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Review Article

Incidence of Malignancy in Bethesda III and IV Thyroid Nodules: A Single-Center Experience

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Abstract

Background: The increased use of screening and ultrasensitive ultrasound has led to a more recent detection of thyroid nodules. Fine needle aspiration (FNA) is employed to diagnose thyroid nodules, with cytology assessed using the Bethesda system. Bethesda III and IV fall within the intermediate risk category for malignancy, with variable risks reported across several studies.

Aim and Objective: This study aimed to determine the malignancy rates of cytology proven Bethesda III and IV thyroid nodules at our institute.

Methods: A retrospective study was conducted on 321 patients (72.9% females) who underwent thyroid surgery, either hemi- or total thyroidectomy, between January 2021 and January 2023 at King Hussein Medical Center. Only those with FNA results classified as Bethesda III and IV were included in our study.

Results: The malignancy rates in our study were 25.8% for Bethesda III and 57% for Bethesda IV.

Conclusion: The malignancy rates in Bethesda categories III and IV thyroid nodules in our study are significantly higher than those suggested by the Bethesda consensus publication but comparable to similar studies published internationally.

Introduction

Thyroid nodules are common, with approximately 5%-7% detectable through physical examination. Their rise is primarily attributed to the increased use of modern imaging techniques, particularly ultrasound [1], as well as computed tomography, magnetic resonance imaging (MRI) and positron emission tomography (PET) [2].

Various studies have reported the prevalence of thyroid nodules ranging from 12%-67% [3,4]. The incidence of malignancy among thyroid nodules varies between 5%-17% among different studies [5,6]. Fine needle aspiration (FNA) is a recognised diagnostic modality for evaluating thyroid nodules, with or without ultrasound guidance [7-9]. The cytology of thyroid nodules undergoing FNA is classified using the Bethesda System for Reporting Thyroid Cytopathology, developed in 2007 [10]. This system allows cytopathologists to employ a standardised system and communicate their interpretations to referring physicians [11], while also guiding further management [11].

The Bethesda system classifies FNA results into six categories: I) nondiagnostic or unsatisfactory, II) benign, III) atypia of undetermined significance or follicular lesion of undetermined significance, IV) follicular neoplasm or suspicious for a follicular neoplasm, V) suspicious for malignancy and VI) malignant [8-11].

Each of these categories has an associated risk of malignancy, as reported in published studies: I) 1%-4%, II) 0-3%, III) 5%-15%, IV) 15%-30%, V) 60%-75% and VI) 97%-99%, according to the study by Cibas et al. [11].

The risk of malignancy for categories I, II, V and VI has been consistent across various studies [5]. In contrast, the malignancy risk for Bethesda categories III and IV has varied significantly among studies conducted in different institutions worldwide, with malignancy risk for Bethesda category III ranging from 15.7%-54.6% and for category IV nodules from 16.8%-72.4% [12-15]. Cibas et al. [11] reported a significantly lower risk than these ranges. The Bethesda system was revised in 2017, maintaining the same six categories but adjusting malignancy risks, particularly for category III, which now has a risk of 10%-30%, and for category IV, which now has a risk of 25%-40% in the revised system [16].

Materials & Methods

The Jordanian Royal Medical Services' ethical committee approved our study at its meeting (17/2024), which took place on December 3rd, 2024, since this study was conducted retrospectively, without using any personal patient information. The outcomes did not have any impact on patient treatment.

We performed a retrospective chart analysis of all patients who underwent thyroid surgery, whether hemi- or total thyroidectomy, at King Hussein Medical Center between January 2021 and January 2023, including 321 patients. Those with FNA results classified as Bethesda III and IV were included in our study, total number was 162 patients.

The inclusion criteria comprised all patients who underwent thyroid surgery with available preoperative and postoperative FNA and histopathology reports.

Specimens were received from the surgery department in a fixed state in 10% buffered formalin. Proper sections were taken and placed in cassettes after gross examination of the specimens grossly. The selected sections underwent multiple steps in the tissue processor to yield wax-infiltrated tissue. The tissue was then embedded in wax to obtain a paraffin cassette, cut via a microtome to obtain a 3-micron-thick slice of tissue on a glass slide, and stained with hematoxylin and eosin stains. The specimens were examined microscopically for the presence of follicular neoplasms or other follicular lesions. Further evaluation of other parameters in follicular neoplasms was conducted, including capsular and/or vascular invasion and the number of vessels involved in cases of vascular invasion.

FNAs, performed by endocrinologist, pathologist or the radiologist, were processed in the pathology department at King Hussein Medical Center. For each case, some slides were air-dried for staining with Diff Quick stain, while others were alcohol-fixed for Papanicolaou stain. Slides were then examined. The diagnosis was made, and results categorized according to the Bethesda System for Reporting Thyroid Cytology.

Ultrasound results using the TIRAD scoring system and the patient's clinical picture were used to determine whether FNA should be done. This was done as if the patient had risk factors such as radiation exposure, a family history of thyroid cancer, changes in voice or lymphadenopathy.

We accessed all patient data through electronic medical records (HAKEEM). The malignancy rate was determined by correlating the cytopathology report with the histopathology report. The statistical analysis was conducted using IBM SPSS software (version 23), employing descriptive statistics; frequency and percentage were employed to represent the categorical data of the study.

Results

A total of 321 patients (72.9% females) underwent thyroid surgery, with a mean age of 46 years. All patients had preoperative cytology and postoperative histopathology reports are available. 104 patients underwent hemithyroidectomy (33%), while the remaining 217 patients had total thyroidectomy.

Table 3 in the appendices shows the patients demographic as

well as statistics of type of surgery done, FNA cytology and histopathology.

Among the 321 patients, 151 were found to be malignant (47%). Of the malignant cases, 120 had papillary thyroid cancer (79.5%), 25 had follicular carcinoma (16.6%) and six had medullary cancer (4%). This has been demonstrated in Figure 1. and also, in table 4 in the appendices.

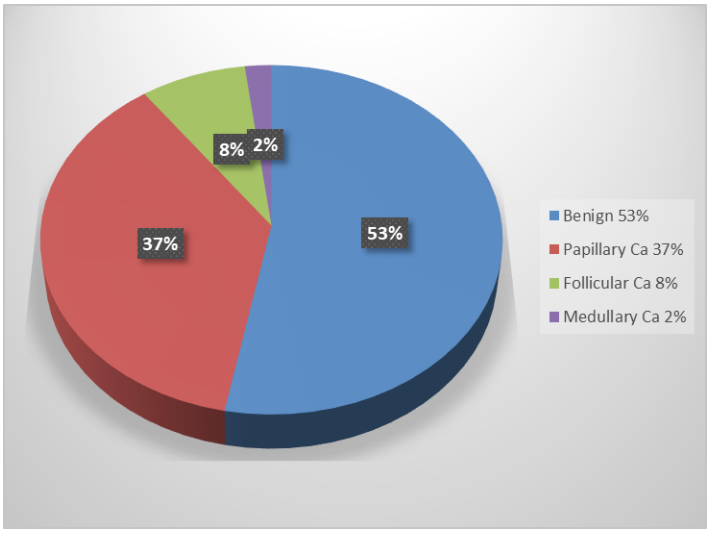

Figure 1: Histopathology Results

The frequency of each Bethesda class was as follows: Bethesda I: 1.2% (four cases), Bethesda II: 22.1% (71 cases), Bethesda III: 30.2% (97 cases), Bethesda IV: 20.2% (65 cases), Bethesda V: 12.8% (41 cases) and Bethesda VI: 13.4% (43 cases).

Extent of surgery	BETHSDA TRUE						Total
HEMI VS TOTAL	1	2	3	4	5	6	
HEMI	3	35	45	19	1	1	104
TOTAL	1	36	52	46	40	42	217
Total	4	71	97	65	41	43	321

Table 1: shows the distribution of cases over all Bethesda stages.

The decision to perform surgery in patients with Bethesda II on FNA cytology was primarily due to large goiter causing compressive symptoms.

Of the total 321 patients, 97 had Bethesda III FNA results and 65 had Bethesda IV FNA results; these groups were included in our study.

Of the 97 cases with Bethesda III, 67% were females; forty-five cases underwent hemithyroidectomy, while the remaining 52 cases underwent total thyroidectomy. Additionally, of the 97 cases, 72 had benign histopathology (74.2%) and 25 had malignant histopathology (25.8%).

The benign histopathology results were as follows: 36 cases with multinodular goiter, 16 cases with hyperplastic nodules, 11 cases with follicular adenoma, seven cases with nodular Hashimoto's thyroiditis and two cases with Hurthle cell adenoma.

With malignant cases, the majority had papillary thyroid cancer: 20 out of 25 total malignant cases (80%), while five cases had follicular carcinoma.

Of the 65 cases with Bethesda IV, 83% were females; nineteen cases underwent hemithyroidectomy, and the remaining 46 cases underwent total thyroidectomy. Of the 65 cases, 28 (43%) had benign histopathology, while the remaining 37 cases (57%) had malignant histopathology.

The benign histopathology results were as follows: 10 cases with multinodular goiter, five cases with hyperplastic nodules, five cases with follicular adenoma, five cases with Hashimoto's thyroiditis and three cases with Hurthle cell adenoma.

The majority of the malignant cases were papillary thyroid cancer, with 22 cases (60%), followed by 13 patients with follicular carcinoma (35%) and two patients with medullary thyroid cancer (5%).

Figure 2 demonstrates the distribution of Bethesda III and IV thyroid nodules in the current study.

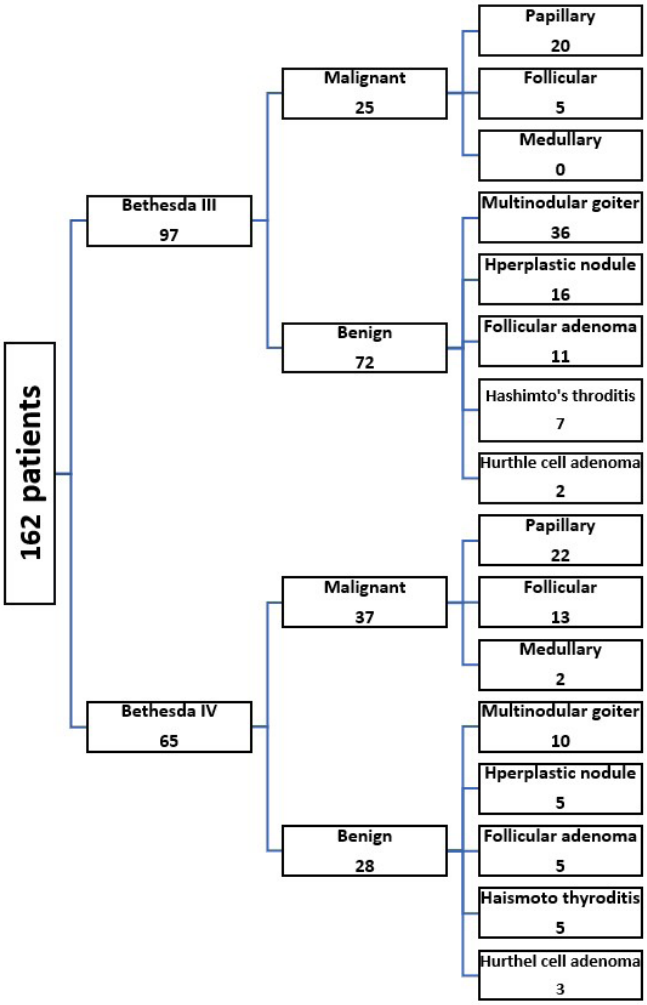

Figure 2: Distribution of patients with Bethesda III and IV, based on disease classification, categorizing them into benign and malignant cases.

The decision between hemi- or total thyroidectomy considered several risk factors, including family history, radiation exposure, compressive symptoms, alarming symptoms in the patient's medical history, like changes in voice and fast growth of the nodule, and alarming features seen on ultrasound. The patient's choice was also considered.

Discussion

Evaluation of thyroid nodules and lesions necessitates comprehensive clinical evaluation and ultrasound reporting, alongside cytopathological assessment. FNA reporting has been successfully standardized using the Bethesda system, which provides clinicians with guidance for management planning. The aim of this system is to achieve consensus regarding the malignancy risk of thyroid nodules. However, the malignancy risk for Bethesda III and IV thyroid nodules remains unclear compared to other Bethesda categories.

Bethesda III presents a management challenge due to its broad spectrum of diagnoses; the first edition of the Bethesda System for Reporting Thyroid Cytopathology in 2007 reported a malignancy probability for Bethesda category III of between 5%-15% [11]. However, the third edition of TBSRTC (The Bethesda System for Reporting Thyroid Cytopathology), released in 2023, revealed a 22% higher risk of malignancy [10].

Different studies have found that the rates of cancer in Bethesda II, V and VI thyroid nodules were consistent. These rates also in line with data from the 2007 Bethesda System for Reporting Thyroid

Cytopathology.

Conversely, malignancy rates for Bethesda III and IV thyroid nodules have varied among different studies: 15.7%-54.7% and 16.8%-2.4% for Bethesda III and IV, respectively [14,15,17,18].

Some studies report a Bethesda III diagnosis rate of 18%-22% [19-22]. However, Ho et al. reported an incidence of only 8% only [23]. In our study, we report a higher diagnosis rate of Bethesda III (AUS/FUS) at 30.2%.

An interesting study by Ronen et al. examined the diagnosis rates of all Bethesda categories between two cytopathologists at the same academic center. The study found that the diagnosis rates of all thyroid Bethesda system (TBS) categories were similar, except for Bethesda III (8.0% and 21.2%, P =.01) [9]. This is a big difference in the frequency of diagnosing Bethesda III, which makes things more difficult for doctors.

Some researchers thought about leaving out Bethesda III (FUS/AUS) from thyroid FNA cytology, but a study by Shi et al. showed that this made the sensitivity of FNA cytology and lead to more false positive and false negative results. [21].

Inabnet et al. reported a large cohort of 21,764 patients who underwent FNA and thyroidectomy across 314 institutions in 22 countries (North America, Europe, Sweden and the UK). Their analysis correlated FNAC findings with surgical specimens, revealing that Bethesda category III was associated with a 32% risk for malignancy, which is higher than both initial and the updated Bethesda system [17].

Additionally, a study [20] from the United Arab Emirates, released in May 2024, examined 1,038 patients who underwent bilateral or unilateral thyroidectomy by a single endocrine surgeon (I.H.) at a tertiary hospital. Of these, 670 had FNA results before surgery, which were used in the study.

The prevalence of cancer in Bethesda III nodules was comparable to that of Bethesda IV, with rates of 33.5% and 33.8%, respectively.

The mean age and gender distribution in the current study were consistent with those in other studies [14,15,18,19]. In our study, the incidence of malignancy in Bethesda III thyroid nodules was 25.8%, while it was 57% in Bethesda IV thyroid nodules.

Table 1 shows that the cancer risk for Bethesda III thyroid nodules was similar to that of other studies. Conversely, the cancer risk for Bethesda IV thyroid nodules was higher in our study than in other studies. This might be because our institute is a tertiary center that gets more cases with a higher risk of cancer.

Table 2 presents a comparison of malignancy risks for thyroid nodules classified as Bethesda III and IV among different studies, including our present study.

	Incidence of malignancy in Bethesda III thyroid nodules %	Incidence of malignancy in Bethesda IV thyroid nodules %
Zahid et al. [13]	29.6%	47.1%
Godoi Cavalheiro B et al. [14]	15.7	16.8
Chirayath et al. [15]	54.7	72.4
Chandra S, et al. [18]	28.5	NA
Yaprak Bayrak, et al. 2020 [19]	25.0	27.6
Iyad Hassan, et al. 2024 [20]	33.5	33.8
Present study	25.8	57

Table 2: Comparison of malignancy risks for thyroid nodules classified as Bethesda III and IV among different studies, including our present study.

		AGE	GENDER	MALIG VS BENIGN	HEMI VS TOTAL	HISTOPATHLOGY	BETHSDA TRUE	BETHSDA CODE
N	Valid	321	321	321	321	321	321	321
	Missing	0	0	0	0	0	0	0
Mean		46.86	.73	.47	.68	.58	3.61	2.19
Std. Error of Mean		.830	.025	.028	.026	.040	.075	.049
Median		46.63[a]	.73[a]	.47[a]	.68[a]	.51[a]	3.46[a]	2.28[a]
Mode		54	1	0	1	0	3	3
Std. Deviation		14.867	.445	.500	.469	.716	1.349	.873
Variance		221.025	.198	.250	.220	.513	1.819	.763
Kurtosis		-.269	-.934	-1.998	-1.438	.972	-.883	-1.582
Std. Error of Kurtosis		.271	.271	.271	.271	.271	.271	.271
Range		85	1	1	1	3	5	2
Minimum		0	0	0	0	0	1	1
Maximum		85	1	1	1	3	6	3
N: number of patients Std: standard								

Table 3: Patients demographics and statistics of type of surgery done, FNA cytology and histopathology.

Type of cancer	Frequency	Percent	Valid Percent
BENIGN	172	53.6	53.6
PAPILLARY	118	36.8	36.8
FOLLECULAR	25	7.8	7.8
MEDULLARY	6	1.9	1.9
Total	321	100.0	100.0

Table 4: Distribution of malignant cases.

Unfortunately, molecular studies are not available at our center; preoperative molecular genetic studies for indeterminate thyroid nodules (Bethesda III and IV) have a high sensitivity in ruling out malignancy and thus assist in avoiding unnecessary surgeries. The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer recommend the use of molecular genetic testing to assess the risk of malignancy in such nodules [5].

Limitations

There were several limitations to our study. Firstly, it was a retrospective study examining record data for pre- and postoperative histopathology and cytopathology records, which precluded the inclusion of clinical or radiological risk factors. Secondly, the number of patients included in our study was relatively small. Lastly, our center is a tertiary referral center, resulting in a higher proportion of patients with a greater risk for malignancy.

We aim to have molecular studies in our center, which will definitely help with risk stratification, and as a result, it would assist with the decision whether to go for surgery and the extent of surgery.

Conclusions

To our knowledge, this study is the first in Jordan to describe the risk of malignancy in Bethesda III and IV thyroid nodules. In our study, the risk of cancer for Bethesda III and IV thyroid nodules was 25.8% and 57%, respectively. These figures are higher than the risks described in the initial Bethesda system report in 2007 but align with the revised risk for Bethesda III in 2017.

Conversely, the risk for cancer in Bethesda IV in our study was higher than in both the original Bethesda system report in 2007 and its revised risk in 2017, but similar to other studies. Our study suggests that, in our clinical practice, categories III and IV thyroid nodules carry a higher risk for malignancy than traditionally understood. Additionally, larger studies in our region are needed to

establish guidelines for managing such nodules.

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