Europrotons

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One of these days, if you end up around a table with physicists and radiation oncologists, and you would like to bring a languishing discussion back to life, try and say the words 'proton therapy'. The chances are that the conversation will restart right away (the problem, actually, might be how to avoid it getting too heated!). In the recent history of radiation oncology it is not easy to find a treatment technology that has given rise to so many discussions. As a consequence, I feel obliged to declare my bias right from the start: after spending about ten years in photon radiation therapy, since late 2005 I have been working as a medical physicist in a project for a proton therapy centre in Trento, in the north east of Italy.

The purpose of this article is not to try and summarize this discussion, nor to bring a personal contribution to it. At the same time, I think that taking a pragmatic approach, and looking at what it is actually happening in terms of active facilities and ongoing proton therapy projects, is a way to bring down to earth the debate on the present and future role of proton therapy.

For the sake of simplicity, we'll discuss here the current activity in the field of proton therapy delivered using a gantry in proton-only facilities. This is not to disregard the relevance of proton therapy of the eye (a technique used to successfully treat thousands of patients), nor to deny the current interest in (carbon) ion therapy, but rather to focus on a)the typical setting of most clinically-oriented proton therapy projects and b) the kind of equipment needed for proton therapy to be an alternative to photon techniques for the whole variety of patients treated in a typical radiation oncology department[1].

With this in mind, we have to state that presently proton therapy in Europe is represented by one centre only, i.e. the Paul Scherrer Institute

[1] An updated list of protons, light ions and heavier charged particles projects can be found at `http://ptcog.web.psi.ch/linksC.html`

(PSI) in Switzerland. Some may argue that PSI is not exactly the *typical* radiotherapy department, and they would be right. This is indeed quite a unique institution, able to combine under the same roof clinical activity, advances in medical physics and developments in beam-delivery technology. This has enabled PSI to become the only proton therapy centre in the world with significant experience in treating patients with pencil-beam scanning.

What is likely to happen in the next five to ten years? Are we going to see physics laboratories following the example of PSI (or GSI, for that matter) and promoting developments in charged particle therapy? This would be perfectly possible, and centres such as PSI will be still crucial in leading technological developments, but the approach of, so to speak, basic physics going towards medicine is likely to be the exception rather than the rule. The current trend, absolutely evident in the US and now more and more clear in Europe too, is in fact the opposite, i.e. hospitals are taking the lead and running projects to build proton therapy centres.

Developments are happening quite fast too: while, as we said, in 2008 there is only one gantry room delivering proton therapy in the whole of Europe, in 2009 we expect to see a second gantry opening at PSI, a gantry room to start operating, in addition to the current treatment lines, at the proton therapy centre of the Institute Curie, in Orsay, France and a new four-gantry facility to open in Essen, in Germany.

What can we expect for sure beyond 2009? Several projects aimed at building a proton therapy centre are currently ongoing in Europe. They are at very different stages: some are close to finalizing the configuration of the equipment, others are going to publish a tender soon, others are at the phase where funding and reimbursement schemes are being discussed and clinical programs are being sketched. As a consequence, while it is quite easy to predict the big picture, i.e. between five and ten years from now most European countries will have at the very least one proton facility in operation, it is more difficult to say where exactly these facilities are going to be, and how they will look like in terms of size and equipment.

All these projects have common challenges to face, and we'll name here a few:

One should think/plan/work on a different scale than for conventional radiotherapy. In the US most proton therapy centres are the result of a single Institution investing in this technology. In Europe, this approach, which is being pursued by the Rinecker Centre in Munich, may turn out to be relatively unusual. The current indications for proton therapy (or, more specifically, the combination between the cost of proton treatment and the patient categories most likely to benefit from it) are such that even a small facility (e.g. with two gantries) should plan to draw patients from a population of 4-5 million people. This, combined with the initial investment needed to start a proton therapy facility, means that most European proton therapy projects are going to be multi-Institutional efforts, with major challenges in terms of patient referral, patient management during and after the treatment course and the difficulties of having different Institutions, each with its own tradition, culture and clinical approach, working together day by day. The timescale is another important aspect: if you start from a greenfield site and you are interested in a 'turnkey' solution, the day your search for a company to build the center officially starts (e.g. the day you publish a tender), you may be more than four years away from treating the first patient. This delay makes it difficult to make the right technological choices, due to a situation that represents the second challenge:

Proton therapy technology is still developing. The vast majority of proton therapy treatments has been delivered so far in treatment facilities where several gantry rooms are served by a single accelerator (be it a synchrotron or a cyclotron) and the beam is shaped by a (double) scattering system. This technique, sometimes dismissed as an approach of the past, is still very much the technique of the present, if we just look at the number of treatments. At the same time, all present and future proton therapy centres are looking at beam scanning as the next step in beam delivery. Beam scanning is a very appealing technique for a number of reasons: by allowing a much more flexible beam delivery, it can address some typical problems of beam scattering, such as the lack of conformity on the proximal side, the need for 'patching' techniques to treat lesions wrapped around an organ at risk, the requirement of patient specific hardware for each field and the neutron dose associated with the aperture. Last but not least, with beam scanning one can deliver 3D intensity modulated proton therapy (IMPT)[2]. However, it is fair to say that proton beam scanning in 2008 is very similar to IMRT *circa* 1998: everyone is talking about it, a few are trying to implement it, and even fewer are actually doing it. At the time of writing (Fall 2008), only one proton therapy centre besides PSI has reported at least one patient treatment with beam scanning (M.D. Anderson, in Houston), while another centre (F. H. Burr at MGH in Boston) is expected to treat the

[2]We use here the term 3D IMPT as it is usually defined in proton therapy (T. Lomax, Phys. Med. Biol. 44(1999), 185-205).

first patient by the end of the year. Furthermore, while it is true that the main technical bottleneck to make beam scanning widely available is represented at the moment by beam delivery technology, one should not forget the need for appropriate treatment planning approaches. If one wants to deliver beam scanning treatments in a variety of clinical situations, where the potential effect of organ motion and/or range uncertainty is a serious concern, one will have to rely on sophisticated delivery and planning techniques, e.g. approaches such as volumetric rescanning and/or robust optimisation. It is safe to say that the treatment of a moving target with proton beam scanning is not yet a solved problem.

From the perspective of a proton therapy project for which the technology has to be chosen for a centre due to start a few years from now, these developments represent a dilemma: should I stay with a proven planning and delivery technique (beam scattering) and be willing to pay the extra money (and time) needed to move to beam scanning at the later stage, or should I trust that by the time treatments will start at the new facility beam scanning will be a proven and robust technique?

To make things even more complicated, two proposals have recently been made for quite radical changes in proton therapy technology: on the one hand, a single-room proton therapy system is under development, where an accelerator is being attached to the gantry. This system tries to address the limitations in size and cost of a single-accelerator multi-room facility and is targeted at hospitals willing to add proton therapy capabilities to their radiation oncology department without building an entire proton therapy centre. Washington University in St. Louis is the first institution expected to acquire this system, while no European project has chosen such a solution so far. Another proposal, which also aims at manufacturing a stand-alone single gantry treatment facility, is even more innovative, being based on a technology (dielectric-wall accelerator) which is completely new in the field of proton therapy. These two approaches, if and/or when successful, might completely change the big picture; however, at this moment it is too early to predict the future impact of these technologies on clinical practice.

Coming back to beam scanning for a moment, there is one more aspect to consider. Those who are familiar with conventional radiotherapy techniques tend to draw an analogy between photons and protons, and say that the transition from scattering to scanning is very similar to the change from conformal photon techniques to IMRT. The analogy is appealing and in many ways justified; as we mentioned earlier, beam scanning does indeed offer more degrees of freedom in planning and delivery, as IMRT does with respect to CRT. However, this analogy misses two points:1) The dosimetric improvements are clear but they might not be as dramatic as from CRT to IMRT, because beam-scattering treatments, in particular when planned by skilled dosimetrists, can produce in many cases very good results; 2) While the transition from CRT to IMRT resulted, in general, in a significant increase in treatment time, pencil-beam scanning may be effective in improving not only the quality but also the quantity of proton therapy treatments. Beam scanning may indeed be one of the tools to be used to face another important challenge for proton therapy in the next years, i.e.

Proton therapy should prove itself as a good technique not only for treatment quality but also for treatment quantity. If you have ever spent some time following proton treatments, you might have noticed one peculiarity: it is not unusual, especially for complex treatments, that the beam is off for most of the time when a patient is in the treatment room. So, you might ask: why should one spend tens of millions of Euros to buy a sophisticated beam delivery system on a gantry, and then waste so much time in the treatment room doing something other than shooting protons? This question is actually less trivial than it may seem, and it may be answered in several ways; one of them is actually to turn the criticism upside down and say that this happens because in proton therapy smaller beam-on-times are often sufficient to deliver better dose distributions than those achievable in IMRT with much larger beam-on-times. However, let's take this question as a serious challenge: can proton therapy produce higher patient throughput without reducing treatment quality and complexity?[3]

There are two complementary approaches one can follow:

> *Use more efficient beam-delivery techniques.* As we said earlier, scattering techniques need two pieces of hardware (aperture and compensator) for each treatment field. This hardware, besides being expensive and time-consuming to produce, can become quite bulky and heavy in the case of large treatment fields, and requires someone to enter the room, remove the old hardware, store it, put the new one in place and exit the room. With beam scanning, one can aim at considerably reducing, if not eliminating, the need for field-specific hardware.

> *Move (part of) the setup procedures outside the gantry room.* Set-up

[3]There is of course a shortcut to increased throughput: treating simpler cases. This quickly leads to a discussion on the balance between clinical and economic priorities. We are not going to open this Pandora's box here.

errors are a very serious concern in proton therapy, where they are potentially associated with range uncertainties and can cause significant discrepancies between planned and delivered dose distribution. As a consequence, daily imaging and on-line correction is the norm. As these operations can be very time consuming, many are attracted by the idea of moving (part of) the set-up procedures into dedicated areas just outside the treatment rooms. For example, PSI implemented a procedure with a dedicated set-up area, connected to the treatment room by a straight passage that facilitates smoothly wheeling in the patient. The new centre in Essen is going to have a set-up room, equipped with MRI imaging, for each gantry room. In our project, too, the plan is to rely on external set-up, at least to some extent. The whole approach might seem counter-intuitive, given that in photon therapy more and more sophisticated imaging tools are brought inside the treatment room. However, this is a clear direction some proton therapy projects are taking, and it will be interesting to compare their results with other centres, such as the University of Pennsylvania, where a similar approach to photon therapy has been chosen and a cone-beam-CT is expected to image the patient in the treatment position.

In conclusion, it should be quite evident that these are interesting times for proton therapy, both in the world in general and in Europe in particular. Many clinical centres are increasingly interested in the technology and are willing to embark on ambitious projects. This is good news for proton therapy, but it is also an indication that the bar has been raised. One thing is to carry out a very promising technique in very few excellence centres on a small numbers of patients. Quite another thing is for the same technique to go 'mainstream', i.e. to be delivered reliably, in a normal clinical setting, on a large scale and at an affordable cost, thus becoming one of the options a radiation oncologist normally has at his/her disposal when choosing a treatment approach.