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REVIEW ARTICLE

Differentiated thyroid carcinoma: diagnosis and dosimetry using ^{124}I PET/CT

F. Capoccetti · E. Biggi · G. Rossi · C. Manni · E. Brianzoni

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Abstract The recent availability of ^{124}I, due in part to the spread of PET scanners, has opened up new possibilities for performing pre-therapeutic dosimetric studies in patients with differentiated thyroid cancer. ^{124}I PET/CT has remarkable clinical potential: for disease staging and the ablation of thyroid remnants, but also for studying patients at high risk or with suspected local relapses and/or metastases; furthermore, it has a low stunning risk. Many clinical studies have shown the superiority of ^{124}I PET/CT versus ^{131}I conventional imaging, which is attributable to the possibility of combining morphological and highly specific functional imaging data, avoiding most of the known pitfalls of ^{131}I scanning. ^{124}I PET/CT can be used to perform dosimetry, avoiding the side effects of ^{131}I, to tailor treatments, instead of using fixed therapeutic activities, and to evaluate mean absorbed doses both to target lesions (thereby allowing adequate therapy planning and staging) and to non-target organs such as the salivary glands. In addition, the concomitant use of 18F-FDG PET/CT allows the detection of non-iodine-avid lesions, discriminating these from simultaneously occurring iodine-positive lesions. This review analyzes clinical studies on ^{124}I PET/CT in patients with differentiated thyroid cancer, and suggests possible future applications.

F. Capoccetti · E. Biggi · C. Manni · E. Brianzoni (✉)
Nuclear Medicine Unit, Oncologic Department, Macerata Hospital, ASUR Marche AV3, Macerata, Italy
e-mail: ernesto.brianzoni@sanita.marche.it

G. Rossi
Medical Physics Unit, Macerata Hospital, ASUR Marche AV3, Macerata, Italy

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Introduction

Expression of the sodium iodide symporter (NIS), the key cellular feature for specific iodine uptake, is an essential prerequisite for the treatment of differentiated thyroid cancer (DTC) [1]. Indeed, for more than 50 years, radioiodine therapy with ^{131}I (RAIT) has been the first line of treatment for patients with DTC after surgery.

The primary objective of RAIT is to achieve ablation of remnants, although it is also used in the treatment of local relapses or metastases, and to improve accuracy in diagnosis and long-term follow-up. However, the use of RAIT is somewhat controversial. The European guidelines [2] categorized DTC as: (1) very low-risk, (2) low-risk, and (3) high-risk. Patients in the first group, being considered to have an excellent prognosis after surgery, do not derive benefit from of RAIT; in other words, in these patients, its high cost and radiobiological risk would not be offset by any clinical improvement in the status of the disease. In high-risk patients, on the other hand, the use of radioiodine is recommended, since the advantages outweigh the risks. For those classified as low-risk, the use of radioiodine may decrease recurrence, but the evidence is not still conclusive. The American Thyroid Association [3] recommends radioiodine ablation for selected patients with 1–4 cm thyroid cancers confined within the gland, who have documented lymph node metastases, other high-risk features (age, tumor size, lymph node status, histology), worrisome histological subtypes (tall cell, columnar, insular and solid variants and poorly differentiated thyroid

cancer), vascular invasion or gross or microscopic multifocal disease.

Correct pre-ablation staging constitutes an important instrument from the perspective of patient management, as it provides a basis for deciding whether or not to use other therapies before or after RAIT, and allows the radioiodine dose to be tailored to the single patient.

Moreover, there is still no general consensus on the amount of radioactivity that can be administered for ablation [2]. Several years ago a fixed empirical activity of 3.7 GBq was administered, but subsequent studies demonstrated that the same success rate could be reached with lower activities, both after thyroid hormone withdrawal and after rhTSH stimulation [4–9]. Fixed empirical activities are also used in cases of local relapse and/or lymph node metastases (5.55–7.4 GBq) and distant metastases (7.4 GBq or more) [3].

According to the only available dosimetric studies, by Maxon et al. [10, 11], the minimum absorbed dose necessary to obtain a high probability of therapeutic success is 300 Gy for ablation of DTC remnants, and 80–100 Gy for complete eradication of metastases, while below 40 Gy no metastatic complete response was found. The activity must, in any case, be chosen in order to avoid exceeding a blood dose of 2 Gy, the threshold above which there is a high risk of serious hematological complications. As the second organ at risk is the lung, when pulmonary metastases are present, the retention of therapeutic activity at 48 h should not exceed 3.0 GBq [10–12]. Thus, there has emerged a need to modulate the amount of radiation in order to improve the efficacy of the treatment while at the same time reducing the associated radiation exposure risks.

In view of these considerations, many centers have adopted a pre-therapeutic dosimetric approach [13–18]. This preliminary assessment should be recommended in pluri metastatic patients, in order to obtain precise individualized dosimetry [2]. Nowadays, diagnostic imaging with ^{131}I SPECT/CT is prescribed before the therapeutic dose of ^{131}I, but this could lead to the stunning effect (for activities of 37–74 MBq) [19–22]. In addition, radionuclide imaging with ^{131}I shows poor spatial resolution and image quality as a result of the effects of high-energy 364 keV gamma emissions leading to septal penetration artifacts; nevertheless, it is used in clinical practice [23–28].

The alternative radiopharmaceutical for staging and/or dosimetry, ^{123}I, is not readily available and has a short half-life. In fact, late imaging with ^{123}I is not possible when using a reasonable amount of ^{123}I activity, a finding that led to questions over whether dosimetry was worth the effort [29].

New horizons have recently been opened up by the PET tracer ^{124}I. The literature contains studies on ^{124}I that date back to 1960 [30], and we have known about the radiotoxicity of ^{124}I for half a century [31], but it is only recently that ^{124}I has actually become available, thanks in part to the spread of PET scanners; in particular, this development was prompted by a phantom study by Erdi et al. [32], who concluded that quantification of ^{124}I is possible. This situation has obviously created new perspectives for ^{124}I PET, especially in relation to the scope for hybrid PET/CT studies.

Imaging with ^{124}I PET/CT

^{124}I is a positron-emitting isotope with a half-life of 4.2 days. It has a cascade gamma (602 keV) with 60 % abundance, and positron emission (23 % decays) suitable for PET/CT imaging [33]. Despite the many high-energy gamma rays (723 keV 10 % abundance and 1691 keV 10 % abundance) associated with the cascade gamma photons, which may create false triple coincidence events, as demonstrated by Pentlow et al. [34], ^{124}I PET imaging is feasible, offering better spatial resolution and diagnostic sensitivity than ^{123}I and ^{131}I SPECT [29], but showing a slightly worse resolution (a difference of about 1 mm), less contrast and more scatter than traditional PET imaging with ^{18}F-FDG [35–37]. Using particular scanner settings, it is also possible to obtain good quality images from ^{124}I PET/CT simultaneously with therapeutic activities of ^{131}I; these acquisitions are suitable for quantitative dosimetric evaluation [38].

In order to obtain visible and evaluable images it is necessary to acquire about 5 min/bed in a 3D PET scanner, after oral or intravenous administration of 25–76 MBq of ^{124}I [39, 40], using hybrid scanners, in order to have attenuation correction and better localization from the anatomical CT study [41]. In accordance with what has long been established [42], the first scan is usually taken at 24 h. It is possible to acquire images for 120 h or more after the radiopharmaceutical administration, which in turn allows better dosimetric studies [39, 43].

Even though 2D PET imaging does not require corrections for spurious events, 3D imaging is the most widespread modality, partly because almost all the available commercial scanners offer only this PET configuration.

The estimated total radiation exposure of diagnostic ^{124}I PET is 5 mSv from the administration of 50 MBq [44] as compared with a whole-body effective dose of 11 mSv from 185 MBq of ^{131}I [45].

To date, no cases of thyroid tissue “stunning” after ^{124}I PET/CT have been reported [35].

Clinical studies

Many clinical studies have shown the superiority of ^{124}I PET/CT versus ^{131}I conventional imaging (planar images

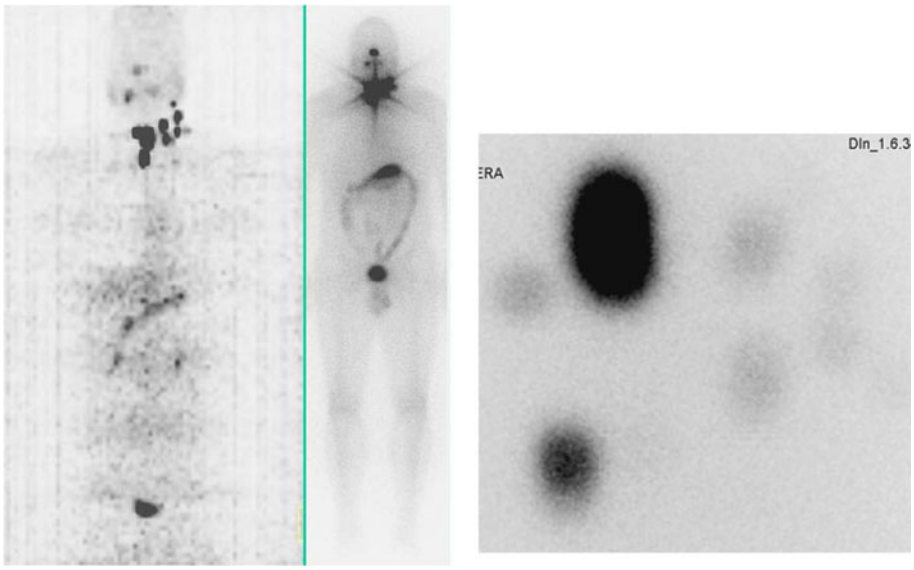

Fig. 1 Lymph node metastases better depicted on ^{124}I PET (on the *left* image) than on ^{131}I WBS (*central* image) with corresponding pinhole image (on the *right* image)

and/or SPECT/CT), which is attributable to the possibility of combining morphological imaging and highly specific functional imaging, avoiding most of the known pitfalls of ^{131}I scanning. This approach could also lead to improved clinical decision-making. See Figs. 1 and 2.

Phan et al. [46] studied the feasibility of ^{124}I PET in 24 patients with histologically proven advanced DTC and compared the findings with those of diagnostic and post-therapy ^{131}I whole-body scans (WBSs). The ^{124}I PET adequately predicted findings on subsequent post-therapy scans, and was shown to be superior to diagnostic ^{131}I and equivalent to post-therapy ^{131}I planar imaging, with abnormal uptake better depicted on ^{124}I PET/CT.

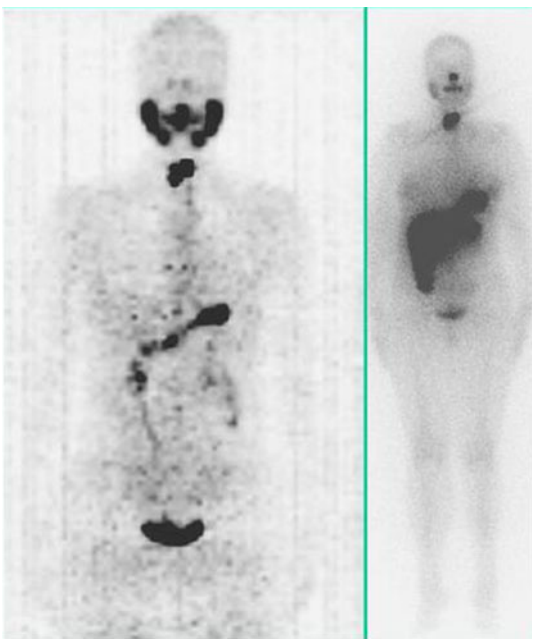

Fig. 2 Example of concordance between ^{124}I PET (on the *left* image) and ^{131}I WBS (on the *right* image)

Capoccetti et al. [41] studied 69 patients with DTC (67 recruited for ablation of thyroid remnants and two affected by pluri metastatic disease) and remarked that the findings of ^{124}I PET/CT and ^{131}I WBS matched in 58 out of 67 patients (87 %). In 12 % of these 67, ^{124}I PET/CT revealed previously unknown lymph node metastases, which changed the *N* stage, and in a further 4 % unknown distant metastases were found.

In fact, ^{124}I PET/CT imaging can also be used to verify the correct assignment of thyroid remnants and lymph node metastases, as shown by Rosenbaum-Krumme et al. [39], who analyzed kinetic quantities by determining the maximum activity concentration and effective half-life of each lesion.

Van Nostrand et al. [47] compared the ability of diagnostic ^{124}I PET images and ^{131}I WBSs to detect residual thyroid tissue and/or metastases. Confirming the results of other studies, they showed that ^{124}I PET allowed them to identify 50 % more sites of radioiodine uptake in 32 % of 25 patients with DTC suggestive of additional residual thyroid tissue and/or metastatic disease.

Recurrence is found in up to 30 % of patients with DTC, although some cases can show elevated thyroglobulin values and negative ^{131}I conventional imaging. In this situation, in which ^{131}I imaging displays poor sensitivity and low yield in detecting metastases in patients who have undergone thyroidectomy [48], some authors [49] have proposed ^{18}F-FDG PET/CT as an instrument allowing selection of patients for surgery, which may be curative.

Freudenberg et al. [50] compared ^{124}I PET/CT and ^{18}F-FDG PET/CT in the detection of recurrent DTC lesions in patients with increasing serum thyroglobulin, thyroglobulin antibodies, or both, but without cervical pathology on

ultrasonography. They studied 21 patients who had previously undergone thyroidectomy and RAIT. The sensitivities for DTC lesion detection were: 49 % for ^{124}I PET, 67 % for CT, 80 % for ^{124}I PET/CT, 70 % for ^{18}F-FDG PET and 91 % for combined modalities. For recurrences the sensitivities were: 60 % for ^{124}I PET, 20 % for CT, and 65 % for ^{18}F-FDG PET. One-third of lesions showed pathological uptake with both ^{124}I and ^{18}F-FDG PET, while the other two-thirds were positive with only one technique. In conclusion, the combination of the two imaging modalities improves restaging in recurrent DTC by enabling detection, on WBSs, of local recurrence or metastases that are often not found if only one technique is applied.

Even though it has been demonstrated that ^{124}I PET/CT is a useful tool, this technique may suffer from other problems or pitfalls: Abdul-Fatah et al. [51] reported that the activity of ^{124}I near the trachea can result in annihilations in the opposite wall of this organ, incorrectly suggesting activity at that location. They found this artifact in 17 % of 29 patients. A different problem may occur in patients with disseminated iodine-avid lung metastases. The lungs are one of the most common sites of distant spread of DTC [52]; indeed, the prevalence of pulmonary metastases at the initial diagnosis is reported to range from 2 to 20 % [53, 54]. Freudenberg et al. [55] demonstrated that visual analysis of ^{124}I PET scans was sufficient in only one out of seven patients affected by disseminated pulmonary disease. On the contrary, quantitative analysis of ^{124}I PET data, using a lung-to-background ratio, allows patients with suspected pulmonary disease to be differentiated from those in whom it is not suspected; however, this criterion cannot be used alone, and must instead be correlated with additional diagnostic tests, such as serum thyroglobulin levels.

^{124}I PET/MRI may also be a useful instrument: in a study of 33 high-risk DTC patients, Nagarajah et al. [56] intra-individually and prospectively compared the lesion detection ability of ^{124}I PET alone and ^{124}I PET used in combination with CT and MRI, considering their ability to characterize a lesion as thyroid remnant tissue or lymph node metastasis, and the consequences of higher detectability on lesion dosimetry. They found that MRI detected more morphological correlates to PET foci than CT did, and 65 % of these lesions were <10 mm in diameter. They concluded that PET/MRI is superior to PET/CT in pre-therapeutic imaging, particularly in lesions measuring <10 mm in diameter, resulting in more precise and individually tailored ^{124}I dosimetry.

Dosimetric studies with ^{124}I PET/CT

Dosimetry using ^{124}I PET is a complex technique whose application needs to be evaluated on an individual, case-by-case basis. It can be used to stage patients with remnants, to determine the optimal administrable activity for remnant ablation, and, in selected pluri metastatic patients, to establish the maximum dose that can be delivered to lesions while avoiding side effects on organs at risk.

The aforementioned problems related to the ^{124}I spectrum can be addressed by the use of a correction factor called recovery coefficient (RC), studied by Jentzen et al. [36] in 2D and 3D modes and evaluated taking into account all the factors affecting this value, such as object shape, background activity spill-in and iterative image reconstruction parameters [57]. These authors concluded that the RC value is not significantly influenced by changes in object shape, whereas reconstruction parameters do have a large effect, especially when an OSEM algorithm with too small a number of iterations is chosen. In addition, ^{124}I PET quantification of lesions smaller than 1 ml, containing very low activity concentrations, was found to be associated with large uncertainties, as confirmed by Capoccetti et al. [41]. Thanks to the long half-life of the tracer, it is possible to acquire images of ^{124}I for up to 120 h after its administration [39]. This advantage makes it possible to structure data acquisition protocols that could be delayed for up to 5 days from ^{124}I administration. The most widely used protocol for pre-therapy dosimetry was developed around serial data collection, for both red marrow and lesion analysis. This model involves serial blood sampling, whole-body counting and serial imaging acquisition for the localization and quantification of lesion activity see Fig. 3.

Freudenberg et al. [40] first applied this model using ^{124}I and a protocol of five PET images (4,24,48,72,96 h), one PET/CT acquisition (25 h), six blood samples (2,4,24,48,72,96 h) and six whole-body counts performed following the same schedule used for the blood samples. The image acquisition makes it possible to study the estimated absorbed lesion dose per GBq of administered ^{131}I, and thus to calculate the minimum effective activity. Through blood collection it is possible to determine the critical threshold that avoids marrow toxicity see Fig. 4.

If there is no anatomical information from CT data, lesion volume can be estimated using a segmentation method [58].

In the case of lesions receiving <80 Gy, the efficacy is reduced [40] and in the event of doses below 40 Gy, an alternative therapeutic option must be chosen [10] see Table 1; see Fig. 5.

Thus, the EANM dosimetry committee has described a pre-therapeutic model for standard operational procedures [59] and explained all the mathematical calculations and the data management in another guideline publication [60].

It is also possible, for the convenience of patients and staff and to reduce healthcare costs, to use a simplified protocol with only two PET points. This option could also

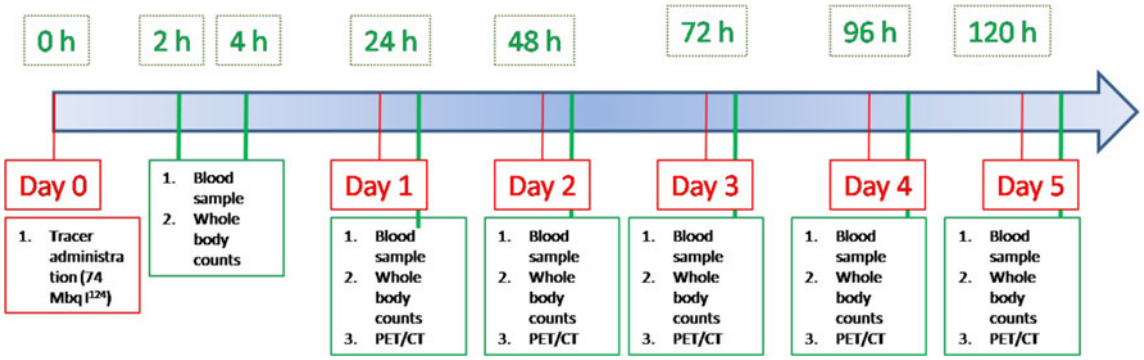

Fig. 3 Dosimetry schedule

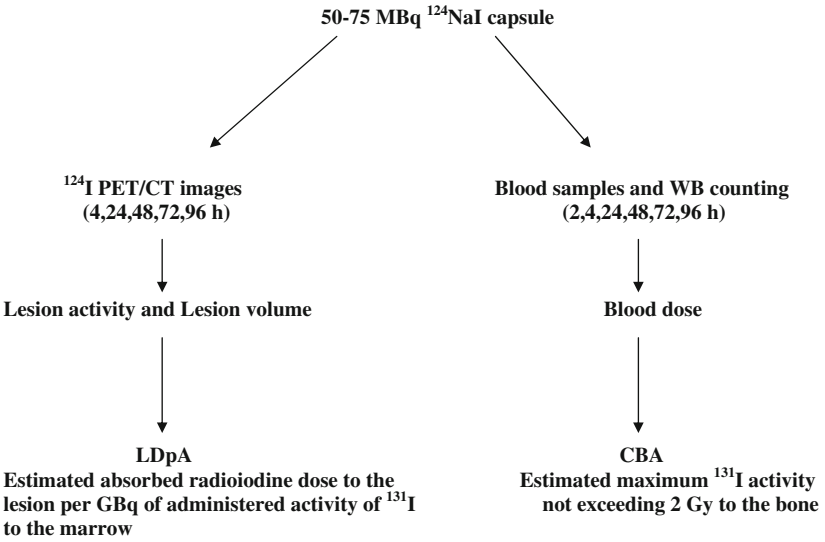

Fig. 4 Determination of ^{131}I activity for radioiodine therapy

Table 1 Dosimetry calculation

Organs	mGy/MBq	Lesions	mGy/MBq
Red marrow	0.273	Thoracic vertebra	8.91
Whole body	0.048	Iliac bone	4.56
Adrenals	0.049	Left superior femur	7.16
Uterus	0.045	Left inferior femur	6.40
Ovaries	0.048	–	–
Liver	0.039	–	–
Kidneys	0.044	–	–

help to make ^{124}I PET/CT dosimetry more widely available and user-friendly [43]. The calculation that obviously follows the data collection can be performed using a standard method (MIRD), or it could be simplified through the use of 3-D software, developed by Sgouros et al. [61] and tested by Kolbert et al. [62]. It is also possible to use more sophisticated methods such as 3-D voxel calculations by either convolution with a dose-point Kernel or Monte Carlo simulation [60].

Evaluation of rhTSH versus thyroid hormone withdrawal in RAIT

As an alternative to thyroid hormone withdrawal, rhTSH stimulation has been shown to be an effective tool for thyroid remnant ablation in patients with DTC [63–67]. The success rate of rhTSH-stimulated remnant ablation using 1–3 GBq of ^{131}I is comparable to that of remnant ablation after thyroid hormone withdrawal, despite the shorter duration of TSH elevation and the faster renal clearance of radioiodine in the euthyroid state [68, 69].

Potzi et al. [70] reported low effective delivered doses to thyroid metastases with rhTSH stimulation compared to thyroid hormone withdrawal, using dosimetric calculations based on tumor and whole-body uptake from ^{123}I scans performed 0, 4, 24 and 48 h after the administration of ^{123}I, and cautioned against empirical radioiodine ^{131}I treatments using exogenous stimulation.

Freudenberg et al. [71], using ^{124}I PET lesion-based dosimetry, delivered adequate radiation doses >300 Gy to remnant thyroid tissue treated using standard therapeutic

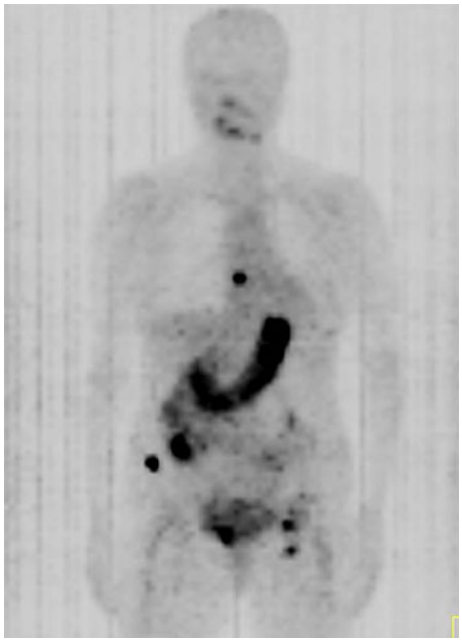

Fig. 5 (^{124}I PET) female patient who underwent dosimetric evaluation

activities of ^{131}I. They concluded that there were no differences between rhTSH stimulation and thyroid hormone withdrawal, and therefore that no modifications of prescribed therapeutic activities were necessary. Regarding distant metastases, the same authors [72], retrospectively comparing mean absorbed doses between groups of consecutive patients receiving ^{124}I PET/CT aided by rhTSH stimulation or thyroid hormone withdrawal, found some indications but no statistically significant evidence that rhTSH administration resulted in a lower radiation dose to DTC metastases than thyroid hormone withdrawal did.

Hartung-Knemeyer et al. [73] studied 198 patients with locally advanced or metastasized DTC, candidates to receive a high-activity therapy, who underwent pre-therapeutic blood dosimetry using ^{124}I. They showed that exogenous, as opposed to endogenous, TSH stimulation could result in a lower blood dose, and that blood doses seemed to be generally higher at first RAIT compared to subsequent RAITs. They concluded that blood dosimetry should become standard practice, as the range of absorbed doses was rather wide.

Evaluation of salivary glands and other organs

Salivary dysfunction is the most common side effect of RAIT, leading to sialoadenitis and occasionally some degree of xerostomia, both of which have a potentially negative impact on quality of life [74]. Stimulation of saliva flow soon after administration of ^{131}I using lemon juice for example is a popular approach for reducing radiogenic damage [75], but only starting 24 h after ^{131}I therapy [76]. Dosimetric studies using ^{131}I and ^{124}I and comparing the well-known dose–effects relationships in external radiation therapy showed that the average absorbed doses in the salivary glands per administered ^{131}I and ^{124}I are too low to induce the observed radiogenic damage. This could suggest an inhomogeneous distribution of iodine in this organ; in fact, Jentzen et al. [77, 78] assessed the effect of chewing lemon slices on the parotid and submandibular glands in patients who underwent pre-therapy ^{124}I PET/CT dosimetry by examining the organ absorbed doses per administered ^{131}I activity. The mean absorbed dose was found to be similar both in the submandibular glands and in the parotid glands, and lower in the non-stimulation group than in the stimulation one. This reduction in the non-stimulation group was significant for the parotid glands, but not for the submandibular glands. These results might demonstrate that lemon juice stimulation shortly after ^{131}I administration increases the absorbed dose to salivary glands.

Conclusions and future perspectives

In a group of patients affected by DTC, a fixed activity-based approach may offer benefits due to its simplicity, with regimens that in most cases remain below toxicity limits. The main disadvantage in using this approach is the failure to consider the individuality of each patient. There may, in fact, be evidence of occasional over- or under-treatment; in addition, the efficacy of each successive treatment in an individual patient might be degraded.

The results of all the considered studies demonstrate that ^{124}I PET/CT is a powerful tool, which can be used both to perform an excellent pre-therapy staging (allowing earlier multimodal interventions than standard empirical protocols do) and to study patients with suspected local relapses and/or metastases, with limited stunning risk thanks to the lower activity injected and the shorter effective half-life of the tracer. PET/MRI is superior to PET/CT in pre-therapy imaging, particularly in lesions measuring <10 mm in diameter, resulting in more precise and individually tailored ^{124}I dosimetry.

^{124}I has not yet been registered, and is currently available only for experimental studies; its cost is comparable to that of many radiopharmaceuticals routinely used in clinical practice. Once registered, it is likely to become more readily available and more widespread.

In conclusion, dosimetric studies calculate individually tailored ^{131}I therapy for the ablation of thyroid remnants with the same success rate as the empirical fixed dose approach, and optimize treatment for patients in the high-risk group, for those with established metastatic disease, and even for cases with measurable thyroglobulin values

and negative ^{131}I imaging, reducing the radiation exposure risks and avoiding the administration of unnecessary activities. By estimating absorbed doses to lesions, it is possible not only to avoid side effects, but also to calculate the probability of cure; on the other hand, it is also possible to choose therapeutic activities in order to avoid exceeding absorbed dose limits not only for organs at risk, but also for the salivary glands and probably other organs too, such as the lacrimal glands, stomach and breast.

This approach, which could be routinely performed in order to obtain fine dosimetry in patients with thyroid cancer, could in the future be used to drive the development of new technologies and techniques in the detection and treatment of other malignancies that express NIS, such as stomach and breast cancer.

Conflict of interest The authors F. Capoccetti, E. Biggi, G. Rossi, E. Brianzoni declare that they have no conflict of interest.

Human and Animal Studies This article does not contain any studies with human or animal subjects performed by the any of the authors.

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