Overview of the 2015 American Thyroid Association guidelines for managing thyroid nodules and differentiated thyroid cancer

Bashar Matti, Ruben Cohen-Hallaleh

ABSTRACT

The last few years have witnessed numerous publications addressing the management of thyroid nodules and differentiated thyroid cancers. The purpose of this review is to provide a simplified summary of the newly released guidelines by the American Thyroid Association. A systematic approach has been recommended to evaluate a thyroid nodule through clinical assessment, measurement of serum Thyroid Stimulating Hormone, neck ultrasonography and Fine Needle Aspiration where appropriate. This is followed by cytology analysis using the Bethesda scoring system to detect malignancy. Once diagnosed, thyroid cancers need to be staged and risk stratification needs to be applied to develop further treatment plans. Lastly, several recommendations have been presented to assure proper follow-up and support for thyroid cancer patients regardless of the treatment received.

Thyroid nodules are common clinical presentations. The purpose of assessing and evaluating them is to detect the presence or absence of malignancy, which occurs in approximately 10% of all nodules.[1] The American Thyroid Association (ATA) has recently published clinical guidelines for the management of thyroid nodules and differentiated thyroid cancer (DTC) in adult patients.[2] This extended document consists of 101 recommendations that span over more than 400 pages. ATA has implemented in these guidelines an evidence based approach in an attempt to answer the variety of the clinically challenging questions related to this topic. Sixteen expert personals were involved in interpreting and analysing the up-to-date information available on this subject over the course of two years. When compared to the previously published guidelines in 2009, it appears that there have been significant changes with a number of new recommendations added and others modified. This review will aim to provide an overview on the main points of the 2015 guidelines using similar sections and recommendations posed in the novel article.

Thyroid Nodule guidelines

This section illustrates the steps in management of thyroid nodules that have been detected through palpation or incidentally while investigating for other illnesses. After careful history and clinical examination, serum Thyroid Stimulating Hormone (TSH) and ultrasonography should be considered first when assessing a thyroid nodule.[3] No role for serum Thyroglobulin measurement and no evidence to support the use of calcitonin serum levels at this stage.[2] Nodules with low TSH should proceed to have thyroid scan (Iodine 123 or Technetium 99m). Hot nodules are generally not cancerous and need evaluation for hyperthyroidism while cold nodules have 5% chance of being cancerous.[3] Cold nodules and nodules

Table 1: ATA sonographic patterns of thyroid nodules with associated risk of malignancy and the recommendations for FNA.[#]

Sonographic pattern	Sonographic features	Risk of malignancy	Recommendation for FNA
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins, microcalcifications, taller than wide shape.	70–90%	FNA of nodules more than 1 cm in largest dimension otherwise repeat US in 6–12 months (Strong recommendation)
Intermediate suspicion	Hypoechoic solid nodule without high suspicion features	10–20 %	FNA of nodules more than 1 cm, otherwise repeat US in 12–24 months (Strong recommendation)
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially (>50%) cystic nodule, with eccentric solid area without high suspicion features	5–10 %	FNA of nodules more than 1.5 cm, otherwise repeat US in 12–24 months (Weak recommendation)
Very low suspicion	Spongiform or partially cystic nodules without high or intermediate suspicion features	<3 %	• FNA or observe nodules more than 2 cm in largest dimension. • 1–2 cm nodules need repeat US in 2 years. • Less than 1 cm nodules require no intervention and no follow-up (Weak recommendation)
Benign	Purely cystic nodules	<1 %	No FNA required but consider aspiration for comfort or cosmesis (Strong recommendation)

adapted from the 2015 American Thyroid association guidelines [2]

with Normal or elevated TSH results should have a neck ultrasound (US) which involves thyroid and cervical lymph nodes assessment (Strong recommendation).

Fine Needle Aspiration (FNA) is the procedure of choice in diagnosing thyroid cancer. Non-palpable, posterior thyroid nodules or nodules with high cystic components should have FNA done under US guidance. Table 1 illustrates the interpretation of sonographic patterns, with estimated risk of malignancy and the recommendations for FNA associated with each.[1,2,4] Multi-nodular thyroid should be assessed in the same manner with consideration to each nodule being a separate entity in the clinical evaluation.[2,5] This is also true for assessment of thyroid nodules in pregnancy with the exception of the Iodine radionuclide scan being contraindicated.[2,6]

Once FNA done, the results should be interpreted using the Bethesda cytology reporting system. Management action post cytology is listed below:[2,7]

1. Non-diagnostic cytology: (1–4% risk of malignancy). Repeat FNA, US guided, with preference to have on-site cytology interpretation (Strong recommendation). Repeatedly non diagnostic with high suspicion US, clinical risks for malignancy or growth in size of nodule requires surgical excision; otherwise close observation can be considered (Weak recommendation).
2. Benign cytology: (0–3% risk of malignancy). No treatment or further immediate investigations (Strong recommendation). Follow-up with US and FNA in one year for high suspicion group, US only in 1–2 years for intermediate suspicion group and US only in more than two years for low suspicion group. If repeated US/FNA is benign then no further follow-up will be required. Adequate dietary iodine intake advised.
3. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance cytology (AUS/FLUS): (5–15% risk of malignancy). Surveillance, molecular testing or surgery

can be considered on a case-by-case basis (Strong recommendation).

4. Follicular Neoplasm/Suspicious for Follicular Neoplasm cytology (FN/SFN): (15–30% risk of malignancy). Surgery or molecular testing in low suspicion groups and carefully selected low risk patients (Weak recommendation).
5. Suspicious for Malignancy cytology (SUSP): (60–75% risk of malignancy). Surgery is strongly recommended. Considering molecular testing only if it may change decision making regarding surgery (Weak recommendation).
6. Malignant cytology: (97– 99% risk of malignancy). Surgical approach is strongly recommended.

The introduction of molecular testing, such as BRAF mutation, in the diagnosis and prognosis of thyroid cancer is considered to be a relatively new approach.[8] ATA made two strong recommendations which highlight the importance of patient's counselling and the consistency in laboratory techniques when molecular testing being utilised.[2] However, due to the lack of sufficient evidence and the limited availability of this approach in New Zealand and Australia, it will not be explored any further in this article.

For cytologically indeterminate nodules (3, 4, 5 groups above), and when the decision has been made for surgical approach, lobectomy is the surgery of choice.[2,9] This is usually true unless the patient is at high risk for thyroid cancer where total thyroidectomy maybe preferential (large nodules more than 4 cm in any dimension, sonographically suspicious, radiation exposure history, familial thyroid cancer, positive molecular testing for cancer). It is also relevant here that for this group of patients, clinical assessment is the main stem for decision making and further investigations, particularly with FDG-PET, are not rendered to be of benefit.[10]

Initial management of Differentiated Thyroid Cancer

Operative intervention is the gold standard for management of Differentiated Thyroid Cancer (DTC).[9] Multiple pre-operative measures should be considered. Neck US and FNA sampling of sonographically suspicious lymph nodes that are more than 8 mm in diameter is strongly recommended.[2,9] Thyroglobulin (Tg) washout analysis of the FNA samples may provide additional information in certain cases (inconsistent sonographic and cytologic features, inadequate cytologic evaluation or cystic lymph nodes) (Weak recommendation). Cross sectional imaging (CT or MRI) with intravenous contrast should also be considered. However, FDG-PET and serum Tg or Tg antibodies testing are not routinely needed prior to the surgery (Strong and weak recommendations respectively).[2,10] Appropriate surgical consent and preoperative examination and assessment of voice should be performed.[11] Laryngeal exam (to detect vocal cord paralysis) should be considered when voice abnormalities noticed, thyroid cancer with posterior extra thyroidal extension or extensive central nodes involvement, or previous history of neck or upper chest surgery and where the recurrent laryngeal or vagus nerves could have been damaged (Strong recommendation).

When it comes to decision making regarding the surgical approach to DTC, ATA makes the following recommendations:[2]

I. Patients with cancer more than 4 cm in size, gross extrathyroidal extension or clinical metastases to nodes or distant sites, should have total or near total thyroidectomy. When the cancer is 1–4 cm in size, unifocal, without extrathyroidal extension or metastasis, then lobectomy should be considered.[12] However, patients with advanced age (>45), high surgical risk, previous history of head and neck radiation exposure or family history of thyroid cancer, are strongly recommended to have total thyroidectomies. Finally, for cancerous nodules less than 1 cm, lobectomy is the recommended approach (Strong recommendation).

II. Completion thyroidectomy should be offered for patients who underwent lobectomy if the histopathological diagnosis suggests the need for it (Strong recommendation).[13] Radioactive Iodine ablation cannot be considered as a substitute to surgery in this instance (Weak recommendation).

III. Therapeutic central node dissection should be performed for all patients with central nodal involvement (Strong recommendation). Similar principle applies for biopsy proven malignant lateral lymph nodes since lateral compartment lymph node dissection is needed. Prophylactic central node dissection is not routinely recommended where no clinical lymph nodes involvement present. However, weak evidence suggests that this should be done for patients with papillary thyroid carcinoma, where there is lateral lymph nodes involvement or advanced primary tumour, ie clinical T3 or T4.

IV. Identification and preservation of Recurrent Laryngeal nerve, External branch of superior laryngeal nerve and parathyroid glands with their blood supply (Strong recommendation).[11] Nevertheless, only weak evidence support the use of intra-operative neural stimulation where feasible.

Post-operatively, staging and risk stratification should be done in order to guide further management and predict disease outcome and prognosis. ATA guidelines endorse the use of the AJCC (American Joint Committee on Cancer) TNM staging and the 2009 ATA Initial Risk Stratification Systems.[2,14] The latter provides additional advantage of predicting disease recurrence or persistence. In the 2015 guidelines, ATA suggests the addition of new prognostic variables such as mutational status of cells when molecular testing applied, degree of lymph nodes invasion and extent of vascular involvement to produce a "modified" initial stratification system (weak recommendation with moderate level of evidence). This information should be accounted for in the histopathology report and according to that, ATA risk stratification system divides patient into three tiers: low, intermediate and high risk. Table 2 illustrates the main features of each group, taking in consideration the modifications introduced in the 2015 guidelines, with the associated risks of disease abstinence or recurrence that applies to each tier.[2] When applying this risk stratification system, it is key to appreciate that these three tiers represents a continuum, rather than a clear cut points, of disease recurrence values ranging from 1% in low risk to more than 50% in high risk individuals. Therefore, individualised approach for interpreting patient results, using the three tiers as a general guide, is highly recommended when management decisions have been made. Also, the initial risk estimates for each patient needs continuous modification and re-application throughout the follow-up period as new clinical materials arise.

Following surgery for thyroid cancer, it is essential to monitor disease status. To do so, multiple investigations should be considered such as serum thyroglobulin (Tg), neck ultrasound and radioactive iodine (RAI) whole body scan. In majority of patients, Serum Tg levels should be lowest 3–4 weeks post-operatively.[2,15] In general, Serum Tg levels less than 1 ng/ml are associated with more favourable prognosis and further intervention may not be needed. This is particularly true for Low and Intermediate risks groups. On the other hand, value more than 10 ng/ml is usually associated with worse outcome and further treatment will likely be needed. RAI whole body scan with or without SPEC-CT can be used when facing difficulties to establish the extent of thyroid residual disease.[16]

RAI therapy (remnant ablation or adjuvant) and TSH suppression (using thyroid hormone therapy Levothyroxine L-T4), are considered the main treatment modalities after surgery.[2,14] Despite the inconsistency of the evidence evaluated, ATA has made multiple recommendations about the target levels for serum TSH. This has been summarised in Table 3.

RAI therapy has been the topic for many studies over the last decade.[16] ATA suggests that RAI therapy is not necessary for low-risk patients but strongly recommended for high-risk group. Prior to RAI therapy or scanning, thyrotropin stimulation by levothyroxine withdrawal has been the gold standard method as it improves the uptake of iodine. The recommended TSH level prior to RAI therapy is more than 30 mIU/L (weak recommendation due to results based on observational studies).[2] Withdrawal protocols suggest stopping Levothyroxine 3–4 weeks prior to RAI therapy. However, if it was to be stopped for more than four weeks, Liothyronine (L-T3) should be used

Table 2: The 2015 ATA risk stratification system.#

ATA Risk Tier	2009 Features	2015 Modifications	Risk: 1. NED$ 2. SI†
LOW	Papillary Thyroid Carcinoma (PTC) with complete resection, no local invasion or distant metastasis, no aggressive histology AND no RAI avid metastases on the first post-operative whole body RAI scan (when performed)	• For PTC, same features as 2009, AND no vascular invasion AND Clinical N0 or pathologic N1 with 5 or less lymphnodes (LN) involvements that are less than 0.2 cm in largest dimension • Intrathyroidal, encapsulated follicular variant of PTC. • Intrathyroidal well differentiated Folicular Thyroid Carcinoma (FTC) with capsular invasion and No or minimum vascular invasion (less than 4 foci) • Unifocal or multifocal BRAF mutated intrathyroid PTC less than 1 cm in size with No extrathyroidal involvement	78–91% 2–7 %
INTERMEDIATE	FTC or PTC with local microscopic invasion, Aggressive histology, vascular invasion AND/OR RAI avid metastasis in the neck	• PTC with Clinical N1 or Pathologic N1 with more than 5 LN involved of less than 3 cm in largest dimension • BRAF mutated PTC that are 1–4 cm in size OR has extrathyroidal involvement	52–63 % 21–34 %
HIGH	Gross extrathyroidal invasion Incomplete resection Distant metastasis (clinical or when Tg results suggestive of that)	• FTC with 4 or more foci of vascular invasion • Pathologic N1 with LN size of 3 cm or more in largest dimension	14–31 % 56–72 %

adapted from table 12 of the 2015 American Thyroid association guidelines [2]
$ NED = No Evidence of Disease detected, † SI = Structurally Incomplete response to initial therapy

with the aim to stop the latter two weeks prior to therapy (strong recommendation).[17] Patients with any ATA risk category who have significant physical or psychological illness that would be exacerbated by hypothyroidism or could not illicit appropriate endogenous thyroid stimulation response, should have recombinant human thyrotropin (Thyrogen or rhTSH) used as an alternative to Levothyroxine withdrawal, in preparation for RAI therapy (strong recommendation).[16,17] ATA also suggests that Thyrogen can be used in low and intermediate risk groups with no evidence of distant metastases. However, no recommendations were made regarding high risk group due to lack of evidence.[2] Patients should be advised to have low iodine diet 1–2 weeks prior to therapy.[16] The dose of RAI recommended should correspond to the physiological status of patients (age, renal function, etc.) and the extent of disease. Low risk groups should have doses as low as 30 mCI while high-risk groups may dictate the use of a

Table 3: ATA recommendation of appropriate TSH suppression levels for each risk group during the initial treatment phase.#

Risk group	TSH level (mIU/l)	Quality of evidence
High	Less than 0.1	Moderate (Strong recommendation)
Intermediate	0.1–0.5	Low (Weak recommendation)
Low, post RAI ablation and serum Tg undetectable	0.5–2	Low (Weak recommendation)
Low with low level serum Tg, with or without RAI ablation	0.1–0.5	Low (Weak recommendation)
Low post lobectomy	0.5–2	Low (Weak recommendation)

adapted from the 2015 American Thyroid association guidelines [2]

dose as high as 200 mCI.[2,16,17] A post therapy RAI scan is strongly recommended. Apart from RAI therapy and TSH suppression, there is no role for other adjuvant systemic therapy, neck radiotherapy or chemotherapy in the initial management of DTC.[14]

Long-term cancer management guidelines

The aim of long term follow-up of thyroid cancer after the initial treatment phase is to detect recurrence and monitor TSH suppression. This is usually done by periodic measurement of serum Tg, Tg Antibodies and TSH.[6,13,15] This ideally should be done using the same laboratory assay technique that is calibrated against CRM457 standards.[2,14] The use of imaging modalities is governed by the clinical and biochemical findings of each patient. The frequency of performing those tests depends on the ATA risk and the response to treatment categories. Table 4 and the following points illustrate the ATA recommendations in this regard.[2,14]

a. In ATA low and intermediate risk groups who show excellent response to treatment: Serum Tg (stimulated or supressed), Tg Antibodies and TSH testing in the first 6–12 months then every 12–24 months thereafter with no need to repeat stimulated Tg testing. Neck ultrasound in the first 6–12 months then every five years thereafter.[18]

b. In all the other groups (indeterminate response, incomplete response or High risk): More frequent neck ultrasound, serum suppressed Tg, Tg antibodies and TSH testing with regular consideration of stimulated Tg analysis, cross sectional imaging, Whole body RAI scanning with or without SPEC-CT and FDG-PET where appropriate.

c. When new lymph nodes detected on ultrasound, those that are more than 8 mm in size and suspicious should undergo FNA biopsy for cytology and Tg assay (Strong recommendation). When positive for cancer, surgical dissection should be considered. Non-suspicious or small nodes can be monitored conservatively (Weak recommendation).

d. In patients with structural or biochemical incomplete response, TSH levels should be kept below 0.1 mIU/l long term, unless significant contraindications present (Atrial fibrillation for instance).

e. Patients with excellent or indeterminate response to therapy who were in the low ATA risk group can have TSH levels at 0.5–2 mIU/L (strong recommendation). However, patients in the high ATA risk, then TSH level should be maintained at 0.1–0.5 mIU/l (weak recommendation).

Table 4: Clinical response of differentiated thyroid cancer following initial therapy with thyroidectomy, with or without RAI therapy.#

Category	Excellent	Indeterminate	Biochemical incomplete	Structural incomplete
Definition	No evidence of disease	Cannot confidently rule disease presence in/out	No localisable disease but suspicious biochemistry	Persistent or newly diagnosed disease
Imaging	negative	Non-specific/negative	Negative	Positive
Suppressed Tg	<0.2 ng/ml	<1	>1	any
Stimulated Tg	<1 ng/ml	<10	>10	any
Tg trend	Persistently low	Declining	Persistent or rising	any
Tg Antibodies level	absent	Absent or declining	Persistent or rising	any
Prognosis: Recurrence and Disease specific death	1–4% recurrence <1% death	15–20% recurrence <1 % death	20% recurrence <1% death	11–50% death dependent on metastasis and extent of disease

adapted from table 13 in the 2015 American Thyroid association guidelines [2]

The ATA guidelines acknowledge the presence of different treatment options for recurrence and metastasis such as Radiofrequency and thermal ablation, ethanol injection of lymph nodes, Stereotactic radiotherapy and using lithium as an adjunct to iodine in RAI therapy.[2,14] However, surgical resection where possible and RAI therapy remain the gold standard.[13,16] Patients who undergo RAI therapy should have appropriate counselling with particular emphasis on potential complications, limitations and the need for ongoing treatment.[18,19] Those patients should have baseline blood count and renal function tests and pregnancy testing for women at child bearing age. Breastfeeding women should not receive RAI and men receiving high doses should be counselled for potential sterility. Since the risk for developing secondary primary malignancy from undertaking RAI therapy is small, additional measures for secondary cancer screening is not needed apart from what is appropriate for that patient's age. Surgical correction for problems arising from RAI therapy, such as nasolacrimal duct obstruction, should be offered where appropriate.[2]

RAI refractory DTC is defined as: 20 cases when the disease tissue does not accumulate iodine, loses the ability to accumulate iodine, some parts accumulate iodine while others do not, or metastasis continues to progress despite adequate RAI dosages. In those instances, continuing to use RAI therapy is strongly not recommended and the prognosis is considered unfavourable. Treatment options include:[2,20]

1. Monitoring: mainly for cancers that have slow progress rate, aggressive monitoring can be considered (Weak recommendation).
2. Directed therapy with surgery or alternatives such as thermal ablation or stereotactic radiotherapy (Weak recommendation).
3. Referral for clinical trial, particularly when considering using toxic agents in which efficacy hasn't been established. (Strong recommendation).
4. Systemic therapy such as kinase inhibitors and cytotoxic chemotherapy with adequate patient counselling and appropriate surveillance for potential adverse effects.
5. In cases with bone metastasis, bone-directed therapy with bisphosphonate or Denosumab can be considered (Strong recommendation).

Outline of the differences between the new (2015) and the old (2009) guidelines

When looking back at the 2009 guidelines, we can see that ATA had generated 80 recommendations, 103 subrecommendations and utilised 437 references.[14] In 2015, 101 recommendations were published, 175 subrecommendations and 1,078 references were utilised.[2] Numerous new recommendations were associated with pre-operative communication and voice check, and the management of RAI refractory DTC. Furthermore, new questions were answered such as the role of FDG-PET and Cross sectional scanning in thyroid nodule assessments and the manner of histopathologic reporting of samples. A comment has also been made regarding the lack of evidence to justify screening in people with familial follicular thyroid cancer. On the other hand, several parts have undergone significant changes. Reporting each section in the new guidelines using the strength of recommendation and the quality of associated evidence, where as in the 2009 version, they used rating from (A) to (I). Sonographic evaluation of nodules to the different subgroups, the use of FNA and the associated cytology interpretation have been substantially changed. A more conservative approach has been adapted in 2015 towards smaller nodules (less than 1 cm) and in surgical approach in general (lobectomy rather than thyroidectomy for low risk cancers) when compared to 2009. The modified ATA stratification system had a number of features introduced as previously mentioned. Target and diagnostic values for TSH and Tg assay respectively have also been revised.

Conclusion

The American thyroid association has published new guidelines in the management of thyroid nodules and differentiated thyroid cancer. These guidelines are evidence based and have been generated after careful consideration of variety of experts' opinions and current literature. Following the discovery of a thyroid nodule,

multiple steps should be considered to appropriately assess the nature of this nodule. This should eventually lead to an appropriate management plan to be put in place with realistic yet effective follow-up regimen. One should always keep in mind that these guidelines were found to aid the clinician in decision making, not as a replacement since treatment strategies must be tailored for each individual patient.

Competing interests:
Nil.

Author information:
Bashar Matti, Surgical Registrar, Auckland District Health board, Auckland City Hospital, Auckland, New Zealand; Ruben Cohen-Hallaleh, Surgical Fellow, Auckland District Health Board, Auckland City Hospital, Auckland, New Zealand.

Corresponding author:
Bashar Matti, Surgical Registrar, Auckland District Health board, Auckland City Hospital, 2 Park Rd, Grafton, Auckland 1023, New Zealand.
bashar_raad@yahoo.com

URL:
https://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1441-9-september-2016/7002

REFERENCES:

1. Remonti LR, Kramer CK, Leitao CB, et al. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. Thyroid. 2015;25(5):538–50.
2. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1–133.
3. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinol Metab Clin North Am. 2007;36(3):707–35, vi.
4. Anil G, Hegde A, Chong FH. Thyroid nodules: risk stratification for malignancy with ultrasound and guided biopsy. Cancer Imaging. 2011;11:209–23.
5. Papini E, Guglielmi R, Bianchini A, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab. 2002;87(5):1941-
6. Gibelli B, Zamperini P, Proh M, Giugliano G. Management and follow-up of thyroid cancer in pregnant women. Acta Otorhinolaryngol Ital. 2011;31(6):358–65.
7. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2009;19(11):1159–65.
8. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab. 2011;96(11):3390–7.
9. Stojadinovic A, Peoples GE, Libutti SK, et al. Development of a clinical decision model for thyroid nodules. BMC Surg. 2009;9:12.
10. Deandreis D, Al Ghuzlan A, Auperin A, et al. Is (18) F-fluorodeoxyglucose-PET/CT useful for the presurgical characterization of thyroid nodules with indeterminate fine needle aspiration cytology? Thyroid. 2012;22(2):165–72.
11. Chandrasekhar SS, Randolph GW, Seidman MD, et al. Clinical practice guideline: improving voice outcomes after thyroid surgery. Otolaryngol Head Neck Surg. 2013;148(6 Suppl):S1-37.
12. Nixon IJ, Ganly I, Patel SG, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery. 2012;151(4):571–9.
13. Untch BR, Palmer FL, Ganly I, et al. Oncologic outcomes after completion thyroidectomy for patients with well-differentiated thyroid carcinoma. Ann Surg Oncol. 2014;21(4):1374–8.
14. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated

thyroid cancer. Thyroid. 2009;19(11):1167–214.

15. Polachek A, Hirsch D, Tzvetov G, et al. Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. J Endocrinol Invest. 2011;34(11):855–60.
16. Bal CS, Padhy AK. Radioiodine Remnant Ablation: A Critical Review. World J Nucl Med. 2015;14(3):144–55.
17. Lee J, Yun MJ, Nam KH, et al. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid. 2010;20(2):173–9.
18. Lamartina L, Durante C, Filetti S, Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. J Clin Endocrinol Metab. 2015;100(5):1748–61.
19. Van Nostrand D. The benefits and risks of I-131 therapy in patients with well-differentiated thyroid cancer. Thyroid. 2009;19(12):1381–91.
20. Schlumberger M, Brose M, Elisei R, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. Lancet Diabetes Endocrinol. 2014;2(5):356–8.