Possible delayed diagnosis and treatment of metastatic differentiated thyroid cancer by adopting the 2015 ATA guidelines

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Abstract

Objective: According to the 2015 American Thyroid Association (ATA) guidelines, thyroid ablation by iodine-131 (I-131) therapy is absolutely recommended only in patients with high-risk differentiated thyroid cancer (DTC). Often distant metastases are not recognized early and they can stay silent for long time. The aim of our study was to retrospectively analyze the prevalence of metastatic disease before and after I-131 and to evaluate the influence of the new ATA guidelines in the management of DTC.

Methods: We retrospectively analyzed 140 patients showing distant metastases. All metastases were detected by whole-body scan after I-131 and confirmed by histology and/or other imaging modalities.

Results: In 26/140 patients metastases were detected before I-131, while in 114/140 were discovered after I-131. Comparing patients with metastases detected before and after I-131, no differences were demonstrated considering age, sex, histotype, tumor size, multifocality of cancer and metastatic localization. Metastatic DTC discovered before radioiodine had higher thyroglobulin and received a higher radioiodine total activity and number of treatments. Considering patients with distant metastases, according to the 2015 ATA guidelines, 38 patients would have been categorized as high risk, 22 as low risk and 80 as intermediate risk. Among intermediate-risk patients, only in 25 cases (31%) I-131 treatment would have been appropriate according to 2015 ATA recommendations; in the remaining 56 cases (69%), I-131 would not have been recommended.

Conclusions: According to the 2015 ATA guidelines, most of metastatic patients would not have been treated after surgery, with the risk of late diagnosis and delayed treatment.

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Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy accounting for 5% of all cancers diagnosed each year in female population (1) and is considered a slowly growing disease with favorable prognosis. The 5-year survival rates for DTC are 99.8% for localized tumors, 97% for tumors with regional metastases and 57.3% for tumors with distant metastases (2). Metastatic DTC patients are a group with lower survival rate; they need an early and appropriate treatment to improve prognosis. Radioiodine therapy can be an effective treatment for metastatic patients and may contribute significantly to their life expectancy (3). In 2015, the American Thyroid Association (ATA) released the new version of the guidelines for the management

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of patients with thyroid nodules and DTC (4), compared to the previous version (5); these guidelines show a huge effort to guide decision making with more than 100 recommendations. Despite this, many doubts and objections are arising about these guidelines (6, 7, 8) and probably they should be a matter of debate and further discussions. One of the major critical issue is the indication for post-operative iodine-131 (I-131); 2015 ATA guidelines in 'Recommendation 51A' and 'Table 14' established that post surgery I-131 treatment should not be routinely performed in patients considered at low risk; this include patients with unifocal microcarcinoma and patients with larger tumor sizes up to 4 cm. Instead, in patients with ATA high-risk, radioiodine therapy is routinely recommended. In patients with ATA low-to-intermediate risk, that is the most commonly observed group, which includes patients with tumor size larger than 4 cm or with microscopic extrathyroidal extension (T3 according to AJCC classification), and patients with central neck and lateral neck compartment lymph nodes metastases (T1–T3, N1a-b), I-131 is not proposed as mandatory and should be considered only for patients with additional high-risk factors (including advanced age, morphological characteristics of nodes, number of nodes). Furthermore, in the description of the adverse features, there are many open questions without clear indications (3, 9); for example, there is no clear definition of advanced age. The term 'consider' is frequently adopted and it opens many clinical scenarios in patient management, making recommendations not univocal and susceptible to different interpretations. Controversial perspectives about I-131 indications could lead to a reduction of the number of patients eligible for radioiodine therapy, potentially missing metastatic disease. Our aim was to retrospectively analyze in a consecutive cohort of patients evaluated in our institute the prevalence of metastatic disease detected before and after I-131 and to evaluated what influence the new ATA guidelines would have had in the diagnostic work-up and/or treatment of metastatic patients.

Subjects and methods

We retrospectively screened 2516 patients who underwent I-131 for DTC after total or near total thyroidectomy from January 2008 until January 2017 using our institutional Radiology Information System. They were admitted to the Nuclear Medicine Department of our Institution for the ablation of thyroid remnant according European Association of Nuclear Medicine (EANM) guidelines (10). Out of these 2516 patients, we identified 140 cases of metastatic DTC (91 female; 49 male; sex ratio F:M 1.9:1). All metastases were confirmed by histology when available and/or other imaging modalities (computed tomography, magnetic resonance imaging, positron emission tomography and ultrasonography).

The patients' age ranged from 16 to 82 years with a mean age of 57.4 ± 16.2; only three patients were pediatric (age less than 18 years) at the time of diagnosis. All patients had histopathological diagnosis of DTC: 58 classic variant of papillary carcinoma, 35 follicular variant of papillary carcinoma, 10 aggressive papillary variants (4 tall cells variant of papillary carcinoma and six poorly differentiated carcinoma), 35 follicular carcinoma and 2 Hurthle cell carcinoma. Tumor size was 3.1 ± 2.2 cm (range: 0.15–7.5 cm), multicentricity of neoplastic lesions was present in 59 cases (42%) and extrathyroidal extension of primary carcinoma in 79 cases (56%). One hundred and twenty-four patients underwent levothyroxine withdrawal for 40 days, replaced by levo-triiodothyronine in the first 20 days and in 16 patients recombinant human thyrotropin (rhTSH-Thyrogen, Genzyme Corporation) was administered intramuscularly with a dose of 0.9 mg over two consecutive days during treatment with levothyroxine, and radioiodine was administered the day after the second injection. All patients followed a low-iodine diet for 2 weeks and the serum thyrotropin (TSH) concentration was higher than 30 mIU/L before radioiodine administration. In patients without antithyroglobulin antibody (AbTg) interference, serum thyroglobulin (Tg) at the time of first radioiodine treatment was 303 ± 329 ng/mL (range: 0.1–1001); AbTgs were positive in 30 patients (21%).

All patients underwent whole-body scintigraphy followed by SPECT/CT scanning on the same day; the imaging was acquired 3–4 days after I-131 administration. Hybrid SPECT/CT scans from skull base to the lung bases were routinely obtained in all patients and additional SPECT/CT scans of other areas were performed depending on whole-body scintigraphy findings.

The administered activity of I-131 first treatments ranged from 1.1 to 7.4 GBq (average: 3.2 GBq) and it was established according to the risk class based on the TNM staging of the American Joint Committee on Cancer/International Union against Cancer currently in use (11) and the status of the disease. Typically, 1.1 GBq were administered to low-risk patients, 1.85 GBq to intermediate-risk patients and a high-dose (3.7 GBq) to high-risk patients. The mean ± standard deviation number of radioiodine therapies per patient was 4.3 ± 2.7 (range:

1–11); the average cumulative I-131 activity administered per patient was 31.8 ± 41.3 GBq (range: 1.1–114 GBq). Baseline characteristics of all patients are summarized in Table 1. The average follow-up time was 70 ± 18 months (range 9–118 months).

All patients gave their written informed consent; ethical statement that approves this study was not required due to its retrospective nature.

Statistical analysis

Statistical analysis was carried out using SPSS, version 23.0 for Windows (IBM). The descriptive analysis of categorical variables comprised the calculation of simple and relative frequencies. The numeric variables were described as mean, minimum and maximum. The statistical significance of the continuous variables was tested with a Student's *t*-test or Mann–Whitney's *U* test and a χ^2 test was performed for the categorical variables. A *P* value of ≤0.05 was considered as statistically significant.

Table 1 Baseline characteristics of 140 patients.

	Average (range)	**Patients, *n*** (%)
Age	57.4 (16–82)	
Male		49 (65)
Female		91 (35)
Histotype		
Papillary		58 (41)
Follicular variant of papillary		35 (25)
Follicular		35 (25)
Aggressive variant		10 (7)
Hurtle cell		2 (2)
Tumor size (cm)	3.1 (0.15–7.5)	
Site of metastases		
Lung		63 (45)
Bone		56 (40)
Lung + bone		16 (11)
Other		5 (4)
Multicentricity		59 (42)
Tg at the time of ablation (ng/mL)	303 (0.1–1001)	
AbTg positive patients		30 (21)
Single RAI activities administrated (GBq)	3.2 (1.1–7.4)	
Cumulative RAI activities administrated (GBq)	31.8 (1.1–114)	
N° therapies	4.3 (1–13)	
Follow-up time (months)	70 (9–118)	

GBq, gigabequerel; N°, number; RAI, radioiodine; var, variant.

Results

Of the 2516 patients evaluated, 140 (5.6%) showed distant metastases of DTC: 55 in the bone, 63 in the lung, 16 in bone and lung simultaneously and 6 in other localizations (Fig. 1). Histological confirmation was achieved in 68 patients, while in another 72 cases other imaging modalities confirmed the presence of metastases. Overall, 26 of 140 (19%) metastases were detected before I-131, while 114 (81%) were diagnosed after I-131. Considering the first group, metastases were localized in the bone in 14 patients, in the lung in 6, in the bone and lung together in 3, in the muscular system in 1 and in the bone and brain in 2 cases; in 15 cases, metastases were diagnosed because of complications or symptoms such as fractures, bone pain, cough, dyspnea, while in the remaining 11 cases, they were incidentally detected with other imaging techniques performed for other reasons. Thus, in these patients, the detection of metastases was the first step, which led to the diagnosis of DTC. All patients with metastases detected before I-131 were considered as ATA high-risk class of recurrence. Instead, in 114 patients with metastases discovered after I-131, 60 (53%) metastases were recognized in the first whole-body scan after treatment, while the other 54 (47%) were detected in the subsequent scintigraphies. Forty-two of 114 were localized in the bone, 57 in the lung, 13 in both the lung and bone, 1 in the brain and 1 in the liver. Among patients with metastases detected after I-131, AbTgs were positive in 27 cases making Tg values unreliable (Fig. 2); in 14 cases with metastases detected at first whole-body scintigraphy and the remaining 13 in subsequent scintigraphies. Stimulated Tg values at first I-131 therapy was 129 ± 174 ng/mL (range 0.1–1001) and was significantly lower compared to patients with metastases diagnosed before radioiodine therapy (438 ng/mL; $P < 0.001$; Table 2). In 29/87 (33%), the stimulated Tg level at the time of I-131 was less than 10 ng/mL, a value conventionally not considered suspicious for distant metastases. Among them, ten had distant metastases detected at the first whole-body scintigraphy after I-131 and 19 in the subsequent course of disease. In the remaining 58 patients, post-operative Tg value was less than 5 ng/mL in 32 cases (55%) and less than 10 mg/dL in 39 (67%). Thus, only in 19 cases post-operative Tg was higher than 10 ng/mL, a value considered suspicious for the presence of distant metastases, and among them, ten were classified as high risk after surgery and before I-131.

Comparing patients with metastases detected before and after I-131, no differences were demonstrated

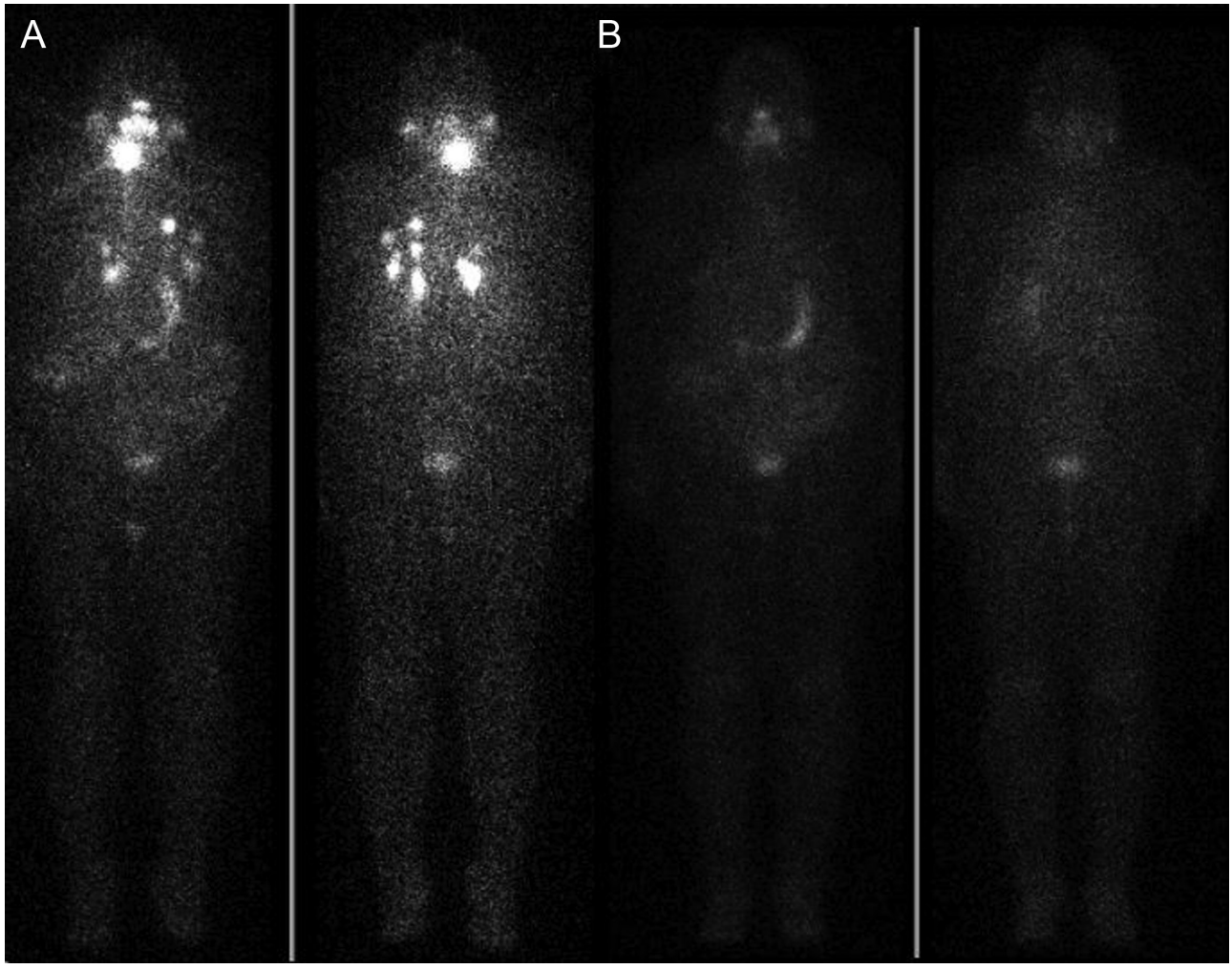

Figure 1

A representative case of a 64-year old woman with a conventional papillary carcinoma with thyroid capsule invasion and microscopic extrathyroidal extension and without cervical pathological nodes (pT3N0 according to AJCC 2010 classification, low-to-intermediate risk according to ATA 2015 guidelines). After thyroid hormone withdrawal, he received 3.7 GBq of I131 for remnant ablation. The TSH level was 58 U/L, serum Tg 7.8 ng/mL and serum TgAb <1 IU/mL. I131 total body planar scintigraphy (A, anterior and posterior views) showing intense uptake of tracer in the upper central area of the neck corresponding to residual thyroid tissue and several bilateral areas of thoracic focal uptakes due to metastatic lung lesions 1 year later, the total body planar scintigraphy (B, anterior and posterior views) showing the disappearance of the previous uptakes with negative stimulated Tg (<1 ng/mL).

considering age, sex, tumor size, histotype, multifocality of primary cancer, presence of AbTg and metastatic localization (Table 2). Metastatic DTC discovered before I-131 received a higher cumulative 131-I activity and number of treatments.

Considering all 140 patients, only 38 (27%) were classified as high risk according to 2015 ATA guidelines after surgery and before I-131 (12 because of gross extrathyroidal extension and 26 because of distant metastases diagnosed before I-131); 22 (16%) were classified as low risk, (tumor size less than 4 cm and without other pathological findings) and 80 (57%) were classified in the in low-to-intermediate risk class (17 patients with tumor size more than 4 cm, 23 with microscopic extrathyroidal extension, 10 with the presence of nodal metastases in central neck compartment and 30 with metastatic lymph nodes in lateral neck compartment). Analyzing the 80 patients classified in ATA as low-to-intermediate risk, 16 presented adverse features potentially relevant for considering I-131 (in six cases due to the histological diagnosis of aggressive

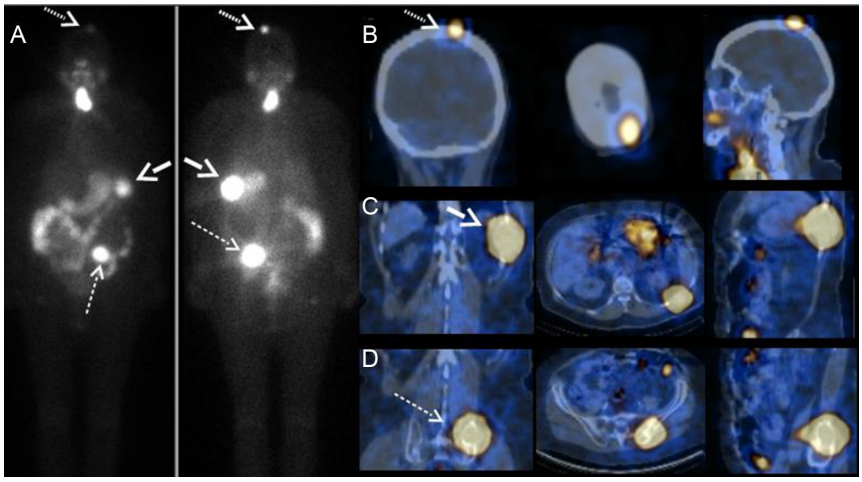

Figure 2
A representative case of 45-year old woman with a follicular carcinoma (pT1b according to AJCC 2010, low risk according to ATA 2015), positive AbTg (75 IU/mL) and undetectable Tg (<1 ng/mL) after rh-TSH stimulation. I131 total body planar scintigraphy (A) after 1.85 Gbq of I131 demonstrating intense uptake in the neck corresponding to thyroidal remnant and three I131 uptakes in the bone: skull (B dashed arrow, coronal, axial and sagittal images), a left rib (C thick arrow, coronal, axial and sagittal images) and the right sacroiliac joint (D thin dashed arrow, coronal, axial and sagittal images). A full color version of this figure is available at https://doi.org/10.1530/EJE-18-0253.

variant papillary carcinoma and in ten due to the presence of increasing number of large lymph nodes, more than 1 cm, and/or clinical evidence of them) and nine had post-operative Tg higher than 10 ng/mL. Thus, only in 25/80 (31%) patients with low-to-intermediate risk, I-131 ablation would have been indicated according to 2015 ATA guidelines recommendations. In the remaining 55 (69%), I-131 ablation of thyroid remnant would not have been recommended (Table 3). Among low-risk group, nobody had elevated post-operative Tg and/or adverse features.

Considering all 2516 patients analyzed between 2008 and 2017, 250 patients (10%) were classified in ATA high-risk group, 1639 (66%) in low-to-intermediate risk and 616 (24%) in low risk.

Discussion

I-131 therapy of DTC was performed for the first time in 1943 (12); since then, the worth and efficacy of I-131 in DTC treatment has been proven in several landmark studies (13, 14), especially in carcinoma with diameter greater than 1 cm (15) and especially in DTC with distant metastases (3). The main aims of post-operative administration of I-131, also called 'ablation', were threefold: (1) to treat any remaining, unknown cancer tissue in the thyroid bed, lymph nodes or other locations; (2) to recognize and prevent recurrences and (3) to destroy any remaining healthy thyroidal cells contributing to make subsequent Tg determination during follow-up as a reliable tumor marker (16). Several authors have demonstrated the role of post- I-131 whole-body scan in the detection of occult distant metastases, mainly in bone and lung; distant metastases are the main cause of death and an early detection offers greater opportunities for a cure (15, 16, 17, 18, 19). Moreover, in recent years, the introduction in clinical practice of single photon

Table 2 Comparison between clinical and pathological features in patients with metastases recognized before or after RAI.

	Metastases before RAI (*n* = 26)	Metastases after RAI (*n* = 114)	*P* value
Sex F:M	17:9	74:40	0.885
Age at diagnosis	62.4	56	0.586
T tumor size (cm)	3	3.1	0.742
Multicentricity	6	53	0.747
Histotype: classic var papillary	6	52	0.612
Follicular var papillary	6	29	
Follicular	14	21	
Aggressive variants	2	8	
Hurtle cell	1	1	
Mean Tg at ablation (ng/mL)	438	129	<0.001
AbTg pos	3	27	0.397
First RAI activity (GBq)	3.6	3.1	0.08
Cumulative RAI activities (GBq)	34.7	27.6	0.003
N° therapies	5.2	3.3	0.02
Metastases: bone	14	42	0.111
Lung	6	57	0.012
Lung + bone	3	13	0.986
Other	3	2	0.102

Ab, antibodies; F, female; GBq, gigabequerel; M, male; N°, number; pos, positive; RAI, radioiodine; Tg, thyroglobulin.

Table 3 Summary of patient's class risk features and indication to RAI following 2015 ATA guidelines.

2015 ATA risk class	pTNM (AJCC 2010)	No. of patients	Adverse features suggesting RAIT	Post surgical potential RAI indication	
ATA high risk ($n=38$)	T4, any N, any M	12	ne	12/12 (100%)	38/38 (100%)
	M1, any T, any N	26	ne	26/26 (100%)	
ATA low-to-intermediate risk ($n=80$)	T3, N0-x, M0-x for tumor size	17	2	2/17 (12%)	25/80 (31%)
	T3, N0-x, M0-x for extension	23	4	4/23 (17%)	
	T1-3, N1a, M0-x	10	7	7/10 (70%)	
	T1-3, N1b, M0-x	30	12	12/30 (40%)	
ATA low risk ($n=22$)	T1a, N0-x, M0-x	2	0	0/2 (0%)	0/22 (0%)
	T1b-2, N0-x, M0-x	20	0	0/20 (0%)	

ne, not evaluated; P, post surgical; RAIT, radioiodine therapy.

computerized tomography-computed tomography (SPECT-CT) acquisition has significantly improved the accuracy and detection rate (20).

In our analysis, we included all patients with distant metastases detected in our center, considering both patients with metastases detected before and after I-131. These two groups were similar seeing the main epidemiological and clinical features (age, sex, size, histotype, multifocality of thyroid cancer, presence of AbTg and site of metastases) as showed in Table 2. Instead, patients with distant metastases detected before radioiodine seemed to have a more aggressive behavior and needed a higher cumulative I-131 activity and a higher number of treatments.

Recent 2015 ATA guidelines have reduced the indication to I-131, suggesting a more conservative approach after surgery and, consequently, determining a significant reduction of candidates for I-131. In our paper, we have demonstrated that 102 patients after surgery would not have had a recommendation for I-131 because they were classified as ATA low and low-to-intermediate risk (22 and 80 respectively). Despite the fact that 25 patients showed the presence of additional adverse characteristics or higher post-operative Tg value (>10 ng/mL) potentially useful in 'considering' the I-131 option, in the remaining 77 I-131 might have been omitted. In these patients, the lack of I-131 could have affected their management, delaying both the diagnosis of metastatic disease and treatment and probably affecting the patient outcome. The high risk of downstaging DTC after surgery with consequent delay in therapeutic decision making should council caution in abandoning a long-established and successful clinical practice. The ATA 2015 guidelines (4) also emphasize the absence of specific studies about I-131 efficacy in the intermediate-risk group. In a recent systematic review, Lamartina *et al*. (21) reported conflicting results on the impact of I-131 treatment on disease recurrence, including in the paragraph dedicated to ATA intermediate-risk patients. The authors concluded that 'more research is needed to understand the therapeutic efficacy in various subgroups of patients in the ATA intermediate-risk category'. A surveillance without I-131 ablation is based on the assumption of an indolent course of DTC but several studies demonstrated adverse outcomes, due to regional or distant metastatic disease (22), in patients that delayed I-131. So far, the hypothesis that a less frequent use of I-131 could be clinically favorable and indicated is based on non-long-term follow-ups papers, often less than 10 years; longer follow-up periods (at least 10–15 years) are needed to assess reliably the effective role of I-131 therapy (23); in the meantime, in our opinion, I-131 remains a reasonable option, especially in the numerous situations where the literature is controversial (24). Avoiding I-131 ablation and subsequent whole-body scintigraphy can imply a systematic understaging of a non-negligible number of metastatic patients, with the only advantage of a mild reduction of the effective radiation dose exposure. It should be underlined that the administered activities are currently lower than those in the past, because 1.1 GBq after thyroid remnant uptake stimulation by recombinant TSH was proven in multi-center trials (25, 26) to be effective in thyroid remnant ablation and comparable to higher activities. Some authors suggested performing a diagnostic pre-ablation I-123 or I-131 (27, 28, 29, 30) scan as an alternative to therapeutic 131I whole-body scintigraphy; however, 123I whole-body scan, independently of the tracer cost, can be sub-optimal due to the short half-life of this radiopharmaceutical, with the risk of missing metastatic lesions with late uptake and, conversely, a 131I scintigraphy performed with diagnostic activity (usually 185 MBq) could be not sensitive enough, especially for SPECT/CT imaging, in comparison with the therapeutic one, especially in case of isolated and

small metastases (31, 32). The importance of an accurate initial staging should be strongly considered, taking into account an acceptable health detriment being adverse effects generally mild and transient especially in post-operative adjuvant I-131 (33, 34). Serum thyroglobulin determination has an important role in post-operative risk stratification, but post-operative Tg levels alone cannot be used as a milestone criterion to recommend for or against I-131. New recommendations include using post-operative Tg measurement (a few weeks after total thyroidectomy either TSH stimulated or not stimulated) as a tool to discriminate between high and low-risk patients and consequently for indication to adjuvant I-131 (35). Moreover, in some cases, Tg can be false negative in recurrent or metastatic DTC patients when there are thyroglobulin antibodies present (36). Different technical problems may involve Tg measurement and need to be carefully considered when using Tg as a marker for the presence of residual thyroid tissue. First, the possible interference from TgAb compromises the use of serum Tg as a tumor marker in immunometric methods (37); second, interferences by heterophilic antibodies, called 'high-dose hook effect', may lead to reporting inappropriately low serum Tg (37, 38, 39); third the variability between different Tg immunoassays should be considered (29, 40). As underlined in ATA 2015 guidelines (4), no precise Tg value cutoffs are established to define what is a complete thyroid removal to omit RAIT. Post-operative Tg value is strongly dependent on the type of determination (stimulated or nonstimulated), type of stimulation (rh-TSH vs withdrawal), the actual level of TSH stimulation and the volume of remnant thyroid tissue (9, 35, 36). In our study, 25% of patients without pre-surgery known metastases had low stimulated Tg values (less than 10 ng/mL), not suggesting the presence of distant metastases, confirming the poor value of post-operative Tg alone in the decision making for I-131. Moreover, also post-operative Tg value seems to be a poor tumoral marker because it may be frequently lower (41). Also in our study, only ten patients presented post-surgical Tg >10 ng/mL in the intermediate group and these Tg values led to radioiodine therapy. We agree that not all DTC patients who are treated with I-131 would really benefit from this therapy, but it is not objectively possible to identify these patients without evidence based criteria, which require large prospective studies with very long-term follow-ups.

This study has several limitations based on its retrospective analysis, the relative small sample of patients analyzed, partially due to the rarity of the metastatic disease in DTC patients, and the lack of histological confirm of every metastasis. In conclusion, our study demonstrates that distant metastases in DTC patients are mainly detected after I-131; the majority of these patients belong to the ATA system low-to-intermediate risk group. By following the 2015 ATA guidelines class risk definition and related indication to I-131, most of metastatic patients would not have been treated with I-131 after surgery, with the risk of missing the presence of metastases and consequent delayed diagnosis and treatment.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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