The minefield of indeterminate thyroid nodules: could artificial intelligence be a suitable diagnostic tool?

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Abstract

Artificial intelligence (AI) is assuming a central role in anatomic pathology for ancillary diagnosis in histology and cytology. AI techniques can analyse large amounts of data and identify patterns that may not be visible to the human eye.

Several studies have explored the potential of such techniques to improve the accuracy and efficiency of thyroid nodule diagnosis and to increase the sensitivity and specificity of thyroid cytopathology. Specifically, the indeterminate categories of 'the Bethesda system for reporting thyroid cytopathology' (TBSRTC) represent a major diagnostic challenge, and articles reported in this review highlight the potential of new AI technologies in improving the accuracy and standardisation of the cytological diagnosis of indeterminate thyroid nodules.

Although a large amount of data supports AI's utility in thyroid cytopathology, further research is needed to integrate and standardise AI-based diagnostic systems in clinical workflows.

Keywords Artificial intelligence; Bethesda system; deep learning; fine-needle aspiration cytology; indeterminate thyroid nodules; machine learning

Introduction

Artificial intelligence (AI) is assuming an increasingly central role in anatomic pathology and represents an emerging tool for ancillary diagnosis in histology and cytology. AI can analyse large amounts of data and identify patterns that may not be visible to the human eye. It can simultaneously process a set of holographic data to allow image recognition and can extract and quantify visual inputs, transforming the subjective qualitative

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items associated with diagnostic imaging into objective quantitative ones.[1−3] AI has been applied to the analysis of histological images of the gastrointestinal tract[4] to diagnose colorectal cancer[5] and to measure histological disease activity in ulcerative colitis.[6] Moreover, it has been employed to diagnose cutaneous basal cell carcinoma[7] and hepatocellular carcinoma.[8] AI has a significant role to play in cytology as well. In fact, AI-assisted cytology systems have been shown to improve sensitivity with clinically equivalent specificity for detecting cervical intraepithelial neoplasia[9] and have also shown promising results in cytology-based screening and colposcopy examination based on image pattern recognition.[10]

In addition, AI has been used to differentiate malignant from benign pancreatic cystic lesions using cyst fluid[11] and exploited in the cytological diagnosis of brain tumors.[12] Moreover, it has been used to assist in reporting urine cytology,[13] and AI-assisted cytology systems have also been developed for early esophageal squamous epithelial lesions.[14]

Nonetheless, several studies have explored the potential of AI techniques such as computer-aided diagnostic systems (CAD), deep learning (DL), and machine learning (ML) to improve the accuracy and efficiency of thyroid nodule diagnosis.[3,15−18]

For example, Wei et al.[19] proposed a new CAD system that uses a convolutional neural network (CNN) to classify thyroid nodules as benign or malignant: this technique demonstrated high diagnostic accuracy and could represent a useful tool to assist clinicians in diagnosing thyroid nodules.

Moreover, also Ozturk et al.[16] proposed a novel CAD system that exploits a genetic algorithm for the risk stratification of thyroid nodules, showing a high accuracy in differentiating between benign and malignant nodules, and similarly, Wan et al.[17] reported a good performance for the classification of thyroid nodules based on a novel AI-assisted diagnostic system generating a dynamic AI ultrasound intelligent auxiliary system. Moreover, Xue et al.,[3] conducted a systematic review and meta-analysis of studies that used AI to diagnose thyroid nodules, showing that these techniques could improve the diagnostic accuracy of thyroid nodules, especially in patients younger than 50. The role of AI in ultrasound imaging applied to thyroid nodules has been analysed by several other authors,[15,20−23] showing that AI systems can provide high diagnostic performances and could be used as effective tools to aid in diagnosing thyroid nodules. Similarly, AI is important in the cytopathological diagnosis of thyroid nodules. AI has been used to quantify objective features in thyroid cytological samples, such as nuclear area and elongation factor,[24] nuclear-to-cytoplasmic ratio and numerous follicular aggregates[25], which could help in the differential diagnosis between benign and malignant lesions.

Literature review

Thyroid fine-needle aspiration cytology (FNAC) is a safe, accurate, cost-effective diagnostic tool[26] used to analyse thyroid nodules that meet specific radiologic criteria according to the American Thyroid Association guidelines.[27] However, thyroid cytopathology is characterised by great variability in literature-reported sensitivity and specificity ranges from 68% to 98% and 56% to 100%, respectively.[28]

The classification system for thyroid cytology is represented by ‘the Bethesda system for reporting thyroid cytopathology’ (TBSRTC),[29] a standardised tiered reporting system that divides thyroid lesions into six groups, each with its risk of malignancy. The Bethesda III and IV categories represent the most challenging categories, the so-called “indeterminate” nodules that represent about 15%−30% of cytologic reports.[30,31]

It is really difficult to standardise the morphological features in such categories (i.e., architectural and nuclear atypia), and this problem has been demonstrated by several studies that showed a quite low interobserver agreement among cytopathologists regarding cytologically indeterminate nodules.[32−35] However, an accurate diagnosis is essential because Bethesda III (atypia of undetermined significance or follicular lesion of undetermined significance) and Bethesda IV (follicular neoplasm or suspicious for a follicular neoplasm) nodules are characterised by risks of malignancy that range from 15.7% to 54.6% and from 16.8% to 72.4%, respectively (according to different studies).[36−38]

Therefore, the indeterminate cytological categories pose important diagnostic challenges, and several studies have tried to find the best tool to reach the most accurate diagnosis. Immunocytochemistry (ICC)[39,40] and molecular markers have been used to improve the preoperative detection of malignancy in FNA thyroid smears with indeterminate cytology.[41−47]

In addition to molecular markers, microRNA expression profiling has also been investigated as a potential diagnostic tool for distinguishing between benign nodules and papillary thyroid carcinomas (PTCs).[48]

Despite these advances, the diagnosis of indeterminate thyroid nodules remains challenging, and a growing number of studies are investigating the possibility of adopting AI to increase the accuracy and standardisation of the cytological diagnosis of indeterminate thyroid nodules (Figure 1).

Already in 1999, Karakitsos et al.[49] used a neural network to classify benign and malignant follicular and Hurthle cell nodules. They reached an overall accuracy of 90.61% on test data and high sensitivity and specificity in distinguishing benign from malignant lesions (respectively 94.9% and 98.9%).

The first attempt to solve the problem of indeterminate nodules was made by Ippolito et al.,[50] who demonstrated that an artificial neural network (ANN) model could distinguish between benign and malignant thyroid lesions with higher sensitivity and specificity compared to standard cytologic criteria and could therefore be a useful tool in the management of indeterminate nodules.

In 2006, Cochand-Priollet et al.[51] extrapolated 25 morphometric nuclear data derived from May Grunwald−Giemsa-stained smears and used statistical classifiers to categorise them as benign or malignant. They found that four parameters (based on nuclear and chromatin features) could aid in distinguishing between benign and malignant thyroid nodules. In the same year, Poloz and Tarkov[52] proposed a neural network algorithm to diagnose thyroid follicular lesions using intraoperative cytological images. They showed that such an algorithm could allow the development a medical expert system. One year after, Shapiro et al.[53] examined several ANN types and designs using nuclear morphological parameters in 197 thyroid follicular tumours (adenomas and carcinomas). The authors showed that ANNs had an accuracy of 87% in differentiating between adenomas and carcinomas, while the accuracy in diagnosing follicular tumours was 97%.

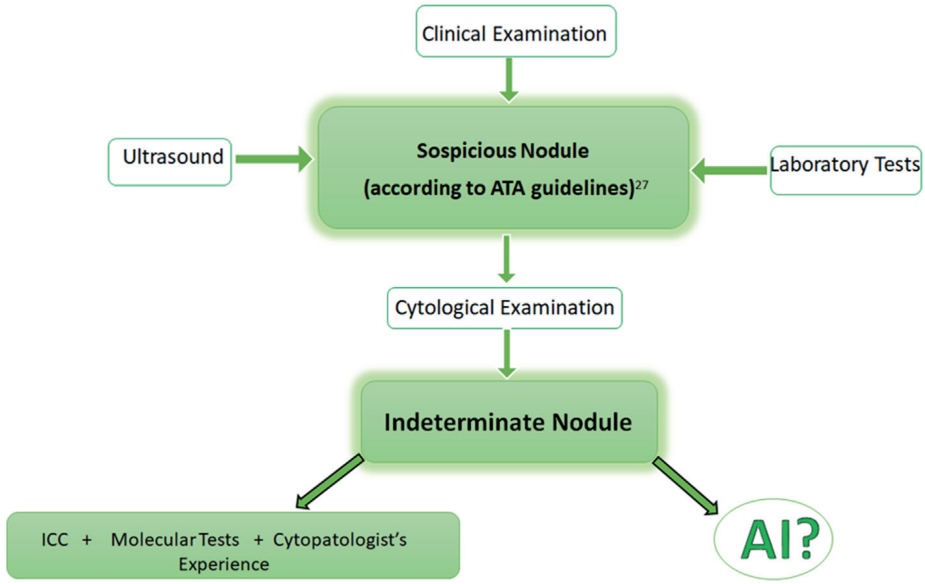

Figure 1 Thyroid nodule management.

Soon after, Daskalakis et al.[54] efficaciously adopted a multi-classifier system to distinguish between benign and malignant nodules based on nuclear texture and morphology, and Varlatzidou et al.[55] showed how the combination of neural networks with morphometry could increase the accuracy of thyroid FNAC, particularly in suspicious follicular neoplasms and in Hürthle cell tumours.

All these studies were performed before the introduction of whole-slide-imaging (WSI) and their main limitation was the use of static images. Gopinath et al. published several manuscripts using pictures taken from the Papanicolaou Society of Cytopathology online atlas, and this is the reason why their results couldn't be broadly applied to real-world practice since the inputs given to the system were too limited: the training data did not reflect the variation observed in daily practice.[56–58] The transition from a traditional semi-manual cytomorphometry-based approach to an automated one is evident in work by Gilshtein et al.,[59] who showed a great diagnostic accuracy of both techniques within the indeterminate Bethesda groups, even if the automated approach based on the association of wavelets analysis with a neural network method achieved the results quicker.

Moreover, the wide adoption of WSI has given a great boost to the application of AI in thyroid cytopathology, which allows for the digitalisation and storage of entire slides.

In this regard, one of the most comprehensive analyses regarding the role of AI in WSI-based thyroid pathology was done by Girolami et al.,[60] who showed comparable diagnostic performances of automated models and expert pathologists, particularly for distinguishing among malignant and benign nodules in the indeterminate cytological categories and between encapsulated lesions with the evaluation of the immunohistochemical expression of different biomarkers.

The importance of AI in diagnosing indeterminate thyroid nodules was remarked by Savala et al.[61] who used an ANN to distinguish between follicular adenoma and follicular carcinoma at cytology, achieving high accuracy in the training set. Moreover, Shih et al.[18] quantified cytological features in thyroid FNACs to develop a diagnostic computer-aided tool to detect papillary thyroid carcinoma within the indeterminate category. However, even if the logistic model adopted by the authors showed good sensitivity for Bethesda III category and was very specific for Bethesda V category (suspicious for malignancy), it was less efficient for Bethesda IV category.

Fragopoulos et al.[62] applied an AI methodology based on the radial basis function (RBF) ANN to thyroid cytopathology. The authors found that such a technique has a high sensitivity, specificity and accuracy in predicting subsequent malignancy at histology.

Dov et al.[63] developed a deep-learning algorithm to identify follicular cell groups, and predict malignancy and TBSRTC category, reaching results comparable with manual performances. Moreover, the same author[64] applied a machine learning algorithm to thyroid fine needle aspiration biopsy (FNAB) WSIs and demonstrated its ability to recognise and screen for regions of interest (ROIs) that could be helpful for the final diagnosis.

Also, Range et al.[65] applied a machine learning algorithm (MLA) to whole-slide thyroid cytopathology images to identify follicular cells and establish the TBSRTC category. The authors found that the MLA has high sensitivity and specificity, similar to a manual review.

More recently, Yao et al. evaluated a machine learning-based digital image analysis technique[66] to analyse cases originally classified as atypical and finally diagnosed as benign or follicular adenomas at histology. In this study, atypical follicular lesions were better subclassified by MLA than by humans. Moreover, Hirokawa et al.[67] and Alabrak et al.[68] showed a remarkable efficiency of AI in diagnosing FTNs, distinguishing between follicular adenomas and follicular carcinomas with high accuracy.

Recently, Kezlarian and Lin[69] made an up-to-date and thorough analysis of literature data regarding the application of AI solutions to thyroid FNAB. The authors summarised all available literature data on the application of AI to thyroid cytopathology, showing that different algorithms have largely improved the diagnostic accuracy of thyroid cytology but emphasising the need for standardisation and larger multicentric datasets. In fact, despite the promising results, AI-assisted cytopathological diagnosis of thyroid nodules has several limits.

As previously stated, larger multicentric datasets and standardisation are needed. Moreover, there may be biases in the data that could affect algorithm performance. Nonetheless, large amounts of high-quality data are needed to train the algorithms and the important size of WSI images in terms of gigabytes, as clearly reported by Dov et al.,[63] could make the functioning of the AI algorithms problematic. Additionally, cytological samples usually contain a low percentage of analysable relevant follicular cells, as shown in a work that aimed to develop an algorithm to identify significant clusters of follicular cells to optimise the computational demands.[70] In addition, cytologic smears often contain intact cells that sometimes form dense clusters of several layers: multiple layer scans are therefore needed with a consequent increase of both acquisition times and storage requirements and lower image quality.[28,71]

Last but not least, regulatory and ethical considerations must be addressed before AI is widely adopted in clinical practice. Data privacy and transparency should be ensured, and the transparency of both study outcomes and data and algorithms sharing should be guaranteed.[72]

Conclusions

Overall, the articles reported in this review highlight the potential of new AI technologies in improving the diagnosis and management of indeterminate thyroid nodules. AI techniques can improve diagnostic accuracy and efficiency and assist cytopathologists in the diagnostic phase, potentially reducing errors. In fact, training AI algorithms on large datasets make it possible to identify patterns that human observers may miss, reducing inter-observer variability and improving diagnostic consistency. However, further research is needed to validate these findings and determine the clinical utility of these tools in diagnosing and managing thyroid nodules. The full potential of AI in clinical practice is still to be discovered, and the application of AI-based diagnostic systems in clinical workflows should be standardised. ◆

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