Ultrasound: how effective is it to predict malignancy pre-operatively in solitary thyroid nodules?

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Abstract
A descriptive, cross-sectional study was conducted from January 2013 to June 2014 among the patients presenting with clinically solitary thyroid nodule, attending to OPD and indoor of ENT department of R G Kar Medical College. A total of 40 cases were selected. They underwent thorough pre-operative evaluation including ultrasonography. They were managed surgically and post-operative histopathology report was considered as the gold standard for diagnosis. Different sonological findings were then corroborated with histopathology report to assess their predictability for malignancy. Nodule size more than 4 cm, spiculated border, punctate calcification and presence of neck node were found to be statistically significant predictor of malignancy. Solid content of a nodule, hypoechoigenicity, elongated shape, absent perinodular halo and disorganized central vascularity were also found to be predictors of malignancy with variable sensitivity and specificity; though they were not statistically significant. Overall, ultrasonography was found to be quite a sensitive, specific and statistically significant imaging modality to characterize solitary thyroid nodules and to predict malignancy pre-operatively.

Introduction:
Thyroid is the largest endocrine organ of human body. This gland can be affected by numerous pathologies, many of which ultimately lead to enlargement of the gland. The enlargement is either generalized (goiter) or nodular. Moreover, the nodules can either be solitary or dominant in a multinodular goiter. Prevalence of thyroid nodule has been shown to be as high as 67% of the population using ultrasonography (USG) as the diagnostic modality. In this study, an attempt will be made to identify different sonologic features of clinically solitary thyroid nodules, with particular emphasis on identification of malignancy pre-operatively.

Materials and methods:
This study was conducted among the patients attending to the outpatients' department (OPD) and from indoor of the E.N.T. Department of R. G. Kar Medical College & Hospital. The patients, who had presented with solitary thyroid nodules clinically and ultimately underwent surgical management, were included in this study. The study period was from January 2013 to June 2014. A total of 40 patients were included in this study; the exclusion criteria being clinically diffuse goiter and multinodular goiter, elderly debilitated patient, inoperable cases due to other co morbid conditions and the patients who opted against surgery. It was a descriptive, cross-sectional study with objectives of calculation of occurrence of different sonologic findings in solitary thyroid nodules, determination of the role of individual sonologic findings in predicting malignancy in solitary thyroid nodules and determination of the sensitivity and predictability of USG in characterization of solitary thyroid nodules. Following presentation, detailed history was taken in each patient and clinical examination was done thoroughly. Thyroid profile was done in each case. USG of the neck was mandatory for all the patients. First of all, the number, lobar involvement and size of the nodule (including Perinodular halo, if any) was measured. Then the content of the nodule was evaluated. In case of cystic nodules (anechoic), it was seen whether it was purely cystic, honeycomb patterned or complex cystic. In case of solid nodules, the nodular echotexture (isoechoic, hypoechoic or markedly hypoechoic) was assessed. Next the following parameters were evaluated in all the nodules:

1) Nodule echotexture - isoechoic, hypoechoic or markedly hypoechoic.
2) Shape - whether elongated or not (Anteroposterior : transverse diameter >1)
3) Borders - spiculated or not
4) Presence and quality of intranodular calcifications - whether punctate (<2mm) without posterior acoustic shadowing or not
5) Perinodular halo
6) Vascularity - whether disorganized central vascularity or not

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In case any neck node was identified, it was evaluated for echogenicity of its hilum, shape, vascularity and presence of intranodular calcification.

Following imaging, cytological evaluation and pre-operative investigations were done. The patients were treated surgically and specimens were sent for histopathological examination. Finally, corroboration of sonological findings was done with histopathology report.

Results and analysis:

For the purpose of results and analysis we compared the pre-operative USG findings with post-operative histopathology results of these 40 patients. Either Fisher exact test (2 tailed) or chi-square test with Yate’s correction was used to calculate p-value in this study. If the calculated p-value is less than 0.05, the test is considered to be statistically significant. The SPSS - version 20 software was used for the purpose of statistical analysis in this study.

Out of 40 cases, 9 (22.5%) were actually malignant, as proved by post-operative histopathology. Rest of the cases (77.5%) were benign. There was clear female preponderance with female : male ration being 4.7:1. However, the rate of malignancy was higher among the males, though the gender distribution was not statistically significant. Most of the cases were among the 30-44 years age group, but the occurrence of malignancy was higher in the lower extreme of ages (less than 30 years). Multinodularity was detected by USG in 27.5% clinically solitary thyroid nodules; however malignancy was more related to solitary nodules with 88.8% sensitivity. No predilection for any particular thyroid lobe involvement was seen. Interestingly enough, malignancy occurred more commonly in nodules involving the left lobe of thyroid.

Most of the nodules were of 2-4 cm in size. Size more than 4 cm at initial presentation was found to be 80.6% specific and statistically significant to predict malignancy. Content-wise, solid nodules (77.7% sensitive) and complex cystic nodules only harbored malignancy. None of the purely cystic or honeycomb lesions were malignant. Hypoechoigenicity was found to be 71.4% sensitive predictor of malignancy among the solid nodules. Elongated shape was found to be 87% specific predictor, though not significant statistically. Presence of a perinodular halo almost always confers benignity to a lesion. Its absence was found to be 88.8% sensitive to predict malignancy. Disorganized central vascularity within a nodule was found to be quite a specific (90.3%) sonological sign, though not significant statistically. Some statistically significant and highly specific signs were present of spiculated border (96.7% specific), presence of neck node (96.7% specific) and punctate calcification within a nodule (93.5% specific).

Overall, ultrasonography was found to be 77.7% sensitive and 83.8% specific to predict malignancy pre-operatively with 58.3% positive predictive value and it was statistically significant (p-value 0.0011 by implementing Fisher exact test- 2 tailed).

Discussion:

All the 40 subjects, who were included in this study, underwent pre-operative evaluation including ultrasonography. The Ultrasonographic findings are compared with post-operative histopathology examination result to find out various objectives of this study.

1) Occurrence of different findings - demography and radiology:

Solitary thyroid nodule was more commonly seen in female than male patients with female : male ratio being 4.7:1. Most of the available literature claims that thyroid nodule is seen more commonly in females. The result is nearer to that of CFJ Russel; according to him 80% are female patients7.

Extremes of ages are known risk factor for malignancy. In our study, all the malignant cases among the male patients were less than 30 years old. Among the female patients, total 7 were malignant cases. Except 1 case, all were less than 30 years old. However, there was no patient with malignancy in our study population, who was more than 45 years old.

27.5% of clinically solitary thyroid nodules were actually multinodal as proved by ultrasonography. But these multinodular cases were not excluded from the study as the study was about the clinically solitary thyroid nodules.

No predilection for the involvement of any thyroid lobe was seen in this study with both right and left lobe harboring 40% of the nodules each, both lobes being involved in 20% cases.

Most of the nodules were 2-4 cm in size (60%) followed by more than 4 cm nodules (30%).

According to content, most were solid nodules (55%) followed by complex cystic nodules (25%). Honeycomb patterned lesion (15%) and purely cystic lesions were rare. Most of the solid nodules were hypoechoic (50%). No hyperechoic nodules were seen.

In our study, only 20% of the nodules were elongated in shape, majority being not elongated or globular. Spiculated border was seen only in 17.5% cases, all other being smooth. Presence of Perinodular halo was a rare sign (15%). Neck node was seen in only 12.5% cases.
75% of the nodules did not have any calcification. Typical punctate calcification was seen in only 15% cases, followed by coarse calcification (10%). Most of the nodules had no radiologically demonstrable vascularity (57.5%) followed by peripheral (27.5%) and disorganized central (15%) vascularity.

2) Predictability for malignancy of individual signs:
According to the analysis of our study, 4 signs were statistically significant to predict malignancy. They were more than 4 cm size of nodule at initial presentation, spiculated border, punctate calcification and presence of neck node. All the other signs, though some of them had good sensitivity or specificity, were not statistically significant.

We found that solitary nodule is more prone to be malignant than multinodular goiter. This corroborates with other studies as well. Though the sensitivity was high (88.8%), it was not statistically proved to be significant.

Size of the nodule at initial presentation was found to be a good predictor of malignancy. The nodules, which are malignant, tend to grow fast and thus present with a large size. In our study, more than 4 cm sized nodule was 66.69% sensitive and 80.69% specific to detect malignancy. This is comparable to the result of study by Hoang JK, et al, but they also concluded that benign nodules can often be very large too. McCoy KL, et al, also opined that nodule size more than 4 cm is a predictor of malignancy; however they found the associated risk to be only 19.3%. In our study, the risk amounted to 50%.

Solid nodules were most commonly associated with malignancy, corroborating with the previous studies. Most importantly, the cystic nodules, which were malignant, were complex cystic nodules. Histopathology proved both of these lesions to be papillary thyroid carcinoma. Thus, we must not forget Hatabu et al, describing the sign “calcified nodule within a cyst”, a complex cystic nodule representing papillary thyroid carcinoma with cystic degenerations. Purely cystic and honeycomb lesions are almost always benign.

Hypoechoic nodules most commonly harbor malignancy among the solid nodules. The sensitivity and specificity of this sign has been found to be variable in literature. As per our study, it is 71-496 sensitive in detecting malignancy.

Spiculated border has been found to be highly specific (96.7%) and statistically significant predictor of malignancy as per our study. The finding of Moon WJ, et al, was quite similar - 91.8% specificity.

Punctate calcification is another highly specific (93.5%) and statistically significant sign. This perfectly corroborates with previous studies - (91-396 - 96.3%) specificity for malignancy. The problem with this sign is that it is not much sensitive (44.49%). In literature, it has been found to be variable, but low - 29% to 51.4%. The cause for this low sensitivity has been cited as papillary thyroid carcinoma presenting with coarse calcification. In our study though, no papillary thyroid carcinoma presented with coarse calcification, but one anaplastic carcinoma did.

Traditionally presence of Perinodular halo has been described to be related with long standing benign lesions. But literature shows that this sign can also be seen in different malignancies. However; in our study, only one malignant case had Perinodular halo. Overall, absence of Perinodular halo was 88.8% sensitive in detecting malignancy.

Papini E, et al. found internal vascular pattern to be 74.2% sensitive and 80.8% specific to detect malignancy. This does not perfectly corroborate with our study. Though the specificity is high (90.3%), the sensitivity has been found to be only 33.3%.

Presence of neck node has been found to be highly specific (96.7%) to detect malignancy, though the sensitivity is poor (44.4%). The plausible explanation of this low sensitivity is that, many a malignancy does not have nodal metastasis at the time of initial presentation. But when a neck node has been found, the risk of the nodule being malignant is high; 80% positive predictive value according to our study.

Overall, lobar distribution, nodular size, spiculated border, punctate calcification and presence of neck nodes were the most important and statistically significant radiological signs.

3) Predictability of ultrasonography to detect malignancy:
Overall, ultrasonography was found to be a quite handy imaging modality for preoperative characterization of solitary thyroid nodules. In our study, ultrasonography has been found to be 77.7% sensitive and 83.8% specific to detect malignancy pre-operatively, which was statistically significant. However, the positive predictive value was 58.3% only. The results are very much comparable to a recent study done by Popli MB and others. They found the sensitivity, specificity and positive predictive value of
ultrasonography to be 81.8%, 87.2% and 59.0% respectively to detect malignancy in thyroid nodules.  

**Conclusion:**  
USG is the imaging procedure of choice for evaluating thyroid nodules. When done by an experienced sonologist, it can predict malignancy with sufficient sensitivity and specificity. The probability of malignancy seemed to be highest when a nodule is more than 4 cm at initial presentation, has spiculated border or punctate calcification and there is associated presence of neck node. Male sex, lower extreme of age and truly solitary nodule are some demographic factors that contribute to the risk of a nodule being malignant. Hypoechoic solid nodules, elongated shape, absence of Perinodular halo and disorganized central vascularity also contribute to the risk of malignancy with variable sensitivity and specificity.

**References:**  