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ORIGINAL ARTICLE

Thyroid Ultrasound Features and Risk of Carcinoma: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Objective: This study was performed to evaluate how well thyroid nodules with nonspecific fine needle aspiration cytology and nonrandom nodules performed symptomatically for thyroid cancer.
Study Design: Cross-sectional & observational study.
Place and Duration: The study was conducted at Jinnah Hospital in July 2012.
Methodology: We included individuals with thyroid nodules who had thyroidectomy after having their nodules assessed by the US were taken into consideration. We only took into account studies where surgical samples have been diagnosed by histology. For full-text evaluation, all of the chosen studies were accessed. Stata v11.0 software was used for all statistical analyses.
Results: There were 52 observational studies totaling 12,816 nodules. 10 studies classified 1852 nodules that had uncertain cytology as a different group. With probabilities ranging from 2.15 to 3.77, all US characteristics of nonrandom nodules were substantially linked with cancer; micro calcifications, discontinuous edges, and a taller than broad form had significant particularities (Sp; 89.8 %, 85.3 %, and 98.1 %) and favorable probability ratios (LHR; 5.16, 4.19, 10.17). The one aspect with the better diagnostic efficacy was lack of flexibility (sensitivity 89.1 %, Sp 88.3 %, and positive LHR 8.19).
Conclusions: Ultrasound characteristics are not an effective way to identify nodules that require fine needle aspiration cytology. To standardize elastography procedures and assess results, particularly in nodules with an undetermined cytology, more research is necessary.
Keywords: Thyroid Ultrasound Features, Risk Of Carcinoma, Systematic Review, Meta-Analysis.

INTRODUCTION

The use of ultrasound is enhancing the identification of thyroid nodules, which are a general finding in the population. Approximately 50 percent of people over the age of forty have thyroid nodularity, which can range in frequency from 19 percent to 67 percent and worsens with age.[1] The necessity to rule out thyroid cancer that is detected in five to fifteen percent of cases based on gender, age group, as well as exposure to other risks is the medical relevance of thyroid nodules.[2]

Papillary thyroid tumors, the sluggish kind of thyroid cancer, are primarily blame for the almost 5-fold rise in thyroid cancer cases during the past fifty years.[3]

Micro calcifications, hypo echogenicity, absence of a halo, greater intranodular vascularity, nodule form, and uneven edges are some US features that have historically been linked to a greater risk of cancer.[4] To identify cancer, neither of these traits, taken alone, appears to be sufficiently trustworthy. Diagnostic accuracy varies from 451.4% to 96.1 %, 80.6% to 82.8%, and 87.8% to 97 %, accordingly, while diagnostic level of sensitivity ranged from 28.3 to 89.3 percent for hypo echogenicity, 56.3 % to 76.6 % for intranodular vascularity, and 28.1 percent to 61.2 percent for micro calcifications.[5] Elastography is a technique used in the US to measure tissue elasticity, has lately been proposed as a way to identify thyroid nodules that are malignant. This method had 92 percent sensitivity and 92 % specificity according to a meta-analysis. But only a couple of studies were considered, and only 3 employed surgical specimens' histology for the final diagnosis.[6] The method for identifying malignant nodules that is thought to be the most precise is fine needle aspiration (FNA) biopsy. It would be very laborious to do biopsies on every patient with a thyroid nodule, and fine needle aspiration (FNA) results have certain constraints. The contraindications are broad and ambiguous and often include people who have a genetic based thyroid cancer, have experienced extensive radioactivity, or have many worrisome ultrasound characteristics.[7] There is no evidence on the likelihood that US characteristics are linked to malignancy, or which combination is more therapeutically relevant. When making treatment decisions for individuals whose fine needle aspiration cytology specimens are either inadequate for identification (10 %) or indeterminate (15 to 30 percent), the latter of which carries a 22 to 32 % cancer risk, US characteristics might be helpful. Sensitivity ranged from 28 % to 89 %, while specificity ranged from 40% to 95 %, according to a meta examining the effectiveness of US to identify carcinoma in thyroid nodules. The greatest diagnostic odds ratio (OR) for cancer was seen in this investigation for shapes that were taller than wider. The research added in the meta-analysis, although, employed cytology rather than histopathology to make the diagnosis for malignant nodules. Additionally, it did not assess the veracity of elastography to predict malignancy.[8] Additionally, there's no explanation of the probability value or likelihood of ultrasound features linked to cancer. In addition to specificity and sensitivity, the probability ratio would offer additional data that might be employed in the therapeutic decision making process for thyroid nodules.[9]

This study's objective was to performed a meta-analysis and systematic review of observation-based researches evaluated the diagnostic value of US features thought to be linked to thyroid malignancy in sick people with unallocated nodules with undefined fine needle aspiration cytology, only using the histology diagnosis of tissue biopsies as the medical assessment.

MATERIAL AND METHODS

The study was conducted at Jinnah Hospital in July 2012. No of the rationale for surgery, observational studies of individuals with thyroid nodules who had thyroidectomy after having their nodules assessed by US were taken into consideration. We only took into account studies where surgical samples have been diagnosed by histology. Using the titles and abstracts as a guide, two independent researchers chose papers that could be qualified. For full-text evaluation, all of the chosen studies were accessed. The phrases "Thyroid Nodule" and "Ultrasound" OR "ultrasonography" OR “Doppler Sonography" was used to search PubMed. The phrases "Thyroid nodule" and "Ultrasound" from EmTree were searched in Electronic databases. In July 2022, the searching phase came to a conclusion. The citations of review papers, earlier meta-analyses, and important papers were also manually searched. Regardless of the primary result or language, all possibly suitable research was taken into account for analysis.

Two researchers examined the histopathological findings, patient characteristics, and US features in the chosen trials. Any disagreements arising from the data extraction were debated until an agreement was achieved. It was determined the exact number of patients with and without the assessed traits and with and without cancer. Taking into account true positives, false positives, and false negatives true negatives, the data was recorded into a computerized spreadsheet.

The ability of the following US characteristics to identify thyroid cancer was assessed: solid form, hypo echogenicity, uneven edges, lack of halo, micro calcifications, central vascularization, single nodule, diversity, taller than wider form, and lack of flexibility. The definition of their existence followed the original study's description.

Using the QUADAS-2 technique, two independent researchers assessed the caliber of the included studies.[10] A third researcher resolved any discrepancies. The current meta-analysis was explained in accordance with the ideas put out.[11]

Statistical Evaluation: To evaluate the prognostic significance of each ultrasound trait for malignancy, the total odds ratio was determined. The statistical heterogeneity between studies was assessed using the chi-square and the twelve tests, and a threshold of p = 1.01 was deemed significant. In the event that there was appreciable heterogeneity across the studies in the preliminary models, risk estimates were determined using a random effects meta-analysis.

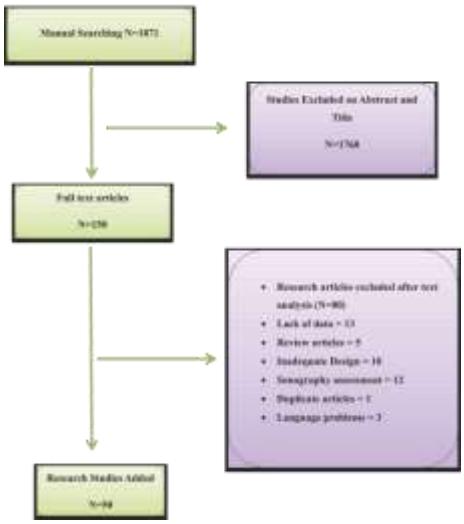
According to the typical amount of malignancy observed in thyroid nodules globally,[12] a mean pre-test likelihood of ten percent was used to compute the pooled level of sensitivity, negative and positive probabilities, and post-test probabilities.[13] A statistical method for summarizing the diagnostic efficacy of a test, the probability value shows how many times commonly individuals with the disease display that specific result than a patient without the ailment.[14] A probability ratio of greater than 10 or less than 0.1 is regarded as substantial evidence to affirm or disprove a certain diagnosis, respectively.[15]

Only individuals with nodules whose cytology was uncertain were involved within a different meta-analysis. Ambiguous cytology was defined in the original article, including those categorized as suspicious. However, fine needle aspiration cytology categorization has evolved over time. Stata v11.0 software was used for all statistical analysis.

RESULTS

The first search brought around 1871 articles, but 1766 of them were disqualified based on the abstract and title. 50 of the 150 papers that underwent full-text evaluation and were chosen for the current study. 12,786 nodules were therefore incorporated into the research. A comprehensive meta-analysis comprised nine trials involving 1760 nodules from individuals with ambiguous cytology aspirates.

Ultrasound Features Perform Diagnostically in All Nodules: With an absolute odds ratio ranging from 2.05 to 37.2 all of the investigated characteristics were substantially related with malignancy. However, the sensitivity of US traits usually linked to malignancy was quite poor, ranging from 26.7% to 63%, meaning that 37% to 73.3% of malignancies wouldn't be identified using these features alone. Micro calcifications, central vascularization, and a taller than wider form are 4 of these traits that demonstrated more specificity compared to the other features, with accuracies of 89.1 %, 80 %, 85.2 %, and 98.1 %, respectively. The range of the positive probability value was 3.13 to 10.17, while the range of the negative probability value was 2.13 to 2.17. A positive test result resulted in a post-test likelihood of malignancy ranging from 14.5 % to 49.0 %, while a negative test result resulted in a post-test likelihood of 3.4 % to 9.8 %, based on a pretest value of 12 %. With a negative and positive LHR of 9.19 and 3.23, respectively, and a sensitivity of 89.1 %, absence of flexibility was the ultrasound trait that demonstrated the greatest diagnostic accuracy.



With the exception of heterogeneity and having a taller than wider form, high statistical variability was found in the examination of all ultrasound traits, hence the random effects method was employed. When all unselected nodules were taken into account, the hysteresis loop and the Egger test indicated a selection bias in the examination of the ultrasound traits of heterogeneity, hypo echogenicity, central vascularization and solidity.

Research Quality: The risk of bias was generally minimal across the included studies. The absence of information indicating whether the US evaluator was masked to the histopathological assessment constituted the most worrying problem. The individual who conducted the ultrasound was unaware of the histopathological diagnosis since US must be done before surgery. Additionally, it was thought that certain studies would have problems resulting from patient selection, typically as they only recruited individuals with cold nodules.

Table 1: Diagnostic performance of each us feature in the differentiation of benign and malignant thyroid nodules in unselected nodules

Features	Level of Sensitivity (percentage)	Specific (percentage)	Positive probability ratio	Posttest likelihood (percentage)	Negative probability ratio	Posttest likelihood (percentage)
Taller	28.1	98.1	10.11	49.1	3.1	9.1
Halo absent	58.2	74.0	6.1	19.2	2.10	8.1
Lack of flexibility	89.2	88.2	8.19	43.1	2.13	3.6
Heterogeneity	49.1	72.1	3.18	16.9	2.14	9.6
Hypo Echogenicity	63.1	64.2	2.16	17.2	2.12	8.1
Solid	73.1	55.1	3.75	16.5	2.11	7.7
Micro Calcifications	41.2	89.1	4.16	28.4	2.18	9.1
Solitary	55.1	62.1	3.63	14.8	2.17	9.2
Central Vascularization	49.3	80.1	4.19	20.1	2.89	9.1
Irregular margins	52.1	84.1	4.19	26.1	2.19	8.4

Likelihood of cancer after a positive test
Likelihood of cancer after a negative result

Performance of US Features in Nodules with Uncertain Cytology: Only a small number of publications particularly included the histopathological diagnosis for nodules with an undetermined cytology. Due to that, just the following aspects were analysed: absence of halo, irregular margins, lack of flexibility, hypo echogenicity, solid structure, and central vascularization, occurrence of micro calcifications, as well as solitary nodule. Only three of them could have their pooled diagnostic accuracy statistics calculated hypo echogenicity, central vascularization, and the occurrence of micro calcifications because a diagnostic test requires over three studies to be analyzed comprehensively. Malignancy was only substantially linked with micro calcifications. However, none of the US traits could accurately predict the likelihood of malignancy in this sample of nodules with an adequate specificity. The characteristic with the highest specificity (98 %) was the occurrence of central vascularization. The range of the positive likelihood ratio was 1.12 to 2.52, while the range of the negative likelihood ratio was 3.16 to 3.15. Assuming a 10 percent pretest likelihood, the posttest likelihood of malignancy varied from 11% to 23.1 % in the event of a positive test as well as from 8.1 % to 11.5 % in the event of a negative test finding.

Table 2: Diagnostic effectiveness of each US characteristic in distinguishing benign from malignant benign cysts in nodules with uncertain cytology

Criteria	Level of Sensitivity (percentage)	Specificity (percentage)	Positive probability ratio	Posttest Likelihood (percentage)	Negative probability ratio	Posttest Likelihood (percentage)
Hypo echogenicity	50.1	58.0	3.12	13.0	2.11	10.1
Micro calcifications	47.1	83.1	4.52	23.8	2.19	8.2
Central vascularization	10.1	98.0	4.13	21.1	2.25	11.2

Likelihood of cancer following a positive test results
Likelihood of cancer following a negative test results

Meta-regression: Less than 10 papers were collected for some characteristics analysis, which precluded the use of a meta-regression. The year of publication and/or the prevalence of cancer in the research sample were included as factors in a meta-regression for the analysis of central vascularization, hypo echogenicity, micro calcifications, solid structure and irregular margins. Neither of these factors, however, was able to meaningfully account for the higher heterogeneity discovered.

DISCUSSION

Taller than wider form, insufficient flexibility, the presence of micro calcifications, and irregular margins were the ultrasound characteristics found in the current meta-analysis to be related with a greater risk and posttest likelihood of cancer. Moreover, none of the ultrasound traits examined separately showed post-test likelihood as well as a clinically meaningful positive likelihood ratio (greater than 10) suggesting malignancy. Most certainly, using both together might increase the danger and likelihood of cancer.[16] Furthermore, because so few studies have examined this issue and they varied about the chosen characteristics, it was not possible to predict the actual malignancy risk by employing the combination of ultrasound features.

The large number of nodules evaluated and the fact that every nodule would include had a histology diagnosis the standard method for making a conclusive diagnosis of thyroid nodules are the strong points of the current meta-analysis. Additionally, the effectiveness of US in nodules with ambiguous cytology was also assessed. This patient population represents the most difficult to diagnose and treat clinically. There are several restrictions on this study. First, there wasn't any evidence on the unique patient traits associated with the risk factors for cancer and the purpose of the operation. Additionally, there weren't enough research to analyze certain US characteristics in individuals with ambiguous cytology, who may be the patients group which might benefit the greatest from using ultrasound as a tool to aid in health-care decisions.

The findings of earlier solitary investigations are supported by our findings. The majority of the ultrasound characteristics had poor sensitivity values, according to Moon et al.,[17] who examined 832 individuals with thyroid nodules. Hypo echogenicity was the sole evidence that had shown a sensitivity of 89.2 %. The sensitivity for malignancy of the taller than wider form, questionable margins, pronounced hypo echogenicity, and macro and micro calcifications ranged from 92.8 % to 99.2 % in the same research. Popovicz et al.,[18] also discovered poor susceptibility levels for the majority of ultrasound characteristics for malignancy among one of the biggest datasets, which included 675 individuals and 1130 nodules. Micro calcifications and characteristics with a taller than wider form demonstrated good applicability, nevertheless.[19] Furthermore, Salmaslioglu et al., discovered that the presence of micro calcifications had a susceptibility of 91.3 % for malignancy in other research involving 549 individuals with nodules goiter.[12] The absence of flexibility had the best diagnostic performance in the current meta-analysis. Either a scale of 1 to 5 (1-3 is indicative of a benign tumor and 4 to 5 of malignancy) or even a scale of 1 to 4 (1 to 2 is suggestive of a benign nodule and 3 to 4 of malignancy) is often used to describe flexibility.[20] Several studies have evaluated the ability of this US component to distinguish between benign thyroid nodules, finding specificity (83.1 to 99 % and 83.1 102 %). This US characteristic was previously identified for chest or colon cancer.[21] The specificity and sensitivity for elasticity were found to be 92 % and 94 %, respectively, in an earlier meta-analysis of 8 trials with a total of 638 nodules identified by fine needle aspiration histopathology. Not all of the analyzed studies had a nodule's final histopathological diagnosis.[22]

The study results further point towards the necessity for even more precise criteria when recommending surgery to individuals whose cytology is ambiguous.[23] This is a crucial logistical problem, as it would aid in making better decisions about which individuals should have fine needle aspiration cytology and, in particular, when surgery should be advised in nodules with ambiguous cytology.[24]

CONCLUSIONS

The current findings demonstrate that there is no single ultrasound characteristic that may accurately diagnose thyroid nodules for malignancy. Moreover, some ultrasound characteristics, such as micro calcifications, a form that is taller Moreover, some ultrasound characteristics, such as micro calcifications, a form that is taller than wider, uneven borders, core vascularization, or lack of flexibility, will likely indicate nodules with a higher risk of cancer. Meta-analyses of specific patient records are ideal because they allow for the development of a risk categorization for thyroid nodule cancer taking into account US characteristics as well as other risk variables to more accurately identify which individuals should have fine needle aspiration and surgical procedures. A novel method called elastography may be useful in identifying people who are more likely to develop thyroid cancer. However, additional research is necessary to standardize the technique methods and confirm its benefits.

Recommendation: The current findings further point to the necessity for more precise criteria when recommending surgery to patients whose cytology is ambiguous. This is a crucial practical issue since it will allow for improved patient selection for FNA and, specifically, will help determine when surgery is necessary for nodules with uncertain cytology.

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Authors' contributions: Dr. Irfan Amjad Lutfi, Dr. Nadeem Siyal, provided the idea of the study and designed experimental data. Dr. Imam Bakhsh, Dr. Hazrat Bilal collected the data for the current study. Dr. Yasir Ali Khoso, Dr. Sajid Ali analyzed the data and drafted the manuscript

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