MICRODOSIMETRY IN GdNCT

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Abstract

In this job we consider to couple NCT with gadolinium as treating agent. The importance of using Gd resides in the Auger electron produced. Auger electrons have a very short range and high energy deposited. Gd has the ability to cross nucleus membrane and build up in nucleus cells and in particular it binds to DNA molecule.We will evaluate interactions and reactions to a nanometer scale, that is DNA scale. The target result of these calculations will be to reach a rough estimation of the treatment length in manner to obtain a considerable damage to the cancer but at the same time to ensure the lowest possible dose to healthy tissue.

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Introduction

NCT is a fascinating kind of therapy if we consider to couple it with gadolinium as treating agent. Studies on this argument are very few and a complete dissertation is really complicated by the plenty and peculiarity of particles emitted by gadolinium.

Particles emitted by (n,γ) interaction

Among the many reactions Gadolinium undergoes by neutrons the one which is the most important for the therapy is $Gd^{157}(n,\gamma)Gd^{158*}$. This reaction generates γ-rays in a very broad range of energies. In 69% of cases these gamma particles generates an internal conversion electron, which create a vacation in an shell close to the nucleus. The nucleus is now in an excited state and it has to de-excite by two ways: emission of characteristic X-rays or generation of an Auger electron cascade. The second case is the one of our interest, in which the vacancy is successively filled by an outer shell electron, which by its own generates a new vacancy, giving a start to a cascade of Auger electrons.

Peculiarity of Auger electrons and Gadolinium and their application to the therapy

The importance of being an Auger electron resides on its very short range and the high energy deposited on such path, that is LET so the Auger electrons can be compared to high LET particles.

A particular gadolinium ability is to cross nucleus membrane and build up in nucleus cells and in particular it binds to DNA molecule. This characteristic, combined with emission of Auger electrons allows to kill cancerous cells breaking DNA molecule and prevents cancer proliferation.

A limitation in early experiments was given by the toxicity of Gd^{+3} ions, so that only a little concentration could be administered to a human being, but recent researches[1] have led to the development of a pharmaceutics compound, XCYTRIN™, which is absolutely non-toxic and has a concentration ratio between nucleus tumor cell and tissue tumor cell up to 15.

Furthermore gadolinium is widely used as contrast agent in MRI, so it could be possible to exploit MRI results for a on line screening in GdNCT therapy.

Micro-dosimetry analysis

All previously listed Gadolinium characteristics makes a very targeted analysis necessary. In particular it is essential to see interactions and reactions to a nanometer scale, that is DNA scale.

Unfortunately this scale is difficult to be handled, especially with non ad hoc Monte Carlo Codes. Even if the code allows to model the DNA geometry there are some difficulties on physics thresholds relative to very low Auger electron energies.

So, after an extensive bibliographic research, we decided to choose MCNP-4C for our simulations. The reason for this choice lies in the fact that all public Monte Carlo Codes are similar in geometry and physics limitations, but MCNP is a more tested and reliable code than others at the Department.

As we decided which Monte Carlo code was to be used, next steps consists of DNA geometry and composition schematization and Auger electron source modelation.

To represent a fragment of chromatin structure we made some simplifications which led us to model the structure you can see in Fig.1.

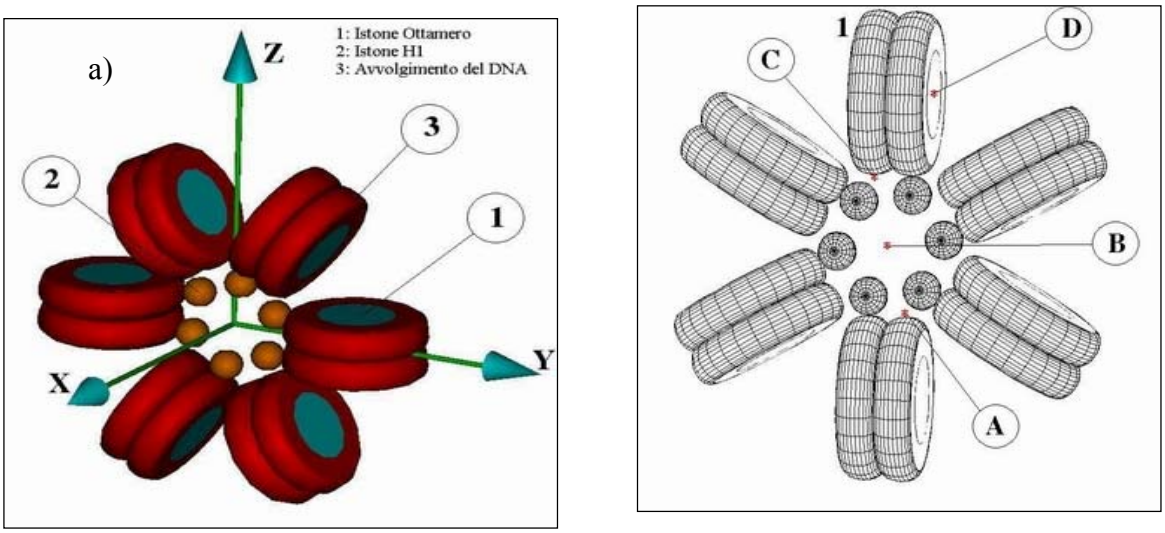

Fig.1.a. Micro-dosimetric model used with simulations. 3D representation of fragment of chromatin fiber model, with its basic components: octamer histone, H1 Histone and DNA wrap; b. Hypothised source positions.

It represents the basic module which composes DNA molecule. This task requested us a great deal of time for the difficulty we found treating nanometer scale. It systematically happened that MCNP-4C had particles leakage. That problem was due to simple precision implemented in the code and after some unfruitful tries we simplified geometry demonstrating the new geometry was in accordance with the more complicated one with a precision of 95%.

DNA composition was a less ungrateful task. For every histone was determined the sequence of protein by which it is composed. Then every chromatin fiber basic element was analyzed through a calculation software which starting from histone proteins allow to determine percentage chemical composition of every single material.

For a complete Auger electron source description we analyzed ^{158*}Gd Auger electron emission spectra showed in Fig.2.

As can be seen in the table some emissions lie under 1keV threshold, that is a physical limitation in MCNP for this kind of particles. So these emissions weren't take into consideration in our calculations. These might seem a rough approximation, but the values we obtained are certainly a sort of threshold limit, that is it will be necessary a less quantity of gadolinium to have therapeutic effects.

Reactions and energy ranges (eV)	Mean energy (eV)	Yield	Stopping range (μm)
Auger KLL	3,47*10^4	9,54*10^-3	2,31*10^1
Auger KLX	4,11*10^4	4,91*10^-3	3,11*10^1
Auger KXY	4,75*10^4	6*10^-4	4,01*10^1
CK LLX	5,33*10^2	4,94*10^-2	1,97*10^-2
Auger LMM	4,77*10^3	3,03*10^-1	6,99*10^-1
Auger LMX	5,92*10^3	1,08*10^-1	1,02*10^0
Auger LXY	7,11*10^3	9,46*10^-3	1,4*10^0
CK MMX	1,84*10^2	3,74*10^-1	4,95*10^-3
Auger MXY	9,12*10^2	9*10^-1	4,44*10^-2
CK NNX	1,12*10^2	2,42*10^0	2,89*10^-3
Auger NXY	1,22*10^2	2,27*10^-1	3,15*10^-3
CK OOX	1,69*10^1	3,9*10^-1	3,39*10^-4
Auger OXY	4,32*10^1	3,73*10^-3	1,04*10^-3

Fig.2.Energy range, mean energy, yield and stopping range of Auger electron generated by $^{157}Gd(n,\gamma)^{158}Gd$.

Results

Micro-dosimetric results

Some interesting results are carried out from the micro-dosimetric calculations[2], in which we would evaluate the energy deposition in the chromatin fiber by Auger electrons.

We have analyzed the energy deposition through the DNA wrap and through the histone octamer in different source positions, as shown in Fig.3 and Fig.4.

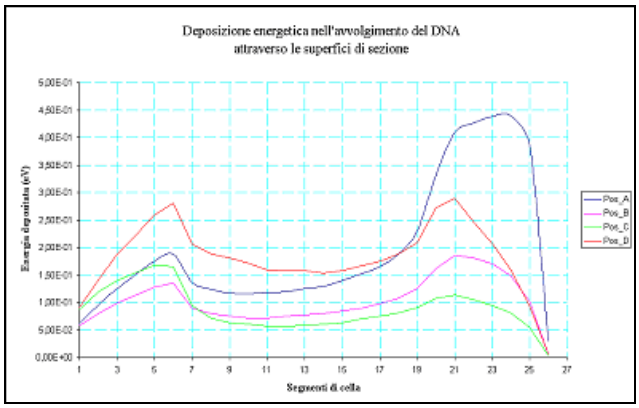

Fig.3. Energy deposition in DNA wrap through segmentation surfaces in four cases cosidered.

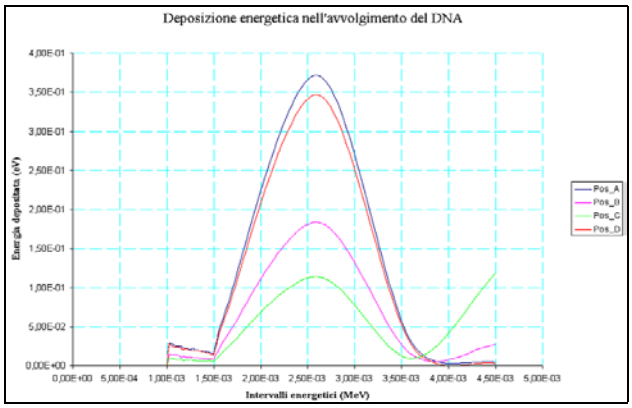

Fig.4. Energy deposition in histone octamer.

In Fig.3 can be observed the same trend for all four cases, more evidence in case of position A of Gd nucleus. We can notice that because of the isotropic source, if the Gd nucleus is in the middle of the histone octamer, position D, the trend is more symmetric than in the other cases.

In the Fig.4 we show the total energy deposition per source particle release, in which can be seen that the energy deposition is peaked around 2.6keV and for position A and D the total energy deposition is twice greater than case position B or C. We can also note that under 1keV there aren't results because of MCNP-4C threshold.

Relative to energy deposition in the histone octamer through the segmentation surfaces, Fig.5, we can observe the same trend for all four positions and, for position D, also a symmetric trend.

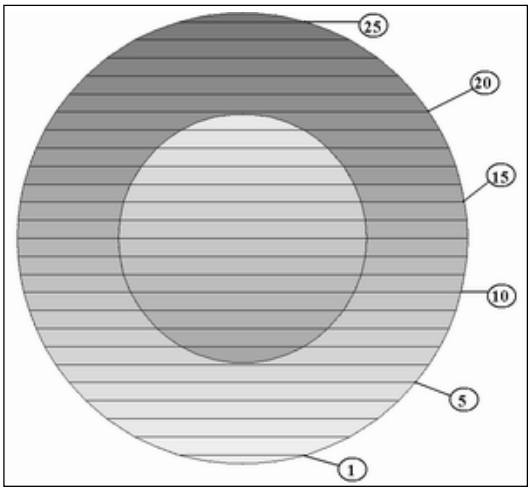

Fig.5 Segmentation used in calculations. External cylinder represent DNA wrap, internal cylinder represent histone octamer. The wrap is sectioned by 25 planes, while histone is sectioned by 13 planes.

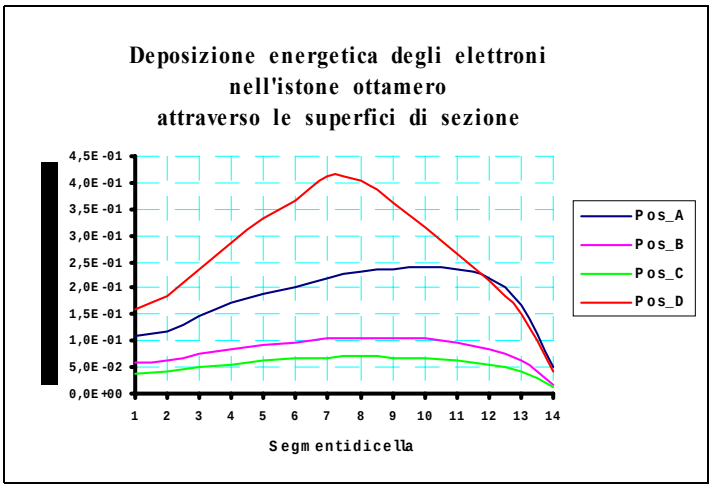

Fig.6 Energy deposition in the histone octamer through segmentation surfaces in four cases considered

Results combined with macro-dosimetric analysis

The target result of these calculations was to reach a rough estimation of the treatment length in manner to obtain a considerable damage to the cancer but at the same time to ensure the lowest possible dose to healthy tissue.

But before we needed to formulate some hypothesis, as first step we suppose a treatment length of about 10 minutes and an incident neutron flux, in the tumour cells of about 3.09E7 n/cm^{2}s. Those results were taken by our macro-dosimetric calculations.

From the micro-dosimetric results we know that, for every conversion electron, there is an energy deposition of about 25,6eV so that 100 (n,γ) reactions are necessary to have one cell death.

If we suppose a 2cm diameter tumour, there must be 2.39E10 reactions/cm^3.

The reaction rate was $T = \Phi_t N_a \sigma_t$ =2.39E10/600 = 4E7 reactions/cm^{3}s, and the number of Gd atoms resulted 5.08E18 nucleus/cm^3.

If we would obtain the Gd mass concentration in ppm, knowing Gd atom weight, 2.6062E-22g, we achieve 1263.6ppm of gadolinium concentration in tumor cells, that is a reasonable mass concentration for cancerous cells.

Conclusions

We can conclude that the use of Gd in NCT must be further investigated.

It can be developed a physic model in which MCNP libraries can be used under 1keV threshold; it can be keep track of Gd distribution between cytoplasm e nucleus; finally can be optimized a source channel able to reach the best neutron flux, such to optimize released dose between tumor and healthy tissue.

Acknowledgements

We want to thank sincerely Prof. Cerullo, Prof. Mazzini, Prof Curzio, Dr Daquino, Ing. Muzi to allow us to get our graduation thesis about NCT, and for their precious advices.

[1] www.pcyc.com

[2] A. MASTRULLO, S. PALMERINI, *Analisis of the use of Gd in NCT* -Graduation Thesis (2003)