Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Michael Goitein & Gudrun Goitein (2005) Swedish protons, Acta Oncologica, 44:8, 793-797, DOI: 10.1080/02841860500402207

To link to this article: https://doi.org/10.1080/02841860500402207

Published online: 08 Jul 2009.

Acta Oncologica, 2005; 44: 793–797

Taylor & Francis
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INVITED EDITORIAL

Swedish protons

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Ten papers in this issue analyze the indications for proton beam therapy within the context of the Swedish population and conclude that there is a sufficient basis for proposing that a proton medical facility be built in the country. In commenting on the papers, we should make the disclaimer that we ourselves are convinced "protoneers". Our own experience predisposes us to be favorable to the conclusions of these studies – although, on the other hand, also to be critical with regards to what it is reasonable to attempt.

These ten papers give a thorough overview of the available clinical data. Taken together with the underlying physical rationale, these data certainly support the proposition that proton beam therapy is a valuable tool in the therapeutic armamentarium. However, so far as clinical results are concerned, while there has been quite a lot of favorable experience, there have been only two randomized studies and very few critical comparisons with historical controls. This is largely due to the fact that, until quite recently, only a few centers have been engaged in proton beam therapy and those that were had limited capacity and a number of constraints such as limited energy, limited technology (e.g. no gantry), and limited beam availability. Furthermore, where the initial experience has been very favorable, subsequent randomized trials have not been thought to be possible on ethical grounds. The experience to date should perhaps be read as a confirmation that the theoretical arguments for proton beam therapy have been upheld in the limited number of situations in which they have been tested.

The physical rationale for proton beam therapy is unimpeachable. Under virtually every scenario, protons deliver less dose outside the target volume than do x-rays – typically they deposit one half or less integral dose to uninvolved normal tissues than do x-rays [1]. This statement holds no matter what the technical approach — it is the case, for example, for intensity-modulated radiation therapy (which can be done with protons just as with x-rays). Glimelius et al. in this issue [2] cite a remarkable 52 published treatment planning comparisons that document this fact. Faced with the possibility of receiving the dose distribution possible through a proton treatment, it is hard indeed to imagine anyone readily volunteering to receive an additional, say, 20 to 30 Gy to a large volume of tissue for which irradiation is not medically indicated.

All this having been said, it is important to appreciate that the application of protons is not without its difficulties and some limitations. With regard to the former, we see it as essential that anyone entering the field of heavy charged particle therapy serve an apprenticeship at one of the existing heavy charged particle centers. The physical/technical limitations include: the management of the influence of internal tissue heterodensities; the substantial problems posed by surgically implanted metallic objects; the lack of superficial skin-sparing; the management of moving target volumes; the unavoidably enlarged penumbra at large depths; the distortion of the dose distribution under conditions of tangential irradiation of structures with strong differences in density (including the skin-air interface); neutron backgrounds (especially

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(Received 10 October 2005; accepted 10 October 2005)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860500402207

problematic when scattered beams are used in pediatric treatments) and so forth. While many of these limitations can be overcome, nevertheless protons are not uncritically appropriate for all patients. One must always keep in mind that the colorful and attractive pictures produced by treatment planning programs may be misleading.

The commonly raised issue, ultimately, is that of economics. Is the drawback of receiving the extra dose delivered by x-rays worth the reduction in cost that they offer? In order to answer this question, one has to know or carefully estimate the extent and clinical significance of the benefit, the difference in cost, and how to juxtapose these in a sensible manner. It seems to us that there is doubt on all these matters. Probably the cost issue is the best understood and, in fact, the additional cost of proton beam therapy is not as great as is often thought. Proton beam treatments, by the time a Swedish facility is built, will probably cost between 1.7 to 2.1 times the cost of IMRT with x-rays [3]. However, it is unclear what the denominator should really be. The cost of some systemic therapies is substantially higher than the cost either of x-rays or protons. When referenced to such costs, the differences in the costs of proton and x-ray therapies are very modest.

Assuming that one knows the cost and the fact that some benefit will accrue from the use of protons, the question remains as to whether the advantage is worthwhile. That is, how high should one set the bar? If one sets it low, then virtually all Swedish cancer patients requiring radiation therapy would benefit from protons; the higher one sets the bar, the fewer the number of patients one would select to receive protons. Thus, in attempting to make number estimates, this issue is a critical one. While the papers presented in this issue try to deal with this matter, it seems to us that the question is so problematic that the kind of analyses presented here are bound to leave doubts in the minds of readers — in both directions.

The papers in this issue approach the question of the value of proton beam therapy by looking at a number of (mostly) common tumor sites and attempting to identify where problems exist in the current therapies and what fraction of these problems might be clinically significantly reduced with protons. Most groups interested in proton beam therapy are led to make such analyses and it is noteworthy how well the existing published reports agree with one another [2]. They all conclude that something like one in seven patients for whom radiation therapy is indicated would benefit sufficiently from treatment with protons to justify the additional cost. In translating this into the number of patients who could be treated in a proton medical facility, one note of caution is in order. The number of patients who will be referred may be significantly less than the number who might benefit. The situation probably differs among countries, but it is an unfortunate fact that many physicians prefer to treat a patient themselves, with the best tools they have at their immediate disposal, rather than refer the patient elsewhere, where the tools are better.

Glimelius et al. [2] present their concept of a Swedish proton medical facility in the context of making it possible to undertake large clinical trials of the efficacy of proton beam therapy. Here, too, we would propose caution. It has proved difficult in the past, as they allude to, to perform randomized trials of protons vs. conventional therapies. The reasons have been partly logistical (how does one persuade the 50% of patients in the control arm to travel hundreds if not thousands of kilometers to receive a treatment they could get in their back yard?), but mainly ethical. Different countries have different standards for the conduct of randomized trials, but it is generally regarded that a fundamental principle of a clinical trial is that of 'equipoise' [4]. Equipoise in this context means that the two (or more) arms of a randomized trial must, in an informed patient's mind, be of equal clinical merit — that there is but a coin-toss between them. In practice it is hard to imagine proposing a new therapy that is not expected to benefit the patient. For equipoise to be satisfied, therefore, there needs to be a possibility of a comparable (from the patient's point of view) downside to the test arm. It is extremely hard to think that the standard of equipoise is met in randomizing between proton beam therapy and therapy using x-rays (provided the best techniques are used for each).

The currently most successful proton treatments — those of base of skull sarcomas and ocular melanomas — would almost certainly not have emerged from the analysis-by-site methodology used in the papers in this issue. Both are rare tumors, seen infrequently, if at all, in most radiotherapy facilities. Yet, hundreds of the former, and thousands of the latter have been treated in the last two decades at only two proton centers. Partly motivated by this observation, we prefer, rather than analysis by tumor type, analysis by clinical and technical problem — some examples of which we now present. It is harder to make estimates of numbers using this type of analysis, but it may better characterize the potential role of a new proton medical facility.

Geometric complexity – shape, size and site

One should bear in mind that the advantage of proton over x-ray radiation therapy is based on geometry and not biology. Any biological (that is, clinical) benefit is secondary to the better geometry of proton beam dose distributions. Consequently, one may predict that the three S's of "shape, size and site (i.e. location relative to radiosensitive structures)" of the target volume will affect the extent to which protons may provide a superior treatment. Every radiation oncologist for whom protons are a therapeutic option knows that patients are often presented at rounds, or are referred to him or her directly, with tumors whose geometry makes them extremely hard to treat well with x-rays. The tumors may lie next to or between critical organs, or may be of a complex shape, such that the dose outside the target volume would be undesirably high if x-rays were used. Such patients are natural candidates for proton beam therapy.

Of course, there may be some clinical situation in which difficult geometries are more usual. For example, it could be that an outer quadrant breast tumor in a patient with positive nodes, which also need irradiation, would be advantageously treated by protons — with good sparing of the heart, lung and contralateral breast — while breast tumors with different geometries might receive much less benefit. In other words, there may be types of tumors for which the use of protons would be highly desirable in a subset of patients.

Thus, the numbers of patients benefiting from proton therapy may be determined less by site or stage than by particular individual geometric problems. To take advantage of such a benefit, it would be desirable that clinicians who might potentially refer patients have access to state-of-the-art comparative proton/x-ray treatment planning in order to participate in the judgment of the possible advantages of protons for a particular patient.

Large tumors

Protons have a false reputation for being most appropriate for the treatment of mainly small target volumes. In fact, their benefit is probably most apparent in the treatment of large tumors where conventional techniques would irradiate an undesirably large fraction of the uninvolved normal tissues. This has been the experience at the Paul Scherrer Institute, for example, where target volumes up to three to four liters in volume have been treated with protons in situations in which conventional therapy would have at best been problematic.

"Large" does not necessarily mean large in the scale of centimeters or tens of centimeters. A tumor is large if its volume occupies an important fraction of the organ or compartment in which it is situated. The treatment of ocular melanomas is a clear example of this. While the proton fields are typically less than 2 cm in largest diameter at this site, the tumors may occupy a third or more of the volume of the globe. It is the ability to nevertheless avoid treatment of the remaining fraction of the globe that accounts for the success of proton beam therapy of ocular melanomas.

Multi-modality therapy

The use of multiple modalities, either concurrently or in close time conjunction, is likely to increase in importance in the future. However, interactions between these therapies can compromise the use of one or more of them. The concomitant use of radio- and chemo-therapy is a case in point. It is not uncommon that chemotherapy has to be interrupted or even halted due to poor patient tolerance of the combined regime. It seems likely that decreasing the volume of tissue receiving significant radiation dose, and in particular avoiding irradiation of specific organs and tissues (such as the esophagus or oral mucosa), will decrease the severity of the interaction. This should lead to fewer treatment breaks, more patients completing their chemotherapy, and may make a higher intensity of either or both of the modalities possible. Again, anecdotal experience supports this hypothesis. For example, at the Massachusetts General Hospital, seven patients were treated with hyperfractionated proton therapy (1.6 GyE [note GyE is the iso-effective (relative to ^{60}Co) dose equal to the physical dose expressed in Gy multiplied by the relative biological effectiveness (RBE), equal to 1.10 in this case], BID, total dose >76 GyE) for advanced nasopharyngeal cancer after they had received neoadjuvant chemotherapy. None of these patients required a treatment break. This is unlike the institution's large experience of radiation treatment of nasopharyngeal cancer, which featured the use of BID x-rays to a lower total dose, where all patients require a break at 38.4 Gy due to severe mucositis. The PSI experience with pediatric treatments in the framework of combined chemo-radiotherapy protocols (since 2004) supports the theory that sparing of, for example, oral and pharyngeal mucosa from radiation dose reduces added toxicities and makes the combined therapy more tolerable.

Hypofractionation

Prolongation of treatment time appears to reduce the likelihood of local control in a number of sites;

e.g. head and neck cancer [5] and uterine cervix [6]. The corollary of this observation is that reduction of overall treatment time — by the use of larger dose per daily fraction, for example — may improve the probability of local control. The lower dose delivered by protons outside the treatment volume should increase the patient's tolerance to higher doses per fraction. The prime example of a situation in which this prediction is confirmed is the treatment of ocular melanoma with protons. Doses of 60 to 70 GyE are routinely delivered in 4 to 5 fractions in 4 to 10 days and are extremely well tolerated [7,8]. Hypofractionation has also been demonstrated in lung cancer with protons [9] and carbon ions [10]. (In the latter case, there is no evidence in these experiences that the better tolerance stems from high LET effects; the tighter dose conformation is quite likely to be the cause and this feature is shared by protons.) Thus, hypofractionation seems to be a promising possibility for proton beam therapy that merits investigation. Should it prove clinically desirable, it would also reduce the cost of the treatments. However, we strongly caution that it would be unwise to base any cost projections on the assumption that fewer fractions will be needed per patient. Reliance on hypofractionation for financial reasons is likely to lead to pressure to treat patients in a medically inappropriate, and even unethical, manner.

The aged or frail patient

The general population is steadily aging and, along with this, it seems likely that there will be a need to treat increasingly older patients. Such patients may be frail and may tolerate radical radiation therapy poorly. Anecdotally, in the Boston experience, patients receiving proton beam therapy often seem to tolerate their radiation treatments better — with fewer treatment breaks and fewer acute side effects reported. Patients transferring from x-ray therapy to proton therapy frequently report a substantial diminution of their symptoms. Thus, it seems likely that protons might be a valuable modality for patients too frail to tolerate conventional radiation therapy easily.

Surgical successes

Protons may, paradoxically, find application in tumors for which current therapies such as surgery are highly successful — though with a high price in terms of preservation of function. The treatment of ocular melanomas is a case in point. Before the use of protons, surgery was the most common approach and, as a cancer therapy, was highly successful. However, it involved enucleation of the eye with its concomitant functional and cosmetic disadvantages. Proton beam therapy has provided very high levels of local control — 99% local control at 5 years in one study [7] and 95% at 15 years in another [11] — while preserving a useful level of function for many patients and, of course, the advantage of preserving the eye for most of them. Thus, it seems that a survey of the surgical experience may turn up a number of promising sites for the application of protons. And, this search may not be problematic for our surgical colleagues. It is likely that their involvement will still be essential — as has been the case for ocular melanomas.

We have already alluded to the fact that there are some technical limitations and complexities in proton beam therapy. The same is true of the clinical applications of protons. To give a few examples:

1. Björk-Eriksson et al. [12] refer to retreatment using protons. The retreatment of patients who have unfortunately suffered a local recurrence of their disease is, of course, an important and very difficult problem, and one hopes that protons can offer an advantage. However, when the high dose retreatment volume encompasses normal tissues which received similarly high doses in the initial treatment, one most likely has to compromise the re-treatment target dose significantly, otherwise one will run into severe problems with any radiation — and protons are no exception. The so-far limited experience with re-irradiation at PSI supports the concept that appropriate dose coverage is mandatory, otherwise rapid tumor progression in the under-dosed regions will occur, and the re-treatment will fail. On the other hand, in one case of re-treatment for local recurrence of a nasopharynx cancer, we have seen that, while a high target dose of 70 GyE controlled the lesion, it also caused after about one year necrosis in the base of skull with neurological complications that made the patient's life more miserable than the local control could compensate for. In summary, we want to warn against making re-treatment a main focus for proton therapy. Cases need to be very carefully selected; the tolerance of previously co-irradiated normal tissues may be much lower than expected. However, protons may well be appropriate when the high dose re-treatment volume only or mainly encompasses adjacent tissues that have previously been irradiated to lesser doses.
2. Intracranial tumors, as Blomquist et al. discuss [13], are a traditional focus for proton- and other charged particle therapy. Unfortunately, the biological behavior of high-grade gliomas and glioblastoma has prevented protons from offering a breakthrough

in the treatment of these lesions. The use of radiation therapy for low-grade gliomas is subject to much discussion. However, the sparing of integral dose to the brain is a crucial issue particularly for young patients. Therefore, protons should be considered for treatment of pediatric low grade gliomas if radiation is to be used at all. In considering the use of protons for irradiation of meningiomas, one has to be careful not to have illusions as to the extent to which normal structures can be spared. It is impossible to deposit protons "one by one" to tiny structures (such as the sheath of the optic nerve) and simultaneously spare adjacent normal tissues. Even the best technology and treatment planning tools cannot overcome the laws of physics.

The use of proton beam therapy needs to be based on a solid clinical rationale. When not, resources are wasted and patient hopes may be wrongly raised. Considerable caution and careful study with good follow-up is needed when doses are pushed above currently accepted levels.

In sum, we are strong supporters of the use of protons. We judge that the arguments given in this issue together, perhaps, with some of the additional thoughts we have presented here — some of which are admittedly speculative — justify our position. If protons were no more expensive than x-rays, a majority of patients would receive proton beam therapy. Common sense suggests, as it has for almost all previous technical innovations, that their undoubted technical advantages will, and do, translate into worthwhile clinical gains. However, in ending, we also would like to sound two notes of caution. First, the high capital cost of protons has the potential to generate primarily financial pressures to achieve a high volume of treatments. Great care must be taken to prevent these pressures from leading to sub-optimal or even inappropriate treatments. Second, we want to emphasize that one must keep in mind that protons are simply a tool — they are no magic bullet. And a tool is no better than the craftsman who wields it. For protons to be exploited, the best minds need to be recruited to use them, and they must undertake extensive training. Any new project must attend to these matters. Otherwise, protons, as with any other tool, could be more disadvantageous than useful.

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