



Thyroid

Correct extent of thyroidectomy is poorly predicted preoperatively by the guidelines of the American Thyroid Association for low and intermediate risk thyroid cancers



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Background. Recent guidelines from the American Thyroid Association recommend thyroid lobectomy for intrathyroidal differentiated thyroid cancers <4 cm. Our aim was to examine histology from patients with cytologic results that were positive or suspicious for malignancy to assess the extent of initial thyroidectomy based on criteria from the 2015 American Thyroid Association guidelines.

Methods. We studied consecutive patients who had either a positive or suspicious for malignancy cytologic diagnosis and under prior American Thyroid Association guidelines underwent initial total thyroidectomy ± lymphadenectomy.

Results. Among 447 patients, high-risk features necessitating total thyroidectomy were present in 19% (72/380) of positive and 15% (10/67) of suspicious for malignancy patients (P = .5). Intermediate-risk features on histology were identified postoperatively in 46% (175/380) with positive and 15% (18/67) with suspicious for malignancy fine-needle aspiration results. In multivariable analysis, preoperative factors associated with intermediate-risk disease included age ≥45 years, women, larger tumor size, positive fine-needle aspiration cytology, and *BRAF V600E* or *RET/PTC* positivity.

Conclusion. When patients are considered for lobectomy under the 2015 American Thyroid Association guidelines, ~60% with positive and 30% with suspicious for malignancy cytology would need completion thyroidectomy based on intermediate-risk disease. The cost and risk implications of the new American Thyroid Association strategy were substantial and better tools are needed to improve preoperative risk stratification.

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Thyroid cancer is increasing in incidence, and an estimated 64,300 new cases were diagnosed in 2016.¹ The increasing incidence is likely multifactorial, although improved detection is a substantial contributor.² Several studies have demonstrated that the diagnosis of small, subcentimeter carcinomas is increasing at the greatest rate.^{3–5} Differentiated thyroid cancer, however, has excellent 10-year survival rates, and the recent trend is toward judicious management to avoid overtreatment.⁶ The 2015 guidelines of the American Thyroid Association (ATA) now advise a risk-directed approach to the management of thyroid cancer. For example, thyroid lobectomy may be sufficient treatment for intrathyroidal, differentiated thyroid cancers <4 cm (ATA recommendation 35).⁶ This observation was based on

findings from studies demonstrating that 1) lobectomy does not affect disease-specific survival,^{7–9} 2) salvage therapy for recurrences is efficacious,¹⁰ and 3) experts now advocate a more selective use of radioactive iodine (RAI)^{6,11}; however, if lobectomy is performed and more aggressive features are seen on histology, such as microscopic extrathyroidal extension or lymphovascular invasion, completion thyroidectomy may be needed to facilitate RAI ablation and/or subsequent surveillance. Thus, recommendations for treatment are now more dependent on the results of the final pathology than previously, and the appropriate extent of thyroidectomy in particular can be difficult or impossible to assess preoperatively.

Results of fine-needle aspiration (FNA) biopsy are used typically to diagnose thyroid cancer and determine if operative intervention is needed. Studies have demonstrated that low-risk differentiated thyroid cancers are often associated with cytologically indeterminate results on FNA.^{12,13} It is unknown if and how frequently initial lobectomy is adequate treatment when preoperative FNA is positive (POS) or suspicious for malignancy (SUSP). The aim of the present study was to examine the histologic features of patients who had

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a POS or SUSP cytologic result and to assess the recommended extent of initial thyroidectomy using criteria from the 2015 ATA Guidelines.

Materials and Methods

Study cohort

The present study was a retrospective review of consecutive patients from May 2007 to December 2012 with preoperative cytology either POS (Bethesda Category 6) or SUSP (Bethesda Category 5¹⁴) who underwent initial total thyroidectomy with or without lymphadenectomy according to the 2006 and 2009 ATA guidelines^{15,16}; this was our routine surgical approach during the study period. Molecular analysis was performed routinely for *BRAF*, *KRAS*, *HRAS*, *NRAS* mutations, and *RET/PTC1*, *RET/PTC3*, and *PAX8/PPARG* rearrangements, as reported previously.¹⁷ Some of these patients have been described previously in other studies. Based on a previous study in which phenotypically similar thyroid cancers were observed in 2 groups (*BRAFV600E* + *RET/PTC* and *RAS* + *PAX8/PPARG*),¹⁷ we analyzed cancer genotype using these same 2 groupings.

After approval by the Quality assessment and quality improvement (QA/QI)-institutional review board, clinicopathologic data were collected. Follow-up including postoperative RAI ablation, suppression with thyroid stimulating hormone, and radiologic surveillance, including neck ultrasonography and whole body iodine-131 imaging, was performed by the treating endocrinologist and/or surgeon based on the extant ATA guidelines.^{15,16} Information on last follow-up interval and date of histologically confirmed recurrent disease was also collected. Mean follow-up for the study population was 52.4 months (0.1–112.6).

ATA risk stratification

Based on the clinicopathologic features, patients were classified retrospectively into ATA high, intermediate, or low risk categories to determine the recommended extent of thyroidectomy per the 2015 guidelines.⁶ Briefly, high-risk tumors were defined here by clinical N1, clinical T4, tumor size ≥ 4 cm, or synchronous distant metastases. Intermediate-risk tumors were defined by extrathyroidal extension, >5 positive lymph nodes, vascular invasion, and/or aggressive histologic variants, including tall cell, hobnail variant, or columnar cell carcinoma. The remainder were classified as low risk.

Statistics

Continuous variables were summarized as means (\pm standard deviation) or medians (interquartile range). Categorical data were summarized as frequencies and percentages. χ^2 test was used for comparison of categorical variables, and Mann-Whitney *U* test was used to compare continuous variables. Univariable analysis was performed using logistic regression. Data were reported as odds ratios and 95% confidence intervals. Variables were introduced into the multivariable model to predict intermediate versus low risk (referent) based on statistical significance and clinical relevance. Multivariable model was adjusted for the following covariates: age (<45 or ≥ 45 years), sex, tumor size (continuous variable), FNA category (POS or SUSP), and mutational status (negative, *BRAF* + *RET/PTC*, or *RAS* + *PAX8/PPARG*). All analyses were performed using STATA 14.1 (Statacorp, College Station, TX).

Results

Patient characteristics

A total of 447 patients were reviewed, including 380 patients with POS and 67 patients with SUSP FNA results. Table I provides

Table I
Study population.

	N = 447 (%)
Age (y)	47.7 (36.3–58.6)
Women	345 (77.2)
Histologic subtype	
Classic PTC	317 (71.2)
Follicular variant PTC	48 (10.8)
Tall cell variant PTC	66 (14.8)
Other	14 (3.2)
Size (cm)	1.5 (1–2)
Size ≥ 4	25 (5.6)
Extrathyroidal extension	229 (51.5)
Multifocal	260 (58.3)
Bilateral	170 (38.2)
Angiolymphatic invasion	272 (61.1)
Positive margins	113 (25.4)
Clinical N1	61 (13.6)
Central compartment LN dissection	406 (90.8)
Pathologic LN positive	231 (51.7)
M1	7 (8.54)
Thyroiditis	154 (34.5)
Mutation data	431
Mutation positive	359 (83.3)
<i>BRAF</i> positive	326 (75.6)
Recurrence	46 (10.3)

Continuous variables are summarized as medians with interquartile range (25th percentile to 75th percentile). Categorical variables are summarized as frequencies and percentages.

the details of the demographic and clinicopathologic features. One POS patient had false positive cytology (0.03%). The overall median age was 47.7 years, and women comprised 77.2% of the study population. Classic papillary thyroid cancer (PTC) was the most common histologic subtype (71.2%), and the median tumor size was 1.5 cm. The majority of PTC had extrathyroidal extension (51.5%), were multifocal (58.3%), demonstrated angiolymphatic invasion (61.1%), and had lymph node metastases (51.7%). Although 38.2% (170/447) had bilateral cancers, only 3% of patients had contralateral cancers >1 cm.

Clinicopathologic characteristics

POS versus SUSP FNA results. We compared the clinicopathologic features of PTC associated with POS FNA to those of PTC with SUSP FNA (Table II). PTC with POS cytology were more often seen in younger patients (median age 46.6 vs 53.7, $P = .021$) and were more likely to have extrathyroidal extension (55% vs 31.3%, $P < .001$), angiolymphatic invasion (65.1% vs 38.8%, $P < .001$), clinical N1 disease (15% vs 5.9%, $P = .047$), central and lateral LN positive disease (54.5% vs 35.8%, $P = .005$), and histologic background thyroiditis (36.8% vs 20.9%, $P = .011$). Eight patients had distant metastases, and the rate did not differ by preoperative FNA cytologic category (POS 6/380, 1.6% vs SUSP 2/67, 2.9%; $P = .4$). Recurrent/persistent disease requiring reoperation was also equally likely in the 2 groups ($P = .6$).

Distribution in ATA risk categories

Overall, 82 (18%), 193 (43%), and 171 (38%) were classified as ATA high-, intermediate-, and low-risk tumors (Table III). Based on the current ATA recommendations for extent of the initial extent of resection for high-risk disease, total thyroidectomy would therefore have been definitively indicated by preoperative staging for only 18%. The proportion of patients with high-risk disease did not differ between patients with POS or SUSP cytology (19% vs 15%, $P = .5$). In the 374 patients who were not high risk, classification into the intermediate-risk category due solely to >5 positive lymph nodes

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