

Malignancy Rates in Thyroid Nodules Classified as Bethesda III and IV; Correlating Fine Needle Aspiration Cytology with Histopathology

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Abstract: Fine needle aspiration cytology (FNAC) is an integral part in the diagnostic work up of thyroid nodules. FNAC reports are based on Bethesda system for thyroid cytopathology which is one of the most commonly used systems worldwide. The main objective of the present study was to evaluate the malignancy rates in Bethesda category III and IV thyroid nodules over a six-year period. 642 thyroid FNAC were performed over a six-year period. The medical records of all these patients were reviewed using electronic patient records. Cases reported to have Bethesda category III and IV were included in the study. Data for these patients were reviewed to determine the relationship between these categories and thyroid cancer. There were 41 cases of category III of which 19 underwent surgery and the malignancy rates were found to be 26.3%. Category IV consisted of 50 cases of which 45 underwent surgery and the malignancy rates were 26.6%. The results from our study are similar to findings in larger multicentric studies which found that malignancy rates for Bethesda category III and IV were 10–30% and 25–40%, respectively.

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Introduction

Distinguishing a benign from a malignant thyroid nodule can be challenging at times. Fine needle aspiration cytology (FNAC) plays a crucial role in the diagnosis of thyroid nodules. Although an imperative investigation, reports at times can be ambiguous and hence perceived differently by surgeons and endocrinologist (Redman et al., 2006). Due to these shortcomings a standardized reporting system such as Bethesda system for reporting thyroid cytopathology plays an important role. Based on this system, thyroid FNAC are classified into six categories which are, category I – non diagnostic, category II – benign, category III – atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), category IV – follicular neoplasm, category V – suspicious for malignancy and category VI – malignant. Introduction of this system of reporting has not only improved the overall quality of reporting FNAC but also reduced the number of unwanted thyroidectomies (Crowe et al., 2011).

Thyroid nodules classified as Bethesda category III are difficult to distinguish as benign or malignant and are reported as atypia of undetermined significance or follicular lesion of undetermined significance. According to the 2017 Bethesda consensus (Cibas and Ali, 2017), risk of malignancy from these nodules is 6–18% when non-invasive follicular thyroid neoplasm (NIFTP) is not considered as cancer versus 10–30% when NIFTP is considered as cancer and can be managed initially with a repeat FNAC.

A few recently published papers have suggested higher malignancy rates associated with Bethesda category III. Bethesda category IV includes follicular neoplasm or suspicious of follicular neoplasm. At a cytological level both follicular cancer and benign follicular neoplasm look identical making it difficult for pathologist to distinguish the two. Identification of either capsular or vascular invasion on FNAC can confirm malignant diagnosis (Ohuri et al., 2010).

The aim of this study is to evaluate the risk of thyroid cancer for Bethesda category III and category IV nodules over a six-year period.

Material and Methods

This is a retrospective observational study of all thyroid nodules with a Bethesda category III and IV results investigated by department of general surgery, surgical oncology and otorhinolaryngology between January 2015 and December 2020. All reports were obtained using the hospitals electronic patient record system. Since no intervention was carried out on patients and this is a retrospective review, ethical committee waiver of consent was approved.

In the case of larger nodules FNAC was performed directly into palpable nodule while in the case of smaller nodules it was done under ultrasound guidance. All FNAC were reported according to Bethesda classification. All category III cases were classified as either AUS or FLUS. All smears were fixed with alcohol and stained with Papanicolaou stain. Following the initial FNAC patients were given the

option of undergoing surgery versus a repeat FNAC in 1–3 months in Bethesda category III.

Inclusion criteria included all patients with Bethesda category III and IV nodules and had operative details and histology available. Patients whose electronic records did not have the above information were excluded from the study. There were 106 patients in total included in this study of which 47 were category III and 59 were category IV. The histopathological reports were compared with FNAC reports in order to determine rate of malignancy.

Results

A total of 642 thyroid FNAC were performed from January 2015 to December 2020. The total number of males was 112 and females 530. Age ranged from 16 to 78 years. Based on Bethesda system there were 18 in category I, 442 in category II, 47 in category III, 59 in category IV, 35 in category V and 41 in category VI (Table 1).

Category 3 was further divided into AUS and FLUS which included 32 and 15, respectively. Out of the 47 cases in category 3, 6 patients were lost to follow-up. Among the remaining 41 cases, 6 (14.7%) had immediate surgery of which 5 (83.3%) were found to be benign and 1 (16.6%) malignant. The remaining 35 (85.3%) underwent repeat FNAC of which 3 (8.5%) were reported as category I, 19 (54.2%) as category II and 13 (37.1%) as category III. Patients with repeat FNAC reported as category III underwent surgery and 9 (69.2%) were benign and 4 (30.7%) were malignant (Figure 1).

There were 59 patients in category IV of which 9 were lost to follow-up. The remaining 50 cases underwent surgery of which 38 were benign and 12 were malignant (Figure 2).

Malignancy was diagnosed in 5 (26.3%) out of 19 cases diagnosed as category III and 12 (26.6%) out of 50 cases diagnosed as category 4 that had undergone surgery (Table 2).

Based on histopathology, benign cases included follicular adenoma, Hashimoto's thyroiditis and nodular colloid goitre while malignant diagnosis included papillary

Table 1 – Patient categorization based of Bethesda System for Reporting Thyroid Cytopathology

Bethesda category	No. of cases (%)
Category I	18 (2.8%)
Category II	442 (68.8%)
Category III	47 (7.3%)
Category IV	59 (9.1%)
Category V	35 (5.4%)
Category VI	41 (6.3%)

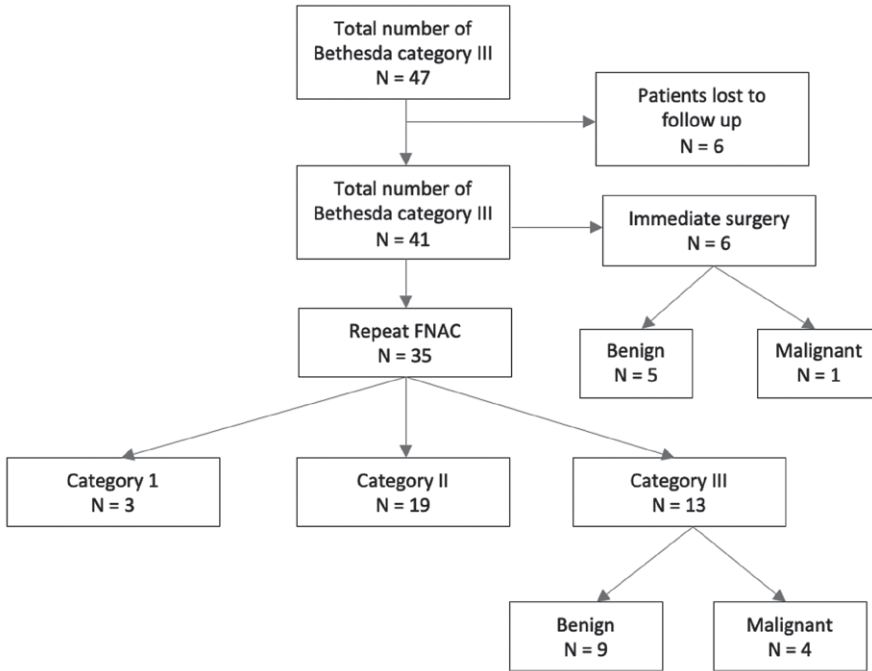


Figure 1 – Flow chart of category III thyroid nodules on fine needle aspiration cytology.

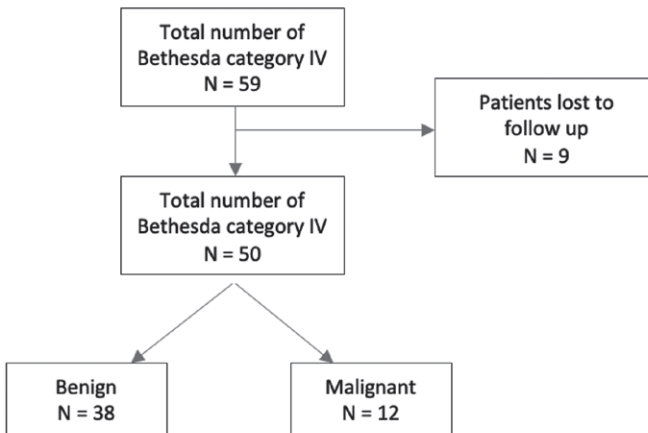


Figure 2 – Flow chart of category IV thyroid nodules on fine needle aspiration cytology.

carcinoma thyroid (PTC), follicular carcinoma thyroid and Hurtle cell carcinoma. The most common type of cancer in category IV was PTC (66.6%) followed by follicular cancer thyroid (25%). The only malignant tumour in category III was papillary cancer thyroid (Figure 3). Among the 5 cases of PTC in category III, 1 case was

Table 2 – Malignancy ratios of thyroid nodules following surgery

	Benign (%)	Malignant (%)	Total
Bethesda III	14 (73.6%)	5 (26.3%)	19
AUS	10 (71.4%)	4 (28.5%)	14
FLUS	4 (80.0%)	1 (20.0%)	5
Bethesda IV	38 (76.0%)	12 (24.0%)	50

AUS – atypia of undetermined significance; FLUS – follicular lesion of undetermined significance

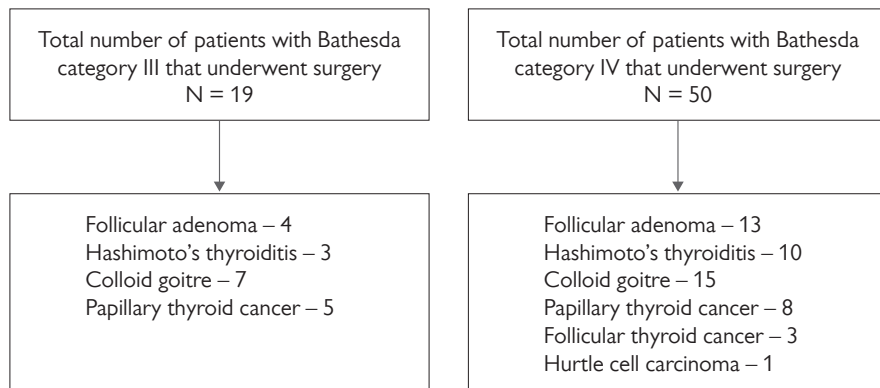


Figure 3 – Flow chart of Bethesda category III and IV and histopathology results following surgery.

NIFTP, 3 were conventional and 1 was tall cell variant. Among the 8 cases of PTC in category IV, there were 2 cases of follicular variant of PTC while the remaining 6 were conventional PTC.

Discussion

Bethesda System for Reporting Thyroid Cytology has played an important role in standardizing reports for thyroid FNAC. The main aim of this system was to have a clear understanding about the potential malignancy rates among various sub categories. The main limitation of this system are category III and category IV where the risk of malignancy remains unclear (Somma et al., 2010). Some researchers have a shared opinion that either by reducing or eliminating certain Bethesda categories, it would help in easy decision-making in patient management. However, studies have shown that eliminating category III or IV increases the rates of false positivity, false negativity and lowers the sensitivity of FNAC (Shi et al., 2009).

In the present study, the mean age was 47 years and there were a greater number of females as compared to males. This was comparable to other published

studies (Ho et al., 2014; Yaprak Bayrak and Erucar, 2020). The present study evaluated FNAC reports of 642 patients with thyroid nodules. Among these patients 7.3% were category III and 9.1% were category IV based on initial FNAC. Some case series reported a much higher incidence i.e., 22.6% were category III and 14% were category IV (Yaprak Bayrak and Erucar, 2020). A case series by Ho et al. (2014) showed similar incidence of category III as the present study.

Malignancy rates in respect to Bethesda category III and category IV will vary from institute to institute with higher rates seen more commonly in multicentric studies. Studies that evaluated a larger population with thyroid nodules showed that malignancy rates in Bethesda category III range from 10–30% while category IV ranges from 25–40% (Ho et al., 2014; Cibas and Ali, 2017). Studies with smaller cohorts showed that malignancy rates can be as high as 40% in category III (Alexander et al., 2012; Canberk et al., 2016). In the present study, malignancy rates were 26.3% and 26.6% for category III and category IV respectively which are similar to studies with a larger cohort. Undoubtedly, these rates play an important role when surgeons need to decide whether patients need surgery or regular observation and follow-up. Mathur et al. (2014) evaluated 4,827 FNAC of which 255 patients with Bethesda category III underwent surgery and malignancy rates were 39%, which is much higher as compared to our study. In another large cohort by Jo et al. (2010) the malignancy rates for category III was 17% and category IV was 25%, which is comparable to our study. Difference in malignancy rates seems to depend on the interpretation of FNAC by various cytopathologist.

In the present study, the malignancy rates of patients that underwent immediate surgery was 16.6% and 28.8% for category III and category IV, respectively. The malignancy rates in thyroid nodules following a repeat FNAC were 30.7% and 26.3% in category III and category IV, respectively. Similar findings were also seen in a study by Yaprak Bayrak and Erucar (2020) where malignancy rates were higher following patients that had a repeat FNAC for category III thyroid nodules. Chirayath et al. (2019) carried out a prospective study to determine malignancy rates in Bethesda category III and IV. They recommended that patients with category III should undergo repeat FNAC while those with category IV can proceed directly to surgery. Papillary thyroid cancer was the most common cancer type in both category III and IV. This was similar to study done Cavalheiro et al. (2018).

Conclusion

This study provides a more accurate analysis of cancer rates in patients with thyroid nodules classified as Bethesda category III and IV, as these patients underwent surgical excision. The study concludes that malignancy rates associated with Bethesda category III and IV are similar to already published data which relates to 10–30% and 25–40%, respectively.

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