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ABSTRACTS

of the

XXIII PTCOG MEETING

held in Cape Town, South Africa
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Oral Session 3

Getting started: the first years of biomedical protons

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Investigations of biomedical applications of the proton beam at Harvard were initiated in 1959 by Dr. William H. Sweet, Chief of Neurosurgery at the Massachusetts General Hospital (MGH), and William M. Preston, PhD, Director of the Harvard Cyclotron Laboratory (HCL). The immediate purpose was to make precisely controlled focal lesions using the Bragg peak as had already been demonstrated a few years earlier by C. A. Tobias and J. H. Lawrence at Berkeley, California, and by B. Larsson and L. Leksel at Uppsala, Sweden. Dr. Sweet was then using surgical techniques to suppress pituitary function to arrest the progression of disease in patients with diabetic retinopathy and certain other conditions. It was thus quite natural to choose to develop the proton beam for pituitary irradiation, especially since the Berkeley group was already reporting promising results using a fully penetrating helium ion beam with rotation of the patient to build up the dose within the target.

Dr. Sweet invited Dr. Raymond N. Kjellberg, then Assistant in Neurosurgery at MGH and Associate in Surgery at the Harvard Medical School, to take charge of the clinical aspects of the investigation, while Preston invited the author to join him in developing the necessary technology. The 160 MeV proton energy available at HCL provides only 17 cm penetration in water, insufficient for the Berkeley style of irradiation. In order to place the Bragg peak accurately within the target a new system was devised using a stereotactic frame to allow rotation of the patient's head about two intersecting axes. This center of rotation was placed at a distance from the beam collimator equal to the depth in water of the Bragg peak. An adjustable water column filled the space between the collimator and the patient's skin to compensate for the patient's surface contour at different points of beam entry. Using orthogonal x-ray images, the position of the patient could be accurately adjusted within the frame to bring the target to the intersection of the axes of rotation. This apparatus was mounted firmly in alignment with the proton beam collimator, using x-ray films to confirm and document the entire aiming procedure. Based on x-ray images of skull bone and soft tissue, a small computed correction (typically 5 mm) was introduced for the difference in stopping power between water and these tissues along the beam path. Thus a remarkably accurate and reliable control of the beam was achieved well before the availability of CT based treatment planning.

Preclinical irradiation of experimental animals, starting in 1959, verified the accuracy of the system and provided useful dose-response data. The first patient, with a highly malignant brain tumor, was treated in 1961. The first pituitary irradiation took place in 1962, and the first arterio-venous malformation (AVM) was treated in 1965. By the time of Dr. Kjellberg's death in December 1993, he had treated more than 2900 patients with the HCL Bragg peak beam delivery system, about equally divided between AVM and pituitary targets.

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Comparative Treatment Planning for Nasopharynx Tumors

Alfred Smith, Judy Adams, John Munzenrider, Norbert Liebsch Department of Radiation Oncology, Massachusetts General Hospital Boston, MA

The second part of Comparative Treatment Planning for Nasopharynx Tumors was the topic of the clinical focus session at the Cape Town PTCOG meeting. The first part was given at the San Francisco meeting in the Spring of 1995. The goals of the study have evolved somewhat since the study was first conceived and are as follows:

The aim of the study was to evaluate the treatment plans provided by various participants for a selected nasopharynx case with the overall goal of determining which modalities and techniques led to the best treatment plan(s). CT scans for the selected case were provided in the AAPM format for each participant. The CT scans contained contours of the target volumes and normal structures. In addition, the participants were provided with target doses, normal tissue tolerance doses, and criteria for margins arising from errors in CT numbers and patient movement. Each participant was requested to send their dose matrices to Tony Lomax at PSI who would calculate dose volume histograms (DVH) for each plan using a common algorithm, grid and format. Tony would then send the DVH data to Andrzej Niemierko (MGH) who would calculate the tumor control probabilities (TCP) and normal tissue complication probabilities (NTCP) for each plan. These biological endpoints would then serve as the basis for the evaluation of all plans.

Daniel Miller (LLUMC) presented the details of the nasopharynx case, the target and normal tissue dose criteria, and the requirements for errors and margins. Judy Adams (MGH) then presented two proton treatment plans, one for fixed modulation and the other using variable modulation. Daniel Miller then presented samples of dose distributions and DVHs calculated by Tony Lomax from dose data submitted by several participants including: proton beams with fixed and variable modulation (MGH); scanned proton spot beams (PSI); standard conformal x-rays (UCSF); intensity modulated, multi-leaf-controlled, X-ray conformal therapy (UCSF); and an optimized, inverse, X-ray plan (Heidelberg). Andrzej Niemierko had faxed the results of calculations for the TCP and NTCP to Cape Town but the hotel delivered them too late for the presentation. These calculations showed that all of the plans had comparable TCPs but had a rather wide variation in NTCPs.

The most interesting aspect of the analysis was the discovery that some of the participants had pulled off the normal structures when the tolerance dose was reached, thus penalizing the target dose, while others delivered the prescribed target doses, letting the normal tissues exceed tolerance dose. This was an unexpected outcome since in the actual clinical situation it is expected that critical structures would not, in general, be given doses in excess of their tolerance. Also, one participant did not use the correct margins. It was decided to negotiate a standard set of criteria for normal tissue tolerance doses which everyone would follow and present the final data at the meeting in Detroit.

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Radiobiological measurements in 66 and 200 MeV proton beams

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As part of preclinical investigations at the NAC proton facility, radiobiological measurements were conducted in 66 and 200 MeV beams. The aim of the study was to establish if any variation in radiation quality relative to Cobalt-60 could be ascertained between different positions on the Bragg curve. Chinese hamster fibroblasts (V-79) were irradiated, either as monolayers or in suspension, to quantify radiation damage in terms of cellular survival. In addition, micronuclei formations in binucleated human lymphocytes were enumerated following exposure to protons and photons. Exposures behind various thicknesses of aluminium in the unmodulated proton beam (200 MeV) yielded surviving fractions with a response profile that mirrored the measured physical depth dose curve. Furthermore, inactivation parameters determined in the plateau region for both the 66 and 200 MeV beams were not significantly different from those determined for identical doses of Cobalt-60. These observations indicate that an RBE of 1.00 should be adopted for clinical use with the shoot-through protocol. In contrast, variations in biological potency were noted in the 200 MeV proton beam that was modulated to give a spread-out Bragg peak (SOBP) of 11 cm. Significant differences in cellular inactivation parameters were observed between cells exposed on the plateau, in the middle and at the distal edge of the SOBP. With respect to the plateau region, RBE values of 1.04, 1.07 and 1.16 were respectively evaluated at the proximal, middle and distal positions. In addition, an RBE of 1.46+/-0.3 was determined at the distal edge where the dose is 32% of that at maximum. Also, higher micronuclei frequencies were determined in lymphocytes exposed at the distal edge compared to those that absorbed the same dose in the plateau region. This resulted in RBE values ranging between 1.03 and 1.30. It is concluded that small but significant variations in beam quality can be associated with decelerating protons and that these differences should be accounted for in order to optimize the therapeutic advantage of the new radiation facility.

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Biophysical modeling of ion-radiation effects II. Cell-survival predictions based on the TC model

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An attempt is being undertaken at LLUMC to develop biophysical models of ion-radiation effects, which will eventually be incorporated in treatment planning programs. At the last PTCOG meeting, a new approach to biophysical modeling of cellular effects caused by ion irradiation was introduced, which is called the two-compartment (TC) model. The basic assumption of the TC model is that there are two classes of energy deposition events in DNA molecules: high- and low energy deposition events, which have different biological consequences. High-energy deposition events may cause complex DNA double strand breaks that are difficult two repair. Conversely, low-energy deposition events may cause no damage or damage that can be mostly repaired. The TC model allows prediction of cell survival based on the energy deposition pattern at the nanometer level. The dose-response curve is described by a second-order polynomial, i.e. linear-quadratic equation, with coefficients that are comprised of physics- and cell-specific parameters. Physics-related parameters were estimated based on previously published Monte-Carlo calculation of energy deposition frequencies in linear DNA segments of 18 nm length [1]. With increasing LET more dose is deposited into high-energy deposition events albeit with decreasing efficiency per unit dose. On the other hand, less dose is deposited in low-energy deposition events but in

this case the efficiency per unit dose increases. Cell-specific parameters were estimated by fitting the TC cell survival equation to V79 cell survival data obtained with proton and alpha particle irradiation of different LETs [2]. A good fit could be obtained without changing these parameters with particle species or energy. It may be concluded that the TC model is based on realistic radiobiological assumptions and that further investigations are useful.

References: (1) Charlton, D.E., Nikjoo, H. and Humm, J.I. Calculation of initial yields of single- and double-strand breaks in cell nuclei from electrons, protons and alpha particles. Int. J. Radiat. Biol. 56, 1-19, 1989. (2) Prise, K.M., Folkard, M., Davies, S. and Michael, B.D. The irradiation of V79 mammalian cells by protons with energies below 2 MeV. Part II. Measurement of oxygen enhancement ratios and DNA damage. Int. J. Radiat. Biol. 58, 261-77, 1990.

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Clinical indications for proton therapy: Introduction.

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Developing new protocols for proton therapy is an issue which has been raised by numerous centres during the latest years. The main reasons for new clinical protocols may be summarised as follows:

A - The proton scenario is rapidly changing; new proton projects have been developed during the latest years or are under development;

B - new centres may need the help and support of the experienced ones;

C – “new-comers” may use the considerable amount of skill and expertise which has been developed and accumulated by the “long-standings” ones;

D – “new-comers” may offer their clinical experience, organization and “manpower” to return the favour to the “long-standing” ones.

To prepare the session and to understand how many people were interested to be involved in a international collaboration to develop common clinical studies a questionnaire was sent out to 24 centres containing three main questions:

1 - how many new patients a year (total number and numbers by tumor site) are usually referred to your centre?

2 - which type of tumor(s), among those usually referred, might be, in your opinion, good candidate(s) for dose escalating protocols? Can you point out five of these?

3 - would you be interested to organise one or more extensive searches (personal data, data from the literature) to provide evidence of the best known local tumor control rates in these tumors? Do you agree that such an analysis may be the first step to start the process toward the production of new clinical protocols?

Some of centres to which the questionnaire had been sent out mailed a complete answer and paperwork. It was clear that most of these people were really interested to the effort and made suggestions as concerns possible tumor sites for new clinical protocols. These proposals are summarised in Table I. On the other side it is evident that protocols have been developed during the past years and are used. Well known protocols have been developed to treat gliomas and other intracranial tumors, chordomas and low-grade chondrosarcomas of the skull base and cervical spine, benign meningiomas,

uveal melanomas, retinoblastomas, AVMs, advanced paranasal sinus carcinomas, carcinoma of the prostate and hepatocellular tumors.
The main aim of the session is to introduce examples of the existing clinical accomplishments and new efforts to establish a possible common method of work for the future. Besides this we hope to close the session with a concrete proposal to be developed and proposed during the next PTCOG meeting.

Table 1. PRELIMINARY ENQUIRY:

POSSIBLE SITES FOR NEW PROTOCOL DEVELOPMENT.

Central nervous system:
- MALIGNANT MENINGIOMA
- ACOUSTIC NEUROMA
- MEDULLOBLASTOMA / PNET
- GLIOMA

Head and neck:
- NASOPHARYNX
- HYPOPHARYNX / BASE OF THE TONGUE
- OCULAR ADNEXAE, ORBIT, LACRIMAL GLAND
- SALIVARY GLAND
- SARCOMAS, ADENOID CYSTIC CARCINOMA

Thorax:
- NON SMALL CELL LUNG CANCER
- UPPER SULCUS TUMOR
- ESOPHAGUS

Abdomen-pelvis:
- PANCREAS
- BILIARY DUCTS
- CERVIX
- RECTUM / RECTO SIGMOID
- RETROPERITONEUM
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Hyperfractionated, accelerated radiation therapy of advanced paranasal sinus carcinoma employing combined proton and photon irradiation

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To examine whether increases in tumor doses delivered to paranasal sinus carcinomas to 76 Gy will improve upon local control, the first of a series of protocols employing precision, tightly conformal, combined proton-photon irradiation for the treatment of advanced head and neck malignancies has been introduced. This successive regimen builds on experience in accelerated hyperfractionation to include the increased targeting accuracy of proton therapy, hoping to spare patients morbid, extensive surgical resections of the orbital contents and premaxillary area. This program has accrued 36 patients thus far, including 3 currently under treatment. Permanently implanted cranial fiducials, in concert with thermoplastic masks and full denture prostheses, are employed to reduce daily positioning inaccuracies to less than 0.5 mm, verified with digitized-film repositioning algorithms. Patients are treated over a 6.5 week period with 3-dimensionally planned photon irradiation (1.8 Gy) in the morning, followed at least 6 hours later by proton irradiation (1.5. Gy) designed to spare the dose-limiting structures of optic nerves, chiasm and brain. All structures, tumor definitions are digitised in concert with the participating surgeon and neuro-anatomist. Follow-up is rigorously defined to include routine neuro-ophthalmologic examination, endocrine evaluation, and alternating CT/MR imaging.

Analysis indicates 27 of the 34 patients to be more than 2 months since completing irradiation with median follow-up = 18 months. Of 25 evaluable patients, 15 are NED (68%) with 5 (20%) alive with partial responses. Organ preservation is a significant goal of this protocol; preservation of sight with control of the primary is achieved in 75% of patients. Overall metastatic rate is 18%. Acute toxicities have included the expected moist skin desquamation and nasal crusting. One patient has realised devascularization of a preaxillary skin graft and another failure of cribiform reconstruction. The increased targeting accuracy implicit in proton therapy has resulted in significantly less oral mucositis and lachrymal gland dysfunction than realised with conventional therapy. No visual untoward effects have been realised with the rigorous follow-up methodologies described above. One patient developed focal brain necrosis in the frontal lobe which has resolved. Statistical predictions based upon dose-response data from pharyngeal wall tumours suggest the protocol-delivered 76 Gy radical dose may ultimately result in as much as a 35% increase in local control. Although the series is not mature, this regimen appears both practical and tolerable, due to improvements in immobilisation, digitised fiducial-based set-up, and combined particle-photon irradiation. The technologies are directly applicable to other tumor sites, specifically nasopharynx and petrous ridge.

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Potential role of proton therapy in the treatment of medulloblastoma/PNET

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Supratentorial volume reduction: One of the important components of radiotherapy (RT) in medulloblastoma/PNET is the irradiation of the whole brain to treat the potential supratentorial implants and the tumor bed. Nevertheless, the irradiation of the whole brain can cause severe neuropsychological and behavioural morbidity. Consequently, a reduction in RT dose or a complete elimination of RT have been proposed as treatment alternatives. We present the results of a CT based dosimetric study in which we attempt to reduce, not the dose, but the irradiated brain volume by treating only the supratentorial "sanctuary" regions (i.e. higher risk for relapse) while delivering an "optimal" high dose to the posterior fossa and tumor residual. Based on the patterns of supratentorial failure in patients treated or not treated to the whole brain (i.e. 60-80% frontal, temporal and intraventricular failures) we defined a reduced target in the supratentorium including the entire ventricular system, the main cisterns, and the subfrontal and subtemporal regions. A comparative dosimetric study is presented in which a three field (two laterals and one posterior) proton plan (spot scanning method) is compared to an :optimal" photon plan including 4 coplanar and 2 non-coplanar fields. The dose distribution was evaluated with dose-volume histograms to examine the coverage of the targets as well as the dose to the non-target brain, brain stem, and optical structures. The prescribed dose to the supratentorial target, posterior fossa, and tumor residual were 30, 54 and 60 Gy, respectively. With both photons and protons all targets received at least 100% of the prescribed dose without exceeding the tolerance dose for the brain stem (54 Gy). Protons and photons delivered respectively 15% and 33% of the prescribed dose to the tumor to 50% of the non-target brain volume. In addition, dose to the optic structures were significantly reduced with protons. In conclusion, modulated proton beams may help to reduce significantly the irradiation of normal brain while treating optimally the supratentorial and posterior fossa regions at higher risk for relapse. A decrease in morbidity can be expected.

Spinal theca irradiation: Despite a constant improvement in the outcome of patients treated for medulloblastoma/PNET with the use of optimised surgical techniques and chemotherapy, extended radiotherapy (RT) to the neuraxis remains a key factor for cure. Nevertheless, RT (photons or electrons) to the spine is associated with a severe morbidity: bone marrow failure, acute upper digestive symptoms, vertebral growth, thyroid hypofunction and cancer induction, cardiac dysfunction, restrictive lung disease and gonadal damage. This toxicity is related to the exit dose of the beams and is particularly severe in young children. The stopping power of protons can potentially reduce the morbidity related to the beam exit while delivering a high, uniform and target-contoured dose to the spinal theca. The results of a comparative dosimetric study are presented in such a way that dose distributions achievable with a posterior modulated proton beam (spot scanning method) are compared to those of a "classic" posterior 6 MV x-ray field. The potential improvements with protons are evaluated relying on dose-volume histograms to examine the coverage of the target as well as the dose to the vertebral bodies (growth plates), heart, etc. The target (i.e. spinal cord) receives the full prescribed dose in both treatment plans. However, 100% but only <20% of the vertebral body volume receives 50% of the prescribed dose with 6 MV x-rays are protons, respectively. More than 80% of the dose prescribed to the target (6 MV x-rays) was delivered to 44% of the heart volume, while the proton beam was able to completely avoid the heart

as well as the thyroid and liver. The present study demonstrates a potential role of proton therapy in decreasing the dose (and toxicity) to the critical structures in the irradiation of the spinal neuraxis in medulloblastoma/PNET. The potential bone marrow growth arrest sparing effects make this approach specially attractive for intensive chemotherapy protocols and for very young children.

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Stereotactic proton irradiation of arteriovenous malformations and meningiomas: the N.A.C. Experience

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Since the start of the proton therapy program in September 1993, 22 patients with arteriovenous malformations and 13 patients with meningiomas have been treated at N.A.C. All patients with AVMs were considered inoperable and the main aim of treatment was to prevent further bleeding. Volumes ranged from 0.4 cm to 64.8 cm (mean 14.6, median 19.6). Dose ranged from 14 Gy in 3 fractions to 34 Gy in 2 fractions. The majority of patients were treated with 3 fractions: this was based on the initial use of the shoot-through technique, but was maintained once Bragg peak planning became available because of the large volume of the lesions treated and the postulated saving of normal brain tissue without loss of effect on the AVM itself. Nine patients are available for follow-up of more than 1 year, and of those 5 are clinically stable, 6 did not bleed again. Two patients were lost to follow-up. One patient has complete obliteration of the lesion on imaging. Almost all of the 13 patients with meningioma were considered inoperable. Volumes ranged from 4.1 cm to 63 cm (mean 16.7, median 11.1) and again most of the treatments were given in 3 fractions for the same reason, namely protection of surrounding normal brain. Doses ranged from 14 Gy in 4 fractions to 33.7 Gy in 3 fractions. The patients have a follow-up of more than 3/12 and of those 1 had a complete response and 3 had a partial response on imaging. A further 2 patients had clinical improvement. One patient was lost to follow-up and 1 had progression (this was a malignant meningioma). So far, 66% of patients with a meningioma showed improvement with proton irradiation.

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Phase I/II clinical trial of heavy charged particles on the HIMAC

J Mizoe, NIRS, Chiba

From June 1994 to August 1995, 55 patients were treated by carbon ions of the HIMAC at NIRS. There are 8 phase I/II study protocols of carbon ions, which are for the H&N, the CNS, the NSCLC, the T3/4 tongue, the liver, the prostate, the uterine cervix and the miscellaneous sites. Currently, phase I/II study protocols for the eye tumor, the esophagus and the bone and soft tissue tumors are being designed.

The initial pilot study for advanced H&N cancer was started from June 1994 and till the beginning of August 1995, a total of 12 patients were treated. Each patients were scheduled to receive carbon ions radiotherapy in 18 fractions over 6 weeks at three fractions per week. Fraction dose was escalated from 2.7 GyE for initial three patients to 3.3 GyE for recent 5 patients by 10% dose step. RBE value of carbon ions for acute reaction of the skin and connective tissues were estimated to be 3.0 at the distal part of the SOBP from preclinical studies.

From October 1994 to February 1995, 3 patients with astrocytoma grade 2 were treated by carbon ions in 24 fractions over 6 weeks at 4 fractions per week. Fraction dose was 2.1 GyE and total of 50.4 GyE was given to the target volume.

A total of 7 patients with malignant gliomas were treated by carbon ions. They consisted of 3 cases of anaplastic astrocytomas and 4 cases of glioblastoma multiforme. At first, patients were treated by conventional X ray of 50 Gy in 25 fractions over 5 weeks for the T2 high area by MRI scans. During the X ray therapy, 2 courses of ACNU chemotherapy were administered. X ray radiotherapy was followed by Carbon ions radiotherapy for the enhanced tumor volume by CT or MRI. Patients were scheduled to receive carbon ions radiotherapy in 8 fractions over 2 weeks at 4 fractions per week. Fraction dose was 2.1 GyE for 7 patients.

A total of 13 patients with NSCLC were treated by carbon ions. They consisted of 10 cases of adenocarcinoma and 3 cases of squamous cell carcinoma. Two cases of stage III patients were scheduled to receive radical operation after carbon ions treatment for the local tumor. Each patients were scheduled to receive carbon ions radiotherapy in 18 fractions over 6 weeks at 3 fractions per week. Fraction dose was escalated from 3.3 GyE for initial 4 patients to 4.0 GyE for recent 3 patients.

The protocols for the liver, the prostate and the uterine cervix were started from April 1995 and 5 cases of the hepatoma, 2 cases of the prostate and 3 cases of the uterine cervix were treated. The purpose of the protocol for miscellaneous sites is to search the candidate diseases for carbon ions therapy. Till the August of 1995, 8 patients were treated by this protocol. Patients were treated in 16 fractions over 4 weeks at 4 fractions in a week. Fraction dose was started from 2.7 GyE. At present time, we have impression that the preliminary results of phase I/II clinical trials showed expected reactions of tumors and normal tissues.

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Clinical protocols and preliminary results of proton therapy for hepatocellular carcinoma, non-small cell lung cancer and esophageal cancer at Proton Medical Research Center, University of Tsukuba

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During a period from 1983 to 1994 approximately 450 patients were treated with proton beams at Proton Medical Research Center, University of Tsukuba. Of the patients 112 with hepatocellular carcinoma (HCC), 18 with non-small cell lung cancer, and 32 with esophageal cancer were treated with curative intents.

Of the 112 patients with HCC, 66 had T3-4 tumors according to the 1987 UICC staging system. Overall survival was 41% at five years after the treatment. For the 48 patients with slightly impaired hepatic functions five-year survival rate was 55%. For those with moderately and severely impaired hepatic functions, three-year survival rate was 41% and 17%, respectively.

Of the 18 patients with non-small cell lung cancer, who were mostly elder persons with various medical disorders, 10 had stage I, four stage II, and four stage III. Five-year survival rate for patients with stage I was 37.5%.

Of the 32 patients with esophageal carcinoma four patients had stage I disease, 14 stage II, and 14 stage III. Five-year survival rates for patients with stage I, for those with stage II, and for those with stage III were 75%, 37% and 43%, respectively.

With encouraging results obtained for patients with these tumors, we will be concentrating on the three tumors in the next few years.

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Example for a dose-escalating protocol: local recurrence of rectal carcinoma.

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This presentation has been prepared to introduce an example of a tumor site for which a radiotherapy could be administered in an optimal way to high dose levels to achieve local cure in as many patients as possible. Local recurrences of rectal carcinoma have been selected and the following data have been presented during the clinical session:

1 - analysis of data from the literature;
2 - retrospective analysis of the results obtained in our Institution in the treatment of this clinical conditions;
3 - a 3-D treatment planning to delineate the problems and difficulties encountered to achieve the purpose of high dose delivery in these patients.

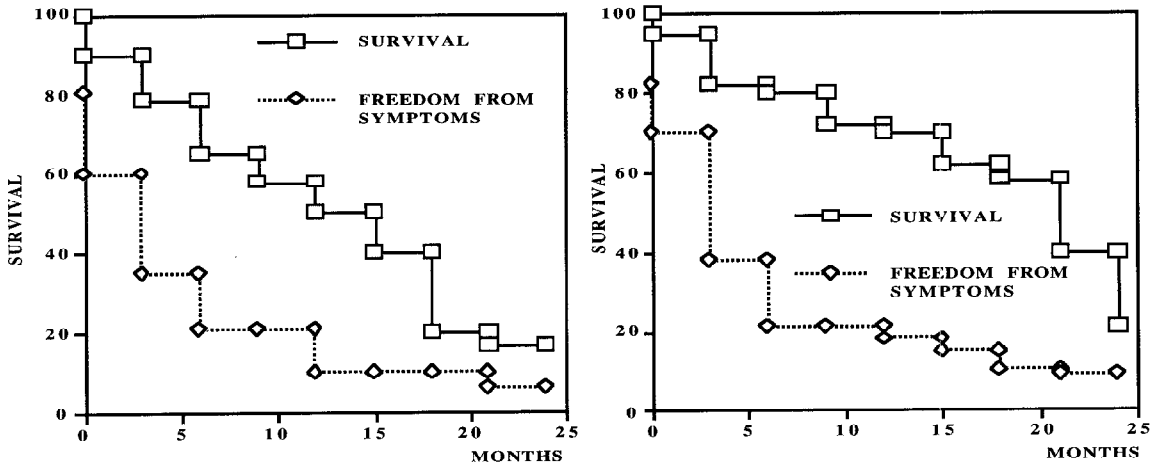
Local recurrence rates after surgery alone in patients with rectal carcinoma have been reported to be between 5 and 69%. A local recurrence is often associated with significant morbidity and palliation with radiation therapy is possible. Survival after local recurrence is short and longterm survival rare.
Although either pre- or post-operative radiation therapy have reduced the incidence of local recurrences in a number of controlled clinical trials, this reduction is prominent when high dose irradiation is used. It

has, however, been suggested that instead of giving all the patients additional irradiation in conjunction with primary surgery, radiation should be reserved until a recurrence appears. In these patients the treatment should be administered in an optimal way to high dose levels and combined with chemotherapy in order to achieve a higher local control of the disease.

Recently Frykholm and coll. (Radiotherapy and Oncology 34 (1995) 185 - 194) have published their results in the treatment of local recurrences of rectal carcinoma. The treatment results of these 159 patients show a cancer-specific 5-year survival of only 6% in a group of previously non-irradiated patients and no 5-year survivor in the other two groups receiving either pre- or post-operative irradiation as a part of their initial treatment. Moreover only 32% of curatively treated patients are locally symptoms free at death or last follow-up examination. About 30% of the death are due to local tumor growth. The retrospective analysis of a group of 143 patients treated in our Department for local recurrence of rectal carcinoma has reached similar conclusions. The results are reported in Figure I and II.

Figure I - Survival and freedom from symptoms in 143 patients treated with doses between 36 and 65 Gy.

Figure II - Survival and freedom from symptoms in 46 patients treated with doses > 50 Gy.



Based upon the present results and data from the literature it is clear that the curative potential of conventional radiation therapy is very limited and these poor results reflect what may be achieved in the clinical practice. In spite of the use of 3-D treatment planning and multiple field technique we have seen that the dose to the target volume may not be increased over the tolerance dose of the rectum. For all these reasons we believe that further improvements cannot be achieved with conventional radiation therapy. Higher local doses can probably be delivered with intraoperative radiation therapy or proton or neutron irradiation resulting in better local cure and, maybe, increased survival although this has not yet been demonstrated in randomized studies.

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Clinical indications for proton therapy: Conclusions.

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During the introduction to the Clinical session Table I has been presented to make an example of how a proposal for a new clinical protocol could be summarized in a simple and understandable way. No numbers or data had been included in Table I so as not to force a decision toward a particular tumor site to be chosen for a future clinical protocol to be developed.

During the final discussion it was clear that some of the participating people were supportive of the initiative. Nonetheless it was pointed out how difficult it could be to take a decision as concerns the selection of a particular tumor site to develop a new clinical protocol to be presented during PTCOG XXIV in Detroit.

The problem that the existing known and active protocols may be not well known to everybody, or might be discussed during a clinical session has been raised by some people. The assembly proposed and accepted, as a basis for the organization of a new session in Detroit, to submit to all the interested people a copy of the "Advanced "paranasal sinus carcinoma" protocol. During PTCOG XXIV the protocol will be illustrated, discussed and, maybe, criticized. Possible modifications to the protocol might be proposed and, even, introduced to existing one so as to make it acceptable to everybody.

As a second topic to be discussed during PTCOG XXIV it has been proposed to present the different treatment options for AVMs.

Table 1: PTCOG XXIII - PRELIMINARY ENQUIRY

TUMOR SITE AND STAGE	IS THE LOCAL CONTROL IMPORTANT?	WHICH IS THE BEST RESULTS? (*)	WHICH IS THE TOTAL DOSE?	IS THE FOLLOWING PROPOSAL FEASIBLE?

(*) Local Control

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Fast Proton Radiography on the PSI Gantry FROG

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In proton radiography the patient is scanned by a proton beam passing through the entire body. Each proton's rest energy as well as its x and y coordinate in front and behind the patient are determined.

Practical considerations require a picture to be accumulated in about 5 seconds. This requires the detector system with readout electronics to be capable of coping with a 2 MHz proton rate.

Scintillating fiber arrays are used as position-sensitive detectors (spatial resolution ~ 1 mm) and the residual range (energy) is measured in a stack of plastic scintillators. The fiber scintillations are detected by multichannel photomultipliers.

A sustained data throughput of approximately 30 MByte per second can be achieved by reducing the number of detector signals using hardwired logic before transmitting the data to the computer.

This work is supported by the Beschleunigerlabor LMU+TUM, Muenchen, and by the Bavarian Ministery for Environment.

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Attenuation of therapeutic heavy-ion beam due to projectile fragmentation

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To superimpose the steep Bragg Peak over the whole tumor volume, the peak is spread out by the ridge filter and the maximum range is shifted roughly by the range shifter and finely by the three-dimensional bolus at HIMAC.

However projectile fragmentation along the beam path in those devices causes an attenuation of the primary particles and may disturb the depth-dose distribution which is essential in the treatment planning.

We have therefore measured the attenuation of 290 MeV/u carbon beam and 400 MeV/u neon beam impinging on a target such as water, polyethylene, polymethyl methacrylate (PMMA), graphite, aluminum or copper. We placed the target between two plate-type plastic scintillators along the beam axis. Changing the thickness of the target, we measured the number of primaries that survived after passing through the target.

The obtained result shows that the attenuation of carbon beam in PMMA and polyethylene agrees well with that in water. This means that one can regard PMMA and polyethylene as water equivalent material also in terms of nuclear attenuation of the carbon beam. We therefore find that it is appropriate to select PMMA and polyethylene as stuff of the range shifter and the bolus respectively in the carbon beam therapy.

We have also determined the total charge-changing cross sections of the carbon and neon beams for the six different target materials from the slope of the measured attenuation. These cross sections were in good agreement with both other experiments and the semi-empirical calculation within the experimental errors.

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Patient supervisory and dosimetry systems for a clinical proton therapy facility

T.J. Fulcher, National Accelerator Centre, Faure, South Africa

The dosimetry system is responsible for measuring the dose to the patient and terminating the treatment once the prescribed dose has been delivered. The dosimetry system also performs various safety checks during an irradiation. The DOS operating system was chosen for the dosimetry system because it is interrupt intensive and the speed of operation is critical. Hardware was developed for the counting of pulses received from recycling integrators. The patient file system checks whether certain patient-specific components are in position (e.g. modulating propeller, degraders, collimator) before an irradiation commences. It is also responsible for configuring the dosimetry system for an irradiation. A multi-tasking operating system was required for the patient file system to enable it to communicate with a barcode scanner (used for checking the patient specific components) and the dosimetry system simultaneously. The National Accelerator Centre's standard of I.B.M.OS/2 was used as the operating system for the patient file system. Both systems were written in the C^{++} programming language.

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Boron Neutron Capture Therapy - Physics

J.F. Crawford, B. Larsson and S. Teichmann, Institute for Medical Radiobiology (IMR, University of Zurich and the Paul Scherrer Institute August Forel-Strasse7, CH-8029 Zurich, Switzerland

About 20% of natural boron is ^{10}B, which has a cross-section of 3840 barns for thermal neutron capture: $^{10}B(n, \alpha)\ ^{7}Li$. The reaction releases 2.8 MeV, usually including a 0.5 MeV γ. The ranges of the of the α and ^{7}Li are 9 μm and 5 μm, about the size of a biological cell.

It was suggested as long ago as 1936 that if a tumour could be loaded with ^{10}B and irradiated with thermal neutrons, energy would be released in the tumour cells. Three problems of conventional radio-therapy would be solved: attacking the tumour precisely, even on the microscopic scale; confining the dose to tumour cells; and treating metastases.

Most neutron production methods generate high-energy neutrons, which, not being captured by the ^{10}B, irradiate indiscriminately; but thermal neutrons cause skin damage, and penetrate only a few cm in tissue. The best compromise energy is 0.1 - 10 keV. Such neutrons penetrate with little damage, and are thermalised in tissue. A fluence of 10^{13} neutrons per square cm over a few hours is needed, together with a ^{10}B concentration of at least 20 parts per million by weight.

During the 1 950's the first patients, with advanced brain tumours,were treated in New England using thermal neutrons, with disappointing results, although the tumour regressed in at least one case. In 1968, the concept was re-introduced in Tokyo, using thermal neutrons from a reactor during surgery. Results are encouraging: a significant number of patients with advanced brain tumours have survived for about a decade.

In the present climate of public opinion, nuclear reactors in hospitals/clinics are intolerable. Several other neutron-production methods are possible: spallation, for which the Paul Scherrer Institute is well placed; ^{252}Cf, which is commercially available; and nuclear reactions, e.g. $^{7}Li\ (p,n)\ ^{7}Be$. A variation on the last method is BNCT brachytherapy, in which neutrons would be produced inside the body by a proton beam on ^{7}Li in a beam tube of diameter about 5 mm.

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Boron Neutron Capture Therapy - Chemistry

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From 1950 until the early 1960s several clinical trials using ^{10}B-enriched borate were performed. The lack of specificity of this compound to the tumour showed the need to develop more convenient boron compounds. During the same period, the polyhedral borane anions $B_{10}H_{10}^{2-}$ and $B_{12}H_{12}^{2-}$ were discovered, and carboranes like closo-1,2- and closo-1,7-$C_2B_{10}H_{12}$ were synthesised. The sodium salts of $B_{12}H_{11}SH^{2-}$ and 1,10-$B_{10}Cl_8(SH)_2^{2-}$ were evaluated for BNCT. The first of them, di-sodium undecahydro-mercapto-closo-dodecaborate (BSH), showed high persistence in tumour and low systemic toxicity, and since 1968 it is used successfully in clinical treatment of glioblastoma multiforme patients. Further, DL-4-dihydroxyborylphenylalanine (BPA) is used in clinical trials for the treatment of melanomas, but the uptake of the L-stereoisomer is favoured.

In order to improve uptake and specificity of boron in tumour cells, some new approaches in synthesising boron-containing compounds have been followed. 4-closo and 4-nido derivatives of DL-4-carboranyl-phenylalanine are under biological evaluation. Asymmetric syntheses of the D and L enantiomers of carboranylalanine were the task of several research groups. Another strategy is to couple the boron-containing compound to a tumour-affinic protein (Antibody, Receptor ligand, Liposomes etc.) and to use the conjugate in BNCT. Further, boron can be localized in the DNA of target cells, when coupled to a pyrimidine derivative or to a DNA dye, respectively. Many other compounds have been synthesised, each using a different approach in binding the tumour cells.

From the chemistry point of view, BNCT is not yet optimised, and progress and success of this therapy mode depend strongly on the progress in different fields in biology, physics, chemistry and medicine. Today we should try to answer the following question: How a sufficient number of ^{10}B atoms can be delivered selectively to cancer cells?

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An interesting case presentation with combined proton and photon radiotherapy

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This patient was a challenge to plan as the diagnostic investigations revealed not only metastatic disease posterior and lateral, but also anterior to the cord in the vertebral body of C1 and C2. The patient was a known case of uterine sarcoma with recurrence of bony and soft tissue metastases in C1 / C2 which had previously already been treated to tolerance. Our planning technique combined a proton beam Bragg peak with two lateral photon beams to obtain the desired result and at the same time avoiding the cord. This planning technique will be presented.

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The C235 IBA-SHI proton therapy cyclotron for the NPTC project - (I) magnetic field mapping and shimming

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At the beginning of 1994, the Massachusetts General Hospital (MGH) of the Harvard Medical School in Boston, MA, USA, selected a team led by IBA to supply the proton therapy equipment of its new Northeast Proton Therapy Centre (NPTC). The IBA integrated system includes a compact 235 MeV isochronous cyclotron, a short energy selection system transforming the fixed energy beam extracted from the cyclotron into a variable energy beam, one or more isocentric gantries fitted with a nozzle, one or more horizontal beam lines, a global control system including an accelerator control unit and several independent but networked therapy control stations, a global safety management system and a robotic patient positioning system.

The present paper presents the system designed for the field mapping in the C235 isochronous cyclotron, the magnetic field measurements and the shimming process used to reach the proper isochronous field.

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The C235 IBA-SHI proton therapy cyclotron for the NPTC project - (II) magnetic system design and construction

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The present paper presents the system designed for the field mapping in the C235 isochronous cyclotron, the magnetic field measurements and the shimming process used to reach the proper isochronous field.

The present paper presents the design and construction of the magnetic system of the C235 isochronous cyclotron, i.e. the overall magnet design, the foundry and machining of the magnet steel and finally the coil and coil power supply manufacturing.

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From multiple fractions to single dose: exploring the unknown

R. Schulte, Department of Radiation Medicine, Loma Linda University Medical Center

Over the last two decades proton radiation therapy has mainly evolved as a multi-fractionated treatment form using conventional fractions sizes, i.e. 1.8-2.0 CGE (Cobalt Gray Equivalent). However, there are many targets where treatment over many weeks may not be required. Giving the total dose in a few fractions or even as a single dose may be adequate if the treatment is given to a well defined target with stereotactic geometric accuracy. There is, however, considerable uncertainty with the respect to the choice of the total dose when unconventional hypofractionated schedules are used. In any case, the late-responding tissue which is included in the treated volume or the proximity of critical structures are the dose-limiting factors. Tolerance doses of dose-limiting CNS structures such as optic chiasm, hypthalmus and brainstem for conventional fraction sizes and single-dose schedules are known from multi-fraction and radiosurgery experience, respectively. For example, the near tolerance dose of the optic chiasm is in the order of 50 Gy when 2 Gy fractions are used, and in the order of 10 Gy when a single dose is given. From this information one may extrapolate tolerance doses to the range of fraction sizes between those two extremes using the reciprocal dose vs. fraction size plot first described by Douglas and Fowler [1]. If the linear-quadratic (LQ) dose-response model is correct this plot should yield a straight line. Assuming an additional time factor, the reciprocal dose plot becomes non-linear. Using the two tolerance limits for the optic chiasm stated above and assuming that the LQ model is correct, a straight line passing through the two data points would yield an alpha-beta ratio of 0.05 Gy. This alpha/beta value seems to be unusually low, as values between 1.5 and 5 Gy have been reported for late-responding normal tissues including CNS [2,3]. Alternatively, an alpha/beta ratio of 2 Gy in conjunction with a time factor of 0.024 Gy/day results in a reciprocal dose line that also passes through the two data points. In this case, the reciprocal isoeffective dose plot becomes nonlinear, and tolerance doses are up to 20% lower than those predicted from a straight line plot. In conclusion, the simple LQ model, i.e. without time factor, may not be adequate to extrapolate isoeffective tolerance doses for fractionation schedules between multiple fractions and single doses and may lead to underestimation of the tolerance dose. A small time factor may have to be included, which, however, needs experimental verification.

References: (1) Douglas, B.C., and Fowler, J.F. The effect of multiple small doses of X-rays on skin reactions in the mouse and a basic interpretation. Radiat. Research 66, 401-26, 1976. (2) Thames, H.D., Hendry, J.H., Moore, J.V., Ang, K.K., and Travis, E.L. The high steepness of dose-response curves for late-responding normal tissues. Radiother. Oncology 15, 49-53, 1989. (3) Thames, H.D., Bentzen, S.M., Turesson, I., Overgaard, M., and Van den Bogart, W. Time-factors in radiotherapy: a review of human data. Radiother. Oncol. 19, 219-235, 1990.

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ICRU Contribution to Uniformity in Dosimetry Protocols

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The ICRU has recently completed the preparation of a Report on **"Clinical Proton Dosimetry. Part I: Beam Production, Beam Delivery and Measurement of Absorbed Dose."**

The composition of the Reporting Committee was as follows: L. Verhey (Chairman), H. Blattmann, P. DeLuca, D. W. Miller (Members), P. Andreo, H. Bichsel, D. T. L. Jones and S. Vynckier (Consultants). H. H. Rossi and A. Wambersie served as Sponsors of the Main Commission.

This Report contains recommendations for the determination of the absorbed dose in a homogeneous water phantom under reference conditions.

The ICRU initiative, which started in 1991, was justified by the fact that, at that time, several dosimetry protocols were applied in the different proton therapy centers worldwide. As a result, in extreme conditions, differences up to 10% could be observed between the doses measured under reference conditions. These differences were due, to a great part, but not only, to different numerical values adopted for quantities such as W/e, stopping powers, etc.

Recent dosimetric intercomparisons performed at the Loma Linda University Medical Center (Spring 1995, involving 13 centers) and in NAC-Capetown (Autumn 1995, involving 5 centers) have shown that an agreement of about ±1% on the dose delivered under reference conditions could be achieved if a common dosimetry protocol such as the ICRU protocol would be applied worldwide. As far as the numerical values of the quantities are concerned, the ICRU protocol recommends:

(1) $W/e = 34.8\ J*C^{-1}$ (±2%)

and

(2) the mass electronic stopping powers for protons contained in ICRU Report 49 (1993).

The ICRU is now preparing a second Report going from reference conditions to clinical conditions, which addresses problems such as treatment planning, dose specification for reporting, radiation quality (and RBE).

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Irradiation system for heavy ion beams coincident with a patient's respiratory motion

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In radiation therapy, it is very important to minimise undesirable dose deposition in normal tissues. However, the target such as a lung or liver cancer is moving by autonomous respiration. Therefore to concentrate the dose on a target only, the irradiating method coincident with a patient's respiratory motion is very effective. Now we are developing the irradiation system of heavy ions synchronised with a patient's respiratory motion at the HIMAC. In our system, a sensitive strain gauge is set on the chest wall to detect the movement of the diaphragm. From the output of the respiratory sensor, the timing signal (TTL level) to request the irradiation is generated corresponding with the expiratory phase because the motion of diaphragm is usually small during expiratory phase. When the timing of respiration corresponds to the extractive timing of beam from synchrotron ring, the beam is extracted by the RF knockout method. Experimental results with beam (400 MeV/u carbon) extraction coincident with a modelled respiratory motion have been demonstrated. The cycle of the synchrotron was 0.3 Hz. Irradiated beam was successfully coincided with respiratory phase. Further the X-ray CT scanner was improved to scan synchronised with a respiratory motion in order to make accurate treatment planning-based CT images. We will report the detail of our irradiation system synchronised with a patient's respiratory motion and the experimental estimation of the dose distributions.

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Real time non invasive diode detector for beam control during patient irradiation

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We have developed a detector based upon silicon diodes put around the hole of one of the collimators :

- the first ring (eight diodes) is used to measure the average intensity of the beam and its centering.
- the second ring of diodes (24 diodes) is placed behind the first ring and a spiral made of lucite (in order to place each diode behind one step of lucite, each step with a different thickness) to measure the Spread Out Bragg Peak.

The detectors are standard PN diodes, with a pseudo-integrator and an amplifier to transform the pulsed signal into a continuous one. The 32 signals are read by a PC and a home-made software handles the data and displays the three informations (intensity, centering, SOBP) twice per second during the treatment. The setup is done during the quality control every morning: offset subtraction, gain calculation from reference conditions (SOBP measured with an ion chamber). This system, used since January 1994, is for the moment just a visual control. As the reproducibility of the range measured for each patient during one week of treatment is ± 0.5 mm, we plan to add this measure to our safety system. First designed for the ophthalmic treatments (73 MeV), a similar detector, with an aluminium ring, is now tested for brain treaments (200 MeV).

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Harvard Cyclotron Lab Operations

A.M. Koehler, Harvard Cyclotron Laboratory, Cambridge, Mass.

HCL operations have been primarily on a fee-for-service basis since 1968, with 90% being related to treatment of patients for two Boston hospitals which pay for the service and bill the patients. All expenses of routine operation must be met from these fees, including operation and maintenance of the cyclotron and buildings. A small amount is assigned to current development and improvement of services and towards the future cost of decommissioning the laboratory. In the fiscal year 1994-95, income to HCL from the large-field fractionated treatments was about 770 K$ ($245 per fraction). Eye treatments yielded 146 K$ ($235 per fraction, usually 5 fractions per patient). Neurosurgical treatments, usually given in one fraction, yielded 61 K$ ($1260 per patient). Fees from other services yielded 242 K$. More detailed data about the operation are available.

Laboratory staff now totals about 19 full time equivalents of whom 13 are assigned to operations. Clinical and patient-care services are provided by hospital staff who work at HCL regularly or on rotation. They are not included in this accounting.

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In-House Maintenance and Improvements of a Clinical Neutron Therapy Facility

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The Seattle clinical cyclotron facility has over the past 11 years been used to treat over 1500 patients with fast neutrons. The system was built and installed by a commercial company (Scanditronix). All maintenance, repair and upgrade work has been carried out by local technical personnel dedicated to the cyclotron operation, with spare parts support from the manufacturer and technical support by hospital building maintenance personnel and on-campus machine shops.

Unlike a medical linear accelerator, where the manufacturers stock spare parts and develop improvements and new features, unique systems such as a neutron or proton therapy machine cannot rely on this kind of support as long as there is only a limited market. In addition, these special machines have longer lifetimes and are not replaced every 12 to 15 years like a linac. This puts the burden to keep the facility up-to-date on the local accelerator staff.

Improvements at the Seattle facility have included the following general areas:

- Performance improvements
- Improvements to system parts, which caused major downtime
- Improvements for streamlined system operation or maintenance
- Replacement of parts which are becoming obsolete

The maximum scheduled downtime has been five days (extended weekends, Friday to Monday or Tuesday). Apart from one 12-day period the system has never been unavailable for therapy for more than three therapy days in a row.

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Operational aspects of the Harper Hospital neutron therapy facility

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The Harper Hospital neutron therapy facility utilizes a 48.5 MeV deuteron superconducting cyclotron with an internal beryllium target to produce a high intensity neutron flux (delivering 48 cGy min^{-1} at the isocenter). The accelerator system was built by Dr. Henry Blosser and his associates at the National Superconducting Cyclotron Laboratory as a joint project between Michigan State University and Harper Hospital. The estimated cost of the system was ~M$3.5. Routine patient treatment started in March 1992 and since that time (to Sept. 1995) 369 patients have received treatment with 10,507 fields.

Total additional staffing required for installation and initial operation of the cyclotron was 4 FET (1 cryogenics tech., 1 electronics tech., 1 cyclotron engineer and 1 physicist). At maturity staffing is ~9 FET (1 physician, 2 RTT, 1 cyclotron eng., 1 cryogenics tech., 0.75 electronics tech., 0.5 machinist, 0.25 nurse, 1 dosimetrist and 1.5 physicists) and annual running costs including all staff except the physician are ~M$1.1 per year. The present best estimate of the maximum achievable patient throughput is ~9500 fields/year, equivalent to 320 patients/year. On average patients are treated with 30 fields in about 10 treatment sessions; most patients receive mixed beam (neutron and photon) therapy. At 60% capacity (the present operating level) the cost per patient treatment session necessary to cover cost would be ~$690. At full capacity (assuming 95% up time) this cost would fall to ~430 per treatment session.

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Operational aspects of particle therapy facilities

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Late 1970's, just after completion of the 12 GeV proton synchrotron complex(PS) at the National Laboratory for High Energy Physics(KEK), a medical facility was proposed. PS has all beam handling features, i.e., injection into a small ring, booster synchrotron, beam transfer from the small one to the large one, 12 GeV main ring, and slow extraction. The accelerators are running periodically. The main ring cycle is variable and now 4.5 sec. The booster is a rapid cycling synchrotron and delivers 500 MeV beam pulses every 50 milli-sec. 9 pulses are injected into the main ring, then other about 80 pulses are delivered to 500 MeV proton users including therapy. Beam on-off and intensities are independently controlled for main ring injection and 500 MeV proton utilization. The booster beam pulse length is several times ten nano-sec. The pulsed beams are switched to one of three users, proton therapy, spallation neutron source and meson physics. The protons are decelerated to 250 MeV by a carbon degrader, then passed to a horizontal or a vertical beam treatment room. Even if the proton therapy has the first priority, the beam pulses are switched to other users during patient setting.

The beam delivery system must be static because of the beam time structure. The system consists of a scatterer and ridge filter. It is simple, dependable and less expensive, suitable for treatment of patients as many as possible. But it requires a large beam emittance to achieve uniform dose distribution at the target volume, in turn, yields big penumbra.

The serious problem of the facility now is machine time. PS has run more than 4000 hours in a year, not continuously, but divided into three long terms. Every term consists of 3-week mode operation, named run, in which 13 days are allocated to medical use, 2 Saturdays are for biology or physics. Other 11 days, Monday through Friday, are for therapy. We had 11 runs in 1994 fiscal year. Machine time is 4 hours a day, 3 hours are for patient irradiation and 1 hour is for dose measurement for treatment.

Number of staff members are 14, including 3 Medical Doctors, 5 physicists and 2 physicians. The KEK PS accelerator division has 25 physicists, 20 technicians and 9 operators from a company. CT images are taken in University Hospital collaborating with its staff. Expenditure in 1994 fiscal year is 1.3 M US$ except salary of the staff members. One tenth is cost of electricity. The 500 MeV protons from KEK are free.

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Operational aspects of the National Accelerator Centre's particle therapy facilities.

J.E. Symons, Division of Medical Radiation, National Accelerator Centre, Faure, South Africa

The National Accelerator Centre (NAC) is a multidisciplinary cyclotron-based nuclear research facility. Beam time is allocated for nuclear physics research; radio-isotope production; and particle therapy using protons or neutrons. The particle therapy program currently (first half of 1995) receives 19% of the scheduled beam time, which includes beam time for bio-medical research with both proton and neutron beams.

The neutron therapy program commenced in September 1988, and the proton therapy program in September 1993. To date (end of September 1995) 723 patients have been treated with neutrons, and 98 with protons. This was at an average of 8.9 fractions per treatment day with neutrons, and 2.8 fractions per treatment day with protons. Proton patients receive an average of 3.1 fractions of 3.1 fields each, while neutron patients typically receive 12 fractions with an average of 2.6 fields per fraction.

Only 3.8% of scheduled neutron fractions, and 3.1% of proton fractions have had to be rescheduled for non-medical reasons. Treatment times with neutrons have dropped over the 7 years of operation from 16 minutes to 12 minutes per field, while with protons it currently takes 25 minutes per field.

The radiation exposure to the therapy staff has, in general, also declined since operations began. The exception to this trend is the average dose to the physicists, which has increased slightly in recent years because of the close involvement of the physicists in proton therapy treatment, and the extensive dosimetry program during the commissioning of the proton therapy facility.

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Operational aspects and organization of a proton facility in the centre of Italy.

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The need for a proton therapy facility in the centre of Italy has been assessed according to the number and tumor sites usually referred to the Departments of Radiation Oncology in this geographic area. Tumors which might benefit from proton treatments have been classified into four categories:

- A - tumors characterized by closeness to highly critical organs;
- B - tumors characterized by prevalent local evolution and low radiosensitivity;
- C - tumors for which protons may be used as a boost on a reduced treatment volume;
- D - advanced or recurrent malignancies in which a longer survival and better quality of life may be obtained.

Out of about 57 millions of people living in Italy approximately 12.000 new patients/year might benefit from proton therapy. Out of these more than two thousand live in the centre of Italy.

Table I reports the minimal specifications of the equipment. The project is based on a turnkey facility including a cyclotron and two treatment rooms (one gantry and one fixed beam). This equipment is similar to the proton accelerator chosen for the Northeast Proton Therapy Centre (NPTC)

Staff members to run the facility will include only a few new employees. Two engineers or physicists will be necessary to keep care of the facility, but may be employed for different purposes too (computer programming or technical developments in patient positioning or related fields). A part of the medical staff, actually working at the University and Hospital Departments, may take care of the routine activities at the proton facility; patient selection and evaluation for proton treatments will be the responsibility of all the present staff members of the Department, according to their specific interests and following common clinical protocols. At least two shifts of two technicians will be necessary for each treatment room a day. Four nurses and two secretaries are required. Dosimetrists and planners represent new figures to recruit although some of them may be shifted from their present activities towards the proton ones.

Fees for the upkeep and technical upgrading of the Centre will be provided by the National Health System and no fee will be charged to the patient.

The cost of a proton treatment has been estimated, in comparison to conventional photon therapy, to be at least 2.5 times higher. Such an extimation has been done considering the high complexity of a proton treatment, the costs for the staff, the medications, the amortization of the equipment and the administration and janitory. In the present extimation telefone, heating and cooling, building amortization and maintenance and electrical consuption of equipments other than the accelerator have not been included. Electric and water consumption have been calculated.

A third treatment room could be added within 5 years from the starting of the clinical activities. Under these circumstances (three treatment rooms) the total number of new patients treated per year could approximatly be around 1000 (one Linac, in fact, usually may treat about 300 - 350 new patients a year).

The total cost for the facility and the building has been estimated to be around 30 millions (US $). According to our funding scheme, including upgrading and maintenance costs, amortization of the overall expenses should be possible within 10 years.

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Operational aspects of the future National Centre for Oncological Hadrontherapy

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A number of aspects related to the operation of the National Centre for Oncological Hadrontherapy (CNAO), the hub of the future RITA network, are discussed. These refer to beam use, power consumption, staff and its cost, financial issues and operation control and safety. The estimates are made on the basis of treating 1000 patients/year at full capacity, with an expected operational life of the Centre of at least 25 years. The beam use assumes that the facility will operate 6 days/week, 3000 hours/year (for both clinical and research activities), for a total of 30,000 fractions. The estimated power consumption for proton operation (equipment and building) is 1000 MW-h/year. When ion operation is implemented the above figure will be higher. The personnel foreseen at regime is 17 people for administration and management, 39 medical staff (physicians, radiation technicians, nurses, etc.) and 42 technical staff (accelerator and medical physicists, engineers, technicians). 14 out of this total number of 98 should be supplied by the associated centres and 84 would instead be on the payroll of the CNAO. The cost of personnel during the construction and running periods have also been evaluated. At full operation the cost of personnel will be about 5,000,000 US dollars. The expected average fee which will have to be charged to the patients to cover the running costs is in the range 10,000 - 15,000 US dollars.

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PTCOG XXIII Facility Operation Requirements Focus Session and results of operations questionnaire

J. Flanz, MGH, Northeast Proton Therapy Center, Boston MA 02114.

A new focus session was organized at the XXIII PTCOG in Cape Town. The topic was the operational requirements of particle therapy facilities. What was attempted was to share operational requirements among treatment facilities. It is hoped that through this, facilities can learn lessons which can both help the planning of new facilities and help existing facilities.

The session included speakers from long time operating facilities and newly planned facilities. It included facilities which use protons, neutrons and heavy ions. Representatives from Hospital based, non-Hospital based, dedicated and shared facilities contributed.

A questionnaire was sent out to compile a list of facility operating parameters and operational requirements. Out of 24 mailings, 16 replies were received. Replies were obtained from all types of facilities. It was not clear at the outset what correlations, if any, could be obtained from the data. While some facilities keep records quite differently from others, there was a good attempt to compare like categories.

There was a range of data reported from facilities with patient treatment totals of from 10's per year to plans for 1000 patients per year. It is interesting to note that there seemed to be correlations between facility staffing with patient treatment and hours of operation despite the different operational characters of the various treatment facilities. There was a large range reported of the percentage of time devoted to research and development. There was some discussion at the PTCOG as the necessity for this at treatment facilities. Finally it is interesting that there was reasonable consistency on average of the percentage breakdown of the types of staff needed by treatment facilities.

The data analysis results are being written up. If the questionnaire respondents approve, then the report will be available for distribution.

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Measurements of scattered radiation at a proton therapy facility

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Prior to the first scheduled treatments at a new 200 MeV proton therapy facility a study was commissioned to ascertain the nature of extraneous radiations produced by ancillary components in the beamline. Estimates of the dose and dose equivalent were obtained in the vicinity of the isocentre using a tissue equivalent proportional counter. The character of the scattered radiation was deduced from the measured single event distributions and varied with lateral displacement from central axis of the primary beam. The final collimator defining the treatment field size was identified as the principal source of fast neutrons to the patient produced in the beamline. Extending beyond the periphery of the final collimator a forward peaked cone of scattered high energy protons was evident. The assessed absorbed dose at the position of the patient due to scattering in the beam delivery system was between 1.0 and 2.7% of the treatment prescription.

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Experimental determination of influence of an ionization chamber wall material on the chamber sensitivity in high energy particle beams

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The influence of an ionisation chamber wall material on the response of the chamber has been investigated in medical beams of high energy protons (200 MeV and 660 MeV) and neutrons (mean energy 350 MeV). A parallel-plate air-filled ionisation chamber with thin wall (metal-coated polyimide film 2.1 mg/cm2 thick) was placed at different depths in a PMMA phantom irradiated by the medical beams. Replaceable radiators, 1.2 g/cm2 thick, were placed in front of the chamber. The resulting ionisation currents, related to monitor readings, have been compared for different radiators. The radiators have been prepared from PMMA, tissue-equivalent plastic, air-equivalent plastic, graphite, aluminium, lead, gold, water, some tissues and some insulating materials. Data obtained allow calculation of the wall correction coefficients required for the determination of absorbed dose in a phantom by means of ionisation chambers. It was shown, that for all the beams considered, the correction coefficients are close to unity and may be neglected for all ionisation chambers with organic material walls.

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Energy spectra in the NAC proton therapy beam

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In order to tailor a proton beam for radiation therapy several beam modification devices are used which affect both the dose distribution and the energy spectrum of the beam. Knowledge of the proton spectra is required for optimizing the beam delivery system and for comparison with theoretical calculations. Proton elastic scattering has been used to measure spectra in the NAC 200 MeV clinical beam. A polyethylene scatterer is located at the treatment isocentre. Two shielded scintillator detector DE/E telescopes are placed symmetrically about the beam axis such that the energy of both the scattered and recoil protons is half the incident beam energy. Multiparameter data acquisition is used to determine the coincident summed spectra under various irradiation conditions. The data demonstrate that there is a negligible low-energy component in the beam. The expected peak broadening is observed when beam modification elements are inserted in the beam.

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A superconducting ring-cyclotron proposal for dedicated proton therapy installations

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A new type of superconducting ring-cyclotron (SRC) with split sector magnets is proposed for dedicated proton therapy installations. The SRC is an isochronous fixed-frequency machine with a small internal ion source, and combines the advantages of conventional superconducting cyclotrons (reduced size, low operating costs) with the ease of access and extraction characteristics of separated-sector cyclotrons. The proposal features four symmetrically arranged 20-ton sector magnets with S-coils and two 106 MHz /2 rf-resonators enclosed in a common vacuum chamber for accelerating proton beams on the 4th harmonic of the orbital frequency up to a maximum energy of 220 MeV. The resonators are placed in opposite valleys between the sector magnets, and by utilising the remaining two valleys for variable-radius extraction the SRC could provide external proton beams of high intensity and quality from 100 MeV up to the maximum energy for direct use in scanning systems, thus eliminating the need and disadvantages of prior energy degradation. Energy changes would be accomplished in a matter of minutes, required for repositioning and tuning the extraction components, because very little retuning of the machine should be necessary. The characteristics of the proposed SRC are examined, and results of investigations into the design of its magnet configuration and rf-resonators are presented and discussed.

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Dosimetry of proton beams at the medical facility of the JINR phasotron in Dubna.

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Radiation therapy with a proton beam has a number of important advantages over conventional radiation therapy. The proton beam allows the maximum dose to be confined to the treatment volume while the dose to surrounding normal tissues is minimized. Realization of these advantages requires higher precision of the proton beam dosimetry.

For absorbed dose rate measurements of therapeutic proton beams we use clinical dosimeters KD-27012 with air-filled thimble ionization chambers VAK-253. Dosimeter calibration was made with the Co-60 source in accordance with the recommendations of the : "Code of practice for clinical proton dosimetry". The use of different parameters for the proton conversion factor calculation is discussed. The energy dependence of the calibrated factor for protons with energy up to 10 MeV is very slight and influence of the proton beam energy distribution is negligible.

The ion recombination correction factors in the thimble ionization chambers for pulsed proton beams and continuous radiation were measured. The ion recombination correction factor for pulsed proton beams from the JINR phasotron is approximately ten times higher than that for continuous radiation and must be taken into account.

It is found that the accuracy of JINR phasotron proton beam dosimetry is about 5%. This accuracy meets the international requirements for the therapeutic proton beams and was confirmed in the intercomparison dosimetry measurements at the National Accelerator Center in Cape Town.

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The NAC proton therapy beam delivery system

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The 200 MeV horizontal proton therapy beam line at NAC was commissioned in September 1993 and a total of 98 patients had been treated up to September 1995. The present proton beam delivery system is designed for a maximum field diameter of 100 mm and was optimized for crossfire plateau irradiations. The beam exits the vacuum system 7 m from the isocentre. A double scatterer plus occluding ring system is used to flatten the beam while a rotating variable-thickness absorber spreads out the Bragg peak. The position of the beam is controlled by two computerized feedback systems acting on two sets of XY steering magnets. Positional information is obtained from quadrant and multiwire ionization chambers. The dose to the patient is monitored by two parallel plate ionization chambers immediately upstream of the final patient collimator. A real time range monitor gives a continuous indication of the range of the incident protons and hence of the beam energy.

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Beam control for proton therapy

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Improvements to the NAC cyclotrons and beamlines were necessary before routine proton therapy could commence. Among these were a fast energy change procedure which could yield stable magnetic fields for 66 MeV and 200 MeV protons in less than an hour, systems to control the beam current and to stop the beam within a few milliseconds, as well as new beam alignment systems. One of the important characteristics of this treatment is the precision with which the dose can be controlled. This requires good angular and positional stability of the proton beam, which is greater than is inherent in the beam extracted from the cyclotron. Thus a two-stage closed-loop control system was developed for steering the beam just before it is delivered to the therapy vault. The first loop keeps the beam stable at the first reference point while the second loop keeps it stable at a second one, several metres down-stream, thus providing the required stability. The system also provides the operator controlling therapy with information about dose rate, penetration profile and position error. This information is also displayed in the cyclotron control room.

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Operation experience of KCCH cyclotron for 10 years and prospect of cyclotron in Korea

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The first cyclotron installed at the Korea Cancer Center Hospital has been utilized for basic medical researches and treatment of cancer patients in addition to production of radioisotopes for 10 years. We have produced Ga-67, Tl-201, I-123, In-111 which are delivered to the hospitals. In this paper the authors also describe past, present, and future for the cyclotron in Korea.

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Patient positioning accuracy for proton therapy using a stereophotogrammetric positioning and monitoring system

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To improve patient comfort and to expand the dose/fractionation options of proton therapy, a unique photogrammetric positioning method is being used at N.A.C. Patients are CT-scanned wearing a full head cast, consisting of two halves, onto which plastic markers are fixed, and the position co-ordinates of the markers are determined. These markers are also visible on MRI (when filled with olive oil), on angiography (when embedded with a ball bearing), and have a reflective surface making them visible to digital cameras. Once the treatment plan is approved, the co-ordinates of the isocentre, beam entry points and markers are stored in the control computer. The patient is seated in the computer-controlled chair, and the markers are co-ordinated using digital photogrammetry with three cameras. These values are then used to calculate the translations and rotations necessary to move the patient into the final treatment position. After the movements are completed the markers are co-ordinated again to check that the patient is in the correct position. When this is checked the beam can be switched on and the patient is closely monitored by the cameras for any movements until the treatment is complete. However, movement of the patient relative to the cast is still possible. Treatment verification films were retrospectively analysed to determine the extent of patient movements relative to the cast. A total of 33 separate mask set-ups have been evaluated. Measurements of the distances between anatomical landmarks and identified markers (metal ball bearings), lying coplanar with the x-ray film, were made and corrected for the variation in magnification factors. Analysis of the relative differences showed a standard deviation of 0.6 mm for the x-axis, with a 95% confidence interval of 0.46 mm - 0.87 mm; 0.66 mm for the y-axis (0.50 mm-0.95 mm) and 0.83 mm for the z-axis (0.66 mm - 1.09 mm). These measurements are within the 1 mm variation which seems to be the accepted standard for stereotactic irradiation.

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Skull contours versus implanted fiducial markers for stereotactic repositioning

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Implanted skull fiducials are currently the preferred method for verification of correct alignment of patients treated with high-dose radiation therapy for intracranial targets [1]. At LLUMC all patients undergoing stereotactic proton irradiation of arteriovenous malformations (AVMs) have at least three implanted fiducial screws, and patient alignment is radiographically verified before treatment using these fiducials. Although the accuracy of this method has been established there are disadvantages such as costs and patient discomfort. We have therefore developed and tested a skull registration technique that uses the external contour of the skull. We are hoping to show that skull contours can provide accurate results in conjunction with the vacuum-assisted bite block immobilization of the patient, which minimizes head rotations. External skull contours are outlined on each CT slice using the auto-threshold contouring option of the MGH/LLUMC treatment planning system. For standard AP and right- or left lateral X-ray projections, skull contours, typically consisting of 70-80 points, are derived. Two dimensional point coordinates with respect to horizontal and vertical reference axes intersecting at the isocenter are stored in contour files. Corresponding external skull contour point sets are extracted from AP and lateral X-ray films taken in the treatment room using a digitizer. All point files are entered into a

contour matching computer program, which uses an iterative algorithm to calculate the transformation required to match the skull contour sets. For 8 AVM patients the new alignment technique was assessed by comparing the results obtained with the new method to those obtained using the skull fiducial method. For movements with respect to the lateral and the vertical patient axis the mean difference ± S.D. between both methods was 0.3 ± 0.6 mm and
0.4 ± 0.9 mm, respectively, which was not significantly different from zero. For the longitudinal axis a statistically significant difference of 0.9 mm ± 0.9 mm ($p = 0.02$, two tailed paired t-test) was found. This systematic difference could be due to the fact that the contours derived from the treatment planning system were too large by about 1 mm. We are planning to optimize the contour algorithm by adjusting the threshold value for auto-contouring of the skull.
References: (1) Gall, K.P., Verhey, L.J., and Wagner, M. Computer-assisted positioning of radiotherapy patients using implanted radiopaque fiducials. Med. Phys. 20, 1153-1159, 1993.

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Suitability of acrylic mask for positioning in proton therapy

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A basic principle of patient positioning at NAC is that it is based on the patient mask, rather than the anatomy directly. Reflective markers, of which the three-dimensional co-ordinates are known, are attached to an anterior head mask. The mask, acting as the patient's 'second skin', is then positioned semi-automatically. Overall positioning would be considered successful if two conditions are satisfied:

(i) The markers are positioned relative to the beam within a given tolerance.
(ii) There is a negligible change in the relationship between the markers and the patient's internal anatomy.

The essence of a successful mask is that the anterior section is pulled as tightly as possible onto the head. Thus, the posterior half must not butt against any part of the anterior section. Also, it was found that movement of the anterior half of the patient's head in the anterior section was minimised by requiring the patient to shave his head, or at least have very short hair. Once the posterior part is attached firmly to the chair, small strains can occur between the posterior part and the patient. Because flexible Velcro strips are used to attach the two halves, minimal distortion is transferred from the posterior to the anterior section and the patient remains firmly held inside the anterior section.

The study to check how reproducibly the patient anatomy is located within the mask was done in three stages. Firstly, the mask was surveyed with a stereo-metrograph to obtain the 'true' positions of the markers. These were determined with a standard deviation of 0.1 mm, 0.2 mm, and 0.1 mm in x, y, and z respectively. Next, the mask was scanned to obtain the CT co-ordinates of the markers. The mean differences from the 'true' values were zero due to the geometrical transformation used, but the standard deviations of these differences were 1.0 mm, 0.6 mm, and 0.6 mm respectively. (The average absolute differences from the 'true' positions were 0.8 mm, 0.6 mm, and 0.5 mm respectively). This gives an idea of the scanner precision under ideal conditions. Thirdly, 6 patients were scanned in their masks to obtain co-ordinates of both markers and bony landmarks. This scan was repeated a week later. The standard deviations of the differences from one week to the next were 0.5 mm, 0.8 mm, and 0.5 mm respectively (the average absolute differences from the 'true' positions were 0.6 mm for x, y, and z). The

mean movements of the patients within the masks, for each direction x, y, and z, were 0.7 mm, with a standard deviation of about 0.5 mm. The movement of anatomical points was thus of the same order as the accuracy with which stationary markers can be determined, and shows that there is minimal movement of the patient from week to week in the cast whilst on the CT table.

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Quantitation of brain movement within the skull associated with head position: its relevance to proton therapy planning

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Since proton beams have the potential to irradiate volumes with a precision of the order of mm, an investigation was undertaken to study possible variation of brain position with respect to the skull, for different head positions. Five adult males (mean age 49, range 33-61 years) in good health, with no history of head trauma or any central nervous system or other condition which could affect the cerebrum or cranium, were imaged with transaxial cerebral magnetic resonance scans. The slices parallel to the orbitomeatal line, were obtained using a T1 sequence, with the patient supine. Immediately after this a repeat scan was obtained using identical slice positions, but with the subject prone. Slice positions were chosen from sagittal scout views. During all scans the subjects had external position markers in fixed positions on the skull exterior. These markers were in a plane determined by the orbitomeatal lines. The distances (d), between marker centres in the median plane and clearly delineated features in high contrast images, were measured in corresponding pairs of slices, obtained in the supine and prone positions for each subject. The cerebral landmarks in the median plane, whose displacements from the markers (both anterior and posterior to the cerebrum) were measured, included the isthmus of the pons, the upper fourth vertical, interpeduncular cistern and midpoints between inferior and superior colliculi. Another set of measurements made at an angle of 20 to the median plane produced consistent results. All measurements were made with a travelling microscope, moving in the same direction to reduce backlash and were repeated by 2 observers without knowledge of any previous results. The difference between d values in corresponding supine and prone images varied with subject and ranged between 1.5 and 4.0 (+/-0.6 mm). The differences remained consistent for a given slice and subject in repetitive determinations. However d varied with brain position. Taking into account the unavoidable inaccuracies in planning, this newly described influence could result in serious underdosages of the target volume.

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EYEPLAN: The Next Generation

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TESTING; an open question: The EYEPLAN planning program has had a major update, requiring equally major testing. Specific operations can be tested individually. Plans generated different routes (eg. using the old program version) can be in detail. Finally, of course, the program is tested in use. However, it seems impracticable to test the program FULLY ie. to follow all possible path combinations with all possible data. What testing is necessary and desirable? Any observations would be most welcome.

FUTURE POSSIBLE DEVELOPMENTS

a) Multiple Fields are already being pioneered at UCSF. However, their use for eye treatments seems more restricted than for conventional radio-therapy. The target volume can already be treated to 100% with a single field, and any reduction of collateral damage is limited by the very restricted choice of possible treatment angles compared to conventional therapy. We await the UCSF experience with great interest.

b) Using Imaging Data: The planning program has two main choices: to use (as now) an object-based model or an image-based one based on MRI or CT scans. If an image-based system is used: 1) the head + eye + lid can be modelled in one relative position only; selective manipulation is impossible: 2) the fixation position involved is known less precisely: 3) lower resolution than ultrasound reduces the accuracy of important measurements such as the eye length: 4) established detailed measurements of eye structure cannot be used: 5) imaging is supine, treatment is upright. Error?: 6) computer processing time increases substantially, giving less freedom to optimise treatment plans: 7) the more realistic and familiar (to a ÒconventionalÓ planner) display may actually obscure detail.

Wholesale conversion to an image-based model therefore seems a retrograde step; rather use scan-derived data as an adjunct to the existing model. The disadvantages of performing scans (extra patient dose, patient distress, planning effort and cost) suggest that they should be confined to specific cases eg. non-spherical eyes or large and irregularly-shaped or anterior tumours.

FUTURE DEVELOPMENT; another open question.

Should EYEPLAN users develop the program locally, or use a centrally-developed version eg. the Clatterbridge one? Arguments cut both ways: specific local needs / response time to requests for change / program integrity dependent on only one person / desire to use a different computer platform versus duplication of effort and the difficulty of taking advantage of other centres' improvements. "One for All and All for One" or :Free-for-all" ? The choice may not be clear, but should surely not go by default.

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The PROXELPLAN system used at NAC for proton treatment planning

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High energy proton therapy treatments at the NAC commenced in September 1993 and a total of 98 patients had been treated up to September 1995. Initially only crossfire plateau irradiations were possible due to limitations in existing treatment planning systems. During 1994 the NAC obtained a sophisticated three dimensional proton therapy planning system which is entirely based on the VOXELPLAN planning system, made available to the NAC by the DKFZ, Heidelberg, Germany together with a proton therapy module which was provided by the Royal Marsden Hospital, UK. The NAC system is now called PROXELPLAN and has been routinely used for proton treatment planning since October 1994. The proton module has been modified and refined by the NAC's Division of Medical Radiation to make it suitable for clinical use.

The main features of the PROXELPLAN system are: (1) Fully 3-D treatment planning (i.e. non-coplanar treatments) based on CT data, (2) Digitally reconstructed radiographs can be obtained and compared with portal X-ray images, (3) Dose volume histograms are calculated, (4) Stereotactic co-ordinates of beam entry and exit points are calculated, (5) Beam shaping is done according to a beams-eye view of the treatment volume and (6) Isodoses are displayed in the different scanned transversal planes as well as in user selected frontal and sagittal reconstructions.

The proton module uses a ray line tracing algorithm which does not permit the accurate calculation of compensators. A pencil beam algorithm is currently under development and preliminary calculations are in good agreement with measured data. Except for the proton module, which is now running on an Alpha VAX computer, the rest of the system is running on a suboptimal hardware arrangement which adversely affects its performance. A dedicated Alpha VAX has been obtained to run the latest generation of VOXELPLAN software which is under beta testing and will be released for clinical use in the near future. In addition to this the proton module will be revised to accommodate patched beams. This will significantly improve the performance of the PROXELPLAN system.

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Semi-automatic conformal proton therapy planning: fast and accurate

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The layout and results of a proton therapy planning system are presented. It utilises a PC (Pentium 90, 32 MB RAM, 300 MB hard drive): input is via 3.5" floppy disc, keyboard and mouse. The software is based on an algorithm employing a differential pencil beam to compute a fully 3D dose distribution for a proton beam having an arbitrary entrance angle. The algorithm checks the density of the substance in the pencil beam's path pixel by pixel and adjusts its penetration depth accordingly. In between density corrections a scattering correction is also applied. The resulting depth dose may be folded with a distribution of appropriate RBE values in order to present iso-RBW curves. In semi-automatic mode, the algorithm determines the energy of the central beam line, so that the maximum of the dose distribution coincides with the isocentres. In addition, the program presents the outline of the target in the beam's-eye-view and supplies the relevant data to cut out a fitting aperture. If required, the algorithm will compute a 3D insert (DISD) for the aperture, so that the pre-set isodose line of the proton beam will follow the distal contour of the target. The system can handle up to 6 beams in different directions, with different apertures and energies. Average handling and computation times are: read-in of one CT image from floppy disc: 2 s, outlining / vectorizing of 1 CT: 2 s , computing one fully 3D dose distribution: 15 s, computing one DISD and resulting dose distribution: max. 1 min.

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