De-escalating Thyroid Cancer Treatment: Indications for Thyroid Remnant Ablation and Adjuvant I-131 Therapy after Surgery for Differentiated Thyroid Cancer

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Abstract

Patients with differentiated thyroid cancer have an excellent prognosis. After the diagnosis of differentiated thyroid cancer most patients undergo a total thyroidectomy followed by radioiodine therapy. In recent years it has become evident that not all patients need extensive surgical treatment and post-operative radioiodine therapy. This article describes the current indications for radioiodine therapy after thyroidectomy for differentiated thyroid cancer.

Introduction

In the Netherlands, approximately 900 patients are diagnosed with thyroid cancer yearly, the most common form being differentiated thyroid cancer (DTC), which makes up around 85% of new cases (1). Patients with DTC generally have a favorable prognosis, with most cases being in TNM stage 1 or 2, with a 10-year disease-specific survival rate of over 90%. The standard treatment for DTC involves surgical removal of the thyroid gland, usually followed by post-operative radioiodine therapy, which is a non-invasive treatment.

Radioiodine therapy involves the oral administration of an activity of radioactive iodine (^{131}I), which is then eventually absorbed by thyroid cells through the sodium-iodide transporter. ^{131}I treatment is a targeted therapy that is effective in treating thyroid cancer and metastatic disease, although it can have side effects such as fatigue and nausea, and may also increase the risk of damage to the salivary glands and secondary neoplasms over the long term. The goal of ^{131}I treatment, as stated in the Martinique criteria, is to postoperatively destroy remaining normal thyroid tissue, to facilitate follow-up and to diagnose and treat microscopic disease and therefore increase recurrence-free survival (2). There are three distinct indications for ^{131}I treatment: i) remnant ablation, to destroy post-thyroidectomy residual thyroid tissue to facilitate thyroglobulin (Tg) follow-up and improve future radioiodine imaging, ii) adjuvant treatment, to destroy subclinical microscopic tumor deposits, for which the risk is high enough to justify ^{131}I therapy to improve disease-specific and overall survival, and iii) treatment of known disease, to destroy post-operatively remaining DTC foci or to treat persistent or recurrent DTC during follow-up.

Despite its use for over eight decades, there are still many controversies surrounding the use of ^{131}I, including which patients would benefit from the treatment, what activity to use and which method of thyroid stimulating hormone (TSH) stimulation to employ. Here we describe the current available evidence for de-escalating DTC treatment and the recommendations of different international guidelines.

Thyroid nodule diagnosis

The Thyroid Imaging Reporting and Data System (TI-RADS) classification is increasingly being used to make the decision for further pathological investigation of thyroid nodules. TI-RADS is an ultrasound-based risk stratification system for thyroid nodules that was published in 2009, although a number of other varieties also exists (3-6). The implementation of TI-RADS has led to fewer fine needle biopsies being performed, resulting in a smaller, and more selected group of patients undergoing surgery. With the implementation of TI-RADS a reduction of unnecessary biopsies of malignant nodules of 20-47% has been described (7). This means that less, but more selected patients undergo surgery, and thus radioiodine treatment.

The guidelines on incidental findings have also changed in recent years (8). There is a more restrictive work-up for incidental thyroid nodules detected on CT or MRI, which also leads to less patients receiving surgery and I-131.

Current guidelines

In 2015, the American Thyroid Association (ATA) provided guidance on the use of ^{131}I for DTC in its guidelines on the management of thyroid nodules and DTC (9). The

European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (NMMI) did not endorse these guidelines (10). In 2019, a joint, multilateral statement was developed during the Martinique meeting (2).

This statement provides updated guidance on the indications for ^{131}I in treating DTC. An overview of the guidelines published since 2015 are summarized in table 1. The guidelines differ in the specific recommendations on indications and prescribed activity.

However, they do all emphasize the importance of individualizing treatment based on the patient's specific clinical characteristics.

Randomized controlled trials

In recent years, four large randomized

Table 1. Guidelines on ^{131}I therapy after thyroidectomy.

	ATA (2015)(9)	Dutch Thyroid Cancer Guideline (2015) (11)	ESMO (2019) (12){Filetti, 2019 #656}	Martinique consensus (2019) (2)	ETA (2022) (13)	EANM/ SNNMI (2022) (14)
Microcarcinoma	Not routinely recommended	N/A	No ^{131}I	Based on individual basis; shared-decision making	No ^{131}I	N/A
Low risk	Not routinely recommended	1.1 GBq	Intensive scientific debate (no ^{131}I vs. 1.1 GBq ^{131}I), should be based on the presence of individual risk modifiers.	Based on individual basis; shared-decision making	Intensive scientific debate (no ^{131}I vs. 1.1 GBq ^{131}I), should be based on the presence of individual risk modifiers.	Indicated, risk-based approach
Intermediate risk	Should be considered	Patient-tailored	Patient-tailored	Based on individual basis; shared-decision making	Patient-tailored	Indicated, risk-based approach
High risk	Routinely recommended	Patient-tailored	All patients, >3700 MBq	Based on individual basis; shared-decision making	All patients, >3700 MBq	Indicated, risk-based approach
rhTSH vs. THW	rhTSH is an acceptable alternative in low-risk or intermediate-risk without nodal involvement; and may be considered an alternative in intermediate-risk with nodal involvement	Low-risk: THW or rhTSH Other: THW	THW or rhTSH	N/A	rhTSH should be the preferred method of preparation	rhTSH or THW; THW for metastatic disease

ATA = American Thyroid Association; ESMO = European Society for Medical Oncology; ETA = European Thyroid Association; EANM = European Association of Nuclear Medicine; Society of Nuclear Medicine and Molecular Imaging; N/A = Not Available; GBq = Gigabecquerel; rhTSH = Recombinant Thyroid-Stimulating Hormone; THW = Thyroid Hormone Withdrawal.

controlled trials have been conducted on the use of ^{131}I for DTC in the setting of thyroid remnant ablation: ESTIMABL (15,16), ESTIMABL2 (17), Hi-LO (18,19) and IoN (20), with a total of 2464 included patients. An overview of the trials is shown in table 2.

The primary focus of the ESTIMABL1 and HiLo trials was to determine whether 1.1 GBq ^{131}I therapy was non-inferior to 3.7 GBq for remnant ablation in low-risk and intermediate risk patients, and whether recombinant TSH (rhTSH) was non-inferior to thyroid hormone withdrawal (THW), in a 1:1:1:1 study design. The results of both trials showed that 1.1 GBq and rhTSH were as effective as 3.7 GBq and THW for remnant ablation in low-risk and intermediate-risk patients. The ESTIMABL2 and IoN trials built upon this conclusion and investigated whether no ^{131}I versus 1.1 GBq ^{131}I was non-inferior in low-risk patients. The ESTIMABL2 trial concluded that no ^{131}I was as effective as 1.1 GBq ^{131}I in low-risk patients. The results of the IoN trial have not yet been published.

Which patients are candidates for ^{131}I treatment?

Generally, guidelines agree that the decision to administer ^{131}I for DTC should be based on the patients' risk of recurrence following surgery and not risk of cancer related mortality. This is different from most other malignancies where treatment is primarily based on the TNM classification of malignant tumors (23). The 2015 ATA guidelines provided a risk stratification system to categorize patients into three groups based on their likelihood of structural disease recurrence: low-risk, intermediate-risk and high-risk, which is illustrated in figure 1 (9). Patients with intrathyroidal DTC and less than 5 lymph node micrometastases (<0.2 cm) are considered low-risk. Patients with aggressive histology, minor thyroidal extension, vascular invasion or more than 5 involved lymph nodes (0.2-3.0 cm) are categorized as intermediate-risk. Patients with gross extrathyroidal extension, incomplete tumor resection, distant metastases or lymph nodes larger than 3 cm are considered high-risk. The patient group with >10 mm DTC without metastases is currently the subject of debate. However, the 2019 joint statement does add that optimal patient selection requires consideration and evaluation of multiple factors beyond postoperative disease status and risk stratification (2). These include post-operative risk assessment, impact on outcomes of interest, side effect profile, patient values and preferences, improved initial staging, facilitate sensitive follow-up, availability and quality of ultrasound, radioiodine imaging, thyroglobulin (Tg) assays and an experienced thyroid surgeon, the presence of anti-Tg antibodies and the preferences of the local disease management team. While some may debate the specific details of the risk assessment criteria mentioned earlier, the fundamental principle remains unchanged: if a patient has multiple

Table 2. Randomized controlled trials on radioiodine therapy for differentiated thyroid cancer.

Study	Trial	Number of patients	Aim	Patient group	Dose administered	Method of TSH stimulation	Conclusion
Schlumberger et al. (2012) (short-term) (15) Schlumberger et al. (2018) (long-term) (16)	ESTIMABL1	726	Remnant ablation	Low risk patients	1.1 and 3.7 GBq	rhTSH and THW	1.1 GBq + rhTSH was as effective as 3.7 GBq + THW
Mallick et al. (2012) (short-term) (21) Dehbi et al. (2019) (long-term) (22)	HiLo trial	438	Remnant ablation	Low- and intermediate risk patients	1.1 and 3.7 GBq	rhTSH and THW	1.1 GBq + rhTSH was as effective as 3.7 GBq + THW
Leboulleux et al. (2022) (17)	ESTIMABL2	730	Remnant ablation	Low-risk patients	No I-131 and 1.1 GBq I-131	rhTSH	No I-131 was as effective as 1.1 GBq I-131
Mallick et al. (2012) (study protocol) (20)	IoN trial	570	Remnant ablation	Low-risk patients	No I-131 and 1.1 GBq I-131	Unknown	Not published yet

GBq = Gigabecquerel; DFS = Disease-Free Survival; TSH = Thyroid-Stimulating Hormone; rhTSH = Recombinant Thyroid-Stimulating Hormone; THW = Thyroid Hormone Withdrawal.

and more severe characteristics that increase the risk of cancer recurrence or thyroid cancer-related death, the indication for post-operative ^{131}I treatment is more strongly recommended.

Patients with unifocal papillary microcarcinoma

For patients with unifocal papillary microcarcinoma (i.e. <10 mm), ^{131}I should be avoided as it leads to overtreatment of disease without any beneficial effect on recurrence and mortality rates, as shown by several retrospective studies (24-27).

Patients with low-risk of structural disease recurrence

Most thyroid cancer patients present with low-risk disease. The benefit of the administration of ^{131}I to low-risk patients after total thyroidectomy remains controversial. Adverse events associated with ^{131}I therapy, such as salivary gland destruction, bone marrow dysfunction and cardiovascular effects, support the trend towards less aggressive treatment for low-risk patients. However, in low-risk patients I-131 can be useful for ablation of thyroid tissue and/or residual disease, allowing for interpretation of serum Tg levels. The ESTIMABL2 trial demonstrated that no radioiodine treatment was as effective as 1.1 GBq ^{131}I in low-risk patients in a three-year follow-up study (17). When further considering that modern high-resolution ultrasound and high sensitivity Tg measurement have superseded diagnostic radioiodine scanning during follow-up, there really does not appear to be any good medical reason left for performing radioiodine therapy for thyroid remnant ablation in this setting. The current trend toward de-escalation of low-risk patients is also present in the surgical management of thyroid cancer. Specifically, hemithyroidectomy is being chosen more frequently over total thyroidectomy in low-risk patients. It is important to note that this approach limits the use of ^{131}I, as not all thyroid tissue is removed.

Patients with intermediate-risk of structural disease recurrence

For patients with intermediate-risk of structural disease recurrence, it is important to consider their individual factors when deciding whether to administer ^{131}I. For patients with a higher-intermediate risk of structural disease recurrence, ^{131}I therapy is shown to be beneficial. However, the available retrospective studies report a wide variety of results regarding the efficacy of ^{131}I. A study that involved 532 patients found that individuals who are over 45 years of age, have tumors that are smaller than 4 cm in size, without extrathyroidal extension any nodal metastases can undergo surgery without ^{131}I safely, advocating for de-escalation of radioiodine therapy (28). On the other hand, a recent retrospective study (n=1487) investigated the correlation between ^{131}I therapy and serum Tg levels (29). The study concluded that ^{131}I is effective in reducing the recurrence in intermediate-risk patients with unstimulated Tg ≤1 ng/mL, or stimulated Tg ≤10 ng/mL. Recurrence was present in 6/1349 (0.4%) of patients in the I-131-group, and 5/138 (3.6%) in the non-^{131}I therapy group. The patients with recurrence (n=11) all had recurrence in the cervical lymph nodes. Another large study (n=21870) also concluded that adjuvant ^{131}I therapy was associated with an improved overall survival in intermediate-risk patients (30). In the prospective HiLo trial, intermediate-risk patients were included, however no clear subgroup analysis was performed on these patients (18).

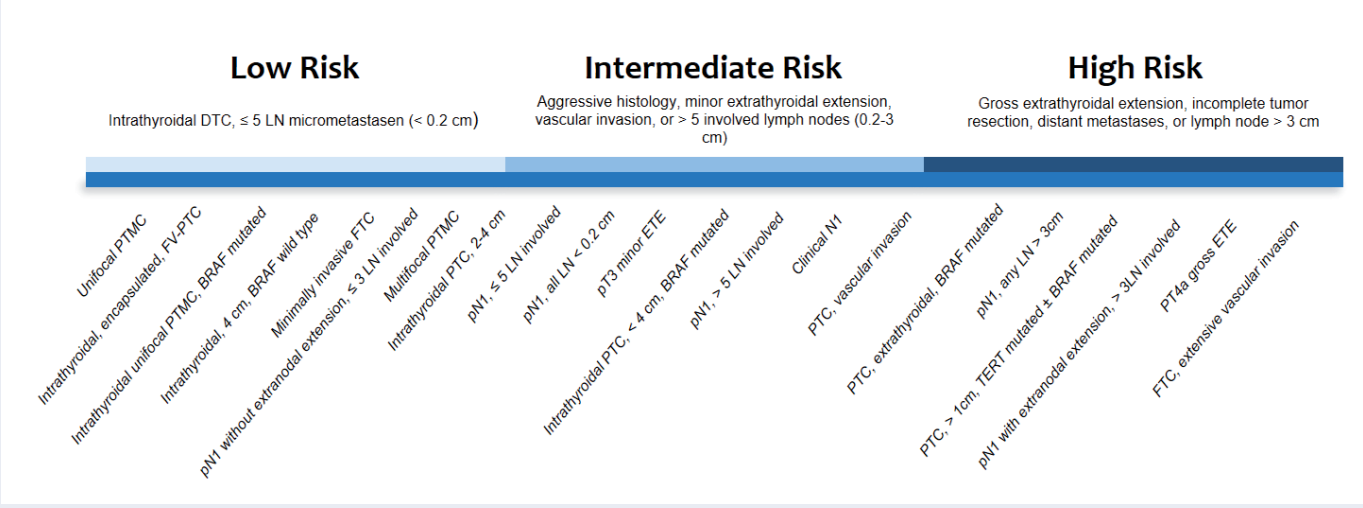

Figure 1. Risk of Structural Disease Recurrence as formulated by the 2015 ATA guidelines.

Certainly, in the intermediate risk patients, the inhomogeneity of evidence does not warrant a hard "yes" or "no" to I-131 treatment. In these patients, the process of shared decision can be of great value.

Patients with high-risk of structural disease recurrence and distant metastases

For high-risk patients and/or patients with distant metastases the use of I-131 is recommended by all guidelines.

Which activities of ^{131}I should be used?

In the context of remnant ablation, patients who are categorized as low-risk can be given an activity of 1.1 GBq after the injection of rhTSH. However, considering that there appears to be no good justification left for performing ^{131}I therapy with thyroid remnant ablation as the only goal, the question is whether there is any role left for this activity level.

On the other hand, for patients with intermediate and high-risk disease in the adjuvant setting, the recommended activity is 5.5 GBq, which should be administered after withdrawal of thyroid hormone, depending on the precise stage of the patient as well as any relevant co-morbidities. For treatment of known disease, an activity of 7.4 GBq or more is typically administered, with the exact amount depending among others on the patient's weight and age; for very high activities well exceeding 7.4 GBq dosimetry is advisable.

What method of TSH-stimulation should be used?

Stimulation with rhTSH is a safe option associated with reduced side effects of ^{131}I and better quality of life. The current recommendations are summarized in table 1. The efficacy of rhTSH for thyroid remnant ablation appears to be equivalent to withdrawal in both the HiLo and ESTIMABL studies. There is lack of prospective studies examining the use of rhTSH in adjuvant treatment, and clinicians should carefully consider its use in this context. Legal regulations permit the use of rhTSH in Europe for initial treatment in patients without distant metastases, but its off-label use in patients with metastatic disease should be evaluated on a case-by-case basis on conjunction with any morbidity the patient may have precluding safe thyroid hormone withdrawal.

Despite the limited evidence, clinicians and patients should have an open conversation to make a shared decision about the best TSH stimulation modality based on their preferences and experiences. Further prospective studies are necessary to evaluate the effectiveness of rhTSH in both the adjuvant setting and the treatment of known disease.

Conclusion

There have been several recent developments in de-escalating thyroid cancer management, with the aim to reduce patient burden without compromising long-term outcomes. In this manuscript we have presented a short overview of latest literature and recent guidelines concerning the use of ^{131}I. The treatment of DTC used to be quite extensive with a total thyroidectomy followed by a high activity of ^{131}I for almost all patients. However, most patients with DTC have an excellent prognosis and this extensive treatment is not necessary for all patients with low and intermediate risk DTC.

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