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The Role of Preoperative Neck Ultrasounds to Assess Lymph Nodes in Patients With Suspicious or Indeterminate Thyroid Nodules

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Abstract

Background and Objectives—Currently there are no recommendations for obtaining a preoperative neck ultrasound for patients with suspicious or indeterminate thyroid nodules. Because a preoperative surgical ultrasound can detect suspicious lymph nodes that could result in ultimately altering surgical management, we chose to study which variables were predictive of this change.

Methods—Medical records of 173 patients who presented between January 2006 and December 2010 with suspicious or indeterminate thyroid cytology were retrospectively reviewed. Clinicopathological variables were analyzed to determine factors predictive of malignancy and a change in operative approach.

Results—One hundred thirty-four of 173 patients were evaluable. Seventeen of 134 (12.6%) of the preoperative ultrasounds were suspicious. Seven of 134 (5.2%) patients underwent a formal lymph node dissection based on ultrasound findings. Size of tumor, Bethesda FNAB category, and male gender were associated with malignancy while thyroid nodule microcalcifications and category of FNAB were associated with performing lymph node dissections.

Conclusion—Thyroid nodule microcalcifications on ultrasound and category of FNAB appear to be the best predictors of metastatic disease. Because the surgical approach was altered in only a few patients, further analysis is needed to delineate whether performing cervical ultrasound for suspicious/indeterminate nodules is cost effective.

Keywords

preoperative neck ultrasound; suspicious or indeterminate thyroid nodule; papillary thyroid cancer; metastases

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INTRODUCTION

Thyroid nodules are common in the United States, occurring in 5 out of 100 women and 1 out of 100 men [1,2]. An increasing number of thyroid nodules are now being detected, which is likely due to the use of higher resolution ultrasound as well as the increased surveillance of patients with thyroid disease [3]. It is important to preoperatively determine whether a thyroid nodule is malignant or benign since up to 15% of thyroid nodules are malignant, and the surgical approach for benign versus malignant nodules can differ significantly [4,5]. Of the differentiated thyroid cancers, papillary thyroid cancer is the most common, representing approximately 90% of all malignant cases [6].

We know that cervical lymph node metastases are present in 20–50% of differentiated thyroid carcinomas [7-11]. Because of the relatively high risk of cervical metastases, preoperative cervical neck ultrasounds have become the standard of care for patients who present with known malignant thyroid nodules [12]. Indeed, studies have shown that preoperative neck ultrasound can detect suspicious cervical lymphadenopathy in up to 30% of cases with resulting alteration in the surgical approach for as many as 14–24% of patients with papillary thyroid cancer [13-16].

Although routine preoperative neck ultrasound in patients with known malignant thyroid nodules is recommended, there are no clear recommendations for the preoperative management of a patient with a suspicious or indeterminate thyroid lesion, nor there are any studies that have examined the impact of preoperative neck ultrasound on the management of these patients [12]. Because of this we chose to examine how often preoperative neck ultrasounds, for patients with suspicious or indeterminate thyroid nodules, detected suspicious cervical lymphadenopathy, thereby altering the surgical management of patients with these lesions. We also examined whether there were certain preoperative clinical factors associated with suspicious nodules that were associated with clinically apparent (either by ultrasound or intraoperatively) suspicious cervical lymphadenopathy. Lastly, we analyzed what clinicopathological factors predicted a thyroid malignancy.

MATERIALS AND METHODS

With IRB approval, a retrospective review of 173 patients who had undergone surgery by a single surgeon for a suspicious or indeterminate thyroid nodule at a tertiary center between January 1, 2006 and December 31, 2010 was performed. In order to capture all patients with suspicious or indeterminate nodules who underwent surgery, we queried the cytology reports in a prospectively collected thyroid tumor database for keywords including the following: “atypia, atypical cells of undetermined significance (ACUS), rule out neoplasm, atypical follicular lesion, follicular lesion, follicular neoplasm, suspicious for follicular/Hürthle cell neoplasm/lesion, suspicious for papillary thyroid cancer, and indeterminate.” Because the Bethesda criteria had not been implemented at Johns Hopkins until 2008, this terminology was needed to capture all reports that were considered suspicious or indeterminate [17]. All cytology specimens, including those from outside institutions, had been reviewed by the Cytology Division at Johns Hopkins Hospital.

Cytology, operative, ultrasound, and final pathology reports were reviewed to determine whether a preoperative neck ultrasound impacted the extent of operation performed (i.e., the addition of central or lateral neck dissection(s)). Patients who did not have a neck ultrasound to evaluate for suspicious lymphadenopathy were excluded. Clinicopathological variables, including: age, sex, race, personal history of head or neck irradiation/exposure to radiation, history of thyroiditis, family history of thyroid cancer, thyroid function (euthyroid, hypothyroid, hyperthyroid), whether the nodule was palpable, whether there was palpable

lymphadenopathy, size of tumor in centimeters (measured by ultrasound), ultrasound focality (unifocal vs. multifocal), presence of thyroid nodule calcifications or intranodular hypervascularity on ultrasound, and fine needle aspiration biopsy (FNAB) category were analyzed to determine factors predictive of a change in operative approach. These factors were also examined to identify predictive factors of malignancy of the thyroid nodule on final pathology. FNAB categories included three groups: ACUS, suspicious for a follicular neoplasm, and suspicious for papillary thyroid cancer [17,18]. Cytology reports for those patients operated on prior to the implementation of the Bethesda criteria at Johns Hopkins in 2008 were categorized as closely as possible to the Bethesda criteria by careful review of the reports; for example, “atypical cellularity” became ACUS, “cannot rule out neoplasm” became follicular/Hürthle cell neoplasm, suspicious became suspicious for papillary thyroid cancer.

All patients with indeterminate or suspicious nodules, determined by FNAB, obtained a preoperative neck ultrasound to detect suspicious lymphadenopathy. A lobectomy or total thyroidectomy was performed at both the surgeon’s and patient’s discretion. Total thyroidectomy plus lateral neck dissections were performed for biopsyproven metastatic lymph nodes in the lateral neck compartment. Central neck dissections were performed on patients with suspicious or indeterminate thyroid nodules who had central cervical lymph nodes that were suspicious on ultrasound or intraoperatively.

A lymph node was considered suspicious on ultrasound if it was noted to be taller than wide, if it had peripheral vascularity, microcalcifications, or lacked a fatty hilum. Suspicious lymph nodes were biopsied by FNA if they were present in the lateral neck only (Levels II–V). A biopsy-proven malignant lateral neck lymph node altered the surgical approach to include a modified lateral neck dissection(s). Suspicious lymph nodes in the central neck (Level VI) were not biopsied, but changed the operative approach to include a formal central neck dissection. All patients who had suspicious central neck lymph nodes had metastatic disease. Patients who were found to have suspicious lymph nodes intraoperatively only, underwent a central lymph node dissection.

Statistical Analysis

Multivariate analysis was performed on the clinicopathological factors to determine predictive factors for malignancy and/or a change in operative approach. Student’s *t*-tests and Wilcoxon Rank sum tests were used to examine continuous variables; chi-squared and Fisher’s exact tests were used for discrete variables.

RESULTS

Patient Demographics

Thirty-two patients did not have preoperative neck ultrasounds performed and were therefore excluded from the study. Seven patients had a normal preoperative ultrasound performed, but still had a central neck lymph node dissection performed due to intraoperative findings. All 7 had metastatic disease. Because these 7 patients had central lymph node dissections performed based on intraoperative findings, and not on the preoperative neck ultrasound, these 7 patients were also excluded from the analysis. Therefore, a total of 134 patients were included in the final analysis; 111 (82.8%) were female and 23 (17.2%), male. The average age of the patients was 49.0 years (SD 13.6). A total of 109 (81.3%) individuals were Caucasian, 9 (6.7%) were African American, 3 (2.2%) were Asian, 6 (4.5%) were Hispanic, 5 (3.7%) were other, and 2 (1.5%) were not classified. Malignant nodules were found in 72 (53.7%) of the patients; all were papillary thyroid cancer.

Surgery Performed

Of the 134 patients, 17 (12.7%) had suspicious cervical neck ultrasound findings as described above. Fifteen patients had suspicious lateral neck nodes and 2 patients had suspicious central neck nodes. Of the 17 patients with suspicious cervical neck ultrasounds, 7 patients (5.2%) underwent a lymph node dissection based on ultrasound findings; 3 patients had central and ipsilateral neck dissections, 2 patients had central and bilateral neck dissections, and 2 patients had a central neck dissection only. Of the remaining 10 patients FNAB of lymph nodes were negative and, therefore no change in operation occurred in these patients. As described above, seven additional patients, who were excluded from the study, had suspicious lymph nodes discovered at the time of surgery and underwent central lymph node dissection; all had metastatic disease. They were excluded because their central neck dissections were based on intraoperative findings and not the preoperative cervical ultrasound.

Clinicopathological Factors

Of the clinicopathological factors analyzed, none of the following were predictive of malignancy on final pathology: age, race, personal history of head or neck irradiation/ exposure to radiation, history of thyroiditis, family history of thyroid cancer, thyroid function, whether the nodule was palpable, ultrasound focality (unifocal vs. multifocal), or intranodular hypervascularity on ultrasound. (Table I.) Size, however was associated with malignancy in that smaller nodules, as measured by ultrasound, were associated with malignancy: median size among patients with a malignancy was 1.6 cm versus 2.4 cm in patients with benign findings ($P = 0.017$). Among the other variables examined, as expected, FNAB category ($P < 0.001$) was significantly associated with nodule malignancy and consistent with the risk stratification of the Bethesda cytological categories. A trend toward significance was also seen for male gender where malignancy was reported in 69.6% of males and only 50.5% of females ($P = 0.094$; Table I).

When analyzing the clinicopathological factors predictive for a change in operation, that is, the addition of a lymph node dissection, nodule microcalcifications were more likely to be present when metastatic disease was detected (13.8% vs. 2.9%, $P = 0.022$). FNAB category ($P < 0.002$) was also significantly associated with the addition of a lymph node dissection. Furthermore, there was a trend toward men being more likely to undergo lymph node dissection than women (13.0% vs. 3.6%, $P = 0.064$; Table II). No other variables were significantly associated with proportional differences in lymph node dissection in bi-variable analysis.

DISCUSSION

It is widely accepted that certain ultrasound characteristics of thyroid nodules make the nodule more or less suspicious for malignancy [7,19-23]. These characteristics include nodule hypoechogenicity, increased intranodular vascularity, irregular or infiltrative margins, and the presence of microcalcifications. While we were unable to include all of these characteristics in our analysis because some of these data were unavailable, we found that smaller size thyroid nodules (measured by ultrasound) and FNAB category were associated with malignancy. While not statistically significant, there was a trend for male gender to be associated with malignancy.

It is unclear why smaller-sized nodules conferred an increased risk of malignancy when the majority of studies have documented the opposite, that larger tumors have a greater risk of malignancy [24-26]. Perhaps lesions that had a more benign appearance on ultrasound were followed longer and grew in size whereas those lesions that were more worrisome on

ultrasound were not followed, but were resected sooner. Prior long-term follow-up was not available to us, however, for detailed examination of this.

The American Thyroid Association (ATA) guidelines recommend that a patient who has a nodule with suspicious characteristics should undergo a FNAB [12]. Based upon the Bethesda criteria, FNAB results are placed into four categories: benign, suspicious/indeterminate, malignant, or non-diagnostic [18]. Our current study only included nodules that had an associated suspicious or indeterminate FNAB result. The suspicious/indeterminate group is further divided into ACUS, suspicious for follicular/Hürthle cell neoplasm, and suspicious for papillary thyroid cancer. The risk of malignancy for each of these subcategories, in turn, is stratified and ranges from 5–15% to 60–75%, respectively [18]. Our findings are consistent with the Bethesda criteria in that the more suspicious the FNAB category, the more likely it is that the nodule is malignant. This statistically significant difference among cytological categories was also associated with an increased risk of suspicious lymph nodes seen on ultrasound in our study.

Males have been shown to be at a higher risk for thyroid cancer than women [24]. Our study also noted this trend toward malignancy for male gender when compared to females. Tuttle et al. [24] described clinical criteria that were predictive of malignancy in patients with indeterminate FNAB. They noted that the risk of malignancy was significantly higher when follicular neoplasia was present in a male (43% vs. 16% for females, $P = 0.007$) and that clinical features such as gender should be systematically integrated into the decision analysis, thereby improving the selection of patients for surgical referral.

Differentiated thyroid cancer metastasizes frequently to cervical lymph nodes. Indeed, micrometastases may occur up to 90% of thyroid cancers [27]. However, the clinical relevance of micrometastases is less apparent than the presence of macrometastases (either detected clinically or by ultrasound), which can occur up to 50% of differentiated thyroid cancers [7-11]. Therefore, when a differentiated thyroid cancer is diagnosed preoperatively, the 2009 ATA guidelines states that a “preoperative neck ultrasound for…cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant cytologic findings on biopsy” [12]. However, within these guidelines, there exists no recommendation for the workup, that is, neck ultrasound, for the evaluation of suspicious or indeterminate thyroid nodules, despite the fact that up to 40% overall of these nodules will be malignant [28-30]. Ultimately, in our study it was the FNAB that altered the surgical approach in several cases. But, originally it is the cervical neck ultrasound that led to obtaining the biopsy, which in turn leads to a change in operative approach; this change occurred in 5% of our patients. We chose to study this because the ATA guidelines do not address an algorithm for suspicious thyroid nodules and patients may not undergo routine evaluation for cervical lymphadenopathy.

Not only has the preoperative management of patients with malignant thyroid nodules been standardized, but there have also been attempts to standardize a routine operative approach. Grant et al. [31] examined the safety and efficacy of an “optimized surgical approach” including preoperative ultrasonography, total thyroidectomy, routine central neck dissection for tumors T1 or greater, and lateral neck dissection for biopsy-proven lymph node metastasis. During a 10-year period from 1996 to 2006, 420 patients underwent this optimized approach. Recurrences developed in 57 (14%) patients: with lymph node metastases occurring in 44 of these patients, soft tissue local recurrence in 5 patients, and distant metastases in 8 patients. However, relapse with lymph node metastases occurred in previously operated fields in only 19 (5%) patients. They therefore concluded that loco-regional recurrence was limited to only 5% of the patients when the extent of the disease was accurately defined preoperatively [31]. This study also reported a significantly lower

locoregional recurrence rate than what had been previously reported in the literature [16]. It also indirectly supports the algorithm of fully evaluating any patient with a known thyroid malignancy, or, as in our study, a suspected malignancy. Because there are no clear recommendations or optimized surgical approach for the preoperative management of patients with suspicious or indeterminate thyroid nodules, we attempted to investigate the efficacy of preoperative neck ultrasound and resulting impact on the surgical management of these patients.

In our study, of the 7 patients whose ultrasound impacted the extent of the surgery performed: 3 patients had central and ipsilateral lateral neck dissections, 2 patients had central and bilateral neck dissections, and 2 patients had central neck dissections alone. The change in extent of surgery was more likely to occur in patients who had microcalcifications of the thyroid nodule on ultrasound. The addition of a lymph node dissection was also more likely to occur in nodules with a more suspicious FNAB category. Lastly, although not statistically significant, it was more common in men compared to women. Even when including the 7 patients who had central neck dissections based on intraoperative findings, rather than ultrasound findings, thyroid nodule microcalcifications and FNAB category still showed a statistically significant risk of suspicious lymph nodes.

Microcalcifications of a thyroid nodule, if present, can be highly specific for papillary thyroid cancer [32]. Bai et al. [33] carry this statement even further and conclude from their study that not only are nodule calcifications suggestive of malignancy, but also have a correlation with metastases and even an association with worse overall patient survival.

Although not previously stated in the literature, our finding of a more suspicious thyroid nodule having a statistically significant increased risk for the addition of lymph node dissection can be extrapolated from the Bethesda criteria. Since a nodule that is suspicious for papillary thyroid cancer has up to a 75% chance of being malignant and a nodule that is ACUS has only a 15% chance of being malignant, it makes sense that a more suspicious nodule would therefore have a more likely chance of having metastatic disease [18].

Ten patients, in addition to the 5 who had modified lateral neck dissections performed, for a total of 15 patients were noted to have suspicious lateral neck lymph nodes; however, biopsy was negative for malignancy in these 10 patients. In the earlier part of the study there were more negative FNAB of suspicious lymph nodes. In the latter part of the study, nomenclature for suspicious lymph nodes was better standardized to allow for better specificity. Of the 8 patients who underwent lymph node biopsy between 2006 and 2007, only 1 (12.5%) was positive, whereas of 7 patients who underwent lymph node biopsy between 2008 and 2010, 4 (57%) were positive. Lymph nodes were often labeled as suspicious earlier in the study period, when in fact they were only “indeterminate or too small to characterize.” As the years have progressed, finite criteria have been established in order to characterize a lymph node as suspicious; these include the lymph node being taller than wide, having peripheral vascularity, microcalcifications, or lacking a fatty hilum [34,35]. We also recognize that some centers also perform FNA washout to measure thyroglobulin to help determine metastases in suspicious lymph nodes [36]. We do not routinely, however, obtain thyroglobulin washout levels in FNA samples of lymph nodes unless a lymph node is clinically very suspicious, but had resulted in a negative FNA biopsy.

CONCLUSION

In conclusion, obtaining preoperative neck ultrasounds altered the extent of surgery in only 7 of 134 (5%) patients who had suspicious or indeterminate thyroid nodules. Microcalcifications on thyroid ultrasound of the thyroid nodule and FNAB category

appeared to be the best predictors of metastatic disease. A previous study of ours that examined the impact of ultrasound on patients with known papillary thyroid cancer also found that thyroid nodule microcalcifications were predictive of metastatic disease [37]. These consistent findings may simply reflect the findings of Bai et al., described above. Although the surgical approach was altered in only a few patients, future analysis may be needed to delineate whether performing a preoperative cervical neck ultrasound in patients who present with suspicious thyroid cytology is cost-effective in preventing a second operation for completion thyroidectomy and/or a lymph node dissection.

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TABLE I

Proportion of Patients With Thyroid Malignancy by Underlying Characteristics

Patient characteristic	Benign (n = 62)	Malignant (n = 72)	*P*-value
Mean age	51.3 years (SD = 13.5)	47.0 (SD = 13.4)	0.059
Gender			0.094
Female	55	56	
Male	7	16	
Race			0.257
Caucasian	53	56	
African-American	5	4	
Other	4	10	
Positive family history	2	5	0.357
History of radiation	4	5	0.555
History of thyroiditis	14	22	0.480
Palpable nodule	46	57	0.488
Palpable lymph nodes	1	0	0.308
Ultrasound focality	34	44	0.463
Microcalcifications	10	19	0.296
Hypervascularity	18	12	0.094
Mean size in cm (ultrasound)	2.5 cm (SD = 1.2)	2.1 cm (SD = 1.4)	0.017*
Thyroid function			0.519
Hypothyroid	12	21	
Euthyroid	47	46	
Hyperthyroid	2	3	
FNAB category of nodule			<0.001*
Suspicious for malignancy	6	32	
Follicular Neoplasm	19	23	
ACUS	37	17	

SD, standard deviation; ACUS, atypical cells of undetermined significance.

*Statistically significant.

TABLE II

Proportion of Patients With Lymph Node Dissections by Underlying Characteristics

Patient characteristic	No lymph node dissection (n = 127)	Lymph node dissection (n = 7)	*P*-value
Male gender	20 (15.8%)	3 (42.9%)	0.064
Non-White race	22 (17.6%)	1 (14.3%)	0.882
Positive family history	7 (5.6%)	0 (0.0%)	0.522
History of radiation	8 (6.4%)	1 (14.3%)	0.416
History of thyroiditis	34 (27.4%)	2 (28.6%)	0.947
Palpable nodule	96 (76.2%)	7 (100.0%)	0.142
Palpable lymph nodes	1 (0.8%)	0 (0.0%)	0.813
Ultrasound focality	74 (58.3%)	4 (57.1%)	0.953
Microcalcifications	25 (2.02%)	4 (57.1%)	0.022 *
Hypervascularity	30 (24.4%)	0 (0.0%)	0.136
Mean size in cm (ultrasound)	2.27 (SD = 1.36)	2.46 (SD = 1.29)	0.722
Thyroid function			0.854
Hypothyroid	31 (25.0%)	2 (28.6%)	
Euthyroid	88 (71.0%)	5 (71.4%)	
Hyperthyroid	5 (4.0%)	0 (0.0%)	
FNAB category of nodule			0.002 *
Suspicious	32 (25.2%)	6 (85.7%)	
Follicular neoplasm	42 (33.1%)	0 (0.0%)	
ACUS	53 (41.7%)	1 (14.3%)	

SD, standard deviation; ACUS, atypical cells of undetermined significance.

* Statistically significant.