




Indication for radioiodine remnant ablation in differentiated thyroid cancer patients: does 2018 Italian consensus change anything?

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Abstract

Purpose We speculated that radioiodine remnant ablation (RRA) could be performed less frequently in differentiated thyroid cancer (DTC) patients, if the recommendations of the 2018 Italian Consensus (ITA) were applied in clinical practice. Therefore, we compared the ITA indications for RRA with the recommendations by the 2015 American Thyroid Association guidelines (ATA).

Methods We retrospectively evaluated 380 consecutive DTC patients treated with surgery and RRA, followed at the Section of Endocrinology, University of Siena, Italy from January 2006 to December 2019.

Results Using ITA a significant increase of DTC patients classified as low or high risk and a significant decrease of patients defined at intermediate risk were observed ($p < 0.0001$). Consequently, the percentage of patients without routine indication for RRA (47.4%, versus 38.2%, $p < 0.0001$) and those with a definite indication for RRA (8.2 versus 1.8%, $p < 0.0001$) was significantly higher compared to ATA. Moreover, using ITA the percentage of patients with a selective use of RRA was lower in comparison to ATA (44.7% versus 60%, $p < 0.0001$). Nevertheless, the prevalence of distant metastases, at post-ablative whole body scan, in patients without indication for RRA, was not different using either ATA or ITA (2.1% and 1.1% respectively, $p = 0.37$).

Conclusion The use of ITA Consensus, in clinical practice, increases significantly the number of patients for whom RRA is not routinely indicated in comparison to ATA guidelines but without differences in delaying the diagnosis of distant metastatic disease.

Keywords Radioiodine · Differentiated thyroid carcinoma · Distant metastases · Remnant ablation

Introduction

Differentiated thyroid carcinoma (DTC), including papillary and follicular tumors, is the most common endocrine malignancy and accounts for more than 90% of all thyroid cancers. Over the past decades, an increasing incidence of DTC has been reported and is mainly due to the detection of small and early-stage papillary tumors, resulting from the improvement of the diagnostic tools (neck ultrasound and fine-needle aspiration cytology) [1, 2]. On the other hand, the rate of cancer mortality does not seem to be increasing. In this regard, different scientific communities developed their own guidelines and consensus to establish the diagnostic and therapeutic

approach for DTC patients [3–5]. For post-surgical radioiodine thyroid remnant ablation, the indications have become more selective and, in clinical practice, they are mainly based on the 2015 ATA three-tiered risk stratification system [3]. Specifically, for patients at low risk, remnant ablation is not routinely indicated [6–10], while for patients at high risk radioiodine therapy is always recommended [7]. For intermediate risk class patients RRA should be considered and the decision to treat or not is based on additional clinicopathological features [7, 10–13]. This stratification system is based on TNM seventh edition [14]. In 2016 the TNM eighth edition was released and several changes have been made that were subsequently applied in clinical practice starting from early 2018 [15]. The main changes involve the minimal extrathyroidal soft tissue invasion which is no longer a component of the tumor T category and the T3 category that have been divided into T3a, including tumor more than 4 cm limited to the thyroid, and T3b comprising tumor of

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any size with gross extrathyroidal extension invading only strap muscles [15]. Consequently, based on the TNM eight edition patients with minimal extrathyroidal soft tissue invasion are currently classified according to the tumor diameter and a great number of patients, previously classified as T3 category, using the TNM seventh edition, have been down-staged to T1 or T2 category. Several studies reported that using the TNM eight edition led to down-stage a great number of patients in the T categories [16–22]. The Italian Consensus, published in 2018, has developed a risk stratification system, similar to ATA but based on TNM eight edition, and provided updated indications for post-surgical RRA [5].

Since T categories are used both in the 2015 ATA guidelines and in the 2018 Italian Consensus for RRA in patients with DTC, we speculated that using the 2018 ITA Consensus a significant increase of DTC patients without indication for RRA could occur in clinical practice.

Therefore, the main aim of our study was to evaluate, in a retrospective cohort of patients with DTC, the distribution of risk classes and the indications for the post-surgical RRA according to the 2018 Italian Consensus and the 2015 American Thyroid Association guidelines. The second aim of our study was to compare the prevalence of metastatic disease that could have been missed if RRA was not performed based on the recommendations of the 2018 ITA Consensus and the 2015 ATA guidelines.

Patients and methods

Study population

We retrospectively evaluated 380 consecutive DTC patients treated with total thyroidectomy, with or without lymphadenectomy, and RRA, followed at our Institute from January 2006 to December 2019. Clinical-pathological features of patients are reported in Table 1. A written consent was given by all patients and data were collected anonymously. The study was approved by local ethical committee.

Methods

All patients were staged according to the seventh and eighth edition of the AJCC/TNM system. In order to predict the risk of recurrence and/or persistence of disease, patients were classified according to the 2015 modified ATA initial risk-stratification system, based on TNM seventh edition, and the 2018 ITA initial risk-stratification system, based on TNM eighth edition.

According to the 2015 ATA guidelines, patients were classified as low risk if they were in T1 or T2 categories without lymph node metastases, as intermediate risk if they belonged to T1–T2 categories with loco-regional metastases

Table 1 Clinical-pathological features of patients ($n = 380$)

Variables	$n = 380$
Age (years)	
Median	47.1
Range	6.7–90.8
Female, n (%)	277 (72.9%)
Surgery, n (%)	
Total thyroidectomy alone	281 (73.9%)
Total thyroidectomy plus lymphadenectomy	99 (26.1%)
Histology, n (%)	
Papillary	352 (92.6%)
Follicular ^a	28 (7.4%)
Aggressive histology ^b , n (%)	80 (21%)
Multifocality, n (%)	177 (44.0%)
Bilaterality, n (%)	126 (33.2%)
Micro PTC, n (%)	112 (29.6%)
Tumor diameter (cm)	
Median	1.5
Range	0.1–8.2
Lymph node metastases, n (%)	121 (31.8%)
Clinical N1	60 (50.4%)
Pathological N1	61 (49.6%)
Distant metastases, n (%)	5 (1.3%)
rhTSH preparation, n (%)	368 (96.8%)
Radioiodine activity MBq	
Median	1850
Range	555–5720
Distant metastases at post-ablative whole body scan, n (%)	21 (5.5%)

^aHistological data were available in 27/28 patients: all of them had a well-differentiated follicular carcinoma with capsular invasion and no or minimal (<4 foci) vascular invasion

^bAggressive histological subtypes: tall cell, columnar cell, diffuse sclerosing, insular, Hurthle cell and poorly differentiated carcinomas

or T3 category, and as high risk if they showed gross extrathyroidal extension (T4 category) or distant metastases (Table 2).

According to 2018 ITA Consensus, patients in T1 category with or without minimal extrathyroidal extension in absence of lymph node metastases were classified as low risk. Patients with aggressive histology, in T1 category with lymph node metastases, T2 category, with or without minimal extrathyroidal extension, and any T1–T2 categories with lymph node metastases were classified as intermediate risk. Patients with T3 and T4 categories and/or with distant metastases were classified as high-risk class (Table 2).

Statistical analysis

Epidemiological data are presented as mean \pm SD or median depending on their distribution. We analyzed 2×2

Table 2 Indications for radioiodine remnant ablation according to ATA and ITA risk classes

Risk class	2015 ATA (TNM 7th ed)	2018 ITA (TNM 8th ed)	Remnant ablation indication
Low	T1a-b, N0-X, M0-X T2, N0-X, M0-X	T1a-b, N0-X, M0-X	Not routinely indicated
Intermediate	T3, N0-X, M0-X T1-3, N1a-b, M0-X	T2, N0-X, M0-X T1-2, N1a-b, M0-X	Should be considered
High	T4, any N, any M M1, any T, any N	T3-4, any N, any M M1, any T, any N	Routinely indicated

contingency tables by the Fisher exact test in order to calculate significant differences in data frequency. Tables with size larger than 2×2 were examined by the Chi-squared test or a numerical approximation of the Fisher exact test, when all cell frequencies were greater than 4 or not, respectively. Statistical analysis was performed using the software Stat-View for Windows version 5.0.1 (SAS Institute, Cary, NC) and the SPSS Statistics version 22.0. A p value < 0.05 was considered statistically significant.

Results

T category according to seventh and eighth AJCC/TNM editions

According to the TNM seventh edition, 138/380 patients (36.3%) were included in T1 category, 50/380 (13.2%) in T2 category, 189/380 (49.7%) in T3 category and 2/380 (0.5%) in T4 category; one patient (0.3%) could not be classified as any T category (Tx). Based on the TNM eighth edition, 267/380 patients (70.3%) were entered in T1 category, 81/380 (21.3%) in T2 category, 27/380 (7.1%) in T3 category and 2/380 (0.5%) in T4 category; any T

category could be assigned to three patients (0.8%) Using the TNM eighth edition, the percentage of patients in T3 category decreased significantly (from 49.7 to 7.1%) while the number of patient in T1 and T2 categories increased significantly in comparison to the TNM seventh edition ($p < 0.0001$) (Fig. 1a).

Risk of persistent/recurrent disease according to the 2015 ATA and the 2018 ITA risk stratification systems

According to the 2015 ATA guidelines, 145/380 (38.2%) patients were classified as low risk, 228/380 (60%), as intermediate and 7/380 (1.8%) as high risk for recurrent/persistent disease. According to the 2018 ITA Consensus, 180/380 (47.4%) patients were classified as low risk, 169/380 (44.5%), as intermediate and 31/380 (8.2%) as high risk for recurrent/persistent disease. We observed a significant increase of patients classified as low and high risk and a significant decrease of patients classified as intermediate risk ($p < 0.0001$) when the 2015 ATA guidelines and the 2018 ITA Consensus were compared (Fig. 1b).

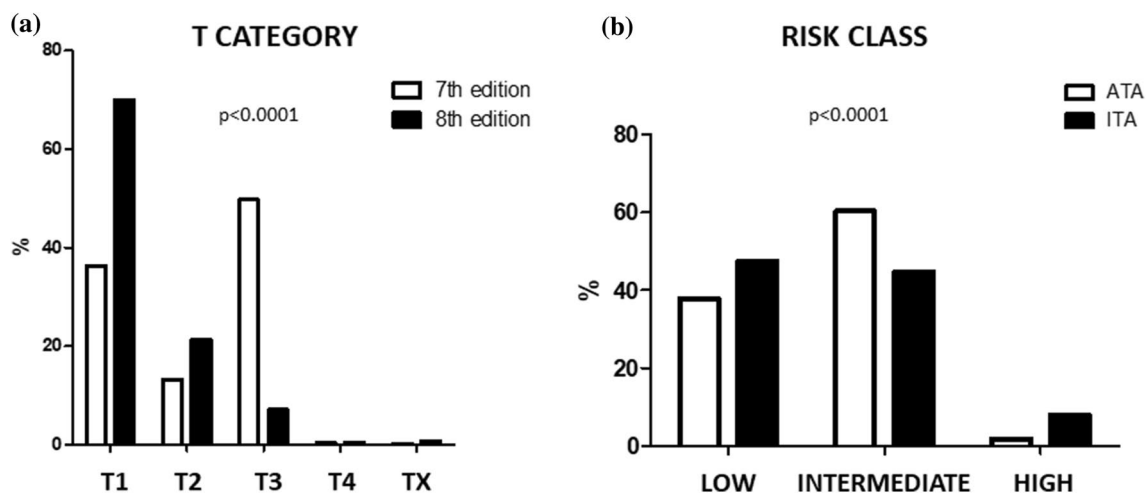


Fig. 1 **a** Distribution of patients based on T category according to TNM seventh and eighth editions; **b** distribution of patients according to ATA and ITA risk stratification system

Indication for RRA according to the 2015 ATA guidelines and the 2018 ITA consensus

According to the 2015 ATA guidelines and the 2018 ITA Consensus, RRA was not routinely indicated in 145/380 (38.2%) and 180/380 (47.4%) patients, respectively. A definite indication for RRA was given to 7/380 (1.8%) patients by the 2015 ATA guidelines and to 31/380 (8.2%) patients by the 2018 ITA Consensus. Finally, a selective use of RRA was recommended in 228/380 (60%) and 169/380 (44.5%) patients according to the 2015 ATA guidelines and the 2018 ITA Consensus, respectively. Using the 2018 ITA Consensus, a significant decrease of patients in whom RRA was not routinely recommended or should be considered, was observed ($p < 0.0001$). A definite indication for RRA was given to a greater number of patients by 2018 ITA Consensus compared to 2015 ATA guidelines ($p < 0.0001$) (Fig. 2).

Distant metastatic disease at WBS in the study population

Metastatic disease at the time of RRA was documented in 69/380 patients (18.2%). Among patients with metastatic disease at post-ablative WBS, 48/380 patients (12.6%) showed lymph node metastases while distant metastases were found in 21/380 patients (5.5%). Metastases were detected in the bones in 8/21 patients (38%), in the lungs in 9/21 patients (42.8%), in the liver in 2/21 patients (9.5%) and in the upper mediastinal lymph nodes in 8/21 patients (38%).

We analysed the correlation between the presence of distant metastases and the indication for RRA in order to estimate the number of missed cases with metastatic disease in the subgroup of patients with no indication for I131 treatment. Specifically, metastatic disease was documented

in 3/142 (2.1%) and in 2/180 (1.1%) of patients with no indication for RRA, according to the 2015 ATA guidelines and the 2018 ITA Consensus, respectively, with no difference between the two groups ($p = 0.37$).

Discussion

Over the past decades, the indication for RRA in DTC patients has become more selective and according to the 2015 ATA guidelines, the recommendations for remnant ablation are based on the AJCC-TNM seventh edition [14]. In 2016 the AJCC released the TNM eighth edition in which the most significant change was the new definition of T3 category [15]. T3 category included, under TNM seventh edition, both tumor with minimal (mETE) and gross extrathyroidal extension. Minimal extrathyroidal extension is a controversial prognostic factor in PTC. In the recent years it has been debated whether mETE per se has an impact on the prognosis of differentiated thyroid carcinoma. More recently, it has been reported that patients with small tumor diameter with mETE had no significant worse outcome compared to patients with large tumor diameter without mETE [23, 24]. According to the eighth edition of TNM, mETE has not been considered as a negative prognostic factor and it was not included in the T3 category [15]. After applying the eighth TNM edition, a significant number of tumors with minimal extrathyroidal extension have been down staged to T1 and T2 categories, according to their greater diameter [16–22]. In our study, more than 80% of T3 tumors were down staged to T1 and T2 tumors by applying the TNM eighth edition. Similar results were reported by Kim et al. in a cohort of 1613 patients: in this study 63% of patients with T3 classification were down staged to T1 or T2 tumor [16].

In the 2018, the Italian Consensus on diagnosis and treatment of differentiated thyroid carcinoma was published [5]. Under item 9, the authors emphasized that the indication for the post-surgical RRA should be given both on the basis of the AJCC/TNM eighth edition and an ATA-like Risk Stratification System. Using the 2018 ITA Consensus, the risk class distribution and the indication for remnant ablation therapy changed significantly. In our study we observed a significantly higher number of patients classified as low (47.4% by ITA Consensus and 38.2% by ATA guidelines) and high risk (8.2% by ITA Consensus and 1.8% by ATA guidelines) and a lower number of patients classified as intermediate risk (44.5% by ITA Consensus and 60% by ATA guidelines). In detail, the decreased rate of intermediate risk and a consequently the higher rate of low risk patients using 2018 ITA consensus were related to the down-staging of tumors with minimal extrathyroidal extension from T3 to T1–T2 category. Furthermore, the increased rate of high-risk patients

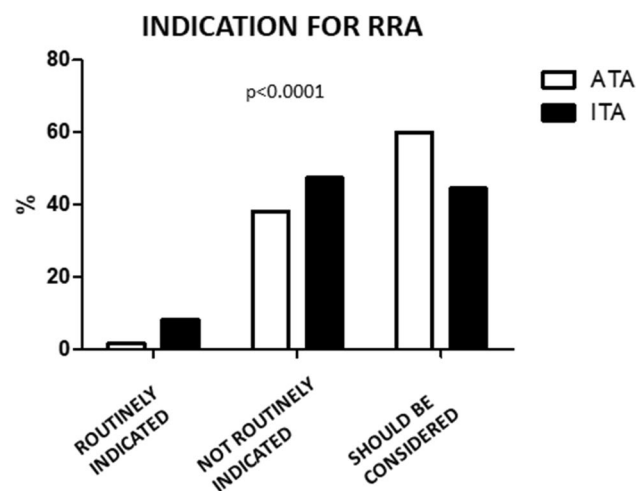


Fig. 2 Indications for radioiodine remnant ablation according to ATA guidelines and ITA Consensus

was due to the up-staging of patients with T3 tumors from intermediate- to high-risk class by 2018 ITA consensus.

Consequently, using ITA Consensus, the definite indication for RRA has raised from 1.8 to 8.2% and the percentage of patients for whom radioiodine was not routinely recommended has increased from 38.2 to 47.4% ($p < 0.0001$). However, decreasing the number of radioiodine-treated patients could imply a hypothetical risk of missing small distant metastases, frequently diagnosed at the post-ablative WBS. In our study, using the 2018 ITA Consensus, the patients with distant metastatic disease undiagnosed in the subgroup of those without indication for radioiodine therapy was 1.1%, similar to that observed applying the 2015 ATA guidelines (2.2%), although the number of untreated patients was higher.

Some limitations of this study are intrinsic to its retrospective design. On the other hand, the data have several strengths including a similar post-surgical therapeutic approach and follow-up in the same institution. In addition, to our knowledge, this is the first study that has validated the recommendation for radioiodine therapy given by the 2018 ITA Consensus.

In summary, the 2018 ITA Consensus has changed significantly the distribution of risk classes in DTC patients and, consequently, also the indication for RRA after surgery. Therefore, the use of 2018 ITA Consensus in clinical practice may significantly reduce the number of patients treated with RRA without any difference in the delayed diagnosis of distant metastatic disease compared to the 2015 ATA guidelines.

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Compliance with ethical standards

Conflict of interest The authors state the absence of any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval The study was approved by local ethical committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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