Particle therapy in clinical practice: Is there enough evidence to justify the current surge in interest?

Enthusiasm for particle therapy has never been as high as it is today throughout the world. There is not only a great interest in the subject but investments are also being made for setting up such facilities in different parts of the world, including in the US and Western Europe; a number of less developed countries are also expressing interest in it. In the US, the interest is largely focussed on proton therapy, whereas centers in Europe and other countries are planning for, and exploring the possibilities of, setting up facilities for both proton and ion therapies (hadron therapy).

Parallel to this boom, there has been a spate of articles and correspondence published in most of the oncology-related journals, presenting the differing viewpoints and the controversies surrounding this new modality. Perhaps the most interesting is the debate published recently in a widely read and reputed oncology journal on the available evidence and the need to generate more data on hadron therapy. The current interest in particle therapy also presents a unique opportunity to discuss the need for evaluation of not only high-precision radiotherapy techniques such as hadron therapy, but also of the other new (and often costly) technology-driven practices in medicine at large.

Let us examine the progress graph of proton and particle therapy in clinical practice. Fractionated therapy employing protons was pioneered at the Harvard cyclotron in the mid-seventies and therefore proton beam therapy cannot really be considered a very novel technique. That particle beam therapy, in general, has several intrinsic physical advantages over conventional photon therapy is more or less accepted. However, the fact is that these techniques have not been adequately explored because of the enormous costs involved in setting up the necessary facilities. The last few years have seen tremendous strides in the field of photon therapy and we are now able to produce considerably improved dose distributions around the target volume. In addition, we have learnt the importance of understanding the fundamental principles regarding the delineation of the target and of critical structures, we have developed improved methods to measure doses and, importantly, we now also know how to verify that the rather complex plans are delivered accurately on the treatment machine on an every-day basis. The confidence that the radiation oncology and medical physics communities have gained over the last few years, particularly with regard to their abilities to sculpt the desired dose distributions around an accurately defined target volume by means of sophisticated conformal therapy techniques and to implement it with a precise check by image guidance, has opened up new vistas; it is now feasible to reexplore the widely recognized physical advantages of the particle beam. I think this is perhaps among the most important reasons for the unprecedented interest in proton and ion therapy that is being witnessed today. Equally important is the recognition that there exists a reasonable prospect for recovering the costs of such high-end, often expensive, treatments for instance, intensity-modulated radiation therapy (IMRT) and image-guided radiotherapy (IGRT)] in most parts of the world. There is thus an increasing belief that it would be worthwhile to explore the attractive field of proton and ion therapies, which has been and continue to be virtually beyond the reach of radiation oncology practice in the vast majority of the centers in the world. In some centers such as in the US, there is actually a belief that proton beam therapy facilities, though expensive business propositions to begin with, may well turn out to be highly profitable enterprises in the long run. This has naturally aroused the interest of a number of private organizations and even generated interest in academic institutions to some extent.

In spite of the fact that proton beams and even ions have been employed in radiotherapy for decades, there is remarkably little published literature demonstrating its superiority over conventional forms of X-ray therapy. This is in part the reason why there is difficulty in evaluating the cost-effectiveness of these technologies. High-end technology in medicine has been always difficult to judge. The last few decades have also
witnessed many new discoveries and the introduction of several novel molecules and agents, which has prompted the academic medical fraternity to lay down certain criteria for the acceptance or rejection a particular ‘advance’ before integrating it into routine clinical practice. One of the criteria is that any new modality or agent must be thoroughly studied in a well conducted and statistically powered randomized controlled trial (RCT) to examine its efficacy. Indeed, RCTs remain the gold standard for proof of efficacy as far as the average researcher and clinician are concerned. There have been several examples, including in oncology, where a seemingly attractive advance identified through phase II data has failed, in RCTs, to display an advantage over the standard practice. A few examples that come readily to mind are myeloablative therapy and bone marrow transplants in breast cancer, the use of erythropoietin to enhance hemoglobin (though at the cost of poorer tumor control), and worse survival after dose escalation by radiosurgery in malignant gliomas. In all these instances, there was impressive data ‘proving’ the superior outcome with these measures as compared to historical cohorts, yet none of them showed any meaningful benefit when tested by a rigorous RCT that obviated the biases in phase data. Applying the same principles for high-end technologies such as hadron therapy, the questions that arise are: 1) Should we not test these technologies in RCTs as well, especially in light of previous experiences and heavy investments; and 2) should we rely only on RCTs or should we also examine other end points as a measure of acceptable success?

Improved dose distributions, especially with scanned pencil beam techniques in proton and ions could be potentially beneficial in several clinical situations. Indications for small ocular tumors and base of skull tumors have been well established but such cases comprise only a small fraction of the patients seen in clinical practice. For hadron therapy to be really considered effective, we have to evaluate its potential in other cancers in which local control has always been an issue, for example, head and neck cancers, cancers of the lung and esophagus, and the so-called radioresistant tumors like sarcomas, melanomas, etc. Relatively small case series reported from centers in the US and Europe have shown evidence in favor of the effectiveness of hadron therapy in providing improved outcomes in a range of tumors; similarly, reasonably large data from Japan on carbon ion therapy (which has several advantages over proton beam therapy) also shows benefits with this technique. However, the available evidence is unfortunately not enough to satisfy the demands of present day rigorous scientific evaluations. Several investigators have pleaded that the dose distributions and Dose volume histograms (DVsH) data is impressive enough to justify the routine use of this technique as well as the human and financial investments. Some researchers even argue that the dose distributions are so good that it may be unethical to conduct, for instance, a randomized trial between ion/proton therapies vs photon therapy. I find this very hard to believe. I certainly would go with the school of thought that suggests that new technologies should be tested just as any novel intervention or drug. It is also true that RCTs alone should not be the sacrosanct standard in evaluation. After all, we did not need an RCT to switch from telecobalt machines to linear accelerators (although in some head and cancer situations, that may be an issue). For that matter, we have embraced IMRT as a standard treatment in many sites without evidence from a large RCT (which, ideally, we should have asked for). However, there exists reasonably strong nonrandomized evidence in favor of IMRT, at least as far as minimization of toxicity is concerned (for example, reduced xerostomia when treating head and neck cancers). A couple of RCTs with IMRT, using patient satisfaction score as the end point, however, failed to show a clear superiority of IMRT over conventional radiotherapy, although there was impressive dosimetric and salivary flow advantages. Our own data on childhood brain tumors revealed a significant proportion of patients as having poor IQ levels even before starting radiotherapy, therefore posing the question of just how much advantage the high-precision technique of stereotactic radiotherapy provides over conventional radiotherapy. The results of this trial should be interesting.

The bottom line is that we must establish stringent, yet reasonably achievable, end points for evaluating emerging and potentially exciting technologies. While it may not be possible to perform a RCT in every site (a few certainly must be attempted), at least a collective effort by the hadron therapy groups in the form of a consortium-based database should be established. The consortium could collect prospective data with clearly defined end points of local control/survivals in dose escalation studies and toxicity end points in various sites with an aim to reduce complications. It is the latter which would be a challenge, for it is difficult to collect such data (eg, in neuropsychological testing) and it may also take several years for the maturation of such data. On the other hand, we must be cognizant of the potential ill effects, howsoever small, of proton and ion therapies. Increased neutron contamination by them could potentially lead to increased carcinogenesis, an effect with considerable implications, especially in children, who paradoxically could be the biggest beneficiaries of ion/proton beam therapy as such. Slightly less stringent end points may also be considered in some sites. Merely treating a large number of patients (as is often the case in such settings) certainly should not be an aim; collecting appropriate data and presenting the same with scrupulous intellectual honesty is the way to go forward.

One of the major issues when implementing expensive modalities in healthcare is justifying their cost, and several methods have been propounded for assessing cost-effectiveness. One method would be to calculate the incremental cost-effective ratio, which estimates the cost involved per life-year/quality-of-life year gained, and different setups have laid down their own criteria for measurement. The World Health Organization (WHO)
advocates that any modality can be considered to be cost-effective if the cost per quality-of-life year gained is less than the country’s gross domestic product (GDP). The proponents of hadron therapy propose that the initial costs of treatment with these techniques may be 2-5 times more than with high-end photon therapy, but that the costs can be recovered by treating a large number of patients. Also, as in the HIMAC model in Chiba, Japan, increasingly hypofractionated treatments are being implemented to maintain the increased number of patients. It should be borne in mind though that the pressure to recover cost may push the envelope and end up accruing more numbers, even if they may lead to the treatment of patients who may not perhaps qualify for these treatments. This makes it even more imperative to generate quality data and define the indications for these expensive treatments as accurately as possible, lest it be confronted with the Titanic and Iceberg story as has been compared in a recent editorial for patients with cancer of the prostate.[9]

As far as the situation in India is concerned, we face a peculiar problem. On the one hand, we are struggling to provide even basic radiotherapy facilities to our patient population, with significant gaps between needs and resources. At the same time, we do have a small but significant proportion of patients with the capacity to pay for the latest treatments. In this regard, India presents a very interesting paradox, with a mix of some of the richest and some of the poorest people in the world, as well as a burgeoning middle class with the wealth and the desire to explore all treatment options. The country does possess the technology and the know-how for maintenance and even initiation of such facilities in some regard in this direction. Therefore, there does exist a case for at least exploring some of these avenues. Having large patient numbers may be an advantage and we may actually be able to provide the answers to some of the difficult questions by conducting appropriate studies as per internationally accepted scientific and ethical guidelines.[10]

REFERENCES
1. Glimelius B, Montelius A. Proton beam therapy: Do we need the randomised trials and can we do them? Radiother Oncol 2007;83:105-9.

Source of Support: Nil, Conflict of Interest: None declared.