



Dosimetry for molecular radiotherapy

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Abstract

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. Proper dosimetric evaluation is the basis of assessing the efficacy of treatment with ionizing radiation to evaluate the efficacy of the treatment and the side effects due to irradiation of healthy tissue. In molecular radiotherapy, made by radiopharmaceuticals administration, 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.

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Review

The use of ionizing radiation for the treatment of cancer is a well-established technique for years [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 magnitude of main interest in radiotherapy is the absorbed dose, D . The absorbed dose in a mass volume dm at point P , is defined as the energy deposited by the radiation in the mass volume [4]. The unit of measurement of the absorbed dose is the Gray (Gy) [5].

It is possible to calculate the Tumor Control Probability (TCP), a quantity that indicates the probability that all the tumor cells will be killed following the administration of a certain amount of radiation equal to a dose absorbed in water [6]. The cell survival study is also carried out on healthy cells, thus building the

so-called probability curve of complications of healthy tissue (NTCP, Normal Tissue Complication Probability) [7].

An effective radiotherapy treatment is characterized by a dose absorbed in water such that the value of TCP is close to 1 (all the tumor cells are killed), while the value of NTCP is close to zero (low probability of complications of healthy tissue).

Proper dosimetric evaluation is therefore the basis of assessing the efficacy of treatment with ionizing radiation to evaluate the efficacy of the treatment and the side effects due to irradiation of healthy tissue.

The first applications of nuclear medicine concerned precisely radiotherapy with radioisotopes. In fact, in the early '40s, the Phosphorus-32 was used for polycythemia and some forms of leukemia [8,9], and subsequently the administration of iodine-131 was adopted for the therapy of thyroid disease [9,10]. From



that moment, the molecular radiotherapy has had a long road to success, with the synthesis of many classes of radiopharmaceuticals and the entering into clinical practice of pure beta emitting particles, electrons, with physical characteristics very advantageous, as Samarium-153 [11] or Yttrium-90 [12].

Radiopharmaceuticals contain atoms emitting β particles, or α particles, bound to molecules able to fix themselves in tumor cells. β and α particles are characterized by a "local" energy deposit, up to a centimeter for the former and a few mm for the latter, for which it is possible to selectively irradiate the tumor cells while saving healthy tissues.

The clinical interest in alpha emitters in Nuclear Medicine molecular radiotherapy is that with these nuclides it is possible to easily eliminate single tumor cells, while this is not generally possible with beta-emitters, while maintaining an acceptable toxicity profile [13].

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.

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 [14], 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 [15]. An innovative method of iterative thresholding for tumor segmentation has been proposed and implemented for a SPECT system [16].

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 [17]

In radioiodine therapy of hyperthyroidism from nodular thyroid disease patient-specific dosimetry has proven to increase therapeutic effectiveness, reducing the recurrence frequency and the need of repeated treatments [18,19].

In recent years, has been demonstrated in many clinical studies using ^{223}Ra -dichloride the safety and efficacy of palliation of painful bone metastases in patients with Castration-Resistant Prostate Cancer (CRPC). ^{223}Ra -dichloride bone metastases therapy acts not only in the palliation of these lesions, but also on the overall survival of these patients) [20,21]. It is demonstrated that correct dosimetric evaluation allows the administration of the highest possible dose with minimal side effects [22,23]. For these reasons therapy with ^{223}Ra -dichloride is intended to be used as a first approach in the case of multiple bone metastases from CRPC, in absence of visceral metastases, not to miss the opportunity to attack the lesions with high doses, calculated pre-therapy, tailored patient per patient, for each lesion [24].

Somatostatin Receptors (SSTR) are over-expressed by well-differentiated Neuroendocrine Neoplasms (NEN), and in particular the SSTR-2 subtype. Therefore, SSTRs are teranostic targets in the NEN that have been known for almost three decades and have established themselves [25]. Somatostatin analogues for SPECT (^{111}In -Octreoscan and the more recent $^{99\text{m}}\text{Tc}$ -EDDA / HYNIC-TOC) 24) or PET (^{68}Ga -DOTA peptides) offer improved disease staging, occult tumor visualization and assessment of eligibility for somatostatin analogue treatment [26]. In patients with neuroendocrine neoplasia, peptide receptor radionuclide therapy is considered very reliable to offer the promising results. The synthesis of new imaging devices has introduced the concept of radiotheranostics, which is important for the localization, typing and staging of cancer in vivo but also and above all, for dosimetric evaluation and individual treatment of patients [27].

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, as seen in the case of thyroid field, bone metastases and neuroendocrine tumors. In other forms of molecular radiotherapy the pre-administration therapeutic dosimetry study is providing promising results, such as in the treatment of primary and secondary hepatic neoplastic lesions with yttrium90-labeled microspheres (SIRT)[28].

From the acquired data and for ongoing studies the dosimetric method based on theranostics can bring its beneficial results in many other applications. *"Dosimetry not only is nice to have and easily performed but also is needed for predicting therapy success and optimizing therapeutic applications of radiopharmaceuticals"*[29].

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