

Main Article

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Abstract

Objective. British Thyroid Association 2014 guidelines emphasised ultrasound assessment of nodules. One ultrasonographic differentiator of debatable relevance is intra-nodular vascularity. This is the first UK study conducted to address this question.

Methods. Ultrasound reports for thyroid surgery patients over 10 years were retrospectively reviewed. Reports documenting ‘intra-nodular vascularity or flow’ were analysed. Reports identifying peripheral vascularity only or no intra-nodular flow formed the control group. Concordance with final histology was used to determine the odds ratio for malignancy.

Results. A total of 306 patients were included, and 119 (38.9 per cent) nodules demonstrated intra-nodular vascularity. Of these, 60 (50.4 per cent) were malignant compared with 42 per cent in the control group. Intra-nodular vascularity was not a statistically significant predictor of malignancy with an odds ratio of 1.39 ($p = 0.18$, 95 per cent confidence interval, 0.86–2.23).

Conclusion. Intra-nodular vascularity in isolation was not a reliable predictor of malignancy. This supports other world literature studies. Although intra-nodular flow should not be relied upon in isolation, interpretation in conjunction with other suspicious findings enhances the predictive value.

Introduction

According to data from Cancer Research UK, thyroid cancer is the 20th most common cancer in the UK, accounting for 1 per cent of all new cancer cases in 2016 with 73 per cent of cases occurring in females and 27 per cent in males. In 2016, UK thyroid cancer incidence rates (European age-standardised) were reported as 8.1 per 100 000 people for females and 3.2 per 100 000 people for males.¹

Despite stable survival rates, the incidence of thyroid cancer appears to be increasing.² It is largely agreed that better imaging detection of incidental microcarcinomas is the main reason for the rising incidence, especially with the increased use of positron emission tomography (PET) scanning for staging or response assessment of malignancy.³ Notably, it is widely established that approximately 30 per cent of 18-fluorodeoxyglucose-avid incidental thyroid nodules detected on PET scanning represent thyroid cancer.⁴ Another contributing factor is the increased detection of incidental earlier stage cancers, particularly papillary thyroid cancers, when thyroid surgery is carried out for presumed benign disease.⁵

Because thyroid nodules are common but thyroid cancer is relatively rare, accurate assessment via ultrasound is critical to determine the need for further cytological evaluation, which is indicated for nodules with indeterminate, suspicious or malignant appearances. To facilitate standardised sonographic assessment of thyroid nodules, the British Thyroid Association guidelines⁶ recommend use of the ‘U’ grading system (see Table 1 below, adapted from the UK National Multidisciplinary Guidelines for Management of Thyroid Cancer).²

As a consequence of this, the quality and reliability of reported findings is of paramount importance. One particular finding that has led to controversy is intra-nodular vascularity, also described as mixed or central vascularity. Although some studies have proposed that intra-nodular vascular flow on colour Doppler sonography may be associated with thyroid malignancy, many studies and meta-analyses outside the UK conclude that this is not a statistically significant predictor of malignancy in isolation.^{7,8,9} Our aim was to conduct the first UK study, to our knowledge, to further address this question.

Materials and methods

All ultrasound reports for patients undergoing thyroid surgery for indeterminate or suspicious nodule(s) at our institution were retrospectively reviewed over a 10-year period from November 2008 to November 2018. Data including age, gender, ultrasound findings and final histopathological diagnosis were obtained. If the ultrasound was reported at another institution and the report was unavailable despite request, these cases were excluded from the study.

Table 1. U grading of thyroid nodules

U1 normal	U2 benign	U3 indeterminate/equivocal	U4 suspicious	U5 malignant
Normal thyroid tissue	Halo, iso-echoic or mildly hyper-echoic, cystic change with or without ring down sign, microcystic/spongiform, peripheral eggshell calcification, peripheral vascularity	Homogeneous, hyper-echoic, solid, halo (follicular lesion), equivocal echogenic foci, cystic change, mixed/central vascularity	Solid, hypo-echoic or very hypo-echoic, disrupted peripheral calcification, lobulated outline	Solid, hypo-echoic, lobulated or irregular outline, microcalcification, globular calcification, intra-nodular vascularity, shape (taller than wide), characteristic associated lymphadenopathy
No follow up required	No follow up required: routine fine needle aspiration cytology not recommended unless high level of clinical suspicion of thyroid cancer	Fine needle aspiration cytology	Fine needle aspiration cytology	Fine needle aspiration cytology

All ultrasound reports with findings of 'intra-nodular vascularity or flow' or 'mixed or central vascularity' were analysed. Reports identifying peripheral vascularity only or demonstrating no intra-nodular flow formed the control group.

Concordance with final histology was used to perform a univariate regression analysis to determine the odds ratio for detecting malignancy for this particular sonographic finding. All analyses were conducted using the Stata® statistics software package.

Because this was a retrospective study with no change in intervention proposed, ethical committee approval was not required.

Results

A total of 306 patients were included in the study. The mean age was 48.6 years with a male-to-female ratio of 22.9:77.1 per cent.

A total of 119 (38.9 per cent) nodules demonstrated intra-nodular vascularity with final histology later confirmed post-operatively. In total, 167 nodules were benign (54.6 per cent) and 139 nodules were malignant (45.4 per cent).

Of the nodules demonstrating intra-nodular flow, 60 (50.4 per cent) were malignant compared with 42.2 per cent (79) in the control group. The results are summarised in the form of a flow chart in [Figure 1](#).

Data analysis using the Stata statistics software package was used to calculate the odds ratio for malignancy attributed to the presence of intra-nodular vascularity or flow.

Intra-nodular vascularity was not a statistically significant predictor of malignancy with an odds ratio of 1.39 ($p = 0.18$, 95 per cent CI, 0.86–2.23).

Discussion

Intra-nodular vascularity in isolation did not appear to be a reliable predictor of thyroid malignancy. This supports the majority of studies in the world literature.^{7,8,9} Notably, this group had a 50.4 per cent malignancy rate which at first glance appears more significant than the commonly quoted 25–30 per cent malignancy rate for thy3f nodules, many of which will undergo diagnostic excision.^{10,11} However, in our series, all nodules had one or more additional features suspicious enough to warrant surgery (e.g. solid nodule, equivocal echogenic foci, disrupted peripheral calcification, microcalcification, presence of pathological lymph nodes, hypoechogenicity, 'taller-than-wide'). The only difference being that in one group, the nodules additionally demonstrated intra-nodular

flow. This is evidenced by the fact that the control group also had a reasonably high malignancy rate of 42.2 per cent.

Because the incidence of thyroid nodules is high but the prevalence of thyroid malignancy is relatively low, there has been considerable interest in determining which sonographic features confer the greatest accuracy for reliably predicting malignancy. A recent meta-analysis by Khadra *et al.* in 2016 showed that intra-nodular flow on Doppler sonography did not accurately predict malignancy.⁹ Moreover, other findings such as nodule size, calcifications, echogenicity, margins and shape also did not appear to accurately predict malignancy when looked at individually. Indeed, the authors noted that no individual sonographic feature reliably differentiated between benign and malignant thyroid nodules.

However, several studies suggest that interpreting intra-nodular vascularity in combination with other suspicious ultrasound findings improves the predictive value.^{12,13} For example, Sebag *et al.*¹³ noted that the combination of hypo-echogenicity, microcalcifications and intra-nodular vascularity increased the specificity and positive predictive value for detecting malignancy. Unfortunately, attempts at multivariate analyses in our study proved unreliable because of collinearity, making interpretation of potential associations difficult and inconclusive.

Our intention was to analyse the histopathology of all nodules removed for suspicion of thyroid cancer, comparing them with their ultrasound reports. We divided the findings into two groups, namely those with and those without central vascularity to study the effect this finding had on malignancy rate. We found it made no difference, and we note that the North American ultrasound classification system, Thyroid Imaging, Reporting and Data System,¹⁴ does not include this variable. The authors quote a Brazilian study by Rosario *et al.*¹⁵ which found that benign and malignant nodules were not reliably differentiated using colour Doppler ultrasound.

From the data in our study, because we analysed all nodules removed for suspicion of thyroid cancer, central vascularity in isolation was very rarely the sole factor in upgrading the U classification from U2 to U3, accounting for 4 out of 65 U3 nodules (6.2 per cent), only 1 of which was malignant. This is likely to be a relatively uncommon occurrence given the multiple factors conferring a U3 classification (see [Table 1](#)).

Following on from this, we speculated whether central vascularity should be disregarded in the likely rare occasions where it is the only abnormal finding. Although we are unable to provide a definitive statement on this, it would appear from our study that when assessing suspicious nodules (U3–U5), intra-nodular or central vascularity does not appear to confer

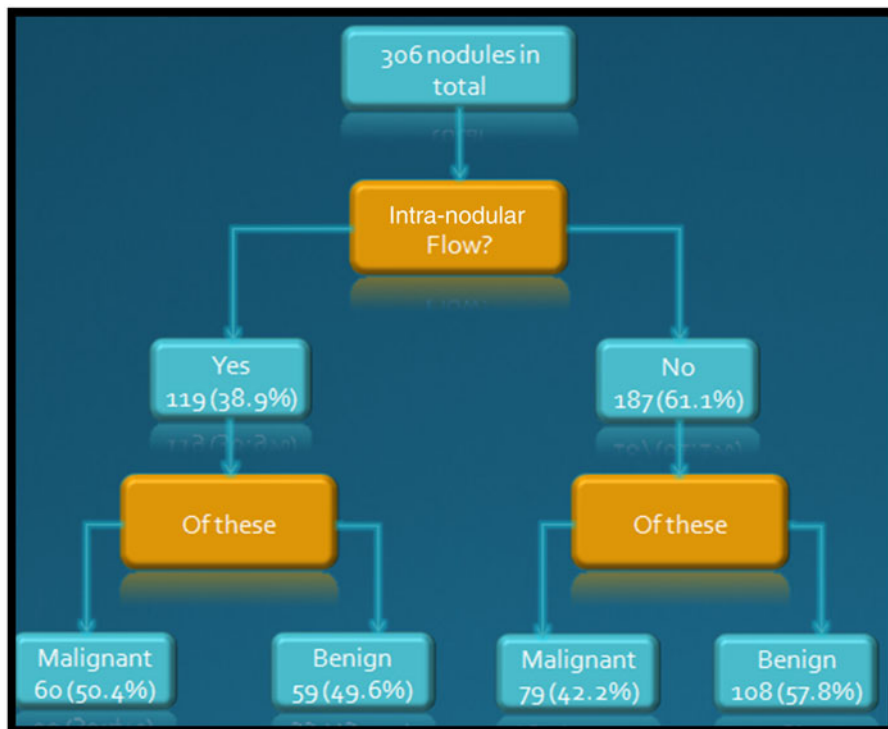


Fig. 1. Summary flow chart of results.

any additional risk for malignancy. This finding supports the fact that the Thyroid Imaging, Reporting and Data System does not include this observation for malignancy risk stratification, and this should perhaps be considered in future British Thyroid Association guidelines.

- Thyroid nodules are common, but thyroid cancer is relatively rare
- Accurate assessment via ultrasound is critical to determine the need for further cytological evaluation
- Significance of intra-nodular vascularity or flow is debatable
- Some studies propose that intra-nodular flow may be a predictor of malignancy, and other studies suggest the converse
- This study showed that in isolation intra-nodular vascularity was not a reliable predictor of thyroid malignancy
- The literature suggests that predictive value is enhanced when combined with other suspicious parameters

To conclude, our study has shown that intra-nodular vascularity is not a statistically significant predictor of thyroid nodule malignancy in isolation, but the literature suggests that the predictive value is enhanced when combined with other parameters. Further larger studies including analyses of different combinations of ultrasound findings will aid identification of the most reliable sonographic patterns for prediction of malignancy.

Competing interests. None declared

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