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ABSTRACTS

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INDEX

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

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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. 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 the autumn of 2005. 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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The Midwest Proton Radiotherapy Institute, an Update.

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The Midwest Proton Radiotherapy Facility (MPRI) was conceptualized in 1996 by a consortium of physicians and physicists. The plan, now in the final stages of execution, proposed that the Indiana University Cyclotron Facility (IUCF) would construct a proton therapy facility and supply beam utilizing the separated sector cyclotron accelerator system. Reconfiguration of the cyclotron experimentation stations began in 2000, with the removal of all equipment and moveable shielding from the high and low bay areas. All existing beam lines were removed downstream from the cyclotron extraction point. The main cyclotron extraction system and radio-frequency (rf) cavity structures were modified to improve extraction efficiency and increase the routine operating energy to 205 MeV. The Cockcroft Walton pre-accelerator will be replaced at the end of this year with a CW RFQ injector that will significantly increase the reliability and stability of the medical beam delivery system [3]. A doubly achromatic extraction beam line was installed and commissioning of the medical beam delivery system was completed in August of 2002. The first of 4 energy selection lines (ES) and two fixed horizontal beam treatment lines were manufactured and the ES has been installed. Commissioning of the ES began in October. A fifth ES line will supply the radiation effects research station (RERS), a radiation research facility available 24 hours a day, 7 days a week.

The horizontal beam lines are currently being installed in the first treatment room and commissioning is anticipated to begin immediately. Two isocentric, rotational gantries will be installed following completion of the horizontal beam lines. A fifth line will supply the full-time radiation effects research station. Standard proton delivery out of the main stage is specified at 500 nA of 205 MeV. The technical details of the fixed horizontal lines will not be presented here; that discussion is beyond the scope of this paper.

Clinic construction began in April of 2002 and will be completed by mid-December. The clinic facility will include 4 examination rooms, 2 offices, a physician conference area, reception area, nurses' station, CT/simulation suite, recovery area and a standard photon therapy linear accelerator room. The patient support facility has been constructed in the IUCF "low bay" area, which was divided into two floors of more than 15 vertical ft. each. The second floor will remain mostly unfinished until the first two treatment rooms are operating at full capacity. Only medical physics and physicians' offices will be located on the second floor until that time. Design, construction and operation of these proton facilities have been accomplished by the proton therapy group at IUCF. Included in this group during the past 6 years are: Chris Allgower, Vladimir Anferov, Mark Ball, George Berg, Chuck Bloch, Brian Broderick, John Cameron, John Collins, Vladimir Derenchuk, Gary East, Dennis Friesel, Chuck Hagen, Brett Hamilton, David Jenner, William Jones, Joe Katuin , Susan Klein, Don Rosselot, A. Niek Schreuder, Jeff Self, Bill Starks, Bill Vanderwerp, and Moira Wedekind.

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Present Status of Proton Cancer Therapy Project at WERC, 2002.

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The present status of the proton cancer therapy project at WERC (the Wakasa Wan Energy Research Center) is reported. The construction of the accelerator complex that consists of a 5 MV tandem and a 200 MeV synchrotron has been finished in 2001 by Hitachi Ltd. The medical beam line comprises two fixed ports, in one of which proton beam is transported from vertical direction, while another from 9.5 degrees above the horizontal direction. The beam check for the flatness of the irradiation field, which is provided by wobbler magnets and tungsten scatterers, has been done. Relative biological effect (RBE) value was also measured by using HSG cells and C3H mice with proton, and was shown to be 1.1.

The first two patients with prostate cancer has been started since June 2002 to have total dose 67.5 GyE for each in 27 fractions as the safety proof examination suggested by the government. Patient positioning was done with the X-ray CT within the accuracy of nearly 1mm at every treatment. The treatment for four other patients will be performed by coming spring 2003.

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Stereotactic proton beam radiation for large cerebral Arteriovenous Malformations

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Stereotactic radiosurgery is an effective and safe treatment for small intracerebral AMV's. Large lesions are more difficult to treat because of dose constraints imposed in order to keep the complication rate acceptable. Proton beam therapy due to its inherent physical advantages has the ability to treat large AMV's with low complication rates. At iThemba labs 61 patients have been treated by the end of December 2001. Excluding patients to early for amv obliteration (n=4) 57 patients have been analyzed. Of those, 34 (56%) had lesions with volumes >/ 14 cc. Of this group, 29 patients were analyzed and 10 (34%) showed amv obliteration. If all evaluable patients with volumes of 10cc or more are analyzed, an obliteration rate of 36% was achieved. Comparison with other studies remains difficult due to variable criteria in volume grouping, documentation of obliteration (angiographically ⇔ MRI/MRA) and pre-radiosurgical embolizations. Taking all these variables into consideration our obliteration rates are similar to somewhat lower than other series. Dose/volume considerations are a major factor in radiosurgical treatment decisions. The low incidence of permanent late side effects in this series opens up the avenue of a dose increase, with expected better obliteration rates for large avm's.

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Phase I/II Study of High Dose Stereotactic Proton Therapy of Brain Metastases.

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Purpose: A prospective phase I/II study was initiated at LLUMC in 1995 to identify patients with single or multiple brain metastases who may benefit from proton radiosurgery, either given as adjuvant boost treatment following whole brain radiation therapy (WBRT), as a salvage treatment for recurrent brain metastases after WBRT, or as the primary treatment without WBRT.

Methods and Materials: Forty-five consecutive patients with brain metastases were treated with proton radiosurgery between June 1995 and July 2002. Seventeen patients received radiosurgery as an adjuvant focal boost to WBRT, 22 patients as salvage treatment after local failure or persistent disease following primary WBRT, and 6 patients as the primary treatment without WBRT. Median age at treatment was 59 years (range 31 – 74 years) and the median Karnofsky performance status (KPS) was 80 (range 50 – 100). In 30 patients the primary tumor was controlled at the time of treatment, while in 15 patients it was uncontrolled. Extracranial metastases were present in 25 patients and absent in 20 patients. Seventeen patients presented with single brain metastases; 28 patients had two or more metastases. The median tumor dose was 20 Gy, prescribed to the 80% isodose curve. Lesions equal or less than 5 cm^3 usually received single-dose treatments, while larger lesions were treated with two fractions. Brain stem lesions or very large metastases in the posterior fossa received 3-4 fractions. Patients were followed until death, with survival time measured from the beginning of the primary or salvage treatment, depending on the

treatment scenario. Using multivariate analysis, the following prognostic factors were evaluated with respect to their influence on survival: KPS, age, primary tumor (controlled vs. uncontrolled), presence of extracranial metastases, number of brain metastases (single vs. two or more) and Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis class (I, II, or III).

Results: Median survival for all patients was 7 months. At the time of analysis, there were three long-term survivors, all of them without evidence for brain metastases at 20, 37.5, and 79 months after treatment, respectively. In the multivariate analysis, only the number of brain metastases predicted survival, i.e., 11.5 months median survival for patients with single metastasis vs. 3 months for those with two or more metastases ($p = 0.012$). Furthermore, it was found that patients in subgroups with different RPA classes had generally better median survival results than those published by the RTOG for patients treated with WBRT alone: RPA class I, 11 months (LLUMC) vs. 7.1 months (RTOG); RPA class II, 6 months (LLUMC) vs. 4.2 months (RTOG); RPA class III, 6.9 months (LLUMC) vs. 2.3 months (RTOG).

Conclusion: Based on a historical comparison with RTOG data, addition of radiosurgery to WBRT, either as an adjuvant or salvage treatment, or as primary treatment in selected patients, seems to offer a survival advantage even in prognostically less favorable patient groups. However, we cannot exclude the possibility that our results are influenced by selection bias due to the relative large proportion of patients receiving radiosurgery as salvage treatment after WBRT.

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Stereotactic Neurosurgery.

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The Cape Town Stereotactic Pointer (CTSP) is a simple device based on the three-dimensional geometric principle that any vector can be defined by two points separated in space, and that this vector can be reconstructed by making use of two such points, each located on one of two parallel planes at a known distance apart. In this device, the feet of the three legs of a tripod define the bottom plane and a horizontal arm mounted on a vertical pivot a fixed distance above the bottom plane defines the top plane. The horizontal arm can both swivel about the pivot and move in and out at the point where it intersects with the pivot. A ball and socket joint is attached to the end of the horizontal arm. The angle and position of the ball and socket joint is set pre-operatively with the aid of a phantom and a printout generated from coordinates determined from the computed tomography (CT) scans. During surgery the tripod is placed on a halo sutured to the patient's scalp. A hollow sleeve passing through the ball and socket joint guides the surgeon's biopsy needle. Work is in progress to develop an interactive image-guided neurosurgical system. This system uses locally developed smart camera technology and the principles of stereo-photogrammetry to track in real time the position of the neurosurgeon's probe in theatre and to display this relative to the lesion on pre-operative CT images.

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Review Proton beam radiotherapy at Clatterbridge: Follow-up of iris melanoma treatments and ARMD controlled trial.

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Iris melanoma treatments: The standard form of treatment for iris melanoma is iridectomy, with iridocyclectomy being performed if the tumour extends to angle or ciliary body. Both procedures are technically straightforward but the surgical iris defect may cause photophobia requiring further treatment.

Proton beam radiotherapy has been used for choroidal melanomas for several decades, with excellent local tumour control. To our knowledge this modality had not previously been used for the treatment of iris melanomas. In view of the limitations of surgical resection and plaque radiotherapy of iris melanomas, there was strong motivation for exploiting proton beams in providing precise, superficial beams for irradiating these iris tumours. In 1994, the first patients were treated at the CCO, using the standard melanoma dose and fractionation (53.1 Gy in 4 daily fractions). At present, over 100 iris patients have been treated. This talk will describe the early results (i.e. longest follow-up) of proton radiotherapy of a treated study group, showing

outcomes in terms of visual acuity, ocular complications and symptoms. The present results have not been described in detail earlier as radiation-induced complications usually take time to appear.

Method: proton treatment plans were prepared according information on a special form, which included: (1) the shape and extent of the tumour; (2) the target area comprising the tumour and safety margins; (3) echographic measurements of distances from cornea to back of lens, cornea to retina, retina to outer sclera, and transverse ocular diameter. Tantalum markers were not necessary. EYEPLAN (3.01) eye therapy program had the possibility of modelling the tumour base on the iris. Treatment was delivered with the pupil fully dilated to reduce the tumour area. The eyelids were fully retracted to improve positioning accuracy with field-light and to minimise cosmetic side effects. The superficial proton beam depths required the use of a flat, thin walled Markus IC. It is concluded that proton therapy of iris melanoma has achieved excellent local tumour control with minimal complications for patients in the study group, with 5 to 8 years follow-up. NB Parts of this talk have been presented at the PTCOG XXXV in Catania.

The ARMD randomised control study, using 18 Gy (proton) dose in 4 fx, was followed through 12 months and 24 months for most treated patients. The method has been described at previous PTCOG meetings (Cape Town 1999 and Berlin 2000). Net benefit in VA was shown at 12 months, however benefit at 24 months is less clearly defined due to several reasons.

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Proton Radiation Therapy at PSI – Experience with Established and Novel Technologies

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PSI took up proton radiation therapy of ocular tumors in 1984 after having built a device for patient treatments at the 70 MeV beam line of the pre-accelerator injector 1. This installation followed the example of the treatment place at the Harvard Cyclotron and was modified according to PSI's (at that time SIN) local conditions and needs. By September 2002, we have treated more than 3500 patients with ocular lesions in close collaboration with the University Eye Hospital Lausanne. Choroidal melanomas present the by far largest group of tumors. Local tumor control is excellent with over 95% at five years, and the detailed analysis of these data proves the fact that local control and survival are strongly related.

A total of 99 patients have been treated by the end of 2001for deep-seated tumors on the spot-scanning gantry,. Forty -eight were female, fifty-one male. Age varied from 7 to 80 years, with a median of 47 years. The tumor groups / histologies were chordomas / chondrosarcomas (37), meningiomas (15), brain histologies (11), soft tissue and bone sarcomas (11), singular metastases (7), nasopharynx cancer (6), prostate (5), esthesioneuroblastoma (2), local tumor relapses (2), basalioma (1), ependymoma (1) and gangliocytoma (1). Follow up time is ten to seventy-one months, median 33 months. Of the ninety-nine patients, 78 were treated with curative intent. Thirteen patients died, nine of whom had been treated with palliative intent.

The group of chordomas (chor.) / chondrosarcomas (ch-sarc.) is divided into 9 ch-sarc. and 7 chord. of the base of skull, 1 occipital ch-sarc., 1 ch-sarc. of the t-spine, 8 chor. of the spine (5 c-, 1 t-, 2 l-spine), 9 chor. of the sacrum and 2 ch-sarc. of the trunk. We saw two local failures: one c-spine chordoma, irradiated with 74 CGE after multiple surgeries, and one skull base chordoma, which relapsed after 72 CGE in the surgical pathways and locally. Out of 37 patients 6 were treated with palliative intent, two died from distant metastases.

Meningiomas were the second largest group with 12 benign and three atypical lesions. One patient died from complications after necrosectomy due to central necrosis of an atypical, multifocal meningioma. Three patients developed optic nerve toxicity after 54 CGE (2) and 64 CGE (1), with the nerve being entirely included in the target volume.

Of the 11 gliomas (9 low, 2 high grade), 8 were locally controlled. Three patients developed necrosis within the high dose region with two patients being symptomatic and needing steroids. On patient died at 31 months from local relapse of a grade II astrocytoma.

Of the eleven sarcomas, 8 are locally controlled. The relapses occurred: at 6.5 months in a pediatric intracranial rhabdomyosarcoma, the patient died at 10 months with local and distant progression; at 14 months in a juvenile rhabdomyosarcoma, which had been treated with only 14 CGE protons plus photons and chemotherapy in Italy; 1 malignant nerve sheath tumor relapsed locally after prior complete resection and irradiation.

Five of the 6 nasopharynx carcinomas were treated curatively with proton-photon combination and chemotherapy, they are locally controlled without distant disease and show no toxicity.

In summary, 86 out of 99 patients are alive five to sixty-six months after proton radiotherapy. Local control was achieved 72 out of 78 curatively irradiated patients and in 10 out of 20 palliative cases. Late toxicity greater grade 2 was found in 6 out of ninety-nine patients.

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Update on the status of the Pencil Beam Scanning Development at IBA, Belgium.

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IBA is a Belgian enterprise offering a turnkey Proton Therapy System. In its actual solution the system uses a double scattering and wobbling technique integrated in the same nozzle for delivering the dose to the patient.

The Pencil Beam Scanning development at IBA concerns the realization of a new nozzle that would offer a higher accuracy in the dose delivery and that would be compatible with the rest of the actual IBA Proton Therapy System. The development was started in 2000 and it is now in an advanced phase with a complete test bench of the nozzle produced and ready for testing together with a prototype of the on-line monitor system.

An update on the status of the development and the related performed tests will be given.

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The robot-based patient positioning system for high precision radiotherapy at iThemba LABS.

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A new patient positioning system for high precision proton radiotherapy is currently being developed at iThemba LABS. This non-invasive system is intended to be used with fixed beam lines, but can in principle be modified to be used with gantry systems. A commercial robot manipulator will be used to transport the patient in the treatment room and to position the patient accurately in the treatment position. The problem of aligning the patient correctly with respect to the treatment beam will be solved by using video images of a set of reflecting markers, which are attached to a custom-made treatment mask that fits the patient accurately. This treatment mask will be used when the CT study of the patient is conducted, and during each radiotherapy treatment session. Multi-camera stereophotogrammetry systems will be used to capture sets of video images of the markers in the CT scanner room, and in two different settings in the radiotherapy treatment room. These images will be analyzed through stereophotogrammetry (SPG) techniques to determine the position coordinates of the markers, which in turn are used to compute the required movements of the robot manipulator to position the patient correctly for each treatment beam. The treatment room will also be equipped with a digital radiographic system, which will consist of the x-ray equipment needed to acquire both stereo and portal radiographs of the patient. The stereo radiographs, together with video images of the treatment mask obtained from one of the SPG systems, will be used to determine the small corrections that may be needed to compensate for the possible misalignment of the treatment mask on the patient. The portal radiographs will be used to verify that the patient is indeed in the correct treatment position. Adequate safety systems will be provided for the robot manipulator.

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Biological Weighting of Absorbed Dose in Radiotherapy

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Absorbed dose is a quantity, which is scientifically and rigorously defined. It is used to quantify the exposure of any biological system to ionizing radiation.

There is, however, no unique relationship between absorbed dose and induced biological or clinical effects, and the quantity absorbed dose alone cannot predict these effects. Other factors have to be considered such as: “time factor”, radiation quality, level of biological effect/endpoint and, more generally, technical conditions under which radiological treatments are delivered. A “weighting factor”, W, is applied to correlate/link absorbed dose and biological effect.

For fractionated external beam therapy, the influence of the dose per fraction is recognized and there is a general agreement on the use of the α/β model to normalize doses for differences in fraction size. There is also an agreement on the numerical values of α/β for late and early tissue reactions (3-4 and 9-10 Gy, respectively). In brachytherapy, the problem is more complex. In addition to the α/β model, a half-time factor for repair kinetics, $T_{1/2}$, has to be introduced ($\approx$2 h for late responding and 1 h for early responding tissues, with larger uncertainties than on the α/β values).

Based on the above assumptions, weighting factors $W_{\alpha/\beta}$ for differences in fractionation, and W_{rate} for brachytherapy applications can be derived. The corresponding weighted doses (expressed in Gy) are $D_{\alpha/\beta}$ and D_{rate}, respectively. The references are the current fractionation (2 Gy per fraction) and the (historical) dose rate of 0.5 Gy per hour.

In hadron therapy (neutrons, protons, heavy ions,..), the RBEs, and their variations, for the different radiation qualities are well documented. From these experimental sets of data, a weighting factor, W_{RBE}, can be derived and applied to the absorbed dose when prescribing the dose to the patient. Selection of W_{RBE} is based primarily on the (experimental) RBE data, but it also implies a medical decision and clinical judgment. W_{RBE} depends on dose and biological system (e.g., late vs early effects), but it often also includes factors such as subtle differences in dose distribution, small changes in time factors (or even personal/exchanged clinical experience).
A similar symbolism can thus be used for all radiation therapy modalities: the biologically weighted dose is the product of the absorbed dose, D, by the biological weighting factor, W. When reporting the treatments, it is important that in addition to the biologically weighted dose (which is expressed in Gy) the absorbed dose is always specified, as well as the applied W factor. When needed, suffices may used to avoid confusion ($D_{\alpha/\beta}$, D_{rate}, D_{RBE}, etc).

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Micronucleus response of human glioma cells to low-LET photons and high-LET p(66)/Be neutrons.

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The benefit of neutron irradiation requires the identification of photon resistance and neutron sensitivity in tissues. The micronucleus (MN) assay was evaluated for this purpose in an *in vitro* model comprising a range of human glioblastoma and neuroblastoma cell lines. We show that p(66)/Be neutrons are 1.43-5.29 times more effective per unit dose in inducing micronuclei than ^{60}Co γ-rays. As cells become more photon resistant the MN yield tends to increase and significant correlations are demonstrated to exist between photon sensitivity and MN yield ($r = 0.66$, $P = 0.07$ and $r = 0.59$, $P = 0.12$ for photon and neutron irradiation, respectively). Determination of mean inactivation dose (Đ) shows that the relative biological effectiveness (RBE) and photon sensitivity are significantly correlated ($r = 0.89$, $P < 0.01$), indicating a potential therapeutic gain for photon resistant cells. Early irradiation damage reflected in the MN response in this panel of cell lines is strongly LET-dependent and emerges as a sensitive indicator of the lethality of irradiation, as indicated by the fact that the neutron dose required to generate a micronucleus is 1.33-5.59 times lower than for photon irradiation. It is also demonstrated that cell lines producing a minimum of 0.17 and 0.35 MN per binucleated cell per Gy of photons and neutrons, respectively, show an RBE advantage.

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Intestinal crypt regeneration for intercomparison of five Neutron Capture Therapy (NCT) beams. (First evaluation).

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As part of an IAEA sponsored program, the beams of 5 NCT facilities have been radiobiologically intercompared using intestinal crypt regeneration in mice as biological system. No boronated compound was administrated, the experiments aiming at determining the RBE of the "free" beam, i.e. of the combination of the gamma (Dγ), the high-LET proton (Dp) and fast neutrons (Dn) components.

Each Center was visited by the same team who performed the experiments in reference conditions and according to the same procedure : control gamma irradiations carried out simultaneously with reactor irradiations ; animals irradiated to the whole body ; application of 6 - 10 increasing doses ranging from 8 to 18 Gy gamma equivalent ; randomization according to beam quality (control gamma *versus* reactor beam) and dose levels ; animal sacrificed 3.5 days after the end of the irradiations. The mice were irradiated per group of 4 and held in a custom made jig. For NCT irradiations, the jig generally formed part of a solid Lucite phantom (approximate dimensions 30 x 20 x 14 cm^3) that was positioned with its front face at the aperture of the beam collimator. The depth of the mice, measured from the mid-line of the abdomen to the front surface of the phantom, ranged between 1.5 cm and 2.6 cm ("clinical depth"). Other depths were also tested in some centers.

Dosimetry was performed at each of the locations where the mice were positioned. The doses reported were measured by the local medical/physics team and are those on which the doses to the patient are based. Proportion of the dose components varied from one NCT beam and from one depth to another: typically the beams at the clinical depth contained 70 - 80% gamma and 30 - 20 % high-LET proton/fast neutrons. Dose rates (at the clinical depth and the center of the field) were substantially different and ranged between ~ 3 Gy /h (Petten) and ~30 Gy/h (M.I.T). Total dose at the edge of the field (~ 20 cm diameter)

was generally lower by 15% than the dose at the center. However, the relative contribution of the different dose component did not vary significantly across the field.

NCT beam RBEs were determined at the level of 20 regenerated crypts per circumference in reference to gamma (delivered with a "high" dose rate of ~ 1 Gy/min). RBEs at the clinical depth (and corresponding NCT dose and irradiation times) were found equal to : 2.2 (5.9 Gy, 113 min) at Petten, 1.7 (7.35 Gy, 70 min) at Espoo, 1.6 (6.76 Gy, 15 min) at Cambridge and 1.4 (8.6 Gy, ~ 60 min) at Bariloche (data for Tokai will be available shortly). RBE at other depths were found to decrease or increase when the gamma contribution increases or decreases, e.g. RBE of the M.I.T beam decreased from 1.6 at 2.6 cm depth (77% gamma) to 1.1 at 10 cm (90% gamma).

Interpretation of the former data is particularly difficult because the physical/dosimetric characteristics of the beams and the dose rates are different. Dose rates of NCT beams fall in the range where the "dose rate effect" (affecting mainly the gamma component) is the most marked. They are thus likely to determine the RBE in a substantial extent, concurrently with the dosimetric/physical characteristics of the beam. Standardization of dosimetry and further assessment of the dose rate effect should make it possible to derive the RBEs for each particular dose component, which is an important step towards harmonization in prescribing, recording and reporting NCT treatment.

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Radiosensitization of neutron damage using a halogenated pyrimidine.

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Background: Bromodeoxyuridine (BrdU) is known to be a sensitizer of biological damage induce by conventional radiation modalities but it is unknown what influence this drug may have following irradiation with neutrons. In general, chemical modifiers of radiation damage are reliant on the modification of radical species and are much less effective in cells exposed to neutrons or other sources of high-LET radiation. Cells in S-phase however, are radioresistant but incorporate BrdU directly into their DNA. Therefore, it is likely that the sensitizing properties of this type of drug may be more appropriate for neutron irradiations. The purpose of this work was to compare the extend of radiosensitization with BrdU in cells exposed to the clinical neutron beam and ^{60}Co gamma rays.

Methods: CHO-K1 cells were grown for 48 hours in medium containing 2 μM BrdU. Before irradiations, cultured monolayers were trypsinized and any unbound drug was rinsed from the cell samples. The clonogenic capacity of treated and control cells were measured one week after irradiations.

Results: The drug alone had no influence on the plating efficiency of cells. Drug plus radiation however, resulted in sensitization with a dose modifying factor of 1.6 ± 0.2 for ^{60}Co exposures. The same degree of sensitization is seen for cells exposed to neutrons (DMF 1.6 ± 0.2). In a second set of measurements these values change to 1.4 ± 0.3 for ^{60}Co and 1.3 ± 0.2 for neutrons.

Conclusion: The dose modifying influence of BrdU is similar for neutrons and conventional low LET radiation. It would therefore be sensible to use BrdU as a sensitizer in neutron therapy for fast growing radioresistant disease.

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ICRU - International Commission on Radiation Units and Measurements: ICRU Activities in the proton beam therapy field.

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The ICRU was created by the First International Congress of Radiology (ICR), in 1925, with the mandate to develop an internationally accepted unit for x-ray exposure. The röntgen ("R") was defined in 1928.

The main current objective of the ICRU is to develop a set of quantities and units, applicable in all fields where ionizing radiation is used, and on which there could be an agreement at the international level. The ICRU also recommends methods for measuring these quantities, after careful and critical review, and comparison of the existing methods.

The following ICRU Reports are especially relevant to the field of proton beam therapy :

- ICRU Report 60 (1998): Fundamental Quantities and Units for Ionizing Radiation.
- ICRU Report 49 (1993): Stopping Powers and Ranges for Proton and Alpha Particles, with Data Disk.

- ICRU Report 63 (2000): Nuclear Data for Neutron and Proton Radiotherapy and for Radiation Protection, with Data Disk.
- ICRU Report 59 (1998): Clinical proton Dosimetry. Part 1 : Beam Production, Beam Delivery and Measurement of Absorbed Dose.

In the field of radiation therapy, the ICRU has been involved for many years in efforts towards improving harmonization and uniformity in reporting. In that respect, the following reports are relevant:

- ICRU Report 29 (1978): Dose Specification for Reporting External Beam Therapy with Photons and Electrons.
- ICRU Report 50 (1993): Prescribing, Recording and Reporting Photon Beam Therapy and ICRU Report 62 (1999): Supplement to Report 50.
- ICRU Report 38 (1985): Prescribing, Recording and Reporting Intracavitary Therapy in Gynecology
- (a revision is in preparation).
- ICRU Report in preparation (2003): Prescribing, Recording and Reporting Electron Beam Therapy.

A report of the same type is in preparation for proton beam therapy : "Prescribing, recording and reporting proton beam therapy". The report, sponsored jointly by the ICRU and the IAEA (International Atomic Energy Agency), is intended to update ICRU Report 59, and to address other issues such as treatment planning, heterogeneity, radiobiology/RBE, etc. Selection of reference points for dose specification, and definition of volumes for reporting will also be discussed.

Terms and concepts, recommended in previous ICRU reports (and already in clinical use), for photon beam therapy should be applied whenever possible. A certain number of issues in proton beam therapy are also encountered in conformal photon beam therapy (e.g. dose heterogeneity within the planning target volume). Therefore, interactions and exchanges are foreseen with the current ICRU Committee on "Prescribing, Recording and Reporting Conformal Photon Beam Therapy".

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Establishing a Proton Therapy Center - A Beginner's Guide to Available Resources.

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Almost five decades after the first human treatment with a proton beam, there are about 20 centers in operation and about another 20 in the planning or construction phase. The recent growth rate of the proton therapy community can be attributed to several factors, principally good patient outcomes and economic competitiveness with more traditional photon and electron beam therapies. Several commercial vendors now offer proton therapy systems, and this relatively recent development may well remove some of the barriers that prevent hospitals from acquiring proton therapy facilities. For example, the hospital no longer needs to mount an expensive and lengthy ground-up design effort. During the construction and clinical phases, the hospital may elect to subcontract portions of the facility operation and maintenance to the vendor, eliminating the hospital's need to recruit and train a large group of technicians and engineers. This very positive trend is increasingly allowing the hospital's technical staff to focus on clinical topics such as patient care, research, and development.

Today, a medical physicist responsible for establishing a new proton therapy program faces a substantially greater effort therapy than would be the case for a conventional radiation therapy. This fact can not be attributed solely to the proton physics and therapy equipment since these are of comparable complexity to those in conventional therapy. Rather, there is a scarcity of widely accepted guides and recommendations for the implementation of the clinical physics and quality assurance programs. In addition, many of the procedures vary substantially between centers. There have been recent efforts toward achieving standardization, *e.g.*, in proton dosimetry, but in general the proton therapy community has not yet standardized and documented its methods to the same extent as in conventional radiation therapy.

Fortunately, much of the information needed to establish a new proton center is available from a variety of sources include the scientific journals, conference proceedings, and hard-to-find internal reports and unpublished manuscripts. In the case of proton dosimetry, there is the interesting problem created by the existence of multiple guides that differ substantially from one another, despite having been published in rapid succession by respected international advisory bodies. Interim guidance is available until the differences are satisfactorily reconciled. In other areas, the recommended practices from external beam photon and electron therapy may be adapted for use in a proton clinic.

In this presentation, we aim to provide the novice proton medical physicists with an overview of literature resources *of practical value* in establishing a new proton center. In particular, we will emphasize the literature that we have found helpful in establishing new proton therapy centers in Boston (Massachusetts General Hospital) and in the planning phase of the

Houston project (University of Texas - M. D. Anderson Cancer Center). We will also briefly mention efforts that are underway to standardize and document the quality assurance of proton therapy.

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The Relative Costs of Proton and X-Ray Radiation Therapy.

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Goals: We have studied the costs of intensity modulated proton therapy and intensity modulated x-ray therapy with the particular goal of understanding their relative differences. We have therefore focussed on analyzing the ratio of the cost per fraction of proton therapy to the cost per fraction of x-ray therapy.

Materials and Methods: We have used a computer spreadsheet tool in which a large number (typically 130) of input parameters characterizing a particular therapeutic modality can be stored. From these parameters a number of derived variables are computed, and from these derived variables the costs of sub-systems, the entire facility, running costs and cost per fraction and per treatment can be computed. The sensitivity of any given variable (e.g. cost/fraction) to any given parameter (e.g. set-up time) can be explored, together with an estimate of the associated confidence interval. The costs of facility construction and facility operation are considered separately.

Key data for the input variables regarding the cost of the therapy equipment (a dominant cost for proton beam therapy) were provided by four commercial vendors. Other costs, such as costs for building construction and shielding or personnel costs, are much more standard and our estimates were primarily based on practical experience.

We considered two scenarios: (1) both facilities operating under current conditions; and (2) future facilities where foreseeable improvements in efficiency and a 25% reduction in the cost of the proton equipment were assumed.

Results: The construction cost of a current 2-gantry proton facility, complete with the equipment, was estimated at 62,500k euros and of a 2-lincac x-ray facility at 16,800k euros. The cost of operation of the facility was found to be dominated, in the case of proton therapy by the business cost (42% - primarily the cost of repaying the presumed loan for facility construction), personnel costs (28%) and the cost of servicing the equipment (21%). For x-ray therapy, the cost of operation was seen to be dominated by the personnel cost (51%) and the business costs (28%). The costs per fraction were estimated to be 1.025k euros for protons and 0.425k euros for x-rays - for a ratio of costs of 2.4 ± 0.35 (85% confidence). In a future facility these costs could be reduced to 0.65k euros and 0.31k euros respectively, leading to a ratio of costs of 2.1. A number of further improvements could be imagined which could reduce the ratio of costs by some 20%.

If, however, the initial capital investment were "forgiven," so that the operating costs need not repay the investment, both the costs and the ratio of costs would be significantly less. We estimate that, under this condition, the future costs of proton and x-ray therapies would be 0.37k euros and 0.23k euros respectively - for a cost-per-fraction ratio of 1.6. This ratio could also be susceptible to a further 20% reduction.

Conclusions: Sophisticated (i.e. intensity modulated) proton therapy is now, and is likely to continue to be, more expensive than sophisticated (i.e. intensity modulated) x-ray therapy. The ratio of costs is about 2.4 at present and could readily come down to 2.1 and, even, perhaps 1.7 over the next 5 to 10 years. If recovery of the initial investment is not required, the ratio of costs would be much lower, in the range of 1.6 to 1.3. The question of whether the greater cost of proton beam therapy is clinically worthwhile is a cost-effectiveness issue. The goal of this study is to contribute to the former arm of this comparison.

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Proposal for documentation – one step towards togetherness

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Our way to the best possible togetherness in particle radiation therapy has to lead us to a careful and meaningful documentation of our daily work in all aspects. We are well trained in writing grant applications to cancer leagues and other foundations, and we are also successful in publishing our results. Technical developments, physics tools or problems and positive medical outcome are subjects to write about. But when we come to really compare these results, we will detect that, though we all document our work, understanding in depth what has been done with a patient is not always so easy. We may ask

ourselves whether this deep understanding is needed, because in the end we want to prove that we can deliver a defined dose to a defined tumor and out comes a defined result. Really? I think: this is no longer sufficient - and not interesting enough for the "non-particle community". Pointing out the "dose bath" provokes resistance rather than interest in a method that can avoid it. Proving "what is better" becomes increasingly difficult as conventional radiation therapy becomes increasingly sophisticated. Therefore we should follow joint guidelines, which help us to prove why! and not only that the performance and medical outcome of particle radiation therapy is excellent if not superior to other radiotherapy modalities.

In the course of the application for reimbursement by the Swiss Health Insurances PSI has delivered a documentation that includes amongst other facts a list of topics, which we felt were necessary to a) document what we have done and b) why the treatment outcome is the way it appears. The *why* is important, though the effort to ask us that question is not minimal. I think we should try to know why we are good as well as why we fail. Clinical symptoms for instance which attract much attention after radiation therapy may have been pre-existing but not perceived and not documented before irradiation. Other therapies, even though they may not be tumor related, may have substantial influence on the patient's tolerance of radiation, repair, response and post-therapeutical status and development. We are not beginners in the field of tumor therapy and radiation therapy in particular. Therefore we can positively stimulate each other's and our own performance by documenting in a standardized though permanently reflected and consequently communicated way.

I would like to emphasize a joint effort to share documentation forms in order to be able to better analyze our results in comparison with other particle centers, other beam qualities, various application technologies and in particular with state of the art conventional radiotherapy. In addition, I see particle therapy very much in the context of combination therapies. If we don't have a particularly good way of documenting clinical, technical and physical facts, particles will be at risk to not be acknowledged for success but rather for the problems, acute side effects, long-term complications and therapy failures. If we want to play a definite role in modern cancer therapy, we should start to play with each other – seriously, now.

You will get the proposed documentation forms from PSI via e-mail, and I would be very happy to receive constrictive critique and support from a vivid community.

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BANG polmer gel dosimetry for 68 MeV protons.

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BANG polymer gel dosimetry using MRI was applied to an ophthalmologic 68 MeV proton beam. The object was to examine the use of BANG gel for the verification of proton fields in eye tumor therapy and to explore the applicability of polymer gel dosimetry in proton therapy under practical aspects. The gel phantoms were irradiated with monoenergetic and modulated proton beams. Magnetic resonance imaging (MRI) analysis was carried out at clinical 1.5 T and 3 T MR scanners. Results show at constant LET a linear relationship between spin-spin relaxation rates and dose. However, depth dose curves in BANG gel reveal a quenching of the Bragg maximum due to LET effects. The depth dose response of the gel for monoenergetic protons and spread-out depth distributions can be calculated based on ionization chamber measurements. Experiment and calculations show good agreement and indicate that BANG polymer gels might become a valuable tool in proton therapy quality assurance.

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Selected Characteristics of Si Diodes with a Nearly Tissue-Equivalent Dose Response.

V. Luckjashin, V. Khrunov, V. Kostjuchenko, D. Nichiporov

Extremely high pulse dose rate of the proton clinical beam at ITEP impedes the use of such an ubiquitous instrument as ionization chamber. This circumstance has stimulated a quest for a field dosimeter that could be used in place of an ion chamber. The research efforts, began in the 1980 together with our Swedish colleagues, have resulted in the development of a

semiconductor detector of our own design. The energy dependence of the newdetector's response to proton irradiation is close to that of tissue. Some of the new detector's characteristics will be presented along with the properties of another, mass-produced and commercially available, semiconductor diode.

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Energy spectra of TLABS' proton therapy beams.

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A proton pair spectrometer has been developed to measure energy spectra of proton therapy beams at the iThemba Laboratory for Applied and Basic Sciences (TLABS). The spectrometer is based on proton elastic scattering in a thin polyethylene radiator and uses two ΔE-E detector telescopes to detect coincident proton pairs. The polyethylene radiator is located at the treatment isocentre and the two ΔE-E detector telescopes are placed symmetrically about the beam axis such that the energy of the scattered and recoil protons satisfying the detection conditions (coincident proton pairs) is half the incident proton energy. The spectrometer was used to investigate the effect of standard beam modification elements on the energy spectra of proton therapy beams produced by the passive scattering beam delivery system. Monte Carlo calculations of spectra of proton therapy beams at the TLABS' proton therapy facility were computed with the MCNPX Monte Carlo code to compare with the experimental results.

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A Secondary Emission Monitor for the iTL Proton Clinical Beamline.

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A secondary emission monitor (SEM) was built and installed in the iThemba LABS (iTL) proton clinical beam line to complement the existing monitor, a plane parallel transmission ion chamber. The circuitry of the SEM is designed so as to facilitate measurements with devices that use either "normal" or "floating" ground. The SEM design and its placement in the beam line allow the monitor to be used for absolute measurements of the primary beam fluence. Results of the SEM evaluation tests will be presented. The new instrument's versatility, good performance and reliability make it an attractive choice as an additional beam monitor and reference detector.

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The implementation of a voxel-based Monte Carlo code for direct dose planning in proton therapy.

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Introduction: The clinical routine treatment with protons is in need of fast and accurate algorithms for dose calculations. While this is already done with the phenomenological description of dose distributions through pencil beam algorithms, there is still demand for alternative methods to verify the calculated dose distributions or to support their accuracy. For this purpose the Monte Carlo technique is well suited. We therefore introduce a voxelbased Monte Carlo code for 3-D treatment planning in proton therapy, which shall be built in a conventional RTP system.

Materials & Methods: The Monte Carlo code is voxelbased and therefore determines, in a simple way, the dose distribution for extended media and arbitrary direction and energies of the protons. Furthermore, each voxel can be assigned a different chemical composition and density. It therefore naturally allows the use of CT-images. In analogy with the Monte

Carlo code *Ptran* (Berger ´93) the transport of protons follows a grouping of events. In this way the code accounts for the inelastic Coulomb interactions with the atomic electrons and the elastic Coulomb interactions with the screened-atomic nuclei in a condensed random walk, describing energy loss and range straggling. Unlike Ptran the non-elastic interactions with the atomic nuclei are treated on an event by event basis. Therefore, the production of secondary particles (protons, etc.) is considered to handle the relevant impact of the dose contribution from non-elastic interactions. Together with the condensed random walk this procedure yields a realistic outcome in respect to the dose distribution from protons. The data used for the Monte Carlo procedure are taken from the reports ICRU49 and ICRU63.

Results: This Monte Carlo code will be presented and compared along with the results of established Monte Carlo codes and experimental data. Furthermore, examples for simple inhomogeneous phantoms will be shown. The aim will be to show the application for arbitrary CT-data-sets, in which the density and chemical composition is given by the HU unit, and the integration into an existing RTP system.

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The proton treatment facility at HMI.

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Since 1998, the Hahn-Meitner Institut Berlin operates a proton beam eye treatment facility in cooperation with the Benjamin Franklin University clinic. At the ion beam laboratory a proton beam with a maximum energy of 72 MeV is available. Due to the limited beam energy only eye tumors can be treated. Ten treatment weeks with 68 MeV protons are scheduled per year. From June 1998 to September 2002, altogether 298 eye tumor patients have been irradiated. 80 % of the proton beam indications are medium-sized, posterior uveal melanomas close to the optic disc and/or macula (distances to tumor base < 3 mm). Other indications are hemangiomas (10 %), iris melanomas (8 %) and conjunctival melanomas (2 %). First results after 3 years follow-up indicate local tumor control rates of 93 %.

Special features of the Berlin eye treatment facility are the treatment chair and the use of X-ray image intensifiers instead of polaroid film for patient alignment. Treatment planning is done using EYEPLAN together with high-resolution CAT scans of the tumor eye in straight-ahead fixation. Additional software is used to verify the EYEPLAN model with the CAT data.

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Transit dose calculations in HDR brachytherapy revisited: the Sievert Integral.

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The transit doses around a HDR ^{192}Ir stepping source is calculated using Sievert Integrals. These have been introduced to build more versatile models whilst not compromising accuracy. Calculations were performed at positions in which, the moving source, instantaneously, had its geometrical centre located exactly between two adjacent dwell positions. The dose rates in these positions were obtained from the Sievert Integrals, making use of absorption coefficients, obtainable from *XMuDat, IAEA Nuclear Data Section*. Discrete step sizes of *0.25 cm* were chosen to calculate the dose rates and the total transit dose at any of the calculation points evaluated. The exercise was repeated by applying the *MCNP 4B* computer code using *ENDF/B-VI* data. Using our Monte Carlo Simulation results as a standard the Sievert Integral calculations produce dose calculation errors ranging from *–32* to *-21 %* for the examples considered. The error introduced by the Sievert Integrals to the prescribed dose for complex implants could be in the neighbourhood of 5 %. For simple implants or standard applicators the error introduced by the transit dose will be acceptable, typically less than *1 %*. The transit doses however need to be calculated more accurately when the source goes through an appreciable thickness of tissue, otherwise assumed to receive negligible radiation dose, before stepping at the proximal dwell site. Using the Monte Carlo simulations a Mathematical Model to correct for the shortfalls of the Sievert Integral is presented.

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