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ABSTRACTS

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A preliminary report of a clinical trial at the new proton therapy facility at Tsukuba.

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We started treating patients with proton therapy at the newly constructed facility in the campus of the University of Tsukuba Hospital in September 2001. Fifty-one patients were entered in the trial as of March 31, 2002. There were 10 men and 32 women. A median age of the patients was 67 years ranging from 11 to 90. Of the patients 17 had hepatocellular carcinoma, 10 lung cancer, six head & neck (H&N) tumors and remaining patients had miscellaneous tumors. We irradiated 59 tumors in the 51 patients. Of the 59 tumors 28 were in the liver, 11 in the lung, 6 in the H&N, remaining 18 in the miscellaneous organs. Of the 59 tumors irradiated 48 were primary tumors and 11 metastatic tumors. Of the 59 tumors 43 were irradiated with proton beams alone and remaining 16 with a combined x-rays and proton beams. We irradiated 20 hepatic tumors in the 17 patients with proton beams alone. Doses given to the 20 tumors were a median of 64.5 Gy in 15 fractions with a range of 50-72 Gy in 10-22 fractions.

We have two treatment rooms with one each rotating gantry. It takes about 15-20 min to irradiate a patient with an average 1.5 ports. The treatment time comprised of 2-10 min of irradiation and 8-15 min of preparation. We currently irradiate 10-15 patients a day. An estimated maximum number of patients to be irradiated in six hours is about 50 patients.

After we obtain a safety approval by the government for the irradiation apparatus, we will proceed to obtain a permission to charge a patient for proton therapy.

Representative cases treated and clinical protocols at the center will be presented.

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Clinical parameters related to the visual acuity in treatment of head and neck.

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In the radiation therapy of head and neck cancer, the preservation of the visual acuity is of paramount importance for both patients and doctors. Between June, 1994 and March, 2000, we treated 163 patients with head and neck cancer, 54 optic nerves (ON) in 30 patients were included in PTV. The median age of 30 patients was 57.2 years (range, 22-79) with 14 males and 16 females. Visual acuity of 54 ON shows no disorder at the treatment of carbon ion radiotherapy. Minimum follow up periods was 2 years.

Median prescribed target dose was 56.0 gray equivalent (GyE) (range, 48-64 GyE) at 3.0-4.0 GyE per fraction per day. (Table 1) The optic nerves were outlined on planning CT to allow dose-volume histograms (DVH) analysis. Average volume was 1.68 ml (range, 0.8-3.1).

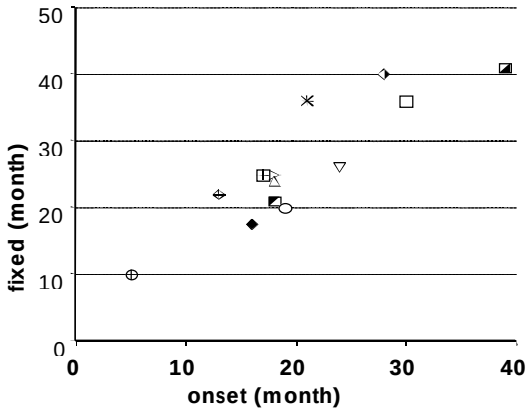
Twelve ON in 10 patients showed the decline of the eyesight in 19.6-month (range, 5-39) and loss of eyesight in 25.6-month after irradiation: the shortest 10 months and the longest 41 months. (Fig. 1)

In this paper, we estimated the relationship between dose and probability of neuropathy.

Table 1. Details of target dose

GyE/fractions	n
48/16	3
48.6/18	1
52.8/16	6
57.6/16	17
64/16	3

Figure 1. Analysis of correlation



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Patient positioning with vacuum bite block for proton therapy of head and neck tumors: First experience and outlook to the future.

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At PSI, patients undergoing proton therapy at the spot scanning gantry are positioned outside the treatment room. Position verification is done on a remote CT by comparison of several CT slices with the slices of planning CT and measurement of several points on scouts view. Patients are brought inside the treatment room in their mould after position verification and necessary corrections have been completed.

For head and neck tumors, patients are positioned with a vacuum bite block, which is a very straightforward procedure to obtain high precision positioning. We will analyze the positioning precision obtained with this system. We will also discuss the time necessary for precise positioning of the patient, the personal required for an optimal use of the irradiation facility and raise the question whether in a new facility, patient positioning should also be done outside the treatment room or preferably inside the treatment room.

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Proton radiation therapy of deep seated lesions at PSI – Update 2002.

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Since PSI took up proton radiation therapy of deep-seated tumors on the spot-scanning gantry, a total of 99 patients have been treated by the end of 2001. 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 fife to sixty-six months, median 30.5 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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Clinical commissioning of Gantry 1 at the Northeast Proton Therapy Center.

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The clinical commissioning of the first gantry at the Northeast Proton Therapy Center (NPTC) qualified the use of the gantry for clinical operations, produced the data necessary for input to, and verification of, the treatment planning system, and established an essential understanding of the operational behavior of the gantry. The commissioning measurements can be divided into dosimetric measurements, geometric measurements, operational and control system verifications, and their interdependencies. The dosimetric measurements focused on exercising the beam nozzle over its full operational range and to quantify the pristine proton peaks and SOBPs over this range. The geometric measurements focused on quantifying the accuracy of the patient positioning devices and the patient alignment with respect to the gantry and nozzle. The operational aspects of the gantry operation also required close scrutiny as the system is, in essence, a software driven system. Commissioning commenced in September 2001 and the first patient was treated on November 8 2001. We present our data acquired for the commissioning tasks, discuss the logistical effort to commence treatments, and the experience in the first phases of clinical operations.

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DVHs analysis of the brain treated by carbon ions for Astrocytoma grade 2.

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The DVHs of the brain, delivered from the patients treated by carbon ions for their astrocytoma grade 2, were analyzed to determine the dose-complication probability for late toxicity.

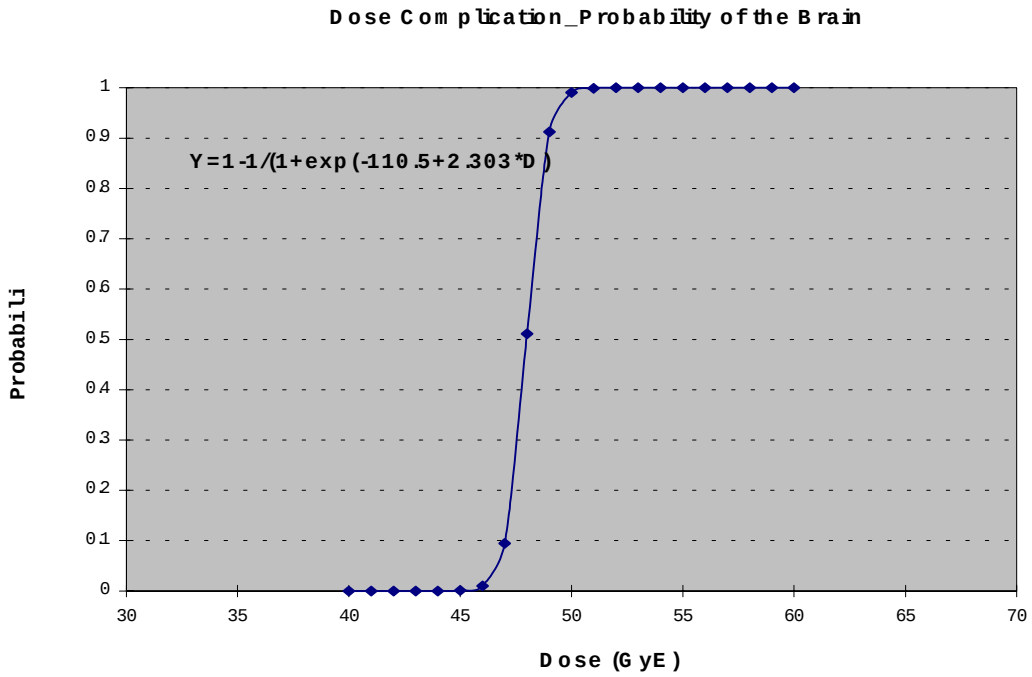
Twelve patients with astrocytoma grade 2 were treated on a phase I/II dose escalation protocol of carbon ions at NIRS between September 1994 and February 2001. Eligibility criteria included biopsy proven astrocytoma grade 2, age between 18 and 80 years, Karnofsky performance sore of 60 or greater, and no infection and no wide degeneration. Median age of the patients was 31 years (range 18-48) with 8 males and 4 females. The sites of disease were consisted of 5 frontal, 2 temporal, 2 basal ganglion, 1 parietal, 1 occipital and 1 corpus callosum respectively.

Fractionation method of 24 fractions through 6 weeks was applied with fraction dose of 2.1 and 2.3 GyE(photon equivalent dose). Of the 12 patients, 4 developed grade 1 and 2 late toxicity of LENT/SOMA MRI Scaling System. Integral DVHs were calculated using planning CT and dose-complication probability was calculated at 10% high dose volume. Calculated equation of logistic model was follows;

$$P = 1 - 1 / (1 + EXP (-110.5 + 2.303 D))$$

P: Probability of late toxicity more than grade 1 (LENT / SOMA MRI Criteria)

D: Dose (GyE) at 10 % volume in integral DVH of the brain



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The prevention of radiation damage on bone due to heavy ion particle radiotherapy.

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Osteoradionecrosis (ORN) of the mandible is a severe complication due to radiotherapy in the head and neck region, which is known as progressive radiation damage. It is a complex metabolic and tissue homeostatic deficiency created by radiation-induced tissue injury. And the occurrence of ORN of the mandible to any extent can cause morbidity and pain second only to the development of recurrence, metastasis or second tumor in the area.

Heavy ion particle irradiation has excessive biological effects than X-Ray irradiation in all of tissues. Until now, we made clear that carbon ion irradiation caused more decrease in trabecular Bone Mineral Density (BMD) than X-Ray irradiation (Fig. 1). Then Schmitt J. has reported that ORN presented with different signal intensities depending on the time elapsed after radiation therapy. We thought that ORN is related to decrease in BMD, and thus, increase in BMD leads to prevention of ORN.

At present, there are two kinds of compounds to improve bone metabolism and to maintain and increase BMD. One has an inhibitory effect of bone absorption acting to osteoclast cells, for example, bisphosphonates, and the other has an enhancing effect of bone formation acting to osteoblast cells like statins. Bisphosphonates, analogs of pyrophosphate, bind to bone at sites of active bone remodeling. In clinical settings of rapid bone turnover and/or excessive osteolytic activity, they have shown to have beneficial clinical effects. Bisphosphonate inhibition of osteolysis in cancer has shown to be effective as an adjunctive therapy for the delay or prevention of cancer-related skeletal morbidity, including bone pain, pathologic fractures. Animal models of bone metastasis prevention by bisphosphonate treatment have provided the preclinical background for the adjuvant use of bisphosphonates in primary cancers.

Thus, we consider bisphosphonate is able to prevent the negative effects of radiotherapy on bone and conduct an experimental study.

In this experimental study, we focus on two kinds of bisphosphonate compounds, which are Etidronate and Pamidronate. 35 Female Wistar rats (3 months old) divided into 7 groups: control, 1.0GyE carbon ion irradiation group, 5.0GyE carbon ion irradiation group, 1.0GyE carbon ion irradiation with Etidronate group, 1.0GyE carbon ion irradiation with Pamidronate group, 5.0GyE carbon ion irradiation with Etidronate group, 5.0GyE carbon ion irradiation with Pamidronate group. The rats were injected with a daily dose of 3mg/kg bisphosphonate subcutaneous administration after whole body carbon ion irradiation 3 times a week for 6 weeks. Then we measured tibial trabecular BMD using peripheral

quantitative computed tomography twice every month. Two of the 1.0GyE carbon ion irradiation groups, which were administrated Etidronaate and Pamidronate, respectively, presented increase in BMD compared with not only 1.0GyE carbon ion irradiation group but also control group. And highly similar results were observed in the 5.0GyE carbon ion irradiation groups with Etidronaate and Pamidronate (Fig. 2).

It is suggested that Etidronate and Pamidronate have been established as effective in the prevention of decrease of BMD due to carbon ion particle irradiation.

Figure 1. The radiation effects in trabecular BMD

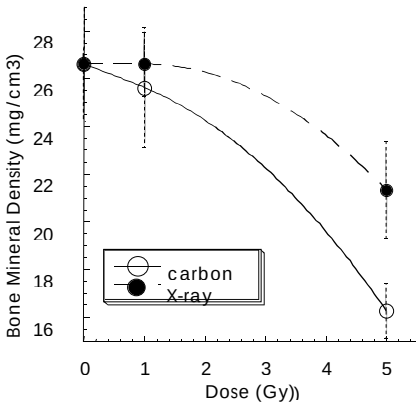
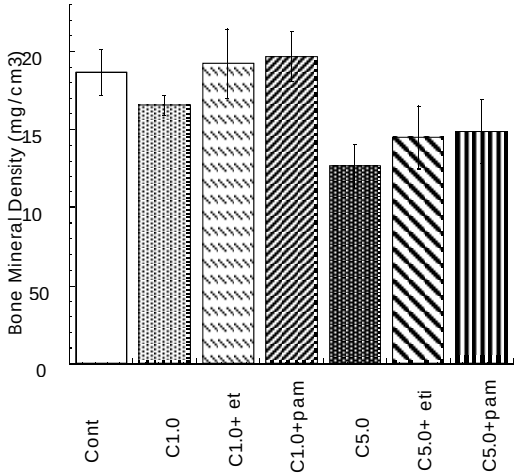


Figure 2. The prevention effects in trabecular BMD



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Dose optimization treatment planning code for proton and carbon ion therapy with a voxel scanning technique.

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We have proposed a new dose optimization analytical code (ANCOD++) dedicated to proton and heavy ion therapy. The objective is to obtain as a solution the optimal set of beam weights distribution. The irradiation technique adopted is an active scanning technique where each of the elementary volumes (voxel) have to be irradiated with a pencil beam. The inverse planning method allows the calculation of the kinetic energies needed to have the maximum energy deposition at the center of the spoted voxel.

The algorithm used consists of iteratively changing the trial incident fluence values of different beams which yields to match the prescribed dose distribution.

A comparison of the analytical estimation and a Monte Carlo simulation with the package GEANT3 shows excellent agreement, indicating that the inverse planning methods for optimizing the plans is efficient enough and allows improving the quality of the treatment planning in a practical time.

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Positron emission Tomography for Quality Assurance of Carbon ion therapy.

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The physical and radiobiological properties of high-energy ions offer the possibility of treating deep-seated, compact and radioresistant tumours with high precision. In delicate therapeutic situations, especially when the tumours are growing in close vicinity to organs at risk, an in-situ verification of the dose localisation is highly desirable. Positron emission tomography (PET) is the only available method for an in-situ and non-invasive monitoring of the precision of the dose application in charged hadron therapy. The physical background is the production of minor amounts of positron emitting radionuclides via nuclear fragmentation reactions following collisions between the incident projectiles and atomic nuclei of the tissue. In the case of carbon ion therapy the most abundant isotopes are ^{11}C, ^{15}O and ^{10}C.

An in-beam positron emission tomograph has been integrated into the experimental carbon ion therapy facility at the Gesellschaft für Schwerionenforschung, Darmstadt (GSI). Its technical basis are components of PET-scanners as applied for radiotracer imaging in nuclear medicine. However, operating PET simultaneously with therapeutic irradiations requires dedicated solutions in detector geometry, data acquisition and processing as well as in tomographic reconstruction techniques.

After more than 4 years of clinical operation first conclusions on the benefit of the in-beam PET method for improving the precision of ion therapy may be drawn. PET is capable of detecting deviations between the prescribed and the delivered spatial dose distribution. Since the distributions of dose and of β^+-activity may remarkably differ for physical reasons, a special technique for identifying dose deviations has been developed: we compare the spatial distributions of the measured β^+-activity with those predicted on the basis of the treatment plan, the anatomical information from computed tomograms of the irradiated region and the time course of the particular treatment fraction [1]. The reasons for dose deviations have been identified as (*i*) unavoidable deficiencies of the physical beam model used for treatment planning, (*ii*) minor errors in patient positioning in combination with steep tissue density gradients in the beam path as well as (*iii*) local and frequently temporary changes in the patient anatomy leading to density modifications of the irradiated tissue. While being rather uncritical in conventional radiotherapy, such slight inaccuracies may severely modify the dose distributions delivered by ions. To quantify these local dose deviations on the basis of PET data, an interactive procedure has been developed.

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Experimental investigation of the potential of in-beam PET for the monitoring of proton therapy.

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Positron-emission-tomography (PET) is potentially a powerful tool for the in-situ and non-invasive control of the precision of the dose application in charged hadron therapy. The clinical implementation of in-beam PET monitoring at the heavy ion tumor therapy facility of GSI Darmstadt has proven the important impact of the method on the quality assurance of high precision carbon ion therapy [1]. In perspective of the dedicated ion beam tumor therapy facility of Heidelberg, Germany, which is planned to deliver particles from protons up to oxygen nuclei, we started to investigate the potential of in-beam PET for the monitoring of proton therapy. The extension is non-trivial, since protons do not suffer the projectile fragmentation reactions originating a sharp maximum of the β^+-activity in close proximity to the dose maximum in the carbon ion case.

Following our previous promising but preliminary investigation [2] entirely based on Monte Carlo simulations, a first experiment was performed: three mono-energetic proton beams in the energy and intensity range suited for the treatment of

deep-seated tumors were completely stopped in blocks of PMMA ($C_5H_8O_2$) positioned in the center of the field of view of the in-beam PET scanner installed at the treatment unit of GSI Darmstadt. The amount of β^+-activity was found to be three times larger than that induced by carbon ions at the same range and the same applied physical dose. The reconstructed β^+-activity distributions were well reproduced in shape by calculations based on experimental cross-sections and on the proton flux given by the FLUKA Monte Carlo code.

Despite the weaker spatial correlation between β^+-activity and dose depth-distributions in the proton case, the presented experiment supports the feasibility of in-beam PET for the in-situ monitoring of proton therapy based on a comparison between measured and realistically calculated β^+-activity distributions, as already implemented for carbon ion therapy.

This work is supported by the Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie of Germany (grant 06DR825).

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Potential use and specifications of a dedicated positron emission tomography system to the hadrontherapy project "ETOILE".

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The Project "ETOILE": Protontherapy has proven to be very useful for cancer treatment by more than fifteen international centers. More recently, Chiba (HIMAC) and Darmstadt (GSI) centers have treated more than 1000 patients with carbon ion beams and have shown the efficiency of carbon ion beams, particularly in case of tumors being either highly radio-resistant or closely localized to sensitive organs (1,2). However, these clinical results are limited by the small number of treated patients. Therefore, the goal of the project ETOILE (*Espace de Traitement Oncologique par Ions Légers Européen)* is to implant a center for hadrontherapy in the French region "Rhône-Alpes" to extend this new approach of cancer treatment. This project is organized with the French institutions (UCB-Lyon1, UJF-Grenoble1, CNRS/IN2P3, CEA/DSM, HCL, CHU Grenoble, CLB…) in collaboration with the CERN and the five other European projects through the network ENLIGHT. The center will be based on a synchrotron of PIMMS type allowing the production of proton and carbon ion beams at the maximal energy of 200 and 400 MeV/nuclei, respectively. The ion beam will be delivered in three treatment rooms through a dynamic raster scanning and monitored *on line* using a dedicated positron emission tomography (PET) system.

PET imaging in hadrontherapy: The penetration of the ion beam through the tissue induces fragmentation of tissue nuclei (mainly water molecules) with proton beams and also of the primary particles with carbon ions beams. This phenomenon generates positron emitting isotopes which can be detected by PET as shown by GSI (3,4). PET can therefore provide a powerful monitoring tool to measure *in vivo* and *on line* the spatial distribution of both the beam and the dose deposition. For this challenging purpose, a dedicated PET system characterized by a high sensitivity and high accuracy has to be studied.

Development of a dedicated PET system: In collaboration with the CERN, ENLIGHT and the Crystal Clear Consortium (CCC), our goal is to study a new generation of PET system based on new design and technologies to achieve better sensitivity and spatial resolution.

Specifications: 1) large field of view and solid angle allowing the positioning of the patient in the beam path, 2) high spatial resolution (> 4 mm) according with the accuracy of the beam, 3) high sensitivity to compensate the low count rate, 4) insensibility to magnetic field and secondary particles effects.

Development: 1) dedicated design using Monte Carlo simulations, 2) denser, faster and brighter scintillating materials (LSO, LuAP), 3) photodetectors such as MaPMT and APD, and rapid front-end electronic.

Research: 1) simulation of the fragmentation phenomenon and realistic PET images, 2) modeling of the fragmented particles and positrons kinetic and of the delivered dose.

Planning: 1) development of bench prototypes for testing the new crystal-photodetector-electronic configurations consisting of block with 64 crystals (2x2x8mm), 1 MaPMT or 2 APD and new front-end electronic, 2) development of microPET prototype based on the precedent tests, 3) feasibility study of a dedicated PET system for hadrontherapy.

Results: The project "ETOILE" will be presented with the preliminary results obtained either by simulation or testing the new detection blocks developed for the microPET system.

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Method to estimate uncertainties of the range calculation associated with patient respiration.

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Purpose: To propose a method for estimating uncertainties of the range calculation in particle radiotherapy associated with organ motion along with patient respiration.
Methods and Materials: A set of sequential CT images every 0.2 seconds was reconstructed from continuous x-ray projection data accumulated by the dynamic scanning mode in helical CT scanner. At the same time of CT data acquisition, respiratory signal of patient and on/off signal of X-ray on CT scanner were recorded. From these data, the timing of each CT image was related with the phase of respiration waveform. These CT images were analyzed in our treatment planning system that included the function converting from CT number to water equivalent path length (WEL). A set of CT images of the patient with liver cancer at upper right lobe was analyzed. The geometrical sizes of the liver and WELs from body surface to iso-center were measured in each CT image.
Results: WEL variations of depth from body surface to iso-center were 6.2mm and 18.9mm at anterior-posterior and posterior-anterior direction, respectively. Liver size was changed to 35.2mm. However these variations were shown to be considerably reduced by gated irradiation.
Conclusion: The proposed method using sequential CT images with respiration waveform was shown to be useful to evaluate the uncertainties of the range calculation associated with patient breathing. The variation of the depth along the beam path was presented in WEL rather than geometrical length.

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Feasibility of radiotherapy using anti-protons.

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We have begun an investigation into the potential use of antiproton beams in clinical radiotherapy. Observed experimentally for the first time in 1955, antiprotons are the antimatter counterpart to protons, with a negative charge and parity and rest mass of 938 MeV/c^2. Antiprotons have depth dose characteristics similar to protons in that they exhibit an energy dependent Bragg peak. The matter-antimatter annihilation event at the end of range is accompanied by the release of nearly 2 GeV, primarily in the form of energetic pi-mesons, but also neutrons, K-mesons and gammas, and of particular interest for therapeutic applications, charged nuclear fragments.

We are using the MCNPX Monte Carlo code developed at Los Alamos National laboratory to evaluate the feasibility of clinical antiproton therapy and in the design of physical experiments. MCNPX combines the traditional MCNP particles (neutrons, photons, and electrons) with the high-energy, multi-particle transport features of the LAHET code package. The intermediate energy model in MCNPX simulates antiproton annihilation and accompanying secondary particle production. The de-excitation of the residual nucleus after proton-antiproton annihilation is modeled using the multistage pre-equilibrium model and multi-fragmentation of light nuclei is based upon the Fermi-Breakup model.

Monte Carlo calculations confirm that the annihilation event produces a significantly larger Bragg peak relative to a proton dose deposition curve. For 150 MeV incident antiprotons, the peak-to-plateau ratio is approximately twice that for protons of a similar energy. The antiproton peak-to-plateau advantage over protons increases as the incident energy is decreased. Perhaps more significantly, a further potential clinical advantage exists in the form of the high relative biological effectiveness (RBE) of the charged nuclear fragments produced in-situ at the end of range.

While gammas resulting from the prompt neutral pion decay have sufficient energy to exit a human, roughly half of the charged pions produced will contribute to a relatively isotropic background dose. Nevertheless, this background is inconsequential relative to the clear physical and biological advantages.

In summary, the use of antiprotons holds significant potential for enhancing the clinical efficacy of focal radiotherapy approaches. Theoretical and experimental studies to evaluate the technique are actively ongoing.

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Everybody is good - How good can we be together?

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Proton Radiation Therapy has developed to the point that it is recognized worldwide as a valuable approach to the treatment of various forms of malignant and even benign diseases. Today's technology and performance originated in physics research institutions, where the physics background, engineering skills, medical competence and excellent partnership between physics and medicine could flourish to remarkable degree and quality. Established indications for proton therapy such as choroidal melanomas, chordomas and chondrosarcomas of the base of skull, AVM's and other tumors have been treated according to technical guidelines and medical protocols at a limited number of institutions. For more than ten years, the international community of people interested in particle therapy has grown greatly, and today about twenty centers worldwide are active in particle radiation therapy, using protons and heavier ions. During this time technologies have changed, the number of indications has, and will continue to, grow, and other local and systemic treatment modalities are changing in parallel and causing a form of competition which did not exist at the time of the founders of particle therapy.

In order to preserve and even strengthen the importance of particles and to create a reliable quality of treatments, the community has to work on new guidelines and protocols, which allow for a) technical and medical comparison of procedures, b) a meaningful standardization of treatments (particularly for "new" indications) and c) transparent analysis of all procedures and results. The situation vis-à-vis conventional radiation therapy has become much more competitive, technically as well as economically, not to mention the psychological aspects of the acceptance of particles. Beam characteristics, devices for beam application, dose prescription, dosimetry, treatment planning and delivery tools such as intensity modulation, homogeneity / inhomogeneity of dose, single / total doses, fractionation, overall treatment time, tumor histology, stage, combination with other treatment modalities – these are only some of the many parameters we have to know and to compare if we want to analyze our procedures and results seriously. Modern tools for data sharing make cooperation much easier than before. The goal of this presentation is to initiate within PTCOG efforts to establish standards and ensure a uniform high quality. This is needed in order to ensure that particle radiation therapy does not degenerate into an expensive nice-to-have therapy but, rather, establishes our existing and upcoming facilities as necessary weapons against a variety of malignant diseases.

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Dosimetric commissioning of the CATANA proton beam for the first patient treatments.

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At INFN-Laboratori Nazionali del Sud (LNS) in Catania, a proton therapy facility, named CATANA, (Cetro di AdroTerapia e Applicazioni Nucleari Avanzate), based on the use of 62 MeV proton beam, has been ralized mainly dedicated to the treatment of shallow tumors (3 cm max), like those present in the ocular region (i.d. uveal melanomas and macular degenerations). The dosimetric beam characterization has been concluded. For this aim different dosimeters have been employed and according to our previous experience. The dosimetric commissioning has been carried out mainly looking at the evaluation of depth dose, lateral off-axis profiles in water, field size dependent output factors, absolute dosimetry and dosimetric beam monitoring system. The results will be extensively presented.

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New high spatial resolution semiconductor microdosimetry in proton therapy.

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In the present clinical practice a single value of RBE is used for the whole treatment planning. However, proton RBE depends on the type of biological endpoint, on the initial proton energy, method of beam delivery, on the depth of beam penetration and size of radiation field. The LET of particles is a main parameter responsible for RBE. The protons themselves can demonstrate LET up to about 80-90keV/micron at the end of the Bragg peak. Recent proton beam simulations with Monte Carlo code GEANT with nuclear interaction module FLUKA for MGH NPTC facility demonstrated a significant contribution to the total dose beside the primary protons could be due to secondary heavier particles alphas, deuterons, tritons and neutrons and secondary low energy protons [1,2]. Also these high LET particles can contribute to RBE of proton beam.

The relative changes in RBE across the beam for different beam size and method of delivery must be the input into the treatment planning system for proton conformal therapy. In this case measurements of dose distribution with ionizing chamber only is not enough for dose planning. Existing experience in proton therapy indicate the need for extensive further studies of RBE of the therapeutic proton beam especially in the distal edge of the Bragg peak [3]. Additionally to in vitro experiments with biological cells the microdosimetry is important method for investigation of RBE properties in conformal PT. Present microdosimetric instrument is based on proportional gas counter and has limited spatial resolution and require TE gas and high voltage operation.

New silicon SOI microdosimeter was developed at the Centre for Medical Radiation Physics, UoW as a part of PT Australian National program. Microdosimeter is based on SOI (silicon-on-insulate) p-n junction array with sensitive volumes of micron sizes similar to biological cells [4]. Advantage of this microdosimeter is high spatial resolution (less than 1 mm) and possibility to measure under the full proton beam. Measurements of microdosimetric spectra were done along the Bragg peak for 210 MeV slow-extracted beam at MGH and pulsed 250 MeV proton beams at KEK in a Perspex phantom.

It was demonstrated that microdosimetric spectra became much harder on the distal edge of the Bragg peak. At the depth of 26 cm, that corresponds to the range of the 190 MeV protons in perspex, contribution of high LET (more than 100keV/u) events was observed. For position behind the Bragg peak contribution to microdosimetric spectra was mostly due to the secondary protons originated by neutrons. Events with LET more than 200 keV/micron were observed for high energy protons in entrance region of the phantom that is in agreement with theoretical model predicting high LET nuclear secondary.

Method of changing the effective size of sensitive site using time rise discrimination technique has been developed and tested.

New microdosimeter is small and require low bias operation. Microdosimetric spectra can be used as experimental input data for RBE based dose planning system in conformal proton therapy for particular proton beam and method of delivery. Also these spectra can be used for verification of Monte Carlo simulations in proton therapy utilizing GEANT and FLUKE codes.

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Investigation about proton beam quality with a mini TEPC.

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Microdosimetric spectra are the imparted energy distributions in micrometric sites due to single interaction events. In proton therapy, the imparted energy distributions are rather wide and their shape varies with the depth and the position inside the irradiated patient. The relative biological effectiveness (RBE) of the proton beam depends on the imparted energy distribution. Therefore RBE changes can be monitored by measuring microdosimetric spectra.

The optimisation of the experimental procedures was already investigated[1]. In this study we have measured microdosimetric spectra at different positions in the SOBP, both longitudinally and laterally with respect to the proton beam axis, behind a bolus used to treat cornea pathologies and near the border of beam collimators. A lucite phantom was used to simulate the ocular tissue.

This study has been performed with a new mini TEPC, the sensitive volume of which has 0.9 mm of diameter (see figure 1). Thanks to the small size of the counter, the radiation beam perturbation was minimized and the position determined with good accuracy.

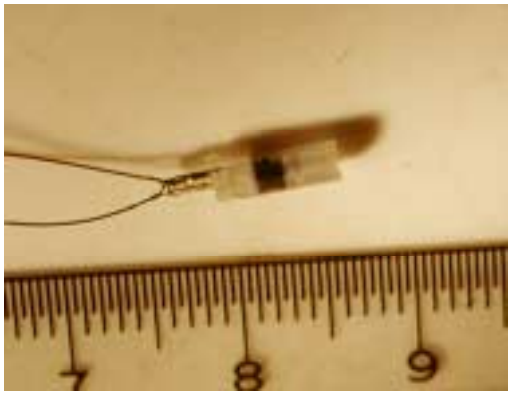

Figure 2. The mini TEPC used in this study.

We have used a weighting function[2] to process microdosimetric spectra and to assess the proton beam RBE in different conditions. Comparison with radiobiological data is rather satisfactory. Since the measured RBE variation can be large (more than a factor 2 in some conditions) and microdosimetric measurements are able to monitor it quite well, why do not take into account microdosimetric experimental information in therapeutic plans?

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Polystyrene versus water calibration of proton beams.

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Previous dosimetry protocols allowed calibrations of proton beamline dose monitors to be performed in plastic phantoms. Nevertheless, dose determinations were referenced to absorbed dose to muscle or water. The new IAEA Code of Practice TRS 398 recommends that dose calibrations be performed with ionization chambers only in water phantoms because plastic-to-water dose conversion factors are not available with sufficient accuracy. These factors are necessary, however, to evaluate the difference in doses delivered to patients if switching from calibration in plastic to the new protocol that requires calibration in water. This work provides measured polystyrene-to-water dose conversion factors for this purpose. Uncertainties in the results due to temperature, geometry, and chamber effects were minimized by using unique experimental set-up procedures. At the peak of non-range-modulated beams, polystyrene-to-water factors ranged from 1.015 to 1.024 for beams with ranges from 36 to 328 mm. For beams with the same ranges and medium sized modulations, the factors ranged from 1.005 to 1.019. These measurement results support theoretical calculations and can be used at clinical proton facilities to increase the accuracy of dose monitor calibrations performed in polystyrene phantoms.

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Monte Carlo calculated versus experimental fluence correction factors in plastic phantoms for clinical proton beams.

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Modern codes of practice for clinical proton beam dosimetry using ionization chambers, recommend to measure absorbed dose to water in a water phantom. However, in situations where the desired positioning accuracy is difficult to achieve in water, it could be convenient to measure in a plastic phantom. In order to account for differences in particle fluence distributions at equivalent depths in plastic and in water, fluence correction factors would be required.

In the present work, fluence correction factors were determined for proton beams with energies between 50 MeV and 250 MeV using the Monte Carlo code PTRAN for PMMA with reference to water. The influence of non-elastic nuclear interaction cross sections is investigated. Two experiments, comparing depth dose distributions in PMMA and in water in 75 MeV and 190 MeV proton beams, were performed to obtain measured information.

The Monte Carlo calculations revealed that differences in proton fluence distributions are almost entirely due to differences in non-elastic nuclear interaction cross sections between PMMA and water. The fluence corrections were found to vary more or less linearly with depth and to be limited to less than 1 % for energies below 100 MeV, whereas for beams with energies above 200 MeV they could amount to 2-5%, depending on the cross section data-set used. The results could as well be represented as a correction per cm penetration of the beam, with a reasonable accuracy. The Monte Carlo calculations yielded values between 0.06% to 0.15% per cm penetration. From the experiments, values rangeing from 0.03% to 0.15% per cm were obtained.

We conclude that below 100 MeV, dosimetry could be performed in plastic phantoms without a dramatic loss of accuracy. On the other hand, in clinical high-energy proton beams, where accurate positioning in water is in general not an issue, substantial correction factors would be required for converting dose measurements in a plastic phantom to absorbed dose to water. Therefore, it is not advisable to use plastic phantoms for measurements of absorbed dose or depth dose distributions in proton beams with energies above 100 MeV.

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Analytical linear energy transfer calculations for proton therapy.

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In treatment planning for proton therapy the physical dose can be calculated with high accuracy, but it is still difficult to predict the corresponding biological effect. Currently a constant relative biological effectiveness (RBE) of 1.1 is widely used, although many experiments indicate that this might be an oversimplification. Therefore models for fast three-dimensional RBE calculation are required to investigate the potential impact of a variable RBE in treatment planning. As the RBE depends on the local energy spectrum, which can be characterized by the linear energy transfer (LET), a model for three-dimensional LET calculation for proton therapy is presented. This analytical model allows much faster LET calculations than Monte Carlo techniques and can therefore be used in iterative treatment planning.

The linear energy transfer describes the mean stopping power weighted by the local energy spectrum at a given point in a radiation field. As the main contribution to the LET is due to Coulomb interactions, nonelastic nuclear interactions are neglected. By assuming a Gaussian energy spectrum and a parameterization for the proton stopping power, an analytical formula for the LET distribution of a single beam in water is derived. It includes range straggling and can be applied to multiple fields and spread-out-Bragg-peaks. LET values in other media can be computed by appropriate scaling of the LET distributions in water. The validity of the analytical model was checked by Monte Carlo simulations. Local energy spectra were obtained with GEANT 3.21 to calculate three dimensional LET distributions.

The analytical LET distributions were compared with Monte Carlo simulations for a variety of cases. Typical clinical energies of 70 MeV and 160 MeV and several widths of the initial energy spectrum were used. In most cases the phantom consisted of water, but also other materials (e.g. bone) were investigated. The Monte Carlo simulations were observed to agree within ±0.5 keV/µm with the analytical calculations.

The analytical model for fast three dimensional LET calculation can now be incorporated into the treatment planning process. It can help to compare different dose delivery techniques in terms of high- and low-LET regions and is well suited for the determination of three dimensional RBE distributions.

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High spatial resolution MOSFET dosimetry: possibility of application in proton therapy

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Metal Oxide Semiconductor Field Effect Transistor (MOSFET) dosimetry has become popular in radiation therapy and particular using medical LINACs and brachytherapy. MOSFET dosimetry allows the possibility of *in vivo* dose measurement, multiple readouts of accumulated dose without deterioration , and small size of the sensors make them useful for catheter applications in brachytherapy.

Recently CMRP has developed an on line MOSFET clinical dosimetry system, which allows simultaneous measurements, accumulated dose and derives dose profile of radiation beam in similar way to a diode system. We demonstrated superior spatial resolution of MOSFET dosimetry in the order of 1-2microns [1]. This makes o MOSFET dosimetry suitable for use in IMRT and Microbeam Radiation Therapy (MRT), where steep dose gradient measurements are essential for QA and dose planning verification. Proton therapy require high spatial resolution dosimetry due to the

sharp penumbra and very steep distal fall-off after the Bragg peak. Limitations of commercially available detectors for dosimetry in proton therapy have been demonstrated in Bragg peak and penumbra regions. [2].

Preliminary investigation of the feasibility of MOSFET dosimetry in proton therapy has been done on a 150-250 MeV proton beam with range in a water about 20-30 cm at KEK proton therapy facility in Tsukuba. Measurements of depth dose profile and lateral beam penumbra in the entrance and in Bragg peak positions has been investigated in water and Perspex phantoms in a 10x10 cm^2 radiation field. MOSFET detectors with thick gate oxide about 1micron and voltage bias +5V during irradiation demonstrated spatial resolution of penumbra measurements in water better than 0.3mm. However essential reduction in ratio of Bragg peak -to entrance measured doses has been observed in comparison with silicon diode. It was 1.5 and 2.6 respectively. This effect was not related to decreasing sensitivity of the MOSFET detectors with accumulated dose but rather was due to increasing LET of protons in the Bragg peak in comparison with the entrance position. Higher LET protons generate more dense ionising tracks in the gate oxide of MOSFET detectors leading to higher recombinations of holes before they are trapped. To avoid this recombination a higher electrical field is required in the gate oxide. It is possible to achieve this by using thinner gate oxide and/or higher gate bias than in an X-ray therapeutic beam.

The experiments with 0.02 micron gate oxide p-MOSFETs in a 100 MeV proton beam demonstrated good agreement with an ionising chamber in the Bragg peak region [3]. However, higher doses should be applied due to reduced sensitivity. These results suggest that "edge on" MOSFET dosimetry can provide high spatial resolution dosimetry for proton therapy but further experiments are required.

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An Analytical Model for Monitor Unit Calculations in Spread-Out Bragg Peak Proton Fields.

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The dose delivered to a patient by an ionizing field is specified and controlled in terms of machine monitor units. A monitor unit, MU, is a fixed amount of charge collected in a reference chamber positioned at a known location in the field and upstream of the patient. The ratio of Gray per MU for a specific patient field is required to convert the therapeutic dose prescription in units of Gray to the machine specification in terms of MUs. This field-specific ratio, referred to as output factor, can be measured. Such measurements are currently the only clinical method for obtaining the required output factor because a rigorous and reliable framework for the determination of the output has not been generally available.

We derive an analytical model for the output factor based on a model derived by Bortfeld and Schlegel (1). Our model provides both an independent verification for measurement as well as a robust method for output prediction without the need for measurement. The model is based on the simple observation that the monitor unit reference chamber measures the entrance dose region of the SOBP (i.e. at d=0 cm) while the dose specification is in the (flat) SOBP plateau region. The output factor thus is simply the ratio of plateau dose to entrance dose. The model in (1) approximates the SOBP entrance region as $D(d) = 100 \big/ 1 + 0.44 r^{0.66}$ where $r = (R - M - d) \big/ M$ and where R is the maximum range, M is the desired SOBP modulation width, and d is the depth. The output factor is thus simply the value of $D(d$=0).

We tested the model against clinical fields planned for the delivery nozzle installed in gantry 1 at the Northeast Proton Therapy Center. The nozzle components of relevance are the first and second scatterers that produce the flat lateral profile and the range modulator that produces the SOBP. The monitor unit reference chamber is mounted downstream of these devices, and is the last device the field passes through before entering the patient or patient-specific beam modifiers. The deliverable clinical ranges are grouped into options, numbered 1 through 8, where each option is a combination of a range modulator and scatterer.

We first verified the fidelity of the theoretical model against measurements for the full range of over 150 SOBP measurements -independent of option considerations – and found good agreement against the theoretically derived model parameters. The model was able to predict the output factor within ±4% (95% CL) compared to these measurements. The model's predictive power significantly improved, however, if each range option was considered separately to yield an output factor accuracy of ±1.8%. For some fields, however, significant discrepancies remained. These remaining

discrepancies are shown to be due to the range compensator, and to a much lesser extent the field size, which can produce significant perturbation in the fluence at the calibration point. We therefore extended the analytical model with a fluence prediction calculation in the plane containing the calibration point and perpendicular to the central axis. The model prediction combined with the computation of the fluence properties at the calibration point provides a complete description of the observed output behavior. We present a full derivation of the model and results and discuss the applicability of the model as a reliable clinical tool for output prediction as an alternative to measurements.

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CVD and natural diamond and silicon detectors in proton beam dosimetry.

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Solid state dosimetry is gaining importance in the field of clinical proton dosimetry mainly due their physical charateristics. In the framework of the CATANA facility development we are develping an R&D program having as main goal the study of natural and CVD diamonds and silicon detectors. In the presentatio main results so far obatined in terms of calibration factors, energy dependence and relative dosimetry applications will be extensively reported.

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The Hounsfield look-up table used for treatment planning at GSI: measurement, accuracy and validation.

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In particle therapy the precision of dose distributions critically depends on the accuracy of the beam's energy and the accuracy of the information about the stopping power distribution in the target. At GSI the different beam energies are stored in a read-only library, the precision of the energies is better than 0.1%. The treatment planning software package TRiP calculates the water-equivalent path lengths for carbon ions in the target based on computer tomographic data of the patients in combination with a Hounsfield look-up table (HLUT).

The first HLUT used for treatment planning at GSI was derived from phantom measurements only. In-situ range verifications using Positron Emission Tomography (PET) during the first patient irradiations indicated that further improvement of the HLUT was desirable. Therefore measurements with animal samples were performed leading to a modification of the HLUT. The new HLUT was validated with radiographic measurements of a frozen pig head. A comparison of measured and modeled data based on either the old or the new HLUT shows that the new HLUT significantly improves the calculation of the water-equivalent path lengths in the target.

Up to now the radiographic measurements were performed by either using a water absorber of variable thickness in front of an ionization chamber or by using a stack of ionization chambers (IC-stack). With these set-ups up to 25 (water absorber) or 280 (IC-stack) selected positions per sample were measured. For further improvements of the HLUT new measuring set-ups are in preparation to allow even faster data acquisition. First experiments using a fluorescent detector have been performed to test fast acquisition of radiographic images – not only point measurements - of a sample from different angles.

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The expected radiation failure rate for optical encoders in the mpri treatment rooms.

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The MPRI patient positioner system uses a commercially available UP-200 robot arm. The control system for this robot arm uses information obtained from absolute optical encoders attached to each rotation axis of the robot arm. An Optical encoder uses light from an LED light source, modified by a mask and intercepted by a photo-detector. This is similar to a normal optocoupler. With the recent data on the radiation sensitivity of optocouplers [1] we can estimate the failure rate of optocouplers and hence for optical encoders in the radiation environment expected in the MPRI treatment rooms. There are generally three major radiation issues affecting optocouplers i.e. ion displacement damage, single event transients and total ionizing dose [1]. In the MPRI case, the dominant part of the radiation environment is secondary neutrons produced by the primary proton beam. The robot's optical encoders will always be outside the primary proton beam allowing us to neglect the total ionizing dose effect. Moreover, single event transients are typically induced by the heavy ions in high-speed devices (>1*Mbps*). Therefore, we base our estimate only on ion displacement damages caused by the secondary neutrons. Optocouplers exhibit degradation in their current transfer ratio when the neutron fluence reaches the level of 10^{12} n/cm^2 [1].

A typical proton radiation treatment requires irradiating a 10×10 cm^2 tumor to 2*Gy* in about 1min. Assuming proton energy loss of 27.2 $MeV.cm^{-1}$ at the Bragg peak, the proton beam fluence required for treating a "thin" tumor (single Bragg peak) to 2*Gy* is $4.6 \cdot x\ 10^8$ $p.cm^{-2}$. Radiation treatment of an extended tumor volume requires multiple Bragg peaks i.e. a Spread Out Bragg Peak (SOBP). This adds a factor of 3.2 to the required beam intensity for a typical 10cm SOBP. Therefore a typical treatment of a one liter (10×10 cm^2) tumor volume requires $1.47 \cdot x\ 10^{11}$ protons. We can estimate the neutron flux to the optical encoders, which would typically be at about 1–2 m distance from the iso-center at a 45-degree angle to the direction of the incident proton beam. The neutron flux (n/cm^2) at 1 m from a target absorbing a single proton can be estimated using the neutron emission angle with respect to the parent proton beam and the kinetic energy of the proton beam [2]. For a 205 MeV proton beam and a neutron emission angle of 45 degrees an estimated fluence of 4.85 x 10^{-6} $n.cm^{-2}$ per proton hitting the target can be calculated. Multiplying this number by the number of protons required for the typical tumor irradiation, one can expect a neutron fluence of 7.13 x 10^5 n/cm^2 in the direction of the robot's optical encoders during each proton treatment. Using a fluence to dose equivalent conversion factor of 40 $fSv/n/m^2$, this flux of neutrons corresponds to 0.29 mSv dose per 2 Gy treatment. A secondary neutron dose measurement during a spot scanning treatment [3] revealed a three times lower neutron dose of 0.1 mSv (or 0.3 fSv/proton) for a similar geometry condition but at a lower energy (177 MeV). We also expect at least a factor of two higher neutron flux due to beam losses in the nozzle as a result of wobbling the proton beam. Measurements of the secondary neutron dose to the patients receiving proton beam treatments at HCL and ORSAY using passive scattering methods, revealed an average neutron dose of 1mSv/Gy [4]. Our estimate is between the two numbers reported and should give a correct order of magnitude value. With the 10^{12} $n.cm^{-2}$ threshold for failure, the optical encoders are expected to operate for more than 1.4 million treatments before failing. This equates to > 20 000 patients at the rate of 3.5 portals and 20 fractions per patient treatment.

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Progress on DICOM for ion therapy.

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The well known DICOM standard [1,2] which was developed to communicate radiological images and related information has been successfully extended to meet the needs of radiotherapy. Users of the standard now have almost five years experience in communicating images, structures, dose distributions, and external and brachytherapy treatment plans

amongst systems from different vendors. This radiotherapy extension has been defined and is being further developed by Working Group 7 (Radiotherapy Objects) of the DICOM Committee. The group consists of representatives of all major vendors of radiotherapy systems and users of such systems.

In mid 2001, WG 7 recognized the need to form a subgroup to elaborate the possibilities of further extending DICOM to describe ion beam treatments. Since then, the group had several meetings where the aim and content of the new extension was discussed in detail. The current draft documents represent input from vendors of treatment units and treatment planning systems as well as users from the USA, Europe, and Japan. Due to the heterogeneous nature of today's ion therapy approaches discussions have sometimes been difficult. However, it is hoped that this new DICOM extension will be available within a time frame of two years.

The general approach for the proposed extension is to define at least two new objects: a RT Ion Plan object and a RT Ion Treatment Session Record object. The RT Ion Plan object will contain the prescribed treatment technique whereas the RT Ion Treatment Session Record object will contain the recorded parameters of the performed treatment.

The basic structure of the RT Ion Plan object is shown in Figure 1. An ion plan may contain of one or more ion beams having two or more control points. Each beam refers to one treatment unit and may have zero or more patient setup and beam modifier entities.

The elements of these basic building blocks will be presented and a detailed description of the control point concept will be given. Furthermore, results from the meeting held at PTCOG XXXVI will be presented.

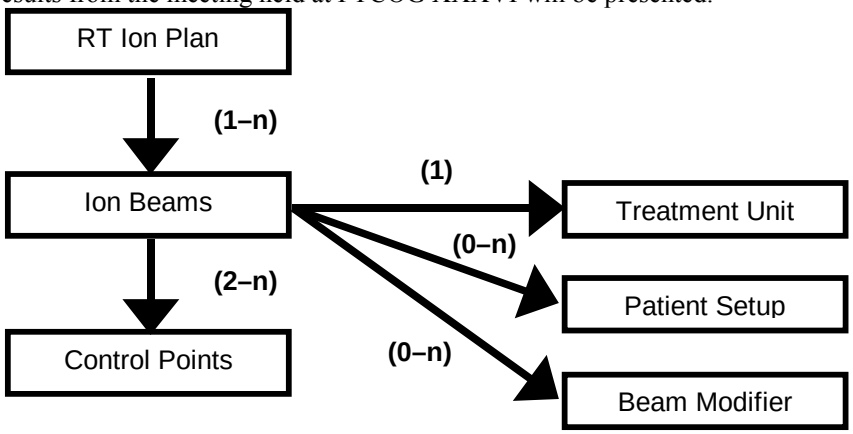

Figure 3. Schematic structure of the new RT Ion Plan object.

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3D conformal radiotherapy (3D-CRT) and IMRT in organ-confined prostate cancer.

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Introduction: The frequent persistence of local residual tumor after radiotherapy of localized prostate cancer has been a matter of concern in the recent literature. Although the true rates of local relapse remain uncertain, recent studies indicated a PSA relapse-free survival of about 60% in patients with stage T1-T2 disease. Moreover, biopsy-proven local recurrences have been reported in up to 65% of patients treated for stage T1-3 disease. Most patients in these reports were treated with doses of 65-70 Gy. Failure to eradicate the disease results from intrinsic resistance of prostate tumor clonogens to these dose levels and from uncertainties in tumor delineation, organ motion, and patient positioning from day to day. Three-dimensional conformal radiotherapy (3D-CRT) has been developed to address some of these issues. 3D-treatment planning is based on the ability to anatomically define each pixel within the entire 3D space of irradiated tissues and to precisely calculate the dose delivered at each point. In the treatment of localized prostate cancer, by means of significant exclusion of

adjacent normal tissues from the high-dose region, 3D-CRT has been shown to reduce the risk of rectal and bladder toxicities. Moreover, 3D-CRT can be effectively used to achieve tumor dose escalation with a significant improvement in local tumor control.
Materials and Methods: Since 1995 we have treated over 700 patients with biopsy-proven prostatic adenocarcinoma with high dose 3D-CRT. All patients were treated in a prone position, with rectum and bladder empty, with a 6-field technique. To ensure reproducible positioning, a custom-made polyurethane-foam half-body cast was produced for each patient. A total dose of 76 Gy in 2 Gy fractions prescribed at ICRU point was administered. Recently, we have acquired dedicated micro-multileaf collimator at both sites and we have therefore gradually abandoned the static approach in favor of a conformal dynamic arc treatment delivery. This mode of delivery has both shown a higher degree of conformality as well as ha better patient throughput. We are currently fine-tuning all quality-assurance procedures required for IMRT delivery which we expect to launch in the next few months.
Results: Acute toxicity was graded according to the RTOG scoring system. Acute gastro-intestinal (GI) toxicity was as follows: 34% G0, 48% G1, 18% G2 and no G3 and G4. Acute genito-urinary (GU) toxicity was as follows: 16% G0, 52% G1, 28% G2, 4% G3 and no G4. It is noteworthy that no interruption of treatment due to acute reactions was recorded. Late toxicity was recorded according to the RTOG scale. Late GI toxicity was as follows: 18% G1, 5% G2, 2% G3 and 1% G4. Late GU toxicity was as follows: 22% G1, 3% G2 and 1% G3. Overall late treatment toxicity greater than or equal to G3 was 3%. No definitive biochemical disease-free survival data can yet be drawn from our series.
Conclusions: Similarly to the experience of several other Institutions we may conclude that conventional 3D-CRT of localized prostate cancer has an excellent acute toxicity profile and a relatively low late toxicity rate at the dose level we have employed so far. While our biochemical disease-free survival data are not yet fully mature for evaluation, we are well aware of the fact that some recent reports indicate that higher doses may be required to achieve better local control and consequently improved biochemical relapse-free survival in localized prostate cancer, especially in high-risk patients. To this end we have embarked upon the challenging project of dose escalation with IMRT.

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Conformal proton beam therapy of prostate cancer-report of long-term PSA-based outcomes in over twelve hundred patients

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Purpose: Conformal proton beam radiotherapy of prostate cancer has been performed at LLUMC since October 1991 The following is an update of our previously reported results.
Materials and Methods: Between 10/91 and 12/97, 1255 patients with localized prostate cancer (defined as stages T1c-T3, PSA < 50 ng/ml) were treated with conformal proton beam radiotherapy to doses of 74-75 CGE (Cobalt-Gray Equivalent) at 1.8-2.0 CGE per fraction. None of these patients underwent prior surgery or received adjuvant hormonal therapy. Patients were assessed at regular intervals during treatment for tolerance to therapy. Follow-up consisted of serum PSA determinations and digital rectal exams every six months until five years post treatment, than annually, with additional testing being performed as appropriate. Biochemical failure was defined as per the ASTRO criteria.
Results: The median follow up is fifty-seven months (range 1-115 months). Overall seven year actuarial Biochemical Disease-Free Survival (BNED) was 66%. BNED survival was strongly influenced by pre-treatment PSA levels (94 vs. 87 vs 73 vs 55% for pre-treatment PSA's of < 4.1 ng/ml, 4.1-10.0 ng/ml, 10.1-20.0 ng/ml, 20.1-50 ng/ml, $p<0.0001$). PSA nadir also correlated with BNED survival (91 vs 76 vs 35% for nadirs of < .051 ng/ml, 0.51-10 ng/ml, > 10 ng/ml, $p<0.0001$). Treatment was extremely well tolerated with a 0.5% incidence of RTOG > Grade 3 late complications. BNED survival rates compare favorably with other modalities (surgery, 3-D CRT), while treatment-related morbidity is less than that which has been reported in large conformal x-ray therapy series
Conclusions: Long-term follow up continues to demonstrate the safety and efficacy of conformal proton beam radiotherapy of prostate cancer.

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Physical and clinical aspects of prostate IMRT with photons.

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Introduction: Intensity modulated radiotherapy with high energy photon fields (IMRTX) can solve two problems of conventional 3D conformal radiotherapy (3DCRT): (1) Conformal treatments of concavely shaped targets can be performed. (2) It is possible to plan and treat concomitant boosts in an easy and elegant way.
Today's IMRTX systems typically consist of three parts: (1) an optimization system to calculate the photon field fluencies (inverse planning system), (2) a multileaf collimator (MLC) which is able to create modulated fields either statically ("step and shoot") or dynamically ("sliding window") and (3) a MLC sequencer, which calculates the MLC steps and/or movements for the intensity modulation.
During the last years IMRTX was established as a routine option in a few hospitals, it is nevertheless still a new and not widely used method. One problem is that the complex delivery technique requires new and time consuming QA procedures. IMRTX of prostate cancer allows the safe application of high doses possibly resulting in an increased relapse free survival without increasing acute toxicity and late morbidity. IMRTX has firstly been introduced for clinical use in 1996 at the MSKCC in New York.
Materials and methods: We are using the Varian IMRT system, which consists of the Cadplan/Helios inverse planning system with integrated MLC sequencer and a dynamic MLC.
A quality assurance system was established which take into account both machine and patient related aspects including systematic dosimetric checks and daily patient set-up verification.
Treatment planning was done according to the so-called SMART technique (Simultaneous Modulated Accelerated RadioTherapy). This concomitant boost technique offers two advantages. Firstly, it allows an increased dose within a specific target region (e. g. prostate) and a reduced dose to the peripheral region (e. g. periprostatic area). Secondly, it keeps the overall treatment time constant while increasing the target dose. In our study the CTV was irradiated with a single dose of 2.0 Gy per fraction whereas the PTV was irradiated with 1.8 Gy simultaneously. With the SMART technique we were able to increase the therapeutic dose significantly from 73.8 Gy to 82.0 Gy without increasing the doses to the organs at risk, especially the rectum.
Results: Treatment was completed safely and without interruption in all 48 IMRTX patients treated so far. Dosimetric pre-treatment results performed for all patients were always very precise. Results of the daily set-up verification revealed a very good patient positioning. Acute radiation side effects were scored according to the Common Toxicity Criteria (Version 2.0). All critical acute side effects showed no significant differences compared to conventionally treated patients. No late radiation toxicity has been observed in our IMRTX patients so far.

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Real time tumor tracking (TULOC): first clinical measurements and plans for applications in prostate irradiation.

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As a contribution to the solution of the organ motion problem we have developed a novel magnetic tracking method which we call TULOC (acronym for TUmor LOCation). The demonstration of its proper functioning in the lab has been described in previous PTCOG-meetings.

In this paper we report on the implementation of TULOC into the clinical environment. A first clinical measurement was accomplished at the LINAC of the University of Zurich Veterinary school. During the irradiation of a dog patient the movements of a chondrosarcoma in the lumbosacral area of the spine were measured. Effects of eddy currents in the LINAC nozzle and in the patient table have been corrected for using special computational methods. The next step will be the gating of the LINAC during dog treatments.

As a first application in human patients, the real time tracking of the position of the rectal wall and with it of the prostate during conformal radiotherapy is in preparation. For this, rectal balloon catheters equipped with TULOC sensors will be used.

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Patient positioning for proton therapy of prostate tumors: First experience and outlook to the future.

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At PSI, patients undergoing proton therapy at the spot scanning gantry are positioned outside the treatment room. Position verification is done on a remote CT by comparison of several CT slices with the slices of planning CT and measurement of several points on scouts view. Patients are brought inside the treatment room in their mould after position verification and necessary corrections have been completed.

For prostate tumors, patients are positioned in an individual mould. A rectal balloon is used to immobilize the prostate. This can be a time consuming procedure to obtain high precision positioning. We will analyze the positioning precision obtained with this system. We will also discuss the time necessary for precise positioning of the patient, the personal required for an optimal use of the irradiation facility and raise the question whether in a new facility, patient positioning should also be done outside the treatment room or preferably inside the treatment room.

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A new superconducting cyclotron to produce 250 MeV light ion beams.

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A four sector compact superconducting cyclotron able to deliver light ion beams with a maximum energy of 250 A MeV has been studied. This cyclotron is mainly designed to accelerate H_2^+ ions to be extracted by stripping. Moreover ions like C, O or Ne can also be accelerated and extracted by stripping. Thanks to the extraction by stripping, two simultaneous beams can be extracted, allowing to performs therapy treatment, interdisciplinary research and radioisotope production using low or medium intensity beam. The use of the extraction by stripping simplify greatly the maintenance of the cyclotron and reduce its activation. The preliminary design model of the magnet circuit has been accomplished with the 3D electromagnetic code OPERA. The design of the main coils and of the cryostat has been investigated too. The isochronous magnetic field, the flutter, and the focusing properties of the cyclotron for different ions will be presented.

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Status of development of installation for proton conformal therapy mass application.

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The proton therapy will become mass, if the proton installation will have cost of the equipment, size of the building, consumption of electric power and cost of operation comparable with the same cost for electron accelerator.

In paper the proton installation is presented, which completely, together with a treatment room, is placed in the radiation protected hall with the sizes 7x13 sq.m, required about 50 KW of the electric power in therapy mode.

Energy of the proton accelerator reaches 330 MeV, that in the future will allow to have on the same installation proton tomography. The experimental sample of the accelerator works, the first full sample of installation with the equipment for therapy is planned to commissioning in 2002, and in 2003 to put two serial samples in clinics of Russia.

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Successful acceleration test of the first module of the proton linac booster "LIBO".

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The linac booster "LIBO" project aims at building a 3 GHz proton linear accelerator to boost the energy up to 200 MeV of the beam from 30 to 70 MeV cyclotrons, which exist in several laboratories and hospitals. A prototype of the first LIBO module was designed, constructed and tested by a collaboration formed by CERN, University and INFN of Milan, University and INFN of Naples, and the TERA Foundation.

Low power RF measurements have shown a good field uniformity and stability along the axis of the four tanks composing the LIBO module. Full power RF measurements at a repetition rate of 100 Hz have been performed at CERN. After a very short conditioning period, an accelerating gradient approaching 30 MV/m has been easily achieved in the tanks, well above the nominal value of 15 MV/m.

In February 2002 in the LNS of INFN in Catania the module was powered with a 3.6 MW RF modulator produced by IBA/Scanditronix. As expected, protons have been accelerated over about 1 meter from 62 MeV to 73 MeV. The particularities of the design and the reasons for the successful performance are discussed.

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Status of TOP Linac Costruction.

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The TOP LINAC (short for ***T**erapia **O**ncologica con **P**rotoni **LIN**ear **AC**celerator*), an innnovative linac for protontherapy in the energy range 65 - 200 MeV is being constructed in the ENEA Frascati Research Centre by a collaboration between ISS and ENEA. The system is intended to be installed in the main Oncologycal Hospital in Rome, Istituto Regina Elena. Up to now funding allowed the construction of a 7 MeV injector and of the first 3 GHz module (up to 13.4 MeV). The injector has been produced by AccSys Company (USA) and is under commissioning at Frascati. The low energy (7 MeV) beam lines for F-18 production and injection in the following accelerating sections are under construction. The first 3 GHz SCDTL module has been completely built. The characteristics of the various accelerator components are presented.

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Recent Improvements on the Proteus 230 for a Flawless System Operation.

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The recent developments accomplished on the Proton Therapy System that is installed and currently operational at the Northeast Proton Therapy Center at the Massachusetts general Hospital in Boston will be presented at the Catania PTCOG conference of May 2002. These developments reflect IBA's wish and also ability to constantly adapt its products to its client's needs, whilst using their experience to this purpose and integrating their suggestions. The new snout family design shall be presented along with the newly designed snout removal system. Examples of the new features that have been integrated into our control system will also be given, such as those that will improve the information readability and also the operation flexibility.

As system availability is a key factor of client and patient satisfaction, a process for the putting into place of a continuous tuning preventive maintenance program and a system fault diagnostic is being reviewed.

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Long term results after proton beam radiotherapy of uveal melanoma.

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In this study, we report on long term results after proton beam radiotherapy (PBRT) of uveal melanoma in terms of survival, local tumor control, eye retention and retention of a useful vision. We identify the risk factors for local tumor control failure and for ocular tumor related death. We present the improvements implemented to increase the rate of local tumor control, and compare the survival rate of patients with locally controlled tumors to those of patients who had to receive a second treatment. We analyze the causes leading to enucleation and to a loss of vision following this conservative treatment approach.

We have treated 2645 patients (2648 eyes) with uveal melanoma, from 1984 through 1999 with proton beam radiotherapy (PBRT). Patients' age ranged from 9 to 90 years, 1284 were men, 1361 women. Largest tumor diameter ranged from 4 to 27.5 mm, tumor height from 0.9 to 15.6 mm. Median follow-up time was 44 months.

Local tumor control probability at 5 years was improved from 90.6 ± 1.7 % for patients treated before 1988, to 96.3 ± 0.6 % for patients treated between 1989 and 1993, and became 98.9 ± 0.6 % for patients treated after 1993. Among 2645 treated patients, 78 (3%) had to receive a second treatment because of tumor regrowth. Our results in terms of local tumor control and the work performed in order to maximize local tumor control have been described in [1].

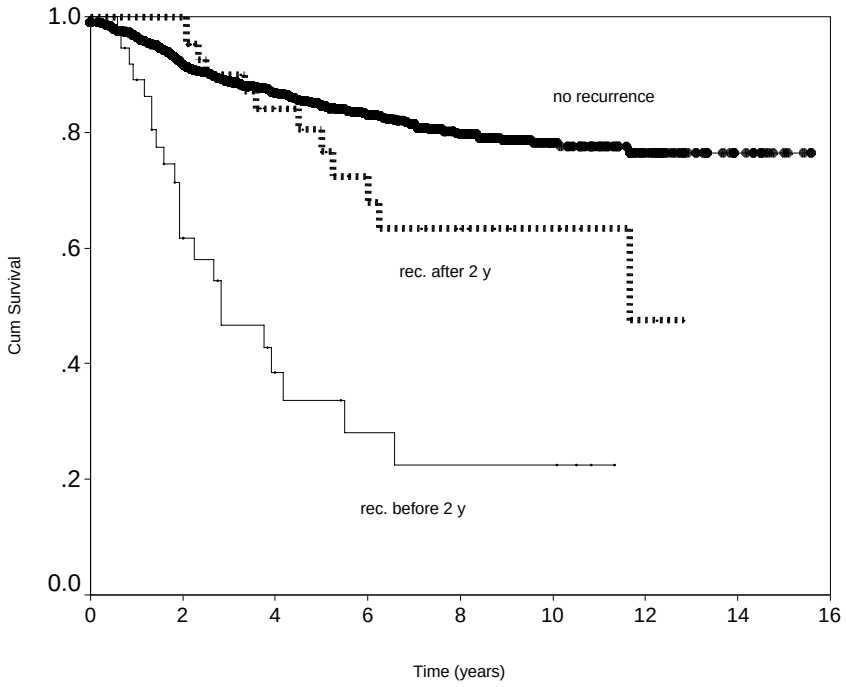

Figure 4. Ocular tumor related survival in function of local tumor control (no recurrence, recurrence two years or more after treatment, recurrence within two years after treatment)

Ocular tumor related survival at 10 years was calculated to 78.2 ± 1.4 % for patients with controlled tumors compared to 22.4 ± 8.9 % for those with tumors recurring within two years after treatment and 63.3 ± 9.3 % for those with tumors recurring more than 2 years after treatment (Figure 1).

The overall eye retention rate at 5, 10 and 15 years after treatment was 88.9%, 86.2% and 83.7%, respectively (Figure 2). In total, 218 eyes had to be enucleated. Enucleation was related to larger tumor size, mainly tumor height, proximity of posterior tumor margin to optic disc, men gender, high intraocular pressure and large degree of retinal detachment at treatment time. After optimization of the treatment technique, the eye retention rate at 5 years was increased from 97.1 % to 100 % for small tumors, from 86.7 % to 99.7 % for medium and from 71.1 % to 89.5 % for large tumors.

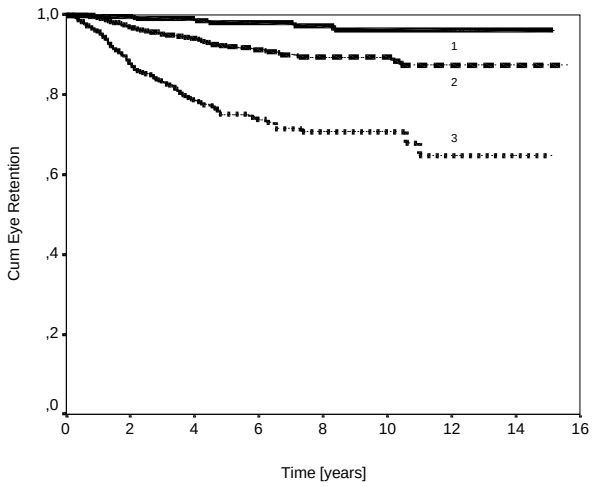

Figure 2. Eye retention rate in function of tumor height **(**1: 401 eyes with a height smaller or equal to 3.0 mm, 7 of them had to be enucleated, 2: 1570 eyes with a height ranging from 3 to 8 mm, of which 94 were enucleated, 3: 677 eyes with a height larger than 8 mm, of which 117 were enucleated)

Larger tumor height, proximity of tumor to optic disc and macula and large amount of retinal detachment at baseline were the parameters identified to lead to poor functional outcome. Ten years after treatment 35 % of the patients with a tumor height smaller or equal 8 mm and 12 % of patients with a tumor height larger than 8 mm still had a useful vision (Figure 3).

Conclusion: Reduced safety margins, large ciliary body tumors, eyelids within the treatment field, inadequate positioning of tantalum clips, and male gender were identified to be the main parameters to impair local tumor control. The improvement of local tumor control rate after 1993 is attributed to changes implemented in the treatment procedure. Our data strongly support that the rate of death by metastases is influenced by local tumor control failure: improvement of local tumor control rate allowed for better survival rate. The treatment technique as used today results in excellent eye retention rates, even in less favorable cases like large tumors and tumors located close to the optic disc. The continuous quality control program allowed to increase the 5-year eye retention rate for all tumor sizes. These findings demonstrate the positive impact of experience and quality control based efforts for treatment technique optimization. We conclude that functional results are strongly influenced by tumor size and location. Even for less favorable cases it is possible to save a useful visual acuity to a small number of patients. Nevertheless, in most of the cases, proton therapy is the only possible conservative treatment approach.

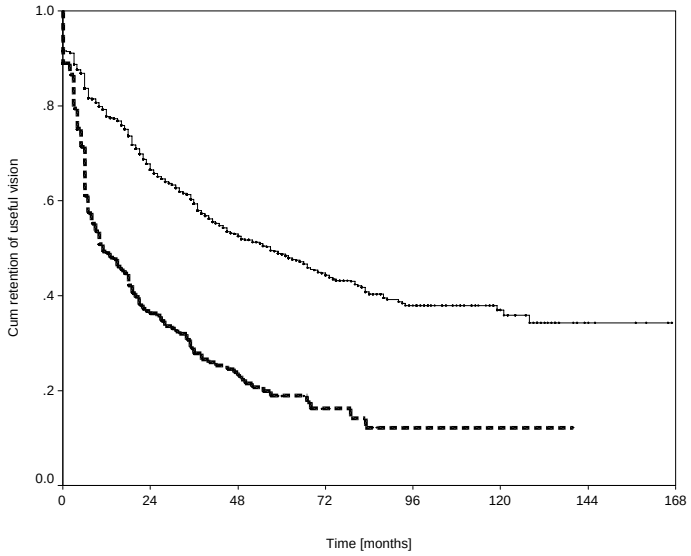

Figure 3. Retention of a useful vision in function of tumor height **(**1: eyes with a height smaller or equal to 8.0 mm, 2: eyes with a height larger than 8 mm)

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Ten years of technical evolutions in the preparation of ocular diseases for protontherapy.

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Since june 1991, a total number of 2040 patients have been treated in Nice using the 65 MeV proton beam. The Eyeplan program was used for all patients. Along these years, we decided to modify some classical approaches in order to be more and more accurate and sure to deliver the dose where it was planned. We first decided to develop the use of bolus in order to flatten the entrance of the beam and therefore be certain that the distal shape is reliable, mainly when we have to use a wedge filter. Bolus are now made of ultrasonographic gel and a thin sheet of plexiglas or transparency. The measurement of the thickness of the bolus has been facilitated by a special apparatus developped in Nice and used in routine. The wedge filters design was also modified to be easy to produce and use. These developments will be presented.

But the main problems is the eye modelization using the Eyeplan spherical representation. The inaccuracies of the modelization were first suspected on wrong clips-limbus measurements, elevated chi-squared values and wrong light fields projections. Changes in eye length sometimes ameliorate the values as well as changes in initial fixation. But these modifications were empiric. Some CT scans were initially performed to check the axial length measured by ultrasonography. But they also demonstrated obviously that the eye is often not at all comparable to a sphere and that the clips position may depend on the eye shape irregularities.

CT scans are now performed systematically for each patient after clips insertion and contoured slice by slice in a standard radiotherapy treatment planning. The set-up of virtual fields, anterior, lateral and cranio-podal allows a comparison with beam's eye view, lateral view and overview issued from Eyeplan. The eye position during CT scan is estimated from anterior and lateral fields rescaled to the magnification of the X-rays of protontherapy simulation, using the Eyeplan function "Determine a true position". This position is given to the model and by superimposing the clips system of CT scan and model at the same scale in the three views, we have the possibility to evidence the discrepancies between the two systems. Some modifications may be rationally introduced on eye length, center of the eye, initial angle of fixation. Practical examples will be given demonstrating the problems encountered and the solutions given using the Eyeplan modelization. The influence of a wrong modelization on dose distribution will also be adressed.

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Statistical analysis on melanoma treatment with proton beam in Nice.

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The Genoa Ocular Oncology Group presents the statistical results of the first ten years of activity with proton beam therapy for ocular melanoma treated in Nice Antoine Lacassagne Cyclotron Biomedical Centre. The sample is composed by 187 patients (48.1% men and 51.9% women) coming from all Italy and treated from 1991 onwards. We consider 7 cases having a tumour stadiation T1, 52 cases T2 and 128 cases T3, with an overall mean age of (60.5 ± 0.4) years. The follow-up mean time is (27 ± 2) months, only a few patients being followed till 96 months. With this therapy we obtain a local tumour control in 96.8% of cases and eye retention in 94.1%. We were able to calculate the tumour regression for the T1+T2 sample as a whole:

Thickness = (3.25 ± 0.11) - (0.049 ± 0.008) · Time (months)

and for the T3 sample alone:

Thickness = (7.07 ± 0.18) - (0.118 ± 0.014) · Time (months).

Eleven eyes were enucleated: five eyes in consequence of tumour relapse (45%) and six because of the appearance of neovascular glaucoma (55%), this pathology being highly brought about by some protons' treatment plannings. In any case,

the most frequent complication was vasculopathy (62.1%), while the 25.9% of cases showed the presence of cataract and about the 13.8% of neovascular glaucoma. Papillopathy appeared in 15.5% of the cases with an average time of appearance of (25 ± 3) months for the sample T1+T2 and of (23 ± 3) months for T3.

Eleven patients (5.9%) died because of metastases' appearance. In all these patients the main metastatic localization was the liver. Only one patient was already suffering from metastases' diseases at the time of the uveal melanoma diagnosis. In our sample, the global survival expectation for protontherapy, estimated by means of a Kaplan-Meier survivorship function, is equal to (0.81 ± 0.08) from 96 months on. The global survival rate after 42 months is calculated to be 91%.

This statistics, the only one available up to now in Italy, will be here onwards extended to the totality of the patients treated by SERAG (South Europe Radiotherapy Group) by means of a specialized clinical folder. The preliminary results of this study allow comparisons among different centre strategies.

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Proton beam radiotherapy of iris melanoma: long term follow-up study in UK.

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INTRODUCTION: 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 tends to cause photophobia, which requires further treatment.

Proton beam radiotherapy has been used for the treatment of ciliary body and choroidal melanomas for several decades, with excellent rates of local tumour control. However, 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 the physical advantages of protons in providing precise, superficial beams for irradiating melanomas of the iris. In 1994, the first patients were treated at the CCO, using the standard melanoma dose and fractionation (53 Gy in 4 daily fractions). At present, 95 iris patients have been treated. This presentation will describe the early results (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 previously 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. Iris treatment planning was performed on the EYEPLAN (1.6/3.xx) eye therapy program, which 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 effects. The superficial proton beam depths (4.5 to 7 mm) required the use of a flat, thin walled Markus IC.

CONCLUSION: Proton beam radiotherapy 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.

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Results of proton and plaque therapy of choroidal melanoma treated in Vancouver.

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Treatment of choroidal melanoma using 70-74 MeV protons from the TRIUMF cyclotron started in 1995 with 68 patients treated by the end of 2001. Patients presently receive 45 Gy (reduced from 50 Gy in 1998) in four daily fractions. The physicians and medical physicists responsible for proton therapy also carry out ^{198}Au plaque therapy for smaller ocular tumors with very favourable results reported (ref). Patients are referred for proton therapy based on tumor size and/or location close to the optic nerve.

This paper will describe the beam line and proton treatment system, some aspects of dosimetry and treatment planning, statistics on the patients treated, and a preliminary report on treatment outcomes.

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Proton beam therapy for wet macular degeneration: the rationale for adding photodynamic therapy.

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Proton Beam Therapy (PBT) is a safe and effective therapy for the wet type of age-related macular degeneration (wet AMD). Over 400 patients have been treated since 1995, with an anterior chamber sparing and lens sparing proton therapy technique. The leaky blood vessel of the wet AMD has closed (stopped bleeding) at a rate of 90% using 14 GyE in a single fraction. The response time for blood vessel closure was 3 to 6 months post proton therapy. The recurrence rate is less than 5 % at 1 year.

The bleeding of this leaky vessel exposes the macula to the caustic substances found in blood. This will eventually cause permanent damage and visual decline. Thus, reducing the macula's exposure time to blood should reduce this damage. There is concern that the bleeding during the response time of PBT might allow additional macular damage and visual decline.

The FDA has approved Photodynamic Therapy (PDT) for the classic type of wet AMD. PDT consists of a photosensitizer that has a higher uptake in rapidly proliferating cells, such as the leaky blood vessel of the wet AMD. A non-thermal laser is utilized to cause cellular death of the blood vessel cells. A randomized study has demonstrated its efficacy, but it has required re-treatment an average of 3.4 times in the first year and 2.1 times in the second year.

The hypothesis is that the combination of PBT and PDT would be synergistic by reducing the exposure time of the macula to blood. PBT has a low recurrence rate but has a 3 to 6 month response time. PDT has a fast response time but high recurrence rate. Using PDT to stop the bleeding during the response time of PBT should reduce the exposure time of the blood to the macula and hopefully improve visual outcome.

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Proton therapy of ocular tumors in Berlin. The experience of the first four years.

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From June 1998 226 pts. have been treated with protons at the Hahn Meitner Institute in cooperation with the University Hospital Benjamin Franklin in Berlin.

This includes 182 uveal melanomas, 14 iris-melanomas, 28 hemangiomas of the choroidea and the retina and 2 patients with other indications. The most cases of uveal melanomas have been treated with the standard fractionation scheme, four

fractions with 15 CGE each, melanomas of the iris have been treated with a total dose of 50 CGE in four fractions and in hemangiomas 20 CGE in four fractions were applied.

Indications for the treatment of choroidal melanomas with protons were tumors within two PD to the optic disc or the macula. The maximum tumor prominence was 7 mm. Since the introduction of endoresection in May 2000 patients with tumor prominence larger than 7 mm were first irradiated with protons and subsequently resected.

Results: Of the 182 uveal melanoms we observed 8 recurrencies. 3 of them underwent enucleation, 3 could be salvaged by TTT, 2 by ruthenium brachytherapy. Due to toxicity further 8 eyes were enucleated. The median followup was approx. 2 years.

Two of the 14 patients with melanomas of the iris were enucleated due to anterior sequment complications. For the remaining patients only minor toxicity has been observed

Most of the patients with ocular hemangiomas had a stabilisation or improvement of visual acuity with only grade I and a few grade II sideeffects. The median followup time for this group was 18 month.

The details will be presented.

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Clinical application of proton beams in the treatment of uveal melanomas: the first therapies carried out in Italy (CATANA project).

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The first Italian proton therapy facility has been realized in Catania, at the INFN-LNS. With its energy (62 MeV proton beam) it is ideal for the treatment of shallow tumors like those of the ocular region: uveal melanomas first of all (the most common primary intraocular malignancy of adults), other less frequent lesions like choroidal hemangiomas, conjunctiva melanomas, eyelid tumors, and afterwards we plan to treat benign lesions like age-related macular degeneration as well.

Since February 2002 three patients with uveal melanoma, coming from different parts of the country, have been treated successfully. All patients had a localized disease, with no systemic metastases, and had specific indications for conservative approach by means of proton beams, depending on their size or location: according to the TNM-AJCC Staging System, one patient was stage I (height 3mm, LTD 10 mm), two stage III (one with tumor invading the ciliary body and the iris periphery, the other had tumor height 7 mm, LTD 17 mm).

The target volume was defined as the tumor plus a safety margin of 2.5 mm, both laterally and antero-posteriorly. The treatment has been carried out in 4 fractions to a total dose of 54.5 Gy (single fraction 13.6 Gy), which corresponds to 60 CGE (Cobalt Gray Equivalent; single fraction 15 CGE), because the relative biological effectiveness (RBE) is 1.1.

The first follow-up is planned 6 months after the end of the treatment.

Scirè: height 3 mm, LTD 6-7 mm, stage I
Allori: h. 5 mm, LTD 15 mm, s. II
La barile: h. 8-9 mm, LTD 9 mm, s. III

Table 3: Staging (TNM-AJCC)

Stage	**Height**	**Diameter***	**TNM**
I	≤ 3mm	< 10mm	T1 N0 M0
II	> 3 and ≤ 5mm	> 10 and ≤ 15mm	T2 N0 M0
III	> 5mm	> 15mm	T3 N0 M0
IV	**Extraocular extension (T4) or any N1 or M1**		

*Lesion diameter is referred to the largest tumor diameter (LTD)

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The experience of 10 years of eye treatments by protontherapy at CPO: from melanomas to other indications.

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Since 1991, 2000 patients have been treated at CPO for ocular diseases.

Based on a well established procedure set up for melanomas, new indications have been treated: iris melanomas (1,4 % patients treated) and haemangiomas (5.7% patients treated).

Clinical requirements (dose, margins) and technical aspects (patient positioning, proton beam line, treatment planning system) adapted to each case will be presented.

The results (1) of a 1062 patients study between 1991 and 1998 with a median follow-up of 38 months are presented : local control was obtained for 97.1 % of patients, the survival rate was 92 % at 2 years and 78 % at 5 years.

A correlation between the different steps of the preparation and treatment and the low rate of local relapse (2.9 %) will be discussed.

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The Italian experimental radiobiological research related to hadrontherapy.

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In the present review, which of course cannot be exhaustive, I'll focus principally on the Italian activities related to hadrontherapy carried out in the framework of Istituto Nazionale di Fisica Nucleare (INFN).

The radio-biological section of the ATER experiment of INFN involved research groups from the University of Milano, the Laboratori Nazionali di Legnaro (LNL) of INFN, the Istituto Superiore di Sanità (ISS), and the Università di Napoli Federico II. It was devoted to the study of the cell inactivation frequency in human cells, normal and tumoural, with different radio-sensitivity to photon irradiation, following low energy proton irradiation. The use of monoenergetic protons could in fact provide useful information on the energy dependence of the biological effectiveness especially at low energies. Results showed that the relative biological effectiveness (RBE) for inactivation with protons of high linear energy transfer (LET) increased with the cellular radioresistance to γ-rays. The cell line with the greatest resistance to γ-rays was the most responsive to the highest LET protons [1].

This study was then continued with the same proton beams and biological samples with the realisation of split-dose experiments, aiming at determining the relationship between the cell recovery from radiation induced damage and the radiation quality [2]. A higher maximum recovery was observed for radiosensitive cell lines in comparison to radioresistant cells, and the recovery potential after split doses was smaller for slow protons in comparison to low-LET radiation.

All proton irradiations were performed at the 7 MV CN accelerator at the LNL, and at the 3 MV TTT-3 Tandem accelerator at the Università di Napoli Federico II. The incident LET on cells was between 7 and 33 keV/μm.

An analogous research was then extended to carbon ions, as carbon ion radiotherapy was started in Chiba (Japan) and Darmstadt (Germany). A systematic study of RBE dependence on the LET of carbons was accomplished which could give useful information for a realistic evaluation of the effective biological dose. RBE values for cell inactivation were found higher then RBE corresponding to proton beams and preliminary results showed that radioresistant tumour to γ-rays could be better treated with high LET particles.

The irradiation facilities used for carbon radiobiology were the Tandem-XTU accelerator at LNL, which delivered carbon beam with energies of 6 MeV/amu and 8 MeV/amu, and the Tandem-ALPI facility, always at LNL, to achieve the energy of 20 MeV/amu. Successively these experiments took advantage from the superconducting cyclotron of the Laboratori Nazionali del Sud (LNS) of INFN, where carbon ions were accelerated up to 62 MeV/amu. Finally, also the therapeutic beams were used for irradiations at the HIMAC facility in Chiba to understand the effects of the secondary ions coming from the projectile and/or target fragmentation.

The studies on cellular clonogenity were enriched by the different research groups investigating other biological end-points, such as DNA fragmentation [3], and chromosome aberrations [4] to assess useful parameters for predictive test in radiotherapy treatment.

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Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors.

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We aimed to assess the potential influence of improved dose distribution with proton beams compared to conventional or intensity modulated (IM) X-ray beams on the incidence of treatment-induced secondary cancers in pediatric oncology.

Two children, one with a parameningeal rhabdomyosarcoma (RMS) and a second with a medulloblastoma (MDB) were used as models for the purpose of this study. After defining the target and critical structures, treatment plans were calculated and optimized, four for the RMS case (conventional X-ray, IM X-rays, protons, and IM protons), and three for the irradiation of the spinal axis in MDB (conventional X-ray, IM X-rays, protons). Secondary cancer incidence was estimated using a model based on Publication #60 of the *International Commission on Radiological Protection*. This model allowed computation of absolute life-time risks of secondary cancer for each treatment plan, based on dose-volume distributions for the non-target organs.

Proton beams reduced the expected incidence of radiation-induced secondary cancers for the RMS patient by a factor of 2 and 2.4 and for the MDB case by a factor of 1.7 and 15 when compared with either IM X-ray or conventional treatment plans, respectively.

The potential for a significant reduction in secondary cancers in pediatric cancers after using proton beams (forward planned or IM) in the treatment of RMS and MBD in children and adolescents represents an additional argument supporting the development of proton therapy for most radiotherapy indications in pediatric oncology.

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Present status of the proton therapy system in PMRC.

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We had constructed "PROBEAT-Tsukuba", that is, the proton therapy system in Proton Medical Research Center, University of Tsukuba. The present system employs two treatment rooms with rotating gantries and a synchrotron with a maximum energy of 250MeV. Clinical trial to generate data for Governments' approval had started in September 2001, and ended before previous PTCOG Meeting held at Tsukuba, November 2001.

Before starting the above clinical trial, we had confirmed several characteristics and functions needed in daily treatments, one of which was to provide the highly stable and reproducible proton beam with simple operation. The beam position measured at the entrance of the irradiation nozzle was kept in 0.5mm without feedback control. This characteristic was realized by Hitachi's RF driven slow extraction scheme and stable power supplies, magnet and so on. Another was the respiratory synchronized operation of synchrotron, which was essential for proton irradiation to the tumor moving with the respiration. High irradiation efficiency was realized by the variable repetition period of our slow-cycling synchrotron, which was synchronized to the patient's respiration signal.

After the previous PTCOG meeting, the present system has been improved significantly. First of all, the intensity of protons extracted from synchrotron and transported to the nozzles has been increased up to the 20nC per pulse, which is rise of 50% from last November. The value of 20nC/p corresponds to 2Gy/min at 0.33Hz operation for the maximum irradiation field (20cm-diameter x 12cmSOBP). The second is the improvement of the respiratory synchronized irradiation system. The respiration signal generating and accelerator control systems have been modified to keep the high irradiation efficiency even in the various and irregular respiration patterns of different patients. The time for beam irradiation to the patient are significantly shortened by these two key advances. There are many advances other than those above, for

example, shortening of the time for changing the treatment rooms, some improvements of treatment planning system, user-interface of accelerator control system and so on. All of them improve the patient throughput of this proton therapy facility.

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Proton beam therapy at the Svedberg Laboratory. a status report 2002.

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The synchrocyclotron at the The Svedberg Laboratory in Uppsala has been utilised for radiotherapy with a maximum energy of 180 MeV. Since 1994 we have been offered 10 treatment weeks per year evenly distributed in time with one week per month, with the exception of July and August. Patients with benign targets have generally been irradiated with protons only. Those with malignant targets have been given a combination of photons and proton beam therapy utilising the protons as a "boost" to a smaller target.

Between 1989 and 2001 we have treated 311 patients with the following distribution:

Meningeomas at the base of the skull	83 patients
Arterio-venous malformations	69
Malignant gliomas	79
Uveal melanomas	20
Other targets	60

Twelve patients with metastasis or tumor growth in the vertebral cord or pelvis have been irradiated in a supine position with one field. All other patients were treated in a seated position, generally with two or three isocentric fields

The incidence of late side reactions has been low. The results of irradiation for each category of patients will be reported and commented.

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CNA, the Italian national centre for proton and carbon ions and related projects.

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The first meeting of the board of the CNAO Foundation was held in November 2001. This Foundation was created by the Italian government with an initial allocation of 10.4 million Euros "to realize the CNA designed by the TERA Foundation". The TERA design is based on the *Proton Ion Medical Machine Study* (PIMMS) that was lead by Phil Bryant at CERN in the years 1996-2000. TERA and Med-Austron personnel contributed to PIMMS, while GSI gave expert advice. More recently TERA has introduced some modifications in the initial project. In particular protons and ions will be injected on many turns by a single short injector, that is placed inside the synchrotron ring and was designed by GSI for the Heidlberg project. These modifications have been adopted also by the ETOILE project in Lyon and by the Karolinska project in Stockholm.

Phase 1 of CNA is based on three treatment rooms with three horizontal proton or ion beams. In one of them a fixed vertical beam will be also available. The present design foresees that the beam is bent vertically by a conventional magnet that is very heavy and power consuming. A project is under way (under the name TESI) aimed at designing a superconducting magnet in collaboration with the University and INFN Section of Genoa and Ansaldo Superconduttori. The coils of this magnet have a special form and are cooled with cryocoolers instead of standard liquid Helium refrigerators. A model of one of the coil is under construction.

For beam diagnostics a novel detector is under development in the framework of the European funded project SUCIMA. The secondary electrons extracted by protons and ions from a very thin aluminum foil will be imaged by a pixel solid state detector, giving continuous online measurements of the intensity, profile and position of the beam in the extraction lines.

A project named PRASSI (*Piani Radioterapici con Adroni e Sistema di Scansione Integrati*) has been submitted together with six hospitals and universities to a financing committee, for the development of an integrated planning, active

scanning and dosimetry system for hadrontherapy. An intermediate milestone consists in producing an atlas of the clinical hadrontherapy indications.

The workshop held at CERN 12-13 February launched the ENLIGHT programme, a European Network for research in LIGht ion Hadron Therapy. It has been signed by ESTRO, EORTC, ETOILE, Karolinska, GHIP (German Heavy Ion Project), Med-Austron, Macarena, TERA and CERN to coordinate the efforts that aim at the construction of national Centres for light ion therapy.

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The Italian project for the development of a proton accelerator for oncological therapy (TOP project).

The TOP Collaboration, ISS/ENEA/IRE, Rome - Italy

In 1993, following a deep analysis of reports issued by TERA (short for ***Te****rapia con* ***A****droni*) Foundation, the Physics Laboratory of the Istituto Superiore di Sanità (ISS, the Italian National Institute of Health) decided to take a primary responsibility in fostering protontherapy in Italy, and enforced the project "Development of the use of protons in oncological therapy".

The idea underlying this project, referred to as TOP (short for ***T****erapia* ***O****ncologica con* ***P****rotoni*), was that a design should have been developed for a compact proton accelerator that could be housed in already existing hospitals, and which required a limited space and limited shielding. Soon after, the Rome Oncological Institute Regina Elena (IRE) accepted to cooperate with ISS to demonstrate the operational validity of the Project and to assume the future responsibility of the clinical activity.

After a 2-year comparative study among different types of accelerators, the construction of a high-frequency proton linear accelerator was approved, and ENEA decided to collaborate with ISS and IRE for the realization of the prototype.

Such a large project, to be developed over several years, required a deep insight into basic research topics in the fields of biophysics, of oncological radiobiology and of dosimetry and microdosimetry, together with a thorough study of the clinical effectiveness and of the treatment planning techniques and the development of information technologies.

For these reasons, the project has benefitted from the collaboration with several institutions, and INFN (**I**stituto **N**azionale di **F**isica **N**ucleare) funded part of the research activity.

A status report of the development of the TOP project will be presented.

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The CATANA (Centro di AdroTerapia ed Applicazioni Nucleari Avanzate) proton therapy beam delivery system.

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The 62 MeV horizontal beam proton therapy facility for the treatment of eye melanoma at the Laboratori Nazionali del Sud (INFN) of Catania, Italy was commissioned in January 2002 and the first three patients were treated in March 2002.

The proton beam exits in air through 50 μm Kapton window placed at about 3 meters from isocenter. Before the window, under vacuum, is placed the first scattering foil made by a 15 μm tantalum.

The first element in air of the beam delivery system is a second tantalum foil 25 μm thick provided with a central brass stopper of 4 mm in diameter.

The double foil scattering system in optimized to obtain an acceptable homogeneity, in terms of lateral dose distribution, minimizing the lateral penumbra and the energy lose.

Range shifter and range modulator are placed downstream the scattering system and mounted in a box. Two diode lasers, placed orthogonally, provide a system for the isocenter identification and for patient centering during the treatment. The emission light of a third laser is spread out to obtain the simulation field.

A key element of the treatment line is represented by the two transmission monitor chambers and by a four sector chamber, implemented to have an on-line control of the dose furnished to the patients and an information on beam symmetry respectively.

Two orthogonal X-Ray images are taken to establish relationship of the tantalum clips, surgically placed on the eye to indicate tumor margins, to the treatment system landmarks.

The patient is treated in a seated position with the head immobilized with a face mask and bite block. The treatment chair has six motorized degree of freedom including the rotation about a vertical axis and it is fully computer controlled.

The main features of the proton beam line will be extensively reported.

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The control system of the CATANA proton therapy facility.

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A very important activity in the framework of the CATANA project, the first hadrotherapy application in Italy, is the development of a fully automated hardware/software interface of the facility as a strategic element designed to guarantee the maximum efficiency and security level both during beam characterization and treatment. Our choices were made according to intrinsic security and redundancy guidelines.

The control system consists of two main components: the operator interface and the interlocks management. The role of the operator interface is the supervisor of the correct functioning of the whole facility. In this sense, we developed a complete set of tools, hardware and software, allowing the operator to achieve reliable results in the most simple and efficient way. All the informations coming from the beam instrumentation are reported in the operator interface together with simple commands to start and stop the beam and to manage the patient file and database. The interlock management is a fully hardware system with the most important aim to guarantee the correct functioning of all the instrumentation used during both beam calibration and patient treatment. The system is able to accept, for security check, three kinds of inputs: analog signals, TTL signals and electric contacts. Furthermore, the same system manages the beam start/stop devices (two valves and one faraday cup) and performs the control of all the voltage level used to supply the instrumentation and the electronics itself. A suited electronic board (the interlock board) was realized in order to accept up to three different inputs; the board must be hardware configured in order to define the kind of input and the logic of the security check. The control logic is cabled in the circuit and a microcontroller manage through a serial port the data exchange with the operator console.

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What are the questions we should be asking about scanning?

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There has clearly been much good work done in the field of scanning and we should acknowledge the excellent results of the groups at PSI, and GSI for example. There have been scanning workshops and Marco Schippers has produced a nice report from one of them. However I would like to use the PTCOG as a forum for a bit of brainstorming about what we should do next. New facilities recently commissioned and under construction are ready to implement scanning. How should this implementation proceed? I am concerned that future scanning designs may be taking too much from the existing implementations. For example the PSI and GSI facilities have particular issues regarding beam time uniformity, dose rate and methods of beam to target motion. The implementation that has been chosen in those cases while very clever, is possibly somewhat specific to those parameters.

It could be useful to identify what is meant by the ideal scanning system. What features are interesting, useful, important, or vital to the success of a flexible clinical program? What are the prerequisites to be able to implement these features? It would be useful then to compare existing and planned facilities with respect to how or indeed which of the features can be implemented. The corollary question to that is: what features are required in the beam delivery system of a Proton Therapy System to implement the most general scanning system?

The next step is to evaluate the necessity of the features of an ideal system. For each facility these features may have a different importance. Finally, it is useful to understand how the design of a facility is affected by the decision of the scanning requirements.

The intention is not to answer all the questions, but to try to ask them, and through a straw-person model, to start the process of evaluation. We have a particular interest in doing this at the NPTC since we hope working together with IBA to implement scanning in the next year or two.

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Studies of optimization methods for dose delivery with A beam scanning system.

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Intensity Modulated Proton Therapy (IMPT) can be implemented at the Northeast Proton Therapy Center (NPTC) using the pencil beam scanning system developed by IBA and the treatment planning system KonRad. The IBA system is designed to perform a continuous scanning, on a raster pattern, of the pencil beam throughout equal-range layers within the target volume. The delivered dose along the scanning lines is modulated by simultaneously varying the scanning speed and the beam intensity. Transition between the target layers is accomplished by varying the proton beam energy. The pencil beam parameters (energy, width, intensity etc.) are calculated by the treatment planning system (TPS) for a discrete spectrum of instantaneous beam positions, or "spots", along the scanning lines. The spacing between the adjacent spots is typically of the order of the width of the pencil beam (σ).

For the purposes of *continuous* raster scanning, one needs to convert the discrete intensity map generated by the TPS into a continuous one. Such conversion may produce a significant discrepancy between the prescribed dose, as planned by the TPS, and the delivered dose. This discrepancy may be minimized by using a much finer spot spacing (e.g. $\sigma/10$) in the fast scanning direction at the planning stage. However, reducing the spot spacing would increase the time necessary for the calculation and, eventually, for treatment. Alternatively, the intensity map calculated by the TPS may be adjusted (optimized) for the use by the delivery system to achieve the desired conformity of the delivered dose.

We have investigated various methods of conversion of a discrete spectrum into a continuous one. The results of the calculation will be presented for the intensity map optimization techniques using, respectively, deconvolution of the planned dose distribution with a pseudo-gaussian distribution, a triangular approximation, and bicubic spline. It will be demonstrated that the desired reduction in the discrepancy between the planned and delivered doses may be achieved without decreasing the TPS spot spacing.

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Beam Scanning Research at LLUMC.

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A dedicated beam line in the research room of the LLUMC proton facility has been used for scanning beam research at Loma Linda since last year. Two scanning magnets followed by a dose monitoring ion chamber are used to control the beam. In this presentation, we discuss recent improvements in beam delivery including production of a 400 mm by 400 mm field size at isocenter, a 5 mm FWHM beam spot, and irregular field shapes using a spot scanning technique. We will present 2-D images of the scanned beam at the entrance region of a patient and discuss where future progress can be made.

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Optimization in proton scanning beams.

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The intensity-modulated proton therapy (IMPT) is a new challenging dimension in tumor treatment. The superposition of Bragg peaks, corresponding to different energies, enables the uniformity of the dose distribution in the target, whereas the dose delivered in the neighboring organs is kept minimal. Compared to conventional techniques, active scanning offers a larger spare of healthy tissue.

Due to its complexity, IMPT treatment planning can only be performed with the help of special optimization algorithms. Due to the presence of the third dimension in the problem (modulation in depth) for each beam, IMPT is more complex than conventional photon IMRT.

Our treatment planning comprises three steps:

The calculation of the dose-deposition coefficients (dose delivered from each spot at predefined voxels inside the irradiated volume) for all beams.

The subsequent optimization of the spot weights (which are proportional to the integral beam current at each spot position), given the prescribed dose(s) for the target(s) and the dose constraints for the organs.

The final calculation of the dose distribution, given the optimal spot weights.

In step b, four optimization methods have been implemented and put into test: the conjugate-gradient algorithm, a method incorporating principles of simulated annealing, the simultaneous optimization used at the Paul-Scherrer Institute (PSI), as well as an algorithm attempting the minimization of the angle between the desired and the delivered dose vectors (generalized sampled pattern matching).

All optimization methods are implemented in such a way as to be independent of the details of the actual beam line; the only input relates to the dose-deposition coefficients. Hence, we can deal with discrete spot scanning (on a regular or irregular grid) as well as with raster scanning (small step size in one direction, i.e., simulating continuous scanning, large step size in another direction).

First results will be presented and discussed.

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Status of the development of a pencil beam scanning system at IBA, Belgium.

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Ion Beam Application is a Belgian enterprise with a unique expertise in particle accelerators technology, with applications spanning from sterilization to radioisotope production for nuclear medicine and to radiotherapy. The Proton Therapy System developed at IBA is a turnkey solution based on a 230 MeV cyclotron, provided with a beam-line, rotating gantries, multi-axis patient couches and a software of control. The actual proposed solution utilizes the passive technique for treatment delivery by means of an advanced system of double scatterers, but a new development based on the pencil beam scanning technique is ongoing and already in an advanced stage [0]. This system allows delivering the correct dose distribution to the target by irradiating it slice after slice with a pencil beam. The energy of the proton beam is selected in order to have the Bragg peak located at the depth of the corresponding target slice. The transversal shape of the target is reproduced by steering the pencil beam in the x and y directions through two scanning magnets as shown in **Figure 5**. The dose distribution as calculated by the treatment plan is deposited by a contemporary modulation of the beam scanning velocity and of the beam current, thus achieving a continuous irradiation in opposition to a voxel scanning technique. The beam spot size at isocenter can be modified by a pair of quadrupoles and may therefore be an optimization parameter in the treatment planning system.

The status of the ongoing development at IBA will be presented.

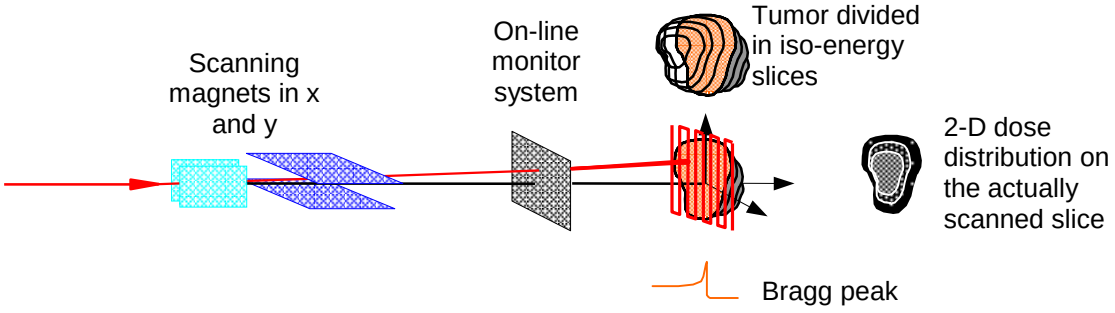

Figure 5. The principle of functioning of the IBA Pencil Beam Scanning System.

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Performances of a pixel ionization chamber to monitor a voxelscan hadron beam

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A planar ionization chamber with the anode segmented in (32x32) pixels to cover an area of (24x24) cm^2 has been tested with an Carbon ion beam at the therapeutical beam line of GSI, Darmstadt (GE).

The chamber has been fluxed with nitrogen and operated with an electric field of 1500 kV/cm.

The read out of each individual channel has been performed with a current-to-frequency converter implemented in VLSI 0.8 μm technology. The whole chamber is served by 16 chips mounted on the frame and close to the pixels to control the noise. The data acquisition is based on a Motorola CPU hosted in a VME crate. The architecture is capable of the read out of a square of (7x7) pixels and to compute the beam center of gravity in about 50 μs. In a voxelscan beam environment the read out time is sufficiently fast to monitor the fluence delivery and the position of the beam several times during each voxel irradiation.

The reconstruction of the center of gravity has been compared to the expected beam position and furthermore the fluence as measured by the chamber has been compared to the expected fluence.

With a beam dimension of ~8.5 mm (FWHM), the position resolution is approximately 0.2 mm.

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Treatment Planning for Broad-Beam 3D Irradiation Heavy-Ion Radiotherapy.

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Since 1994, medical accelerator complex HIMAC at NIRS has been delivering therapeutic carbon beams to over one thousand patients. [1] In order to further improve dose-tumor conformity in heavy-ion radiotherapy, the idea of broad-beam 3D irradiation was proposed, where the range shifter and the MLC system are dynamically controlled in accordance with the delivered dose to longitudinally scan the minimally spread-out Bragg peak through the treatment target while keeping the optimum irradiation field. [2,3,4] The treatment control system of HIMAC has been modified to deal with this new delivery technique and here we summarize the modification to the treatment planning system. [5]

In broad-beam 3D irradiation, a treatment target is divided into slices along depth and a sequence of slice-wise irradiations forms an optimum dose distribution by prescribing appropriate dose weights to each slice. The weights are optimized to maximally flatten the effective dose over the target volume. The conversion from physical dose to the effective dose is 1.43 times RBE value at 10% survival fraction for HSG cells to retain the clinical dose scale at HIMAC. [6,7] In comparisons with the conventional 2D irradiation, the consistency of the biophysical model was verified and the improvement of dose distribution has been observed in simulations for actual cases.

As to the employed dose conversion, we apparently ignore the dose dependence of RBE and therefore the effective dose should not be considered as the photon-equivalent dose. However, we decided to keep this historical dose scale concluding that there would be little benefit in improving the photon-dose equivalency while sacrificing the dose consistency within the same treatment system and losing direct applicability of the established clinical protocols for the conventional 2D irradiation.

An enhancement to the HIMAC treatment planning system has been made to consistently deal with the broad-beam 3D irradiation in addition to the conventional 2D irradiation. The achieved high integrity of the system enables seamless transfer to the new irradiation technique for the regular clinical practices.

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Treatment Planning for Carbon ion Therapy.

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For the GSI carbon ion therapy unit a treatment planning system (TPS) has been developed that accounts for the dynamic beam application using active energy variation in combination with beam scanning. Moreover, the scanner control parameters are optimised to yield a homogeneous biological effective dose in the target volume. The underlying biological model takes into account the fragmentation of the carbon ions and the biological efficiency for the resulting mixed particle field in tissue as a function of beam energy, depth in tissue and tumour type.

The TPS for carbon ions thus allows to optimise treatment plans that exhibit a very high degree of dose conformation to the target volume in addition to the enhanced biological efficiency of carbon ions. With this treatment planning program the treatment of 130 patients at GSI with carbon ions has been performed. The majority of these patients was treated for tumours of the skull base (clivus chordoma and chondrosarcoma) but also 7 patients with sacral chordoma were treated. The results for the progression free survival after 2 years are very promising (83% for the clivus chordoma and 100% for the chondrosarcoma).

Currently several planning studies for the planned Heidelberg facility are ongoing that investigate the application of carbon ions for different tumor types and locations in comparison to other advanced techniques like IMRT with photons. In addition the limitations in the accuracy of the applied dose distributions due to uncertainties (e.g. in the range calculation) are assessed.

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Ammonium tartrate and alanine ESR detectorsfor proton beam dosimetry.

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In this work we discuss the results of an experimental study aimed to evaluate the dosimetric properties of ESR dosimeters, 1 mm thick, realized at the Università di Palermo using alanine or ammonium-tartrate as sensitive substance; the dosimeters were irradiated with the 60 MeV clinical proton beam at the Clatterbridge Centre for Oncology at different depths inside a water equivalent phantom, to study the dependence of their response on dose and on proton energy. The relative effectiveness was significantly different from unity only at the lowest tested proton energy (13 MeV). This result,

together with dose dependence and time stability of the response, indicates that ammonium tartrate ESR dosimeters could find application in proton therapy, as well as alanine ones.

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Investigation on LET dependence of glow curve characteristics of thermoluminescent materials irradiated with proton beams.

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Different types of LiF thermoluminescent detectors (TLD100 and GR200) were irradiated with the 60 MeV clinical proton beam at the Clatterbridge Centre for Oncology, at different depths inside a water equivalent phantom. Glow curve deconvolution and analysis were carried out to gain deep understanding on the relationship between characteristics and concentration of the doping materials, and kinetic parameters of the glow curve, such as activation energy and peak temperature. The results showed a decrease in sensitivity with increasing LET of proton beam for both type of dosimeters; moreover, no variation was evident in the glow curve of TLD100 irradiated with proton with various LET, whereas the glow curve of GR200 showed some dependence from LET, suggesting that new TL defects are induced.

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Physical characteristics of lucite compensator used for conjonctival melanoma treatment.

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The purpose of lucite compensator is to treat the whole conjonctiva while sparing the inner part of the eye.

We fit the range of proton to the depth to be treated by using a suitable thickness of some material. The compensator is roughly, a semi spherical accessory. The material used is lucite as it is easy to machine.

The shape of these personnalized spherical compensator depend on the diameter of the eye, the thickness of sclera to be treated, the thickness of lid and ultrasonographic gel used as bolus and the maximum range of proton beam needed to treat all the conjonctiva. The width of modulation does not influence the shape of the compensator but the dose distribution as the homogeneity depends largely of this value.

A computerized programme has been made and the coordinates are sent to a milling machine, in our worshop, where these compensators are manufactured.

The compensator is positionned in a fixed and reproducible way at the end of the optic bench using a lucite support whearing also the personnalized collimator for the patient. The quality control of treatment includes the verification of the compensator position.

The Eyeplan programme does not give the possibility to modalize this kind of accessory and it was essential to verify experimentally the feasability and reliability of such an accessory. We used a little water phantom with a (1x 0.5mm) diode which automatically scans the beam in the three directions. We verify the dose distribution in different perpandicular and parallel planes. We are able to superimpose the eye géometry with the measured dose distribution.

We will present details of this compensator and dose distributions and we will discuss the influence of modulation on dose distribution.

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Technical requirements and indications of protontherapy for conjunctival melanomas.

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Conjunctival melanomas mainly benefit from surgery and post operative low energy roentgentherapy or electrontherapy. For some cases, after multiple relapses, a conservative surgical procedure is no more possible. Therefore multirelapsing conjunctival melanoma often lead to a salvage enucleation or exenteration although the eye itself is not affected by the melanoma. Radiotherapy (including low-energy X-rays, electrons, protons) has been used to treat some of

these melanomas but give a more or less important dose to the inner eye. A technique of protontherapy allowing an homogeneous irradiation of the whole conjunctiva with a total protection of the inner eye is proposed as an alternative for these patients.

The natural history of the disease implies to treat both bulbar and lid conjunctiva, because of the existence of kissing lesions, but generally allows to spare the inner part of the eye. The target volume to be considered is very large. It includes at least half of the total surface of the conjunctiva, in order to try to avoid further relapses at the margin of the treated volume.

The techniques developped for the treatment of uveal melanomas using the medical proton beam in Nice have been extrapolated to the treatment of multi-relapsing conjunctival melanomas. The beam has to pass through the lid but must respect the internal structures of the eye, in order to preserve the visual outcome.

The technical principles of the treatment are as follows : - the clips are inserted on the eye for localisation of the target volume and repositionning purpose, - a bolus is set-up on the lid to give a homogeneous flat entrance for the proton beam collimated to the size of the tumor, - the beam passes through a semi-spherical plexiglass compensator to adapt the range of the proton beam to the shape the inner sclera and let the protons irradiate the thickness of sclera and conjunctiva. The compensator is individually customized from a plexiglas block by a computerized milling machine. The dose distribution is homogeneous and gives the whole dose to the lid and bolus as well as to the conjunctiva.

From 1992 to the end of 2001, 49 cases have been treated. The dose fractionation currently used is 6 fractions of 5.2Gy (36 Gy cobalt equivalent) followed by a boost of 2 fractions of 7 to 9.1 Gy, depending on the clinical status.

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Raman spectroscopy of irradiated tissue samples.

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Tissue samples No. I (skin of mice, normal and tumor) and tissue samples No. II (skin of a woman, normal and tumor) of about 1 mm thickness were irradiated by 24 MeV protons from the Munich Tandem Accelerator. The samples were sealed in thin wrappers of plastic foil. The plateau region of the protons traversing the samples delivered doses of 1, 7, and 50 Gray (samples No. I) and 0.5, 5, and 50 Gray (samples No. II).

The samples were analysed using Raman spectroscopy at the Institute of Chemical Technology in Prague by measuring the intensity of signals sensitive to radiation damage. Effects depending on the delivered dose for both tissues were found: A significant decrease with increasing dose occurs for the amide I line. Aromatics dominantly present in the non-irradiated tumor tissue are destroyed during the irradiation and the Raman spectrum for the highest dose approaches that of the normal skin with less pronounced lines of aromatics.

Acknowledgments: Work supported by the Bavarian Ministry of Environmental Affairs and the Ministry of Education of the Czech Republic.

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Long term results of proton beam radiotherapy for small posterior choroidal melanoma.

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In recent years several groups have used transpupillary thermotherapy for the treatment of small posterior choroidal melanoma. Preliminary results have been presented [1]. We will review the outcome of proton radiotherapy in patients presenting with small posterior choroidal melanoma in terms of survival, local tumor control, eye retention, and retention of a useful degree of visual acuity.

This is an institutional case series. Data have been collected prospectively. 236 patients with unilateral choroidal melanoma treated between March 1984 and December 2000 with proton radiotherapy. Patients were included in the analysis when they met the following inclusion criteria: Largest tumor diameter smaller or equal to 12 mm, tumor thickness smaller or equal to 4 mm, anterior tumor border located posterior to equator, retina not infiltrated by tumor, optic disc not infiltrated by tumor. No hemorrhage, no lens opacities, no effraction of Bruch's membrane, no extrascleral extension present at treatment. The following outcomes are reported: overall and cause specific survival, local tumor control, eye retention, retention of useful vision

The results at 15 years after treatment are as follows: The overall survival rate was 85.0 ± 4.1 %. Ocular tumor related survival was 92.8 ± 2.4 %. The local tumor control rate was 96.8 ± 1.7 %, four eyes had to receive a second treatment because of tumor recurrence. The eye retention rate was 96.1 ± 2.0 %, three eyes were enucleated because of treatment complications. 51.1 ± 4.9 % of the patients still had useful vision.

We conclude that proton beam radiotherapy is a very effective treatment technique in terms of patient survival rate, long-term local tumor control, retention of the eye, and even retention of a useful degree of visual acuity.

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Centre for accelerator science imaging and medicine at the Daresbury Laboratory in the north west of the United Kingdom.

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This important proposal should be considered in two parts: -

4GLS (the 4th generation light source) is one of the major components of **CASIM** to be based at Daresbury Laboratory in the U.K. It is essentially a suite of accelerator-based light sources designed to complement the ESRF and 'Diamond 'by providing state-of-the-art radiation in the low energy photon regime – from the far infrared to the extreme ultraviolet. This will provide a great boost for imaging of the structure and dynamics of biological tissue, materials and even molecules.

2. **SIRIUS**:

The SIRIUS proposal centres on a radioactive beam facility to be situated at Daresbury Laboratory. A 230 MeV proton cyclotron will produce a high intensity proton beam, which will act as the driver to produce exotic radioactive nuclei by bombardment of selected targets. These nuclei will be subjected to post-acceleration to energies of a few MeVs per nucleon. This facility will form the basic infrastructure for UK experimental nuclear science that currently takes place in laboratories abroad, and will be used to study such diverse fields as materials, biomedical science and astrophysics.

The same accelerator will be used to provide the basis for proton therapy, with the therapy beam operating in parallel with the nuclear physics beam. The medical research facility will be unique within the UK, and will extend the role of proton therapy in the UK to higher energies than presently available. Proton therapy is presently restricted to the treatment of ocular tumours on the 62 MeV therapy beamline of the Douglas Cyclotron at Clatterbridge Centre for Oncology (CCO). The higher energy protons from SIRIUS will be used to study the treatment of deep-seated tumours such as spinal chordoma and chondrosarcoma, and other tumours situated close to critical structures. Applications where a low integral dose is required will also be investigated to determine optimal treatment techniques.

SIRIUS will also produce clinical isotopes in support of clinical research and service programmes across the north-west. The proposal will allow for the production of limited quantities of a wide range of high purity isotopes for potential clinical research use, as well as the production of semi-commercial quantities of isotopes for common clinical service use.

The proposed facility links fundamental science at Daresbury with clinical research throughout a network of leading medical institutes centred in the north-west, but extended across the UK.

SIRIUS and the proposed medical facility can be constructed within 5 years from the point of funding, at a cost of around £50M. The design incorporates flexibility for future developmental upgrade.

4GLS and SIRIUS have had great international support and are under consideration for peer review and ministerial approval.

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Status report of proton treatment facility at NCC (Kashiwa).

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The proton therapy system at National Cancer Center Hospital East (Kashiwa) was approved as a Medical Device by Japanese government in early 2001, and the clinical treatment has been started as the advanced medical technology. Specialized in clinical use, the system is equipped with the double scattering system and the ridge filter system for irradiation field formation devices. Fixed energy cyclotron (C235) and the energy selection system (ESS) can provide very stable and optically identical beams. In order to provide the same doze distribution at different gantry angles, the beam at the gantry entrance section is tuned to be X-Y symmetric and almost parallel , which enables us to omit quadrupole magnets in this section. Automatic tuning of flat irradiation field is performed by lateral movement of 2nd scatterer according to the flatness monitor signal, which will realize a sequential treatment at three irradiation ports. The number of ridge filters necessary for treatment is reduced by using a single ridge filter for one SOBP but different energies. The shape of ridge is optimized for different stepwise energies from ESS and different fine degrader settings.

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The design and implementation of a heavy ion therapy database.

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A database system of carbon ion therapy to be used for the analysis of planning data as well as treatment records has been designed and implemented. This database will give investigators access to the imaging and character data since the start of the clinical trials June 1994.

A schematic diagram of the system is shown in Fig.1. The database is created on an Oracle relational database management system running on a Sun workstation. We implemented a DICOM v3.0 (1) including radiotherapy extensions. The MergeCom Toolkit (Merge Technologies Inc., Milwaukee, U.S.A.) was used. Data were mapped to DICOM standard objects; however, limited numbers of private attributes were introduced for ion therapy specific objects since ion therapy was not supported yet.

All the saved planning data and treatment records of 1200 patients have been loaded into the database with a software tool. In routine use, planning data and treatment records saved in storage disks are loaded into the database on-line every night. Besides this, GUI tools used to load data manually as well as to edit loaded data are prepared.

User can access database with standard WWW browser to search and retrieve information. A DICOM RT viewer has been developed to view and retrieve RT images, dose distributions and structure set. The system has been fully tested.

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Potential advantage of 99-TC-methoxy-isobutil-isonitrile (MIBI) - spect in association with CT and MR imaging in delineation of target volume for high grade gliomas: preliminary results.

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The MIBI is a substrate of P-glyocoprotein that is codified by the gene of multidrag resistence 1 and is an efflux pump for several cytotoxic drugs. Literature data show that MIBI uptake is correlated with cell metabolism and positivity to

99Tc-MIBI SPECT with vascularization and density of tumor cells. We studied functional imaging (MIBI-SPECT) in addition to morphological studies (CT, MR) in order to assess the potential advantage in target delineation for conformal radiotherapy (CRT) of high-grade gliomas.

Five patients affected by high-grade glioma and candidate to conformal radiation therapy (CRT) have been enrolled in this study to date. All patients were immobilized by head-rest and thermoplastic mask. Contiguous spiral CT (Highspeed, GE) and MR T1-weighted images with gadolinium (Contour, GE) were obtained with 3 mm thickness. The SPECT study was done by a two headed gamma-camera (Varicam, Elshint). After 740 MBq of 99Tc-MIBI injection. FOV was set to 25 cm and the matrix varied from 512x512 for CT to 128x128 pixels for SPECT. The 3 images set was matched using the software of the treatment planning system Pinnacle 6.0i, ADAC. Preliminary phantom study showed that registration errors were comparable with the SPECT pixel size, i.e. 0.2 cm. The extension of the lesion detectable by SPECT was assumed as biological target volume (BTV). For each patient the BTV and GTV were drawn by the same physician on SPECT, CT, and MR. Then the outlined volumes and of the regions of mutual intersection were calculated and compared.

The average volumes of GTV obtained by CT and MR were 61.0 cm3 and 59.6 cm3 respectively and the average volume of the overlapping region only 45.3 cm3. The average BTV outlined on SPECT was 55.6 cm3 and the average volumes of the overlapping region of CT and MR were 39.9 cm3 and 49.5 cm3. Looking at the images, the BTV was well correlated with the most part of GTV delineated on T1-weighted MR images and the difference between BTV and MR-GTV could be due to necrotic areas within the tumour (MIBI negative). In some cases, a marginal extension of BTV outside the MR-GTV (less than 3 mm) was seen; this finding could be related to partial volume effect due to the low matrix of SPECT or to the high background of MIBI of some structures such as choroid plexus and skull base.

This preliminary experience showed a tight relation between BTV drawn on MIBI-SPECT and GTV on MR T1-weighted images. In particular, MIBI positive area was evident in the GTV volume meaning a region with higher clonogenic cell density suitable for possible biologically based boost by using CRT with IMRT techniques or particle therapy.

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Development of 3 Tesla Magnet-in-magnet for a compact synchrotron.

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A strong magnetic field as high as 3 Tesla with little saturation effect in iron pole is possible in Magnet-in –Magnet concept. This concept was originally invented at a Snowmass2001 with a motivation to increase the magnetic filed of 2 Tesla in the Pipetron magnet which was limited by an iron saturation effect[1,2]. The magnet-in-Magnet concept is applicable not only to superconducting magnet but also to a conventional electromagnet. We have fabricated and tested a magnet capable of generating a magnetic field from 0 Tesla to more than 3 Telsa by a small model magnet. Magnetic field measurement was performed and its result is presented. Prototype actual size MiM magnet may be constructed to make a compact synchrotron for a future dedicated medical synchrotron of small size.

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Presentation of the IBA Therapy Control Software.

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This presentation will reflect Ion Beam Applications (IBA) experience with the *Therapy Control System* (TCS)[*] at Massachusetts General Hospital (MGH). It will describe several aspects of the TCS software, concentrating on interfaces, infrastructure and technologies rather than the technical details.

During the first section the IBA *Therapy Control System* functional requirements will be presented as well as our software characteristics such as safety, reliability, performance, portability and scalability.

The second section will highlight both system and software architectures and its evolution based on MGH experience. This section will also address the interface to third-party components (Patient Alignment System and Treatment Planning).

The final section will mention some perspectives for the future. An overview of current TCS developments (including Graphical User Interface prototype) will then be presented.

[*]*TCS product:*
The Therapy Control System (TCS) from IBA performs five main functions. The system is designed to 1) extract and manage the beam up to a target point, 2) manage clinical prescriptions and translate them into equipment parameters, 3) bring patients to a treatment position with high level of safety concerns, 4) manage an irradiation (beam delivery and quality checks) and 5) monitor equipment (such as security of magnets) and human safety interlocks (such as beam authorization).

The system design contains the various functions that will be completed for the system to be operational in Wobbling and Pencil Beam Scanning.

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Preliminary test of ^{123}I production with proton induced reaction.

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In the framework of the CATANA project and R&D program is under development studying the optimal condition for the production of radioisotopes of medical interest with nuclear reactions induced by high energy protons. Particularly 62 MeV proton beam produced by the INFN-LNS Superconducting Cyclotron has been used. Our initial attention has been devoted to the ^{123}I production mainly looking at its high interest for nuclear medicine applications.

In this work has been realized a preliminary test of ^{123}I production irradiating some targets of ^{124}Te evaporated on aluminum backing.

The used reaction is ^{124}Te(p,2n)^{123}I, the targets were irradiated at different energies, obtaining the best activity for 123I at 23 MeV. The preliminary results will be extensively reported.

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Effects of proton beam irradiation on uveal melanoma. The experience of the Oncology Eye Center of Genoa, Italy.

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A review of 187 patients with uveal melanomas, who were treated by proton beam irradiation between 1991 and 2001, showed that 11 (5,9 %) of these patients have thus far required enucleation of the affected eye. Most common clinical reasons for enucleation were neovascular glaucoma (72 %), tumor regrowth (9 %) and total retina detachment (18 %). Enucleation was performed on average 25 months after irradiation (min. 3, max. 36). These irradiated melanomas were of mixed cell type in 4 cases (40%), spindle in 3 cases (30%) and epithelioid in 3 cases (30%). Some degree of necrosis was seen in 40 % of cases. Overall, the median number of mitoses per 40 high-power filed in these irradiated tumor was 0. These findings together with the immunophenotypic characteristics will be discussed.

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The physical results for proton treatment at National Cancer Center, Kashiwa.

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In 1997, the proton-treatment facility that has the therapeutic AVF cyclotron accelerator (C235) is constructed at National Cancer Center Kashiwa[1-2]. The facility has 3-irradiation ports (rooms) that are 2-rotationg gantry ports and 1-horizontal fixed port. The C235 can accelerate proton to 235MeV with the beam intensity of 300nA. The external diameter is a very compact with about 4m. The radio frequency is 106MHz, the accelerating voltage is about 60kV, and the harmonic number is 4.

The proton beam therapy began at the end of November 1998. It has been curing 109 patients by the present. Also, the proton therapy system at our hospital got an approval as medical equipment from the Japanese government in April 2001. And the proton therapy at our hospital was approved as a high advanced medical technology from the Japanese government in July 2001. The treatment expenses are 2883,000 yen (about $22,000) uniformly. However, by influence of a high proton treatment cost in Japan, the increase of patient number for the proton therapy is presently difficult and is concerned with a political problem.

A beam stability of the C235 has an important relation with the uniformity of an irradiation field and is a very difficulty. The measured result indicated that the incident beam position against the 2.5-% dose uniformity must be into the 0.5- and 6.6-mm circles with the double-scattering and wobbler methods, respectively[3]. The treatment planning of proton therapy is done with the gantry angles of 5-degrees step. Therefore, the beam transport parameters at proton energies of 110, 150, 190 and 235MeV are beforehand adjusted by 30-degree step and the parameter of the 30-degrees interval is revised it.

Table 6. A summary of physical data for proton treatment of 109 patients by a treatment site.

	patient number	plan number	gate number	non-coplanar	av. gate number	target volume [ml]	target size [mmϕ]	range [mm-wet]	energy [MeV]
Head&Neck	53	62	124	18	2.0	160.1	107.1	114.9	125.3
Liver	26	31	61	0	2.0	182.5	106.9	130.1	134.6
Lung	13	14	38	0	2.7	95.6	87.6	101.0	116.3
Prostate	16	16	32	0	2.0	125.5	98.9	225.7	184.9
other	1	1	1	0	1.0	77.4	137.8	108.7	121.3

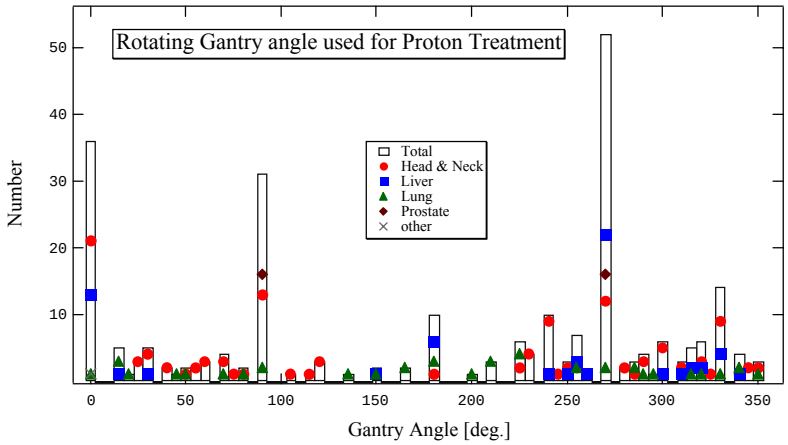

Figure 1. A use rotating gantry angle for 109 patients by a treatment site.

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The study of a target autoactivation by using a proton beam for therapy - part 2.

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Heavy charged particle therapy is excellent radiotherapy that has highly the local control of cancer. The beam control of the high precision is needed for the therapy. Recently, the research of the imaging irradiation in the patient body that used positron emitter production is done at some facilities of heavy charged particle therapy. There are a way of using a positron emitter beam and a way of using autoactivation by incident and target nucleus. Therefore, we did the study of the autoactivation by using a proton beam for therapy that is one of the heavy charged particle. The autoactivation with proton beam is the reaction by target fragmentation. The distribution of positron emitter products shows the passage information of the incident beam in patient body.

We had done the first report about this study of a target autoactivation with a proton beam for therapy by the conference (XXXIV in Boston) of the last year. The viewer of the proton dose distribution (irradiated field) in patient body just after the proton irradiation was confirmed with a medical PET at NCC Kashiwa as the study results[1-3]. We must examine various kinds of reaction mechanism for a development of a highly precise conversion tool from the dose distribution to the produced positron emitter nucleus distribution, because this reaction has strong dependence of a target. Therefore, we construct the detection system for the research on SB1 course at HIMAC. The system is constructed with large positron camera and each small NaI(Tl) detector array for measurement of the reaction cross section by a proton energy dependence.

In this work, $^{12}C(p,X)^{11}C$,^{10}C reaction cross sections were investigated by irradiating the proton beam to $(CH_2)n$ target, as the experimental data is lacking. The proton beam energy and intensity were respectively 230MeV and 5×10^7pps. Pair annihilation gamma rays from the positron emitter nucleus produced by the reaction in the target were measured with the detection system. The average $^{12}C(p,X)^{11}C$,^{10}C reaction cross sections at relative energy of 79.7MeV to 186.5MeV deduced from the experimental results were 53.3±3.3mb and 0.97±0.84mb, respectively.

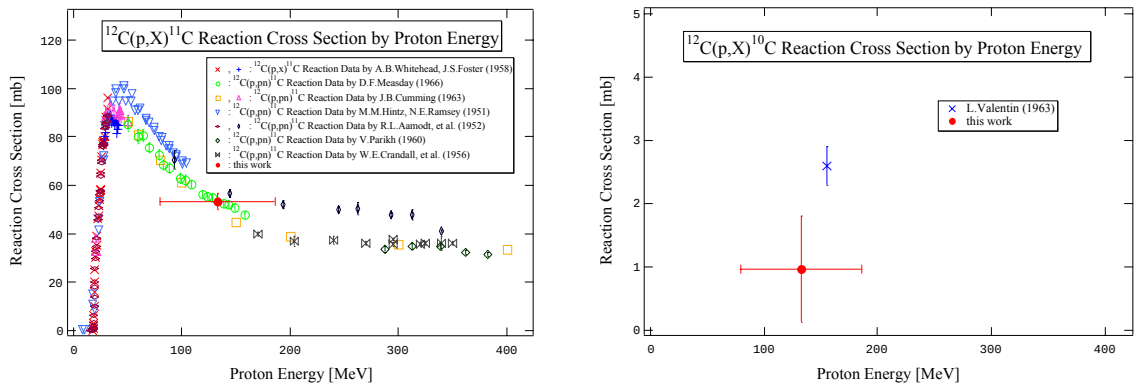

Figure 7. These figures are the summary of the reaction cross section data by a proton energy. The left and right figures show the data by the $^{12}C(p,X)^{11}C$ and $^{12}C(p,X)^{10}C$ reactions, respectively.

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Radiochromic film employed as a dosimeter to characterize a clinical proton beam.

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The characterization of the 62 MeV proton beam, employed at INFN-LNS (Laboratori Nazionali del Sud) in tha CATANA (Centro di AdroTerapia ed Applicazioni Nucleari Avanzate) facility to treat some ocular tumors (uveal melanomas and macular degeneration), needs the use of several type of dosimeters with different properties and qualities. Among these, radiochromic films are widely appreciated for their excellent spatial resolution (≈ 200 μm), their two dimensional response after a single exposure and because they are particularly suitable for the characterization of irregular and small field (output factor ≈ 1).

These films allow to study, with great precision, especially the transversal dose distribution of the proton beam and don't need chemical development (necessary for radiographic films); moreover, radiochromic films are made of a equivalent tissue material and their response is independent from proton energy.

Also radiographic films were used in comparison with radiochromic films.

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Relative dosimetry with ionization chambers for the CATANA project.

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It is well known that in the radiotherapy techniques with accelarators machines a system of ionization chambers is used in order to perform functions necessary to deliver the treatment. Here it is presented the solution adopted by the CATANA group with particular interest to the system architecture, design and behaviour which is in perfect agreement with standard models available in litterature. At LNS INFN in the CATANA project, the system for the on-line beam monitoring is composed by three modular ionization chambers: two monitor chambers and a quadrant chamber. All the chambers, located along the beam line, are transmission ionization chambers and free in air. The acquisitions of the electrical signals produced inside the active volumes allow, by means of appropriate calibrations, the measures of the integral dose, the dose delivered per unit of time and the shift of the center of the proton beam with respect to the geometrical axis of the treatment line. Saturation effetcs have been investigated at very high dose rates; results show that when the electric field is about 85V/mm the lost of signal due to the recombination effects is 1% at 20Gy/min. (the treatment dose rate is 15Gy/min.) and less than 5% if dose rate is increased up to 100Gy/min.

No feedback system has been activated, but if a measure moves from its programmed value more than a certain programmed threshold, an interlock signal is automatically generated in oreder to stop the beam.

In treatment condition the chambers are calibrated in terms of delivered dose (for a fixed dose rate); as the dose is strongly dependent from the treatment situations the calibration is performed on each patient day by day.

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The use of thermoluminescence detectors for proton dose distribution measurements.

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At INFN-Laboratori Nazionali del Sud (LNS) in Catania a proton therapy facility, named CATANA, (Centro di AdroTerapia e Applicazioni Nucleari Avanzate), based on the use of 62 MeV proton beam, has been realized mainly for to the treatment of shallow tumors (3 cm max), like those present in the ocular region (i.d. uveal melanomas and macular degenerations). The dosimetric beam characterization has been already practically concluded. For this aim different dosimeters have been employed and according to our previous experience. Thermoluminescent Detectors (TLD) have been exetensively used. Nevertheless TLD are widely used in conventional radiation therapy, their use in the protontherapy field is relatively new. Otherwise we believe that TLD should represent a cost effective solution when a very reduced perturbation of irradiation field is required like in the case of the eye treatment with proton beams. In this work our experience gained using LiF TLD (1x1x1 mm^3) for lateral and axial dose distribution measurements and output factor determination will be extensively presented also comparing their features with other dosimeters.

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Respiration synchronized irradiation system and beam efficiency.

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In our proton treatment, the lung and liver cancer has been treated with respiration-gating irradiation system. By using the system, beam efficiency was decreased, and extra time was required to complete the irradiation. In this paper, our respiration-gating system, time data and beam efficiency is presented. We are now trying to use head-mounted display system, by which patient can visualize his/her own respiratory and gating signal, to improve beam efficiency.

	No. Pts	No. Pts with Gating	Available Data	minimum	maximum	average
1998/1999	19	5	3	19.8%	27.1%	23.0%
2000	19	12	12	25.3%	45.7%	34.5%
2001	59	20	20	26.9%	50.3%	36.0%

Table 1 Patient number and beam efficiency (beam on time / irradiation time).
% data means the average beam efficiency of each patient

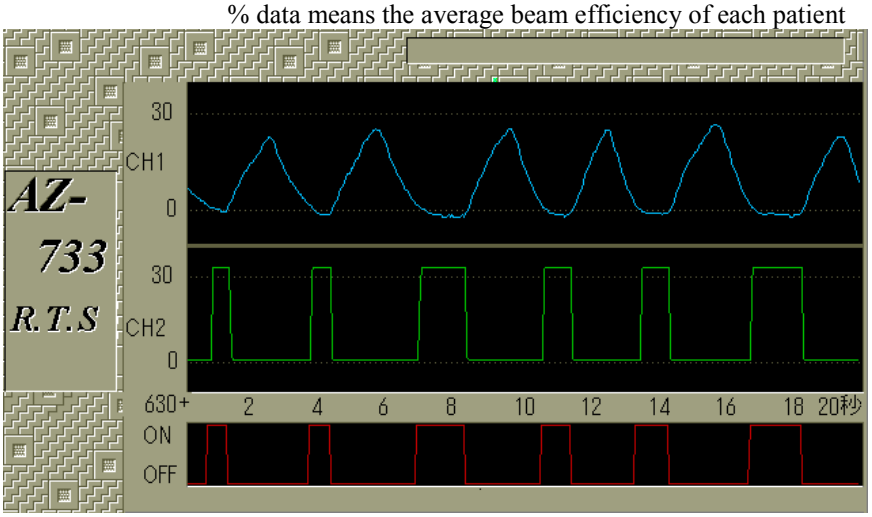

Figure 1 Respiration-Gating Irradiation System
CH1; Respiratory signal
CH2; Actual Beam On/Off Signal

Red; Gating signal by strain gauge

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A specialized clinical folder for choroidal melanoma treatment.

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A specialized electronic clinical folder has been developed in order to collect all the data coming from patients affected by eye melanoma and treated by means of proton radiotherapy. This product is aimed to gather the patients' first medical examination (personal data, tumor stadiation, size and localization, visual acuity, and so on), the treatment planning parameters and all other follow-up data. It is the logical evolution of NORMA (Network Oriented Radiological and Medical Archive) [1.], an original project designed in the framework of the TERA Foundation. NORMA was a *client/server* system written in Java and based on the World Wide Web (WWW) protocols. As it was noticed that this program was too difficult to be maintained in an hospital network, we projected and implemented a much more user friendly tool based on Microsoft ACCESS. Each collaborating center taking part in the project will have a copy of the program in order to follow a common standard. Each center's database will be afterwards transferred to all the other labs by e-mail as an attachment. In order to preserve the patients' privacy, no personal information is sent.

This database has been carefully projected with the aim of simplifying a consecutive statistical elaboration. For this reason it has been approved by SERAG (South Europe RAdiotherapy Group) to be used as the standard tool for a multicenter statistical analysis about every proton beam treatment performed during the past ten years in Antoine Lacassagne Cyclotron Biomedical Centre of Nice, France.

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Monte Carlo simulations using PTRAN and MCNPX for dose and spectral calculations in clinical proton beams.

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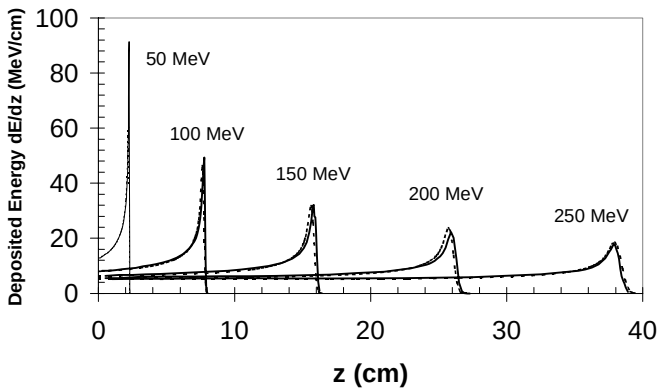
The number of patients treated with hadron beam radiotherapy has increased significantly in recent years, especially in the USA and Japan. In Europe, the number of hadron therapy facilities has increased slowly. Plans to commission a hadron beam capable of delivering 230 MeV/amu beams of primarily protons but also heavier ions is taking shape in the UK (the CASIM project at Daresbury). Accurate dosimetry and treatment planning are prerequisites in these beams for successful radiotherapy treatments.

In this work, preliminary results of a study to determine the usefulness of hadron Monte Carlo (MC) simulations in proton therapy are reported. The proton transport code PTRAN, extensively used by us in a modified form in the past, was compared against the new all-particle code MCNPX, derived from the well-known code MCNP. Dose and spectral distributions in water were calculated for 10-250 MeV protons.

The results show that calculated depth doses with the two codes are in good agreement, with the largest differences in the energy region for ocular treatments (50-65 MeV). Secondary particles such as neutrons, deuterons, alpha particles etc were found to have a minimal effect on dose distributions but inclusion in the transport of these particles required calculation times which were roughly twice as long. Lateral dose distributions for pencil beams and more realistic beams with a Gaussian lateral profile at the phantom surface were found to show small differences at different depths, with PTRAN profile slightly narrower. Significant differences were found in calculated proton spectra at the depth of maximum dose in the Bragg peak.

It is concluded that MCNPX is a valuable tool for simulations in clinical proton dosimetry, but that the small differences between MCNPX and PTRAN warrant further investigation.

Figure 1. Energy deposition of proton beam (per primary proton) as a function of depth in water for 50-250 MeV protons calculated by MCNPX (full lines) and PTRAN (dashed lines).



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Potential for a Radiotherapeutic Gain from an Anti-Proton Beam.

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Antiprotons have radiobiological characteristics which suggest they should be evaluated for a potential advantage over protons in clinical practice. They may provide a steeper gradient of biological dose between a localized tumor and adjacent normal tissues than is currently achieved with proton therapy, and with an even larger advantage over conventional external beam x-ray therapy.

Besides the physical advantage of a high Bragg-Gray peak, the potential exists for enhancement of biological dose differentials resulting from:

a. the high RBE of the high-LET charged nuclei which result from the antiproton annihilation

b. the short distance (e.g. 30 microns) traveled by the charged particles, resulting in the high LET effects being concentrated within the target volume

c. a relative insensitivity to the effect of a low alpha-beta ratio for some tumors on the differential in response between them and late-responding normal tissues. This may be relevant to such slowly proliferative tumors as prostate, meningiomas, chordomas, etc.

d. a relatively low oxygen enhancement ratio for the ionizing particles

e. a high kinetics gain factor associated with high LET beams

Experiments are planned to test these principles.