I. Introduction

The main purpose of this meeting was to discuss radiation biology implications and issues for the design of light ion particle therapy (LIBT) clinical trials. This is a sequence of IAEA’s Consultant Meeting on Particle Therapy in the 21st Century, held in November 2014, on which the IAEA report “Particle Therapy in the 21st Century: Relevance to Developing Countries” was based.

Light ion therapy (LIBT) currently includes the therapeutic application of protons and carbon ions in radiation oncology. It is considered an excellent tool for highly precise, conformal dose delivery. Importantly, not much is known about the radiobiological basis of LIBT, particularly with ions other than protons. In vitro radiobiological studies on the RBE of charged particles regarding clonogenic cell killing demonstrated a bell-shaped dependence on LET with significant dependence also on the particle charge (Durante, M., New challenges in high-energy particle radiobiology. Br J Radiol, 2014. 87(1035): p. 201306262014). However, little is known about other “classical” effects, such as DNA damage and repair, or even on so called non-targeted radiation effects or - most importantly - on in vivo pathobiological mechanisms and individual radiosensitivity to LIBT. This also applies to OER.

Based on these considerations, the IAEA Technical Meeting (TM) on “Radiation biology implications and issues for the design of light ion therapy (LIBT) clinical trials” was organized in November 2015. The detailed program of the meeting and the list of participants are attached. This meeting was covering various aspects of LIBT, regarding radiobiology, clinical radiooncology, and implementation in low-and-middle-income countries (LMIC).

II. Radiobiology

The presentations and discussions on radiobiological aspects mainly focused on LIBT-specific (bio)dosimetry and ongoing preclinical studies - in vitro and some in vivo. Based on the discussions during the session, requirements for new studies and optimization of procedures and endpoints, as well as new (biology-based) research directions were identified. This section of the report is based on the following presentations and the respective discussions, and gives an idea and summary of the aspects presented by the individual experts.
The selection of models for LIBT radiobiological research is critical. This applies to in vitro models, but particularly to animal models and their endpoints. They may have some major limitations. In vitro models essentially should include various tumor as well as normal tissue lines, in order to be conclusive. Specific endpoints need to be investigated after irradiation in a therapeutic beam setting. Tumour endpoints need to focus on various positions within the SOBP, but normal tissue endpoints must include, in addition, a panel of positions also in the entrance track before the SOBP as well as behind the SOBP (particularly for ions beyond protons). Radiation-induced carcinogenesis can hardly be studied in animals, and in many instances, the biology of tumor induction and the biology of the resulting tumors are different from those in human patients. Here, the selection of models is of major importance and seems to require discussion in international research groups.

Investigations on the dose-dependence of RBE, fractionation effect, dose-dependence studies for main morbidity endpoints (in vitro as well as in vivo) are urgently required. These however, must be based on well-defined exposure conditions, but also must demonstrate their relevance for (specific) clinical endpoints and outcome parameters. One open question is the study of combinations of LIBT with standard chemotherapy, biologically targeted agents or even immunotherapy. Such investigations must include clinically relevant treatment protocols, but also must guarantee that the drugs tested are still in use in patients when the study results become available.

Some key questions with regard to the radiobiology of LIBT are:
- Are there qualitative differences in (endpoint-specific) radiobiology between LIBT and photons. If yes, what are their quantitative consequences?
- Can these differences be assessed before or early during the course of treatment, as predictive factors, on the basis of genomics, endpoint-specific radiopathology or non-targeted effects?
- Can these factors than also be applied to subject patients to the most effective treatment strategies (stratification)?

### III. Clinical aspects

With regard to clinical aspects of LIBT, the presentations and discussions mainly concentrated on options for achieving clinical evidence for the benefit from LIBT with regard to tumor effects (for specific indications) and/or treatment related adverse events (in...
association with specific indications), the optimization of the design of biology–based clinical trials, and the identification of effective and potentially radiation quality-specific, biology-based combination therapies. The following presentations provided the basis for the discussions.

Mack Roach III (USA) Challenges to Heavy Particle Radiation Therapy: NAPTA (North American Particle Therapy Alliance)
Berta Roth (Argentina) Argentinian plans for building a new proton radiation therapy facility
Siddhartha Laskar (India) Particle Therapy in India: The Need, Challenges & Opportunities
Søren Bentzen (Denmark/USA) “Particle therapy: Can we get the evidence we need?
Manjit Dosanjh (CERN) CERN OPENMED Facility
Tatsuaki Kanai (Japan) Carbon therapy in Japan
Jiade Lu (China) Clinical trials evaluating carbon ion radiation therapy in the management of head and neck malignancies: Challenges and Opportunities
Andrea Ottolenghi (Italy) Research on radiation quaLIBTy and hadron therapy: where are we? What is to be done?
Stephanie Combs (Germany) Clinical trials at the proton therapy in Germany
Marco Durante (Germany/Italy) New directions in LIBT
Stanislav Vatnitskiy (Austria) Current developments in light ion beam therapy technology
Wolfgang Dörr (Austria) Biologically based treatment planning

One of the most important aspects for comparative clinical trials is the harmonization of dose reporting (e.g. in GyE), as there are currently different reporting systems, which do not allow for the comparison between the administered dose in individual or groups of centers. This particularly refers to dose parameters related to specific morbidity endpoints. In this aspect, it is essential to document and publish absorbed doses to the major OAR in general or to endpoint-specific OAR subvolumes. Else, no comparison of adverse event incidences between different centers related to dose/dose-distributions will be feasible.

One open question is the optimization of LIBT treatment plans with regard to RBE and/or OER in the tumor-specific target volumes and OAR (sub)volumes in different positions in the SOBP (tumor) and the entire LIBT beam track. However, based on this particular optimization procedure, a therapeutic gain of LIBT over state-of-the art image-guided high-precision photon therapy needs to be demonstrated, as mentioned in the introduction of this report.

Normal tissue complication probability (NTCP) models may need to be adjusted or even developed for LIBT, based on preclinical investigations. However, they need to be supported and validated by clinical observations; in return, these adjustments may then be used for optimization of photon models. Tumor control probability (TCP) models are usually more reliable, but may also be improved. This particularly relates to specific effects of LIBT on the
immune system.
There are several phase-III trials on the effects of LIBT ongoing. However, their design is mostly pretty complex and hence the results are hard to interpret. Importantly, comparison of the results between studies is largely impossible due to this complexity factor. Therefore, clinical investigations might start as observational studies. These studies might include a gradual replacement of photons by LIBT, also in combination studies. For the latter, similar strategies with regard to the combination treatment with photons and LIBT need to be followed.
In any case, however, a detailed, structured and long-lasting follow-up of the patients is required, particularly regarding morbidity. This is a prerequisite for the identification of potential institutional deviations. Options for this might be represented by ROSIS (www.rosis-info.org) and/or SAFRON (rpop.iaea.org/RPOP/RPoP). For the role of the LIBT-induction of second tumors, particularly in pediatric cancer therapy, the role of neutrons in active scanning vs. passive scattering systems compared to photons needs to be identified. Moreover, a system for detailed recording and reporting of doses and dose distributions, also out-of-field, is required.
In general, the clinical studies should be based on hypotheses generated in specifically designed preclinical investigations. If necessary in order to gain sufficient patient numbers, these studies need to be coordinated on an international cooperative basis. They need to be carefully designed, and the data achievability, also for retrospective analyses, must be guaranteed; here, leaf sequencing algorithms (leaf motion calculator [LMC]) also need to be considered.
In some member states of IAEA, however, the options for participation in such clinical trials will be less favorable. Therefore, an international harmonization particularly with regard to reimbursement regulations for participation in clinical trials as well as for data sharing options and their legal basis may have to be established. If LIBT must be performed on a non-trial basis, then the treatment protocols need to be based on established clinical practice. However, even then there must be an algorithm for structured follow-up in order to identify deviations from the generally observed outcome and morbidity parameters.
Key questions that were raised in the discussion within this section were:
- What are the proper and promising indications? A randomized study on re-irradiation of head and neck cancer was suggested, but the suitable HNT site(s) remained unclear.
- What is the role of hypofractionation?
- How to handle and respond to novel biologically targeted or combination therapies or combinations with immunotherapies?
- Are phase-I/II studies required?

III. Conclusions
Proton radiotherapy today should no longer be considered experimental, as there is ample experience from its application over two last decades for a number of specific indications in a large number of patients. For many other indications, however, there is no evidence of the superiority of LIBT over high-precision photon therapy. LIBT with ions other than protons must, in contrast, should be considered as an experimental modality for most commonly diagnosed malignancies as an experimental modality. In situations with unknown superiority of LIBT, a clear benefit of LIBT needs to be proven in order to justify costs, particularly for therapy with ions beyond protons. Hence, clinical trials comparing different modalities of LIBT and state-of-the art photon therapy are ongoing and further investigations - including
precise documentation of (long-term) toxicities - are needed. Uncertainties on the RBE - particularly for other endpoints - are a major concern. Moreover, more extended radiobiological data, along the entrance track of the beam as well as within the SOBP, are required as a basis for precise treatment planning and predictive mathematical modeling of the effects of LIBT. Dosimetry of LIBT is challenging, particularly because of fragmentation and neutron contributions to the total dose, also in regard to passive scattering vs. active scanning procedures. This lack of knowledge may be overcome e.g. by on-line dosimetry, biophysical dosimetry and biodosimetry.

With regard to the clinical situation, besides indications and toxicities mentioned above, open questions include the effect/potential of LIBT hypofractionation down to single dose administration, as well as suitable combinations with conventional chemotherapy, targeted agents or immunotherapy. Long-term toxicities may be different from those after photon treatment, particularly with regard to effects in the heart and CNS and to second cancers.

A structured research program on an international level is required, which must - besides the radiobiology/-oncology community - also integrate partners from e.g. radiation physics, radiation chemistry, general cancer biology research, immunology and others. These research activities might be coordinated by IAEA.

One option might be a Coordinated Research Project (CRP) related to LIBT.

Country reports are attached in the Annex I.
Annex I

Countries’ reports

IAEA Technical Meeting (TM)

Radiation biology implications and issues for the design of light ion beam therapy (LIBT) clinical trials

IAEA Headquarters, Vienna, Austria
11 – 13 November 2015
ARGENTINA
Instituto de Oncología Angel H. Roffo
Dra. Bertha Roth

National Plan of Nuclear Medicine

- Argentina belongs to the range of countries with medium to high incidence of cancer (170-240 x 100,000)
- Malignant tumors are the leading cause of death among people from 40 to 64 years old.
- In 2012, 61,866 people died from cancer. Without discrimination by sex, the most frequent cancer was lung (14.9 %), followed by colorectal (11.3%), breast (9%) and prostate (6.1%)

Currently, Argentina has 290 nuclear medicine centers and 100 radiotherapy centers. Approximately 80% are private and 20% are public. Most of them are located in Buenos Aires and surroundings areas. An important part of the population has no access to the high technology applied to Health (including radiotherapy).

The NATIONAL PLAN OF NUCLEAR MEDICINE is an initiative of the Ministry of Federal Planning. It aims at providing to different regions of Argentina with Nuclear Technology applied to Health for the Prevention, Control and Treatment of various chronic Non Communicable Diseases (including Cancer).

Specific objectives of the National Plan of Nuclear Medicine are:

- **Social Inclusion.** To ensure the fairness and accessibility of the population to nuclear medicine and radiation therapy services.
- **Technology.** Each Center will have infrastructure and equipment with technology of high complexity, according to world standards.
- **Human Resources.** Professionals and technicians will be trained resulting in not only more job opportunities but also a steady development of the communities.

A Proton Therapy and Advanced Radiotherapy Center has been included into the National Plan of Nuclear Medicine. With a population of 40 million of people, the potential number of patients in Argentina that could benefit from Protons is 8,000-12,000 per year. The Proton Therapy Center will be the first in Latin America.
Biologically based treatment planning

W. Dörr, Austria

Radiotherapy in general is a highly personalized treatment form, as it is primarily adjusted to the individual characteristics of the tumour of each single patient. These features include tumour entity (radioresistant tumors supposed to be planned for higher doses compared to radiosensitive tumor entities) and tumor size (higher equieffective doses considered for large compared to small tumors). Also, tumor localization relative to OAR is considered on an individual basis. For example, a superficial tumour at the outer part of a thigh might be planned to receive a higher dose compared to an identical tumor within the pelvis or even only at the inner part of the thigh. One more aspect is the localization of a high-dose volume within an OAR, which may be located in more sensitive or resistant parts (kidney pole vs. hilus), or in positions where similar radiation effects are associated with more or less severe clinical consequences (confluent mucositis at the lips vs. buccal mucosa). Moreover, radiotherapy dose prescription, treatment planning and delivery are adjusted to the specific characteristics of the patient, such as anatomy, concomitant diseases and/or physiological performance of OAR. In all these instances, light ion therapy (LIT), associated with a higher dose conformity to the planning target volume (PTV) and/or with an increase in the PTV dose, may be instrumental in achieving the optimum outcome. In this aspect, however, the conformity and associated dose (and thus the outcome, e.g. cure probability) realized by photon radiotherapy is of major relevance. In situations where the PTV can already receive a near optimum dose with photon therapy, the advantage of LIT may be minor and not detectable.

One other aspect of biologically based radiotherapy planning is the adjustment to the specific biology of individual tumor sub-volumes, which may require higher doses for sterilization. These can be sub-volumes representing with hypoxia, or high metabolic (glucose consumption, amino acid transport, etc.) or proliferation rates. Such sub-volumes may be identified by specific functional imaging procedures. Also in such situations, LIT may assist to optimize the (intra-PTV) dose distributions. The benefit compared to photon therapy, however, again is dependent on the dose that might be achieved with photons.

Finally, LIT - like photon radiotherapy - may be combined to chemotherapy or drugs targeting tumor-specific biological pathways. If LIT is associated with the induction or alteration of such biological pathways in contrast to photons, and if these pathways can be targeted, then this may open new approaches for LIT-specific targeting.
The development of major components of the equipment that will be installed and currently used at light ion beam therapy (LIBT) facilities is performed either by the major suppliers of turnkey facilities or within cooperation of accelerators producers with several industrial and scientific partners. Currently two types of the accelerators are used in clinical practice—cyclotrons and synchrotrons, both with different footprint size. A cyclotron has an advantage for scattered and scanned beams in terms of beam intensity and stability, while a synchrotron allows pulse to pulse energy variation for scanned beams and has acceptable footprint to generate a set of different light ions for medical applications. The only scanning beam delivery systems will be installed on all new planned facilities to allow efficient treatment of deep seated tumours. The modern facilities are equipped with the robotic patient alignment systems (PAS). The major components of the PAS consist of the robotic patient positioner, that can move in 6/7 ways in order to select the ideal beam entrance angle of the ion beam; anti-collision system, and the 2D-3D patient position verification system with x-ray source, image capture devices, anti-collision system and control and image processing software with which the position of the patient is determined prior to irradiation and can be fine-tuned automatically.

The LIBT facilities require comprehensive image, data and patient information management software that centralizes LIBT process and is accessible by multi-disciplinary teams across multiple locations and will giving to doctors and physicists flexibility to choose the optimal treatment solutions and workflow. A range of integrated medical software components are usually integrated at LIBT facility with the treatment planning system (TPS). Modern TPSs are extended with state-of-the-art functionalities to support planning for LIBT to optimize the scanning pattern for discrete as well as line scanned beams. Characteristics of the beam delivery system, like dose rate and spot size, are also the subject to optimization. For physical dose calculation two algorithms are currently used, pencil beam and Monte Carlo, to serve both normal clinical use as well as research needs. To verify delivery of light ion beams PET and prompt gamma imaging will be the most promising modalities and some of the systems are already in clinical use.
CERN, ENLIGHT and BioLEIR

Manjit Dosanjh, 12 November 2015

CERN, the European Organization for Nuclear Research, physicists and engineers are probing the fundamental structure of the universe. CERN was founded in September 1954, the same month and the year the 1st patient was treated with protons in Berkeley.

The prime technologies which have been developed at CERN over the past 60 years in order to carry out this research are accelerators, detectors, and computing. These technologies have been successfully applied to other fields of application and research including many in the field of medicine.

The Proton-Ion Medical Machine Study (PIMMS) aimed at producing a synchrotron design optimised for treating cancer patients with protons and carbon ions. The proposed design was detailed in two reports issued in 2000; it was further perfected by TERA, and then implemented at two treatment centres: CNAO in Pavia (Italy), which opened in 2011, and MedAustron in Wiener Neustadt (Austria), which is planned to start treating patients in 2016. Beyond the initial design study, CERN has contributed to the realization of the CNAO and MedAustron treatment centres, in particular with expertise in accelerators and magnets and with training of personnel. Both projects have been accomplished through networks of national and international collaborations. PIMMS aimed at producing a synchrotron design optimised for treating cancer patients with protons and carbon ions. The proposed design was detailed in two reports issued in 2000. The PIMMS concept was further enhanced by TERA, and then implemented at CNAO and MedAustron. Beyond the initial design study, CERN has contributed to the realization of the CNAO and MedAustron treatment centres, in particular with expertise in accelerators and magnets, and with training of personnel. Both projects have been accomplished through networks of national and international collaborations.

In 2014, the CERN Medical Applications (CMA) Office was established with a mandate to coordinate and structure activities and resources related to medical applications within the organisation, and to catalyse collaborations with external partners. The challenge and aim for the CMA Office is to ensure that state-of-the-art technologies and know-how developed at CERN are used or modified to provide clinical end-products that are valuable for the medical community. In order to help with this International Strategy Committee (ISC) was formed to advise the CMA. ISC selected BioLEIR/OPENMED as a priority activity and supported via endorsement letters directly and via international community and international organisations e.g. IAEA.

OPENMED/BioLEIR

The need for an open-access facility for R&D with ion beams in the context of medical applications was first raised at the ENLIGHT meeting in 2005 in Oropa. This was echoed by a request from the multidisciplinary scientific community at the 2010 Physics for Health workshop, where CERN was asked to take the lead on this initiative. In 2012, the possibility of modifying the existing CERN Low Energy Ion Ring (LEIR) accelerator to establish
OPENMED/BioLEIR was evaluated in an open brainstorming session, again with a broad positive answer from the medical and radiobiological communities.

OPENMED intends to provide suitable ion beams for a multitude of interdisciplinary studies, including radiation biology, nuclear physics models for medicine, detectors and instrumentation for dosimetry, diagnostics, and imaging. OPENMED will complement the existing or planned beam lines for this kind of multidisciplinary research, providing ample beam time without the constraints of a clinical setting. Ideally, all centres hosting research beam lines should form a pan-European collaborative network that will allocate beam time to researchers in an effective and concerted way.

CERN has proven experience in international cross-disciplinary scientific collaboration for a common research purpose and for training. OPENMED researchers will benefit from existing knowledge at CERN in accelerator physics and experimental techniques. Most importantly, the general infrastructure needed to host the research community already exists at CERN, thus significantly reducing the cost of establishing such a facility.

**Unique features of the facility would be:**

- Internationally shared expertise, collaboration with leading universities, research facilities and industry
- Beam time availability for 8 months each year
- A range of ions from proton to neon at the first stage, but using higher energies and other ions relevant for space radiobiology as a second phase
- Versatile energy, charge, mass, beam switching and pulsed capabilities
- Versatile biological end station for optimal sample configuration and analysis
- Comprehensively investigate complex physical and biological parameters that control radiation cell killing efficiency under highly controlled conditions.
- Provide accurate data for the modelling of radiation effects for proton and ion beam clinical applications
- Study comparative beam ballistics and dosimetry in humanoid phantoms and so improve predicted physical dose distributions.
- Provide a range of beams and infrastructure for developing new instrumentation.

**ENLIGHT** is a network of research centres, institutions, and scientists, involved in the research, promotion, and realization of hadron therapy in Europe. CERN has been active in ENLIGHT since its birth: in fact, the inaugural meeting took place in the Laboratory in 2002. Since 2006, the ENLIGHT Co-ordination office is at CERN. ENLIGHT was established to coordinate European efforts in using ion beams for radiation therapy, and to catalyse collaboration and co-operation among the different disciplines involved. ENLIGHT had its inaugural meeting in February 2002 at CERN, and was funded by the European Commission (EC) for its first 3 years (2002-2005).
Despite the end of the EC funding, in 2006 the network members decided to maintain ENLIGHT alive, with the primary mandate of developing strategies to obtain the necessary funding for hadron therapy research, and to establish and implement common standards and protocols for treating patients. The current membership exceeds 400 participants from more than 20 countries across Europe. Between 2008 and 2015, four EC projects have been started under the umbrella of ENLIGHT, for a total funding of 24M Euro: PARTNER, ULICE, ENVISION and ENTERVISION. All these projects are directed towards different aspects of developing, establishing, and optimising hadron therapy.
The Shanghai Proton and Heavy Ion Center (SPHCIC) started its phase 2 registration trial (the “IONTRIS” trial) in June 2014, and completed the study treatment in late December 2014. The hospital was approved by the Chinese FDA for patient care in March 2015 after the successful completion of the clinical trial.

The one-year results of the IONTRIS Trial

A total of 35 patients were accrued in the IONTRIS trial. Nineteen, 10, 4, 1 and 1 patients have prostate, head and neck, pulmonary, liver and abdominal sarcoma respectively. Twenty-two patients received carbon-ion radiotherapy (CIRT) and the rest had proton therapy. The 12-month overall survival was 100%, and the progression-free survival was 97.1%. Only one patient with colon cancer with lung metastasis had local progression in the pulmonary foci irradiated after partial response. We consider the outcome of the trial favorable at this time.

Current practice at SPHIC including clinical research

SPHIC started routine patient care in May 2015. By November 2015 we have treated approximately 140 patients and the majority received carbon therapy. Disease treated include chordoma, nasopharyngeal cancer, adenoid cystic carcinoma, oral/oropharyngeal cancer, liver cancer, pancreatic cancer, prostate cancer, sarcoma, lung cancer, and several other conditions.

We consider clinical research as an important integral part of our practice, thus have already initiated a number of trials. In this meeting I used head and neck as an example. The current focus of our head/neck research is re-irradiation using carbon-ion for locally recurrent nasopharyngeal cancer (NPC) since we consider recurrent NPC after IMXT is resistant to another course of photon therapy. And the physical and biological features of particle therapy can benefit this group of patients over IMXT. Other trials being planned in head/neck cancer including randomized trials to compare the effectiveness of CIRT versus proton in chordoma and GBM.

Challenges in the treatment of head/neck cancer with CIRT including the uncertainties in the optimal dose/fractionation for different pathologies. The outcome from our NPC re-CIRT protocol may not be applicable to other pathologies such as SCC and sarcoma. Clinical trials may answer some of the important questions that we have on CIRT, but the mechanism of the improved efficacy will need the support from translational studies and basic research.
Light ion beam therapy: Can we get the evidence we need?

Søren M. Bentzen, PhD, DMSc

Worldwide there is currently a major capital investment in LIBT. This happens despite the lack of robust level I evidence for a relevant patient-level benefit from LIBT vs. standard photon radiotherapy (XRT). To make LIBT sustainable in the longer term, clinical evidence for improved outcomes after LIBT will be required.

Presently, the main exception from this general observation is for childhood malignancies managed with radiation therapy where the reduced integral dose to non-target tissue in combination with the reliable registry-based estimates of the risk of treatment-related second malignancies after XRT produce a strong case for LIBT. In countries with a national health service, the top priority for investment in LIBT would be to secure the required capacity to meet the needs for pediatric radiation oncology. Such facilities should be located in centers of excellence with adequate funding and infrastructure for conducting clinical trials aiming at testing the comparative effectiveness of LIBT over photon RT in non-pediatric indications to the extent that the capacity is there.

Ions heavier than protons are potentially of interest due to possible radiobiological differences in action compared with XRT as well a less lateral scatter from the beam. The issues related to RBE means that the introduction of these radiation modalities must be regarded more experimental than proton beams. These types of treatments should be tested in the setting of carefully planned clinical trials.

The LIBT hypothesis is that ion beams in some indications will improve the therapeutic ratio relative to that of XRT. In other words, it is necessary to show that tumor control is improved with non-inferior toxicity or alternatively that toxicity is lowered with non-inferior tumor control.

RBE is a key consideration when designing trials comparing different radiation modalities. For XRT the default assumption is that RBE=1.1. There are data, however, showing that RBE could vary with dose-fractionation as well as the type of endpoint. This raises statistical issues as regards sample size requirements; estimating RBE with a reasonable precision, say a 95% confidence interval with a width of ±5% would generally require trials with 1000-2000 patients for typical values for the steepness of the dose-response curve.

Radiation therapy is a complex intervention and the first challenge in a head-to-head comparison of LIBT vs. XRT is to specify the two treatments to such a degree that the comparison is informative and potentially credible for the wider community once the outcome of the trial is known. Trials of modified XRT have in many cases failed to confirm the expectations from clinical radiobiological modeling, examples are the RTOG 0617 dose-escalation trial in NSCLC and the Pollack hypofractionation trial; or the trial has given rise to unexpected secondary observations, an example is the significant increase in early non-parotid related toxicity in the UK PARSPORT trial when parotid function was spared using
IMXT. This illustrates the strength of randomized comparisons over model based or registry based approaches.

In the absence of evidence from randomized controlled trials, registry based comparisons may be of value. However, it is important to recognize the limitations to registry studies especially when the question is comparative effectiveness of therapies. Despite a variety of statistical methods, multivariable models or propensity score adjusted analyses, it remains difficult to ensure that the groups receiving two competing treatments are balanced with respect to all other factors than the therapy used.

Also in this case, there are exceptions; most notably second solid malignancies where incidence estimates will almost certainly have to come from registry data in large cohorts rather than from prospective trials. It seems reasonable to assume that case-selection biases are less of an issue for second malignancies than for many early and late toxicities.

So, which tumor types would be good candidates for testing in controlled clinical trials of LIBT vs. XRT? Ideally where local progression is a major mode of failure, where the tumor shows a dose-response relationship and where treatment success is limited by relatively high-grade (late) toxicity. One example fulfilling these criteria would be re-irradiation of recurrent or second-primary squamous cell carcinoma of the head and neck. Also, here it is important to specify the tumor sub-site and the toxicity profile to be addressed. Another example could be combinations of RT with drugs showing relatively high-grade toxicity from the combination.
BACKGROUND: The ultimate goal of any radiation therapy technique or technology has been to deliver the required radiation dose to the target tissue and minimise the dose to the surrounding normal tissues to as less as possible. By reducing the dose to the surrounding normal tissues one may be able to reduce the early and delayed side effects of radiation therapy. This is especially important while treating young children because the normal growth and development of the child can get severely affected by high doses of radiation to normal structures like muscle, bone, brain, heart, eyes etc.

PHYSICAL & BIOLOGICAL BASIS OF PARTICLE THERAPY: Charged particle therapy is a technology with potential for improving the therapeutic ratio in cancers and has been known as early as 1946. Charged particle therapy replaces the photon (energy) beam of conventional radiation (X-rays, gamma rays or electrons) by a stream of protons or other sub-atomic particles (collectively known as ‘hadrons’) or by heavier bodies such as carbon ions. Their greatest impact (known as the Bragg peak) is delivered as they come close to the end of their path, after which point they have virtually no impact.

Protons are charged and have similar radiobiologic (RBE) properties as x-rays; whereas heavy charged particles such as carbon and neon ions possess high LET properties.

CURRENT CLINICAL APPLICATIONS: These unique physical & biological properties of particle beams (Hadron beams) along with the complex delivery system allows highly conformal delivery of physical radiation dose to the tumour with minimal dose to the surrounding normal structures, thereby allowing optimal radiation dose delivery without significant side effects. This is of special significance in the treatment of tumours that are located close to vital body structures, tumours considered resistant to radiation, and in the treatment of children as they are highly susceptible to the long term adverse effects of radiation. The sites where particle therapy has been of maximum clinical benefit are paediatric cancers, bone & soft tissue tumours, prostate cancers, lung cancers, & head & neck tumours (skull base & paranasal sinuses).

GLOBAL INFRASTRUCTURE FOR PARTICLE THERAPY: As per updated statistics (March 2014) from the Proton Therapy Co-operative Oncology Group (PTCOG) database, currently there are 42 Proton therapy and 7 Carbon Ion facilities functional globally. These facilities are located in the United States & Europe except for 14 centres located in Japan, China & South Korea. Tata Memorial Centre (TMC), Mumbai will be the first government supported academic centre in the subcontinent to provide this advanced radiation therapy technology for service, research & education.

The relatively slow progress in the development & clinical use of particle therapy can be attributed primarily to four main reasons: 1) Very high establishment cost 2) Large size of equipment/facility & the need for refinements in technology i.e. dosimetry/ gantry/ patient positioning systems/ image & dose verification etc. 3) Higher levels of expertise required compared to conventional radiotherapy and 4) Rapid developments happening in the field of ra-
diation therapy using photons (IMRT, IGRT, SRT, Helical Tomotherapy etc.) 5) Lack of robust clinical outcomes data to support use of particle therapy.

SIGNIFICANCE OF TMC (Tata Memorial Centre) AS NATIONAL FACILITY FOR HADRON BEAM THERAPY: The Tata Memorial Centre, Mumbai is a comprehensive cancer care centre. The centre is a grant in aid institution under the Department of Atomic Energy, Govt. of India, with a motto of Service, Research & Education. The centre registers 55-60 thousand new cancer patients every year from across the country & the neighbouring region. The centre has a robust teaching & research infrastructure and is currently involved in institutional & multinational research protocols with the IARC, IAEA, ESTRO, RTOG etc.

Global statistics indicate that approx. 15-20% of patients receiving radiation therapy would be eligible/ benefit from treatment using proton beams. In India approx. 50,000 children are diagnosed with cancer every year. Approx. 2000 of them would potentially benefit with proton beams. Similarly a much larger number of patients in the adult age group would also benefit from proton beam therapy. The facility at TMC would benefit patients in both paying & non-paying categories (40:60 in TMC). Availability of the therapy facility in TMC will make this state of the art treatment facility accessible to a large number of deserving patients from within the country & the surrounding region.

RESEARCH & DEVELOPMENT OF TECHNOLOGY

Interest has been growing in exploring the distinct radiobiological properties of charged particles. The biological impact of charged particles in terms of DNA damage is known to be higher for charged particles than photons. Calculated in terms of their relative biological effect (RBE) compared to photons, carbon ions have an RBE of 3–4, while that of protons is around 1.1. This raises the possibility that tumours that respond poorly to conventional radiation may respond better to carbon ion therapy. This would be of particular benefit in certain cancers of the salivary gland, sarcomas, bone tumours etc. Currently there is limited data to support or refute the use particle therapy for various clinical indications.

With the available expertise and research infrastructure at TMC and other affiliated DAE institutions, we will be able to generate valuable high quality robust scientific information to support or refute the use of particle therapy for treatment of cancers (both paediatric & adults).

It will also be an opportunity for undertaking research related to high & low LET radiation biology. Scientists/ physicists from TMC/ BARC (Bhabha Atomic Research Centre) / TIFR (TAta Institute for Fundamental Research) & RRCAT (Raja Ramanna Centre for Advanced Technologies) will also have an opportunity to work in tandem with companies involved in the development & functioning of Hadron facilities & undertake research activities related to heavy charged particle technology. This could also be an opportunity for indigenous development of technology in the future. It is thus appropriate that TMC with the support of DAE (Govt. of India) should try to establish a common platform for Clinicians, Physicists, Scientists, & Manufacturing Industry representatives from within the country & abroad to collaborate for further advancement of this complex technology.
Research on radiation quality and hadrontherapy: where are we? What is to be done?

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In the last few years several collective attempts have been made to define an agenda highlighting key questions, uncertainties and research needs relative to radiation quality issues, their applications to radiation protection and to the optimization of medical procedures, e.g. in hadrontherapy. A critical analysis will be presented starting from the results of a workshop organized by the EU network of excellence DoReMi [1] on Radiation Quality in 2013 [2], the EU Allegro Project [3] which ended in 2011, and the ongoing EU ANDANTE project [4] that will be concluded by the end of 2015. The outcomes of these projects will be starting points for a general analysis of the research needs in hadrontherapy.

As is known, proton therapy takes advantage of the favourable depth-dose curve, since the LET (Linear Energy Transfer), and therefore the dose, increases with increasing depth up to near the end of the particle’s range (Bragg peak). The main added value of carbon ions is the larger increase of the LET with depth and, as a consequence, of the relative biological effectiveness in the Bragg peak region (corresponding to the tumour region). Indeed the clustering properties (i.e. the high number of ionizations and excitations in volumes of a few nanometers) of high LET radiation in the tumour region can cause complex lesions in biological targets, this way affecting the repair ability and consequently the biological effectiveness, and the tumour control probability, (TCP).

The future of hadrontherapy will depend on key elements of clinical relevance, in the reduction of the integral dose (with a reduction of the risk of secondary tumours), in the possibility of increasing the dose without a significant increase of the risk of complications (normal tissue complication probability, NTCP), in organ preservation and in the possibility of increasing the dose in radio resistant tumour volumes (e.g. due to hypoxia). The rules of evidence-based and personalized medicine need to be applied to compare the effectiveness of hadrontherapy with the techniques used to date in the treatment of tumours.

Among the various research topics of importance for hadrontherapy (such as research on hypofractionation protocols, motion management, out-of-field doses and particle spectra), special attention will be given to radiobiology research in terms of questions and problems (e.g. radiobiological modelling in clinical practice, genetic susceptibility, bystander and abscopal effects, the role of stem cells and cancer stem cells), together with specific examples on the in vitro/in vivo issue. Furthermore, to better understand the action of radiation on complex systems (such as the crosstalk between the tumour microenvironment and the immune system) a multi-scale approach will be discussed prior to concluding with future perspectives, such as the potential effectiveness of combined radio- and immuno-therapies.

The importance for the research in hadrontherapy of networking activities at international level (e.g. within European consortia) and at local level (e.g. within structures like cancer research centers), will be also addressed.

[1] Low Dose Research towards Multidisciplinary Integration
[3] Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy
[4] Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the analysis of second malignant neoplasms following paediatric radiation therapy
A unit of clinical dose, which is used for estimating clinical responses of patients to the carbon absorbed dose, GyE, has been used at the National Institute of Radiological Sciences (NIRS) and also at the Gesellschaft für Schwerionenforschung mbH (GSI), although their respective definitions are completely different. In both facilities, the unit GyE has been defined as physical dose multiplied by relative biological effectiveness (RBE). But the values of RBE used in clinical treatment planning are completely different. In this clinical dose definition, the RBE value for 10 % survival level of Human Salivary Grand Tumor cell (HSG) is taken.

The ‘clinical dose’ used in Japan is mathematically defined as follows,

\[
D_c(z) = c \times RBE(\text{center}; 0.1) \times d(\text{center}) \times \frac{d(\text{center}; 0.1)}{d(z; 0.1)} \times \frac{d(z)}{d(\text{center})}
\]

In this definition, the clinical dose is separated into two part, RBE × dose at the center of the SOBP, \( c \times RBE(\text{center}; 0.1) \times d(\text{center}) \), and the dose distribution relative to the SOBP center, \( \frac{d(\text{center}; 0.1)}{d(z; 0.1)} \times \frac{d(z)}{d(\text{center})} \). In the designing the clinical dose, the latter part of relative dose distribution is designed to be 1. Then, the clinical dose in the SOBP will be constant value of \( c \times RBE(\text{center}; 0.1) \times d(\text{center}) \). We can use this clinical dose like physical dose in the treatment planning system.

The clinical results of TCP can be analyzed with the LQ model in the above frame work of clinical dose system by introducing the variation of the sensitivity \( \alpha, \Delta \alpha \).

Large part of the variation of the sensitivity, \( \Delta \alpha \), will be contributed by oxygen effect. We examined how large or how small the oxygen effect is in our treatment of carbon ions. A simple Poisson-like distribution is assumed on the P(O2) distribution. And using 2 dimensional OER map on LET and P(O2) developed by Scifoni at GSI, we calculated clinical dose distribution in the circumstance of the above P(O2) distribution in our frame of clinical dose. The obtained clinical dose distribution was relatively flat in the SOBP. And when normalizing the clinical dose at the center of the SOBP, variation due to the oxygen effect was the same order as the variation of the sensitivity deduced by TCP calculation.

More accurate and detailed studies on the tumor responses should be done for evaluating the carbon therapy.
Biological Research at HIMAC, NIRS:
Biological Advantages of Carbon-ion Irradiation for Cancer Therapy
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Physics and chemical features of the particle beam have contributed greatly to the clinical outcomes of particle radiotherapy (RT). For example, the excellent dose distribution has significantly reduced adverse events, and also is contributing to the local control due to the higher dose delivery into the tumor. Moreover, it has become clear that there are additional properties affecting biological reactions, which cannot be explained by RBE.

The control of cancer stem-like cells greatly affect clinical outcome, since they usually are resistance to conventional radiation. In contrast, Cui et al demonstrated that carbon ion irradiation (C-ion IR) could effectively reduce the cancer stem-like cells in both *in vitro* and mouse model experiments.

Metastasis is a common issue for cancer treatments. Even for particle beam RT, which has a higher effect on local control, the regulation of micrometastasis is a crucial matter for clinical outcomes. Several mouse model experiments clearly showed C-ion IR suppress metastasis, even though the irradiated dose does not affect tumor growth. In addition, combination therapy of C-ion IR and DC immunotherapy demonstrated that C-ion IR was significantly enhanced by the combined effect with dendritic cell therapy. On the other hand, the actual dose of photon beam required is more than that calculated on the base of RBE, indicating C-ion IR is effective in activating immunity.

It is well known that cancer cells sometime acquire treatment-resistance and also malignancy after treatments. For example, tumor vessels are increased and metastatic abilities are enhanced. We evaluated the potential of cancer cells to acquire malignancy after repetitive irradiation by C-ion beams or photon beam, by using in vitro and mouse models. Our results indicated that repetitive irradiation by photon beam induced shortening of the survival rate by enhanced metastasis. However there were no significant changes after C-ion IR. The results are in line with previous reports that
tumor angiogenesis is induced by photon irradiation but not by C-ion IR.

Since applications for particle beam therapy are expected to expand in the future, it is an important problem to reveal the long-term effects on the young and in children. Imaoka et al showed by using the rat mammary cancer model that RBE of radiation-induced carcinogenesis is changed by the exposed age.

These unique biological effects, which cannot be fully explained by physical and chemical characteristics, make it difficult to predict the biological effects of the particle beam. However, understanding the underlying mechanisms of such effects might be important to develop clinical outcomes of particle RT.
APPLICATION OF BIODOSIMETRY TECHNIQUES TO DETERMINE THE BIOLOGICAL EFFECTS OF HEAVY IONS IN HUMAN LYMPHOCYTES

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Biomarkers are important in assessing the exposure and for predicting future adverse health outcomes. The development of cellular and molecular biomarkers is an important goal in cancer research. A study involving multiple end points following irradiation was initiated in our laboratory using human blood lymphocytes from three healthy donors. Human cells were irradiated with different doses (0.10 to 1.0 Gy) of Carbon (290MeV/u, LET 70 keV/micron) ions at National Institute of Radiological Sciences, Chiba, Japan. Gene expression profiles using microarray analysis were generated from blood lymphocytes irradiated at G0 state to identify signature genes of exposure to heavy ion radiations. Chromosome alterations induced were detected by using fluorescence in situ hybridisation (FISH) using telomere/centromere specific probe as well as by multi-colour FISH. A dose dependent increase in the extent of DNA damage and double strand breaks formation was observed in the study. Cytogenetic analysis revealed a dose-dependent increase in the percentage chromosome aberrations such as dicentrics and translocations. In this study, it appears that carbon ions produced greater and complex chromosome aberrations compared to gamma rays. Microarray analysis revealed that low doses of carbon ion irradiation induced differential gene expression. Collectively, our results indicate that irradiation with low doses of carbon ions induces varied molecular and cellular changes including chromosomal aberrations. Gene expression profiles are very distinct from those of gamma radiation exposure. The results obtained in this study would, hopefully, provide us with functional relevance of early biomarkers of exposure as well as in the manifestation of heavy ion therapy. It is anticipated that such biodosimetric techniques could be of clinical significance in treatment planning.
Radiobiological testing of new ProTom technology at the Proton Therapeutic Complex in Ružomberok, Slovakia

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In order to evaluate DNA damage induced by protons at low and radiotherapeutic doses at the therapeutic proton complex at Ružomberok, Slovak Republic, lymphocytes from umbilical cord blood (UCB) of radiation induced effects at doses of 50 cGy and higher. Factorial analysis of variance in the whole studied dose range has shown no significant effect of radiation quality on number of γH2AX and 53BP1 foci. The ratio of proton-induced foci to γ-ray-induced foci was 0.86 ± 0.16 (53BP1) and 0.99 the same four probands were irradiated in the dose range of 1 - 200 cGy with γ-rays and protons (200 MeV, irradiation in the Bragg peak). DNA repair γH2AX/53BP1 foci were analyzed by fluorescent microscopy and flow cytometry. Statistically significant effects of radiations were detected by fluorescent microscopy at all doses higher 1 cGy. Almost all distributions of foci in irradiated cells fitted to the Poisson distribution. In general, there was no significant difference in the levels of γH2AX and 53BP1 foci in irradiated cells. Flow cytometry was less sensitive and detected 0.34 (γH2AX) as measured by fluorescent microscopy and 0.99 ± 0.16 (γH2AX) as measured by flow cytometry at the radiotherapeutic dose of 2 Gy. To conclude, both flow cytometry and fluorescent microscopy indicated that the average value of relative biological efficiency (RBE, 200 MeV, irradiation in the Bragg peak) at radiation doses ≥ 20 cGy was about 1.0. Our data that RBE increased at low doses < 20 cGy are relevant both to the development of treatment modalities and exposures that take place during space exploration and should be verified by further studies.

In order to study distribution of dose over tumor and healthy tissues during proton therapy, anthropomorphic human phantom was established with special chambers for physical/biological dosimeters which are filled up with tissue equivalent plastic. Computer model of the human phantom for 3D dose simulations was built. Computer simulations of the absorbed dose and scattered radiation distributions were performed with MARS Monte Carlo simulation package in anthropomorphic human phantom. Irradiation procedure was modeled with four tumor locations, relevant proton beam energies being used. Distribution of the scattered (mostly neutron) dose over the phantom body was calculated. Based on obtained data we conclude that biological dosimetry using sensitive endpoints to study DNA repair foci may be used in anthropomorphic human
phantom to define dose distribution in tumors and healthy tissues for optimizing radiation treatment and assessment of side effects including secondary cancer.

Acknowledgements. Structural EU Funds (Protonbeam, ITMS: 26220220129), the Slovak Research and Development Agency (APVV 0669-10), the VEGA Grant Agency (2/0150/11) of the Slovak Republic, the National Scholarship Program of the Slovak Republic (SAIA), and the Joint Research Project of the Slovak Academy of Science and Russian Academy of Medical Science.
Mapping RBE effects at the cellular level: Impact for clinical radiotherapy

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Our understanding of the effectiveness of different radiation qualities at the cellular level is built on the physics of track structure, with increasing ionization density, quantified as linear energy transfer (LET) leading to more complex or clustered DNA damage which cells have difficulty in repairing. This is thought to drive differences in relative biological effectiveness as LET changes and is known to be influenced by a range of factors including dose, dose-rate and intrinsic radiosensitivity. Although significant studies on RBE/LET relationships have been reported, the data suffers from significant variability and is only available in a limited range of models and for a small range of endpoints [1,2]. Even though trends of increasing RBE with LET have been reported, for protons a clinical RBE value of 1.1 is currently used for treatment planning. Recently we have performed comparative studies of pristine versus spread-out-Bragg Peak comparisons of DNA damage and repair alongside survival and show a high resolution that the RBE value of 11 underestimates the biologically effective dose by around 18% and leads to some increase in range of the protons. This correlates with increased residual DNA damage [3,4]. Recent studies have started to assess the impact of biology on the RBE value. For example in a comparative study of 17 lung cell models exposed to the same energy protons the RBE for survival varied from 0.88 to 1.6. Underpinning this was an involvement of deficiencies in the Fanconi Anemia pathways and is a good exemplar of trying to develop mechanistic understanding of the mechanistic basis of RBE effects [5]. Our understanding of the biological consequences of radiation exposure is based on a DNA damage model despite the fact that a complex signalling based biology underlies the responses of tumour and normal tissues to radiation exposures. There is a pressing need to expand preclinical studies to characterise RBE dependent biological processes and their mechanistic basis. Despite experimental studies highlighting an impact of bystander and abscopal responses the role of these in particle therapies needs to be elucidated [6].

References

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Defining the rate-limiting step in proving the clinical value of heavy charged particle radiotherapy (HCPRT) requires an understanding of how it should be compared to conventional and or proton radiation. Without this knowledge, fraction size, total dose, tumor site selection and the magnitude of the benefit expected can’t be accurately estimated. As a result, the design of phase III randomized trials required to provide level I evidence of benefit can’t be optimized. Conducting non-optimized phase III trials may result in the false negative conclusion, suggesting that HCPRT does not improve the outcomes of cancer patients. The degree to which in vivo and/or in vitro studies can be used to help answer these questions is unknown but based on the poor correlation between the genomic responses of mouse models to mimic human inflammatory diseases, we must be leery about their use. As a result, confident conclusions about the use of HCPRT in humans will require trials in humans. The first Phase I/II clinical trial involving the application of HCPRT were initiated at the University of California, San Francisco/Lawrence Berkeley National Laboratory (UCSF-LBNL) in 1975. After delivering HCPRT ion treatments to nearly 2,500 patients the facility at Berkeley Lab was closed by the Department of Energy (DoE) in 1992, due to budget constraints. However, on February 10, 2015, the U. S. President’s Office of Science and Technology Policy announced the National Cancer Institute’s selection of two P20 Planning Grants. The North American Particle Therapy Alliance (NAPTA) is a collaborative effort between leading academic institutions in the U.S., U.S. National Laboratories, and leading PBRT centers in Japan and Germany, Our proposal entitled: “NAPTA: Optimizing clinical trial design and delivery of particle therapy for cancer” was one of the recipients. NAPTA P20 had as an overall specific aim to complete a pilot research project showing how we can develop “new knowledge” in radiobiology into treatment planning for assessing biological dose distributions. Over the next several years, in collaboration with a number of national and international investigators and laboratories, we will launch a series of trials leveraging existing technology to challenge the null hypothesis that HCPRT is required to improve survival and local control of selected cancers. This research area, will allow us to finally address the key 7 major challenges to advancing this field, which we call by the acronym “RESIDUE” (Radiobiology; Exchange of info; Size/weight of accelerators/gantries; Integration; Define patient population; Uncertainties of dose and range; and Evidence of clinical effectiveness and cost-effectiveness). We believe that the rate limiting step is addressing “new knowledge” required to understand the radiobiology of HCPRT vs SBRT using photons or protons and the impact of these treatments on immune responses is a critical area of research.

References: