ORIGINAL ARTICLE

MANAGEMENT AND ASSESSMENT OF INDETERMINATE (U3) THYROID NODULES: A 5-YEAR MULTISITE RETROSPECTIVE STUDY

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Background: The U grading of Ultrasound scan (USS) is used to assess the likelihood of malignancy in a thyroid nodule and help determine those that warrant an FNAC confirmation. All those of a U3-5 warrant an FNAC for confirmation and typing. This study aims to review the follow-up practice and the likelihood of picking up a malignancy on subsequent USS and FNAC, for those determined as an indeterminate U3 nodule. **Methods:** We retrospective reviewed the trust database (Portal) for patients who had a U3 nodule reported on USS identified, and clinical, operative and outcomes data were analysed. **Results:** 258 scans were identified over a 5-year period. The average age was 59 (range 15-95) years old at first USS with a female to the male sex ratio of 4:1. The average number of USS that each patient prior to final diagnosis had averaged at 2.8 (range 1–12). Of those with an initial Thy status, 64 (33%) were benign (Thy2) and a further 49 (25%) were non-diagnostics (Thy1). Over time, only 7 nodules were upgraded to a potential malignancy. Of those who underwent surgery, a final histological diagnosis was obtained in 41 cases. Only Thy1, 2 and 3f produced benign final histology results. **Conclusion:** For those indeterminate (U3) nodules of Th1-3f, electing for a watch and wait management strategy is reasonable for up to 2.5 years and 4 follow-up scans at an interval of 6–12 months should be implemented. A Thy2 result on a U3 nodule should not be taken as completely reassuring, a high index of suspicion of malignancy must be maintained.

Keywords: Thyroid nodule; Diagnostic imaging; Fine-needle aspiration cytology; US scan

Citation: Patel R, Conybeare A, Panesar H, Badrol S, Sood S. Management and assessment of indeterminate (U3) thyroid nodules: A 5-year multisite retrospective study. J Ayub Med Coll Abbottabad 2023;35(2):216–9.

DOI: 10.55519/JAMC-02-11305

INTRODUCTION

In 2016, the Journal of Laryngology and Otology produced new guidance for the management of thyroid cancer in the United Kingdom, based on the 2014 British Thyroid Association (BTA) Guidelines.[1] This stated that ultrasound scanning (USS) of the nodule or goitre is a crucial investigation in guiding the need for fine needle aspiration cytology (FNAC) and that FNAC should be considered for all nodules with suspicious ultrasound features (U3-U5).[1] The U and Thy systems are now the most commonly used in the UK.[2]

The ultrasound "U" classification of thyroid nodules has been developed by the British Thyroid Association (BTA) as part of their 2014 guidelines on the management of thyroid cancer 1.

It allows for the stratification of thyroid nodules as benign, suspicious, or malignant based on ultrasound appearances termed U1-U5. This is used to streamline further investigation and management. The U grading of USS is used to assess the likelihood of malignancy in a thyroid nodule and help determine those that warrant an FNAC confirmation. U1 (normal thyroid tissue) has a 0% malignancy rate; U2 (benign nodule) has a 13.6–18.2%; U3 (indeterminate/equivocal) has a 30.4–39.4%; U4 (suspicious) has a 40–65.9%; and U5 (malignant) has an 85.1–100% chance of being a malignant nodule.[3,4] All those of a U3-5 warrants an FNAC for confirmation and typing.[5] The Thy system of FNAC interpretation predicts the likelihood of a nodule being malignant. Thy5 (diagnostic of malignancy) has a 98–99% malignancy rate. Thy4 (suspicious of malignancy) has a 68-70% malignancy rate; Thy3 (indeterminate) has a 9.5–43% chance of malignancy (higher with Thy3f than Thy3a); Thy2 (benign) still has a malignancy rate of <3% and Thy1 (non-diagnostic) has a 4.5–8.5% malignancy rate[5]. Therefore, these results are taken in conjunction with the USS and a Thy2 and Thy1 should be repeated (initial sample only taken due to USS suspicion).[1,5]

The new guidance recommends that U1 and U2 nodules do not require an FNAC unless certain statistically significant risk factors for malignancy are identified.[1,4]

These include:

- Age less than 20 years or over 60 years
- Firm nodule on palpation
- Rapid nodule growth
- Fixation to adjacent structures
- Vocal cord paralysis
- Regional lymphadenopathy
- History of neck irradiation
- Family history of thyroid cancer
- U3 to U5 nodules require further investigation with FNAC

Diagnostic hemithyroidectomies and total thyroidectomies were recommended for those with Thy3f or Thy4 (follicular lesion or suspicious of thyroid cancer); and with tumours greater than 4cm or with suspicious features respectively.[1] U2 and U1 lesions can be reassured and discharged.[5] However not all patients fit nicely into these categories of reassurance or surgery and many end up having repeated USS and FNACs, especially those U3 Thy1-3 nodules. Add to this the increase in the discovery of incidental thyroid nodules and the back log from the coronavirus pandemic there is an increasing burden on our radiology departments that warrant a degree of rationale[6]. We, therefore, decided to review our own departments' follow-up practice and the likelihood of picking up a malignancy on subsequent USS and FNAC, for those determined as a U3.

MATERIAL AND METHODS

This is a retrospective analysis of The Shrewsbury and Telford Hospitals NHS Trust current usual practice over a 5-year period (1 January 2017 – 31 December 2021). A search on our PACS system for "U3 nodule" on USS over this period produced 258 results. 58 records were excluded as being multiple episodes for the same patients. One record was excluded as a U4 being mistyped in the report. One episode was excluded as being a parathyroid adenoma when correlated with parathyroid imaging using technetium-99m sestamibi (MIBI) and confirmed on subsequent surgery.

Four patients had yet to be seen by ENT and no FNAC had yet been obtained (initial USS reports in our department are returned to the requester with a suggestion of FNAC needing to be requested if U3-5). 194 patients were therefore included. Their electronic records were accessed for clinic letters, histology results cytology reports and USS reports. Data was collected on age at first USS, sex, past medical history, number and dates of any follow-up scans, along with any U stage changes, FNAC attempts, results and changes, thyroid surgery and other management, final histology and date of death (with permission of institutional board review.

RESULTS

The average age was 59 (range 15–95) years at first USS with a female-to-male sex ratio of 4:1 (Figure-1). Four patients died of unrelated causes (2 breast malignancies, one pneumonia and one severe sepsis). Of those alive, 66 are still being followed up, 12 for a proven malignancy. 54 are therefore still in the system without a proven malignancy. 2 of these are to review the contralateral side and one refused to be discharged after being followed up with repeat USS and FNAC for 7 years with no change.

The average number of USS that each patient prior to final diagnosis had averaged at 2.8 (range 1–12). 101 of these were originally by a radiographer who cannot perform an FNAC, therefore would have been referred back to the requester, advising USS guided FNAC be requested. 143 had more than 2 USS however, with 10 having more than 4 USS. The mean average amount of time between the first and second USS was 81 (9–601) days, between the second and third was 156 (7–690) days, between the third and fourth was 158 (15–756) days and between the fourth and third USS was 246 (42–1117) days. Of the initial Thy status, 64 (33%) were benign (Thy2) and a further 49 (25%) non-diagnostic (Thy1). 10 (5%) were too deep to obtain an FNAC, however, 31(16%) were just not done (Figure-2). Twenty of these Thy2 however were downgraded to U2 on subsequent USS. A further 2 were superseded by a more invasive malignancy, 3 are more in keeping with thyroiditis, 1 is under 16 and has been referred to the paediatric thyroid team, 1 opted straight for a diagnostic hemithyroidectomy and 2 are still pending cytology results. There is no obvious reason why the other two have not had a FNAC.

Over time, only 7 nodules were upgraded to a potential malignancy (Figure-3), the last being at 976 days (2.7 years) in a patient being treated for a more invasive concurrent malignancy first and choosing to continue a watch and wait management during this time. This was all within 6 USS (Figure-4). Most were within 3 USS and 240 days (0.66 years). Of those who underwent surgery and a final histological diagnosis was obtained (41(21%) with a further 2 patients on the waiting list), 9 (22%) were malignant with a further 1 non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). Figure-5 shows the results in relation to the Thy status. Only Thy1, 2 and 3f produced benign final histology results, although interestingly as many Thy2 FNACs produced final malignant histology as benign, indicating the importance of maintaining suspicion with a U3 USS (although the numbers are small). 19% of Thy1 (high compared with published data) and 15% Thy3f were confirmed malignant (low compared with published data,[1,5] however when put with the Thy3a, it was in keeping (27%) and may just be more in related to the low numbers).

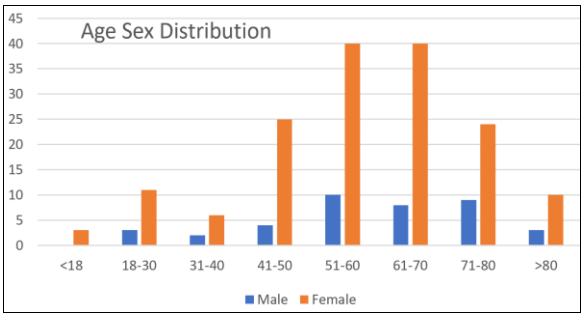

Figure-1: Average age (years) at first USS with a female-to-male sex ratio

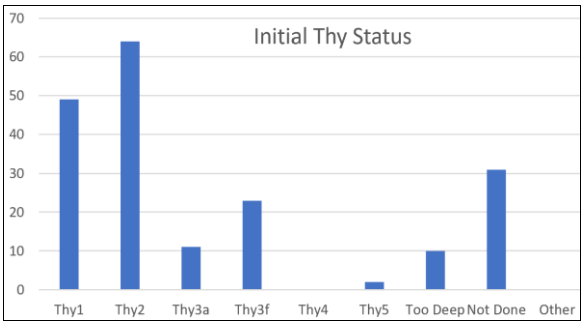

Figure-2: Initial Thy status of patients

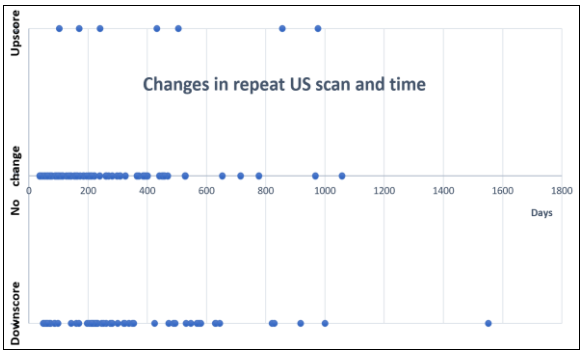

Figure-3: Changes in repeat USS at the time (days)

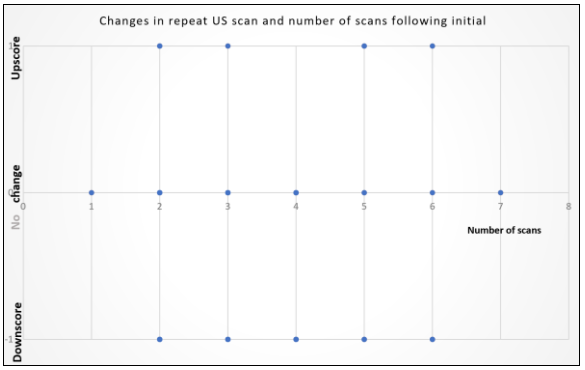

Figure-4: Changes in repeat USS at the time (days) and the number of scans after the initial scan (n)

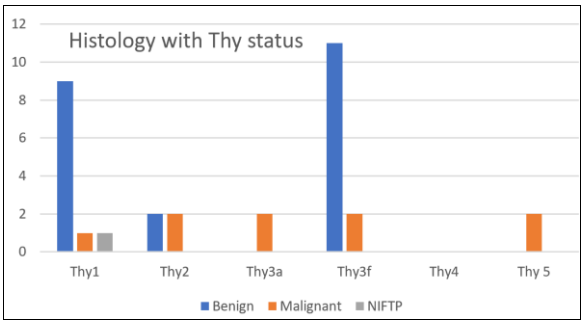

Figure-5: Histology Classification with Thy Status

DISCUSSION

Some thyroid nodules can elude initial diagnosis with USS (U staging) and FNAC (Thy status) and can end up having multiple repeat USS and FNAC tests. This is both inconvenient for the patient and excessive use of limited resources, particularly in the post-coronavirus pandemic radiology department. Add to this the increasing number of diagnosed thyroid nodules and our limited resources begin to become quite stretched.[3] It is therefore important for both the clinician and patient to have some guidance as to how long to continue investigations before a benign nodule can safely be assumed. From the review of the data in our department, no malignancy was found after 976 days from the first USS and even this one had valid reasons why diagnostic surgery was not undertaken by the patient (despite being offered). No guidance if 100% safe (U2 nodules have a 13.6–18.2% malignancy rate)[3,4] and clinical suspicion must be taken into account. However, for those indeterminate (U3) nodules of Th1-3f electing for a watch and wait for management, it is reasonable to limit this to 2.5 years and 4 follow-up scans at an interval of 6–12 months as suggested by Arambewela.[3,7]

However, it must also be noted that a Thy2 result on a U3 nodule should not be taken as completely reassuring as we had two U3 Thy2 patients have a final histology of malignancy and therefore an index of suspicion must be maintained.[8,9] Certainly, a repeat USS & FNAC after an interval of time would not be unreasonable.[9,10]

CONCLUSION

For those indeterminate (U3) nodules of Th1-3f, electing for a watch and wait management strategy is reasonable for up to 2.5 years and 4 follow-up scans at an interval of 6–12 months should be implemented. However, it must also be noted that a Thy2 result on a U3 nodule should not be taken as completely reassuring as we had two U3 Thy2 patients have a final histology of malignancy and therefore a high index of suspicion must be

maintained. A repeat USS & FNAC after an interval of time would not be unreasonable as an additional management strategy.

Limitations: The data set used here, although, over a 5-year period, only one institution's data set and therefore differences may be found across sites. We, therefore, recommend further studies in other institutions before our recommendations are considered more nationally. In addition, the number of full final histologies is small and therefore could skew the data set. Some data is yet to be completed as patients are still in the system. It would be important to instigate the suggested changes within our clinical setting and re-evaluate the results of the changes to enable a more accurate data set.

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Acknowledgement: None Stated.

Patient consent: Patient consent for publication Obtained

Provenance and peer review: Not commissioned; externally peer-reviewed.

AUTHORS' CONTRIBUTION

RP, AC, HP are the first authors of this article. RP, AC, performed data collection and wrote the manuscript. RP, AC, HP, SB performed data collection and reviewed drafts of the manuscript. RP, HP, SS reviewed drafts of the manuscript. SS designed the study and reviewed drafts of the manuscript. All authors have reviewed the final version and have consented to publication.

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Submitted: September 12, 2022	*Revised: October 17, 2022*	*Accepted: December 6, 2022*

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