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Sonographic Predictors of Thyroid Cancer: A comprehensive Systemic Review and Meta-analysis.

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ABSTRACT

Objective: To evaluate Effectiveness of thyroid ultrasound in detecting cancer among nodules with uncertain fine-needle aspiration performed symptomatically for thyroid cancer

Material and Method: We included individuals with thyroid nodules with thyroidectomy following ultrasonography (US) examination. In order to ensure precise confirmation of malignancy or benign status, only studies where the surgical specimens were clearly identified by histological analysis were taken into consideration. All relevant studies were obtained in full text for the systematic review and meta-analysis in order to provide a thorough assessment. Stata v11.0 software was used for statistical studies, including pooled estimates and diagnostic performance computations.

Results: A total of 12,816 nodules were found in 52 observational investigations. 1852 nodules with unclear cytology were categorized as a separate category in 10 investigations. All US characteristics of nonrandom nodules were significantly

associated with cancer, with probabilities ranging from 2.15 to 3.77; microcalcifications, discontinuous edges, and a taller than broad form had favorable probability ratios (LHR; 5.16, 4.19, 10.17) and significant particularities (Sp; 89.8%, 85.3%, and 98.1%). Lack of flexibility was the only factor with superior diagnostic effectiveness (sensitivity 89.1%, Sp 88.3%, and positive LHR 8.19).

Conclusion: Malignant thyroid nodules cannot be diagnosed by a single ultrasound feature. Certain sonographic characteristics suggest higher cancer risk, and combined assessment with clinical factors improves patient management. Elastography shows potential but requires further validation

Keywords: Thyroid Ultrasound, Thyroid Cancer, Meta-Analysis, Effectiveness.

INTRODUCTION

Ultrasound has become one of the most used imaging tools for assessing the thyroid gland. Ultrasound, which is non-invasive, safe, affordable, and capable of creating high-resolution pictures, can identify even very minute abnormalities inside thyroid tissue. The detection of thyroid nodules has improved dramatically as ultrasonography has become more widely used in regular medical examinations and diagnostic investigations. Thyroid nodules are localized lumps or abnormal growths inside the thyroid gland that are quite frequent in the general population. Many people with thyroid nodules have no symptoms, and the nodules are frequently detected inadvertently during imaging exams for other medical reasons [1].

According to epidemiological research, thyroid nodules are more frequent in middle-aged and older persons. When adults over the age of forty are evaluated with ultrasonography, almost half of them have at least one thyroid nodule. Overall, the prevalence of thyroid nodules varies with demographic, ranging from 19% to 67%.This large variance is caused by changes in age distribution, gender, iodine consumption, environmental variables, and the sensitivity of the diagnostic procedures utilized [2]. One distinguishing feature of thyroid nodules is that their frequency rises with age. As people age, the thyroid gland's structure changes, increasing the likelihood of nodular development. In addition, thyroid nodules are more frequent in women than males. Despite the fact that the majority of thyroid nodules are benign (non-cancerous), a tiny percentage may be indicative of thyroid cancer, which makes them clinically significant. To rule out cancer, thyroid nodules must be evaluated medically. According to research, between 5 and 15 percent of thyroid nodules are cancerous. The likelihood of cancer is determined by a number of risk factors, such as the patient's age, gender, history of radiation exposure to the head and neck area, family history of thyroid cancer, and environmental variables [3]. Due to this possible danger, doctors employ diagnostic techniques such fine-needle aspiration cytology, laboratory testing, clinical examination, and ultrasound imaging to identify if a thyroid nodule is benign or malignant.

Microcalcifications, hyperechogenicity, lack of a halo, increased intranodular vascularity, nodule shape, and uneven edges are some US characteristics that have previously been associated with an increased risk of cancer.4Neither of these characteristics alone seems to be reliable enough to detect malignancy [4].The diagnostic level of sensitivity ranged from 28.3 to 89.3 percent for hyperechogenicity, 56.3 percent to 76.6 percent for intranodular vascularity, and 28.1 percent to 61.2 percent for microcalcifications, while the diagnostic accuracy varied from 451.4% to 96.1 percent, 80.6% to 82.8%, and 87.8% to 97%.[5].

Elastography, a method used in the United States to test tissue elasticity, has recently been suggested as a means of detecting cancerous thyroid nodules. A meta-analysis revealed that this approach has 92% sensitivity and 92% specificity. However, only a few studies were taken into account, and only three used the histology of surgical tissues to make the final diagnosis.SixFine needle aspiration (FNA) biopsy is considered the most accurate technique for detecting malignant nodules. Every patient with a thyroid nodule would require a biopsy, and the results of fine needle aspiration (FNA) have limitations. People who have a genetically based thyroid cancer, have been exposed to high levels of radiation, or have several concerning ultrasonography features are frequently among the various and unclear contraindications [6,7].

The possibility that US traits are associated with cancer or which combination is more therapeutically useful are not supported by any data. US features may be useful for choosing a course of therapy for patients whose fine needle aspiration cytology specimens are either insufficient for diagnosis (10%) or indeterminate (15–30%), the latter of which entails a 22–32% malignancy risk.A meta-analysis of the efficacy of US in detecting cancer in thyroid nodules found that sensitivity ranged from 28% to 89% and specificity ranged from 40% to 95% [8]. In this study, forms that were taller than broader had the highest diagnostic odds ratio (OR) for cancer.

Malignant thyroid nodules were frequently diagnosed using cytology rather than histology in prior research that were part of earlier meta-analyses. Cytology often refers to fine-needle aspiration cytology (FNAC), which involves examining thyroid nodule cells under a microscope. FNAC is a widely used, less invasive diagnostic technique, however because it only examines individual cells rather than the entire tissue structure, it occasionally yields ambiguous or inconclusive results. On the other hand, the gold standard for verifying malignancy is histopathology, which entails analyzing the whole tissue taken from a biopsy or surgical specimen. Consequently, the accuracy of earlier research' findings about the actual incidence of thyroid cancer may have been compromised by their primary reliance on cytology [9].

Another drawback of previous studies was that they did not assess elastography's potential to predict thyroid cancer. An

sophisticated ultrasound method called elastography is used to evaluate the elasticity or stiffness of tissue. Malignant thyroid nodules are generally stiffer than benign nodules, so elastography can potentially improve the diagnostic accuracy of ultrasound. Previous meta-analyses may have overlooked crucial information on this method's utility in detecting malignant nodules by failing to evaluate it. Additionally, the probability values or likelihood of particular ultrasound findings being connected to thyroid cancer were not adequately explained by earlier research. Thyroid nodules with uneven borders, microcalcifications, hypoechogenicity, a taller-than-wide form, and enhanced vascularity can all be seen by ultrasound. But merely recognizing these characteristics is insufficient; medical professionals also need to know how well each characteristic predicts cancer [10,11]. The degree to which a certain ultrasound characteristic raises or lowers the possibility that a nodule is malignant can be determined using statistical techniques like probability ratios (also known as likelihood ratios). While sensitivity and specificity characterize a diagnostic test's overall effectiveness, likelihood ratios provide more practical information that can assist clinicians assess the possibility of malignancy and guide treatment options for patients with thyroid nodules [12].

Because of these limitations, the current study sought to conduct a systematic review and meta-analysis of observational studies assessing the diagnostic usefulness of ultrasound characteristics associated with thyroid cancer. The study focused on individuals who had unclassified or ambiguous thyroid nodules with unclear fine-needle aspiration cytology findings, which are notoriously difficult to identify. Crucially, this research included histological diagnosis from tissue biopsies as the reference standard, which ensured a more accurate and dependable determination of whether the nodules were indeed benign or malignant than in earlier investigations. By doing this, the study aimed to enhance clinical decision-making in the treatment of thyroid nodules and ascertain the actual diagnostic significance of ultrasonography features in predicting thyroid cancer.

MATERIAL AND METHODS:

The study took place in July 2012 at Jinnah Hospital. Regardless of the rationale for surgery, observational studies including individuals with thyroid nodules who had thyroidectomies after their nodules had been assessed by ultrasound (US) were taken into consideration. The study was limited to studies where the surgical specimens were verified by histological inspection. To choose studies that satisfied the eligibility requirements, two separate researchers went through the titles and abstracts of the discovered papers. After that, every chosen study was obtained for full-text evaluation. The terms "Thyroid Nodule" and "Ultrasound," "Ultrasonography," or "Doppler Sonography" were used to conduct a thorough search of the PubMed database. Additionally, to find pertinent papers, electronic resources were searched using the EmTree keywords "Thyroid Nodule" and "Ultrasound."

The search process concluded in July 2022. A manual search was also conducted for the citations of review articles, previous meta-analyses, and significant works. All potentially relevant research was taken into consideration for analysis, regardless of the main outcomes. In the selected studies, two researchers looked at the histopathological results, patient characteristics, and US features. Disagreements resulting from the data extraction were discussed until a consensus was reached. The precise number of patients with and without cancer, as well as those with and without the evaluated characteristics, was ascertained. The data was entered into an electronic spreadsheet, accounting for true positives, false positives, and false negatives.

The following US features were evaluated for their capacity to detect thyroid cancer: solid form, hypoechogenicity, uneven edges, lack of halo, microcalcifications, central vascularization, single nodule, diversity, taller than wider form, and lack of flexibility. The definition of their existence was based on the description found in the initial investigation.Two separate researchers evaluated the quality of the included studies using the QUADAS-2 method [13]. Any disparities were settled by a third researcher. The explanation of the current meta-analysis was in line with the concepts presented [14].The overall odds ratio was calculated in order to assess each ultrasonography trait's predictive importance for cancer [15]. The chi-square and twelvet tests were used to evaluate the statistical heterogeneity between the studies, and a p-value of 1.01 was considered significant. A random effects meta-analysis was used to calculate risk estimates in the case that there was significant heterogeneity across the studies in the initial models. The pooled level of sensitivity, negative and positive probabilities, and post-test probabilities were calculated using a mean pre-test likelihood of 10% based on the average amount of cancer found in thyroid nodules worldwide [16].

The probability value, a statistical technique for evaluating a test's diagnostic effectiveness, indicates how frequently people with the illness exhibit a certain result compared to a patient without the condition [17].A probability ratio of less than 0.1 or more than 10 is considered significant evidence to support or refute a certain diagnosis, respectively [18]. A separate meta-analysis included only those with nodules whose cytology was unclear. The original article defined ambiguous cytology, which included those classified as suspicious. Nonetheless, the classification of fine needle aspiration cytology has changed throughout time. All statistical analyses were conducted using Stata v11.0 software.

RESULTS:

Approximately 1871 articles were found in the first search, but 1766 of them were rejected because of the abstract and title. Fifty of the 150 publications that were evaluated in full text were selected for this study. Consequently, 12,786 nodules were included in the study. Nine studies totaling 1760 nodules from people with unclear cytology aspirates were included in an

extensive meta-analysis.

Ultrasound Features Perform in All Nodules

All of the examined traits had a significant correlation with cancer, with absolute risks ranging from 2.05 to 37.2. However, the sensitivity of US characteristics often associated with cancer was quite low, ranging from 26.7% to 63%. This means that 37% to 73.3% of cancers would not be detected by these characteristics alone. With accuracies of 89.1%, 80%, 85.2%, and 98.1%, respectively, microcalcifications, central vascularization, and a taller than broader morphology showed more specificity than the other parameters. Positive probability values ranged from 3.13 to 10.17, while negative probability values ranged from 2.13 to 2.17. Based on a pretest value of 12%, a positive test result produced a post-test chance of malignancy ranging from 14.5% to 49.0%, whereas a negative test result produced a post-test risk of 3.4% to 9.8%. The ultrasound characteristic that showed the highest diagnostic accuracy was the lack of flexibility, with a negative and positive LHR of 9.19 and 3.23, respectively, and a sensitivity of 89.1%.

The random effects technique was used since the evaluation of all ultrasonography properties revealed considerable statistical variability, with the exception of heterogeneity and having a taller than broader shape. The hysteresis loop and the Egger test revealed a selection bias in the analysis of the ultrasonic characteristics of heterogeneity, hypoechogenicity, central vascularization, and solidity when all unselected nodules were considered.

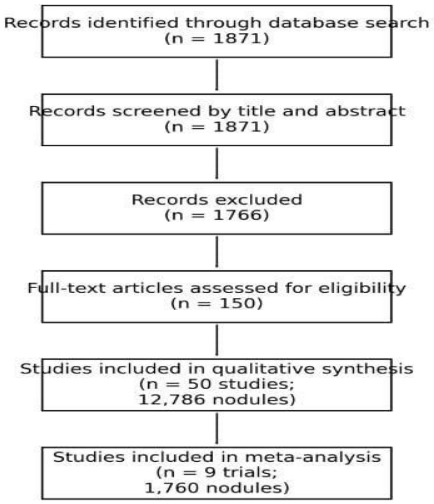

Fig 1: Prisma Flow Diagram

In most of the included research, there was minimum chance of bias. The most concerning issue was the lack of information on whether the US assessor was blind to the histopathology evaluation. The histological diagnosis was unknown to the person doing the ultrasound since US must be performed prior to surgery. Additionally, it was believed that certain studies would have issues with patient selection, usually because they only included people with cold nodules.

Table 1: Diagnostic Performance of US features with Benign and Malignant Thyroid Nodules in Unselected Nodules

Features	Sensitivity Level (%)	Specific (%)	Positive Probability ratio	Post-Test Likelihood (%)	Negative Probability ratio	Post-Test Likelihood (%)
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-calcification	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

Performance of US features in Nodules with Uncertain Cytology:

The histological diagnosis for nodules with an unknown cytology was only found in a few papers. As a result, only the following characteristics were examined: the lack of a halo, uneven borders, lack of flexibility, hypoechogenicity, solid structure, central vascularization, the presence of micro calcifications, and a single nodule. Because a diagnostic test necessitates the thorough analysis of more than three studies, only three of them could have their pooled diagnostic accuracy statistics produced for hypoechogenicity, central vascularization, and the incidence of microcalcifications. Only microcalcifications were significantly associated with malignancy. Nevertheless, none of the US characteristics were able to reliably and sufficiently specify the probability of cancer in this nodule group. The presence of central vascularization was the feature with the highest specificity (98%). The positive likelihood ratio ranged from 1.12 to 2.52, and the negative likelihood ratio ranged from 3.16 to 3.15.The posttest likelihood of malignancy varied from 11% to 23.1% in the case of a positive test and from 8.1% to 11.5% in the case of a negative test result, assuming a 10% pretest risk.

Table 2: Performance of US features in Nodules with Uncertain Cytology

Features	Sensitivity Level (%)	Specific (%)	Positive Probability ratio	Post-Test Likelihood (%)	Negative Probability ratio	Post-Test Likelihood (%)
Hypo Echogenicity	50.1	58.0	3.12	13.0	2.11	10.1
Micro-calcification	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

Meta-Regression:

A meta-regression could not be used since less than ten articles were gathered for some attributes analysis. A meta-regression was used to analyze central vascularization, hypoechogenicity, microcalcifications, solid structure, and irregular margins, taking into account the year of publication and/or the cancer prevalence in the research sample. However, the increased heterogeneity seen could not be well explained by any of these variables.

DISCUSSION:

The current meta-analysis identified ultrasonography features that were associated with a higher risk and posttest probability of cancer, including taller than widerform, inadequate flexibility, the presence of microcalcifications, and irregular edges. Furthermore, neither post-test likelihood nor a clinically significant positive likelihood ratio indicating malignancy were present in any of the ultrasound characteristics that were analyzed independently. Combining the two might undoubtedly raise the risk of developing cancer [19].Additionally, it was not able to estimate the real malignancy risk by using the combination of ultrasound features because so few research have looked at this topic and they differed on the chosen criteria.

The present meta-analysis's strong aspects include the huge number of nodules analyzed and the fact that each nodule had a histology diagnosis, which is the conventional way for getting a definitive diagnosis of thyroid nodules. Furthermore, the efficacy of US in nodules with unclear cytology was evaluated. This group of patients is the hardest to diagnose and treat in a clinical setting. This study has a number of limitations. First, there was no proof of the specific characteristics of the patient linked to cancer risk factors or the reason for the procedure. Furthermore, there was insufficient study to assess specific US features in people with unclear cytology, which may be the patient group that would benefit most from utilizing ultrasonography as a tool to help with health-care choices.

Our results corroborate those of previous single experiments. Moon WJ et al. [20], who looked at 832 people with thyroid nodules, found that most ultrasonography features had low sensitivity values. The only data that demonstrated an 89.2% sensitivity was hypoechogenicity. In the same study, the sensitivity for malignancy of the taller than broader shape, dubious margins, noticeable hyperechogenicity, and macro and micro calcifications varied from 92.8% to 99.2%. In one of the

largest datasets, which comprised 675 people and 1130 nodules, Popovic et al.[21] likewise found low susceptibility levels for most ultrasonography features for malignancy. Nevertheless, microcalcifications and features with a taller than broader shape showed good applicability [22]. Additionally, in another study comprising 549 people with nodules and goiter, Salmaslioglu et al. found that the presence of micro calcifications had a susceptibility of 91.3% for malignancy. In the current meta-analysis, the best diagnostic performance was found when flexibility was absent. Flexibility is frequently measured on a scale of 1 to 5 (1-3 is suggestive 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) [23]. Numerous investigations have assessed this US component's specificity (83.1 to 99% and 83.1 to 102%) in differentiating between benign thyroid nodules. This US trait has been linked to colon or chest cancer in the past [24]. An previous meta-analysis of eight studies with a total of 638 nodules detected by fine needle aspiration histology revealed that the specificity and sensitivity for elasticity were 92% and 94%, respectively. Not every study that was examined had a definitive histological diagnosis for a nodule [25].

The study findings also suggest that even more exact standards are required when suggesting surgery to people whose cytology is unclear [26].This is an important logistical issue since it would help determine which patients should have fine needle aspiration cytology and, in particular, when surgery should be recommended for nodules with unclear cytology [27].

CONCLUSION:

In current findings, malignant thyroid nodules cannot be accurately diagnosed using a single ultrasonographic characteristic. However, several features are linked to a higher risk of cancer, including microcalcifications, a taller-than-wide form, uneven borders, core vascularization, and decreased flexibility. By combining ultrasonography characteristics with other clinical and demographic factors, meta-analyses of individual patient data enable risk assessment and improve patient selection for fine-needle aspiration and surgical intervention. New methods, such elastography, might improve the detection of high-risk nodules, but more research is needed to establish clinical value and standardize methodology.

Conflict of Interest: None.

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