PROTON THERAPY CO-OPERATIVE GROUP	Chair	Secretary
	Michael Goitein Ph. D. Department of Radiation Oncology Massachusetts General Hospital Boston MA 02114 (617) 724 - 9529 (617) 724 - 9532 Fax	Daniel Miller Ph. D. Department of Radiation Medicine Loma Linda University Medical Center Loma Linda CA 92354 (909) 824 - 4197 (909) 824 - 4083 Fax

ABSTRACTS

of the

XXIV PTCOG MEETING

held in Detroit, Michigan, USA

April 24-26 1996

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PTCOG nasopharynx treatment planning intercomparison

A. Smith, Massachusetts General Hospital; A. Lomax, Paul Scherrer Institute; D. Miller, Loma Linda University Medical Center

The Treatment Planning Working Group has continued to develop and implement the tools necessary to carry out treatment planning intercomparisons. We will perform studies for a number of disease sites and will continue to expand the number of participants so that the study will include a complete representation of proton beam delivery and treatment planning methods as well as challenging treatment plans using photons.

The following capabilities have been implemented using the Internet: transmission of patient CT data sets, including contours of treatment targets and normal tissues, to participants; transmission of 3-D dose distributions to PSI where they will be converted into a common format and Dose Volume Histograms (DVHs) calculated; and transmission of the DVHs to MGH where biological models will be used to calculate the Tumor Control Probabilities (TCPs) and Normal Tissue Complication Probabilities (NTCPs).

The Nasopharynx data set and Treatment Planning Protocol have been sent to: MGH, Loma Linda, Univ. of CA San Francisco, and Univ. of Wisconsin, USA; PSI, Switzerland; DKFZ, Heidelberg; NAC, South Africa; and Clatterbridge, United Kingdom. The treatment planning protocol has been revised since the South Africa meeting to include new dose constraints for the parotid and submandibular glands. At the time of the Detroit meeting new dose distributions (following the revised protocol) from three facilities had been submitted: PSI, using spot scanned protons; MGH, using passively scattered protons, and DKFZ, using intensity modulated x-rays.

Data were presented in Detroit for the submitted treatment plans. A treatment plan was also presented from UCSF which followed the old protocol. The presentations included: representative dose distributions for 4 CT slices; DVHs for all target volumes and normal tissues; TCPs for the target volumes, and NTCPs for representative normal tissues.

The data presented in Detroit should be regarded as preliminary because the treatment plans continue to be refined and the analysis is incomplete. After the meeting we found that one institution had not followed the protocol for treatment planning margins and also found discrepancies in some of the DVHs used for the calculation of TCPs and NTCPs. These findings may change the rank ordering of TCPs that was presented in Detroit and will perhaps change some of the NTCPs. In light of this on-going analysis we will not present any final results or conclusions in this report. We also expect to receive treatment plans from other institutions which will be included in the study.

The discussions after the presentations in Detroit centered around the relative merits of the proton plans which were presented and the intensity modulated x-ray plan. It was pointed out that our study should include direct comparisons of intensity modulated protons with intensity modulated x-rays because intensity modulation represents a more optimum use of both modalities. Any direct comparison of x-rays and protons which uses equivalent beam delivery parameters (both using intensity modulation, or numbers, directions, and weighting of static fields, etc.) will result in superior dose distributions for protons. The quantification of the improvements which can be achieved with protons and the assessment of their clinical implications should be a central element in the treatment planning intercomparisons.

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Proton therapy in 1996: a world wide perspective.

J. M. Sisterson, Harvard Cyclotron Laboratory, Harvard University.

It is more than 30 years since the first patients were treated with proton beams and the annual number of patients treated world wide is still increasing. New proton therapy facilities are under construction, some of them hospital-based, and others are in the planning stages. The current status of proton therapy world wide and patient treatment statistics through 1994 will be presented.

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Arteriovenous malformations: the NAC experience.

F. Vernimmen[1], J. Wilson[2], D. Jones[3], N. Schreuder[3], E. De Kock[3], J. Symons[3], [1]Dept. of Radiation Oncology, Tygerberg Hospital, Cape Town, [2]Dept. of Radiation Oncology, Groote Schuur Hospital, Cape Town, [3]NAC Cape Town.

Since the start of proton therapy at NAC in September 1993, twenty eight patients with arteriovenous malformations have been treated. Almost all the patients were referred for proton therapy because they were considered inoperable by their referring neurosurgeon. This has resulted in a patient group with either big lesions or lesions located in critical areas of the brain.

Mean volume of the AVM's was 19.3 cc with a median of 14.6 cc and a range of 0.4 - 64.8 cc. The number of AVM's greater then 15 cc was 13 or 46%. Patient's age ranged from 4 to 59 years, with a median of 33 years.

The treatment was usually delivered in 3 fractions, aiming for an single fraction equivalent (SFE) dose of 17 - 25 GyE.

Of the 28 patients, 11 have been followed up for 1 year or more. Of those 11 patients, two are lost to follow up. Of the remaining 9 patients, 1 had a complete obliteration, and one died of progressive disease. One patient was clinically well until she had a bleed at 6 months causing neurological symptoms. All remaining patients are clinically well, with no permanent neurological deficit, and no further bleeding.

Our treatment schedule has resulted in a very low obliteration rate, but with no permanent neurological damage and no bleeding, once the latent period has passed.

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Preliminary results of carbon-ion therapy at NIRS

H. Tsujii, J. Mizoe, T. Miyamoto, S. Morita, M. Mukai, T. Nakano, H. Kato, T. Kamada, K. Morita, Research Center of Heavy Charged Particles, National Institute of Radiological Sciences, Chiba, Japan

In 1994 the clinical trial of heavy ion therapy was begun at the National Institute of Radiological Sciences (NIRS) using carbon-ions generated by a medically dedicated accelerator (HIMAC: Heavy Ion Medical Accelerator in Chiba). The HIMAC is the world's only heavy ion accelerator complex dedicated to medical use in a hospital environment. There are three treatment rooms with fixed apertures as well as rooms for physics and biological research studies. Judging from the results of preparatory experiments as well as LBL experiences, we decided to use carbon ions in the initial clinical studies. Preparatory to clinical application, preclinical studies were performed on five human cell lines cultured *in vitro* and mouse skins to estimate RBE values relative to photons and to fast neutrons as well. The RBE values of

carbon-ions for subacute skin reactions were estimated to be 3.0 at the distal part of the SOBP. Interdisciplinary working groups were organized to design protocols for phase I/II carbon ion therapy, in which the main purpose was to investigate radiation-related toxicities as well as tumor response in HIMAC carbon ion therapy. The protocols were designed for various tumor sites including the head and neck, brain, lung, liver, uterine cervix, and prostate. In the phase I/II studies for these tumors, the initial doses employed were 10-20% lower than those possibly tolerable for musculo-connective tissues. The doses have been escalated by 10% increments for every 3 to 5 patients based on careful observation of the normal tissue morbidities as well as tumor responses. During June 1994 and February 1996, the total of 104 patients were treated. As with radiation-related toxicities, none of the patients experienced any type of major radiation-related morbidities. Although the follow-up periods are still too short and radiation doses initially employed may be rather conservative, the preliminary results appear to demonstrate promising effects of carbon-ion therapy in selected tumors. Despite we gave relatively low doses for cancer control, the local controls are not so bad in those tumors other than malignant gliomas. For this ultra-radioresistant tumors, adequate dose fractionations have not possibly been met.

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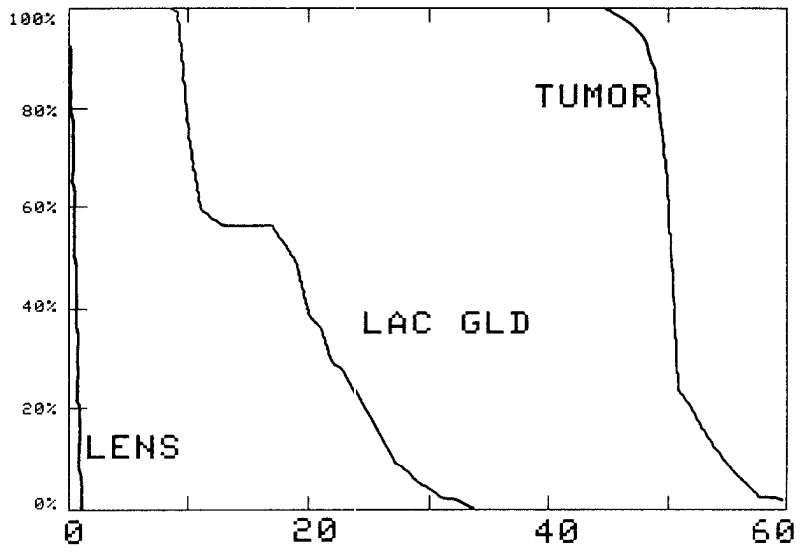
Proton radiation therapy for orbital and parameningeal rhabdomyosarcoma.

E. B. Hug, J. A. Adams, J. E. Munzenrider, Massachusetts General Hospital, Boston and Harvard Cyclotron Laboratory, Cambridge, MA.

Purpose: Conventional megavoltage x-ray therapy of the orbit concomitantly delivers significant doses to important, normal structures resulting in adverse late side effects. Possible cataract formation, risk of glaucoma, pituitary gland deficits, unnecessary brain irradiation and cosmetic effects on developing facial structures are of particular concern in the pediatric patient. In an effort to reduce irradiation of non-target tissues a technique has been designed and implemented utilizing 160 MeV Protons.

Material and Methods: Following CT-based 3D-treatment planning two pediatric patients (both age 7) with orbital, and one adult patient (age 27) with parameningeal rhabdomyosarcoma and orbital involvement underwent fractionated Proton Therapy and Chemotherapy since January 1995. Total radiation doses to macroscopic/microscopic targets of 50/40 CGE and 55/40 CGE for orbital and 65/59 CGE for parameningeal primary were prescribed, 1.6 to 2.0 CGE (Cobalt Gray Equivalent) per fraction. Dose-Volume-Histograms (DVH's) were generated to ascertain target coverage, and to quantify irradiation to lens, globe, optic nerve(s), chiasma, pituitary gland and brain parenchyma.

Results: DVH's demonstrate significant reduction in volume irradiated and dose per volume for all normal tissues compared to standard fractionated x-ray treatment. This effect was most pronounced in the ability to spare anterior ocular structures (lens, cornea, eyelids) as well as lacrimal gland, optic chiasm and pituitary gland. DVH's for one girl with orbital rhabdomyosarcoma treated to 50 CGE (macrosc. target) are illustrated (y-axis = volume, x-axis = dose). Proton therapy was well tolerated and acute side effects were within the expected range. Adequate observation time will be needed to evaluate long term effects and tumor control.



Conclusion: The unique physical properties of Protons can reduce or eliminate unnecessary irradiation of normal tissues, which should translate into improved structural and functional outcome. In addition, increasing the target doses while respecting normal tissue tolerances might further improve local tumor control for selected sites.

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Conformal radiation therapy for retinoblastoma: comparison of various 3D proton plans

M. Krengli, J. A. Adams, E. B. Hug, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, and Harvard Cyclotron Laboratory, Cambridge, USA

Introduction: Conventional megavoltage radiation treatment for retinoblastoma can result in potentially severe cosmetic and functional long-term side effects. In an effort to minimize these side effects the 160 MeV, fixed, horizontal proton beam of the Harvard Cyclotron Laboratory with lateral field arrangement has been used in 12 patients with unilateral and bilateral retinoblastoma since 1986. In the present study different tumor locations in the retina have been assumed and various field approaches have been tested to optimize the dose distribution to target and non-target tissues.

Material and Methods; CT-scans were obtained with three different eye positions: straight, temporal, and nasal rotations. Eye positions were secured by placement of a vacuum silicon suction cup centered on the cornea.

Three tumor locations have been assumed: temporal, central, and nasal. Tumor volume, microscopic target and critical structures were drawn on the 3D treatment planning system. Microscopic target was defined as any retina posterior to the equator. The following critical structures were outlined: lens, orbit bone and soft tissues, optic nerve, lacrimal gland, controlateral eye, temporal and frontal lobes, pituitary gland.

3D-treatment plans were performed. Different oblique beam arrangements for various eye positions were compared with the previously used lateral beam orientation with straight eye position. A 45° oblique antero-lateral field with intra-rotation of the eye was chosen for tumors in central and temporal locations.

Two different arrangements were studied for nasal location of the tumor: a 30° oblique antero-medial field with outward rotation of the eye and a 45° oblique antero-lateral field with inward rotation of the eye. Doses of 46 CGE (Cobalt Gray Equivalent) to the tumor and 40 CGE to the secondary target were prescribed.

Results: With full coverage of the tumor target and microscopic target, isodoses on the 3-D treatment plans and dose-volume histograms demonstrated no difference in the ability to spare the lens. The maximum dose at the posterior pole of the lens was < 15 CGE.

For all three tumor locations (temporal, central, and nasal) dose-volume histograms demonstrated improved dose distribution by using a 45° oblique latero-anterior field. The advantage was particularly evident for orbital bone and soft tissues. No difference was appreciable for the optic nerve. Even for nasal tumor location the use of a 30° oblique medial anterior field did not show any advantage when compared to the lateral proton beam. Neither plan delivered significant dose to pituitary gland, controlateral eye, or brain tissue.

Conclusions: Recent advances in general anesthesia permit greater freedom of treatment positioning in infants. By using immobilization mask and vacuum suction cup it is possible to implement high precision proton beam techniques to homogeneously irradiate tumor and microsopic target and reduce irradiation of non-target tissues. In this study the treatment plan comparison of oblique fields vs. lateral field indicates improved sparing of non-target tissues with 45° oblique lateral anterior field orientation for temporal, central, and nasal tumor locations.

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An analysis of acute and late toxicity in a randomized study of pion vs. photon irradiation for stage T3/4 prostate cancer.

T. Pickles, G. Goodman, M. Dimitrov, G. Duncan, C. Fryer, P. Graham, M. McKenzie, J. Morris, D. Rheaume, I. Syndikus. BC Cancer Agency, Vancouver, Canada.

Introduction: 219 patients with T3/4,N0/X,M0 prostate cancer were randomly assigned to pion or photon radiation therapy in a phase 3 study between 1990 and 1994.

Method: After giving informed consent, patients were randomly allocated to treatment with pions (33-34.5Gy? in 15 fractions in 3 weeks) or photon irradiation (66Gy? in 33 fractions in 6.5 weeks). Pion patients were treated with a direct anterior field. The target volume (90% isodose) was the clinico-radiologic extent of the disease plus a 1cm margin, except posteriorly where it was 5mm. Pion patients were treated with an empty bladder as the duration of treatment was approximately 30 minutes. Photon patients were treated with 4-field (78%) or arc radiotherapy (20%), +/- custom blocking. The target volume was the tumour plus 1 - 1.5cm. Photon patients were treated with the bladder full.

Results: This report is confined to an analysis of toxicity. Median follow-up is 32 months. The mean treatment volume (90%) in the two arms are pion 325cc, photon 413cc, (Wilcoxan rank sum test, $p<0.0001$). Overall the incidence of acute toxicity is greater in the pion arm, ($?^2$ $p=0.02$), and is accounted for entirely by increased bladder toxicity ($?^2$ $p=0.0005$). Late toxicity overall is significantly reduced in the pion arm, (all RTOG grades, log rank $p=0.009$). The incidence of serious toxicity (grades 3 and 4) does not differ between arms. The incidence of late rectal toxicity is significantly reduced in the pion arm (log rank $p=0.0001$ grades 2-4). The incidence of grade 2-4 bladder and bowel late toxicity does not differ (log rank $p=0.6$ and 0.3)

Interpretation: Increased acute bladder toxicity in the pion arm is likely related to the treatment of pion patients with an empty bladder, and the short overall duration of treatment. Reduced late rectal

complications in the pion arm may be a result of tighter posterior margins to the 90% isodose, although the fall off in pion dose distal to the end of the SOBP from 90 to 50% is 2cm. In addition the planning of pion patients took into account the rising RBE seen along the SOBP to give a uniform biologic dose along the SOBP. There is no indication from this study that the late tissue RBE of pions is higher than the acute RBE. Consideration of the variation of RBE with SOBP is important in particle therapy planning.

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With conformal photon irradiation, who needs particles?

J. D. Forman, Gershenson Radiation Oncology Center, Karmanos Cancer Center, Harper Hospital and Wayne State University, 3990 John R., Detroit, MI, USA.

Neutron irradiation has been proven superior to photon irradiation in terms of survival and disease-free survival, but with considerably more than equal late toxicity. However, the comparison group in the two RTOG studies was far below what would be standard or even optimal photon therapy. The patients receiving photon irradiation did not receive conformally delivered and designed photon irradiation. Doses of only 7,000 Centrigray were utilized, whereas many investigators are using much higher doses. Finally, neo-adjuvant or adjuvant hormonal therapy was not a component of the treatment.

In 1996 it has been shown that higher than standard doses of conformally delivered photon irradiation can be safely delivered with increases in histological and clinically determined local control. In addition a neo-adjuvant hormonal therapy has been shown to significantly reduce the rate of clinical and bio-chemical failure and increase the disease-free survival. Therefore, it is postulated that although neutron treatment is proven to be better than photon treatment by itself, there are other means of accomplishing improvement over photon treatment that may allow for comparable results to the neutron treatment.

One of these options that has been tested is the use of combined hyperfractionated external beam radiotherapy and neo-adjuvant hormonal therapy. In a Phase I-II dose escalation protocol at Wayne State University, 49 patients have received escalated dose hyperfractionated external beam radiotherapy with or without hormonal therapy. A summary of the results shows no Grade 3 or 4 Gi or GU complication. In addition, of patients receiving both hyperfractionated photon irradiation and neo-adjuvant hormone therapy, 100% of these patients had a post-radiation biopsy that showed either marked therapeutic effect or was completely negative. In view of these results it appears possible that neutron type survival improvements could be accomplished with dose intensification using photons in combination with neo-adjuvant hormonal therapy. However, at the present time, this remains completely hypothetical and must be proven in a clinical setting before it can be said that comparable results can be achieved without the use of neutrons.

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Update of Loma Linda experience with conformal proton treatment of prostate cancer

C. Rossi et al., Loma Linda University Medical Center, Loma Linda, CA, USA

Purpose: A study was developed to evaluate the use of combined photons and protons for the treatment of locally advanced carcinoma of the prostate. This report is a preliminary assessment of treatment-related morbidity and tumor response.

Methods and Materials: One hundred and six patients in stages T2b (B2), T2c (B2), and T3 (C) were treated with 45 Gy photon-beam irradiation to the pelvis and an additional 30 Cobalt Gray Equivalent (CGE) to the prostrate with 250 MeV protons, yielding a total prostate dose of 75 CGE in 40 fractions. Median follow-up time was 20.2 months (range: 10 - 30 months). Toxicity was scored according to the Radiation Therapy Oncology Group (RTOG) grading system; local control was evaluated by serial digital rectal examination (DRE) and prostate specific antigen (PSA) measurements.

Results: Morbidity evaluation was available on 104 Patients. The actuarial 2-year rate was Grade l or 2 late morbidity was 12% (8% rectal, 4% urinary). No patients demonstrated Grade 3 or 4 later morbidity. Treatment response was evaluated on 100 patients with elevated pretreatment serum PSA levels. The actuarial 2-year rate of PSA normalization was 96%, 97%, and 63% for pretreatment PSAs of >4-10, >10-20, and >20 respectively. The 13 patients with rising PSA demonstrated local recurrence (3 patients), distant metastasis (8 patients), or no evidence of disease except increasing PSA (2 patients).

Conclusions: The low incidence of side effects, despite the tumor dose of 75 CGE, demonstrates that conformal protons can deliver higher doses of radiation to target tissues without increasing complications to surrounding normal tissues. The initial tumor response, as assessed by the high actuarial rate of normalization with pretreatment PSA $\leq$ 20, and the low rate of recurrences within the treatment field (2.8%) are encouraging.

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Actuarial control of PSA in patients irradiated with fast neutrons for prostate carcinoma

F. Richard[1], M. Octave-Prignot, P. J. Van Cangh[2] and P. Scalliet[1] , [1]Department of Radiation Oncology, [2]Department of Urology, Clin. UCL St LUC 1200 Brussels, Belgium

Since March 1978 up to December 1995, four hundred fifty patients have been treated with fast neutrons for prostatic adenocarcinomas at the cyclotron " CYCLONE" of Louvain-La-Neuve.

The different parameters analyzed were the rate of PSA decline (PSA half-live), the PSA nadir and the post-nadir PSA trends for patients with locally advanced carcinomas treated with mixed beam therapy (3 neutron fractions and 2 photon fractions a week) with a total dose of 66 Gy equivalents given on the prostatic area in 33 fractions over 7 weeks.

In the facility of Louvain-La-Neuve, 363 patients out of 450 have been treated radically . The other patients, with incomplete treatments, or with stages D2 treated for local evolution of the disease, or lost for follow-up were excluded from the present analysis.

The majority of the patients were locally advanced stages C of the disease. Hundred and three patients received adjuvant hormonal therapy before or during irradiation or had an orchiectomy at the time of diagnosis. They were not included in this series. Twelve patients treated for recurrences after radical prostatectomy and 39 patients treated postoperatively after adenectomy or radical prostatectomy were also excluded from this series.

Before 1990, PSA values were not systematically available, reason why 115 patients were not evaluable because a lack of pretreatment PSA values. Finally, only 54 patients were fully evaluable for the endpoints mentioned above.

In this study, initial (pretreatment) PSA values correlated significantly with clinical stage and disease outcome with a good prognostic implication of a low initial PSA. Probability to obtain a PSA < 1 ng/ml after radical irradiation is dependent on pretreatment PSA. With initial PSA value < 10 ng/ml, PSA value decrease to less than 1 ng/ml in the majority of the cases. The rate of fall after radiotherapy, or clearance of PSA does not appear to have a prognostic value. The importance of PSA normalisation (< 1 ng/ml) is confirmed as far as long term PSA control is concerned. When the PSA nadir exceeds 4 ng/ml, ultimate progression is almost certain. However if the normalization of PSA is a favourable prognostic factor, even an undetectable nadir PSA is not a guarantee of long term control.

As compared to other series of prostatic adenocarcinomas treated with photons only, there is no difference in the rate of PSA reduction or in the initial PSA value which is still compatible with a low PSA nadir and a long term PSA control in the present series. The number of patients evaluable for these particular endpoints was small and do not allow to draw a definitive conclusion.

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The effect of local/regional tumor recurrence on survival for patients with carcinomas of the prostate: results from NTCWG protocol #8523

T. W. Griffin[1] and T. F. Pajak[2], [1]Department of Radiation Oncology, University of Washington, Seattle, WA, USA, [2]Statistical Center, Radiation therapy Oncology Group, Philadelphia, PA, USA.

Although the local/regional treatment of prostate cancer is a subject of intense research in the United States and around the world, the effect of local/regional tumor recurrence on the subsequent survival of patients with this disease continues to be a subject of debate and has yet to be adequately defined. An updated analysis of NTCWG 8523 (a study with significantly different local/regional tumor recurrence rates on the two treatment arms) was accomplished in an attempt to answer this question.

From April 1986 to October 1990, 178 patients were randomized on a prospective, multi-institutional study (NTCWG 8523) comparing external beam photon irradiation to neutron irradiation for patients with high grade T2 or T3 - 4, N0 - 1, M0 adenocarcinomas of the prostate. Patients entered into this study now have a minimum of 5 years follow-up information. As previously reported, there is a significant difference in local/regional tumor recurrence rates between the two treatment arms (now 40% for photons vs. 14% for neutrons at 7 years). The cause of death was prostate cancer in 43% of photon treated patients vs. 28% of neutron treated patients at 7 years. The effect of local/regional tumor recurrence on subsequent survival was evaluated using the Cox regression model with treatment, grouped Gleason scores (2-6 vs. 7-10) and grouped stage (B2/C vs. D) as covariates.

The results of this multivariate analysis reveal that the relative risk of dying for a man suffering a local or regional recurrence of his prostate cancer is 2.80 times the risk for a man without a local/regional tumor recurrence in this patient population ($p < 0.001$).

These findings have significance for studies investigating local/regional treatments of prostate cancer.

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Evaluating the therapeutic gain of conformal mixed photon/neutron irradiation in localized and locally advanced adenocarcinoma of the prostate

J. D. Forman, P. Kocheril, P. Chuba, S. Reddy, J. Ruby, T. Alpinheim, C. Orton, R. Sharma, R. Maughan, Gershenson Radiation Oncology Center, Karmanos Cancer Center, Harper Hospital and Wayne State University, 3990 John R., Detroit, MI, USA.

In order to evaluate the therapeutic ratio of conformal mixed photon/neutron irradiation, four prospective dose finding studies have been conducted in patients with localized and locally advanced adenocarcinoma of the prostate. The goal was to evaluate the optimal field arrangements, block configuration, neutron and photon dose, both separately and cumulatively in order to maximize the therapeutic gain of mixed neutron/photon irradiation as compared with conformal photon irradiation alone.

Between January 1992 and the present, 280 patients with non-metastatic prostate cancer have been treated on a number of dose finding protocols involving the use of conformal neutron and photon irradiation. Neutron and photon treatments have been delivered with completely conformal axial, non-axial and non-coplanar 9-20 neutron gray and photon doses have ranged from 18-46 photon gray. Follow up has been conducted in the usual manner with history and physical including digital rectal examination, bio-chemical evaluation, including PSA determination and planned post treatment ultrasound guided biopsies at 12-18 months after treatment in all patients. Toxicity has been evaluated and scored according to the RTOG toxicity grading scale. These results have been compared to concurrently treated patients treated with conformal photon irradiation alone at a dose of 6,900 centigray or locally advanced prostate cancer patients treated on a hyperfractionated dose escalation protocol to a dose of 7,800 or 8,300 centigray.

In order to evaluate the therapeutic gain of neutron/photon irradiation, an estimated RBE was determined for each of the following end points. These end points included histologically determined local control, bladder toxicity, rectal toxicity, potency, hemotologic toxicity as well as skeletal muscle injury in the region of the pelvis. Iso-effect end points were available for histological local control. In the patients with locally advanced prostate cancer, 85% of patients treated with 15 neutron gray plus 18 photon gray had negative post radiation biopsies. This was statistically identical to the 95% of patients with negative biopsies at 8,300 cent gray on the locally advanced hyperfractionated protocol. From this a 2 Grade per fraction dose was calculated to determine the iso effect of dose and an RBE for the prostate cancer of 4.0 was calculated. Next, an iso effect end point for rectal injury was obtained. This was available for patients with both locally advanced prostate cancer who received elective pelvic lymph node irradiation and earlier stage prostate cancer in which pelvic lymph node irradiation was not a component of the treatment. It was calculated that the RBE for rectal injury was 3.3 including pelvic irradiation and 2.9 excluding pelvic irradiation. Thus, the RBE for rectal injury was both lower than that for histological control and there was a demonstrable volume effect in RBE. With respect to chronic bladder injury, there was a statistically significantly higher rate of chronic Grade 2 bladder toxicity in patients receiving standard fractionation conformal photon irradiation alone. Therefore, although an iso effect end point was calculable for locally advanced patients treated with hyperfractionated photons or neutrons including pelvic irradiation, no such iso effect point could be calculated for low volume irradiation with neutrons since the neutron treatment had a statistically significantly lower rate of complications. For large volume treatment, the RBE was calculated to be 3.3. For small volume irradiation the RBE was estimated to be less than 2.9. For the end points of potency and hemotological toxicity, an RBE was calculated a 3.0 with no demonstrable volume effect. Finally with respect to skeletal muscle injury, it was found through a series of MRIs in patients with subjective hip muscle stiffness, that patients developed myositis in the obturator internis, obturator externis and gluteus medius muscles. This coincided with the high dose

volume irradiation from the non axial conformal neutron and axial neutron ports. From this an RBE for skeletal muscle was calculated at 4.0. In addition, a 2 Gray per fraction threshold dose of 6,200-6,400 centigray was estimated.

In conclusion, the therapeutic gain of conformal mixed neutron and photon irradiation in nonmetastatic prostate cancer is in the range of 1.25-1.35. Thus, for a dose of mixed neutron/photon irradiation that would deliver a 2 Gray per fraction photon equivalent dose of 8,400 centigray, the equivalent dose to the rectum is 7,300 centigray and to the bladder, is in the range of 7,100 centigray. With this type of therapeutic gain significant advances in the management of non-metastatic prostate cancer are anticipated.

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Sensitization of brain tumor cells to fractionated fast neutron irradiation

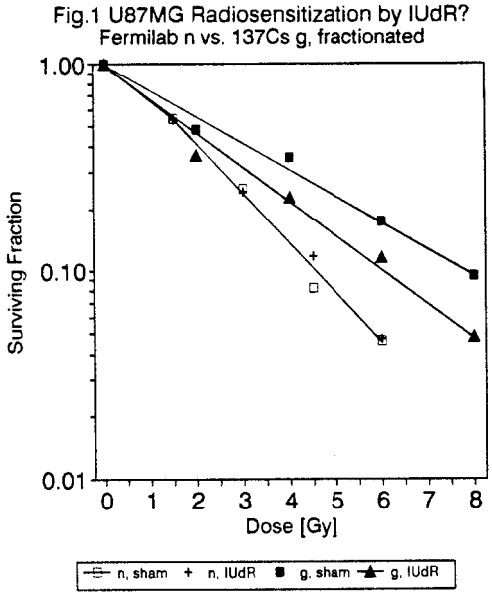
E. R. Blazek, C. Carpenter, W. Chen, A. J. Lennox, B. Pientak, and T. Kroc, Rush-Presbyterian-St. Luke's Medical Center and Fermi National Accelerator Laboratory, Chicago, IL 60612 and Batavia, IL 60510

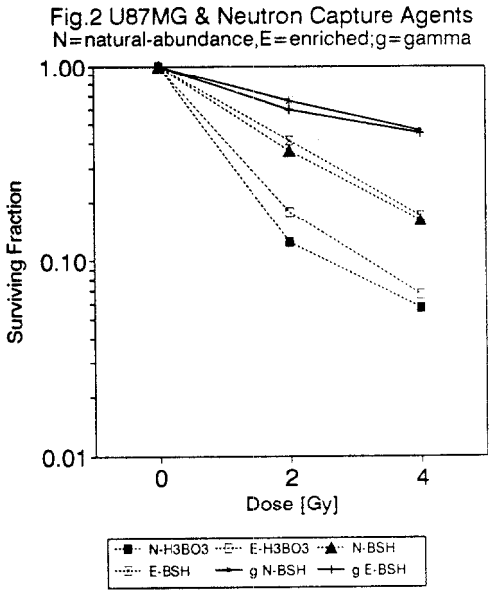
The inability of conventional external beam photon radiotherapy to control high-grade astrocytomas demands alternative approaches. We are studying whether, in the Fermilab fast neutron beam [p(66)Be(49)] either (1) iododeoxyuridine or (2) boron neutron capture agents can radiosensitize human anaplastic astrocytoma U87MG cells or rat gliosarcoma 9L cells *in vitro.* Most *in vitro* cell survival experiments are performed with single radiation doses, rather than clinically-fractionated irradiation. Use of single fractions overestimates the killing achievable by doses larger than the clinical fraction dose and inherently cannot detect changes in effective survival due to delaying sublethal damage or slowing of interfraction repopulation. For these reasons, we study survival after clinical fractions separated by realistic intervals.

Figure 1 shows survival curves for U87MG cells subjected to either 2-Gy daily fractions of ^{137}Cs gamma radiation, or to Fermilab fast neutrons. Cell were grown in the presence or absence of 5 ?M IUdR from 4 d before the initial radiation fraction until after the final fraction. For both gamma radiation and neutrons, the 24 h interval allowed full repair of sublethal damage, as indicated by the purely exponential (shoulderless) survival curves. IUdR radiosensitized U87MG cells to gamma radiation, with a dose modification factor of 0.75 at a survival of 0.1. This is consistent with many reports of IUdR sensitization of various cell lines to *single-fraction* gamma radiation. IUdR did not, however, sensitize U87MG cells to fractionated neutron radiation. We do not understand the reason for its inactivity with neutrons; other preliminary experiments suggest that IUdR *does* sensitize 9L cells to fractionated neutron irradiation.

We also attempted to determine whether tumor cell killing by fast neutrons might be enhanced by capture of target-moderated neutrons by boron neutron capture agents. We exposed cells to either natural abundance (18% ^{10}B) or isotopically-enriched (97% ^{10}B) forms of either sodium borocaptate (BSH) or boric acid (H_3BO_3) at *identical chemical concentrations.* Cells were then irradiated with ^{137}Cs gamma rays or with Fermilab neutrons after their passage through 9 cm of D_2O to enhance the fluence of slow neutrons. Figure 2 shows that cell killing did not depend upon isotopic enrichment of the capture agent for the active ^{10}B nucleus, hence there is no evidence that neutron capture occurred either for the gamma control (as expected) or the neutron beam. Comparison of Fig. 2 with Fig. 1 shows that BSH strongly protected the gamma-irradiated cells from killing. In retrospect, this could have been predicted from the ability of sulf-hydryl compounds to quench hydroxyl radicals. BSH appears to have modestly protected the neutron-irradiated cells, while boric acid sensitized these cells compared to drug-free controls. We conclude that in experiments testing for additional cell killing by neutron capture reactions, the

appropriate control is not a drug-free cell population, but rather a cell population exposed to the same chemical concentration of capture agent with a different level of isotopic enrichment.





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D-T neutrons for therapy - Detroit re-visited

L. Cranberg

On April 6, 1979, a ten-member ad hoc Committee of the Committee for Radiation Oncology Studies, chaired by William E. Powers, M.D., met in Detroit at the request of Vincent deVita, M.D., Director of the National Cancer Institute, to hear my proposals for, and criticisms of, the NCI program to develop D-T neutron generators to treat cancer with monoenergetic 14-MeV neutrons, and on NCI programs for neutron dosimetry.

The criticisms focused on the neglect of proven D-T neutron sources using rotating targets at Lawrence Livermore Laboratory and the University of Hamburg, and of my proposed design (Int. J. Rad.Onc.Bio.Phys. 3, (1977) 393), in favor of accelerators with fixed or gaseous targets. The neglect of measurements of neutron energy spectra for proper determination of neutron dose was also a concern. My proposals and criticisms, and the compelling technical reasons underlying them, were not included in the report to Dr. Devita of May 9, 1979.

But in the following years my patented claims for rotating targets with ten-fold increased target lifetime were fully confirmed at Hamburg. At the same time the failure of Cyclotron Corporations' solid target machine brought bankruptcy in 1983. This account is confirmed in essentials by Dewhirst et al., (J. Nat. Cancer Inst. 85 (1993) 951). Today all D-T accelerators other that the one at Hamburg have closed, while the Hamburg machine is out-of-date and seriously short of neutron intensity. The Livermore machine for reasons not yet understood, was never used for therapy. A paper by H.H. Barschall, "The Production and Use of Neutrons for Cancer Treatment", American Scientist, 64 (1976) 668 also neglected rotating target machines proposing a gas-target design.

The fact that we do not yet have adequate neutron energy spectral data on cyclotron sources used for therapy is another reminder that my criticisms of 1979, and oft-repeated since then, are still unheeded. Until those data are available, neutronic calculations such as are now standard in the reactor industry, are not on the horizon for neutron therapy.

The lessons we can learn from this unhappy history, as we revisit Detroit seventeen years later, will be discussed. Obviously, the accelerator development program of NCI failed to develop the long-sought D-T generator of monoenergetic 14 MeV neutrons for proper clinical trials of fast neutron therapy. Where is the remedy to be sought? Probably the answer is in private philanthropy or private commercial development, where support had been very fruitful here at the Gershenson Radiation Oncology Center for a cryogenic cyclotron.

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In-vivo dosimetry in neutrontherapy utilizing 7LiF dosimeters: preliminary results

J.-M. Denis, Th. Loncol, N. de Patoul, S. Vynckier, P. Scalliet, Service de Radiotherapie, Cliniques Universitaires St. Luc, Avenue Hippocrate 10, 1200 UCL-Bruxelles, Belgium.

Neutrontherapy has been performed at Louvain-la-Neuve utilizing a multileaf collimator since 1991. Determination of the output factors for clinical conditions with the MLC needs the knowledge of the collimator and phantom scatter of the neutron beam. Based on these data, a semi-empirical algorithm is applied for the determination of the exposure under clinical conditions [1].

It is generally recognized that in-vivo dosimetry is a final and last check of all procedures applied before the irradiation of the patient. At Louvain-la-Neuve we studied systematically the response of the 7LiF (TLD700) thermoluminescent dosimeters in the p(65)+Be neutron beam. The same method for calibration in-vivo dosimeters as described by Leunens et al [2] was followed. In a first instance our TLD's were calibrated with reference to a TE ionization chamber at the entrance of the phantom. Dose equilibrium was assured utilizing a small 5 mm A-150 cap, which at the same time assured the packing of 5 TLD's. The calibration at the exit of the phantom will be studied in a second step.

Under these conditions, the response of the dosimeters relative to the ionization chamber was studied for different conditions, relevant for the clinical applications. We will present these results together with some preliminary in-vivo dosimetry results which were initiated approximately 2 months ago (± 50 measured points).

References: [1] S. Vynckier, N. de Patoul, J.-M. Denis, A. Wambersie Dosimetry of p(65)+Be neutron beams, produced by means of a multileaf collimator at Louvain-la-Neuve. Proceedings of the EORTC Heavy Particle Therapy Group Workshop, Brussels, March 1993. [2] G. Leunens, J. Van Dam, A. Dutreix, E. Van der Schueren. Quality assurance in radiotherapy by in-vivo dosimetry. Radiotherapy and Oncology, 17 (1990).

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Determination of the absorbed dose from the flux measurements: potentialities of the Faraday cup and activation methods.

V. Kostjuchenko[1], D. Nichiporov[1], and E. Grusell[2], [1]Institute for Theoretical and Experimental Physics, Moscow, Russia, [2]The Svedberg Laboratory, Uppsala, Sweden.

The issue of absolute dose measurements with Co-60-calibrated ion chambers was settled after 13 proton clinical centers participated in dosimetry intercomparisons held at the Loma Linda University Medical Center in April 1995. However, the question whether the methods based on flux measurements can be used for determination of dose remained open.

The use of activation detector (AD) has been shown [1] to provide the accuracy of absorbed dose calibrations compliant with the requirements set forward by international recommendations (AAPM Dosimetry Protocol, ECHED Code of Practice).

In experiments performed at ITEP in collaboration with the Svedberg Laboratory specialists, three independent methods of flux measurement were in intercompared. The Faraday cup (FC) employed in the experiments belonged to the Svedberg Laboratory, whereas the current monitor and the activation detector, the standard method of dosimetry at ITEP, were part of the ITEP dosimetry equipment. All three detectors had independent calibrations. The number of particles in the beam measured with these instruments differed by less than 1.7%. The absorbed doses in the central part of the beam measured with the AD and FC differed by +/-0. 7%. This fact, combined with the results presented in [1] allows one to assert that AD and FC can provide the accuracy of absolute dose measurements within the +/-5% error boundary. As the monoenergetic nature of the beam was judged to be an important condition, an uncollimated beam was used. The results of [2] also confirm the importance of the use of a monoenergetic beam in the FC experiments.

The following features of the activation detector make it more appealing than other flux-based dosimeters: (i) the beam flux is measured directly, making beam profile measurements unnecessary, (ii) the behavior of the mass stopping power and the $^{12}C(p,pn)^{11}C$ excitation function curves in the therapy interval of proton energies (80 - 200 MeV) compensate for the contribution into the dose from protons with the quoted energies [3].

References: [1]. D. Nichiporov, V. Kostjuchenko, A. Molokanov, J. Karlin, and S. Vatnitsky. Intercomparisons of proton clinical beams in Russia in light of the Loma Linda intercomparisons. To be presented at the XXIV PTCOG meeting, Detroit, April 24-26, 1996. [2]. E. Grusell, U. Isaaksson, A. Montelius, and J. Medin. Comparative measurements with Faraday cup and ionization chamber in an uncollimated proton beam. Abstracts of the XX PTCOG meeting, Chester, UK, May 16-18, 1994. [3]. B. Larsson and B. Sarby. Equipment for radiation surgery using narrow 185 MeV proton beams. GWI-R 5/74, April 1974.

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Microdosimetric investigations in the fast neutron therapy beam at Fermilab-work in progress

K. Langen[12], A. J. Lennox[2] and P. M. DeLuca[1], [1]University of Wisconsin-Madison, Department of Medical Physics, Madison, WI, USA. [2]Neutron Therapy Facility at Fermi National Accelerator Laboratory, Batavia, IL, USA

Until recently is was not feasible to perform microdosimetric measurements in the fast neutron therapy beam at Fermilab. This is due to the very high instantaneous dose rate (> 15 Gy/s) in this beam resulting from its low duty cycle (< 0.043%). Through modification of the beam chopper settings a 10^{-5} reduction in instantaneous dose rate could be achieved (Kroc 1995), allowing microdosimetric measurements to be performed in the beam.

Employing microdosimetric techniques, several characteristics of the neutron therapy beam are being investigated and a feasibility study on the utilization of boron neutron capture in this fast neutron therapy beam will be performed.

One investigation will focus upon the conversion factor that relates absorbed dose in ICRU tissue to absorbed dose in A-150 plastic. Carbon and oxygen kerma factor ratios relative to A-150 plastic, which are needed to calculate this conversion factor, are measured using a set of Rossi counters that are made with A-150, C, O, Zr and ZrO_2 walls.

Furthermore we want to utilize the qualitative information provided by the microdosimetric event spectra to determine changes in radiobiological effectiveness of the beam with field size and depth in tissue.

It will also be investigated if boron neutron capture can be utilized in this fast neutron therapy beam to selectively enhance the tumor dose. An increase in the thermal and epithermal fluence component will be attempted using beam filtration. Monte Carlo codes will be used to simulate the effects of the beam filtration. The boron dose enhancement will be measured using a regular A-150 wall counter and a A-150 + 200 ppm B-10 additive wall counter.

Initial results will be presented.

Reference: Kroc T. K. (1995), Low intensity configuration at NTF for Microdosimetry and Spectroscopy, Fermilab TM-1940.

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A multi-institutional interactive network for intracranial arteriovenous malformations: design, implementation and initial experience

R. P. Levy[1,2,4], R. W. M. Schulte[1], G. K. Steinberg[2], K. A. Frankel [1,2,4], D. W. Miller[1], M. P. Marks[2,3], J. D. Slater[1], B. Lane[3], L. Heilbronn[4], J. M. Slater[1], [1]Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, CA; Departments of [2]Neurosurgery and [3]Radiology, Stanford University Medical Center, Stanford, CA; and [4]Division of Life Sciences, Lawrence Berkeley Laboratory, University of California, Berkeley, CA

Purpose / Objective: Proton irradiation is advocated for treatment of selected neoplastic disorders and intracranial arteriovenous malformations (AVMs), because of the favorable dose-localization and dose-distribution of proton beams. Patient treatments in the United States to date, however, have been constrained by the limited number of existing proton facilities. In order to make proton treatment accessible to more investigators of the radiation medicine community, and to serve a larger patient population base, a multi-institutional collaborative network has been established to permit proton

treatment planning and related radiologic imaging procedures to be performed at collaborating medical institutions geographically separated from the proton irradiation facility.

Materials & Methods: Patients with symptomatic inoperable AVMs are accepted into the irradiation protocol after evaluation by a multi-institutional team of radiation oncologists, neurosurgeons and interventional neuroradiologists. After placement of fiducial skull screws, patient are immobilized for stereotactic neuro-imaging, treatment planning and (subsequent) proton treatment procedures by a non-invasive relocatable head-immobilization system, consisting of a vacuum-assisted dental fixation device, a vacuum-secured stereotactic head-frame and interchangeable CT and angiographic localization devices. Via a multi-institutional data transfer network, the treatment planning team uses digitization software to correlate angiographic and MRI data for iterative delineation of target volumes on each CT slice of interest. Treatment plans are similarly developed in collaborative fashion. Patient alignment at treatment is verified radiographically with respect to the implanted fiducials. "Small" lesions (< 10 cm^3) are typically given central maximum doses of 25 GyE (assuming RBE = 1.1), usually in one fraction. Larger lesions are given maximum doses of 20 to 25 GyE, usually in two fractions. Treatment planning is designed to contour the 80-90% isodose surface to the periphery of the target volume. A lower dose is considered for lesions in unusually sensitive locations (e.g. brain stem) or for patients who where previously irradiated.

Results: Extensive quality assurance studies performed prior to treatment of the first patient demonstrated that targets localized by stereotactic diagnostic procedures at collaborating institutions could be repositioned with respect to the proton beam with an accuracy of better than 1.0 mm. From December 1993 through March 1996, 50 patients with 59 discrete (non-adjacent) AVM target volumes have been treated. Twenty-one small AVMs (mean, 4.6 cm^3; range, 0.9 - 9.9 cm^3) were treated with doses of 20.0 - 27.5 GyE (mean, 24.0 GyE) in one fraction (13 patients) or two fractions (8 patients). Thirty-eight larger AVMs (mean, 38.7 cm^3; range, 10.7- 112 cm^3) were treated with doses of 17.6 - 25.0 GyE (mean, 21.6 GyE) in two fractions (36 patients) or one fraction (1 patient) Transient focal seizures occurred acutely in two patients. Two patients developed symptomatic edema, responding well to transient treatment with steroids. One patient died several months after developing progressive venous sinus thrombosis which began 3 months following irradiation; the site of thrombosis was remote from the high-dose region and was not considered to be related to the radiation treatment. No other acute or permanent late sequelae have been observed to date. Preliminary MRI and/or CT imaging data available in 19 patients (median follow-up time, 9.5 months; range, 3-23 months) showed absent flow in one patient (5%),decreased flow in eight patients (42%) and unchanged flow in 10 patients (53%). Long-term follow-up is in progress.

Conclusion: A regional multi-institutional network has been established for collaborative proton treatment of patients with intracranial AVMs. The methodologies employed have been found to be satisfactory for stereotactic irradiation procedures. Treatment-related toxicity has thus far been infrequent. Obliterative AVM response at this early stage following irradiation has been encouraging The regional collaborative approach described above can be extended to other participating institutions and may be used for the treatment of other intracranial and extracranial disorders where proton irradiation may be benefical.

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Iterative target delineation for stereotactic irradiation of AVMs using angiography, CT and MRI

R. P. Levy[1,2,4], R. W. M. Schulte[1], K. A. Frankel[1,2,4], G. K. Steinberg[2], M. P. Marks[2,3], [1]Department of Radiation Medicine, Loma Linda University Medical Center, Loma Linda, CA; Departments of [2]Neurosurgery and [3]Radiology, Stanford University Medical Center, Stanford, CA; and [4]Division of Life Sciences, Lawrence Berkeley Laboratory, University of California, Berkeley, CA.

Introduction: Optimal target volume delineation for stereotactic irradiation of arteriovenous malformations (AVMs) is problematic, especially for larger lesions geometrically altered by embolization or microsurgery. Angiography has greater resolution than MRI and CT for defining an AVM's extrema in anteroposterior and left-right dimensions in any given axial plane, but it yields limited information regarding the surface contours of irregular lesions. MRI and CT, however, often disclose the presence of apparently normal brain tissue within these angiographic extrema. In this report, we quantify modifications in the target volume resulting from iterative treatment planning using multi-modality imaging data.

Methods: Iterative target delineation was performed for 20 consecutive AVMs >10 cm^3. Angiographically defined extrema were transformed into CT space on a 2-mm-slice-by-slice basis. These initial target volumes were quantified and then modified by a multi-disciplinary team after review of all available imaging data. After iterative treatment planning, volumes were calculated for final targets, presumed normal tissue excluded and additional AVM target included.

Results: Initial target volumes ranged from 15.3 to 96.1 cm^3 (mean, 43.6 cm^3). Final targets ranged from 10.7 to 114.0 cm^3 (mean, 38.4 cm^3). Presumed normal tissue excluded by iterative planning ranged from 2.6 to 47.0 cm^3 (mean, 15.5 cm^3). Additional AVM, usually obscured originally by embolization material, was newly included in all cases (range 0.3 to 57.8 cm^3; mean, 10.3 cm^3).

Conclusions: Iterative target volume delineation can result in significant modifications from angiographically defined volumes. In our experience, substantial amounts of apparently normal tissue were excluded from the final target, and additional vascular abnormalities were identified for inclusion in the final target. We conclude that an iterative multi-modality approach to target volume delineation for large and complex AVMs should be investigated further.

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On-line PET imaging of radiotherapy beams

D. W. Litzenberg[1], F. D. Becchetti[1], D. A. Roberts[1], R. Ronningen[2], A. M. Vander Molen[2], J. A. Brown[2], R. K. Ten Haken[3], [1]University of Michigan, Dept. of Physics, Ann Arbor, MI, [2]Michigan State University, NSCL, E. Lansing, MI, [3]University of Michigan, Dept. of Radiation Oncology, Ann Arbor, MI

We have performed PET imaging studies of the positron-emitting activity created in water and tissue phantoms by proton and $^{12}C^{6+}$ radiotherapy beams using a prototype imaging system. These beams were produced at Michigan State University's National Superconducting Cyclotron. During proton experiments a 150 MeV, l nA, beam with a 10 second period and a 50% duty cycle was used. Data was collected between beam pulses and after beam delivery. Beam duration varied from 10 seconds to 20 minutes with data acquisition continuing as long as an additional 60 minutes. Other experiments were conducted in which continuous, 150 MeV/u, l nA, proton and $^{12}C^{6+}$ beams were imaged immediately after beam

delivery. A typical image of a one dimensional activity distribution containing roughly one thousand counts requires 5 seconds of data acquisition in the case of proton beams and 10 seconds for $^{12}C^{6+}$ beams. Images at various times during the beam delivery will be presented. Using the decay data it is also possible to determine the amount of oxygen, and other elements, as a function of depth along the beam path, thus providing information on tumor blood perfusion and tissue hypoxia for subsequent treatment planning. Results will be presented for both proton and $^{12}C^{6+}$ beams.

Similar experiments were also conducted using the University of Michigan's 50 MeV racetrack microtron. Water, gelatin and Lucite phantoms were irradiated by a 2 cm x 2 cm bremmstrahlung beam created by a 50 MeV electron beam. Images were acquired off-line with data acquisition starting within a minute after the beam. Some preliminary results from these experiments will also be presented.

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Radioprotection shielding measurements for 200 MeV protons

A. Mazal, K. Gall[1], S. Michaud, C. Nauraye, S. Delacroix, J. F. Botolier and M. Louis, Centre Protontherapie d'Orsay, Orsay, France, [1]Massachusetts General Hospital, Boston, MA, USA

Microdosimetric spectra, absorbed dose and dose equivalents have been obtained behind different thicknesses of concrete (0.3 m, density 2.2 g/cm^3), at different angles (0-90^o) and for two targets: copper and water, with a 200 MeV proton beam at Orsay. Conventional and modified rem counters (extended energy range, as presented by Birattari et al, 1990) were used as well as two tissue equivalent proportional counters and an ion chamber for gamma measurements. The response of these detectors and the attenuation coefficients will be presented.

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The project of proton treatment facility at the National Cancer Center Hospital East, Kashiwa

T. Ogino, N. Moriyama, S. Yoshida, S. Ebihara, National Cancer Center Hospital East, Kashiwa city, Chiba 277, Japan

National Cancer Center (NCC) has determined to build a dedicated proton treatment facility, and has obtained the funds last year. The facility will be built at its Kashiwa campus (National Cancer Center Hospital East), located at 30 km apart from its Tokyo campus. The proton accelerator will be a fixed 235 MeV cyclotron made by Sumitomo Heavy Industries Ltd. There will be three treatment rooms: two with isocentric gantries and one with fixed horizontal beam. The nozzles will include double scattering system and wobbler scanning system for beam spreading laterally. One of the gantries will be attached with multi-leaf collimator (less than 1 cm width each). Treatment couches can be move iso-centrically to enable to do non-coplanar irradiation. Respiration gating system will be introduced. The patient positioning will be done under real time digital fluoroscopic imaging. There will be a dedicated helical CT scanner and a MRI unit for treatment planning. The building will provide approximately 4,500 net square meter, and building construction will start soon. We hope the beginning of patient treatment will be in the first quarter of 1998 at the latest. This project will be carried out in collaboration with the National Institute of Radiological Sciences (NIRS) in Chiba.

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Stereotactic neutron radiosurgery system

S. Song[1], Z. Lu[1], X. Zheng[1], [1]Shenzhen OUR Science Development Co. LTD, China, N. Hu[2], [2]Deparment of Physics, Nan Jing University, China

The advantages and disadvantages of neutron radiosurgery are reviewed in this article. It is known that, according to the dose distribution inside human body, in neutron radiosurgery, the radiation dose on the human skin and the superficial tissues is very high. In order to reduce this radiation dose, the solution is to spread the radiation dose on the surface of the human body onto a larger area. The isocentric rotatory radiosurgery system recently adopted world wide embodies this thought. To evaluate the quality of the neutron radiosurgery system, we roughly define a parameter of "Therapeutic Ratio" as the ratio of the radiation dose on the targeted tumor per unit of volume to the radiation dose on the surface skin per unit of depth per unit of area. It is of significant importance for neutron radiosurgery to raise this ratio. To further increase this therapeutic radio of neutron radiosurgery, a scheme of stereotactic neutron radiosurgery is proposed by OUR Co.. Its schematic diagram is shown in Fig. 1. The neutron beam produced from an accelerator is collimated onto the lesion of the patient. The whole neutron beam can rotate around the axis vertical to the lesion, with the variable radius of the rotating circle, thus, a serial of isocentric circular conical surfaces are formed. Therefore, with the sufficient radiation dose on the targeted tumor, the dose on the normal skin and tissues is greatly reduced. Part of the physics diagram of such a neutron radiosurgery system is shown in Fig. 2. From the diagram, we can see: the proton beams bombarding onto the target are bent into different angles when the bending magnet B6 rests in different positions, therefore, the neutron beams hit into the human body at different incident angles; in the meantime, B6 rotates 360° around the axis vertical to the surface of the human body, thus, the above mentioned stereotactic neutron radiosurgery system is formed.

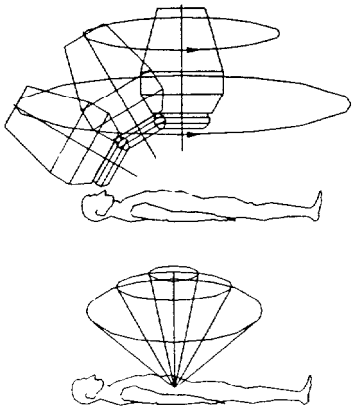

Fig. 1

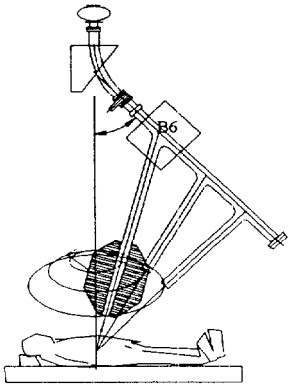

Fig. 2

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Monte Carlo calculations as shielding design tools for heavy charged particle accelerators

S. Agosteo[1], A. Fassr[2], A. Ferrari[3], P.R. Sala[3], M. Silari[4], P. Tabarelli[5], [1]Politecnico di Milano, Dipartimento di Ingegneria Nucleare, Via Ponzio 34/3, 20133 Milano, Italy, [2]Stanford Linear Accelerator Center, Radiation Physic Department, MS 48, P.O. Box 4349, Stanford, CA 94309, USA, [3]Istituto Nazionale di Fisica Nucleare, Sezione di Milano, Via Celoria 16, 20133 Milano, Italy, [4]CERN, 1211 Geneve 23, Switzerland, [5]Fondazione per Adroterapia Oncologica, Via Puccini 11, 28100 Novara, Italy

Complete set of data on secondary angular and energy distribution of particles emitted from thick iron and tissue targets for 100, 150, 200, 250, 400 MeV primary protons was computed by two Monte Carlo codes, LCS and FLUKA. Results agree with literature data.

The attenuation of secondaries through ordinary concrete (TSF 5.5) from 0 to 6 m was completely studied with FLUKA code in 18 angular bins (from 0^o to 180^o) for two different concrete geometries (sphere and slab). A comparison between the results obtained in the two geometries shows an independence on geometry. At forward angles results show a build-up effect increasing with energy and it becomes very important for 400 MeV protons where attenuation does not seem to follow an exponential behaviour. As lateral target dimension is large, no build-up effect is shown for large angles because the intranuclear cascade is fully developed in the target. The source terms and attenuation lengths obtained fitting data with the classical two parameter formula were compared with calculated and experimental data available in the literature. The agreement is in general satisfactory. Photon and secondary proton percentage to total dose equivalent for each angle and primary proton energy was also computed. The photon contribution becomes important at low energy and large angles, while proton contribution is not negligible for 400 MeV primary protons and forward direction.

Neutron attenuation was computed through different ordinary concretes for 100 MeV protons on thick iron target. Results show a decreasing of concrete thickness to obtain the same neutron attenuation with hydrogen and boron percentage. Furthermore for large angles photon contribution increases with hydrogen content.

Calculations of secondary attenuation through TSF 5.5 for 177.5 MeV/n alphas on thick water and steel targets and for 337 MeV/n neon ions on thin copper target were also performed. Results show a strong build-up effect up to 60 cm for forward angles, high values for the attenuation length but small source term per ion because neutron emission both from thick targets and from thin one is very low. The behaviour of the attenuation length versus emission angle is similar for protons and ions. This work is still in progress, simulations with other ions and other targets are going to do.

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Nuclear data for Monte Carlo calculations in neutron and proton therapy and description of a new ICRU report committee

M. B. Chadwick, University of California, Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM 87545, USA

Monte Carlo radiation transport calculations of absorbed dose in neutron and proton therapy require high-quality nuclear data. I shall describe recent work performed for the Lawrence Livermore National Laboratory PEREGRINE program, to provide evaluated nuclear cross sections for neutrons and protons

with energies up to 250 MeV incident on biologically-important elements. The evaluated data is determined by using nuclear model calculations which have been benchmarked to cross section measurements - particularly recent results from Louvain-la-Neuve, Los Alamos, UC-Davis, and Faure. In the case of neutron reactions, integral benchmarks against kerma measurements are performed.

The International Commission on Radiation Units and Measures (ICRU) has initiated a new report committee, chaired by Prof. H.H. Barschall, on nuclear data needed for neutron and proton therapy. This activity, which utilizes some of the above data, will be described.

Further descriptions of this work can be found on the World Wide Web at: file://t2.lanl .gov/pub/publications/c12nse/ and file://t2.lanl.gov/pub/publications/o16n14/

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Monte Carlo calculations in neutron therapy

A. Ross, Department of Medical Physics, University of Wisconsin, Madison, WI, USA.

The Monte Carlo transport codes LAHET and MCNP are currently being used to calculate neutron fluence spectra at three facilities; The National Accelerator Center (NAC) in Faure, South Africa, Fermi National Accelerator Laboratory (FNAL) in Batavia IL, and Harper Hospital in Detroit MI. These codes use a combinatorial geometry scheme to define cells in a three-dimensional coordinate system. The calculations start with LAHET transporting the projectiles (either a proton or deuteron pencil beam) through a Be target. The NAC and FNAL facilities produce high energy neutrons using the p+Be reaction, while Harper Hospital uses the d+Be reaction. Other differences include the thickness of Be and the type, size, and composition of the filters and collimators. Calculations of neutron fluence spectra have been made for each facility under a variety of operating conditions (e.g. field size and filter combination). A discussion of the operating parameters of each facility and detailed comparisons of the calculated fluence spectra will be presented. The calculations of the NAC spectra will be compared the recent fluence measurements by Jones et al. Kerma spectra and absorbed dose calculations for each facility will also be presented and compared to measured values.

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Modeling of proton treatment nozzles with the LAHET Monte Carlo code.

J. V. Siebers and M. M. Traynor, Loma Linda University Medical Center

The LAHET Monte Carlo radiation transport code has been used to model proton beam transport through the Loma Linda proton therapy beam lines. Both primary protons and nuclear secondaries were included in the transport. Particle straggling was evaluated with both the LAHET range straggling routines, and using the Landau-Vavilov energy straggling routines from GEANT.

Proton beam transport was initiated after the last bending magnet but before the nozzle SEM foils. Transmission ion-chambers were modeled as material slabs located at the detector location, while the multi-wire ion chamber was modeled in detail. Beam-line apertures and scattering foils were also modeled in detail. The range modulator wheel was modeled as a sequence of pie-piece shaped slabs centered on the beam center-line. To eliminate the spatial dependence of the proton beam exit energy, particle phase space coordinates were rotated by a random angle about the beam center-line after the modulator wheel.

Calculated depth dose and lateral profiles agree well with measurements. A comparison between use of the default LAHET range straggling routines and the Landau-Vavilov energy-straggling routines of GEANT shows that energy-straggling improves agreement between measured and computed depth dose profiles.

LAHET output is being interfaced to the PEREGRINE treatment planning Monte Carlo by providing the phase space coordinates of particles exiting the final beam line transmission ionization chamber. These are then evaluated to determine phase space distributions that PEREGRINE can perform its source sampling on.

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Characterization of particle therapy radiation sources for use with PEREGRINE, the all particle Monte Carlo dose calculation code

L. J. Cox[1], C. L. Hartmann Siantar[1], A. E. Schach von Wittenau[1], J. V. Siebers[2], M. Traynor[2], [1]Lawrence Livermore National Laboratory, [2]Loma Linda University Medical Center

PEREGRINE is a data driven, All Particle Monte Carlo radiation transport code that can calculate 3D dose distributions from most types of clinical radiation sources. It is designed to be used within existing treatment planning programs as the dose calculation engine. PEREGRINE uses the best available nuclear and atomic databases for particle interaction cross sections. It also requires the input of source characterization data to simulate the incident radiation.

Photon, Electron, Neutron and Proton sources can be defined as the primary radiation sources. Source data can be derived from measurements of source spectra and/or beamline modeling studies. The PEREGRINE source model and the derivation of source parameters from Monte Carlo beam line modeling will be discussed.

A PEREGRINE model of a 250 MeV doubly scattered proton beam (LLUMC Gantry 3) has been derived from LAHET calculations. It will be presented as the model on which to build other particle therapy source definitions for PEREGRINE. Preliminary depth-dose and profile calculations will be presented and compared to measurements.

Sample calculations will also be shown for idealized neutron sources. Comparisons will be made between neutron-only calculations and coupled neutron, secondary charged particle and photon calculations. Also discussed will be the state of the available databases for nuclear and atomic interations. PEREGRINE currently used the data derived from ENDL, ECPL and EGDL for particle energies less than 20 MeV and the recently created evaluated database PCSL for particle energies up to 250 MeV. The need to extend PCSL to more isotopes for proper beamline modeling will be addressed.

This work was performed under the auspices of the U.S. Department of Energy by the Lawrence Livermore National Laboratory under contract number W-7405-ENG-48.

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PROTOX - a proposal to develop high energy proton beam radiotherapy in Oxford, U.K.

D.J. Cole[1], H. Weatherburn[1], G. Walker[2] and P. Williams[2]. [1]Dept. Clinical Oncology, Oxford Radcliffe Hospital, Headington, Oxford, OX3 7LJ, U.K., [2]Rutherford Appleton Laboratory, Chilton, Didcot, Oxon, OX11 0QX, U.K.

In 1995 the Department of Clinical Oncology, Oxford Radcliffe Hospital (ORH) and the Rutherford Appleton Laboratory (RAL) agreed to collaborate to develop a proton radiotherapy facility (PROTOX), using the existing 800 MeV proton beam at RAL.

A variable 70 - 250 MeV treatment beam will be extracted from the RAL synchrotron and delivered into an existing radiation-protected hall which will accommodate three treatment rooms each with isocentric gantries to deliver conformal proton therapy using the spot scanning technique.

This facility will provide the first high energy proton radiotherapy centre in the UK for the treatment of chordomas and chondrosarcomas of the base of skull and cervical spine. This technique has been shown to improve progression-free survival in these rare tumours.

The principle tumour site to be investigated with this project will be early prostate cancer. Conventional photon radiotherapy often fails to eradicate the primary disease and it may be that dose escalation to 75 - 80 Gy, which is achievable with conformal proton therapy will substantially improve local control without any increase in normal tissue effects. Randomized controlled clinical trials comparing conformal proton therapy with state of the art photon therapy will be performed to determine whether the disease-free and overall survival can be improved with proton therapy.

There will be programmes for studying proton radiobiology, dosimetry, target definition and tumour response.

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Construction of the NPTC equipment - status report and recent results

S. Laycock and Y. Jongen, IBA, Louvain-la-Neuve, Belgium

As is well known in the protontherapy community, IBA is providing the protontherapy equipment for the North-eastern Proton Therapy Center (NPTC). Since the contract signature in April 1994, IBA together with its team members, General Atomics and Sumitomo Heavy Industries, have completed most of the design and have commenced fabrication of the equipment.

The cyclotron magnet is fully mapped and shimmed, an overview of the mapping and beam dynamics calculations together with the expected extraction efficiency shall be given. The results of the ion source bench tests, showing its good linearity, low noise and rapid switch on and switch off, shall be presented. We are now in the process of installing the vacuum system and starting up the RF.

The beam transport system together with its instrumentation is fully designed with the magnets in fabrication. The gantries are fully designed and a subcontract is expected to be let around the time of the PTCOG meeting. The design of the nozzles approaches completion. Two special 6 axis patient positioners are being designed. The architecture of the control system and safety system is completed.

An overview of the system design and progress shall be given.

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Status of the TERA project

M. Krengli, Massachusetts General Hospital, Boston, USA and Fondazione TERA, Novara, Italy

The TERA project, launched in Italy in 1991 with the aim to introduce hadrontherapy in Italy and treat patients with protons and light ions, is now a collaboration of about 150 physicists, physicians and engineers. It is financed by the TERA Foundation, INFN (National Institute for Nuclear Physics), and ISS (Istituto Superiore di Sanita')It is basically organized on three lines of activity:

- construction of a National Centre for Oncological Hadrontherapy (CNAO), equipped with a synchrotron to accelerate protons and ions and capable of treating more than 1,000 patients a year;
- construction of a certain number of Protontherapy Centres, each equipped with proton accelerator of small dimensions (Compact Accelerator Project, PACO) , possible cheap, and capable of treating about 200-300 patients a year;
- creation of a network (Rete Italiana Trattamenti Adroterapici, RITA), connecting the CNAO and the Protontherapy Centres to public and private hospitals in Italy and abroad.

The initial project of the **CNAO**, realized with the collaboration of National Institute of Nuclear Physics (INFN) and CERN (Geneva), is collected in the Blue Book edited by the INFN National Laboratories in Frascati. During the last months this project has been reviewed and has been decided that the facility will be realized in three steps:

- installation of a synchrotron for protons and ions and three treatment rooms for protontherapy: one equipped with gantry and two with fixed beams for eye and other treatments; this facility will be capable of treating about 600 patients a year;
- building of two other treatment rooms equipped with gantry, to treat more than 1,000 patients a year;
- installation of the injector and the equipment to treat patients with carbon ions.

The cost of the first step is about 85.000 millions lire (about 60 M$) and will be covered by public and private funds. The construction is planned to start in 1998 and should end in 2002. The CNAO will be realized in Milan close to the European Institut of Oncology (IEO), directed by Prof. U. Veronesi, where a few members of the TERA Group are already working. The most important scientific and medical institutions in Milan are interested in this project and a collaboration is being established with the Policlinico (Faculty of Medicine of the University), the Neurologic Institut "Besta", the Hospital "San Matteo" in Pavia, the Foundation "Clinica del Lavoro" in Pavia, and the Politecnico (Faculty of Engineering of the University).

For the **Compact Accelerator Project (PACO)** four different machines have been studied and compared: a high field pulsed proton synchrotron, a weak-focusing proton synchrotron, a superconducting cyclotron, and a linear accelerator. The most interesting solutions from the technical and financial point of view are the superconducting cyclotron and the linac accelerator. In December 1995 the ISS in Rome, which is in charge of the building of a prototype, choose the linac accelerator. A 3Ghz Linac will be realized in two steps: a first part of 70 MeV for eye treatments and a second part until 200 MeV for deep tumors. Funds have been allocated by ISS.

The **network project (RITA)** is under development: a few italian centres of the TERA collaboration are connected and a software to exchange information and images using World Wide Web has been tested. In particular the "Laboratori Nazionali del Sud" of INFN in Catania (Sicily) has been connected to the network, in view of the trasformation of the superconducting cyclotron (which is running) in a facility to produce proton beam for the therapy of eye melanoma (Progetto Catana). The network is very

important in order to optimize the access of the patients and permit the exchange of information between the members of a national community of physicians and health physicists, thus contributing to the development of the clinical research and to the definition of treatment protocols.

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The proton therapy partnership in the centre of italy.

R. Santoni[1], M. Bucciolini[1], N. Taccetti[2] and G. Biti[1], [1]Radiation Therapy Department, University of Florence, V.le Morgagni 85, 50134 Firenze, Italy and I.N.F.N., [2]Physics Department, University of Florence, Largo E. Fermi 2, 50100 Firenze, Italy and I.N.F.N.

A project for a new proton therapy facility, in the centre of Italy, has been developed and it is based on a partnership among five Universities (Firenze, Bologna, Pisa, Siena and Perugia) as well as the corresponding Hospitals and Regional Governments of Toscana, Emilia Romagna and Umbria. The total population living in this central area of our Country is about ten millions of people. The need for a new proton facility in the Centre of Italy is based on the number of patients usually referred to the Radiation Oncology Departments in this area and tumors site candidate for Proton Therapy.

Tumors which might benefit from proton treatments have been classified into four categories:
A - tumors characterised by closeness to highly critical organs;
B - tumors characterised 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 all over the Country. Out of these more than two thousand live in the centre of Italy.

Minimal requirements for facility have been established and presented during PTCOG XXIII in Cape Town. 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. The medical staff, actually working at the University and Hospital Departments, will be in charge of the clinical activities at the new proton therapy Centre; 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. 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 estimation has been done considering the high complexity of a proton treatment, the costs for the staff, the medications, the amortisation of the equipment and the administration and janitor. In the present estimation telephone, heating and cooling, building amortisation and maintenance and electrical consumption of equipment 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 be 1000 after 5 or 6 years of full clinical activity (based on the assumption that one Linac may treat about 300 - 350 new patients a year and may be compared to a Proton treatment room) 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, amortisation of the overall expenses should be

possible within 10 years. The general organisation of Project is presented as well the minimal clinical and physical requirements for the facility.

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Progress report on HIMAC Facility

K. Kawachi, Y. Sato, S. Yamada, T. Kanai, M. Endo, E. Takada, T. Murakami, A. Kitagawa, M. Kumada, M. Kanazawa, K. Noda, M. Torikoshi, S. Minohara, N. Miyahara, N. Matsufuji, H. I. Koyama, H. Tomura, Y. Futami, J. Yoshizawa, S. Kohda, H. Ogawa, A. Itano, A. Higashi and N. Araki, National Institute of Radiological Sciences, Chiba-shi 263, Japan

Two years have passed since the completion of HIMAC (Heavy Ion Medical Accelerator in Chiba) facility at NIRS (National Institute of Radiological Sciences). During these two years, there have been several improvements of facility and progress of the operational techniques, such as the increasing of highly charged particle beam intensity at ion sources, the progress of beam extraction technique at synchrotron, the reduction of the beam switching time at high energy beam transport system, the improvements of control software at irradiation system, et. al.. These improvements and progress have conferred a great benefit on the users of the HIMAC beams as well as the clinical trials of heavy ion therapy.

The fluctuation of the extracted beam spill was considerably improved by reducing the ripple current of the quadrupole and dipole magnets to the level of sub-ppm.

A gated irradiation technique with respiratory motion has reached to the practical use for treatment. We have adopted a transverse rf field resonated with a horizontal betatron tune, so called “rf knockout extraction”, which is possible to respond quickly to a trigger signal for an irregular respiration. To minimize the irradiation time, a repetition rate of 0.3 Hz and a duty factor of 50 % was selected as an operational pattern of synchrotron. When the beam off signal is generated during the beam extraction, the residual beam in synchrotron is aborted by deceleration of the beam.

3-D irradiation technique using a broad beam is still under developing. A ball shaped target of 7 cm in diameter in water phantom was irradiated three dimensionally with this technique. It is found that the total system including the wedge type absorber and multileaf collimator was satisfactorily controlled, and quite reasonable dose distribution and uniformity were obtained from this experiment. However, we have to develop a special treatment planning system for the practical use at the next step.

The following HIMAC up-grade and technical improvements are also under going:

1. An ECR ion source of 18 GHz was developed for the purpose of heavier particle acceleration.
2. We succeeded in the time-sharing acceleration at injectors. Now, we are preparing to deliver different ions to the different beam lines or rooms, simultaneously.
3. The construction of the secondary beam lines has been started.

Furthermore, we are intensively studying the developments of a junction line between upper and lower rings, and a synchrotron operation by a storage-ring mode.

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Proton Therapy in Moscow: the State-of-the-Art

N. N. Alexeev, S.I. Blokhin, V. M. Breev, V. S. Khoroshkov, E. I. Minakova, Institute of Theoretical and Experimental Physics, Moscow, Russia

Routine proton irradiation at ITEP PTF resulted in total 2800 patients treated by 1996. Only two of three procedure rooms operated in 1995. The future of hospital-based multichannel PTF with dedicated accelerator has been intensively discussed with Moscow authorities. Moscow Oncological Hospital #62 situated 15 km far from Moscow was considered to accommodate the facility. The Moscow Government Decision is expected this summer/fall.

H- ion acceleration test has been carried out at ITEP synchrotron. H- ions were preaccelerated up to 700 KeV, 3 mA beam current. It is planned to get 200 Mev internal beam by the end of the year.

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The hadron radiotherapy centre in Krakow - a project based on 20 years of clinical experience with fast neutrons

M. P. R. Waligorski[1,2], P. Olko[2], J. F. Skolyszewski[1], A. Budzanowski[2], [1]Centre of Oncology - M. Sklodowska-Curie Memorial Institute, ul. Garncarska 11, 30-115 Krakow, [2]The Henryk Niewodnicza ski Institute of Nuclear Physics, ul. Radzikowskiego 152, PL-31342 Krakow, Poland

The aim of the Project is to establish in Krakow a modern centre of radiotherapy which would exploit beams of protons and neutrons (i.e. hadrons) from the AIC-144 isochronous cyclotron of the Institute of Nuclear Physics in Krakow, producing 60 MeV proton and 30 MeV deuteron beams. The Centre of Hadron Radiotherapy created as a result of this Project would be the only centre in Poland in which clinical work in this area would be carried out. This centre would satisfy national needs for treating ocular melanoma and clinically indicated fast neutron radiotherapy, and produce selected medical radioisotopes. The Centre would also offer research and training opportunities for about 50 physicians, physicists, biologists and engineers and allow them to actively develop modern techniques of treating cancer in close cooperation with laboratories abroad. We estimate that a sum of about 4M US$, invested over a period of four years into the present infrastructure of at least the same value, would allow us to install and adjust the AIC-144 cyclotron at the Institute of Nuclear Physics in Krakow, to equip the proton ocular therapy and fast neutron radiotherapy facilities, and to partially support the necessary research work in this area. We plan to treat about 300 patients a year and to produce small quantities of selected medical radioisotopes. Under our current funding of about 0.3M US$ from the National Committee for Scientific Research, we are now installing the AIC-144 cyclotron. This project is carried out in collaboration with the Jagiellonian University Department of Ophthalmology of the Collegium Medicum and the Institute of Molecular Biology, and with the Department of Physics and Nuclear Techniques of the University of Mining and Metallurgy (AGH) in Krakow. We believe that establishment of the Hadron Radiotherapy Centre at the Institute of Nuclear Physics in Krakow is justified by the many years' clinical and research experience of the teams engaged in this Project and especially by the fact that for the past twenty years neutron radiotherapy and ocular brachytherapy have been carried out in Krakow, that the main accelerator infrastructure already exists, significantly easing the financial burden of creating this Centre, and that the siting of the Institute of Nuclear Physics in Krakow is convenient for out-patient treatment.

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Intercomparisons of proton clinical beams in Russia in light of the Loma Linda intercomparisons.

D. Nichiporov[1], V. Kostjuchenko[1], A. Molokanov[2], J. Karlin[3], and S. Vatnitsky[4], [1]Institute for Theoretical and Experimental Physics, Moscow, Russia. [2]Joint Institute for Nuclear Research, Dubna, Russia. [3]Leningrad Institute for Nuclear Research, St. Petersberg, Russia. [4]Loma Linda University Medical Center, Loma Linda, CA, USA.

In April 1995, thirteen proton therapy centers of ten countries participated in an international proton dosimetry intercomparison held at the Loma Linda University Medical Center. Neither of the three Russian proton clinical facilities - ITEP (a) in Moscow, JINR (b) in Dubna, and LINP (c) in St. Petersburg - had on opportunity to join this project due to economical and technical reasons. The issue of accuracy of absolute dose measurements has, however, received serious attention in Russia: absolute dosimetry intercomparisons of dose were conducted in 1981 and in 1992-93. An overview of the latest results was reported at the PTCOG XX meeting in Chester, UK.

Unfortunately, the two sets of intercomparison data - for the Russian and the Loma Linda groups - could not be compared because no center participated in both of the projects. After the Dubna specialists took part in an additional dose measurement project completed at the National Accelerator Centre in South Africa in October 1995, and employing the ITEP/NIST (d) intercomparison data it became possible to establish a comparison chain between the Russian and the Loma Linda sets of the intercomparison results. The ratios of doses measured at the Russian centers to the Loma Linda mean dose are given in the table below.

Institution	Irradiation Geometry	
	SOBP	Plateau (Unmodulated)
ITEP, Moscow	1.010	1.019
JINR, Dubna	1.022	1.021
LINP, St. Petersburg	-	0.971

Results of the indirect Russia/Loma Linda comparison show that (i) absolute dosimetry at all three of the Russian institutions meet the present requirements formulated in international dosimetry protocols (1,2,3), (ii) field detectors used in dose measurements introduce no significant errors into the final results, (iii) the use, when possible, of common physical factors for determination of dose is highly desirable, (iv) the comparison results confirm the viability of the ITEP standard dosimetry method based on the $^{12}C(p,pn)^{11}C$ monitor reaction.

(a) Institute for Theoretical and Experimental Physics
(b) Joint Institute for Nuclear Research
(c) Leningrad Institute for Nuclear Physics
(d) National Institute of Standards and Technology, Gaithersburg, USA

References: [1]. AAPM Report No. 16. Protocol for Heavy Charged-particle Therapy Beam Dosimetry. AAPM New York, 1986. [2]. S. Vynckier, D.E. Bonnett, and D.T.L. Jones Code of Practice for Clinical Proton Dosimetry. Radiotherapy and Oncology, vol. 20, pp 53-63, 1991. [3]. S. Vynckier, D.E. Bonnett, and D.T.L. Jones Supplement to the Code of Practice for Clinical Proton Dosimetry. Radiotherapy and Oncology, vol. 32, pp 174-179, 1994.

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Comparative treatment planning: age related maculopathy

A. Mazal, L. Schwarz, F. Lacroix, H. Mammar, S. Delacroix, L. Desjardins, J.L. Habrand, Centre Protontherapie d'Orsay, Orsay, France

A comparison of different dose distributions with beams of photons, electrons and protons are presented for the treatment of age related maculopathies. While the relative dose distribution is logically better for proton beams, the real discussion should be orientated towards the problem of absolute dose and fractionation. There are also some practical considerations (the patient set-up could be even easier with proton beams!) and epidemiological aspects to be taken into account, as only a few proton facilities are available and a large population is affected. The impact of such a choice on the use of proton facilities and on the national health system should be carefully evaluated.

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A water calorimeter for high-energy protons

H. J. Brede[1], J. Heese[2], O. Hecker[1], R. Hollnagel[1], H. Kluge[2], and M. Morgenstern[2], [1]Physikalisch-Technische Bundesanstalt (PTB), Bundesallee 100, D-38116 Braunschweig, Germany, [2]Hahn-Meitner-Institut (HMI), Glienicker Str. 100, D-14109 Berlin, Germany

The PTB is developing a water calorimeter as a primary standard for absorbed dose from protons with energies above 60 MeV. At present, two main sources of uncertainty limit the accuracy of the absorbed dose determination in water: Firstly the heat defect of the protons in water, and secondly the temperature measurement in the water absorber.

An especially designed calorimeter regulates the temperature gradient in the water absorber and allows the heat defect of the water to be determined. The linear energy transfer dependence of the heat defect in water, the calorimeter design, measurement methods, and preliminary calculations of the calorimeter's time-dependent response will be presented.

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Summary of the ICRU proton dosimetry report

L.J. Verhey[1] and D W. Miller[2], [1]University of California San Francisco, Dept. of Radiation Oncology, L-75 Box 0226 CA 94143-0226, [2]Loma Linda University Medical Center, Dept. of Radiation Medicine, 11234 Anderson St., Loma Linda, CA 92354.

At the annual meeting of the ICRU Commission held in Remsheid, Germany in September, Part I of the Report on Clinical Proton Dosimetry was provisionally accepted for publication. Many modifications to the earlier draft were discussed and approved at that meeting and the final acceptance depends only on verification that these modifications were included. The modified Report was submitted to the ICRU reviewers in January.

The ICRU Proton Dosimetry Report is intended to promote uniformity of standards that will provide a basis for world-wide comparison of clinical results and allow the development of meaningful inter-institutional clinical trials. Part I includes a description of the interaction of protons with matter, methods of beam production, clinical beam characteristics, methods for beam monitoring and specific recommendations for dose calibration. Part II will deal with the influence of patient shape and tissue heterogeneity on dose distribution, treatment planning considerations, microdosimetry and relative

radiological biological effectiveness of protons compared to photons. The Report Committee for Part II has been appointed and is now beginning their deliberations.

The Part I Report makes a number of recommendations which can be summarized as follows:

1. A standard A-150 TE or graphite thimble ionization chamber having a Co-60 calibration factor is the recommended reference dosimeter for proton dosimetry. The chamber should be open and filled with ambient air and sized appropriately for the size of the proton beam. Acceptable methods of Co-60 calibration include those based on exposure, on air kerma and on absorbed dose to water.

2. Recommended values of dosimetric parameters are included in the Report. Recommended stopping powers for protons are from ICRU Report 49. The recommended w-value for protons in air is 34.8 J/C. Chamber-specific factors for Co-60 irradiations are included.

3. When possible, a water, graphite or A-150 calorimeter should be used to confirm the proton calibration factor calculated for the reference chamber. Thermal defect corrections are discussed in the Report.

4. Fluence-based calibration methods, such as those based on the Faraday Cup are recommended as a secondary method only when the energy and effective area of the beam can be accurately determined or calculated. The uncertainties of such methods are thought to be larger than those associated with ionization chambers or calorimeters.

5. The proton absorbed dose should be specified in water. Although not of critical importance, it is recommended that water or other tissue-like phantoms be used for measurements.

6. Measurements should be made in a phantom at a point where the dose if fairly uniform. In general, this should be at the center of the SOBP. Phantoms should have transverse dimensions significantly larger than the beam cross-section.

7. Efforts should be made to intercompare dosimetry between institutions. This can be through direct intercomparison with ionization chambers, indirectly through the serial use of traveling calorimeters, or even mailed integrating dosimeters. When possible, such dosimetric intercomparisons should be combined with microdosimetric and radiobiological intercomparisons.

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Planning and implementing a Swiss radio-oncology network

A Lomax[1], O Ratib[2], R Miralbell[3], T Boehringer[1], L Cozzi[4], P-A Tercier[5], [1]Department of Radiation Medicine, Paul Scherrer Institute. [2]Department of Hospital Informatics, University Hospital of Geneva. [3]Department of Radio-Oncology, University Hospital of Geneva. [4]Department of Radiotherapy and Nuclear Medicine, San Giovanni Hospital, Bellinzona.s [5]Department of Radio-Oncology, University Hospital of Lausanne.

Commissioning of the PSI gantry for proton therapy will shortly be completed and it is expected that the first patients will be treated in late spring. In order to make the facility, which is not hospital based, more accessible to potential users, a network for the exchange of patient data relating to radiotherapy is being developed. The initial aim of this is to allow the radio-oncology centers of the Swiss hospitals to remotely evaluate the potential of proton therapy for individual patients through the comparison of treatment plans. As this project requires the eventual exchange of many data types between a number of commercial treatment planning systems (TPS's), it has been divided into three phases.

1. Exchange of patient CT and volumes of interest (VOI's).
2. Export (and import) of dose matrices from and to treatment planning systems.
3. Complete exchange of all radiotherapy data types (including DVHs, beam geometry etc)

The PAPYRUS data exchange protocol has been selected for the phase1 development. This is fully DICOM 3.0 compatible, but has an extension which allows for the polygonal representation of VOIs within the same data structure. In cooperation with treatment planning manufacturers, a common software package is being developed for the conversion of this format to the local TPS formats. Data will be transferred initially using FTP with the view to providing a more secure network in the future. On completion of phase 1, it will be possible to exchange the minimum data required for plans to be performed at both the referring clinic and PSI. For phase 2, we are proposing to represent dose matrices within the same PAPYRUS framework, and are currently in negotiations with the TPS manufacturers to determine the feasability of this approach for the import and export of dose matrix data.

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Positron beam therapy

F. Becchetti[1], D.Litzenberg[1], M. Skalsey[1] and R. Ten Haken[2], [1]Dept. of Physics, Univ. of Michigan, Ann Arbor, MI, [2]Dept. of Radiation Oncology, Univ. of Michigan, Ann Arbor, MI

We and others have developed on-line PET imaging systems for deducing the dose distribution of proton, heavy-ion, ?-ray electron radio-beams. By imaging the secondary production of short-lived positron emitting nuclear products such as ^{15}O and ^{11}C (see e.g. our contributed abstract to this meeting as well as D. Litzenberg et al. IEEE-NS 43, No. 1 (Feb. 1996) pp. 154-158 and references cited there). In addition to the low production yields for this type of imaging, hence limited statistics for accurate depth profiling there is the difficulty of correlating the PET image with the actual dose profile of the primary beam in tissue. Thus, positron-emitting secondary ion beams such as ^{11}C have been proposed and tested as an alternative to using stable ion beams since these beams can be monitored via PET more directly. In addition to the fragmentation problem intrinsic in using any heavy-ion beam for radiotherapy, the cost of a facility to produce ^{11}C or a similar beam (even protons) is a major limitation to wide-spread clinical use. In contrast, at least from the cost of the accelerator and gantries needed, it appears feasible to produce positron beams with sufficient intensity and energy (E = 20 to 50 MeV) to be useful for certain types of radiotherapy and which could be imaged directly in vivo using an on-line PET system. As with electron-beam therapy, multiple scattering and range-straggle are a limitation, but it appears that suitable, externally-applied magnetic fields could possibly reduce these effects.

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Robotic approaches for patient positioning systems

A. Mazal, R. Ferrand, J. C. Rosenwald, J. L. Habrand and F. Lafortune, Centre Protontherapie d'Orsay, Orsay, France

A very high reproducibility in patient positioning is obtained in proton treatments based on specific contention systems, a radiological control using fiducial markers or anatomical information and DRRs, and patient positioning systems of different technologies. At CPO, we have been using a robotic approach for the positioning of ophthalmic treatments since 1991. More recently, the same system has been used for the treatment of intracranial targets (seated patient). For the second treatment room (couch approach), different proposals are under evaluation, including the modification of conventional tables for radiotherapy, industrial robotics or specific prototypes. These proposals and our specific choice will be presented.

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Study of a small proton beam field

Y. Takada, Institute of Applied Physics, University of Tsukuba

As the proton field shrinks in size, its specific depth-dose distributions (Bragg curve) change due to the multiple Coulomb scattering in a specimen and the finite width of initial beam divergence. The peak-to-plateau ratio decreases and lateral region of the same Bragg curves disappears. We usually use a collimator to generate a small beam from a large-size beam. In that case, the surface scattering at the collimator partially contribute the dose distribution as the aperture of the collimator gets smaller. These facts affect two aspects of proton therapy. The one is the discrepancy between results of proton treatment planning using the large beam algorithm and real dose distribution for small target. The other is related to the mixing of different proton paths. If there is a prominent imhomogeneity in the target region, or there is a rapid change of integrated electron density along the beam path in the adjacent region of the target, such mixing of different proton paths affects the depth-dose distributions even if the target size is not so small. So it is important to consider these effects of finite initial beam phase and the multiple Coulomb scattering in the target in order to understand the proton dose distribution. We measured the depth-dose distributions and lateral distributions of small-size proton beam collimated by the 67 mm-long brass collimator with an aperture diameter of 20 mm. We measured the dose distributions using the Therados water-phantom detector. A Monte Carlo program has been developed to calculate the proton dose distribution in water. It takes the Multiple Coulomb scattering effects, energy straggling effect, the effect of nuclear target fragmentation to the dose, the surface scattering effect of the collimator, into account. The initial beam condition is also calculated by the Monte Carlo methods. The measured results was compared with the calculations. The measured results are partially reproduced by the calculations at present. Since our present model of calculation is not so precise, there remains the room for improvement. We also measured the depth-dose distributions of the model phantom to demonstrate the effects of the mixing of the different proton paths. The phantom is made from the Mixed-DP which is a mixture of wax and pine resin equivalent to human muscle to diagnostic X-ray. The 54-mm-thick Mixed-DP has a 40-mm-long cylindrical hole of 20 mm in diameter. Results of measurements showed the prominent mixing of different paths. These studies will be useful to obtain the kernel function of the pencil beam algorithm and to evaluate the results of various proton treatment planning.

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A BNCT facility based on an ESQ-accelerator

B. Ludewigt, W. T. Chu, and R. Donahue, E. O. Lawrence Berkeley National Laboratory, University of California

An epithermal neutron beam suitable for BNCT can be produced via the ^{7}Li(p,n) reaction. Very high current proton beams can be produced by an electrostatic quadrupole (ESQ) accelerator. LBNL and UCSF have formed a collaboration including other West Coast medical centers for the pursuit of a BNCT research program and the development of an accelerator-based BNCT facility. Work has began towards the conversion of an existing ion injector located at the Berkeley Lab into an ESQ accelerator by replacing the accelerator column and upgrading the power supply. Neutron production and moderator and filter assemblies were modeled in order to determine the useful epithermal neutron flux as a function of the proton beam energy. The results of three-dimensional Monte Carlo simulations suggest that the optimum proton energy for BNCT is about 2.3 MeV, significantly less than the 2.5 MeV most often found in the literature. The converted injector will be able to produce a 7.5 mA proton beam at a maximum energy of 2.5 MeV. The lithium target requires aggressive cooling because of the total heatload of about 20 kW and the low melting point of Li-metal. An engineering analysis indicates that such a target can be water cooled. The preliminary design is an adaptation of the microchannel absorber concept which provides for the convective cooling of an aluminum substrate coated by a thin ^{7}Li-layer. A finite element analysis showed that the temperature of the ^{7}Li-surface can be kept far below the melting point. Preliminary results from Monte Carlo simulations of neutron production, moderation, and filtering indicate that a 7.5 mA proton beam will produce a useful neutron flux of about 1 x 10^{9} $n_{epi}/(cm^{2}$ s). The ultimate goal of the research effort is the development of technology for BNCT treatment centers at hospitals based on ESQ-accelerators which can deliver up to 100 mA proton beams.

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A novel 2.5 MeV D-D neutron source

G. H. Miley, Fusion Studies Laboratory, University of Illinois, 100 NEL, 103 South Goodwin Avenue, Urbana, IL 61801-2984

Inertial electrostatic confinement (IEC) methods have been applied to develop a novel neutron source, whereby fusion reactions occur from accelerated deuterium ions interacting with a deuterium plasma target.[1] Present devices offer 10^{6} - 10^{7} 2.5-MeV D-D n/s during steady-state operation.[2] Consequently, the IEC neutron source is currently competitive with Cf-252 sources, but offers a number of advantages, including an on-off capability, longer lifetime without deterioration in strength, and minimum radioactivity involvement. Thus the IEC provides an excellent laboratory neutron source for a variety of clinical research projects. Several companies are currently planning manufacturing facilities to produce a commercial IEC source, although some research laboratories have already fabricated their own units.

Two basic geometries have been developed - a spherical unit[1] and a cylindrical unit.[3] Spherical units, having vacuum vessel diameters ranging from 15 cm to 60 cm, have been operated, while current cylindrical units are approximately 12 cm in diameter by 1 m long, although much smaller cylindrical designs are under development. Basically, the spherical unit provides a “point” source of neutrons, while the cylindrical device provides a line source. The principle of operation of the two devices is quite similar

- either a grid or hollow tube cathode is employed to produce a plasma discharge and simultaneously extract and accelerate ions towards either a small spherical central plasma core or a linear core region, where neutron-producing fusion reactions occur.

Research is currently underway to increase the neutron source strength to 10^8 - 10^9 2.5-MeV n/s, and to provide a 14-MeV proton source at the same strength. If successful, these upgraded devices will greatly expand the utility of the IEC. Both will employ pulsed power technology to take advantage of the fact that the reaction rate scales strongly with current. A large peak pulse current with repetitive pulsing provides a high time-averaged reaction rate while minimizing power input.[4] Even larger units have been envisioned that would involve larger power supplies and carefully designed active cooling systems to remove waste heat. A design study for such a unit has been carried out to examine its application to boron neutron capture therapy (BNCT).[5] Assuming the technology can be successfully developed, the availability of such units would enable siting of dedicated local clinical facilities for BNCT, as opposed to the restricting this therapy to centralized fission reactor facilities.

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Simultaneous Macro and Micro dosimetry for Boron Neutron Capture Therapy with a MOSFET probe.

A. B. Rosenfeld[1], G. I. Kaplan[1], M. G. Carolan[1], B. J. Allen[2], C. Kota[3], M. Yudelev[3], R. L. Maughan[3], J. N. Mathur[1], [1]Department of Physics, University of Wollongong, Wollongong, NSW, 2522, Australia, [2]St George Hospital Cancer Care Centre, Kogarah, NSW, 2517, Australia, [3]Gershenson Radiation Oncology Centre, Harper Hospital, Wayne State University, Michigan 48201, USA.

The measurement of the average absorbed dose provides an inadequate characterisation of the biological effect of radiation in a mixed gamma-neutron radiation field, for short range radiation such as immunotherapy with alpha emitting isotopes or for boron neutron capture therapy (BNCT). In these cases the distribution of energies deposited on the micron scale of typical cell volumes is the most important characteristic of such radiation fields.

Metal-oxide-semiconductor structures (MOSFETs) are quite suitable for the application to measurements of average integral absorbed dose due to their very small sensitive volume of SiO_2 and the simplicity of readout based on threshold voltage changes [1]. The usefulness of semiconductor p-i-n and MOSFET dosimeters for dosimetry in BNCT has already been demonstrated by us [2,3]. The proposed new approach to MOSFET dosimetry uses simultaneous measurement of integral absorbed dose in the SiO_2 layer and on-line measurement of energy deposited in the small micron volumes of the source and drain p-n junctions. The former is determined by measuring the change in threshold voltage of the MOSFET and the latter is recorded using traditional on-line pulse amplitude analysis.

MOSFETs with a thick gate oxide were investigated. MOSFET design was suitable for the use of two lids only to obtain high sensitivity integral mode as well as effective count mode . The pulse height distribution of charges from reversed biased source of MOSFET and threshold shift were measured under irradiation from Co-60, Sr-90 and alpha particles from Am-241 (5.5 MeV) and Po-210 (5.3 MeV). The energy spectrum showed a broad peak in count mode, corresponding to the deposited energy from alpha particles in the micron size depletion volume of the source of p-n junction. There was very little response from electrons and gamma photons due to low interaction probability with this volume. However, although photons and electrons do not contribute to the pulse height spectra they do make a strong contribution to the threshold shift due to ionization and charge trapping (not collection) in the SiO2 layer, giving a contribution to the absorbed dose. The integral response of MOSFET to alpha particles with the flux expected for BNCT was linear up to 10E8 particles/cm^2. All these properties suggest a new and promising approach to macro-micro dosimetry with paired MOSFETs (one covered with B-10) in BNCT.

The advantages of such a dosimeter includes its small size, which avoids perturbation of the radiation field within the phantom, and the ability to measure the LET spectrum and dose on line as well as modelling the effect of the spatial distribution of B-10 relative to the cell when exposed to alpha and Li-7 radiation during BNCT. Using these detectors and fast pulse readout we can model the effect of cell size on the LET spectrum just changing low voltage on the detector. The experimental data on deposited energies from alpha particles of Am-241 for different size of silicon cells will be presented. The MOSFETs can also be used on-line at full reactor power for such measurements.

This new approach was initially tested using the MOSFET probes with and without B-10 converters in a water phantom exposed to a fast neutron therapy beam at Harper Hospital, Wayne State University.

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BOPP: Cytotoxicity, pharmacokinetics and intracellular localization in a human glioma cell line

D. Deen[1], J. Afzal[2], E. Blakely[2], A. Bollen[2], D. Callahan[2], W. Chu[2], L. Hu[1], S. Kahl[1] and T. L. Phillips[1,2], [1]University of California, San Francisco, CA, and the [2]Ernest Orlando Lawrence Berkeley National Laboratory, Berkeley, CA.

In preparation for Phase I clinical trials with the boronated protoporphyrin BOPP (Kahl and Koo, J. Chem. Soc. Chem. Commun., 1769, 1990), we have investigated some *in vitro* characteristics of BOPP with a human glioma cell line (SF-767), and the *in vivo* biodistribution of BOPP in a canine model. The SF-767 cell line from the Brain Tumor Research Center Tissue Bank at the University of California, S.F. was derived from a grade 4 malignant glioma (Oredsson et al., Cancer Res. 43:4606,1983). Selective tumor uptake of BOPP has been reported in CBA mice bearing an implanted intracerebral glioma with tumor ratios as high as 400:1 relative to normal brain (Hill et al., Proc. Natl. Acad. Sci. USA 89, 1785, 1992). In collaboration with W. Bauer at INEL we have analyzed boron content to determine BOPP uptake in exponentially growing tumor cells over a range of concentrations including 0.01, 0.05 and 0.1 mM for 24, 48 and 72 hours. We find BOPP uptake appears to saturate within 24 hours, and cytotoxicity studies indicate approximately 50% cell killing with exposure to 0.07 mM BOPP for 24 hours. In studies using the fluorescence microscope, the fluorescence of BOPP allows one to determine the intracellular localization of the compound. Hill et al., 1992 reported discrete localization into perinuclear mitochondria. We also observe discrete BOPP sub-cellular localization, distributed into punctate perinuclear bunches, but our co-localization studies with rhodamine-123 indicate that the BOPP (20 ?g/ml for 32 hours) appears primarily to accumulate in a non-mitochondrial site with adequate proximity to the nucleus for effectiveness in boron neutron capture therapy. The pharmacokinetics, tissue localization and toxicology of BOPP in normal adult male beagle dogs also has been investigated. Three sets of four dogs have been exposed to BOPP (35 mg/kg) for 25 hrs, 79 hrs or 10 days. At the end of the exposure period, tissue specimens from numerous organs were taken for either tissue fixation and embedding for later microscopic examination of ultrastructure or for analysis of boron content. Clinical toxic effects have been mild and transient and have consisted of some vomiting, nausea, and peripheral vasodilation seen as erythema and scleral injection. Boron associated with BOPP appears to be concentrated in the liver, lymphatic tissues and the adrenal glands of canine subjects. Boron levels in the cerebrum, cerebellum, CSF and intraocular fluid remained at or below 1 ?g/g at all time points. Plasma boron pharmacokinetics appear to follow a multicompartment behavior with a long terminal half-life. Clinicopathologic findings during these studies found several significant effects of BOPP administration. Transient increases in white blood cell counts, decreases in red blood cell counts and a mild increase in bilirubin were most consistent among the subjects. Additionally, an increase in the liver enzymes AST and ALT was found in two dogs studied for greater than 79 hours. Preliminary histopathologic examination of livers of these subjects suggest some changes in the morphology of the liver. Supported by the Office of Energy Research, U. S. Department of Energy under contract No. DE-AC03-76SF00098.

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RBE data needed for designing clinical trials with new radiation therapy beams

J. Gueulette, V. Gregoire, S. Vynckier, A. Wambersie and P. Scalliet, UCL-Cliniques Universitaires St-Luc 1200 Bruxelles

In radiation therapy with non-conventional radiation beams, the doses are currently reported in terms of absorbed dose (in Gy) and equivalent (or weighted) photon doses. The equivalent photon doses correspond to the doses which would have been prescribed and/or delivered to the patient with photons and are obtained by multiplying the doses of the concerned radiations by their clinical RBE. RBE not only varies with the type of the radiation and its energy but also with different factors, especially the biological endpoint studied and the dose per fraction (or the fractionation) applied. Moreover, in proton- and heavy ion therapy, the RBE varies with the position in the spread out Bragg peak.

The dose accuracy required in radiotherapy is 3.5%. Therefore it is important to determine the RBEs as accurately as possible since *uncertainties in the RBE values lead to equal uncertainties in the derived equivalent photon doses*. This raises the problem of determining a "reference" RBE, which deals with the choice of the biological endpoints and the irradiation conditions (fractionatian) that are relevant for each particular clinical situation: biological systems based on the study of the late tolerance of healthy tissues at 2 Gy per fraction have been proposed (e.g. lung tolerance in mice evaluated by LD50/180 after Irradiation in 10 fractions). The use of reliable RBE values is one of the essential condition for comparing the clinical results of different radiation qualities.

The problem is particularly crucial when designing *cooperative* trials. Indeed, it is well know that for a given particle and a given nominal energy, the RBE might significantly vary from one centre to another according to the technical characteristics of the beam production and beam delivery. Radiobiological intercomparisons are thus compulsory. They should be performed using a relatively simple biological system able to monitor precisely the variations of the reference RBE. Different high-energy neutron beams and proton beams have been intercompared for the regeneration of the intestinal crypts in mice after single irradiation. This system was found easily exportable and showed its ability to disclose RBE variations as small as 4 - 5%.

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Use of MOSFET gamma dosimeters and silicon P-I-N diode neutron dosimeters for epithermal neutron beam mixed field dosimetry.

M. G. Carolan[1,3], B. J. Allen[1,2], A. B. Rosenfeld[1], J. N. Mathur[1], [1]Department of Physics, University of Wollongong, Wollongong NSW 2500 Australia, [2]St. George Cancer Care Centre, Kogarah NSW 2217 Australia, [3]Illawarra Cancer Care Centre, Wollongong NSW 2500 Australia.

Dose measurements using MOSFET gamma dosimeters and PIN diode neutron dosimeters have been performed in phantoms exposed in the Petten High Flux reactor BNCT epithermal neutron beam and have been reported previously[1]. These measurements made use of MOSFET dosimeters and PIN diode neutron dosimeters as well as epithermal resonance activation foils. Good agreement was found between measured and Monte Carlo calculated thermal neutron fluences in tissue equivalent cylindrical and anthropomorphic head and trunk phantoms. All Monte Carlo dose calculations were done using the Los Alamos MCNP code. Good agreement between experiment and calculation was also observed for PIN diode neutron dose measurements close to the surface of the phantoms. At depth however a systematic

discrepancy was observed with Monte Carlo calculations under estimating the diode and epithermal resonance foil responses and the MOSFET gamma dosimeter response. Further sensitivity calculations on the model have been performed to elucidate these discrepancies.

It was necessary to adjust the hydrogen density in the Monte Carlo models of the phantoms to allow for dehydration of the tissue equivalent gel. When this was done good agreement was obtained between measured and Monte Carlo predicted neutron doses.

To obtain agreement between the calculated gamma dose and the experimental response of the MOSFET detectors it was necessary to determine the neutron response function of the MOSFET by making a detailed MCNP model of the MOSFET TO-18 packaging and the LiF/epoxy neutron cover. Numerous separate MCNP runs were done with neutrons of different energies incident on the MOSFET. In this way an energy dependent neutron response function was derived. When this response function was used to correct the experimental MOSFET gamma response good agreement was observed between MOSFET gamma dose measurements and MCNP calculations.

Our results indicate that MOSFETs and PIN diodes can be useful in validation of Monte Carlo treatment planning systems and mixed radiation dosimetry in general. However, the packaging of the devices has a marked effect on performance. For gamma measurements in neutron fields, particularly epithermal and thermal neutron fields the devices should have minimal iron and nickel encapsulation in order to minimise neutron sensitivity.

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Biological effectiveness of absorbed dose in BNCT and BNCEFNT

C. Kota and R. L. Maughan, Gershenson Radiation Oncology Center, Harper Hospital and Wayne State University, 3990 John R., Detroit, MI, 48201.

The absorbed dose in tissue, in both boron neutron capture therapy (BNCT) and boron neutron capture enhanced fast neutron therapy (BNCEFNT), consists of varying contributions from secondary charged particles of different energies, and hence of different values of biological effectiveness. In the present study, the utility of proportional counter microdosimetric measurements to predict the biological effectiveness of the total absorbed dose has been investigated.

The dual counter microdosimetric technique[1] was used to measure the single event spectra of the absorbed dose. This technique employs two 1/2” LET counters with A150 tissue equivalent walls. The wall of one of the counters has 50 ?g/g of ^{10}B incorporated in it to simulate a tissue containing 50 ?g/g of ^{10}B. Spectra measured with both counters at the point of interest are manipulated to obtain the single event spectra of the individual gamma, neutron and boron neutron capture reaction dose components. The two counters were filled with a propane based tissue equivalent (TE) gas to a pressure of 17 torr to simulate a 0.5 ?m diameter spherical, unit density tissue volume and were operated at a voltage of + 600 volts. Measurements were made in an epithermal neutron beam for BNCT and in a fast neutron beam for BNCEFNT.

The spectra of the individual dose components in the epithermal beam were scaled to the representative fractional dose contributions from these components, in tumor and normal tissue. From these spectra, the event frequency in various microscopic volumes was calculated for each dose

component. Through these calculations, the validity of assuming independent action by these individual components has been investigated. From the single event spectra of the neutron dose component, the possibility of changes in its RBE, due to changes in the neutron energy spectrum has been investigated.

The single event spectra in the neutron beam for BNCEFNT were analyzed using the formalism outlined in the Theory of Dual Radiation Action for calculating the RBE from the single event spectra. RBE values were calculated for the absorbed dose in this beam with and without contribution from the boron reaction. It is found that the RBE of the enhanced dose is very similar to that of the fast neutron dose.

The practical applications of the microdosimetric measurements are discussed.

Reference: [1. Kota C. and Maughan R.L., "A dosimetry system for boron neutron capture therapy based on the dual counter microdosimetric technique," *Bulletin du Cancer/Radiotherapie,* In Press (1995).

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3D treatment planning for 14 MeV- neutrons

R. Schmidt, T. Frenzel, A. Krull, L. Ludemann, T. Matzen, Abteilung Strahlentherapie,
Universitatskrankenhaus Eppendorf, Universitat Hamburg, Germany

Three-dimensional treatment planning is now widely used in radiotherapy with high energy photons. Special tools, for example beam's-eye view (BEV) and dose-volume histograms (DVH) are developed to simulate the shape and position of the beams and to evaluate the dose distribution in the target and the organs at risk. 3D visualization is used to asses the dose distribution with respect to the target, the organs at risk, and anatomical landmarks obtained from CT data.

For the adaptation of 3D treatment planning for neutrons several modifications have to be taken into account:

neutron and photon dose separation
attenuation correction for heterogeneities
kerma correction for heterogeneities
modified inverse square law

For the corrections of heterogeneities can be obtained pixel by pixel from the hounsfield units of the CT slices.

For the application of absorbers the algorithms used in photon treatment planning have to be checked for their validity in neutron therapy.

At our department standard blocks made out of steel are used to reduce the dose to critical organs. The ring model, originally developed for photon treatment, could be modified to be used with neutrons, too. This implies that the neutron dose is separated into its primary and scatter components, arising from concentric rings around the point of interest. A comparison between measurements in a water phantom and corresponding calculations demonstrate the attainable accuracy.

For the DT neutron generator, used for patients treatment at our institution, a commercially available treatment planning system was modified to enable the coplanar calculation of three-dimensional treatment plans for neutrons. The matrices containing the CT-, VoI-, and dose- data are transferred to avisualization system developed at our hospital. This system is used to render the 3D dose matrix together with anatomical data and the regions of interest. The mode of shaded surfaces and transparency simulates a three-dimensional impression of the rendered structures.

A realistic case of a neutron treatment will be used to clarify the different steps of the 3D treatment planning procedure and its implementation into clinical use.

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Musculoskeletal toxicity of neutron-photon therapy for prostate cancer

P. J. Chuba, R. Soulin[1], J. Romero[1], P. Kocheril, M. Yudelev, R. Sharma, R. Maughan, and J. D. Forman, Gershenson Radiation Oncology Center, and Radiology Department[1], Harper Hospital, Karmanos Cancer Institute, Detroit, MI 48201.

Hip stiffness was found to be a common complaint among patients treated with mixed neutron-photon radiation for prostate cancer. Most patients complained of difficulty in shoe-tying or leg-crossing (mild hip stiffness), however some also had pain, limitation of range of motion, or limitation of activity (moderate to severe hip-stiffness). The dose-response relationship and mechanism of this phenomenon were studied for 132 patients treated using five different dose-levels. Neutron doses delivered ranged from 9 Gy to 20 Gy and photon doses ranged from 0 Gy to 38 Gy. The severity of hip stiffness was assessed by using a grading scale. Some hip stiffness (>Grade 0) was observed in 40 out of 132 patients (30%). In 24 patients (18%) this hip stiffness was mild, in 10 patients (7.5%) the hip stiffness was considered moderate, and in 6 patients (4.5%) hip stiffness was found to be severe. The incidence of musculoskeletal toxicity was significantly higher in patients treated with a larger proportion of dose given with neutrons $p = 0.001$). Clinical findings could be correlated with pelvic magnetic resonance imaging (short inversion time recovery sequence images) performed in 18 patients. Dramatically increased signal intensity reflecting muscle edema was observed in the obturator internus, obturator externus, and gluteus medius muscles involved in hip movement. The location of these structures within the pelvis corresponded with the dose distribution of neutron radiation suggesting a direct causal relationship of high LET radiation on muscle damage. By using mixed conformal neutron-photon radiation and limiting the neutron dose to less than 13 Gy, severe musculoskeletal toxicity could be avoided.

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Neutron therapy for glomus tumours, a possible new indication

F. Vernimmen, Dept. of Radiation Oncology, Tygerberg Hospital, Cape Town.

Glomus tumours are slow growing histologically benign tumours arising along the nerves causing clinical signs and symptoms that are a function of the site of origin. For those lesions arising in and around the skull base surgical treatment is technically challenging and usually associated with cranial nerve dysfunction. Irradiation is an well established alternative to surgery and some authors even prefer irradiation as the primary treatment modality. The problem with irradiating these lesions is that they rarely completely disappear on follow-up investigations, although the patients have symptomatic improvement

On the grounds that these tumours are slow growing and the fact that only moderate doses of radiation are needed (45 Gy-50 Gy), the author started investigating the value of neutron therapy for these tumours. The objective is not to achieve better " Control", but to evaluate if these lesions wouldn't shrink quicker or even disappear completely on follow-up investigations.

Up to date three patients have been treated at NAC with neutron therapy. Using 3-dimensional treatment planning a dose of 17 nGy was given in 12 fractions over 4 weeks. One patient has a complete radiologically response after 8 months, One patient is lost to follow-up and the third patient has only recently been treated.

The complete response at 8 months is interesting and it might be worthwhile to further investigate the role of neutron therapy for glomus tumours, because if a high complete radiologically response is observed this would make irradiation an even more acceptable alternative to surgery.

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The lack of benefit of neo-adjuvant hormonal therapy when given in conjunction with mixed neutron-photon irradiation for non-metastatic prostate cancer

P. G. Kocheril, F. Shamsa, J. D. Forman, Barbara Ann Karmanos Cancer Institute, Wayne State University Department of Radiation Oncology, Detroit, Michigan, USA

Background: The only two proven methods in randomized studies of increasing the biochemical and local control in the treatment of prostate cancer with photon irradiation are the addition of neo-adjuvant hormonal therapy to photon irradiation or the use of neutron irradiation.

Purpose: To evaluate for the presence of a additive benefit when combining neo-adjuvant hormonal therapy with conformal mixed neutron-photon irradiation.

Methods and Materials: From November 1992 to December 1994, 151 men received conformal neutron-photon irradiation as part of three prospective phase II/III protocols. Seventy-six patients (50%) received NAHT and 75 did not (50%). Biochemical control and local control were determined with periodic prostate specific antigen (PSA) determinations, and post-radiation biopsies. The differences between groups were evaluated by chi-square, nonparametric Wilcoxon test and Fisher's exact tests with a level of significance of 0.05.

Results: There was no difference between the two groups by age, stage, pretreatment PSA level or Gleason score. With a median follow-up of 16 months, there was no difference in the biochemical control rate (NAHT + RT: 84% vs. RT: 80%, $p = 0.5$) or the post-radiation negative biopsy rate (NAHT + RT: 85% vs RT: 76%, $p = 0.3$). A subgroup analysis excluding the most favorable subsets of patients (PSA < 10, or Stage < T2c, or Gleason score < 7) was performed. One hundred fourteen patients were analyzed and the groups were well balanced. No difference in biochemical (NAHT + RT: 80% vs. RT: 72%, $p = 0.4$) or local control (NAHT + RT: 83% vs. RT: 73%, $p = 0.4$) was once again found.

Conclusions: No additive benefit is detectable when NAHT is given in conjunction with conformal mixed neutron-photon irradiation. Neo-adjuvant hormone therapy in combination with photon irradiation appears to exhibit its primary benefit through increased local control. Since local control is already high with neutron irradiation, no additional benefit was seen with NAHT in biochemical control or local control.

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Acute and late reactions of fast neutron therapy in patients with head and neck cancer - the Krakow experience

B. Sas-Korczynska and J. Skolyszewski, Department of Radiotherapy, Centre of Oncology - M. Sklodowska-Curie Memorial Institute, Garncarska 11, 31 - 115 Krakow Poland

Between 1978 and 1989, 164 patients with advanced head and neck cancer were treated with fast neutron beam therapy at the Centre of Oncology in Krakow. Three schedules of dose fractionation were used: 114 patients were given the dose 12 - 13.2 Gy in 20 fractions, 17 patients received 10 - 12 Gy in 10 fractions, and 33 patients received 10 - 13 Gy in 5 fractions. Complete remission after therapy was observed in 58 (35.4%) patients, but only twenty six patients survived two years without disease. There were no significant differences in survival rates between patients treated with the three different dose fractionation schedules. Twenty four patients developed severe late complications after neutron therapy: oral cavity mucosal necrosis (8 pts), mandible necrosis (6 pts.), severe laryngeal oedema (9 pts.), and cervical myelopathy (1 patient).

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Neutron radiotherapy for salivary gland tumors at Harper Hospital.

E. Ben-Josef, S. Devi, J. Fontanesi, A. Aref, Gershenson Radiation Oncology Center, Karamanos Cancer Institute, Wayne State University, Detroit, MI.

Several retrospective analyses and a prospective randomized study have suggested advantage for neutrons over photons in the treatment of malignant salivary gland neoplasms. The cyclotron at Harper Hospital became available for clinical use in 1991. We report our experience in 22 patients treated since. Median age was 58.5 years. Twenty patients were treated at primary occurrence, two for recurrence. Tumors originated in the parotid gland (10), maxillary sinus (4), oral cavity (3), submandibular gland (2), base of tongue (2) and nasopharynx (1). Histology included adenoidcystic carcinoma (59%), mucoepidermoid carcinoma (18%), adenocarcinoma (14%), epithelial myoepithelial carcinoma (4%) and acinic carcinoma(4%). Stage distribution was I (14%), II (8%), III (14%) and IV (64%). Patients were treated with surgical resection followed by radiotherapy (11) or definitive radiotherapy (11). Of the former, resection margins were involved with tumor (37%), close (25%) or unknown (13%). Ten patients received mixed photon/neutron irradiation (mostly postoperatively) and twelve patients received neutrons alone. Patients treated after radical resection received a median dose of 19.76 NGy (neutrons alone) or 6.79 NGy plus 40.06 Gy (mixed beam). When radiotherapy was used alone, median dose was 18.2 NGy (neutrons alone) or 14.65 NGy plus 17.93 Gy (mixed beam). With a median follow-up of 1.6 years (1.8 years in living patients), 5 patients have relapsed locally and 4 patients have died. Actuarial 2-year survival and local control were 80% and 56%, respectively. All relapses and deaths occurred in patients who could not have surgery. Complications developed in 4 patients (severe complications in 2 patients). All complications occurred in patients treated with neutrons only (18.7-20.4 NGy, 1.7 NGy/fx). We believe that the better control observed in patients treated with surgery is the result of a selection bias. Nevertheless, further investigation of the role of debulking surgery in locally advanced tumors is warranted. Our results suggest an advantage to the use of mixed beam over neutrons alone.

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Biophysical aspects for fast neutron therapy planning

K. H. Hover[1], P. Pihet[2], T. Loncol[2], S. Gerdung[2], [1]Deutsches Krebsforschungszentrum, Heidelberg, Germany, [2]Universite Catholique de Louvain, Belgium

Various irradiation modes, including the computer-controlled dynamic irradiation and the application of "small" fields for stereotaxy, were examined and used at the neutron device in Heidelberg for the optimization of the physical dose distribution. In biophysical treatment planning of neutron therapy, the *relative biological effectivity* (RBE) has to be taken into consideration. Though an overall "clinical RBE" is taken into account at all treatment units, this is not the case for the variations of the RBE within the treatment volume. However, microdosimetric measurements and biological dose-effect functions have shown that, especially in the case of dynamic irradiation therapy, these variations in the RBE have to be accounted for.

Microdosimetric measurements: In this paper, we will investigate how the beam quality and thus the RBE vary in angle-weighted dynamic irradiation therapy on the basis of the selected irradiation parameters. Microdosimetric measurements were performed in various locations in a plexiglas phantom. The probe was a tissue-equivalent proportional counter with tissue equivalent gas. In a single-beam configuration, the physical beam quality was measured for various angles of incidence (0°, 22.5°, 45°, 67.5°, and 90°). Microdosimetric measurements in various locations in a phantom were also performed for a dynamic irradiation for the same dose level.

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A multiblade trimmer for neutron therapy

D. T. L. Jones, A. N. Schreuder, J. E. Symons, P. J. Binns, H. A. Smit and A. Mueller, National Accelerator Centre, P O Box 72, Faure, 7131 South Africa

At present shaping of the NAC neutron beam to spare healthy tissue and critical organs is accomplished by using a limited set of 12 cm thick tungsten blocks. For practical reasons only two blocks per field can be used. Although adequate for most treatments these blocks are heavy, difficult to mount and time-consuming to align. Although over 800 patients have been treated to date in several neutron therapy protocols very few prostate cases have been treated. A new protocol for such treatment is presently being formulated, for which better conformation of the treatment field to the tumour shape is very important. Obviously the ideal solution to improve beam shaping is to replace the existing rectangular jaw collimator with a multileaf or multirod device. The cost and the disruption that this would cause to the clinical program ruled this option out.

Comprehensive experiments were undertaken in order to assess the requirements for a steel multiblade post-collimator device (trimmer). These included narrow beam attenuation and dose distribution measurements as well as the determination of the spatial resolution of the blades. The results showed that two parallel opposed sets of 15 cm thick steel blades, 1 cm wide, would provide effective beam blocking with approximately 15% transmission. Tungsten was not considered because of the cost of material and machining. The limited distance between the end of the existing collimator and the isocentre (35 cm) means that some of the distal fixed components, mainly borated polyethylene and lead shielding, will have to be removed to accommodate the new device. A microdosimetric investigation showed that the leakage radiation was not significantly different if the distal components were replaced by 15 cm of steel, provided at least 5 cm of borated polyethylene was mounted upstream of the steel.

A totally mechanical apparatus, permanently fixed to and rotating independently of the existing collimator, has been designed to provide shaping for field sizes up to 15 x 15 cm^2. Shaped polystyrene cut-outs will be pneumatically driven onto the blades from the outside edges to form the required beamshapes. The blades will be locked in position by lateral pneumatic pressure. For larger rectangular fields (up to 26 x 26 cm^2) the blades will be completely retracted. To reduce activation 2 or 3 sets of high purity iron blades will be made, which will allow the blades to be changed on a regular basis. The device will still permit the mounting of the present tungsten blocks, which may be required for the larger fields and for more effective blocking of critical organs in the shaped fields.

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New LiF:Mg,Ti thermoluminescent detectors for hadron radiotherapy

P. Olko[1], P. Bilski[1], M. Budzanowski[1] and M. P. R. Waligorski[1,2], [1]The Henryk Niewodniczanski Institute of Nuclear Physics, ul. Radzikowskiego 152, PL-3 1342 Krakow, Poland, [2]Centre of Oncology - M. Sklodowska-Curie Memorial Institute, ul. Garncarska 11, 31 115 Krakow, Poland

LiF:Mg,Ti thermoluminescence detectors, commercially available for over 30 years eg. from Harshaw as TLD-100, TLD-600 and TLD-700, are widely applied in dosimetry for conventional radiotherapy due to their high stability and reproducibility, linear response up to 1 Gy and good tissue-equivalence for photons. Several studies were performed to apply LiF:Mg,Ti detectors also for heavy charged particle and neutron dosimetry by exploring the different response of particular peaks in the glow-curve on ionization density. In neutron dosimetry, pairs of ^{7}LiF/^{6}LiF detectors were used to discriminate between neutron and gamma doses by exploring differences in cross sections between Li-6 and Li-7 isotopes. However, for densely ionizing particles, interpretation of detector response in terms of absorbed dose is difficult due to the complex glow-curve structure with overlapping peaks, supralinear response above about 3 Gy 60Co ?-ray dose and a 4-10 times lower TL efficiency of the main dosimetric peak with respect to 60Co ?- ray doses.

The main goal of this work was to adjust the properties of LiF:Mg,Ti detectors to the needs of hadron radiotherapy dosimetry by extending the linearity of response at doses above 1 Gy and by increasing the relative TL efficiency after doses of high-LET particles. LiF:Mg,Ti detectors in the form of 4.5 x 0.5 mm pellets were manufactured at the Institute of Nuclear Physics, Krakow, Poland by cold pressing 80-200 mm powder and sintering pellets just below the LiF melting point. 6 batches of detectors were prepared with Ti content varying from 4.3 to 130 ppm. The dose-response of all detectors was studied for 0.05, 0.5 and 5 Gy of 137Cs and 60Co gamma-rays. Relative TL efficiency h, was investigated for 5.3 MeV stopping alpha-particles. Response for thermalized neutrons from Pu-Be source was investigated and compared with the response of conventional TLD-100, TLD-600 and TLD-700.

We found that with increase of molar concentration of Ti above the conventionally used 13 ppm, which is the optimum concentration for photon dosemeters, the onset of LiF:Mg,Ti supralinearity was suppressed and TL efficiency increased. For Ti concentration of 40 ppm and after 5 Gy of Cs-137??-rays no supralinear response of the main dosimetric peak was observed and a relative TL efficiency for stopping Am-241 ?-particles increased from 0.33 (Cti = 13 ppm) to 0.51 (Cti = 40 ppm) and 0.61 (Cti = 130 ppm). For thermalized neutrons the TL signal per unit exposure was approximately doubled for 40 ppm Ti detectors. An additional advantage of 40 ppm Ti detectors is a decrease of the height of peak 5 in the glow curve which enables better separation of main dosimetric and high-temperature peaks without d convolution. For higher Ti concentrations the glow-curve structure strongly changes, making the practical application of such detectors more difficult.

LiF:Mg,Ti detectors with increased Ti concentration appear to be a promising new material for proton, heavy charged particle and neutron dosimetry

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A spectrum integrated convolution model for therapeutic fast neutron beams

M. F. Moyers[1], J. L. Horton[2], A. L. Boyer[3] and L. T. Myers[4], [1]Loma Linda University Medical Center, Loma Linda, CA, [2]M.D. Anderson Hospital, Houston, TX, [3]Stanford University, Stanford, CA, [4]University of Pennsylvania.

Convolutions of energy spread kernels with available energy distributions allows calculations of three-dimensional dose distributions for fast neutron therapy beams incidents upon heterogeneous materials. The use of fast Fourier transform techniques has been effective at reducing the time required to do these calculations. This report describes a method to further reduce the time for calculations by integrating the available energy at each point in the patient from the primary neutron, scattered neutron, and photon components of the beam over their respective spectrums and convolving each with an effective kernel. The technique for determining the spectrum of the scattered neutron component and generation of the spectrum weighted effective kernels will be described. Comparisons of measured and calculated doses for flat water phantoms will be given. Dose distributions with a wedge and a flattening filter inserted will also be shown.

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Implementation of quality assurance program for Harper Hospital fast neutron therapy unit.

M. Yudelev[1], R. L. Maughan[1], K. McEnhill[1] and E. Blosser[2], [1]Gershenson Radiation Oncology Center, Karmanos Cancer Institute, Harper Hospital and Wayne State University. Detroit, Michigan, [2]MedCyc Corp. East Lansing, Michigan.

The Quality Assurance (QA) program for Harper Hospital Superconducting Cyclotron Fast Neutron Therapy Unit is designed to be uniform with the QA program for other teletherapy machines in this institution. In general, it is based on recommendations of MPM TG-40. However, certain unique features of the superconducting cyclotron as well as the peculiarities related to neutron radiation and dosimetry single out the performed procedures from conventional therapy units. The program can be divided into three major groups: maintenance of the cyclotron and related hardware; QA of the neutron beam dosimetry and treatment delivery; safety and radiation protection.

The procedures involving maintenance of the cyclotron and liquid helium production systems are performed by the technical personnel. In the cyclotron the ion source is being cleaned every ten days to two weeks and the cathode is replaced every two to three months. The RF coupler is replaced quarterly. The oil and turbo-mechanical pumps of the vacuum system are checked, greased and replaced periodically. The log of the parameters of the liquid helium production system is kept and the maintenance of the helium compressors and the liquefier is performed.

The QA tests of the neutron beam dosimetry and treatment delivery are performed on daily, monthly and annual basis. These tests are the beam output constancy, the monitor system calibration, the field flatness an symmetry, the beam alignment with optical devices, the mechanical and radiation isocentricity, the patients set-up aids as well as the treatment port verification system. The beam output

constancy together with the symmetry and flatness are checked daily using Tracker System 90100 (Keithley, Inc. Model 35360A) in 25 x 25 cm^2 at 2.5 cm depth and standard distance of 182.9 cm. The results are compared with the performance of the segmented monitor chamber. The daily output is analyzed in terms of percentage deviation from the average value of previous measurements. Immediate action level is set when the measured output exceeds ±3% of the average value. The neutron beam flatness and symmetry are checked at points 10 cm from the central axis in both in-plane and cross-plane directions. The absolute calibration of the monitor ion chamber is performed monthly in a water phantom following the recommendations of the International Protocol for Fast Neutron Beam Dosimetry (ICRU Report 45). The calibration of the monitor system is adjusted if exceeds ±2%. The monthly QA checks also include the mechanical alignments, lasers, light/radiation coincidence as well as the test of the X-ray system. The ionization chambers used for neutron dosimetry are calibrated annually in 60Co beam.

The tests off the interlock safety system are performed daily and on a quarterly basis. They include conformation of warning flashing lights, test of door switches, by-pass key and emergency switches operations. These are pass or fail tests and require immediate action in case of failure.

The radiation exposure to the staff involved in the operation of the neutron therapy unit is monitored by means of personnel dosimeters on daily and monthly basis. The results are recorded in the log-book at the end of each day of cyclotron operation. The monitoring of individual exposure allows to take action if someone exceeds the ALARA limits. The radiation levels around the neutron therapy vault are monitored on monthly basis in 12 separate locations by means of personnel dosimeters.

The comprehensive QA program for Harper Hospital Superconducting Cyclotron Neutron Therapy Facility ensures safe and reliable operation of the unit and allows to maintain the standard of treatments comparable to that of conventional radiation.