PARTICLE THERAPY CO-OPERATIVE GROUP

Chair
Gudrun Goitein M. D.
Paul Scherrer Institute
Division of Radiation Medicine
Villigen PSI CH-5232
Switzerland
+41 56 310 35 12
+41 56 310 35 15 Fax
gudrun.goitein@psi.ch

Secretary
Janet Sisterson Ph. D.
Northeast Proton Therapy Center
Massachusetts General Hospital
30 Fruit Street
Boston MA 02114
617 724 1942
617 724 9532 Fax
jsisterson@partners.org

ABSTRACTS

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The status of ion beam therapy at the end of 2001.

J. M. Sisterson, Northeast Proton Therapy Center, Massachusetts General Hospital, Boston, MA.

By January 2003, 33,398 patients worldwide have been treated with proton beams and 3,860 with ion beams. The status of ion beam therapy through 2001 is discussed and details of patient treatments for selected sites presented. At the end of 2001, there were 21 operating proton therapy facilities, including several hospital-based dedicated facilities. Seven of these facilities were limited to treating eye tumors only. Carbon ions were available at two facilities in Japan and one in Germany. All existing centers used either a cyclotron or a synchrotron and several facilities had one or more gantry to provide beams at any angle to the patient. For several treatment sites, there are good long-term follow-up results, increasing the interest worldwide in having proton or ion beams more readily available. As a result many new facilities are under construction or being planned and some existing facilities are being upgraded.

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Overview of Proton Therapy in Boston: Initial Clinical and Research Experience at the Northeast Proton Therapy Center (NPTC @ MGH).

J. E. Munzenrider, Massachusetts General Hospital, and Harvard University Medical School, Boston, Massachusetts, 02114, USA

The Northeast Proton Therapy Center (NPTC) was specifically designed for clinical radiotherapy at MGH, and began treating patients in November 2001. This represented continuation of proton radiotherapy in Boston, performed with the 160 MEV beam at the Harvard Cyclotron Laboratory (HCL) between 1961 and April 2002. The clinical utility of the HCL was limited by the energy and fixed horizontal orientation of the beam. In addition, the HCL was relatively remote from the clinical facilities at the Massachusetts General Hospital (MGH). Reported here is the total population treated at the HCL, highlights of those treatments, a description of the NPTC and its first 18 months of operation, and the clinical research program planned for the new facility.

Total HCL population: A total of 9,116 patients were treated at HCL. 3,687 patients received single fraction stereotactic radiosurgery (PBSRS), the only treatment technique employed until 1974, when a fractionated treatment program began. 2,980 uveal (eye) melanoma patients received five proton fractions, and 261 patients with "wet" macular degeneration and patients with choroidal metastases each received 2 fractions. Conventionally fractionated proton treatment, combined with megavoltage photon treatment, was given to 2,188 patients. That category included 786 patients with chordomas and chondrosarcomas of the skull base and cervical spine, 324 with soft tissue (166) and bone (158) sarcomas, 308 with CNS tumors, 243 with prostate cancer, 187 with head and neck cancers, and 340 patients with other tumor types.

Summary of proton treatment results at HCL: The excellent results of PBSRS in small CNS lesions have contributed to the widespread incorporation of that technique into current clinical practice. Local control rates with fractionated proton beam therapy in choroidal melanomas (96% at 10 years) have been confirmed at both PSI in Switzerland and in Nice, France. Local control rates greater than 80% at 4 years in advanced para-nasal sinus carcinomas, and 94% at 10 years have in skull base chondrosarcomas have been achieved. Male skull base chordoma patients enjoy progression-free survival rates of 81% and 65% at 5 and 10 years, respectively. Corresponding rates for females are 65% and 42%, respectively.

Current status of the NPTC: One gantry became operational in November, 2001. Uveal melanoma treatments began on 4/1/2002. The second gantry will become available in June 2003. A stereotactic treatment station and a fixed beam treatment station, both formerly employed at HCL, will be installed and available for treatments in the relatively near future. Through April 30, 2003, a total of 341 patients had been treated at NPTC, including 141 uveal melanomas, 87 chordomas and chondrosarcomas, and 7 medulloblastomas.

New clinical research program for NPTC: Availability of the second gantry in June 2003 will allow expansion of the clinical research program, which now includes protocols for skull base and cervical spine chordomas, and retinoblastomas. Inactive protocols for patients with benign, atypical and malignant meningiomas, and with functioning pituitary adenomas will be reactivated. New protocols will include Phase I studies in medically inoperable and local advanced lung cancer, and in hepatomas. Phase I/II trials are planned for both early and locally advanced prostate cancer. Phase II trials will study paranasal sinus and nasopharyngeal carcinomas and pediatric patients with medulloblastomas and bone and soft tissue sarcomas. A phase III trial of protons versus photons in rectal carcinoma is also planned.

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The University of Texas M.D. Anderson Cancer Center Proton Therapy Facility.

A. Smith[1], W. Newhauser[1], M. Latinkic[1], A. Hay[1], B. McMaken[2], J. Styles[3], J. Cox[1], K. Hiramoto[4], K. Suzuki[4], and N. Nishimura[4], [1]University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA, [2]Sanders Morris Harris, Houston, TX 77002, USA, [3]The Styles Company, Houston, TX 77098, USA, [4]Hitachi, Ltd., Hitachi, Ibaraki 319-122, Japan

The University of Texas M.D. Anderson Cancer Center (MDACC), in partnership with Sanders Morris Harris Inc., a Texas-based investment banking firm, and The Styles Company, a developer and manager of hospitals and healthcare facilities, is building a proton therapy facility near the MDACC main complex at the Texas Medical Center in Houston, Texas USA. Hitachi, Ltd., Japan will supply the major equipment (accelerator, beam lines, gantries, nozzles and treatment couches) for the facility. The MDACC Proton Therapy Center will be a freestanding, investor-owned radiation oncology center offering state-of-the-art proton beam therapy. The facility will have four treatment rooms: three rooms will have rotating, isocentric gantries and the fourth treatment room will have capabilities for both large and small field (e.g. ocular melanoma) treatments using horizontal beam lines. There will be an additional horizontal beam room dedicated to physics research and development, radiation biology research, and outside users who wish to conduct experiments using proton beams. The first two gantries will each be initially equipped with a passive scattering nozzle while the third gantry will have a magnetically swept pencil beam scanning nozzle. The latter will include enhancements to the treatment control system that will allow for the delivery of proton intensity modulation treatments. The proton accelerator will be a 250 MeV zero-gradient synchrotron with a slow extraction system. The facility is expected to open for patient treatments in early 2006. It is anticipated that 675 patients will be treated during the first full year of operation, while full capacity, reached in the fifth year of operation, will be approximately 3,400 patients per year. Treatments will be given up to 2-shifts per day and 6 days per week.

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Developing a National Proton Facility in Australia.

M. Jackson, Royal Price Alfred Hospital, Camperdown, NSW 2050 Australia

Proton therapy is widely regarded as the optimal form of radiotherapy treatment but has proven difficult to introduce in many countries.

The reasons for this include: the assumption that cancer will soon be cured, its high initial cost, perception that IMRT is good enough, lack of support from manufacturers, low status of radiotherapy and radiation oncologists, high cost effectiveness of traditional radiotherapy, the need to import equipment, senior radiation oncologists are exhausted by many years of fighting for resources, excessive desire for uniform resource allocation, reluctance to make ambit claims of benefit, obsession with “evidence based medicine”, and differences between the assessment of pharmaceutical and physical medical interventions.

The question for a small, poor or mean country is whether to wait for more centres in Europe, USA and Japan to treat patients and publish results or to try to solve these problems themselves.

Possible approaches include: encouraging patient groups to want the best treatment, using private finance to reduce or delay the cost to the government, stressing the benefits of raising the profile of radiation oncology, appealing to national pride, potential payments from using the beam for scientific and engineering research, and lobbying by equipment suppliers.

Logical arguments based on dose distribution such as reduced second malignancies and long-term complications, less interaction with chemotherapy and the high integral dose from IMRT seem to have little effect on our colleagues but are better accepted by other specialists and the public.

Other glamorous medical interventions rarely require such extensive justification on the basis of evidence or logic. We need to learn from these successes without compromising the integrity of a truly useful and cost effective advance in cancer management.

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Zibo Proton Therapy Center: Progress Report.

G. Gevers, Ion Beam Applications, Avenue Einstein 9, 1348 Louvain-la-Neuve

The goal of this talk is to give an update of the work that has been accomplished during the last semester on the installation of the First Proton Therapy Center in China (Wan jie Hospital - Zibo city - ROC).

The installation of the Proton Therapy equipment began at the end of last year. Our installation phase was started just after a very fast building construction phase (less than 12 months). The activities carried out during this winter as well as those ongoing and the future goals will be briefly presented.

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The ACCEL Superconducting Cyclotron: A Driver for Proton Therapy.

M. Schillo, ACCEL Instruments GmbH, Germany

A 250 MeV Medical Cyclotron with superconducting coils is being developed at ACCEL, starting from a proposal of the National Superconducting Cyclotron Laboratory (NSCL) [1] and in close cooperation with NSCL and PSI [2]. This accelerator covers especially well all the needs for a proton therapy facility. The first machine is currently under construction for the PSI PROSCAN project and will be delivered in autumn 2003. The second, identical machine is being built for the Rinecker Proton Therapy Center (RPTC) project in Munich, where ACCEL supplies the complete proton therapy equipment for the facility with four gantries and one fixed beam. All gantry nozzles will be equipped with fast scanning beam delivery systems. In combination with the special cyclotron features the whole facility can be considered as IMPT ready.

The essential features of the cyclotron design will be described. The issue of the advantages of a superconducting coil magnet versus the operation of a cryogenic system will be discussed.

References:

[1] H. Blosser et al., Proposal for a Manufacturing Prototype Superconducting Cyclotron for Advanced Cancer Therapy -- MSUCL-874 (1993).

[2] H. Reist, P. Sigg, S. Adam, T. Blumer, J. Duppich, U. Kalt, A. Mezger, E. Pedroni, P.A. Schmelzbach, T. Stammbach and J. Zichy; Specifications for the PSI Medical Accelerator, PSI Technical Note TM-85-01-01, 25. April 2001

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Beam commissioning and development aspects of the MPRI fixed beam line nozzle – interesting aspects about using ridge filters.

N. Schreuder, C. Allgower, J. Olmsted, S. Klein, V. Anferov, M. Ball and B. Starks, Midwest Proton Radiotherapy Institute + Indiana University Cyclotron Facility, 2401 N. Milo B. Sampson Lane, Bloomington, 47408 Indiana, USA

The first phase of beam commissioning and development tests on the MPRI fixed beam line nozzle was completed by the end of March 2003 when the IUCF cyclotrons were shut down for a period of two months. During this shutdown period, a new RFQ injector and the Energy Selection (ES) lines for the second and third treatment rooms, will be installed. Both these treatment rooms will be equipped with rotating gantries supplied by IBA. After the shutdown period the beam and nozzle configuration tests will be repeated prior to commissioning the 12 cm beam for the first patient treatments scheduled for July 2003. The construction of the MPRI outpatient clinic has been completed in January 2003 and the first patients have been admitted to the clinic for medical examinations.

In contrast to the initial plans of using only active beam spreading methods, it was decided to use for the start-up phase, a passive scattering system to spread the beam to a maximum diameter of 12 cm at the isocenter. A classical double scattering system was designed by Bernie Gottschalk and proved to work very well. The use of upstream-located ridge filters in conjunction with the passive scattering system was also investigated. It was, however, concluded that the ridge filters for larger SOBPs (made from Al or Brass) introduced too much scatter in the nozzle and it was not possible to obtain a flat beam at isocenter using a simple passive scattering system. A downstream rotating propeller was therefore introduced successfully to modulate the beam. The design of the IUCF beam lines allows for modifying the beam energy in each of the

ES lines prior to injecting the beam into the treatment rooms. Each treatment room has its own ES line. This means that the beam nozzles must be able to accept any energy between 60 and 206.5 MeV and the passive scattering system must be able to function over a large energy range. Our solution is to use two first scatterers with different scattering but the same energy loss characteristics. In addition to changing the first scatterer we also decided to move the selected first scatterer down the beam axis as a function of decreasing incident energy. This allows for maintaining as required beam spot size on the second (contoured) scatterer. Both first scatterers exhibit the same energy loss to the beam, which obviates the need to adjust the beam range in water definition as a result of changing the first scatterer.

The current nozzle configuration, beam data and interesting aspects observed during the development stages with special reference to the use of ridge filters will also be presented. The effect of moving the first scatter position along the beam axis will also be discussed.

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Pencil Beam Scanning System for Proton Therapy Center – Houston.

K. Matsuda, R. Shinagawa, H. Akiyama, K. Hiramoto, W. Newhauser*, A. Smith*, Hitachi, Ltd. Power & Industrial Systems, 7-2-1, Omika-cho, Hitachi-shi, Ibaraki-ken, 319-1221 Japan, *University of Texas MD Anderson Cancer Center, Houston, TX 77030

A proton beam facility for the Proton Therapy Center - Houston (PTC-H), which offers state-of-the-art proton beam therapy, is under construction. For the facility, Hitachi and M.D. Anderson Cancer Center (MDACC) are developing a pencil beam scanning system. This system has the ability to irradiate a field of 30cm by 40cm laterally and from 4g/cm2 to 30g/cm2 distally. A discrete spot scanning technique is employed for lateral scanning, i.e., the proton beam is switched off before the pencil beam position is changed. This scanning scheme is less sensitive to the fluctuations of the proton beam intensity delivered by the accelerator. The control system and the safety analysis will be simpler for an irregular shaped target. A narrow pencil beam is scanned using two orthogonal scanning magnets. Two parallel plate ionization chambers measure the fluence of the transmitted proton beam. The synchrotron extraction scheme is terminated and the proton beam is switched off by a trigger signal from the ionization chamber unit. A multi-wired ionization chamber located near the patient measures the position and size of each pencil beam. For depth scanning, i.e., to change from one scanning layer to another, the energy of the proton beam supplied by the accelerator system is changed. The proton beam accelerator system, a synchrotron and a beam transport system, has the ability to change the beam energy from pulse to pulse. This pencil beam scanning system will be installed in one of the three rotating gantries in the facility. First treatment with the pencil beam scanning system is scheduled to start on the mid of 2006.

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Prototype of an Objective Patient Positioning System for Precise Radiotherapy Using Phase Measuring Topometry.

St. Kloeck[1] and R.G. Mueller[2,3,4], [1]Kantonspital Muensterlingen, Switzerland, [2,3]Inst. of Med. Phys. and Radiooncology University of Erlangen-Nuremberg, Germany, [4]Lifebeam AG, Erlangen, Germany

INTRODUCTION: Modern technologies in radiotherapy like IMRT and hadrons demand precise patient positioning more than ever. Using phase measuring topometry a system was developed which allows an objective positioning including more than 200.000 3d data points of patient's unmarked surface. This way an objective positioning system has been realized.
METHODS: Using structured light with sinus like intensity distribution and different linear frequency of the pattern it is possible to detect the patients surface in a space of about 50*60*40 cm³ (in width, length, depth). The system, which we call *TOPOS*, needs as hard ware two light sources, to projectors and two detectors (ccd-cameras). Under optimised conditions more than 200.000 surface points of the patient can be acquired in about one second with an accuracy of better than 1mm in all dimensions. We developed a software which allows the technicians quick control and repositioning of the patient inside the treatment room. The very advantage of the system is the fact that it can be used without any harm for personal and patients as well.
RESULTS: The system shows good performance. The optical measured surface points are easily to be matched with CT or MRI surface. Herewith a very realistic relation between surface and internal organs becomes possible. CT data - the basis of each treatment planning in radiotherapy - can be checked with *TOPOS* and in almost every case table tilt of CT becomes

evident. *TOPOS* allows objective patient positioning and storage of data. With the end of the treatment regimen history, average and maximum deviations can be recorded.

DISCUSSION: *TOPOS* turns out to become an universal tool in radiotherapy. Not only passive patient positioning but also the calculation of deviation vectors (min. 6) for active table track are possible. There exist a lot of additional features which can be managed with *TOPOS* as e.g.

- automatic repositioning,
- patient movement control,
- respiratory gating,
- matching, fitting and fusion with CT or MRI
- check and correction of CT or MRI data,
- collision detection including patient's body,
- patient position correction during treatment session
- position verification, recording, reporting, statistics.

CONCLUSION: *TOPOS* improves patient positioning and gives insight in restrictions of the spatial accuracy of CT data for treatment planning. *TOPOS* allows patient positioning, repositioning, and movement tracking inside the treatment room and outdoors. *TOPOS* serves an objective link to the planning CT and realizes objective positioning verification and reporting.

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The Potential of Table Top Lasers for the Production of PET isotopes and in the long term Proton Therapy.

K. W. D. Ledingham, Department of Physics, University of Strathclyde, Glasgow G4 0NG, Scotland

In the last few years high intensity lasers have developed to such a degree that by focussing these on thin targets MeV beams of protons can be generated. These lasers can be made table-top in size and sufficiently intense to generate short lived PET sources. In the longer term proton and heavy ion therapy is another vision. Ultimately the potential for developing these systems as a cheaper and smaller alternative to conventional nuclear technology may be realised.

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On the Characterization of Spread-Out Bragg Peaks and the Definition of 'Depth' and 'Modulation'.

B. Gottschalk,, Harvard High Energy Physics Laboratory, 42 Oxford St., Cambridge, MA 02138, USA

We describe a model-independent analysis of measured spread-out Bragg peak (SOBP) data. The proximal rise, flat top and distal drop of the SOBP are fit with separate polynomials. In addition to the three sets of polynomial coefficients, the breakpoints between segments are parameters of the fit. The intersections of the fitted polynomials provide a robust and precise definition of the corners of the SOBP, even when the proximal corner is quite rounded as occurs with beam gating.

Based on the corners we define d_100, the depth of penetration at full dose, and m_100, the extent in depth or 'modulation' at full dose. The overall procedure also defines the 100% level itself, as well as other quantities useful in quality assurance. These include the entrance dose, the slope of the SOBP, the range-equivalent depth d_80, and the steepness of the distal drop.

In our notation the definitions of depth and modulation most widely used at present are d'_90 and m'_90. The prime means that these definitions rely on a horizontal line drawn at the 90% dose level, rather than one which follows the slope (if any) of the SOBP. We argue that d_100 and m_100 are more convenient definitions and ought to be adopted as standard in charged particle radiation therapy. They are more convenient mathematically, for QA, and for the hardware designer, and are at least as convenient for the treatment planner. To illustrate these points we discuss a retrospective analysis of a large data set from the Northeast Proton Therapy Center (NPTC).

A ZIP file which may be downloaded from http://huhepl.harvard.edu/~gottschalk/ contains a complete article in PDF format, a DOS executable fitting program, program instructions, source code, and two test cases.

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Range verification.

R. Slopsema, Ion Beam Applications s.a., Avenue Einstein, 9, 1348 Louvain-la-Neuve in collaboration with H. Kooy, NPTC, MGH

In proton therapy, it is of the utmost importance to accurately control the beam energy and hence the proton range in a patient.

For this purpose, the IBA system is equipped with a device that allows a real-time measurement of the proton energy. This device monitors the proton energy throughout the whole irradiation and can pause the treatment in the instance of discrepancy between the expected and the measured range in patient.

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Range Compensator Design Based on RPL Depth Smearing.

J. Wolfgang, Northeast Proton Therapy Center, Massachusetts General Hospital 50 Fruit St., Boston, MA 02114

Range compensator design algorithms, such as the one employed in the CMS/FOCUS treatment planning suite, are based on radiological path length (RPL) ray traces extending from the source to the distal edge of the target volume. As has been noted in other efforts in this area (1), this method often results in an under dosing of the distal volume of the target as RPL methods do not account for extreme depth and density gradients at the distal target surface. Our algorithm corrects under dosed points generated by the RPL compensator by calculating the RPL to the distal target depth z of the under dosed point and then smearing this RPL value at constant depth z to nearby compensator elements within a radius proportional to the beam sigma at the under dosed point. This smearing is accomplished by removing compensator material from the nearby elements, thereby shifting the distal edge of the spread out Bragg peak from beam passing through these elements to the same physical depth z as the under dosed point. Comparing this approach to the simple RPL generated compensator, we have seen an improvement in the target dose coverage, increasing the minimum dose from 65% of the mean target dose to over 85% for some cases.

References: (1) P. Petti, Phys. Med. Biol. 42 (1997) 1289-1300

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The impact of respiratory motion on proton dose distributions.

E. Rietzel[1,2], J. Adams[1], T. Harris[1], C. Willett[1], N. Choi[1], and G. Chen[1], [1]Massachusetts General Hospital, Boston, USA, [2]Gesellschaft für Schwerionenforschung, Darmstadt, Germany

At Massachusetts General Hospital we started the acquisition of time resolved CT-data last year. For each patient typically 5-10 complete volumetric CT-data sets over a respiratory cycle are obtained. At each couch position data are acquired in cine mode for approximately the duration of the patient's breathing cycle. About 10-15 images per couch position are reconstructed, equally distributed over the acquisition time. This results in typically 1000-1500 images per patient. Correlated to the CT-data acquisition the motion of the patient's abdominal surface is recorded. Based on the surface motion the reconstructed slices are resorted into different volumes, each representing a specific phase of the patient's breathing cycle.

Based on the 4DCT-data changes in radiological path length due to the respiratory motion can be calculated for each patient. We have started to study the impact of respiratory organ motion on proton dose distributions. The perturbations of dose distributions as well as the changes of DVHs during the patients' breathing cycles are analyzed. The 4D dose distributions can not yet be summarized. For adding the doses the voxel correspondence between the different phases of the breathing cycle are needed (works in progress). At the PTCOG meeting case studies of 4D proton dose distributions as well as DVHs for different breathing phases will be presented.

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A Pencil Beam Scanning system in a Double Scattering Nozzle.

C. Brusasco, and D. Prieels, Ion Beam Applications, Chemin du Cyclotron 3, 1348 Louvain-la-Neuve, Belgium

Pencil beam scanning is in vogue today and is probably the most advanced technology in radiotherapy. On the other hand, this dynamic beam delivery system raised several new questions upon safety when compared to the well-known and largely used double scattering technique.

These questions are particularly relevant when choosing options for a new Proton Therapy Center. In order to face this situation, IBA will be proposing a single nozzle that can deliver treatments in both double scattering and pencil beam scanning mode during the same treatment day.

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New insights into radiation damage by charged-particles using microbeams.

M. Folkard, K. Prise, G. Schettino, C. Shao, N. Zyuzikova, S. Gilchrist, O. Belyakov*, B. Vojnovic, and B. Michael, Gray Cancer Institute, PO Box 100, Mount Vernon Hospital, Northwood, HA6 2JR UK, *RAREF, Univ. Columbia, New York, USA.

The Gray Cancer Institute has been involved in the development and application of microbeams of ionizing radiation in a radiobiological context since the early 1990's. The strength of the micro-irradiation technique lies in its ability to deliver precise doses of radiation to selected individual cells (or sub-cellular targets) *in vitro*. Our microbeam uses a 1μm diameter bore glass capillary to vertically collimate protons, or helium ions accelerated by a 4MV Van de Graaff. Using $^{3}He^{2+}$ ions, 99% of cells are targeted with an accuracy of ±2μm, and with a particle counting accuracy >99%. Using automated cell finding and irradiation procedures, up to 10,000 cells per hour can be individually irradiated. The facility is being used to study a range on 'non-targeted effects' such as the bystander effect, intracellular signalling, adaptive responses and genomic instability. Bystander studies using low energy particles show that up to 7% of the cells on a dish are damaged, even though only one cell on the dish is targeted with just a few particles. This occurs irrespective of whether the nucleus or cytoplasm is targeted. Most recently, fluorescent antibody staining (using markers such as H2AX) techniques have been used to highlight regions of DNA damage within individual cells.

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Specification of beam parameters for intensity-modulated proton therapy

A. Trofimov, T. Bortfeld, J. Flanz, H. Kooy, and K. Jokivarsi, Massachusetts General Hospital, Northeast Proton Therapy Center, 30 Fruit St, Boston, MA 02114, USA

Purpose: To find the most useful beam parameters for intensity-modulated proton therapy (IMPT). Among the many relevant parameters we will focus on (i) the size of the initial proton pencil beam, (ii) the dynamic range of the intensity modulation, and (iii) the speed of the scanning.
Methods: For our studies we used the KonRad-pro inverse planning system developed at the German Cancer Research Center that is under further development at NPTC. First we compared IMPT plans for different initial pencil beam sizes. The comparisons were done for various paraspinal and head&neck cases using pencil beam sizes of 3, 5, and 8 mm. Ideally, the pencil beam width should be dominated by the multiple Coulomb scattering (MCS) in the patient. Because the standard deviation (sigma) of the beam resulting from MCS is in the order of 2% of the range, we guessed that the initial beam sigma should be less than that, i.e. less than 3 mm for a range of 15 cm. To spare critical structures proximal to the target volume, where the MCS is smaller, the width of the initial pencil beam should be even smaller. For the dynamic range study (ii) we compared IMPT plans with continuous intensity modulation and those stratified into a number of discrete levels (10 to 100). Finally, for the study of the scanning speed we simulated the interplay effect between respiratory motion and scanning, and looked at the averaged total dose after 30 fractions, as well as at the variation around the average.
Results: (i) For the cases under considerations, we saw significant improvements by reducing the pencil beam size from 8 to 5 mm. Only minor improvements were found by a further reduction to 3 mm. As for the dynamic range (ii), 30-50 intensity levels gave near optimum results in all cases. The simulation of the scanning speed (iii) revealed resonance effects

(maximum variation) at scan times per intensity layer in the order of 10 s, which were much reduced at scan times of 1s. Multiple (3 times) paintings of the same intensity layer delivered at evenly spaced intervals over the breathing period resulted in a reduction of the variation far above the statistical effect (square root of 3).
Conclusions: Our simulations using different parameter settings showed that for clinical cases it is not generally necessary to push the parameters to their physical limits. Beam sizes of 5 mm (sigma), dynamic ranges of 30-50, and scan times per layer of 1s seem to produce dose distributions that are sufficiently close to the theoretical optimum.

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Proton dose calculations in heterogeneous media: Effects on IMPT treatment planning.

H. Szymanowski, S. Nill and U. Oelfke, German Cancer Research Center (DKFZ), Dept. of Medical Physics, Heidelberg, Germany

For the planning of intensity modulated proton therapy treatments, the dose calculation engine plays a crucial role not only in the assessment of the treatment plan quality but also in the determination of the optimised particle fluence. An important issue is thereby the accurate prediction of the dose while irradiating complex inhomogeneous patient regions.

Most of dose calculation algorithms currently used in clinics are based on the standard (1D) pathlength scaling applied along the central axis of the pencil beam. Only the energy loss due to the material traversed is considered, but neither the depth nor the scattering properties of the inhomogeneities are taken into account. An improved proton dose calculation algorithm based on a two-dimensional scaling of proton pencil beams in water has therefore been developed and validated. It has been shown with Monte-Carlo simulations that the accuracy of proton scattering predictions in various media at various positions can be significantly improved by an additional scaling of the lateral proton pencil beam fluence. In order to integrate the improved dose algorithm into a CT based treatment planning system, a calibration curve relating the lateral scaling factors to the CT Hounsfield numbers has been introduced using a stoechiometric method, additionally to the standard stopping powers to Hounsfield numbers calibration.

The new dose calculation algorithm together with its CT calibration curves has been integrated into the inverse treatment planning system KonRad. The effects of the dose calculation method on IMPT treatment planning were investigated for patient cases with inhomogeneities such as lungs, air cavities and bony structures. Each IMPT plan was determined twice, using the (1D) and the (2D) pencil beam scaling methods, resulting into (1D)- and (2D)-optimised fluence matrices. The final dose distributions based on these optimised fluence matrices were computed with the (1D) and the (2D) proton pencil beam scaling methods. For the (1D)-optimised fluence matrices, severe differences were observed between the final dose distributions computed with both scaling methods, e.g. for the irradiation of a 60 cm^3 target volume located in lung by five intensity modulated proton beams, the respective dose distributions showed significant deviations in the order of 10%.

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A simplified RBE model and its application in planning studies for protons.

J. J. Wilkens and U. Oelfke, DKFZ, Dept. of Medical Physics, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany, e-mail: j.wilkens@dkfz.de, u.oelfke@dkfz.de

While a constant RBE is used at most operating proton facilities, the clinical impact of a variable RBE in proton therapy is still under investigation. For theses studies, a fast and easy method for RBE calculations in treatment planning would be useful. It would allow extensive investigations into the potential effects of a variable RBE, e.g. in inverse treatment planning. We therefore propose a simplified RBE model for this purpose, which describes the RBE as a function of dose, linear energy transfer (LET) and phenomenological tissue parameters.

In the framework of the linear-quadratic model, one can easily derive a dose-dependent expression for the RBE from dose-effect curves for x-rays and protons, which are each described by the parameters alpha and beta. For protons, these parameters obviously depend on the local energy spectrum or radiation quality. Inspired by experimental results of cell survival measurements, we assume that the alpha parameter for protons is a linear function of the dose-averaged LET (as long as the LET does not exceed a certain limit, beyond which alpha would decrease), while beta is independent of LET.

Together with a recently developed model for the LET in therapeutic proton beams, this yields a simple algorithm for the calculation of a variable RBE.

The LET and RBE models were applied to a variety of treatment situations. Calculated RBE distributions for single Bragg peaks as well as for spread-out Bragg peaks (SOBP) agreed qualitatively with experimental results and previous studies. The model was employed to investigate RBE effects for various values of the tissue parameters, e.g. to estimate the shift of the distal edge in a SOBP, which is important for determining safety margins to organs at risk. For a typical SOBP for the treatment of ocular tumours (70 MeV, 15 Gy per fraction), this shift was observed to be up to 1 mm in depth. It was further possible to integrate the RBE model into an objective function for the optimization of SOBP's. With this approach, the relative weights of the single Bragg peaks could be easily optimized to yield a homogeneous biological effect in the SOBP instead of a homogeneous physical dose.

Although the proposed model consists only of a few simple formulas, it reproduces the basic dependencies of RBE on dose and LET observed by 'in vitro' experiments. This makes it a fast tool for investigating the effects of a variable RBE in planning studies and in the optimization of SOBP's. The simplified model has also potential applications in inverse treatment planning for deep seated tumours in intensity modulated proton therapy.

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Web-Based Peer Review of Radiotherapy Treatment Planning Data.

J. R. Palta and V. A. Frouhar, Department of Radiation Oncology, University of Florida, Gainesville, FL, and USA.

Purpose/Objective: Advances in imaging have enhanced our ability to create a complete anatomical and functional 3D model of each patient, which facilitates the use of advanced-technology radiation-therapy delivery tools. It also makes it possible to highly conform dose distributions to the target volumes while sparing the surrounding critical structures. Therefore, the task of safely implementing these advances for patient treatments in radiation therapy around the world will require innovative and efficient methodologies of clinical quality assurance. It requires an electronic infrastructure that will allows the transmission of voluminous multimodality clinical data for rapid review, archiving and data mining, while maintaining patient confidentiality.

Materials/Methods: The Resource Center for Emerging Technologies (RCET) at the University of Florida has designed and developed an infrastructure for a distributed database, visualization and analysis system for collecting, sharing and distributing information for remote peer review of advanced technology imaging, radiotherapy plan data, and demographics information. The system is a four-tier web-based system, which provides a secure auto-anonymizing and auto-archiving of clinical data. The system supports DICOM-RT and RTOG clinical data formats. It can also import any electronic image. A suite of PC based application software, NetSys and WebSys, provide facilities for clinical data preparation and submission as well as tools for automatic data retrieval, modification and resubmission. The visualization tools are designed specifically for radiotherapy applications, which provide multi-view, 3D, DRR and Portal images with editing capabilities available in advanced treatment planning systems.

Results: The NetSys software assists participating institutions in collecting, visualizing, and submitting clinical data objects to the RCET database. It anonymizes the data before it is transmitted. It automatically creates an electronic folder of all submitted data that may consist of textual information, multiple image sets, and treatment planning information for each submitted case. The RCET system has proven to be of practical use in remote peer review. It has enabled radiation oncologists to get an expert opinion on almost real time basis.

Conclusion: The picture archiving and radiotherapy archiving system designed at UF will enable the PTCOG member institutions to organize, submit, review and share large amount of clinical data. The web-based secure private network infrastructure provides an opportunity for real time peer review.

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CASIM project: the evolution of a project.

J. Shaw (CCO), C. Hall (CLRC, Daresbury) and A. Kacperek, (Cyclotron, CCO)

:Key milestones for the Sirius part of CASIM

SIRIUS for nuclear physics and isotope production, proposal published.	January 1999
Byers announcement that Diamond would be at RAL	13th March 2000
The North West Science Review (NWSR) (a.k.a. the Smith committee) called into being. Its remit to 'exploit Manchester's health corridor' and Daresbury's strength in instrumentation. £25 M committed to fund the implementation of the committee's recommendations. Additionally £25 m pledsged for biotechnology core facilities.	13th March 2000
Interdisciplinary Accelerator Centre (IAC) proposed at DL- start of what was to become CASIM	June 2000
NWSR issues call for bids for the £25 M. Byers announces a North West Science and Daresbury Development Group (NWDDG). Its remit to make a proposal of how Daresbury fits in the NW scientific and industrial development. Due to report to Byers by end of December 2000.	9th June 2000
Manchester consortium bid: Institute for Functional and Molecular Imaging - aimed at the NWSR.	
Deadline for NWSR bids reached.	1st August 2000
NWSR announces results of bid: £26 M for the North West. Main CASIM bid passed on to the North West Science and Daresbury Development Group. IFMI, which included the Daresbury medical imaging, awarded £5.7 M. Daresbury's part was £1.5 M for x-ray imaging and PET instrumentation.	16th October 2000
NWSDDG (Smith committee) report to Byers.	March 2001
Byers announce £150 M for CASIM. £100 M for Sirius, £50 M for 4GLS. Maggie Pearson asked to head up the proton cyclotron side.	March 2001
'This is CASIM' Meeting. Plus breakout meetings afterwards.	25th April 2001
CASIM bid - draft version issued.	July 2001
PTCOG in Boston attended by CASIM members.	11-13th June 2001
CASIM Medical Applications Technical Group set up various workshops Neurology, Oncology, Radioisotopes and Proton Therapy.	August, 2001
Proton therapy workshop, International CASIM Proton Therapy Consensus Meeting. Manchester Science Museum.	3-4th September 2001
Sirius part of CASIM passed to NHS for review. NHS ask NCRI for report on proton therapy in the UK. All goes quiet.	Sometime in 2002
Official announcement that Sirius would not be funded	March 2003
4GLS science case accepted	December 2001
4GLS gateway 1 passed (business case)	November 2002
4GLS funded for prototype.	April 2003

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Proton radiotherapy – potential areas for clinical research.

R.E. Taylor, Cookridge Hospital, Leeds, UK. LS16 6QB

Radiotherapy (RT) plays an important role in the management of children with cancer. The aim is to achieve local tumour control while minimising long-term effects. Proton RT has an established role in the treatment of children with chordomas and chondrosarcomas of the skull base. However experience is still relatively limited, and the knowledge base will benefit from additional clinical studies. Following treatment of CNS tumours the most important long-term effects are neuropsychological. Proton RT may have a role in the treatment of children with tumours requiring involved field RT, e.g. low-grade glioma, by achieving homogeneous irradiation of the target volume and minimising dose to the surrounding brain. Planning studies comparing proton RT with conformal RT techniques would need to include analyses of whole brain DVHs, with calculation of NTCP, and radiation doses to OARs – eyes, inner ears, pituitary, hypothalamus, and optic chiasm.

For children with medulloblastoma the role of proton RT for the posterior fossa boost could be assessed. Also proton RT for the spinal component of craniospinal RT may have potential for homogeneous irradiation of the spinal axis, while sparing structures anterior to the spine, such as the heart. For non-CNS tumours orthopaedic long-term effects may compromise function or be cosmetically harmful. Proton RT has the potential for homogeneous irradiation of the target volume while reducing the magnitude and/or extent of the 'low dose bath' area outside the target volume, which may be clinically relevant for long-term effects. The role of proton RT could be explored for children with tumours adjacent to critical structures, such as paraspinal tumours. Some children with retinoblastoma require 'lens sparing' or orbital RT. Long-term effects of irradiating the orbit include enophthalmos, dry eye and cataract and potentially distressing orbital hypoplasia. The use of a precisely collimated single proton beam may have the potential for reducing irradiation of orbital structures surrounding the target volume.

For over 25 years research into the management of children's cancer has been coordinated by the United Kingdom Children's Cancer Study Group (UKCCSG). The establishment of a proton therapy research programme in collaboration with the UKCCSG would significantly enhance the international status of UK paediatric oncology research.

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Case Report: Proton Craniospinal Irradiation For Pediatric Medulloblastoma.

L. Yonemoto, Loma Linda University Medical Center, Loma Linda, CA

Purpose: Radiation therapy for the treatment of medulloblastoma significant toxicity to the cochlea, vertebral bodies, thorax, abdomen, and pelvis and negatively impact on the child's quality of life. We report the first two patients receiving craniospinal (CSI) with proton radiation therapy

Method and Materials: Two 3-year-old children with stage M3 medulloblastoma were treated with CSI using a proton beam. Proton therapy eliminates the exit dose in the thorax, abdomen, and pelvis, and significantly reduces the dose to the cochlea and vertebral bodies. Patients received 36 Gy to the craniospinal axis, followed by an 18 Gy boost to the posterior fossa. The cranium was treated with a right and left anterior oblique field and an AP patch field to the cribriform plate. The posterior fossa was treated with one field daily alternating between the PA, right posterior oblique, and left posterior oblique fields. In each case, the range was adjusted to stop the beam just proximal to the cochlea. The spinal axis was treated with 3 matching PA fields; the beam was halted at the posterior third of the vertebral body. The matchline was shifted weekly. An isocentric gantry permitted treatment of the entire craniospinal axis with a single patient set-up. Diagnostic x-ray generators permitted pre-port, diagnostic-quality x-ray films for patient alignment and field matching.

Results: CSI delivered via a conformal proton beam eliminated exit dose into the thorax, abdomen and pelvis, and reduced the dose to the cochlea and vertebral bodies. The daily treatment set-up, with general anesthesia and pre-porting, was readily reproducible and verifiable. Chemotherapy was administered concurrently and resulted in no significant reduction in blood counts. Treatment was tolerated well. Acute side effects were minimal, consisting of mild nausea, decreased appetite, and alopecia. Both patients completed therapy without difficulty.

Conclusion: Proton CSI of medulloblastoma in children was well tolerated and is a reproducible technique. Both patients were treated with significant reduction of dose to many normal tissue structures that can impact the child's quality of life. Further follow-up is necessary to determine the long-term benefit.

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Treatment of Medulloblastoma with Spread-Out Bragg Peak (SOBP) Treatment Fields.

H. M. Kooy, J. A. Adams, S. Rosenthal, S. Michaud, J. Flanz, S. Bradley, and N. Tarbell, Northeast Proton Therapy Center, Massachusetts General Hospital and Dept. of Radiation Oncology, Harvard Medical School, Boston MA 02114

We present our techniques for planning and delivering the full-course treatment for medulloblastoma including the full cranial and spinal axis irradiation fields and the posterior fossa boost. The clinical objectives are to treat the full cranial and spinal axis volumes, comprising all volumes containing spinal fluid, to 23.4 or 36 CGE (depending on clinical stage) to control potential seeding from the original tumor volume and to treat the posterior fossa, the site of the original tumor volume, to a total of 54.0 CGE.

Conventional treatment with photons irradiates significant non-involved tissue volumes, such as internal organs, and internal cranial structures, such as the auditory system. The excessive exposure to these non-involved areas, from photon exit dose, often complicates the delivery of concurrent chemotherapy. The use of protons significantly reduces, often to subclinical levels, the dose to these volumes. We present details of our treatment planning for medulloblastoma, with specific emphasis on the problem of matching field edges given the multiple fields required to treat all target volumes. The treatment delivery technique is an excellent demonstration of our ability to precisely position and verify the patient alignment using the isocentric features of our gantry and patient positioning device.

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Molecular Pathology of Gliomas : Its impact on therapy?

C. Walker, Clatterbridge Cancer Research Trust, Clatterbridge Hospital, Bebington, Wirral CH63 4JY

Although gliomas are generally considered radioresistant, some tumours do respond well to radiotherapy, but currently there are no clinical means to predict radiosensitivity. As in other cancers, biological factors from host and tumour components, such as angiogenesis and the ability of tumour cells to undergo apoptosis, are thought to contribute to responsiveness. With the recognition that anaplastic oligodendrogliomas are likely to respond to chemotherapy, histopathological diagnosis plays an important role in the clinical management of glioma patients. However, gliomas are frequently histologically heterogneous and their diagnosis is notoriously difficult and subject to inter-observer variability. Revised WHO criteria and changing diagnostic trends have resulted in oligodendroglial neoplasms, previously diagnosed in approximately 4% of gliomas, now being reported in up to 33% of these tumours. In consequence, it is not clear from previous clinical studies whether the glioma histological subtype influences response to radiotherapy.

Recent research has suggested that gliomas may be subdivided according to the genetic alterations that they possess, but that this classification may differ from the pathological classification. Oligodendrogliomas are likely to have loss of heterozygosity of chromosomes 1p and 19q, while astrocytomas are more likely to have loss of chromosome 17p and mutation in p53. Investigations of histologically heterogeneous gliomas have shown that gliomas are in general more homogeneous in their genotype than their phenotype. The molecular classification is likely to play an important role in future clinical management. For example, loss of 1p/19q may be predictive of chemosensitivity, while loss of chromosome 10 may be a marker for poor prognosis in high-grade gliomas.

To elucidate the complex parameters that influence the therapeutic response of gliomas, in Liverpool, we are adopting a multidisciplinary approach in prospective studies of gliomas undergoing defined chemotherapeutic or radiotherapeutic protocols. Comparisons are being made of the histopathology, molecular pathology and biology of these tumours from *in vivo* imaging studies and laboratory investigations of gene expression patterns. These factors are being compared with the radiological response to therapy and clinical outcome.

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A Treatment Option for Glioblastoma Multiforme.

U. Linz, Forschungszentrum Jülich, Germany

For decades, the treatment of glioblastomas (GBM) has been among the most challenging fields in oncology. Heterogeneity of the tumors, their infiltrating growth, high sensitivity and low regeneration capacity of the surrounding brain tissue or the selective permeability of the blood-brain barrier are some of the factors which determine the therapeutic difficulties. The standard treatment consisting of surgery, radiotherapy and often chemotherapy has not led to a significant improvement in survival during the last thirty years.

An analysis of more than 200 treatment protocols for GBMs including unusual fractionation schemes, brachytherapy, intraoperative irradiation, application of neutrons or BNCT, a plethora of chemotherapeutics, gene and immunotherapy concepts has led to a new proposal with carbon-based ion beam therapy as central element. The multimodality regimen comprises surgery and adjuvant therapy, as well. However, in contrast to conventional treatments the algorithm is changed.

Based on radiobiological and pharmacological reasoning the concept envisions an initial chemosensitivity assay and in case of lacking resistance a chemotherapy step with a BBB permeable drug. Ion beam therapy and a cytoreductive surgical step are to follow. Efficiency should further be increased by reducing the overall treatment time.

It is expected that the suggested treatment scheme is safe, that it will yield survival rates which match at least the best results obtained so far and it is hoped that it can achieve all this with less reoperations and a good quality of life of the patients.

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Carbon Ion Radiotherapy for Malignant Gliomas.

J. Mizoe and H. Tsujii, Hospital, Charged Particle Research Center, NIRS, Chiba, JAPAN

Purpose: To investigate the preliminary results of combined therapy with X-ray, chemotherapy and carbon ions for malignant gliomas.

Methods and Materials: From October 1994 to February 2002, 48 patients with histologically confirmed malignant gliomas (16 anaplastic astrocytoma and 32 glioblastoma multiforme) were enrolled into phase I/II clinical study of carbon ion radiotherapy. Their age ranged from 18 to 78 and, mean age of 53 years. By gender, they comprised 29 male and 19 female patients. Locations of disease were 20 frontal lobe, 10 temporal lobe and so on. Twenty-seven patients underwent partial resection, 8 subtotal and 8 macroscopic total resections prior to radiotherapy.

Treatment involved the application of 50 GyE/25 fractions/5 weeks of X-ray followed by carbon ion radiotherapy of 8 fractions/2 weeks. ACNU of 100 mg/m2 were administrated in 1st and 4^{th} or 5^{th} week of X-ray therapy. Carbon ions dose was escalated from 16.8 to 24.8 GyE by 10 % incremental steps after confirmation of the safety of each dose given previously.

Results: There were 9 cases with grade 2 acute skin reaction but there was nor grade 3 or higher-grade tissue reaction. The late reactions included, 2 cases of grade 2 brain reaction (RTOG) and 3 cases of grade 2 brain reaction (LENT/SOMA, MRI) out of 48 cases. There was no grade 3 or higher-grade reactions until the date of analysis.

Median progression free survival (m-PFS) of AA was 31 months and that of GBM 7 months. Mean survival time (MST) of AA was 35 months and that of GBM was months. In AA patients, MST was 20 months for the low dose group (16.8 ~ 20.0 GyE, 6 patients) and not reached (NR) for the high dose group (22.4 ~ 24.8 GyE, 10 patients). MST of GBM patients were 7 months for the low dose group (16.8 GyE, 7 patients), 18 months for the middle dose group (18.4 ~ 22.4 GyE, 23 patients) and NR for the high dose group (24.8 GyE, 5 patients).

Conclusion: Preliminary results of combined therapy of X-ray, ACNU and carbon ions show the clinical utility of carbon ion radiotherapy for malignant gliomas because of the increased control and survival rate according to the carbon ion doses. These results delivered to a new protocol for malignant gliomas treated only with carbon ion radiotherapy from April 2002.

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Spinal Cord Tolerance to High Dose Fractionated 3D Conformal Proton-photon Irradiation as Evaluated by Equivalent Uniform Dose and Dose Volume Histogram Analysis.

L. Marucci, A. Niemierko, N. J. Liebsch, F. Aboubaker, M. C. C. Liu, and J. E. Munzenrider, Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA.

Purpose: to evaluate cervical spinal cord tolerance using equivalent uniform dose (EUD) and dose volume histogram (DVH) analysis in patients treated with high dose 3D conformal fractionated proton-photon therapy for chordoma and chondrosarcoma of the cervical spine and cervico-occipital junction.

Patients and methods: 3D dose distributions were available in 85 patients who received high dose 3D conformal fractionated proton-photon treatment between November, 1982 and May, 2000. Median and mean patient ages were 49 and 44.6 years, respectively (range 3-74 years). Nine patients were $\leq$ 18 years of age. Specific patient characteristics were tabulated for all patients, including age, history of smoking, diabetes and/or hypertension, and previous surgeries. Median and mean follow-up was 45 and 41.3 months, respectively (range 2-117 months). Median and mean prescribed doses were 75.7 and 76.3 CGE (CGE = proton Gy X RBE 1.1), respectively (range 68.6-83.5 CGE). Dose to the center and the surface of the cervical spinal cord was constrained to be $\leq$ 55 and $\leq$ 67 CGE, respectively, in 72 patients. In 13 patients randomized to receive a prescribed dose of 82.9 CGE, cord center and surface constraint doses were $\leq$ 58 and $\leq$ 70 CGE, respectively. EUD, the uniform dose biologically equivalent to the non-uniform dose actually delivered, multiple cord dose parameters and dose-volume-histograms were calculated for each patient. Specific cord parameters studied included cord length and volume treated, and maximum, mean, and minimum doses to the cord center and surface. Spinal cord toxicity was graded using the EORTC/RTOG Late Effects scoring system.

Results: Thirteen patients experienced Grade 1-2 toxicity, which did not further progress. Four patients had Grade 3 toxicity, including 2 of the 13 patients treated with the higher cord dose constraints. Median and mean times to onset of cord toxicity were 5.6 and 11.3 months, respectively (range 2.5-49.2 months). For the total population, the actuarial probability of surviving free of any cord toxicity, and of surviving without Grade 3 cord toxicity was 0.78 ± 0.05 and 0.94 ± 0.03 at 5 years, respectively. For patients treated with the lower and the higher cord dose constraints, actuarial probability of surviving without any cord toxicity was 0.80 ± 0.05 and 0.63 ± 0.16 at 5 years, respectively ($p=0.31$ on log rank test). Total dose and proton dose to the cord surface and center did not differ significantly between the 68 patients without toxicity and the 17 patients with toxicity. There was also no difference in the two groups in either the volume or the length of the cord treated. Mean EUD was 54.4 CGE in the first group and 54.7 CGE in the second. By Cox proportional hazards and by logistic regression analysis, the only factor that significantly impacted the probability of cord toxicity was the number of surgeries the patients had undergone before radiation therapy ($p= 0.021$). Specifically, cord complications developed in 9 of 25 patients (36%) with 3 or 4 surgeries, and 8/60 patients (13.3%) with 1 or 2 surgeries. There were no statistically significant differences between the two groups in the other parameters examined.

Discussion and conclusion: Using conformal 3D proton techniques, prescribed doses ranging from 68.6 to 83.5 CGE were delivered to tumors abutting or compressing the cervical spinal cord, while constraining the dose to the cord center and cord surface to 55-58 CGE and 67–70 CGE, respectively. Actuarial probability of surviving without Grade 3 toxicity at 5 years was 0.94 ± 0.03 for the total group. The only factor significantly impacting toxicity was the number of surgeries before radiation, suggesting that the integrity of the normal musculo-skeletal supportive tissues and vascular supply may be more important factors than the radiation dose itself. These data also suggest that the cervical spinal cord dose constraints used in treating these patients with 3D conformal proton-photon radiation therapy are appropriate.

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Parameters of dosimetry are prognostic factors of local control for chordoma and chondrosarcoma of the base of the skull and the cervical spine treated by a 3D conformal irradiation with a combination of photons and protons.

L. Feuvret[1], G. Noël[1], J.-L. Habrand[2], C. Haie-Méder[2], H. Mammar[3], D. Pontvert[3], D. Hasboun[4], R. Ferrand[1], G. Boisserie[4], A. Beaudré[2], G. Gaboriaud[3], J.-J. Mazeron[1,4], [1]Centre de Protonthérapie d'Orsay. BP 65, 91402 Orsay Cedex, France, [2]Institut Gustave Roussy, 39, rue Camille Desmoulins, 94805 Villejuif Cedex, France, [3]Institut Curie, 5, rue d'Ulm, 75005 Paris, France, [4]Pitié Salpêtrière Hospital, AP-HP, 49-83, Bd de l'hôpital, 75651 Paris Cedex 13, France

Background: prospective analysis of local tumour control and survival in 90 consecutive patients treated with fractionated photon and proton radiation for a chordoma or a chondrosarcoma of the base of the skull and the cervical spine.
Material, Methods and Patients: between December 1995 and December 2000, 90 patients with a median age of 51.3 years (10-85), were treated using the 201 MeV proton beam of the Centre de Protonthérapie d'Orsay (CPO). There were 38 females and 52 males. There were 64 chordomas and 26 chondrosarcomas. Irradiation combined high-energy photons and protons. Photons represented 2/3 of the total dose and protons 1/3. The median total dose delivered within gross tumour volume was 67 Cobalt Gray Equivalent (CGE) (range : 22-70).
Results: With a median follow-up of 33 months (3-74), 25 tumours failed locally. The 3-year local control rates are for chordomas and chondrosarcomas 60% and 91%, respectively.
On univariate analysis, prognostic factor of local control were age ($p = 0.018$), pathology subtype ($p = 0.048$), minimal dose delivered in GTV ($p = 0.014$), % of GTV receiving 90% of the total prescribed dose ($p = 0.02$), % of GTV receiving 95% of the total prescribed dose ($p = 0.003$) and GTV out of the 95% isodose line ($p = 0.006$).
On multivariate analysis, independent prognostic factors of local control were % GTV receiving 95% of the prescribed dose (RR : 3.8, CI95% [1.2-11.6], $p = 0.017$), minimal delivered dose (RR : 2.9, CI95% [1.2-6.9], $p = 0.015$).
Conclusion: In base of the skull and cervical spine chordomas and chondrosarcomas treated by a 3D conformal irradiation with photons and protons, dosimetric parameters are main prognostic factors of local control.

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Optimal PTV margin for proton therapy of prostate cancer: Analysis of interfraction motion and patient position-related motion.

T. Ogino, K. Nihei, S. Ishikura, and M. Kawashima, Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Purpose: To define the optimal margin for proton therapy of prostate cancer by analyzing interfraction motion (IFM) and patient position-related motion (PRM).
Material and methods: Thirteen patients with localized prostate cancer treated by combination of photon/proton therapy were included in this study. Radiotherapy consisted of 50 Gy/25 fx photon beam followed by proton boost of 26 GyE/13 fx. All patients were instructed to urinate and drink half a liter of water 30 minutes before each treatment and to have a regular bowel movement. For patient immobilization, both legs were fixed by vacuum cushion in supine position.
Method 1) Analysis of IFM; all patients underwent pelvic CT sans 3 times during the course of radiotherapy. Contours of prostate and the pelvic bone were delineated on RTP system and the center of prostate (CoP) relative to a bony landmark was defined. The differences of CoPs were measured 3-dimensionally between the CT scans.
Method 2) Analysis of PRM; before each proton therapy, 3-dimensional positioning verification was performed using image subtraction method with digital radiography. We presented the detail of this technique elsewhere. Three-dimensional patient-setup deviation was measured in 169 treatments of 13 patients from the couch movement to correct the misalignment.
Results: The IFMs were -0.49 +/- 2.18 mm (Mean +/- 2SD) in right-left (RL), 1.04 +/- 6.42 mm in cranio-caudal (CC), and 0.88 +/- 4.18 mm in antero-posterior direction (AP). The recommended PTV margin for IFM was 3 mm in RL, 8 mm in CC, and 6 mm in AP. Conventional patient-setup produced the PRMs of 1.93 +/- 4.44 mm (Mean +/- 2SD) in RL, 0.97 +/- 2.58 mm in CC, and 1.51 +/- 4.26 mm in AP. The PTV margin combining both IFM and PRM needed at least 9 mm in RL, 11 mm in CC and AP.
Conclusions: The PTV margin for proton therapy of prostate cancer may be reduced by daily positioning verification with our technique, but we should not miss the target by underestimating the IFM.

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Proton Radiation Therapy of Prostate Cancer: Ten -year Results from Loma Linda University Medical Center.

C. J. Rossi Jr (et al.), Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, California, U.S.A.

Purpose: We analyzed results of conformal proton radiation therapy for localized prostate cancer, with emphasis on biochemical freedom from relapse (bNED).
Methods and Materials: Analyses were performed for 1,255 patients treated between October 1991 and December 1997. Outcomes were measured on primarily in terms of biochemical relapse.
Results: The overall ten-year biochemical disease-free survival rate was 73%, and was 90% in patients with initial PSA $\leq$4.0; it was 87% in patients with post-treatment PSA nadirs $\leq$ 0.50. Rates dropped with rises in initial and nadir PSA values. Patient age (< 60 v. > 60 years) at time of treatment did not have a statistically significant impact on bNED survival. Long-term survival outcomes were similar to those reported for radical prostatectomy.
Conclusions: Conformal proton radiation therapy yielded disease-free survival rates comparable to those reported for prostatectomy. Dose-escalation strategies are being implemented to further improve long-term results.

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Preliminary results of proton therapy for stage I non-small cell lung cancer.

T. Ogino, K. Nihei, S. Ishikura, M. Kawashima, H. Nishimura, and H. Ikeda, Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Purpose: To assess the feasibility and efficacy of high dose proton therapy for stage I non-small cell lung cancer (NSCLC).
Patients and methods: We started a phase I dose escalation study of proton therapy for stage I NSCLC in December 1999. Patients received escalating dose of proton therapy in 20 fractions over 5 weeks (level 1: 70 GyE, level 2: 80 GyE, level 3: 88 GyE, level 4: 94 GyE, level 5: 98 GyE). Dose limiting toxicity included grade 4 radiation dermatitis and other grade 3 non-hematologic toxicities.
Results: Ten patients were enrolled in the phase I study. Every 3 patients were enrolled in level 1-3. One patient in level 4 suffered symptomatic radiation pneumonitis, resulting in closure of the study. Additional 17 patients were treated on an off-study basis. Thirteen patients received 88 GyE and 4 patients with poorer pulmonary function received 80 GyE. Patients characteristics were as follows: median age 75 (range 67-87), male/female: 21/6, Stage IA/IB: 13/14, squamous/adenocarcinoma/others: 13/11/3. The numbers of patients who received 70/80/88/94/98 GyE were 3/7/16/1/0, respectively. Grade 1 acute toxicities were observed as following incidences; radiation dermatitis: 21, esophagitis: 1, fever: 1. No grade 2 or greater acute toxicities were observed. With regard to late toxicities, grade 1 chest pain in 3 and grade 1/2/3 radiation pneumonitis (RP) in 15/2/1 were observed. No patients with stage IA disease suffered grade 2 or greater RP, while all grade 2/3 RPs were observed in 3 patients with stage IB disease. With a median follow-up period of 8.7 months (2.7 - 37 months), 1- and 2- year overall survivals were 100% and 78%, respectively. Patterns of failure were: loco-regional: 1, regional lymph node: 3, distant: 2. Two patients died of cancer.
Conclusion: Acute toxicities of high dose proton therapy for stage I NSCLC are acceptable. As late toxicities, radiation pneumonitis is not negligible. Longer follow-up duration is necessary to evaluate the treatment efficacy.

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PROG 92-14: Proton Therapy in Locally Advanced Oropharynx Cancer, Ten-year report of the accelerated fractionation protocol.

L. Yonemoto, LLUMC CA USA

PROG 92-14 is a combine proton/photon protocol treating advance stage oropharynx cancer, which paralleled the concomitant boost arm of RTOG 90-03. PROG 92-14 a concomitant boost protocol had higher dose and shorter duration (75.9 Gy in 28 treatment days) as compared to RTOG 90-03's concomitant boost protocol (72 Gy in 30 treatment days).

Twenty-nine patients with locally advance squamous cell carcinoma of the oropharynx cancer were treated from 10/91 to 6/02 at LLUMC with follow-up from 2 to 96 month. The Clinical Tumor Volume (CTV) included the Gross Tumor Volume (GTV) and subclinical sites was treated with photons with 3-port ENT fields to 50.4 Gy at 1.8 Gy fraction over 28 days. The GTV included all sites of gross disease and was treated with protons to 25.5 CGE at 1.5 CGE fraction over the last 17 days of photons, with at least 6 hours between bid treatments.

The 5-year disease free survival was 65%, and the local regional control was 84%. The 2-year local regional control was 93% that compares with RTOG's concomitant boost are of 55% and standard arm (70 Gy with 2 Gy fractions over 35 treatment days) of 46%. Late morbidity was 11% grade 3, and with no grade 4 or 5 morbidity.

Conclusion: The PROG 92-03 provides excellent local regional control and disease free survival. The toxicity is no greater that other radiation therapy with lesser doses. The next protocol would use protons for the CTV to further decrease the morbidity. Also radioprotectors will be evaluated for additional decrease in morbidity.

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Applying the NPL Alanine dosimetry service to low-energy clinical proton beams.

H. Palmans[1], R. Thomas[1], A. Kacperek[2], P. Sharpe[1], A. DuSautoy[1],and F. Verhaegen[3], [1]Centre for Acoustics and Ionising Radiation, National Physical Laboratory, Middlesex, UK, [2]Douglas Cyclotron, Clatterbridge Centre of Oncology, Wirral, UK, [3]Medical Physics Unit, McGill University, Montreal, Canada

The usefulness of alanine dosimetry in clinical proton beams has been previously demonstrated. NPL has developed an alanine service for photon dosimetry. In this work, the application of this service to low-energy proton beams is investigated. Various aspects related to the use of alanine detectors in proton beams are discussed in more detail than has been done before. A procedure is outlined to derive stopping powers and non-elastic nuclear interaction cross sections for alanine consistent with the recommendations in ICRU reports 49 and 63. The water-equivalence (or phantom-equivalence) of alanine is investigated using the Monte Carlo codes PTRAN and MCNPX. The LET-dependence of the alanine response is discussed and various models are fitted to experimental data from the literature. The influence of these data on calculated depth dose distributions and perturbation factors has been evaluated using a modified version of the Monte Carlo code PTRAN. Perturbation correction factors for alanine pellets have been calculated by Monte Carlo and analytical methods. An experiment with a stack of alanine pellets in a PMMA phantom was performed in a 60 MeV proton beam and is compared with theoretical results and experimental results from other investigators.

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Low energy proton beam dosimetry with plane parallel chambers using NPL electron and ^{60}Co calibrations.

R. Thomas[1], H. Palmans[1], and A. Kacperek[2], [1]Centre for Acoustics and Ionising Radiation, National Physical Laboratory, Middlesex, UK, [2]Douglas Cyclotron, Clatterbridge Centre of Oncology, Wirral, UK

IAEA TRS 398 [1] recommends that proton dosimetry using ionisation chambers be based on absorbed dose calibrations. In the absence of a service for the calibration of chambers directly in terms of proton beam absorbed dose, TRS 398 provides factors to convert a chamber calibration in terms of photon or electron beam absorbed dose to one in terms of proton beam absorbed dose.

This work, carried out in a 60 MeV proton beam at the Clatterbridge Centre for Oncology, compared measurements with four different types of chamber arriving at determinations of absorbed dose by two separate routes following the TRS 398 protocol, in both modulated and unmodulated beams, starting from either a photon beam or an electron beam calibration.

All chambers had been calibrated at NPL in terms of absorbed dose, and included thimble chambers of type NE 2561 and NE 2611, and NACP 02, Markus and Roos parallel plate chambers. The parallel plate chambers were calibrated in both ^{60}Co and electron beams whilst the cylindrical chambers were calibrated only in ^{60}Co.

In a modulated beam the dose ratio, parallel/thimble, varied between 0.995 and 1.018 depending on the type of parallel plate chamber and on the choice of starting calibration, photon beam or electron beam absorbed dose. For the same beam and starting calibrations, the dose ratio parallel/NACP obtained using Markus and Roos chambers varied between 0.987 and 1.008.

In an unmodulated beam (in which only the parallel plate chambers were used) the ratio parallel/NACP varied from 0.986 to 1.019 for Markus and Roos chambers with photon beam and electron beam calibrations. The unmodulated beam has much larger dose gradients and so these measurements are more sensitive to chamber position.

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Dose imaging with an Ar-CF_4 filled scintillating GEM.

Th. Delvigne[2], S. Fetal[3], C. W. E. van Eijk[2], F. Fraga[3], J. de Haas[2], R. Kreuger[2] and J. M. Schippers[1], [1]Paul Scherrer Institut, WBGA/C16, 5234 Villigen, Switzerland, [2]Interfacultair Reactor Instituut, TU Delft, Mekelweg 15, 2629 JB Delft, the Netherlands, [3]LIP Coimbra - Department of Physics, University of Coimbra 3004-516 Coimbra Portugal

The properties of a gaseous scintillation detector based on a Gas Electron Multiplier (GEM) system have been investigated. This detector, which combines the dosimetric advantages of a gas-filled detector with the relatively simple read-out of the signal by means of a CCD camera, is developed for use as a two-dimensional position sensitive dosimeter in radiation therapy with protons. Using 150 MeV protons, the light yield of a double GEM system has been measured as a function of gas composition (ratio Ar-CF_4) and operating voltage. We found that a mixture of 95%-5% gives the most light in absolute sense as well as per primary electron. At stable operating conditions 1.5 times more light is detected compared to the light yield of a conventionally used Gd_2O_2S:Tb phosphor screen. This means that the light yield is by far sufficient for standard dosimetry applications (doses ~1 Gy) and it opens possibilities in low dose applications and on-line control of treatments employing a scanning beam.

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MRI Interrogation of BANG Gel Proton Dose Visualisation for a 62 MeV Cyclotron.

J. N H Brunt[1], A. Kacperek[2] and T. Quine[1], [1]Physics Department, and [2]Douglas Cyclotron Unit, Clatterbridge Centre for Oncology, Bebington, near Liverpool, CH63 4JY, England

Our objective is to find a method of gel dosimetry with a satisfactory combination of dose discrimination and geometrical precision to analyse the proton dose distributions used for ocular treatments. In previously published work [1], results using Magnetic Resonance (MR) interrogation of BANG-25 polymer gel were encouraging, despite relatively large uncertainties in relaxation rates (R1 or R2).

Last year, we replaced our 0.5 Tesla MR scanner with a 1.5 Tesla scanner. We have now conducted equivalent experiments with BANG-25 gel. Within a single phantom, we irradiated several test fields (Bragg peaks, range shifted, blocked, wedged and abutted fields), and several calibration fields (using a collimated, fully modulated beam), allowing the dose distributions to be directly compared to ionisation chamber measurements (tracable in turn to the regional secondary standard). Our MR interrogation has included analysis of computed pure T1 and T2 images as before. Additionally, we have examined the feasibility of using background correction of T2-weighted images (for which scan durations are relatively short) to achieve acceptable calibration curves and dose-depth distributions.

In comparison with our previously published work, we have achieved improvements in spatial resolution and dose discrimination. Additionally, we have observed significantly higher Bragg peak to entrance dose ratios (> 4.0).

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BANG polymer gel dosimetry in eye tumour therapy.

J. Heufelder[1], M. Pfaender[3], L. Lüdemann[4], G. Grebe[2], and J. Heese[1], [1]Hahn-Meitner-Institut Berlin, Augentumortherapie, [2]Technische Fachhochschule Berlin, Medizinphysik, [3]Klinik für Strahlentherapie, Charité – Campus Mitte, Humboldt-Universität zu Berlin, [4] Klinik für Strahlenheilkunde, Charité – Campus Virchow, Humboldt-Universität zu Berlin

Using polymer gel it is possible to measure three dimensional dose distributions of ionising radiation. Phantoms with BANG-1 and BANG-3 gel were irradiated using a 68 MeV proton beam at the eye tumour therapy beam line of the Hahn-Meitner-Institute in Berlin. Up to twelve treatment fields consisting of mono energetic Bragg-curves, spread out Bragg-curves of circular fields (diameter 20 mm) and spread out Bragg-curves of patient fields were applied to single phantoms. Magnetic resonance imaging was used to obtain the gel dose distributions. Results were compared to water phantom ionization chamber measurements.

BANG polymer gels show a significant quenching of Bragg-peaks compared to ionisation chamber measurements. BANG-3 gel was found to be not suitable for further investigations with 68 MeV protons. With BANG-1 wedge slopes and irregular field forms could be verified. From our experiences, we can state that polymer-gel is suited for quality assurance in proton therapy on principle.

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An Overview Of Uveal Melanomas And Their Treatment.

B. Damato, Royal Liverpool University Hospital/Clatterbridge Centre for Oncology, UK

About 90% of uveal melanomas involve choroid with almost half of these extending close to fovea or optic nerve. Survival probability is related to chromosomal abnormalities and tumour diameter. Metastasis usually precedes ocular symptoms so that ocular treatment is mostly aimed at preventing pain, if possible conserving a useful eye.

Where choice exists, treatment is selected according to tumour size and location as well as the patient's priorities with respect to local tumour control, visual function, comfort, and cost. Most patients undergo radiotherapy, delivered with a plaque or proton beam. Phototherapy is less reliable at achieving tumour control but useful as adjunctive therapy to confirm tumour destruction and suppress exudation after radiotherapy. Trans-vitreal 'endoresection' is controversial and performed only for small, juxtapapillary tumours when it offers the best chance of preventing visual handicap. Trans-scleral local resection of choroidal tumours is useful for large tumours, either as an alternative to radiotherapy or for treating severe exudative retinal detachment after radiotherapy. Surgical removal of iris and ciliary body tumours causes severe ocular morbidity so that there is growing interest in radiotherapy for such tumours.

Our experience indicates that exudative retinal detachment and neovascular glaucoma are mostly caused by intra-tumoral radiation-vasculopathy, which explains why these complications are prevented by adjunctive treatment of the irradiated tumour and not by altering radiation technique.

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Proton beam radiotherapy of iris melanoma.

B. Damato, A. Kacperek, M. Sheen, K. Sztanko, and R. D. Errington, Royal Liverpool University Hospital/Clatterbridge Centre for Oncology, UK

The standard form of treatment for iris and ciliary body melanomas is local resection, but this inevitably causes an extensive iris defect, which results in cosmetic deformity and photophobia. It is possible to deal with such problems using a painted contact lens, but this is not tolerated by many patients. Surgical resection can also cause cataract and lens instability, which makes it difficult to perform cataract surgery. Another severe problem is ocular hypotony, which can be intractable. For these reasons, since 1994, we have treated almost 100 patients with proton beam radiotherapy for iris and/or ciliary body melanoma. In 40% of patients, more than two clock hours of ciliary body, iris and/or angle were involved. At the latest visit, 99% of eyes were retained, with 91% having visual acuity of 6/12 or better. The main complication was cataract, which was readily treated.

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The rationale of combining Proton Therapy and Photodynamic Therapy for Wet Age-Related macular Degeneration.

L. Yonemoto, Loma Linda University Medical Center, Loma Linda, CA, USA

The rational for the treatment of the "wet type" of Age-Related Macular Degeneration is based on the clinical, radiobiological and physics of proton beam.

A dose escalation trial demonstrated a dose response to single fraction protons. Actuarial lesion control at 21 months was 36% for 8-GyE patients and 89% for 14-GyE patients; 77% of patients with controlled lesions achieved improved/stable visual acuity, compared to 44% with uncontrolled lesions. Actuarial mean visual loss for proton-treated macula was zero at 24 months. No treatment-related morbidity was seen, based on Radiation Therapy Oncology Group criteria [1,]2.

The technique is similar to the treatment of ocular melanoma. The patient is immobilized with a mask and look at the positioning light. Lid retractors and anterior chamber sparing technique with proton beam were used to reduce dose to critical structures [3].

Assuming the eye is an extracranial brain extension and the microvessels are similar properties to the brain's microvessels, there is rationale to continue investigating various dose and fractionation schemes [4].

References: [1] Yonemoto LT, Slater JD, Friedrichsen EJ, et al. Phase I/II Study of Proton Beam Irradiation for the Treatment of Subfoveal Choroidal neovascularization in Age-Related Macular Degeneration: Treatment Techniques and Preliminary Results. . Int. J. Radiation Oncology Biol. Phys. Vol. 36, No. 4 pp. 867-871, 1996. [2] Yonemoto LT, Slater JD, Blacharski P, et al. Dose Response in the treatment of Subfoveal Choroidal Neovascularization in Age-related Macular Degeneration: Result of a Phase I/II dose escalation study using conformal proton radiation therapy. J Radiosurg 3(2000) 47-54, 2000. [3] M.F. Moyers, R.A Galindo, L.T.Yonemoto, et al. Treatment of SNVM with Proton Beams. Presented at the 38th annual meeting of the American Association of Physicist in Medicine, Med. Phys. 26 (5), 1999. [4] Archambeau JO, Mao XW, Yonemoto LT et al. What is the Role of Radiation in the Treatment of Subfoveal Membranes: Review of the Radiobiologic, Pathologic, and Other Considerations to Initiate a Multimodality Discussion. Int. J. Radiation Oncology Biol. Phys. Vol. 40, No. 5 pp. 1125-1136, 1998.

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EyePlan: the story so far - where next?

M. A. Sheen, Clatterbridge Centre for Oncology

Treating ocular tumours with protons imposes particular requrements on the treatment planning program to be used. At the time of the first such treatments at Massachusetts General Hospital using the Harvard cyclotron, no suitable program existed and EYE was specially written for the purpose. This was further developed at PSI in Switzerland, and subsequently, as EYEPLAN, at Clatterbridge. The latest incarnation, EyePlan, transfers the program to a Windows platform for greater ease of use and to give scope for future developments. The great majority of ocular proton treatments worldwide are planned using one version of EYEPLAN or another.

This talk traces the development of EyePlan so far, and looks at current developments and suggests what will, or should, happen to it in the future.

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Stitching Fundus Photos Together for Eye Planning.

J. M. Collier[1], A. Can[2], G. Yang[3], H. Iyer[3], and B. Roysam[3], [1]Massachusetts General Hospital, [2]Woods Hole Oceanographic Institution, [3]Rensselaer Polytechnic Institute

In an ongoing project funded by the National Science Foundation, called the Center for Subsurface Sensing and Imaging Systems (CenSIS), there has been work at RPI to stitch together fundus photos of the retina in aid of laser surgery of the eye[1] into a single mosaic photo. This work developed the algorithm of finding the blood vessels of the retina in the various photos and matching the branch points and cross over points. This works very well for laser surgery patients because their retinas are clear and undistorted. Patients with ocular melanoma present a number of serious problems to this technique. First there may be regions of the retina without good blood vessels. Secondly the tumor bulges into the eye, distorting the spherical geometry of the normal retina, and this leads to a parallax problem for different camera angles into the eye. Finally the depth of field of the camera is small enough that not all of the retina with tumor will be in focus in any one photo. Nevertheless even with these limitations the current program can stitch photos together in many cases. The result is the equivalent of a single wide angle fundus photo centered on a chosen input photo, but with much higher quality than the usual wide angle photo.

The goal is to use this result in the EYEPLAN, whose latest version can display such photos under the wide angle fundus diagram of the eye that is used for drawing the tumor base. This presents the opportunity to confirm the information from surgery about the relation of the edge of the tumor to the marker rings and more accurately define the tumor margin in regions, usually posteriorly, where rings could not be placed. However there are two major caveats in this. The relation of the clips to the structures of the eye is still dependent on knowing the gaze direction of the patient at simulation. While comparison of clip-to-limbus distances give some confidence within the uncertainties of those measurements, there is no independent information of the rotation of the eye about its own axis.

Ongoing work seeks to produce more usable mosaic by smoothing the edge between photos and choosing the ‘best’ pixel to display in the final result instead of an overlay of all pixels from all input photos. In addition there is work to overcome the limitation of the current algorithm by providing two new ways of making the correlation. The first will be

allowing a human to pick common points among the input photos, and the second will use a texture mapping system. Long term goals include making use of ultrasound to produce a 3D image model of the eye, with the ultimate dream of replacing the replacing the marker ring based model with this image-based model.
References: [1] A. Can, et al, A Feature-Based, Robust, Hierarchical Algorithm for Registering Pairs of Images of the Curved Human Retina, IEEE Transactions on Pattern Analysis and Machine Intelligence, 24(3) p347

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Comparative CT-based Planning for Proton Treatment of Ocular Melanoma –Eyeplan vs. Octopus.

D. Cordini, H. Fuchs, J. Heufelder, and H. Kluge, Hahn-Meitner-Institut Berlin GmbH, Augentumortherapie, Glienicker Straße 100, D-14109 Berlin

About 5 years ago we started proton beam therapy of eye tumours, mainly ocular melanoma with close vicinity to centrally situated risk organs as macula, optic disk, and nerve. We use the standard system Eyeplan (Vers. 1.2B) for therapy planning. Due to the often critical tumour location, for planning we include additional informations from actual CT records among the usual data extracted from fundus photography and ultrasound. For each patient, we match the conventional Eyeplan eye model with the CT images and fit it to "real eye" individually. In most cases, CT superposition results in a subsequent correction of the eye model and, thus, leads to a better correspondence to the whole geometrical subset of clinical input data.

For enhancement of planning precision, the new planning tool Octopus (*) has been developed that merges helpful features to a single platform, i.e. 1. direct access to digital fundus and patient CT records, 2. free modelling, and 3. a pencil beam algorithm for calculation of dose distributions. In our presentation, we will demonstrate the steps within the powerful planning procedure and show preliminary results from comparative planning of Eyeplan vs. Octopus.

(*) Developed in collaboration with DKFZ Heidelberg, Germany.

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UK High Energy Proton-Particle Radiotherapy Facility: Outline case for Imperial-UCL and associated NHS Trusts project.

B. Jones, , Imperial College School of Medicine, Department of Clinical Oncology [Cancer Centre], Hammersmith Hospital, London W12 OHS

Executive summary:

- There exists an opportunity to establish the first high-energy proton radiotherapy facility in the UK as a joint project between Imperial and University College.
- Proton dose distributions are more favourable than those obtained even from the best available linear accelerator treatments and, for an anticipated increasing range of tumour sites, allow reduced radiation side effects and/or improved tumour control.
- Proton beams are created in a cyclotron and have unique properties, which make them an excellent choice for the treatment of certain rare malignant tumours, particularly those close to the central nervous system.
- At present patients with such conditions are referred (with DH funding) to France or the USA for proton therapy.
- There is currently a major investment programme in the UK aimed at updating ageing linear accelerator equipment in national radiotherapy Centres, there remains a presently unfilled need for a national Centre capable of providing proton therapy.
- Initial costs of providing proton therapy is high and central government support would be required.
- The longer-term national benefits may be considerable for patients and for the advancement of clinical science.
- The UK should undoubtedly start R & D programmes using high-energy protons.

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Proton therapy in Sweden: Current activities and future visions.

E. Blomquist, Uppsala Hospital, Sweden

Since 1989 more than 360 patients have been treated with protons at The Svedberg Laboratory in Uppsala. The available beam time has been limited to ten weeks per year i.e. in general one week per month for irradiation with protons. Most patients treated had intracranial targets, about half of those were benign (AVM's or meningeomas). The results have been encouraging and the demands on advanced radiotherapy are increasing. Representatives from most University Hospitals in Sweden have now decided to fully investigate the possibility of how to design and build a hospital-based proton beam therapy center located in Uppsala. The committee work on the subject is in rapid progress.

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RBE corrections in BED equations: should we use a constant factor or variable factors which are linked to fraction size?

B. Jones, R. G. Dale and A. Carabe-Fernandez, Imperial College School of Medicine, Department of Clinical Oncology [Cancer Centre], Hammersmith Hospital, London W12 OHS

Classical radiobiological experiments demonstrate that RBE varies inversely with dose per fraction. We have recently shown how this variable RBE effect may be included in biological effective dose (BED) equations through incorporation of RBE_{max}, the maximum RBE occuring at zero dose.

The modified BED formulae indicate the conditions under which th continuous scale of RBE correction with changing dose per fraction can lead to increased tumour control relative whilst respecting a defined normal tissue iso-effect. However, the differences in the adjusted dose are small in the case of high energy protons, for which RBE_{max} values may be as small as 1.2, and the use of a conventional generic correction factor of a 10% change in dose for all doses per fraction seems to be reasonable in practice. Although clinical outcomes might be further improved by the continuous BED correction system, it would be difficult to detect such changes within clinical trials unless very large numbers of patients were used. The same restriction applies to in-vivo animal experiments where there is less biological heterogeneity.

For radiation modalities with higher RBE_{max} values (e.g. neutrons and carbon ions), application of radiobiologically-based BED corrections should be more appropriate than use of a fixed generic value for all fraction sizes, particularly since the range of RBE variation is variable in different tissues. The predicted gain in therapeutic index is more substantial for carbon ions than for protons.

There are two areas of concern with respect to linear quadratic modelling: low and high doses respectively. Work in progress includes the following refinements of the linear quadratic:-

1. The phenomenon of low dose hypersensitivity, sometimes referred to as induced repair (IR) can be well simulated by the reasonable assumption of dose related saturation of repair enzymes.
2. For large doses per fraction, chromosome breakage saturation effects (Poisson statistics applied to compensate for the "wasted dose" effect of multiple breaks per individual chromosome) can be used to produce cell survival curves that become reasonably log-linear at higher doses. Such corrections may be more appropriate for radiosurgery, or where large dose per fraction (>6 Gy) is used.

These modifications have implications for RBE calculations. In particular, both changes predict reduced variation in RBE with dose per fraction.

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RBE Study in Clinical Proton Beams.

A. G. Molokanov[1], T. A. Fadeeva[1], N. L. Shmakova[1], F. Spurny[2], B. Vlcek[2], [1]Joint Institute for Nuclear Research, Dubna, Russia, [2]Nuclear Physics Institute, Prague, Czech Republic

Proton clinical beam contains particles with high linear energy transfer (LET). Secondary heavy charged particles produced from nuclear interactions and degraded protons at the Bragg peak region are particles with high LET. These particles could enhance the Quality Factors (QF) and the Relative Biological Effectiveness (RBE) of the proton beam.

The method of the LET spectra measurement with track etched detectors allows one to determine the influence of high LET particles to the dosimetric characteristics of proton clinical beams - absorbed dose, equivalent dose and the value of the RBE. For the RBE calculation from the measured LET spectra the Biological Weighting Function [1,2] was used.

Track detectors were irradiated in the different depth of proton clinical beams with the primary energies of 155 and 200 MeV at the JINR (Dubna) phasotron. The LET spectra between 10 and 700 keV/mm were measured by means of the CR-39 track etch detectors and automatic optical image analyzer LUCIA-II at the NPI (Prague). Due to the increased number of high LET particles with a depth of proton beam penetration, radiobiological characteristics of the clinical proton beam changed with the depth as well.

The relative contribution of the high LET particles to absorbed dose increases from several per cent at the beam entrance to several tens of per cent at the Bragg peak region. The value of the RBE increased from about 1.0 at the beam entrance to about 1.25 at the Bragg peak. These values must be taken into account during beam production and using.

We have carried out two radiobiological experiments to investigate the RBE of 150 MeV clinical proton beam. The irradiation of the Chinese Hamster V79 cells were performed at two points of the depth-dose distribution – at the beam entrance and at the Bragg peak. Reference irradiation was performed with ^{60}Co γ-rays. The RBE values calculated from these survival curves for different depth and survival fractions (SF) demonstrate that the increasing of RBE values depend on SF level and on the depth of the beam penetration. The values of RBE obtained by two independent methods are in a good agreement with similar investigations [3,4].

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Proton conformal radiation therapy and radiosurgery of intracranial targets at the Dubna: Technique and early results.

Ye. I. Luchin, Yu. G. Budjashov, E. P. Cherevatenko, V. N. Gaevsky, I. A. Gulidov*, A. V. Iglin, A. G. Molokanov, G. V. Mytsin, S. V. Shvidkij, Joint Institute for Nuclear Research (JINR), Dubna, Moscow region, Russia, *Medical Radiological Research Center of the Russian Academy of Medical Sciences, Obninsk, Moscow region, Russia

Purpose: Proton three-dimensional radiation therapy and radiosurgery is, at the present time, a powerful modality to decrease normal-tissue integral dose significantly while achieving a highly conformal dose distribution in the target area. Especially this is advantageous for many critically located and complex-shaped intracranial tumors and arteriovenous malformations. Purpose of this report is presentation of developed technique of 3D proton radiation therapy in Dubna and early results of clinical using.

Material and method: After difficulties during economic transformations in 1990, proton accelerator of the JINR began to run more time that was enough to re-start proton therapy clinical program in Dubna. In-patient radiation therapy department has been organized in the local hospital. During 2000-2001 years one procedure room has been modified to satisfy requirements for precise stereotactic radiation treatments. Technological steps of the proton treatment are as follows. 1) Manufacturing of head immobilizing devices. There are two kinds of thermoplastic masks – Loma Linda style and "Orfit" produced one. 2) Imaging studies: high resolution CT with up to 99 2-mm slices on the "GE hi-speed" apparatus. MRI usually used as visually correlated image. 3) 3D treatment planning. We are using three-dimensional treatment planning system "TPN" that has been developed at the Loma Linda University Medical Center. This is early version of the "OptiRad-3D" system that is now presented at the market. The system was modified to incorporate the Dubna proton beams. Often treatment plans have been duplicated with local less sophisticated planning system. 4) Manufacturing of beam modifying devices – individual cerrobend apertures, compensating boluses. 5) Realization of the treatment plans and beam position verification relatively to bone landmarks. Digital reconstructed radiographs (DRRs) with projection of target, isocenter and bone landmarks were calculated and printed. Alignment Rx-films were compared with DRRs during irradiation sessions. Alignment accuracy was about 1mm.

Early clinical experience: Forty-four patients with 52 separate intracranial targets received 3D-proton conformal radiation therapy or radiosurgery at Dubna since April 2001. There were 19 meningiomas (benign, atypical, anaplastic), 7 malignant gliomas, 6 metastasis, 6 AVM, 2 acoustic neurinomas, 1 pituitary adenoma, 1 plasmocytoma, 1 low-grade gliomas and 1 chordoma. Radiosurgery (1-3 fractions) irradiation applied for relatively small targets. Maximum total doses were 20-27 GyE. Hypofractionated regimen of 10-15 fractions has been used for larger size and critically located targets.

Dose per fraction was 3-4 GyE with traditional for proton RBE=1.1. Total equivalent doses were calculated by the linear-quadratic formula and were equal to 56-60 GyE-a/b to the target margin. Some patients received conventionally fractionated (30-33 fraction) proton conformal radiation therapy. Early results demonstrated that developed technique of proton irradiation allow to deliver proton dose to the target volume precisely.

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The water equivalence of solid materials used for dosimetry with small proton beams.

U. Schneider[1], P. Pemler[1], J. Besserer[1], M. Dellert[2], M. Moosburger[2], J. de Boer[2], E. Pedroni[3], and T. Boehringer[3],
[1]Division of Medical Physics, Department of Radiation Oncology and Nuclear Medicine, City Hospital Triemli, 8063 Zürich, Switzerland; [2]Department of Physics, University of Munich, Garching, Bavaria; [3]Department of Radiation Medicine, Paul Scherrer Institute, 5232 Villigen-PSI, Switzerland

Various solid materials are used instead of water for absolute dosimetry with small proton beams. This may result in a different dose measurement to that in water, even when the range of protons in the phantom material is considered correctly. This dose difference is caused by the different cross sections for nuclear scattering in water and in the phantom materials.

To estimate the magnitude of this effect, flux and dose measurements with a 177 MeV proton pencil beam with a width of 0.6 cm (FWHM) were performed. The proton flux and the deposited dose in the beam path were determined behind water, lucite, polythylene, teflon and aluminium of different thickness. The number of out scattered protons due to nuclear reactions was determined for water and the different materials. The number of scattered protons relative to water were found to be 1.20 for lucite, 1.16 for polyethylene, 1.22 for teflon and 1.03 for aluminium. The out-scatter relative to water is plotted as the squares in figure 1.

For comparison we plotted with diamonds in figure 1 also the quotient of the non-elastic nuclear interaction probability of Janni's data table of the materials relative to water.

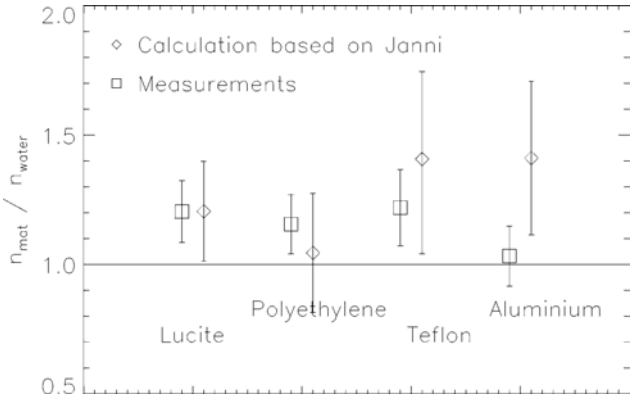

FIGURE 3. Number of scattered protons in different materials relative to water. The squares represent the results of the measurements and the diamonds label the data from Janni's tables.

The difference between the deposited dose in water and in the phantom materials, respectively, in the center of the proton pencil beam was estimated from the flux measurements, considering the different range of protons in the materials. The dose deviation was also measured with an ionisation chamber. The estimated dose difference to water in 15 cm water equivalent thickness was -2.3% for lucite, -1.7% polyethylene, -2.5% for teflon and -0.4% for aluminium. It should be noted that the dose error is as larger as deeper the effective point of measurement is located.

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