Editorial

# Managing Bethesda IV thyroid nodules in an iodine-deficient population

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According to the latest global cancer data released by the American Cancer Society, thyroid cancer has one of the highest incidences amongst all cancers worldwide, ranking thirteenth overall and sixth among women (1). While most thyroid cancers present as thyroid nodules, the vast majority of thyroid nodules diagnosed on ultrasound evaluation are benign (2). Therefore, risk stratification systems have been developed to aid clinicians with the management of these nodules. Following the detection of ultrasound features suspicious for malignancy, cytological examination by fine needle aspiration (FNA) is the gold standard approach for the evaluation and management of thyroid nodule pathology. The Bethesda System for Reporting Thyroid Cytopathology is the most commonly utilized diagnostic guide for interpreting cytomorphological data from FNA biopsies and predicting malignancy risk (3). Nodules with Bethesda categories of III–V are considered to have indeterminate risk of malignancy, and their management can depend on multiple nodule-specific and patient-related factors. Nodules classified as Bethesda IV present a particularly difficult challenge for clinicians and patients, who must consider a multitude of variables to ultimately decide between a wide array of possible treatment options (4).

According to the 2015 American Thyroid Association (ATA) management guidelines for adult patients with thyroid nodules, a diagnostic lobectomy is the preferred surgical approach for Bethesda IV nodules in the absence of factors that may warrant a total thyroidectomy, such as those with highly suspicious ultrasound patterns, greater than 4 centimeters (cm) in size, family history of thyroid cancer, history of radiation exposure, or bilateral nodules under certain conditions (5). Still, there are disagreements in the literature regarding the optimal management of these nodules, as multiple studies have found both higher and lower rates of malignancy among Bethesda IV nodules than those reported in the 2015 ATA guidelines, and therefore support more conservative management with a repeat FNA or observation, or more aggressive treatment with a total thyroidectomy, depending on characteristics specific to the patient and nodule (6-8). Adding further complexity to this issue, molecular testing has played an increasingly important role in the evaluation of Bethesda IV nodules in recent years, as these tests provide additional information about the presence of certain genetic mutations and other molecular alterations which can help stratify the risk of harboring malignancy and thereby guide the management of these nodules (6,9,10). In light of the many possible management options for Bethesda IV thyroid nodules, numerous studies have investigated the utility of different clinical, radiological, cytological and biochemical features for guiding their management (11,12).

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One such research article, recently published by Loderer *et al.* in *Gland Surgery*, reports on the results of a retrospective cohort study in which the authors evaluated the selected surgical approach, and rate of malignancy on final surgical pathology, among 320 patients with Bethesda IV nodules in an iodine-deficient region of Italy (13). The authors performed the study at the Operative Unit of the General Surgery Clinic of the University Hospital of Parma, Italy, from January 2010 to December 2020, both before and after the release of the 2015 ATA guidelines. The authors found that, spanning this entire decade, the rates of thyroid lobectomies performed for Bethesda IV nodules remained low, while total thyroidectomies were the more frequently selected procedure. Although they reported an overall increase in the rate of lobectomies performed for Bethesda IV thyroid nodules relative to total thyroidectomies after the publication of the 2015 ATA guidelines (from 7.2% to 41.5%), the lobectomy rate remained lower than that of total thyroidectomy (58.5%) even after 2015. The authors suggest that the increased rate of total thyroidectomies performed for patients with Bethesda IV nodules in their population is based on the relatively high incidence of carcinoma found in patients with these nodules (28.8%), frequent need for adjuvant radiometabolic therapy by patients diagnosed with thyroid carcinoma (66% among patients for whom this information was available), and the high rate of multiple (56.9%) and bilateral nodules (39.7%), presumably due to the high prevalence of iodine-deficiency in their population. Furthermore, the authors demonstrated that increasing nodule size, specifically greater than or equal to 4 cm, correlated with increasing malignancy rate (40.9%) as well as with higher rates of local and lymphovascular invasion.

Of particular interest is the high rate of multiple and bilateral nodules encountered in this iodine-deficient population of Italy, which the authors acknowledge played a prominent role in the decision to perform total thyroidectomy for most patients. It is well-known that low iodine levels lead to reduced thyroid hormone production, hindering the negative feedback mechanisms of the hypothalamic-pituitary-thyroid axis, and promoting secretion of thyroid stimulating hormone and continued stimulation of the thyroid gland (14). This process likely leads to the higher rates of thyroid disorders, goiter, thyroid nodularity, and papillary thyroid cancer observed in iodine-deficient populations (15-17). In fact, one study found that thyroid hyperplasia and hypertrophy can occur within six months of iodine deficiency (15). Even though the widespread availability of iodized salt has helped to curb iodine deficiency worldwide, a meta-analysis performed in 2022 showed that the prevalence of thyroid nodules remains relatively high in iodine deficient regions today (18). While each nodule that is greater in size than 1 cm carries an independent risk of malignancy, and therefore having multiple nodules of this size should statistically increase the risk of thyroid carcinoma, it has been shown that patients with multiple thyroid nodules have the same risk of harboring malignancy as those with solitary nodules (19,20). Therefore, the decision to perform total thyroidectomy for patients with a Bethesda IV nodule in the setting of multiple additional nodules remains controversial.

Another key finding noted by the authors is that, in their study population, increasing nodule size correlated with increased malignancy risk, and that nodules greater than 4 cm in size had statistically greater rates of malignancy, as well as local and lymphovascular invasion, than smaller nodules. Based on these findings, the authors recommend total thyroidectomy for patients with Bethesda IV nodules that are greater than 4 cm in size. These statements are in agreement with the 2015 ATA guidelines for the management of thyroid nodules, which similarly state that total thyroidectomy should be considered for patients with nodules at indeterminate risk of malignancy that are greater in size than 4 cm (5). However, evidence for the correlation between increased nodule size and higher malignancy risk for Bethesda IV nodules in the literature is inconsistent, with many studies reporting no correlation between nodule size and malignancy rate (21,22). While this study does provide additional support for the selection of total thyroidectomy as the surgical approach for large Bethesda IV thyroid nodules due to their higher rate of malignancy, the decision on the optimal management option should involve the consideration of all patient and nodule-specific variables that influence the probability of harboring malignancy, the additional risks associated with performing a total thyroidectomy, as well as patients' personal preferences. Therefore, the most meaningful conclusion which can be drawn from Loderer's study is that, for patients residing in iodine-deficient regions, nodule size and the presence of bilateral nodules should be considered along with the multitude of other relevant parameters when making an evidence-based and shared decision with patients about the management of a Bethesda IV nodule.

While this article provides valuable insights about thyroid nodule management, there are certain limitations inherent to its retrospective cohort study design, such as

potential selection bias and the reliance on a retrospective review of medical records, which certainly cannot not capture all the variables which influence malignancy risk among Bethesda IV nodules. Additionally, the study focuses on a very specific patient population in a single hospital in Parma, Italy, and thus, the generalizability of these results to other populations with different genetic and environmental characteristics is limited. Additional prospective studies, with larger and more diverse cohorts, will be necessary to validate these findings and explore other potential factors that may influence the risk of malignancy, and optimal management approach, for patients with Bethesda IV thyroid nodules. Overall, the findings of this study emphasize the need for a tailored approach to the management of Bethesda IV nodules which considers the iodine status of the patient in addition to other clinical, radiological, cytological, and biochemical factors. Finally, clinicians should employ a shared decision-making strategy that incorporates each patient's unique preferences, and management decisions should only be made once patients have been properly counseled on all available treatment options and the relative risks that accompany each.

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## References

1. Kitahara CM, Schneider AB. Epidemiology of Thyroid Cancer. Cancer Epidemiol Biomarkers Prev 2022;31:1284-97.
2. Durante C, Costante G, Lucisano G, et al. The natural history of benign thyroid nodules. JAMA 2015;313:926-35.
3. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017;27:1341-6.
4. Almquist M, Muth A. Surgical management of cytologically indeterminate thyroid nodules. Gland Surg 2019;8:S105-11.
5. 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;26:1-133.
6. Kim NE, Raghunathan RS, Hughes EG, et al. Bethesda III and IV Thyroid Nodules Managed Nonoperatively After Molecular Testing With Afirma GSC or Thyroseq v3. J Clin Endocrinol Metab 2023;108:e698-703.
7. Zahid A, Shafiq W, Nasir KS, et al. Malignancy rates in thyroid nodules classified as Bethesda categories III and IV; a subcontinent perspective. J Clin Transl Endocrinol 2021;23:100250.
8. Yaprak Bayrak B, Eruyar AT. Malignancy rates for Bethesda III and IV thyroid nodules: a retrospective study of the correlation between fine-needle aspiration cytology and histopathology. BMC Endocr Disord 2020;20:48.
9. Hier J, Avior G, Pusztaszeri M, et al. Molecular testing for cytologically suspicious and malignant (Bethesda V and VI) thyroid nodules to optimize the extent of surgical intervention: a retrospective chart review. J Otolaryngol Head Neck Surg 2021;50:29.
10. Lee E, Terhaar S, McDaniel L, et al. Diagnostic performance of the second-generation molecular tests in the assessment of indeterminate thyroid nodules: A systematic review and meta-analysis. Am J Otolaryngol 2022;43:103394.
11. Talmor G, Badash I, Zhou S, et al. Association of patient characteristics, ultrasound features, and molecular testing with malignancy risk in Bethesda III-V thyroid nodules.

Laryngoscope Investig Otolaryngol 2022;7:1243-50.
12. Öcal B, Korkmaz MH, Yılmazer D, et al. The Malignancy Risk Assessment of Cytologically Indeterminate Thyroid Nodules Improves Markedly by Using a Predictive Model. Eur Thyroid J 2019;8:83-9.
13. Loderer T, Bonati E, Donato V, et al. Malignancy risk in Bethesda class IV thyroid nodules in an iodine deficient region. Gland Surg 2023;12:884-93.
14. Sun Y, Teng D, Zhao L, et al. Iodine deficiency is associated with increased thyroid hormone sensitivity in individuals with elevated TSH. Eur Thyroid J 2022;11:e210084.
15. Carlé A, Krejbjerg A, Laurberg P. Epidemiology of nodular goitre. Influence of iodine intake. Best Pract Res Clin Endocrinol Metab 2014;28:465-79.
16. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018;14:301-16.
17. Xu T, Ren Z, Li S, et al. The relationship of different levels of high iodine and goiter in school children: a meta-analysis. Nutr Metab (Lond) 2021;18:46.
18. Mu C, Ming X, Tian Y, et al. Mapping global epidemiology of thyroid nodules among general population: A systematic review and meta-analysis. Front Oncol 2022;12:1029926.
19. Marqusee E, Benson CB, Frates MC, et al. Usefulness of ultrasonography in the management of nodular thyroid disease. Ann Intern Med 2000;133:696-700.
20. 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;87:1941-6.
21. Jinih M, Faisal F, Abdalla K, et al. Association between thyroid nodule size and malignancy rate. Ann R Coll Surg Engl 2020;102:43-8.
22. Valderrabano P, Khazai L, Thompson ZJ, et al. Association of Tumor Size With Histologic and Clinical Outcomes Among Patients With Cytologically Indeterminate Thyroid Nodules. JAMA Otolaryngol Head Neck Surg 2018;144:788-95.

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