



An Institutional Analysis of Malignancy Rate in Bethesda III and IV Nodules of the Thyroid

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Abstract

Background: Bethesda III and IV nodules constitute a problematic entity, with previous reports demonstrating a large variability in their malignancy rate between different institutions and regions.

Methods: A retrospective analysis recognized patients who underwent thyroidectomy due to Bethesda III and IV nodule between 2011 and 2016. The primary outcome was to identify the malignancy rate in these nodules. A secondary outcome was to recognize predictors of malignancy in these patients.

Results: During the study period 176 thyroidectomies were performed due to Bethesda III/IV lesions. This group had a mean age of 47.1 years \pm 14.6 years and 73.9% were females. They had a mean of 1.6 \pm 1.0 nodules per patient and a mean size 30.6 mm \pm 16.6 mm. Total thyroidectomy was performed in 48.3%, and lobectomy in 51.7%. Malignancy was identified in 109 patients (61.9%) on final pathology, leading to the performance of completion thyroidectomy in 47/91 (51.6%) of the patients who first underwent lobectomy. Patients with benign and malignant pathologic results had similar mean age, gender distribution, number and size of nodules. Significantly more patients with malignancy were found to have positive family history of thyroid cancer when compared to patients with benign nodules (7.3 vs. 0%, respectively, $p=0.02$).

Conclusion: This study emphasizes the vast inter-institutional and regional variability in malignancy rate in Bethesda III/IV nodules, a finding which can guide an informed dialogue with patients and endocrinologists, and assist in determining appropriate management. The presence of positive family history of thyroid carcinoma may justify a more aggressive approach to these patients.

Keywords: Bethesda III and IV; Follicular lesion; Malignancy; Variability; Family history

Introduction

Thyroid nodules are an extremely common clinical entity, and can be identified in 19% to 68% of cervical Ultrasounds (US) [1,2]. US-guided Fine Needle Aspiration (FNA) biopsy is the diagnostic procedure of choice for the evaluation of nodules of more than 1 cm diameter [1]. These results are interpreted using the Bethesda System, with an overall accuracy of approximately 80% [3,4].

Bethesda V and VI nodules carry a high risk of malignancy (45% to 75% and 94% to 99%, respectively), and therefore surgery is recommended [4]. Bethesda II nodules are associated with a very low malignancy rate (0% to 3%), and therefore clinical and sonographic follow-up is generally recommended [4]. However, Bethesda III (Atypia of Undetermined Significance [AUS] or Follicular Lesion of Undetermined Significance [FLUS]) and Bethesda IV (Follicular Neoplasm [FN] or suspicious for FN) nodules constitute a problematic entity, with reported malignancy rates of 6% to 30% and 10% to 40%, respectively [4]. The recommended management for Bethesda III and IV cases is thyroidectomy, however molecular testing is a further diagnostic option [4]. The preoperative uncertainty regarding malignancy leads to difficulty in deciding the appropriate operation for some patients (total thyroidectomy or lobectomy), and results in frustration for endocrinologists, surgeons, and patients alike.

Previous reports have demonstrated a large variability in the malignancy rate of follicular lesions between different institutions and regions [5,6]. This can be attributed to different interpretations by pathologists examining the cytological FNA specimens [7,8]. The objective of this investigation

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Table 1: Comparison of patients with benign and malignant postoperative pathological results.

Variable	Benign (N=67)	Malignant (N=109)	p Value
Age (mean, years)	49.0 ± 15.9	45.9 ± 13.8	0.17
Females (%)	45 (67.2%)	85 (78.0%)	0.11
Number of nodules (mean)	1.7 ± 1.2	1.4 ± 0.9	0.08
Size of largest nodule (mean, mm)	33.6 ± 17.5	28.8 ± 15.8	0.06
Microcalcifications on sonography (%)	8 (11.9%)	13 (11.9%)	0.99
Preoperative history of neck radiation (%)	0 (0%)	2 (1.8%)	0.27
Family history of thyroid cancer	0 (0%)	8 (7.3%)	0.02

was to determine the malignancy rate of Bethesda III and IV nodules at a referral university hospital with a high-volume endocrine surgery service. In addition, this study aimed to identify preoperative characteristics that predict malignancy in these nodules.

Materials and Methods

The study was conducted following the approval of the institutional review board according to the World Medical Association Declaration of Helsinki 2008. A retrospective analysis and chart review was performed collecting data of patients who underwent thyroidectomies for thyroid nodules between January 1, 2010 and December 31, 2016. Both total thyroidectomies and thyroid lobectomies were included in the analysis. Patients of all ages with a preoperative diagnosis of a Bethesda III or IV nodule were included in the study, while those diagnosed with Bethesda I, II, V and VI nodules were excluded from analysis.

Data collected included demographic characteristics, preoperative US findings, FNA cytology results (performed either within or outside our institution), intraoperative findings, and postoperative histopathologic reports. The primary outcome of the investigation was to identify the malignancy rate in Bethesda III and IV lesions operated at our institution. A secondary outcome was to attempt to recognize preoperatively-identifiable factors that may predict malignancy in patients with follicular lesions.

It is our institutional policy not to perform frozen section analysis during the operation for Bethesda III and IV cases. Lobectomy patients with a postoperative diagnosis of malignancy subsequently underwent completion thyroidectomy if indicated, in accordance with the 2009 and 2015 American Thyroid Association guidelines [1,9].

Statistical analyses were performed using Statistical Software (SPSS version 20.0, SPSS, Inc). In order to identify differences between patients with benign and malignant pathology, univariate analysis with t test and chi square was utilized, as appropriate, and a $p < 0.05$ was considered statistically significant for all comparisons. Data are presented as the mean (SD).

Results

Between January 1, 2010 and December 31, 2016, 920 thyroidectomies were performed, of which 176 (19.1%) were due to Bethesda III (14/176) or IV (162/176) lesions. The mean age of this study group was 47.1 years ± 14.6 years (range 19 years to 89 years), and 73.9% were females. The preoperative US demonstrated a mean of 1.6 ± 1.0 nodules per patient (median 1.0, range 0 to 6), and a mean diameter of the largest nodule of 30.6 mm ± 16.6 mm. The preoperative FNA biopsy was evaluated at our institution in 115/176 patients (75.3%) and at outside laboratories in 61/176 (34.7%).

Eighty-five patients (48.3%) underwent total thyroidectomy and 91 (51.7%) underwent lobectomy as an initial procedure. Postoperative complications included transient hypocalcemia in 7.4% (13/176), transient Recurrent Laryngeal Nerve (RLN) injury in 3.4% (6/176), and permanent RLN injury in 0.6% (1/176).

The final postoperative pathology demonstrated malignancy in 109 patients (61.9%), leading to the performance of completion thyroidectomy in 47/91 (51.6%) of the patients who first underwent lobectomy. The rate of malignancy in Bethesda III and Bethesda IV patients was 35.7% (5/14) and 64.2% (104/162), respectively. There was no significant difference in the rate of malignancy between FNA biopsies performed and examined within our institution and those examined at an outside laboratory (63.5% vs. 59.0%, $p = 0.56$).

Follicular Variant of Papillary Thyroid Carcinoma (FV-PTC) was the most common type of malignancy demonstrated on the histopathology evaluation, accounting for 85/109 (78.0%) of cases. This was followed by PTC (23/109) and follicular thyroid carcinoma (1/109). The mean tumor diameter was 25 mm ± 16 mm (range 1 mm to 68 mm), 47/109 (43.1%) of carcinomas were multifocal, and 28/109 (25.7%) involved the contralateral lobe. Extrathyroidal invasion was identified in 8/109 (7.3%) and lympho-vascular invasion in 14/109 (12.8%).

Table 1 compares patients whose final postoperative pathological result showed malignancy to those who were found to have benign nodules. Neither patient age nor nodule size predicted risk for malignancy. Significantly more patients with malignancy were found to have positive family history of thyroid cancer when compared to patients with benign nodules (7.3% vs. 0%, respectively, $p = 0.02$). The risk of malignancy was 60.1% (101/168) and 100% (8/8) in patients negative and positive family history of thyroid cancer, respectively ($p = 0.02$).

Discussion

This investigation evaluated patients who underwent thyroidectomy (either lobectomy or total thyroidectomy) after a preoperative diagnosis of Bethesda III and IV nodules, at a high volume endocrine surgery referral center. The rate of malignancy in this cohort was 61.9%. A positive family history of thyroid cancer was the only preoperative factor associated with malignancy. The preoperative and operative approach to Bethesda III/ IV nodules has been a topic of great interest in recent literature, and this current study adds to the available literature by demonstrating the variability of rate of malignancy in different centers and regions.

The malignancy rate of Bethesda III and IV nodules in our study is higher than that reported in the literature [4]. In a previous study from our institution that analyzed the correlation between

preoperative FNA biopsies and postoperative pathologic results in thyroid surgery patients operated between 1994 and 2004, Mazeh et al. [5] demonstrated a malignancy rate of 42.5% in those with a preoperative FNA diagnosis of follicular lesion. The same author later compared these results to those of a different institution, demonstrating significant inter-institutional variation in the rate of malignancy in these lesions (42.5% vs. 23%, $p < 0.05$) [6]. Mijović et al. [10] similarly published their institutional results, demonstrating relatively high malignancy rates of 48% and 62% in follicular lesions and Hurthle cell lesions. Maia et al., [11] reported a 51.3% malignancy rate in Bethesda IV nodules.

The substantial variability of malignancy rate among different institutions emphasizes the clinician's obligation to acknowledge the malignancy rate in Bethesda III/IV lesions at their center and region. This familiarization can greatly facilitate an informed dialogue with the patient and endocrinologist, and assist in discussing and determining the appropriate operation for the patient.

Molecular testing has recently been proposed as a useful adjunct to the cytological analysis in the differentiation between benign and malignant thyroid nodules. More than 60% of thyroid cancers harbor at least one identified gene mutation [12,13]. Molecular testing has been widely described in the analysis of Bethesda III/IV nodules, and is an additional diagnostic option in recently-published recommendations [4]. For such a test to be useful in a clinical setting, it must possess the ability to accurately "rule out" malignancy, and therefore must be a test with a high Negative Predictive Value (NPV). A study published by Alexander et al., [14] validated the utilization of a gene-expression classifier (Afirma), demonstrating a relatively high NPV of 95%, 94%, and 85% in Bethesda III, IV, and V nodules, respectively. However, it must be noted that the rates of malignancy in these Bethesda groups were 24%, 25%, and 62%, respectively. In any such test, as the prevalence of the disease (in this case, the rate of malignancy) increases, the NPV of the test decreases [15]. Therefore, clinicians must be aware that in centers or regions in which the reported malignancy rate in Bethesda III/IV nodules is high, the usefulness of molecular testing to rule out malignancy may be limited.

This current study demonstrated an association between family history of thyroid cancer and the presence of malignancy in a Bethesda III/IV nodule. Although it is widely reported that family history increases the risk of malignancy in thyroid nodules in general, to the best of the authors' knowledge, this association has not been reported in the Bethesda III/IV subgroup [9]. It is possible that a more aggressive approach is justified in the management of these nodules when a positive family history is conveyed. In our study however, no association was demonstrated between nodule size and risk of malignancy, a finding that has been described in previous publications [16].

This study has several limitations. Patients analyzed were those that underwent surgery, and those with thyroid nodules that were not operated were excluded from the analysis. This effect should be minimal however, because the general institutional recommendation during the study period for the management of Bethesda III/IV lesions was surgery, due to the limited availability and cost of molecular testing. In addition, the retrospective nature of the investigation constitutes a disadvantage, and prospective studies are definitely required.

Conclusion

This study demonstrates a malignancy rate of 61.9% among patients diagnosed preoperatively with Bethesda III/IV nodules, emphasizing the vast inter-institutional and regional variability in this rate. This finding should urge clinicians to further investigate their institution's Bethesda III/IV malignancy rate, which can guide an informed dialogue with patients and endocrinologists, and assist in deciding upon appropriate surgical management and further diagnostic testing. In addition, the presence of positive family history of thyroid carcinoma may justify a more aggressive approach to these patients.

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