Outcome of Subclassification of Indeterminate (Thy-3) Thyroid Cytology into Thy-3a and Thy-3f

Catherine Brophy^a Rania Mehanna^a Julie McCarthy^c Antoinette Tuthill^d
Matthew S. Murphy^b Patrick Sheahan^a

Departments of ^aOtolaryngology – Head and Neck Surgery and ^bEndocrinology, South Infirmary Victoria University Hospital, and Departments of ^cCytopathology and ^dEndocrinology, Cork University Hospital, Cork, Ireland

Key Words

Thyroid · Cytology · Thy-3 · Thy · Follicular lesion of uncertain significance · Atypia of uncertain significance

Abstract

Objectives: The British Thy system is a widely used classification system for reporting thyroid fine-needle aspiration (FNA) cytology. The Royal College of Pathologists in 2009 recommended the subdivision of the Thy-3 (indeterminate) category into Thy-3a (atypia) and Thy-3f (follicular neoplasm). Our objective was to examine the malignancy rates of Thy-3a and Thy-3f cases at our institution and to investigate whether the risk of malignancy in Thy-3a cases is reduced by FNA on a different occasion showing benign cytology. **Methods:** This is a retrospective study of 748 thyroid nodules undergoing 1,032 FNAs, with indeterminate (Thy-3) cytology subdivided into Thy-3a and Thy-3f. Cases were correlated with final histology in surgical cases. Incidental carcinomas occurring outside the biopsied nodule were discounted. **Results:** A total of 109 nodules had a final cytological diagnosis of Thy-3a, of which 67 underwent surgery, with an incidence of malignancy of 13.4% (9/67); 90 nodules had a final cytological diagnosis of Thy-3f, of which 84 underwent surgery, with an incidence of malignancy of 17.9% (15/84). The difference in malignancy rates was not signifi-

cant ($p = 0.51$). The incidence of malignancy in nodules with benign and Thy-3a cytology on separate occasions was not significantly different from cases with a single Thy-3a cytology. **Conclusions:** Thyroid nodules with Thy-3a cytology have a slightly lower risk of malignancy than Thy-3f cases. However, the difference is not significant and does not appear to be reduced by FNA on a separate occasion showing benign cytology. Management decisions for patients with Thy-3a cytology should be taken carefully to avoid missing cancers.

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Introduction

Thyroid nodules are common, being present by palpation in up to 5% of individuals and by ultrasonography (US) in up to 50% [1]. While the overwhelming majority are benign, it is estimated that the incidence of cancer in clinically apparent thyroid nodules is between 5 and 15% [2].

Fine-needle aspiration (FNA) cytology has demonstrated high utility in the diagnosis of thyroid nodules. In an effort to stratify thyroid nodules according to risk of malignancy in a consistent fashion, a number of tiered clas-

sification systems for thyroid cytology have been devised. The most widely used systems are the American Bethesda system [3], and the British Thy system [4]. The British Thy system is widely used in many countries both within and outside Europe. The major advantage is the numerical nomenclature which facilitates ease of use and understanding by cytologists, endocrinologists, and surgeons. In this system, an inadequate aspirate is designated Thy-1, benign cytology as Thy-2, indeterminate as Thy-3, suspicious (for malignancy) as Thy-4, and malignant as Thy-5.

Limitations of FNA arise for nodules which are reported as having an indeterminate cytology (Thy-3). While the majority of these cases transpire to be benign, surgical excision with histological examination is frequently necessary to make a definitive diagnosis.

In order to enhance the sophistication of the British Thy system in dealing with indeterminate cytology results and to facilitate the triage of such cases into those which require immediate surgical excision and those which can be followed without immediate surgery, the Royal College of Pathologists (RCP) in 2009 proposed the subclassification of Thy-3 aspirates into Thy-3a (atypia) and Thy-3f (follicular neoplasm) [4]. The Thy-3f category is used for cases which are cytologically suspicious for a follicular or Hürthle cell neoplasm (analogous to the Bethesda follicular neoplasm category), whereas the Thy-3a category is used for cases demonstrating cytological or architectural atypia or other features which raise the possibility of neoplasia but which are insufficient to enable placing into any other category – analogous to the Bethesda AUS (atypia of undetermined significance) or FLUS (follicular lesion of undetermined significance) categories.

Although the subclassification of Thy-3 cytology into Thy-3a and Thy-3f subcategories has been adopted by many institutions, there is, to date, little or no published data in the literature regarding the outcomes of this subclassification. The purpose of the present study was to examine the malignancy rates of Thy-3a and Thy-3f nodules at our institution and to investigate whether the malignancy risk of Thy-3a cases is reduced in cases where FNA performed on a separate occasion is reported as showing benign cytology.

Methods

The present study comprised a retrospective review of all thyroid FNAs performed at our institution, an academic teaching hospital, between January 2011 and December 2013. Inclusion criteria were cases of thyroid cytology reported according to the British Thy system as Thy-3a and Thy-3f.

FNA was performed in nearly all cases under US guidance with a laboratory technician present on-site to assess adequacy and to optimally prepare the sample. After multiple passes through the nodule, aspirated material was spread onto glass slides and air-dried. In addition, needle rinse material was sent in CytoLyt solution.

Thyroid cytology was reported by a small team of cytopathologists with an interest in thyroid cytology using the British Thy classification, with subclassification of Thy-3 aspirates into either Thy-3a or Thy-3f. Samples categorized as Thy-3a category include those showing cytological atypia but at a level considered insufficient to place confidently into a higher category. This may be due to architectural atypia in the form of a mixed macro- and microfollicular pattern where a definite distinction between a follicular neoplasm and a hyperplastic nodule is not possible. Also included in the Thy-3a category are samples with little colloid relative to the cellularity, aspirates with atypical cyst lining cells, and samples in which some atypia is noted but assessment is compromised by obscuring blood or preparation artefact. Finally, this category includes samples where there are focal cytological changes that are most probably benign but where papillary carcinoma cannot be confidently excluded. The Thy-3f category was used for samples which are predominantly microfollicular in architecture and thus likely to harbour a follicular neoplasm (but which may turn out on histological examination to be a hyperplastic nodule, adenoma or carcinoma). Samples that are composed almost exclusively of Hürthle cells were also categorized as Thy-3f. Follicular variants of papillary carcinoma without clear nuclear features may fall into this group. At our institution, we have also included sparsely cellular samples that are predominantly microfollicular in the Thy-3f category. In accordance with institutional policy, all cases of Thy-3 or higher-risk cytology were listed for discussion at thyroid or head and neck cancer multidisciplinary meetings.

In the case of patients who had undergone FNA of the same nodule on more than one occasion with discrepant results, then for the purpose of the present study the final cytological diagnosis was taken as the higher-risk cytological diagnosis. Thus, any nodule which had undergone a Thy-3a and Thy-3f aspirate on different occasions was considered to have a final cytological diagnosis of Thy-3f, whereas the Thy-3a category included cases which underwent FNA on a separate occasion showing benign cytology. Cytology was correlated with final histology. Final histology was considered malignant only if cancer was found within the biopsied nodule. Incidental carcinomas occurring outside the biopsied nodule were not included in the malignant category.

Statistical analysis was performed using Prism 6. Comparisons on 2 × 2 contingency tables were performed using a 2-tailed Fisher exact test. Student's *t* test was used to test for significant differences in normally distributed data. Permission to conduct the research was obtained from the Institutional Research Ethics Board.

Results

During the study period, 1,032 thyroid FNAs were performed on 748 thyroid nodules in 677 patients. The final cytological diagnosis in the 748 nodules was benign (Thy-2) in 415 cases (55.6%), indeterminate (Thy-3) in

Table 1. Characteristics of nodules in Thy-3a and Thy-3f categories

	Thy-3a (n = 109)	Thy-3f (n = 90)	p value
Male:female	13:93	16:70	0.23
Age, years	50.2 (29–82)	51.9 (20–81)	0.47
Nodule size ¹ , mm	33.4 (7–64)	33.1 (7–74)	0.92

Values are means (range). A total of 3 patients in the Thy-3a group and 4 patients in the Thy-3f group had bilateral nodules included.

¹ Mean size given for surgical cases.

Table 3. Outcome of Thy-3a cases undergoing more than 1 diagnostic FNA on different occasions

FNA results	Cases	Cases undergoing surgery	Malignancy
Thy-2 → Thy-3a	19	11	3
Thy-3a → Thy-2	19	1	0
Thy-3a → Thy-3a	9	5	0
Thy-3a → Thy-3f	10	9	2
Thy-3f → Thy-3a	1	1	0
Thy-3a → Thy-4/5	2	2	1
Total	60	29	6

209 (27.8%), suspicious for malignancy (Thy-4) in 12 (1.6%), positive for malignancy (Thy-5) in 32 (4.3%), and inadequate in 80 (10.7%).

Of the 209 cases with Thy-3 cytology, 10 were excluded due to not having been subclassified into Thy-3a or Thy-3f. Thus, 199 thyroid nodules, occurring in 192 patients, formed the final study population. The final cytological diagnosis was Thy-3a in 109 nodules and Thy-3f in 90 nodules; 3 patients had bilateral Thy-3a nodules, and 4 had bilateral Thy-3f nodules. Table 1 shows the characteristics of the nodules in the 2 groups.

Overall, 67 of the cases with Thy-3a cytology and 84 cases with Thy-3f cytology proceeded to surgery. Nodules with Thy-3f cytology were significantly more likely to undergo surgery than those with Thy-3a cytology ($p = 0.0001$). Among nodules with Thy-3a cytology, the mean size of cases undergoing surgery was 33.4 mm, which was significantly larger than that of 21.9 mm among cases not undergoing surgery ($p < 0.0001$). There was no significant difference in the incidence of calcifications among Thy-3a cases proceeding to surgery (8/67) versus those not undergoing surgery (6/42; $p = 0.77$).

Table 2. Final histological diagnosis

	Thy-3a (n = 109)	Thy-3f (n = 90)	p value
Surgery	67	84	0.0001
Cancer	9 (13.4%)	15 (17.9%)	0.51
Papillary carcinoma	7	10	
Conventional	4	4	
Follicular variant	3	5	
Oncocytic (Hürthle cell) variant	0	1	
Follicular carcinoma	2	3	
Hürthle cell carcinoma	0	2	
Incidental carcinoma outside biopsied nodule	5 (7.5%)	8 (9.5%)	0.77

Table 4. Outcome of Thy-3f cases undergoing more than 1 diagnostic FNA on different occasions

FNA results	Cases	Cases undergoing surgery	Malignancy
Thy-2 → Thy-3f	5	5	2
Thy-3f → Thy-2	0	0	0
Thy-3a → Thy-3f	10	9	2
Thy-3f → Thy-3a	1	1	0
Thy-3f → Thy-3f	1	1	0
Thy-3f → Thy-4/5	1	1	1
Total	18	17	5

Table 2 shows the final histological diagnosis according to cytological subcategory. The incidence of malignancy among Thy-3a cases was 13.4% and among Thy-3f cases 17.9%. The difference was not significantly different ($p = 0.51$).

Among the entire series, there were 60 nodules with Thy-3a cytology that had undergone more than 1 diagnostic FNA (excluding inadequate FNAs) and 18 nodules with Thy-3f cytology that underwent more than 1 diagnostic FNA. The results of the asynchronous FNAs and the outcomes of these cases are shown in tables 3 and 4.

Among the cases with asynchronous Thy-3a and Thy-2 (benign) results which proceeded to surgery, the incidence of malignancy was 25% (3/12; table 3). This was not significantly different from that in cases undergoing surgery after a single FNA showing a Thy-3a result (6/50; $p = 0.36$). The incidence of malignancy in cases with asynchronous Thy-3a and Thy-3f results undergoing surgery was 20% (tables 3, 4).

Within the Thy-3a category, there were no significant differences between patients with cancer and those without in age (43.9 vs. 51.3 years, $p = 0.16$) or nodule size (27.1 vs. 33.3 mm, $p = 0.25$). Similarly, there was no significant differences between patients with cancer and those without in the Thy-3f group in age (51.8 vs. 52.0 years, $p = 0.97$) or nodule size (29.0 vs. 34.0 mm, $p = 0.30$).

Discussion

Since the publication of the 2009 guidance document by the RCP [4], the subdivision of indeterminate (Thy-3) thyroid aspirates into either Thy-3a or Thy-3f has been incorporated into thyroid cytology reporting at our institution. The purpose of the present study was to investigate the malignancy rates in indeterminate thyroid nodules since the incorporation of this subclassification into our practice. Our results showed a slightly higher malignancy rate in Thy-3f cases (17.9%) than in Thy-3a cases (13.4%). However, the difference was not statistically significant.

To our knowledge, there are no published studies to date comparing malignancy rates in Thy-3a and Thy-3f nodules. Lobo et al. [5] reported Thy-3f to be associated with a 28% positive predictive value for malignancy. However, the number of Thy-3a cases undergoing surgery in their series was too small for analysis. There is some data from other researchers who devised their own systems for subdivision of Thy-3 aspirates into higher- and lower-risk categories before publication of the RCP guidelines, with a higher incidence of malignancy being found in the higher-risk categories [6, 7]. On the other hand, our malignancy rates are broadly in line with the expected risk of malignancy according to the RCP guidance document, wherein a Thy-3a diagnosis is expected to confer a 5–15% risk of malignancy and a Thy-3f diagnosis a 15–30% risk of malignancy [4]. Our results would also appear to be consistent with published series reported according to the Bethesda system, when the Thy-3f category is considered analogous to follicular neoplasm, and the Thy-3a category is considered analogous to the Bethesda category of AUS/FLUS [8, 9]. However, there is wide variation in the reported malignancy rates for these categories. Typical reported malignancy rates in the literature for follicular neoplasm cytology range between 16 and 35% [10–14] and for AUS/FLUS cytology between 4.5 and 22.5% [10–12, 15–19], but with malignancy rates as high as 27–48% reported by some authors [20–23].

Besides the variability in reported malignancy rates for the AUS/FLUS category, one of the other recognized

challenges for the Bethesda system has been the high variability in the use of this category [21, 24]. According to the National Cancer Institute State of the Science conference, the use of this category should be restricted to 5–7% of thyroid FNAs [3, 8, 9]. However, the reported range of cases reported as AUS/FLUS ranges from 1 to 29% [18, 19, 23, 25]. The RCP guidance document [4] does not give a recommended proportion for the Thy-3a category. In the present study 12.7% of all aspirates (131/1,032) were reported as Thy-3a, which is higher than the National Cancer Institute recommendation of 5–7%, but well within the norms of published data.

One of the major benefits of subclassification of indeterminate thyroid cytology into higher- and lower-risk subcategories is to facilitate the triage of cases for immediate excision (Thy-3f) versus those which may be managed conservatively, usually with repeat US-FNA (Thy-3a) [26]. Among the series classified according to the Bethesda system, support for a conservative management protocol for AUS/FLUS cases comes from series which have reported that up to half or more of such cases may be reclassified as benign by repeat FNA [19, 27, 28]. However, most cases undergoing repeat FNA in these studies did not undergo surgery and thus did not have histological correlation [27, 28], or no information regarding surgery was given [19]. Other authors have recently questioned the conservative management of AUS/FLUS lesions based on the high incidence of malignancy in cases which do undergo surgery [22]. In the present study, the risk of malignancy among Thy-3a cases was small, though not insignificant. Notably, among Thy-3a cases undergoing surgery which underwent FNA on a separate occasion which was reported as benign, the risk of malignancy was 25%, which was not significantly different from that of Thy-3a cases which underwent immediate surgery, suggesting that when histological correlation is available, the risk of malignancy in Thy-3a cases may not be significantly offset by FNA on a different occasion being reported as benign. However, nearly all cases with asynchronous benign and Thy-3a results undergoing surgery had a Thy-3a result following an initial benign result, and thus we do not know whether it would have made any difference if an initial Thy-3a result had been followed by a benign cytology.

The optimum management of Thy-3a cases remains controversial. Our findings would suggest that these cases have a significant risk of malignancy, which is not necessarily reduced by benign FNA on a separate occasion. Such cases should be discussed at a multidisciplinary meeting, with management decisions additionally in-

formed by other characteristics such as sonographic features, which may be useful in identifying patients with a higher risk of malignancy [29, 30]. In most cases, management options will be either immediate surgery or follow-up with repeat US-FNA. Where there is a high degree of suspicion based on adverse clinical or sonographic features, immediate surgery may be the preferred option. Surgery might also be considered for nodules >4 cm, as if such cases transpire to be cancers, then based on size criteria they will be upstaged to at least intermediate risk cancers [31]. For other cases, interval US-FNA may be reasonable, with a low threshold for surgery if repeat FNA is atypical or other adverse features develop. However, even if repeat FNA is benign, such cases should be kept under continued close follow-up.

Possible future directions for the further work-up of Thy-3a cases may include the use of genetic analysis panels, including testing for BRAF-V600E mutation [32–35] and immunocytochemistry [19]. However, the utility of BRAF-V600E mutation analysis in cases with low-risk Bethesda cytology has been disputed [36], and thus further research in this area is clearly needed.

Weaknesses of the present study include its retrospective nature, and the inability to exclude confounding of the analysis of malignancy rates between Thy-3a and Thy-3f cases due to a significantly greater proportion of Thy-3f cases undergoing surgery, or selection bias among Thy-3a cases which did proceed to surgery. However, this weakness is common to all studies examining the outcomes of low-risk thyroid cytology and is compounded by the very indolent natural history of most cases of thyroid cancer such that lack of significant nodule growth,

even over a lengthy period of follow-up, is not sufficient to infer absence of cancer [37]. A further weakness was the small numbers, particularly of patients undergoing repeat FNA, which may have left our study under-powered. Finally, we did not include an analysis of sonographic features which may be predictive of malignancy risk or be important in case selection for surgery. On the other hand, the strengths of this study include the universal and consistent application of the Thy system to all nodules undergoing FNA during the study period, with subdivision of nearly all Thy-3 cases into Thy-3a or Thy-3f, and the review of all cases with Thy-3 or higher risk cytology at multidisciplinary thyroid cancer meetings.

Conclusion

Although the risk of malignancy is slightly higher in thyroid nodules with Thy-3f cytology than Thy-3a cytology, the difference is not statistically significant. Great care should be taken in management decisions for patients with Thy-3a cytology results, with due consideration of other factors including nodule size and sonographic and clinical features. For cases not undergoing surgery, repeat US-FNA should be performed, with continued close follow-up of cases even with benign cytology.

Disclosure Statement

The authors have no conflicts of interest to declare. No funding was received for this study.

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