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Thyroid

Comparison between 2015 ATA guidelines and Italian Consensus for DTC management. A commented report

Confronto critico fra le linee guida ATA e il Consensus italiano sul trattamento del DTC

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SUMMARY

The 2015 ATA guidelines and 2018 Italian Consensus have produced a series of generally concordant recommendations on clinical and therapeutic management of thyroid nodules and thyroid carcinoma. Currently, the goals of treatment are to achieve the highest disease-free survival rates through the best ratio between minimum invasiveness and cost/impact on quality of life. By analysis and comparison of the ATA Guidelines and Italian Consensus, we highlighted and commented upon the key points of differentiated thyroid cancer management. Furthermore, the aim of this work is to identify and promote uniform clinical approaches among all specialists who treat differentiated thyroid cancer and represent a starting point for a consensus drafted by the Italian Society of Otolaryngology - Head and Neck Surgery.

KEY WORDS: guidelines, differentiated thyroid cancer, consensus, thyroid, thyroid nodule

RIASSUNTO

Le linee guida ATA 2015 e il Consenso Italiano 2018 hanno prodotto una serie di raccomandazioni generalmente concordanti sulla gestione clinica e terapeutica dei noduli tiroidei e del carcinoma tiroideo. Attualmente, gli obiettivi del trattamento prevedono il raggiungimento di alti tassi di sopravvivenza libera da malattia, un miglior rapporto tra minima invasività e costo/impatto sulla qualità della vita. Analizzando e confrontando le Linee Guida ATA e il Consenso Italiano abbiamo evidenziato e commentato i punti chiave sulla gestione differente dei tumori tiroidei. Inoltre, lo scopo di questo lavoro è identificare e promuovere approcci clinici uniformi tra tutti gli specialisti che trattano il cancro differenziato della tiroide e, infine, rappresentare un punto di partenza per un consenso redatto dalla Società Italiana di Otorinolaringoiatria - Chirurgia Cervico Facciale.

PAROLE CHIAVE: *linee guida, carcinoma tiroideo differenziato, consenso, tiroide, nodulo tiroideo*

Introduction

Differentiated thyroid cancer (DTC) has recently emerged as one of the most rapidly increasing human cancers worldwide. Nowadays, a large majority of these cancers is constituted by small non-palpable papillary thyroid tumours, whose prognosis is generally excellent. The widespread diffusion of high sensitivity diagnostic tools like thyroid sonography (US) and cytology on fine needle aspiration (FNA) has enhanced its diagnosis. Hence, the need to review and update diagnostic and therapeutic strategies has emerged as a fundamental priority.

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In 2015, the American Thyroid Association (ATA) released the revised version of the guidelines (GL) for the management of thyroid nodules and DTC [1]. Compared to the previous revision (2009) [2], there are many novelties for diagnostic work-up and treatment of DTC. The most relevant concerns the selection of thyroid nodules amenable to cytological evaluation by FNA, routinely recommended in nodules ≥ 1 cm only, even if with highly suspicious US pattern. Moreover, the restraint of total thyroidectomy (TT) followed by post-operative radioactive iodine (RAI) ablation and suppressive therapy for high-risk cases of DTC only, while the intermediate or low-risk cases can be managed more conservatively.

In 2018, six scientific Italian Societies involved in cure of patients affected by thyroid cancer developed the "Italian Consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies" [3]. They produced a collection of practical statements on selected relevant issues in the management of thyroid nodules and cancer, based on an adaption of ATA GL according to the Italian scenario and expert opinion of the multidisciplinary panel.

The aim of this paper is to analyse the two different guidelines, underlying the differences and similarities to identify and promote standardised clinical approaches among all specialists who treat differentiated thyroid cancer. This paper could also be used as a basis for a hypothetical Italian Society of Otolaryngology - Head and Neck Surgery guidelines drafting.

Materials and methods

ATA GL [1] and IC [3] were reviewed. The 24 topics covered in IC were taken as reference points, as are considered a summary of the most relevant diagnostic and therapeutic issues. We grouped items into macro areas to produce a uniform publication. Differences and similarities between the two sets of recommendations, their implications in clinical practice, the grey areas in understanding and disseminating the GL, together with the most relevant topics in areas of future research, were highlighted.

Diagnosis

US

Thyroid US usually represents the first imaging study in the evaluation of thyroid nodules, thanks to its high predictive value, ease and reproducibility of the techniques, lack of exposition to ionising radiation, non-invasiveness, repeatability, and low cost, even if operator dependent. US allows, based on nodule size and number, structure and echogenicity, margins and shape, calcification, vascularity and elastography, to stratify the risk of malignancy and to select nodules which should undergo FNA. The ATA GL describe 5 different US patterns, defining high, intermediate, low, very low suspicion and benign classes. The IC instead proposes a simplified scheme with only 3 classes of risk: low-US-risk (Class 1), intermediate-US-risk (Class 2) and high-US-risk (Class 3). Both classifications are based on previously specified US characteristics (IC is based on EU-TIRADS criteria) [4]. Table I compares the two GLs. Each category defines a dimensional cut-off as an indication to FNA. According to the IC, US-guided FNA is recommended in Class 3 thyroid nodules > 10 mm in diameter, and in Class 2 nodules > 20 mm. For Class 1 nodules, the indication is restricted to lesions > 20 mm, only if symptomatic, increasing in size, associated with high-risk factors, or before surgery or percutaneous therapy. Nodes < 5 mm nodes should be monitored by US even if they show high-risk US features. For high-risk nodules of 5-9 mm the IC admits the possibility to proceed both with FNA and US monitoring, based on clinical characteristics and patient preference. FNA is recommended for subcapsular, posterior or paratracheal lesions, for suspicious lymph nodes, extra-thyroid spread and clinical thyroid cancer risk factors. The ATA GL states that FNA should not be performed on nodules ≤ 1 cm, thus making the diagnosis of papillary micro carcinomas impossible. To conclude, both GLs consider features of US nodules to be more relevant than size in defining the risk of cancer, and to select nodules to submit to FNA. In general, a more invasive approach is limited to carefully selected cases. The main difference in GLs is the possibility, given by the IC, to perform FNA in nodules 5-9 mm.

FNA

Cytological examination is essential in the choice of therapeutic strategy: it allows a US suspicious nodule to be classified into cytological categories, according to increasing risk of malignancy. Nodules can be stratified from probably benign (false negatives < 3%) to almost certainly malignant (probability ~100%). The main pitfall of cytology is the risk stratification of follicular pattern and/or oxyphilic (Hürthle) cell lesions (vascular/capsular invasion is not evaluable on cytology), classified as indeterminate. Overall, 10-15% of FNAs provide inadequate results, while a diagnosis of follicular/oxyphilic lesions of indeterminate significance is made in 10-20% of FNAs [5]. Although several molecular analyses have been proposed to overcome this diagnostic pitfall, the proper clinical management of indeterminate nodules is still debated.

The cytological reports used in the GL are different. The ATA refers to the Bethesda classification system [6], while

Table I. Comparison between ultrasound risk categories and indications to FNA.

Italian Consensus		ATA Guidelines	
Risk definition	**Cut-off for FNA**	**Risk definition**	**Cut-off for FNA**
Class 1 (EU-TIRADS 2-3)	≥ 20 mm	Benign	No biopsy
		Very low suspicion	≥ 20 mm
		Low suspicion	≥ 15 mm
Class 2 (EU-TIRADS 4)	≥ 20 mm	Intermediate suspicion	≥ 10 mm
Class 3 (EU-TIRADS 5)	≥ 10 mm 5-9 mm → consider patient characteristics and preference	High suspicion	≥ 10 mm

IC uses the classification proposed in 2014 by AIT-AME-SIE and SIAPEC-IAP [7]. Bethesda classification includes 6 diagnostic categories: (I) non-diagnostic/unsatisfactory; (II) benign; (III) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); (IV) follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), a category that also encompasses diagnosis of Hürthle cell neoplasm/suspicious for Hürthle cell neoplasms; (V) suspicious for malignancy (SUSP) and (VI) malignant. The Italian classification also includes 6 categories, which are: TIR 1/TIR 1C (non-diagnostic/cystic nodule), TIR 2 (benign nodules), TIR 3A (low-risk indeterminate lesion), TIR 3B (high-risk indeterminate lesion), TIR 4 (suspicious nodule) and TIR 5 (malignant nodule).
The two systems show slight differences and there is clear parallelism in the respective risk classes and management (Tab. II). In evaluation of cytologically indeterminate nodules, the ATA GL give a greater role to molecular testing, which in Italy currently has a very limited use possibly due to its high cost. When surgical treatment is chosen, specific recommendations on the extent of resection according to the clinical situation are made.

Other investigations

US is the most sensitive imaging technique for examination of thyroid gland and neck lymph nodes: both the ATA and IC recommend it for all patients undergoing thyroidectomy for malignant or suspicious cytologic findings. In case of US suspicious cervical lymph nodes (≥ 8-10 mm, according to ATA GL), US-guided FNA for cytology and/or thyroglobulin (Tg) assessment in the needle washout is strongly suggested, if this could change surgical management. Cross-sectional imaging studies (CT and MRI, both with contrast medium) of the neck, mediastinum and lung are recommended after US in case of advanced disease clinical suspicion (invasive primary tumour and multiple or bulky lymph node involvement). Tracheal and/or oesophageal endoscopy should be considered in case of suspected aerodigestive tract invasion. Routine preoperative ^{18}FDG-PET scans are not recommended by the ATA and not even mentioned in the IC. Serum Tg and anti-thyroglobulin antibody (TgAb) determination is not recommended. Serum calcitonin measurement as a screening test for medullary thyroid carcinoma is recommended by the IC for all patients with thyroid nodules at diagnosis, or at least for patients undergoing surgery. The ATA currently does not express opinions on this issue (no recommendations, insufficient evidence), while in previous editions it was not recommended as it is not cost-effective [2,8]. The comparison of preoperative imaging and laboratory testing is summarised in Table III.

Tumour treatment

DTC Surgery

The long-standing debate on the best surgical strategy for these cases has been stimulated by the last edition of ATA GL, which significantly differs from the previous one. The 2009 edition proposed a more aggressive strategy, and total thyroidectomy was considered the best option for (almost) every tumour > 1 cm, independently of the evidence of loco-regional or distant metastases [2]. This approach was justified by retrospective data suggesting improved outcomes (in terms of both recurrence and survival) after total thyroidectomy [9-13]. Furthermore, it allows performance of radioiodine remnant ablation, easing a follow-up strategy based on US studies and serum Tg surveillance.
The 2015 edition of ATA GL outlines a more conservative attitude, with surgical strategy depending on the actual risk of recurrence/death of each patient. This change has been the consequence of an overwhelmingly increased diagnosis of small and early-stage tumours. Most, according to more recent studies [14-18], are low-risk tumours characterised by similar optimal outcomes when treated with loboisthmectomy or total thyroidectomy. Moreover, the additional complications risk observed in total thyroidectomy has led

Table II. Comparison between cytological risk categories and therapeutic management. FNA Fine needle aspiration US ultrasonography.

Italian Consensus	Risk of malignancy	Recommended management	ATA Guidelines	Risk of malignancy	Recommended management
TIR 1 TIR 1C	Undefined	Solid nodules: repeat FNA (consider core-needle biopsy). Cystic nodules: clinical and US follow-up. Consider diagnostic surgery for persistently non-diagnostic solid nodules > 1 cm with suspicious clinical and US features, or in the case of growth (> 20% in two dimensions). The best surgical choice for a single nodule is lobectomy. Total thyroidectomy if contralateral nodules, and/or specific risk factors, patient's choice.	I Non-diagnostic	1-4%	Repeat US-guided FNA Consider surgery for nodules with high suspicion sonographic pattern, in the case of growth (> 20% in two dimensions), or if clinical risk factors for malignancy are present. The best surgical choice for a single nodule is lobectomy. Total thyroidectomy if contralateral nodules, and/or specific risk factors, patient's choice.
TIR 2	< 3%	No treatment, unless surgery is indicated for clinical reasons: large-size (> 4 cm) and symptomatic nodules, nodules that develop suspicious US changes or increase in volume, hyperfunctioning nodules > 3 cm. Local treatment techniques (laser or radiofrequency) may be considered.	II Benign	0-3%	No treatment, unless surgery is indicated for clinical reasons: growing nodules of large size (> 4 cm) causing compressive or structural symptoms, or clinical concern. Nodules with high suspicion US pattern: repeat US and US-guided FNA within 12 months. Nodules with low to intermediate suspicion US pattern: repeat US at 12-24 months.
TIR 3A	5-15%	Follow-up if favourable clinical and US features; a repeat FNA is recommended; molecular testing can be a useful adjunct. Surgery in the other cases.	III AUS/FLUS	5-15%	Consider repeat FNA (or a second opinion review of the cytopathology slides) and molecular testing. If both not performed or inconclusive, either surveillance or diagnostic surgery, depending on clinical risk factors, US pattern and patient preference
TIR 3B	15-30%	Surgery as preferred option. Close follow-up may be proposed to selected patients with favourable clinical and US features (after discussion of treatment options); molecular testing can be a useful adjunct.	IV FN/SFN	15-30%	Diagnostic surgery is the long-established standard of care. Molecular testing may be an alternative option, to supplement malignancy risk assessment data (consider informed patient preference)
TIR 4	60-75%	Surgery in most cases (as for TIR 5 category). Molecular testing for better characterisation may be considered in selected cases.	V SUSP	60-75%	Surgery Molecular testing may be considered, if such data would be expected to alter surgical decision making
TIR 5	> 98%	Surgery Close follow-up may be offered to patients with very low-risk papillary microcarcinomas (see Item 5), and to elderly patients with incidentally discovered papillary cancers, at high surgical risk and without evidence of extra thyroid spread.	VI Malignant	97-99%	Surgery Consider active surveillance in (A) patients with very low risk tumours (e.g., papillary microcarcinomas without evident metastases or local invasion, and no cytologic evidence of aggressive disease), (B) patients at high surgical risk, or (C) with a relatively short life expectancy, or (D) with concurrent medical/surgical issues that need to be addressed first.

to suggest loboisthmectomy for low-risk patients, especially in low-volume thyroid surgery centers. In low-risk non-confirmed patients, the possibility of second-step surgery can be recommended on a case sensitive basis. The IC has substantially endorsed the recommendations of the ATA (summarised in Table IV). Both IC and ATA consider,

Table III. Comparison of preoperative staging imaging and laboratory test.

Imaging/Laboratory	Italian Consensus	ATA Guidelines
Neck ultrasound	Yes	Yes
FNA lymph nodes + Tg on needle washout	Yes	Yes (if ≥ 8-10 mm in the smallest diameter)
CT/MRI	Yes (for advanced disease only)	Yes (for advanced disease only)
Tracheoscopy and/or oesophagoscopy	Yes (for suspected aerodigestive tract invasion)	Yes (for suspected aerodigestive tract invasion)
18FDG-PET	No	No
Tg/TgAb determination	No	No
Calcitonin determination	Yes	?

Table IV. Recommendations for total thyroidectomy or lobo-isthmectomy (equal for ATA and IC).

Total thyroidectomy (at least one of the following)	Thyroid cancer > 4 cm Extrathyroidal macroscopic extension (ETE) (cT4) Clinically apparent lymph node metastases (cN1) Distant metastases (cM1)
Lobo-isthmectomy	Thyroid cancer ≤ 1 cm No ETE No clinical evidence of lymph node metastases (cN0) No distant metastases cM0
Lobo-isthmectomy or total thyroidectomy	Thyroid cancer 1 to 4 cm No ETE No clinical evidence of lymph node metastases (cN0) No distant metastases cM0

among several risk factors, previous head and neck exposure to ionising radiation to be of particular relevance in the choice of total thyroidectomy, i.e. mandatory if post-surgical radioiodine treatment is expected. The ATA also emphasises that patient referral to high-volume thyroid surgeons is associated with superior outcomes, and this should be considered in cases with more extensive disease.

Papillary microcarcinoma treatment

A particular category of DTC is papillary thyroid microcarcinoma (PTMC), defined as a papillary carcinoma ≤ 1 cm in size. Most of these tumours have an indolent behaviour, as shown by prospective studies in Japan on many patients with biopsy-proven PTMCs not submitted to surgery and followed for 15 years according to an active surveillance protocol [19-22]. Unfortunately, neither clinical aspects nor cytology can reliably differentiate the minority of PTMCs that will significantly progress from the majority of indolent PTMCs. Likewise, isolated molecular biology (BRAF mutation) is not able to identify microcarcinomas with a more aggressive attitude, but the concomitance of BRAF with other oncogenic mutations (PIK3CA, AKT1, TERT promoter, or TP53) may be a specific marker of a less favourable outcome of PTC [23-26].

For PTMC ATA recommends loboisthmectomy if there are no other indications for total thyroidectomy, but admits the possibility to consider active surveillance as an alternative in selected patients with very low-risk tumours (e.g., PTMC without clinical evidence of metastases or local invasion, and no cytologic evidence of aggressive disease), high surgical risk because of comorbid conditions, relatively short life expectancy (e.g., serious cardiopulmonary disease, other malignancies, very advanced age), or concurrent medical or surgical issues requiring priority care. However, a clinical conundrum can be envisioned in the advice by the ATA against performing FNA in nodules ≤ 10 mm, thus preventing the possibility of diagnosis of PTMC. The IC instead admits FNA also in high-US-risk nodules between 5 mm and 9 mm in size.

In IC, active surveillance may be considered for very low-risk PTMC in particular situations: high risk surgical patients; patients who refuse surgical treatment; patients potentially eligible to controlled clinical trials. The decision requires a thorough discussion with the patient, and a careful clinical and cytological risk stratification. Active surveillance is not recommended in case of neck irradiation history, US extra-thyroid extension, subcapsular or posterior localisation, multifocal or bilateral tumour, coexistence

of Graves' disease, suspicious lymph node involvement, aggressive cytological features and BRAF mutation. If a conservative approach of watchful waiting is selected, neck US examination every 6 months in the first two years and once a year thereafter is recommended.

Completion thyroidectomy

Both the ATA and IC state that a completion thyroidectomy must be offered to those patients to whom a total thyroidectomy would have been chosen if the diagnosis of thyroid cancer had been available before the initial surgery. The IC specifies that completion thyroidectomy is mandatory for DTCs > 4 cm, or with ETE and/or lymph node metastases, or in case of aggressive variants. This latter indication, not considered by the ATA, must be kept in mind for thorough patient information: in some cases suitable for limited surgery, the indication for total thyroidectomy can emerge from histological examination. It is worth noting that recent publications have reported that up to 43.5% of patients who meet ATA preoperative criteria for lobectomy would require a second operation due to high-risk features on final pathology [27,28]. The ATA GLs also state that in selected cases radioiodine ablation of the remaining lobe can be considered as an alternative to completion thyroidectomy. However, data regarding long-term outcomes are limited and suggest a slightly higher proportion of patients with persistent detectable Tg. This approach never caught on in European countries, and therefore the IC does not take it into consideration. Both the ATA and IC agree on the equality of surgical risks between a two-stage thyroidectomy and primary total thyroidectomy. The IC, however, points out that this is true in specialised centers, and stresses the importance of avoiding any contralateral dissection in the first surgery. Finally, the ATA advises against prophylactic lymph node dissection for cN0 disease, while the topic is not appraised in the IC.

Lymph node treatment

A large proportion of patients with papillary carcinoma have regional lymph node metastases at the time of diagnosis, mainly in the central neck compartment. Lymph node metastases significantly increase the risk of locoregional recurrence, especially if multiple and bulky, and/or with extracapsular nodal extension, but the impact on overall survival is little if any.

The role of therapeutic lymph node dissection is well established whenever metastatic nodal disease is discovered at preoperative investigations (cN1) or intraoperatively. In these cases, both the ATA and IC confirm the indication of therapeutic lymph node dissection.

The risk of subclinical nodal metastases in DTCs cN0 raises the question of prophylactic lymph node dissection. Today there is general agreement that prophylactic lateral neck dissection is not an option: the ATA does not even address the topic, while the IC states that it is only advisable in cN1 patients. On the contrary, the role of prophylactic central neck (level VI) dissection (pCND) for cN0 disease remains controversial. Several lines of clinical evidence led to consider pCND appropriate, as in this area lymph node metastases are frequent and often not evident on preoperative imaging [29] or at the time of surgery. Furthermore, the procedure allows more precise staging of the disease, and reoperation in the central neck for nodal recurrence is challenging and carries a non-negligible risk of complications. On the other hand, in several studies pCND has shown little or no improvement in long-term outcomes, while increasing the chances of temporary and permanent morbidity (especially hypoparathyroidism) [30,31]. The ATA proposes a cautious attitude and a careful assessment of the risk-benefit ratio. The 2009 edition stated that pCND may be performed in clinically uninvolved central neck lymph node PTC patients, and that near total or total thyroidectomy without pCND may be appropriate for small (T1/T2), non-invasive, clinically node-negative PTCs and most follicular cancers. The decision of whether to perform a pCND is then made considering available surgical expertise, and a simple near-total thyroidectomy may be safer in less experienced surgical hands [2]. The 2015 edition takes an even more cautious attitude, stating that pCND (ipsilateral or bilateral) should be considered in patients with advanced primary tumours (T3/T4) or cN1b, or if lymph node involvement extent could be useful for planning further therapeutical steps, and that a thyroidectomy without pCND can be considered appropriate for small (T1/T2), non-invasive, cN0 PTCs and for most follicular cancers. The IC endorses the ATA GL recommendations (Tab. V), but also suggests considering an ipsilateral pCND with immediate frozen section examination in selected patients. It can be argued that ipsilateral pCND may represent the best compromise between the conflicting need to minimise the risk of complications, and to guarantee maximum local radicality and accurate staging.

Pathological report

The ATA staging system follows the AJCC 7th edition/TNM Classification System for DTC [32] while the more recent IC follows the 8th edition [33]. A complete pathology report should indicate, besides the basic tumour features for histological classification and staging (according to the TNM classification of AJCC/UICC), status of resection margins

Table V. Comparison of indications for neck dissection.

	Central compartment dissection		Lateral compartment dissection	
	Prophylactic	Therapeutic	Prophylactic	Therapeutic
ATA Guidelines	cN1b → recommended cT3-cT4, or if useful for planning further steps in therapy → allowed	cN1a → recommended	No	cN1b → recommended
Italian Consensus	cN1b → recommended cN0 → ipsilateral + immediate frozen section examination allowed in selected patients	cN1a → recommended	No	cN1b → recommended

(involved/uninvolved) and additional information that is useful for risk assessment. The latter includes: presence of vascular invasion and number of invaded vessels (< 4/≥ 4), number of lymph nodes examined/involved by tumour, size of the largest metastatic focus and presence/absence of extra nodal extension.

The histopathologic evaluation should also identify and report variants of thyroid carcinoma: more unfavourable outcomes (tall cell, columnar cell, and hobnail variants of PTC; widely invasive follicular thyroid carcinoma; poorly differentiated carcinoma), or those that may show a more aggressive behaviour (solid and diffuse sclerosing variants of PTC); more favourable outcomes (encapsulated follicular variant of PTC without invasion, renamed in 2016 "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" NIFTP [34]; minimally invasive follicular carcinoma); associated with familial syndromes (cribriform-morular variant of PTC often associated with familial adenomatous polyposis [FAP], follicular or papillary carcinoma associated with PTEN-hamartoma tumour syndrome). Following the TNM 8th edition, the histological report should describe the predominant histotype and, if present, a minor component of either an aggressive variant or a less differentiated tumour type (poorly differentiated or anaplastic); if metastatic deposits are detected in lymph nodes, histology should specify whether they are micrometastases (< 2 mm in size); immunohistochemical and molecular analyses, when performed, should be reported or there should be a reference to any additional report.

The IC also reports the indications on the requirements of the cytological report. It must specify the technique used to obtain the sample and include essential clinical information, such as functional status, location, number, and size of lesions analysed, their structure and US pattern.

Post-surgical treatment

When?

The postoperative AJCC/UICC TNM (both 7th and 8th edition) staging system provides reliable information on the risk of death from thyroid cancer, but it does not adequately predict the risk of recurrence. In 2009, the ATA GL proposed an Initial Risk Stratification System to predict the risk of recurrence and/or persistence of disease after surgical treatment [2]. This system classified patients as having low/intermediate/high-risk of recurrence and helped to adequately plan disease surveillance and therapeutic strategies. The 2015 edition has re-proposed this classification (Tab. VI), with some updates (including specific DTC histology, multifocality, extent of vascular invasion or extent of metastatic lymph node involvement, extrathyroidal extension, and completeness of surgical resection). This risk stratification plays a key role in therapeutic management decisions, and particularly regarding the indications for RAI treatment after surgery.

Following the ATA GLs, the goal of postoperative RAI administration includes *remnant ablation* to facilitate detection of recurrent disease and initial staging; *adjuvant therapy* to improve disease-free survival by theoretically destroying possible, but unproven foci of residual disease; *therapy* to improve disease-specific and disease-free survival by treating persistent disease in higher risk patients.

The indication for RAI administration after thyroidectomy depends on the stage of disease and risk stratification. In the ATA GLs, RAI remnant ablation is not routinely recommended for low-risk patients, it should be considered in ATA intermediate-risk cases and is routinely recommended

Table VI. ATA risk classification system for structural disease recurrence approved by IC. DTC Differentiated thyroid cancer, LN lymph node.

High risk	Gross extrathyroidal extension Incomplete tumour resection Distant metastases Lymph node > 3 cm
Intermediate risk	Aggressive histology Minor extrathyroidal extension Vascular invasion > 5 involved lymph nodes (0.2-3 cm)
Low risk	Intrathyroidal DTC ≤ 5 LN micrometastases (< 0.2 cm)

for patients in a high-risk category. The IC, in agreement with the last ATA GL, considers that the indication for post-surgical RAI ablation should be established based on the AJCC/UICC TNM staging (8th edition) and the Initial Risk Stratification System, also considering serum Tg levels (on thyroid hormone therapy or after TSH stimulation) and neck US. For ATA low-risk patients (T1a-b, N0-X, M0-X) RAI remnant ablation can be avoided, especially when basal serum Tg or TSH-stimulated Tg are undetectable or < 5 ng/ml, and neck US is negative. For patients with intermediate or low-to-intermediate risk (T1-2, N1a-N1b, M0-X) RAI ablation should be considered (advanced age, larger tumours, macroscopic or clinically evident lymph node metastases, extra nodal extension or vascular invasion, aggressive histology). Finally, in high risk or intermediate-to-high risk patients (T3-4, any N, any M) RAI administration is routinely recommended.

A post-therapy whole-body scan (WBS), with or without SPECT/CT, is recommended by the ATA to inform disease staging and document RAI avidity of any structural disease. The IC does not dwell on this point, probably because in Italy post-therapy WBS is routinely performed.

How?

Since DCT cells retain NIS (sodium/iodide symporter) expression, although reduced in comparison to normal thyroid cells, high TSH levels are necessary to promote RAI uptake. Preparation for thyroid ablation can be performed through two approaches: thyroid hormone withdrawal (THW) and recombinant human TSH (rhTSH) administration. If THW is planned, both ATA GL and IC agree that LT_4 should be withdrawn for 3-4 weeks. Liothyronine (LT_3) can replace LT_4 in the initial weeks, but it must be withdrawn in the last 2 weeks. Serum TSH levels will confirm the appropriate stimuli, and a level > 30 mU/L is generally recommended. Compared to THW, the use of rhTSH is associated with similar rates of successful ablation and superior quality of life around the time of RAI administration, since hypothyroidism is avoided. However, long-term outcome data are still limited, and this has led to some restrictions on the indications of rhTSH use when the risk of recurrence or death is high. Indeed, rhTSH is currently approved by many international authorities for use in preparation for RAI remnant ablation in patients who do not have evidence of distant metastases. Both the ATA and IC state that rhTSH can be an alternative to THW in patients with ATA low and intermediate-risk DTC without extensive lymph node involvement. Conversely, in patients with ATA high-risk DTC, loco-regional or distant metastases and higher risk of disease-related mortality and morbidity, additional controlled data from long-term outcome studies is needed to recommend rhTSH preparation for RAI treatment.

Finally, rhTSH preparation should be considered in patients with DTC of any risk level who cannot tolerate hypothyroidism due to concomitance of severe comorbidities (including psychiatric conditions), or who are unable to obtain TSH elevation by THW (for these cases the Italian Medicines Agency (AIFA), according to law 648/96, approved the use of rhTSH) (Tab. VII). Both GLs recommend cautious use of RAI therapy in patients with brain or proximity to the spinal cord or superior vena cava metastases. In these cases, the onset of an acute swelling of metastatic tissue can cause neurological damage or superior vena cava syndrome. To limit the risk, the institution of temporary high-dose corticosteroid therapy is recommended.

A low iodine diet (LID) is suggested for 1-2 weeks (but for IC a restriction on the use of iodised salt is not necessary); avoiding iodine-containing drugs and iodinated contrast medium is emphasised. A possible previous high-dose iodine exposure should also be considered when planning the treatment schedule. Measurement of urinary iodide excretion is recommended only in case of suspected iodine contamination.

The IC points out the following recommendations not specifically addressed by ATA: RAI treatment must be performed in protected hospitalisation with collection of the patient excreta (the obligation derives from the Italian law 187/2000, transposition of the European directive 97/43 MED); at discharge, the patient and his family must be provided with written information and instructions on daily behaviour, to respect the dose limits for the population and the dose constraints for family members or caregivers; in case of travel across international borders or via airport, a form (including the date of treatment, the radionuclide, the administered activity and the treating facility) must be provided, since radiation detection systems can be triggered.

Pregnancy is an absolute contraindication to ^{131}I therapy, and the ATA recommends women of childbearing age to have a negative screening test for pregnancy prior to RAI administration. Thereafter, according to both GLs, pregnancy should be avoided for 6-12 months. In breastfeeding women RAI therapy should be deferred until breastfeeding or pumping has been stopped for at least 6 weeks (3 months for ATA), as the mammary gland intensely concentrates iodide during lactation. In men, conception should be avoided for 4 months (3 months for ATA); sperm banking could be considered in young patients with distant metastases likely requiring high cumulative activities.

Which dose?

Selection of the most appropriate activity to be administered is important: for remnant ablation in patients with low/intermediate-risk, both ATA and IC suggest a low ac-

tivity use (approximately 30 mCi for ATA, 30-50 mCi for IC). Higher activities (up to 150 mCi for ATA, 100 mCi or more for IC) should be considered if RAI is intended for patients at high risk of persistent/recurrent disease.
Both ATA and IC mention three basic approaches to RAI therapy for loco-regional disease or distant metastases: administration of empiric fixed activities, therapy determined by the upper limit of blood and body dosimetry [bone marrow (blood) dosimetry in the IC], and quantitative tumour or lesion dosimetry (lesion-based dosimetry in the IC). There are no data supporting the superiority of one approach over another, so that the choice is left to the experience and resources of the single institution. ATA only reports that dosimetry methods are often reserved for patients with unusual situations, such as extensive lung metastases, renal failure, children and the elderly. When an empiric activity is chosen, IC specifies that an amount of ^{131}I ranging from 3.7 and 7.4 GBq (100-200 mCi) is appropriate for most patients. The ATA agrees but recommends avoiding activities exceeding 150 mCi in patients over 70 years. Both state that the cumulative activity that can be administered must be assessed on an individual basis, because it depends on various factors such as response to therapy, age and onset of deterministic adverse effects. Re-treatment should be performed not earlier than 6-12 months from previous treatment.
Both the ATA and IC agree that empirical RAI treatment can be considered in selected cases with biochemical disease, but without evidence of structural disease. The indications are limited to patients with high or rising serum Tg levels, or rising TgAb levels, and negative structural or metabolic imaging. There is no consensus on the cut-off value of serum Tg above which a patient should be treated, but a relevant aspect is Tg (or TgAb) increase over time. Another important element in selecting patients for empiric RAI therapy is the result of ^{18}FDG-PET scanning, since ^{18}FDG-PET positive tumours generally do not concentrate RAI. The recommended activity to be administered is 100-200 mCi for ATA and 100-150 mCi (3.7-5.2 GBq) for IC. Both GLs agree that if the post-therapy scan is negative, the patient should be considered to have RAI-refractory disease and no further RAI therapy should be administered. On the contrary, if persistent not-resectable disease is localised, further treatment courses can be considered if evidence of clinical benefits is provided. The most compelling benefit evidence from empiric RAI therapy is in the case of pulmonary micrometastases.

RAI complications

The ATA and IC agree that RAI therapy is reasonably safe, but may be associated with a low risk of early and late-onset complications, especially after higher individual and cumulative doses. The most common early side effects are nausea, taste disturbances and sialadenitis. Late-onset complications include salivary and lacrimal gland damage (with xerostomia, xeropthalmia and salivary or nasolacrimal duct obstruction), bone marrow depression, pulmonary fibrosis, gonadal disfunction, and secondary malignancies. The risk of secondary malignancies (including bone and soft tissue cancers and leukaemia) is very small and dose related; according to ATA it does not warrant specific screening. Both GLs agree that in women RAI therapy does not increase the risk of infertility, miscarriage and foetal malformations. In men, RAI therapy may be associated with temporary oligospermia, and permanent infertility can result from cumulative damage after multiple treatments.

RAI-refractory DTC

According to the ATA, radioiodine-refractory disease occurs when (in patients with appropriate TSH stimulation and iodine preparation): malignant metastatic tissue does not ever concentrate RAI, tumour tissue loses the ability to concentrate RAI, RAI is concentrated in some lesions but not in others, or metastatic disease progresses despite significant concentration of RAI. The IC adheres to the same criteria but by unifying the first two categories. The definition of any of these possibilities depends on imaging (post-therapy ^{131}I WB scan, combined with other imaging modalities). When DTC is defined as RAI refractory, there is no indication for further RAI treatment.

Systemic therapy

Systemic therapy is mentioned, by both the ATA and IC, in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic and/or imminently threatening disease, not otherwise amenable to local therapies. The purpose of therapy is to reduce the growth rate and tumour burden, improve progression-free survival and control symptoms. Kinase inhibitors (KI) are currently considered the first line of therapy, and sorafenib and lenvatinib are approved for clinical use in the US and EU. These agents are associated with numerous adverse effects as well as serious and potentially fatal risks. In view of this, both GLs always recommend considering possible alternatives to their use, such as surgery or other localised approaches (including radiation therapy or thermal ablation). Moreover, the ATA highlights the importance of an experienced care team and exhaustive patient information.
Conventional chemotherapy has historically produced disappointing results. The ATA and IC agree that today it can be exceptionally indicated in cases where KI are ineffective or cannot be used.

Follow-up

Early follow-up identifies disease-free patients who consequently require less aggressive management strategies, and those with residual disease who may need closer surveillance and possible additional therapies.

For both GLs, the initial follow-up evaluation should be performed at 3-6 months from initial treatment by serum Tg (on l-thyroxine therapy), serum TgAb measurement and neck US (thyroid bed and central and lateral nodal compartments). For both the ATA and IC, follow-up should be performed every 12-24 months. The IC states that follow-up should be performed periodically, according to the patient's risk factors and Tg levels and suggests prolonging follow-up frequency after 5 years, but continuing lifelong.

Serum Tg is the most specific and sensitive marker in monitoring patients with DTC [35]. Even if most laboratories currently use immunometric, ultra-sensitive assays (sensitivity ≤ 0.2 ng/ml), the patient is recommended to always perform the assay in the same laboratory because of possible measurement differences.

After total thyroidectomy and radioiodine remnant ablation, undetectable serum Tg levels (either basal or TSH-stimulated if basal Tg is undetectable) and negative TgAb are predictive of a disease-free status with a negative predictive value close to 100%.

Sometimes (low-risk patients not submitted to RAI ablation, incomplete ablation cases, suboptimal remnant) a detectable Tg does not allow precise assessment of a patient's status. Therefore, both GLs recommend monitoring the trend of Tg overtime, as stable or declining Tg levels are reassuring, whereas a Tg increase suggests residual/recurrent disease. Both the ATA and IC agree that TgAb should be quantitatively assessed whenever serum Tg is evaluated. Following total thyroidectomy and remnant RAI ablation, TgAb usually disappears over a median of about 3 years in patients without evidence of residual disease. Increased TgAb values over time may serve as a surrogate marker of residual normal thyroid tissue or tumour, while declining TgAb levels are considered a good prognostic sign.

Neck US has a primary role in follow-up, especially when serum Tg is not a reliable marker, because thyroid cancer often spreads or recurs in cervical lymph nodes or thyroid bed. To confirm suspicious US findings, both the ATA and IC recommend US-guided FNA for cytology and Tg measurement in the washout fluid. However, the ATA GL states that suspicious lymph nodes should be biopsied only if greater than 8-10 mm in the smallest diameter, and a positive result would change management; otherwise, they may be followed-up without biopsy.

The IC states that other functional (whole-body RAI scan, ^{18}FDG-PET) and/or cross-sectional (CT, MRI) studies should be considered in patients with a high risk of persistent disease only, when response to therapy cannot be adequately classified with first-level tools. ATA accurately defines the role of each imaging technique. In particular, ^{18}FDG-PET/CT can be indicated in high-risk DTC patients with elevated serum Tg and negative WB scan after therapeutic doses of RAI. It may also be considered as part of initial staging in poorly differentiated thyroid cancers and invasive Hürtle cell carcinomas, especially patients with other evidence of disease on imaging or with elevated serum Tg levels, or as a prognostic tool in patients with metastatic disease to identify those at highest risk of rapid disease progression and disease-specific mortality. In this regard, the ATA emphasises that ^{18}FDG uptake on PET in metastatic DTC patients is a major negative predictive factor for RAI treatment response and an independent prognostic factor for survival.

Post-treatment risk stratification

In the 2006 edition of the ATA GLs, the idea of re-evaluating the risk of recurrence/death after initial treatment were considered to modulate follow-up intensity and adapt therapeutic decisions to the clinical situation of each individual patient [8]. The subsequent 2009 and 2015 editions of the GL updated and developed this concept, which is now being adopted by the IC.

Initial risk stratification analyses the risk of recurrence and disease specific mortality, and can define the type of surgery and the indication for RAI administration (Tab. VI). Both the IC and ATA recommend dynamic use of this classification to evaluate the response to initial therapy and consider any changes of the calculated risk during follow-up. This allows an individualised approach to ongoing management and avoids aggressive, needless treatment of patients initially classified at intermediate or high risk, who are free from disease after initial therapy. Table VIII compares the two classifications and related classification criteria. According to the ATA, the response to treatment can be defined as follows:

- *excellent*, in case of stable basal Tg levels, consistent with the presence of a normal thyroid lobe, and negative US;
- *biochemical incomplete*, when unstimulated Tg is inappropriately high and/or increases over time in the presence of similar TSH levels, with negative US;
- *structural incomplete*, in the presence of morphological evidence of disease, regardless of Tg values;
- *indeterminate*, in case of non-specific US findings and/or non-evaluable Tg trend.

IC refers only to initial therapy response and does not include the indeterminate response.

Table VII. Indications for rhTSH in the preparation for RAI therapy of patients with metastatic DTC in Italy, according to the law 648/96.

Indications	Examples
Patients whose serum TSH cannot be raised (at least 30 μU/mL) because of concurrent clinical conditions	Primary or secondary hypopituitarism Functional metastasis
Patients with underlying comorbidities making iatrogenic hypothyroidism potentially risky	Previous cerebral stroke or TIA Cardiomyopathy (NYHA grade III or IV) Severe renal failure (stage 3 or superior) Serious mental disorders (severe depression, psychosis)

Table VIII. Response-to-therapy category comparison. Tg thyreoglobulin.

	Italian Consensus	ATA Guidelines
Category	Definition	Definition
Excellent response	Negative or non-specific structural or functional imaging findings *and either* Suppressed Tg < 0.2 ng/mL *or* TSH-stimulated Tg < 1 ng/mL	Negative imaging *and either* Suppressed Tg < 0.2 ng/mL *or* TSH-stimulated Tg < 1 ng/mL
Biochemical incomplete response	Negative imaging *and* Detectable basal Tg *or* Detectable stimulated Tg *or* Rising anti-Tg antibody levels	Negative imaging *and* Suppressed Tg ≥ 1 ng/mL *or* Stimulated Tg ≥ 10 ng/mL *or* Rising anti-Tg antibody levels
Structural incomplete response	Structural or functional evidence of disease With any Tg level With or without anti-Tg antibodies	Structural or functional evidence of disease With any Tg level With or without anti-Tg antibodies
Indeterminate response		Nonspecific findings on imaging studies Faint uptake in thyroid bed on RAI scanning Detectable basal Tg, but <1 ng/mL Detectable Stimulated Tg, but <10 ng/mL *or* Anti-Tg antibodies stable or declining in the absence of structural or functional disease

L-thyroxine therapy

DTC express the TSH receptor on the cell membrane and respond to TSH stimulation by increasing rates of cell growth. Hence, TSH suppression using supraphysiologic doses of LT_4 has traditionally been considered a cornerstone in long-term management of DTC patients to decrease the risk of recurrence. This attitude is no longer strictly followed for various reasons: several studies have demonstrated that TSH suppression may improve outcomes in high-risk patients, while its benefit is more uncertain in low-risk cases; the appropriate degree and duration of TSH suppression in long-term follow-up is unknown, especially in high-risk patients judged free of disease; the administration of supraphysiological doses of LT_4 induces a state of subclinical thyrotoxicosis, which can cause adverse effects. Thus, the choice of optimal TSH for individual patients should balance the potential benefit of TSH suppression with its possible harm.

The ATA gives indications on TSH suppression after initial therapy and in long-term follow-up based on the clinical situation and response to treatment (Tabs. IX, X). The IC recommends similar management of levothyroxine therapy. In patients with excellent response to initial treatment (and in those with indeterminate response, according to ATA), levothyroxine therapy should keep TSH in the low/normal range (0.5-2 mU/L).

However, high-risk patients at diagnosis with an excellent (or indeterminate) response to therapy, ATA suggests maintaining a moderate suppression of TSH (0.1-0.5 mU/L) for up to 5 years.

For both the ATA and IC, patients with persistent biochemical disease should undergo Tg, TgAb determination and

Table IX. Initial TSH suppression according to ATA Guidelines. Tg thyreoglobulin.

Clinical situation/response to treatment	Optimal TSH values
High-risk thyroid cancer patients	< 0.1 mU/L
Intermediate-risk thyroid cancer patients	0.1-0.5 mU/L
Low-risk thyroid cancer patients who have undergone or not remnant ablation, with undetectable Tg levels	0.5-2 mU/L
Low-risk thyroid cancer patients who have undergone or not remnant ablation, with low Tg levels	0.1-0.5 mU/L
Low-risk thyroid cancer patients who have undergone lobectomy	0.5-2 mU/L (even without LT4 therapy)

Table X. TSH suppression in the long-term follow-up according to ATA Guidelines.

Clinical situation/response to treatment	Optimal TSH values
Patients with a structural incomplete response	< 0.1 mU/L
Patients with a biochemical incomplete response	0.1-0.5 mU/L
High-risk thyroid cancer patients with an excellent or indeterminate response	0.1-0.5 mU/L for up to 5 years
Patients with an excellent or indeterminate response (especially if at low-risk for recurrence)	0.5-2 mU/L
Patients with an excellent or indeterminate response, who not have undergone remnant ablation	0.5-2 mU/L

neck US every 6-12 months. For these patients, both GLs suggest moderate (TSH 0.1-0.5 mU/L) or complete (TSH < 0.1 mU/L) suppression, depending on the overall clinical context. A Tg or TgAb increase (especially when the doubling time is < 12 months, as pointed up by the IC) suggests progression and requires further morphological investigations to identify structural disease.

For persistent structural disease, both the ATA and IC agree on adopting an individualised follow-up programme that considers multiple clinical-pathological factors, including the location, size, growth rate, ability to concentrate radioiodine and intensity of ^{18}FDG-PET uptake. In these high-risk patients, TSH should be maintained at < 0.1 mU/L.

Legal issues

The IC state that the guidance should not replace clinical judgement and should be used to complement informed clinical choices. Informed consent is mandatory to reduce medical conflicts by discussing different clinical choices with the patient and by taking into consideration any expression of dissent. This topic is not covered by the ATA GLs.

Discussion

GL on diagnosis and management of thyroid nodules and differentiated thyroid carcinoma have been drawn up periodically by various national and international scientific societies, and the most recent were published simultaneously or even after the ATA GL [36-40]. The ATA GLs arguably represent the leading clinical practice recommendations regarding DTC management. However, they were developed predominantly by North American experts. European experts sometimes have different perspectives and divergent viewpoints, depending on epidemiological, methodological, practical and medico-legal differences [41]. These considerations explain the opportunity of the IC, which adapts the ATA GLs to current practice and expert opinions in Italy. The result has been the series of general and homogeneous recommendations on the clinical and therapeutic management of thyroid nodules and DTC that was reviewed.

Currently, the goal of treatment is to achieve the highest disease-free survival rate, with less invasiveness and minimal cost and impact on the patients' quality of life. This trend, which envisages a therapeutic approach decidedly more conservative than in the recent past, finds justification in both the epidemiological evolution of DTC (smaller tumours, diagnosed in the early or even preclinical phase, with a generally favourable prognosis) and in the excellent results from large series of patients.

Clinical data emerge from both prospective and retrospective studies.

In 1993, an observational clinical trial began in Kuma Hospital (Japan) with the aim of comparing surgery with active surveillance (AS) in low-risk papillary microcarcinomas. Patients, adequately informed, were free to choose between the two options. About two years later, Tokyo's Cancer Institute Hospital also began a stackable AS programme, and subsequently several authors from around the world reported their experience of AS for PTMC. Therefore, the

currently available data are plentiful and represent an AS experience of about 25 years on thousands of patients with low-risk papillary microcarcinomas. They confirm a low rate of disease progression during AS and the absence of impact on treatment efficacy or outcomes [19-22,42,43].

The ATA GLs are based on mainly retrospective studies. This is one critical point, as they are founded on the analysis of cases treated in an outdated manner (total thyroidectomy for tumors > 1 cm that eliminates the problem of frequent neoplasm multifocality, facilitates follow-up and allows radiometabolic treatment).

Therefore, some prognostic variables that we consider almost irrelevant today, such as neoplastic microfoci in the contralateral lobe, minimal extra-thyroid invasion, or micrometastases in the central neck compartment, may no longer be so when a significant proportion of DTCs are treated with lobectomy and do not receive radioiodine after initial surgery.

Taking these last concepts into consideration, the appropriateness of the management proposed by ATA and IC, which is clearly less invasive and tailored to the individual patient, can only be assessed in the next years, analysing the rates of recurrence/persistence of disease (re-surgery rates), and a possible but unlikely increase of cancer-specific mortality. We hope that molecular analyses on cytological samples and surgical histological material will be able to provide further reliable guidance on the most appropriate therapeutic management. Therefore, it appears essential that the therapeutic options, especially if placed in the "grey areas", are discussed with patients by providing full information about the advantages and potential disadvantages of each choice.

Conclusions

By analysing and comparing the ATA and IC GLs, we highlighted the key points of management of DTC. GLs are essential to inform clinical decision-making and harmonise clinical practice among all specialists dealing with DTC. We also highlighted different consideration of GLs to allow the specialist (especially otolaryngologists and head and neck surgeons) to better tailor clinical management to the specific patient.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

GA data collection, writing and editing the manuscript, EC editing the manuscript, MF editing the manuscript, AP editing the manuscript, RRG editing the manuscript, GS conception and design of the study, editing and supervision, NP conception of the study, editing and supervision.

Ethical consideration

Ethical review and approval was not required for the study. Both guidelines have been drawn up following the requirements of the World Medical Association's Declaration of Helsinki.

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