Original Article

Contribution of I-131 SPECT/CT uptake on the dynamic risk assessment of papillary thyroid cancer

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Background: Nowadays, dynamic risk stratification (DRS) is the chosen strategy for monitoring papillary thyroid cancer (PTC). However, other variables contribute information to optimise monitoring. The objective of this study was to analyse the quantitative parameters of the single-photon emission computed tomography/computed tomography (SPECT/CT) imaging after treatment with post-surgical I-131 uptake, and to analyse those that predict a non-excellent response (NER) at 1 year of monitoring as well as their predictive capacity.

Methods: A retrospective observational study was designed that included patients diagnosed with PTC and treatment with I-131. Monitoring was based on the DRS at 1 year comparing the patients that have an excellent response (ER) with those who have a response less than excellent (NER). For the study of the biokinetics of the I-131 in the post-surgical thyroid remnants, SPECT/CT images were acquired, as well as the following variables: the absorbed activity per the administered activity, percentage of remnant uptake at 2 and 7 days post-administration; and the accumulated activity over time.

Results: Fifty-seven patients were studied and 103 remnants. Of them, 19.30% obtained NER. Among males, there was a higher percentage of NER, 45.45% while among females, 82.61% obtained ER (P=0.102). As for the surgical technique, the patients with ER, 78.26%, underwent total thyroidectomy (TT) with bilateral central lymph node dissection. Most of the patients who had TT, bilateral central and unilateral lateral lymph node dissection had NER (45.45% *vs.* 8.70%) (P=0.027). The I-131 absorbed activity per administered activity was greater for ER [13.8 (28.85) *vs.* 4.63 (5.66)], the accumulated activity 0.12 *vs.* 0.04 (P=0.017) and the percentage of administered activity at 2 days (P=0.003). The variables associated independently to a NER were the male gender (P=0.009), the percentage of administered activity at 7 days (P=0.043) and the absorbed activity per administered activity (P=0.014). The predictive capacity of the model was area under the curve (AUC) [95% confidence interval (CI)] of 0.816 (0.720–0.912).

Conclusions: In PTC follow-up, the male gender, the absorbed dose, and the percentage of absorbed dose at 7 d should be considered along with the DRS, as tools to support future decision-making.

Keywords: Papillary thyroid cancer (PTC); dynamic risk stratification (DRS); I-131 single-photon emission computed tomography/computed tomography (I-131 SPECT/CT); quantitative parameters

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Introduction

The incidence of thyroid cancer has been increasing worldwide in recent years, with a higher trend among younger patients (1). According to the latest histopathological classification of thyroid cancers, papillary thyroid cancer (PTC) continues being the most common subtype and represents 85% to 90% of all thyroid cancers (2). The main PTC treatment is surgery, which can be associated or not with I-131 therapy after thyroid hormone suppression. The objectives of the I-131 therapy include remnant ablation, adjuvant therapy, or the treatment of persistent diseases (3). It ultimately improves disease-free survival, potentially eliminating suspicious, but unconfirmed, residual diseases, especially in patients with a high risk of recurrence of the disease (1).

In order to optimise the follow-up strategy of the patient, different prognostic classifications have been used. An example of this are the TNM (tumor, node, metastases) or MACIS (metastases, age, completeness of resection, invasion extrathyroidal, size of tumour) scales (4,5). The main information that they contribute is to know which tests must be conducted on the patients during the follow-up, their frequency, and the objective values for thyroid-stimulating hormone (TSH) suppression. In this way, a stricter follow-up is carried out on patients with a higher risk of recurrence. In 2008, Tuttle *et al.*, for the first time, proposed a new dynamic system that takes into account the evolution of the disease as the therapies are administered, in such a way that, after the initial follow-up of 1 or 2 years, it is possible to reclassify the patients depending on their response to the treatment (6). Today, and after validating the system by different authors for PTC treatment management it reclassifies patients as excellent, incomplete biochemical, incomplete structural, and indeterminate responses depending on the course of the disease (7,8).

Despite the fact that the PTC is characterised by a low mortality rate and long survival period, it significantly affects the patients' quality of life and health. Therefore, the diagnosis, therapy and standardised monitoring are fundamental. The serum level of thyroglobulin (Tg) is the principal tool for monitoring, as it is a specific indicator that reflects the burden of thyroid tissue in the body, including normal tissue and primary and metastatic tumours of the PTC. Changes in the serum levels of Tg are usually earlier and more sensitive than the imaging of structural lesions, serving as an important indicator for assessing tumour remnants, recurrence or metastasis. It not only reflects the post-operative state of PTC but it can also be used to assess the initial risk of recurrence and the response to treatment (9). However, the presence of Tg antibodies (TgAb) can cause a decrease in the Tg serum values and even lead to false negatives, reducing the sensitivity of the Tg for monitoring the disease (10).

In recent years, it has been demonstrated that single-photon emission computed tomography/computed tomography (SPECT/CT) is capable of accurately quantifying the absorption of radioactive isotopes associated with advance software packages (11). In addition, if individualised dosimetry is applied, very precise parameters are obtained that help in making decisions such as the calculation of the dose of I-131 for patients in special situations (12,13). Data with such precision can be obtained such as the uptake values and the absolute concentration of radioactivity in the absorption sites. Furthermore, it is possible to use these parameters to assess the therapeutic response in patients with PTC and characteristics as precise as mutations in the BRAF V600E gene, which gives a lower avidity for I-131, (14,15). However, the contribution of dosimetry parameters following post-surgical treatment with I-131 to the dynamic risk response in the initial assessment has not been evaluated.

For this reason, the main objective of this study was to determine which quantitative parameters of SPECT/CT imaging predict a non-excellent response (NER) at 1 year of follow-up in PTC. The secondary objectives are also to evaluate the clinicopathological differences between patients who obtained an excellent response (ER) and those who did not and to establish a predictive capacity model for the

ER based on dosimetric and clinicopathological variables. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-2188/rc).

Methods

We designed a retrospective observational cohort study. The population studied was made up of patients with diagnosis of PTC underwent surgery and with postoperative I-131 from July 2016 until January 2018 in Basurto University Hospital. We selected the population of patients with PTC because during the follow-up period there were no cases of follicular thyroid cancer, due to its low incidence as reported by other authors (16). The criteria for inclusion were: histological diagnosis of PTC treated with total thyroidectomy (TT) and I-131 with quantitative evaluation of the SPECT/CT images by means of dosimetry and annual follow-up of the dynamic risk response. The criteria for exclusion were: incomplete thyroidectomies, recurrence of PTC, prior therapy with I-131, patients with distant metastasis and patients with thyroiditis (neither Hashimoto's nor Graves'), incidental cancers or microcarcinomas. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The Basurto University Hospital. Individual consent for this retrospective analysis was waived.

The variables analysed in the study were: demography (sex and age), surgical technique, tumour staging based on the seventh edition of the TNM classification of the American Joint Committee on Cancer because it was the last classification published when the study was started; and the following pathological characteristics: tumour size, BRAF mutation, number of affected lymph nodes, clinically significant nodes, id est, one metastatic node >2 mm or more than five nodes >2 mm, histological type according to the criteria of the pathologist (follicular or classical variant), desmoplastic reaction, bilateral disease, minimal extrathyroidal extension diagnosed after the analysis of pathological anatomy, and multifocality.

The surgical technique was decided after evaluating the characteristics described in the preoperative ultrasound study, the tumour size, the lymph node study and the result of the sample obtained through core needle biopsy (CNB), according to the Multidisciplinary Thyroid Pathology Committee. In all cases, TT was performed with complete resection of the gland, without visible thyroid remnants. In addition, patients underwent sentinel lymph node technique with preoperative staging using N0 ultrasound, as described in the literature (17).

After obtaining the definitive histological results of the sample, the dose of I-131 was decided in the Multidisciplinary Thyroid Pathology Committee. Different ablative or adjuvant activities of I-131 were administered, following the recommendations of the American Thyroid Association (ATA) guide depending on the state of the post-operative disease and the established risk (3). These activities were 1,110, 3,700 or 5,550 MBq. All of them after stimulation with two doses of 0.9 mg of recombinant TSH during two consecutive days, 24 and 48 hours before the administering of the isotope.

In order to study the biokinetics of I-131 after surgery, SPECT/CT images were acquired on the post-operative thyroid remnants of each patient at 2 and 7 days after the treatment with I-131. The patient was admitted to the Cruces University Hospital to receive the I-131 treatment and the first SPECT/CT images were obtained two days later. The patient was discharged from the hospital and returned 7 days later for a new SPECT/CT image sequence. At 7 days, the uptake of I-131 is considerably lower, with very little deposition in other anatomical sites. Once the image sequences were obtained at 2 and 7 days, their values were analyzed by dosimetry at the work station. This analysis allowed identifying the thyroid remnants and their location (*Figure 1*). In the case of obtaining more than one uptake focus in the same patient, they were analysed independently. The activity of the thyroid remnants was quantified by a threshold-based method. The following variables were analysed: the absorbed activity according to the administered activity, the percentage of I-131 uptake at 2 and 7 days, and the accumulated activity over time.

Two SPECT/CT scans targeting the cervical region with automatic body contouring were performed for each patient at intervals of 2 and 7 days following administration. The SPECT/CT acquisitions were carried out using a dual-head General Electric (GE, Fairfield, CT, USA) Infinia Hawkeye gamma camera, which has a crystal thickness of 9.5 mm (3/8 in) and is fitted with High-Energy General-Purpose collimators. A helical CT scan was conducted with a pitch of 1.9, lasting 130 seconds, utilizing a voltage of 120 kVp (the minimum available setting) and a current of 2 mA. The CT was utilized for the purpose of SPECT attenuation correction. SPECT projections were gathered at 60 angular positions, each lasting 45 seconds. A matrix size of 128×128 was used, resulting in a voxel size of 0.4423 cm^3. A photopeak energy window centered at

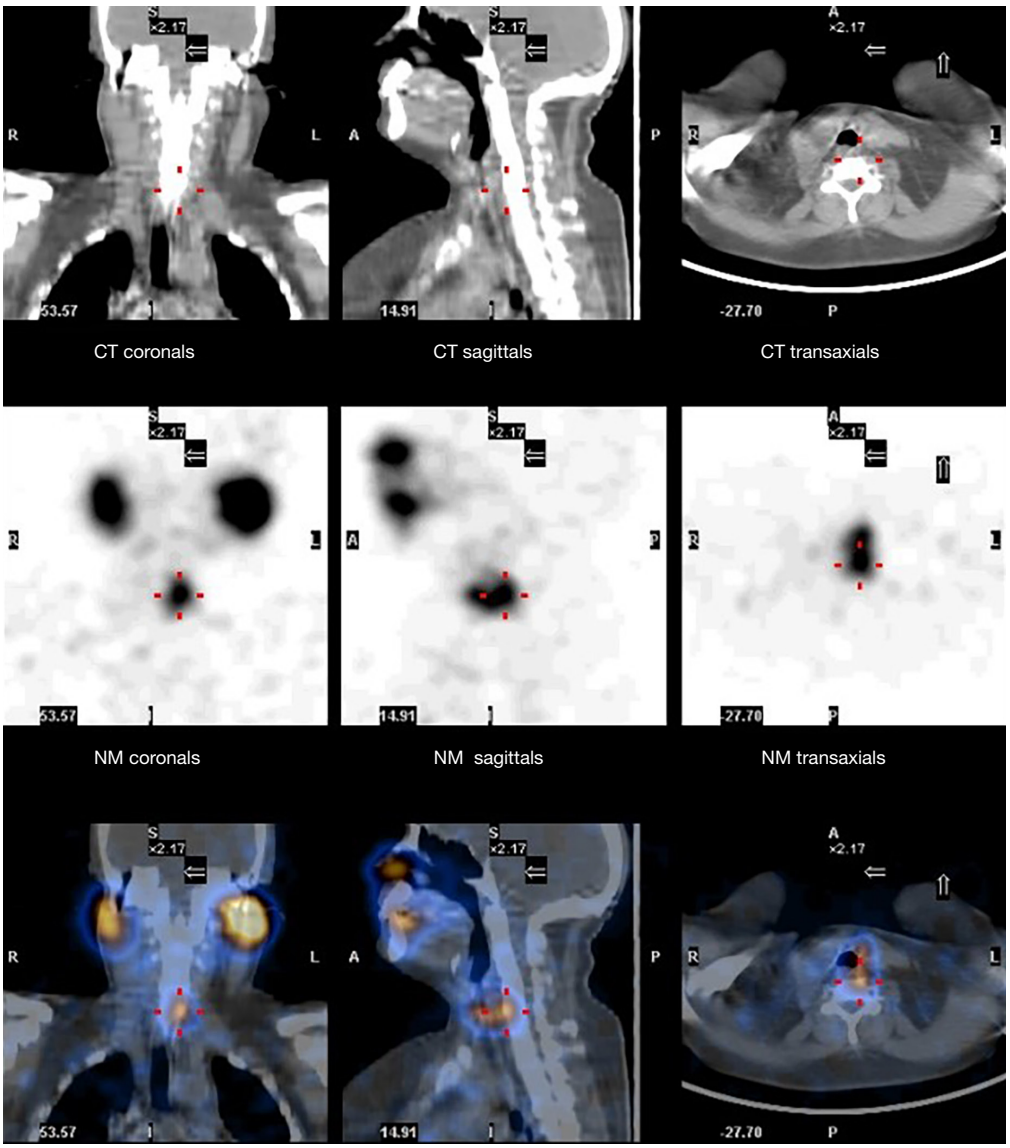

Figure 1 The SPECT/CT images correspond to a screenshot of the workstation, in the coronal, sagittal and transaxial planes. The last line represents the hybrid union between the CT images of the first line and the gammagraphy of the second line. Thus, we obtain qualitative information on the exact anatomical location of the thyroid remnants, close to the surgical bed, and it allows us to differentiate them from the natural accumulation of the isotope in other anatomical places, such as in this case, the salivary glands. A, axial plane; CT, computed tomography; L, left; NM, Nuclear Medicine; P, posterior plane; R, right; S, sagittal plane; SPECT, single-photon emission computed tomography.

364 keV, with a width of 20%, was employed. For scatter correction, a dual-energy window method developed by GE was implemented, which included an additional energy window centered at 297 keV, also with a width of 20%. The reconstruction of SPECT images was performed using the ordered subsets expectation maximization (OSEM) algorithm on a GE Xeleris workstation, incorporating 2 iterations and 10 subsets, along with a Butterworth filter that had a critical frequency of 0.5 cycles/cm and a power of 10 (order 5).

To measure remnant activity, SPECT/CT imaging of the IEC-Standard 61675-1 image-quality phantom was used, which comprised six spheres filled with I-131, positioned within a cold background. The spheres varied in volume

from 0.5 to 26.5 cm^3 and displayed activities ranging from 1.2 to 10.6 MBq. During the evaluation, it was observed that implementing a 5% threshold around each sphere yielded an activity estimate within a 10% margin of error. Additionally, it was noted that the count ratio, referred to as f30, obtained using a 30% threshold alongside the 5% threshold remained relatively stable across different sphere volumes. As a result, the remnant counts in patients were determined by first applying a 30% threshold to reduce the inclusion of counts from surrounding tissues, followed by the application of the established count ratio f30. The resulting counts were then converted to activity using a calibration factor derived from SPECT imaging of a large cylindrical phantom containing a homogeneous solution of I-131 (18).

The response on the second day of treatment with I-131 was measured based on the maximum Tg values. Patients with antithyroglobulin antibodies (AbTg) were excluded due to possible interferences in the measurement of Tg. In all cases, 24 hours after the second dose of recombinant human TSH (Thyrogen®) (rTSH), the value of thyroid-stimulating hormone (TSH) was greater than 50 mIU/L. Therefore, it was interpreted as valid without including this variable in the study.

It was decided to determine the dynamic risk stratification (DRS) at the 1-year follow-up of the patients according to the recommendations of the ATA guide. Thus, in order to facilitate the analysis, the patients were classified into two groups: those with ER (basal Tg <0.2/mL and, when it was available, stimulated <1 ng/mL with negative AbTg and normal cervical ultrasound) and a response less than excellent (NER) (incomplete biochemical, incomplete structural or indeterminate responses).

Statistical analysis

For the descriptive analysis, the mean and standard deviation (SD) were used for the quantitative variables, and frequencies and percentages for the qualitative variables.

For the comparison of the quantitative variables between the ER *vs.* NER groups, we used the *t*-test of mean comparisons or the Wilcoxon non-parametric tests in case the normality requirement was not met. For the comparison of the qualitative variables, the Chi-squared test or Fisher's exact test was used.

In order to study the factors associated with ER, the multivariate logistic regression model was used. The data were presented by the odds ratio (OR) along with confidence intervals (CIs) of 95%. The predictive capacity of the model was evaluated by means of the area under the curve (AUC).

For all the analyses a statistically significant result was considered as P<0.05. The analyses were performed using the programme SAS for Windows statistical software, version 9.4 [Statistical Analysis System (SAS) Institute, Inc., Carey, NC, USA].

Results

The epidemiological data of the sample being studied is presented in *Table 1*. Of the 57 patients who underwent post-surgical I-131 treatment and completed the 1-year follow-up, 11 of them (19.30%) obtained a response less than excellent (NER). Among the male group, the percentage of NER was higher than ER (45.45% *vs.* 17.39%). However, among women, the percentage of ER was higher (82.61% *vs.* 54.55%), although the difference was not significant (P=0.102). The mean age was 53.72 (SD =12.96) years, with the NER group being younger, although without significant differences (47.27 *vs.* 55.26 years, respectively, P=0.065). As for the surgical technique, within the group of patients with ER, the majority underwent TT with bilateral central lymph node dissection (73.68%). The patients who underwent TT, bilateral central lymph node dissection and unilateral lateral dissection mostly had a NER (45.45% *vs.* 8.70%). These differences were significant (P=0.027). In relation to the rest of the variables, the group with responses less than excellent was more frequently the classic variant (81.82% *vs.* 54.35%), the mutation of the BRAF V600E gene (72.73% *vs.* 45.65%); extrathyroidal extension was more frequent (36.36% *vs.* 28.26%); tumour size was greater (2.03 *vs.* 1.83 cm); there was a higher number of affected lymph nodes, and the Tg levels were higher 48 hours after treatment with I-131 (42.91 *vs.* 17.93 ng/mL). However, these differences were not statistically significant.

Data on the administered activity are shown in *Table 2*. We analyzed if the distribution of I-131 activities is different in ER and NER, by means of a Fisher exact test. In both the ER and NER groups the most frequently administered activity was 3,700 MBq, for which reason there was no statistically significant differences in the administered activity of I-131 for the complete response and the less than complete response groups.

The analyses of the uptake according to DRS can be observed in *Table 3*. The SPECT/CT uptake study was

Table 1 Analysis of the population studied according to their response: ER and NER

General variables	Total (n=57)	ER (n=46)	Response less than excellent NER (n=11)	P
Gender, n (%)				0.102
Female	44 (77.19)	38 (82.61)	6 (54.55)	
Male	13 (22.81)	8 (17.39)	5 (45.45)	
Age (years), mean (SD)	53.72 (12.96)	55.26 (11.96)	47.27 (15.50)	0.065
Surgical technique, n (%)				0.027
TT	5 (8.77)	5 (10.87)	0 (0.00)	
TT + BCND	42 (73.68)	36 (78.26)	6 (54.55)	
TT + BCND + LND	9 (15.79)	4 (8.70)	5 (45.45)	
TT + BCND + BND	1 (1.75)	1 (2.17)	0 (0.00)	
Histologic type, n (%)				0.170
Follicular variant	23 (40.35)	21 (45.65)	2 (18.18)	
Classical variant	34 (59.65)	25 (54.35)	9 (81.82)	
BRAF mutation, n (%)				0.325
BRAF wt	24 (42.11)	21 (54.35)	3 (27.27)	
BRAF mut	33 (57.89)	25 (45.65)	8 (72.73)	
Desmoplastic reaction, n (%)				0>0.99
Present	21 (36.84)	17 (36.96)	4 (36.36)	
Absent	36 (63.16)	29 (63.04)	7 (63.64)	
Multiple foci, n (%)				0.498
Yes	24 (42.11)	18 (39.13)	6 (54.55)	
No	33 (57.89)	28 (60.87)	5 (45.45)	
Minimal extrathyroid extension, n (%)				0.716
Yes	17 (29.82)	13 (28.26)	4 (36.36)	
No	40 (70.18)	33 (71.74)	7 (63.64)	
Tumour size (cm)				0.57
Mean (SD)	1.87 (1.04)	1.83 (1.03)	2.03 (1.13)	
Median (IQR)	1.5 (1–2.5)	1.65 (1–2.5)	1.5 (1.3–3)	
Affected lymph nodes				0.07
Mean (SD)	2.54 (4.26)	2.33 (4.37)	3.73 (3.74)	
Median (IQR)	0 (0–3)	0 (0–2)	2 (0–9)	
Thyroglobulin 48 hours (ng/mL)				0.57
Mean (SD)	21.32 (65.53)	17.93 (56.54)	42.91 (103.18)	
Median (IQR)	2 (1.05–4.6)	2.8 (0.5–4.60)	2 (0.9–3.90)	

Table 1 (*continued*)

Table 1 (*continued*)

General variables	Total (n=57)	ER (n=46)	Response less than excellent NER (n=11)	P
Clinically significant nodes, n (%)				0.260
Yes	16 (28.07)	11 (23.91)	5 (45.45)	
No	41 (71.93)	35 (76.09)	6 (54.55)	

BCND, bilateral central neck dissection; BND, bilateral neck dissection; BRAF mut, BRAF mutation; BRAF wt, BRAF wild type; ER, excellent response; IQR, interquartile range; LND, lateral neck dissection; NER, non-excellent response; SD, standard deviation; TT, total thyroidectomy.

Table 2 Activity of I-131 administered after total thyroidectomy

I-131 activities	Total (n=56)	ER (n=45)	NER (n=11)	P
1,100 MBq	7 (12.50)	7 (15.56)	0 (0.00)	0.402
3,700 MBq	42 (75.00)	33 (73.33)	9 (81.82)	
5,550 MBq	7 (12.50)	5 (11.11)	2 (18.18)	

Data are presented as n (%). ER, excellent response; MBq, megabecquerels; NER, non-excellent response.

Table 3 Analysis of the uptake of I-131 according to the response to treatment

Dosimetric variables	Total (n=103)	ER (n=81)	NER (n=22)	P
Absorbed dose/administered activity				0.002
Mean (SD)	11.84 (25.96)	13.80 (28.85)	4.63 (5.66)	
Median (IQR)	7 (2.35–12.34)	8.10 (3.66–13.27)	2.35 (1.40–5.56)	
Accumulated activity				0.017
Mean (SD)	0.10 (0.23)	0.12 (0.25)	0.04 (0.05)	
Median (IQR)	0.06 (0.02–0.11)	0.07 (0.03–0.12)	0.02 (0.01–0.05)	
Activity at 2 d per administered activity (%)				0.003
Mean (SD)	0.09 (0.12)	0.10 (0.13)	0.04 (0.06)	
Median (IQR)	0.05 (0.02–0.11)	0.06 (0.03–0.11)	0.02 (0.01–0.04)	
Activity at 7 d per administered activity (%)				0.053
Mean (SD)	0.02 (0.05)	0.02 (0.06)	0.00 (0.01)	
Median (IQR)	0 (0–0.01)	0 (0–0.02)	0 (0–0.01)	

d, day; ER, excellent response; IQR, interquartile range; NER, non-excellent response; SD, standard deviation.

performed based on thyroid remnants after TT. In each patient there were between 1 and 3 thyroid remnants that were analyzed independently. Therefore, the total number of remnants was greater than the number of patients, 103. The absorbed activity per administered activity of I-131 (DTBRA/A administered) (Gy/GBq) was significantly distinct between the two groups, with the highest mean for the ER group, 13.8 (SD =28.85) *vs.* 4.63 (SD =5.66) respectively (P=0.002). The differences in the accumulated activity over time between the two response groups was also significant (P=0.017), with a higher accumulated activity for the group with a better response, 0.12 (SD =0.25) *vs.* 0.04 (SD =0.05), respectively. Furthermore, there were statistically significant differences in the percentage of uptake between activity administered at 2 days (P=0.003) and, although without reaching statistical significance at

Table 4 Multivariate analysis: variables related to non-excellent response

Variables	OR (95% CI)	P
Gender (male *vs*. female)	4.84 (1.48–15.86)	0.009
Activity at 7 d per administered activity (%)	0.29 (0.09–0.96)	0.043
Absorbed dose/administered activity	0.88 (0.79–0.97)	0.014
AUC (95% CI)	0.816 (0.720–0.912)	–

AUC, area under the curve; CI, confidence interval; d, day; OR, odds ratio.

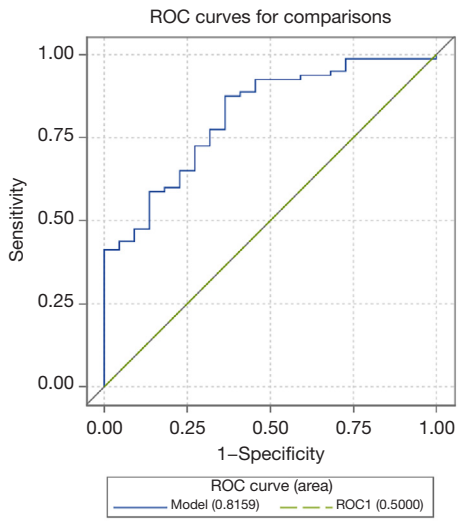

Figure 2 ROC curve for predictive model of variables related to non-excellent response. ROC, receiver operating characteristic.

7 days (P=0.053), higher values were obtained in both variables for the group with an ER [0.10 (0.13) *vs.* 0.04 (0.06), P=0.003 and 0.02 (0.06) *vs.* 0.00 (0.01), P=0.053].

The multivariate analysis to analyse the variables associated with a NER can be seen in *Table 4*. The only variables that were associated independently to the one NER were the male gender (P=0.009) and the activity absorbed according to the administered activity (P=0.014). As suggested, the gender variable showed large differences between NER and ER, although these are not significant (P=0.102), probably due to the limited sample. Although the Chi-squared test showed significant differences (P=0.0463), we had to use the Fisher exact test due to the existence of cells with expected count less than 5, and the P value of the Fisher exact test was P=0.102. However, for the multivariate analysis, we decided to include as possible covariates those with P<0.15 in the univariate analyses, since it could be that with the adjustment of other variables they would be significant. Therefore, the variable gender was considered for the multivariate model, becoming significant. In this regard, men have 4.84 times more probability of obtaining a NER in comparison to women. In addition, in terms of dosimetry, the increase of one unit in the percentage of administered activity at 2 days is associated with a decrease of 71% in the probability of a NER. Likewise, the increase of one unit in the absorbed dose is associated with a decrease of 12% in the probability of a NER. The predictive capacity of the model including the two dosimetric variables was AUC (95% CI) of 0.816 (0.720–0.912) (*Table 4*, *Figure 2*).

Discussion

Nowadays, PTC is considered a malignant pathology with a high cure rate. However, it is essential to carry out both the correct treatment and effective follow-up that detects the patients with high probabilities of recurrence. In our study, at 1 year of monitoring, 19.3% of patients obtained a NER, that is, incomplete biochemical response (the majority), incomplete structural or indeterminate response. The proportion is somewhat higher than other series, but this is due to the fact that our studied population excluded those with a better prognosis who did not require I-131 treatment (19). Among the males, the percentage of NER was higher than that of ER (45.45% *vs.* 17.39%). This was not the case for the females, who obtained a higher percentage of ER (82.61% *vs.* 54.55%), which shows once again the poor prognosis of men compared to women, as has been commented in previous studies (1,3,6,20). It is worth highlighting the decision not to include microcarcinomas. This was based on the fact that, according to the latest recommendations, I-131 therapy is not indicated in these patients, and therefore, dosimetry would be impossible (3). In addition, patients with thyroiditis were not included, since this condition could affect the I-131 uptake and, therefore, the calculation of dosimetric values (21).

As for the surgical technique, most of the patients with an ER were those who underwent TT with bilateral lymph node dissection (78.26%). It is striking that the majority of patients who underwent TT, bilateral central lymph node dissection and unilateral lateral lymph node dissection had a NER, 45.45%, compared to the small percentage of those who did obtain an ER, 8.7%. In both types of surgery, lymph node dissection was therapeutic. The indication for therapeutic surgery in cases of central metastases is already established in the literature, so these results support what has already been published (22). Therefore, we can reaffirm that patients with central metastases, if they undergo therapeutic lymph node dissection surgery, have a greater probability of an excellent prognosis. This is not the case if the disease is more widespread, if the metastases are in the lateral compartment, even with radical surgery, the outcome is more likely to be less than excellent, results in line with what has already been published (23). To confirm these conclusions, it would be appropriate to design studies with more evidence, larger patients series and a robust study design.

With respect to the clinicopathological variables, it can be highlighted that the classic variant was more common than the follicular within the group of patients with a non-excellent result. This result is similar to what has been published, as it could point to a slightly more pronounced aggressiveness in the classic variant (19,20). It is interesting to highlight that another of the histological characteristics that is more closely associated with a NER was that of having a V600E mutation of the *BRAF* gene. Today, there are still controversies regarding the prognostic significance of this mutation; some authors have found an association with higher mortality, more aggressive variants, and ultimately a poorer prognosis (24-27). Others, on the contrary, have found their results to be inconclusive (28). Our team already studied the relationship between the mutation and its association with the I-131 treatment, concluding a greater resistance to this therapy in the group of patients who presented the mutated gene (14). Nonetheless, the significance of a mutation cannot be overlooked, as these arise biologically from the accumulation of genetic errors which inherently entail a higher degree of aggressiveness, and therefore a worse response. In the same way, the extrathyroidal extension was more frequent in patients with a poorer response. This condition has already been considered by the ATA guide as a factor of poor prognosis and to be taken into account when deciding a treatment, for which reason our results agree with what has already been published (3). In line with this, the number of affected lymph nodes is also higher in the group of patients with a NER; therefore, this should be considered when designing a follow-up strategy for these patients. These results have also been considered in the literature by several authors (29). Finally, the Tg was higher at 48 hours from the I-131 treatment (42.91 *vs.* 17.93 ng/mL) which denotes greater residual tissue or poor response to the I-131 treatment, as published in the literature (30). Although none of these differences were statistically significant, probably due to the size of the sample, it would be interesting to consider them for future studies.

As for the administered I-131 activity, both in the complete response group and in the group with a less than complete response, the most frequently administered activity was 3,700 MBq. This activity is what is usually administered in patients that require an ablative strategy, as indicated by the guidelines and according to the latest consensus (31).

In the PTC evaluation, SPECT/CT imaging is increasingly being used due to its ability to anatomically locate precisely the abnormal lesions that accumulate radiotracers. This can be used as a tool to predict the risk of recurrence and therefore the decision on treatment (12). However, the analyses of the quantitative parameters of these images are limited. Recently, some authors have published their papers on the relationship between these parameters and the effectiveness of ablation (6). In our study, the uptake in SPECT/CT is done based on the thyroid remnants after administering post-surgical I-131. It is important to emphasise that the analyses were done quantitatively through dosimetry, which implies greater precision of information than that which can be obtained when it is only done qualitatively. The absorbed activity per dose of administered activity of I-131 was significantly different between the two groups, being greater for the excellent-response group. In the same way, the differences in the accumulated activity over time between the two response groups were also significant, with the higher accumulated activity observed in the group with a better response. This indicates that not only does better absorption of I-131 imply a better response, but also a greater I-131 activity accumulated over time is also going to imply a better response to therapy. Regarding the uptake percentage, at 2 days from administering I-131, a significant difference was observed, obtaining an ER in those who present a higher percentage of uptake. These results support the idea that when I-131 uptake is greater, the

treatment will be more effective and therefore, the response to the therapy will be excellent.

In line with this, the multivariate analysis reveals that being male implies being 4.84 times more likely to obtain a NER at 1 year of monitoring after I-131 therapy in comparison with females. Once again and as was published on several occasions in the literature, the male gender is a risk factor that implies a less favourable prognosis for thyroid cancer (20). Furthermore, in terms of dosimetry, by increasing one percentage point of absorbed activity at 7 days, the probability of a NER decreased 71%. This result is more striking than that corresponding to the absorbed dose, since, in this case, by increasing by one unit of absorbed dose, the probability of a NER only decreases by 12%.

Although it is not the objective of the study to review the proposals on DRS that have been made over the years, there have been authors who have proposed other research models such as adding the telomerase reverse transcriptase (TERT) promoter to redefine the dynamic risk (32). Thus, we have opened a new line of research with the contribution of dosimetric variables, not proposed until now. However, as has been emphasized, it would be advisable to carry out long-term studies with a larger number of patients to validate this proposal. This model presents a predictive uptake of 0.816 (0.720–0.912). With this result, it can be considered useful as a tool associated with the DRS, contributing greater information in order to individualize the prognostic monitoring strategy and in this way, future decision-making during the follow-up of the patients with PTC.

The fundamental limitation of the study is the small sample size, in addition to the usual limitations of an observational study and therefore we must be cautious when generalizing it. However, these cases were selected to reflect the common clinical practice, with standard histological variants. For this reason, other types of studies should be designed with a larger population to confirm the results. In second place, the follow-up of the patients was done after 1 year; therefore, a longer follow-up would be beneficial to assess the impact of the analysed dosimetric variables on prognosis.

Conclusions

In conclusion, observed patients with PTC and lymph node metastasis of the central compartment who underwent TT with therapeutic lymphadenectomy had an ER after 1 year of monitoring in 78% cases. In addition, the quantitative parameters obtained from SPECT/CT imaging after I-131 treatment, specifically the absorbed dose, the percentage at 2 d, and the accumulated activity, can be useful in assessing the risk of recurrence at 1 year in patients with PTC. Lower levels of these parameters imply a less than ER to treatment. Lastly, the male gender, the absorbed dose and the percentage of absorbed dose at 7 d can be incorporated as a tool in DRS after 1 year of follow up in PTC patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The Basurto University Hospital. Individual consent for this retrospective analysis was waived.

References

1. Francis GL, Waguespack SG, Bauer AJ, Angelos P,

Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S; American Thyroid Association Guidelines Task Force. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2015;25:716-59.
2. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, LiVolsi VA, Papotti MG, Sobrinho-Simões M, Tallini G, Mete O. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol 2022;33:27-63.
3. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
4. TNM Classification of Malignant Tumours, 7th Edition.
5. Powers PA, Dinauer CA, Tuttle RM, Francis GL. The MACIS score predicts the clinical course of papillary thyroid carcinoma in children and adolescents. J Pediatr Endocrinol Metab 2004;17:339-43.
6. Tuttle RM. Risk-adapted management of thyroid cancer. Endocr Pract 2008;14:764-74.
7. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 2010;20:1341-9.
8. Castagna MG, Maino F, Cipri C, Belardini V, Theodoropoulou A, Cevenini G, Pacini F. Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur J Endocrinol 2011;165:441-6.
9. d'Herbomez M, Lion G, Béron A, Wémeau JL, DoCao C. Advances in thyroglobulin assays and their impact on the management of differentiated thyroid cancers. Ann Biol Clin (Paris) 2016;74:21-7.
10. Mariotti S, Barbesino G, Caturegli P, Marinó M, Manetti L, Pacini F, Centoni R, Pinchera A. Assay of thyroglobulin in serum with thyroglobulin autoantibodies: an unobtainable goal? J Clin Endocrinol Metab 1995;80:468-72.
11. Zhang Q, Xu W. Correlation analysis of I-131 SPECT/CT uptake parameters with the success ablation treatment of thyroid remnant in patients with low-intermediate-risk differentiated thyroid cancer. Nucl Med Commun 2022;43:1051-7.
12. Klubo-Gwiezdzinska J, Van Nostrand D, Atkins F, Burman K, Jonklaas J, Mete M, Wartofsky L. Efficacy of dosimetric versus empiric prescribed activity of 131I for therapy of differentiated thyroid cancer. J Clin Endocrinol Metab 2011;96:3217-25.
13. Holst JP, Burman KD, Atkins F, Umans JG, Jonklaas J. Radioiodine therapy for thyroid cancer and hyperthyroidism in patients with end-stage renal disease on hemodialysis. Thyroid 2005;15:1321-31.
14. Domínguez-Ayala M, Mínguez-Gabiña P, Paja-Fano M, Bilbao-González A, Expósito-Rodríguez A, Rodeño-Ortiz de Zarate E. The role of BRAF V600E mutation in post-surgical 131I therapy in papillary thyroid carcinoma: a study based on SPECT-CT uptake analysis. Q J Nucl Med Mol Imaging 2023;67:83-92.
15. Domínguez Ayala M, Expósito Rodríguez A, Bilbao González A, Mínguez Gabiña P, Gutiérrez Rodríguez T, Rodeño Ortiz de Zarate E, García Carrillo M, Barrios Treviño B. BRAF V600E mutation in papillary thyroid cancer and its effect on postoperative radioiodine ((131)I) therapy: Should we modify our therapeutic strategy? Cir Esp (Engl Ed) 2018;96:276-82.
16. Miranda-Filho A, Lortet-Tieulent J, Bray F, Cao B, Franceschi S, Vaccarella S, Dal Maso L. Thyroid cancer incidence trends by histology in 25 countries: a population-based study. Lancet Diabetes Endocrinol 2021;9:225-34.
17. Expósito Rodríguez A, Corta Gómez I, Domínguez Ayala M, García Carrillo M, González García AI, Gutiérrez Rodríguez MT, et al. Ganglio centinela en la metástasis ganglionar por cáncer papilar de tiroides: validez diagnóstica y aplicación en la práctica clínica. Cir Esp 2022;100:416-21.
18. Mínguez P, Flux G, Genollá J, Delgado A, Rodeño E, Sjögreen Gleisner K. Whole-remnant and maximum-voxel SPECT/CT dosimetry in (131)I-NaI treatments of differentiated thyroid cancer. Med Phys 2016;43:5279.
19. Steinschneider M, Pitaro J, Koren S, Mizrakli Y, Benbassat C, Muallem Kalmovich L. Differentiated Thyroid Cancer with Biochemical Incomplete Response: Clinico-Pathological Characteristics and Long Term Disease Outcomes. Cancers (Basel) 2021.
20. Li P, Ding Y, Liu M, Wang W, Li X. Sex disparities in thyroid cancer: a SEER population study. Gland Surg 2021;10:3200-10.
21. Happel C, Bockisch B, Leonhäuser B, Sabet A, Grünwald

F, Groener D. The influence of thionamides on intra-thyroidal uptake of 131I during radioiodine-131 treatment of Graves' disease. Sci Rep 2023;13:21190.
22. Goepfert RP, Clayman GL. Management of the central compartment in differentiated thyroid carcinoma. Eur J Surg Oncol 2018;44:327-31.
23. Kim HI, Kim TH, Choe JH, Kim JH, Kim JS, Kim YN, Kim H, Kim SW, Chung JH. Surgeon volume and prognosis of patients with advanced papillary thyroid cancer and lateral nodal metastasis. Br J Surg 2018;105:270-8.
24. Shi X, Liu R, Basolo F, Giannini R, Shen X, Teng D, et al. Differential Clinicopathological Risk and Prognosis of Major Papillary Thyroid Cancer Variants. J Clin Endocrinol Metab 2016;101:264-74.
25. Henke LE, Pfeifer JD, Baranski TJ, DeWees T, Grigsby PW. Long-term outcomes of follicular variant vs classic papillary thyroid carcinoma. Endocr Connect 2018;7:1226-35.
26. Li J, Zhang S, Zheng S, Zhang D, Qiu X. The BRAF V600E mutation predicts poor survival outcome in patients with papillary thyroid carcinoma: a meta analysis. Int J Clin Exp Med 2015;8:22246-53.
27. Liu C, Chen T, Liu Z. Associations between BRAF(V600E) and prognostic factors and poor outcomes in papillary thyroid carcinoma: a meta-analysis. World J Surg Oncol 2016;14:241.
28. Henke LE, Pfeifer JD, Ma C, Perkins SM, DeWees T, El-Mofty S, Moley JF, Nussenbaum B, Haughey BH, Baranski TJ, Schwarz JK, Grigsby PW. BRAF mutation is not predictive of long-term outcome in papillary thyroid carcinoma. Cancer Med 2015;4:791-9.
29. Cao YM, Zhang TT, Li BY, Qu N, Zhu YX. Prognostic evaluation model for papillary thyroid cancer: a retrospective study of 660 cases. Gland Surg 2021;10:2170-9.
30. Stevic I, Dembinski TC, Pathak KA, Leslie WD. Transient early increase in thyroglobulin levels post-radioiodine ablation in patients with differentiated thyroid cancer. Clin Biochem 2015;48:658-61.
31. Ahuja S, Avram AM, Dillehay G, Greenspan BS, Gulec S, Van Nostrand D. The Martinique Principles. J Nucl Med 2019;60:1334-5.
32. Kim TH, Ki CS, Kim HS, Kim K, Choe JH, Kim JH, Kim JS, Oh YL, Hahn SY, Shin JH, Jang HW, Kim SW, Chung JH. Refining Dynamic Risk Stratification and Prognostic Groups for Differentiated Thyroid Cancer With TERT Promoter Mutations. J Clin Endocrinol Metab 2017;102:1757-64.

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