer (LET) increases and as a consequence, also the RBE. As only a small part of the total energy of a high-energy proton is deposited with this higher LET, the clinical importance of this increase near the end of the range is usually considered to be small. However, the increased RBE at the distal fall-off of the SOBP, if this is close to a risk organ, may be of clinical relevance. This has not yet been fully explored and there is, with the presently used dose planning systems, no possibility of taking these effects into account.

The similarities in the biological effect of protons with photons and electrons are an important aspect in the clinical situation, as all clinical experience gained during decades concerning the relations between dose and fractionation pattern and adverse effects when using conventional radiation qualities can be immediately translated to protons. This together with the possibility of creating dose distributions that more effectively spare normal tissues at risk make protons ideally suited to the treatment of malignant tumours.

Algorithms in dose planning systems handling 3D CT studies

Three different principles can be used in algorithms for calculation of dose distributions in tissues penetrated by a high energy proton beam. In order of increasing potential accuracy, they are (i) depth penetration (ray tracing) algorithms; (ii) pencil kernel (pencil beam) algorithms; or (iii) Monte Carlo algorithms (14). At present only the first two can be implemented clinically with reasonable calculation times, and of these, only ray tracing algorithms have calculation times making interactive work at a computer workstation possible. A way to work is to optimize dose plans with a ray-tracing algorithm and then do a more refined calculation of the resulting dose distributions with the more accurate pencil beam algorithm. The most important weakness of the ray-tracing method is the inability to give a correct representation of dose distributions in the vicinity of tissue inhomogeneities, such as borders between soft tissue and lung or bone tissues. Although the more accurate calculations can be made with pencil beam algorithms, this calculation problem reflects a fundamental property of proton beams when used for radiation therapy; the resulting dose distributions are very sensitive to the exact position of air cavities and bone structures. In general, it is advisable to avoid beam directions passing through complicated bone or air structures. These effects are particularly strong when the border surfaces have longer sections that are parallel or close to parallel with the beam direction (14–16). A pencil beam algorithm is also better suited for calculating dose distributions from scanned beams, and can cope with inhomogeneous fluence distributions. With the evolution of the calculating speed of computers, Monte Carlo algorithms can be foreseen to be a useful method for calculating proton dose distributions before long.

Where is the greatest need for protons?

Some years ago, a working group reached the following conclusions about where the potential benefits from proton therapy are likely to be the greatest (17). They were divided into four categories:

1. Highly localized tumours characterized by their close proximity to vital structures. Typical examples of this group are uveal melanomas and sarcomas of the skull base. It was estimated that these patients are willing to travel long distances to be treated. In a population of 20 million (the Nordic countries), it can be estimated that 150–200 individuals yearly could be candidates for proton therapy (based upon the estimates made by Bonnelli et al. (17). These tumour patients are already today offered proton therapy at selected sites worldwide (18–20).
2. Localized tumours inadequately controlled by conventional radiotherapy where protons would offer the prospect of increasing the tumour dose without exceeding the tolerance of surrounding normal tissues. Examples are prostate cancer and undifferentiated thyroid tumours.
3. Tumours for which local tumour control might be improved by adding a proton boost to conventional treatment. Examples are head and neck tumours and oesophageal cancers.
4. Advanced conditions for which conventional photon radiotherapy is ineffective and where treatment could be improved by giving all or a part of it with protons. Examples are pancreatic tumours and malignant gliomas.

In addition to these four categories, we would like to add a fifth group:

5. Large irregular tissue volumes at risk of containing tumour cells close to organs not at risk of containing any tumour cells but at risk of being damaged by the radiation doses needed to eradicate the tumour cells. A typical example is a woman with breast cancer operated with a segmental resection with positive axillar lymph nodes, where the remaining breast and the regional lymph nodes in the axilla, fossa supraclavicularis and parasternal regions are at risk of containing tumour cells and often routinely irradiated (21, 22). Particularly the heart, but also the lungs are at risk for late toxicity. Using a single proton beam (see below), the dose to the risk organs could be more or less eliminated. Other examples are the spinal cord at risk of containing tumour cells in paediatric medulloblastomas and other primitive neuroectodermal tumours (PNET) (23) and the retroperitoneal tissues after inadequate removal of a soft tissue sarcoma (24). In these cases,

tumour control would not be improved since this is often already very high, but the risk for late toxicity could probably be substantially reduced. In these instances, protons not only compete with conventional external radiotherapy, but in the future also with more effective cytostatic drug treatments. The costs, acute and late toxicities, and thus the relative merits of these treatments are not known.

In this context, it is thus clear that the development of proton therapy does not only depend upon what happens with conventional radiotherapy but with all therapeutic modalities. Radiotherapy then requires relatively high investment costs, but running costs are comparatively low (25). Chemotherapy, on the other hand, has very small investment costs for the hospitals (regular patient rooms, pumps), but high running costs, accentuated when more recently developed, and thus expensive drugs, are used.

What is the best conformal technique?

In order to reach sufficiently high radiation doses without exceeding normal tissue tolerability, various 'conformal' techniques have been developed and recently implemented with photons and electrons (26). With few exceptions, these techniques mean that the number of beams increases over the presently used standards of 3 or 4 beams. These multiple beams (sometimes also rotational beams are used) imply that the dose to the vulnerable organs can be kept safely low for late organ-specific toxicity, but the integral dose in the total body volume remains virtually the same (27). This 'radiation bath' may not immediately cause any relevant toxicity, but it means that much larger volumes are at risk, for example for secondary radiation induced malignancies. This may actually be of even greater concern than previously recognized in the light of the relatively higher biologic effects from doses in the range of 0.1–0.5 Gy (28). These doses correspond to the 5–20% isodoses, when daily fractions of 1.8–2 Gy are used.

When using protons for conformal treatment, considerably fewer beams can be used while still reaching the same tumour doses and the same upper doses to particularly selected risk organs. Thus, the integral dose can be kept much lower, and the tissue volumes within the 5–20% isodose curves considerably smaller. The clinical relevance of these gains is at present not known, but they may be particularly important in children and younger patients.

Brachytherapy, whether interstitial or intra-cavitary also has the capability to deliver a high dose to the tumour target while limiting the dose to surrounding tissues (29). The relative merits of brachytherapy compared to 'external' conformal techniques are not properly known. Since one or only relatively few high fraction doses are used in brachytherapy, it is not yet possible to include this modality in the predictive studies, because there is insufficient knowledge of the biological correspondents.

Estimations of potential therapeutic gains

Several studies have compared the dose distributions of protons and photons. However, most of the studies do not fulfil the above-mentioned criteria, i.e. they have usually only analysed a single patient, compared dose distributions only, and the conventional dose plans have been a treatment commonly used today. Therefore, albeit of interest to show the potential of protons at the variety of tumour sites, they are of limited value as arguments for future investments. They may, however, point to tumour types of interest for further investigation.

Brain and other CNS tumours. In two studies, one in paediatric brain tumours and one in a cortical glioblastoma, it was shown that the dose to the tumour tissue could be increased at the same time as a reduction in the dose to normal brain was possible (30, 31). More recently (32) the risk of a 10% decrease in IQ after a 30 Gy prophylactic tumour dose to supratentorial tissues in the treatment of paediatric medulloblastomas/posterior fossae PNET using protons with spot-scanning algorithms from PSI was compared to the risk of (i) the conventional two-beam technique presently used world-wide, (ii) a six-beam, conventionally produced, but optimized 6 MV x-ray plan, or (iii) a computer optimized 9 beam 'inverse' 15 MV x-ray plan. Three beams were used for the proton plans. Compared to the presently used treatment, all further optimized techniques could substantially reduce the risk of lowered IQ in patients with both high-risk and low-risk features. The proton plan fulfilled this task better than the other techniques, although the differences towards the other optimized techniques were relatively limited. For a four-year-old patient, the estimated risk decreased from 80% using the presently used treatment, to 51% using 'handmade' beams, to 40% using 'inversely' planned beams and to 38% using protons.

The same group has also analysed the role of protons compared with 6 MV photons for prophylactic spinal cord irradiation in the same tumour types. The proton beams could entirely avoid dose contributions to the heart, liver, thyroid and gonads, and significantly reduce the dose to the vertebrae bodies (33). This risk organ sparing effect could be of relevance for the acute tolerability, particularly in combination with chemotherapy, since it spares bone marrow and, above all, for late toxicity from the mentioned organs/structures.

Head and neck cancer. It has been shown that higher tumour target doses and/or lower doses to critical organs could be achieved using protons rather than photons in the treatment of maxillary sinus cancers (34) and carcinomas of the tonsillar region (35). We have compared the dose distributions that can be achieved using protons as a boost after a conventional full-dose treatment with 2 Gy to 66 Gy to patients with locally advanced (T3-T4) hypopharyngeal carcinomas. As can be seen in Fig. 3, five additional

boost doses of 2 Gy (possible to deliver today at The Svedberg Laboratory, Uppsala, Sweden) result in a dose distribution that spares tissues outside the hypopharynx compared with the use of photons. Assuming a maximum slope in the dose response curve (γ) of 2 for hypopharynx cancers, this dose increment would increase TCP by about 25%. Evaluation of NTCP for the hypopharynx itself and for the adjacent tissues is not possible to predict owing to the lack of adequate parameter values.

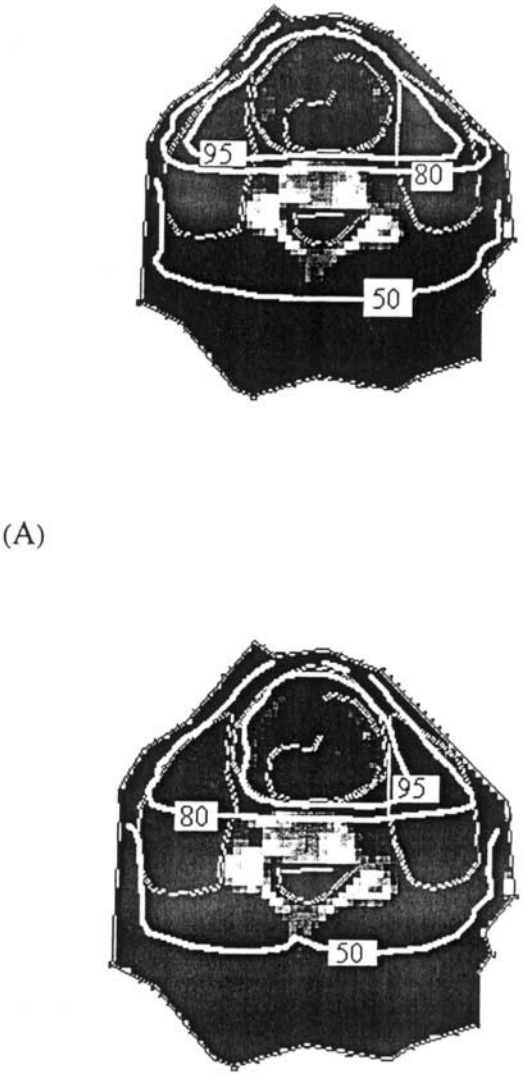

Fig. 3. Dose distributions, in % of prescribed dose, in a representative transverse section, for (A) an x-ray plan and (B) a proton boost plan in a patient with a hypopharyngeal carcinoma, stage T4N0M0. The patient was first planned with 5 MV x-rays to 66 Gy followed by either five 2 Gy fractions with 5 MV x-rays or with 180 MeV protons to the primary tumour. Note that the 95%-isodose curve covers a smaller volume using protons than x-rays.

Lung cancer. Similar to the situation for brain tumours and head and neck cancers, it was shown (36) that, for the treatment of non-small-cell lung cancer, protons can increase the tumour dose while maintaining a sufficiently low dose to the contralateral lung volume.

Oesophageal cancer. In a comprehensive study of five patients with primary oesophageal cancer (T2-3 N0M0) it was shown that, on an average, TCP could increase from 7% using x-rays to 46% using protons alone or 27% using protons as a boost after photons (37). The tumour doses that could be reached with protons amounted to 73–95 Gy, whereas they were limited to 48–58 Gy using photons unless an overly high normal toxicity was accepted. The choice of model, coefficients in the model, clonogenic cell density, acceptable risk organ tolerability influenced the TCP. The choice of these parameters did, however, not change the ranking or the absolute difference between the techniques as long as clinically reasonable choices in coefficients were selected.

Spinal cord tumours. In a study using a patient with a Ewing sarcoma growing around the cervical spinal cord, it was shown that protons had therapeutic advantages over conventional radiotherapy, even if this was planned with treatments not yet possible in practice (38). While keeping the dose to the spinal cord at a level that caused a maximum of 1% expected NTCP, the mean dose to the tumour target could be increased from 54 Gy, using a 'conventional' conformal treatment plan, to 61 Gy using a further optimized plan using an arc treatment with asymmetric beams, and to 68 Gy with laterally opposed proton beams. Sensitivity analyses indicated that this resulted in a gain in TCP that was greatest (10% units) using an α-value of 0.4 Gy^{-1} corresponding to relatively radiosensitive tumours. This study was performed as a cooperative study between the Departments of Oncology in Gothenburg, Sweden, which performed the conventional plans, and the Department of Oncology in Uppsala, Sweden, which carried out the proton plans and the evaluations.

Rectal cancer. Tatsuzaki et al. (31) demonstrated that the volume of bowel treated to the 90% isodose could be reduced to approximately half using protons rather than conventional photon beam arrangements for the postoperative treatment of rectal cancer. In a more comprehensive study, Isacsson et al. (39) investigated six medically inoperable patients with locally advanced tumours in stage T3-4 NXM0. Accepting a maximum of 5% expected NTCP in any organ (the small bowel was usually the dose-limiting organ), protons resulted in an average TCP of 75% compared with 64% using x-rays. The TCP was 71% if the protons were used only during the boost after 50 Gy. The benefit derived from using protons was greater in the three patients with a tumour located in the mid- and upper rectum rather than in the lower third of the rectum. Several attempts to further optimize the conventional three- or four-beam techniques were made, but none of

them could substantially increase TCP over that reached by the presently used standard treatments.

Prostate cancer. In an extensive study of 20 cases of locally advanced prostate cancer, it was shown that a two-beam proton technique yielded distinct advantages in one-third of the cases over three- or six-beam megavoltages conformal x-ray techniques (40). The gain was sensitive to changes in the parameter values of the NTCP model. The sensitivity analyses did not, however, encompass more recent information on the volume dependence of the rectal wall (A Nahum, pers. comm.). Therefore, it is possible that the true gains may be larger than was reported in the study.

Other pelvic tumours. Studies in cervical cancer (41, 42) found that it was possible to reach higher doses using protons when irradiating either the primary tumour or para-aortic lymph nodes.

Sacral chordomas. A single, posterior proton beam can result in lower doses to adjacent risk organs, particularly the urinary bladder and rectum if the chordoma is located in the middle and lower parts, and the small bowel is located more cranially, than can be reached with 'optimized' three- or four-beam photon techniques (Fig. 4).

Breast cancer. Measurements of doses in a phantom showed that dose contributions to the lungs and the heart were lower using a proton arc treatment compared to an electron arc treatment of the chest wall, e.g. in the treatment of the scar after breast cancer surgery (43).

Treatment of the remaining breast after a segmental resection is a challenge if the adjacent lymph nodes are to be included at the same time. Several solutions using multiple beams of photons and electrons have been proposed (21), but none of them can solve the problem accurately. A single proton beam, whether using passively scattered or scanned beams, can create the desired dose homogeneity in the target volumes with very low-dose contributions to the lung and the heart (Isacsson & Glimelius, unpublished data). Thus, the slight, but still potentially important risks of late morbidities can be eliminated.

CONCLUSIONS

It is increasingly evident that the geometric advantages of high-energy protons relative to conventional rays will be translated into improved tumour controlled rates and/or less risk of late morbidity in a number of tumour types. These advantages will also be present when protons are compared to the radiotherapy that it is foreseen will be available at the most advanced university hospitals worldwide in the next decade. However, the magnitude of the advantage cannot, at present, be estimated with any accuracy due to the lack of appropriate calculating algorithms in dose planning systems and the limited knowledge of the clinicobiological equivalence.

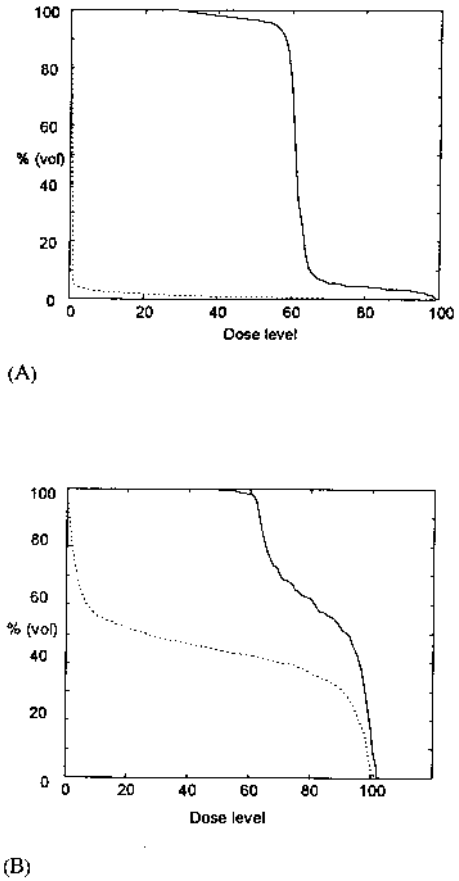

Fig. 4. Dose volume histograms for the bladder (A) and the rectum (B) for a four-beam 21 MV x-ray plan (—) and a single posterior 180 MeV proton beam plan (---) for a 78-year-old woman with an 8.5 cm large inexstirpable chordoma occupying the middle and lower parts of the sacrum.

The greatest advantages of protons have, by tradition, concerned well-demarcated targets close to sensitive structures. Typical examples of this are uveal melanomas and benign or malignant tumours close to the base of the skull. These rare tumours will be treated continuously with protons at selected facilities world-wide. The potential advantages seen in comprehensive comparative dose planning studies in other localized, and often more common tumour types like prostate cancer, thyroid cancer and other malignancies close to the spinal cord, provide the motivation to ensure that existing and planned proton facilities treat these tumours in properly controlled clinical trials so that the magnitude of a benefit can be accurately assessed and the predictive models improved. Other high technology conformal photon techniques could also achieve high target doses in these tumours with a dose below a certain threshold dose in one or a few classical risk organs, but will always result in higher total body integral doses.

In addition to the 'localized' tumour types, it is possible that the quantitatively greatest advantage of protons in the

future will be to decrease the risk of late morbidity when treating large irregular volumes at risk of containing tumour cells. A single-scanned proton beam could, for example, accurately cover the remaining breast and the regional lymph nodes after breast-conserving surgery for a breast cancer with axillary lymph node metastases and, at the same time, more or less completely exclude dose to the adjacent parts of the lungs and the heart at risk for late morbidity. A similar treatment is impossible with electrons or photons. Similarly, the brain and the spinal cord at risk of containing medulloblastoma cells may be irradiated with no dose to the thyroid, heart and female gonads and a limited dose to the vertebrae. In children and young adults having a life expectancy of several decades, this sparing of critical organs and structures is a great advantage.

The high investment costs for proton therapy have hampered its development. It has been estimated that the cost of protons compared to photons will be two or three times as high (44). No comparison of costs is available for the costs involved in the improvement of the conventional armamentarium aimed at even higher conformation of the beams than is presently possible. Furthermore, owing to the lack of a more precise estimate of the clinical gains, the cost effectiveness of protons, or any other high technology radiation development, is not known. In the light of the comparably low cost of standard radiotherapy, in spite of the high investment costs in buildings, 3D dose planning systems, accelerators and gantries (25), it is likely that future development of the entire radiation process will be cost-effective in comparison with other cancer treatments, or several medical interventions in other diseases.

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