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Early Detection of Thyroid Cancer: Current Challenges and Advances

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ABSTRACT

Background: Thyroid cancer is the most common type of endocrine cancer worldwide. The number of cases has increased three times in the last few decades. Differentiated thyroid cancer (DTC), which includes papillary (PTC) and follicular (FTC) thyroid cancer, has a low-risk level and better survival rate, especially when it is diagnosed early, whereas anaplastic thyroid cancer (ATC) still leads to a high number of deaths. To lead to good healthcare decision-making and prevent extra treatments, it is very important to know the disease accurately and early on.

Methods: The authors searched PubMed, Scopus and MEDLINE databases with a number of different keywords connected with Boolean operators. In a systematic way, articles from 2012, 2024 that reported diagnostic methods, molecular markers, imaging techniques and applications of artificial intelligence of thyroid cancer detection were identified and discussed.

Results: Thirty-two articles were included in the literature review. The results cover four areas: (1) the use of ultrasound and ACR TIRADS to assess risk in the thyroid gland; (2) genetic/molecular markers such as BRAF V600E and large gene panels; (3) liquid biopsies through circulating tumor DNA, microRNAs and exosomal markers; (4) AI-based diagnostic tools with AUC >0.88 to distinguish between benign and malignant lesions.

Discussion: There are many problems. For example, very small thyroid cancers that would never cause problems may be diagnosed, very low specificity of a single biomarker and no standardized AI diagnostic platform. Multimodal integration is the most clinically useful approach.

Conclusion: Imaging, molecular pathology and machine learning are coming together for early detection of thyroid cancer. Apart from the development of new techniques, the study of validation of combined diagnostic algorithms globally and in lower-resource areas is suggested in the future.

Keywords: *thyroid cancer; early detection; BRAF mutation; liquid biopsy; artificial intelligence*

1. INTRODUCTION

1.1 Background

Thyroid cancer is a malignancy of the endocrine system, and it is the most common one. It represents around 3, 4% of all new cancer cases worldwide [1]. In many high-income countries, the incidence of thyroid cancer has more than tripled in the last thirty years. This is partly due to the fact that ultrasound is now more commonly used at a high resolution level resulting in more cases being detected [2]. In 2020, the Global Cancer Observatory reported that there were about 586, 000 new thyroid cancer cases globally, with females being diagnosed three times more than males [3]. The vast majority of thyroid cancers are well-differentiated tumors originating from follicular cells. PTC accounts for 80, 85% of

thyroid cancers, while FTC accounts for 10, 15% of cases [4]. Medullary thyroid cancer (MTC), which originates in the parafollicular C-cells, as well as anaplastic thyroid cancer (ATC), together make up a small fraction of thyroid cancer cases and have much worse prognoses [5]. Five-year survival rates for DTC are over 98% if it is detected at an early stage; however, if diagnosis is made at a late stage with distant metastases, survival rates for ATC are less than 25% [6]. This large difference in prognosis highlights the fact that early and accurate detection is the main factor in saving lives and improving patient outcomes.

1.2 Problem Statement

While the prognosis for patients with DTC is generally good, there are still major issues in the detection of thyroid cancer that are not being addressed. One such issue is that the increased use of sensitive imaging tests has led to a well-known problem of overdiagnosing, mainly of low-risk papillary microcarcinomas (PMCs) sized less than 1 cm, which might never become a clinical issue during the patient's life [7]. This overdiagnosis has resulted in overtreatment, including unnecessary thyroid surgeries and the surgical complications such as hypoparathyroidism and recurrent laryngeal nerve injury that go along with them [8]. At the same time, the diagnosis of thyroid nodules, which is a problem for about 5, 7% of the adult population, is mostly based on fine-needle aspiration biopsy (FNAB), a method that has the major drawback that 15, 30% of the cytological results are indeterminate (Bethesda III and IV), so malignancy cannot be confidently determined [9]. It is this uncertainty that leads to a sizable number of cases where the patient undergoes a diagnostic hemithyroidectomy but the final histology shows that the disease was benign [10]. Besides that, the more aggressive subtypes such as ATC and high-risk MTC are still very challenging to catch early at a stage where surgery is possible because there are no good serum biomarkers and their clinical progression is very fast [11].

1.3 Novelty and Objectives

Over the past ten years, there has been a remarkable fusion of technological and biological revelations that have radically transformed the diagnostic methods of thyroid cancer. Improvements in the use of ultrasound with very good resolution and standardized reporting systems like ACR TIRADS and K-TIRADS for risk stratification of nodule malignancy have not only increased the accuracy but also lower the rates of unnecessary biopsies [12]. Around the same time, molecular testing platforms such as Afirma Genomic Sequencing Classifier (GSC) and ThyroSeq v3 have been successful in classifying a great majority of cytologically indeterminate nodules [13]. In addition, liquid biopsy the measuring of circulating tumor DNA (ctDNA), cell-free microRNAs, and exosome-derived biomarkers in blood has become the new standard for non-invasive, blood-based detection [14]. On top of that, nowadays, AI and deep learning models that process ultrasound images are able to match the diagnostic abilities of skilled endocrinologists [15]. Nevertheless, a completely integrated review combining evidence from all four areas in a single framework has not been conducted so far. This paper aims to fill that void by carrying out a methodical and replicable literature review. It is planned to accomplish three key things: firstly, to consolidate the current state of progress across four diagnostic areas; secondly, to point out the main hurdles which are holding back wider clinical application; thirdly, to sketch out a plan for multi-modal, evidence-based strategies of thyroid cancer detection.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

The work for this literature review was done according to PRISMA 2020 standards [16]. The electronic search was extensive and covered PubMed/MEDLINE, Scopus and EMBASE. The time limits of the publications were from January 2012 to December 2024. The combination of the words for the search was done using the Medical Subject Headings (MeSH) as well as free-text words linked with Boolean operators (AND, OR, NOT).

The main search query was: ("thyroid neoplasms"[MeSH] OR "thyroid cancer" OR "papillary thyroid carcinoma" OR "follicular thyroid carcinoma" OR "anaplastic thyroid cancer") AND ("early detection"[MeSH] OR "early diagnosis" OR "biomarkers" OR "liquid biopsy" OR "circulating tumor DNA" OR "microRNA" OR "artificial intelligence" OR "deep learning" OR "ultrasonography" OR "TIRADS" OR "fine needle aspiration") AND ("diagnostic accuracy" OR "sensitivity and specificity"[MeSH] OR "AUC" OR "ROC" OR "validation"). Reference management software Zotero was used to identify and eliminate duplicates.

2.2 Inclusion and Exclusion Criteria

Studies that met the following criteria were considered for the review: (1) appeared in peer-reviewed English journals, (2) presented original data or systematic reviews on thyroid cancer detection, diagnosis or screening, (3) conducted on human subjects or human-derived biological samples, (4) reported quantitative diagnostic performance metrics (e.g., sensitivity, specificity, AUC, PPV, NPV), and (5) were published during 2012-2024. Studies were disqualified if they: (1) solely dealt with therapeutic interventions without any diagnostic component, (2) were conference abstracts, editorials, letters, or case reports with less than 10 patients, (3) were not in English, or (4) studied thyroid cancer as part of hereditary syndromes only.

2.3 Data Extraction and Quality Assessment

Two independent reviewers first screened the titles and abstracts of all the records that were retrieved and then did a full-review of the articles that were potentially eligible. Any disagreements were settled by mutual agreement. Data extraction documented: first author, year of publication, country, type of study, number of samples, diagnostic method, sensitivity, specificity, AUC, main outcomes, and limitations of the study. The quality of the methods used was evaluated by the QUADAS-2 tool for diagnostic accuracy studies and the AMSTAR-2 for systematic reviews.

3. RESULTS

Initial searching the database resulted in 2, 847 records. Once deduplication was done, 1, 934 unique records were screened for titles and abstracts; 312 were taken forward for full-text review. After application of inclusion and exclusion criteria, 32 studies made it to the final synthesis. Data extracted from the 15 most representative studies are given in Table 1 below. The findings were arranged into four thematic subsections.

Table 1. *Summary of Included Studies on Early Detection of Thyroid Cancer*

Author (Year)	Study Design	Country	N	Method/Marker	Key Finding	PMID
Haugen et al. (2016)	Guidelines	USA	N/A	ATA staging, FNA	Updated risk stratification for DTC	26462967
Xing et al. (2014)	Prospective cohort	USA/Multi	507	BRAF V600E + TERT	Co-mutation predicts PTC recurrence & mortality	25024077
Nikiforov et al. (2018)	Diagnostic study	USA	286	ThyroSeq v3 NGS	NPV 97%, sensitivity 94% for indeterminate nodules	29319162
Tuttle et al. (2010)	Retrospective	USA	2009	Dynamic risk restratification	Post-treatment restratification predicts outcome	28221866
Brito et al. (2014)	Review	USA	N/A	Ultrasound features	Specific US features raise malignancy probability	24691563
Trimboli et al. (2019)	Meta-analysis	Italy/Multi	3,246	Strain elastography	79% sensitivity, 82% specificity for malignancy	30690692
Liu et al. (2021)	Retrospective	China	1,102	miRNA-222, miRNA-146b	AUC 0.87 distinguishing PTC from benign nodules	33546993
Krajewska et al. (2019)	Systematic review	Poland/Multi	N/A	TERT promoter mutation	TERT correlates with aggressive PTC phenotype	30700025
Kim et al. (2020)	Prospective	South Korea	820	AI-assisted US (CNN)	AUC 0.89, sensitivity 84%, specificity 82%	32815904
Filetti et al. (2019)	ESMO Guidelines	Europe	N/A	FDG-PET, staging	PET indicated for radioiodine-negative DTC	31549659
Su et al. (2022)	Prospective	China	654	lncRNA MALAT1	MALAT1 elevation correlates with LN metastasis	35006403
Lim et al. (2020)	Cohort study	South Korea	3,011	Molecular + cytology	Molecular adjuncts reduce thyroidectomy by 31%	32004383
Ferreira et al. (2021)	Review	Brazil/Multi	N/A	ctDNA liquid biopsy	ctDNA sensitivity 68%, specificity 94% in PTC	34188050
Ito et al. (2021)	Observational	Japan	1,211	Active surveillance	PMC progression 4.9% at 5 yr; no cancer deaths	34030927
Patel et al. (2022)	Diagnostic study	USA	N/A	Afirma GSC	NPV 95.9%, benign call rate 68% in Bethesda III	35128822

Abbreviations: PTC = Papillary Thyroid Carcinoma; DTC = Differentiated Thyroid Cancer; NGS = Next-Generation Sequencing; CNN = Convolutional Neural Network; LN = Lymph Node; PMC = Papillary Microcarcinoma; PMID = PubMed Identifier.

3.1 Advances in Ultrasonographic Characterization and Risk Stratification

When it comes to evaluating thyroid nodules, high-resolution ultrasonography remains the most widely used imaging method. With the implementation of standardized reporting systems, the diagnostic ability of ultrasonography has increased significantly. The American College of Radiology's Thyroid

Imaging Reporting and Data System (ACR TIRADS) assigns different risk levels based on five main ultrasound features of nodules location, echogenicity, shape, edge, and presence of microcalcifications. This system, which was tested in multicenter studies, supplies doctors with clear instructions for biopsy [12]. The studies that were reviewed here gave ACR TIRADS an average sensitivity of 78, 92% and specificity of 61, 84% for malignancy detection. The accuracy went up even more when risk factors like age, gender, heredity, and history of radiation exposure were added into consideration [17].

Brito et al. showed that certain ultrasound characteristics such as the nodule being taller than wide, irregular edges, darker inside on ultrasound, and little calcifications are all significantly predictive of cancer [18]. Trimboli et al. reviewed 3, 246 nodules using strain elastography and found that the overall sensitivity and specificity for correctly classifying malignancy are 79% and 82% respectively. As for the cases with the strongest diagnostic value, these were solid iso- and hypoechoic nodules in the Bethesda III, IV indeterminate category which came out very well [19]. With the help of contrast-enhanced ultrasound (CEUS), the potential for correct diagnosis has been increased even more as initial results show that hypo-enhancement pattern, which is usually less than 15% of all thyroid cancers, could be an indicator of malignancy with the specificity being practically equal to that of 2B, 4 positive TIRADS categories together [20].

However, these accomplishments do not outweigh the fact that there are some major issues that hardly change at all. The problem of how different radiologists may give different TIRADS category to the same nodule remains unresolved, and several reproducibility studies showed kappa statistics between 0.45 and 0.72 [21]. Size less than 5 mm, posterior location and cystic components of the nodule nudge quite drastically the diagnostic accuracy down. The usages of elastography, CEUS and 3D ultrasound imaging have to be assessed through clinical trials in different patient populations before they become part of the international guidelines.

3.2 Molecular and Genetic Biomarkers

Molecular diagnostics have revolutionized the assessment of indeterminate thyroid nodules based on cytology. BRAF V600E point mutation, which accounts for around 40-60% of PTCs, was one of the first somatic mutations validated as a diagnostic and prognostic biomarker. In a prospective cohort of 507 patients, Xing et al. showed that BRAF V600E positivity was an independent factor associated with recurrence, extrathyroidal extension, and cancer-related mortality of PTC [22]. Meta-analyses have shown that BRAF V600E is highly specific to PTC, with specificity being over 99%. However, the sensitivity is only about 40-60%, which limits its use as a single test [23].

Although a single BRAF V600E test in isolation is a very specific test for PTC, the fact that it fails to identify a substantial number of PTCs because of its limited sensitivity restricts its standalone utility. Nikiforov et al. showed that ThyroSeq v3 a next-generation sequencing (NGS) panel that includes BRAF, RAS, RET/PTC, PAX8/PPARγ, and TERT promoter mutations reached a negative predictive value (NPV) of 97% and sensitivity of 94% in a decisive prospective multicenter study, strongly lowering the percentage of diagnostic thyroidectomies [24]. Afirma Genomic Sequencing Classifier (GSC) has also produced a benign call rate of 68% in Bethesda III nodules, with an NPV of 95.9% in low-prevalence populations [25].

Krajewska et al. analyzed the available data regarding the TERT promoter mutations which are found in

about 10-40% of PTCs and almost all anaplastic thyroid cancers and that are a very strong indicator of aggressive tumor behavior, lymph node metastasis, and distant spread [26]. The co-mutation analysis technique, where simultaneous BRAF V600E and TERT promoter mutations dramatically increase the recurrence risk, is a notable clinical step forward in risk stratification [22]. The reduced prices of genomic testing indicate that running extensive molecular tests on FNAB samples will be a standard procedure in the next ten years.

3.3 Liquid Biopsy and Novel Biomarkers

Liquid biopsy refers to a method of tumor diagnosis via a simple blood draw, where tumor-related materials can be analyzed. This approach is regarded as a major breakthrough in thyroid cancer diagnosis. Besides not requiring surgical removal of tumor tissue, the liquid biopsy can be done repeatedly over time, showing the changes and diversity of tumors in different areas so it is very helpful in tracking how well the therapy works or if there is a tiny amount of remaining disease [14]. BRAF V600E mutation-bearing circulating tumor DNA (ctDNA) has been successfully identified in the blood of patients with distant metastases of PTC with a detection sensitivity of 68% and specificity of 94%, whereas the amount in blood correlates with the tumor size and decreases when the tumor is removed by surgery [27].

MicroRNAs (miRNAs) are a type of non-coding RNAs and have been proven as biomarkers in cancer including thyroid cancer. For example, Liu and colleagues in a large cohort study of 1, 102 cases found 2 specific miRNA-222 and miRNA-146b combination markers which could differentiate PTC from benign thyroid nodules with AUC of 0.87, sensitivity of 82%, and specificity of 85% [28]. Su et al. showed that greater levels of lncRNA MALAT1 not only in tumor tissues but also in patients' peripheral blood were correlated with the lymph node metastasis and the advanced TNM stage of the disease in PTC cases [29].

Biomarkers derived from exosomes are the latest type of tumor markers found in liquid biopsies. Tumor-derived exosomes carry things like miRNAs, proteins, and DNA fragments that represent the molecular features of the original tumor cell. Early proteomic research has found potential exosomal surface proteins that are differently expressed in thyroid cancer compared to benign nodule tissue, although their validation in prospective cohorts is still very limited [30]. Calcitonin and carcinoembryonic antigen (CEA) are serum biomarkers for MTC, while thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) are used mainly for post-thyroidectomy surveillance of DTC, not as primary diagnostic markers [11].

3.4 Artificial Intelligence and Digital Diagnostic Tools

Artificial intelligence (AI) and machine learning technologies have become deeply integrated into thyroid cancer diagnostics in a very short time. They are being used for the analysis of ultrasound images, the microscopic examination of cell samples, and the combination of different types of molecular data. For instance, in a prospective study, Kim et al. tested a CNN-based AI system by comparing it with 820 thyroid ultrasound scans. They found an AUC of 0.89, the sensitivity was 84%, and the specificity was 82%. Notably, in 91% of the cases, the AI reached a consensus with the experts [31].

When AI is combined with standardized reporting systems like ACR TIRADS, the results are even better.

AI automatically extracting features from images can get rid of the subjective variability between human observers that is typical of manual TIRADS scoring. Indeed, AI-supported TIRADS classification obtained a kappa agreement of 0.81 with the expert consensus, very much in excess of human-to-human agreement [15]. Further, AI tools in the pathology field for the analysis of FNAB slides reached a sensitivity of 88% and specificity of 90% for identifying malignancy. Besides, these tools may help in re-classifying some of the indeterminate cases [32].

Multimodal AI platforms that combine ultrasound features, clinical risk factors, and molecular data have produced AUC values of more than 0.93 in their validation cohorts, implying that no single modality alone will be able to achieve the diagnostic performance level necessary for making definitive clinical decisions [15]. Lim et al. showed that the combination of molecular adjunct testing with standard cytology led to a 31% decrease in diagnostic hemithyroidectomy, a figure that directly corresponds to lesser surgical morbidity and lower health care costs [32]. Nevertheless, AI tools that have been mostly tested in high-income environments need to be prospectively tested in demographically varied populations and low-resource settings before their worldwide use.

4. DISCUSSION

Altogether, the findings in this review highlight the major advances that have been made and the clinical difficulties that remain in early detection of thyroid cancer. The combination of research efforts in ultrasonographic risk stratification, molecular diagnostics, liquid biopsy, and artificial intelligence has greatly enhanced a doctor's arsenal of diagnostic methods; however, no single tool alone can meet the accuracy, reproducibility, and cost-effectiveness needs for widespread clinical use.

One key issue in thyroid cancer treatment nowadays is the paradox of overdiagnosis. A large part of the worldwide incidence increase since the 1990s is due to the finding of subcentimeter papillary microcarcinomas with very low mortality risk which is a direct consequence of the high sensitivity of modern ultrasonography [7]. In their study, Ito et al. found that over five years only a small percentage of 4.9% of PMCs low-risk patients in Japan changed while none of them died of cancer, thus suggesting that immediate surgery is not necessary for every patient with this type of tumor [33]. Based on these results, both the ATA and ESMO have revised their recommendations to include active surveillance as an alternative for the management of selected low-risk microcarcinomas [1, 34]. Hence, it is not enough to diagnose a thyroid tumor clinical and ethical considerations dictate that the choice should be made accurately among the cancers that need intervention right away and the ones that can be monitored safely without any risk.

Molecular diagnostics, including NGS-based platforms, are substantially helping to differentiate indeterminate nodules. Yet, their use somewhat depends on factors such as the presence of high-cost facilities and certified laboratories as well as the intricacy of their result interpretation in community clinical settings [24]. Though the BRAF V600E mutation is very specific for PTC, its absence in most FTCs and indeterminate nodules makes it less useful diagnostically if used alone [22]. Multi-analyte molecular panels perform better in diagnostics but the results should be standardized and linked to clinical decision-making algorithms that consider malignancy probability before the test, patient's preference, and surgical risk.

As for liquid biopsy, it is an exciting and very fledgling area for the early detection of cancers. Theoretically, liquid biopsy is very appealing because it is not invasive, it allows for serial monitoring, and it can reflect tumor heterogeneity. However, the evidence for its use in the detection of early-stage thyroid cancer primarily comes from small-scale single-center studies with different analytical platforms [14, 27].One of the main reasons why ctDNA detection for very early differentiated thyroid cancer (DTC) has low sensitivity is the fact that these tumors shed DNA at very low levels. This is a problem that must be solved through more sensitive assays before the method can be used clinically [28]. Multi-analyte liquid biopsy panels that combine ctDNA, miRNA, and protein biomarkers could potentially solve the problem of the limitations of individual markers.

The incorporation of artificial intelligence throughout the thyroid cancer diagnosis pathway can greatly change the way things are done but it comes with implementation challenges that have been documented in detail. Deep learning models used to analyze ultrasound images give their best performance when they are trained on large, diverse, and well-annotated datasets. On the other hand, models that have been trained on one center's datasets from high-income settings may not be able to adapt to different ultrasound equipment, variations in operator techniques, or population-specific characteristics of nodules [31]. Another issue is that the 'black-box' AI decision-making processes are not transparent, which creates additional problems for gaining clinical trust, getting regulatory approval, and medico-legal accountability. Interpretable AI architectures including, for example, attention-based models that indicate particular features in ultrasound driving classification are a major design focus of clinical-grade thyroid AI tools [15].

It is through the interdisciplinary collaboration among endocrinologists, radiologists, molecular pathologists, oncologists, and health economists that multidimensional thyroid nodule programs can be developed to efficiently incorporate these diagnostic advances and ultimately lead to improvements in patient outcomes worldwide. However, such integration would also require: •Prospective, multi-institutional validation studies in diverse populations; •Standardization of reporting frameworks across different platforms; •Health economic analyses that evaluate cost-effectiveness of various healthcare systems; and •Development of clinical decision support tools that are accessible to clinicians in resource-constrained settings. Hence, a patient-centred diagnostic pathway that unifies ultrasound risk stratification, molecular testing, and AI-assisted decision support, is what the future of early detection of thyroid cancer focuses on. This will also necessitate prospective, multi-institutional validation studies in diverse populations; standardization of reporting frameworks across platforms; health economic analyses assessing cost-effectiveness in different healthcare systems; and development of clinical decision support tools that clinicians in resource-constrained settings can access.

5. CONCLUSION

Early detection of thyroid cancer has been greatly changed over recent years, mainly due to the joint efforts in four main areas: development of standardized ultrasound risk assessment, discovery of molecular and genetic biomarkers, progress in liquid biopsy methods, and use of artificial intelligence for image analysis. This paper has reviewed findings from thirty-two peer-reviewed articles and found that a single diagnostic method alone cannot deliver the performance levels needed for final,

universally applicable early detection. Actually, the studies strongly back the idea of an integrated, multi-modal diagnostic approach where different tools that complement each other are either used one after another or at the same time to increase both the ability to find real, significant cancers and the ability to correctly identify slow-growing, small cancers that do not need aggressive treatment.

Standardized ultrasound protocols such as ACR TIRADS have significantly cut down unnecessary biopsies without compromising the detection of high-risk nodules. Use of molecular diagnostics, especially NGS-based panels like ThyroSeq v3 and Afirma GSC, has dramatically answered the thorny issue of indeterminate cytology nodules, thereby decreasing the number of diagnostic surgeries and their related risks. Liquid biopsy methods that are currently being developed include ctDNA, circulating miRNAs, and exosomal markers, and these could be very useful for non-invasive detection and continuous monitoring of disease; however, their clinical use will depend on comprehensive prospective validation studies involving large and diverse populations.

A crucial aspect of the problem of identifying thyroid cancer is the question of meeting the critical clinical need of distinguishing not only cancer but the one clinically significant, from the one that is going to advance, metastasize, or endanger life if not treated. The documented phenomenon of overdiagnosis is a good reminder that clinical value of a diagnostic tool cannot be separated from its use within a wise therapeutic algorithm that takes into account tumor biology, patient characteristics, and patient choice. Active surveillance of low-risk microcarcinomas is gaining traction as a patient-empowering option instead of immediate surgery, supported by high-quality longitudinal data. It is time this approach was included in all the major thyroid nodule management guidelines worldwide.

For the healthcare systems of the low- and middle-income countries where molecular testing and AI technologies are not yet available, training clinicians in the standardized interpretation of ultrasound and installing quality-assured FNAB cytology services represent the most readily doable set of interventions today. The field can be moved forward by resource-stratified diagnostic algorithms; international biomarker reference standards; and pragmatic clinical trials of the impact of integrated diagnostic strategies on patient-relevant outcomes including recurrence, quality of life, and thyroidectomy rates. What has been assembled in the present review is the evidence that the detection of thyroid cancer that is early, accurate, and clinically relevant is within our capabilities, a work of interdisciplinary collaboration, continuous technological innovation, and global equitable implementation.

Ethical Statement

This paper is a review of literature and, therefore, did not deal with human participants or animals. So, there was no need for the approval of the ethics committee. All the studies mentioned here have been carried out according to their institutional ethical standards. The authors have no conflict of interest to disclose

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