**Exploratory Workshop**

Physical and Engineering Sciences (PESC)

European Medical Research Councils (EMRC)

# SCIENTIFIC REPORT

# Advanced Instrumentation for Cancer Diagnosis and Treatment

**Oxford, September 23rd to 26th 2008**


Convened by

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## Executive Summary

1. The workshop was attended by 25 participants from 8 European countries and CERN, with a mixture of instrumentation, radiation and medical physicists, hadron therapy specialists and clinical oncologists.
2. The workshop focussed the need for better imaging during therapy, the development of better treatment models and the subsequent treatment planning, accurate measurement of radiation dose and micro-dosimetry delivered to patients during treatment, particularly involving protons and light ions such as Carbon.
3. Protons or light ions like carbon deposit more radiation in the tumour through the increased ionisation at the end of the range (the "Bragg peak") than in the healthy tissue between the tumour and the surface skin. While Charged Particle Therapy is certainly effective, there is significant scope for improvement in instrumentation, to monitor and control the dose delivery and distribution, including the development of *in vivo* and real-time dose-distribution measurements and feedback.
4. The workshop was organised in a deliberately open way, with substantial time for discussion. The combination of oncologists, radiobiologists, medical physicists, experts in instrumentation and in other areas of physics in a single workshop has been very beneficial, and it would be useful to encourage the organisation of an international meeting with a similarly broad attendance to discuss charged particle therapy.
5. There is a need to train a new generation of workers in this field, perhaps through a European school to offer both training and information about Charged Particle Therapy, targeted at those who were interested in learning more about CPT, in part to reinforce the publicity campaign.
6. There is a need for a rigorous database of conventional and charged particle therapies, with sufficient information about the patient histories so that samples of similar patients treated under the best available conditions can have their outcomes compared.
7. There is already an impressive range of instrumentation available for calibrating, monitoring, measuring and controlling the delivery of the treatment plan, but improvements in imaging during therapy are required to enhance the targeting of the dose on the tumour while reducing the dose delivered to adjacent healthy tissue. In-beam PET (ibPET), ultrasound and new imaging techniques that can track organ motion during treatment would in principle allow much more efficient dose delivery, and reduce the possibility of delivering part of the dose to the surrounding healthy tissue. Single particles scanning techniques also need to be studied.
8. Improvements in instrumentation will allow therapy and treatment plans to take advantage of improvements in accelerator and beam transport technologies.
9. The workshop was successful in bringing together a very broad range of specialists to assess the "state of the art" in instrumentation for Charged Particle Therapy.

## 1. SCIENTIFIC CONTENT OF THE EVENT

The workshop was attended by about 25 participants from 8 European countries and CERN, with a mixture of instrumentation, radiation and medical physicists, specialists from hadron therapy centres and clinical oncologists. The workshop focussed on the issues surrounding the need for better imaging during therapy, the development of better treatment models and the subsequent treatment planning, accurate measurement of radiation dose and micro-dosimetry delivered to patients during treatment, particularly involving protons and light ions such as Carbon. There is also a clear need for a better system to collate the available data to assist in the development of treatment planning. Improvements in accelerator and beam delivery technology, to achieve faster energy scanning for example, were also needed. The workshop took place in the Physics Department of the University of Oxford, with accommodation provided by Keble College. The relaxed and informal atmosphere, allowing the work to continue well into the evening over dinner, greatly added to the usefulness of the meeting.

Cancer is still a feared disease, and rightly so. There can be few people who do not know of a relative or friend who has undergone radical surgery and/or radiotherapy and/or chemotherapy as part of the treatment of cancer. Although there have been many recent advances in understanding the genesis of cancer, and many improvements in diagnosis and treatment so that cancer is not the invariably terminal illness that it once was, cancer remains a major heath concern. While some cancers may be preventable through life-style choices, restrictions in environmental pollution and possibly through designer pharmacology and genetic counselling, there will always be a base level requiring treatment. Despite the improvement in cancer diagnosis and treatment, many therapies are also very aggressive and unpleasant – fear of cancer is understandable. There is roughly a one in eight chance of getting a cancer before the age of 65, and the probability rises to about one third for the whole life; cancer is a mostly a disease of an aging population. Perhaps even more distressing is the, albeit rare, incidence of cancer in young children, where the aggressive nature of the treatments can lead to permanent impairment.

Radiotherapy, usually using x-rays generated from a 6-10MeV electron linear accelerator, is an effective therapy, but because the x-rays are penetrating and have an approximately exponential distribution of deposited energy as a function of depths, a relatively large volume of healthy tissue receives a substantial radiation dose. Charged Particle Therapy, using protons or light ions such as carbon, offers the prospect delivering the same dose while delivering considerably less dose to healthy tissue and, because of the specifics of the energy loss mechanisms, can deliver little or no dose to organs located close to but behind the tumour (see Figure 1).

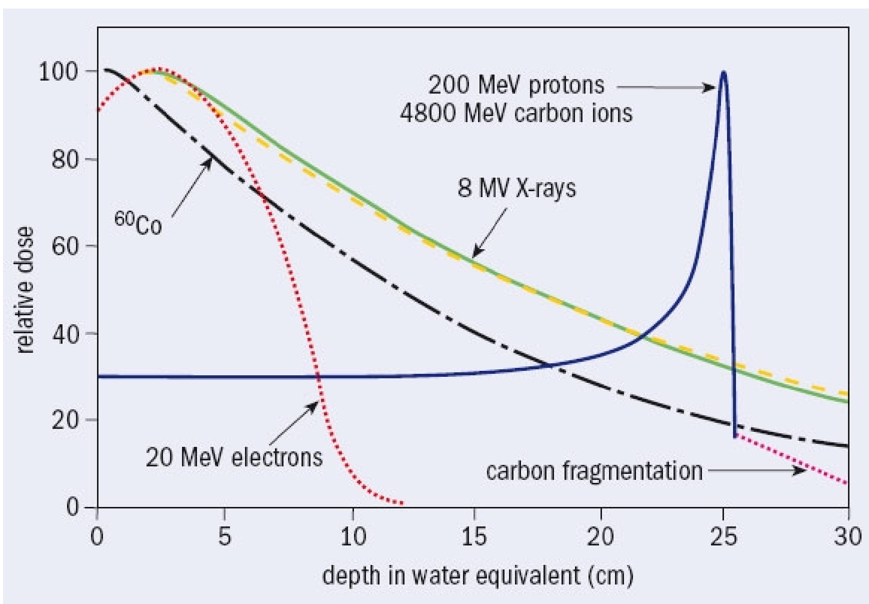


Figure 1: Depth-dose curves for various radiotherapies

With protons or light ions like carbon, if the incident energy is properly set, more radiation is deposited in the tumour through the increased ionisation at the end of the range (the “Bragg peak”) than in the healthy tissue between the tumour and the surface skin. With x-rays or electrons, more energy is deposited in healthy tissue than in the tumour (unless the tumour is located about 2cm below the surface) when irradiated from a single direction. With x-rays, it is *essential* that a deeply located tumour is irradiated from several different directions, whereas with protons or light ions, a small tumour can be treated effectively from just one or two directions.

So far, about 63,000 patients have been treated with charged particles. Over 55,000 have been treated by Protons (mainly for eye cancers using relatively low energies and simple fixed beams), ~4500 with carbon ions, ~2000 with helium ions, ~1000 with pions and around 400 with other ions. The earliest treatments were in Berkeley in 1954 with protons, and most early facilities were based in physics laboratories in Belgium, Canada, Japan (2), Russia, Sweden, Switzerland and the US (6), with inevitable inadequate cancer imaging if compared with modern standards, and limited beam availability. These have mostly closed, the last (Harvard) in 2002, in order to relocate facilities to a hospital setting. Since then, around 30 new facilities have been built in 13 countries, most in hospitals, led by the Japan (7) and the US (6), and including China, France, Korea, Italy, Korea and South Africa. Interestingly, the first hospital-based proton therapy facility was at Clatterbridge in the UK, which started in 1989, just before Loma Linda in the US (1990), although Clatterbridge is 62MeV and can treat only cancers in the eye. At least 22 more facilities are planned, being extended or under construction around the world (Austria, China, France, Germany, Italy, Japan, Slovakia, South Africa, Taiwan, US…). While Charged Particle Therapy is certainly effective, there is significant scope for improvement in instrumentation, to monitor and control the dose delivery and distribution, including the development of *in vivo* and real-time dose-distribution measurements and feedback.

The workshop was organised in a deliberately open way, with substantial time for discussion. After an overview of the objectives for the ESF to support such initiatives, there were seven workshop sessions, covering various aspects of Charged Particle Therapy and the available and potential instrumentation. Each of these sessions had presentations from participants covering the current status and plans, and reviewing the options and opportunities for development. The combination of oncologists, radiobiologists, medical physicists, experts in instrumentation and in other areas of physics in a single workshop has been very beneficial, and it would be useful to encourage the organisation of an international meeting with a similarly broad attendance to discuss charged particle therapy. There is also a need to train a new generation of workers in this field, perhaps through a European school to offer both training and information about Charged Particle Therapy, targeted at those who were interested in learning more about CPT, in part to reinforce the publicity campaign.

There is a need for a rigorous database of conventional and charged particle therapies, with sufficient information about the patient histories so that samples of similar patients treated under the best available conditions can have their outcomes compared. This would allow the identification of any “holes” in the data and the development of a programme for further measurements. This is particularly true for ions such as carbon, where better measurements of fragmentation cross-sections and biological end-points and access to clinical data are required. In addition, a comparison between the data and models used for treatment planning is required. There is also a need for further work on the issue of radiobiological modelling within the treatment planning process and the measurements required to benchmark the models.

There is already an impressive range of instrumentation available for calibrating, monitoring, measuring and controlling the delivery of the treatment plan. However, improvements in imaging during therapy are required to enhance the targeting of the dose on the tumour while reducing the dose delivered to adjacent healthy tissue. There are a number of techniques that are in use, but where there are good prospects for development, including in-beam PET (ibPET) and ultrasound. However, there is a real need to devise new imaging techniques that can track organ motion during treatment, since this would in principle allow much more efficient dose delivery, and reduce the possibility of delivering part of the dose to the surrounding healthy tissue. This requires the development of detectors able to work in real time. Further, the use of prompt particles, produced by the therapy itself, would be beneficial as no additional radiation would be required to produce an image. There is also a need for detectors able to count single particles, as this is also important for micro-dosimetry, for example if re-scanning is used for carbon ion beams for organ motion. This requires larger area detectors, together with the appropriate integrated electronics, for example using CVD diamond material. In-vivo dosimetry is being investigated, which will lead to major improvements in quality assurance, to confirm the radiation range and position determination during therapy, which requires the use of, for example, prompt photons, prompt protons, neutrons, etc; in particular, neutron production and neutron detection techniques need to be understood and studied.

Improvements in instrumentation will allow therapy and treatment plans to take advantage of potential improvements in accelerator and beam transport technologies. It would be highly desirable to be able to vary the energy of extraction at significantly higher rates, up to several hundred Hz, particularly if re-scanning is used.

Independent from the choice of accelerator technology, there is considerable scope for improvement to the beam transport and its delivery to the patient. If fast variable energy extraction could be achieved, there is a need for improved performance beam transport systems. There is a clear clinical need for gantries, but novel technologies are required to reduce the size and cost, and to increase the scanning speed. The size and cost of the gantries is likely to restrict the growth of carbon therapy.

Finally, there is a clear need for a campaign of publicity about the benefits of Charged Particle Therapy. While some countries, in Europe, the US and Asia, are leading in this area, there are several countries where there seems to be little public awareness, and some resistance to its introduction by the medical profession, presumably largely because of the cost. There is a clear need for patients to be monitored for several years after treatment, and for the results to be recorded carefully and in a standard way, so that the results can be widely disseminated. Authoritative, clinically robust, reports are likely to be essential in convincing Governments and other healthcare providers of the benefits of Charged Particle Therapy, and the needed to invest in such facilities.

## 2. ASSESSMENT OF RESULTS AND CONTRIBUTION TO FUTURE DIRECTION OF THE FIELD

The workshop was successful in bringing together a very broad range of specialists to assess the “state of the art” in instrumentation for Charged Particle Therapy. This is essential if the benefits of advanced instrumentation are to meet the requirements of the clinicians. It was also very timely. The EU issued a call for proposals (HEALTH-2009-1.2-4) on “Novel imaging systems for in vivo monitoring and quality control during tumour ion beam therapy” at the beginning of September 2008, just three weeks before the workshop. Many of the participants in the workshop will be participants in a proposal to be submitted in response to this call, and the workshop provided the opportunity to build the appropriate network of contacts, and to review the challenges, assess the options and rehearse the arguments. If this bid is successful, the impact of the workshop will already have been significant.

In the “Conclusions and Recommendations”, a number of actions were identified to consolidate the work covered by this workshop, and to extend its scope to the international arena. Although Charged Particle Therapy has been an experimental therapy for more than 50 years, it is still represents only a small part of the cancer therapy armoury. There is scope for a significant expansion of this technology. However, as the technology is rolled out, there will be an increasing need for more advanced instrumentation to monitor and control the dose delivery. Particularly important is the suggestion that there should be an international conference with a similar mixture of instrumentation, radiation and medical physicists, specialists from hadron therapy centres and clinical oncologists.

Although not really a result, the format of the workshop, with a lot of time for discussions, both formally in the sessions and informally in the evenings, was an important element in achieving the final outcome.

***Acknowledgements***

The organisers would like to thank the European Science Foundation for their support for this workshop, The John Adams Institute for Accelerator Science and the Physics Department of the University of Oxford for their help with the facilities. We also gratefully acknowledge the friendly and efficient service from Keble College over the accommodation, Wolfson Hertford Colleges for their provision of the reception and workshop banquet, and the al-Shami restaurant for a memorable dinner.

## 1. CONCLUSIONS & RECOMMENDATIONS OF THE ICPTESF WORKSHOP

- Bringing together oncologists, radiobiologists, medical physicists, experts in instrumentation and in other areas of physics in a single workshop has been very beneficial.
  - ➢ It is recommended that an ESF International Conference is organised to bring together the same communities on an international scale to discuss charged particle therapy.
  - ➢ It is also recommended that a school is organised for those in Europe who have an interest in charged particle therapy, but do not necessarily work in the field, and would like to learn more about it.
- There is a need to collate the existing data on the use of charged particles for therapy, especially carbon ions. This would allow the identification of any "holes" in the data and the development of a programme for further measurements. In addition, a comparison between the data and models used for treatment planning is required. The International Atomic Energy Agency (IAEA) has initiated in 2007 a Co-ordinated Research Project on this.
  - ➢ It is recommended that an ESF Exploratory Workshop jointly with IAEA is held to discuss the issue of radiobiological modelling within the treatment planning process and the measurements required to benchmark the models.
- A greater awareness of the benefits of charged particle therapy is required in some countries in Europe.
  - ➢ It is recommended that an effort is made to have experts in the field invited to give presentations at the meetings of appropriate bodies in these countries.
- Improvements in imaging during therapy are required. In-beam PET has already been shown to work in this area and further improvements are already being worked on. Ultra-sound imaging also has potential for this application. Of particular interest, however, is imaging during organ motion and current techniques do not appear to be adequate for this. There is scope for novel technology in this area.
  - ➢ It is recommended that an ESF Exploratory Workshop is organised to study imaging during therapy, in particular in the case of organ motion.
- The use of detectors able to count single particles is important for micro-dosimetry, for example if re-scanning is used for carbon ion beams for organ motion, and for other applications. Larger area detectors able to do this, along with the appropriate integrated electronics, need to be developed. One candidate for this might be CVD diamond material, which has already been shown to work in this area.
- Faster variation in beam energy directly from the accelerator is required, of the order of a few hundred Hz, especially if re-scanning is used.
- There is a clear clinical need for gantries, but the size and cost of these is likely to restrict the growth of carbon therapy. Novel techniques need to be studied to reduce the size and increase the scanning speed, e.g. fixed field, super-conducting magnets.
  - ➢ It is recommended to hold a multidisciplinary ESF Exploratory Workshop to study the reduction in size and power consumption of gantries.
- Using particles produced by ions during therapy for radiation range confirmation and/or position determination would provide good quality assurance, e.g. using prompt photons, prompt protons, neutrons, etc. In particular, studies of neutron production are necessary, together with neutron detection techniques.
- A number of different techniques for doing in-vivo dosimetry are being investigated, but none are currently universally accepted. There is a requirement to develop novel technologies for this purpose.
  - ➢ It is recommended that an ESF Exploratory Workshop is organised to study both existing and possible novel techniques for in-vivo dosimetry.
- The usefulness of carbon therapy is currently not limited by the knowledge of the beam parameters in the accelerator, so improvements over the state-of-the-art in beam diagnostic techniques are currently not required.
- There is a need for careful recording and wide dissemination of clinical follow-up of patients treated with hadron therapy. This information is essential if the case is to be made to governments to invest in this kind of facility.

## 3. FINAL PROGRAMME

| | |
|---|---|
| **Tuesday 23rd** | |
| Morning | |
| 09:00-09:30 | Malgorzata Tkatchenko and Vladimir Bencko: “ESF Introduction” |
| 09:30-10:15 | Bleddyn Jones “Toward a UK charged particle research facility” |
| 10:15-11:00 | Carmen Ares “Spot scanning proton radiation therapy: Paul Scherrer Institut experience” |
| 11:00-11:15 | Coffee |
| 11:15-12:30 | All: discussions |
| 12:30-14:00 | Lunch + discussions |
| Afternoon | |
| 14:00-14:45 | Thomas Haberer “The Advantages of Particle Therapy and the status of the Heidelberg Iontherapy Center” |
| 14:45-15:30 | Piero Fossati “Treatment delivery from the patient perspective: potential indication, set-up and organ motion issues at CNAO” |
| 15:30-16:00 | Tea |
| 16:00-16:45 | Marco Durante “Current plans for research in heavy-ion therapy at GSI” |
| 16:45-17:30 | All: discussions |
| **Wednesday 24th** | |
| Morning | |
| 09:00-09:45 | Vincenzo Monaco (a) “Activities in Torino on hadrontherapy” (b) ”Development of a treatment planning system” |
| 10:30-11:00 | Coffee |
| 10:30-12:30 | All: discussion |
| 12:30-14:00 | Lunch + discussions |
| Afternoon | |
| 14:00-14:45 | Lukas Tlustos “Latest developments in spectroscopic X-ray imaging: characteristics, performance, remaining challenges and anticipated benefits” |
| 14:45-15:30 | Fabio Sauli “AQUA: Advanced QUality Assurance for Hadrotherapy at CNAO” |
| 15:30-16:00 | Tea |
| 16:00-16:45 | Manjit Dosanjh “European Network for Light Ion Therapy ENLIGHT” |
| 16:45-17:30 | All: discussion |
| **Thursday 25th** | |
| Morning | |
| 09:00-09:45 | Tony Lomax “Future directions and current challenges of proton therapy” |
| 09:45-12:30 | All: discussion |
| 12:30-14:00 | Lunch & discussions |
| Afternoon | |
| 14:00-15:00 | All: discussion |
| 15:00-15:30 | Tea |
| 15:30-16:15 | Nicolas Freud ”Monitoring the Bragg peak location by means of prompt measurements” |
| 16:15-17:00 | Monika Rebisz-Pomorska “Diamond detectors” |
| 17:00-17:30 | All: discussion |
| **Friday 26th** | |
| Morning | |
| 09:00-10:00 | All: discussion |
| 10:00-10:30 | Coffee |
| 10:30-12:30 | All: Concluding discussion and review of the workshop |
| 12:30-14:00 | Lunch and close |

## 4. STATISTICAL INFORMATION ON PARTICIPANTS

In all the statistic below the two ESF representatives, Prof Bencko and Prof Tkatchenko, were always included.

Age structure: half of the participants were in their late thirties, early forties.

Gender repartition: Out of a total of 27 participants, 7 (26%) were women and 20 (74%) were men.

Countries of work: The participants were from 10 different countries, listed in the table below together with the number of participants from each country.

| Country of work | Number of participants |
|---|---|
| UK | 6 |
| Belgium | 1 |
| Check Republic | 2 |
| Denmark | 1 |
| France | 5 |
| Germany | 3 |
| Italy | 2 |
| Netherlands | 1 |
| Portugal | 1 |
| Switzerland | 5 |

Of the 5 participants from Switzerland 3 were from CERN.

The number of participants from UK exceeded by 1 the maximum set by ESF. The convenors asked and obtained permission for this in order to supplement their expertise in the field of particle physics with expertise in healthcare.

Industry: there was one representative from industry (IBA in Belgium)

Background: The table below reports the various backgrounds of the participants together with the corresponding number of participants.

| Background | Number of participants |
|---|---|
| Biology | 1 |
| Biophysics | 1 |
| Epidemiology | 1 |
| Industry | 1 |
| Instrumentation (applied) physics | 7 |
| Medical physics (radiotherapy) | 8 |
| Oncology | 2 |
| Particle physics | 6 |

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