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Current practice in intermediate risk differentiated thyroid cancer – a review

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Abstract
Although the overall prognosis for differentiated thyroid cancer (DTC) is excellent, a subset of patients will experience disease recurrence or may not respond to standard treatments. In recent years, DTC management has become more personalized in order to enhance treatment efficacy and avoid unnecessary interventions.
In this context, major guidelines recommend post-surgery staging to assess the risk of disease persistence, recurrence, and mortality. Consequently, risk stratification becomes pivotal in determining the necessity of postoperative adjuvant therapy, which may include radioiodine therapy (RIT), the degree of TSH suppression, additional imaging studies, and the frequency of follow-up.
However, the intermediate risk of recurrence is a highly heterogeneous category that encompasses various risk criteria, often combined, resulting in varying degrees of aggressiveness and a recurrence risk ranging from 5 to 20%. Furthermore, there is not enough long-term prognosis data for these patients. Unlike low- and high-risk DTC, the available literature is contradictory, and there is no consensus regarding adjuvant therapy.
We aim to provide an overview of intermediate-risk differentiated thyroid cancer, focusing on criteria to consider when deciding on adjuvant therapy in the current context of personalized approach, including molecular analysis to enhance the accuracy of patient management.

Keywords Thyroid neoplasms · Thyroid cancer · Differentiated thyroid cancer · Radioactive iodine therapy · Iodine radioisotopes · Neoplasm recurrence · Therapy · Treatment outcome · Intermediate-risk papillary thyroid cancer

1 Introduction

Over the past decade or so, the management of thyroid cancer has undergone a significant transformation, primarily driven by the rising global incidence of thyroid cancer [1, 2]. This surge in incidence can be largely attributed to the increased accessibility of diagnostic tests like neck ultrasound (neck-US), computed tomography (CT), and magnetic resonance imaging (MRI). Additionally, ultrasound-guided aspiration punctures have played a pivotal role in the increased detection of low-risk papillary thyroid carcinomas (PTC) [3].

Although the overall prognosis for differentiated thyroid cancer (DTC) is excellent, a portion of DTC patients will experience disease recurrence or may not respond to standard treatments [4]. In order to improve treatment effectiveness and reduce unnecessary interventions, the management of DTC is evolving towards a more personalized approach.

In this context, the 2015 American Thyroid Association (ATA 2015) guidelines recommend evaluating the risk of disease persistence or recurrence, as well as the risk of mortality [1]. This assessment is crucial for determining the necessity of postoperative adjuvant therapy, which may include radioiodine therapy (RIT), the degree of TSH suppression, the need for additional imaging exams, and the frequency of follow-up [5].

The ATA recurrence risk stratification categorizes DTC tumors into low, intermediate, and high-risk groups (see Table 1 and Table 2). Among these, the intermediate-risk

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Table 1 Risk stratification of recurrence and disease persistence of differentiated thyroid carcinomas proposed by the 2015 ATA guidelines

Low Risk (< 5%)	(I) Papillary carcinoma with the following characteristics: • Absence of vascular invasion and local or distant metastases; • Complete tumor resection • Absence of tumor invasion of tissues or locoregional structures • Subtype that does not have aggressive histology; • Absence of lymph node involvement or up to 5 micrometastases of up to 2 mm (II) Follicular subtype papillary carcinoma encapsulated intrathyroidal (III) Well-differentiated follicular carcinoma with capsular invasion and no or < 4 foci of vascular invasion (IV) Unifocal or multifocal papillary intrathyroidal microcarcinoma including mutated BRAFV600E (if known)
Intermediate Risk (5–20%)	(I) Microscopic invasion of the tumor into the perithyroid soft tissues; (II) RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan (III) Aggressive histology (For example: tall cell, hobnail variant, columnar cell carcinoma) (IV) Papillary carcinoma with vascular invasion; (V) Lymph node involvement < 3 cm or up to 5 lymph nodes with micrometastases < 2 mm; (VI) Multifocal papillary microcarcinoma with extrathyroidal extension (ETE) and BRAFV600E mutation (if known)
High Risk (> 20%)	(I) Macroscopic tumor invasion of perithyroid soft tissues (II) Incomplete tumor resection (III) Distant metastases (IV) Postoperative serum thyroglobulin suggestive of distant metastasis (V) Lymph node involvement ≥ 3 cm in the largest dimension (VI) Follicular thyroid carcinoma with extensive vascular invasion (> 4 foci)

category is the second most prevalent, accounting for 25 to 35% of all cases. This group exhibits significant heterogeneity, with various risk criteria that can be combined, resulting in varying degrees of aggressiveness and a risk of recurrence that ranges from 5 to 20% [1]. Furthermore, there is not enough data on long-term prognosis for these patients.

Table 2 A refined assessment of the characteristics regarding the rate of recurrence and disease persistence according to the 2015 American Thyroid Association (ATA) Guidelines. * Varies with tumor size and other histopathological and molecular features

	Tumor Characteristics	Estimated Recurrence Rate %
High Risk	Follicular cancer with > 4 foci of vascular invasion	30 – 55%
	T4a tumor with invasion of local structures	30 – 40%
	Extranodal extension in > 3 lymph nodes	40%
	Tumor > 1 cm with TERT mutation	40%
	Metastatic lymph node > 3 cm	30%
	BRAF mutation + extrathyroidal extension	10 – 40%
Intermediate Risk	Papillary thyroid cancer with vascular invasion	15 – 30%
	Clinical N1 or > 5 metastatic lymph nodes	20%
	BRAF mutation without extrathyroidal extension and tumor < 4 cm	10%
	Microscopic extrathyroidal extension	3 – 9%
	Aggressive histology Variable*	
Low Risk	Any number of metastatic nodes but all < 0.2 mm	5%
	Up to 5 metastatic nodes	5%
	2—4 cm intrathyroidal papillary carcinoma	5%
	Multifocal micropapillary carcinoma	4 – 6%
	T1 without microscopic extrathyroidal extension and up to 3 metastatic lymph nodes	2%
	Minimally invasive follicular carcinoma	2 – 3%
	Intrathyroidal and < 4 cm, BRAF wild-type	1 – 2%
	Intrathyroidal micropapillary carcinoma BRAF mutated	1 – 2%
	FV-PTC, Intrathyroidal and encapsulated	1 – 2%
	Unifocal micropapillary carcinoma	1 – 2%

Unlike low- and high-risk DTC, the available literature is contentious, and there is no consensus regarding the prescription of adjuvant therapy [1, 5–9].

While currently accepted prognostic factors include patient's age, histological variant, initial disease extension, and the size of the primary tumor, a significant percentage of patients are not accurately classified solely based on these variables. Indeed, it is necessary to consider additional factors for a more individualized approach, including the experience of the surgeon and specialist physician, the geographical region, accessibility to healthcare services (including the availability of serum thyroglobulin (Tg) tests and the quality of neck-US), economic considerations, and the patient's values and preferences [10]. Molecular analysis also offers an effective way into a more personalized approach for patients in this category [11].

The aim of this publication is to review potential indicators that can aid in decision-making regarding the optimal surgical approach, the prescription of radioiodine therapy, and the recommended follow-up procedures, both initially and after restaging. It is important to note that this review is not applicable to children under 18 years of age.

2 Lobectomy or total thyroidectomy?

Due to the relatively low risk of persistent disease and recurrence of some thyroid cancers, lobectomy has emerged as a viable alternative to total thyroidectomy [1]. The primary objective is to optimize oncologic outcomes, specifically disease-specific and disease-free survival, while minimizing surgical morbidity and the long-term effects of treatment [12, 13]. Indeed, the complication rate associated with total thyroidectomy is higher than that of thyroid lobectomy, even when performed by experienced surgeons. Furthermore, this complication rate increases significantly for low-volume surgeons. In a study based on a dataset of 62,722 hospitalizations in the USA, the overall complication rate for lobectomy was 7.6% when performed by high-volume surgeons (those with over 99 cases per year) and 14.5% for total thyroidectomy. These numbers escalated to 11.8% and 24.1%, respectively, for low-volume surgeons [14].

Additionally, a prospective cohort study in patients with low to intermediate risk DTC showed that health-related quality of life (HRQOL) in the short-term postoperative period is better following lobectomy compared to total thyroidectomy, although there was no difference in long-term results (after 6–12 months) [15].

For the intermediate-risk group, the available data on patients' outcomes are conflicting, as summarized in Table 3. Some studies suggest that lobectomy does not result in any disadvantage in terms of recurrence-free survival (RFS) or disease-specific survival (DSS) [12, 13, 16–18]. In their respective studies, which included matched-pair analyses with propensity score matching for potential prognostic clinical and histological factors, Liu J et al. found that among 341 pairs of patients, there was no significant difference in the 10-year RFS rate between patients treated with lobectomy and total thyroidectomy (77.4% vs. 80.2%, $p = 0.622$), nor in the DSS rate (97.2% vs. 98.4%, $p = 0.554$)

Table 3 Major studies assessing lobectomy x total thyroidectomy in intermediate-risk DTC

References	Country	Number of Intermediate-risk patients	Mean follow up (months)	Lobectomy	Total thyroidectomy	Difference in patients' outcome
Liu et al. [12] Single center retrospective study, 2019	China	620	125	341	279	No
Xu et al. [13] Single center retrospective study, 2023	China	530	60	265	265	No
Adam et al. [14] Multicentric restropective study, 2014	US	15,134 N1 4722 ETE 10,521 multifocality	82	6849	54,926	Yes
Park et al. [16] Single center retrospective study, 2017	Korea	170	103	-	-	No
Momesso et al. [17] Multicentric restropective study, 2016	US and Brazil	74	101	34	28	No
Vaisman et al. [18] Single center retrospective study, 2011	US	75	60	-	-	No
Colombo et al. [19] Single center retrospective study, 2021	Italy	39	113	12	27	Yes
Dobrinja et al. [20] Multicentric retrospective study, 2021	Italy	564	median 29 months	65	499	32% needed completion thyroidectomy

[12]. Similarly, Xu S et al. reported that among 265 pairs of patients, there was no significant difference in the 5-year RFS rate between patients treated with lobectomy and total thyroidectomy (92.3% vs. 93.7%; p = 0.77) [13].

On the other hand, a retrospective study, including 61,775 patients from the National Cancer Institute Database with DTC tumors ranging from 1.0 to 4.0 cm, indicated that when some histological features of intermediate risk such as extrathyroidal extension and lymph node metastases are present, patients tend to benefit from total thyroidectomy. In fact, prior to adjusting for these pathologic criteria, overall survival was slightly better for patients who underwent total thyroidectomy compared to those who had lobectomy at 5 years (97.2% vs. 96.9%), 10 years (92.9% vs. 91.4%), and 14 years (86.6% vs. 84.4%), with a p-value of 0.001 [14]. Colombo et al. also showed that structurally incomplete responses were significantly more frequent among patients treated with lobectomy (42% vs. 7% with total thyroidectomy; P = 0.010) [19]. Furthermore, an Italian multicentric retrospective study showed that 32% of intermediate-risk patients treated with lobectomy required completion thyroidectomy [20].

The decision regarding the need for total or completion thyroidectomy hinges on several critical factors, including the risk of cancer recurrence, the indication for adjuvant RIT, and the requirement for a highly sensitive tumor marker (Tg) to detect potential recurrences [21].

To better decide on the extent of thyroid surgery, it is important to consider both the preoperative characteristics of the tumors and the post-operative histological features. Pre-treatment characteristics that may warrant total thyroidectomy encompass the presence of a rapidly growing thyroid nodule, lymph node involvement, a history of radiation exposure and a family history of thyroid cancer, the both latter implying an increased risk of contralateral or multifocal disease. Additionally, if molecular testing is available and performed before surgery, the presence of BRAF and TERT promoter mutations may justify total thyroidectomy due to their aggressive nature [22]. For elderly patients, it is essential to account for comorbidities and assess the risk associated with a potential second surgery [23].

Intermediate-risk histological features that warrant considering adjuvant RIT often need a completion thyroidectomy (Table 4). These features encompass aggressive subtypes of PTC, such as hobnail, tall cell, or columnar carcinoma, as well as multicentric disease. In case of multicentric disease, there is a higher risk of residual disease in the contralateral lobe, making completion thyroidectomy more suitable [23, 24]. Specifically, the tall cell subtype of PTC is frequently associated with multifocal and bilateral disease, further underscoring the need

Table 4 Summary of the studies addressing controversial factors in recommending RIT for Intermediate-Risk Thyroid Cancer

Controversial Factors	Benefit from RIT	No benefit from RIT
Microscopic extra thyroidal extension	*Perros et al. [39] *Zerdoud et al. [40]	*Mallick et al. [33] *In MPTC: AL-Qahtani et al. [41] *In MPTC: Kim et al. [42] *Ahmaddy et al. [43] *Forleo et al. [44] *Diker-Cohen et al. [45]
Vascular invasion	*Wreesmann et al. [51] *Puga et al. [52] *Creach et al. [53]	*In MPTC: AL-Qahtani et al. [41]
Lymph node metastases	Creach et al. [53] In MPTC: Kim et al. [42] If > 1 lymph node metastases: Zhao et al. [92]	*In MPTC: AL-Qahtani et al. [41] *In < 45 y patients: Sacks et al. [93] *For level VI lymph node metastases: *Wang et al. [37] *Han et al. [38]
Agressive histology	In MPTC: AL-Qahtani et al. [41] Kazaure et al. [49] Regalbuto et al. [50]	*Sawka et al. [48]
Tg level value	*sTg ≥ 10 ng/mL: Gao et al. [60] *If sTg > 1 and ≤ 10: Webb et al. [56] *usTg ≤ 1 ng/mL and sTg levels ≤ 10: Tian et al. [59]	*If sTg ≥ 10 ng/mL: Du et al. [35]
BRAF mutation	*Boucai et al. [69]	*Xing et al. [64] *Agrawal et al. [65] *Liu et al. [67] *Sabra et al. [66] *Leboulleux et al. [70]

for total thyroidectomy [25]. Conversely, microscopic extracapsular extension may not be an immediate indication for completion thyroidectomy. Numerous publications have shown that minimal extrathyroidal extension does not necessarily result in a worse prognosis [23, 26–28]. However, the presence of lymph node disease detected after lobectomy may justify completion thyroidectomy with neck dissection, depending on the size and number of lymph node metastases [23].

Despite careful preoperative patient selection and intraoperative evaluation to exclude extrathyroidal extension or lymph node metastases, approximately 30% of patients may ultimately require completion thyroidectomy. This is often due to higher-risk features that can only be confirmed after comprehensive histopathological and molecular analyses of the tumor [29]. Importantly, retrospective studies have shown that, if necessary, completion thyroidectomy does not result in significantly higher morbidity compared to an initial total thyroidectomy [23, 30, 31]

3 Radioiodine therapy (RIT) in intermediate risk: for whom? (Fig. 1)

The benefits of RIT for intermediate-risk thyroid cancer patients have been a subject of extensive discussion in the literature. The term "Radioiodine Therapy" broadly encompasses three main objectives: (I) ablation of remaining thyroid tissue to facilitate follow-up, (II) adjuvant treatment to eliminate suspicious neoplastic remnants undetected in imaging studies, with a focus on enhancing disease-free survival, and (III) treatment of macroscopic residual disease or known relapse, with the aim of improving overall survival and progression-free survival, either for curative or palliative purposes [3, 32].

Traditionally, most patients with DTC received postoperative RIT as standard care. However, the approach has changed in recent years into a more personalized management model, where RIT recommendations are based on

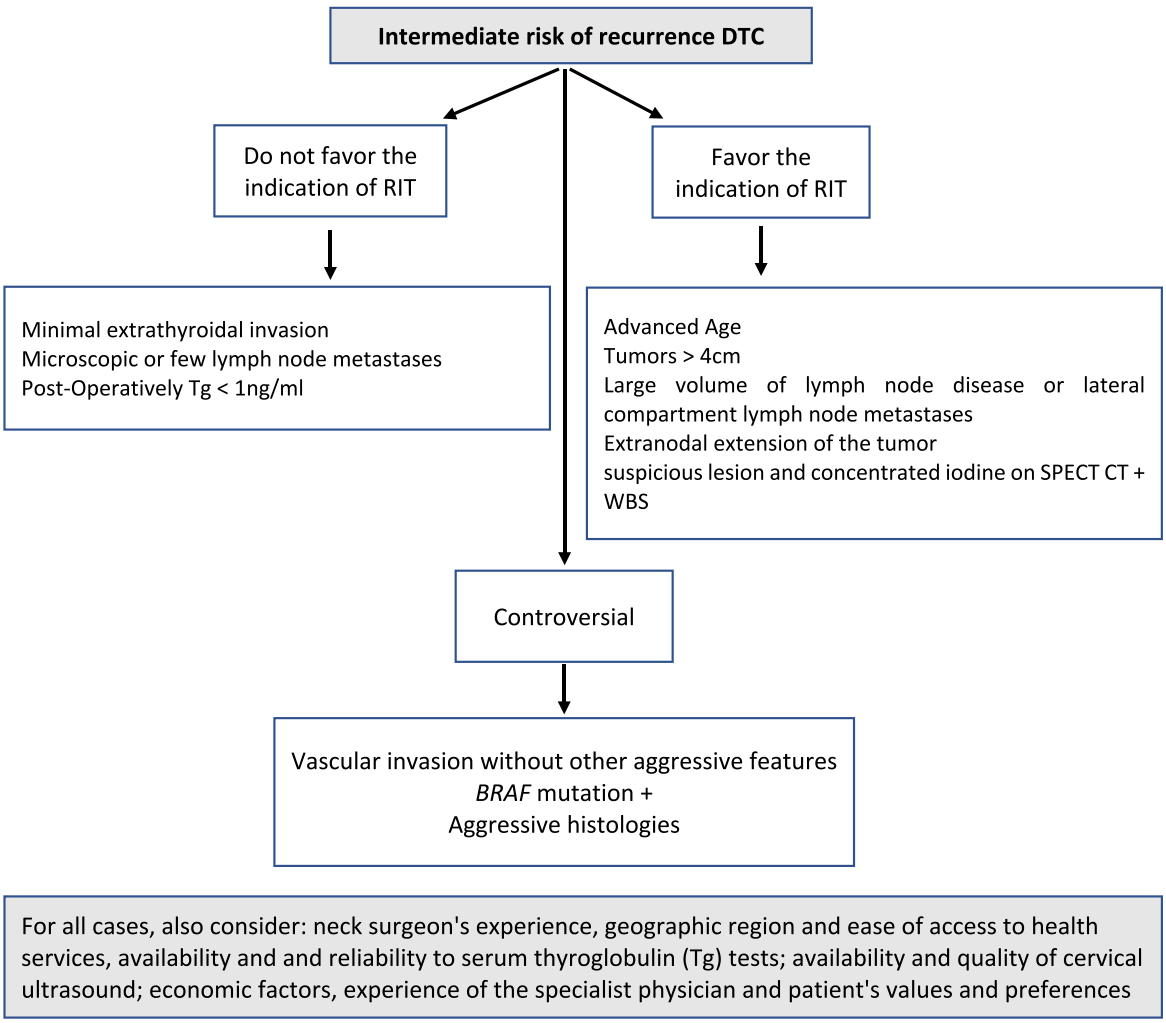

Fig. 1 Factors that may influence the decision to indicate RIT or not in intermediate-risk DT patients

clinical and pathological features, especially for the intermediate risk group. According to the ATA 2015 recommendations, RIT is not usually necessary for low-risk patients, highly recommended for high-risk patients, and should be considered on an individual basis for intermediate-risk patients.

The lack of standardized recommendations for intermediate-risk patients stems from the absence of prospective, multicenter, and randomized studies that could provide substantial evidence supporting adjuvant RIT in this group. The intermediate-risk category is notably diverse, incorporating a range of tumors with varying risk profiles and degrees of aggressiveness, making it challenging to establish universal RIT guidelines. Recurrence rates vary widely within this category, ranging from 5 to 20%. In a personalized approach, the decision to recommend adjuvant RIT and determine the appropriate radioactive iodine (^{131}I) activity should consider several factors, including initial prognostic indicators, surgical reports, anatomopathological descriptions, post-operative Tg levels, and anti-thyroglobulin antibodies (ATg). Additional considerations include neck-US, other imaging exams, and the presence of relevant genetic markers.

Low to low-intermediate-risk patients do not appear to benefit from adjuvant RIT. Nonetheless, it can still be administered using lower doses of ^{131}I, typically around 1.1 GBq after recombinant human TSH (rhTSH) stimulation, for ablative purposes [1, 33–36].

For instance, the impact of RIT remains a topic of debate for patients with intermediate risk and lymph node metastases, as the benefits of RIT appears to vary depending on the size and location of the involved lymph nodes. Some studies suggest potential benefits, even for micro papillary thyroid carcinoma (MPTC) with lymph node involvement, while others do not support this conclusion. Wang et al. [37] found no significant difference in 5-year central compartment nodal recurrence-free survival between PTC patients treated with RIT and those without RIT. A meta-analysis of 79 studies also failed to show a significant improvement in survival or reduced risk of persistent disease or recurrence in patients under 45 years old with microscopic central compartment lymph node metastases. Han K et al. [38] showed that the recurrence-free survival of intermediate-risk PTC patients did not significantly differ between those who received postoperative RIT and those who did not, especially for patients with negative extranodal extension and a low number of metastatic lymph nodes.

The role of minimal extrathyroidal extension (mETE) as a risk factor for persistent PTC in patients at the intermediate-risk category remains a subject of controversy. The British Thyroid Association (BTA) [39] and French Societies [40], recommend the use of RIT based on the presence of mETE. However, some studies suggest that although mETE may raise patients' risk classification, it does not necessarily lead to a poor response to initial treatment [33, 41–44]. In fact, these studies have failed to demonstrate a discernible benefit of adjuvant RIT in reducing the risk of recurrence in case of mETE [33, 41–44]. A meta-analysis conducted by Diker-Cohen et al. [45] indicated that mETE does increase the risk of recurrence in patients with DTC, but the absolute increase in risk is relatively small, especially in patients with N0 disease, where the risk remains within the low-risk category for recurrence. They also showed that mETE has no impact on disease-related mortality and should not change tumor stage. Tran et al. [46] have shown that while mETE may not be an independent prognostic factor in multivariate analyses, it can provide valuable information about disease biology and serve as a surrogate marker for several closely associated adverse features.

For patients in the high-intermediate risk category (comprising patients aged over 55 years, those with tumors larger than 4 cm, a significant volume of lymph node disease, multiple lymph node involvement, lateral compartment lymph node metastases, and vascular invasion), adjuvant RIT with 3.7 GBq of ^{131}I following rhTSH stimulation has demonstrated greater efficacy due to the increased risk of recurrence or distant metastasis, especially for cases with aggressive histology [1, 3, 47]. However, there may be exceptions for patients with aggressive histology, as available data can be inconclusive. In such cases, patients with BRAF mutations tend to benefit less from RIT, as they often have lower NIS expression, which affects their ability to concentrate ^{131}I [48]. Nevertheless, some studies have indicated a reduction in the risk of recurrence after RIT for aggressive variants of PTC [41]. Kazaure et al. [49] and Regalbuto et al. [50] have shown that patients with diffuse sclerosing and tall cell histological subtypes who did not receive RIT had a 4.9- and 2.1-times higher likelihood of mortality compared to those who received RIT. For the time being, the overall risk–benefit assessment leans in favor of RIT.

The significance of vascular invasion (VI) as a predictor of distant metastasis and its potential role in RIT benefits are also subjects of debate, particularly in well-differentiated PTC. Different studies have yielded varying results. In their retrospective study Wreesmann et al. [51] found a significant association between VI and factors such as tumor size greater than 4 cm, extrathyroidal extension, distant metastasis, and radioiodine treatment. However, in the multivariate analysis, VI did not emerge as an independent predictor of distant recurrence-free survival. In contrast, Puga et al. [52] showed that lymphovascular invasion, including lymphatic invasion alone, was significantly linked to a higher likelihood of persistent or recurrent disease, especially among patients who did not undergo RIT, compared to those without lymph vascular invasion. This suggests that VI may have implications for the likelihood of disease recurrence. Creach et al. [53] also demonstrated the benefits of RIT for patients

with VI, indicating a potential advantage in these cases. Furthermore, Al-Qahtani KH et al. [41] provided evidence that adjuvant RIT with a dose of 150 mCi or higher enhances Disease-Free Survival (DFS) in patients with thyroid microcarcinomas and VI. In summary, the potential benefit of adjuvant RIT in well-differentiated PTC cases characterized by the presence of VI and the absence of other aggressive features remains uncertain, with studies yielding mixed results [51]. Further research is needed to clarify the role of VI in guiding treatment decisions for these patients.

By reviewing the relevant literature, it becomes evident that clinicopathological features have primarily guided the RIT decision-making process. However, it is crucial to recognize that relying on these criteria alone may be insufficient to accurately predict patients' risks of recurrence and metastasis, as patients' real-time status may be influenced by their initial treatment. This highlights the need to assess the postoperative status.

In this context, postoperative thyroglobulin (Tg) level plays a significant role in assessing the risk of recurrence and the effectiveness of RIT in patients with DTC. Several studies have consistently shown that elevated postoperative stimulated thyroglobulin (sTg) levels, typically above 1–2 ng/mL, are associated with an increased risk of recurrence [54–56]. Conversely, sTg levels below this threshold generally indicate a state of remission, suggesting a lower risk of recurrence [57, 58].

Tian et al. [59] conducted a propensity score matching (PSM) analysis to investigate the effectiveness of RIT in reducing the recurrence risk of intermediate-risk PTC in patients with low Tg levels. They found that RIT could decrease the recurrence risk of intermediate-risk PTC in patients with unstimulated Tg (usTg) levels of ≤ 1 ng/mL or sTg levels of ≤ 10 ng/mL. This suggests that RIT may be beneficial for these patients, even if their Tg levels are relatively low. A comprehensive meta-analysis [56] involving 3947 patients with DTC across fifteen studies, focusing on sTg values ranging from $>$ 1–2 ng/mL and $<$ 10 ng/mL, supported the notion that patients with postoperative sTg levels below 10 ng/mL, in the absence of anti-thyroglobulin antibodies (ATg), tend to have a significantly improved prognosis following RIT compared to those with higher sTg levels. Importantly, only 6% of these patients were found to have persistent disease after RIT, indicating a favorable response to treatment. Additionally, in a multicenter prospective study with a median follow-up of 10.6 months, it was observed that 80% of DTC patients with sTg levels ≥ 10 ng/mL, even when presenting more adverse clinicopathologic characteristics, maintained a non-structurally incomplete response after receiving 5.55 GBq (150 mCi) of ^{131}I [35]. Gao et al. [60], in a retrospective analysis of 423 low- and intermediate-risk DTC patients, concluded that pretreatment sTg levels are essential indicators in RIT decision-making and efficacy evaluation. They found that DTC patients, particularly in the intermediate-risk group with sTg levels ≥ 10.0 ng/mL, would benefit from aggressive RIT. In summary, postoperative sTg level is a valuable indicator for assessing the risk of recurrence and guiding RIT decisions in patients with thyroid carcinoma. While elevated sTg levels are associated with a higher risk, some studies suggest that RIT can still be effective in cases with low to moderately elevated Tg levels, depending on the specific patients' clinical characteristics. Although additional evidence is needed to establish an optimal sTg threshold for selecting patients who would benefit from RIT [36, 48], it is reasonable to consider omitting RIT for those with lower sTg levels below 1.0 ng/mL.

In addition to serum Tg levels and neck-US, radioiodine whole-body scintigraphy (WBS) performed with single-photon emission computed tomography-computed tomography (SPECT/CT) has emerged as a valuable tool for postoperative staging and patient selection for RIT. This approach offers several advantages, including enhanced image quality and improved capabilities for identifying foci of abnormal ^{131}I uptake. These improvements make image interpretation and post-surgical staging more efficient, contributing to the assessment of risk of disease persistence and recurrence [61]. A study conducted by Avram et al. found residual disease or suspicious regional metastases in 35% of cases and distant metastases in 8% of cases among 320 patients, which modified the initial staging for 4% of younger patients and 25% of older patients [62]. In another study, pre-ablation WBS performed with SPECT/CT after surgery and before RIT, combined with serum thyroglobulin levels, modified the baseline risk stratification for 15% of patients, ultimately impacting the clinical management of 29.4% of the study's population [47]. Collectively, these modalities assist in patient selection for RIT and determining the most appropriate radioactive iodine activity for their treatment [62, 63]. A retrospective analysis conducted at a single center in Brazil, involving 301 intermediate-risk patients who underwent total thyroidectomy and RIT, showed that 17.3% of them had metastases detected through diagnostic ^{131}I WBS (DxWBS) and/or post-therapy WBS (RxWBS). Specifically, DxWBS identified metastases in 10.6% of patients, including instances of unexpected distant metastases. When combined with single photon emission computed tomography-computer tomography (SPECT-CT), DxWBS more frequently detected ^{131}I-avid metastases, especially in the case of lymph node metastases (13.1% vs. 4.2% for planar WBS, $p = 0.015$). These DxWBS findings led to modifications in patient management in 8.3% of cases. Importantly, a pretherapy sTg level below 1 ng/mL was associated with a low rate of false negatives for the presence of metastases (5.2%). This ability to exclude metastasis was further enhanced when combined with a negative DxWBS, as only 2.7% of patients with sTg levels below 1 ng/mL and a

negative DxWBS showed metastases on post-therapy WBS [63].

In recent years, risk stratification based on molecular markers has emerged as a promising strategy for the personalized management of thyroid cancer [64]. This approach carries particular significance for DTC, given its high incidence and the well-established prognostic value of specific molecular markers [1–3, 5, 7, 32].

It has been observed that PTC carrying the *BRAFV600E* mutation often display a poor response to RIT [64–67]. This resistance to ^{131}I treatment appears to be associated with the expression of genes involved in iodide uptake and metabolism, which are pivotal indicators of the differentiated state of follicular thyroid cells. In contrast, RAS-mutated PTCs exhibit a low MAPK-dependent transcriptional program due to negative feedback regulation. They also tend to maintain the expression of iodine metabolism genes and generally exhibit an affinity for radioiodine [68]. Nevertheless, a subset of BRAFV600E-mutated PTCs does respond to radioiodine therapy. In these cases, tumors still show relatively preserved expression of thyroid differentiation genes and higher expression of MicroRNAs targeting the transforming growth factor β (TGFβ) signaling pathway. Activation of this pathway suppresses the expression of thyroid-specific genes [69]. Moreover, in the ESTIMABL 2 trial, among patients initially categorized as "low-risk" DTC, over half of them carried the BRAFV600E mutation and 25% had the tall-cell variant, which reclassified some of them as intermediate-risk patients. Nevertheless, the trial demonstrated that a follow-up strategy without the use of ^{131}I was noninferior to an ablation strategy [70]. An emerging and clinically significant question revolves around the reliability of molecular markers in predicting the resistance of thyroid carcinomas to ^{131}I. Heterogeneous gene mutations may contribute to variations in tumor morphology, gene expression, and individual clinical characteristics. These markers have the potential to become pivotal prognostic factors for decision-making in radioiodine therapy. However, further evaluation is necessary to fully understand the impact of these mutations on disease progression.

Regarding the benefit of RIT in improving the survival of intermediate-risk patients, there is a lack of randomized clinical trials due to the indolent nature of DTC and its long-term survival. Conducting such trials would require an impractically large number of patients, extended follow-up periods, and significant associated costs [71]. In a nationally representative study using the Surveillance Epidemiology and End Results (SEER) database, Podnos et al.[72], and in a single-institution study with extensive patient follow-up conducted at the Mayo Clinic by Hay et al. [73], conclusive evidence supporting a survival benefit for RIT in the overall patient population was not found. It is important to note that neither study specifically examined the intermediate-risk patient subgroup. On the other hand, one study did demonstrate a survival benefit with RIT in a subset of intermediate-risk patients. Similarly, another study found a benefit in disease-free survival within a subset of patients with stage T2-T4 disease, but it was a smaller, single-center study [74]. Moreover, Ruel et al. [8] conducted a study involving 21,870 intermediate-risk patients defined by the American Thyroid Association risk criteria and American Joint Commission on Cancer staging (T3, N0, M0 or Mx, and T1–3, N1, M0, or Mx) over a mean follow-up of six years. They reported that RIT was associated with improved overall survival (OS) in all patients ($p < 0.001$). This benefit was also observed in subgroup analyses among patients younger than 45 years ($n = 12{,}612$, $p = 0.002$) and those 65 years and older (median OS 140 vs. 128 months, $n = 2{,}122$, $p = 0.008$). After adjusting for demographic and clinical factors, RIT was linked to a 29% reduction in the risk of death, with a hazard ratio of 0.71 (95% confidence interval 0.62–0.82, $p < 0.001$). For patients under 45 years, RIT was associated with a 36% reduction in the risk of death, with a hazard ratio of 0.64 (95% confidence interval 0.45–0.92, $p = 0.016$).

Table 4 provides a summary of the studies addressing controversial factors in recommending RIT for intermediate-risk DTC. Figure 1 illustrates the factors that can influence the decision to recommend or not RIT in intermediate-risk DTC patients.

4 Initial follow-up

Risk stratification for early disease persistence and recurrence should be used to guide management recommendations during the first 1–2 years of follow-up. However, it is crucial to adapt new recommendations based on the response to the initial therapy, aiming for a more precise and individualized long-term management and follow-up plan [5].

The most significant shift in risk estimation as a function of therapy response is observed within the intermediate-risk group. In this category, the estimated risk of recurrent or persistent structural disease, initially at 18%, diminishes significantly to just 2% in patients with an excellent treatment response. Similarly, a select few high-risk patients who respond exceptionally well to therapy experience a substantial reduction in the risk of recurrent or persistent structural disease, declining from 66 to 14%. Conversely, low-risk patients who exhibit an incomplete response to therapy see their risk of persistent structural disease increase from 3 to 13% [5]

Obtaining a clinical outcome with serum thyroglobulin (sTg) levels below 1 ng/mL and a negative imaging test is closely associated with a higher likelihood of showing no clinical evidence of disease. Furthermore, a combination of negative neck ultrasound (neck-US) and suppressed

Tg levels below 1 ng/mL also presents a high probability of an excellent response, especially in low-risk (94%) and intermediate-risk (90%) patients within the initial 2 years of follow-up [5]. As a result, the necessity to conduct sTg testing should be approached with an individualized perspective, considering factors like the sensitivity and reliability of the available Tg assay, the quality of neck-US, and the cost associated with sTg testing.

Furthermore, several potentially crucial variables that could account for unexplained variations, beyond what current staging systems cover, include the impact of additional therapies administered after the 2-year re-stratification, complications stemming from therapy that may alter overall survival or affect the ability to detect recurrent disease, and the influence of the initial genotype on tumor aggressiveness, therapy response, or the ability to detect recurrent disease [75]After total thyroidectomy, the size of the presumably benign thyroid remnant is usually small, resulting in very low or often undetectable serum thyroglobulin (Tg) levels. Currently, even without postoperative radioiodine therapy, most patients can be followed up with serum Tg, with TSH suppression according to the stratification of risk of recurrence and disease persistence, and with imaging examination. For intermediate-risk patients, the TSH goal should be between 0.1–0.5 mU/L. An undetectable Tg level is comforting, as is a low but detectable level. In the latter case, the serum Tg should be monitored over time: a decline or stable Tg is reassuring, while an increase should prompt imaging to locate and treat the disease [1, 55]

5 Initial risk reassessment and prognosis

Numerous studies have consistently demonstrated that an excellent response to treatment, defined as the presence of a normal neck ultrasound (neck-US) and suppressed thyroglobulin (Tg) levels below 0.2 ng/mL or serum Tg (sTg) below 1 ng/mL [1], significantly reduces the initial risk of persistent or recurrent disease. This shift downgrades the risk level from intermediate to low, with an associated risk of only 1–2% [76]. Such patients, constituting 57–63% of intermediate-risk patients, can benefit from a less intensive follow-up regimen, which involves monitoring serum Tg and anti-thyroglobulin antibodies (ATg) every 12–24 months, undergoing cervical ultrasound (US) every 3–5 years, and having TSH levels maintained in the lower normal range (0.5 to 2 mUI/L) in the event of increasing tumor markers [77].

Conversely, patients exhibiting an incomplete structural response to treatment, accounting for 19–28% of intermediate-risk patients, face an increased risk of persistent disease at the conclusion of follow-up, despite additional treatment measures [76]. For these individuals, a comprehensive clinical and biological monitoring plan is recommended, involving frequent monitoring of serum Tg and ATg levels every 3–6 months. TSH suppression should be maintained at levels below 0.1 mUI/L, unless contraindicated [77]. Additionally, they should undergo more frequent cervical US assessments and other imaging staging procedures, including computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and [18F]2-fluoro-2-deoxy-D-glucose—positron emission tomography/computer tomography (18FDG-PET-CT), if there is suspicion of metastatic or progressive disease. For cases of persistent or recurrent disease, further treatment options such as reoperation for cervical lymph node dissection and/or a second round of Radioactive Iodine Therapy (RIT) may be necessary. The latter helps diagnose RIT-refractory disease, particularly when there is a lack of radioactive iodine (RAI) uptake in known secondary lesions or when 131I-positive lesions continue to progress after treatment [1, 77].

Patients with an indeterminate response to treatment, making up 8–23% of intermediate-risk patients, are typically defined by criteria such as suppressed thyroglobulin (Tg) levels at 0.2–1 ng/mL or serum Tg (sTg) at 1–10 ng/mL, positive stable/declining anti-thyroglobulin antibody (ATg) levels, or non-specific findings in imaging. Similarly, patients with an incomplete biochemical response to treatment, accounting for 21–22% of intermediate-risk patients, are characterized by criteria like negative imaging results, and suppressed Tg levels exceeding 1 ng/mL or sTg levels over 10 ng/mL, along with positive rising ATg levels. While these groups generally have a favorable prognosis [5, 78], the risk of recurrence can reach up to 20% [76]. Therefore, they should undergo clinical and biological monitoring, including serum Tg and ATg levels, every 6–12 months, with mild TSH suppression maintained within the range of 0.1 to 0.5 mUI/L. Additionally, more frequent cervical ultrasound (US) and other staging imaging should be considered when there is suspicion of metastatic or progressive disease [77].

Several risk factors have been associated with a non-excellent response to treatment in intermediate-risk Differentiated Thyroid Cancer (DTC). These factors include lateral cervical lymph node metastasis [79], the size of the largest focus of lymph node metastasis [80], larger tumor size [81], and post-operative stimulated serum thyroglobulin levels exceeding 10 ng/mL [28, 79]. The utility of BRAF status in dynamic risk stratification (DRS) analysis remains inconclusive due to conflicting data. While two studies suggest that BRAF mutation [82] and complete molecular testing [81] may enhance DRS, another study indicated that BRAF mutation did not significantly improve the differentiation of risk groups [83].

DRS offers a reliable prediction of patient status at the final follow-up in individuals treated with total thyroidectomy and Radioactive Iodine Therapy (RIT). Additionally,

criteria for defining the response to treatment in patients treated with total thyroidectomy without RIT or lobectomy have been established, enabling the prediction of the risk of structural disease during the follow-up period [76, 77].

6 Prognostic role of the 18FDG-PET-CT and the molecular markers

Some intermediate-risk patients can benefit from undergoing 18FDG-PET-CT, not only when there is a well-established suspicion of persistent or recurrent disease during follow-up, but also at the time of the initial Radioiodine Therapy (RIT) [84]. This is particularly relevant for patients with aggressive histological subtypes, such as tall cell, columnar cell, squamous differentiation, diffuse sclerosing, hobnail, and solid/trabecular variants, including tumors harboring a BRAF V600E mutation.

Persistent disease identified on pre-ablation 18FDG-PET-CT scans has been observed in 13 to 33% of intermediate-risk patients [85, 86], with a higher frequency (53%) noted in cases with aggressive histology [87]. Pre- ablation 18FDG-PET-CT can be performed under TSH stimulation, resulting in a slight increase in sensitivity, though with limited clinical benefit. The results should be compared to Radioiodine Whole-Body Scintigraphy (RAI-WBS) findings. Tumors with aggressive histology are more likely to exhibit FDG-positive but iodine-negative lesions, indicating a refractory disease [84, 88].

18FDG-PET-CT also plays a prognostic role, both during the initial treatment and follow-up, especially when there is a rising trend in suppressed thyroglobulin (Tg) or anti-thyroglobulin antibody (ATg) levels. Its sensitivity increases with higher serum Tg levels and larger tumor foci. However, in cases of highly proliferative disease and those with a short Tg doubling time, the sensitivity can be very high, even in the presence of low Tg levels [88].

If available, molecular testing can provide valuable risk stratification for intermediate-risk patients. The BRAF mutation, which is the most frequent mutation in Differentiated Thyroid Cancer (DTC) (~60%) and present in almost 90% of the tall cell variant [89], is a marker of more aggressive tumor behavior, associated with lymph node metastasis, extrathyroidal extension (ETE), and higher recurrence rates. As a result, small tumors in the 1–4 cm range are considered at intermediate risk of recurrence when the BRAF mutation is present, and at high risk if there is a concomitant BRAF and TERT promoter mutation [1, 77].

Additionally, Yip et al. propose a molecular-based risk stratification of DTC using a commercially available molecular testing panel (ThyroSeq version 3). The intermediate-risk molecular-based group includes BRAF V600E, other BRAF-like alterations, and DNA copy number alterations, but lacks additional molecular features to further refine this cohort. In their case–control study, the molecular-based risk classification accurately stratified the risk of distant metastasis, which aligned with the expected risk of structural disease recurrence for the ATA risk groups [90].

Recently, Pizzimenti et al. suggested that in intermediate-risk patients, assessing the BRAF V600E mutation could be useful at the initial treatment stage to identify patients who might benefit from higher doses of 131I or other potential therapies, such as immunotherapy, particularly for those with higher expression of PD-L1 [82].

Finally, molecular testing can also predict tumor behavior and RIT refractoriness, as tumors harboring a BRAF V600E mutation exhibit significantly lower differentiation scores in The Cancer Genome Atlas (TCGA) cohort when compared to RAS tumors [91].

7 Conclusion

Intermediate-risk differentiated thyroid cancers encompass a highly diverse group of patients, characterized by varying combinations of risk factors, resulting in different levels of disease aggressiveness. Managing this patient category is a subject of debate, as there is no consensus regarding the recommendation and benefits of adjuvant therapy, given the limited availability of long-term prognosis data. In the current era of personalized medicine, decisions regarding treatment should consider multiple factors, including the patient's age, histological subtype, initial disease extent, and the size of the primary tumor. Additionally, the surgeon's experience, geographical location, access to healthcare services, the availability of serum thyroglobulin tests, the quality of neck ultrasound, economic considerations, and the patient's personal values and preferences all play a role in the decision-making process. Molecular analysis is emerging as a valuable tool for tailoring treatment to the individual needs of patients within this group.

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