Acta Oncologica, 2005; 44: 798–800

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INVITED EDITORIAL

Protons. A step forward or perhaps only more expensive radiation therapy?

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In this issue of Acta Oncologica a series of review papers exploring the possible role of clinical application of protons came to the conclusion that protons may be suitable for 15% of the irradiated Swedish cancer population [1]. Having followed the development in radiation therapy for 30 years, I have reflected a bit on these calculations. Much of the progress in the past history of radiation therapy has been technology driven in the sense that when new machines were developed, giving radiation with new obvious advantages, these were simply used by enthusiasts followed by the other institutions in due time. This can be seen for introduction of high voltage radiation, where for example a Van de Graaff machine was built in 1943 in Bergen against the advice from the leaders at the Norwegian Radium Hospital, an institution that acquired high voltage equipment 10 years later [2]. Similarly there was no formal randomized trial proving that the cobalt unit when first introduced yielded better radiation results than conventional radiation. As far as I know the major promoter for its use was the recommendation from prof. Gilbert Fletcher at MD Anderson Cancer Centre [3]. Also the introduction of conformal radiation in the 1990s was more or less conceptually accepted with only few clinical controlled studies, but a series of model treatment planning studies were published [4]. The modern intensity modulated therapy (IMRT) is widely implemented [5] in most countries based on concepts initially largely developed and published in Acta Oncologica by prof. Anders Brahme [6]. Most major departments are currently investing money in equipment, training and research to implement IMRT for selected patient groups. The future focus has the past years been moved more to the biological properties of the cancer cells, i.e. the accurate localization of the part of a tumour that needs a higher dose and the registration of the actual response to exposure for radiation [7–11]. One may therefore ask whether protons represent a new paradigm shift in radiation oncology, making the efforts to implement IMRT obsolete?

The background for the proposal is mainly based on the concept that the radiation can be more precisely enveloped around the target volume (tumour with risk volume) with protons than conventional radiation including IMRT techniques. This is a relevant issue as there seems to be a potential doubling of late secondary cancers due to increased integral doses in areas outside the target when using multiple fields in IMRT [12,13]. Recently a treatment planning study indicated much lower lifetime risk for secondary cancer after proton therapy compared with IMRT, but the risk for IMRT was particularly high in children with medulloblastoma [14]. I could not find any specific publications addressing secondary cancer after proton therapy, despite that 43.000 patents have been exposed to this treatment modality [1]. In the papers better shielding of critical normal tissues surrounding the tumour are frequently stated. This is, however, a statement that should be tested as similar claims were put forward when conformal radiation based on CT-delineation of tumours was introduced. In fact it turned out that treatment volumes had to be increased to encompass the visualized tumour, just as often as they could be reduced. There is therefore a clear limit which cannot be passed with any radiation. A safety margin must prevail.

Another concern is the response of normal structures included in the irradiated volume if the sparing

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860500456120

of surrounding normal tissue will allow a higher dose. I also would like to see more data on vascular tolerance for protons.

Before introduction of a clinical study a clear and measurable hypothesis should be stated, based on a summary of the current knowledge. In the paper on pediatric tumours, 4 clinical studies and a few case reports comprising less than 100 patients totally were cited [18]. One should also note that the reported studies comprise posterior fossae chordomas and brain tumours in four small studies and a few case reports. Despite this limited experience and only about 3 years follow up, they estimated that 80-100 children currently given radiation may benefit from proton radiation. One should bear in mind that the series are small and collected over long time periods, making it open for selection biases. The confidence limits for any result are obviously large.

One may further ask whether protons always represent the optimal radiation therapy. I must admit that there are good physical arguments in favour of protons [19,20]. On the other hand, much better results than current results may emerge from IMRT and not the least from better diagnostic procedures disclosing the biological properties of a tumour and selection of areas where appropriate radiation can selectively be deposited as mentioned above. If secondary cancer is an increasing problem, the lowest radiation deposition in normal tissues may in fact be achieved with light ions [21,22], but then new uncertainties concerning high LET effects in normal tissues may be introduced due to denser ionizations which is considered beneficial for tumour destruction.

Personally I do not think it is reasonable to apply protons for almost all types of cancer in the current situation. A scientific project must select some type or a limited type of tumours where the proper protocols can be followed and the acquisition of necessary documentation can be monitored resulting in reliable data to prove the benefit of protons. It is disturbing to see that 43.000 patients have been currently treated with protons and only a few sufficiently large series giving a reliable amount of data have been published, as for eye melanomas and chordomas [23,24]. I find also hepatocellular carcinomas as particularly interesting as protons seem to yield at least as good tumour control as surgery with lower morbidity [25,26]. Before any particular tumour entity should be included in a study, a clear statement should be given on the magnitude of expected benefit in terms of better local tumour control and for reduction in local side effects that the authors think is appropriate for the inconvenience of sending all patients and relatives to a single institution in Sweden to have their proton therapy. Thus a testable hypothesis is necessary.

The present series of papers eccoes the enthusiasm for the use of protons at the research cyclotron in Uppsala I can remember 20 years ago [27], but this has hereto not lead to a paradigm shift in radiation oncology in Sweden. A modern clinical proton facility gives better possibilities for patient treatments than the present facility, but only a focused project will probably have a better chance of success. I am afraid that I am not fully scientifically convinced of the arguments put forward in the estimates provided in these papers, but I hope that the Swedish initiative will precisely define which patients who in the future will benefit from the best possible radiation techniques.

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