Gadolinium dosimetry, a problematic issue in the neutron capture therapy. Comparison between experiments and computational simulations.

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Abstract. In GdNCT the interested isotope is $^{157}$Gd that captures neutrons with (n, $\gamma$) reaction and also emits internal conversion and Auger electrons. These electrons have an important effect on DNA strands, mainly due to the property of gadolinium to link to DNA. The emitted gamma rays partially interacts with tumours but mainly diffuse in the body damaging healthy tissues. Therefore in the study of Gd therapeutical effect both dosimetric and microdosimetric analyses must be performed. At Pisa University, in the last years some works were performed by NCT group. At the present these researches are continued on these topics carrying out also a PhD thesis. In this frame some simulations, using MC code, were performed in order to evaluate the dose distribution due to Gd reactions. It is however necessary to calibrate the calculations on experimental results, though they are scarce in GdNCT. Some experiments with $^{157}$Gd were performed by Milan group using gel dosimetry [1,2,3]. Therefore some computational comparisons were done. In these article the results of this comparisons are shown and discussed.

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1. Introduction

As predicted by Locher [4] also the use of gadolinium in vice of boron was proposed in NCT in more recent studies [6,7,8,9,10,11,12]. It derived mainly from the consideration of quite higher neutron capture cross sections of gadolinium (49700 barns in natural composition) vs. boron (3835 barns for B-10) that implies a huge dose delivery in proximity of the tumour region. Furthermore we can take advantage from the experience gained in use of Gd as contrast agent in MRI. It has been estimated that a tumour concentration of up to 1000 ppm $^{157}$Gd can be achieved with 0.5 mmol kg$^{-1}$ body weight of Gd-DTPA.

The research on the use of gadolinium as a neutron absorber in NCT, even if appears quite complex, seems to present some promising future applications [5]. Therefore this kind of research earns to be carried out. In this field, the aim of this work is to do a first attempt of comparison between experimental (gel dosimeter) and computational (MC simulations) results.

Gadolinium neutron capture reactions release prompt gamma rays, internal conversion electrons, X-rays and Auger electrons. The spectrum of the secondary particles emitted by gadolinium (mainly electrons) is manifold and, among others, the presence of strong spreads out the dose delivery to a broad region, limiting the selectivity of the therapy. The photons emitted in the (n, $\gamma$) reaction interact with the tissues and deposit energy over a longer path length than the boron reaction products. This is the main drawback of GdNCT. However if $^{157}$Gd uptake is isolated strictly to tumour, and the tumour is on the order of some cm$^3$, then an additional effect will supplement the attenuation of the capture photons: decreasing photon intensity will be encountered with increasing distance from the tumour site according to a $1/r^2$ relationship and tissue absorption.

Conversion and Auger electrons are also emitted after the Gd neutron capture, at hundreds of discrete energies. These electrons have energy-dependant ranges in water as short as 0.8 μm at 5 keV, with the range increasing with increasing electron energy. The most commonly emitted electron energies however have ranges that are many times the dimensions of a single cell (approximately 10 μm), but also electrons with very low energies are emitted, and these are characterized by a short range, bringing a very high contribution to the local dose delivery in GdNCT. The least energy necessary to produce “double strand breaks” (DSB) in DNA is about 20 eV. For 500 eV electrons the probability to have DSB is about 1 [13]. It has been demonstrated that “single strand breaks” (SSB) and DSB may be produced in DNA also by very low energetic electrons (about 5 eV) via a process called “electron attachment” [14]. If the Auger emitter atom is linked to the nucleus of a cell the electron RBE values are very high. Therefore the problem of the therapy efficacy is, above all, of chemical/pharmaceutical kind.

In order to verify the results, both microdosimetric (tumour dose) and “macrodosimetric” (healthy tissue dose) evaluations are necessary.

The last researches on GdNCT took in consideration:

- the study of direct DNA damage from Auger electrons emitted by “DNA seeking” Gd compound [5,20],
- the possibility to utilise Gd in addition to BNCT (Gd-BNCT) [15] specially to reach and kill also the quiescent (non-boron-uptaking) cells,
- further pharmaceutical researches of highly selective Gd carrier drugs, because the efficacy of present GdNCT agents (Gd-DTPA and Gd-DOTA) is low, due to the insufficient number of tumour cell nuclei incorporating Gd [16].

Particularly Japanese researchers are most active on GdNCT and experiments in vitro and in vivo on animals have been done and recently presented in ISCT-11 [17, 18, 19].
2. Experimental in-phantom dosimetry

Measurements of gamma dose and of thermal (<0.5 E\text{v}) neutron flux have been performed in tissue-equivalent phantom having different composition. The detectors utilised to this aim are:

1) Gel-dosimeters that allows imaging and profiling all dose components.
2) Thermoluminescence dosimeters (TLD), for measurements of gamma dose and thermal neutron fluence in some reference positions
3) Activation foils, for inter-comparison of thermal neutron fluence values

A gel dosimeter is a gel matrix in which a chemical dosimeter is incorporated. The here utilised dosimeters are FAX (Ferrous-Sulphate/Agarose/Xylenol) gel dosimeters in form of layer, and the spatial distribution of the absorbed dose is achieved by measuring visible-light optical transmittance through the irradiated gel layers, imaged with a portable instrumentation, suitably designed and set up in the laboratory\[1\]. NCT can take advantage of this dosimeter: in fact it is possible to design the gel matrix in order to obtain good tissue-equivalence for thermal neutrons and for all kinds of secondary radiation. Moreover, by properly changing the gel isotopic composition, it is possible to separate all the contributions to the absorbed dose, by means of a properly developed method and utilising suitable algorithms.\[27, 2\]. From the dose images obtained with this method, dose profiles can be quickly extracted and compared with Monte Carlo simulation results.

For in-phantom dosimetry measurements, a cylindrical volume made of gel has been set up, containing a region with accumulation of both \(^{10}\text{B}\) (35 ppm) and \(^{157}\text{Gd}\) (100 ppm) and an amount of both the isotopes lower for a factor 3.5 in all the gel around this volume\[3\]. The phantoms were in the form of cylinder, with 16 cm of diameter and 14 cm of height and the internal volume with higher accumulation of \(^{157}\text{Gd}\) and \(^{10}\text{B}\) was a coaxial cylinder of 6 cm if diameter. Phantoms have been exposed in the epithermal column of 5 kW TAPIRO fast reactor (ENEA, Casaccia) faced to the collimator and with the cylinder axis fitting the beam axis.

The measured dose contributions are the doses due to gamma-radiation, fast neutrons, charged particles and electrons. The electron dose has been obtained by means of suitable analysis of the responses of gel layers with and without gadolinium respectively.

Three phantoms have been prepared:

- **Phantom 1 (Ph1)** - Polyethylene shell filled with gel containing 10 ppm of \(^{10}\text{B}\) and 28,6 ppm of \(^{157}\text{Gd}\)
- **Phantom 2 (Ph2)** - Like Ph1 but with inserted a cylindrical volume (3 cm high, 7 cm in diameter) containing 35 ppm of \(^{10}\text{B}\) and 100 ppm of \(^{157}\text{Gd}\) in order to simulate a tumour
- **Phantom 3 (Ph3)** - Polyethylene shell filled with gel containing only 10 ppm of \(^{10}\text{B}\)

These phantoms were irradiated in the epithermal column of TAPIRO fast reactor at the ENEA Casaccia Centre Italy) (figure 1).
The TAPIRO reactor is a highly enriched (235U) fast neutron reactor with nominal power: of 5 kW (thermal). The neutron flux (at core centre) is $4 \times 10^{12}$ cm$^{-2}$ s$^{-1}$. Thermal or epithermal facilities can be introduced in the main column. An epithermal column has been designed and constructed for experimental research on BNCT. Phantom have been exposed in such an epithermal column, faced to collimator [28].

In fig. 2, a gel dosimeter after irradiation in a phantom exposed in the TAPIRO epithermal column is shown. The dosimeter is placed on a plane light source in order to detect, by means of a CCD camera, the image of visible light transmittance from which the absorbed dose image is finally obtained.

In fig. 3, the thermal neutron flux profiles obtained for the three different phantom types are shown. In fig. 5, the gamma dose profiles vs. depth along the axis of the three studied phantoms are also shown. The figure shows the dose rates in the central axis of phantom Ph2, containing 10 ppm of $^{10}$B and 28.6 ppm of $^{157}$Gd and with simulation of a tumour with 35 ppm of $^{10}$B and 100 ppm of $^{157}$Gd.

The total electron dose has resulted to be a very low percentage of the total dose in the examined configuration. Here, the region with accumulation of $^{157}$Gd is a cylinder (3 cm in height, 7 cm of diameter). If the same concentration of gadolinium would be accumulated in smaller volumes, then the total gamma dose would be lower and the relative electron dose higher.

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3. Monte Carlo flux and dose calculations

At DIMNP since long time a wide activity in Monte Carlo (MC) neutron and photon calculation is carried
out on fission and fusion reactors and on shielding. About ten years ago also BNCT (in order to evaluate the efficiency of TPS and accelerators driven neutron sources) was added to these activities [21]. In this frame we have developed an original TPS based on the use of PET slices able to individuate the position of $^{18}$F labelled $^{10}$B atoms [22]. We have also developed a new kind of accelerator driven neutron source based on D-T reaction designing the shaping assembly in order to reach an epithermal neutron spectrum at the end of the channel [23].

During this activity on computational analyses of NCT we have tested some world diffused MC programs, namely FLUKA [24], MCNPX [25], PENELOPE [26]. Each of this programs presents a lot of different performances that were carefully analysed, concluding that none of this program is able to fully meet our requirements, particularly for the low energy electron calculations.

Therefore we choose, as a first guess, MCNPX that optimize the capabilities and flexibility, combined with our experience. In fact, in this code it is possible to follow all nuclear particles behaviour taking into account all nuclear reactions, also using the models present in the code when tabular data are not available. However the generation of conversion and Auger electron source needs to be explicitly modelled in the neutron cross section library. When we use the MCNPX code with the MISC5XS1 library (which contains the $^{157}$Gd) the electrons associated with neutron capture are not in the cross section library, whilst the characteristic X-rays that accompany the conversion process are included in the emission spectrum. So it is correct to use MCNPX to evaluate neutron and photon (X and gamma) doses but it is difficult to evaluate the electron dose using this cross section library. Therefore our calculations will be considered only as “macrodosimetric” calculations. Also in this case it is necessary to calibrate the calculations on experimental results, though these are scarce in GdNCT bibliography.

Our work in future will be address to find and implement cross sections files with explicit modelling of IC and Auger secondary yield. At the present these researches are continued and also a PhD thesis is carrying out.

4. Comparison

In the field of NCT research a collaboration is in progress between Milan (University and INFN group) and Pisa (DIMNP). In this frame the results of physical measurements performed by researchers of Milan University at the TAPIRO reactor (ENEA, Casaccia) on phantoms containing B and Gd listed at the previous point 2.1) were used to compare our calculations with this experimental results in order to test their reliability also when Gd atoms are present.

Figures 3 and 4 show the comparison between experimental and calculated behaviour of thermal neutron flux (< 1 eV) and figures 5 and 6 show the comparison between experimental and calculated behaviour of gamma dose due to (n, ) reactions and experimental results.

The comparison between experimental data and MCNPX calculation also with the limiting statements previously expressed, seems to be satisfactory.

The trend of the lines is practically the same and the noticeable thermal flux depression in presence of gadolinium is confirmed. Also larger gamma flux in Gd containing phantoms is confirmed.
5. Conclusions
The task of this work was to compare experiments with computational simulation of materials containing gadolinium. In fact published experimental data are poor or non-existent and so the experiments done by University of Milan are very important.

The computational simulations performed at the University of Pisa meets the proposed task and are quite interesting. These preliminary comparisons gave good results and the work deserve to be continued.

The future work will be oriented in modifying the code energy limits and in preparing suitable electron sources and low energy cross sections tables.

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