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RESEARCH ARTICLE

Reducing non diagnostic thyroid cytology using on-site adequacy assessment performed by junior medical staff

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ABSTRACT

Objective: To assess efficacy of bedside cytology assessment of thyroid fine needle aspirate samples performed by junior medical staff compared to cytologists.

Methods: Retrospective analysis was performed of 1490 thyroid fine needle aspirates. Samples were divided into three groups: cellular adequacy assessment performed by cytologists, interns, and no onsite adequacy assessment (blind). A 45-minute training session was provided to medical interns with the aim of identifying whether adequate cellular material was demonstrated, as defined by the Bethesda criteria. The primary outcome was the rate of nondiagnostic samples, and the secondary outcome was the number of fine needle aspirate passes required to reach sample adequacy.

Results: The incidence of non-diagnostic samples for the cytologist, blind, and intern groups were 6.90%, 17.1% and 14.0% respectively ($p<0.001$). There was no statistically significant difference in non-diagnostic rate between the blind and intern groups. Significantly more aspirates required more than two passes in the cytologist group (74.8%) and blind (94.7%) compared to the intern group (58.7%, $p<0.001$).

Conclusions: On-site adequacy assessment performed by cytopathologists is the gold standard for minimising non-diagnostic thyroid FNAs, however, medical staff with minimal anatomical pathology experience can be trained to perform on-site adequacy assessment and improve outcomes with the implementation of a simple targeted training program.

Keywords: Thyroid nodule, Thyroid ultrasound, Cytology, Aspiration biopsy.

Introduction

Thyroid nodules are a common occurrence within the general population, with a prevalence of approximately 27%[1-4]. The general incidence of thyroid nodules has substantially risen over the last decade resulting from increased ultrasound usage[5]. Most thyroid nodules are incidental and do not require further treatment, however a small proportion of these may be malignant and thus need to be identified in a timely manner[6-8]. Thyroid ultrasonography is the first step in assessment of thyroid nodules, and certain sonographic features including size, shape, echotexture and presence of calcification are predictors of potential malignancy[7,9-11]. The Thyroid Imaging Reporting and Data System (TIRADS) is a risk-stratification system that classifies thyroid nodules based upon their sonographic appearance and is used to guide further management: investigation with fine needle aspirate (FNA), observation or no further work up. (Table 1a and 1b)[12,13].

Table 1a. ACR TIRADS classification system

Sonographic feature	Points
Composition	
Cystic or spongiform	0 (automatically TIRADS 1)
Mixed cystic and solid	1
Solid or almost completely solid	2
Echogenicity	
Anechoic	0
Hyper/isoechoic	1
Hypoechoic	2
Very hypoechoic	3
Shape	
Wider than tall	0
Taller than wide	3
Margin	
Smooth	0
Ill-defined	0
Lobulated/Irregular	2
Extra-thyroidal extension	3
Echogenic foci (one or more options)	
None	0
Large comet-tail artifact	0
Macrocalcifications	1
Peripheral calcification	2
Punctate echogenic foci	3

Table 1b. ACR TIRADS classification system continued.

Total point score	TIRADS Classification	Likelihood of malignancy
0	TIRADS 1 – Benign	0.3%
2	TIRADS 2 – Not suspicious	1.5%
3	TIRADS 3 – Mildly suspicious	4.8%
4-6	TIRADS 4 – Moderately suspicious	9.1%
>6	TIRADS 5 – Highly suspicious	35%

Fine needle aspiration biopsy is widely accepted as the gold standard for diagnosis of thyroid nodules due to its high diagnostic accuracy and low risk of complications[14,15]. The main drawback of FNA, however, is the high rate of non-diagnostic tests of up to 30% due to inadequate sampling[16-21]. The incidence of nondiagnostic samples is dependent on the skill of the operator as well as the presence of a dedicated cytology technician to determine the adequacy of an FNA sample at the time of procedure[17,22-24]. In the case that a nondiagnostic sample was obtained, current literature recommends repeat FNA[19,25].

During the COVID pandemic, there was a paradigm shift in the implementation of the thyroid FNA clinic in the department of Radiology at Monash Health, a large quaternary teaching centre in Victoria, Australia. Traditionally all FNA samples were assessed for cellular adequacy at the bedside by a cytologist who would direct repeat samples in the event of an acellular/paucicellular specimen. The introduction of an onsite cytology service at Monash Health had previously reduced the nondiagnostic FNA rates to 14.6% from 36.7% (as compared to blind FNA) as illustrated by Tan et al[26]. The 2020 COVID pandemic related staffing shortages disrupted this service with withdrawal of onsite cytology support; the FNA service was continued without onsite cytology assessment leading to a rebound in non-diagnostic rates. These patients were then recalled to have a repeat procedure, which further stressed an already long waiting list for thyroid FNAs. As a result, a new initiative was implemented from August 2022 whereby a medical intern (first year doctor) working in the department underwent a 45-minute training session with a consultant pathologist to determine cellular adequacy of a FNA slide specimen. A total of three interns were trained over one academic year.

The aim of this study was to determine if medical interns with minimal training could improve the diagnostic yield of thyroid FNAs and thus reduce the burden of a busy thyroid clinic, improve patient access to key health services, and reduce unnecessary invasive testing.

Materials and Methods

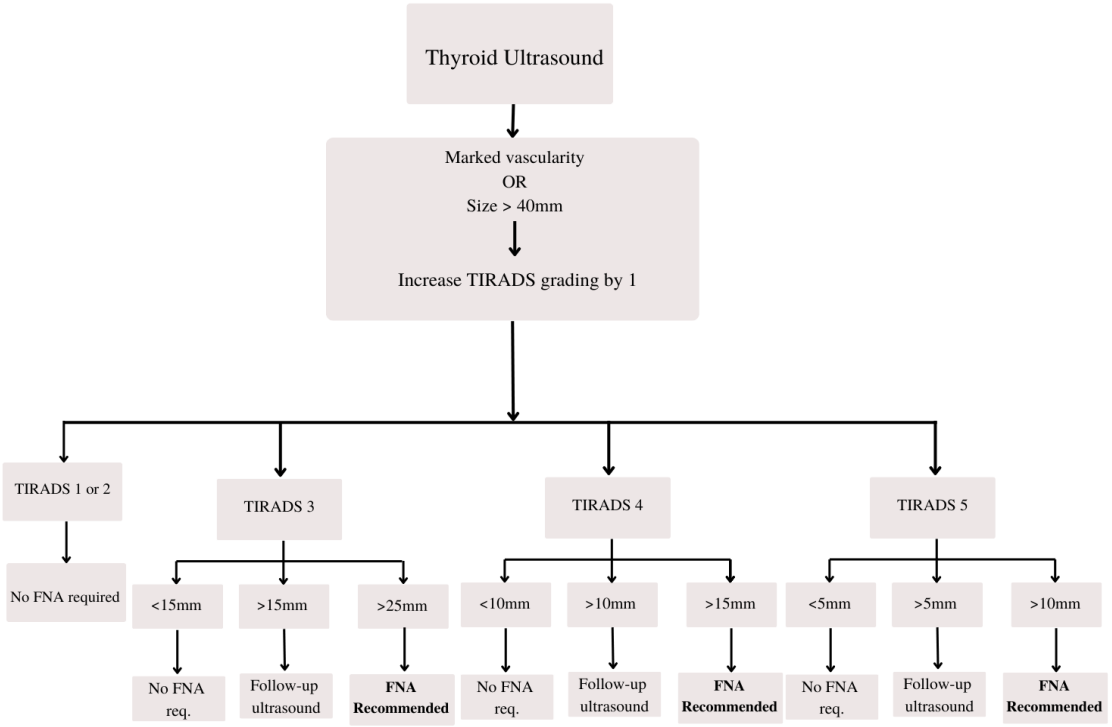
A retrospective analysis was performed of 1490 cases of thyroid FNAs performed by the diagnostic imaging department at a major tertiary hospital over the course of 6 years. All patients referred for FNA had thyroid nodules identified on a prior thyroid ultrasound. Thyroid ultrasounds were reported in accordance with the TIRADS classification system - there are multiple variations on this

classification system developed by different institutions, including the ACR TIRADS, K-TIRADS, and EU-TIRADS, however in this study referral for FNA was based on the American College of Radiology (ACR) TIRADS classification guidelines[13,27,28]. This classification system has been prospectively evaluated and has demonstrated a high degree of sensitivity[29]. Nodules classed as TIRADS 3 and above, in combination with meeting a certain size cut-off were deemed at increased risk and had FNA recommended (Figure 1). In addition, the TIRADS score for all nodules greater than 4 cm was increased by one point based on institutional guidelines as these have been shown to carry a significant risk of malignancy[30]. Significant vascularity of the nodule was also assessed and assigned one point as per institutional guidelines as malignant nodules have been demonstrated to show increased vascularity[31,32]. Marked vascularity was defined as significantly increased doppler flow within the nodule compared to surrounding thyroid tissue.

FNAs were performed either by radiologists or by radiology trainees undergoing accredited radiology training under the Royal Australian and New Zealand College of Radiologists (RANZCR); the degree of operator experience varied depending on roster allocations. Indirect supervision was provided by a consultant radiologist at all times. For the purposes of this study a junior operator was defined as either a first or second year radiology trainee, whilst a senior operator was any radiology trainee with three or greater years of seniority, or a consultant radiologist.

FNA samples were obtained using a 25-gauge needle under sonographic guidance. At least two separate passes were made into each thyroid nodule, and samples were sent as slides as well as washings in CytoLyt solution for cell block preparation. A haematoxylin and eosin stain was immediately performed on each slide and examined under light microscopy to assess for cellular adequacy. Additional passes were made based upon the bedside cellular adequacy assessment or in cases without adequacy assessment, clinician judgment of the macroscopic appearance of the sample was applied. Repeat passes were continued until an adequate sample was identified or up to a maximum of 5 passes.

Figure 1. Recommendations for FNA based on TIRADS grading



Ethics approval was obtained via the Monash Health Human Research Ethics Committee. Data was collected in a de-identified format by a senior sonographer overseeing the FNA clinic. Subsequent cytology results were followed up on the hospital's electronic medical record (EMR) system. The cytology diagnosis was reported according to the Bethesda system for reporting thyroid cytopathology[33]. Of particular interest in this study was the subgroup identified as Bethesda class I or "nondiagnostic or unsatisfactory". The key criterion for a non-diagnostic sample is acellularity, defined as less than 6 clusters of follicular cells each containing a minimum of 10 cells. However, there are other criteria which are more ambiguous, including acellular specimens containing abundant colloid, or specimens containing only cyst contents (macrophages). In these cases the diagnostic category was determined by the expert opinion of the reporting pathologist.

A 45-minute face to face teaching session was organized for the medical radiology intern at the commencement of each 10-week rotation. All interns were trained by the same anatomical pathologist. The primary purpose of the tutorial was to help the medical intern differentiate between thyroid follicular cells and other cells including macrophages, lymphocytes, and erythrocytes. The medical intern was provided example slides from each

Bethesda diagnostic category to gain an appreciation for a broad spectrum of potential cellular morphology. The focus for the intern was to identify whether there was adequate cellular material within the sample obtained, as defined by the Bethesda criteria.

Subgroup analysis was performed between three groups: Adequacy assessment performed by a cytologist (Cytologist group), no assessment (Blind FNA group), and assessment performed by a medical intern (Intern group). Continuous data was analyzed using one-way analysis of variance (ANOVA). Student's T-test was used to compare means of two continuous variables. Categorical data was compared using the Pearson Chi-Squared test. P values of less than 0.05 were deemed statistically significant.

The primary endpoint was the rate of nondiagnostic samples in each subgroup. The secondary outcome was the number of passes required to reach sample adequacy.

Results

A total of 1490 FNAs of thyroid nodules were undertaken between the dates of 01/01/2017 and 07/03/2023. Of these, 787 FNAs had bedside cytology performed by a pathology technician, 114 performed by a diagnostic imaging intern, and 589 FNAs were performed blind (Table 2). The mean patient age was higher for the intern group (62.4±13.6 years) compared to the cytologist (58.5±15.1 years) and no cytology groups (59.6±15.2 years, p=0.0244). There was no statistical difference in sex distribution between subgroups (p = 0.208). The mean nodule diameter was 26.4 ± 13.7mm, and there was no difference in nodule size between groups (p=0.449). 25% of nodules were graded as TIRADS 3 or below, 52.8% were TIRADS 4, and 22.2% were TIRADS 5. There was no difference in the distribution of TIRADS scoring between the three subgroups (p=0.309).

Two passes were performed in 18.9% of FNAs; 56.4% of nodules required 3 passes and 24.7% required 4 passes. Significantly less FNAs were completed in only two passes in the cytologist group (25.2%) and blind FNA (6.4%) compared to the intern group (41.2%, p<0.001). More than twice as many patients underwent a third pass in the blind group compared to the intern group (68.9% vs 33.3%, p<0.001)). More third passes were also performed in the cytologist group compared to the intern group (50.3% vs 33.3%, p<0.001)). There was no difference in the number of FNAs requiring four or more passes between the three groups.

Table 2. Thyroid FNA subgroup analysis.

	Cytologist	Blind FNA	Intern	Total	
N	787	589	114	1490	
Sex, F (%)	580 (73.7%)	438 (74.3%)	92 (81.0%)	1110 (74.5%)	p=0.208
Age (SD)	58.5 (15.1)	59.7 (15.2)	62.4 (13.6)	59.2 (15.0)	p=0.0244
Number of passes					p<0.001
2	198 (25.2%)	37 (6.35%)	47 (41.2%)	282 (18.9%)	
3	396 (50.3%)	406 (68.9%)	38 (33.3%)	840 (56.4%)	
≥4	193 (24.5%)	146 (24.8%)	29 (25.4%)	368 (24.7%)	
Bethesda					P<0.001
I	54 (6.9%)	101 (17.1%)	16 (14.0%)	171 (11.5%)	
II	572 (72.7%)	395 (67.1%)	83 (72.8%)	1050 (70.5%)	
≥III	161 (20.4%)	93 (15.8%)	15 (13.2%)	269 (18.0%)	
Seniority					p<0.001
Junior	320 (40.7%)	227 (38.5%)	75 (65.8%)	622 (41.7%)	
Senior	467 (59.3%)	362 (61.5%)	39 (34.2%)	868 (58.3%)	
Nodule size mm, (SD)	26.1 (14.3)	26.6 (13.0)	27.7(13.3)	26.4 (13.7)	p=0.449
TIRADS Classification					p=0.309
≥3	206 (26.2%)	136 (23.1%)	30 (26.3%)	372 (25.0%)	
4	396 (50.3%)	331 (56.2%)	59 (51.8%)	786 (52.8%)	
5	185 (23.5%)	122 (20.7%)	25 (21.9%)	332 (22.2%)	

869 FNAs were performed by senior operators, and 621 were performed by junior operators. The non-diagnostic rate of FNAs performed by senior operators was lower (10%) compared to junior operators (13.5%, p=0.0358) (Table 3). 65.8% of FNAs in the intern group were performed by junior operators, which was significantly greater than both the no cytologist (38.5%) and cytologist group (40.7%, p<0.001).

Table 3. Comparison of FNA non-diagnostic rate of senior versus junior operators.

	Junior	Senior	p=0.0358
Diagnostic	537 (86.5%)	782 (90.0%)	
Non-diagnostic	84 (13.5%)	87 (10.0%)	

In total, 171 specimens yielded non-diagnostic cytology results (11.5%). Of the samples which were adequate for diagnosis, 1050 (70.5%) were benign, whilst 269 (18%) were Bethesda III or above (suspicious for malignancy or malignant). The lowest incidence of non-diagnostic FNA (Bethesda I) was in the cytologist group (6.90%) compared to the blind FNA (17.1%) and intern groups (14.0%, $p<0.001$). There was no statistically significant difference in non-diagnostic rate between the blind FNA and intern groups ($p=0.626$). 72.7% of nodules in the cytologist group were benign, which was not significantly different compared to the intern (72.8%) and blind FNA group (67.1%) ($p=0.151$). The highest incidence of nodules suspicious for malignancy or malignant (Bethesda III or greater) was in the cytologist group (20.4%), compared to both the blind and intern groups, were which 15.8% and 13.2% respectively ($p=0.031$).

Discussion

The primary outcome of this retrospective study was to determine whether bedside cytology performed by medical interns with minimal cytopathology training would be comparable to cytologists, and ultimately reduce the non-diagnostic rate when compared to blind FNA. The non-diagnostic rate of both blind FNA and intern cytology exceeded the Bethesda system's recommendation of an overall non-diagnostic rate of less than 10%[33], though was comparable to non-diagnostic rates quoted in pre-existing literature[19,34]. The data definitively demonstrated that cytology performed by pathology technicians reduced the non-diagnostic rates as compared with blind FNAs and onsite assessment by interns. It should be noted, however, that in comparison to Tan et al's study which was previously conducted at the same health service, the non-diagnostic rate of cytologists was comparable to that of intern cytology in the current study (14.7% vs 14.0% respectively)[26].

A Systematic review published by Witt et al (2013) demonstrated the benefits of on-site adequacy assessment with pooled meta-analysis showing an improvement in rate of diagnostic FNA from 83% to 92%[24]. In this review, all on-site adequacy was performed by qualified cytopathologists. The non-diagnostic rate of adequacy assessment performed by cytopathologists as well as the non-diagnostic rate of blind FNA were both comparable to this current study. However, this review also highlighted the heterogeneity in clinical practice across different centers; notably, there was limited data reported on the number of passes performed for each FNA, which has a significant impact on the diagnostic yield. For example, in Zhu's et al's study (2007), it was demonstrated that the non-diagnostic rate decreased from 25% with three or less passes to 1.4% for 6 passes[17]. Furthermore, the epidemiology of thyroid nodules can vary significantly across population cohorts and with time, which can ultimately affect the yield of thyroid FNAs. Therefore, the cumulation of patient factors and differences in clinical practice make it difficult to make a direct comparison between this study and prior studies. This may also explain the difference in non-diagnostic rate of FNA performed by cytologists between this study and Tan et al's data which was collected at the same center[26].

One potential benefit of intern cytology demonstrated in this study was the significantly lower number of passes required per nodule. Cytology performed by an intern was seven times more likely to only require two passes per nodule compared to blind FNA. The lower threshold to perform further sampling in the blind FNA group may stem from uncertainty of the operator due to the inability to microscopically assess the sample; thus, further samples may be taken to reduce the likelihood of a non-diagnostic FNA. However, despite more than twice as many third passes being taken, there was no improvement in diagnostic yield compared to the intern group. This suggests that intern cytology was able to accurately identify samples which were definitively adequate, thus avoiding the need for unnecessary sampling, reducing procedure time and improving patient comfort. Whilst cytologists demonstrated a lower non-diagnostic rate compared to the intern group, more passes were also required to achieve this, which may partly explain the difference in non-diagnostic rate between cytologists and interns.

Unfortunately, during the transition from blind FNA to intern cytology, there was concurrently a shift in the rostering of the thyroid FNA clinic, with junior operators being more frequently rostered to perform the procedures. This was reflected in the results, with almost twice as many FNAs being performed by juniors in the intern group. Operator experience has been shown to affect non-diagnostic rate both in this study and in previous studies, thus adding a confounding variable in this study[16,35]. Resultantly, the true benefit of intern cytology may be underestimated in this study.

Further limitations of this study are reflective of the fact that the intern cytology program is a newly implemented initiative with limited prior experience to draw upon. As a result, the low sample size of intern cytology render it more difficult to ascertain the true efficacy of this program; prospective data collection with a larger sample size would be a beneficial follow-up study to further assess its viability. Additionally, the teaching program is currently in its first iteration and needs further refinement to ensure consistency and improved reliability. One discrepancy described previously was the difference in the rate of repeat sampling (more than 2 passes) between cytologists and interns; the lower incidence of repeated sampling in the intern group likely represents a higher threshold to repeat FNAs which may result in more inadequate samples being accepted. The teaching program could be adjusted to reflect this to improve the sensitivity and diagnostic yield of future iterations of interns at the slight cost of specificity.

In summary, the data presented in this study demonstrates that on-site adequacy assessment performed by a qualified cytopathologist remains the gold standard for minimizing non-diagnostic thyroid FNA rates. However, this pilot has demonstrated the potential of intern-performed cytology to be a simple, fast, and cost-effective way of improving the efficacy of thyroid FNAs. More importantly, this initiative has brought forth a new framework for performing thyroid testing, highlighting that a simple teaching program can significantly improve outcomes for thyroid testing by reducing the need for unnecessary sampling which will increase clinic efficiency and be better tolerated by patients.

Additionally, it has demonstrated that cytology may not necessarily have to be performed by highly trained cytologists - whom many centers may not be able to readily access - and can in fact be performed with minimal training. This gives hospitals much more flexibility in resource utilisation and raises the possibility of recruiting either more junior doctors or nursing staff into this role. Multiple considerations must be made, however, to balance the benefits of intern cytology (decreased cost, greater accessibility) with the potential risk of increased non-diagnostic rates compared to dedicated cytologists.

Conclusion

On-site adequacy assessment performed by cytopathologists is the gold standard for minimising non-diagnostic thyroid FNAs, however, medical staff with minimal anatomical pathology experience can be trained to perform on-site adequacy assessment and improve outcomes with the implementation of a simple targeted training program.

Conflict of Interest Statement:

The authors have no conflict of interest to declare.

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