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# Nuclear therapy: From the beginning to dosimetry to theranostics

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**Abstract**
The paper deals with nuclear therapy from its beginnings to its growth in the clinic. Briefly illustrates the therapeutic effect of radiation. Subsequently it deals with dosimetry and its importance in obtaining therapeutic effects. Finally, it addresses the issue of theranostics and its contribution to the affirmation of nuclear therapy.

**Keywords:** nuclear therapy, dosimetry, theranostics

## Introduction

The use of ionizing radiation for the treatment of neoplasms has been a well-established technique for years that goes by the name of radiotherapy [1, 2].

The main purpose of a radiotherapy treatment is to induce the death of all the tumor cells following the administration of a certain amount of radiation. However the damage to the cells by the ionizing radiation is a random process; there is therefore a non-zero probability that some cells survive radiation [3].

The quantity of main interest in radiotherapy is the absorbed dose, *D*. The absorbed dose in a volume of mass *dm* at the point *P* is defined as:

$$D = \frac{dE}{dm}$$

Where *dE* is the energy deposited by the radiation in the mass volume *dm*.[4] The unit of measurement of the absorbed dose is the *Gray (Gy*), defined as *1Gy = 1 Joule / kg*. With the same irradiation, the absorbed dose values are specific for the irradiated medium [5].

Regarding the possibility that some cells can survive radiation, the cell survival studies after irradiation with ionizing radiation is possible to calculate the probability of local tumor control (TCP Tumor Control Probability). TCP indicates the probability that all tumor cells are killed following the administration of a certain amount of radiation equal to an absorbed dose D in water [6]. If on average at a certain dose *D* are killed *a(D*) cells, the probability $P_D(n)$ that *n* cells survive follows the Poisson distribution given by the formula:

$$P(n) = \frac{a(D)^n e^{-n}}{n!}$$

TCP is therefore defined as:

$$TCP(D) = P_D(n = 0) = e^{-a(D)}$$

The cell survival study is also performed on healthy cells, thus constructing the so-called Normal Tissue Complication Probability (NTCP) curve. An effective radiotherapy treatment is characterized by a dose absorbed in water such that the TCP value is close to 1 (all cancer cells are killed), while the NTCP value is close to zero (low probability of complications of healthy tissue) [7-9].

In addition to radiation from external beams, the radiotherapy effect can be obtained internally by administering drugs labeled with radioactive isotopes, by means of their nuclear radiations [10, 11].

These particular drugs (radiopharmaceuticals) are chemical compounds characterized by a molecule called vector which possesses physical-chemical-biological requisites for the specific organ, tissue or physiological process of clinical interest, to which was added a radioactive isotope [12].

Once administered, orally, parenteral or other routes of administration, due to their pharmacodynamic characteristics, these drugs reach the organs, or functional systems that we are interested in reaching to obtain the deposit of radiations in the site to be treated. Nuclear Medicine therapy, also before known as radio-metabolic, consists in labeling those drugs with radionuclides that emit a "curative" type of radiations such as beta- or alpha-particles.

Treatment with radioactive isotopes was the first clinical application of Nuclear Medicine, when, at the beginning of the '40s, Phosphorus-32 was used for the polycythemia and some forms of leukemia and was subsequently adopted the administration of Iodine-131 for therapy of thyroid disease [13-15].

Nuclear Medicine treatment, also called Molecular Radiotherapy, has a very low risk, for example, to cause the occurrence of tumors in the treated subjects, so that often these therapies are also used for benign diseases. Nuclear medicine technology is now regarded as an essential tool for diagnosis, palliation, therapy, and theranostic applications [12].

Since Nuclear Medicine is an integral part of modern healthcare, the use of radioactive nuclides tagged biomolecules, evaluating their distribution in human bodies by SPECT or PET systems, provides longitudinal sets of volumetric and quantitative images that can be used to

diagnose a wide range of disease and/or assess response to disease specific treatments [16]. For this purpose, the various radiopharmaceuticals are labeled with radioisotopes emitting radiations that are easily detectable outside the body such as gamma rays and positrons.

As mentioned before one of the nuclear radiation predominantly used for therapeutic purposes are the beta particles emitted by unstable nuclei of various elements such as iodine-131, yttrium-90 or the newer Lutetium-177 or Holmium-166. The small distance covered by corpuscular radiation emitted by utilized isotopes helps to make a more targeted treatment and, since all the radiated energy is released in a small space, thus irradiated cells cannot repair the damage that their DNA have suffered, then running into death.

The relatively path length is about 0.8–5 mm and low linear energy transfer (LET) is of approximately 0.2 keV/μm [17]. The relatively long range of these particles results in a rather pronounced crossfire effect that can affect the cells to be treated, but also contributes to the non-specific toxicity of non-targeted tissues. Beta emitters such as 90Y or 188Re, with these long range properties are more suitable for treating large and poorly perfused tumors, but less suitable for targeting small metastases as their energy would be deposited outside the target volume. In case of small lesions to be treated, it is preferable to use low-energy beta radiation, such as those emitted by Lutetium-177 [18]. The half-life of these beta emitting radioisotopes is also very important for therapeutic efficiency, making it more useful to use radioisotopes with longer half-lives [19].

Raised recently a clinical interest towards alpha emitters in Nuclear Medicine therapy, that derives from the fact that with these nuclides it is possible to easily delete individual cancer cells, while this is not generally possible with beta emitters, while maintaining an acceptable toxicity profile.[20] Alpha particles have much higher energy (4-9 MeV) and travel into tissues only over a few cell diameters (i.e. 40-100 μm), thus offering the exciting prospect of matching the specific nature of the molecular targeting cell with radiation. Alpha particles emitting drugs have a higher Biological Effective Dose (BED) of the most energetic beta particles, thus allowing more targeted treatments.

The simple physical basis of the difference between alpha and beta rays is the ratio of their masses, that is about 8000 to 1. This enormous difference, together with the electric charge, greater however only of a factor of 2, and energy emissions, higher only by a factor of 10, implies that alpha particles travel with non-relativistic speed (about 1/20 of the speed of light), while beta ones have a speed practically equal to the light speed. The slower speed of the alpha radiation therefore results in a much shorter route than that of the electrons in the middle traversed, thus resulting in a Linear Energy Transfer (LET) much higher, measured in keV/micron.

The 5.9 MeV and 8.4 MeV alpha LET are 80 keV/micron and 61 keV/micron, respectively, while those of beta of 100 and 500 keV are 0.2 and 0.5 keV/micron.

This much higher LET generate ionization density along the path much higher and a much shorter range of route of the alpha particles, compared to beta ones. Both characteristics have very important implications for radionuclide therapy and dosimetry.

The ionization density has a strong influence on the shape of the survival curve as a function of the dose. Low LET radiation (photons and electrons) induces 3-9 ionizations on a distance of 3 nanometers. The alpha particle has such a short route that few cell diameters, typically 5, are crossed by each particle. The concentration of ionizations along the alpha route is so high that a single shot to the DNA is able to kill a single cell.

It is clear that in the case of beta rays, the mean dose concept is significant, even if considered on a macroscopic volume that can be small like a voxel of medical application scanners (the size of a few millimeters).

The concept of average dose is not significant however, with alpha rays, or, rather, slightly predictive of biological effects, because the same amount of energy deposited by a projectile directed to the cell membrane could give completely different biological effects to the cytoplasm or inside the nucleus.

The first clinical applications of alpha emitters are of recent date and relate to the use of Radium-223 for the treatment of bone metastases [21]. In fact, the Radium-223 behaves in nature as a mimetic of calcium, and then reaches, once administered, the bone lesions with higher calcium turnover. In this case the therapeutic effect, in addition to causing a net reduction in the painful symptoms, also demonstrated a significant increase in survival, on average estimated at 3.6 months. The aforementioned short route alpha leaves also unharmed neighboring tissues, particularly the bone marrow.

Other alpha emitters in study are the Bismuth-212 (synthesizable with a 244Ra/212Bi generator) which, as its isotope Bismuth-213, can be chelated into special carrier. Another nuclide is Astatine-211which, similar to iodine, can bind a covalent, bond to carbon atoms of other molecules [22, 23].

As mentioned before, the molecular radiotherapy (MRT) is clinically used for about 75 years. Yet, despite this long history of clinical use, there is no established dosimetric practice for calculating the dose absorbed by tumor targets or organs at risk. As a result, treatment protocols have often evolved based on experience with a relatively small number of patients. Each of them is given a similar activity but, potentially, widely varying absorbed doses. All this is in contrast with what happens in modern external beam radiotherapy, where the dose is tailored as precisely as possible, thanks to devices for defining the target area more and more precise, thanks to the contribution of medical physicists for the simulation of the calculation of the dose and increasingly collimated accelerators for the protection of nearby healthy organs [24].

The absorbed dose that can be delivered to tumor lesions, in the case of targeted radiotherapy, is limited by toxicity to the organs at risk. So this situation is capable of constraining the prescription activity to be administered, in order to minimize the dose to the organs at risk thus reducing to a maximum the possible side effects [25]. So an accurate and personalized evaluation of absorbed dose to organ at risk and tumor lesions should be performed to guide activity prescribing decisions and since treatment planning is a real challenge, the best way to execute it consists of a customized 3D dosimetry, based on Monte Carlo calculations [26].

The dosimetric evaluation can take place either after treatment, to evaluate the real effectiveness of the treatment, or before treatment, to determine the maximum tolerated activity to limit irradiation of healthy tissue [27].

In molecular radiotherapy the radiation sources are not localized, but are distributed in the various organs and tissues involved both in the chemical processes and in the physiological pathway of the molecule that constitutes the radiopharmaceutical. Furthermore, the distribution of the radiopharmaceutical is not fixed over time, but varies according to the chemical and physiological processes typical of each patient. For these reasons the dosimetric evaluation in the region of interest (either it the organ at risk or the lesion to be treated) must take into account both the irradiation due to the presence of multiple sources (the various tissues in which the molecule is involved) and the retention (uptake) and elimination (clearance) times of the radiopharmaceutical.

The basis of a correct dosimetric evaluation for the use of radiopharmaceuticals in nuclear medicine consists in a precise measurement of the radionuclide activity in the sites of interest. Radionuclide activity can be measured by two-dimensional scintigraphic images, or by SPECT or PET tomography [28], depending on the radionuclide used and patient comfort. It is clear for the quantification of the activity values, that a three-dimensional imaging is preferred in cases where a superimposition of several springs in the scintigraphic images is suspected [29]. An innovative method of iterative thresholding for tumor segmentation has been proposed and implemented for a SPECT system [26].

On the basis of what has been said it can be stated that: *"Dosimetry not only is nice to have and easily performed but also is needed for predicting therapy success and optimizing therapeutic applications of radiopharmaceuticals"*[30]

We said before that in nuclear medicine there is the possibility of calculating the dose received from a lesion to be treated before performing molecular therapy. In fact, there is often the possibility of administering a radiopharmaceutical able to concentrate in the lesion, labeled with a gamma –emitting, or positron emitter, isotope useful for detection with diagnostic equipments (SPECT or PET) and so calculate the amount dose received. In this way it will be possible to calculate the exact dose to be administered of the same molecule, labeled this time with an alpha or beta particles emitter for therapeutic purposes. This is what is called theranostics in nuclear medicine [31]

A clear example of theranostics applied since the dawn of nuclear medicine is represented by pathologies of the thyroid gland. In fact, the use of iodine in this case was applied first in therapy than in diagnostics, but the current use involves a diagnostic phase with Iodine-123, which emits only gamma radiation, while the subsequent therapeutic phase is carried out with iodine-131 which emits beta particles. In this way it is also possible to perform a fairly precise dosimetric calculation [32, 33].

Equally significant is the case of therapy with Radio-223, as mentioned above an alpha particle emitter, for bone metastases of prostate and breast cancer. In fact, the behavior of this radiopharmaceutical mimics calcium metabolism. The same goes for the radiopharmaceutical for skeletal diagnostics, MDP labeled with Technetium-99m, an emitter of only gamma radiation. The preventive diagnostics with this last radiopharmaceutical allows a valid calculation of the optimal therapeutic dose of Ra-223 [34-36].

In conclusion, the principle of theranostics and its introduction into the clinical practice of nuclear medicine in the field of molecular radiotherapy, has allowed us to considerably implement obtained results in multiple clinical situations [37].

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