ABSTRACTS

13th International Congress on

Neutron Capture Therapy

"A new option against cancer"

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Edited by A. Zonta, S.Altieri, L. Roveda and R. Barth

ENEA
Italian National Agency for New Technologies,
Energy and the Environment

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BEAM DOSIMETRY

BEAM DOSIMETRY – talk

Progress in gadolinium utilization in NCT

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The evaluation of improvements in the use of gadolinium in cancer therapy (GdNCT), through the Treatment Planning System (TPS) assessment, is one of the topics currently analyzed by our group. In this paper the most recent results of this research are presented.
At first an intensive updated evaluation of the Gd compounds toxicity was performed identifying the Motexafin Gadolinium [1] as the best. Afterwards, the spectrum of IC and Auger electrons was calculated using an original method. As a second step, the energy deposit in DNA was defined through the PENELOPE code [2], exploiting the evaluated electron source. Taking into account that the electron yield and energy distribution are related to the neutron beam spectrum and intensity, the shaping assembly architecture was optimized through computational experiments [3].
Finally the study of GdNCT was performed from two different points of view: macrodosimetry using MCNPX, with calculation of absorbed doses both in tumor and healthy tissues, and microdosimetry using PENELOPE, with the determination of electron EBR through the energy deposit. The equivalent doses were determined combining these two kinds of data, introducing specific figures of merit to be used in TPS.

A detailed Monte Carlo accounting of radiation transport in the brain during BNCT

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Whereas $^{10}B(n, \alpha)^{7}Li$ is the collision type central to BNCT, other types of nuclear collisions do take place in the patient. In addition to these nuclear collisions, different types of atomic interactions occur as the beam is incident on the brain. Apart from the neutrons and their subsequent progenies, contaminating gammas (in the case of reactors) or photons (in the case of linear accelerators), present in the beam, generate cascades of particles of their own. In BNCT cases, therefore, a variety of collision and interaction event types, scatter fractions and dose components must be taken into consideration. Detailed accounting of the above not only provides better understanding of radiation transport in the human body during BNCT, but such knowledge also affects the design of the facility, as well as treatment planning, imaging and verification for a given BNCT agent. Of the methods of investigation currently available, only Monte Carlo simulation could provide the detailed accounting and breakdown of the quantities required. We report Monte Carlo simulation of a realistic anthropomorphic voxel phantom and show how these quantities change by different ^{10}B concentration ratios. We have chosen the ^{10}B biodistribution to be the variable of interest, since it is not accurately known, is frequently approximated and is a crucial quantity on which dose calculations are based.

Angle- and energy-differential neutron spectrometry for the SPES BNCT facility

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The design of the SPES BNCT installation relies on the production of neutrons from a beryllium target bombarded with 5 MeV protons. Before the construction of the facility, Monte Carlo simulations are necessary for the evaluation of geometry and materials of the apparatus which moderates the fast neutron source spectrum and produces a collimated thermal neutron beam. A complete set of double differential data, i.e. angle- and energy-differential neutron spectra produced by the beryllium target, is necessary to perform these simulations. While data are available in the literature for 4 MeV protons on beryllium, double differential fluence measurements for 5 MeV protons are currently being done at the INFN-LNL CN Van de Graaf accelerator utilizing the "BINS" device based on superheated emulsions. This spectrometry approach was introduced over ten years ago and has been tested extensively, including at the BNCT installations of Studsvik (Nyköping, Sweden) and Casaccia (Rome, Italy). The current version of the BINS spectrometer uses a superheated emulsion of dichlorotetrafluoroethane which is sequentially operated at 30, 35, 40, 45, 50 and 55 °C, and thus provides a series of six sharp thresholds covering the 0.1-10 MeV neutron energy interval. The BINS response matrix is virtually orthogonal, with threshold responses nested and spaced in quasi-isolethargic bins. This makes BINS ideally suited for spectrum unfolding using "few-channel" techniques, where the number of detectors is much smaller than the number of energy bins used for the unfolding. Deconvolution of the data is performed with the code MAXED, which uses standard maximum entropy and allows for a rigorous handling of *a priori* information. The analysis of our first neutron spectrometry measurements at angles of 0, 40, 80 and 120 degrees is presented and discussed in this paper.

Radiation Field Characterization of the NCT Research Facility at IEA-R1

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A NCT (Neutron Capture Therapy) research facility was constructed at IEA-R1 reactor. The facility installed at beam-hole (BH) number 3 can be described to be consisted of 2 modules:
- an inner BH module: with the filter, sample and shielding arrangement sets and
- an out of wall module: with biological shielding room surrounding the sample positioning/removing table.

Neutron/gamma spectra can be modulated by a set of filters interposed between the reactor core and the sample position. The biological shielding at the end of the BH was designed and constructed to allow the extraction of the sample (and the inner shielding with it) even with the reactor on. This feature together with a remote controlling sample positioning/removing system enable controlling the sample exposition time (dose).

The present work intends to show the results from a series of simulations performed in order to select the best set of moderators so to get an optimized thermal neutron radiation with small gamma ray contamination at the radiation sample position

Experiments with activation foils and thermoluminescent dosimeters, which have been performed to characterize the field and check the adequacy of the simulations, will also be shown. Actual thermal neutron radiation conditions are 32.2 ± 0.1 Gy/h of dose rate with 25% of gamma contamination for a 3.5 MW reactor operation power.As the sample irradiation region is inside BH, sample size is limited to a cylindrical enclosure of 30.0 cm height by 12.8 cm in diameter and therefore due to its size limit, the facility is not suited to carry any treatment. Field modulation and time exposition control possibilities of this facility provide adequate radiation conditions to perform NCT research experiments.

An in-vivo comparative study between the standard and PET-based approach using BDTPS

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Previous studies dedicated to the evaluation of the best approach for a treatment plan more consistent with the clinical findings opened a *vexata quaestio*, which is still an open issue as demonstrated by the fact that BNCT treatment plans are only partially based on the pre-evaluation of the macroscopic boron distribution. For example, the evaluation of the T/N ratio through pre-irradiation PET scanning is undoubtedly a major improvement.
The present article shows that the Treatment Planning System (TPS) response is evidently different if it is applied with two approaches: on one hand, the definition of the target and other regions takes into consideration the tumour morphology obtained through CT scanning (*standard*). On the other hand, the target and other regions definition is based on the evaluation of the PET scanning of the same patient (*PET-based*).
In particular, the case study is a 74 years old woman, affected by parotid progressive cancer. The PET scanning permitted to evaluate a T/N ratio equal to 5. The same patient has been CT scanned for the morphology reconstruction in the TPS. BDTPS (Boron Distribution Treatment Planning System) is a TPS designed, implemented and in-phantom tested at JRC-IE in collaboration to University of Pisa. It is possible to use this TPS in both approaches. In particular, PET data are integrated directly by the system in the post-processing evaluation of the ^{10}B dose. The other doses (gamma, nitrogen and hydrogen) mainly present in BNCT are also calculated.
The comparison between the two approaches gives a clear indication that the PET-based TPS offers more information in the peripheral area of the tumour, where the standard approach overestimates the boron dose. Consequently, the treatment plan calculates an irradiation time, insufficient to deliver a proper therapeutic dose in the area surrounding the main tumour core. The follow-up confirms the PET-based TPS findings.
Additionally, the PET scanning helped to evaluate properly the T/N ratio, especially in zones where this ratio is too close to the unity. In this case, significant collateral damage occurs limiting the efficacy of BNCT. BDTPS can be applied to other capture therapies, such as GdNCT. Therefore, a PET-based treatment planning is a key for the most effective NCT.

Importance functions approach to neutron beam optimization for tumor therapy

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The idea of BNCT consists of selectively incorporating ^{10}B in malignant tumor and after irradiating tumor by thermal neutrons arising the secondary radiation destroys the tumor sells with minimal harm for healthy tissue. To treat a malignant tumor BNCT utilizes a binary method. The first step involves administering a cancer-seeking pharmaceutical that has been loaded with ^{10}B. An ideal drug is harmless to the patient and is absorbed in cancerous cells far more selectively than in normal tissue cells. The second step is irradiation of the patient by soft neutron beam. ^{10}B has a very high thermal neutron capture cross section of 4000 barns and decays immediately into high LET particles via $^{10}B(n,\alpha)^{7}Li$ reaction, as well as 480 keV γ ray in 93% of the reactions. The energy of combined high LET particles is largely confined within the diameter of a single cell, thus targeting a large radiation dose preferentially to malignant cells without significantly irradiating dose healthy tissue. Because BNCT is a binary therapy, advances in both boron delivery and in neutron beam shaping are important to improving the quality of treatment.

A wide variety of different neutron spectra can be produced by various neutron sources (reactors, accelerators tuned to different proton energies or utilizing different target materials) and various moderator assemblies. The clinical efficacy of each spectrum must be evaluated by extensive Monte Carlo modeling with program such as MCNP. Generally this is done in two-step process.
The first step involves modeling the "pure" beam to determine the spectrum that will be applied to the patient. The next step consists of determining the filter which will form the best neutron specter for tumor treating.
Optimizing neutron beams for treatment is primarily a matter of designing moderators and filters to produce a spectrum which limits the unwanted "background" doses while maximizing the penetration of the beam and maintaining a high enough dose rate to treat in a reasonable amount of time. Optimization studies usually have involved hundreds of Monte Carlo simulations to compare properties of different neutron beams and filter constructions.
Small changes in tumor parameters or RBE values can produce drastic changes in the performance of different neutron beams. Usually, the only way to determine the effect of changing involved in BNCT treatment is to return many Monte Carlo processes, each of which can take hours or days.
To accelerate the process of performing a great number of Monte Carlo simulations with different sources the importance functions approach was developed. The idea of this approach is based on the dose distributions from number of the delta neutron sources having the definite energy (energy group). The developed method of applying importance functions to reduce a Monte Carlo simulation for different variable sources is quite powerful. Using the number of such importance functions it can be defined what energy for neutron source more preferable, not only for tumor but for healthy tissue too.

Determination of the irradiation field at the research reactor TRIGA Mainz for BNCT

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The TRIGA Mainz (TRIGA = Training Research Isotope production General Atomic) is one of two research reactors operated at German universities. The TRIGA Mainz can be operated in the steady state mode with a maximum power of 100 kW_{th} and in the pulse mode with a peak power of 250 MW_{th}. With respect to a future application of the boron neutron capture therapy (BNCT) at the research reactor TRIGA Mainz the basic characteristics of the radiation field in the thermal column must be determined. So far neutron and gamma fluxes in the thermal column were determined using thermoluminescence detectors (TLD) with a new developed energy-compensation filter system as well as thin gold foils, and a semiconductor detector.
The TRIGA Mainz with a graphite thermal column provides a source of well-thermalized neutrons suitable for physical research or biological and medical irradiations. This thermal column shall be used for the irradiation of an explanted liver with thermal neutrons for a liver metastases therapy. BNCT was first realized at the TRIGA Pavia, Italy as follows: after a patient accumulates pharmaceutical ^{10}B mainly in the tumour tissue, the liver is explanted, irradiated with thermal neutrons and reimplanted (auto--transplantation).
Concerning the proximity between the transplantation centre and the treatment reactor, the TRIGA Mainz has a unique advantage in Europe.
The basic characteristics of the radiation field in the thermal column as beam geometry, neutron and gamma-ray energies, angular distributions, neutron flux as well as absorbed gamma and neutron doses must be determined in a reproducible way.
Measurements of the photon dose and the neutron flux in this mixed neutron-gamma radiation field have been performed using different TLDs, gold foils and a semiconductor detector.

The employed TLD materials were CaF_2:Tm (TLD-300) and LiF:Mg,Ti with different ^{6}Li concentrations and thicknesses. They have been used to determine the photon dose contributions in a plexiglass phantom and free in air over the whole length of the central radiation channel of the thermal column for reactor powers between 10 W and 100 kW. The TLDs were analysed at the "Forschungszentrum Karlsruhe" and calibrated at the thermal neutron beam of the GKSS research reactor (GeNF) in cooperation with the PTB. This beam at GeNF provides a negligible photon dose.
The thermal column of the TRIGA Mainz shall be reconstructed to allow the irradiation of an organ with thermal and epithermal neutrons and to establish an irradiation facility for medical purposes at the reactor facility. A further aim is to measure photon and neutron dose with small and thin TLDs inside the liver during the treatment.

Characterisation of the epithermal beam at the TAPIRO reactor

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In order to perform the characterisation of the epithermal beam at the 5 kW fast reactor TAPIRO (ENEA, Italy), an irradiation area has been set up in the reactor hall; the area is large enough to allow the experimental characterisation of the beam and it is sufficiently shielded to permit operating the reactor up to 10% of the maximum nominal power. The beam characterisation began in 2007. Various techniques for neutron fluence and gamma dose measurements in-air and in-phantom were employed to verify the design parameters, using the standard 12×12 cm^2 beam aperture configuration. The thermal and epithermal neutron fluence rates were measured with activation techniques based on bare and cadmium-covered gold and indium foils, nickel and manganese foils. The spatial homogeneity of the neutron beam over the aperture was verified using a number of TLDs and gold foils at some selected points. Neutron spectrometry was performed at the beam port with a set of five Bonner spheres. As far as the fast neutron spectrometry is concerned, two different sets of bubble detector spectrometers have been employed. Also, some preliminary measurements of the gamma component were carried out by means of TLDs and an ionization chamber. Monte Carlo calculations were performed in order to complement the measurements and provide comparison with the experimental results. The intercomparison of the measurements obtained with the different techniques is discussed in this work.

The basic theory for 10BNCT with thermal neutrons

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The basis of the theory is the value of effective mass of substance irradiated by thermal neutrons as we introduce it. The values of the effective mass corresponding to the various irradiation conditions can be measured in model experiments or in certain cases theoretically calculated. The theory we introduce ties the physical conditions of irradiation, neutron, nuclear and atomic data, 10B concentration in the irradiated area to the maximum absorbed dose rate in the irradiated object by simple algebraic expressions.

The results of calculations of the following values are presented in table 1:

- The effective mass of biological tissue – Meff for the narrow neutron beam;
- Effective thickness of biological tissue – meff for the broad neutron beam (the broadness of the neutron beam is related to the diffusion length of neutron in biological tissue);
- Values of thremal neutron flux density - φth corresponding to the maximum dose rate of 30 Gy/hr given 10B concentration is 30ppm;
- Kerma of fast neutrons Kfast corresponding to 3 Gy/hr given the fraction of fast neutrons in the beam is 0.25.

Table 1.

Beam	Meff, g	meff, g/cm^2	φth, 1/cm^{2}s	Kfast, Gy·cm^2
Narrow	2,0	–	2,6·109	9,5·10-13
Broad	–	3,2	1,3·109	20·10-13

Neutron irradiatin techniques to reduce skin dose and to improve therapeutic dose distribution using thermal neutron filter

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Introduction: Clinical studies of boron neutron capture therapy (BNCT) for a malignant brain tumor and for a head-&-neck cancer are being performed using JRR-4 in Japan Atomic Energy Agency (JAEA). In most of the clinical trials at JRR-4, dose given to a patient has been controlled according to limitation of not tolerance dose of brain but skin dose. This is attributed to the fact that contamination of thermal neutron component (-0.5eV) in epithermal neutron beam of JRR-4 is higher than other reactors' one such as KURR and FiR-1. This study aims to investigate how reduce the thermal neutron contamination in the neutron beam and how enhance the therapeutic dose around tumor region.

Material: To reduce the thermal neutron component in the epithermal neutron beam, we attempted to set a thermal neutron filter on the beam line just before beam port of JRR-4 facility. Material of the filter was applied a composite of enriched Li-6 fluoride and Teflon compound. To verify the performance of the filter, several preliminary estimations were carried out using MCNP-5, a neutron and photon transport calculation code. In these estimations, calculation conditions such as enrichment of Li-6, thickness of the filter were changed, and then neutron spectrum and neutron fluxes for free in air condition and dose distributions in a cylindrical water phantom were estimated for each condition. The results were compared with the conventional epithermal neutron beam of JRR-4.

Results and Discussions: The comparison results of neutron spectrum on the free in air condition proved that application of the filter was effective to reduce ratio of thermal neutron component in the beam. And in the estimations for the phantom irradiation, by setting a filter consisting of 50% enriched Li-6 fluoride: 50%wt and Teflon: 50%wt (thickness: 5mm), the thermal neutron flux at phantom's surface reduced approximately 30% compared with the conventional filter-less beam. In case of estimation applying clinical condition of JRR-4's BNCT, as normalizing by maximum skin dose: 10Gy-Eq, application of the 50% enriched Li-6 filter enabled to enhance the maximum therapeutic dose about 10% and the dose at 5cm in depth about 20% than the values of the filter-less beam.
A prototype of the thermal neutron filter with 50% enriched Li-6 was made and has been installed to JRR-4. We begin to perform several characteristic measurements of the filter.

Neutron Flux Mapping inside a PMMA and a RANDO Phantom using Indirect Neutron Radiography

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Boron dose in a tumour, which is an important indication of effectiveness in Boron Neutron Capture Therapy (BNCT), is an integrated value of boron spatial distribution multiplied by neutron spatial distribution over the tumour volume.
The neutron spatial distribution in a phantom is generally determined by calculation using neutron transport code like MCNP, and is confirmed by a few measured points using activation foils. Due to the limitation of counting capacity, the measured spatial resolution of neutron distribution is quite poor.
Hence, any delicate difference between the calculation and the reality can not be found through the measurement. In order to provide a high resolution, two-dimensional neutron flux mapping in a phantom to be compared with the calculation and to provide direct information of the trend of neutron distribution, indirect neutron radiography is proposed in this study. For the sake of demonstration, a 1-mm thick plastic plate with 0.1-mm thin, pure copper foil attached on the surface is irradiated in a cubic PMMA phantom at different depth by a 14-cm diameter epithermal neutron beam in the THOR.
The activated copper is then attached on an imaging plate (BAS-III) for exposure. After the readout of imaging plate, a high resolution image with a pixel size of 50μm is formed. The center 14cm by 14cm square is then cut into a 25 by 25 matrix for the purpose of comparison, where each group size is 5.6mm by 5.6mm. The statistical error of each group value is less than 1% which is comparable to the conventional activation measurement. As to the time cost, the whole procedure normally takes less than three hours. The same methodology is also applied in a RANDO phantom. The result shows that the indirect neutron radiography can be a quick and reliable method to provide a two-dimensional neutron spatial distribution in a PMMA and a RANDO phantom.

BIOLOGY

BIOLOGY – talk

What is the future for boron neutron capture therapy?

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Over the past 25 years, BNCT research has progressed relatively slowly but steadily with the greatest progress in the field of clinical studies, and specifically its application to a variety of malignancies other than high grade gliomas and melanomas. These include meningiomas, cancers of the head and neck region, and under very special circumstances, the treatment of hepatic metastases of colon cancer. However, there are a number of key areas where little, if any, significant progress has been made. First and foremost among these has been the lack of new boron delivery agents that have advanced to clinical use since the introduction of boronphenylalanine (BPA) for the treatment of melanoma in 1989 and gliomas in the early 1990s. Improvement in drug delivery and the development of the best dosing paradigms for both BPA and sodium borocaptate (BSH) are of major importance and still have not been optimized. This is not only important for brain, but also extracranial tumors. Dosimetry for BNCT still is based on treating to normal tissue tolerance, based on blood boron values rather than any realtime information on the boron content of the residual tumor that is to be irradiated. The ultimate goal would be to move BNCT to the same level as other types of radiation therapy where dosimetry is quite precise. Another major problem has been the total dependence on nuclear reactors as neutron sources for BNCT, and despite much effort a clinically useful accelerator source has yet to be sited in a hospital and used for therapy. Even though there are many reasons for the failure to develop randomized clinical trials, the simple fact of the matter is that until BNCT is put to this test, it will not gain the credibility of a broad community of physicians who are treating cancer patients. Although, the survival statistics for patients with high grade gliomas are almost as dismal now as they were 25 years ago, the introduction of temozolomide in combination with photon irradiation has produced a modest 2.5 month increase in median survival, which raises the bar of what has to be achieved in order to make BNCT a clinically useful modality. Getting clinical results that are equivalent to external beam photon irradiation will not be sufficient. Finally, recent experimental studies with the F98 rat glioma model combining X-irradiation with intracerebral delivery of carboplatin (Clin. Cancer Res., 13:5195-5201, 2007) have yielded survival data better than those that we ever have obtained with BNCT. Therefore, the final, and most important question that must be addressed is, "How can BNCT survive as a treatment modality if and when there are more widely applicable and less costly alternatives?"

A novel boronated-porphyrin as a radio-sensitizing agent for boron neutron capture therapy of tumours: *in vitro* and *in vivo* studies

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A water-soluble [meso-tetra(4-nido-carboranylphenyl)porphyrin] (H_2TCP) bearing 36 boron atoms was studied for its accumulation and its radio/photo-sensitization efficiency towards murine melanotic melanoma cells. The amount of H_2TCP in the cells increased with the porphyrin dose in the incubation medium up to 100 μM with no significant dark toxicity. Fluorescence microscopy observations showed that the porphyrin was largely localized intracellularly.

Based on these "in vitro" results our investigations were pursued using the B16F1 melanotic melanoma subcutaneously transplanted in C57/BL6 mice as "in vivo" model. Phormacokinetic studies were performed by injection of H_2TCP intratumorally (1 mg/kg) andintravenously (10 mg/kg). At 0.5 h after i.t. administration or at 24 h after i.v. injection, the amount of ^{10}B in the tumour were about 60 ppm and about 6 ppm, respectively. The distribution of H_2TCP in the tumour after intravenous or intratumoural injection was also assessed by fluorescence microscopy analyses.
Under these conditions, preliminary BNCT studies were carried out using a new thermal column called HYTOR (HYbrid Thermal spectrum sHifter TapirO Reactor) inserted in the fast nuclear reactor Tapiro at ENEA Casaccia, Italy. The mice were exposed to HYTHOR radiation field for 20 min at a reactor power of 5 kW. In spite of different amounts of ^{10}B in the tumour at the irradiation time, a significant delay in tumour growth (5-6 days) was induced by neutron irradiation in the two groups of injected (intratoumorally and intravenously) mice with respect to control mice simultaneously transplanted exposed to the thermal neutron radiation but not injected with the porphyrin.
The response of the melanotic melanoma to H_2TCP-BNCT was compared with that obtained by irradiation after intraperitoneal injection of boron-phenylalanine.

In vitro neutron dosimetry of F98 and endothelial cultured cells

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BNCT is biologically-target rather than physically targeted therapy: boron uptake in neoplastic cells and its relative concentration with respect to normal cells should be considered as the two main limiting factors for therapy. Recent studies demonstrated in vitro how BPA is taken by multiplying cells and its correlation with the cell cycle phase. However, the mechanism of BPA uptake and the parameters drawing the kinetics of influx end elimination of BPA are still not clarified. This multidisciplinary group already investigated the incorporation of ^{10}B in two different cell type, a neoplastic F98 type and normal endothelial type (Umbilical Vein Endothelial Cells, HUVEC), and set up a methodology based on capillary electrophoresis-electrospray mass spectrometry and HR-ICP-MS for the quantification of ^{10}B-boronophenylalanine inside the cells (2005). The present study is aiming to investigate the cell damage after incorporation of BPA-fructose under controlled condition, assessing the level concentration of boron inside the cell.
The kinetic of incorporation and release of BPA have been determined for F98 and HUVEC cell line during *log*-phase: the release (*wash-out*) of BPA-Fr was assessed after removal of the growing medium, as performed before the irradiation with neutrons. On the bases of the kinetic of accumulation, multiple irradiation tests of two cultured cells have been performed with thermal neutron: the contribution to citotoxic and clonogenic damage after the numerous capture events was only produce by the intracellular ^{10}B at the moment of the irradiation.
The antiproliferative effects of neutron irradiation after BPA-Fr incubation were assed using MTT assay: no cytotoxic effects were detected at concentration lower than 110 $mg \cdot ml^{-1}$ ^{10}B equivalent, that demonstrated that no chemosensitivity is present at lower concentration.
Because longer time of incubation with ^{10}B-BPA found in our studies to increase the intracellular boron concentration (cells in different cellular cycle phase probably exhibit different uptake of aminoacid analogue compounds) an incubation time of the drug of 18 hours was set up.
The study was performed on the two above mentioned models with thermal neutron beam available at the ENEA TAPIRO facility.
After neutron irradiation antiproliferative test using MTT assay, performed after 6 cell cycle (cell sample analysed in double using 6 well flask). The analysed Survival Fraction (SF) allow to calculate the main radiobiological parameters. Preliminary results of the ongoing studies will be presented.

Monitorisation of BNCT efficiency using biochemical oxidative stress and apoptosis parameters

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Boron neutron capture therapy is based on the selective delivery of boron-10 to tumor cells. Approximately 10^9 ^{10}B atoms per tumor cell are necessary to produce four to five αparticles per cell, but studies of radiation-induced apoptosis suggest that BNCT also may be cytotoxic via other mechanisms so that the required number of ^{10}B atoms actually may be less. The aim of our paper is to find new biochemical mechanisms such us the oxidative destruction involved in tumoral cell cytotoxicities mediated by oxygen reactive species.
Materials and methods: RS1 hepatoma –bearing rats were given single i.p. injection of 30 mg ml^{-1} of a BPA: fructose 1.0:1.1 molar solution. Mice were anaesthesiated and irradiated 2 hours with a $1.655*10^9$ n $/cm^2$ epithermal fluency beam. Tumor, blood, and liver tissue sample were removed and assayed for boron biodistribution, oxidative stress and apoptosis induction.
Results**:** Our results show preferential capture of BPA at tumoral level with a maximum value at 3 hours after the administration., the lipid peroxides level measured in blood is increasing two times at the hepatoma bearing rats than in normal control, also the caeruloplasmin Cu-oxidase activity growth from 168 I.U. to 330 I.U., the albuminic thiol-groups are decreasing from 267 μmol/l at 107 μmol/l , at at liver level of tumor bearing rats sacrificed one hour after the irradiation can be observed an increase of apoptosis rate, suggesting the implication of free radicals in the apoptotic pathway.
Conclusions: The BPA administration possibly induce methabolic pathways wich involves the oxigen consumption, and after the irradiations the cytotoxicities is done by oxigen free radical production The biochemical parameters of oxidative stress can be used in monitoring the evolution of hepatoma, the modifications after BPA administration and the irradiation effects.

Accumulation of ^{131}I-BSH in melanoma B-16 and surrounding tissues of mice following different methods of compound administration

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The heightened attention is recently given to combined application of BNCT and fast neutron therapy. The local delivery of significant boron amount to tumour is a primary problem both for BNCT and for the mixed therapy.
Depending on tumour localization it is reasonable to use various methods of compounds administration: intravenous, intra-arterial, intratumoral (into metastases), and pricking around the tumour zone. Not only concentration of ^{10}B in tumour tissues but also the degree of boron accumulation in tumour cells is important for the effective realization of BNCT. In this regard, the purpose of the research was to study distribution of sodium mercaptododecaborate, labeled with radioactive iodine (^{131}I-BSH), in melanoma B-16 and surrounding tissues following various methods of compound administration: intraperitoneal, single and double intratumoral and also under tumour administration. The ratio between accumulation of ^{131}I-BSH in tumour cells and intercellular space depending on method of compound administration was also studied.
The studies were carried out on male C_{57}BI/6 mice with melanoma B-16 subcutaneously implanted in hind leg. ^{131}I-BSH (0.1 ml) was administrated into tumour (single and double) and under tumour with 0.15 MBq radioactivity. Content of the labelled compound in tumour and surrounding tissues (blood, skin, muscle) was measured in 15 min, 30 min, 1 h and 3 h after the administration by the radioactivity level of decapitated under narcosis animals. The intraperitoneal (0.2 ml, 0.3 MBq) and single intratumoral (0.1 ml, 0.15 MBq) administrations of ^{131}I-BSH were performed for studies of cellular and intercellular accumulation of the compound in tumour tissue. The tumour was removed from the hind leg in 3, 6 and 12 h (after intraperitoneal administration) and in 0.5, 1 and 2 h (after intratumoral administration). Then it was comminuted and trypsinized at constant mixing (37 °C, 15 min).

The cellular suspension was centrifuged for 15 min at 2000 r/min. The supernatant and the sediment were selected in tubes for radioactivity measuring.
The studies of ^{131}I-BSH distribution in melanoma B-16 and surrounding tissues by different methods of compound administration showed that the high content of ^{131}I-BSH in the tumour was reached in all cases. The most compound accumulation was observed in 1 h after administration. The percentage of administrated ^{131}I-BSH per 1 g of the tumour were 11.60±1.68 % and 11.26±0.88 % for single and double intratumoral administration, respectively, and 10.69±2.54 % for administration under tumour. In this case the ratio of radioactivity in melanoma B-16 and surrounding tissues was more than 3 for majority of mice.
The study of ^{131}I-BSH accumulation in tumour cells showed considerably larger compound accumulation in intercellular space (65.3% and 63.0%) in comparison with the cellular content (34.7% and 37.0%) in 3 and 6 h after intraperitoneal administration. The ratios became identical in 12 h. There were approximately equal compound accumulations in intercellular space and tumour cells during the study (0.5-2 h) at single intratumoral administration of ^{131}I-BSH.
The results of studies allow to consider the intratumoral administration of sodium mercaptododecaborate to be a perspective for combined application of neutron capture and fast neutron therapy.
The researches were supported by the Russian Federation President Grants Council (grant № MK-4562.2007.7) and the International Science and Technology Center (ISTC) (project № 3437).

Biodistribution and Imaging studies on F98 rat glioma by convection enhanced delivery of transferrin targeting PEG liposomes encapsulate both BSH and iodine contrast agent

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In the last ICNCT we reported the effectiveness of transferrin (TF)-PEG liposome (BSH), with regard to its ability to target the tumor cells and to accumulate more boron atoms in the tumor tissues. However, systemic administration of these compounds has some problems, including unexpected boron distributions to other organs, limited accumulation by BBB, infiltrative nature of the glioma, and so on. To solve these problems, in the present study we adopted convection enhanced delivery(CED) as the way of drug administration. Furthermore we developed a novel liposomal boron delivative drug which encapsulated not only BSH but also iodine contrast agent (Iomeprol), so that it has become possible to trace distribution of the drug by clinical imaging. We evaluated two boron carriers, PEG liposome(Iomeprol+BSH) and TF-PEG liposome (Iomeprol+BSH) administered by CED as a boron delivery system into the rat brain tumor model.
Methods: We prepared F98-brain tumor bearing rats and administered each boron carrier, PEG liposome(Iomeprol+BSH) and TF-PEG liposome(Iomeprol+BSH) by CED over 30 minutes at a rate of 0.33μl/min. In the definite time after CED, we performed computed tomography scan to evaluate the distribution of these drugs and euthanized them. And then we evaluated boron concentration of tumor, normal brain and blood by inductively coupled plasma atomic emission spectrometry (ICP-AES).
Results: Drug distributions were well recognized by CT scan. The difference of tumor boron concentration between PEG liposome(Iomeprol+BSH) and TF-PEG liposome(Iomeprol+BSH) showed the largest at 48 hours after CED, and values at that time were 3.4μg^{10}B/g in PEG liposome(Iomeprol+BSH) and 38.3μg^{10}B/g in TF-PEG liposome(Iomeprol+BSH).
Conclusions: We showed the effectiveness of TF-PEG liposome(Iomeprol+BSH). Especially the combination of CED and TF-PEG liposome(Iomeprol+BSH) enables a precise targeting on tumor tissues and following the trace of the drug in each tumor-bearing rat.

Do the Various Radiations Present in BNCT Act Synergistically?
Cell Survival Experiments in Mixed Alpha-Particle and Gamma-Ray Fields

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In BNCT, as with all high-LET therapy regimes, a significant fraction of the dose may be contributed by low-LET components. The components of such mixed fields may show a synergistic interaction and produce a greater biological effect than would be the case for independent action of the different radiation types. Such a synergy has important implications for treatment planning in BNCT and other mixed field therapies and in the interpretation of clinical results.
Some evidence for such an interaction has been previously reported by McNally *et alii* (1988) who irradiated mammalian cells with alpha particles or X-rays following a 'priming' dose of alpha particles. Other workers, including Suzuki (1993) and Murray *et alii* (1975) also report synergism under certain conditions. However, there is no unequivicol evidence of a significant synergistic effect between high and low-LET radiations. Further data are needed, not only to develop a better understanding of possible effects, but also for the development of improved mathematical models which can be applied clinically.
To this end a novel irradiation setup has been created at the Medical Research Council in Harwell which allows simultaneous irradiation of cells by cobalt-60 gamma-rays and plutonium-238 alpha-particles. The setup allows for variation of dose and dose rates for both sources along with variation of the alpha-particle energy. Cell survival measurements have been carried out for mixed alpha-particle and gamma-ray fields using V79-4 cells and compared with the results from exposures to the individual components under identical conditions. Doses for the two components were chosen to be approximately equally effective, *i.e.* 0.5, 1.0, 1.5 and 2.0 Gy of alpha-particles and 3.5, 5.4, 7.1 and 8.6 Gy of gamma rays, producing respectively surviving fractions of 0.4, 0.15, 0.08 and 0.03. Following irradiation cells were left for 2 hours at 37°C to allow for cellular repair before processing.
The survival curve obtained for the mixed field exposures was found to be only slightly different from that obtained by addition of the individual surviving fractions; the survival curve parameters fitted to the linear-quadratic model being $\alpha = (0.423 \pm 0.038)$ Gy^{-1}, $\beta = (0.0242 \pm 0.0047)$ Gy^{-2} for the mixed fields and $\alpha = (0.407 \pm 0.078)$ Gy^{-1}, $\beta = (0.0224 \pm 0.0095)$ Gy^{-2} for the addition of the individual components.
Thus it appears that there are no significant synergistic effects of combined alpha-particles and gamma-rays under the conditions of these experiments.

High-LET Dose and Microscopic Uncertainties in an Irradiated Cell Population

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The probability distribution of specific energy deposited by radiation in a microscopic site is described by the microdosimetric multi-event density function and thus applies only to an infinite population of sites. The mean of this density function is the dose D. However, when a cell irradiation is performed, a finite sample of such volumes is implicated. The (unknown) average dose actually deposited in them will be different from D, and some measure of how close the point estimate is likely to be to the true value is necessary.
In this work, we show that a $(1-\alpha)$% confidence interval for the sample average dose can be calculated knowing the population mean dose D and the microdosimetric quantity z_D, the dose-mean specific energy. As an example, we analyze a hypothetical survival experiment where ^{10}B thermal neutron capture reactions are produced. For a spherical cell nucleus 10 microns in diameter and a uniform distribution of boron reactions, the z_D value is 0.41 Gy.
In order to get a 95% confidence interval for the sample average boron dose of length no more than 2%, the number of cells to be seeded for a given survival point is $N=1.57\text{x}10^4/[DS(D)]$, where D is the dose in Gy for that point and $S(D)$ the survival due only to the boron component.

This implies that the number of cells needed to achieve an uncertainty of 2% at 1 Gy is two orders of magnitude larger than for photons. Likewise, if a survival point is measured by considering for example a hundred surviving cells, the total uncertainty is 25% for a mean boron dose of 1 Gy. If the microdistribution of reactions is not uniform, both z_D and D must be calculated on a microdosimetric basis. This shows the importance of taking into account the stochastic aspects for specifying dose uncertainties associated to survival points, especially when high-LET radiation and low doses are involved.

Study of Hela cell Damage Effect Induced by ^{7}Li Ions Irradiation

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NCT is an experimental form of treatment that requires the infusion of an element such as Boron or Gadolinium and exposure of the patient to a Neutron Beam from a nuclear reactor.
It is a two component or binary system, based on the nuclear reaction that occurs when the stable isotope ^{10}B is irradiated with low energy or thermal neutrons to yield highly energetic particles including 1.47MeV of helium-4 (^{4}He) nuclei (i.e., α particles) and 0.84MeV of recoiling Lithium-7 (^{7}Li) ions. The emitted α particles and ^{7}Li ions are largely high linear energy transfer (LET), producing more severe damage than low LET (such as X-rays, γ-rays and electron) radiation resulting in the increase of cell death. The short range in tissue of these two particles (<10 μm) allows localized energy release in tumor cells, saving the surrounding healthy tissue. These particles exhibit characteristics of high energy transfer (LET) radiation and have enhanced biologic effects. Therefore, It is essential to study the mechanism of tumor cell damage induced by α particles and ^{7}Li ions radiation. Here, α particles and Lithium ions were produced by ^{241}Am radiation source and HI-13 tandem accelerator at China Institute of Atomic Energy (CIAE) respectively to simulate ionizing radiation in Boron Neutron Capture Therapy (BNCT) process. The effects of heavy ion radiation on Hela cells were investigated with a 30MeV ^{7}Li irradiation.

Molecular Targeting of the Epidermal Growth Factor Receptor for Boron Neutron Capture Therapy of EGFR Positive Gliomas

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In the present report we will summarize studies carried out over the past 5 years on molecular targeting of the epidermal growth factor receptor (EGFR) and its mutant isoform, EFGRvIII, for BNCT of the F98 rat glioma. EGF or the monoclonal antibodies (mAbs), cetuximab (IMC-C225) and L8A4, which recognize wildtype EGFR and EGFRvIII, respectively, were heavily boronated using PAMAM dendrimers (BD). These were chemically linked to the targeting vehicles by means of heterobifunctional reagents. Biodistribution studies revealed their preferential localization in receptor (+) gliomas following intracerebral (i.c.) administration by either intratumoral (i.t.) injection or convection enhanced delivery (CED). Tumor boron values ranged from 35-60 μg/g and normal brain values were 4-6 μg/g.
BNCT was carried out at the Massachusetts Institute of Technology Research Reactor (MITR-II) 12-14 d after tumor implantation and 24 h following i.c. administration of the boronated EGF or mAbs, administered by either i.t. injection or CED, either alone or in combination with i.v. BPA.
Following BNCT, the mean survival times (MSTs) of rats bearing $F98_{EGFR}$ gliomas that had received BD-EGF or BD-C225 by i.t. injection were equivalent (43 d.), compared to 54 d. following CED without i.v. BPA and 70 d. with it. Untreated or irradiated control animals had MSTs of 26-28 d. and 31-34 d., respectively, compared to 39-40 d. for rats that had received i.v. BPA. The best survival data were obtained in rats bearing $F98_{EGFRvIII}$ gliomas that had received CED of BD-L8A4 either alone or in combination with i.v. BPA (71 d. and 85 d., respectively).

Studies carried out in rats bearing a 1:1 mixture of $F98_{EGFR}$ and $F98_{npEGFRvIII}$ glioma cells demonstrated that it was essential to target both receptors in order to obtain an optimal therapeutic effect. Based on these observations, we have concluded that EGFR targeting vehicles are useful, but not stand-alone boron delivery agents and that they should be used in combination with BPA, BSH or other low molecular weight delivery agents.

BNCT Inhibits Second Primary Tumor Recurrences in Experimental Oral Cancer

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In previous studies we demonstrated the efficacy of BNCT mediated by BPA, GB-10 or the combined administration of (BPA+GB-10) to control tumors with no normal tissue radiotoxicity in an experimental model of oral cancer in the hamster cheek pouch. This model allows for the study of field cancerized tissue around the induced tumors, an issue of great clinical relevance because second primary tumor recurrences occur in field cancerized areas, jeopardizing the therapeutic success of anti-tumor therapies. The aim of the present study was to evaluate the potential inhibitory effect of BPA-BNCT, GB-10-BNCT and (BPA + GB-10)-BNCT on the development of second primary tumors from hamster cheek pouch field cancerized tissue, employing the BNCT protocols that proved highly successful in controlling hamster cheek pouch tumors in previous studies.
We developed an experimental model of field cancerization in the hamster cheek pouch that mimics human oral field cancerized mucosa. Employing this model we performed biodistribution studies with BPA (15.5 mg B/kg), GB-10 (50 mg B/kg) and [BPA (31 mg B/kg) + GB-10 (34.5 mg B/kg)] to evaluate boron content in blood, field cancerized tissue and normal tissues and perform the corresponding dosimetric calculations. BNCT studies were then performed at the RA-6 Reactor hyperthermal neutron facility in Bariloche. The response of field cancerized tissue to BPA-BNCT, GB-10-BNCT and (BPA + GB-10)-BNCT and beam only (n=7-9 animals per group) was monitored periodically upto 8 months post-treatment employing macroscopic follow-up and tumor volume assays as end-points. The clinical status and body weight of the animals were also evaluated. The total physical dose to pouch field cancerized tissue ranged from 4 to 8 Gy. At different time-points some of the animals were sacrificed for histological analysis. A group of 20 cancerized, sham-irradiated animals served as controls. Four groups of 10 non-cancerized hamsters were treated respectively with each of the three BNCT protocols and with beam only to study the effect on normal pouch tissue.
All three BNCT protocols induced a highly statistically significant inhibitory effect on the development of tumors from hamster cheek pouch field cancerized tissue. In the case of BPA-BNCT and (BPA + GB-10)-BNCT, the inhibitory effect reached a maximum of 100% and persisted at 100% at the last time point evaluated (8 months). The inhibitory effect of GB-10-BNCT reached a maximum of 100% but faded after 2 months post-treatment. As from 5 weeks of follow-up several of the tumors that developed in cancerized non-treated hamsters were larger than 10 mm^3 and some even exceeded 50 mm^3. Conversely, as from 5 weeks post-treatment and until the last time point evaluated, the tumors that did develop in the BPA-BNCT and (BPA + GB-10)-BNCT groups never exceeded volumes of 10 mm^3. Beam only exerted a transient but significant inhibitory effect on tumor development from field cancerized tissue. Normal tissue did not exhibit radiotoxic effects at any of the time-points evaluated. Overall, the macroscopic inspection and histological analysis of the cancerized pouches treated with BPA-BNCT and (BPA + GB-10)-BNCT revealed that at 8 months post-treatment the field cancerized pouch tissue was similar to non-cancerized, normal pouch tissue.
The present study provides evidence that BNCT induces a marked inhibitory effect on tumor development in field cancerized tissue with no radiotoxicity in normal tissue and is capable of reverting at least the histological hallmarks of field cancerization.

In the case of BPA-BNCT and (BPA + GB-10)-BNCT the inhibitory effect persisted until the last time-point evaluated (8 months) whereas in the case of GB-10-BNCT it faded after 2 months. The difference between protocols could be attributed to the differences in the mechanisms of action of the different boron compounds, i.e. cellular targeting via BPA-BNCT and vascular targeting via GB-10-BNCT.
BNCT protocols that were proved effective to control hamster cheek pouch tumors would also inhibit local regional recurrences caused by the development of tumors in field cancerized tissue, confering on BNCT a potential additional clinical application.

Development and Characterization of a Small Animal Irradiation Facility for Boron Neutron Capture Therapy (BNCT) Research at the RA-3 Research Reactor: Application to BPA-BNCT for Oral Cancer

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The National Atomic Energy Commission of Argentina (CNEA) has constructed a thermal neutron source for use in BNCT applications at the RA-3 research reactor facility located in Buenos Aires. A tunnel in the graphite thermal column enables the insertion of samples while the reactor is in normal operation. The free-field neutron flux spectrum was measured at the irradiation location by nuclear activation techniques employing a variety of foils to cover the energy range from thermal to about 1 MeV. The thermal neutron flux was also measured employing self-powered nuclear detectors (SPND). The foil measurements indicated that the free-field thermal flux was 7.1 x 10^9 n/cm^{2}s^{-1}and the fast neutron flux was 2.5 x 10^6 n/cm^{2}s^{-1} with estimated uncertainties of 8%, indicating a very well thermalized neutron field with negligible fast neutron dose.
The gamma dose rate at the irradiation location was 5.0 ± 0.6 Gy/h. Having previously demonstrated the efficacy of BPA-BNCT to treat tumors in the hamster cheek pouch oral cancer model at the RA-6 Reactor hyperthermal neutron facility, we performed some initial studies of BPA-BNCT at the RA-3 facility to evaluate the feasibility of treating hamster cheek pouch tumors with no radiotoxic effects in normal tissues in the new facility, taking into consideration that the whole body of the animal would be exposed to the thermal neutrons.
Three animals bearing a total of 11 tumors were irradiated 3 hours after ip administration of BPA (15.5 mg B/kg). The total physical dose delivered to tumor and normal tissue respectively was 3.4 ± 0.4 Gy and 2.1 ± 0.3 Gy. Potential whole body radiotoxicity discouraged the administration of higher tumor doses. At 30 days post-BNCT we observed 55% tumor control (complete remission 9.1%) with no normal tissue radiotoxicity.
These results were encouraging but further escalation of the tumor dose required a modification of the irradiation apparatus to avoid unacceptable escalation of the whole body dose. In order to shield the body of the animal from the neutron flux while exposing the everted cheek pouch bearing the tumors, we developed an enclosure fabricated from plates composed of a 6 mm layer of lithium carbonate enriched to 95 % in lithium-6 sealed between thin sheets of Lucite.
The hamster pouch bearing tumors is everted out of the enclosure and onto a protruding shelf. A Lucite hamster phantom was constructed for measurements to determine the spatial distribution of the thermal and above-thermal flux based on activation of copper-gold flux wires. The wire measurements showed that the thermal neutron flux at all locations within the shield container is at least a factor of 20 lower than the flux on the shelf. A new set of BNCT irradiations employing the shielding device was performed in 8 hamsters bearing a total of 58 tumors.
The total physical dose delivered to tumor and normal body tissue respectively was 5.50 ± 0.67 Gy and 0.62 ± 0.09 Gy. Tumor control was 70% (complete remission 56.6%) with no normal tissue radiotoxicity. The significant reduction in whole body dose offers the possibility of further increase in tumor dose, provided the radiotolerance of precancerous tissue surrounding tumor is not exceeded.

RA-3 is a useful irradiation facility for BNCT-related small-animal studies. Additionally, comparative studies with other facilities such as RA-6 and RA-1 will allow for enlightening radiobiological studies on the effect of the different dose components of BNCT since these other facilities have different neutron spectra than RA-3.

Boron Neutron Capture Therapy of Liver and Lung Coloncarcinoma Metastases: an *in vitro* Survival Study

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The management of tumors disseminated in explantable organs by means of BNCT is particularly favourable. The possibilty to perfuse the isolated organ, withdrawing the residual boronated compound, and to expose it entirely to the neutron flux, let BNCT to better show its peculiarity i.e. selectively kill neoplastic ^{10}B enriched cells sparing normal ^{10}B lacking tissues. Being BNCT effectiveness tightly dependent on the amount of the endocellular boron at the time of neutron irradiation, the occurrence of the discarge of a fraction during the perfusion procedure is a questionable point in terms of therapeutic efficacy. In order to investigate the incidence of the endocellular boron loss, caused by the boronated compound deprivation, the boronophenylalanine (BPA) cell uptake and its washout were checked *in vitro* on the DHDK12TRb (DHD) rat coloncarcinoma cell line and *in vivo,* on BD-IX rats, affected by liver metastases induced by DHD cells injection, following BPA removal by the organ perfusion. The dose-dependent cell survival was studied on the same cell line. Results on the DHD cells show a time and concentration dependent boron accumulation capability. Cell harvesting as like as time and temperature of permanence in boron deprived medium influence boron loss, that can reach substantial levels. Nevertheless the retained intracellular fraction results in a TD_{50} for an absorbed dose of 0,29 Gy. *In vivo* data of ongoing studies show more favourable cellular behaviour in terms of retained boronated compound suggesting that the organ perfusion cannot invalidate the BNCT therapeutic efficacy.

Radiobiological Studies in a Human Cell Line of Undifferentiated Thyroid Cancer (UTC) for BNCT

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In previous studies we demonstrated the efficacy of BNCT for the treatment of UTC using ^{10}BPA (p-borophenylalanine) alone and combined with ^{10}BOPP (2,4-bis (α,β-dihydroxyethyl)-deutero-porphyrin IX). In the present work we evaluated in vitro the mechanisms of damage induced by BNCT by cytokinesis block micronuclei assay (CBMN) and by the cell fraction survival using a colorimetric assay of viability (MTT). We also calculated the relative biological effectiveness factor (RBE) of the neutron beam and the compound biological effectiveness (CBE) values for BPA and BOPP. Exponentially growing human cells of UTC (ARO) were distributed into the following groups: 1) BPA (10 ppm ^{10}B) + neutrons; 2) BOPP (10 ppm ^{10}B) + neutrons; 3) neutrons alone; 4) gamma-rays (^{60}Co). The cells were irradiated in the thermal neutron beam of the RA-3 (flux= 7.5 10^9 n/cm^2 sec).
The irradiations were performed during different times in order to obtain total physical doses between 1-5 Gy (±10%). The frequency of micronucleated binucleated UTC cells and the number of MN per micronucleated binucleated cells showed a dependent dose relationship until around 2 Gy. The response to gamma rays was significantly less than the other treatments.
The irradiation with neutrons alone and neutrons + BOPP showed curves that didn't differ significantly and showed less DNA damage than neutrons + BPA. The number of MN per micronucleated binucleated cell showed that high physical doses from BNCT treatment modified the distribution, increasing the frequency of micronucleated cells with 4 or >4 MN. A decrease in the survival fraction as a function of the physical dose was observed for all the treatments. We also observed that neutrons and neutrons + BOPP did not differ significantly and that BPA is the more effective compound. The RBE and CBE factors calculated from CBMN and MTT assays, respectively, gave the following values: beam RBE: 4.4 ± 1.1 and 2.4 ± 0.6; CBE for BOPP: 8.0 ± 2.2 and 2.0 ± 1; CBE for BPA: 19.6 ± 3.7 and 3.6 ± 1.3. These values represent the first experimental values obtained for the RA-3 in a biological model and will be useful for future dosimetric experimental studies of the application of BNCT to UTC**.**

Bystander effect induced mutagenicity in HPRT locus of CHO cells followed BNCT neutron irradiation

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To investigate bystander mutagenic effects induced by alpha particles during boron neutron capture therapy (BNCT), we mixed cells that were electroporated with borocaptate sodium (BSH), which led to the accumulation of ^{10}B inside the cells, and cells that did not contain the boron compound. BSH-containing cells were irradiated with alpha particles produced by the ^{10}B(n,α)^{7}Li reaction, whereas cells without boron were only affected by the ^{1}H(n,γ)^{2}H and ^{14}N(n,ρ)^{14}C reactions.
The lethality and mutagenicity measured by the frequency of mutations induced in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus were examined in Chinese hamster ovary (CHO) cells irradiated with neutrons (Kyoto University Research Reactor: 5 MW).
Neutron irradiation of 1:1 mixtures of cells with and without BSH resulted in a survival fraction of 0.1, and the cells that did not contain BSH made up 99.4% of the resulting cell population. The molecular structures of the mutations were determined using multiplex polymerase chain reactions (PCRs).

Due to the bystander effect, the frequency of mutations increased in the cells located nearby the BSH-containing cells compared with control cells. Molecular structural analysis indicated that most of the mutations induced by the bystander effect were point mutations and that the frequencies of total and partial deletions induced by the bystander effect were less than those induced by the original neutron irradiation.
Previously, we reported that the dimethyl sulphoxide (DMSO) or ascorbic acid showed the protective effect on cell killing and mutagenicity against the neutron irradiation. We here compare the effect of bystander mutation induction of short-lived radicals and long lived-radicals. The treatment with DMSO, which acts as a short-lived radical scavenger, reduced bystander mutation induction of neutrons. Furthermore, the ascorbic acid post-irradiation treatment, which acts as a long-lived radical scavenger, reduced much more bystander mutation induction of neutrons than the short-lived radical scavenger did.

Molecular targeting of CD44 for Mesothelioma

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Malignant pleural mesothelioma (MPM) is an aggressive and refractory tumor caused by asbestos exposure. Therapy of MPM is required the multidisciplinary treatment; surgery, chemotherapy, and radiotherapy. However, surgery (extrapleural pneumonectomy) is limited to the locally advanced MPM. The chemotherapeutic regimens with Pemetrexed have resulted in an improved tumor response, but the median survival duration is only 12 months from the date of diagnosis.
Radiotherapy including intensity-modulated radiotherapy (IMRT) is limited utility because the extensiveness of the tumor requires large fields and it is impossible to administer tumoricidal doses without injuring the adjacent lung and mediastinal organs. BNCT is expected to be a breakthrough strategy for MPM, because it is suitable for the therapy of diffuse and invasive tumor. However, the success of BNCT depends on the selective delivery of ^{10}B–atoms to tumor cells to supplement the attenuation of thermal neutron. We focused CD44 for the targeting therapy of MPM, because a large amount of CD44 is expressed on the MPM cells. We developed Hyaluronan (HA) - ^{10}B conjugate for the targeting of BNCT. We also used the Hemagglutinating Virus of Japan Envelope (HVJ-E) as a vehicle of ^{10}B, because it can eradicate tumors and mechanism through which it induces antitumor immune responses. However, the application of HVJ-E is limited to the local administration because of the hemagglutination. So we developed the novel HA and HVJ-E conjugate(Cationized HA HVJ-E; CZ-HA-HVJ-E) incorporating BSH to diminish the side effect of HVJ-E. We examined basic characteristics and antitumor efficacy of CZ-HA-HVJ-E Compound.

1) The hemagglutination test; The hemagglutination of CZ-HA-HVJ-E was diminished by Cationized-HA. 2) Binding ability and gene transfer efficiency of CZ-HA-HVJ-E to MPM cells; CZ-HA-HVJ-E with Quantum Dot 655(Qdot655) or with luciferase gene showed significant higher fluorescence or higher transfection efficiency than HVJ-E. Furthermore, these preferences to the MPM cells were diminished by the CD44 neutralizing antibody. 3) Cytotoxicity of CZ-HA-HVJ-E BSH to MPM cells with BNCR; CZ-HA-HVJ-E BSH showed the higher cytotoxicity than BSH by BNCR after only 30 minutes contact of each BSH compound. 4) Anti-tumor efficacy of CZ-HA-HVJ-E BSH for MPM pleural dissemination model; CZ-HA-HVJ-E BSH efficiently suppresses the local growth of MPM cells *in vivo* with BNCR. These results suggest that the CD44-targeted delivery of ^{10}B with HA is a potentially useful modality for MPM.

Cell Survival Measurements, with and without Boron, in an Accelerator Produced Epithermal Neutron Beam: A Proposal for a Radiobiological Intercomparison of BNCT Facilities

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The accelerator-based BNCT facility at Birmingham has been previously used for cell survival measurements and data from these irradiations presented at earlier ICNCT conferences (Mason 2004). The purpose of the work to be presented here is to extend these data using more clinically relevant conditions of temperature, growth conditions and cell lines. A further aim is to establish a standard simple and reproducible protocol for the international comparison of the biological effectiveness of different BNCT facilities.
Three cell lines are being used for these experiments: V79 Chinese hamster cells and M095K and M095J human glioma cells. V79 cells are widely used in radiobiology research, and the use of these for international comparisons is ideal. However, M095K and M095J cells are of more relevance for BNCT purposes.
Initial results for irradiations with V79 cells in 50 ppm of boron-10 (as boric acid) indicate an approximate 8 to 10-fold increase in cell killing at all depths over non-borated cells. This is in broad agreement with previous data using a reactor-based neutron beam (Mill 1994).
A standard set-up and protocol for comparison purposes will be presented. This will be based on a large rectangular water phantom maintained at a temperature of 37 °C. V79 cells will be irradiated attached to T25 flasks placed at set depths within the water phantom and containing two different concentrations (0 and 50 ppm) of boron-10 (as boric acid). It is hoped that a number of groups will participate in a biological inter-comparison of their BNCT irradiation facilities.

Inhibition of Tumor Growth of Mouse Colon Cancer Cell Line by Boron Neutron Capture Therapy & Immunotherapy

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Cytotoxic effects of locally injected ^{10}B entrapped cationic liposome (COATSOME-EL) on mouse colon cancer were evaluated with thermal neutron irradiation.
^{10}B entrapped COATSOME-EL was prepared. After thermal neutron irradiation of mice injected with ^{10}B entrapped COATSOME-EL, 2 x10^6 immature dendritic cells (DC) were injected intratumorally. Colon26 tumor growth was suppressed in the groups of BNCT and BNCT with DC injections relative to controls. After one month observation of tumor growth, the splenocytes of tumor bearing mice were isolated, and were transferred to other same strain mice by intraveneous injection. Then, half million of colon26 cells were challenged.

The growth of colon26 tumors was highly suppressed in mice that received spleen cells from DC-treated mice, suggesting that anti-tumor immunity was induced by DC treatment.
These data showed that direct DC immunotherapy could be enhanced the anti-cancer effect of BNCT and had the possibility of use in clinical use in near future.

BNCT for oral squamous cell carcinoma cells with p53 gene mutation

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Purpose: Mutation in p53 tumor suppressor gene is a genetic alternation observed in oral squamous cell (SCC) frequently. However, the role of p53 gene in sensitivity of oral SCC to boron neutron capture therapy (BNCT) had not been investigated intensively. In this study, we examined the effect of BNCT on oral SCC cells with p53 gene mutation.
Material and methods: Oral SCC cells showing either wild-type p53 (SAS/neo) or mutated-type p53 (SAS/mp53) were used. Surviving fractions were mesured by clonogenic assay. Cell viability was measured by MTT assay. Apoptotic cells were evaluated by flow cytometry and nuclear DNA staining. The cell cycle and cell cycle-related proteins were examined with flow cyctometry and Western blot analysis. BNCT for cultured cells was performed in the presense of boronophenylalanine (BPA) in the medium at KUR.
Results: When SAS/neo and SAS/mp53 cells were subjected to BNCT at a physical dose of 6 Gy, more suppressive effects on colony formation and cell viability were observed in SAS/neo cells as compared with SAS/mp53. Cell cycle of SAS/neo was arrested at the G1 and G2 checkpoints, but that of SAS/mp53 was arrested at the G2 checkpoint only. Western blot analysis revealed the phosphorylation of p53 and up-regulation of p21 at 6 h after BNCT, and the up-regulation of Wee1 and phosphorylation of cdc2 in SAS/neo cells at 12 h after BNCT. Although, there were no changes in p53, and p21, up-regulation of Wee1 and phosphorylation of cdc2 at 12 h after BNCT were observed in SAS/mp53 cells. Apoptotic cells with DNA fragmentation were increased at 6 h after BNCT in SAS/neo cells, and at 48 h after BNCT in SAS/mp53 cells.
Conclusions: These results suggest that oral SCC cells with mutated p53 gene are more resistant to BNCT than those with wild-type p53. Inhibitory effect of BNCT on SAS/neo cells can be ascribed to arrest at the G1 and G2 checkpoints and apoptosis associated with G1 arrest, but that on SAS/mp53 cells be ascribed to the arrest at the G2 checkpoint and apoptosis associated with G2 arrest. BNCT must inhibit oral SCC cells in p53-dependent and p53-independent mechanisms.

Feasibility Study of the Utilization of Boron Neutron Capture Therapy (BNCT) in Diffuse Lung metastases in a Rat Model

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In order for BNCT to be eligible for clinical application in lung tumour disease, three fundamental criteria must be fulfilled; there must be selective uptake of boron in the tumour cells in respect to surrounding healthy tissue, biological effectiveness of the radiation therapy and minimal damage or collateral effects of the irradiation on the surrounding tissues. In this ongoing study, we evaluated the biological effectiveness of BNCT by *in vitro* irradiation of rat colon-carcinoma cells previously incubated in boron-enriched medium. One part of these cells was re-cultured *in vitro* while the other was inoculation via the inferior vena cava to induce pulmonary metastases in a rat model.
We observed a post-irradiation cell viability of 0.05% after 8 days of cell culture. At four months follow-up, all animal test subjects that received irradiated cells were alive while no animal survived beyond one month in the control group that received non-treated cells. ($P<0.001$ Kaplan-Meier). These preliminary finds strongly suggest that BNCT has a significant lethal effect on tumours cells and post-irradiation surviving cells lose their malignant capabilities. This radio-therapeutic potential warrants the investigation BNCT in *in vivo* lung tumour metastases.

Selective uptake of p-boronophenylalanine by osteosarcoma cells for boron neutron capture therapy

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Osteosarcoma is the most common non hematologic cancer type that develops in bone. Current osteosarcoma treatment relies on surgical resection associated with adjuvant chemotherapy and frequently requires the entire limb amputation. The incidence of distal recurrences reduces the survival rate to less than 60%. These poor data request to set up a new therapeutic approach aimed to restrict the surgical removal meanwhile acting a radical treatment. Boron neutron capture therapy (BNCT) could be a valid alternative or integrative option in case of osteosarcoma management. In this particular application field two main characteristics of BNCT could be turned in advantage: the selectivity of the therapeutic action and the possibility to deprive the circulatory system from the residual boronaded compound.
Aim of the present work is to investigate the feasibility of employing BNCT to treat knee osteosarcoma. An animal tumor model was developed in Sprague-Dawley rats by means of an intrafemoral injection of UMR-106 osteosarcoma cell line at the condyle site. The tumour to normal tissue ^{10}B ratio was determined injecting boronophenylalanine (BPA) as boron carrier. The endocellular compound uptake was previously *in vitro* checked on the referred cell line and results evidence an adequate cell accumulation capability. Despite preliminary *in vivo* data don't completely support the required prerequisite for BNCT applicability, they encourage us to express a positive judgement.

BORON IMAGING

BORON IMAGING – talk

Rapid biopsy processing for secondary ion mass spectrometric (SIMS) analysis

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The efficacy of boron neutron capture therapy depends on the preferential accumulation of a sufficient amount of ^{10}B in the cancer cell. The determination of the presence of ^{10}B *within* the cell is thus of critical importance. One technique that shows considerable promise in this regard is secondary ion mass spectrometry (SIMS). Critical requirements of the sample preparation for high vacuum chemical imaging techniques such as SIMS are that the tissue or cell viability is preserved faithfully and chemical redistribution is minimised. For tissue samples these criteria are typically met by plunge freezing the biopsy in liquid propane, cryostating (-20°C), thaw-mounting and freeze-drying. This process is not readily reproduced in a clinical theatre setting and is not easily applied to the tiny needle biopsies collected for routine diagnostic or other purposes. To this end, we have developed a rapid technique of tissue preservation and presentation that circumvents cryostating, and that is suitable in a clinical setting and for SIMS and complementary analysis.
Using this technique, tissue is available for SIMS analysis within 30s of removal from the patient. Importantly for sub-cellular chemical imaging, the sample temperature is maintained at -80°C or below throughout the entire processes, minimising the possibility of ionic redistribution of highly diffusible ions such as B^+. Viability was confirmed by vital dye staining and showed good preservation, especially in cell aggregates. Under H&E light microscopy, cellular morphology was excellent and architectural integrity was acceptable. Tissue integrity in SIMS is being explored by K:Na and ^{10}B uptake ratios.

CR-39 neutron imaging of biological samples at clinical linac's

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CR-39 track-etch detectors have been used for obtaining ^{10}B thermal neutron capture induced images of biological, including human lung previously perfused with ^{10}BPA, samples. Thermal neutrons production by means of a photo-neutron converter installed in front of the head of clinical linear accelerators is the method recently developed in Italy within the PhoNeS (Photo Neutron Source) collaboration and already tested at several hospital linac's (Trieste, Rome, Como, Turin, Rionero in Vulture, Campobasso, Salzburg).

Such a method was applied for the present study at the Turin Molinette Elekta SLIT 25 MV e-linac with the PhoNeS converter since December 2007. The group has used already calibrated CR39 extensively used also for dosimetric measurements. Several biological samples (thickness ~10㎜, area ~ 1cm^2), prepared by the clinical and biological units, have been positioned between couples of CR39 layers (37 x 13 x 1 mm^3 in size) within the PhoNes cavity and irradiated with ~10^{11} n cm^{-2} thermal neutron fluence, operating the linac at 400 MU/min (nominal pre-conversion dose rate) and integrating a total of ~$7 \cdot 10^4$ MU in ~3 h ~10^4 s . After etching the CR39 layers, 2h in NaOH (6N) at 90 ^oC, ~10㎜ diameter holes, corresponding to α and ^{7}Li products of neutron capture by ^{10}B, are clearly observed at the microscope with densities of the order of 1-2 $\cdot 10^3$ mm^{-2} following the features of the corresponding previously overlaying tissues. A specific sideways illumination procedure has allowed the recording of digital photographic camera high resolution images which are made available for comparison with histological ones and the determination of tissue ^{10}B concentrations.

Basic Methodology for Application to BNCT Using *In Vivo* Boron Imaging

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Boron neutron capture therapy (BNCT) has been reported to be effective in some kind of cancers. Positron emission tomography (PET) is very important method from a view point of evidence-based medicine (EBM). Capacity for taking the boron-10 compound is variety in each cancer so that PET study using fluoroboronophenylalanine (FBPA) is very effective as application to each cancer. In this report, it is a purpose to arrange the methodology for extended application to BNCT.
A basic method for the research of the extended application has been performed by *in vivo* measurement using PET with F-18 labeled FBPA. Each tumor was confirmed histopathologically, and each location was considered with MRI. The optimal administering method was arranged, and intra-venous or intra-arterial injection was performed to a patient with cancer. The time-activity curve was obtained by PET and the kinetic constants were calculated using an assumption kinetic model.
In patients with breast cancer, they were measured by FBPA-PET. Radioactivity accumulated 60 min after intra-venous injection of FBPA. The tumor to normal (T/N) ratio was 4.2. It has demonstrated the possibility to apply BNCT to breast cancer. In patients with oro-pharyngeal cancer, the catheter was put on the external carotid artery, and radioactivity was accumulated after the injection, but gradually decreased. The radioactivity curve in the lesion within the area of external-artery was suited to those of simulation from the model using following “probability equation”.

$$PB(n+1) = PB(n)\,(1 - 2*K(B\text{-}A)) + K(B\text{-}A).$$
$$PB(n) = a + b*p^n.$$

where $PB(n)$ is probability of a concentration in compartment B (tissue),
and A means arterial compartment.

It was able to be confirmed to boron imaging that simulation and the measurement value were corresponding in intra-venous or intra-arterial condition. Further, it may be possible to simulate boron concentration in tumor tissue by the “diffusion equation” for BSH. This method can be performed by the concept of PS-products (permeability-surface area). It may be possible to adopt for practical use.

PET pharmacokinetic analysis to estimate boron concentration in tumor and brain as a guide to plan BNCT for malignant cerebral glioma

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Introduction: To plan the optimal BNCT for patients with malignant cerebral glioma, estimation of the ratio of boron concentration in tumor tissue against that in the surrounding normal brain (T/N ration of boron) is important. We report a positron emission tomography (PET) imaging method to estimate T/N ratio of tissue boron concentration based on pharmacokinetic analysis of amino acid probes.
Methods: Twelve patients with cerebral malignant glioma underwent 60 min dynamic PET scanning of brain after bolus injection of ^{18}F-borono-phenyl-alanine (FBPA) with timed arterial blood sampling. Using kinetic parameter obtained by this scan, T/N ratio of boron concentration elicited by one hour constant infusion of BPA, as performed in BNCT, was simulated on Runge-Kutta algorithm. ^{11}C-methionine (MET) PET scan, which is commonly used in worldwide PET center as brain tumor imaging tool, was also performed on the same day to compare the image characteristics of FBPA and that of MET.
Result: PET glioma images obtained with FBPA and MET are almost identical in all patients by visual inspection. Estimated T/N ratio of tissue boron concentration after one hour constant infusion of BPA, T/N ratio of FBPA on static condition, and T/N ratio of MET on static condition showed significant linear correlation between each other.
Conclusion. T/N ratio of boron concentration that is obtaied by constant infusion of BPA during BNCT can be estimated by FBPA PET scan. This ratio can also be estimated by MET-PET imaging. As MET-PET study is available in many clinical PET center, selection of candidates for BNCT may be possibile by MET-PET images. Accurate planning of BNCT may be performed by static images of FBPA PET. Use of PET imaging with amino acid probes may contribute very much to establish an appropriate application of BNCT for patients with malignant glioma.

Calibration of the prompt gamma ray spectroscopy facility in Petten for ^{10}B concentrations up to 2000 ppm

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At the BNCT facility in Petten, the Netherlands, ^{10}B concentrations are measured with the Prompt Gamma Ray Spectroscopy (PGRS) facility which is situated at one of the horizontal beam lines of the High Flux Reactor. Up until recently, the quantities of ^{10}B are determined in 1cc samples of blood, urine and/or tissues, following calibration of the facility, using certified ^{10}B solutions, ranging from 0 ppm up to 200 ppm and by fitting a calibration curve of a second order polynomial through 8 measurements. The concentrations of blood and tissue were always below the 200 ppm and therefore within the calibration range. However, recently, urine samples containing up to 1500 ppm have been measured. These values are outside the calibrated region and the fitted results were based on extrapolation of the fitted curve. In this study, newly certified ^{10}B solutions between 200 ppm and 2000 ppm are measured in order to verify if the previous extrapolation is justified. The outcome is that in the Petten PGRS set-up, two calibration curves are necessary. From around 450 ppm another fitted curve is needed as beyond this the self-shielding of the ^{10}B influences the results. This value of 450 ppm is confirmed by simulating the whole set-up with MCNP. With the new calibration curve, some patient cases with high ^{10}B concentrations in urine were analysed retrospectively, and the ^{10}B-concentrations changed up to 30%.

Study of a Monolithic Silicon Telescope for BNCT Applications

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The aim of this work is to study the feasibility of employing a monolithic silicon telescope for measuring the boron concentration in histological samples for BNCT (boron neutron capture therapy) applications. At the LENA reactor (Pavia, Italy) this information is derived by irradiating with thermal neutrons an histological sample (doped with boron) placed on a surface barrier silicon diode. This device measures the distribution of the energy deposited by alphas and ^{7}Li ions generated by neutron absorption on boron. The lower energy part of the spectrum is distorted by secondary electrons (produced by photon background) and by protons generated via the ^{14}N(n,p) reaction in tissue.
The monolithic telescope consists of a ΔE and an E stage built on the same chip, about 2 μm and 500 μm thick, respectively. The ΔE – E structure permits to discriminate between different types of particles. This feature can be exploited to improve the accuracy of the boron concentration estimate.
A detector with a sensitive area of 1 mm^2 was irradiated (in vacuum) bare, faced with a boron implanted silicon chip (standard by NIST) and coupled to a thin sample of rat lung charged with boron. The contribution of protons generated via direct interaction of neutrons with the detector (nitrogen in the dead layer) was estimate. Alphas and lithium ions produced by neutron capture on boron resulted to be well-separated. Moreover, events due to protons generated in tissue by neutron capture on nitrogen were identified and discriminated. The minimum detectable energy was reduced to about 40 keV.
A direct comparison of the estimate of boron concentration in an histological sample obtained with the monolithic silicon telescope and with the silicon diode (present technique) will be presented and discussed.

Boron concentration measurement in lung tissue by charged particles spectrometry

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The measurement of the boron concentration in tissues is one of the fundamental aspects of Boron Neutron Capture Therapy. This work describes a method based on the spectroscopy of the charged particles emitted in the reaction ^{10}B(n,α)^{7}Li induced by thermal neutrons. Thin slices of tissue containing ^{10}B are cut at low temperatures, deposited on mylar supports and irradiated under vacuum in a thermal neutron field.
The charged particles emitted by the sample are collected by a silicon detector and their spectrum is analyzed. The mass stopping power of the irradiated tissue is used to calculate the mass of the sample from which the charged particles originated. In this way the boron concentration can be determined by relatively easy calculations.
In this paper the potentiality and the limits of this technique are described and an example of an application to the measurement of the boron concentration in rat lung tissues is presented.

In vivo ^{19}F MR Imaging and Spectroscopy for the BNCT optimization

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Introduction: Boron Neutron Capture Therapy (BNCT) is a binary radio-therapeutic modality based on the cytotoxic effects of highly ionizing particles released in the $^{10}B(n,\alpha)^{7}Li$ reaction. To improve the BNCT effectiveness for malignant gliomas, C6 rat glioma model was used because of its similarity to the human glioblastoma. Aim of this work was to evaluate *in vivo* the spatial distribution and pharmacokinetics of 4-borono-2-fluorophenylalanine (^{19}F-BPA) using ^{19}F magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). Moreover the effect of L-DOPA as potential enhancer of ^{19}F-BPA tumour uptake was evaluated.

Methods and Materials: Eight male Wistar rats (300-350g) were anesthetized and a C6 cell suspension (10^6 cells in 10µl) was stereotatically implanted in the right hemisphere. Fourteen days after tumour implantation, rats were infused with a ^{19}F-BPA-fr-complex solution (300mg/kg(bw)) within carotid artery. Two rats were also injected intraperitoneally with a L-DOPA solution (100mg/kg(bw)) 24h before infusion. ^{1}H, ^{19}F-MRI images were acquired at 7T using the Spin-Echo (SE) sequence.
Echo-Time (TE)/Repetition-Time (TR)) were (40/2500)ms and (4.6/1800)ms for ^{1}H and ^{19}F scans respectively.
To perform pharmacokinetics studies blood samples were collected from the femoral vein at different times (1-2.5-5h) after infusion.

Results: Boron distribution mapping of ^{19}F-BPA was performed, *in vivo*, using ^{19}F-MRI. Selective ^{19}F-BPA bio-distribution in C6 tumour-bearing rats was revealed by superimposing the ^{19}F image with the corresponding ^{1}H image acquired for the anatomical correlation. Characteristic uptake of ^{19}F-BPA in C6 glioma showed a maximum at 2.5h after infusion as confirmed by both ^{19}F images, collected at different times (2.5-3.5-5h) after infusion, and ^{19}F spectra acquired on blood samples. Furthermore, increased ^{19}F-BPA tumour uptake after L-DOPA pre-treatment was assessed using ^{19}F-MRI.

Conclusion: This study shows the ability of ^{19}F-MRI to selectively map the bio-distribution of ^{19}F-BPA in C6 tumour-bearing rat and provides a useful method to perform pharmacokinetics studies using ^{19}F-MRS.

Neutron autoradiography with a silicon detector in a hospital environment

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In the framework of the INFN PhoNeS project a system to perform neutron imaging has been developed and tested at the radiotherapy unit of the S. Anna Hospital in Como with a Varian Clinac 2100C/D. Imaging is performed by neutron autoradiography with a non depleted self-triggering microstrip silicon detector, exploiting neutrons photo-produced by the Linac. Some boron doped samples were put on the surface of the detector and irradiated: the alpha particles produced in the reaction $^{10}B(n,\alpha)^{7}Li$ are detected and the result is a 1D scan of boron concentration. Dedicated readout electronics allows to acquire the data in the inter-bunch period in order not to blind the detector with the primary gamma beam. This real-time system is independent from the specific molecule containing the boron and it allows studying its concentration in cells using different carriers. The imaging detector has been tested with different samples: solutions of boric acid with different concentrations, boron resin, biological samples of urine containing BPA and BSH and finally with ^{10}BPA-Fructose complex perfused human lung samples. The paper will present the results in terms of minimum detectable concentrations and of kinetic curves.
The measurement uncertainty is <10% and can be improved using better techniques to deposit the samples on the support. The minimum detected amount of ^{10}B was 25 ng and the spatial resolution can be easily improved to 50 μm even if this is not a constraint.

BORON IMAGING – poster

Determination of boron in tissue using neutron-autoradiography and ICP-MS

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Due to the encouraging results of the BNCT research on non-resectable liver metastases in Pavia / Italy within the recent years, a close cooperation was formed between the University of Mainz, Germany, the Research Center Karlsruhe, Germany, and the University of Pavia. Expecting a clinical study of samples provided by 15 patients that suffer from liver-metastases of colorectal carcinoma, two methods for tissue analysis have been prepared. The boron concentration in the tissue is evaluated in Mainz by two different analytical methods: Neutron-autoradiography using CR-39 films and ICP-MS. CR-39 films overlaid with tissue slices which contain ^{10}B are irradiated at the TRIGA Mainz and the TRIGA Pavia and then analyzed.

The University of Mainz is equipped with a TRIGA Mark II reactor and a university hospital, which is an ideal situation for BNCT treatment in the way it was performed in Pavia, Italy, in 2001 and 2003.

In cooperation with the BNCT group in Pavia, a method for autoradiographical analysis of tissue samples was developed. Until now, neutron-autoradiography was mostly used for qualitative analysis. We will present a method for both qualitative and quantitative analysis that is based on graphical data only. This method consists of several algorithms designed especially for this purpose.

The samples are provided by the university hospital of the University of Mainz. After a BPA infusion, liver samples are taken from different positions and depths of the organ, then frozen in liquid nitrogen and cut to thin slices (10-40 µm).

The CR-39 films are irradiated in the thermal column of the reactor with a fluence of $\Phi = 3.15 \cdot 10^{11}$ n/cm² at a thermal reactor power of 1 kW. The films are then developed by placing them in NaOH (3 M) for different times between 60 and 120 minutes at 70 °C. Before doing so, they are cleaned in an ultra-sound bath for 10 minutes. Images of the films are taken with a light-microscope and then examined by means of several algorithms.

The algorithms were created using MATLAB as the program code and work fully automatically for quantitative analysis. The algorithms correct attributes like contrasts, exposure to light, particle borders etc. and then via segmentation render the tracks caused by the ionized radiation. Thus, the picture is converted into a matrix that is fit for further analysis.

Using the features of the program it is possible to determine the nature of the different tracks, the etching speed of the different tracks, their size, number and the area they cover. Hence it is possible to determine also the concentration the concentration.

The determination of the boron concentration is assisted by measurements with an ICP-MS (Agilent 7500). The tissue samples are digested and liquefied in a microwave oven and then prepared for the measurement by the ICP-MS.

We will present the neutron-autoradiography including the mathematical algorithms, the comparison measurements with ICP-MS and first results of the study.

The Present Situation and Problems of the Analysis of Boron Micro-Distribution in Tumor Cells Using PIGE

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We have applied micro particle induced X-ray emission (micro-PIXE) to determine inter- and intracellular distribution of boron-10 (^{10}B). Because the energy of micro-PIXE from ^{10}B is too low, we employed a method to detect gamma-ray produced from the nuclear reaction of ^{10}B (p, γ) ^{7}Be, namely particle induced gamma-ray emission (PIGE).
Cultured 9L gliosarcoma cells on Mylar film were exposed to sodium borocaptate (BSH). To analyze the inter- and intra-cellular distribution of ^{10}B in 9L gliosarcoma cells, 1.7MeV proton beam collimated to 1μm diameter were irradiated and emission gamma-rays were detected. We directly analyzed the inter- and intra-cellular distribution of ^{10}B in 9L gliosarcoma cells using micro-PIGE. These results showed that the distribution of ^{10}B atom was correctly measured. The distribution of ^{10}B should have the same distribution of 9L gliosarcoma cells and some ^{10}B atom showed same distribution of 9L gliosarcoma cells. However, there was significantly high background and the detection of true boron atom was not easy.
Further investigation is necessary for a higher spatial resolution and optimization of the measurement time or improvement of the sampling method. In future, this method will be applied to analyze the intracellular micro-distribution of the capture atoms and development of new drugs for NCT.

The Accumulation of MRI Contrast Agents in Malignant Fibrous Histiocytoma for Gadolinium Neutron Capture Therapy

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Neutron-capture therapy with gadolinium (Gd-NCT) has therapeutic potential, especially that gadolinium is generally used as a contrast medium in magnetic resonance imaging (MRI). Thus, both diagnosis and treatment can be carried out simultaneously. Future success of clinical Gd-NCT trials will depend on both the visualization of tumor cells on enhanced MRI and the selective large accumulation of gadolinium compounds in individual tumor cells. Consequently, we conducted this study using a human sarcoma cell line, malignant fibrosis histiocytoma (MFH) Nara-H. First, we investigated whether the accumulation of gadolinium in the cells could be detected by the MRI system. We used both the commercially available MRI contrast (Gd-DTPA) and the biodegradable and highly gadopentetic acid (Gd-DTPA)-loaded chitosan nanoparticles (Gd-nanoCPs) prepared by a novel emulsion-droplet coalescence technique.
After MFH was cultured, an adequate number of cells produced in the initial culture were harvested and re-seeded in three cell-culture flasks. Ten days thereafter, the first flask was used as the control and incubated with fresh culture medium for 12 hrs. The second and third flasks were incubated for 12 hrs with Gd-DTPA and Gd-nanoCPs suspension, respectively, in fresh culture medium. The culture medium of the three flasks was then aspirated, and the cells were washed and collected into three falcon tubes by detachment with trypsin and centrifuged. The pellet was collected and the supernatant was discarded. The three falcon tubes were then set into the 3-tesra MRI system to obtain signal intensities from each pellet by the Spin Echo method.
The longitudinal relaxation time (T1) was calculated by changing the Repetition Time (TR) under the same Echo Time (TE). The amount of Gd in the sample was then determined by inductively coupled plasma atomic emission spectrography (ICP-AES).

Our results showed that the accumulation of gadolinium in cells treated with Gd-nanoCPs was larger than that in cells treated with Gd-DTPA. In contrast, and compared with the control, Gd-DTPA was more effective than Gd-nanoCPs in reducing T1. The higher numerical reduction of T1 implies that the enhancement effect on tissue was higher on enhanced MRI examination. This contrast suggested that the larger accumulation exerted the adverse effect of lowering the enhancement of MRI. Future studies are warranted to gain insight into the therapeutic potential for Gd-NCT.

Biological Evaluation of Boronated Unnatural Amino Acids as New Boron Carriers

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There is a pressing need for new and more efficient boron delivery agents to tumor cells for use in Boron Neutron Capture Therapy (BNCT). A class of boronated unnatural cyclic amino acids has shown a remarkable selectivity to tumors in animal and cell culture models, far superior to currently used agents in clinical BNCT. One of these amino acids, 1-amino-3-boronocyclo-pentanecarboxylic acid (ABCPC), has shown a tumor to blood ratio of 8 and a tumor to normal brain ratio of nearly 21 in a melanoma bearing mouse model.

This work represents further biological characterization of this compound for tumor targeting in an EMT6 murine mammary carcinoma mouse model and a T98G human glioblastoma cell line. Female BALB/c mice bearing EMT6 tumors were injected with the fructose complex form of racemic mixtures of *cis*- and *trans* isomers of ABCPC in identical concentrations. Boron concentrations were measured in the tumor, blood, brain, skin, and liver tissues at 1, 3, and 5 hr post injection.

These observations revealed a remarkable difference in racemic mixtures of *cis* and *trans* isomers in tumor targeting by boron. This implies that further separation of the L and D forms of this compound may potentially enhance tumor targeting to an even higher degree than that provided by the racemic mixtures. Since these measurements were made in homogenized tumor and normal tissues, little is known about the subcellular location of the boron arising from the various isomeric forms of the amino acid.

To study subcellular delivery of boron from ABCPC in T98G human glioblastoma cells, we employed secondary ion mass spectrometry (SIMS). SIMS ion microscopy is capable of quantitatively imaging elemental (isotopic) gradients in cells and tissues at 500 nm spatial resolution. The T98G cells were exposed to the nutrient medium containing 100 ppm boron of a mixture of both L and D isomers of ABCPC in the form of a fructose complex for 1 hr. For a direct comparison with L-*p*-boronophenylalanine (BPA), another batch was exposed to BPA-fructose at a concentration of 110 boron ppm for 1 hr.

Following these treatments, the cells were fast frozen, freeze-fractured with a sandwich method, and freeze-dried prior to SIMS analysis. Within an hour of exposure, ABCPC delivered twice the level of boron than did BPA to T98G human glioblastoma cells with a partitioning of intracellular to extracellular boron of 3/1. SIMS imaging revealed that boron from ABCPC was distributed throughout the cell, including the nucleus, with minor heterogeneity.

These encouraging observations of the superiority of ABCPC over BPA in quickly delivering boron to tumor cells provide compelling support for further isomeric separations of ABCPC into the D and L forms for enhanced tumor targeting and continued testing of these compounds as new boron carriers in boron neutron capture therapy.

Towards prompt gamma spectroscopy for monitoring boron distributions during extracorporal treatment of liver metastases by boron neutron capture therapy: a Monte Carlo simulation study

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Boron Neutron Capture Therapy (BNCT), a binary modality selective form of radiation therapy, is based on the ^{10}B (n,α) ^{7}Li reaction: the emission of a high energetic α particle and a recoiling Li particle after thermal neutron capture in ^{10}B.
After the first successfully treatment of diffuse liver metastases at the TRIGA reactor in Pavia (2001), the Essen- Petten group investigates an extra corporal irradiation at the BNCT irradiation facility at the HFR Petten (The Netherlands).
A set up constituted by a rotating PMMA container with a liver, surrounded by PMMA and graphit for liver BNCT has already been performed in High Flux Reactor (HFR), Petten, the Netherlands providing homogeneity in thermal neutron field in the liver phantom. Thus treatment of an isolated liver with thermal neutrons is promising. It is necessary during BNCT treatment to perform spatial determinations of each dose contribution, both in tumour and in healthy tissue. In this work, the feasibility of boron distribution measurements during treatment by BNCT has been studied for the set up with a liver phantom and the gamma ray telescope of Petten. To achieve this objective, the telescope with germanium detector was simulated using Monte Carlo code MCNPc2 to collect the prompt gamma rays (478 keV) produced during the BNCT. Within the phantom, the tumour is represented by small sphere with 65 ppm ^{10}B and it is positioned in four positions for our study. Using a GeHP detector in a telescope, gamma ray 478 keV emitted by small specific region can be detected and the reconstruction formalism can calculate absolute boron concentrations using the simulated gamma ray rates.

Positron Emission Tomography: a crucial role for BNCT?

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Positron Emission Tomography (PET) has become a key imaging tool in clinical practice and biomedical research to quantify and study biochemical processes *in vivo*. Physiologically active compounds are tagged with positron emitters (e.g. ^{18}F, ^{11}C, ^{124}I) while maintaining their biological properties, and are administered intravenously in tracer amounts (10^{-9} – 10^{-12} M quantities). The recent physical integration of PET and Computed Tomography (CT) in hybrid PET/CT scanners allows a combined anatomical and functional imaging: nowadays PET molecular imaging is emerging as powerful pharmacological tool in oncology, neurology and for treatment planning as guidance for radiation therapy. The in vivo pharmacokinetics of boron carrier for BNCT and the quantification of ^{10}B in living tissue were performed by PET in the late nineties by W. Kabalka in USA (1997) and Y. Imahori in Japan (1998), using compartmental models based on PET data.

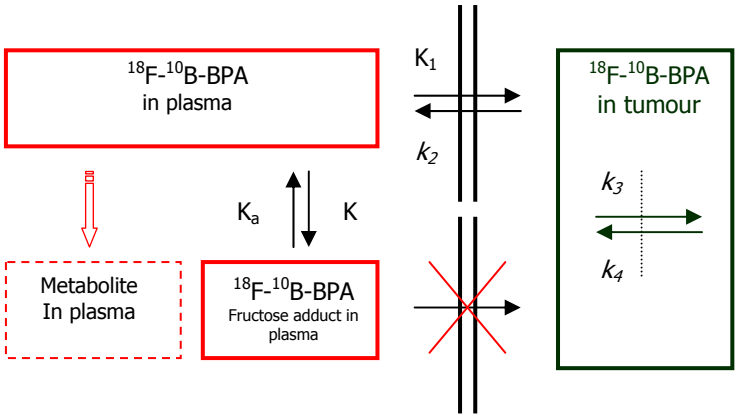

Figure: example of three-compartment model of L-^{18}F-BPA adopted for assessing the pharmacokinetic of BPA in patients. Rate constants K_1 [ml• g^{-1}•min^{-1}], k_2 [min^{-1}], $k3$ [min^{-1}], k_4 [min^{-1}] used in the four-parameters model for ^{18}F-^{10}BPA. K_a and Kb represent the dissociation/association process of the fructose-BPA adduct. The ^{10}B extraction in tissues can be calculated from the values of K_1, k_2, k_3, k_4 obtained by PET with ^{18}F-BPA and the input function of L-BPA

Nowadays PET and PET/CT have been used to address the issue of pharmacokinetic, metabolism and accumulation of BPA in target tissue. Imahori reported a method for the quantitative measurement of boronated drug uptake in patients with high grade gliomas, based on the use of L-[^{18}F]-BPA, i.e. the labelled analogue of L-BPA. The estimated values of ^{10}B-concentration of BPA can be calculated from a four rate constants model applied to a dynamic study by PET using ^{18}F-BPA as a tracer. With this approach the ^{10}B-concentration was assessed at the time of neutron irradiation in patients to be treated with BNCT after L-BPA administration.

Following a similar approach, recent applications have demonstrated the potential of PET imaging for the assessment of BPA accumulation in lesions different from high-grade glioma. ^{18}F-BPA has been used in recurrent cancer in the oral cavity and cervical lymph node metastasis (2007), low-grade brain tumours, such as schwannoma and meningioma (2006), head and neck malignancies (2005) and metastatic malignant melanoma (2003). These early clinical findings with ^{18}F-BPA /PET led to study the transport and the net influx and accumulation of BPA, and to show the capability of PET to screen the different types and different grades of tumour lesions as candidates for BNCT. The added value of the use of L-^{18}F-BPA and PET/CT in BNCT is to provide key data on the tumour extraction of ^{10}BPA versus normal tissue and to predict the efficacy of the treatment based on a single-study patient analysis.

Due to the complexity of a binary treatment like BNCT, the role of PET/CT is currently to design new criteria for patient enrolment in treatment protocols: the L-^{18}F-BPA/PET methodology could be considered as an important tool in newly designed clinical trials to better estimate the concentration ratio of BPA in the tumour as compared to neighbouring normal tissues. Based on these values for individual patients the decision could be made whether a BNCT treatment could be advantageous due to a selective accumulation of BPA in an individual tumour. This approach, applicable in different tumour entities like melanoma, glioblastoma and head and neck malignancies, make this methodology as reliable prognostic and therapeutic indicator for patient undergoing BNCT.

Aromatic aminoacid analogues mimetic of BPA transport : use of *O*-(2-[^{18}F]fluoroethyl)-*L*-tyrosine in experimental animal model of F98 Glioma

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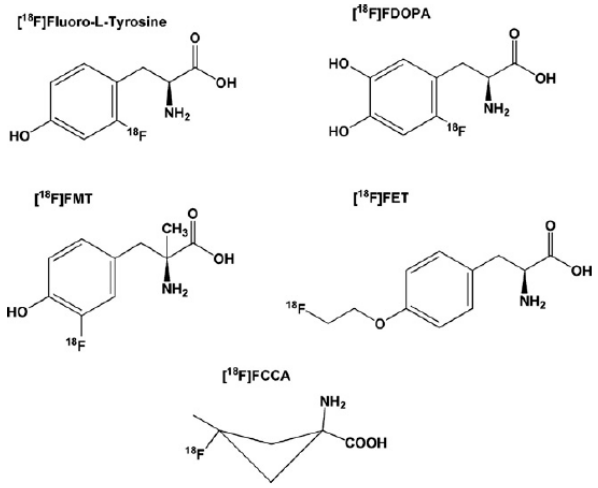
A number of recent applications demonstrated the potential of radiolabeled aromatic aminoacids with Positron Emission Tomography (PET) for brain tumour imaging: the mechanism is similar to other metabolic substrate and it is based on their specific accumulation in neoplastic cells, probably linked to an increased expression of amino acid transporters, but not due to their incorporation in proteins.



Although fluorine-18 (109.7 min half-life) is the most interesting radionuclide for the preparation of PET radiopharmaceuticals, the labeling of amino acids with fluoride-18 is often difficult, particularly in aromatic positions (the use of the molecular F_2, is on the contrary chemically unsuitable and is limited to a few PET centres provided of special equipment and cyclotron targets). An alternative way of labelling aromatic systems with fluorine-18 involves the introduction of a fluoroalkyl group to an aromatic position, rather than by direct labelling with a fluorine atom.

In this class a promising molecule for its applicable in neurooncology is the *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET), one the first ^{18}F-labeled amino acids. The tracer demontrated high in vivo stability, low uptake in inflammatory tissue and suitable uptake kinetics for clinical imaging.

The main objective of this work is to demonstrate the feasibility of a novel approach for experimental BNCT, with a special focus to *micro*imaging for the real assessment of the homogeneity and extent of accumulation of these class of aminoacid in tumour and surrounding healthy tissue. The goal of this study is then to use the FET to screen tumours lesions in experimental model with a small field of view PET, so called, *micro* PET. The *micro* PET-FET approach could lead to the assessment of the transport and the net influx and accumulation of FET molecule, as analogue to BPA. A correlation between BPA and FET pharmacokinetic, mainly linked to different affinities of transporters, could give numeric parameters useful for the assessment of boron loading in tumour and healthy tissues. The study present study was performed on implanted rats at the 3rd week after the tumour implantation (F98 glioma cell line).

In the frame of this project was developed a simple and convenient remote controlled, one-pot synthesis module for FET, based on an automated Gilson module (mod. *Aspec XL*) with opportune hardware and software modifications performed in our laboratories. The radiosynthesis was performed via no-carrier-added ^{18}F-fluorination of N-trityl-*O*-(2-tosyloxyethyl)-L-tyrosine-tert-butylester with subsequent deprotection under nonaqueous conditions in the presence of tetra-butyl ammonium hydrogen carbonate/carbonate. Deprotection of the intermediate FET derivative is performed in presence of trifluoroacetic acid in trichloromethane followed by solid-phase extraction. The FET containing HPLC eluent can be used for studies without purifications. The radiochemical purity is not less than 98% and the typical uncorrected radiochemical yield is higher than 40%; the total synthesis time is less than 90 min.

Measured Relative Distribution of Boron in Brain, Liver and Kidney in Rats

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The success of BNCT is partly depends on the uniformity of boron carrier distribution in tumor. Rat model implanted with C6, 9L and F98 glioma cells has been widely utilized for the assessment of new therapeutic modalities.
An experiment is undergoing on a rat's body to measure the boron distribution in brain, kidney and liver cells. After injection of a neutral solution containing boric acid and borax in a rat heart, the rat was sacrificed and the brain, kidney and liver were dissected. Then the frozen organs slices sandwiched within two pieces of CR-39 were bombarded with thermal neutrons. The alpha tracks registered on CR-39 after being etched in 6.25 molar NaOH at 65 °C for 60m were viewed on an optical microscopy equipped with a digital camera.. The boron distributions in different parts of organs were assessed by alpha track counting. Following Figure are only for reviewing purposes.

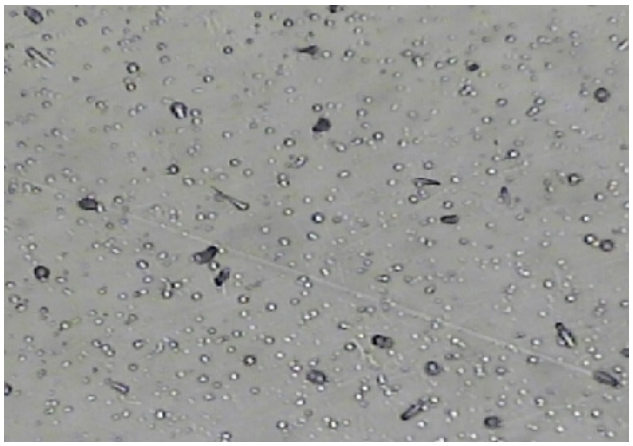

Photo 1 - Ion tracks on plastic of rat's forebrain

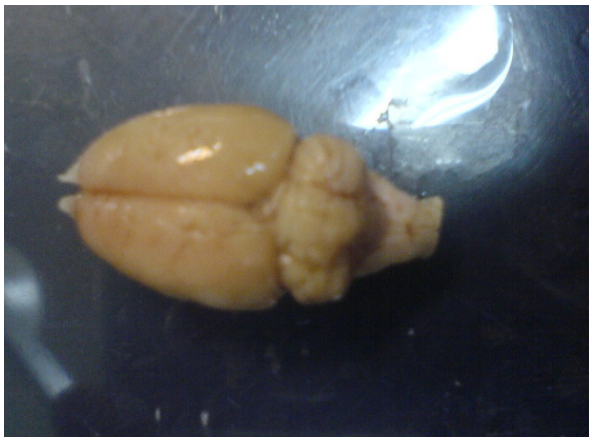

Photo 2 - Total brain of rat

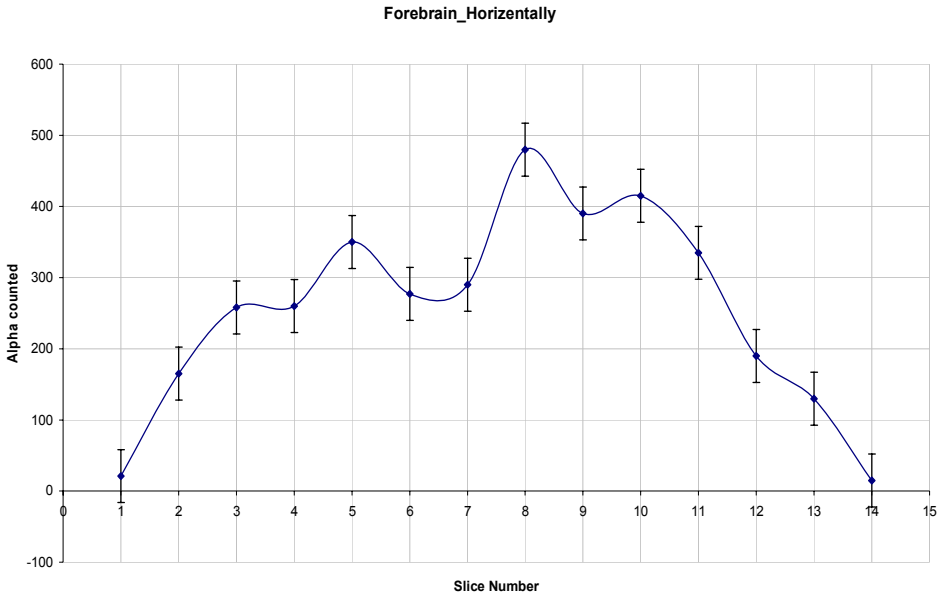

Fig. 1 - Boron distribution in rat forebrain

T2 Corrected Quantification of L-*p*-Boronophenylalanine-Fructose Complex Using Proton MR Spectroscopy

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Purpose: L-*p*-Boronophenylalanine-Fructose Complex (BPA-F) is widely used as a boron-10 carrier in boron neutron capture therapy (BNCT) for malignant brain tumor, skin melanoma, as well as head and neck cancer. In this study, we aimed to establish T2 corrected quantification method of BPA-F concentration using proton MR Spectroscopy (MRS).
Materials and Methods: The cylindrical water phantom containing BPA-F, Choline (Cho), Creatine (Cr), N-acetyl-aspartic acid (NAA) was used for experiments. The concentrations of BPA-F were 1.5, 3.0, 5.0, 7.5 and 10 mmol/kg. The concentration of Cho, Cr and NAA were 3.0, 5.0 and 3.0 mmol/kg each. Proton MRS was performed using a clinical 1.5-T super-conducting MR whole-body system (Philips Gyroscan ACS-NT Intera). Data were acquired by using a point resolved spectroscopy (PRESS) sequence with TR 2000 ms, TE 30, 230, and 490 ms. The volume of interest was a single-voxel of 20 x 20 x 20 mm^3. The signal intensities of BPA-F and internal water were corrected by T2 relaxation time. The absolute concentrations of BPA-F were calculated by proton MRS using an internal water signal as a standard.
Results: We have identified several characteristic resonances. The chemical shift of BPA-F in phantom was corrected using a choline peak as a standard. The biggest BPA-F peaks were detected around 7.1 to 7.6 ppm. We consider that the biggest peaks are well suited for the quantification of BPA-F. The T2 relaxation time was 314.3 ± 10.8 ms (mean ± standard deviation (SD)) in BPA-F, 885.1 ± 39.7 ms in internal water. The calculated BPA-F concentrations were almost same as the actual concentration of BPA-F and the correlation coefficient was 0.99.
Conclusions: We were able to quantify the concentration of BPA-F in phantom using a 1.5-T clinical MR machine. Our BPA-F quantification method was very simple and non-invasive, also it has high accuracy. Therefore, our results indicate that proton MRS can be potentially useful technique for in vivo BPA quantification in BNCT.

CHEMISTRY AND PHARMACOLOGY

Conjugates of boron clusters with derivatives of natural chlorin and bacteriochlorin

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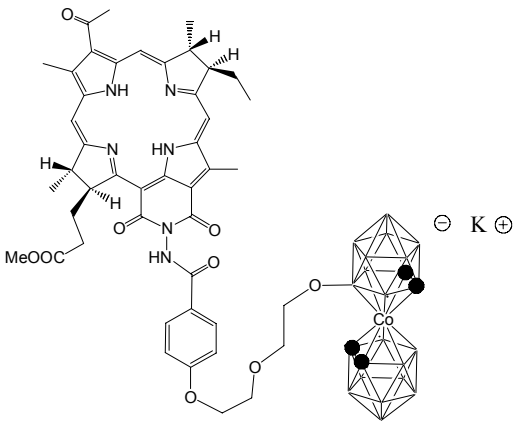
The subject of this presentation is a design of conjugates of polyhedral boron compounds with chlorin and bacteriochlorin which could be used for delivery of boron to tumor for boron neutron capture therapy (BNCT). Previously a new derivative of natural bacteriochlorophyll *a*, namely, a cycloimide bacteriochlorin *p* conjugate with the *closo*-dodecaborate anion, was prepared.
Now new ways of synthesis of conjugates of chlorins and bacteriochlorins with cobalt bis(dicarbollide) anion $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$ were developed. For acylation of exocyclic amino group of bacteriochlorin N-amino cycloimide, cobalt bis(dicarbollide)-based carboxylic acid was prepared by the ring opening reaction of cyclic oxonium derivative of cobalt bis(dicarbollide) with *p*-hydroxybenzoic acid. Condensation of the acid with bacteriochlorin N-amino cycloimide in the presence of 1,3-dicyclohexylcarbadiimide and N,N-dimethylaminopyridine results in conjugate **1**. Another approach was used for synthesis of chlorin conjugates with cobalt bis(dicarbollide) anion. Aminolysis of pheophorbide *a* with diaminoalkanes $NH_2(CH_2)_nNH_2$ (n=2,4,6) resulted in the corresponding chlorin *e6* derivatives with spacers of different length between the porphyrin macrocycle and terminal amino group. The opening 1,4-dioxane ring in cyclic oxonium derivative of cobalt bis(dicarbollide) with these amines gives conjugates **2a, 2b** and **2c,** where the chlorin macrocycle and the boron unit are separated by flexible and rather long spacer. *In vitro* study of the prepared conjugates revealed their effective accumulation in cancer cells.



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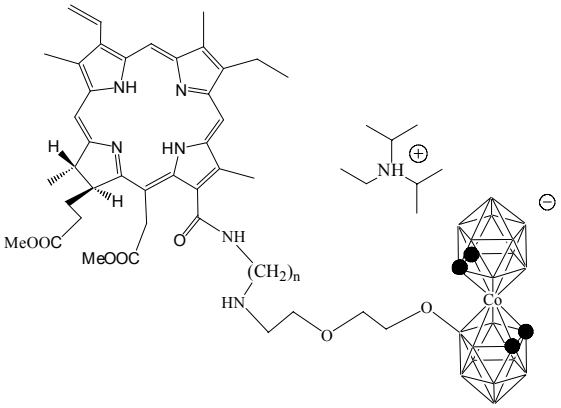

2 **a: n=2**
b: n=4
c: n=6

Suitability of boron carriers for boron neutron capture therapy for hepatoma *in situ*. Accumulation of boron in malignant and normal liver cells with L-boronophenylalanine, mercaptoborane and boric acid

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Introduction: Heptocellular carcinoma remains widely prevalent in tropical Africa and south-east Asia. Its prognosis is extremely poor unless the tumor was diagnosed in an early stage and resected before metastasis. Therefore, BNCT may provide an alternative therapy for treatment of hepatocellular carcinoma.
Materials and methods: In this study, the suitability of L-boronophenylalanine (BPA), mercaptoborane (BSH) and boric acid (BA) was evaluated on the basis of organ-specific boron distribution in normal rat tissues. The intracellular concentrations of BA, BPA and BSH were further examined in human hepatoma HepG2 cells and liver Clone 9 cells. Tissues and cells were digested, and boron concentration was analyzed by ICP-AES. BPA, BSH and BA were intraperitoneal injected into rats for 1 to 3 hours with corresponding boron concentrations of 7, 25, and 25 mg/kg body weight, respectively. With the use of 25 ug B/mL media of BPA, BSH and BA, the intracellular uptake of boron in HepG2 and Clone 9 cells were compared.
Results: The accumulation ratios of boron to blood to liver, pancreas and kidney were 0.83, 4.16 and 2.47, respectively in BPA treated rats, and 0.75, 0.35 and 2.89, respectively in BSH treated rats at 3 hours treatment. However, boron does not appear to accumulate significantly in soft tissues in BA treated rats. Boron concentration in 4 h treated HepG2 and Clone 9 cells were 95 and 53 ppm in BPA treated ones, 24 and 16 ppm in BSH treated ones, 52 and 32 ppm in BA treated ones, respectively. It showed that the accumulation rates of BPA, BSH and BA in HepG2 cells were higher than that of Clone 9 cells. Boron concentration in BPA, BSH and BA treated HepG2 cells were 1.8, 1.5, and 1.6-folds that of Clone 9 cells at 4 h, respectively.
Conclusion: For *in situ* BNCT of hepatoma, normal organs with high boron concentration and adjacent to liver may be damaged in neutron irradiation. BA was more suitable for using as a boron carrier for particular combination treatment with other boron drug for BNCT of hepatoma. These preliminary results provide useful information on BNCT for hepatoma.

Interaction of charged boron clusters with biologically relevant molecules

Detlef Gabel, Tanja Schaffran, Jingyu Li

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Boron clusters offer the advantage for BNCT that a considerable number of boron atoms can be attached *via* a single chemical bond. Past experience has shown that of the icosahedral structures, *o*-carborane requires solubilizing groups when this cluster should form part of a molecule which is to be transported through the blood stream. The base-degraded *nido*-carborane is anionic, it appears, however, to bear some toxic potential. The dodecaborate anion carries two negative charges, and depending on the counter ions, the cluster and its derivatives are very water-soluble. In view of the charge, it was surprising to find the sulfhydryl derivative BSH being firmly bound to cell membranes and even in the nucleus of cells. More recently, we found that BSH interacts with liposomes as models for cell membranes and induces leakage and aggregation.
We have expanded this investigation to cover other heteroatom substituents and a systematic variation of chain lengths of *N*-substituted derivatives of $B_{12}H_{11}NH_3^-$. The initial interaction appears to be through charge. Depending on the substition of the cluster, hydrophobic effects increase, and the cluster derivatives behave more and more amphiphilicly.

Binding to membranes occurs with all derivatives tested. Membrane potentials (measured as zeta potential) as low as –120 mV have been recorded, some of the most negative numbers for liposomes ever measured. Such strong polarization changes of membranes might lead to cellular effects even without further amphiphilic components added.
Surprisingly, the trihexylammonio-undecahydrododecaborate acted also as an efficient inhibor of acetylcholine esterase, despite the fact that the natural substrate, a cation, and the inhibitor, an anion, carry opposite charges.
When using charged clusters as boron carriers, their potential amphiphilic character must be taken into account. A thorough investigation in simple model systems of the toxic potential of the compounds can help to screen compounds and identify possibly detrimental effects.

Delivery of a Cholesteryl Ester Mimic to Human Prostate Cells via Low-Density Lipoprotein Receptor Mediated Endocytosis

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The use of a boron-containing cholesteryl carborane ester compound (BCH) with boron neutron capture therapy (BNCT) for the treatment of prostate cancer is under investigation. Specifically, the *in vitro* uptake and release kinetics of BCH by human prostate cancer cells (PC-3) and human prostate normal cells (RWPE-1) is under study. For this delivery method, BCH is incorporated into a liposomal formulation and extruded through various membranes to fabricate BCH-containing liposomes of various sizes. The concentration of BCH in the liposomes, as well as their size, is varied in order to provide the optimum conditions for cellular uptake and retention of the BCH. Size analysis is performed using Asymmetric Field Flow Fractionation (AFFF) combined with multi-angle light scattering (MALS). Following analysis of the liposome sizes, the formulation is added to the growth medium of the cell populations and incubated for varying time scales. Cellular uptake of the BCH is analyzed using high performance liquid chromatography (HPLC) adapted for the specific detection of BCH and its degradation fragments. Additionally, cells are incubated in fresh media following exposure to the liposomal formulation to quantify the release of the BCH compounds by the cells. Following this analysis, a comparison can be made between the uptake and release kinetics of the cancerous and normal cell populations to determine the therapeutic ratio and identify an optimal radiation window for subsequent thermal neutron irradiation.

The New and Comprehensive BNCT Program of the International Institute of Nano and Molecular Medicine

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At this time, the elegant and potentially most powerful radiotherapeutic method for the selective control of cancer and other diseases has reached a point of stagnation in what should have been accelerating development in both therapeutic scope and clinical acceptance. This situation has been previously discussed and the root cause attributed not to the lack of development of radiomedicine and nuclear engineering, etc., but the fixation of the BNCT research program, as it existed, upon the sterilization of aggressive *Glioblastoma Multiforme* as its principal objective. The terms GBM and BNCT became synonymous while the BNCT proof-of-principle was linked to the success of GBM therapy.

The intellectual dedication to GBM was aggravated by the presence of the blood brain barrier, the very high tumor concentration of ^{10}B required for effective therapy (100 μM or higher) which overwhelms the exquisite targeting methods available for the delivery of modern pharmaceuticals (1 μM or lower) and the absence of a boron agent "pipeline" culminating in the rapid *in vivo* evaluation of promising agents using thermal neutrons and small, tumor-bearing animals. The present availability of only BSH, BPA, and GB-10 as boron agents suitable for human use and the fact that these species were first discovered in the 1955-1970 time period, points out the need of new chemistry and pharmacology for future rapid progress in BNCT and the translation of this science to other, as yet unidentified, applications. Boron agent discovery and evaluation is the weak point in the BNCT suite of past accomplishments.

In 2006 the University of Missouri Medical School created the International Institute of Nano and Molecular Medicine (I^2NM^2) headed by the author and devoted to a number of new areas encompassing boron and including nanoscience, chemistry, pharmacology, imaging, chemical biology, boron neutron capture therapy, radiation biology, and radiochemistry among others. The presence of the 10 MW university research reactor (MURR) allowed the construction of a new high-flux thermal neutron beam for the exclusive use of the I^2NM^2. The I^2NM^2 has just completed a 30,000 square foot research building very near both the MURR and small animal facilities. The research building is fully equipped for chemical synthesis, computational chemistry, nanoscience, cell biology, and related interests. The I^2NM^2/MURR complex is further enhanced by on-campus collaborations with various departments in the Medical School and Hospital, College of Veterinary Medicine, School of Engineering, the Truman Hospital, and College of Arts and Sciences. Off-campus, the I^2NM^2/MURR complex collaborates with the Idaho National Laboratory in the area of nuclear science.

The primary purpose of the I^2NM^2/MURR complex is to rekindle interest in BNCT in the US by assembling the necessary boron agent pipeline, which has never existed in the past. A variety of appropriate diseases will be studied, including rheumatoid arthritis. *Glioblastoma Multiforme* therapy will not be pursued.

Synthesis, Toxicology and Biodistribution of the First Porphyrin Bearing the *closo*-Monocarbaborane Anion $[-CB_{11}H_{11}]^{-1}$

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Of all the boron clusters potentially available as sources of boron for boron neutron capture therapy, derivatives of *closo*-monocarbon carboranes such as $[HCB_{11}H_{11}]^{-1}$ and $[HCB_9H_9]^{-1}$ have received the least attention. These sources, however, offer some potential advantages over the more traditional $B_{10}C_2H_{12}$ isomers. Their inherent permanent mono-anionic charge renders their derivatives considerably more water-soluble, and their higher boron weight percentage and greater resistance to cage degradation compared to 1,2-$B_{10}C_2H_{12}$ are also advantageous. Until recently, the primary barrier to their more widespread application in BNCT has been the lack of a convenient synthesis. Hardie and coworkers recent application of the Brellochs reaction of formaldehyde with *nido*-$B_{10}H_{14}$ now provides a simple, high-yield route to these *closo*-monocarbaborane starting materials.

We will describe the preparation, characterization and preliminary toxicity and biodistribution experiments of the first porphyrin derivative of $[HCB_{11}H_{11}]^{-1}$. Lithiation of the parent anion followed by carbonylation provided the carboxylic acid $[1\text{-}HOOC\text{-}CB_{11}H_{11}]^{-1}$ which was then reacted with oxalyl chloride to provide the corresponding acid chloride. This product was not isolated but was reacted *in situ* with 2,4-bis(1,2-dihydroxyethyl)-6,7-bis[2-(methoxycarbonyl)ethyl]-1,3,5,8-tetramethylporphyrin, a bis-glycol porphyrin that formed the porphyrin framework for our BOPP compound. The resulting anionic, tetra-carborane ester porphyrin is thus the $[-CB_{11}H_{11}]^{-1}$ analog of BOPP. As expected, it has considerable aqueous solubility. Preliminary toxicology testing demonstrated little systemic toxicity when given by intravenous bolus injection at doses up to 100 mg/kg. We will also describe the results of biodistribution experiments carried with this compound in nude rats bearing the intracerebral U-87 MG human glioma model.

On-Line Blood Boron Detection using ICP-AES and ICP-MS during BNCT

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A reliable estimation of the blood boron level for the treatment field is a prerequisite for successful BNCT. The quantification of the boron concentration for such estimation can be done with several methods, including inductively coupled plasma atomic emission spectrometry (ICP-AES), mass spectrometry (ICP-MS), spectrofluorometric and direct current atomic emission spectrometry (DCP-AES) methods, and by prompt gamma photon detection methods.
As part of the ongoing Finnish BNCT clinical trial protocols, the patients were infused with concentrations of 290 to 500 mg BPA per kilogram of total body weight. The boron concentrations were analyzed with ICP-AES and ICP-MS from a total of 73 whole blood samples. The results were compared with each other to assure the congruency of the quantification in case the analyzing method has to be changed during the treatment (e.g. for technical reasons). Additionally, the effect of wet ashing on the outcome was studied.
The average value of samples analyzed with ICP-MS was 6 % lower than with ICP-AES coupled to wet ashing (R^2=0.88). The average value of samples analyzed with ICP-MS without wet ashing was 9 % higher than with ICP-AES (R^2=0.99). The correlation between the results of ICP-MS with wet ashing and ICP-MS or ICP AES without it were good (R^2: 0.97 to 0.98).
The blood boron concentration analyzed with ICP-AES correlated well to the values of ICP-MS with wet ashing of the sample matrix, which is generally the reference method. The feasibility to use these methods parallel during the treatment secures the reliability of the boron quantification, noticing the accuracy requirements of the dose determination for the patient irradiations.

Aggregation of Nucleoside-Boron Cluster Conjugates in Aqueous Solutions and its potential effect on behavior as boron carriers for BNCT

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A number of potential boron carriers for BNCT have been synthesized and tested. Regrettably, in spite of the continuous efforts to develop suitable boron carrying drugs, the clinical applications of boron derivatives are limited so far to two molecules, L-4-(dihydroxyboryl)phenylalanine (BPA) and the sodium salt of thioborane anion ($Na_2B_{12}H_{11}SH$, BSH).
A large group of compounds studied are boron cluster derivatives and their conjugates with biomolecules. Boron clusters are characterized by exceptional hydrophobicity or at least amphiphilicity, the property which may facilitate the cellular uptake of the carborane-bearing compounds through cellular membranes. Simultaneously, the same quality may promote formation of different assemblies (aggregates) in aqueous solutions.

Surprisingly, in spite of extensive biological and pharmaceutical research on boron-cluster-containing conjugates, with few exceptions, very little attention was paid to the solution behavior of these molecules in aqueous media. It is obvious that the aggregation process could reduce the concentration of active boron-containing molecules in the solution, their pharmacokinetics and metabolism.
Herein we show the first evidence that boron-containing nucleoside conjugates have a tendency to associate in water solutions. The size, charge, and exoskeletal pattern of the boron cluster can strongly influence the aggregation. The observed phenomenon can be of importance in better understanding of biological properties of boronated nucleosides and in designing of boronated nucleosides based drugs such as boron carriers for BNCT and antiviral agents.

The potential of transferrin-polyethyleneglycol liposomes encapsulating GB-10 as ^{10}B-carriers for boron neutron capture therapy

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Purpose: To evaluate decahydrodecaborate-^{10}B (GB-10)-encapsulating transferrin (TF)-pendant-type polyethyleneglycol (PEG) liposomes as tumor-targeting ^{10}B-carriers for boron neutron capture therapy.
Materials and Methods: A free mercaptoundecahydrododecaborate-^{10}B (BSH) or decahydrodecaborate-^{10}B (GB-10) solution, bare liposomes, PEG-liposomes or TF-PEG liposomes were injected into SCC VII tumor-bearing mice, and ^{10}B concentrations in the tumors and normal tissues were measured by γ-ray spectrometry. Meanwhile, tumor-bearing mice were continuously given 5-bromo-2'-deoxyuridine (BrdU) to label all intratumor proliferating cells, then injected with these ^{10}B-carriers containing BSH or GB-10 in the same manner. Right after thermal neutron irradiation, the response of quiescent (Q) cells was assessed in terms of the micronucleus frequency using immunofluorescence staining for BrdU. The frequency in the total tumor cells was determined from the BrdU non-treated tumors.
Results: TF-PEG liposomes showed a prolonged retention in blood circulation, low uptake by reticuloendothelial system and the most enhanced accumulation of ^{10}B in solid tumors. In general, the enhancing effects were significantly greater in total cells than Q cells. In both cells, the enhancing effects of GB-10-containing ^{10}B-carriers were significantly greater than BSH-containing ^{10}B-carriers, whether loaded in free solution or liposomes. In both cells, whether BSH or GB-10 was employed, the greatest enhancing effect was observed with TF-PEG liposomes followed in decreasing order by PEG liposomes, bare liposomes and free BSH or GB-10 solution. In Q cells, the decrease was remarkable between PEG and bare liposomes.
Conclusion: In terms of biodistribution characteristics and tumor cell-killing effect as a whole, including Q cells, GB-10 TF-PEG liposomes were regarded as promising ^{10}B-carriers.

Development of Boron Nano Capsules for Neutron Capture Therapy

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Boron neutron capture therapy (BNCT) is a binary cancer treatment based on the nuclear reaction of two essentially nontoxic species, ^{10}B and thermal neutrons, and high accumulation and selective delivery of boron into tumor tissue are the most important requirements to achieve efficient BNCT. We have focused on boronated liposomes for boron delivery system. We recently developed the *nido*-carborane lipid, which has a double-tailed moiety conjugated with *nido*-carborane as a hydrophilic function. We investigated active targeting of the boronated liposomes to solid tumors by conjugation of transferrin onto the surface of their liposomes and achieved a boron concentration of 22 μg ^{10}B/g tumor by the injection of the liposomes at 7.2 mg ^{10}B/kg body weight with longer survival rates of tumor bearing mice after BNCT. However, the mice injected at higher boron concentrations resulted in mortality. In order to overcome this problem, we focused on mercaptoundecahydrododecaborate (BSH) as an alternative hydrophilic function of boron lipids. BSH is a water-soluble divalent anion cluster and significantly lowered toxicity, and has thus been utilized for clinical treatment of BNCT. In this paper, we report synthesis of *closo*-dodecaborate containing boron lipids and their liposomal property. Our design of the boron lipids is based on biomimetic composition of phosphatidylcholines in order to meet a sufficiently low toxic requirement. We prepared boron lipids-containing PEGylated liposomes (Boron Nano Capsules) and examined their BNCT effect using tumor (colon 26) bearing mice. The suppression of tumor growth was observed in the mice injected with the boron liposome after BNCT and some of tumors were completely disappeared.

Measurement of BPA in the Blood by Fluorometry

○Koji Ono, Genro Kashio, Minoru Suzuki, Shin-ichiro Masunaga, Yuko Kinashi, Noriko Fujii

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It is indispensable to know the boron concentration in the blood in BNCT. B-10 and B-10/B-11 are being measured by the prompt gamma-ray spectrometry and ICP, respectively. When using one kind of boron compound, this procedure is sufficient. But, occasionally two kinds of boron compounds, i.e., BPA and BSH, are simultaneously used. In this situation, we have to know the boron concentration originating in each compound in order to translate a physical dose into a biologically X-ray equivalent dose (Gy-Eq). And B-10 concentration must be measured during the short neutron irradiation time. Then, a simple discrimination measuring method of BPA and BSH is strongly desired.
BPA emits fluorescence when it is excited with ultraviolet rays. So, we have an idea to use fluorometry. The solution of BPA-fructose complex was added to the heparinized human blood samples at the B-10 level of 0ppm to 60ppm. Then, small amount of PBS was added to adjust the volume of sample depending upon the volume of BPA solution added at first. Centrifugation was carried out, and plasma was separated, and this plasma was diluted 7 times in volume by 99% ethanol. After vigorous shaking, centrifugation was carried out again. Thereafter, supernatant was filtered with the deproteinization membrane filter. The same ethanol was added to this filtered sample and diluted to 200-350 times finally. This dilution sample was excited with 257nm ultraviolet rays, and the amount of emitted fluorescence of 275nm was measured. The reading value of the 0 ppm fluorescence was equal to it of ethanol. The fluorescence was directly proportional to the boron concentration precisely. Slope of the line depend upon the dilution scale factor of the sample by ethanol, and the measurement sensitivity of B-10 at 0.5 ppm has been achieved. Moreover, BSH did not show measured values.

New dodecaborate cluster lipids and cholesterol derivatives for BNCT

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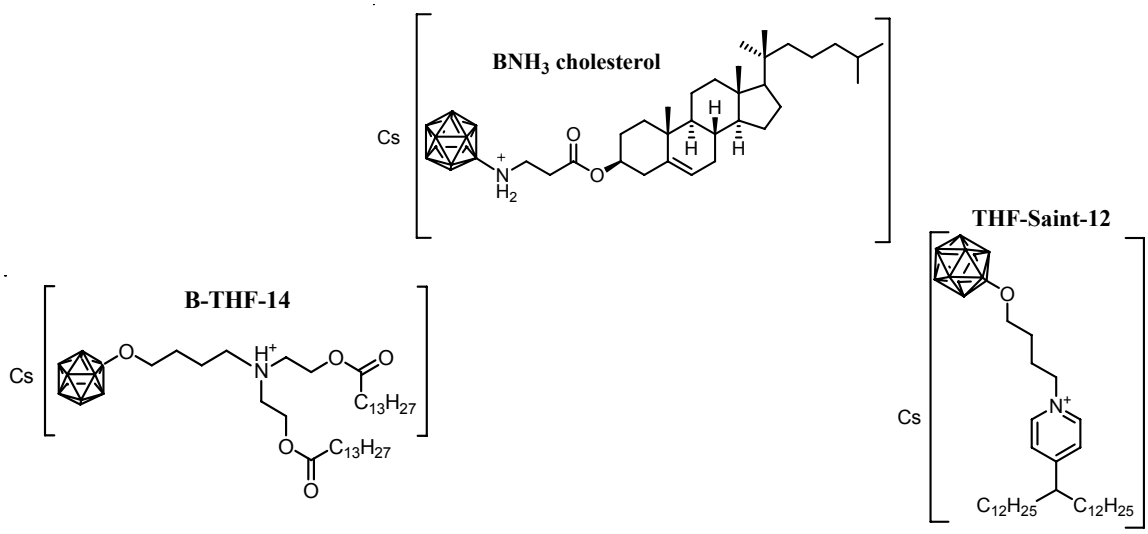
For efficient boron neutron capture therapy (BNCT) high accumulation and selective delivery of boron into the tumor tissue are the most important requirements. In the literature only a few boron-containing lipids are described. Lemmen reported a carborane-containing ether lipid and Nakamura described a nido-carborane cluster lipid. Also only a few cholesterol derivatives are known. Nakamura recently reported dodecaborate-conjugated cholesterols; a cholesterol-carborane conjugate and a cholesterol carborane ester compound are described before. We synthesized dodecaborate cluster lipids and cholesterol derivatives to prepare liposomes for a boron delivery system. It is also possible to functionalize liposomes (targeting).
We have synthesized new dodecaborate cluster lipids *B-THF-14* and *B-Dioxane-14* by nucleophilic ring opening reactions of the tetrahydrofurane or dioxane derivative of the dodecaborate cluster. Cryo-TEM pictures showed formation of boron cluster-containing liposomes when an equimolar mixture of the boron lipid, DPPC and cholesterol was used. The toxicity determination of the lipids is in progress.
We also obtained new dodecaborate cluster SAINT lipids *THF-Saint-12* and *Dioxane-Saint-12* with the same procedure. Boronated liposomes could be obtained with an equimolar mixture of DMPC/cholesterol/THF-Saint-12. Other boron-containing SAINT derivatives are in work.
Novel dodecaborate cluster cholesterol derivates have been synthesized. A THF derivative and a dioxane derivative could be obtained by nucleophilic ring opening reaction. Moreover we synthesized a BNH_3 derivative. First we introduced the linker bromoacetyl bromide at the hydroxyl group of cholesterol and then we carried out a nucleophilic substitution with the deprotonated BNH_3.



New Approach to Incorporation of Boron in Tumor-Seeking Molecules

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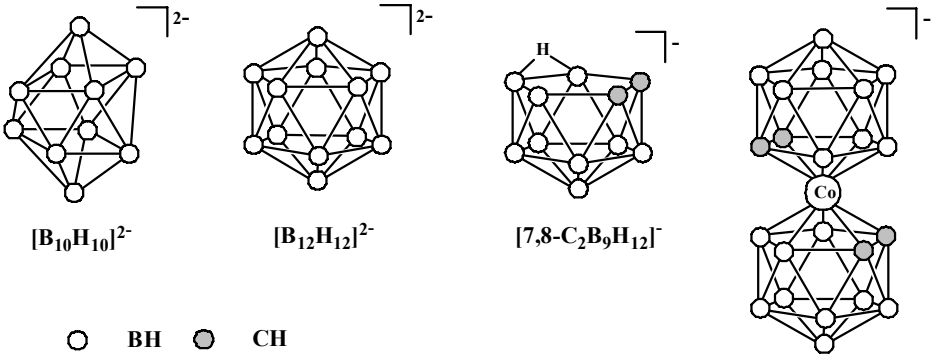
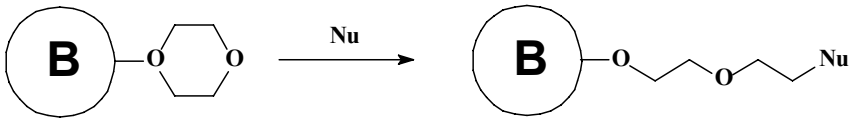
Cyclic oxonium derivatives of polyhedral boron hydrides are relatively new class of boron compounds having great potential for modification of various types of organic and bioorganic molecules. Nucleophilic ring-opening of cyclic oxonium derivatives of polyhedral boron anions (*closo*-$[B_{10}H_{10}]^{2-}$, *closo*-$[B_{12}H_{12}]^{2-}$, *nido*-$[7,8\text{-}C_2B_9H_{12}]^-$, *closo*-$[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$) is proposed to be a new synthetic methodology for incorporation of boron moieties in tumor-seeking molecules.



$[B_{10}H_{10}]^{2-}$ $[B_{12}H_{12}]^{2-}$ $[7,8\text{-}C_2B_9H_{12}]^-$

$[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$

Cyclic oxonium derivatives of polyhedral boron hydrides are easily available and their ring opening reactions with various nucleophiles result in functional derivatives with terminal hydroxy, amino, acid, amino acid, etc. groups that can be used for their conjugation with tumor-targeting biomolecules. Alternatively, active nucleophilic sites being in the presence in biomolecules can be used for direct introduction of boron units.



The use of cyclic oxonium derivatives of polyhedral boron hydrides for preparation of amines, acids and aminoacids, as well as for synthesis of boron-containing conjugates with porphyrins and carbohydrates will be discussed.

A new boron carrier – detection and intracellular uptake of boronated porphyrin ' EC032 '

Takao Tsurubuchi [1], Tetsuya Yamamoto[1], Kei Nakai[1], Fumiyo Yoshida[1], Makoto Shirakawa[2], Manabu Ueno[3], Masahide Matsuda[1], Yoshinori Nakae[4], Akira Matsumura[1]

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Purpose: To improve the therapeutic effect of BNCT, sufficient amount of boron and neutron delivery in tumor tissue is important. We measured the toxicity and intracellular uptake of a newly developed boronated porphyrin ' EC032 ' as a new boron carrier. This compound has a tumor selective porphyrin frame and also has a cage of boron. The fluorescence based ^{10}B concentration measuring methods was verified.
Materials and Methods: 1. *Toxicity study:* Toxicity effect of EC032 on tumor cells such as C6, 9L rat gliosarcoma cells, U87, U251 human glioblastoma cells are examined using MTS assay in comparison with sodium borocaptate (BSH).
2. *Fluorescence study*: C6, 9L, U87, U251 cells were incubated with 20 μM EC032 in the conditioned medium for 30 min, 1h, 2h, 6h, 12h in the 96-well microplate. The cultured medium was washed three times with PBS. The cells were pipetted and minced with Triton-X. The fluorescence intensity of the sample in the well was measured by microplate reader. The excitation wave length was 405 nm and the emission wave length was 670±10 nm. Cells of the same condition were trypsinized and counted. Then the intracellular uptake of EC032 were determined.
3. *Measurement of ^{10}B concentration*: We evaluated the correlation between inductively coupled plasma atomic emission spectroscopy (ICP-AES) and fluorescence intensity detected by microplate reader. C6, 9L, U87, U251 cells were incubated with BSH and EC032, which were respectively added to the conditioned medium at a ^{10}B concentration of 30μg/ml. The incubation times were 6 and 24 h. The cultured medium was washed once with PBS.

The cells were counted and pretreated by wet ashing method. Then the intracellular ^{10}B concentration was measured by ICP-AES. Using the another part of the same sample, fluorescence intensity of the sample was measured by microplate reader.
Results: *1:* The LD_{50} of the EC032 was less than 1000μM. *2:* The intracellular uptake of EC032 increased until 24 hours after its exposure to C6, 9L, U87, U251 cells. *3:* There was linear correlation between ICP-AES and fluorescence intensity about measurement of ^{10}B concentration.
Furthers will be discussed.

Enhancement of *p*-Boronophenylalanine Uptake into Subcutaneous Rat Gliosarcomas: Synergy of Benserazide and L-dopa

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[3] *KLIFOVET AG, 80689 Munich, Germany (present affiliation)*

Objective*:* A synthetic, boronated analog of tyrosine, *p*-boronophenylalanine (BPA), selectively accumulates in certain malignant neoplasms, including human glioblastoma multiforme and rat 9L gliosarcoma (9LGS). BPA is used as a boron-10 delivery agent in clinical trials of boron neutron-capture therapy (BNCT). 9LGS cells exposed to levo-dopa (L-dopa) *in vitro* show increased avidity for BPA thereafter. Since L-dopa is rapidly catabolized by dopa decarboxylase, we exposed the rats to the decarboxylase inhibitor benserazide prior to L-dopa to test enhancement of BPA uptake into rat brain 9LGS tumors *in vivo*.
Method*:* Benserazide and L-dopa were injected i.p. sequentially before i.p.-administration of BPA into male Fisher 344 rats bearing subcutaneous 9LGS gliosarcomas. Boron concentrations were measured in tumors and blood sampled over a 4h period after BPA-injection.
Result: Pretreated tumors accumulated boron at average concentrations of 69.3 ± 7.6 μg/g 2h and 80.1 ± 9.1 μg/g 3h after BPA injection, boron enhancements of 50% ($p = 0.001$) and 65% ($p < 0.001$), respectively, when compared to non-pretreated tumors at the same time points.
Conclusion: Analogous pretreatment should be tested as a possible enhancer of boron uptake from BPA into more malignant rat gliomas *in vivo*.

Structural Characterization of Carborane-loaded Liposomes on the Nanoscale Using Scattering Techniques

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Transport and delivery of boron-containing compounds for Boron Neutron Capture Therapy (BNCT) depends on the stability and structural properties of the loaded carriers. In the case of liposome-based delivery, the insertion of drug modifies the physico-chemical equilibrium within the carrier. This is due to the self-organized nature of liposomes, which are formed by self-assembly of amphiphilic molecules such as phospholipids. Properties like spontaneous bilayer curvature and bending elasticity may change upon incorporation of purely hydrophobic or amphiphilic drugs, leading to modifications in bilayer thickness, liposome size, and possibly destruction. Small angle neutron and X-ray scattering (SANS, SAXS) are powerful methods with nanoscale resolution for the characterization of objects in solution. After a quick introduction to the method, examples of inclusions of (amphiphilic) sugar-based carboranes and (strongly hydrophobic) porphyrazine incorporated into different phospholipid vesicles will be presented and discussed. It will be shown that incorporated amounts can be deduced from neutron transmission experiments, and that their effect on structural parameters of the liposomes can be directly followed by small angle scattering. It is hoped that these first steps will contribute to the understanding and optimisation of the complex interactions between boron-guest molecules and carrier systems.

Pharmacokinetic and proteomic profiles of urine samples after application of boron-10 carriers

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[2] *Strahlenklinik, Universitätsklinikum Essen, Germany*

Clinical investigations of the distribution and the metabolism of the ^{10}B-containing compounds that are available for clinical trials (*closo*-undecahydro-1-mercaptododecaborate, BSH, and ^{10}B-phenylalanine, BPA) are very important.
Many efforts had to be made to perform quali-quantitative assay of drugs in fluid and tissue samples. In particular, we have developed a rapid and quantitative method that permits the determination of BSH and BPA, based on flow-injection electrospray tandem mass spectrometry (FI/ESI-MS/MS)[1]. This approach allows, in a short time (about 2 min for analysis) and high sensitivity (LOD 50 fmol), the identification of the main important drugs (^{10}BSH and ^{10}BPA) used in BNCT studies[2].
In addition, for the understanding of the biochemical and physiological differences between tumour and normal cells and using these differences in compound design, synthesis and targeting, it is very important to investigate protein profiles related to different physiological states or to describe the effect of bioactive compounds. In our laboratory, we use shotgun proteomic approach, based on two-dimensional chromatography coupled to tandem mass spectrometry (2DC-MS/MS). This methodology provides a great improvement over gel-based analysis, and it is a powerful technology for clinical proteomic investigations[3].
In this context, urine samples obtained from BNCT patients were investigated to characterize both the level of boron-containing compounds and the protein profiles using FI/ESI-MS/MS and 2DC-MS/MS approaches, respectively. The main results obtained by the "integrated metabolomic and proteomic clinical studies" will be presented.

Boron-containing polymers for conjugation to antibodies

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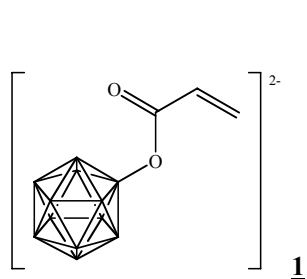
Boron neutron capture therapy (BNCT) is a two-step radiotherapy. A selective radiation effect on tumor cells is achieved by first targeting the tumor with non-radioactive ^{10}B and then exposing it to low energy neutrons. For the success of BNCT a key requirement is to selectively deliver a relatively high amount of boron compound to the tumor cells. But to minimize the damage to normal tissue the boron concentration in the surrounding normal tissue cells should be kept low.
In order to improve the efficacy of BNCT, various approaches have been employed to deliver the ^{10}B compounds to the tumor tissue, including the use of macromolecules such as monoclonal antibodies.
The aim of the work is to synthesize polymers containing the dodecaborate cluster. These macro-molecules must have functional terminal groups such as carboxy-, hydroxy-, amino- or mercaptogroups for binding them to antibodies.
In order to achieve this, some monomers could be synthesized for polymerization. Examples are an acrylic acid derivative of the hydroxydodecaborate cluster (BOH) **1**, a styrene derivative of the ammoniododecaborate cluster (BNH_3) **3** and epoxy derivatives of BOH and mercaptododecaborate cluster (BSH) **4**.



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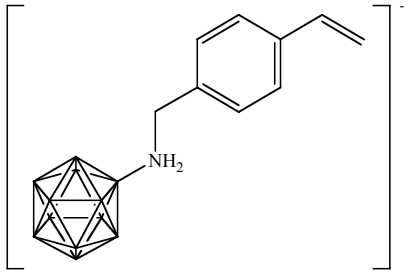

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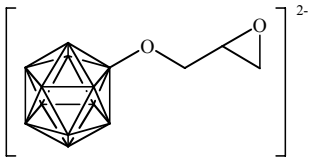

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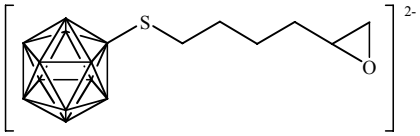

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The polymerization initiator must contain functional groups to integrate them into the polymers. With these functional groups the synthesized polymers can be bound to the antibodies.

Boronated DNA Metallointercalators for Boron Neutron Capture Therapy

H. Y. Vincent Ching[1], Philippa A. MacKay[1], Louis M. Rendina[1]

[1] *School of Chemistry, The University of Sydney, Australia*

It has been demonstrated that boronated drugs which are localised in the cell nucleus exhibit greater cytotoxic effects upon thermal neutron capture than an equivalent amount of ^{10}B distributed on the cell surface or evenly throughout the cytoplasm. The ability of certain metal complexes containing planar aromatic ligands that bind to DNA by intercalation is well documented. Rendina and co-workers have recently prepared a series of 2,2':6',2"-terpyridineplatinum(II) complexes with thioalkylcarborane ligands, which are able to target chromosomal DNA in tumour cells, and also exhibit *in vitro* anti-cancer properties. This novel class of agents would potentially couple the biological effects of the neutron capture reaction with the avid DNA-binding reaction either additively or perhaps synergistically and, indeed, the platinum may also act as a radiation sensitizer. Furthermore, radiolabels such as ^{195m}Pt can be utilised to monitor cellular uptake and biodistribution of the drug *in vivo*.
Recently we undertook the synthesis, characterisation and biological studies of a related series of boron-rich diiminеplatinum(II) complexes containing carboranylpyridylmethanol ligands such as bis[1-(1,12-dicarba-*closo*-dodecaboranyl)4-pyridylmethanol](1,10-phenanthroline)platinum(II) nitrate. A dramatic improvement in the aqueous solubility of these agents has been successfully achieved by exploiting the host-guest properties of β-cyclodextrin, the cavity of which can readily accommodate the hydrophobic carborane cage. The key results of this work will be presented.

DNA-targeted Gadolinium Compounds for NCT

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^{157}Gd can potentially be used for neutron capture therapy. The advantage of ^{157}Gd is that it possesses the largest effective nuclear cross-section of all naturally-occurring elements (2.55×10^5 barns), approximately sixty times that of ^{10}B. The energetic particles released from the nuclear capture reaction, e.g. Auger electrons, are capable of destroying malignant cells as long as they are localised near key cellular components such as DNA due to their short range. Indeed, it has been demonstrated that if BNCT agents can target chromosomal DNA they are two to five times more effective at achieving cell death than an equivalent amount of agent evenly distributed throughout the cytoplasm.

Recently we have synthesised and fully characterised a novel gadolinium agent linked to a DNA intercalator. Studies have been carried out which show promising cell uptake results with this prototype. A preliminary X-ray fluorescence mapping study of both treated and untreated B16 murine melanoma and A549 human lung carcinoma cells has been performed. The key results of this work will be presented.

Biodistribution of BPA and BSH after single, repeated and simultaneous administrations for Neutron-Capture Therapy of Cancer

Ichikawa Hideki[1], Emi Taniguchi[1], Takuya Fujimoto[2], Yoshinobu Fukumori[1]

[1] *Faculty of Pharmaceutical Sciences and Cooperative Research Center of Life Sciences, Kobe Gakuin University, Japan*
[2] *Orthopaedic Surgery, Hyogo Cancer Center, Akashi, Japan*

The aim of the present study is to elucidate biodistribution of BSH and L-BPA after administration of their solutions in different manners in order to enhance boron accumulation in tumor.
Greene's melanoma (melanotic No. 179 cell, D1-179) was allowed to proliferate subcutaneously in the left thigh of 5 weeks old Syrian hamsters, weighing 80-90 g, until it reached 10 mm in diameter at 10 days after implantation. After i.v. administration of BSH and/or BPA, boron concentrations in blood, liver, spleen, muscle, skin, kidney, lung, brain and tumor were determined.
BSH was fast eliminated from all tissues in normal and tumor-bearing hamsters. The extremely high boron concentrations after administration of BSH were observed in liver and kidney. Boron was long-term retained in tumor, muscle and brain after administration of BPA-Fr solution. The long retention in tumor and muscle seemed to relate to a high cell-uptake and/or cell-affinity of L-BPA as an analog of essential amino acid, phenylalanine. The higher and retained boron accumulation in brain with BPA-Fr, compared with BSH, would indicate that L-BPA could pass through the blood-brain barrier slowly. The blood concentration-time profiles of both compounds would be comparable. In the tumor-bearing hamsters, the maximum boron concentration reached 36 μg B/g in tumor at 3 hr after administration of BPA-Fr at 500 mg BPA/kg. This is high enough to induce an effective NCT. The AUC_{tumor}, T/B ratio and T/N ratio of BPA-Fr were much higher than those of BSH. The fast elimination from the blood and the low accumulation in the skin in addition to the high accumulation and the long retention in tumor clearly contributed to the favorable biodistribution characteristics of L-BPA. The boron concentrations in the tumors were 13, 36 and 41 μg B/g wet tissue at 3 hr after rapid i.v. injection at dose of 250, 500 and 1000 mg BPA/kg, respectively. The tumor concentration increased with the dose, but the concentration at the dose of 1000 mg BPA/kg seemed to be not as high as that expected from those at 250 and 500 mg BPA/kg. Thus, the common use of a dose of 500 mg BPA/kg in clinical NCT would be reasonable. When both BSH and L-BPA were administered simultaneously, the concentrations corresponding to the sum of concentration with each compound were observed in all tissues. In this case, the boron concentration in tumor was 37 μg B/g at 3 hr after administration. The repeated injection of BPA-Fr solution was carried out just when the tumor concentration reached the maximum after the first injection of BPA-Fr solution. The boron concentration in tumor was 52 μg B/g at 3 hr after the second i.v. injection. At 12 hr after the second administration, the boron concentration in the tumor was still 20 μg B/g which was high enough to induce effective NCT. This suggested that the repeated rapid injection based on the proposed protocol might make NCT more effective.
The detailed, basic biodistribution data demonstrated in the present study will be useful for constructing a better treatment procedure.

Delivery of BPA using Nanosuspension Formulations for Neutron-Capture Therapy of Cancer

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[2] *Orthopaedic Surgery, Hyogo Cancer Center, Akashi, Japan*

The aim of the present study is to explore nanosuspension formulations of L-BPA as an alternative to the solution systems, which can exhibit more beneficial biodistribution of boron, especially a higher accumulation in the tumor than the L-BPA solutions.
In order to prepare the nanosuspension formulations, a conventional aqueous suspension containing L-BPA and a stabilizer (either Solutol® HS 15 or soybean lecithin) were wet-milled using a planetary ball mill (Planetary micro mill PULVERISETTE 7, Fritsch, Germany), and then sonicated for 30 min at room temperature. Greene's melanoma (melanotic No. 179 cell, D1-179) was allowed to proliferate subcutaneously in the left thigh of 5 weeks old Syrian hamsters, weighing 80-90 g, until it reached 10 mm in diameter (typically at 10 days after implantation). After intravenous (i.v.) administration of the BPA nanosuspension, boron concentrations in blood, liver, spleen, muscle, skin, kidney, lung, brain and tumor were determined by ICP-AES.
BPA nanosuspensions stabilized with lecithin (BPA-NS-LE) or Solutol® HS 15 (BPA-NS-SO) with the particle size of 366 and 215 nm, respectively, were obtained successfully. BPA-NS-LE was found to induce high renal toxicity even at the dose of 250 mg BPA/kg. In contrast, no toxicity was observed in the case of BPA-NS-SO at the dose of 250 mg BPA/kg, although such a renal toxicity appeared again at the dose of 500 mg BPA/kg. The maximum boron concentration reached 19 μg B/g in tumor at 3 hr after administration of BPA-NS-SO at 250 mg BPA/kg. This value was significantly high in comparison with that of BPA-fructose complex solution (13 μg B/g in tumor). Although the nanosuspensions were efficient delivery systems, the limitation of dose arising from the renal toxicity made higher accumulation in tumor impossible. The particle sizes of nanosuspensions prepared here did not seem to be small enough to fully utilize the enhanced penetration and retention (EPR) effect in the tumor and to escape the uptake by reticuloendothelial system. Consequently, the BPA molecules might distribute into most tissues after dissolving in the blood followed by the i.v. injection of BPA-NS-SO while the particulate BPA would be trapped in the liver.
Thus, the BPA-NS formulated in this study was halfway in accumulating boron in tumor. One next target of the research is to improve the particle characteristics such as particle size reduction and further surface-modification, which are expected to lead to better biodistribution of BPA for NCT.

Carborane-Containing Phosphonium Salts For Boron Neutron Capture Therapy

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Phosphonium salts such as tetraphenylphosphonium (TPP) chloride and methyl-triphenylphosphonium (TPMP) iodide are known to accumulate selectively in the mitochondria of cancer cells. This is due to their lipophilic and cationic properties which allow them to traverse the mitochondrial membrane of the tumour cell, in which the membrane potential is generally elevated compared to that of a normal, healthy cell. *In vivo* and *in vitro* uptake studies have shown a high tumour : healthy tissue ratio (~ 40 : 1) for these agents which is approximately an order of magnitude more selective than agents currently being used in the clinic for Boron Neutron Capture Therapy (BNCT). Phosphonium salts containing dicarba-*closo*-dodecaborane (carborane) could act as new cancer-selective, boron delivery agents to mitochondria, organelles that play a critical role in the regulation of apoptosis.
We have recently conducted the synthesis, characterisation, and cell-uptake studies of boronated phosphonium compounds. These include the $[PCH_3Ph_2\text{-}1,12\text{-}C_2B_{10}H_{11}]^+$ I^- salt as well as $[PPh_2CH_3\text{-}7,8\text{-}C_2B_9H_{11}]$ and $[PPh_2CH_3\text{-}7,9\text{-}C_2B_9H_{11}]$ zwitterions. A highly water-soluble derivative containing a tetraethyleneglycol group $[PPh_2(1,12\text{-}C_2B_{10}H_{11})((CH_2CH_2O)_3CH_2CH_2Br]^+$ Br^- has been prepared and characterised, and cell-uptake studies have been undertaken. The key results of this work will be presented.

Disposition of TF-PEG-liposome-BSH in tumor-bearing mice

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Objectives: Boron neutron capture therapy (BNCT) requires high concentration and selective delivery of boron (^{10}B) to the tumor site. To further improve the drug delivery in BNCT, we conducted a study by devising transferring-conjugated polyethylene-glycol liposomes encapsulating sodium borocaptate (TF-PEG-liposome-BSH).
Materials and Methods: Cancer-bearing mice were created by implanting SAS, the oral squamous-cell carcinoma (SCC) cell line, under the dorsal skin of BALB/c mice. When the tumor cell mass diameter reached approximately 1 cm, we administrated three types of boron delivery systems (BDS): BSH, PEG-liposome-BSH and TG-PEG-liposome-BSH. We measured the concentration of ^{10}B over time at the tumor site, blood, spleen, and kidney.
Outcome and Discussion: Results confirmed that ^{10}B concentration increased at the tumor site over time and that TF-PEG-liposome-BSH is significantly effective as BDS. These findings suggest that TF-PEG-liposome-BSH is an effective therapy for oral SCC.

Effect of Surface Modification on Characteristics of Gadolinium-Loaded Chitosan Nanoparticles for Neutron Capture Therapy of Cancer

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As a nanoparticulate device for controlled delivery of Gd, we have been developing gadolinium-loaded chitosan nanoparticles (Gd-nanoCPs). In our previous studies, significant tumor-growth suppression in vivo could be achieved by neutron-capture reaction after intratumoral (i.t.) injection of Gd-nanoCPs. The aim of present study is to apply Gd-nanoCPs to a nano-device for delivering Gd to the tumor site via intravenous injection. For this purpose, a surface modification of the intact Gd-nanoCPs with lecithin was carried out and its effect on the dispersing stability, suppression of Gd-release and cellular interaction behaviours was evaluated.
Gd-nanoCPs were prepared by using chitosan with a degree of deacetylation of 100% and gadopentetic acid (Gd-DTPA) through the w/o emulsion-droplet coalescence technique. The Gd-nanoCPs thus prepared were dispersed in phosphate buffer solution (pH 7.0) and then coated with soybean lecithin by the thin film hydration method. The lecithin-coated Gd-nanoCPs (LC-Gd-nanoCPs) thus obtained were characterized in terms of their particle size, zeta potential and Gd-release in human plasma. Furthermore, cellular toxicity, adhesion and uptake were assessed by incubation of either the intact Gd-nanoCPs or LC-Gd-nanoCPs with the mouse melanoma cells (B16F10) for 12 hours.
The particle size of the intact Gd-nanoCPs was 197 nm where ultrasonic irradiation was carried out just before the particle sizing since the intact Gd-nanoCPs tended to be flocculated immediately after preparation. In contrast, the particle sizing was possible for the LC-Gd-nanoCPs even without ultrasonication (the particle size was 217 nm), indicating that the lecithin-coating improved dispersing stability of the Gd-nanoCPs. The zeta potential of the intact Gd-nanoCPs was 24.8 mV, whereas that of LC-Gd-nanoCPs became a negative value, i.e., −20.8 mV, possibly due to the lecithin-coating.

The intact Gd-nanoCPs showed a rapid Gd- release with an initial burst of around 50% in the human plasma, and the release was completed within 3 hours. Contrary, Gd-release from the LC-Gd-nanoCPs was strongly suppressed; approximately 80% of Gd still remained in the nanoparticles even at 12 hours, and gradually released after that. Thus, surface modification with lecithin was effective to suppress the Gd-release. No significant cytotoxicity was seen in both the intact Gd-nanoCPs and LC-Gd-nanoCPs within the feed Gd concentration up to 10 ppm. The amounts of the cellular adhesion and uptake of Gd in the intact Gd-nanoCPs were twice higher than those of LC-Gd-nanoCPs, suggesting that negatively charged LC-Gd-nanoCPs are likely to diminish their cellular interaction through the electrostatic repulsive force against the tumor cells.

Scheme of Screening Studies of New Compounds

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Screening of new substances requires maximum simplicity and availability of research methods in combination with reliability of the results. At the stage of screening, we suggest the research should be limited to cell-level studies and pharmacokinetic studies in small laboratory animals. The purpose of such studies is estimation of survival of a tumor cell culture after irradiation of the cell homogenate in the presence of the compound being studied, and estimation of ^{10}B uptake at administration of the compound to the organism. These studies are feasible using compounds with natural ^{10}B content.
The efficiency of the suggested approach can be illustrated by the example of the aminoacid derivative of cobalt bis(dicarbollide) (AA): good water solubility of its sodium salt, 18 boron atoms in the structure, and relatively low toxicity make this compound an object of regard.
In vitro studies in murine melanoma B-16 cell culture have shown AA to be twice more effective than BPA by the criteria of colony growth rate and cell survival. The estimation was carried out at equal ^{10}B concentrations in the cell homogenate under the dose of 15 Gy (thermal neutron flux).
At the same time, at intratumoral administration of AA in rats, the ^{10}B concentration in tumor in 5 minutes post administration was at a level of 5 μg/g of tumor, smoothly decreasing to 3 μg/g by 120 minutes post administration of AA. The content of ^{10}B in other tissues of rats (muscle, blood, urine) does not exceed 1 μg/g. At intravenous administration of AA, the content of ^{10}B in tumor, muscle, kidney, and liver tissues was below 1 μg/g. The primary route of AA excretion is in urine in 10-15 inutes. In all cases, the animals received equal amounts of ^{10}B of 30 μg in a volume of 0.2 ml. The screening study resulted in revealing that AA is incapable of accumulating in tumor, as it is not oncotropic. Quantification of ^{10}B in biological samples by prompt gamma analysis was carried out on the facility implemented at the horizontal channel HEC-9 of the IRT MEPhI Reactor; the facility provides reliable determination of ^{10}B in amounts of 1 μg/g and above with an accuracy of at least 10%.
Thereby, the suggested scheme of screening studies allows a sufficiently simple estimation of the prospects of the compound being investigated in terms of its applicability as an NCT agent.

Glycosylated Carbaboranylphosphonates for Use in BNCT-Anti-Cancer Treatment

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Since the introduction of boron neutron capture theory (BNCT) by *Locher* in 1936, several investigations toward synthesizing useful compounds, including derivatives of amino acids, porphyrins, liposomes, monoclonal antibodies, and epidermal growth factors, were carried out and reviewed. Until now, only BPA (L-*para*-boronophenylalanine), its fructose complex, and BSH (sodium mercapto-*closo*-dodecaboronate) made it into clinical trials on high-grade gliomas and melanomas.

Nevertheless, their complete pharmacokinetical behavior and biodistribution are uncertain and need to be further investigated.
Our group focuses on the attachment of glycosides to carbaboranylphosphonates, which combines the boron-bearing part with a hydrophilic, less toxic, and tumor-selective moiety (e.g., Figure 1).

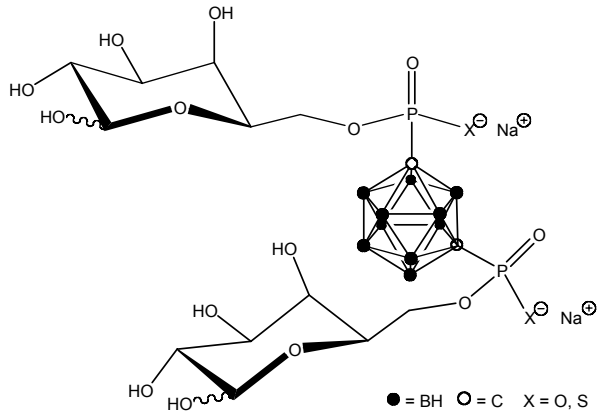

Fig. 1 - Galactosylphoshonate conjugates of *m*-carbaboranes

Previous work showed that carbaboranylphosphates have higher selectivity for some tumors,[3] but they were still too toxic and lipohilic. It was also observed that galactose derivatives have increased selectivity compared to their pyranose analogues.
Toxicity studies on HeLa cells were carried out and will be presented, as will our current biodistribution studies on BALB/C mice. Toxicity and biodistribution studies on related glucose and mannose derivatives are planned.

Synthesis of complex glycosilated carboranes for BNCT

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A large number of boron containing molecules, conjugated with different natural and non-natural compounds, have been synthesized. Among different boron-containing constructs, carboranes containing carbohydrates have recently raised interest. The sugar moiety, in fact, not only is able to confer water solubility to the otherwise hydrophobic boron cluster, but also could have a targeting effect on tumor cells. On the other hand, it has been suggested that the sugar part would hamper the product to cross the BBB or the cell membrane, and it has been shown that such conjugates can have undesired side effects. Moreover another main problem in BNCT is the determination of the "in vivo" distribution of the products. In order to have new compounds which can help to face such problems we decided to synthesize new carborane-containing hybrids. The compounds obtained, apart from the sugar and the carborane, also contain a third moiety constituted by an amino acid or a probe. Such derivatives should allow either the conjugation with peptides or proteins for an improved delivery of the product, or the monitoring the biodistribution of the products.
The synthesis of the new compounds will be described. The compounds have been obtained starting from new carboranes scaffold on which a protected amino acid, a fluorescent probe or a nitroxide probe together with a common lactose unit have been introduced.

Boronated Cyclic Peptides As Tumor-Specific Agents for Boron Neutron Capture Therapy

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It is well-established that non-selective, biologically-active compounds tethered to a molecule which is capable of selectively binding to tumor-associated markers have been shown to be successful in dramatically improving tumor:organ ratios within a few hours of intravenous drug administration. The present study focusses on combining peptidic ligands with boron-containing entities to afford a new class of conjugates for use in Boron Neutron Capture Therapy (BNCT). To maximise tumor cell destruction, the compound must exhibit some degree of selectivity toward tumors. This requirement may be addressed by using small peptides containing the cyclic RGD motif known to bind to integrin receptors which are over-expressed on tumor cells and are involved in tumor angiogenesis and metastasis. Boronated cyclic peptides thus have the potential to deliver ^{10}B selectively to tumor cells.
We have recently synthesized and characterized a series of compounds consisting of a tumor-targeting cyclic RGD peptide and a variety of boron moieties, as well as heavy-atom analogues for use in cell imaging by means of synchrotron X-ray fluorescence (XRF). The key results of this work will be presented.

Synthesis and evaluation of a novel liposome containing BPA-peptide conjugate for BNCT

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Yohei Yamamoto[1], Kenichi Aburai[2], Yuusaku Yokoyama[2], Hiroaki Okuno[2], Akira Matsumura[1]

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[2] *Faculty of Pharmaceutical Sciences, Toho University*

Boron neutron capture therapy (BNCT) is a tumor-selective radiation modality which depends on a sufficient cellular uptake of Boron (^{10}B) followed by irradiation with a beam thermal or epithermal neutrons. ^{4}He and ^{7}Li particles are produced during the neutron capture reaction and damage DNA, which lead to cell killing. Regarding BNCT, the short radiation range of ^{4}He and ^{7}Li particles is decisive for the distribution of ^{10}B. Thus, successful treatment of cancer by BNCT requires the selective delivery of relatively large amounts of ^{10}B compound to malignant cells. The estimated boron concentration required for effective therapy is in the range of 20–30 μg ^{10}B per g tissue. However there have been no ideal boron compounds fulfill on these conditions (the conditions should include low toxicity, water solubility, low distribution in normal tissue……).
We aimed at securing the concentrations of enough ^{10}B in BNCT by developing new drug delivery system. We have designed and developed a novel lipid analog, and succeeded in development of the new boron component liposome with it. It consisted of three different kinds of amino acid derivatives and two fatty acids, and could react directly with the peptide synthesized first on resin by Fmoc solid-phase synthesis.
The lipid mixture by the constant ratio was dissolved in organic solvent. It was prepared by the conventional lipid-film method. The resulting liposomes was extruded through polycarbonate membrane using an extruder, yielding the peptide-modified liposome.
The liposome containing the lipopeptide which give various functions exhibited efficient cellar uptake and effective concentrations of ^{10}B.
With this liposome, chemical characteristics, cytotoxicity and in vitro biodistribution will be discussed.

Boron compound delivery to oral squamous cell carcinoma cells using transferrin conjugated PEG-liposomes

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To improve outcomes of boron neutron capture therapy, it is critical to selectively deliver boron and increase the absolute value of boron concentration in the tumor. It is pertinent to deliver as much boron compound as possible within the tumor cells.
We conducted this study using a drug that sodium borocaptate(BSH) encapsulated transferrin(TF) targeting polyethylene glycol(PEG)-coated liposomes.
Findings showed a concentration of ^{10}B over time once TF-PEG-liposome-BSH was activated in oral squamous cell carcinoma cells *in vitro*,in comparison with PEG-liposome-BSH or liposome-BSH or bare BSH. Findings also indicated that ^{10}B remained in the tumor cells *in vitro* for an extended period of time.
Study findings suggest the efficacy of TF-PEG-liposome as a drug carrier and the possibility of improving treatment outcomes of BNCT in the future.

Synthesis of new dodecahydro-*closo*-dodecaborate cluster containing compounds

Andrea Vöge[1], Detlef Gabel[1]

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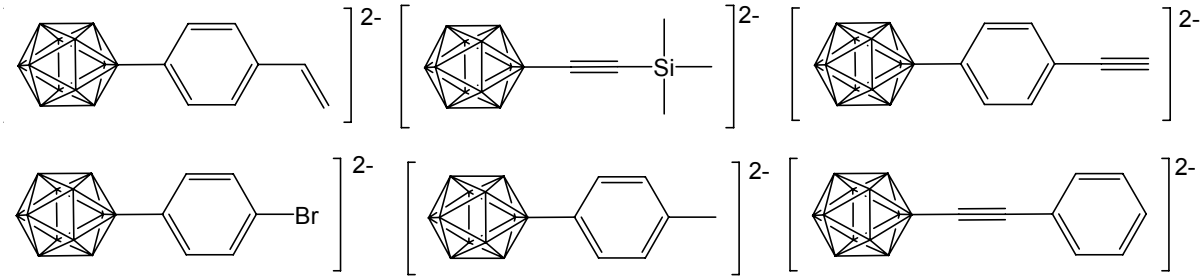
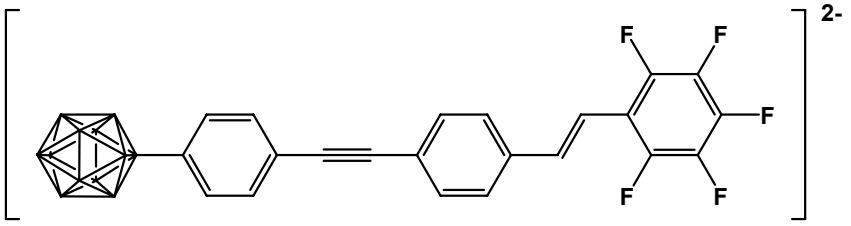
When specific compounds for boron neutron capture therapy (BNCT) are to be prepared, the cluster must be covalently attached to organic moieties. $B_{12}H_{11}SH^{2-}$ (BSH) is clinically used for BNCT of glioblastoma and is taken up in tumor tissue without additional target units.
The aim was to synthesize new dodecahydro-*closo*-dodecaborate cluster derivatives with hydrophobic residues so that the grade of accumulation in tumor cells would be higher compared to BSH with the polar thiol group. We suppose that these cluster derivatives pass the cell membrane easier than BSH. The new cluster derivatives shown below could be prepared by palladium catalyzed coupling reactions. They offer the possibility for further modifications.



One example for a modification of one of these intermediates is shown below. Fluorinated drugs are used because of their hydrophobicity and the slow degradation, so they are effective for longer time. The fluorine and boron containing compound obtained via a Sonogashira coupling can be a new interesting drug for BNCT.



Nanoparticle Fabrication by a Technique of Pulsed Laser Irradiation in Liquid for Boron Neutron Capture Therapy Agent

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Faculty of Engineering, Kagawa University, Japan[1]
National Institute of Advanced Industrial Science and Technology (AIST), Japan[2]

p-boronophenylalanine (BPA) and mercaptoundecahydrododecaborate (BSH) are clinically used for BNCT, whereas these compounds contain slight amount of B. Because highly concentrated boron in tumor cell is absolutely imperative for effective therapy, enormous dose of BPA and BSH is necessary, which imposes strain on a patient. Boron carbide (B4C) nanoparticle is attractive material for BNCT in recent days, because of a high concentration of boron atoms and its inertness. Mortensen et al. reported the size reduction of B4C grain by ball milling for BNCT agent.1) In this study, we obtained B4C particles encapsulated with graphite layer by pulsed laser irradiation of B particles in liquid phase with less contamination. The obtained particle with surface graphite layer is useful for surface modification of the particle for multiple biological functionalization. Thus, this unique B4C particle prepared by the pulsed laser irradiation in liquid has great potential for BNCT application.
Reagent-grade B powder (99.995 %, Aldrich Chemical Company, Inc.) was dispersed in ethyl acetate (99.5 %, Wako Pure Chemical Industries, Ltd.). 6 ml of the suspension including 0.24 mg of B was irradiated with the third harmonic (355 nm) of Nd:YAG laser operated at 10 Hz with pulse width of 7 ns and a maximum output on suspension level of 1.5 J cm-2 in a glass vessel. The suspension was agitated using a magnetic stirrer during irradiation.
Figure 1 shows SEM image of obtained particles by pulsed laser irradiation of B in ethyl acetate. Mean size of these spherical particles were 237 nm. Figure 2 depicts HRTEM image of obtained particle surface. According to selected area electron diffraction pattern, the obtained particle included B4C crystal. The turbostratic graphite layer was observed on the particle surface. Therefore the obtained particles including B4C crystal were encapsulated by graphite. Carboxyl group can be attached on the graphite layer surface of particle by subsequent acid treatment. The modified surface is benefical for further surface modification of the particles toward biomedical functionalization. Thus, the B4C particles obtained by this technique have a possibility for BNCT agent. Preliminary results on the stability against aggregation in phosphate buffer saline will also be presented.

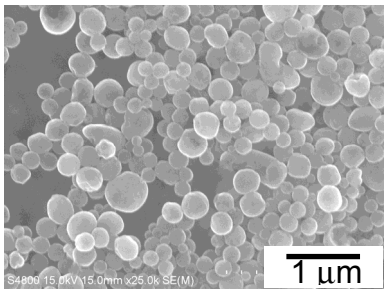

Fig. 1 - SEM image of particles obtained by laser irradiation of B in ethyl acetate

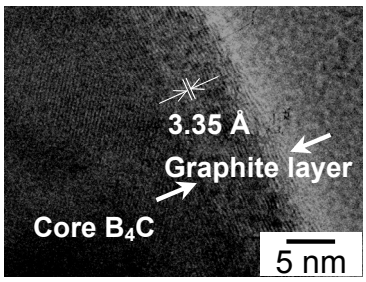

Fig. 2 - HRTEM image of surface of particle obtained by laser irradiation of B in ethyl acetate

Carboranyl Porphyrazines: Synthetic Aspects and Molecular Properties

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Among the challenges precluding the widespread use of BNCT has been the difficulty in achieving selective delivery of large quantities of boron nuclei to malignant cells. In an attempt to contribute to this issue we have recently developed an effective strategy to synthesize a new family of boronated porphyrazines to be delivered through the membrane of cancerous tissues as such or with the help of liposomes.

Herein we describe the synthesis and the basic physico-chemical properties of several neutral octa-*closo*-carboranyl-alkylthio-porphyrazines as well as of their water-soluble counterparts obtained by mild deboronation of the *closo*-polyedra.
Preliminary studies indicate that these compounds show negligible cell toxicity and, compared with BPA, a good cellular uptake, which encourages further studies for their evaluation as potential BNCT sensitizers.

Rational design of boron-rich compounds targeting human thymidine kinase for BNCT

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The drugs currently used in the clinics for BNCT can discriminate tumor cells versus healthy ones at best in the 5:1 ratio. In most cases, the target is not known. To improve drugs' selectivity, it is imperative to identify molecular target(s) of the drug in the cell nucleus.
In this context, 12 ^{10}B rich analogs of human thymidine kinase 1 (TK1) substrate (thymidine) have been recently designed (Fig. 1). TK1's function is the phosphorylation of thymidine to form building blocks of DNA (thymidine monophosphate): one of these analogs has the best kinetic efficiency relative to the natural substrate of TK1, and *in vivo* studies showed that it is efficiently incorporated in cancerous cells. Unfortunately, however, the production of thymidine monophosphate analogs is still much slower than in the natural substrate.
We are using computational methods to design new boron ligands with improved reactivity. We performed docking calculations based on the large X-ray structural information available on the human TK1 and homologous, N. Ostermann *et al.,* enzymes.
The compounds turn out to bind similarly to the natural substrate (Fig. 2). We are currently performing molecular dynamics and QM/MM calculations to shed light on the reaction mechanism of the compounds and compare it to that of the natural substrate. Knowledge of the structure of the transition state may allow the design of new ligands with faster reaction kinetics. These in turn may be incorporated faster in cancerous cell nuclei than the current ones. To the best of our knowledge, this is the first computer-aided, structure-based drug design approach in BNCT.

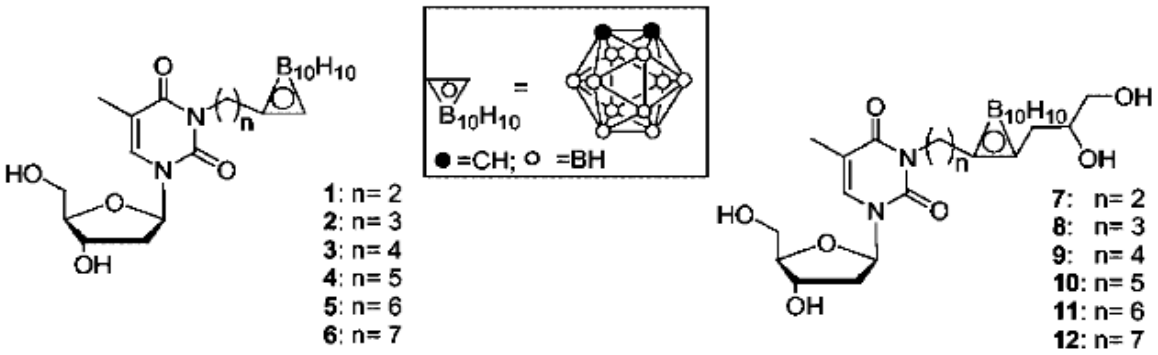

Fig. 1 - The boron-rich analogs of deoxythymidine drawn for BNCT, as proposed in A.S. Al-Madhoun *et al, Cancer Research* **64**, 6280 (2004)

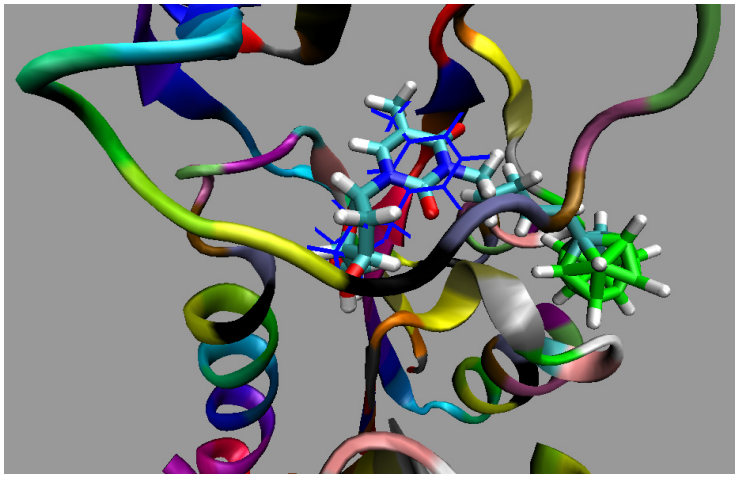

Fig. 2 - The predicted binding pose of one of the deoxythymidine analogs with a five-methylene spacer between thymine and the boron cage, in comparison with the natural substrate (in blue)

Boron carriers for BNCT: state of the art and new perspectives deriving from nanotechnology

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The efficient treatment of cancer by BNCT demands the selective delivery and marked accumulation of ^{10}B in malignant tumor tissues, whereas the B concentration in the cells of surrounding normal tissue should be kept low to minimize the damage to normal tissue. Clinically, two boron delivery agents have been used for BNCT, namely sodium borocaptate (BSH) and p-borono-phenylalanine (BPA), a dihydroxyboryl derivative of phenylalanine. Both these agents have limitations.

To improve the efficacy of the BNCT of cancers, considerable effort has been directed toward the development of new means of selective targeting of ^{10}B to tumors. Ideally, a boron delivery agent for BNCT should fulfill the following conditions: (I) non-toxic at the clinically relevant dose(s) (II) minimum concentration of 20–30 μg of ^{10}B/g per gram of tumor tissue; (III) high tumor/normal tissue and tumor/blood concentration ratios; (IV) rapid clearance from blood circulation and normal tissues, but persistence in tumor; (V) water solubility; and (VI) chemical stability.

In order to meet these requirements, several classes of boron delivery agents have been designed and synthesized over the years. Examples of these compounds include boron-containing amino acids, functionalized polyhedral borane clusters, biochemical precursors of nucleic acids and DNA-binding agents, porphyrin- and carbohydrate- derivatives, peptides, boron-conjugated biological complexes, such as boronated- monoclonal antibodies, -epidermal growth factors, and -carborane oligomers, and liposomes. Promising approaches may come from nanotechnologies and entail the use of targeted and tailored nanoparticles, being developed as “intelligent” drug delivery systems. For example, targeting, imaging and treatment of brain cancer (the latter being difficult to reach by conventional drugs) has been shown to be improved by nanoparticles simultaneously loaded with an anticancer drug and a contrast agent. Notably, a recent study by Mortensen et al (Bioconjugate Chem 2006, 17, 284) has put forward the intriguing hypothesis that *ad hoc* surface modifications of boron carbide nanoparticles may allow their use for, and the development of, T-cell guided BNCT.

Non-tumor specificity of polyhedral borane cages toward C6 tumor cells

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Mercaptoborane (BSH) is one of the therapeutics for use in current BNCT. However, the controversy concerning the mechanism of tumor uptake of this species still existed. Nonetheless, we have recently reported that the T/B ratio was generally less than 1.0 (av. 0.6) for human malignant glioma specimen on our regimen and concluded that the BSH is non-specific boron carrier. We now investigated the uptake mechanism and in-vitro BNCT effect of the dianionic dodecahedral borane cage itself (without the SH moiety) and its several cage-degraded and cage-expanded mono- and dianionic derivatives, including decaborane, undecaborane and their dimeric cages, using C6 gliosarcoma cell line.
Toxicity of anionic polyhedral borane derivatives onto the C6 cells was observed by Cell titer 98 aqueous one solution Cell proliferation assay, IC_{50}: $(NH_4)_2B_{10}H_{10}$ = $6.66x10^{-2}$ M, $K_2B_{12}H_{12}$ = $4.54x10^{-2}$M, BSH=$2.75x10^{-2}$M. Neither any boron uptake nor null boron enhancement ratio in the tumor cells was observed under our experimental conditions. The boron concentration in tumor cells after boron loading was under detectable limit by PGS and ppt-order quantitative determination by particle tracks reading method. There was no significant difference of surviving fraction between the groups those who received the borane derivatives and those with the boron-free control group.
BSH might pass through the cell membrane via conjugate form with some amino acid or amine, etc. Carborane cage itself is chemically stable, highly water soluble and permeable through cell membrane. Therefore, use of carborane cage as boron carrier is beneficial, in part, for accumulation of boron atoms into tumor cells by conjugating with some biological active moiety.

Carborane derivative drugs inserted in liposome as an effective strategy for Boron Neutron Capture Therapy

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Liposomes are the most accredited drug delivery system and, currently, the only one approved for clinical trials, though different promising nanosize vectors have been designed and prepared.
In all cases, it has been established that optimising biomedical applications requires extensive physico-chemical characterization at the molecular and meso-scale level. Factors like overall size, surface charge and drug insertion modality are of primary importance to understand the interaction between loaded vectors and cellular or tissutal substrates.
Here we report on the use of three liposomal formulations, made with different lipid components , i.e. the positively charged DOTAP, the zwitterionic DOPC and the negatively charged DOPA, in order to obtain positive, zwiterionic and negative aggregates, respectively. In addition to this, all liposomes contained the zwitterionic phospholipid DOPE as a fusogenic element.
Liposomes were loaded with carborane-derived drugs, i.e. o-closocarboranyl β-lactoside and 1-allyl-o-closocarboranyl-2- hexylthio-porphyrazine and tested for BNCT efficacy on model cell cultures.
The chosen cell line was the DHDK12TRb rat coloncarcinoma cell line, which is able to induce liver metastases in BD-IX rats and has been largely used in recent years to study the uptake capability of standard BNCT drugs, such as borophenyl-alanine (BPA). This cell line therefore represents an interesting model for comparative purposes.

Preliminary experiments were also carried out on the murine melanoma B16F10 cell line.
Boron uptake was determined by measuring alfa particle emission with the alpha spectrometry technique. Fixed amounts of cells were deposited on mylar disks and irradiated in the thermal column of the TRIGA Mark II reactor (University of Pavia). Boron concentration was thus obtained by analyzing the charged particles spectra emitted in the ^{10}B (n, α) $\rightarrow$ ^{7}Li reaction, which were detected by a thin silicon detector.
The results of boron uptake were analyzed in terms of both inserted drug and liposome properties. Toxicity effects were also investigated and a comparison was made with the behaviour of BPA on the same cell lines.
In general, an improved performance of the newly prepared ^{10}B delivery systems was demonstrated.

CLINICAL MATTERS/BIOMEDICAL APPLICATION

BPA uptake and distribution in GBM and normal brain is determined by extensive functional LAT-1 transporter expression which does not correlate with proliferative marker PCNA distribution

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[1]*Department of Neurosurgery, School of Medicine, University of Birmingham, Birmingham, UK*

Boronophenylalanine (BPA) functions as a vehicle for the delivery of B10 to target cells. Enhanced uptake of BPA into human target GBM tumour cells has been demonstrated. The mechanism of preferential uptake of BPA into tumours is thought to be due to upregulation of the metabolic linked amino acid transporter LAT-1. LAT-1 and tyrosine uptake have also been linked as markers for proliferative activity. In this study we have investigated the distribution of LAT-1 in GBM and normal brain compared to the distribution and incidence of elevated PCNA expression (a proliferative marker). In addition we have tested immediate GBM biopsy tissue and normal brain for uptake of BPA and selectively tested blockade of BPA uptake via LAT-1 with phenylalanine and BCH.
Four populations of cells are identified by dual immunostaining for PCNA and LAT-1. PCNA positive LAT-1 positive, PCNA positive LAT-1 negative (20%) PCNA negative LAT-1 positive, PCNA negative LAT-1 negative. BPA uptake into tumours rose to 30µg/g but much less in normal brain. In both cases uptake was unaffected by tyrosine levels but inhibited by phenylalanine and BCH a specific inhibitor of LAT-1. If inhibition is complete, then most of BPA uptake into GBM is explained by LAT-1 activity
The uptake data confirm the functional importance and specificity of LAT-1 in concentrating BPA in cells, and indicate from the direct competition for uptake between phenylalanine and BPA, that BPA is handled in the same manner as the normal amino acid.
These results indicate a markedly more comprehensive distribution (85% of tumour) of uptake capacity for BPA that does not correlate with proliferative markers. This supports the concept that BPA can act as a more efficient vehicle for BPA entry than was originally thought both in and around the tumour mass. A proportion of PCNA expressing non LAT-1 expressing cells may form a better target for standard radiotherapy or other cell-cycle conditional treatments. This study emphasizes the critical requirement of determining that the potential of BNCT must be based on in vivo biomarker approaches (e.g. LAT-1 distribution) as well as reliable neutron beams.

A novel approach to the study of ^{10}B uptake in human lung by ex-vivo ^{10}BPA perfusion

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[5] *INFN –Turin, Italy*
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[7] *Universitas Studiorum Insubriae, Como, and INFN, Milan Bicocca, Italy*
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[10] *Dipartimento di Fisica Nucleare e Teorica, Università di Pavia*

Research in BNCT concerns several fields as uptake of ^{10}B carriers, evaluation of RBE for different tumours, study of response to neutron capture therapy of different pathologies. Up today, experimental data are mainly obtained in animal models. In this work a new technique is proposed, to use human samples to investigate ^{10}B uptake in lung adenocarcinoma.

In patients surgically treated following "golden standard" for lung adenocarcinoma, the ablated part containing the tumour is perfused with ^{10}BPA solution in controlled conditions. After resection, perfusion of pulmonary lobe containing the tumour is carried out in an extracorporeal perfusion circuit employing a roller pump and a second pump to maintain a sufficient high fluid-water temperature (37 °C). Isolated lobar arteries and veins are incannulated by paediatric cannulas. Crystalloid priming solution is used with adding of blood. Ventilation is provided by a paediatric extracorporeal oxygenator. After perfusion, the biological material is frozen and samples are prepared from normal, peritumour and tumour tissue, placed on Cr-39 thin layers and on slides for the histological analysis. ^{10}B concentration in various samples is evaluated by exposure to thermal neutron field provided in the PhoNeS cavity installed at Elekta SLIT 25MV e-linac. This ex-vivo perfusion technique could represent an innovative method to be applied to different tumour pathologies, opening a new experimental field for widely studying BNCT applications in human samples.

Boronophenylalanine uptake in C6-glioma model is dramatically increased by L-DOPA preloading

Silvia Capuani[1,2], Tommaso Gili [1,2], Marco Bozzali[3], Salvatore Russo[4], MD, Paola Porcari[1], MS, Cesare Cametti[1,5], PhD, Emanuela D'Amore[6], Bruno Maraviglia[2,5], PhD, Giuseppe Lazzarino[7], PhD, [8]Francesco S. Pastore, MD

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[2]*Enrico Fermi Center, Rome, Italy*
[3]*Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy*
[4]*Victor Horsley Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, London, United Kingdom*
[5]*Physics Department, University "La Sapienza", Rome, Italy*
[6]*Serv. Qual./Sicurezza Sperim. Anim., Istituto Superiore di Sanità, Rome, Italy*
[7]*Department of Chemical Sciences, Laboratory of Biochemistry, Univ. of Catania, Catania, Italy*
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Purpose: Boron Neutron Capture Therapy (BNCT) is a radio-therapeutic modality, based on the cytotoxic effects of $^{10}B(n,\alpha)^{7}Li$ reaction, used for the treatment of malignant gliomas. One of the main limitations for BNCT effectiveness is the insufficient intake of ^{10}B nuclei in the tumour cells. This work was aimed at investigating the use of L-DOPA as enhancer for boronophenylalanine (BPA) uptake in the C6-glioma model. The investigation was first performed *in vitro*, and then extended *in vivo* to the animal model.
Methods and Materials: BPA accumulation in C6-glioma cells was assessed, using Radiowave Dielectric Spectroscopy, with and without L-DOPA preloading. Two different L-DOPA incubation times (2 and 4 hours) were investigated, and the correspondent effects on BPA accumulation were quantified. C6-glioma cells were also implanted in the brain of 25 rats, and tumor growth was monitored by Magnetic Resonance Imaging. Rats were randomly assigned to two experimental branches: 1) intra-carotid BPA infusion; 2) intracarotid BPA infusion after pre-treatment with L-DOPA, administrated intra-peretoneally 24 hours before BPA infusion. All animals were sacrificed, and assessment of BPA concentrations in tumor tissue, normal brain, and blood samples was performed using High-Performance Liquid Chromatography.
Results**:** L-DOPA preloading induced a massive increase of BPA concentration in C6-glioma cells only after a 4 hour incubation. In the animal model a significantly higher accumulation of BPA was found in the tumor tissue of rats pre-treated with L-DOPA as compared to the control group ($p<0.0001$). Conversely, no significant difference was found in the normal brain (sampled in both cerebral hemispheres) and blood samples between the two animal groups.
Conclusions**:** This study suggests the potential use of L-DOPA as enhancer for BPA accumulation in malignant gliomas eligible for BNCT. According to our results, this new strategy is expected to increase BNCT efficacy in absence of any additional risk of toxicity.

A Cancer Research UK pharmacokinetic study of BPA-mannitol in patients with high grade glioma to optimise uptake parameters for clinical trials of BNCT

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This presentation describes results from a human pharmacokinetic study which began recruitment in December 2007. The trial is an open-label, noncomparative, nontherapeutic study of BPA-mannitol in patients with high-grade glioma, who will be undergoing stereotactic brain biopsy as part of the diagnostic process before definitive treatment. The study is designed to achieve the following:

- to optimise the dose and uptake parameters for BPA-mannitol for use in future clinical trials of Boron Neutron Capture Therapy (BNCT),
- to evaluate the toxicity profile of BPA-mannitol, and
- to investigate the pharmacokinetic profile of BPA in the new mannitol-based formulation.

The study investigates the route of infusion (intra venous or intra carotid artery) and in each case will assess the effect of administration of mannitol as a blood-brain barrier disrupter. All cohorts will receive a 2 hr infusion of BPA-mannitol, and for some cohorts an additional mannitol bolus will be administered at the beginning of this infusion.

Measurements are made by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) of ^{10}B concentration in samples of blood, urine, extra-cellular fluid in normal brain (via a dialysis probe), brain tissue around tumour and tumour tissue. Additional analysis of the tumour tissue is performed using Secondary Ion Mass Spectrometry (SIMS).

The first patient was part of the cohort having intravenous (IV) infusion without mannitol bolus. No serious clinical problems were experienced and the assay results can be compared with available patient data from other BNCT centres. In particular we note that the peak ^{10}B concentration in blood was 28.1 mg/mL for a total BPA administration of 350 mg/kg which is very consistent with the previous BPA-fructose experience reported by the Helsinki group.

The presentation will focus on the clinical methodology and the derived boron pharmacokinetic data.

Clinical results and radiation dose of BSH, BPA-based non-operative BNCT with additional external beam irradiation

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Purpose: We have shifted from BSH-based intra-operative BNCT to BSH, BPA-based non-operative BNCT since 2005. In this study, we evaluated the clinical course and outcome of non-operative BNCT with additional external beam irradiation, and analyzed BNCT radiation.

Material and Methods: We have applied the modified BNCT in 6 patients (7 times of BNCT) with glioblatoma. 250 mg/kg of BPA and 100mg/kg of BSH were given to patient intravenously. BNCT radiation dose was evaluated with physical boron dose and weighted total (boron and gamma) dose JAERI Computational Dosimetry System (JCDS). Irradiation time was prescribed that normal brain tissue dose did not exceed 12 Gy(w). We analyzed BNCT dose in gross tumor volume (GTV) and clinical target volume (CTV). GTV was concomitant with enhancement area on Gd-MRI. CTV was concomitant with high intensity area on T2-weighted MRI. External irradiation was applied in three patients after BNCT.

Results: Irradiation time was 29.2±8.8 min. Blood boron concentration in BPA and BSH were 17.8±5.4 and 33.8±9.1 ppm, respectively. The maximum skin and normal brain tissue dose were 10.3±2.5 and 12.5±2.3 Gy(w), respectively. The minimum boron physical and weighted total (boron and gamma) dose in GTV were 7.8±2.5 Gy and 27.7±8.7 Gy(w), respectively. These doses in CTV were 4.2±1.1 Gy and 15.2±4.3 Gy(w), respectively. 5 patients were died of tumor recurrence at the primary site. The mean survival time was 19.6 months after BNCT. Only one patient is survived for 14 months with no neurological deficits. There were no patients suffered from acute radiation injury.
Conclusions: The clinical results of BSH, BPA-based non-operative BNCT with additional external irradiation was equal to that of BSH-based intra-operative BNCT. The former method was safe and less adverse effect. A dose-escalation is needed for further improvement of clinical outcome.

BPA-Based BNCT in the Treatment of Glioblastoma Multiforme: A Dose Escalation Study

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Purpose: We evaluated safety and efficacy of escalating doses of boronophenylalanine fructose (BPA-f) as the boron carrier for BNCT in the treatment of glioblastoma multiforme (GBM). The highest tolerated dose of BPA-f is unknown in this setting.
Patients and Methods: Patients with histologically diagnosed GBM were eligible to this prospective, phase I-II single-centre trial. BNCT was given a few weeks after brain surgery. No conventional radiotherapy or cancer chemotherapy was allowed. The first 12 patients received BPA-F 290 mg/kg, following which the BPA-f dose was planned to be escalated as follows: 330 mg/kg (n=1), 360 mg/kg (n=3), 400 mg/kg (n=3), 450 mg/kg (n=3), and 500 mg/kg (n=3). Further 6 patients were planned to be treated at the level of maximum tolerated dose -1 (MTD-1). BPA-f was administered intravenously as 2-hr infusion prior to epithermal neutron irradiation at the FiR 1 BNCT facility. The normal brain average maximum dose was restricted to 10 Gy (W). The NCI common toxicity grading v2.0 was used in evaluating adverse effects. ClinicalTrials.gov trial identifier NCT00115453.
Results: Thirty patients were entered in May 1999 to April 2005. The MTD was reached at 500 mg/kg, where 3 of the 8 patients developed severe central nervous system toxicity (grade 3, n= 2; grade 4, n=1). All but one patient have died. The patient alive received BPA-f 500 mg/kg and has been followed up for 39.0 months following BNCT. No association between the BPA-f dose and duration of survival is evident in this small series. The median survival times are 13.4, 11.0, 16.9, 21.9 and 14.7 months in the dose groups of 290, 330/360, 400, 450 and 500 mg/kg, respectively.
Conclusion: The MTD is reached at the BPA-f dose level of 500 mg/kg, when BPA-f is administered intravenously over 2 hours prior to neutron irradiation. The dose of 450 mg/kg was selected to be used in further studies.

Outcome of the First Twelve Patients with Locally Recurred Inoperable Head and Neck Cancer Treated in the Finnish Head and Neck Cancer BNCT Trial

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Background**:** Head and neck cancer patients whose disease recurs locally after surgery and radiation therapy generally have poor outcome. We evaluated safety and efficacy of boron neutron capture therapy (BNCT) in the treatment of 12 patients who had locally recurred, inoperable head and neck cancer. We

have reported earlier results based on a median follow-up time of 14 months (Kankaanranta et al. IJROBP 2007;69:475-82), and now report outcome based on a median follow-up of 31 months.
Patients and Methods: All patients had inoperable, recurred, locally advanced (rT3, rT4 and/or rN2) head and neck cancer. Prior treatments consisted of surgery and conventionally fractionated photon irradiation to a cumulative dose of 56 to 74 Gy administered with or without concomitant chemotherapy. Tumor responses were assessed using the RECIST criteria and adverse effects using the NCI common toxicity grading v3.0. Intravenously administered boronophenylalanine-fructose (BPA-F, 400mg/kg) was used as the boron carrier. Ten patients received BNCT twice; 2 were treated once.
Results: Ten (83%) patients responded to BNCT, and 2 (17%) had tumor growth stabilization for 5.5 and 7.6 months. The median duration of locoregional tumor control was 10 months (range, 1 to 36.0+ months). Six (50%) patients developed metastatic disease. The median survival time was 13 months. Three (25%) patients were alive at the time of the analysis with follow-up of 30+, 31+ and 36+ months as calculated from the date of first BNCT. One of these patients is alive without cancer recurrence (at 36+ months) with a good quality-of-life. One patient developed retinal toxicity, but otherwise no unexpected late toxicity was recorded.
Conclusions**:** BNCT is effective in the treatment of inoperable, locally advanced head and neck carcinoma that recurs at a previously irradiated site, and deserves further study.

Effectiveness of Boron Neutron Capture Therapy for Recurrent Head and Neck Malignancies

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Introduction: Recurrent head and neck malignancies (HNM) are often radio-/chemo-resistant and show extensive growth, necessitating a wide resection including surrounding tissues. To avoid severe impairment of oro-facial structures and functions, it is necessary to explore new treatments for HNM. Boron neutron capture therapy (BNCT) is tumor-cell targeted radiotherapy that has significant superiority over conventional radiotherapies in principle.We have, first in the world, treated with BNCT for a patient with recurrent parotid gland carcinoma in 2001.
Material and Methods: So far for 6years, we have treated with 42 times of BNCT for 26 patients with a recurrent HNM who were composed of 19 squamous cell carcinomas (SCC), 4 salivary gland carcinomas and 3 sarcomas. All of them had received standard therapy and had developed recurrent tumors for which there were no other treatment options. All of the patients received in principle a combination of BSH:5g and BPA:250mg/kg or BPA:500mg/kg alone administered iv.
Results: 21 out of 26 patients (81%) were advanced stage IV. 14 out of 26 patients (54%) had developed regional lymph node metastases. Distant metastases were developed in 6 cases under treatment. (1) ^{10}B concentration of tumor/normal tissue ratios (T/N ratio) of PET studies were SCC: 1.8-5.7, sarcoma: 2.5-4.0, parotid tumor: 2.5-3.7. (2)Regression rates were CR: 12cases (46%), PR: 10cases (39%), PD: 3cases (12%), NE (not evaluated):1case. Response rate was 85%. 9 patients (35%) were disease free survival. (3)BNCT improved QOL, PS and survival periods. (4)Survival periods after BNCT were 1-72 months (mean: 13.6 months). 6-year survival rate was 24% by Kaplan-Meier analysis. (5) Adverse events were brain necrosis, osteomyelitis and transient mucositis and alopecia.
Conclusions**:** These results indicate that BNCT represents a new and promising treatment approach for recurrent or far advanced HNM without other treatment options.

Survival benefit from Boron Neutron Capture Therapy for the newly diagnosed glioblastoma patients

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Objective: Since 2002 to 2007, we applied boron neutron capture therapy (BNCT) for >50 cases of malignant gliomas (MGs) with epithermal neutron irradiations. Recently, we showed the early radiographical improvement of malignant glioma patients by our modified BNCT, simultaneous use of BPA and BSH. In this time, we focused on the survival benefit from BNCT for the newly diagnosed glioblastoma patients.
Methods: BNCT group including 21 newly histological confirmed glioblastoma patients treated with surgical removal followed by BNCT in Osaka Medical College during 2002 to 2006. Ten patients were treated with BNCT only, and in the other 11 patients, 20 to 30 Gy fractionated external beam X-ray irradiation (XRT) was combined after BNCT. No chemotherapy was applied until tumor progression was observed.
Results: Treatments were well tolerated. Any kinds of acute systemic or local severe toxicity were not demonstrated. Mean over all survival of the patients treated by BNCT was 20.7 and the median was 15.6 months with 2-years survival of 25%. Stratification by RPA criteria showed 6, 6, 8 and 1 patients in class III to VI, respectively. Three patients out of 6 in class III and 1 of 8 in class V are alive at the end point of this study. All the patients in class IV and VI had died. Median survival time for the BNCT group compared to the RTOG database was as follows: 20.6 months vs. 17.9 months for class III; 16.9 months vs. 11.1 months for class IV; 13.2 months vs. 8.9 months for class V.
Conclusion: The RTOG RPA prognostic criteria were helpful in establishing which class of glioma patients could potentially benefit from BNCT. BNCT showed a survival benefit in all of the RPA classes of the RTOG database not only for the good prognosis group.

Boron Neutron Capture Therapy for Patients with Melanomas of Head-and-Neck

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With the approval of the Nuclear Safety Bureau of the Japanese Government and the Medical Ethics Committees of Kawasaki Medical School and Kyoto University, we have conducted clinical trials on patients with mucosal melanomas in head-and-neck at the Japan Research Reactor No. 4 (JRR-4) since 2005.
To date, we have treated 10 patients with head-and-neck mucosal melanomas: 4 with melanomas in the nasal cavity (Nos. 1, 3, 8 and 9), 3 in the paranasal cavity (Nos. 5-7), 2 with metastatic melanomas of the neck lymphnodes (Nos. 4 and 10), and 1 in the lacrimal sac (No. 2).
The tumor/blood ratio obtained from 18F-BPA-PET study was adopted to the dose estimation before neutron irradiation and dose evaluation after BNCT using JCDS. The tumor/blood ratio of 3.0 was adopted when no tumor was detected by PET study due to small tumor volume.

Neutron irradiation was performed using an epithermal beam at a reactor power of 3.5 MW after intravenous administration of BPA in fructose solution at a dose of 500 mg/kg body weight. The tumor dose at the deepest part and the dose of both normal skin and mucosa were planned more than 20 Gy-Eq and less than 15 Gy-Eq, respectively.
Four patients (Nos. 1, 3, 5 and 9) showed a complete response (CR) and 5 patients showed a partial response (PR). Only one patient (No. 7) showed no response. Two patients (Nos. 1 and 4) suffered from normal-tissue damage (both grade 2 RTOG/EORTC acute reaction). Both of them were cured within a few months. Four patients (Nos. 4, 5, 9 and 10) died due to distant metastasis. However, no local recurrence of melanoma has been observed in 2 CR patients and no regrowth of melanoma in 2 PR patients.
BNCT is a promising treatment for achieving local control of mucosal melanomas.

Boron Biodistribution Study in Colorectal Liver Metastases Patients in Argentina

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The TAOrMINA project developed and employed a new method for BNCT treatment of multifocal unresectable liver metastases based on whole liver autograft. The surgeons of the Roffo Institute in Argentina propose a new technique based on partial liver autograft. In situ BNCT treatment of liver metastases is also being considered. In all three scenarios boron biodistribution is pivotal to deliver the necessary doses to achieve tumor control (≥ 40 Gy-eq) and spare healthy liver (≤ 15 Gy-eq). In addition, both whole and partial autograft techniques involve liver perfusion with University of Wisconsin solution (UW) and hypothermal preservation in UW during neutron irradiation. Thus, the boron concentration in healthy liver and metastases following perfusion and immersion in UW will reflect a clinical scenario more adequately. This issue has not been addressed to date.
The aim of the present study was to determine boron concentration in blood, liver and tumor tissue following an intravenous infusion (1.5 hs) of BPA-F (100 or 300 mg/kg) in 5 (to date, March 2008) colorectal liver metastases patients scheduled for surgery. Blood, liver and tumor samples were taken 80-220 minutes after the end of the infusion depending on surgical procedures. Tissue samples were evaluated pre and post perfusion and immersion in UW. Degree of perfusion varied with the surgical procedure and was not always representative of perfusion in an autograft scenario. One set of samples was proccesed for inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis. A second set of samples was fixed in 10% buffered formalin for histological analysis, and a third set of samples was stored in liquid nitrogen for future boron microdistribution studies.
Overall linearity was verified for BPA doses of 100-300mg/kg. Intact liver boron concentration (escalated to 300 mg BPA/kg) ranged from 12-18 ppm whereas intact tumor boron concentration ranged from 24-36 ppm. Intact liver boron concentration and concurrent blood boron values exhibited a liver/blood ratio close to 1. Intact tumor/liver boron concentration exhibited a ratio of 2-3/1. Tumor uptake revealed considerable heterogeneity. Boron concentration fell by approximately 30% in healthy liver post perfusion and immersion in UW. In most of the cases boron loss from tumor tissue post-perfusion and immersion in UW was less than 20%. The ratio of tumor tissue/liver post perfusion and immersion in UW ranged from 1.5-3.3. Histological analysis of the present samples and previous studies by Roveda et al. (2004) and Wittig et al. (2008) suggest that absolute tumor boron concentration would be considerably higher if the values reported herein are corrected for percentage of metabolically active tumor parenchyma.
Based on the boron concentrations reported so far and dose considerations at the RA-3 thermal neutron facility, ex-situ treatment of liver metastases at RA-3 would be feasible.

Current practices and future directions of therapeutic strategy in glioblastoma: survival benefit and indication of BNCT

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Concomitant and adjuvant use of temozolomide with conventional photon radiotherapy, the new standard post-operative therapy for GBM, has demonstrated a significant survival advantage compared to radiotherapy alone, and shows minimal additional toxicity. The median overall survival (OS) time in a randomized control trial was 14.6 months with temozolomide plus radiotherapy and 12.1 months with radiotherapy alone. Recently, image-guided surgery utilizing fluorescence with 5-aminolevulinic acid, neuronavigation and intraoperative MRI has enabled more complete resections of contrast-enhancing tumor, resulting in survival prolongation. Dose escalation studies in radiotherapy have been designed as case series of small numbers of selected patients who underwent additional stereotactic radiosurgery, fractionated proton beam radiation or other conformal radiotherapy. The better outcome following these radiotherapies, in which median OS varies from 9.5 months to 25 months, is in part the result of patient selection.

Previous BNCT clinical studies for GBM have been also designed as case series of small numbers of selected patients. To assess the feasibility of BNCT, indication and survival time in BNCT were compared to those in standard radiotherapy and high-dose proton therapy in our institute. Fifteen of consecutive 68 patients with newly-diagnosed GBM underwent BNCT were categorized according to the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) and the European Organization for Research and Treatment of Cancer (EORTC) RPA. The survival data of the 15 patients were compared with previously reported RPA-based survival data determined using standard therapies or high-dose radiotherapies. In the 68 patients with newly-diagnosed GBM, 15 were treated with BNCT, 17 were treated with high-dose proton/X-ray therapy and other 36 patients were treated with standard X-ray radiation therapy. Age, performance status, and extent of surgery were compared among three different radiation modalities in relation to survival time. The possibility of negative bias was also assessed by comparing survival data between standard X-ray radiation cases and previously reported new standard chemotherapy (TMZ) with standard radiation therapy.

Eligibility analysis showed relatively better survival in eligible patients. The median OS (25.7 months) and 2-year survival rate (56.2%) in the patients with BNCT appear to be superior to those of RTOG Class III and EORTC Class III in both standard therapy and reported high-dose therapy. In the patients who underwent standard X-ray radiation and ACNU-based chemotherapy, OS and 2-year survival rate was 14.2M and 17.9%, respectively. This data is similar to that of standard X-ray radiation with TMZ.

Although part the favorable prognostic data is caused by selection bias, BNCT for GBM has still shown survival benefit. Randomized trials of comparably selected patients are required to demonstrate conclusively that prolonged survival is a result of this tumor-selective radiotherapy. Emerging and standard therapies for GBM will be also systematically reviewed.

BNCT for Skin Melanoma in Extremities: Updated Argentine Clinical Results

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As part of phase I/II Melanoma BNCT clinical trial conducted in Argentina in a cooperative effort of the Comisión Nacional de Energía Atómica (CNEA) and the Instituto de Oncologia Angel H. Roffo (IOAHR), 7 patients (6 female – 1 male) received 8 treatment sessions covering 10 anatomical areas located in extremities. Mean age of the patients was 64 years (51-74). The 8 treatments were performed between October 2003 and June 2007.
All patients presented multiple subcutaneous skin metastases of melanoma and received an infusion with ~ 14 g/m^2 of boronophenylalanine (^{10}BPA)-fructose followed by the exposition of the area to the hyperthermal neutron beam at the RA-6 reactor. The maximum prescribed dose to normal skin ranged from 16.5 to 24 Gy-Eq and normal tissue administered dose varied from 15.8 to 27.5 Gy-Eq.
Taken into account the evaluable nodules, 69.2% of complete response and 30.7% of no changes were seen. The toxicity was acceptable, with 3 out of 10 evaluated areas showing ulceration (30% toxicity grade 3).

The peptide modified BSH highly uptaking into the glioma cells

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Boron neutron capture therapy (BNCT) is a targeted approach to radiotherapy that significantly increases the therapeutic ratio against the malignant brain tumor relative to conventional radiotherapeutic modalities. In our BNCT group, we use the two kinds of Boron compounds in the clinical field (2001, Miyatake et al). One is the boronophenylalanine (BPA) and the other is sodium borocaptate (BSH). These two compounds works in the different uptaking mechanisms and compensates for each other's faults. But one of the most difficult problem is that the BSH can not get into the cell. To improve the effectiveness of BSH delivery, we modified the peptide to the BSH.
We observed the BSH localization in the microscope and confirmed the BSH in the glioma cells. This modified BSH could get into the glioma cell very effectively. We want to show the effectiveness of this modified BSH compound compared to the traditional BSH compound. In future, we think this modified BSH compound can become good help in clinical BNCT field.

Determination of Boronophenylalanin (BPA) in healthy liver and tumour tissue of patients with liver metastasis of colorectal carcinoma

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Patients suffering of colorectal carcinoma develop distant metastases in 50 to 80% with the metastases being confined to the liver in almost half of those cases.
BNCT in patients suffering from multiple liver metastases was established at the University of Pavia with the first case being treated by Pinelli et al in Dec. 2001 [1]. Here, BPA was administered intravenously before explanting the liver and irradiation in the thermal column of the TRIGA-Reactor in Pavia. An accumulation of BPA in tumour vs. healthy liver tissue of 6:1 was determined here. Noteworthy is that the tissue samples were collected before explanting the liver.
The surgical process requires extensive experience in the field of liver transplantation and preservation of the liver during the extracorporeal treatment. This includes perfusion of the liver artery with preservation solution and reducing the liver temperature to 4 °C.
The question remains whether there are any wash-out effects during this procedure and if yes, will the accumulation remaining in tumour tissue still be enough for the irradiation therapy?
We plan to implement BNCT for colorectal liver metastases at the University of Mainz on cooperation with the University of Pavia. The conditions in Mainz are excellent as both the transplant center and the irradiation facility are in a close distance.
Our project will be performed in two steps. The first step will be to determine the accumulation of BPA in tumour and healthy liver tissue in patients after partial liver resection and washing the liver specimen with preservation solution. Provided satisfying results we would proceed with step 2 which is to treat a patient with multiple liver metastasis and extracorporeal irradiation of the whole liver.
So far we have obtained the approval of the German Administration for Medical Products (BfArM) and the Ethical Committee for the first part of our project. This is to examine a total of 15 patients with colorectal liver metastases who need a partial liver resection and to determine the accumulation of BPA in tumour and healthy liver tissue. BPA would be administered in a concentration of 200 mg/kg intravenously and blood samples will be collected during the surgical procedure. The liver specimen will be examined at the Institute of Nuclear Chemistry in Mainz with autoradiographic methods and ICP-MS. In case of an accumulation of BPA in tumour vs. healthy liver tissue of at least 3:1 in 3 patients we would proceed with the remaining 12 patients.

Comparison of BNCT and GdNCT Efficacy in Treatment of Canine Cancer

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The purpose of this study was to evaluate and to compare the efficacy of antineoplastic action of NCT types (BNCT and GdNCT) in most malignant canine tumors.
The study was carried out in dogs with oral cavity melanoma and osteosarcoma – the most malignant canine tumors. In these types of cancer, the prognoses are often poor, the life span is not longer than 2-3 months, and according to recent studies, the incidence of these canine malignancies gradually rises.
The study has been carried out in 33 dogs with oral cavity melanoma, and 9 dogs with osteosarcoma. Dogs with spontaneous melanoma of oral cavity and osteosarcoma of extremities were selected by the

results of clinical examination. In all dogs, tumor stage II B was detected. The diagnosis was confirmed in a histological study of biopsy material.
The dogs with oral melanoma were divided into the following groups: 1) 5 dogs treated with neutrons only, 2) 14 dogs treated using BNCT; 3) 14 dogs treated with GdNCT.
Osteosarcoma patients were divided in two groups: 1) one dog underwent BNCT; 2) GdNCT was performed in 8 dogs. In osteosarcoma cases, NCT was a part of complex osteosarcoma treatment.
Irradiations were carried out at the NCT facility of the IRT MEPhI reactor. In cases of melanoma treated with neutron beam, antineoplastic effect was very low: incomplete regression - in 80% of cases, and full regression - in 20% of cases. Recurrence was detected in 100% cases. In BNCT group, full regression was diagnosed in 78% of dogs, and the recurrence rate was very low -14% only in the cases of incomplete regression. In the GdNCT melanoma group, full regression was detected in 44% of dogs, and in 56% - incomplete regression; recurrence was diagnosed in 46% of cases.
In osteosarcoma cases, BNCT-based complex treatment showed full tumor regression 2.5 months after the irradiation of the bone autograft. The GdNCT group showed complete tumor necrosis in 100% of cases.
For superficial soft-tissue tumors, such as oral melanoma, BNCT is the most effective method of treatment. The effect of GdNCT in melanoma cases is lower and depends on intratumoral concentration of ^{157}Gd. Optimal ^{157}Gd concentrations are 10-15 mg/ml.
In tumors of interstitial origin, such as canine osteosarcoma, GdNCT appears to be an effective method of treatment, as secondary irradiation is optimal for these tumors. GdNCT gives an opportunity to administer the Gd-containing drug intratumorally, perform in vivo irradiation, and to achieve full tumor necrosis after one session of GdNCT.
For epithelial-cell tumors, such as melanoma, the ^{10}B-containing cell is the main target of damage, and for stromal tumors, such as osteosarcoma, drugs accumulating in the extracellular space should be administered preferably.

Clinical results of BNCT for malignant brain tumors in children

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Purpose**:** It is very difficult to treat the patients with malignant brain tumor in children, especially under 3-year-old because the conventional irradiation cannot apply due to the damage of normal brain tissue. However, BNCT has tumor selectivity such as it can make damage only tumor cells. We evaluated the clinical results and courses in patients with malignant glioma under 15-year-old.
Material and Methods: Among 183 patients with brain tumors treated by our group using BSH-based intra-operative BNCT, twenty-three patients were under 15-year-old. They included 4 patients under 3-year-old. There were 3 cerebral GBMs, 6 anaplastic astrocytomas, 7 primitive neuroectodermal tumors (PNET), 6 pontine gliomas and 1 anaplastic ependymoma.
Illustrative cases and Results: All GBM and PNET patients were died. Five of 6 pontine glioma patients were died. 4 of 6 anaplastic astrocytoma and 1 anaplastic ependymoma patients were alive.
Case1: 1-year-old, female, anaplastic ependymoma
The patient had a huge mass in right frontal lobe. She was suffered from transient left hemiparesis one year after BNCT. MRA and angiography demonstrated moyamoya phenomenon on right middle cerebral artery. We performed in-direct bypass surgery. Recent MRI demonstrated no tumor recurrence and brain atrophy.
Case 2: 6-year old, female, glioblastoma
The patient had a huge mass in right frontal lobe. Abnormal enhancement was recognized 8 months after BNCT. Residual tumor cells were recognized histopathologically in salvage surgery. She was died of CSF dissemination 1 year after BNCT.
Conclusion: BNCT can apply to malignant brain tumors in children, especially under 3 year-old in stead of conventional radiation. Although it can achieve the local control in the primary site, it cannot prevent CSF dissemination in patients with glioblastoma.

Can boron neutron capture therapy prolong the survival of recurrent malignant glioma patients?

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Objective: We have applied tumor selective particle radiation known as boron neutron capture therapy (BNCT) to malignant brain tumors. We report the survival benefit of BNCT for newly diagnosed glioblastoma patients with special reference to the results of RTOG RPA classes (Submitted for publication). As there has been no standard treatment for recurrent gliomas so far, it has been difficult to evaluate the results of BNCT for recurrent malignant gliomas. Here we introduce the survival benefit of BNCT for recurrent malignant glioma patients, with special reference to new RPA classification based on phase 1 and 2 trials applied for recurrent malignant gliomas advocated by New Approaches to Brain Tumor Therapy CNS Consortium (NABTT) in J Clinical Oncology 25:2601-2606, 2007.
Methods: Since 2002, we have treated 22 cases of recurrent malignant gliomas with BNCT. All cases had been treated by standard treatment including radiotherapy mainly by XRT prior to BNCT. After BNCT, patients were followed by MRI and F-BPA-PET. Cause of death was estimated by these modalities. Also overall survival was evaluated with special reference to RPA classes advocated by NABTT as above.
Results: All cases showed radiographical improvement at once. The median survival time (MST) of BNCT-treated recurrent gliomas was 11 months, while that of total NABTT cases (N=333) was 7 months. MST of NABTT RPA classes were 25.7, 17.2, 3.8, 10.4, 5.6, 6.4 and 4.9 months for classes 1 to 7, respectively. The MST of BNCT-treated cases were 43, 22, 11, 8, 7, 22 and 11, for classes 1 to 7, respectively. In each RPA class, BNCT showed good survival benefit for recurrent gliomas patients, although case numbers were limited. Especially BNCT could prolong the most poor RPA class 7 from 4.9 months (NABTT) to 11 months as MST. Three cases were lost due to uncontrollable radiation necrosis, 10 were lost due to dissemination and 5 were lost by local recurrence.
Conclusion: BNCT could prolong the survival of patients with recurrent gliomas not only for the good prognosis group but also for the poor prognosis group.

Feasibility of Boron Neutron Capture Therapy for spinal malignant tumors

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Treatment of spinal malignant tumor is currently ineffective. The characteristics of supine are serial organ, small volume, and severe QOL impairment is bring about by small neuronal damage. The present study aimed to investigate the feasibility of BNCT as a tumor selective charged particle therapy for spinal tumour from a view point of preventing normal spine.
Previous report showing the tolerance dose of the spinal cord was 13.8Gy-Eq for radiation myelopathy, and the dose as low as 11Gy-Eq demonstrated no spinal damage on experimental animal model. We calculate the tumor dose and the normal spine dose on a virtual model of spinal cord tumor patient with JCDS treatment planning system. The present study made use of boronophenylalanine (BPA). In these calculate, conditions are set as follows, Tumor/Normal (T/N) ration is 3.5, Blood boron concentration is 12 ppm, tumor boron concentration is 42 ppm, Relative Biological effectiveness (RBE) of the tumor and normal supine are 3.8 and 1.35, respectively. We examine the optimise neutron irradiation by changing the beam direction and number.
Simple opposed two field irradiation achieved 28.0Gy-Eq as minimum tumor dose and 7.3Gy-Eq as maximum normal spinal dose for example. The BNCT for the spinal cord tumor therefore feasible when sufficient T/N ratio could be achieved. F-BPA PET imaging for spinal tumor patients could support for this study.

The Accelerator Based BNCT Project in Kyoto University Reactor Institute

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In Japan, BNCT by epithermal neutron was started in Kyoto University Research Reactor Institute in 2001. Especially, the first success in the world of BNCT for recurrent head and neck cancer accelerated clinical BNCT research, and the cases increased explosively.
We also applied BNCT to liver cancers with multiple lesions or lung cancers including malignant mesothelioma. To advance BNCT research further, the project of accelerator based BNCT was started.
An accelerator maker manufactures a cyclotron with an acceleration proton energy of 30MeV and an electric current of 2mA, and the high-speed proton obtained with the cyclotron is made to collide with Be target. The neutrons are slowed down to obtain the epithermal neutrons for BNCT. Moreover, BPA and BSH, which are other important factors in BNCT, are manufactured by the drug manufacturing company according to manufacturing process of a drug for medical use GMP. Preparations are started in order to begin the clinical trial for the approval as medical device and drugs from authority in the spring of 2009.
As compared with the tumor dose distribution given by KUR neutrons on the condition of 10 Gy-Eq at the highest normal brain dose, cyclotron neutron BNCT system can give 20 Gy-Eq of tumor dose at the cerebrum median section in place of <15 Gy-Eq in KUR.
If the neutrons are also delivered from contra-lateral side on the same condition, the sum total dose at the median section will reach 40 Gy-Eq. This dose is aimed as the minimum tumor dose in the present clinical BNCT research.
Expansion of an indication of tumors and improvement in the anti-tumor effects can be easily expected.

Dynamic Infrared Imaging of Melanoma and Normal Skin in Patients Treated by BNCT

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Since the early 1980s, clinical applications of infrared imaging have received renewed attention mainly due to the availability of improved technologies, and the serious efforts of some groups in establishing infrared imaging protocols as part of a multi-imaging cancer detection strategy, particularly for breast cancer.
We recently initiated a program aimed to investigate the suitability of dynamic infrared imaging for following-up nodular melanoma patients treated by BNCT. The reason that makes infrared imaging attractive is the fact that it constitutes a functional and non-invasive imaging method, providing information on the normal and abnormal physiologic response of the nervous and vascular systems, as well as the local metabolic rate and inflammatory processes that ultimately appear as differences in the skin temperature.
An infrared camera, with a focal plane array of 320x240 uncooled ferroelectric detectors and modified optics is employed, with a minimum focus distance of 1.5 m. It provides a video stream of the infrared emission in the 8-12 μm wavelength band. A double blackbody is used as reference for absolute temperature calibration.
After following a protocol for patient preparation and acclimation, a basal study is performed. Subsequently, the anatomic region of interest is subjected to a provocation test (a cold stimulus), which induces an autonomic vasoconstriction reflex in normal structures, thus enhancing the thermal contrast due to the differences in the vasculature of the different skin regions. Radiation erythema reactions and melanoma nodules possess typically a faster temperature recovery than healthy, non-irradiated skin. However, some other non-pathological structures are also detectable by infrared imaging, (e.g. scars, vessels, arteriovenous anastamoses and injuries), thus requiring a multi-study comparison in order to discriminate the tumor signal. Besides the superficial nodules, which are readily noticeable by infrared imaging, we have observed thermal signals that are coincident with the location of non-palpable nodules which are observable by CT and ultrasound. Diffuse regions of faster temperature recovery after a cold stimulus were observed between the 3rd and 6th weeks post-BNCT, concurrent with the clinical manifestation of radiation erythema. The location of the erythematous visible and infrared regions is consistent with the three-dimensional dosimetry calculations.
We conclude with these preliminary studies that the thermal spatial signatures observed by dynamic infrared imaging are well correlated with the clinical observations as well as with the findings of high-resolution Doppler ultrasound and CT.

Efficacy of BNCT for GBM: Assessment of clinical results from Studsvik, Sweden

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Twenty-nine patients with newly diagnosed GBM were treated in a phase II study at Studsvik, Sweden, using a protocol with 6 hour infusion and a total dose of 900 milligram of L-BPA per kilo body weight, prior to irradiation with epithermal neutrons. A report of the study has recently been published by the investigators.
In the present report the clinical results have been compared to results from the phase I/II study involving 53 patients at Brookhaven National Laboratory, where a protocol with a 2 hour infusion of L-BPA was used, and with results obtained from a large randomized phase III trial, with conventional radiotherapy combined with concomitant and adjuvant temozolomide as the experimental arm and radiotherapy only as

the reference arm. The pre-treatment prognostic status of the patients in the various studies was taken into consideration when comparing the clinical results.
Comparison of the two BNCT studies established a clear advantage of the prolonged infusion protocol used at Studsvik. The median survival time (MST) in the Studsvik study was significantly longer than that observed in the radiotherapy only arm in the phase III study and the level of side effects was similar. The MST was also at least as long as that observed with radiotherapy plus temozolomide and the frequency of WHO grade 3-4 adverse events was more than three times lower in the BNCT study.
It is proposed that BNCT should be particularly advantageous in the case of patients with bad performance status (RPA class V), where the benefit of temozolomide is marginal and where the MST in the Studsvik study was significantly longer than that achieved with radiotherapy only. It is suggested that the present results should be verified in a randomized phase III trial.

Boron Neutron Capture Therapy for Head and Neck Epithelial Carcinomas other than SCC

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Background**:** Based on the reports that success of BNCT in treating mucoepidermoid carcinoma of the parotid gland, we have been conducting BNCT clinical trial on recurrence or locally advanced epithelial carcinomas in the head and neck since October 2003.
Patients and Methods**:** Six patients were treated with BNCT at KUR or JRR-4 from October 2003 to September 2007. The histologic type of carcinoma, recurrence or primary region, and TNM staging in each patient were as follows: *Patient 1*: high grade mucoepidermoid carcinoma; submandibular grand, rN2a, *Patient 2*: adenoid cystic carcinoma (ACC); submandibular grand; rT3, *Patient 3*: ACC; maxillary sinus; rT4, *Patient 4*: acinic cell carcinoma; palotid gland; T4N0M0, *Patient 5*: ACC; lacrimal sac; T4N0M0, *Patient 6*: ACC; maxillary sinus; T4N0M0.
The tumor/normal-tissue boron concentration ratio (T/N ratio) obtained from ^{18}F-BPA-PET study was adopted to the dose estimation before neutron irradiation and dose evaluation after BNCT using SERA or JCDS. Neutron irradiation was performed using an epithermal beam at a reactor power of 5.0 MW (KUR) or 3.5 MW (JRR-4) after intravenous administration of BPA in fructose solution at a dose of 500 mg/kg body weight. The tumor dose at the deepest part and the dose of both normal skin and mucosa were planned more than 20 Gy-Eq and less than 15 Gy-Eq, respectively.
Results**:** All patients demonstrated regional complete response (CR). *Patient 6* suffered from dermatitis (grade 2 RTOG/EORTC acute reaction) that exceeded the tolerance level. However, dermatitis was cured within a few months after BNCT. *Patient 1* showed metastasis to subcutaneous tissue of the neck 19 months after BNCT. *Patient 4* had brain involvement 12 months after BNCT. At present, all the patients are living, surviving 4 to 51 months after BNCT.
Conclusion**:** This study shows that BNCT is a quite effective therapy for the epithelial carcinomas of the head and neck. Based on the promising results and the sample size, further research is warranted on this method.

Boron neutron capture therapy for newly-dignosed gioblastoma: pilot study in Tsukuba

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Background: Neutron capture therapy (NCT) theoretically allows a unique tumor-cell-selective high-LET particle radiotherapy. The survival benefits and safety of NCT were evaluated in 15 patients with newly diagnosed glioblastoma multiforme (GBM).
Methods: Seven patients received intraoperative (IO-) NCT and 8 patients received external beam (EB-) NCT. Sulfhydryl borane (BSH, 5g/body) was administered intravenously 12 hours before neutron irradiation. Additionally, *p*-dihydroxyboryl-phenylalanine (BPA, 250 mg/kg) was given 1 hour before irradiation to the 8 patients who underwent EB-NCT. EB-NCT was combined with fractionated photon irradiation.
Results: Five of 15 patients were alive at analysis for a mean follow-up time of 20.3 M. In 11 of 15 patients followed up for more than one year, 8 (72.7%) maintained their Karnofsky Performance Status (KPS; 90 in 6 and 100 in 2). The median overall survival (OS) and time to progression (TTP) for all patients were 25.7 M and 11.9 M, respectively. There was no difference in TTP between the IO-NCT (12.0 M) and EB-NCT (11.9 M) groups. The 1- and 2-year survival rates were 85.7% and 45.5%, respectively. Three IO-NCT patients and 1 EB-NCT patient suffered transient orbital swelling accompanied by double vision (Grade 2); 1 of the 3 IO-NCT patients suffered post-epileptic brain swelling (Grade 4) requiring surgical intervention.
Conclusions: This NCT pilot study in 15 patients with newly diagnosed GBM showed survival benefits, suggesting that the neutron capture reaction may function sufficiently to control tumors locally, and that further optimized studies in large series of patients are warranted.

Feasible Evaluation of Neutron Capture Therapy for Local Recurrenced Breast Cancer

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Local recurrenced breast cancer is one of the most difficult neoplasms to cure and there is a need for new combinated therapy. If sufficient boron compound can be targeted accurate to the tumor, Boron Neutron Capture Therapy (BNCT) can be applied to local recurrenced breast cancer. We are planning BNCT to patients of local recurrenced breast cancer.
In this study, we performed a preliminary dosimetry with a phantom model of the mammary gland at Kyoto University Research Reactor (KUR), and a feasibility dosimetry with JCDS at JRR4 reactor of Japan Atomic Research Institute.
We performed preliminary dosimetry of a phantom model of the mammary gland with thermal neutron irradiation (OO-0011 mode) on LiF collimation at KUR. The thermal neutron flux was 5.16 E+08 cm-2s-1 at the surface of phantom. The blood boron concentration is estimated to 30 ppm, tumor boron concentration is also estimated to 90 ppm according to tumor/blood ratio is 3 and skin/blood ratio is 1.2. Tumor RBE dose is estimated to 47 Gy/h, and skin RBE dose is 12.4 Gy/h.
In case of advanced breast cancer, we performed the feasibility estimation of 3D construction of tumor according to the MRI imaging of a patient with epithermal neutron mode at JRR4.

The blood boron concentration (ppm) and tumor/normal tissue ratio are estimated to 24, 3.5, respectively. Skin RBE dose is ristricted to 10 Gy/h, the maximum tumor RBE dose, minimum tumor RBE dose, and mean tumor RBE dose are 42.2, 11.3, and 28.9 Gy-Eq, respectively, in half hour irradiation.
In this study, we showed the possibility to apply BNCT to local recurrenced breast cancer. We can irradiate tumors selectively and safety as possible, reducing the effects on neighboring healthy tissues.

Liver autotransplantation according to a "modified orthotopic piggy-back" technique

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We performed orthotopic liver autotransplantation in 2 patients treated by Boron Neutron Capture Therapy (BNCT) for diffused liver metastases from colorectal cancer; the method includes neutron irradiation of ex-situ liver inside a nuclear reactor.
Reconnection of the liver after BNCT was rather difficult; total extracorporeal circulation (ECC) set-up was required; the V.Cava (VC) reconstruction was performed by the interposition of a dacron-prothesis and required a long time; several post-operative complications were registered.
To simplify the procedure and to shorten the operating time as well as the time of total ECC we propose a "modified orthotopic piggy-back technique" for liver autotransplantation.
Methods: We developed the method in the swine model (25 kg). After hepatectomy the VC flow was preserved by interposing a goretex-prothesis by 2 end-to-end anastomosis. The vascular reconnection of the liver was performed by a side-to-side Cava-prothesis anastomosis with lateral clamping of the prothesis so that the VC flow was uninterrupted during the reconnection.
Results: The mean time for VC reconstruction was 54+/- 8 min.; the mean time for side-to-side VC-prothesis anastomosis was 13 +/- 4 min.
Conclusions: In our previous BNCT experiences the reconstruction of supra-hepatic VC was rather difficult and the interposition of a prothesis (20 mm diameter) was required in the reconstruction of infra-hepatic VC; 3 end-to-end sutures were performed and the mean time of total ECC was 5.30 hrs including portal Vein reconstruction (15 min.). The time required to treat the liver in the nuclear reactor was 45 minutes. In the post-operative period we registered not inconsiderable morbidity.
The "modified piggy-back technique" could shorten the times of liver reconnection and of total ECC, infact VC reconstruction by interposition of a prothesis could be carried out during the anhepatic phase, when the liver is away for neutron irradiation; then the VC flow could be immediately restored. Nonetheless, this is not a reason to completely forget a veno-venous bypass, to avoid the inevitable congestion of the splanchnic system in situations without poorly developed porto-systemic collateral circulation. Finally to perform a side-to-side VC-prothesis anastomosis by lateral clamping of VC is easier and faster than to perform end-to-end anastomoses with the liver in situ. All this should decrease the risk of afterbleeding and, owing to the reduced time of total ECC, potential haemodynamic disruption and circulatory instability should be reduced.

Irradiation of an Explanted Pig Liver at the HFR Petten

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As part of a research project between the University Hospital Essen and the JRC Petten to perform BNCT to an explanted organ, a liver was taken from a pig in the operating theatre for animals at the Central Animal Facility of the Medical Faculty in Essen. The pig liver was placed into a standard plastic bag, normally used in organ transportation, which was then filled with a copious amount of preservation fluid and placed into an organ-transport box, which was partially filled with water/ice.
The box was collected and transported to Petten by car. On arrival 3 hours later, the liver was placed into the special PMMA holder and loaded into the custom-built Liver-Irradiation-Facility (LIF). Air supply provided by cold gun sprays gave a temperature of 5–10 °C around the liver holder throughout the irradiation, which lasted 3 hours exactly. The liver was then brought back to Essen.
It was noted that the liver was more radioactive than expected, in comparison to a patient irradiation. The measured radiation level directly following radiation was almost 200μSv/h on contact but after only about 15 minutes, the only remaining activity was from ^{24}Na, with, 4 hours after irradiation, about 100μSv/h.
The exercise highlighted where improvements are needed, including: writing of Standard Operating Procedures; documentation files fulfilling the legal requirements for human irradiation; a treatment plan; better temperature control, including calibration of the cold guns; but also the availability of "simple" equipment, such as ice, cleansing material (tissue, alcohol, etc.).
The overall exercise was part of an on-going feasibility study and is one of the first important steps, i.e. testing of the transport logistics and the irradiation device (LIF) and should be seen as one of a number of steps needed prior to a full human treatment.

Uptake of BSH and/or BPA in human xenografts on nude mice

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Boron neutron capture therapy (BNCT) relies on the preferential delivery of a ^{10}B-compound to tumor cells. Sound knowledge on the ^{10}B-uptake in tumors but also in surrounding healthy tissues is of fundamental importance for developing the method. The ^{10}B-uptake as delivered by the compounds sodium mercaptoundecahydro-*closo*-dodecaborate (BSH) and L-para-boronophenylalanine (BPA) was investigated in 4 human tumors (sarcoma (S3), melanoma (MV3), glioblastoma (U87MG), adenocarcinoma (PC-3)) and a murine sarcoma (MuEs) xenografted in nu/nu mice by prompt gamma ray spectroscopy ($n \geq 8$). After BPA-injection alone ^{10}B-accumulation was observed in all tumors (tumor-blood ratios: 2.0-2.4). BSH injection alone led to tumor-blood ^{10}B-ratios of 0.8 -1.5 with significantly higher ratios for the MV3 and S3 tumors. A co-application of drugs increased the absolute ^{10}B-concentrations in tumors but failed to improve the tissue-blood ^{10}B-ratio. The significantly different uptake of BSH in different tumors underlines the need to further investigate the possibilities of this drug for BNCT.

Uptake of BSH and BPA in head and neck squamous cell carcinoma in human patients

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Purpose**:** Boron Neutron Capture Therapy (BNCT) might overcome problems encountered with treatment of advanced squamous cell carcinoma of head and neck (SCCHN) especially hypoxia, relative radio-resistance and location near critical organs. This trial investigates the uptake of the compounds sodium mercaptoundecahydro-closo-dodecaborate (BSH) or L-*para*-boronophenylalanine (BPA) in SCCHN.
Experimental Design: In a controlled prospective clinical trial (EORTC 11001) 3 patients were infused with BSH, 3 patients with BPA prior planned resection of the malignant lesion. Samples of tissues and blood were analyzed for the ^{10}B-concentration with prompt gamma ray spectroscopy.
Results: Adverse effects from compounds did not occur. After BPA-infusion the mean ^{10}B-concentration ratio tumor/blood was 4.0 ± 1.7. Mean ^{10}B-concentration ratios between tumor and healthy tissue were 2.1 ± 1.2 for muscle, 1.3 ± 0.5 for skin and 1.4 ± 0.01 for mucosa, respectively. After BSH-infusion the mean ^{10}B-concentration ratio tumor/blood was 1.2 ± 0.4. The ^{10}B-concentration ratio between tumor and healthy tissues was 3.6 ± 0.6 for muscle, 1.4 ± 0.5 for skin and 1.0 ± 0.3 for mucosa.
Conclusions: BPA and BSH deliver ^{10}B to SCCHN to an extent that substantiates the potential of BNCT to treat this tumor. Mucosa and skin are the most relevant organs at risk for both compounds, whereas high ^{10}B-concentrations in blood reveal the vasculature of healthy organs at risk for a BSH-mediated BNCT. More efforts are necessary to better understand the metabolism of BSH. The simultaneous application of both drugs can be justified.

Recurrent thyroid cancer: a case for BNCT? Results from the EORTC trial 11001

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Purpose: Recurrences of differenciated thyroid cancer after surgery and radioiodine therapy have the tendency to dedifferentiate and especially to loose their ability to store iodine, making their treatment challenging. Boron Neutron Capture Therapy (BNCT) might offer an opportunity to treat such tumors. This trial collected data on the uptake of the compounds sodium mercaptoundecahydro-closo-dodecaborate (BSH) or L-*para*-boronophenylalanine (BPA) in recurrent thyroid cancer.
Experimental Design: In a controlled prospective clinical trial (EORTC 11001) 4 patients were infused with BSH, 3 patients with BPA prior planned resection of the malignant lesion. Samples of tissues and blood were analyzed for the ^{10}B-concentration with prompt gamma ray spectroscopy.
Results: Adverse effects from compounds did not occur. After BPA-infusion the mean ^{10}B-concentration ratio tumor/blood was 1.7 ± 0.8. Mean ^{10}B-concentration ratios between tumor and healthy tissue were 0.9 ± 0.3 for muscle and 0.6 ± 0.3 for skin. After BSH-infusion the mean ^{10}B-concentration ratio tumor/blood was 0.9 ± 0.2. The ^{10}B-concentration ratio between tumor and healthy tissues was 1.9 ± 0.3 for muscle and 0.8 ± 0.2 for skin.
Conclusions: BPA and BSH do not deliver enough ^{10}B to recurrent thyroid cancer to justify BNCT. The very poor accumulation of both compounds in the tumor tissue raises the question if prior therapies have changed the perfusion of the area of interest prohibiting the transport of the drugs. Another hypothesis to explain our results for BPA could be a poor expression of the L-amino acid transport protein in this tumor as compared to other malignancies.

Pharmacokinetic of BSH - results from EORTC trials

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Introduction: Since its first clinical use in 1967 neither the pharmacokinetic, nor the metabolism nor the uptake mechanisms of Sodium mercaptoundecahydro-*closo*-dodecaborate (BSH, $Na_2{}^{10}B_{12}H_{11}SH$) are fully understood. Originally designed for BNCT of brain tumors, BSH is assumed to target brain tumors by crossing the pathologically permeable blood-brain-barrier (BBB) in the tumor but not the intact BBB that protects healthy brain. Some data on pharmacokinetics are available after single dose of BSH. The analysis was conducted to provide supplementary information to design further clinical trials, improve safety and obtain clearance to use the drug by regulatory authorities.
Materials and methods: The ^{10}B-concentration in blood after BSH-infusion in patients who where treated in the frame of the EORTC trials 11961 and 11001 were analyzed with Prompt Gamma Ray Spectroscopy at the HFR Petten. Three different cohorts of patients were identified:

- Group 1: patients who received a therapeutic dose of BSH (DOSIS) preoperatively (n = 14). Data on uptake in tissues and glioblastoma are available.
- Group 2: patients who received BSH (DOSIS)for the treatment of glioblastoma in 4 fractions on 4 consecutive days (n = 26).
- Group 3: patients who received a low dose of BSH preoperatively (n = 10). Data on uptake in a multitude of tissues and in different tumors exist. Long observation periods could be achieved in some cases.

Data were analyzed using the scientific pharmacokinetic software Kinetica 4.1.1. (InnaPhase Corporation, Philadelphia, USA) in addition to the data analysis system TOPFIT 2.0. Non compartmental as well as compartmental analyses were performed. For compartmental analyses, open compartment models with zero-order input and first-order elimination were chosen. In addition, multiple dose calculations were performed.

Results: Based on a sufficient observation period and adequate numbers of blood drawings, a three-compartment model can best describe the kinetic of BSH in blood. In these cases, terminal half-life of BSH was calculated to be 50-170 h, the mean ^{10}B-clearance from the blood was 18 +/- 10 ml/min. The intra-individual Pharmacokinetic of BSH was linear over the dose range.

Multiple infusions of the drug did not influence the pharmacokinetic, thus neither accumulation of the drug, nor a change in clearance were detectable.

Conclusions: To describe the pharmacokinetic profile of BSH, a sufficient period of time for blood sampling has to be used. The pharmacokinetic results from this study consolidate of those previously reported.

CNAO: The Italian Hadrontherapy facility

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CNAO will be a dual center capable of providing therapeutic beams of protons and carbon ions with maximum energy of 400 MeV/u. At the beginning, it will be equipped with three treatment rooms with fixed horizontal and vertical beam lines. In a subsequent phase, two more rooms with a rotating gantry are foreseen. An active spot scanning dose delivery system will be employed. Initially, 80% of the treatments will be carried out with carbon ions. All patients will be treated within clinical trials to assess carbon ion indications with an evidence-based methodology. Seven disease-specific working groups have been developed: lung tumors, liver tumors, sarcomas, head and neck tumors, central nervous system lesions, eye tumors and pediatric tumors. The last two groups will be treated mainly with protons. In the first phase, CNAO will focus on head and neck cancers, treating inoperable, residual or recurrent malignant salivary gland tumors, mucosal melanoma, adenocarcinoma and unfavorably located SCC (nasal and paranasal sinuses). Carbon ions will be employed as a boost in the treatment of locally advanced, poor prognosis, SCC of the hypopharynx and tongue base. Bone and soft tissue sarcomas of the extremity will be treated with a limb-sparing approach, and trunk sarcomas will be treated with exclusive or post-operative irradiation. Skull base tumors (chordoma and chondrosarcoma), recurrent or malignant meningioma and glial tumors will be treated with carbon ions.

After sufficient expertise has been gained in coping with organ motion, CNAO will start treating thoracic and abdominal targets. HCC will be treated in inoperable patients with one or more lesions that can be included in a single CTV. Early stage NSCLC will be treated. In the second phase, two more groups on gynecological malignancies and digestive tumors (esophageal cancer, rectal cancer, pancreatic cancer) will be created.

BNCT for recurrent oral cancer and metastasis of cervical lymph nodes

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Recurrent oral cancer and metastasis of cervical lymph nodes often resist chemo-/radiotherapy and invade surrounding tissues. We have treated recurrent oral cancer and metastasis of cervical lymph nodes after conventional treatments (including a case no treated conventional treatments) by BNCT. We report the characteristic effect in 6 cases for oral cancer and metastasis of cervical lymph nodes.
In 2 cases, spontaneous pain decreased immediately after BNCT. In all cases, osteomyelitis of maxillary bone and xerostomia have not appeared. Mucositis was appeared in all cases, but more mild rather than the case treated by conventional radiotherapy. Clinical response is PR-PD. Three of 6 patients are alive. BNCT contributes to improvement of the Q.O.L. of the patient.

Dose distribution and clinical response of glioblastoma treated with external beam boron neutron capture therapy

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The dose distribution and failure pattern after treatment with the external beam BNCT protocol were retrospectively analyzed.
BSH(5g/body) and BPA(250mg/kg) based BNCT was performed in 8 patients with newly diagnosed glioblastoma. The gross tumor volume (GTV) was defined as the residual gadolinium-enhancing volume. CTV-2 and CTV-3 was defined as GTV plus a margin of 2cm and 3cm, respectively. Additional photon irradiation, total X-ray dose of 30Gy was given to T2 high intensity area on MRI.
Three of 8 patients were alive at analysis for a mean follow-up time of 20.3 months. The post-operative median survival time of 8 patients was 27.1 months (95%CI 11.8-42.4). The minimum tumor dose of GTV, CTV-2, and CTV-3 averaged 29.8±9.9 Gy, 15.1±5.4 Gy, and 12.4±2.9 Gy, respectively. The minimum tumor non-boron dose of GTV, CTV-2, and CTV-3 averaged 2.0±0.5 Gy, 1.3±0.3 Gy, and 1.1±0.2 Gy, respectively. The maximum brain dose, skin dose, and average brain dose was 11.4±1.5 Gy, 9.6±1.4 Gy, and 3.1±0.4 Gy, respectively. The correlation between dose distribution and failure pattern after BNCT will be also discussed.

Cost Analysis of Radiotherapy, Carbon Ion Therapy, Proton Therapy and BNCT in Japan

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Purpose: To evaluate more accurate data on the precise costs of BNCT, we analyzed the costs of conventional radiotherapy, heavy particle therapy, proton therapy and BNCT. An aggregate cost calculation of accelerator, buildings, equipments and staff requirements was performed.
Materials and methods: There are two heavy ion medical accelerator centers, four proton centers and two reactors for medical use in Japan. Two BNCT centers based on accelerator are planning. The cost of radiotherapy per patient was estimated based on accreditation reports of each center.
Results: The major cost components are the cost of accelerators or facilities, buildings, equipments, medical and non medical staff, materials and overhead. Initial construction cost of medical accelerator center was 16000 million yen for heavy ion, 3200 million yen for proton center, 2000 million yen for BNCT based on accelerator. The renovation cost of JRR-4 for BNCT was 4000 million yen. The cost of the accelerator was 8000-12000 million yen for heavy ion, ca. 3750 million yen for proton, 1500-1000 million yen for BNCT. As for depreciation calculation, the building was calculated on the basis of 47 years, and the accelerator was calculated on the basis of 20 years. Equipment requirements: simulator, treatment planning system, dosimetry was ca. 600 million yen. The total costs of each center including staff and overhead per year were 1170 million yen, 556 million yen and 186 million yen respectively. The average cost per patient varies in a stepwise fashion, according to the number of the patients: 7.17 (pts<200)- 3.93(400<pts) million yen for heavy ion therapy, 4.08-2.39million yen for proton therapy, 3.61-2.56 million yen for intra-operative BNCT, 2.11-1.06 million yen for BNCT without op.
More accurate and details data on precise cost of radiotherapy based on accelerator will be presented.

Intra-arterial Infusion of Boron-10 (10B) compound in Boron Neutron Capture Therapy for Patient with Maxillary Cancer: a case report

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Introduction: We started Boron neutron capture therapy (BNCT) for head and neck malignancies for the first time in the world in 2001 and have achieved successful results. The selective accumulation of 10B-compound into tumor-tissue compared with surrounding normal-tissue(T/N ratio) is especially critical in BNCT. To improve the T/N ratio we administrated boronophenylalanine(BPA) intra-arterially (ia-BPA) and performed BNCT. The T/N ratio was remarkably rose as well as we had expected, and achieved good results.
Materials and methods: 61 year-old woman was diagnosed as having an adenoid cystic carcinoma(ACC) of maxilla and then underwent one course of neoadjuvant chemotherapy and subsequently partial maxillectomy. Histopathological examination and MRI revealed that the tumor mass was partially left in the pterygoid palatal fossa. We tried BNCT on the rest tumor by two different methods of boron compound infusion.
Result: A preferential accumulation of ia-BPA in the tumor was observed (T/N ratio =7.6) compared with that (T/N ratio=2.5) administrated intravenously BPA(iv-BPA) by the 18F-BPA-PET study. She received twice iv-BPA and ia-BPA mediated BNCT with Kyoto University Research Reactor. BNCT caused 97% regression of the tumor and slight side-effect (less than Grade 2 by NCI-CTC) 2 months after BNCT.
Conclusion: Intrarterial boron compound infusion remarkably raised the T/N ratio which should play crucial role in BNCT.

Boron neutron capture therapy (BNCT) for diffuse or multiple pleural tumors: case reports of two cases

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Two patients with diffuse or multiple pleural tumors, malignant pleural mesothelioma (MPM) and lung sarcoma, received boron neutron capture therapy (BNCT). In both cases, due to extensive spread of the tumor through entire pleural space, BNCT was performed twice for treating the tumors in the upper and those in the lower portion on the separate day. In each case, the tumors regressed or remained stable in size for 3-6 months following BNCT. Palliation of chest or back pain and short of breath was successfully provided just within a few days after BNCT. No acute adverse events greater than grade 2 was observed. In patient 1, Grade 2 lung toxicity was observed 7 months after the treatment.
Further clinical study is warranted for revealing the effectiveness of BNCT on palliation or control of pleural tumors.

MEDICAL PHYSICS/DOSIMETRY

A preliminary inter-centre comparison study for photon, thermal neutron and epithermal neutron responses of two pairs of ionisation chambers used for BNCT

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The dual ionisation chamber technique is the recommended method for mixed field dosimetry of epithermal neutron beams. Its importance has been long recognised and it has featured highly in the dosimetry exchange programme of the MIT BNCT group.
This paper presents initial data from an ongoing inter-comparison study involving two identical pairs of ionisation chambers used at the BNCT facilities of Petten, NL and of the University of Birmingham, UK. The goal of this study is to evaluate the photon, thermal neutron and epithermal neutron responses of both pairs of TE(TE) (Exradin T2 type) and Mg(Ar) (Exradin M2 type) ionisation chambers in similar experimental conditions. At this stage, the work has been completed for the M2 type chambers and is intended to be completed for the T2 type chambers in the near future.
Photon calibration: The photon responses of the ionisation chambers were obtained in 6 and 10 MV clinical photon beams at the University Hospital Birmingham. Photon calibration factors ratios (Petten/Birmingham) of 1.077 ± 0.006 and 1.029 ± 0.005 were found for the M2 and T2 type chambers, respectively.
Thermal neutron sensitivity: The thermal neutron sensitivities of the M2 type ionisation chambers were determined using the thermal neutron beam available at the Low Flux Reactor, Petten. Ratios of the raw data measured for each chamber indicate a ratio of (Petten/Birmingham) of 0.980 ± 0.007 for the M2 chambers.
BNCT epithermal neutron beam: Measurements in a reference PMMA cubic phantom were performed using the M2 type ionisation chambers in the epithermal neutron beam of the High Flux Reactor, Petten. At a depth of 2.5 cm, a ratio of the raw data for the chambers yields a sensitivity ratio (Petten/Birmingham) of 0.985 ± 0.008.

LVR-15 Reactor Epithermal Neutron Beam parameters – results of measurements

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The construction of the epithermal neutron beam at a horizontal channel of LVR-15 reactor was completed in year 2000. A group of patient was treated in the project "Pre-clinical trials of brain tumors". In the long term the facility at the reactor is utilized for the study of physical and biological aspects of BNCT. In the part of physics the periodic verification of parameters (as international comparison, too) and the development of appropriate dosimetry methods are included. In the part of biology the biological effectiveness of the beam has been evaluated on different biological models (cell cultures, immature rat brain, mouse intestine crypt regeneration).
The basic characteristics of the beam are neutron spectrum, neutron dose rate, and gamma dose rate. Number of different detector types and methods has been used for the measurement. The results of the following methods are presented in the paper:

- Set of activation monitors of different nuclides irradiated in free beam. For the measurement Au, Cu, In, La, Mn, Ni, Sc and W foils were used. The neutron spectrum is evaluated using an adjustment procedure which provides a means for combining reaction rates of neutron monitors

with a calculated neutron spectrum resulting in the determination of an optimal estimation of the thermal, epithermal and fast neutron fluence rates and their uncertainties.

- Sets of activation monitors irradiated in a water phantom. Depth profile of induced activities is measured with Au foils, In foils, and Au foils in Cd cover.
- Depth profile of thermal neutrons in the water phantom measured with Si semiconductor detector with ^{6}LiF converter.
- Photon absorbed dose and fast neutron kerma rate in tissue measured using twin ionization chambers (M2 Exradin), one made of Mg flushed with Ar, and the second made of TE/TE A150 plastic flushed with TE gas.
- Dose mapping with thermoluminescence dosimeters (TLD).
- The gel dosimeters used for imaging of separate part of dose (gamma, fast neutrons, boron). These dosimeters are laboratory-made Fricke gel layers. The absorbed dose is deduced by pixel-to-pixel manipulations of light transmittance images detected by means of a CCD camera.
- Monoblock neutron spectrometer (Bonner type) developed and verified in real conditions of reactor beam. It consists of polyethylene (PE) cylindrical block with Cd and PE with boron shielding. Seven detectors of thermal neutrons are inserted in seven measuring channels with different thickness of PE for on-line measurement in geometry of scattered beam.

The investigation of neutron capture therapy with nanodosimetric methods I: nanodosimetric radiation quantities

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Radiation-induced damage to cells is dominated by the pattern of inelastic interactions in sub-cellular targets. Thus the effectiveness and the quality of ionizing radiation should be defined in terms of quantities directly related to the particle track structure. We present in this work a new concept for characterizing radiation quality which is based on the assumption that the initial damage to the DNA is mainly due to the number of ionizations (the ionization cluster size) directly produced by single ionizing particles within short segments of the DNA or in the near neighbourhood. The application of this concept requires a detailed knowledge of the frequency distribution of the ionization cluster size due to the interaction of single ionizing particles in target volumes of nanometric dimensions (nanodosimetry). We check the validity of this concept for BNCT by comparing nanodosimetric quantities derived from calculated cluster-size distributions with data from radiobiological experiments.

Dose imaging in a thorax phantom with lung-equivalent volume at the epithermal neutron beamof LVR-15 reactor

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A phantom (Ely) has been prepared for dose imaging in BNCT lung treatment. The phantom is made with layers of polyethylene and PMMA, suitably settled to simulate part of a thorax trunk. In this phantom, a volume having the shape of a truncated cone is filled with a laboratory-made lung-equivalent material. This lung-substitute is properly prepared with water, a gelling agent (gelatine) and a surfactant (sodium-dodecyl-sulfate) to increase the surface tension. By means of appropriate whipping, some air is incorporated in the gel matrix and a gel foam is finally obtained, with a mass density of 0.35 g/cm^3 as established for the lung of ICRU 44 adult man. Also the electron density, measured by TAC analysis, has resulted to be that of ICRU- 44 man-lung.

In Ely phantom, the lung substitute volume has been cut, in horizontal or vertical plane, in order to insert layers of gel dosimeters to obtain dose images. The gel dosimeters are laboratory-made Fricke gel layers having thickness of 3 mm. The absorbed dose is deduced by pixel-to-pixel manipulations of light transmittance images detected by means of a CCD camera. By placing in the Ely phantom lung, during the various exposures, dosimeters with different isotopic content it is possible to obtain, by applying suitable algorithms, the images of the various dose components: the therapeutic dose from B-10 reactions, the photon dose and the fast neutron dose.
Dose mapping with thermoluminescence dosimeters (TLD) are in project too. To this purpose, LiF:Mg,Ti (TLD-700 and TLD-600) and CaF_2:Tm (TLD-300) chips are utilised.
Dose distribution has been measured at epithermal neutron beam of LVR-15 reactor. Parameters of the source are mentioned in the paper. Principal experimental results have been compared with the calculation using MCNP method.

Tumor Control and Normal Tissue Complication in BNCT Treatments of Nodular Melanoma: A Search for Predictive Quantities

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Introduction: Dose data for tumor control of cutaneous melanomas and toxicity in normal skin are barely documented in BNCT. In conventional (fractionated) radiotherapy, where a great amount of such data is available, dose distribution in tumors is highly homogeneous and tolerance doses consider fractionation schemes. This is not the general situation in BNCT. Based on a previous work that investigated the possible influence of tumor size and total equivalent dose on the observed local tumor response, we have extended the analysis including all the available data for patients treated as part of the CNEA-Roffo Phase I/II clinical trial of cutaneous melanoma. Also, in order to study different factors that may be related with observed skin toxicity of our patients, we have analyzed several figures of merit derived from the skin dose distributions. The resulting patient ordering with regard to these parameters was compared with the acute skin toxicity graded as erythema and ulceration.
Materials and Methods: The local responses of 104 subcutaneous nodular lesions in 7 patients were analyzed with regard to different parameters such as minimum or mean photon-equivalent doses, and tumor volume. A logistic regression analysis based on a generalized linear model was performed, and doses, either by themselves or jointly with tumor volumes, were alternatively assessed as possible predictors for the tumor response.
Cumulative dose-area histograms were computed for all treated patients and several figures of merit were evaluated to investigate their possible influence on the observed acute skin toxicities. Inspected figures of merit were: maximum dose to the skin, skin area that received at least some reference dose (i.e., 15, 18, and 20 Gy-Eq), mean dose in the 100 and 200 cm^2 of skin that received the highest doses, the probability of normal tissue complication (*NTCP*), and the probability equivalent uniform dose to the skin (*PEUD*).
Results and Discussions: Neither minimum nor mean equivalent doses were found to be, by themselves, good predictors of tumor response. However, when the tumor volumes is incorporated as a second explicative variable, doses (minimum or mean dose) substantially increased their significance and become critical variables together with tumor volumes (p-values < 0.05). Regarding skin toxicity, all the evaluated figures of merit derived similar results: ulceration is present among the cases for which these parameters take the highest values.

The investigation of neutron capture therapy with nanodosimetric methods II: Monte-Carlo simulations and experiment

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For the assessment of the biological effectiveness of ionizing radiation the track structure of the ionizing particles is of particular importance. In particular, the number of ionizations which are produced along the particle track during the traverse of a volume element filled with matter is a characteristic feature.
We investigate in this work the frequency distributions of clustered ionizations produced by the fissions fragments created in BNCT by means of measurements and Monte Carlo simulations. We present preliminary results for α-particles in the energy range from 0.1 MeV to 2 MeV, measured in a nanodosimetric volume of the size of a DNA-segment using an ion counting nanodosimeter. The comparison between experimental results and Monte Carlo simulations shows a good agreement regarding the energy dependence of the mean cluster size and the frequency distributions of clustered ionizations as a whole as well, thus providing a powerful tool for characterizing radiation fields on the basis of nanodosimetric quantities.

Neutron Spectra Measurement and Comparison of the HFR and THOR BNCT Beams

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This study focuses on the measurement and comparison of BNCT epithermal neutron beams in the HFR and THOR for the sake of further dose comparison and exchange. Neutron spectra of the HFR and THOR BNCT beams were determined using multiple activation foils. A home-made, user-friendly computer program named SAND-EX, which is an extended version of SAND-II, was developed for the purpose of spectrum adjustment. The latest neutron cross-section libraries of ENDF/B, IRDF and JEFF were processed by PREPRO 2007 and NJOY for the SAND-EX and MCNP calculations. The neutron transport code MCNP was applied to determine the necessary self-shielding correction factors. All the foil measurements were performed at the center of the beam exit and counted by well-calibrated High Purity Germanium (HPGe) detectors. Each irradiation was normalized and monitored under respective on-line, real-time neutron monitoring systems in the HFR and THOR. Both initial spectra were adjusted and expanded into the well-known 640-group structure. A sophisticated spectrum adjustment procedure was adopted to ensure the continuity of the adjusted fine-group spectrum. The measured ideal reaction rates and the calculated values derived by MCNP and SAND-EX are matched well within a maximum difference of 4%; most of them are within a difference of 2%.
The measured total beam intensities of the HFR and THOR epithermal neutron beam are 3.78×10^8 and 1.60×10^9 neutron/cm^2-sec, respectively. As to the epithermal neutron fluence rate, it is 3.41×10^8 for the HFR and 1.33×10^9 for the THOR beam. The adjusted spectra indicate that the THOR beam has a larger portion (11%) of thermal neutron (<0.5 eV) than the HFR beam (2.9%); the fast neutron fluence rate (>10 keV) of the initial spectra are both underestimated compared to the measured results. The fast neutron dose and dose curve in a PMMA phantom were also calculated and compared using MCNP.

The gadolinium as a powerful additive for enhancing the neutron sensitivity of ESR dosimeters

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Along with the NCT development and with the use of thermal neutrons for radiotherapeutic purposes, many efforts have been devoted to the beam characterization in order to optimize the therapy procedures. Reliable dosimetric measurements should be able to determine the various components (neutronic and photonic) of the mixed beam usually employed for therapy.
We have studied the effect of the gadolinium addition on the neutron sensitivity of alanine and ammonium tartrate ESR dosimeters exposed to a mixed (n, gamma) field mainly composed by thermal neutrons. We have chosen the gadolinium nucleus because of its very high capture cross section to thermal neutrons. Furthermore, in the nuclear reaction with thermal neutrons Auger electrons and internal conversion electrons are ejected, which in turn release their energy in the neighbourhood of the reaction site. The gadolinium presence hugely (up to a factor 30) enhances the sensitivity to thermal neutrons of dosimeters with gadolinium with respect to those without gadolinium for both organic molecules used. On the other hand, the presence of gadolinium reduces the tissue equivalence because of its high atomic number (Z = 64). Therefore, we analysed the ESR response of these dosimeters as a function of the gadolinium concentration inside the dosimeter in order to find the optimum compromise between the increase of sensitivity to thermal neutrons and the reduction of tissue equivalence. We experimentally found that a low concentration of gadolinium oxide (of the order of 5% of the total mass of the dosimeter) can improve the thermal neutron sensitivity more than 13 times without reducing significantly the tissue equivalence.
We completed our study through a Monte Carlo simulation aimed at obtaining information about the reliability of this powerful tool in predicting the response enhancement achievable with the addition of gadolinium in alanine and ammonium tartrate dosimeters. The computational values obtained through simulation have been compared with the experimental results and a good agreement has been found.

Experimental feasibility studies on a SPECT tomograph for BNCT dosimetry

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In 94% of neutron captures in boron, the resulting ^{7}Li ion is emitted in an excited state and decays immediately through a characteristic 478 keV prompt gamma ray. The attenuation coefficient for this photon in tissue is about 0.1 cm^{-1}, hence this γ ray escapes from the body to a large extent. Its detection thus offers the possibility of a measurement of the boron dose. In previous work, we have designed a prototype of a Single Photon Emission Tomography system for this purpose. After taking 20 projections of 41 bins the system can reconstruct boron dose maps of 21x21 voxels of 1 cm^3 size each. This dosimetry image would give spatial information not available with the current methods and will not depend on the great uncertainties in the boron concentration determination required to calculate the boron dose from the thermal neutron field.
In this work we show experimental results obtained at the accelerator based facility of the University of Birmingham with a prototype consisting of four $LaBr_3$(Ce) scintillator detectors and their collimators and shielding. The shielding consists of paraffin, cadmium and ^{6}Li to thermalize and capture neutrons and lead to shield from γ background. The lead collimators were designed in order to obtain a 1cm resolution at the beam axis. A water-filled cylindrical head phantom containing two 3cm in diameter cylinders filled with a ^{10}B solution (tumor models) has been used for the experiments.

A one-dimensional profile at fixed angle was measured across the tumors. The spectra show the difficulties in quantifying the 478 keV peak area due to its Doppler broadened shape, its overlapping with the low-energy tail of the intense 511 keV pair annihilation peak and the high γ background. A least square algorithm has been used for fitting each spectrum. Although improvements must be made to reduce the background count-rate in the detectors, the acquired projection shows that the proposed system should be feasible.

BNCT dosimetry performed with a mini twin TEPC

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The BNCT radiation field is complex because different beam components are mixed, each one having different relative biological effectiveness (RBE). Microdosimetry with tissue-equivalent proportional counters (TEPC) has proven to be an ideal dosimetric technique for mixed radiation fields, because it is able both to measure the absorbed dose and to assess the radiation field relative biological effectiveness with good accuracy. An ideal detector for BNCT should contain two TEPCs, one detector loaded with, while the other one without ^{10}B in order to record all beam components with a unique measurement. Moreover, such a detector should be of tiny size in order to be able to measure in the intense BNCT radiation fields without significant pile-up effects. TEPCs have been shown to be pretty good dosimeters for mixed radiation fields. In this paper the first mini twin-TEPC counter for BNCT is presented, as well as first measurement at the new HYTHOR thermal irradiation facility at TAPIRO nuclear reactor and comparison with related Monte Carlo calculations.

Implications for Clinical Treatment from the Microdosimetry of Boron Neutron Capture Therapy

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Boron neutron capture therapy has now been used for several malignancies. Most clinical trials have involved glioblastoma multiforme. There have been a few studies on malignant melanoma that has metastasized to the brain. The glioblastoma results have been encouraging but have not achieved the success that many expected. The results for malignant melanoma have been very promising but with too few patients for conclusions to be drawn. Since these early trials, there have been treatments on undifferentiated thyroid carcinoma, hepatic metastases from adenocarcinoma of the colon, and head and neck malignancies. These tumors also responded well to boron neutron capture therapy. Glioblastoma is a infiltrative tumor with distant individual tumor cells which would imply that the therapy fails due to those distant individual cells but the recurrence is on the edges of the main tumor body. The microdosimetry of boron neutron capture therapy can provide an explanation for this observation. Codes written to examine the microdosimetry of boron neutron capture therapy have been used to explore the effects of near neighbor cells. The near neighbor cells can contribute a significant additional dose depending on the geometry. Different geometries have been explored and demonstrate that tumors that grow by direct extension have a greater near neighbor effect. Whereas, infiltrative tumors lose this near neighbor dose which can result in a significant decrease in the dose for cells that do not have optimal boron loading. These results help to explain clinical results obtained to date and imply that tumors with small closely packed cells that grow by direct extension will be the most amenable to boron neutron capture therapy.

A Feasibility Study of Dose Estimation with SPECT Technique after BNCT Irradiation

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Since December 2001, at the Heavy Water Neutron Irradiation Facility (HWNIF) of Kyoto University Reactor (KUR), boron neutron capture therapy (BNCT) has been expanded to the tumors of various body parts, such as neck, liver, lung, etc.. The motion ranges and shape changes of these parts are larger, differently from those of head. Then, the accuracy is limited for the dose estimation. In BNCT irradiation, various radioactive nuclei are generated in and around the target volume. By measuring the distributions of these nuclei with the technique of single photon emission computed tomography (SPECT), the more accurate post-irradiation dose estimation can be expected.
A dose-estimation code system "SERA" was used in the simulation for the distributions of the radioactive nuclei generated near the target volume. The distributions of the respective radioactive nuclei were calculated using the neutron flux distribution obtained by SERA, with the reaction crosssections and decay constants. The result for a head and neck cancer irradiated during 1.5 hour is described as an example.
It was confirmed that Cl-38 and Na-24 could be measured by SPECT for soft tissues. The radioactivity densities for Cl-38 and Na-24 just after the irradiation were calculated to 100 to 1000 Bq/cm^3 in and around the target volume.
For a detector of the SPECT system, it was assumed that the distance to the deepest voxel of 1 cm^3 was 20 cm and the effective detection-field size was 1 cm^2. The count rate for the gamma rays of these nuclei from the deepest voxel was estimated to 2×10^{-3} to 2×10^{-2} s^{-1}. For the counting within the statistical error of 10 percent, 1 to 14 hours are necessary. In focusing the shallower voxel, the necessary counting time was estimated to 5 to 60 minutes when the distance between the detector and the voxel was shortened to 6 cm.

Monte Carlo simulation of the current obtained with ionisation chamber detectors in mixed fields of neutrons and gammas

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It does not need to be understated that good measurements regarding BNCT dosimetry are of critical importance. Above all, the calculations for patient treatment planning are initially based on these measurements. Indeed, well understood dosimetry of mixed neutron and gamma fields is necessary to explain the outcome of the many experiments performed. It is believed that the sometimes confusing and not understandable outcome in BNCT research is due to incorrect dosimetry, i.e. misleading measurements. The most commonly used detector to describe the absorbed neutron and gamma doses is the ionisation chamber. To understand better the behaviour and complexities of this detector, the collected and measured current has been directly simulated using MCNPX. This Monte Carlo code is able to track neutrons, gammas and electrons all around and inside the ionisation chamber. The calculated dose deposited by the electrons in the gas is proportional to the current measured.
Furthermore, the protons and alphas due to reactions in the wall and/or gas materials can also cause ionisations and thus add to the current. A custom-made program was written to simulate this contribution. The problem in such a study is that disagreement between simulated and measured current can be caused by the computer code and/or measurement set-up and/or unknown influences of source and/or materials. Consequently, the model of the ionisation chamber, as well as the neutron and gamma source descriptions, needed to be validated step-by-step. After having obtained enough confidence in the model it could be concluded that ionisation chamber measurements can be significantly affected by neutrons, i.e. energy dependence. Neutrons can increase the measured current due to unknown and non-detectable beta-, proton- and/or alpha-producers in the wall material and gas. This part of the dose only exists with the presence of the ionisation chamber.

Collective Analyses of Clinical Outcomes: Globally Advancing BNCT

Kent J. Riley

Boron neutron capture therapy has successfully developed the scientific infrastructure for clinical programs through multidisciplinary collaborations within individual groups around the world. These centers have independently demonstrated the safety, feasibility and promise of BNCT in clinical trials with small numbers of patients. To advance the modality beyond this stage of development and so facilitate a broader understanding in the radiotherapy community, research must now seek to determine definitive endpoints such as toxicity, tolerance dose, therapeutic response and efficacy. The established system as it exists today is unlikely to fulfill these goals because they require many more patients and greater resources than any one center can sustain. While standardizing treatment protocols across centers would facilitate combining trial data and achieve this aim, this is impractical in the near term due to the independent nature of the various clinical programs already underway and the substantial resources needed that may discourage participation from the new developing centers in the world.

A new type of collaborative effort *between* centers is now needed to both retrospectively and prospectively integrate results of clinical irradiations to advance the overall aims of BNCT. The NCT group from the Massachusetts Institute of Technology (MIT) leads an International Dosimetry Exchange for this purpose that includes groups from clinical centers at the Joint Research Centre (JRC) of the European Commission, Petten (The Netherlands), Nuclear Research Institute, Rez (Czech Republic), VTT, Espoo (Finland), Studsvik, Nyköping (Sweden), Brookhaven National Laboratory (BNL, USA), the Comisión Nacional de Energía Atómica (Argentina), Kyoto University Research Reactor (Japan) and the Japanese Atomic Energy Research Institute (Japan). This group has published a series of reports, culminating in recently completed analyses that evaluated differences in dose specification between centers in Europe and the USA.

Individual dose components calculated from treatment plans formulated by the participating centers were compared to MIT measurements and differences ranged from 4 to 370%.

Among centers using BPA, the maximum dose to brain determined for the same nominal specification of 10 Gy(w) is significantly higher than at BNL by 32% (Harvard-MIT), 43% (VTT), 49% (JRC) and 74% (Studsvik). These findings should provide a more accurate interpretation of clinical results reported by the centers and facilitate rigorous collective analyses of trial data for the first time. Each center freely contributed resources and scientific results to this collaboration and the modest efforts have proven worthwhile for both the participants, and the community as a whole.

Another stage in this collaboration is set to begin with physicists renormalizing treatment plans using a common dose specification. Comprehensive analyses of all trial data accrued by each of these centers although now possible in principle may be unrealistic because each center understandably wishes to protect their results and wants to retain control over interpreting therapeutic response. However, simpler, more restricted but nonetheless useful analyses such as dose-limiting toxicity are more feasible if for example, the frequency and severity of adverse events can be separated from data regarding therapeutic outcome and submitted for tabulation together with other centers. Analyses based on these data will help define a more precise specification of dose limits and increase information sharing between clinical programs. This will benefit both existing centers that seek to develop follow-on studies possibly involving different tumors or more advanced boron delivery agents as well as new centers who should be encouraged to participate so as to avoid needlessly duplicating previous studies. Given the inherent benefits for all participating clinical centers and the entire BNCT research community it is incumbent upon all of us to identify a way to cooperate toward these aims and to advance BNCT while preserving the academic or proprietary interests of each participant.

Calculations of the Dose Distribution in the Lungs of a Rat Model Irradiated in the Thermal Column of the TRIGA Reactor

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To test the possibility to apply Boron Neutron Capture Therapy to the lung tumors, some rats are planned to be irradiated in the thermal column of the TRIGA reactor of the University of Pavia.
Before the irradiation, lung metastases will be induced in BDIX rats, which will be subsequently infused with BPA. During the irradiation, the rats will be positioned in a box containing designed to shield the whole animal body except the thorax area.
In order to optimize the irradiation set-up and to design a suitable holder, some MCNP calculations were performed. A rat model was constructed using the MCNP geometry capabilities and was positioned in the box.
The Teflon walls of the holder were filled with lithium carbonate and a window was opened in correspondence of the lungs zone. Different shapes of the holder and of the window were tested and analyzed in terms of the dose distribution obtained in the lungs and of the dose absorbed by the other radiosensitive structures in the rat.
The results of the calculations and the best configuration of the holder will be presented and discussed.

Evaluation of all Dose Components in the LVR-15 Reactor Epithermal Neutron Beam Using Fricke Gel Dosimeter Layers

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In a previous experiment at the epithermal column of the LVR-15 reactor in Rez, dose images with gel dosimeters had been evaluated without a proper procedure for separating the fast neutron dose. Therefore to obtain gamma dose profiles a hypothetical fast neutron dose distribution has been assumed. The resulting gamma dose trend was not quite satisfying.
A more complete experiment has been then carried out, aimed to obtain experimental images of dose components by means of gel dosimeters.
FriXy gel dosimeters are chemical dosimeters based on Fricke solution that are suitable to reconstruct bidimensional distributions of the absorbed dose; by means of proper variations of their isotopic composition, they can provide dose images due to the different radiation components. These dosimeters, based on an aqueous solution, are shaped in form of gel layers (3 mm thick) and are inserted in water equivalent phantoms. A CCD camera system is used to measure the gel optical density, before and after irradiation; the difference of optical absorbance of visible light at 585nm is proportional to the absorbed dose. Therefore, by pixel-to-pixel elaboration of the acquired grey level images it is possible to obtain dose images.
A particular care has been given to the fast neutron dose component, that has been obtained utilizing a couple of gel made of light and heavy water respectively. Exploiting the different recoil energies of protons and deuterons, it is possible to separate gamma and fast neutron doses by elaborating the images with proper algorithms requiring data that have been calculated with Monte Carlo simulations (MCNP5).
The measured distributions of the photon dose together with the therapeutic boron dose are shown; they are compared with Monte Carlo simulations and with data acquired with other methods.
The agreement between different techniques is in generally satisfying.

Preliminary liver dose estimation in the new facility for irradiation of biological samples at the RA-3 Reactor

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As a part of the project concerning the irradiation of a section of the human left liver lobe a preliminary estimation of the expected dose was performed. To obtain proper values as inputs for the calculation, neutron flux and gamma dose rate characterization were carried out using adequate portions of cow or pig liver covered with demineralized water simulating the preservation solution. Irradiations were done inside a container specially designed to fulfill temperature preservation of the organ and a reproducible irradiation position (which will be of importance for future planification purposes).
Implantable rhodium based self-powered detectors were developed in order to obtain neutron flux profiles both external and internal. Implantation of SPND was done along the central longitudinal axe of the samples, where lowest flux is expected.
Gamma dose rate was obtained using a neutron shielded graphite ionization chamber moving along external surfaces of the samples.
The internal neutron profile obtained resulted homogenous enough to allow for a single and static irradiation of the liver.

For dose estimation, irradiation condition was set in order to obtain a maximum of 15 Gy-eq in healthy tissue. Additionally, literature reported boron concentrations of 47 ppm in tumor and 8 ppm in healthy tissue and a more conservative relationship (30 ppm / 10 ppm) were used.
To make a conservative estimation of the dose the following considerations were done:

i. Minimum measured neutron flux inside the sample was considered to calculate dose in tumor (~5 10^9 n cm^{-2} s^{-1}).
ii. Maximum measured neutron flux (considering both internal as external profiles) was used to calculate dose in healthy tissue (~8.5 10^9 n cm^{-2} s^{-1}).
iii. Maximum measured gamma dose rate was considered for both tumor and healthy tissue (~12.5 Gy/h).

Tumor tissue dose was 71 Gy-eq for 47 ppm of B-10 and 43 Gy-eq for 30 ppm, for a maximum dose of 15 Gy-eq in healthy tissue. As can be seen from these results, even for the most conservative case, minimum tumor dose will be acceptable from the treatment point of view, which shows that the irradiation conditions at this facility have quite good characteristics for the proposed irradiation.

TLD-700 glow curve shape for determining thermal neutron fluence and gamma dose in BNCT beams

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The measurement of the photon dose in radiation fields having suitable characteristics for boron neutron capture therapy (BNCT) requires properly studied methods because thermal/epithermal neutron flux is very high and produces a significant contribution to the response of most dosimeters. A simple method has been proposed and tested for obtaining both photon dose and thermal neutron fluence using a single dosimeter.
The method has originated from some peculiarities appeared during studies regarding thermoluminescent dosimeters (TLD). TLDs are particularly convenient for mapping neutron fields, because, owing to their small volume, they do not sensibly perturb the neutron field. TLD-300 phosphors are very convenient for measurements in large phantoms, where the gamma dose is mainly due to the 2.2 MeV photons generated by the neutron reactions with H, but when reactor background constitutes large part of the gamma field, their utilizations is very problematic because of the noticeable dependence of the response on photon energy. Therefore, for measurements in free beam or in small phantoms, TLD-300 is not a good solution.
During an extensive study on LiF dosimeters, the glow curve (GC) of a TLD-700 exposed, in phantom or in free beam, to thermal/epithermal neutron beams has been carefully studied. It was observed that, after having subtracted from the GC the contribution of the gamma dose, the resulting TL curve has a shape very similar to that of TLD-600. A simple algorithm has therefore been formulated to obtain both thermal neutron fluence and gamma dose from the GC of a single TLD-700.
The algorithm requires the calibration of the dosimeter to photons and to thermal neutrons, and the ratio between the two main peaks of the GC of a TLD-600 irradiated with thermal. If only the TLD-700 gamma calibration is available, only the photon dose is obtained, but in a simple way, without the necessity of subtracting the thermal neutron contribution.
In-phantom and in-free-beam measurements have been carried out to test the method. The results have been compared with those obtained with other experimental methods. The feasibility of the method was so confirmed.

Neutron self-shielding effects and correction factors for foil activation measurements used in BNCT dosimetry

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It is common practice in BNCT to activate Manganese and Gold foils via the (n,γ) capture reaction to determine the thermal neutron flux. Further, the experimentally determined reaction rates can be used, using Freudenreich's theoretical approach, to derive the Nitrogen (N) and Boron (B) reaction rate, from which the N and B kerma can be deduced. For solid metal foils, the experimentally determined reaction rates require correction for flux depression caused by self-shielding.
In this paper, these self-shielding factors were determined by simulation in MCNPX, and compared with previous values determined by our group. Foil correction factors were calculated for two types of foil, one set being 'solid' foils [Mn/Ni (88% Mn by wt.) of approx 35 mg mass, Au of approx 50 mg], the other being dilute foils [MnAl (1% Mn by wt.), AuAl (1% Au by wt.)]. The non-dilute gold foils exhibit the largest flux depression, perturbing the flux by as much as 100% at shallow depths and 20% at depths approaching 10cm. The non-dilute Mn/Ni foils cause a consistent 5% perturbation at all depths along the central axis of the phantom. Simulations show that the dilute foils, both MnAl and AuAl, perturb the field by less than 1%.
Experimental work will be presented to assess the validity of these calculated correction factors in the standard Large Water Phantom. The use of such foil types to accurately determine thermal neutron fluence for neutron spectra which are not well moderated will also be assessed/discussed.
We will also show that even the large correction factors we have determined for solid Au foils at shallow depths have relatively small (approx. 2%) impact on the determined B and N kerma when evaluated with the Freudenreich method.

BNCT Beam Monitoring, Characterisation and Dosimetry

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Work has been recently carried out at the University of Birmingham Neutron Capture Therapy facility to relocate two neutron monitor chambers (Centronic ^{235}U fission chambers) and to locate a third chamber closer to the source. IEC requirements for monitoring radiotherapy beams require the chamber to be in the 'treatment' beam. The problem then arises of neutrons backscattering from patient or phantom affecting the counts at these detectors which are to be located within a 2.5cm layer of Lithium polyethylene shielding surrounding the exit port of the treatment facility.
To investigate monitor chamber neutronic coupling, MCNPX mesh tallies were calculated over the entirety of the shielding surrounding the beam exit port. Chamber sensitivity to neutron energies was accounted for by use of the tally multiplier card to multiply track length estimates of flux by the ^{235}U total fission cross-section. Tallies showed uncertainties of less than 1%.
The original monitor chamber position is separated from the patient / phantom by 20mm of Li-polythene, as chambers are located in the back of the 25mm Li-polythene beam delimiter, adjacent to the graphite neutron reflector. Experimental coupling of 2.3± 0.2% was observed with the large water phantom (40 x 40 x20cm), and the corresponding MCNP prediction was 2.6± 1%.
Changing the monitor position to be within the Li-polythene delimiter, separated from the patient /phantom by 12 mm Li-polythene was predicted by MCNP to reduce the count-rate by a factor of 2.5 ± 0.1. This was verified experimentally as a factor of 2.4 ± 0.1, making typical detector count-rates at 1mA proton current of approx 4000 cps. This change of position was predicted to increase the phantom coupling to 3.9 %, which remains to be verified experimentally.
Note that coupling is anticipated to be negligible (<1%) for other smaller phantoms and for actual patients, but experimental validation of this will be presented in this paper.

A Computational Dosimetry Tool for the study of tumor doses and skin toxicities in BNCT

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Introduction: The Comisión Nacional de Energía Atómica of Argentina and the oncology center Instituto Ángel H. Roffo initiated the phase I/II clinical trial of peripheral melanomas in 2003. Since then, a total of 7 patients with 88 nodular lesions in 10 anatomical areas were treated using the hyperthermal neutron beam of the RA6 reactor at the Centro Atómico Bariloche. During all these years, natural difficulties and questions regarding tumors and normal tissues raised: how to determine doses in small tumors that could not be delineated in medical images, and how to prescribe the dose in normal skin to deliver a safe treatment while imparting control doses to tumors when dose distributions are very inhomogeneous. These concerns motivated the development of a computational tool that helps guide physicians through location and delineation of tumors in medical images, and allows the study of normal skin dosimetry by computing specific figures of merit that cannot be obtained with the routinely used treatment planning system. In this work, we present the main features of the developed computational system and show some examples of its use. The applicability and usefulness of the present tool to other treatments are also discussed.
Materials and Methods: The system was programmed in Matlab, using the graphical user interface capability. After loading input data involving medical images, parameters relevant to the treatment plan evaluation, and calculated physical doses (such as those generated by MCNP with NCTPlan model), the tool allows to compute and visualize the 3D superficial dose distribution in the skin, and to calculate cumulative dose-volume and dose-area histograms for this organ, as well as for tumors. A registration of the 3D reconstruction and a picture of the anatomy facilitates the delineation of tumors on the medical images: the picture helps to locate tumors in the 3D model and the TAC slices corresponding to each tumor are identified for subsequent delineation. Also, this registration allows to estimate the dose values in tumors that are too small to appear in the images.
Results and discussion: The new tool made it possible to complete the tumor dosimetry of the Argentine treatments of cutaneous nodular melanoma, since it allowed to deal with lesions that were difficult or impossible to identify in medical images with the previous available capabilities. Also, the computation of skin dose distributions and related figures of merit were performed, aiming to initiate an analysis of their possible correlation with the observed skin toxicity.

Monte Carlo modelling of the influence of boron microdistribution on BNCT microdosimetry

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Fundamental studies of the efficacy of boron neutron capture therapy (BNCT) including dosimetric and radiobiology studies are currently being undertaken following the commissioning of an accelerator based neutron source. An improved understanding of the relationship between the boron microdistribution and treatment efficacy is sought, which includes the modelling of the relative biological effect (RBE) of the various components of the beam including the boron induced high-LET Li and He ions. Track structure information, generated by the TRIM and PENELOPE Monte Carlo codes, has been used to predict single event spectra for boron-bearing cells exposed to neutrons. These quantities are dependent on the precise microdistribution of the boron in cells. Particle tracks are post processed in order to improve the efficiency of simulations. Strategies to determine unbiased event spectra include the tallying of energy deposition on a regular grid in the form of a list that is further processed to determine the energy deposited within the micron dimension volume of interest.

Calculations are benchmarked against measurements made with a tissue equivalent proportional counter (TEPC) microdosimeters, where small quantities of boron and gadolinium have been introduced into the wall material. Single event spectra are converted into specific energy spectra which describe the effect of multiple events at dose levels used for in vitro experiments. The intercomparison of modelling with measured spectra and RBE from in vitro experiments assists in devising approaches for optimizing treatments. The work supports an emerging understanding of the complex interactions between high and low-LET components of the radiation field.

Boron Neutron Capture Therapy (BNCT) dosimetry by synthetic single crystal diamond

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We report on a new solid state dosimeter, based on Chemical Vapor Deposition (CVD) single crystal diamond fabricated at Rome "Tor Vergata" University laboratories. The dosimeter can be used for direct neutron dose measurements in medical physics and in Boron Neutron Capture Therapy (BNCT). Two single crystal diamond detectors are fabricated in a p-type/intrinsic/metal configuration and are sandwiched together with a Boron containing layer in between the metallic contacts (see Fig. 1). Such a boron layer is used as a converting material for thermal neutrons through the $^{10}B(n,\alpha)Li$ nuclear reaction. In this way, both the 0.83 MeV Lithium and the 1.47 MeV alpha particles are simultaneously detected and a good signal to noise ratio is obtained.
The use of the proposed diamond dosimeter prototype also allows to easily meet some peculiar physical and technical requirements such as human tissue equivalence, small size, high sensitivity, radiation hardness and linearity with dose.
Neutron irradiations were performed at the Frascati Neutron Generator (FNG) using the 14.8 MeV neutrons produced by the T(d, n)^{4}He reaction. Thermal neutrons were then produced by slowing down the 14.8 MeV neutrons through a cylindrical polymethylmethacrylate (PMMA) moderator. The diamond dosimeter was placed in a vertical hole located in the center of the moderator. The products of $^{10}B(n,\alpha)Li$ nuclear reaction were observed together as a single peak at 2.3 MeV, that is $E_\alpha + E_{Li}$ in the Pulse Height Spectrum (PHS) analysis. Stable performance, high reproducibility, efficiency, resolution and good linear behavior of the count rate versus the incident neutron photon flux were observed.

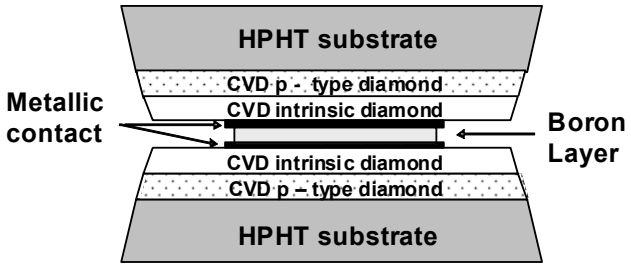

Fig. 1

Construction of an analytic dosimetry tool for BNCT

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The intention of this work is to provide the basis of a methodology to build a deterministic model of the $^{10}B(n,\alpha)^{7}Li$ reaction rate distribution in Boron Neutron Capture Therapy, as a function of space variables, boron concentration and other variables, such as incidence angle. The model has to be valid in homogeneous isotropic environments and also in different kinds of heterogeneous environments, to be extended eventually human body, so that for a given variable set, the reaction rate is known.
The main part of the work is based on precise calculations with the MCNPX code. Calculations are made in different possible cases in order to determine how the different variables interact with each other. The first step is to build the analytic function in a simple homogeneous environment. This construction is done with statistical estimation and numerical methods such as least squares estimation. Those methods are combined with the analytic solution of the radiation transport equation. The calculations are then extended in more complex heterogeneous environments in order to build the dependence of the variables with each other.
The second point is to determine analytically the dependence of the reaction rate with the different variables and know which characteristics of the reaction rate function vary or not with the environment. The dependence is also determined using numerical methods, first in simple environments, then in more complex environments. The study of interaction and dependences leads to the construction of a valid model, as an explicit function of all the chosen variables. This model gives for a given boron concentration the reaction rate that determines the dose. This model is implemented in a code written in C, named ALDEDO.

Testing of a gel equivalent to liver to perform neutron characterizations

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Several characterizations are needed in the frame of the project of irradiation of sections II-III of the human left liver lobe. For trials including neutron irradiation, samples remain with a certain level of activity that avoids their promptly discarding. To not use biological materials, that degrades and add the requirement of proper conservation up to their safe disposal, gel phantoms with non-residual activation were developed and their behavior under neutron irradiation was studied and compared to the one already obtained in previous studies using a pig liver.
Considering that response to neutrons depends mainly on the hydrogen content of the human tissue, materials chosen to construct phantoms equivalent to sections II-III of the left liver lobe were demineralized water and 2% agarose ($C_{12}H_{14}O_2(OH)_4$). The solution, still in its liquid phase, is poured into specially designed polyethylene bags in order to reproduce the portion of liver to be treated. To cover the variability range of sizes and weights in humans, three phantoms were prepared: 180, 240 and 300 g.
Implantable rhodium based self-powered detectors were used to obtain neutron flux profiles in the developed phantoms, both external and internal. Implantation of SPND was done along the central longitudinal axe of the samples, where lowest flux is expected. Irradiations were carried out under the same conditions that are previewed for the liver, i.e. inside the acrylic container and covered with demineralized water to simulate preservation solution.
Phantoms construction was quite simple and its durability very good. Handling in order to insert instrumentation was easy.
Obtained internal neutron profile resulted very similar to the obtained for the pig liver, which showed that it is possible to use the phantoms to perform neutron characterizations.

An Estimation of Activation for Target Volume due to BNCT at Kyoto University Reactor

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Not only the (n, α) reaction of B-10, but also various activation reactions occur in boron neutron capture therapy (BNCT). The dose due to the activation near the target volume is negligible level compared with the dose received during a BNCT clinical irradiation. But, the estimation of the dose due to the activation is important from the viewpoints of the exposures for the patient and the public. The quantitative simulations were performed for the activation near the target volume in BNCT.
The epi-thermal neutron irradiation at the Heavy Water Neutron Irradiation Facility (HWNIF) of Kyoto University Reactor (KUR) was assumed. The neutron flux distribution near a target volume was obtained using a dose-estimation code system "SERA". The activation rate distribution for each nucleus in the various human tissues was calculated from the neutron flux distribution with the reaction crosssection and the decay constant.
The result for the brain tumor irradiated to the parietal lobe during one hour is described as an example. The radioactivities of Cl-38, Na-24, K-42 and P-32 were larger as arranged in order, for the soft tissues such as brain, etc. just after the irradiation. For the bone, the radioactivities of Ca-49, Na-24, Cl-38 and K-42 were larger as arranged in order. The total radioactivity due to this irradiation was estimated to approximately 1.2 MBq.
The gamma-ray emitting nuclei such as Cl-38 and Na-24 are important in the viewpoint of the external exposure to the public. The dose due to these nuclei is sufficiently smaller than the limitations of the discharge criteria for nuclear medicine diagnosis and brachytherapy in Japan. However, it is thought that the residual radioactivities should be recognized for a few hours for Cl-38 and for a few days for Na-24.

BNCT beam monitoring with recombination chamber

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The paper presents the new measuring method for quality assurance or *on-line* monitoring of the BNCT beam intensity and composition, using a specially designed recombination chamber.
Recombination chambers are high-pressure, ionisation chambers which operate in unsaturated mode, under conditions of initial recombination of ions. Parallel plate recombination chambers are known as the detectors which can be used in order to determine the dose rate and several parameters associated with radiation quality of mixed radiation fields. Specially designed chambers can operate correctly also at high dose rates of therapeutic beams. The system presented in the paper uses a special, double recombination chamber which contains two sets of electrode pairs. Details of the chamber design will be discussed in the paper.
The measuring method is based on continuous determination of a quantity denoted as recombination index of beam quality RIBQ. During the measurements, one of the electrode sets is polarized with the high voltage, which ensures the conditions close to saturation (few hundreds volts), while the second one with lower voltage (between 20 and 50 volts). Ionization current measured by the second set of electrodes depends on initial recombination of ions, hence on LET spectrum at the depth of the gas cavity. RIBQ is determined from the difference between ionization currents measured by the first and second sets of electrode pairs. The minimum time needed for reading and display of the data is about 1 s for the dose rate and 10 s for RIBQ. It was shown experimentally that the system can detect the change of the gamma and neutron contributions to the absorbed dose at the level of about 0.5% of the total dose.

Microdosimetry Study of THOR BNCT Beam Using the Tissue Equivalent Proportional Counter

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Boron neutron capture therapy (BNCT) is a cancer treatment modality using the nuclear reactor and the boron compound drug. In Taiwan, Tsing Hua Open-pool Reactor (THOR) has been modulated for the basic research of BNCT for years. A new BNCT beam port was built in 2004 and used to prepare the first clinical trial in the near future. This work reports the microdosimetry study of the THOR BNCT beam by means of the tissue equivalent proportional counter (TEPC). Two self-fabricated TEPCs (the boron-doped versus the boron-free counter wall) were introduced. This dual TEPC system was applied to measure the lineal energy distributions in air and water phantom irradiated by the THOR BNCT mixed radiation field. Dose contributions from component radiations of different linear energy transfers (LETs) were analyzed. Applying a lineal energy dependent biological weighting function, r(y), to the total and individual lineal energy distributions, the effective relative biological effectiveness (RBE), neutron RBE, photon RBE, and boron capture RBE (BNC RBE) were all estimated at various depths of the water phantom. Minimum and maximum values of the effective RBE were 1.68 and 2.93, respectively. The maximum effective RBE occurred at 2 cm depth in the phantom. The averaged neutron RBE, photon RBE, and BNC RBE values were 3.160±0.020, 1.018±0.001, and 1.570±0.270, respectively, for the THOR BNCT beam.

In-phantom dose imaging with polymer gel dosimeter layers

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In-phantom dose distribution measurements are important for validating Boron Neutron Capture Therapy treatment planning protocols. The method for spatial determination of absorbed doses in thermal or epithermal neutron fields, based on Fricke-xylenol-orange-infused gel dosimeters in form of layers, has revealed to be very reliable. By means of the properly developed procedure, gel-layer dosimeters give the possibility of obtaining the spatial dose distribution of each dose contribution in thermal/epithermal neutron fields. The possibility of utilising, with the same methodology, polymer gel dosimeters has been studied. The main advantage of such a dosimeter would be the absence of ion diffusion and therefore the possibility of performing dosimeter analysis also a long time after irradiation.
The studied dosimeter is polyacrylamide gel (PAG), in which a polymerization process appears as a consequence of the absorbed dose. The dosimeters, in form of layers (3 mm thick) having suitable shape, have been optically analysed. Visible light absorbance has been imaged with a CCD camera by detecting the light transmittance through the dosimeters.
Nowadays, wide interest has been pointed to the application of BNCT to liver metastasis treatments. So, in this work the polymer gel appropriateness has been studied by comparing the results obtained in a cylindrical phantom having a volume near to that of an explanted liver. Couples of gel layers, one containing a suitable concentration of ^{10}B and the other without, have been settled in the central plane of the phantom. The phantom has been exposed in the thermal column of the Pavia's TRIGA reactor.
Gamma and boron dose images have been obtained and depth dose profiles along the beam axis have been extracted. The results obtained with polymer and Fricke gel dosimeters have been compared. Dose images and profiles have shown similar trends, but they do not fit well. Polymer gel dosimeters have so proved that further research is necessary in order to optimize the dose imaging method based on polymer gel layers.

Exploring a Boron-Sulphur Neutron Capture Therapy

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In the most commonly used version of neutron capture therapy, ^{10}B is being used to induce reactions (n,α) (Barth et al. 2005). We study the possibility of inducing a similar reaction using the nucleus of ^{33}S, for which the reaction cross section presents resonances for keV-neutrons, the highest peak occurring for 13.5 keV. By means of Monte Carlo simulation of point-like sources of neutrons of this energy, we show an enhancement effect on the equivalent dose in a four component standard tissue by the addition of both type of atoms, at the places where they are delivered. This motivates further research in a combined technique because both additions complement each other.

Accumulation of Boron Compounds to Tumor with Intrarterial Administration of Boron Entrapped Water-in-Oil-in-Water Emulsion by Using Neutron Capture Autoradiography

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The cytotoxic effect of boron neutron capture therapy (BNCT) is due to a nuclear reaction between ^{10}B and thermal neutrons. It is necessary to accumulate the ^{10}B atoms to the tumor cells selectively for effective BNCT. In order to achieve an accurate measurement of ^{10}B concentrations in the biological samples, we employed a technique of neutron capture autoradiography (NCAR) of sliced samples of tumor and normal tissues using CR-39 plastic track detectors. The CR-39 alpha-track detectors attached with samples were exposed to thermal neutrons in the thermal column of the JRR3 reactor of Japan Atomic Neuclear Institute. We obtained NCAR images for VX-2 tumor in rabbit liver after injected BSH entrapped water-in-oil-in-water (WOW) emulsion by intrarterial injection via proper hepatic artery. The ^{10}B concentrations in the VX-2 tumor and normal liver of rabbit were estimated by means of alpha-track density measurements. In this study, we can increase the selective accumulation of ^{10}B atoms in the VX-2 tumor by intrarterial injection of boron entrapped WOW emulsion until 7 days after injection. Therefore, we will be able to apply boron entrapped WOW emulsion to BNCT for hepatocellular carcinoma, and NCAR technique for detection of effective ^{10}B carrier in BNCT for cancer.

NEUTRON SOURCES

Collaborative Characterization of the KG 2,5 Accelerator Epithermal Neutron Beam in Obninsk

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A comprehensive measurement campaign was carried out in May-June 2007 with the aim of characterizing the accelerator-based epithermal neutron beam in Obninsk, Russia.
Measurements were performed with activation detectors and ionization chambers both free-in-air and in a water phantom. VTT and IPPE used their own chambers and activation foils and all the activity measurements were performed on site. This exercise provides an opportunity to intercalibrate equipment and methods and also to compare the results with those obtained at other facilities.
The results of the measurement campaign will be presented and compared to MCNP calculations performed at IPPE. Conclusions about the clinical suitability of the beam will be drawn.

The BSA modeling for an Accelerator-Based BNCT facility for treating shallow skin melanoma at INFN LNL

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The SPES-BNCT ongoing project of the INFN is committed to the final design and installation at Legnaro National Laboratories (LNL) of an accelerator-based thermal neutron facility for BNCT treatment of the of extended skin melanoma, in the framework of SPES (Selective Production of Exotic Species) project. The neutrons will be produced via the $^{9}Be(p,xn)^{9}B$ reactions by a 5MeV, 30mA proton beam into a thick beryllium target. The resulting neutron spectrum is tailored using a beam shaping assembly (BSA) which has been fully designed using the MCNPX transport code.The beam quality at the design stage is evaluated based on in-air figures of merit and fulfills all the current recommend limits at the 10x10 cm^2 irradiation port, having a thermal neutron flux of about $1.2 \cdot 10^{9} cm^{-2} s^{-1}$ with a prominent thermal-to-total neutron flux ratio of 0.99.A mapping of the neutron and gamma dose rate over the patient-facing wall is done. The AB-BSA facility performance is finally compared to two reactor-based facilities, showing a reduction of two orders of the non thermal component of the beam. Finally a wall by wall neutron and gamma dose rate characterization of the facility is done.

Feasibility Study for the Upgrade of a Compact Neutron Generator for NCT Application

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The Plasma and Ion Source Technology Group at Lawrence Berkeley National Laboratory (LBNL, California, USA) has been developing for over 10 years the design several Compact Neutron Generators (CNG) for medical and industrial applications based on the nuclear fusion reactions.
In 2001, an agreement between the Italian non-profit association Eurosea Committee (Turin) and LBNL was signed for the development of a prototype of CNG for medical uses.
At the end of 2004 this prototype called EUROSEA 001 was installed and tested at the Experimental Physics Department of the Turin University.

It is basically composed of three main elements: a source of deuterium ions, a low voltage electrostatic accelerator and a titanium target. The radio frequency antenna (13.5 MHz) is used to produce deuterium ions which, properly accelerated by the potential difference in vacuum chamber, hit the target (at 120 kV) generating neutrons. The deuterium ions are extracted from some multi-circular windows on the source chamber wall and hit the titanium target, where the nuclear fusion reactions among deuterium nuclei occur with generation of fast neutrons.
This prototype allows to produce until $1x10^{11}$ n/s and its dimensions do not exceed 50 cm.
Eurosea Committee and Lawrence Berkeley National Laboratory have investigated different approaches for upgrading the present neutron generator Model EUROSEA 001. The goal is to increase the neutrons yield from $1x10^{11}$ n/s to $2x10^{12}$ n/s without changing the size of the neutron generator.
This can be achieved extracting the deuterium ions from long slits perpendicular to the axial source instead of using multi-circular windows on the source chamber wall. By this way the beam power is spread in a larger area on the the titanium target avoiding cooling problem that can dramatically decrease the neutron production.
This is very important for a therapeutic application of the NCT because the increase of the neutron production will allow a sensible reduction of the treatment time of the patient.
The upgraded CNG, together with dedicated neutron moderators, can be an interesting source for NCT application, providing both epithermal both thermal neutrons.
The modification proposed does not affect the main characteristics of EUROSEA 001, namely, high compactness (dimensions do not exceed 50 cm.), safety (neutron production is stopped when the electrical supply is turned off) and simplicity of assembly and operation throughout the life cycle.
Eurosea Committee and Lawrence Berkeley National Laboratory plan to continue to investigate different solutions for CNG upgrade.

Be target development for the accelerator-based SPES-BNCT facility at INFN Legnaro

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An accelerator-driven thermal neutron beam facility, aimed at the BNCT treatment on skin melanoma, is going to be installed at the INFN Laboratori Nazionali di Legnaro (LNL) in the framework of SPES (Selective Production of Exotic nuclear Species) project. The intense proton beam delivered by the 5 MeV, 30 mA, cw RFQ accelerator which is the SPES driver, is next to being completed. After a feasibility study lasted two years based on SPES driver constraints, two original, beryllium-based, neutron converter concepts have been at the purpose designed, in collaboration with the STC Sintez of Efremov Institute in S. Petersburg. Both full-scale prototypes, constructed at the end of 2004 and 2005, successfully passed a series of both operative and critical electron beam full-power test conditions, thus proving the thermal-mechanical design criteria followed. The remaining radiation damage tests, using high intensity proton and neutron beams, to both assess the target reliability and the operative lifetime, is currently under way. The status of art about the neutron converters development and test is reported.
The LNL-BNCT project will therefore mean to represent a challenge to provide an intense thermal neutron beam and a fundamental test bench for an operative, accelerator-based BNCT facility concept, with respect to the current reactor-based ones.

High power accelerator-based boron neutron capture with a liquid lithium target and new applications to treatment of infectious diseases

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A new conceptual design for Accelerator-based Boron Neutron Capture Therapy (ABNCT) facility, based on the high-current low-energy proton beam from the linear accelerator at SARAF (Soreq Applied Research Accelerator Facility) and a forced-flow liquid-lithium target is described. A novel approach utilizing BNCT for the treatment of infectious diseases is under investigation.
SARAF is based on a superconducting linear accelerator currently being built at Soreq Nuclear Research Center (Israel). The accelerator is planned, during its first year, to generate a proton beam of up to 4 MeV energy at 2-4 mA intensity. The high-intensity beam, together with the linac ability to adjust the beam energy, can be utilized to produce a high-intensity neutron source that has the potential to meet the requirements of a clinical BNCT facility of deep-seated tumors via the ^{7}Li(p,n)^{7}Be reaction near threshold (proton energy between 1.88 MeV and 2 MeV). This reaction together with a moderator/reflector assembly, allows the optimization of the neutron energy for maximum therapeutic benefit (0.5 eV- 10 keV). A major problem of lithium targets is to sustain and dissipate the power generated by the high-intensity proton beam. A liquid-lithium target, based on a forced liquid-Li flow, is currently being built at Soreq NRC. This target is designed both to produce neutrons through the ^{7}Li(p,n)^{7}Be reaction and to serve as power dump for up to a 20 kW proton beam. The accelerator facility and the neutron source setup will be described.
Such an ABNCT facility can be applied to a wide variety of clinical application, from cancer therapy to a novel approach in treatment of infectious diseases associated with biofilms. Biofilm is a microorganism mode of growth and bacteria in a biofilm can be up to 1500 times more resistant to antibiotics and immune chemicals. We seek to apply the BNCT methodology to such cases. Since the biofilm develops on medical devices such as prosthetic knees or hips, BNCT could provide a non-invasive procedure that is less threatening to the patient, costly effective and reduces the development of resistance to common antibiotics. Possible problems which can be targeted by this approach include biofilm inflammations such as: implants and prosthetic devices, Cystic Fibrosis, infectious kidney stones. Feasibility experiments evaluating the boron neutron capture effectiveness on bacteria annihilation are taking place at the Soreq nuclear reactor tangential tube and will be presented.

Neutrons for BNCT from the Near Threshold ^{7}Li(p,n)^{7}Be on Thick Li-target

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The near threshold ^{7}Li(p,n)^{7}Be reaction for 1.900MeV incident mono-energetic proton on thick Li-target was studied as possible practical implementation of an accelerator-based neutron source for BNCT. Neutron fields from near threshold reactions on thick targets are not suitable for BNCT because they are highly contaminated with gamma rays. In this study, we considered a number of target assembly configurations, particularly related to the thickness of the Li-target, with the aim of reducing the gamma rays in the neutron irradiation field.

Results of our parametric survey using Monte-carlo simulation showed that one of the practical approches to near threshold neutron production via the $^{7}Li(p,n)^{7}Be$ reaction would be to include an effective gamma ray shield if thick targets are to be used. A 2mm-thick Li-target having with 50 mm width and 50 mm length which could be established easily than thin Li-target of a few micron meter. Candidate gamma absorbers would be Bismuth and Lead and the suitable the boron dose enhancer (BDE)[1] is Polyethylene. The optimum physical dimensions and configuration of the gamma absorber and BDE were determined by means of the PD(hcp), PD(gamma) and TPD [1, 2,3]. The details of this study will be reported in the conference.

Development of a TESQ accelerator for BNCT

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In this work we describe the present status of an ongoing project to develop a Tandem-ElectroStatic-Quadrupole (TESQ) accelerator for Accelerator-Based (AB)-BNCT at the Atomic Energy Commission of Argentina in Buenos Aires. The project goal is a machine capable of delivering 30-40 mA of 2.4 MeV protons to be used in conjunction with a neutron production target based on the $^{7}Li(p,n)^{7}Be$ reaction slightly beyond its resonance at 2.25 MeV. These are the specifications needed to produce sufficiently intense and clean epithermal neutron beams, based on the $^{7}Li(p,n)^{7}Be$ reaction, to perform BNCT treatment for deep-seated tumors in less than an hour. An electrostatic machine is the technologically simplest and cheapest solution for optimized AB-BNCT. The machine being designed and constructed is a folded TESQ with a terminal at 1.2 MV. In parallel also a tandem, with a 0.8 MV terminal voltage, with an ESQ chain inside the acceleration tube, and injected by a 0.8 MeV pre-accelerator is being evaluated. Such machines are conceptually shown to be capable of transporting and accelerating a 40 mA proton beam to 2.4 MeV. The general geometric layout, its associated electrostatic fields, and the acceleration tube from ion source to neutron production target are calculated using a 3D finite element procedure. The first design and construction of an ESQ module is discussed and its electrostatic fields are investigated theoretically and experimentally. Beam transport calculations through the accelerator are briefly presented. Likewise, work related to neutron production targets is described. Ion source, electronic hardware developments and the control system for the machine, based on optical fiber links and LAN-RS422 communication, are also briefly described.

Neutron producing target for BINP accelerator based neutron source

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Innovative accelerator based neutron source for BNCT is under going to start operating now at Budker Institute of Nuclear Physics, Novosibirsk. One of the main elements of the facility is lithium target producing neutrons via threshold $^{7}Li(p,n)^{7}Be$ reaction at 25 kW proton beam with energies 1.915 MeV or 2.5 MeV. The conception of optimal target and results of investigation of radiation blistering and lithium layer were presented at previous NCT Congress. During the last two years the neutron target had been manufactured, assembled and placed into facility. Optimization of the target is carried out with the Monte Carlo simulation code MCNP. Some diagnostics are prepared for neutron generation that the planned within the next two months. In the report, the neutron producing target design is given, results of target testing and possible neutron generation are described, results of simulation of neutron spectra are presented.

High Energy Proton Application to BNCT Neutron Source (2) - Epithermal Neutron Genrator Using 400MeV Protons -

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A proton linear accelerator is being constructed in J-PARC (Japan Proton Accelerator Research Complex) project of JAEA (Japan Atomic Energy Agency). A transmutation experimental facility and a beam dump of the high energy beam will be also planned to be constructed in the second stage of construction. Hence, we are proposing a BNCT neutron source facility of BNCT (Boron Neutron Capture Therapy) using the 400 MeV proton beam drawn into the beam dump. The beam current available is 75μA, i.e., total power of 30 kW.
An epithermal neutron generator for BNCT has been studied. The neutron generator utilizes the spallation reaction of tantalum and it is equipped with two collimators, horizontal and vertical irradiation holes, to facilitate patient setting. The collimators are set at right angles to the proton beam because the contamination of fast neutron dose can be reduced by using neutrons emitted at 90 degrees with respect to the proton beam. The shape and size of the moderators and the collimator are optimized by neutronics calculations with the MCNPX code. The iron moderator is 90 cm long and the length of Fluental moderator is 30 cm, and it has been found that a high epithermal neutron beam whose quality meets the IAEA recommendations has been obtained at the aperture of the collimator.
The beam current required for one hour treatment is estimated to be 45μA or about a half of the total beam current. Therefore, the proton beam current is so strong that more sophisticated idea, e.g. neutron and gamma shielding, can be incorporated into the design. The remaining beam current of 30μA may be disposed into the beam dump through the target. The heat load of the target will be mitigated in this way. The target structure will be also studied to maintain the integrity of the target.

Epithermal neutron generator based on Be(p,n) reaction using 30 MeV proton cyclotron accelerator at KURRI

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Two hundred and seventy five clinical trials have been performed using the boron neutron capture therapy (BNCT) at Kyoto University Research Reactor Institute (KURRI). More clinical trials will be carried out to show the effectiveness of BNCT. Moreover, a sufficient neutron yield obtained by using an accelerator-based neutron source that can be located near the hospital is required for the further development of BNCT.
Some groups are already investigating a neutron source using spallation reactions between several tens of MeV protons and heavy materials such as lead, tungsten, and tantalum. As for the combination of several tens of MeV protons and a beryllium target, the examination was excluded because of the contamination of a fast neutron in the treatment beam. However, we confirmed that a sufficient epithermal neutron yield based on Be(p,n) reaction with an optimum beam shaping assembly could be obtained. Our system has the advantage of lower activity and larger neutron yield of targets as compared with the spallation reactions involving heavy materials. Our system consists of a cyclotron accelerator promising a proton beam of ~1 mA at 30 MeV, beam transport system, beam wobbler system for heat reduction on the beryllium target, target cooling system, beam shaping assembly, multileaf collimator, and an irradiation bed for patients in both sitting and decubitus positions. The reaction between a proton and the beryllium target emits a high energy neutron at up to ~28 MeV in the 0° direction.

The 0° neutron yield is the largest. Further, the moderator system consists of lead, iron, calcium fluoride, and aluminium for shaping an epithermal neutron beam. This beam can sufficiently treat a patient with an irradiation time of less than 45 min and a normal dose of less than 12.5 Gy-eq with a boron concentration of 45 and 13 ppm for tumor and normal tissue, respectively. The CBE factors for tumor and normal tissue are 3.8 and 1.3, respectively. The RBE factor for nitrogen, hydrogen, and gamma rays are 3.0, 3.0, and 1.0, respectively.
On the basis of the investigation described above, we have started fabricating cyclotron accelerator-based neutron sources. The installation of these systems will begin at KURRI in August 2008. In this presentation, we will report the performance of our epithermal neutron generator system in detail.

Design of a Accelerator- Based Neutron Source for Neutron Capture Therapy

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In order to use the neutron capture therapy for the treatment of deep-seated tumours neutron beams of suitable energy, current, safety and compactness are needed. In this contribution we firstly illustrate the advantages (and disadvantages) in terms of therapeutic gains of the different neutron beam choices and then the design for an accelerator neutron beam is proposed. In detail the GEANT-3/MICAP simulations shows that a high tumour control probability with sublethal dose at healthy tissues can be achieved, in most cases, by using neutron beams of a few keV energy, with a flux of about 10^9 neutrons/cm^2 s. In this energy range therapeutic neutron beams with high-spectral purity could be produced by accelerator-based neutron sources through a suitable neutron reaction. In particular it will be shown that the feasibility of a solution based on a small radio frequency quadrupole for a proton beam current of 30 mA and an energy of 2 MeV. An appropriate choice of the function parameters of the RFQ (modulation, efficiency of acceleration, phase shift, etc.) allows one to design relatively compact accelerators, which could eventually lead to setup hospital-based neutron capture therapy facilities.

Opportunity using of neutron pulse sources at combined boost neutron capture therapy

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Neutron capture therapy (NCT) utilizes thermal (epithermal) neutrons interaction with a substance of high specific capture cross-section resulting in secondary local irradiation of a target (tumour cells). NCT neutron accelerators, generators and nuclear reactors serve as sources of neutron fields.
An absorbed doze in the target at neutron capture therapy is formed by radiation of quite broad energy spectrum including densely and sparsely ionizing radiations (both as primary, and as secondary). Interaction of radiations of different energies can produce synergetic effect.
The choice of optimal source of neutrons for NCT is based not only on physico-dosimetric parameters (the flux, a power spectrum, contribution of accompanying photon radiation) but on parameters of stable formation of therapeutic beams, type of radiation and availability of neutron sources.
The important features of significant number of physical research installations generating neutron beams are pulse character of radiation in a wide frequency range, various forms of an impulse and variable porosity.
Role of the dose rate in formation of therapeutic effect is still a key problem in teletherapy as whole and neutron capture therapy in particular.
A great deal of scientific data on biological effects of densely ionizing radiation, different types of neutrons in the first place are obtained at MRRC. Methods for combined neutron-photon and boost NCT are developed, proved and tested in the clinic. Effectiveness of treatment of more than 500 patients with various malignant tumour is very high.

Preliminary work on formation of neutron beam for therapeutic purposes on linear accelerator KG-2,5 (Obninsk) and reconstruction of the medical block for neutron therapy on reactor WWR-c (Obninsk), standardization of neutron fields and modeling of NCT are carried out. Clinical testing is planned to be started in this year. Pilot technologies developed at the Center will serve as the basis for design of "baby" clinical accelerator.

Russian experience in neutron therapy includes neutron teletherapy at the nuclear reactor BR-10 (Obninsk), cyclotron U-120, E_n=6.3 MeV (Tomsk), and neutron generator NG-12I, E_n=12-14 MeV (Snezhinsk), as well as neutron ^{252}Cf-brachytherapy in Obninsk and Moscow. New facilities are constructed at the nuclear reactors (Moscow, Obninsk), accelerator KG-2,5, portable neutron generators (Moscow, Obninsk).

It is necessary to continue study of regularities of formation of biological response to pulse radiation to prognosis a further development of neutron therapy. Radiobiological and biophysical experiments on BARS-6 (pulse reactor, the dose rate up to 10^7 Gy/s), pulse neutron generators (duration of an impulse from nanosecond to μs), and also linear accelerator KG-2,5 and reactor BR-10, allow us to make a conclusion that the effect of the dose rate (in the given range of the absorbed dozes) of neutron radiation on formation of radiobiological effects is insignificant. The conclusion allows to consider sources of pulse neutron radiation as promising installations for neutron therapy.

Accelerator-Driven Sub-Critical Multiplier for BNCT

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A novel, highly compact, fusion neutron source (CNS) based on a coaxial electrostatic accelerator is under development at the Lawrence Berkeley National Laboratory. This source is designed to generate up to ~10^{12} D-D n/s. This source intensity is an order of magnitude too small for Boron Neutron Capture Therapy (BNCT) applications. The objective of this study was to assess the feasibility of using a small, safe and inexpensive subcritical fission assembly (SCM) to multiply the fusion neutrons by a factor of ≥30. The overall design objective was to get a treatment time for deep seated brain tumors that does not significantly increase beyond one hour when the effective multiplication factor of the SCM is k_{eff} = 0.98. Through the introduction of our optimized subcritical fission assembly and of an optimized beam-shaping-assembly (BSA), the required treatment time was reduced by a factor of 18.

There are two major parts to this study: the optimization of the Sub-Critical Multiplier (SCM) and the optimization of the Beam Shaping Assembly (BSA), including the reflector for both sub-systems. The SCM optimization objective is to maximize the current of neutrons that leak out from the SCM in the direction of the patient, without exceeding the maximum permissible k_{eff}. Minimizing the required uranium inventory is another objective. SCM design variables considered include the uranium enrichment level in the range not exceeding 20% ^{235}U (due to proliferation concerns), SCM geometry and dimensions, fuel thickness and moderator thickness. The optimal design of a SCM is made of 20% enriched uranium metal arranged as follows: two cylindrical fuel shells surround the CNS coaxially and four circular fuel elements are located in-between the CNS and the BSA. Two optimal BSA designs were identified; one for maximizing the dose rate to a deep seated tumor and the other for maximizing the total dose that can be delivered to a deep seated tumor. The former offers the minimum treatment time whereas the latter offers a larger lethality range.

Overview of the IBA Accelerator-Based BNCT System

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During the last few years, IBA started the development of an accelerator-based BNCT system. The accelerator is a Dynamitron built by RDI in USA and will produce a proton beam of 20 mA at 2.7 MeV. Neutrons will be produced by the $^{7}Li(p,n)^{7}Be$ nuclear reaction by directing the proton beam on a thin lithium target. The neutron energy spectrum will be tailored using a dedicated beam shaping assembly (BSA) surrounding the target.
This presentation makes a summary of the present status of the development. After a description of each subsystem, some design issues, solutions and experimental tests will be discussed.
For instance, the high proton current on target induce blistering problems and cooling issues. Both of these can be tackled by a careful choice of the materials and a good target design. Other tests include activation measurements with a low current neutron beam shaped with a close-to-final but versatile BSA design.
According to the outcome of all tests performed so far, the future BNCT system should perform as expected.

Beam Shaping Assembly with Liquid Lithium Target for Neutron Production in BNCT

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The neutron intensity and gamma ray contamination at the intended irradiation point in a patient are among the challenges faced by accelerator-based neutron sources for BNCT. Additionally target heating problems have to be considered in the practical realization of ABNS in order to maintain the integrity of the target especially for long irradiation times. With the Li(p,n) reaction, neutron intensity can be addressed by using proton energies much higher than the reaction threshold. However, this introduces more gamma rays yielding in the target; therefore the beam shaping assembly (BSA) design should be able both to adjust neutron energy and to reduce contaminant gamma rays to acceptable levels.
We have studied a BSA design based on a liquid Li-target and a proton energy of 2.50MeV for the ^{7}Li(p,n)^{7}Be. Investigated were target thicknesses in the millimeter order while considering the mechanical possibility of a flowing liquid lithium metal. From the viewpoint of reducing contaminant gamma rays in the neutron field, the configuration of the BSA includes an optimized gamma absorber (Bismuth or Lead) near the target, heavy water moderator and lithiated polyethylene collimator. A Monte-Carlo simulation-based parametric survey of each component of the BSA was performed and the resulting neutron irradiation field was analyzed. The characteristics of irradiation field produced by the BSA were evaluated by means of the PD(hcp), PD(gamma) and TPD. The details of studies will be shown in the conference.

Comparison between a TESQ accelerator and a reactor as neutron sources for BNCT

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In this work, the performance of an accelerator-based neutron source design has been compared with that of a modern fluoride-filtered reactor-based epithermal beam having near-optimal quality for treatment of deep seated tumours in relation to its applicability for BNCT. The accelerator is a Tandem-ElectroStatic-Quadrupole (TESQ) accelerator which is a design under development at the National Atomic Energy Commission (CNEA) in Buenos Aires, Argentina based on the ^{7}Li(*p,n*)^{7}Be reaction, relatively close to its energy threshold.
The reactor is the Massachusetts Institute of Technology reactor upgraded with a Fission Converter Beam (MIT-FCB) and improved with an 8mm thick ^{6}Li Filter. The comparison has been done by means of data reported on the MIT-FCB + ^{6}Li Filter performance and MCNP simulations on our TESQ design considering the neutron fluxes provided by the two sources and the doses delivered in a human phantom by both devices. The results show a deeper advantage depth (AD) for the TESQ which turns out to be a promising alternative to a reactor-based BNCT treatment.
Our calculations show that the TESQ facility may reach a 98% Tumour Control Probability at 6.4 cm inside the brain in a 27 minutes treatment keeping the maximum healthy tissue RBE dose at 11.6 RBEGy (considering 12.5 RBEGy as the maximum allowed healthy tissue dose) utilizing 34 cm of moderator and a 30 mA proton beam.

Thermal Neutron Flux for NCT Application by means of Compact Neutron Generators

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In 2001, an agreement between the Italian non-profit association Eurosea Committee (Turin) and The Plasma and Ion Source Technology Group at Lawrence Berkeley National Laboratory (LBNL, California, USA) was signed for the development of a prototype of Compact Neutron Generators (CNG) based on fusion reactions for medical uses.
At the end of 2004 this prototype called EUROSEA 001 was installed and tested at the Experimental Physics Department of the Turin University. The prototype allows to produce until $1x10^{11}$ n/s and its dimensions do not exceed 50 cm.
Then, Eurosea Committee and Lawrence Berkeley National Laboratory have investigated different approaches for upgrading the present neutron generator Model EUROSEA 001. The goal is to increase the neutrons yield from $1x10^{11}$ n/s to $2x10^{12}$ n/s without changing the size of the neutron generator.
EUROSEA 001 and its upgrade version seem to be very interesting thermal neutron sources for tissue sample irradiation tests and therapeutic applications respectively.
In order to set up a suitable assembly for the production of thermal neutron fluxes, the CNGs have to be coupled with a moderating-reflecting assembly devoted to slow down fast neutrons (2.45 MeV) and increase thermal neutron population.
To meet this goal the proposed assembly presents a central region containing the CNG (*neutron source*), an inner moderating region (*moderator*) devoted to slow down fast neutrons and an outer reflecting region (*reflector*) devoted to limit thermal neutron leakage back-scattering the neutrons.
The assembly proposed has been studied by means of MCNP code version 4C. Neutron and photon fluxes have been evaluated inside the inner moderating region in several points. Neutron and photon fluxes have been evaluated and compared with the recommended values for the application of NCT.
An extensive set of simulation have been performed. The results show that the CNGs, coupled with a suitable moderating-reflecting assembly, give thermal neutron fluxes matching all the spectral purity parameters for the application of NCT (for instance in case of liver cancer treatment). Moreover, using EUROSEA 001 UPGRADE, a thermal neutron flux higher than $1x10^{9}$ n cm^{-2} s^{-1} is reached in the dedicated irradiation region.
Eurosea Committee and its partners plan to set up EUROSEA 001 UPGRADE and continue to study different solutions based on CNGs in order to perform irradiation of tissue samples and NCT in hospitals.

The Study of Physics and Thermal Characteristics for In-hospital neutron irradiator (IHNI)

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$MNSR_S$ (Miniature Neutron Source Reactor) are low power research reactors designed and manufactured by China Institute of Atomic Energy (CIAE). $MNSR_S$ are mainly used for NAA, training and teaching, testing of nuclear instrumentation. The first MNSR, the prototype MNSR, was put into operation in 1984, later, eight other $MNSR_s$ had been built both at home and abroad. For $MNSR_S$, highly enriched uranium(90%) is used as the fuel material.
The IHNI is designed for Boron Neutron Capture Therapy(BNCT) based on Miniature Neutron Source Reactor(MNSR). The reactor with thermal power 30kW is an undermoderated reactor of pool-tank type, and UO_2 as fuel, light water as coolant and moderator, and metallic beryllium as reflector. The fission heat produced by the reactor is removed by the natural convection.
The paper gives the calculating results of critical mass and the worths of central control rod, auxiliary control rod, reactivity regulator and neutron beam equipments. The parameters at thermal and small thermal ports and at epithermal port were calculated by optimizing combination of kinds of material by MCNP code. The dynamic feature research was done by RELAP5 code when the reactivities of 3 mk, 4.5mk and 6mk were inserted respectively, the results shown that the reactor power can be limited to safe level by itself owing to the Doppler effect of fuel element and moderator negative temperature effect when the 6mk reactivity was inserted to reactor.

The Physics Experimental Study for In-hospital Neutron Irradiator

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$MNSR_S$(Miniature Neutron Source Reactor) are low power research reactors designed and manufactured by China Institute of Atomic Energy (CIAE). $MNSR_S$ are mainly used for NAA, training and teaching, testing of nuclear instrumentation. The first MNSR, the prototype MNSR, was put into operation in 1984, later, eight other $MNSR_S$ had been built both at home and abroad. For $MNSR_S$, highly enriched uranium(90%) is used as the fuel material.
The In-hospital neutron irradiator(IHNI) is designed for Boron Neutron Capture Therapy(BNCT) based on Miniature Neutron Source Reactor(MNSR).
On the both sides of the reactor core, there are two neutron beams, one is thermal neutron beam , and the other opposite to the thermal beam, is epithermal neutron beam. A small thermal neutron beam is specially designed for the measurement of blood boron concentration by the prompt gamma neutron activation analysis(PGNAA).
In this paper, the experimental results of critical mass, worth of the top Be reflectors, worth of the control rod, neutron flux distribution and other components worth were measured, the experiment was done on the Zero Power Experiment equipment of MNSR.

Pulsed Neutron Source for Boron Neutron Capture Therapy - Initial Simulation Results

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In this work a feasibility study for using an irradiation with pulsed neutron flash generated by a Dense Plasma Focus device for BNCT treatment is presented. The use of short powerful neutron pulse in BNCT could in principle produce the desiderate effect with a considerable less total absorbed dose. Through Monte Carlo (MC) simulations this experimental configuration could be described and each pulsed deposited dose and dose power estimated. A detailed MC simulation based on the Geant4 toolkit was implemented to evaluate neutron pulse characteristics (pulse duration and spectrum) after its penetration through a moderator. Then, the neutron flux and dose deposition in a human phantom was study. A second MC simulation step is performed to evaluate the dose deposition in a cluster with healthy and cancer cells.

High Energy Proton Application to BNCT Neutron Source
(1) - Outline of J-PARC project and Transmutation Experimental Facility -

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Japan Atomic Energy Agency and High Energy Proton Accelerator Research Organization (KEK) precede the Japan Proton Accelerator Research Complex (J-PARC) project. J-PARC consists of a 600 MeV proton linac, a 3 GeV synchrotron, a 50 GeV synchrotron and research facilities for basic science like particle physics and applied sciences. Within the project, Transmutation Experimental Facility (TEF) is planned to build in the second phase of the project. TEF aims at studying the physics and engineering feasibility of accelerator driven system (ADS) that is suitable for transmutation of long-lived radioactive wastes. TEF consist of two buildings; Transmutation Physics Experimental Facility (TEF-P) and ADS Target Test Facility (TEF-T). Because of the requirement of low-power operation of critical assembly in TEF-P, beam dump will be located at the end of the beam transport system for TEF-P. In the present plan, a 400MeV-30kW proton beam will be delivered to the beam dump.
It is well known that the proton-induced spallation reaction is an endoergic reaction and is convenient to obtain bright neutron source for basic science. It is also useful for Boron Neutron Capture Therapy (BNCT) which is conducted using fission reactors, and an accelerator driven BNCT neutron source will be realized because the spallation neutron has an energy spectrum similar to that of fission neutron. Hence, we are proposing a BNCT neutron source facility using the beam dump of TEF-P. The neutron spectrum provided by the spallation reaction will also be useful for various simulations such as neutron effects for soft and hard errors of micro-electronic devices.
In the presentation, outline and the current plan of J-PARC and TEF will be presented and installation plan of spallation target and beam ports specialized for BNCT will be discussed.

The INR Neutron Sources for Neutron Capture Therapy

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Physical project of neutron sources for the Neutron Capture Therapy is proposed. The spallation neutron source is based on a pulsed beam provided by the high-current Proton Linac of the Moscow Meson Facility of the INR RAS in Troitsk of the Moscow region. The INR Proton Linac is operating now with proton energy (160 – 209) MeV, pulse current above 10 mA, beam pulse repetition rate up to 100 Hz and pulse length till 200 μs. The spallation neutron source produces fast neutrons with average intensity up to 10^{15} n/s and average neutron energy about 0.5 MeV. The neutrons from the proton irradiation tungsten target is collimated and modified into thermal and epithermal neutron fluxes for neutron capture therapy.
Liquid-crystalline DNA-Gd nanoparticles, as a potential biomaterial for NCT were investigated on the thermal neutron beam. Secondary photons from irradiated biology sample containing nanoparticles were registered using both Xenon gamma spectrometer and BGO scintillation detector.
Another neutron source is based on a DT neutron generator. Neutron generation produces fast neutrons with intensity up to $5 \cdot 10^{12}$ n/s using deuteron beam with the average current up to 20 mA.
The converter, reflector and filters of tungsten, bismuth, lead, beryllium, aluminium, graphite and polyethylene were used for produce thermal and epithermal neutron fluxes. Biology samples containing cells and DNA-Gd nanoparticles were irradiated the thermal neutrons to investigate Ralative Biological Effectiveness and cell killing effect of secondary photon and electron radiation from liquid-crystalline DNA-Gd nanoparticles.

Perspectives for the Application of Plasma Focus Technology to Neutron Capture Therapy

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One of the major problems in the widespread diffusion of neutron capture therapy installations, both for research and treatment purposes, is the lack of safe neutron sources. By safe it is meant a source that satisfies at leats three requirements: 1) doesn't rely upon even small quantities of fertile/fissile materials; 2) doesn't rely upon the strong emissions of radioisotopes; 3) can be switched off and turned on at will. In 2002 we presented a preliminary design for a thermal neutron source based on the Plasma Focus technology for TAORMINA-like treatment protocols. The Plasma Focus (PF) technology in fact satisfies all the three requirements mentioned above. PF machines can produce fast neutrons by triggering D-D or D-T nuclear fusion reactions in a repetitively generated pulsed plasma discharge. Deuterium and Tritium are used at fairly low values of pressure (a few hundred Pa), so that only small amounts of these gases are required.
The typical neutron yield per discharge is proportional to the square of the input energy E which is stored in a high voltage capacitor bank. For D-D reactions and for E = 50 kJ, the neutron yield results to be about $2.5 \cdot 10^{10}$ n/discharge, while for D-T reactions at the same input energy the yield is about $2.5 \cdot 10^{12}$ n/discharge. For these values of E it is possible to build PF machines capable of 1 Hz discharge repetition rates with a continuous workload up to total neutron yields for a D-T plasma of about $3 \cdot 10^{14}$ n in 2 minutes. In the present paper we present a different PF design which can accommodate two special types of irradiators, one that can be used to provide thermal neutrons for TAORMINA-like treatments, and another that can provide epithermal neutrons for standard protocols. The PF end-user can shift between these two at will depending on the day-by-day needs. Evaluations of the performances of the two irradiators will be presented by Montecarlo (MCNP code) simulation of the neutron transport processes.

First neutron generation in the BINP accelerator based neutron source

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Pilot innovative facility for neutron capture therapy was built at Budker Institute of Nuclear Physics, Novosibirsk. This facility is based on a compact vacuum insulation tandem accelerator which is designed to produce proton current up to 10 mA. Epithermal neutrons are proposed to be generated by 1,915 MeV protons bombarding a lithium target using $^{7}Li(p,n)^{7}Be$ threshold reaction. The results of the first experiments on neutron generation are reported and discussed.

NUCLEAR ENGINEERING

Reactor based BNCT facilities: current status and future prospects

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Until now few nuclear research reactor-based neutron beams have been available to treat patients with neutron capture therapy (NCT), however an increasing effort exists to develop accelerator-based neutron sources for NCT essential for a wide use of NCT at specialized radiation therapy centers around the world. Today, dependent on reactor facility-based BNCT, the clinical trials studies are planned to test the efficacy and safety of NCT in a wider spectrum of malignancies. Extensive clinical trials in BNCT are currently conducted only at two facilities, the JRR-4 in Japan and the FiR 1 in Finland. For multicenter trials and in case of a rapid extension of BNCT more neutron facilities should be opened for clinical trials. In several cases nuclear reactors may also be a competitive neutron source for new BNCT facilities.
A nuclear reactor offers an intense and reliable source of neutrons for BNCT. Modernization and refurbishment of an existing reactor or construction of a new research reactor might open possibilities for a new BNCT facility. Other possible advantages are a reasonable additional cost of the reactor operation to be covered by the BNCT activity and availability of skilled personnel to develop and operate a BNCT beam facility. The major prerequisite is interaction with a research hospital with radiation therapy units.
In this work the current status and future prospects of the existing and planned reactor-based BNCT facilities are evaluated. Past, current and future activities at the existing and planned BNCT facilities are reviewed. Emphasis is put on the analysis of the research and development environment and business plans for BNCT. Location of the reactor, its availability for BNCT and appropriate treatment environment are of importance. The capabilities of the facilities, like beam properties and patient positioning, are analysed from the viewpoint of application of BNCT to various tumour sites.
This work is done in collaboration with and to support the Technical Working Group on Research Reactors (TWGRR) at the IAEA.

Preliminary modeling of BNCT beam tube on IRT in Sofia

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Technical Design of the research reactor IRT in Sofia is being in process of elaboration. It includes an arrangement for BNCT facility for tumour treatment.
Modelling of geometry and material composition of filter/collimator for the BNCT beam tube on IRT has been carried out following the beam tube configuration of the Massachusetts Institute of Technology Reactor and taking into account an ability to include the tube in to IRT reactor geometry. Transport neutron and gamma calculations performed for the model have shown that the facility will be able to supply epithermal neutron flux about 5.10^9 n/cm^{2}s, with acceptable quality, which is close to the best value reached in the world until now.
For the BNCT beam tube collimator an analysis of its shape optimizing in accordance with the results obtained for TAPIRO research reactor in Italy have been performed.

Program for reconstruction of experimental equipment of tangential horizontal experimental channel (HEC) No7 of IR-8 reactor at RRC "Kurchatov institute" for medical, biological and physical research using capillary neutron optical systems (CNOS)

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For the tailoring of neutron and photon beam spectra a thin hydrogen-containing scatterer that we developed earlier and set of filters that slow down and absorb fast neutrons will be used. The scatterer will be situated inside the channel on the axis of reactor core. Such neutron source produces beams with the most advantageous spectrum for NCT, CNOS and medical and biological in vivo studies.
We plan the construction of medical block for NCT with thermal and epithermal in the physical hall of the reactor. The traditional collimators will be used for tailoring of broad beams and for in vasion NCT the cone-shaped focusing CNOS will be used to achieve high neutron flux density. The distance from the axis of the reactor core to the channel end is 2.5m. Thermal neutrons flux density at the end of the channel after the biological shielding will be 3·109 1/cm^{2}s, and for epithermal – 109 1/cm^{2}s given the reactor power of 8 MW. The ratio of thermal neutrons flux to the 2.2 MeV neutrons flux is equal to 80. Kerma of fast neutrons is equal to 8·10-13 Gy·cm^2.
The second end of the HEC No7 is planned to be equipped with various CNOS for tailoring of focused, qausiparallel, and extra clean thermal neutrons beam along with the set of collimators for tailoring of beams with various intensities and spectral composition. The distance from the axis of the reactor core to this end of HEC is 6.5m.
Using these neutron beams and other equipment various experiments will be conducted: a wide range of medical and biological in vivo studies including NCT, fundamental and applied studies for solid state and nuclear physics, neutron radiography. HEC No7 experimental equipment is designed for broad range of specialists in various spheres of science and technology.

Modification of the thermal column of the TRIGA Mainz for the treatment of liver metastasis

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In 2001 the BNCT method was successfully applied for the extracorporeal treatment of liver metastases at the University of Pavia. Due to this promising result the BNCT project shall be established at the University of Mainz in a close collaboration with the University of Pavia.
The requirements for the therapy in Mainz are ideal: Like the TRIGA reactors in Finland (Espoo) and Italy (Pavia), the TRIGA Mainz is well suited for BNCT. Its irradiation facility is easily accessible, there is sufficient flexibility concerning irradiation times and it is located close to Mainz Medical University Hospital.
The TRIGA Mainz can be operated in the steady state mode with a maximum power of 100 kW_{th} and in the pulse mode with a peak of 250 MW_{th} for a period of less than 100 ms. It has four beam tubes and a thermal column which shall be reconstructed for the treatment of an explanted organ. Therefore, medical and technical requirements as well as the legal regulations must be considered.
In order to determine the optimal parameter for the planned therapy and for the design of the thermal column calculations were done using the MCNP-code as well as the transport code ATTILA. On the basis of the calculations, the reconstruction of the thermal column will be carried out.

The irradiation facility must provide a homogenous thermal neutron field over the organ and a negligible gamma field at the irradiation position. To guarantee constant irradiation conditions in the thermal column during the treatment, online monitoring of the gamma and neutron component is desirable. The irradiation, handling and transport time for the explanted liver should be as short as possible. To maintain the organ in adequate extracorporeal conditions during the irradiation time, a special confinement which allows the placement of the organ in the thermal column and ensures storage of about 4 °C during the irradiation must be designed.
Two possible configurations are being discussed for the irradiation of the liver. An overview of the concept for of the reconstruction of the thermal column will be given as well as an schedule of the whole procedure.

Prompt Gamma Activation Analysis of ^{10}B and Gd in Biological Samples at the MEPhI Reactor

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The neutron radiation analysis facility with use of monochromatic neutrons implemented at the IRT MEPhI Reactor was upgraded in order to improve the analytical parameters of ^{10}B determination.
The neutron flux at the sample position is 2.7×10^6 n/cm^{2}s. Methods have been developed for quantitative measurement of ^{10}B and Gd in pharmacokinetic studies. The facility is capable of measuring 1 to 3 μg of ^{10}B in biological samples with an error of not more than 10%. The detection limit of the facility is 0.3 μg of ^{10}B.

Conceptual design of a liquid metal small fast reactor for BNCT

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The fourth generation reactor with high economical efficiency, high safety, high amount minimization of wastes, and nuclear proliferation resistance has been studied throughout the world. Five concepts of a supercritical-pressure light water cooled reactor, a lead alloy-cooled fast reactor, a very high temperature reactor, a high temperature gas cool reactor, and a molten salt reactor are presented. These innovative atomic power systems are superior to the physical performance of the present light water reactor system. Development of these reactor system aims at attaining social targets, such as a contribution to the economic society by reservation of energy security, maintenance of the technical base by activation of the atomic power industry, and creation of new industry, and much more improvement in social receptiveness. In order to reduce the investment risk of a building program and electricity demand with uncertainty, development of a small modular type reactor has been considered from view points of technical program as well as social and institutional maintenance. A small modular type reactor is generally less 350 MWe, and is called for corresponding to multi-purpose use such as high-temperature heat supply, hydrogen manufacture and neutron use as well as the power generation.
In this paper, the conceptual design of the lead-alloy cooled fast reactor ENHS+ was studied for consideration of both a high burn-up reactor using spent fuels of PWR and medical use by BNCT in reference to the ENHS(The encapsulated Nuclear Heat Source) which is currently examined at U.S. Department of Energy. The results are as follows:

1) The optimal fuel composition (93%U(1.5%EU)+7%Pu) was determined by use of general PWR spent fuels, and the reactor core design was done with nuclear calculation code (SRAC2003 and SLAROM/CITATION-FBR), and KCODE in MCNP for an ENHS+ reactor core. An effective multiplication factor (burn-up=0) was 1.026, and the critical state could be resulted in maintaining for 30 years or more.

2) Another design study of epithermal neutron beam for BNCT installed at ENHS+ reactor was carried out using Monte Carlo transport code MCNP. An AlF3 /PbF2 was used as a neutron filter /moderator. The beam hole was surrounded by Li-poly. To absorb extra neutrons outside the reactor shield. The void layer inside the beam hole was prepared to avoid attenuation of the beam intensity as well as improvement of beam directionality. The irradiation position was at distance of 248 cm from the core. An epithermal neutron beam with an intensity of $1x10^{10}$, and fast neutron dose and gamma-ray dose per an epithermal neutron of $2x10^{-15}$ and $4x10^{-15}$ $Gycm^2n^{-1}$, respectively , could be produced at irradiation port for the power of 25MWt .

These results would suggest the conceptual design of next generation reactor with multipurpose use.

New irradiation facility for biological samples at the RA-3 reactor thermal column

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A new irradiation facility was developed in the RA-3 reactor in order to perform trials for the treatment of liver metastases using BNCT.

RA-3 is a production reactor that operates continuously 5 days a week and it had a thermal column with an access tunnel of small cross section, not accessible during operation.

The objective of the work was to perform the necessary modifications to obtain a facility to irradiate a portion of the human left liver lobe, in a highly thermalized neutron spectrum, with a thermal flux around 10^{10} n cm^{-2} s^{-1}, as isotropic and homogeneous as possible, with the possibility of introducing on line instrumentation and without interfering with the regular production.

Main modifications consisted in obtaining an access tunnel inside the thermal column with the suitable dimensions, reducing gamma dose rate in the irradiation position and constructing properly shielded entrance gates enabled through a logical control for the safe operation (introduction and withdraw of samples) with the reactor at full power.

Conventional activation foils techniques and a neutron shielded graphite ionization chamber were used for the preliminary characterization of the irradiation site in air.

The facility was constructed and resulted very practical and easy to use. The operation was authorized by radioprotection personnel after checking that the levels of radiation had no significant changes compared to the registered before the modification.

A highly thermalized and homogenous irradiation site was obtained. Measures in the empty cavity showed a thermal flux near 10^{10} n cm^{-2} s^{-1}, a cadmium ratio of 4100 for gold foils and a gamma dose rate of around 5 Gy/h.

Neutron Field Characterization for Accelerator Based BNCT with Low Energy Neutron Spectrometer Based on Position Sensitive ^{3}He Counter

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At present development of new neutron sources based on a particle accelerator is underway would wide for boron neutron capture therapy (BNCT). Though nuclear reactors were used for a long time as the neutron source, accelerator based neutron sources have recently been advantageous taking into account its easy-to-use and acceptable performance. However, when using an accelerator, various secondly particles would be emitted simultaneously and act as a troublesome background, and initially produced neutrons have a high energy and thus should be moderated largely.

Moreover, in these circumstances, patients should be positioned close to the neutron source to keep a strong neutron flux intensity so that the BNCT will be completed within about 1 hour. This indicates that inside a relatively narrow space neutrons should be moderated, simultaneously shielding unnecessary secondary particles. Since this is not an easy job, it is known that it becomes quite hard to make an acceptable background-free neutron field for BNCT. It consequently means, characterization of such neutron fields will have to be a critical issue to confirm the availability of the neutron sources for BNCT. In the present study, a low energy neutron spectrometer has been thus designed and developed to figure out the accelerator based neutron source performance.
As well known, a technique to measure neutron spectrum over 10 keV is already established, e.g., with a scintillation detector. However, below 10 keV there was no straightforward way. In the present study, an easy-to-use low energy neutron spectrometer is aimed at so as to cover quite a wide dynamic range of 6 decades from thermal to epi-thermal region. This wide dynamic range is a crucial requirement especially for BNCT.
The presently proposed spectrometer is based on a ^{3}He proportional counter, which is 50 cm long by 5 cm in diameter with a gas pressure of 0.3 MPa. It is quite unique that the spectrometer is set up in parallel with the incident neutron beam and a reaction depth distribution is measured by it as a position sensitive detector. Recently, a prototype detector has been developed and the signal test is now underway. The present paper summarizes how and why the present spectrometer would play a critical role in BNCT, together with the feasibility and design study result, and the fabrication process details.

Building of Scientific Information System for supporting BNCT Development in Bulgaria

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An arragement of Boron Neutron Capture Therapy (BNCT) facility is foreseen within the reconstruction of the research reactor IRT of the Institute for Nuclear Research and Nuclear Energy of the Bulgaria Academy of Sciences (INRNE). The application of the BNCT has more than 30 years history. BNCT has been carried out in the Netherlands, Germany, Finland, Italy, the Czech Republic, Russia, Japan, USA and Argentina. A big amount of knowledge is collected during this period. A lot of new information on BNCT is periodically published in the scientific journals. To collect and sort this knowledge a centralized scientific information system for supporting the development of BNCT on IRT is being built. The work is done under contract with the Ministry of Science and education of Republic of Bulgaria. The system consists of server, two workstations and four mobile computers.
The data on application of BNCT available until now is collected and put into the information database. The system is also providing access to seven international journals publishing on BNCT and its applications for tumor and other diseases treatment. The web server interface will make possible the access of the researchers from Bulgarian organizations, jointly working in BNCT, to the national requirements, norms, legislation, regulations, ethical rules and/or codes of conduct the BNCT in the country. The sorted data will help the students and the young specialists, just starting in the field of BNCT to quickly enter into this interdisciplinary area. The system will help building and developing of network between Balkan countries. The systems' power and flexibility allows further improvement, by integrating a centralized formal information system that will manage the process of establishment of BNCT on IRT. It will play a very important role for elaboration and application of BNCT facility in Bulgaria. The information system will help more intensive developing of the national network between the INRNE, the Medical University in Sofia, the National Centre of Radiobiology and Radiation Protection, the Institute of Experimental Pathology and Parasitology and Institute of Electronics of the Bulgarian Academy of Sciences, and the Faculty of Physics of Sofia University, as well as its enhancing with interested institute from Balkan countries. Human, social and economical results due to the BNCT for many patients from Balkan region are expected.

Performance of a New Composite Single-Crystal Filtered Thermal Neutron Beam for Neutron Capture Therapy Research at the University of Missouri

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The University of Missouri (MU) Institute for Nano and Molecular Medicine, the Idaho National Laboratory (INL) and the University of Missouri Research Reactor (MURR) have undertaken a new collaborative research initiative to further the development of improved boron delivery agents for BNCT. The first step of this effort has involved the design and construction of a new thermal neutron beam irradiation facility for cell and small-animal radiobological research at the MURR.
In this paper we present the beamline design with the results of pertinent neutronic design calculations. Results of neutronic performance measurements, initiated in February 2008, will also be available for inclusion in the final paper.

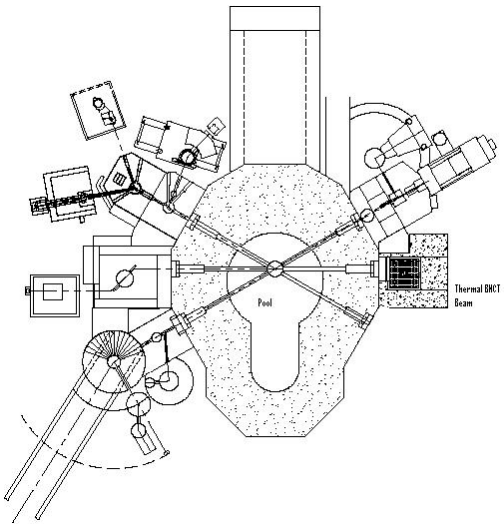

Fig. 1 - MURR core, shielding, and beamlines

The new beam will be located in an existing 152.4 mm (6') diameter MURR beam tube extending from the core to the right in Figure 1. The neutron beam that emanates from the berylium reflector around the reactor is filtered with single-crystal silicon and single-crystal bismuth segments to remove high energy, fission spectrum neutrons and reactor gamma ray contamination. The irradiation chamber is downstream of the bismuth filter section, and approximately 3.95 m from the central axis of the reactor. There is sufficient neutron flux available from the MURR at its rated power of 10 MW to avoid the need for cryogenic cooling of the crystals. The MURR operates on average 150 hours per week, 52 weeks a year. In order to take advantage of 7800 hours of operation time per year the small animal BNCT facility will incorparate a shutter constucuted of boral, lead, steel and polyethylene that will allow experimenters to access the irradiation chamber a few minutes after irradiation.
Independent deterministic and stochastic models of the coupled reactor core and beamline were developed using the DORT two-dimensional radiation transport code and the MCNP-5 Monte Carlo code, respectively. The BUGLE-80 47-neutron, 20-gamma group cross section library was employed for the DORT computations, in keeping with previous practice for analysis of a number of other NCT neutron facilities worldwide. The standard ENDF/B Version 6.8 cross section libraries were used with MCNP, except that special calculated cross section sets for the single-crystal bismuth and silicon filters in the MCNP calculations were provided to MU and INL specifically for this study by the Korean Atomic Energy Research Institute and, independently, by North Carolina State University. Cross sections for the amorphous bismuth and silicon files on the BUGLE-80 library used with DORT were modified to account for the single-crystal form of these materials using correction factors computed using MCNP.

A number of parameter studies were conducted, independently varying the thicknesses of the silicon and bismuth filter sections to find an optimum that maximizes the thermal neutron flux while maintaining the fast-neutron and gamma components of the beam within acceptable ranges. Both the DORT and MCNP beamline optimization computations led to the conclusion that the silicon filtering section should be approximately 55 cm in thickness and the bismuth section should be 8 cm in thickness. The total estimated thermal neutron flux delivered to the irradiation location by the filtered beam, integrated to 0.414 eV, is approximately 9.0 x 10^8 neutrons/cm^2-s. The calculations also yielded an epithermal and fast-neutron kerma of approximately 1.0 x 10^{-11} cGy-cm^2.
Construction of the beamline is currently underway and initial foil activation measurements to characterize the free-field neutron flux spectrum at the irradiation location were undertaken in February 2008. Measured results obtained so far indicate that the neutronic performance of the beam is within the expected range.

Specific Features of Implementation of a Clinical Base for Neutron Capture Therapy of Cancer at the IRT MEPhI Reactor

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An irradiation base has been implemented at the IRT MEPhI Research Reactor for research in the field of neutron capture therapy (NCT) of malignancies.
An irradiation room was built at the horizontal tangential channel HEC-4 with a thermal neutron beam, for preclinical NCT studies. Currently, on this facility, preclinical NCT studies are carried out in cell cultures, small laboratory animals, and dogs with spontaneous malignancies. Over 80 dogs have undergone the NCT procedure with use of ^{10}B-containing (boronphenylalanine) and Gd-containing (Dipentast) compounds.
However, this facility is inapplicable for clinical trials, as the restricted size of the irradiation room prevents location of a human patient; also, the spectrum of the channel contains no epithermal neutrons necessary for treating deep-seated tumors, primarily brain tumors. In order to solve these problems, it was proposed to build an irradiation unit for clinical NCT studies on the HEC-1 channel that extends through the thermal column.
For this purpose, the thermal column is being redesigned, i.e. dismantling major part of graphite and replacing it with the unit of combined aluminum-based shaper of the thermal / epithermal neutron spectrum. For this, the axis of the channel is shifted for 25 cm from its initial position in order to decrease the contribution of the direct radiation of the core. The existing shutter will be replaced with a shutter of a new rotary design; a special collimating device will be installed at the outlet of the beam. The proposed reconstruction design is based on computational studies under MCNP-4c2. The prospective beam is supposed to provide epithermal, and thermal neutrons, or their combination in required proportion with use of a ^{6}Li-containing filter. The calculations have shown feasibility of a beam of thermal and/or epithermal neutrons of more than 1.0x10^9 n/cm^2s with concomitant total dose of fast neutrons and photon radiation not more than $8 \cdot 10^{13}$ Gy per unit thermal or epithermal neutron flux. Basic results of the calculations have been confirmed in experimental studies.
This neutron beam will be the base of a clinical NCT irradiation facility for the treatment of both surface and deep-seated tumors. Currently, a detail design of the reconstruction has been developed; the rotary shutter with the collimator, and blocks of the combined epithermal neutron spectrum shaper have been manufactured.
After the reconstruction of the HEC-1 channel and construction of the irradiation room at the IRT MEPhI Reactor, the first Russian base for specialized experimental and clinical studies on NCT of malignant tumors will be created. Works on implementation of the medical NCT base are supposed to be completed by 2010.

Characterization of a Thermal Cavity in the PhoNeS photo-neutron converter for BNCT research

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Recently, a feasibility study demonstrates that it is possible to obtain interesting thermal and/or epi-thermal neutron fluxes (> 10^7 n cm^{-2} s^{-1}) by using a dedicated photo-neutron converter applied to the high energy (> 18 MV) e-linac head. In this work, neutrons produced by GDR reaction in the High Z core (lead) are moderated to lower energies in a closed treatment cavity, suitably shaped to obtain uniform neutron field and low gamma and fast neutron contaminations. The experimental results concerning the cavity characterization, obtained at Elekta SLIT 25MV accelerator, are presented.
Neutron spectrometry and dosimetry is carried out by passive and active detectors and gamma and fast neutron contamination is evaluated inside the cavity. All the experimental results are compared with MC simulations performed by MCNPX, MCNP-GN codes. Accurate measurements of neutron and gamma background, inside and outside the treatment room, have been performed, as well as the evaluation of the residual activation. The encouraging results show that this device could represent the first in-hospital neutron source for BNCT research and application, useful for exposure to thermal neutrons of cells and biological samples.

Redesign of the RA-6 reactor BNCT facility

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The pool type reactor RA-6, located in Bariloche, Argentina, is undertaking a power uprate to 2 MW and low enriched uranium core conversion in order to improve current applications and to develop new ones.
It´s BNCT facility has been widely used for experimental models development and human clinical trials during the last years.
Nowadays the hyperthermal BNCT beam is also under redesign, in order to make the most of the upcoming increasing in reactor power.
Using verified computational tools, an overall augment in beam's quality was sought, focusing in lowering the fast neutrons and gamma contaminations to the beam, and increasing the lower energy spectrum for therapeutic purposes.
The inclusion of a shutting system was also thoroughly analyzed in order to improve the beam availability.
This task was performed by using the transport code MCNP5 v1.40, beginning with the criticality calculation of the foreseen low enriched uranium core configuration, coupled with the filtering calculation and obtaining a final *by track surface source* at the outer border of the reactor pool tank. This source was used to evaluate the performance of several changes in geometry and composition, such as the inclusion of PTFE as final filtering stage, swapping of the gamma shielding and neutron moderator, geometry of the prolongation of the collimator (to fit irradiation specifications), etc.
An efficient triple-staged shutter design was attained, and its performance was fully characterized.
Nonetheless further modeling showed that a much more optimized design could be achieve if administrative restrictions to the facility operation were assumed in such a way that the shutting system could be avoided.
In the final design, maximum dose rates values in a model of the reference water-filled phantom were about 0.9 and 10 cGy/min for gamma and fast neutron, while the thermal flux was 1.9×10^9 n/cm²sec.
This comprises an in-phantom increase in the foreseen thermal dose of ~80%, whilst decreasing the fast neutron contamination 33%, and increasing the gamma dose rate in 10% compared with the current hyperthermal beam.

A simulation study for the radiation shielding of a treatment room for AB-BNCT

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The radiation shielding design of an Accelerator-Based BNCT treatment room has to accommodate two different concerns: radiation protection of the facility staff and personnel outside of the treatment room, and the radiation protection of the patient within, mainly avoiding undesirable contamination in the dose delivered to the patient due to inner wall scatter (specially the 2.2 MeV gamma background from the neutron capture in the hydrogen present in the concrete and the reflected neutrons).
This work presents an MCNP simulation study of the radiation dose outside the room walls as a function of its thickness (the neutrons were generated by the ^{7}Li(p,n)^{7}Be reaction at 2.5 MeV).
The results show good agreement with data presented in the literature (S. Costes et al., LBL Report 39450, 1996) (for 1% ^{10}B loaded walls).

Furthermore, we have evaluated the dose outside of the room walls for other ^{10}B concentrations and for ^{6}Li as a neutron absorber (which does not produce gamma contamination). From our calculations, walls of about 1 m thickness keep the dose rates below 25 μSv/hr.
In a second part, the dose around a phantom patient head was calculated with and without inner wall shielding. In this case the inner walls were covered with polyethylene loaded with 5% ^{6}LiF. Significant decreases in the thermal neutron and gamma dose were obtained for the shielded case which appears as a useful alternative to diminish the unwelcome dose on the patient.

Design study to further optimise the Birmingham orthogonal accelerator epithermal neutron beam

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A detailed study has been carried out on comparing various moderator and reflector materials in order to quantify any improvements that can be made to the current Birmingham facility.
The motivation for optimising and re-modelling the treatment facility was to maximize the dose to tumour tissue while keeping the weighted dose to healthy brain tissues below 12.5 Gy. Five key indices were calculated for three moderator materials (Fluental, MgF_2 and Teflon) and two reflector materials (Graphite and Lead):

1. Treatment Time
2. Therapeutic Ratio (TR) at 6.5cm into the brain
3. Max TR is the ratio of Maximum Tumour Dose to Maximum Tissue Dose
4. Advantage Depth (AD) and
5. Skin dose

Changing the graphite reflector to one made of lead (for 25 cm Fluental moderator) delivered a substantial improvement. It resulted in an increase in beam quality in terms of Therapeutic Ratio and AD. The AD increased from 9.1 to 9.8 ±0.1cm, the TR at 6.5 cm deep from 2.23 to 2.75 and the max TR from 5.34±0.05 to 5.40±0.05, with a 10 % reduction in treatment time from 198 minutes to 176 minutes.
In order to increase the dose rates obtained with the MgF_2 moderator / lead reflector, and thus reduce the treatment time, it becomes necessary to compromise beam quality. By moving to a shorter moderator depth of 18.1 cm treatment time was brought down from 258 minutes to 146 minutes. The change in other key indices being AD from 9.1±0.1 to >10cm, the TR from 2.23 to 2.76 and the max TR from 5.34 ±0.05 to 5.26 ±0.03 when compared to the current facility.
Further calculations will be presented to show that the addition of a Li-Si filter does not affect our choice of the optimum length of moderator and reflector, and to quantify the effect of an additonal patient collimator on beam performance indices.

BNCT of explanted livers using a suitably shaped neutron spectrum and irradiation box

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A combination of a suitably shaped irradiation box and neutron energy spectrum to treat explanted livers is here presented. Thermal neutrons have a very low penetration capability inside the human tissue thus, in order to get an as much as possible uniform distribution of thermal neutron flux inside the irradiated organ, a mix thermal/epithermal neutron beam has been found more appropriate. Moreover, to flat the neutron distribution it turned out to be useful also adopting an irradiation box with concave lateral walls. Computational results obtained taking as reference the research beam that was available at the Studsvik BNCT facility (Sweden) are here reported.
The thermal neutron flux inside the irradiation box along the beam axis is distributed within -5%/+7% of its average value. The total dose to the healthy tissue is distributed within -3%/+5%.

Limiting the maximum health tissue dose to 10 Gy-eq, at a reactor power of 150 kW the irradiation time is equal to 11 minutes while the total tumor dose ranges between 43.5 and 50.0 Gy-eq.

Construction Design of a PGNAA Facility for Boron Concentration Measurement in THOR

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For BNCT animal or clinic trials the information of boron concentration in blood is a prerequisite. In order to accurately measure the boron concentrations in blood as a function of time after boron compound infusion a PGNAA facility was designed and is being under construction in the E-2 beam port nearby the BNCT epithermal neutron beam of the Tsing Hua Open-pool Reactor (THOR). The E-2 beam tube extending from the core edge passing through water pool and concrete shield and having a length of about 4 meters consists of two sections: a 8"-diameter front section with part in water region and part in concrete region followed by a 10"-diameter rear section.
The design objectives are both to pursue a thermal neutron fluence rate at the exit of the beam tube as high as it is possible with a level at least higher than 1.0 x 10^7 $cm^{-2}s^{-1}$ and to reduce the fluence rates of fast neutrons and gamma rays to a level as low as possible. MCNP calculations with a geometry model consisting of a collimator embedded with bismuth and graphite filters were carried out.
It was found that the embedding of filters consisting of 20-cm bismuth and 30-cm graphite to attenuate gamma rays and moderate neutrons would dramatically reduce the thermal neutron fluence rate at the beam exit by about three orders of magnitude. The position of the filters along the beam tube had only mild effect within a factor of two on the exit beam intensity. In order to preserve the prior criterion of maximizing the thermal neutron fluence rate we were forced to sacrifice the objective of suppressing fast neutrons and gamma rays. Finally, taking into account the fabrication practice blank concrete collimator plugs with a length of ~1.6 meters and an aperture of 1 and 2 inches, respectively in diameter were adopted. The thermal neutron fluence rates at the beam exit were calculated to be ~3.82 x 10^7 and ~1.55 x 10^8 $cm^{-2}s^{-1}$ for 1″- and 2″-aperture plugs, respectively for an isotropic entrance total neutron fluence rate of 10^{12} $cm^{-2}s^{-1}$, of which ~ 70% are thermal neutons, when THOR operating at 1 MW. The designed thermal neutron fluence rates will be verified by measurements in the near future.

Development of a miniature neutron beam monitor for boron neutron capture therapy

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Clinical studies of boron neutron capture therapy (BNCT) are being performed using JRR-4 in Japan Atomic Energy Agency (JAEA). To measure thermal neutron fluxes given to a patient, we are developing a SOF (Scintillator with Optical Fiber) detector as a miniature thermal neutron monitor. The SOF detector consists of a small amount of plastic scintillator which was painted by Li-6 fluoride, a plastic optical fiber, a photo-multiplier tube and a discriminator. A photon signal generated from the scintillator are relayed though the optical fiber onto Photon Counting Unit. The SOF detector has a feature that the detector can be set up on a patient directly due to compact and flexible.
To verify applicability of the SOF detector for the BNCT, several characteristic measurements were performed at JRR-4. The results demonstrated that the SOF detector could measure in real-time the thermal neutron flux at inside collimator and on a patient. Furthermore, we confirmed that the SOF detector located on the patient could monitor movement of the patient during irradiation. However, the verification also proved that the SOF detector had deterioration character when the SOF detector was applied in higher neutron field for long time.

To determine absolute value of the neutron intensity in the higher neutron intensity field, the measurement value of the SOF detector should be corrected by other techniques.
As the results, we have invented a new hybrid neutron beam monitoring system combined the SOF detector and SPND (Self Powered Neutron Detector). The SPND has an advantage for strong anti-deterioration against the higher neutron intensity, though the time response is slower than the SOF detector. The SPND has practical accomplishment as application for neutron monitoring in reactor core. And the SPND can be manufactured to compact like the SOF detector. By combining the SOF detector and the SPND, the deterioration character of the SOF detector is corrected by the SPND and the fast time-response as the advantage of the SOF detector complements shortcoming of the SPND. Development of the hybrid neutron monitoring system enables us to measure the thermal neutron flux given to a patient in real-time, even in high neutron intensity.
A prototype of the hybrid neutron monitoring system has been constructed and then several experiments will be being performed to verify the system's performance. Early results of the verification proved that the system has sufficient performance for the BNCT in practical use.

Study of irradiation port position for accelerator beam shaping assembly operated $^{7}Li(p,n)^{7}Be$ neutron producing target

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Two possible position of irradiation port – on beam axis and under 90 degree to proton beam axis for accelerator based beam shaping assembly is discuss. Results of calculated absorbed dose distribution from the point of view beam shaping assembly optimisation are presented. Possible optimum configuration of BSA is discuss. Results of neutron spectra measurement are presented for optimised beam shaping assembly with irradiation port located under 90 degree to proton beam axis. Discussed results of absorbed dose measurements at accelerator KG-2.5 with water phantom and beam shaping assembly with irradiation port under 90 degree to proton beam axis. Advantage of 90 degree irradiation port positioning is discussed.

Transport of high-intensity proton beams through a TESQ accelerator

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Within the framework of an ongoing project to develop a Tandem-ElectroStatic-Quadrupole (TESQ) accelerator for Accelerator-Based (AB)-BNCT at the Atomic Energy Commission of Argentina in Buenos Aires we discuss the transport of a high-intensity proton beam. The project goal is a machine capable of delivering 30-40 mA of 2.4 MeV protons to be used in conjunction with a neutron production target based on the $^{7}Li(p,n)^{7}Be$ reaction slightly beyond its resonance at 2.25 MeV and to be ultimately installed at a hospital site. This significant ion current is necessary given the values of the relevant nuclear cross sections. In these intense beams, constituted by charged particles of equal sign, there are significant repulsive space charge effects. Hence it is convenient to ressort to devices capable of providing strong and effective transverse focusing, independently of the accelerating fields. In this work we describe in some detail the calculations performed through the focusing and accelerating electrostatic quadrupoles and axially symmetric structures. We have integrated the envelope equations including the external transverse focusing and longitudinal accelerating fields, the repulsion due to space charge effects and the finite emitance of the beam. The accelerator geometry has been explored, preserving a modular design concept, in order to minimize the beam size and hence the possible beam losses along the machine. In particular a procedure has been developed to optimize the matching between the axially symmetric extractor-preaccelerator and the accelerator itself.

Increase the beam intensity for BNCT by changing the core configuration at THOR

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The Tsing Hua Open-pool Reactor (THOR) is TRIGA-conversion type with maximum reactor power of 2MW. Radioisotopes production and BNCT research are two major utilizations for this reactor. The radioisotopes are activated using the vertical tube in core while the BNCT facility is a horizontal neutron beam distance from the core center about 2 meters. In order to balance both utilizations for fixed reactor power at THOR, the fuel elements should be rearranged to increase the beam intensity for BNCT clinical purpose, and keep the radioisotopes production rate at the same time.
In this article, we will consider several core configurations and run the core calculation with MCNP to obtain the neutron distribution in core. Therefore, neutrons produced in core will be traced along the BNCT beam to obtain the neutron intensity at the beam exit. Comparing the neutron intensities both in core and at the BNCT beam exit for several core configurations, the preliminary results show that the BNCT beam intensity can be increased without decreasing the neutron intensity in core. Based on these simulation results, the fuel elements were rearranged during the annual repair period in 2007. The BNCT beam intensity was measured again, and the results showed that the BNCT beam intensity could be increased by 50%.

Converter and shields design for the BNCT facility at MARIA reactor in Poland

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BNCT facility in the Institute of Atomic Energy in Otwock-Świerk is now under construction at one of horizontal channels of the research reactor Maria. The concept of the facility involves the use of a fission converter at the end of the horizontal channel H2 of the reactor. The location of the converter changed comparing with the earlier presented concepts. It was decided that the external part the uranium converter will be placed inside the channel. The paper will show the present concept of the facility and evaluation of radioprotective shields. Radiation hazard in the therapeutic room is due to neutrons and gamma radiation from the uranium converter. The risk from neutrons can be easy reduced by using the shields matched to the converter/filter/moderator system. These parts are not sufficiently defined at this phase of project. The neutron radiation outside the channel will be eliminated by polyethylene moderator and thermal neutron absorber (boron carbide, cadmium plate) placed before the lead shield. Gamma radiation constitutes the main source of radiation risk in the therapeutic room. It is assumed that the basic part of converter shield will be the frontal lead wall which has to be partly dismountable in order to enable evacuating the parts of filter/moderator system and converter. As the converter will be placed inside the concrete shield of reactor, so this shield will serve also for the converter. Additional shields will be needed for movable transport container which has to be designed for the facility.
In order to determine the gamma source in the converter, the Monte Carlo ORIGEN code was used. The results showed that the frontal lead wall should be 30 cm thick. Its inner part should be covered with 20 mm thick layer of boron carbide. The transport container's wall should be 10 cm thick.

TREATMENT PLANNING

Comparison of different MC techniques to evaluate BNCT dose profiles in phantom exposed to various neutron fields

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The absorbed dose in BNCT (Boron Neutron Capture Therapy) consists of several separate radiation dose components (gamma dose, fast neutron dose, thermal neutron dose and boron dose), with different physical properties and biological effectiveness. In order to assess the clinical efficacy of the beams used for the therapy, determining the dose profiles both in healthy and tumour tissue, Monte Carlo techniques are used. This paper presents a comparison between dose profiles calculated along the beam axis inside different phantoms with two MC techniques: Monte Carlo radiation transport code MCNP and BNCT treatment planning program SERA - Simulation Environment for Radiotherapy Application.
In this study MCNP is used as a reference tool. A preliminary test of SERA is performed using mono-energetic and mono-directional neutron beams (size 10x10 cm^2) directed onto a simple water phantom. Then, BNCT treatments planning with epithermal and thermal neutron beams on tissue equivalent phantoms (such as head, liver, lung) are simulated with both MC codes and dose profiles are calculated.

Neutron Beam Source Definition Techniques for NCT Treatment Planning

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Constructing an accurate description of a neutron beam is critical to achieving accurate calculations of dose in NCT treatment planning. Because it requires producing an adequately accurate representation of the 5-dimensional probability distribution describing the spatial, energy, and angular characteristics of a neutron beam, source definition is perhaps the most difficult aspect of treatment planning. This paper compares two different methods of neutron beam source definition. The first method, the "surface source" method, involves conducting a detailed simulation of the neutron beam line and recording the characteristics of all particle histories exiting the beam line to a phase space file. The particle tracks from the resulting phase space file are sampled in subsequent simulations of transport through the patient geometry for treatment planning. The primary benefit of this method is that it introduces no significant approximations into the source description, which should lead to improved dose accuracy. Drawbacks of this method include the extremely large (GB) size of the unportable binary files, lower computational efficiency, increased start-up times for parallel computations, and limitations on the number of particles that can be run, which also limits dose precision. The second method, representing the beam characteristics as a set of probability distributions (using the MCNP general source definition card, SDEF) does not suffer from these shortcomings, but may involve significant approximations and loss of information that reduce the accuracy of computed doses. The fact that the probability distributions for the source characteristics (energy spectrum, spatial distribution, angular distribution) may be inseparable is problematic to this method.
Simulations in this study were performed using the MCNP Monte Carlo radiation transport code. The MIT Fission Converter beam, which has a well-validated MCNP model, was used as the test case.
To construct the probability distributions for the SDEF source, particle track information was read from the surface source file and scored into a 4D array of radial, energy, polar angle, and azimuthal (defined

relative to the radial vector) angle bins. This information was analyzed to construct probability distributions for the source variables in different regions of the radius-energy phase space. Each source type (surface source file and SDEF) was used to simulate transport of the beam through a voxel model of an ellipsoidal head phantom where doses were calculated, as in a treatment planning simulation. The initial calculations with the SDEF produced significant, 13-14% errors in dose relative to calculations with the surface source file. Using a patched version of MCNP that could represent the radial dependence of the azimuthal angle that we observed, the error in the thermal neutron and boron doses at D_{max} was reduced to 1.9%. Differences in other dose components were not statistically significant. Further improvements in accuracy may be possible at the cost of further increases in source complexity.

Comparative study of dose calculations with SERA and JCDS treatment planning systems

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Background: Three treatment planning systems developed for clinical BNCT use are SERA developed by INL/Montana State University group, NCTPlan developed by the Harvard-MIT and the CNEA group and JCDS developed by JAEA in Japan. In order to compare clinical outcomes between the BNCT groups, it is important to compare the dose calculations with the different treatment planning codes. Previously, performance of the SERA and NCTPlan has been compared in various studies.
Methods: In this study, the dose calculations performed with SERA and JCDS systems were compared in single brain cancer patient case at the FiR 1 epithermal neutron beam. A two-field brain cancer treatment plan was performed with the both codes. The dose components to normal brain, tumor and planning target volume (PTV) were calculated and compared in case of each radiation field and combined fields. Isodose contours and the maximum, minimum and average doses in regions of interest were compared.
Results and conclusions: Calculations with the treatment planning systems for the thermal neutron induced (B-10 and nitrogen) dose components and photon dose were in good agreement. Higher discrepancy in the fast neutron dose calculation was found. In case of combined two-field treatment plan, overall discrepancy of the total maximum weighted dose was ~3% for normal brain and PTV and ~4% for tumor.

Development of a multi-modal Monte-Carlo radiotherapy planning system

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A new multi-modal Monte-Carlo radiotherapy planning system (developing code: *JCDS-FX*) is under development at Japan Atomic Energy Agency (JAEA). This system builds on fundamental technologies of JCDS (JAEA Computational Dosimetry System). This system will be released for public use in the fairly near future.
JCDS, a Monte-Carlo treatment planning system for boron neutron capture therapy (BNCT), has many advantages based on practical accomplishments for clinical trials of BNCT performed in JAEA. The advantages and features have been taken over to JCDS-FX. In dosimetry work, JCDS has applied voxel calculation method to calculate complicated 3D-model effectively. JCDS-FX also employs voxel calculation techniques, but more detailed voxel model consists of 1x1x1mm voxel cell or pixel based voxel cell can be made.

By applying the minute voxel model, calculation accuracy at boundary region between air and tissues in particular can be improved. Therefore the function is effective in particular for the dosimetry for head-&-neck cancer involving complicated geometry.
One of the features of the JCDS-FX is that PHITS has been applied to particle transport calculation. PHITS is a multi-purpose particle Monte-Carlo transport code, application of PHITS enables us to evaluate doses for not only neutron and photon but also proton and heavy ions. Therefore, the JCDS-FX with PHITS can evaluate total doses of a patient by a combined modality therapy, for example a combination of BNCT and proton therapy. And in the study of BNCT with an accelerator, we can perform not only design of the BNCT facility involving proton accelerator but also detailed dosimetry including proton-neutron target source.
Furthermore, JCDS-FX can deal with PET's images to construct a patient's model in combination with CT and MRI images. By using PET images, tumor regions which may be invisible by CT or MRI are picked out properly, and then boron dose distribution can be also determined according to the PET value at each region.
To verify calculation accuracy of the JCDS-FX with PHITS, some dosimetry for an irradiation condition with a cylindrical water phantom and for an actual clinical study performed at JRR-4 were performed, and then the results were compared with calculation results obtained by JCDS-MCNP. Calculations for neutron and photon fluxes and several doses were in good agreement with the calculations of JCDS-MCNP. These results demonstrated that JCDS-FX was applicable to the treatment planning of BNCT in practical use.
Several features and performances of the new multi-modal Monte-Carlo radiotherapy planning system are presented.

MCDB Monte Carlo Dosimetry Code System and Its Applications

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MCDB (Monte Carlo Dosimetry in Brain) treatment planning system (TPS) is developed for BNCT. This system consists of a medical pre-processor, a dose computation and a post-processor. MCDB TPS automatically produces the input file from CT and MRI image data. In Monte Carlo dose calculation, a several accelerated measures, such as the fast track technique, mesh tally matrix and material matrix, are increased. The center point method is used to determine the density of the mixture material in boundary voxel. Furthermore, the combined multi-voxel models according to the depth in phantom are investigated. In this paper, we proposed a real patient model. A 3-D reconstruction and the input of MCDB and MCNP is automatically produced. The simulation is done by MCDB and MCNP, respectively. The same results as MCNP are achieved. However, MCDB is faster by factor of 3.4 in computational speed with respect to MCNP. In addition, MCDB can do the parallel computation if necessary. The test shows that the MCDB TPS confirms the suitability of BNCT clinical trials. It satisfies the clincal requirement for computational time (< 2 CPU hours and the error < 4%)
A 30 kW reactor has been built for BNCT in Beijing, China. MCDB is planning to be used in the programs. The tests will do no long time.

Validation of the Accuracy of BNCT Treatment Planning System THORplan

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THORplan is a treatment planning system developed at Tsing Hua University, Taiwan for BNCT purpose. It is recently developed with user-friendly interface using Interactive Data Language. While developing the homogeneous model of THORplan, analysis was carried out to provide a guideline of the proper way of doing material grouping.
In this article the accuracy of the THORplan is validated by comparing results of Snyder phantom calculation with the analytical results of MCNP. Neutron source from THOR epithermal neutron beam is used as the source for the calculation. Comparisons of results include neutron/gamma ray flux/dose in the transverse, coronal and sagittal directions. The difference of the thermal, epithermal, and fast neutron flux along the centerline of beam direction, the coronal-horizontal, and the sagittal-horizontal lines are found to be within 2%. The difference of doses agree within 3% except at cells located at the tissue interface. Due to the limitation of thickness of image slides, tissue assignment of voxels crossing interface may not exactly represent the original situation, which is the main cause of the dose difference.
The results of SERA and NCTplan are also included for comparison. Preliminary results show that SERA overestimates and NCTplan underestimates the thermal neutron flux by 3~5% in most locations. Larger errors are found near the surface. The probable causes of difference among these three treatment planning systems will be accessed.

Acceleration of Monte Carlo based treatment planning:
criteria when adjoint calculations are faster

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Up until now, treatment planning in Boron Neutron Capture Therapy is only performed using Monte Carlo-based techniques. The conventional radiotherapy community has become more interested in such techniques, as they are impressed by the accuracy that can be achieved with Monte Carlo calculations. However, a disadvantage of the method is still the long times needed to obtain results with reliable statistics. Although computer power becomes faster and cheaper over the years, it is still impossible to calculate a hundred or more different beam positions within a few days, which is the time a treatment planner in BNCT normally needs to produce an acceptable plan.
With more calculated beam positions, a better treatment plan can be composed which should maximise the dose in the tumours whilst sparing the organs at risk. In normal (forward) Monte Carlo calculations, the particles start at the beam opening and travel into the tissue where they may or may not hit a target, e.g. tumour, organ at risk. In adjoint Monte Carlo calculations, the particles start at the target and travel out of the tissue to where the information is recorded. This information can be translated as if the particle started at the place of recording. With this method, the same information is gathered as with forward Monte Carlo but instantly all around the irradiated tissue.
In a realistic head phantom with 10 organs at risk and 10 tumours, the adjoint techniques are 1.8 to 3.3 times faster than the forward MC calculations when 1020 different orientations of a gamma beam with a diameter larger than 5 cm are simulated.In the case of a neutron beam, the adjoint technique is faster by 6.6 to 20 times, than the forward MC. In general, in case of small diameter beams, adjoint MC calculations are only preferable for a large number of beams and a small number of regions of interest. For larger beam sizes, fewer beams and/or many regions of interest, the adjoint method is more favourable than the forward calculations.

Assessment of Dose Rate Scaling Factors Used in NCTPlan Treatment Planning Code for the BNCT Beam of THOR

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Tsing Hua Open-pool Reactor (THOR) at Tsing Hua University in Taiwan has been used to investigate the feasibility and to enhance the technology of boron neutron capture therapy (BNCT) for years. A rebuilt epithermal beam port for BNCT at THOR was finished in the summer of 2004, following-on researches and experiments were performed to hasten the first clinical treatment case of BNCT in Taiwan in the near future. NCTPlan, a Monte Carlo-based clinical treatment planning code, was used to calculate the dose rate distributions of BNCT in this work. A self-made Snyder head phantom with a servo-motor control system was irradiated in front of the THOR BNCT beam exit. The phantom was made from a 3 mm shell of quartz wool impregnated with acrylic casting resin mounted on an acrylic base, and was filled with water. Gold foils (bare and cadmium-covered) and paired ion chambers (one with graphite wall and filled with CO_2 gas, another with A-150 plastic tissue equivalent wall and filled with tissue equivalent gas) were placed inside the Snyder phantom to measure and estimate the depth dose distributions in the central axis of the beam. Dose distributions were contributed due to the dose components of thermal neutrons, fast neutrons, photons and emitted α particles from B-10 compounds in the irradiation of BNCT. Comparison and analysis between computed and measured results of depth dose distributions were made in this work. Dose rate scaling factors (DRSFs) were defined as normalization factors derived individually for each dose component in the BNCT in-phantom radiation field that provide the best agreement between measured and computed data. This paper reports the in-phantom calculated and experimental dosimetry and determined DRSFs for the BNCT beam of THOR.

BNCT treatment planning using THORplan

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The BNCT at Tsing Hua with the newly organized clinical team of Taipei Veterans General Hospital (TVGH) is aiming at clinical trials of GBM and "head and neck cancer" in two years from now. Improvements and validations of the treatment planning system THORplan developed at Tsing Hua University is one of the important tasks at present.
In this article THORplan developed at Tsing Hua University is used for the treatment planning of a GBM patient assuming to be irradiated by the THOR epithermal neutron beam. The neutron source for THORplan is the THOR epithermal neutron beam calibrated by measurements.
The results of flux distributions, depth-dose distributions, isodose contour and DVH for each tissue from the treatment planning system will be shown. The results of using SERA will be included for comparison. The details of the features of THORplan will be introduced.

BNCT: treatment plans and neutron dose evaluation using a Monte Carlo code

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Introduction: the purpose of this work is the analysis and optimization of the dose delivered to the patient during a BNCT treatment. The work has been carried out at the Kyoto University Reseach Reactor Institute (KURRI) at Osaka, Japan. In particular the aim was to analyze the dose-volume histograms (DVH) for brain, lung, liver and head-neck tumours and to compare some different beam geometries for each treatment plan. An evaluation of dose inside several phantoms has been also performed by using Monte Carlo simulations (MCNP code).
Methods and Materials: some treatment plans for brain, lung, liver and head-neck tumours have been developed with different beam geometries using SERA (Simulation Environment for Radiotheraphy Applications). For each tumour, a dose analysis has been executed and a comparison among the different geometries has been done.
Some Monte Carlo simulations have also been performed by using both an Am-Be neutron source and the neutron flux obtained from the Kyoto University Reactor.
Results: for brain tumours, the use of three beams delivers a dose of 2.1 Gy-Eq to tissue and a dose of 31.8 Gy-Eq to tumour, but there is a great lack of homogeneity.
For liver tumours, we have noticed that three beams (anterior A, posterior P and right side R), compared with two opposite beams (AP) and two orthogonal beams (AR), provide the greatest therapeutic gain factors for tumours in the right lobe and quite similar therapeutic gain factors for tumours in the left lobe.
For lung tumours, a treatment plan with six beams (compared with one using two or four beams), is the best compromise between a good cover of tumoral tissue and a protection of normal tissues with a mean of 35 Gy-Eq delivered to tumours and a mean of 5.5 Gy-Eq to the left lung, that is the healthy tissue that receives the biggest dose.
With regard to Monte Carlo simulations of dose distribution in phantoms, some curves that represent neutron dose inside different tissues have been created by considering different concentrations of the boron delivery agent (boronophenylalanine, BPA). We have found that the value of dose from neutron interaction with ^{10}B depends not only on ^{10}B concentration inside tissues (a bigger concentration produces a bigger dose), but also on the tissue density. In fact tissues with a density considerably different from that of water receive a lower dose. Another dose contribution is given by the presence in tissues of ^{14}N: however this dose contribution is lower compared with the previous one and it is influenced both by the tissue density and the percentage of nitrogen inside the tissue. Finally we have found that after a depth of about 4 cm, the delivered dose decreases very quickly and this is probably the biggest drawback of BNCT technique: it can't treat deep tumours.
Conclusions: BNCT can be used in several types of tumours and it seems to be very promising in the treatment of tumours near the surface of the body. It would be useful in case of particular tumours that are not treatable by using traditional radiotherapy.

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