Particle Therapy in the 21st Century: Relevance to Developing Countries

Vienna International Centre
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The following document reports the discussion that took place during a consultant meeting organized by IAEA in Vienna from 11th to 14th of November 2014 and summarizes its conclusions.

1. Introduction

Radiotherapy (RT) is a well-established treatment modality in multidisciplinary cancer care. Radiotherapy has been used for more than a century for both curative and palliative treatments, alone and in combination with other modalities of care. In the last 20 years radiotherapy has undergone impressive technological development mainly in three directions: better target volume definition, better dose conformation, better day to day patient positioning reproducibility and image guidance allowing greater accuracy of dose delivery. Target volumes are now routinely contoured in three dimensions (3D) using high resolution imaging, with MRI and PET scanning in addition to CT for target definition. Gross tumour volume (GTV) can now be more precisely identified thanks to this multimodality imaging approach. Dedicated surgical and pathological studies that have quantified the risk of nodal involvement for various tumours have informed the process of clinical target volume (CTV) definition in many sites. Several special radiotherapy techniques are used in clinical practice for selected indications including intraoperative radiotherapy, brachytherapy, orthovoltage therapy, neutron therapy and electron beam radiotherapy; but the vast majority of treatments are performed with external beam photon radiotherapy (EBRT). The ability to conform dose to complex shaped targets has increased dramatically with the improvement in delivery techniques, going from 2D-RT to 3D-RT to intensity modulation (IMRT) and stereotactic RT. Margins between CTV and planning target volumes (PTV) have been reduced thanks to improved accuracy in patient positioning with daily imaging in treatment position, i.e. image guided RT (IGRT) and improved strategies to cope with organ motion (such as real time tumour tracking).

Photon RT is generally considered to be a mature technique, which is ultimately limited by basic physical properties, the most important being the exponential depth-dose curve. In the case of the lower photon energies, tissues shallower than the target may receive more dose than the target itself (entrance dose) and tissues deeper than the target receive a dose that (albeit to smaller volume) may be comparable to that received by the target (exit dose). This can only be improved by increasing the number of irradiated fields to achieve geometrical focusing.

Particle therapy (PT) is a kind of external beam radiotherapy that uses positively charged particles such as protons and carbon ions instead of photons. These particles have more favourable intrinsic physical properties displaying a finite adjustable range (“zero” exit doses) and an inverse depth dose profile (Bragg peak), which reduces entrance dose to about 50% of the dose delivered in a clinically relevant target. As a consequence, particle therapy can achieve a marginally better dose distribution in the target with substantially better sparing of surrounding healthy tissues compared to the most advanced photon RT techniques.

PT with protons can be considered an excellent tool for conformal dose delivery. Historically, the theoretical advantage of PT has been recognized since the forties, and the first patient was treated in the US in 1953. For four decades PT was an experimental technique employed only in physics laboratories that dedicated part of their time to medical applications. In 1991, the first hospital based PT facility became operational in Loma Linda, California. For the next fifteen years, PT was available only in a very limited number of centers worldwide, and was used mainly in rare cancers such as skull base and spine sarcoma and uveal melanoma, although prostate cancer has also been
treated from the beginning. In the last ten years, there has been an exponential growth of new facilities, a rapid increase in patients treated and several new indications including paediatric cancer, lung cancer, breast cancer and pancreatic cancer. This accelerated spread of PT has been due partially to encouraging results achieved by pioneering institutions and partially to developments in target definition and patient positioning that have made the additional precision of PT more necessary and profitable. Today more than 120,000 patients have been treated with PT worldwide.

The physical properties of carbon ions are very similar to those of protons. They have a sharper lateral fall off which is advantageous, but they have a distal tail of dose beyond the Bragg peak which is due to nuclear fragmentation: as a first approximation dose distributions achievable with carbon ions can be considered almost superimposable to those achievable with protons. Carbon ions are employed for their radiobiological properties. Like all positively charged particles each carbon ion delivers dose through multiple ionization events whose mean distance decreases along the particle path. The mean ionization density can be described by a physical parameter called linear energy transfer (LET) that is the energy deposition of a particle in a unitary length along its track. When mean ionization density becomes comparable or shorter than the DNA double helix diameter (high LET) a single particle is capable of producing clustered damage to the DNA. This damage is hard to repair and is relatively insensitive to the common factors that determine sensitivity to low LET radiation, such as oxygenation, the phase of the cell cycle and the viability of apoptotic and repair pathways. Carbon ions have a low LET (mean ionization length much bigger than DNA diameter) in the entrance plateau and reach high LET in the Bragg peak. Not only do they deliver a high dose in the target but the dose delivered there is also radiobiologically more efficient. They have consequently been used in attempts to target tumour subpopulations that cannot be adequately controlled even with high doses of low LET radiation, or in other words to treat “radioresistant tumours”.

Carbon ions have been used in a clinical setting since 1994 at the National Institute of Radiological Sciences (NIRS) in Japan. To date, more than 10,000 patients have been treated and seven more clinical facilities are now in operation in Japan, Europe and China. More facilities are under construction; nevertheless carbon ion radiotherapy is still significantly less available than proton PT. In some countries (e.g. Germany) treatments with carbon ions are considered more of an experimental approach than proton beam therapy. In line with this perspective, carbon ion treatments are allowed in Germany in the frame of clinical trials. Some experts voice the need for more robust data on the relative biological effectiveness (RBE) of carbon ions because of its potential for late normal tissue toxicities.

There is at present a hot debate on the actual value of PT. On the one hand, several experts advocate that its physical advantages are self-evident and that ultimately PT will replace photon RT for most if not all indications, just as LINAC based photon RT has all but replaced cobalt units in developed countries. At the other end of the spectrum, several scientists claim that PT should be considered strictly experimental, and that the number of new facilities should be limited until clinical benefit is proven within prospective randomized clinical trials. For the past fifty years, and although many technological developments in RT have been introduced without randomized data, the routine use of PT is perceived as requiring a higher burden of scientific evidence due to the significantly higher costs involved.
2. Purpose of meeting

The purpose of the meeting was to review all issues related to new PT facility projects, focusing on developing countries whilst not excluding high income developed countries. More specifically the aim of the meeting was to explore the potential role of IAEA in providing advice and support to Member States that sought help with such projects.

3. Work done and results achieved

In the four days of the meeting, fruitful discussions took place that led to consensus on many topics among all participating experts; in some areas consensus was not reached.

Topics discussed here mostly focus on the areas where a consensus was reached.

Indications

All experts agreed that indications for proton therapy and for carbon ion radiotherapy are still subject to clinical research. Up to now no head to head randomized clinical trial of particle therapy versus photon RT has ever been completed. Several ongoing randomized phase III trials in the US are comparing particle therapy to photon RT (e.g. the NRG BN001 trial for GBM, the NRG LU 001 trial for NSCLC) but not one of them has been completed so far. Defining a comprehensive list of indications for particle therapy is beyond the scope of this Consultants’ Meeting. A rational use of particle therapy must take advantage of its physical and radiobiological properties. Proton therapy should be used in situations in which its improved dose distribution can achieve a better sparing of non-target healthy tissues, which can be expected to decrease clinically observable unwanted side effects. Proton therapy should also be used in situations where its improved dose distribution allows safe dose escalation with potential to increase local control. Carbon ions should be used in situations where sub optimal local control is achieved with low linear energy transfer (LET) radiation because of intrinsic low radio-sensitivity of the disease or of a subpopulation of tumour cells. Carbon ion radiotherapy should also be used in situations in which its favorable physical properties (mainly its sharp penumbra) can achieve significantly better sparing of critical organs at-risk (OAR) compared to photons or protons. There is also an emerging area of research, involving the potential impact of heavy particles on the local disease, and the induction of immune stimulatory responses and its impact on the control of systemic disease.

Prerequisite to build a particle facility

There was general agreement among the experts that the main prerequisite for planning and building a particle therapy facility is the existence of local conditions that guarantee a fair chance of success.

While the status of photon radiotherapy in a country can be an indicator for the availability of local expertise and infrastructures, the existence of sufficient LINAC based facilities or wide availability of IMRT is not a prerequisite for building particle facilities. Therefore adequate access of a population to less complex types of photon radiotherapy should not be considered mandatory for planning a particle therapy facility.

The Agency has a policy to assist its Member States in the transition from 2D radiotherapy to 3D-CRT and IMRT. A detailed list of prerequisites is defined in an IAEA document (IAEA TECDOC-1588).
supports requests from countries and facilities that satisfy the prerequisites and discourages requests from facilities that fail to meet them, as such projects are likely to fail and result in a waste of resources. There was agreement between the experts and the Agency to initiate a process that through future meetings will produce a similar document for particle therapy.

It was agreed that allocation of limited resources to one or another specific project in healthcare has ethical implications that need to be analyzed either in the framework of freedom of private enterprise (for private funding) or national health policy (for public funding) rather than this meeting. The prerequisite list will focus on the achievability of any given project.

Several examples of European particle facilities which were completed but never treated patients were analyzed; experience gained from those cases is reflected in the following recommendations.

**Clinical research in new facilities**

There was general agreement that many aspects of proton therapy and almost all aspects of carbon ion radiotherapy are still in need of clinical research. Coordination of clinical research is a challenging task but the past years have seen a huge effort in this area at both the national and international level.

Critical issues for clinical research in particle therapy were discussed with general agreement that a major funding problem exists even in large and well established facilities in affluent countries. More specifically the cost of data management and trial design which is typically covered by industry in drug research is a limiting factor in most institutions. Long term follow up is another critical issue particularly for patients residing far from the facility. Those patients are typically willing to move for treatment but may comply sub-optimally with long travel for follow up. Moreover, loss to follow up is unlikely to be random and may for instance occur more often when patients have either extremely good or extremely bad outcomes, thereby biasing data interpretation. Strategies to improve follow up compliance may include web based interviews or other specific remote tools such as smartphone application or social network based tools. All the experts agreed that despite the challenges, long term follow up data are of paramount importance. The Agency may play a role in creating and distributing web based tools to facilitate follow up. Those tools may be useful not only for developing countries but for the whole particle community.

There was general agreement that participation in clinical trials and new clinical trial design is not mandatory for new facilities. A project that employs established treatment protocols and focuses on clinical activity rather than research should not be discouraged.

If the project has a focus on clinical research, prerequisites should be more stringent and assess also the quality of existing research infrastructure and links with academic institutions. Moreover, the resources and personnel necessary for data management should be assessed critically and country specific strategies to optimize compliance to follow up should be devised. All participants agreed on the high potential value of shared patient data and pooled data analysis whilst acknowledging the many legal and practical factors that hinder the creation of a shared patient database containing treatment and follow up data. These include the privacy issues, data ownership issues, data format issues and the substantial cost of creating, maintaining and updating such a database.

**Facility commissioning**
Facility commissioning was discussed in detail. Commissioning is defined as the set of all tests performed by the facility staff after the vendor and the facility staff have completed the acceptance tests and delivered/accepted the product. There was general agreement that commissioning should not be carried out solely by the vendor. There was also general agreement over encouragement of a peer review of the commissioning process although it cannot be considered mandatory. The Agency could play a significant role in supporting the peer review process. There was agreement that cost of commissioning should be specifically addressed in the planning phase. Commissioning cost should include all the necessary specific hardware and the cost of outsourced expertise. During commissioning the facility is operational but is neither treating patients nor producing revenues and this delay impacts on the business plan. The recommended or minimal duration of commissioning could not be defined as it depends on the specific kind of equipment. Commissioning should be linked with personnel training. A document formalizing the commissioning procedure of a particle therapy facility may be a possible IAEA undertaking.

**Training**

All the experts agreed that training of personnel in the initial planning phase is of paramount importance for the success of a project.

Specific training of radiation oncologists and medical physicists is the most relevant issue but other professional roles such as therapists and nurses should also be taken into account. Pre-existing expertise in advanced photon RT is necessary and should be complemented with specific particle training. The experts agreed on the need to train the whole facility team and the need to educate the whole referral network.

A selected number of radiation oncologists and medical physicists should receive extensive hands on training in active facilities. For these “groundbreaking” staff members, the first step should consist of attendance at a short course, for instance the PTCOG educational, the ESTRO course on particle therapy, the PSI winter school or NIRS courses, complemented by self-study. This should be followed by a long term fellowship in an active facility. Definitive agreement over the ideal or minimal lengths of hands on training was not achieved, but a duration of 6-12 months was considered reasonable. This groundbreaking ‘core’ should then help train the entire staff, taking advantage of additional web based e-learning tools. The experts recommended that IAEA explore the possibility of initiating an e-learning project for particle therapy. The burden and cost of training on the active facility site can be substantial. At present, few facilities have established long term training programs for newcomers in the field and the need to compensate the trainer is widely acknowledged. After the meeting, NIRS decided to initiate a residency program in carbon ion RT for foreign medical doctors. There was general agreement that training costs should be identified in the initial budget of any new project. It was not possible to give a final recommendation on the suggested and minimal budget for training but the figures of 0.5 – 1 M USD were considered to be a reasonable order of magnitude.

Proton therapy and carbon ion radiotherapy are not equivalent and each has its peculiar issues both on the physical and medical side. Training should be focused on the particle that will be used in the planned facility.

The need to educate the referral network was highlighted with a specific focus on multidisciplinary treatments. Referring patients to active facilities during the planning and building phase is suggested
as a way to raise awareness to indications for particle therapy, and to inform other physicians (especially surgeons) of specific needs (e.g. spacer insertion for bowel displacement, low artifact stabilization devices for spinal surgery, extent of necessary debulking, etc.)

**Equipment choice and integration**

There was general agreement that the kind of equipment to be built in a new facility must be linked to the planned clinical use. A low energy, fixed line, passive scattered proton beam is perfectly adequate to treat uveal melanoma and such a facility may address a real clinical need. There was general agreement that new facilities should be encouraged to utilize established technology rather than novel designs that have never been used in clinical practice. Accelerators used worldwide for particle therapy are basically synchrotrons and cyclotrons; several new concepts are under study such as linacs, laser driven proton acceleration and dielectric wall acceleration. The experts agreed that established technology should be considered as first choice; nevertheless it is not possible to discourage the use of new technologies. The use of innovative designs should be attempted only by groups with highly specialized pre-existing expertise. The time frame of such projects should be considered more uncertain. As the cost of the accelerator is only part of the total cost of the facility, there was general agreement that novel accelerator design whose main purpose is cost reduction should be assessed critically within the whole project framework.

There was an in depth discussion on the issue of gantries: a definitive agreement was not reached. For proton therapy the majority of experts were of the opinion that a gantry is mandatory even though the question of whether a full 360° rotation is necessary or a gantry with more limited angles (200°-280°) can be adequate did not reach consensus. There was even a minority opinion that under given conditions a fixed beam facility may be justifiable, and its limitations may be partially solved with dedicated imaging and immobilization devices (e.g. vertical CT, rotating cradle, treatment chair). There was general agreement that the absence of a gantry limits the range of treatable diseases. Gantries are much less available for carbon ion beams than for proton (currently only one in the world, in Heidelberg); however, there are several projects of carbon ion gantries in different stages of development including one isocentric 360° superconductive gantry that will be built in NIRS in 2015. With regard to carbon ion facilities, the majority of the experts advocated the need for a gantry, but, reflecting the state of the art, it was felt that no specific recommendation could be given.

Integration of all subsystems was analyzed as a critical issue. Having a whole facility built by a single vendor was suggested as a possible solution. A more detailed discussion revealed that relevant parts of a facility such as the treatment planning software (TPS) or the Oncology Information System (OIS) are not typically provided by hardware companies. This issue was handled carefully by the experts as it was considered inappropriate to issue any recommendation that may favor one vendor over another. Moreover, none of the vendors are currently able to provide all of the required hardware and software. There was general agreement that the accelerator, beam lines, dose delivery systems, patient positioning system, patient position verification system, TPS, OIS, organ motion coping devices and overall control system should be fully integrated. There was agreement that a single entity (and a clearly identified person) should be responsible for the integration of all subsystems. Finally, there was agreement that integration should not only rely on compatibility but should be verified in operational conditions and that the person responsible for integration should put in place specific problem solving strategies.
**Maintenance and back up**

Maintenance was considered by all experts to be a critical issue. It was agreed that maintenance should be a separate item in any project, provided either via an external maintenance contract with the vendor, a dedicated in-house maintenance team or a combination of the two. The cost and duration of maintenance should be analyzed using existing facilities as a benchmark.

The problem of machine breakdown and consequent long (more than one week) treatment interruptions was discussed. The many critical aspects of a back-up agreement with another facility were analyzed including the need of replanning, sharing of medical responsibility, logistics for the patient and need to triage patients to different options for fall back treatment.

**Organ motion**

There was general agreement that organ motion represents a more critical issue for particle therapy than for any other kind of high precision RT. Respiratory motion, peristaltic motion, cardiac activity, stomach, rectum and urinary bladder filling may all impact negatively on the planned dose distribution. Active scanning is even more prone to organ motion induced plan degradation compared to passively scattered beams due to the interplay effect. There was general agreement that a new facility should initially treat fixed targets and attempt moving target treatments only when sufficient expertise has been gained. There was no definitive agreement on the recommended or minimal necessary interval from start of clinical operation to beginning of moving target treatments, but a period of 1 year was considered reasonable.

**Management; relationship with stakeholders**

There was general agreement that good project management is a key factor for the success of setting up a new facility. A strong project manager with previous experience in complex large scale projects is mandatory. The project manager should be supported by a core team with specific medical and technical expertise in radiation oncology, medical physics and accelerator physics. The experts agreed that the medical component of the project should be at least as important as the technical one from the very initial planning phase. Projects developed in a particle physics environment that focus on the production of a particle beam, planning to define details of its medical use in a subsequent phase, are not to be encouraged. Local and national authorities should be involved during the planning phase. The potential impact of existing radioprotection regulation on clinical operation should be analyzed together with the regulatory body and, if possible, regulation should be tailored to the particle therapy setting. As an example, it was quoted that in some eastern European countries a particle therapy facility would be considered a nuclear site, and therefore personnel would not be allowed to work beyond 13:00 in the afternoon. In some other countries, shielding must be scaled according to the maximum instantaneous dose rate, which for certain types of active scanning may result in gross overestimation. Economic sustainability of the facility should be analyzed within the national framework together with the paying third party (be it private insurance or national health security). In the long run even a sound project will not succeed if the cost of therapy it provides cannot be borne by the national health system of the country. Facilities targeting a paying patient population should be approached differently from those relying on a third party payer.
There was general agreement that local medical societies should be involved in a project at the initial planning phase.

**Patient throughput**

Annual patient throughput is a key factor for the financial sustainability of a project and the experts agreed that it should be estimated realistically.

Patient number depends mainly on four factors:

1) **Facility capacity**

Capacity should be evaluated in terms of treatment sessions deliverable per day. This aspect must be analyzed through modeling the timing of patient entrance in the treatment room, set up, position verification, dose delivery and patient exit. Number of fields delivered per day and ancillary procedures such as coping with respiratory motion, 3D in room imaging or general anesthesia clearly impact on the single fraction duration. Foreseen duration of simple treatments, complex treatments, paediatric treatments (with or without anaesthesia) and treatments of moving targets should be estimated separately. Parallelism issues must be analyzed. Rooms can be considered independent from each other only if beam delivery time and switching time between rooms are negligible compared to overall session duration. Sessions deliverable per day must reflect the expected patient mix (complex and long versus simple and short treatments) and the number of rooms (discounted for suboptimal parallelism).

2) **Fractionation schedules**

Fractionation schedules should reflect the expected patient mix and be based on established fractionation schemes. Experimental or unproven hypo-fractionated regimens should not be used in patient throughput calculations. Of course hypo fractionated treatment can be investigated in a scientific setting, and especially with carbon ion have a strong radiobiological rationale, but it should not be used to artificially increase patient throughput in the business plan.

3) **Patient recruitment**

It is not realistic to assume that all available treatment slots will be filled from the start. The business plan should allow adequate time and resources for establishing referral networks. A formal epidemiology analysis of potential patients should not be considered adequate without an analysis of patterns of care before the particle facility construction and an analysis of competing therapeutic options. The experts agreed that a new facility should either be built in, or be closely related to, an existing oncological hospital. The linked hospital should already be capable of attracting a significant number of patients who are candidates for particle therapy. It was not possible to define the minimum percentage of patients who could be assumed might self-refer, but 20%-30% was considered a reasonable amount even though according to local condition it may be as low as 5%. The creation of a referral network should be part of the project and should involve contact during the construction phase with scientific and medical societies, centers of relevant surgical expertise, and physicians treating patients in the target population in active facilities (including overseas).

4) **Personnel**
Personnel should not be estimated on the figures routinely used for advanced photon RT. Specific issues of particle therapy should be considered, e.g. the need for medical physicists for complex and time-consuming QA.

Throughput may be analyzed in terms of treatment sessions delivered per year or patients treated per year. The second option permits the use of existing facilities as a benchmark.

Patients treated per year by the vast majority of particle facilities are available online on the PTCOG website: http://www.ptcog.ch/index.php/ptcog-patient-statistics

A business plan that estimates a number of patients per year substantially larger than that achieved in existing facilities, must be considered extremely suspicious.

As a reference we report number of patients treated in 2013 according to PTCOG:

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<th>Country</th>
<th>Location</th>
<th>Facility Name</th>
<th>Patients treated 2013 (estimated)</th>
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These data are extrapolated from PTCOG website subtracting the total number treated up to 2012 from the total treated up to 2013. *The HIBMC number of 1689 refers to patients treated within two years (2012 and 2013). These data may not be completely accurate as they reflect what each facility communicates to PTCOG and depend on the month in which the total is assessed. As an example from the PTCOG website we can calculate for HIMAC (NIRS, Japan) the figure of 670 patients treated in 2013 whereas the real figure is 999. In 2013 CNAO has treated 129 patients. Once again the real number is slightly different from the one (128) reported on the PTCOG website; nevertheless the table gives a good estimate of patients throughput. In 2013 no facilities worldwide, regardless of number of treatment rooms, patient mix and pre-existing expertise, treated more than one thousand patients.

**Business plan and feasibility study**

The experts suggested that the Agency support new facilities with a simple tool to guide the initial planning phase. It was suggested that a template for a particle facility business plan be created which could be provided to any applicant and also made available online. There was agreement among the experts to encourage feasibility studies before the start of a project. It was suggested that the Agency produce a list of questions for a low cost simple feasibility study adapting an existing tool devised by the European Bank of Investment. The feasibility study could be the initial step to be performed, even before seeking the Agency’s aid and before going through the formal prerequisite assessment. Business models of other, photon based, advanced RT facilities active in the same country may be a relevant benchmark. Cases of financial failure and of successfully run facilities may provide a key to common aspects such as referral network and reimbursement. Nevertheless the specificity of particle therapy should be considered and a business plan should not be imported from any photons facility.

**Shared database**

All the experts agreed that an international patient database would be an invaluable tool. It was suggested that an imaging intensive database would be needed, allowing access to anonymized patients’ data including treatment plan, follow up imaging, and clinical outcome and toxicity. All the experts agreed that such a database would be extremely useful. However, it was considered an ambitious project that requires separate analysis in a different framework.

There was agreement that a patient database of more limited scope could be useful for new projects. It was agreed that the database should include sample plans describing in detail “good
particle practice”. This database could be used as a benchmark by new facilities during their learning curve. The experts encouraged the Agency to explore the possibility of supporting the creation of such a database.

4. Conclusions

The expert meeting was successful in establishing a team with all relevant expertise that was able to cooperate fruitfully. There was an impressive degree of agreement between experts from different continents with different backgrounds. A PT facility project was recognized as a project at high risk of failure both in high and low-middle income countries. The IAEA initiative to investigate this field and support new facilities is to be commended; the Agency may play a key role in enhancing a new PT facility project’s chance of success. The most critical issues were identified and discussed. In many of them the potential role of IAEA was outlined. The final result of this meeting is summarized in the following recommendations which IAEA is encouraged to give to new facilities. During the discussion, topics were identified that may be of interest to the IAEA and merit specific attention. These topics may become side projects within the main framework of the IAEA interest in PT. IAEA could promote research in particle therapy including radiobiology. IAEA could create tools for the initial planning phase of a PT facility, including a template for a business plan, a list of questions to be employed as an initial feasibility analysis and a list of prerequisites for PT akin to the existing list for switching from 2D to 3D-CRT. IAEA could start a process for e-learning in particle therapy taking advantage of its excellent established expertise in web-based learning tools and involving a broader community of PT experts. IAEA should start a process to facilitate web-based follow up, developing dedicated tools that may ultimately be useful not only for PT but also for broader patient populations. IAEA should foster the creation of a “good particle practice” database, gathering optimal plans for several body sites and diseases. This database could be useful as a benchmark during the learning phase of a new facility. If the Agency continues its involvement in this field, subsequent meetings will be necessary both on the general topic and addressing the specific side projects.

5. Recommendations

The following recommendations were agreed:

Recommendations that the Agency is encouraged to give to new facilities

- The Project Mission should be identified and shared with all relevant national stakeholders from the beginning
- National regulatory authorities and all relevant stakeholders should be involved from the beginning of the project Strong project management skills are essential
- A small core group with multidisciplinary skills and specific experience is essential (as a minimum: radiation oncologist, medical physicist, health administrator)
- A feasibility study is recommended before starting a new PT facility (including cancer epidemiology, access issues and links to an oncology hospital and scientific and professional societies)
• Pre-existing expertise in the clinical use of advanced radiotherapy technology must be available in the consortium planning the facility

• Leveraging of existing local medical infrastructure is encouraged (with a special consideration for paediatric patient multidisciplinary care)

• Established technologies should be considered first. Original and new technologies can be considered at a later stage, but a higher level of pre-existing expertise is necessary, including expertise in the specific issues of medical application

• Patient throughput should be realistic and be defined taking into account:
  - Patient recruitment
  - Number of deliverable fractions (allowing for complex and simple treatments)
  - Personnel availability
  - Number of fractions per patient
  - Anticipated case mix

• Patient throughput at existing operational facilities (PTCOG listings) should be considered as a reference

• Integration and communication between systems (accelerator, beam delivery system, TPS, OIS, patient positioning and verification) are major issues. Preferably one single individual should adopt overall responsibility for the integration of all systems

• Given that the main cost is not the accelerator system, careful attention should be paid to the equipment/procedures in the treatment room including the gantry and all software and interfaces

• Particle therapy education of selected staff (medical physicists, radiation oncologists and RTTs) is strongly recommended. Courses, distance learning and practical fellowships are all needed and must be complemented with in-house training of the full staff

• Vendors should provide specific education and training on the use of their systems

• During the planning/building stage the host medical institution is encouraged to send selected patients to existing facilities for PT; this creates local awareness and experience and fosters collaboration

• The host medical institution is encouraged to establish a referral network

• Commissioning of the completed facility is the responsibility of the local staff. Collaboration with existing facilities with similar technologies is encouraged as well as external peer-review

• In the initial clinical phase established treatment protocols should be employed

• Before attempting high complexity treatments (e.g. moving target), adequate successful experience in simpler scenarios should be obtained
6. Extended synopsis

6.1. From basic physics to projects and protocols in particle therapy

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I. Introduction

In this work, we present some examples of the direct relationships between basic physical interactions of charged particles (with fields and matters) and macroscopic effects, affecting the feasibility and specifications of building new clinical facilities, preparing treatments and setting new clinical protocols.

II. Increasing electric and magnetic fields ... to reduce investments costs

Charged particles like protons and heavier ions interact with electric and magnetic fields. Electric fields accelerate those particles providing the ability to penetrate in tissues with a therapeutic range, while magnetic fields can bend their trajectories. Many of the efforts to conceive compact machines have been oriented towards the optimization of strong magnetic fields to concentrate the orbits in circular machines (e.g., cyclotrons and synchrotrons) and focalizing them till the extraction (e.g., use of cryogenic coils to saturate the magnetic circuits). The most recent result in this direction has been to mount a cryogenic synchrocyclotron in the gantry itself.

In a different approach, for linear accelerators the research is oriented towards high electric fields, either into insulated dielectric walls or plasma based, but their feasibility still need to be proven.

Efforts to conceive compact gantries at lower cost is also related to magnetic fields (to bend the beam trajectory towards an isocenter), and on strategically decisions such as conceiving 180° rotation gantries and, even now, re-discussing the optimal use of fixed lines for selected cases.

Compact accelerators and gantries (integrated in a single room or as separate parts in single or multiple rooms) are required to reduce the bulk size of the treatment area and costly components, and so the investment costs, what is one of the key factors to facilitate the evolution of particle therapy projects. Present costs for technology of an accelerator and a single room is in the order of 20-25 M$, still high, but with a sensitive reduction compared to just a few years ago [1,2].

III. Microscopic interactions with matter (beam line and patients) and macroscopic effects

1. Nuclear collisions of charged particles with matter create secondary particles such as neutrons, having a direct incidence on shielding, activation and dose to patients with high RBE. These interactions produce also some activation in the patient itself, what can be used as an indirect way of in vivo dosimetry or range verification in patients with PET (also detected with prompt gammas produced in these interactions). Finally, for heavy ions, nuclear collisions produce fragments with larger range than the primary particles, creating a tail with high RBE after the Bragg peak, what can be a serious limit in the choice of particles and incidences for therapy.
2. The collisions with electrons are the basis for the therapeutic approach, as they produce ionization and through that the biological and the clinical effect. The energy deposited is represented by the stopping power, which increases at low energies (so at the end of the range), creating a peak in the dose distribution known as the Bragg peak. This big advantage of this ballistic feature has also a weak point: the uncertainties related to where exactly the peak is placed in depth in the patient in real clinical situations. In some cases with complex inhomogeneities, with movements or organ deformations, the evaluation of the risk will be the factor of choice of a treatment plan based on its robustness more than on the « best » theoretical dose distribution. The high ionization in the track of different particles at different energies, measured by its LET, is at the origin of a differential biological effect, represented for ex by the RBE, giving the main interest to have clinical research using heavier ions. This high ionization can affect also the response of dosimetric detectors (saturation, quenching ...) reducing the accuracy of dose measurements if the effect is not well understood.

3. The multiple scattering of particles has several consequences, as for ex : they can be positively used to increase the beam size with scatterers («passive techniques»), but they also increase the beam lateral penumbra into the patient (up to values larger than those of photon beams used in clinics) for both large passive beams and small pencil beams, and they also degrade the distal dose fall-off in presence of complex inhomogeneities.

For all these cases, the treatment planning system must be able to take into account the macroscopic effects of these interactions in the dose modeling. It must also evaluate the robustness of a plan and be able to produce new fast plans adapted to any change in the patient, with the accuracy required to avoid performing massive quality controls for every patient/plan or beam.

IV. Effect of time patterns, beam intensities and beam shaping on clinical protocols

Different accelerators and beam delivery systems have also different time patterns (from continuous to pulsed beams with low or high frequency), beam intensities (relative « low » or « high ») and shapes (dynamic pencil beam vs. passive scattered wide beams). All these specifications affect directly or indirectly some parameters of the implementation of clinical protocols, for ex: easiness to produce intensity modulated beams and then higher conformation to a given tumour (opening dose escalation approaches) and/or reducing doses to critical organs or integral doses (eg. for paediatrics). They also affect the management of clinical constraints such as dealing with organ movements, the production of neutrons directed towards the patient, the effects of very high dose rates [3], the patient throughput ... As state of the art, there is a clear tendency to move towards pencil beam scanning, incorporating modern IGRT tools (ex CBCT or CT in room) and range verification devices, trying to manage the organ movements (in particular interplay effects with scanned beams) and moving towards the implementation of real adaptive techniques of treatment for the « patient of the day »... as with photons.

V. Conclusion

The knowledge of the basic physics of interactions of charged particles with fields and matter and their links with macroscopic parameters is necessary to optimize dosimetric and clinical protocols as well as to lead the technological development in order to reduce investment and operational costs, necessary to warranty the evolution of particle therapy.
VI. References


6.2. User’s guide on implementation of light ion beam therapy facility

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1. Introduction

There are many factors to consider in deciding what kind of equipment to purchase to implement light ion beam therapy facility. Specifications for generic light ion beam treatment facility equipment have been provided by Moyers and Vatnitsky [1]. These specifications can be used by a potential customer as a template to develop their own specifications or as a comparison guide to a manufacturer’s proposals. Current presentation provides some guidance to the potential customers acquiring this type of equipment.

2. Selection of equipment

Typical layout of the light ion beam therapy facility includes accelerator complex, high-energy beam transporting lines to irradiation rooms, equipped with fixed beam delivery lines or gantries, patient alignment systems (PAS) and medical software management systems (MSMS) with treatment planning system (TPS). Currently two types of accelerator complex are used in practice: synchrotron-based and cyclotron-based. The selection of the proper complex can be followed by the analysis of several factors:

- Maximal energy (Proton therapy: Eye therapy 60-80 MeV, Deep-seated tumours 150-250 MeV; Ion beam therapy: 100-450 MeV/u),
- Intensity (beam current of 1 nA leads to a dose rate of 2-4 Gy/min, i.e. treatment time of a couple of minutes. If the efficiency of the beam transport and shaping systems is about 5%, then beam current of 20 nA has to be sent from the accelerator to support required dose rates.
- Time structure (because of saturation effects in detectors and dose rate dependent biological effects, continuous beams are preferred.
- Compactness of the accelerator, simplicity for use and maintenance, low cost.

The customer should decide either on Cyclotron: fixed output energy, energy variation requires post acceleration energy selection (activation of hardware is a problem). On the other side: continuous
beam current of 10μA or more provides high dose rate and stable beam output that can be precisely controlled; either on synchrotron: energy variable from pulse to pulse, maximum beam intensity is limited to ~ 2.4 x 10^12 pulses/min.

The next issue to be decided is beam shaping system that consists of devices spreading the beam laterally and varying the depth of penetration to sufficiently cover the target with dose while minimizing the dose delivered to normal tissues. Passive scattering technology uses patient specific devices: apertures and boluses (compensators) and is widely implemented. The selection of accelerator complex with scanning beam delivery has several advantages: no patient-specific devices, no patient-specific calibrations – computer generated control, more flexible dose delivery patterns with possibility for intensity modulation and inverse planning optimization. But the customer has to take into account that scanning systems are more expensive, less reliable and require more stable beam delivery system; dosimetry is more difficult and organ motion consideration is more critical.

The need of isocentric gantry is motivated by several reasons: beams should be directed from any angle to the patient in a fixed supine position as CT scanning for treatment planning is performed with the patient fixed in the treatment position. Turning a supine patient, as is required with a fixed beam, reduces precision and can influence organ motion. Most proton facilities employed several types of the gantries; however, only one carbon beam gantry is in use).

To align the patients with respect to the treatment beams different PAS are used. The major components of the PAS consist of the patient positioner (PP), devices to register the patient to the PP, devices to immobilize the patient with respect to the PP, a collision avoidance and detection system (CADS), and the patient position verification system (PPVS) that itself consists of x-ray sources, image capture devices, image processing software, and alignment software. The various solutions for PPs using industrial robots are generally compliant to the radiotherapy specifications and combine high flexibility with reasonable prices and sufficient life times. The selection of a robotic PP may be a good solution but the user should also consider the need of a pit to lower the robot below the floor surface and allow for a low-height table top position, otherwise the use of ceiling-mounted system is a choice [2]. If the use of a patient transporter is planned, then the compatibility of the docking system of the transporter and robotic PP should be considered.

The focus of the treatment planning process is to develop a treatment plan which fulfills the physician's prescription and simulates the application of this plan to a patient. This is facilitated through the use of a TPS. A primary difference in the treatment planning process for conventional beams and light ion beams is the need to account for the biological effects of light ion beams on tissue.

The MSMS is used to schedule and document various aspects of the course of treatment and may also be used for billing. The MSMS may interact with the TPS, beam delivery system, hospital information system (HIS), and other systems so the compatibility of the MSMS with these other systems must be taken into account.

The initial costs for a facility include not only the light ion beam equipment but also CT, PET, and MRI scanners, treatment planning workstations and dosimetry equipment, office and medical equipment, and a building to put them in. The salaries for the staff that must perform acceptance testing and commissioning of the equipment for use before the first patient is treated must also be
included. Reference [2] summarizes some of these estimated costs for a typical four-room facility. Once the facility is treating, additional expenses are incurred such as supplies, and maintenance contracts. Moyers and Vatnitsky [2] provided examples of the number of patients per day that could be treated in a four room facility for different mixes of complexity of treatment. Assuming a 50%/50% mix of simple and complex treatments, a four-room facility could expect to treat just over 200 patients per day and receive an annual reimbursement of over $66 M at typical 2009 reimbursement rates (USA data). If one assumes the lifetime of the equipment is 25 years, the facility would be reimbursed over $1.6 B. Unfortunately, most potential users wanting to build a light ion facility have difficulty finding willing investors because the investors want their money and profit returned within 3 to 5 years, not 10 to 25 years.

Follow estimates from [2] equipment costs for a facility treating with carbon ions in addition to protons are almost double that of protons with slightly higher costs for maintenance contracts and upgrades. Assuming that reimbursement for carbon ions is identical to that for protons, there is smaller profit with an associated large uncertainty of financial success. This makes the acquisition of a carbon ion facility impossible without philanthropic or government support.

References


6.3. Proton Therapy: Rationale, clinical outcomes and future directions

Gita Suneja, Zelig Tochner

INTRODUCTION

A central tenant of radiation therapy delivery is to maximize tumour control probability (TCP) while minimizing normal tissue complication probability (NTCP). Balancing TCP and NTCP, and thereby creating a favorable therapeutic ratio, is particularly challenging for tumours located in close proximity to critical normal structures uninvolved with tumour [1]. Proton therapy is a type of non-invasive radiation which uses charged particles instead of X rays to more precisely deposit radiation dose as compared with traditional external beam radiation therapy. Proton therapy has the capacity to minimize entrance and exit dose, decrease integral body dose, and spare normal tissues, organs at risk, or previously irradiated tissue [2]. Therefore, proton therapy may deliver biologically equivalent doses of radiation with more precision and less treatment toxicity than conventional photon radiation. In this chapter, we present a summary of the rationale, clinical outcomes, and future applications of proton therapy to low and middle income countries.

CLINICAL EVIDENCE AND OUTCOMES

Skull Base and Brain Tumours
Chordomas and chondrosarcomas are rare, indolent tumours with a natural history of poor local control and invasion of surrounding structures. Safe maximal resection followed by radiation therapy is the treatment of choice, however even with multimodality treatment; local recurrence continues to be a common pattern of failure. With conventional photon radiation, dose is limited by the tolerance of the brainstem or spinal cord. In contrast, proton therapy has been used to increase the dose delivered to the tumour while sparing dosing to adjacent critical normal structures. Prospective randomized trials comparing photons and protons have not been conducted, however retrospective data demonstrates a high probability of local control with proton therapy, in the range of 45–80% local control at 5 years for chordoma and 98% at 5 years for chondrosarcoma. One prospective study of 100 patients treated with combined modality treatment (photons plus protons) to a dose of 67 cobalt gray equivalents (CGE) showed a 3-year local control rate of 71% for chordoma and 85% for chondrosarcoma. Clinical data for proton therapy in skull base tumours demonstrates superior outcomes compared with conformal photon therapy.

Similarly, dose limiting toxicity is seen in parenchymal brain tumours which are located close to critical structures such as optic nerves, optic chiasm, pituitary gland, hippocampus, temporal lobes, brainstem, and spinal cord. The effect of treatment toxicity is even greater with benign and low-grade tumours, such as meningioma, that have a high chance of cure. Even with highly conformal techniques such as IMRT, late neurocognitive deficits can be seen months to years after radiation therapy. One retrospective study evaluating the use of combined photon/proton therapy for atypical meningioma after surgical resection showed a local control rate of 61% and 2-year overall survival of 95%. In other series treating low grade meningioma with protons alone or after surgery, local control rates of 92–100% were reported with minimal severe toxicity. A small phase I/II study of 20 patients with resected grade 2 and 3 glioma treated with 68–80 CGE of proton therapy showed local control and overall survival rates comparable to outcomes reported in patients treated with photons in the past. The possibility of safely escalating radiation dose for malignant brain tumours may exist with proton therapy.

Ocular Tumours

Ocular melanoma can be a locally aggressive and potentially fatal disease. Enucleation was previously the favored approach for local control, however in recent year, organ preservation with radiation therapy and other ablative techniques have emerged as a reasonable alternative to surgical resection. Doses of 50–70 CGE in five fractions yield local control rates of 95% and eye preservation rates of 90%. Proton therapy is especially effective for large, posterior tumours that are difficult to reach with conventional techniques, such as brachytherapy. The existing evidence suggests high rates of organ preservation and disease control with proton therapy.

Prostate Cancer

Prostate cancer is among the most common male cancers in the world, and detection of early stage, low-risk cancer is particularly high in countries where screening PSA is readily available. Options for the treatment of localized prostate cancer include surgery or radiation therapy with or without hormone therapy. When available, the preferable method of radiation treatment for most men is IMRT to reduce genitourinary and gastrointestinal toxicity. Two prospective randomized clinical trials have investigated the role of proton therapy in the treatment of prostate cancer. The first was a trial of 202 men with stage T3-T4 prostate cancer comparing 75.6 Gy delivered with photons (50.4 Gy) followed by proton boost (25.2 CGE) to 67.2 Gy with photons. While the proton boost did not
improve overall survival, local control was improved in the subset of patients with high tumour grade. The second trial compared 70.2 CGE delivered with photons to 79.2 Gy delivered with photons and protons in 393 men with T1b-T2 disease and PSA < 15 ng/mL. The rate of biochemical failure was 32.4% for the lower dose (photon only) arm and 16.2% for the higher dose (proton boost) arm. Other phase I/II and retrospective studies using proton therapy alone or in combination with photon therapy show favorable local control outcomes and toxicity profile. No randomized clinical data comparing protons alone to photons alone currently exists. The greatest benefits of proton therapy for localized prostate cancer include dose escalation and reduction in mean integral dose to the normal tissues of the pelvis, which may translate into fewer secondary malignancies following treatment for prostate cancer.

Lung Cancer

Lung cancer is not only common, but also highly lethal with universally poor long-term survival. The standard of care for early stage non-small cell lung cancer is surgical resection. However, excellent local control results have been achieved with stereotactic body radiation therapy in medically inoperable patients. Two prospective non-randomized trials have examined the use of hypofractionated proton therapy to a dose of 50–60 CGE in 10 fractions. In the U.S. study, 3-year local control was 74% and 3-year overall survival was 72%. In the Japanese study, 2-year local control was 60% and 2-year overall survival was 80%. More recently, a study of 18 patients with early stage non-small cell lung cancer treated with proton therapy to 87.5 CGE in 35 fractions showed a 2-year local control rate of nearly 90%, and a 2-year overall survival of 70%. Additionally, two retrospective studies demonstrated local control rates in the 80% range for patients with early stage disease treated with proton therapy.

The standard of care for locally advanced non-small cell lung cancer is concurrent chemotherapy and radiation, occasionally before or after surgical resection. The recently published results of a phase II study of proton therapy with concurrent chemotherapy for unresectable stage III non-small cell lung cancer show very promising results with median survival of 29 months and minimal toxicity. Proton therapy may offer significant advantage over photon therapy for treatment of lung cancers due to the reduction of the low dose bath created by photons as they exit the lung. This may decrease incidence of acute esophagitis and pneumonitis, and may completely spare the uninvolved lung from receiving excess radiation dose. However, lung motion and lung density changes during respiration present challenges in proton treatment planning and dose verification.

Hepatocellular Carcinoma

Radiation therapy has been used in the treatment of unresectable hepatocellular carcinoma; however treatment with photon therapy is limited by excess dose to surrounding liver parenchyma in patients with already compromised liver function. Several retrospective studies and prospective non-randomized trials demonstrate favorable results with proton therapy. Retrospective data from Japan using 60–76 CGE showed 5-year local control rates of 85% with 5-year overall survival around 25%. The low survival was partially explained by co-existing liver cirrhosis in many individuals with hepatocellular carcinoma. The three prospective non-randomized studies used proton doses between 63 and 76 CGE, and showed local control rates of 60–88%. Local control rates were higher with higher doses of proton radiation, suggesting that dose escalation may be beneficial in hepatocellular carcinoma. The use of proton therapy for other gastrointestinal cancers has been
limited; however there may be a role for its use in unresectable pancreatic and esophageal cancers in the future.

Head and Neck Cancer

Cancer of the head and neck is challenging to treat due to the large number of critical normal structures located in a small, confined space. Both acute toxicity and long-term treatment-related morbidity from surgery and radiation are high. Proton therapy has been investigated for treatment of head and neck cancers, particularly nasal cavity, paranasal sinus, and nasopharyngeal tumours that are generally not amenable to surgical resection. Two retrospective studies using combined photon/proton treatment plans to doses of 75–76 CGE demonstrated 5-year local control rates of 84% for oropharyngeal cancer and 74% for other head and neck cancers. Two other retrospective studies used proton therapy alone to doses of 60–70 CGE and showed 2-year local control rate of 50% for recurrent nasopharyngeal carcinoma and 1-year local control of 77% for sinonasal cavity tumours. Other less common head and neck tumours such as olfactory neuroblastoma and malignant melanoma have also been treated successfully with proton therapy (local control 84–88% at 1 to 3 years post treatment). The treatment of head and neck cancer with proton therapy is evolving, particularly as new methods for modulating beam shape and size (such as intensity modulated proton therapy) become more readily available.

Paediatric Malignancies

Paediatric malignancies are uncommon, but devastating to patients, families, clinicians, and society at large when they occur. Aggressive treatments are intended to cure children who have many decades of life ahead of them, however late toxicity from the treatments can alter the patient’s quality of life in the future. Nearly 50% of paediatric solid tumours are brain tumours, and unfortunately radiation therapy has deleterious effects on the developing brain. Adverse effects of radiation therapy are also reported in growth and development of soft tissues, bones, and nerves. Maintaining the delicate balance between achieving treatment efficacy while minimizing toxicity is a challenge, and proton therapy provides a unique opportunity to minimize long-term treatment toxicity in children treated for cancer. As such, proton therapy has been used to treat medulloblastoma, ependymoma, craniopharyngioma, rhabdomyosarcoma, neuroblastoma, and many other paediatric tumours in various sites all over the body.

There are numerous dosimetric studies which demonstrate the superiority of proton therapy in sparing normal tissue and decreasing total integral dose. Clinical data has been published for orbital rhabdomyosarcomas demonstrating excellent local control of 85%. When compared to historical controls, sparing of the optic structures, optic chiasm, and temporal lobes were found to be greater. Similarly, retrospective data examining the use of protons for craniopharyngioma, a benign but locally destructive tumour, has shown excellent local control results of 94% with minimal toxicity, particularly in patients with subtotal resection. Another retrospective study in children with ependymoma treated with proton therapy shows excellent disease control while sparing normal structures such as cochlea, the hypothalamus, and temporal lobes. The treatment of paediatric malignancies is one of the most important applications of proton therapy, particularly in cases where craniospinal irradiation is required. The potential reduction of severe late toxicity and decreased risk of secondary malignancies provide compelling rationale to further investigate the use of proton therapy in paediatric malignancies. Emerging data on the efficacy and toxicity profile of proton
therapy for a variety of paediatric malignancies will be forthcoming as more children are referred to proton therapy centres for treatment.

FUTURE DIRECTIONS

Direct comparisons between proton therapy and photon therapy (IMRT, conventional conformal radiotherapy) cannot be made without randomized clinical trials. However, the existing data provides a strong case for the superiority of proton therapy for carefully selected patients, particularly those with ocular tumours, base of skull tumours, or paediatric malignancies. Furthermore, randomization of patients to a less conformal radiation technique may not be ethical, and there is ongoing debate about whether true equipoise exists given the current data. The need and feasibility of prospective clinical trials comparing protons to photon beam therapy is the subject of a heated debate among radiation oncologists today.

While newer radiation techniques such as IMRT have improved local control and decreased late toxicity as compared to conventional conformal treatment, the larger number of monitor units required and multiple fields used may increase the volume of normal tissue exposed to radiation, and therefore increase the risk of secondary malignancy. One of the major benefits of proton therapy is the reduction in integral dose, which may eventually result in decreased risk of secondary malignancy as compared with photon therapy.

At present, studies examining the use of proton therapy in nearly every tumour site are ongoing at facilities around the world. At the University of Pennsylvania Medical Centre, we have used proton therapy to spare breast tissue in young women with mediastinal lymphoma, to spare connective tissue in patients with sarcoma, and to minimize normal tissue toxicity in re-irradiation cases when a second course of radiotherapy is required after tumour recurrence. As the dosimetric parameters and delivery techniques of proton therapy continue to evolve, in particular the use of the pencil beam scanning technique to create high conformal proton plans, the applications of proton therapy will continue to grow.

RELEVANCE TO DEVELOPING COUNTRIES

At present, the cost of proton therapy is higher than photon therapy due to initial investment in equipment and infrastructure, as well as ongoing operational costs. In the future, the cost of building and maintaining a proton therapy facility will decrease due to increased demand, competition among commercial companies, and the development of compact accelerators. While cost-effectiveness of proton therapy is an active area of research and debate, the available data suggest that the treatment is cost-effective in appropriately selected patients.

Current estimates approximate that 15% of patients radiated for cancer in Europe have an indication for proton radiation, and while the proportion may be lower in developing countries, there is still a need for many patients. Currently, the most urgent priority in low and middle income countries is to establish access to basic cancer screening and treatment services. With the ongoing shortage of radiotherapy centres and skilled personnel in developing countries, the establishment of proton therapy centres may not be feasible in the near future. However, one option to increase access to proton therapy is multinational investment in the development of regional “centres of excellence,” where proton therapy can be administered to patients referred from a large catchment area. Specialized training and exchange learning can be developed between countries such that local care
providers and oncologists will be able to identify cases most likely to benefit from proton therapy, such as children with curable malignancies, and make appropriate referrals to the regional proton centre.

CONCLUSION

In theory, any tumour can be controlled by radiation therapy if the appropriate dose of radiation is administered. In practice, the safe delivery of a very high dose of radiation is not feasible with standard radiation techniques due to the tolerance of surrounding normal tissues. Proton therapy represents a major advance in the delivery of radiation therapy that offers the advantage of effective tumour control while minimizing acute and late morbidity. Clinical implementation of proton therapy has been based on the dosimetric advantages and promising early clinical results. At present, the establishment of a proton therapy centre requires considerable financial investment, as well as physics and clinical expertise. Validation of the existing technology and techniques can be achieved in a reasonable time frame if multicentre collaboration is implemented worldwide. Our hope is that as the clinical utility of proton therapy continues to be realized, the cost of this novel therapy will decrease and access for appropriately selected patients will increase worldwide, including low and middle income countries.

6.4. Recent progress in carbon ion radiotherapy at NIRS-HIMAC

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In Japan, the decision for a medical use of heavy ions was made in 1984 as one of the main projects of the first comprehensive 10-year strategy for cancer control. Heavy ion medical accelerator in Chiba (HIMAC) was the world’s first heavy ion accelerator complex dedicated to clinical research. The accelerator complex took almost 10 years to design and construct, and was completed by the end of 1993. After 6 months of commissioning of the facility, in June 1994, clinical trials using carbon ion beam generated from the HIMAC were initiated.

Since then, Japan has been the front-runner in carbon therapy, which so far has shown to be superior to conventional radiation therapy in terms of both dose localization (spatial dose distribution) and biological effect. Owing to these properties, carbon therapy provides a safer, faster, and more definitive result than conventional approaches. 1) Acceleration of very high-velocity (approximately 80% of the speed of light) of the carbon ions is necessary to penetrate deeply in the human body. Until recently, this required a huge facility. NIRS’s original HIMAC facility, with its 42-m diameter double synchrotron rings, required approximately 33 billion yen for its construction. NIRS developed a new, smaller accelerator that was equivalent in performance and capacity to the current HIMAC facility, at a cost of one-third of the original. A demonstration accelerator was installed at Gunma University, Japan, and has been in operation since March 2010 and showing good performance.

From June 1994 until May 2014, more than 80 protocols were conducted in an attempt to determine the optimal dose-fractionation and irradiation method for the treatment of specific diseases. The
HIMAC passive beam delivery system has been showing reliable and stable performance for the last 20 years, and a total of more than 8,000 patients had been registered for treatment. The categories of disease that can be treated in routine clinical practice include lung cancer, prostate cancer, head and neck cancer, skull base tumours, ocular melanoma, bone and soft tissue sarcoma, liver cancer, pelvic recurrences of rectal cancer, pancreatic cancer, uterine cervical cancer, breast cancer and re-irradiation after conventional radiotherapy, among others. The number of patients has increased every year, and the facility has reached a capacity permitting more than 1000 patients to be treated each year. The clinical trials began with a small dose per fraction. At first, the average number of fractions was around 18. All these early trials were carried out as dose-escalation studies. It was found that a very high dose per fraction could be administered because of the better dose distribution of carbon ion beams. In addition to the high physical selectivity of carbon ion beam, the biological properties associated with the high-LET carbon beam, low DNA repair, cell cycle nonspecific activity, and low OER are well-known effects that facilitate cancer eradication. Hence, a protracted fractionated regimen is not advantageous in carbon therapy. Therefore, we started performing less fractionated or hypo-fractionated radiotherapy. When using such treatments, the overall treatment time should be shorter, and the effect of repopulation is limited. The average number of fractions could subsequently be reduced from 18 to 12–13. Over the last several years, this reduction of fraction number has led to remarkable improvements in patient throughput at the NIRS.

At present (May 2014), seven heavy ion treatment facilities are operating around the world; four of them are located in Japan. Construction of the more advanced facility has been undergoing at Kanagawa Prefectures and another two or three facilities are at planning stage in Japan. Overseas, around 10 facilities are being planned or implemented in the following countries: France, Austria, China, South Korea, Malaysia, Saudi Arabia, UAE, Russia and USA (Mayo Clinic etc). European and American manufacturers hold the majority share of the world’s advanced medical equipment and devices market. However, as far as carbon therapy is concerned, Japan enjoys a superior position in competitiveness with respect to equipment manufacturing techniques and clinical experience. More than 10,000 patients treated with carbon therapy worldwide, almost 80% were treated at the NIRS and other facilities in Japan. Japan has the potential to continue to be the world leader in this field.

A clinical research using the pencil beam scanning was in operation with the original fully automated patient positioning system since May 2011. Good performance of this new carbon beam delivery system has been confirmed at NIRS. Regarding the compact superconducting magnet mounted rotating gantry, several magnets were already made and have been testing at NIRS. The NIRS new gantry will be expected to be in operation within a few years.

References

6.5. The Evolving Role of Proton Therapy for Paediatric Patients

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Many paediatric malignancies are treated with multi-modality treatment including surgery, chemotherapy, and radiation therapy. While radiotherapy (RT) can be an integral component of therapy for local tumour control, it is associated with a significant risk of acute and long-term effects. RT has been associated with increased risk of late mortality, development of second cancer, neurocognitive, endocrine, pulmonary, and cardiac dysfunction, growth abnormalities, and other various chronic health conditions in children, all due to the increased sensitivity of maturing tissues. Strategies to decrease the potential toxicities related to radiation include: 1) overall dose reduction or elimination of RT 2) reducing the margins of radiation therapy target volumes and 3) limiting the target volume to the post-chemotherapy target volume, 4) use of radiosensitizing chemotherapy, 5) technological advances to increase conformality of the high dose radiation and monitoring the low dose areas. Over the years, there have been major advances in radiation techniques, delivery and treatment planning; perhaps the most significant recently are the use of intensity-modulated radiation therapy (IMRT) and proton radiotherapy. Below is a summary of comparison to x-ray based IMRT and proton therapy (PRT)

<table>
<thead>
<tr>
<th>Feature</th>
<th>IMRT (x-ray)</th>
<th>Proton Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation field</td>
<td>Multiple</td>
<td>Few</td>
</tr>
<tr>
<td>Dose distribution</td>
<td>Large volume</td>
<td>Limited to tumour</td>
</tr>
<tr>
<td>Scatter</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Availability</td>
<td>Widely available</td>
<td>Selected centers</td>
</tr>
<tr>
<td>Personnel time and effort</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cost</td>
<td>High</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Because paediatric cancer survival rates have continuously improved over the last several decades, attention has turned to the reduction of treatment related toxicities while maintaining high rates of tumour control. The use of conformal RT techniques is an important advance in realizing this goal.

It was recognized early on that the Bragg peak and the lack of an exit dose distal to the target volume could yield a therapeutic gain for patients requiring RT. PRT also planning incorporates the increased relative biologic effectiveness (RBE) and linear energy transfer (LET) difference by using a correction factor of 1.1. These characteristics of PRT are particularly advantageous for children because of the reduction in the overall the integral dose and maintenance of therapeutic doses to the tumour volume. Currently, many dosimetric studies that compare PRT to best available x-ray based RT consistently demonstrate significantly improved normal tissue sparing. Predictive modeling
studies support a calculated risk reduction of several late toxicities including secondary malignancies, cardiac toxicity and infertility. Now, clinical data are now emerging that quantify actual clinical benefit to paediatric patients. Continued multi-institutional and multi-national efforts are ongoing to accumulate data on children treated with PRT so that information can be collected more rapidly and robustly to understand and optimize PRT use further.

Proton radiotherapy is an emerging modality that holds great promise to reduce the treatment related late effects in long-term survivors of childhood cancer by sparing dose to normal tissues. Further technological advances including intensity modulated proton therapy (IMPT) and image guided techniques will allow even higher conformality of the radiation dose. Better understanding of the RBE and LET across the Bragg peak will allow another dimension of refinement in PRT planning. In 2013 over 700 children were treated in the United States with PRT. Currently, 14 centers in the US provide proton beam radiotherapy for children, and it is anticipated the number of patients treated with this technology will continue to increase. Continued comparative studies and clinical trials with long-term follow up are needed to quantify the benefit proton beam therapy paediatric cancer patients.

6.6.  Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas at NIRS, Japan

Reiko Imai, Tadashi Kamada

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A clinical trial was launched in 1996 to evaluate the safety and efficacy of carbon ion radiotherapy for bone and soft tissue sarcomas excluding head and neck (above C2) sarcomas. A phase I/II study was carried out between June 1996 and February 2000 (1). This study presented a dose escalation study starting from a total dose of 52.8 GyE (3.3GyE per fraction) using fixed16 fractionations over 4 weeks. The eligibility criteria of the study were as follows: 1) confirmation of pathological diagnosis 1) diagnosed as unresectable tumour, 2) less than15cm in diameter 3) no systemic metastases, 4) no metal instrumentation 5) no severe infection in the tumour site, 6) no prior radiotherapy for the tumour site excluding radiation-associated sarcoma. The 64 lesions of 57 patients were enrolled into the study. At the time of 2011 this study produced local control rates of 89% at 1 year, and 63% at 3 years and 5 years, respectively. The overall survival rates were 82% at 1 year, 47% at 3 years, and 37% at 5 years, respectively. Regarding the results of both the local control and the overall survival rates, there were significant differences between the tumours irradiated at a total dose of 57.6GyE or less and 64.0GyE or more. Grade 3 RTOG acute reactions to the skin were observed in 7 of the 17 patients treated with 73.6GyE. The dose escalation was halted at the dose of 73.6GyE/16Fr. These findings made it clear that a total dose of 70.4GyE/16 Fr. was the maximum applicable dose to tumours close to the skin, while a total dose of 73.6GyE was possible in cases having sufficient space between the skin and the tumour. The subsequent fixed-dose phase II clinical trial using irradiation at a total dose of 70.4GyE/16Fr or 73.6GyE/16Fr over 4 weeks started in April 2000 and moved into the Advanced Medicine approved by Ministry Health, Labour and welfare in October 2003. The protocol was succeeded after the approval. In the study 594 sarcomas of 575 candidates have been
enrolled as of August 2013. The 589 lesions of 570 patients followed for six months or longer were analyzed. Seventy-five % of all treatment sites were in pelvis and 19% were spine and paraspinal lesions. The most common sarcoma treated with carbon ion radiotherapy was sacral chordoma, chondrosarcoma was in the second and osteosarcoma was in the third largest group. The median age of all patients was 58 years old ranging from 11 to 87. In 589 lesions 72% was applied to by70.4GyE and in 10 patients 73.6GyE. Sacral chordoma and spinal sarcoma were applied at a total dose of 67.2GyE and 64GyE, respectively. The 2-year and 5-year local control rates were 84% and 69%, respectively at the time of 2013. The 2-year and 5-year overall survival rates were 78% and 58%, respectively. The toxicity was acceptable level at less than 2% skin/soft tissue late G3/4 toxicity in the study. There were none of recurrent tumours irradiated at the total dose 73.6GyE, however G3 skin toxicity was observed in 3 patients. These late skin reactions suggested to be related to as follows: 1) total irradiated dose 2) tumour invasion to subcutaneous skin, 3) a large tumour volume, 4) sacrococcygeal involvement, 5) previous surgery, 6) additional chemotherapy and 7) irradiation using 2 ports. It was possible to prevent over grade 3 skin reactions by irradiation using over 3 ports in order to reduce the dose administered to the skin surface. The incidence of Grade 3 and higher late akin reactions in the patients receiving a total dose of 70.4GyE with over 3 ports has been within the acceptable level. Through the dose escalation trial and the subsequent fixed dose trial, it was revealed that carbon ion radiotherapy provided local control and survival benefits without unacceptable morbidity for patients with bone and soft tissue sarcomas that were either difficult or impossible to cure using other modalities.

Sacral Chordoma

Among the bone and soft-tissue sarcomas treated with carbon ion radiotherapy at NIRS, sacral chordoma accounted for the largest proportion (2). The sacrum houses the sacral nerves, which innervate the excretory functions and ambulation. Depending on the involvement site of the tumour to the sacral bone, excision of these nerves causes permanent gait, excretory and other disabilities, and it impairs the patients’ quality of life. Therefore, curative surgery for sacral chordoma (sacrectomy) is one of the most invasive surgeries. Sacral chordoma frequently occurs among the elderly population, who are also often contraindicated for surgery. Between June 1996 and Mach of 2012,175 patients with sacral chordoma who didn’t undergo prior surgery were enrolled in the trials on carbon ion radiotherapy. The median age of the 175 patients was 67 years. The median tumour diameter was 9 cm. The carbon ion dose ranged from 64.0GyE to 73.6 GyE. In 70% of the patients tumours extended up to S2 and higher. The median clinical target volume was 340cm3. The median follow up period was 62 months. Five-year overall survival and 5-year local control rates were 82% and 76%, respectively. The median local recurrent time was 40 months ranging from 13 to 119. The ambulatory in 97% of the patients remained with or without supportive devices. Six patients experienced severe sciatic nerve complications disturbing ambulatory and had impairment of their ordinary life. As for chordoma the longer survival is expected compared to other high grade sarcomas due to the slow-growing tumour characteristics. The sustainability of good quality of life provided by carbon ion radiotherapy is important.

Osteosarcoma

Osteosarcomas of the trunk constituted the third largest group among our study. For the treatment of osteosarcomas of the extremity, which develop with a high incidence among youth, the paradigm based on a combination of surgery and chemotherapy has been well-established, and carbon ion
radiotherapy is unlikely to outweigh their advantages. For the 78 patients with unresectable osteosarcoma of the trunk the 5-year local control and 5-year overall survival rates were 62% and 33%, respectively (3). Tumour located at the pelvis in 61 patients, the spine and paraspinal sites in 15 patients, and others in 2 patients. The median applied dose was 70.4GyE in a total of 16 fixed fractions over 4 weeks. The median diameter of the tumours was 9 cm. As reported in the literature, in the cases of unresectable osteosarcoma, the survival rate was 10% or less. Therefore, carbon ion radiotherapy appeared to provide a survival benefit for unresectable osteosarcomas. The tumour volume was prognostic factors for the survival and local control rates. Thirty-eight patients who had a clinical target volume <500 cm3 had a 5-year overall survival rate of 46% and a 5-year local control rate of 88%, while 40 patients who had a clinical target volume >500 cm3 had a 5-year overall survival rate of 19% and a 5-year local control rate of 31%. For unresectable osteosarcoma of the trunk, carbon ion radiotherapy will be the mainstay treatment.

2 IMAI, R., KAMADA, T., SUGAHARA, S., et al., Carbon ion radiotherapy for sacral chordoma, Br J Radiol. 84 (2011) 48-54.

6.7. ENLIGHT (The European Network for Light ion Hadron Therapy) and OPEN-MED

Manjit Dosanjh, CERN

The European Network for Research in Light-Ion Hadron Therapy (ENLIGHT), which had its inaugural meeting at CERN in February 2002, was established to coordinate European efforts in using light-ion beams for radiation therapy. Funded by the European Commission (EC) for three years, ENLIGHT created a multidisciplinary platform, uniting traditionally separate communities so that clinicians, physicists, biologists and engineers with experience in ions could work together with a common goal.

In 2006 the EC funding for the network came to an end and a brainstorming amongst clinicians, oncologists, physicists, radiobiologists, information and communication technology experts and engineers—from around 20 European countries—took place at CERN. During this ENLIGHT workshop, the community felt and agreed that ENLIGHT was a key ingredient for future progress, and therefore should be maintained and broadened, called ENLIGHT++. The aim of ENLIGHT++ network is twofold: to maintain and enlarge the European network of Institution and specialist which work in the field of Light Ion Therapy and to sponsor the research in fields of common interests for the development of the cutting edge and technically advanced clinical facilities. The primary mandate of the coordinator is to develop strategies for securing funding necessary for the continuation of the initiative in its two fundamental aspects, research and networking and ensure collaboration and training in this multidisciplinary pan-European platform.
Presently it provides a common European platform for fostering and coordinating collaborations between national research activities related to hadrontherapy, encompassing such various fields as proton and light ion accelerators, detectors, image reconstruction and processing, radiobiology, oncology, and clinical research. Under the umbrella of ENLIGHT, in FP7 there were four EC funded projects: PARticle Training Network for European Radiotherapy (PARTNER) www.cern.ch/PARTNER, Union of Light Ion Centre in Europe (ULICE) www.cern.ch/ULICE, European NoVel Imaging System for ION therapy (ENVISION) www.cern.ch/ENVISION and Research Training in 3D Digital Imaging for Cancer Radiation Therapy (ENTERVISION) www.cern.ch/ENTERVISION. All these projects are directed towards the various aspects of developing, establishing and optimizing hadron therapy and training the future experts.

The initiatives involve integrating clinical, biological and technical knowledge as well as training the future generation at a European level, so that hadron therapy becomes widely available for the benefit of all European inhabitants. Specifically its aims to:

- Identify the critical topics and focus the research on key-areas in order to define and develop particle therapy and extend its benefits throughout Europe and eventually worldwide, complementary to other treatments.
- Develop a common European platform to validate the efficacy of hadron therapy, starting first with the most advanced dual ion facilities, in Heidelberg and Pavia soon to be joined by MedAustron.
- Develop the technical expertise and widespread knowledge for a therapeutic use of particle therapy and create the appropriate professional know-how needed for European-wide expansion.
- Enhance the cost effectiveness of hadron therapy by improving quality of life and reducing the overall cost of treatment.
- Integrate hadron therapy within the best available multi-disciplinary management of cancer treatment.
- Train the future scientists needed for this emerging field.

ENLIGHT’s key vision is the promotion and the optimization of hadron therapy for cancer treatment at a pan-European level

The radiobiology community is lacking beam time for systematic studies on the biological impact that different particles at different energies have on cells and biological material, detector development and imaging as well fragmentation studies and treatment planning.

The use of LEIR (at CERN) for such a biomedical research was requested and proposed, as it is an already existing infrastructures that could be used to provide the research community with relevant beams. Additionally, the energies of the ions that can be accelerated in LEIR are similar to those required for clinical use which makes it well suited to provide beams needed for in depth investigations needed for better understanding and optimization of particle therapy.

Studies are underway to find the simplest and cheapest way of using the LEIR accelerator while still maintaining its current operational performance for LHC physics operation. For LHC operation, LEIR only needs a fast beam extraction line and a new slow extraction scheme will have to be implemented. A short transfer line will bring the ions to a horizontal beam line with energy in the range of 200 to 430 MeV/nucleon for most ions of interest, with the option of a lower energy
vertical line to be installed as a second step. The LEIR injector can generate only one type of ions at a
time, and therefore a bio-medical facility using several different ions cannot be operated in parallel
to physics runs. Thus, an upgrade of the LEIR injector system is required, including a second ion
source and Radio Frequency Quadrupole (RFQ) optimized for other ions of interest for bio-medical
research.

A dedicated facility will not only provide the necessary beam time in large time blocks, but also
foster closer collaborations between research teams from different countries to rapidly move the
field of hadron therapy forward. We envision a scenario similar to the large collaborations typical of
high-energy physics, where many teams from different institutions and countries work side by side
on specific pieces of a puzzle, pursuing one common goal.

CERN has a strong tradition in hosting international collaborations, a scientific and technical support
infrastructure, and an excellence in science achieved over the many years of operation, making it the
ideal place where such a project could be initiated and propagated. But CERN does not only mean
physical infrastructures; it is mainly a crossroad of competences and expertise of people. Working
side by side with researchers from many other areas of physical sciences, computer science, and
mathematics is expected to spark new ideas that will lead to new approaches to the existing
problems.

Both ENLIGHT and OPEN-MED are in the same spirit of open collaborative research for improving
cancer treatment and outcome.

6.8. Particle Therapy – Review of costs

Eduardo Rosenblatt – IAEA

Over the past decades there has been a growing concern about high and rising medical costs (1). The
rapid diffusion of new technologies has been proposed as a major contributing factor in this rise.
Hadron therapy is an example of such a technological evolution in radiation therapy for which the
financing and the value for money are heavily debated.

In a study published in 2003, Goitein and Jermann found that sophisticated (i.e., intensity-
modulated) proton therapy was and was likely to continue to be, more expensive than sophisticated
(i.e., intensity-modulated) X-ray therapy. The ratio of costs was about 2.4 at the time of the
publication and could readily come down to 2.1, and even, perhaps 1.7 over the following 5 to 10
years. If recovery of the initial investment would not be required, the ratio of costs would be much
lower, in the range of 1.6 to 1.3. The question of whether the greater cost of proton beam therapy is
clinically worthwhile is a cost-effectiveness issue. The goal of this study was to contribute to the
former arm of this comparison.

Proton therapy may offer potential clinical advantages compared with conventional radiation
therapy for many cancer patients. Due to the large investment costs for building a proton therapy
facility, however, the treatment cost with proton radiation is higher than with conventional
radiation. It is therefore important to evaluate whether the medical benefits of proton therapy are
large enough to motivate the higher costs. Ludkvist et al. (2) assessed the cost-effectiveness of
proton therapy in the
treatment of four different cancers: left-sided breast cancer, prostate cancer, head and neck cancer, and childhood medulloblastoma. A Markov cohort simulation model was created for each cancer type and used to simulate the life of patients treated with radiation. Cost and quality adjusted life years (QALYs) were used as primary outcome measures. The results indicated that proton therapy was cost-effective if appropriate risk groups were chosen. The average cost-per-QALY gained for the four types of cancer assessed was about €10.130. If the value of a QALY was set to € 55 000, the total yearly net benefit of treating 925 cancer patients with the four types of cancer was about € 20.8 million. Investment in a proton facility may thus be cost-effective. The results of this study must be interpreted with caution, since there is a lack of data, and consequently large uncertainties in the assumptions used.

In a study comparing IMRT with IMPT, Konski et al. (2007) concluded that even when based on the unproven assumption that protons will permit a 10-Gy escalation of prostate dose compared with IMRT photons, proton beam therapy is not cost effective for most patients with prostate cancer using the commonly accepted standard of $50,000/QALY. Consideration should be given to limiting the number of proton facilities to allow comprehensive evaluation of this modality.

In a work by Jakel et al. (2007) the cost-effectiveness of carbon ion radiotherapy (RT) for patients with skull base chordoma was analyzed. Primary treatment costs and costs for recurrent tumours were estimated. The costs for treatment of recurrent tumours were estimated using a sample of 10 patients presenting with recurrent chordoma at the base of skull at DKFZ. Using various scenarios for the local control rate and reimbursements of carbon ion therapy the cost effectiveness of ion therapy for these tumours was analyzed. Results: If local control rate for skull base chordoma achieved with carbon ion therapy exceeds 70.3%, the overall treatment costs for carbon ion RT are lower than for conventional RT. The cost-effectiveness ratio for carbon RT is € 2 539 per 1% increase in survival, or € 7692 per additional life year. Conclusion: Current results support the thesis that carbon ion RT, although more expensive, is at least as cost effective as advanced photon therapies for these patients. Ion RT, however, offers substantial benefits for the patients such as improved control rates and less severe side effects.

Existing data do not suggest that the rapid expansion of hadron therapy as a major treatment modality would be appropriate. Further research into the clinical and cost-effectiveness of hadron therapy is needed. The formation of a European Hadron Therapy Register would offer a straightforward way of accelerating the rate at which we obtain high-quality evidence that could be used in assessing the role of HT in the management of cancer. (Lodge 2007)(3).

Evidence on the cost-effectiveness of particle therapy is scarce. Adequate reimbursement is necessary to support such innovative yet costly treatments. For now, model-based economic evaluations performed at least from a health care perspective may help us to gain evidence-based insight into cost-effectiveness. (Pijls-Johannesma,2008)

Particle therapy has potentially a better therapeutic ratio than photon therapy. However, investment costs are much higher. A study by Peeteres et al. (2010) provided an estimation and comparison of the costs of these therapies. Within an extensive analytical framework capital and operational costs, cost per fraction, and four tumour specific treatment costs were calculated for three facilities: combined carbon-ion/proton, proton-only, and photon. Results: Capital costs for the combined, proton-only and photon facilities are: € 138.6 million, € 94.9 million, € 23.4 million. Total costs per year are: € 36.7 million, € 24.9 million, € 9.6 million. Cost per fraction is: € 1128 (€ 877–
Cost ratio particle/photon therapy is 4.8 for the combined and 3.2 for the proton-only facility. Particle treatment costs vary from €10,030 (c-ion: lung cancer) to €39,610 (proton: head & neck tumours). Cost difference between particle and photon therapies is relatively small for lung and prostate cancer, larger for skull-base chordoma and head & neck tumours. Conclusion: Investment costs are highest for the combined carbon-ion/proton facility and lowest for the photon facility. Cost differences become smaller when total costs per year and specific treatment costs are compared. Lower fractionation schedule of particle therapy might further reduce its costs.

Elnahal (2012) Purpose: Proton beam therapy (PBT) centres have drawn increasing public scrutiny for their high cost. The behaviour of such facilities is likely to change under the Affordable Care Act. We modelled how accountable care reform may affect the financial standing of PBT centres and their incentives to treat complex patient cases. Methods and Materials: We used operational data and publicly listed Medicare rates to model the relationship between financial metrics for PBT centres and case mix (defined as the percentage of complex cases, such as paediatric central nervous system tumours). Financial metrics included total daily revenues and debt coverage (daily revenues daily debt payments). Fee-for-service (FFS) and accountable care organizations (ACO) reimbursement scenarios were modelled.

Sensitivity analyses were performed around the room time required to treat noncomplex cases: simple (30 minutes), prostate (24 minutes), and short prostate (15 minutes). Sensitivity analyses were also performed for total machine operating time (14, 16, and 18 h/d). Results: Reimbursement under ACOs could reduce daily revenues in PBT centres by up to 32%. The incremental revenue gained by replacing 1 complex case with noncomplex cases was lowest for simple cases and highest for short prostate cases. ACO rates reduced this incremental incentive by 53.2% for simple cases and 41.7% for short prostate cases. To cover daily debt payments after ACO rates were imposed, 26% fewer complex patients were allowable at varying capital costs and interest rates. Only facilities with total machine operating times of 18 hours per day would cover debt payments in all scenarios.

Conclusions: Debt-financed PBT centres will face steep challenges to remain financially viable after ACO implementation. Paradoxically, reduced reimbursement for noncomplex cases will require PBT centres to treat more such cases over cases for which PBT has demonstrated superior outcomes. Relative losses will be highest for those facilities focused primarily on treating noncomplex cases.

Vanderstraeten et al. (2014) compared three types of facilities using both a business model and an activity-based costing (ABC) model. Both calculation methods were valid and complementary. The financially most attractive option of a publicly sponsored carbon-only centre should be balanced to the clinical necessities and the socio-political context.

Many of the novel strategies (IMRT, IGRT, SBRT) have rapidly gained acceptance, and have been widely adopted in daily practice along with specific reimbursement in many countries. This is contrary to the case of proton therapy, for which it remains heavily debated as to whether the expected benefit justifies the higher capital and operating costs. Particle therapy is associated with considerable investment costs, hence there is a need to balance its costs to the clinical benefits.

References


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*Patient benefits from ion beam therapy: results of an Austrian epidemiological survey*

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*User’s guide to implementing a light ion beam therapy facility*

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*Proton therapy yesterday, today and tomorrow*

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*From basic physics to projects and protocols in particle therapy*

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*Current challenges in particle beam therapy*

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*Potential role of high LET particle therapy in multidisciplinary cancer care in the next 10 years: needs for cooperative research and planned structural investments*

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*Recent progress in carbon ion therapy at NIRS-HIMAC*
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The current status of carbon ion radiotherapy in Gunma University: its role in education and dissemination of particle therapy

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CERN and the ENLIGHT programme for particle therapy in Europe

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The evolving role of proton therapy for paediatric patients

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Clinical and operational aspects of proton beam delivery—from double scattering to pencil beam scanning

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Radiobiology aspects of particle therapy

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Carbon ion radiotherapy for bone and soft tissue sarcomas at NIRS, Japan
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Opening remarks

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Scientific Secretary

Review of costs in particle therapy facilities

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Meeting Agenda: Consultants Meeting on
“Particle Therapy in the 21st Century: Relevance to Developing Countries”
Applied Radiation Biology and Radiotherapy (ARBR) Section – Div. of Human Health
Vienna Austria, 11-14, November 2014

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<tr>
<td>10:30 – 11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 – 12:30</td>
<td>Clinical trials</td>
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<td></td>
<td>Methodological issues: trial design that does not escalate prescription dose but rather dose on dose limiting organs. Case control studies as alternative to randomization in paediatric oncology</td>
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<td>12:30 – 14:00</td>
<td>Lunch</td>
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<tr>
<td>14:00 – 15:30</td>
<td>Carbon ion radiotherapy dose prescription recording and reporting</td>
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<td>15:30 – 16:00</td>
<td>Coffee break</td>
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<tr>
<td>16:00 – 17:00</td>
<td>Dosimetry and commissioning of particle therapy facilities</td>
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**Thursday 13**

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>9:30 – 10:30</td>
<td>Present and future of compact cyclotrons</td>
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<td>10:30 – 11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 – 12:30</td>
<td>Carbon ion and concomitant systemic and specific targeted therapy</td>
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<td>Lunch</td>
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<td>14:00 – 15:30</td>
<td>The costs problem</td>
<td>Health economy issues: Which methodology</td>
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<td>9:30 – 10:30</td>
<td>Platforms to share clinical data: registries, surveys. Shared patient database for carbon ion toxicity and common validation of specific dose constraints</td>
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<td>10:30 – 11:00</td>
<td>Coffee break</td>
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<tr>
<td>11:00 – 12:30</td>
<td>Training and education in particle therapy</td>
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<td>12:30 – 14:00</td>
<td>Lunch</td>
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<td>14:00 – 15:30</td>
<td>For every particle: organ motion coping procedure and QA for passive and active beams.</td>
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<td>15:30 – 16:00</td>
<td>Coffee break</td>
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<td>16:00 – 17:00</td>
<td>Future developments and IAEA role.</td>
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Vienna 11 November, 2014