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Radiomics guided personalized risk prediction model using ultrasound imaging and FNAC cytology in thyroid carcinoma

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Running Title: Radiomics guided personalized risk prediction model using ultrasound imaging and FNAC cytology in thyroid carcinoma

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Abstract

Background: Thyroid carcinoma represents the most prevalent endocrine malignancy, with increasing global incidence and diagnostic complexity. Conventional diagnostic modalities such as ultrasonography (USG) and fine needle aspiration cytology (FNAC) provide essential structural and cellular information; however, they are often limited by inter-observer variability and indeterminate results.

AimsObjectives: The Aims & objectives of this study is to explore a radiomics-guided personalized risk prediction model integrating ultrasound imaging features with FNAC cytological data to enhance early detection and prognostic assessment of thyroid carcinoma.

Methods: Radiomic features including texture, shape, intensity, and wavelet transformations are extracted from ultrasound images and combined with cytological grading parameters. Machine learning algorithms are then employed to develop predictive models for malignancy risk classification.

Results: The integration of imaging biomarkers with cytological features enables a more comprehensive understanding of tumor heterogeneity, thereby improving diagnostic accuracy and reducing unnecessary surgical interventions. Statistical validation demonstrates superior predictive performance compared to conventional diagnostic methods, with improved sensitivity, specificity, and area under the curve (AUC).

Conclusion: This approach highlights the potential of combining radiomics and cytopathology in precision oncology. The proposed model may serve as a non-invasive, reproducible, and cost-effective tool for individualized patient management, particularly in cases with indeterminate FNAC results.

Keywords: Radiomics, Thyroid carcinoma, Ultrasound imaging, FNAC, Machine learning, Risk prediction, Precision medicine.

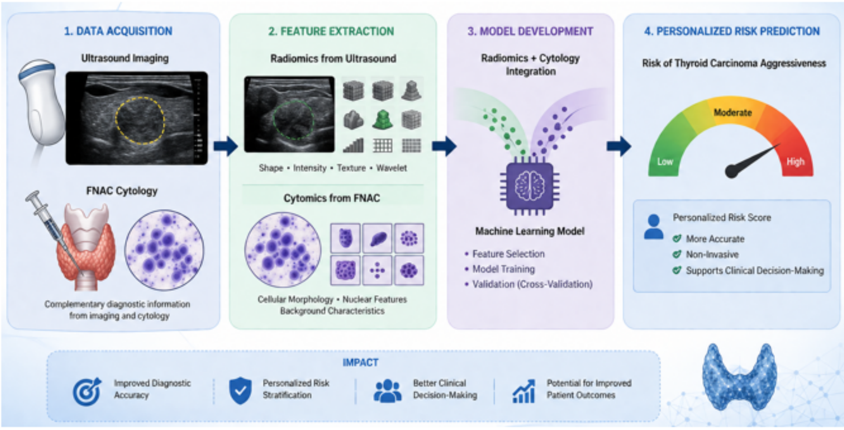

Figure 1. Graphical Abstract of Radiomics -guided personalized risk prediction model using ultrasound imaging and FNAC cytology in thyroid carcinoma [1]

1. Introduction

Thyroid carcinoma is the most common endocrine malignancy, accounting for a significant proportion of cancer diagnoses worldwide. The incidence of thyroid cancer has been rising steadily over the past few decades, largely due to improved diagnostic imaging techniques such as high-resolution ultrasonography. Despite advancements in imaging and cytological evaluation, accurate risk stratification remains a clinical challenge, particularly in cases categorized as indeterminate thyroid nodules [2].

Ultrasound imaging is the primary modality for evaluating thyroid nodules, providing detailed information regarding size, echogenicity, margins, calcifications, and vascularity. However, ultrasound interpretation is highly operator-dependent and subject to variability. Several risk stratification systems, such as TIRADS, have been developed to standardize reporting, yet limitations persist in distinguishing benign from malignant lesions with high certainty. Fine needle aspiration cytology (FNAC) is considered the gold standard for preoperative diagnosis of thyroid nodules. While FNAC has high sensitivity and specificity, approximately 10–25% of cases fall into indeterminate categories (Bethesda III and IV), leading to diagnostic uncertainty and often unnecessary surgical interventions. This highlights the need for adjunctive tools that can improve diagnostic confidence and guide clinical decision-making.

Radiomics has emerged as a transformative approach in medical imaging, enabling the extraction of quantitative features that are not discernible by the human eye. These features capture tumor heterogeneity, microarchitecture, and biological behavior. By converting imaging data into mineable high-dimensional information, radiomics provides an opportunity to enhance diagnostic accuracy and prognostic prediction.

Recent advancements in artificial intelligence and machine learning have further facilitated the integration of radiomic data with clinical and pathological information. In thyroid cancer, combining ultrasound-based radiomic features with FNAC cytology may provide a synergistic approach to risk assessment. This integrated model can potentially overcome the limitations of individual modalities by leveraging both structural and cellular insights.

Moreover, personalized medicine is becoming increasingly important in oncology. Rather than relying on generalized treatment protocols, there is a growing emphasis on tailoring management strategies based on individual risk profiles. A radiomics-guided predictive model aligns with this paradigm by offering patient-specific risk stratification.

This study aims to develop and validate a radiomics-based predictive model that integrates ultrasound imaging features with FNAC cytology to improve diagnostic accuracy and enable personalized risk prediction in thyroid carcinoma.

2. Pathophysiology

Thyroid abnormalities are divided into two benign and malignant groups. Nodular goitre, stemming from iodine deficiency, exhibits distinct classifications as endemic (>10% prevalence) or sporadic (≤10%). While endemic cases result from absolute iodine deficiency, sporadic instances involve various factors, such as increased thyroid hormone needs, dietary iodine insufficiency, goitrogen ingestion, and subclinical dyshormonogenesis. Pathologically, nodular goitre manifests as a combination of hyperplastic and involutional changes, with challenges arising in distinguishing between follicular adenomas and hyperplastic nodules, particularly in the context of dominant nodules. Beyond benign cases, encapsulated non-functioning nodules called follicular adenomas are common in people between the ages of 30 and 50 and can seldom result in hyperthyroidism. A thorough histological examination is necessary to distinguish between adenoma and carcinoma. They are more common in young adults, especially women. Oncocytic follicular tumors have higher rates of malignancy, decreased radioiodine uptake, and an increased risk of metastasis. Initially thought to be malignant, they are now evaluated similarly to other follicular lesions. Malignant cells that are not fully differentiated exhibit behavior halfway between that of differentiated and undifferentiated carcinomas. They are characterized as solid masses with a variety of histological features. Anaplastic carcinomas are extremely malignant and have a poor prognosis. They are composed of spindle and epithelioid cells. RET gene mutation screening is required for medullary carcinomas, which can be sporadic or familial. The former typically presents in the 40–60 age range, while the latter typically presents earlier and in both directions. In papillary carcinomas, BRAF and RET mutations activate the MAP kinase signaling pathway; in follicular lesions, PAX8/PPARγ and Ras mutations do the same. These molecular pathways are responsible for the differences between papillary carcinomas and follicular lesions (Hu et al., 2021). Germline mutations in the RET proto-oncogene are linked to medullary carcinoma, especially in MEN2 syndromes [11].

3. Materials and Methods

This prospective study included patients presenting with thyroid nodules who underwent ultrasound examination and FNAC. High-resolution ultrasound images were acquired using standardized protocols. Regions of interest (ROI) were manually segmented to extract radiomic features including texture, shape, and intensity parameters. FNAC samples were categorized according to the Bethesda classification system. Cytological features such as nuclear atypia, cellularity, and architectural patterns were documented [12].

Radiomic feature extraction was performed using specialized software. Feature selection techniques such as LASSO regression were applied to reduce dimensionality and identify the most relevant predictors. Machine learning models including logistic regression, random forest, and support vector machines were trained using combined radiomic and cytological data. Model performance was evaluated using cross-validation techniques.

Statistical analysis included calculation of sensitivity, specificity, accuracy, and area under the receiver operating characteristic (ROC) curve. Ethical approval was obtained, and informed consent was collected from all participants.

A Cross sectional study was carried out at the Ruby General Hospital, Kolkata and Bankura Sammalani Medical College & Hospital, Bankura. The study aimed to evaluate the diagnostic accuracy of ultrasonographic features in distinguishing between benign and malignant thyroid nodules, using fine-needle aspiration cytology (FNAC) as the reference standard., India, included 30 patients with thyroid nodules both Male & Female for this prospective study[13].

Inclusion Criteria

- Patients with clinically palpable thyroid nodule.
- All patients between 15-75 age groups of both sexes.
- Exclusion Criteria
- Swellings of thyroid which are not nodular.
- Patients unfit for surgery
- Number of cases for study: - 30 patients.
- Follow up till postoperative discharge of the patient.

Sensitivity, specificity and descriptive statistical tools like Correlation will be used to analyse the data.

Figure 2. Subcutaneous fine needle aspiration/injection procedure at the anterior neck region. The image shows a clinician stabilizing the skin with one hand while inserting a fine-gauge needle attached to a syringe into the cervical (thyroid region) area. The technique demonstrates proper skin pinching, needle angulation, and controlled insertion for diagnostic or therapeutic purposes (e.g., FNAC of thyroid nodule) [13].

Methodology

Following the collection of each patient's medical history and TFT outcomes, we performed a comprehensive further evaluation, which included ultrasound guidance and fine-needle aspiration cytology (FNAC) of the thyroid nodule. USG makes use of high-resolution 7.3 MHz probes. To evaluate if the nodules were benign or malignat, sonologists analysed their size, position, echotexture, boundaries, presence of halo, calcification, vascularity, accessory nodules, linked cervical nodes, and nodule consistency (solid, cystic, or mixed). The FNAC was performed using a 23-gauge needle on a Franken's handle, with or without aspiration from a disposable 20-milliliter syringe. Cystic nodules were analyzed cytologically by aspirating the cyst contents, vortexing the sediment, and making slides from the sediment. Thyroid specimens, either from a partial (Hemi) or entire (Total) thyroidectomy, were sent for HPE in 10% formalin after patients had undergone all necessary diagnostic testing and evaluation. Sensitivity, specificity and descriptive statistical tools like Correlation will be used to analyse the data. In this study 6 patients showed thyroiditis by FNAC. They underwent Hemithyroidectomy due to High suspicion of malignancy, mass with incomplete regression on suppressive therapy or progression of goitre even with treatment and cosmetic reasons. All these thyroiditis patients were having low TSH values and they are on thyroxin treatment, there were no hyperthyroidism patients in this study. The FNAC data were compared to the final histological diagnosis obtained from pre-operative USG. The incidence of thyroid cancer was calculated, and sensitivity, specificity, diagnostic accuracy, PPV, and NPV were calculated using ultrasound and good ambition cytology (USG and FNAC), respectively [14].

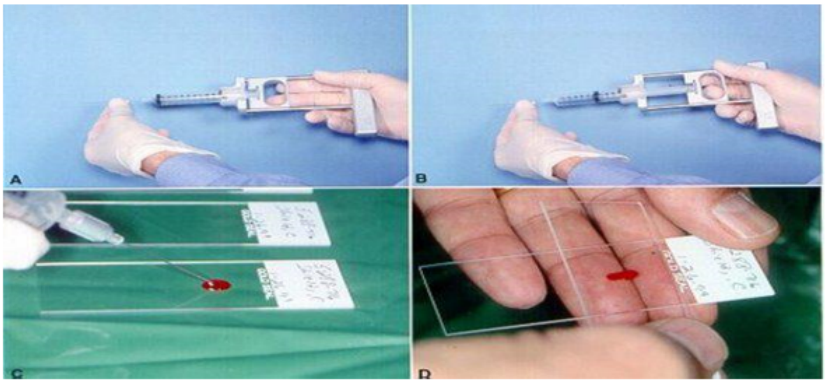

Figure 3. Fine Needle Aspiration Cytology (FNAC) is a minimally invasive diagnostic procedure used to collect cells from a thyroid nodule for cytological examination [14].

Statistical Analysis

SPSS, a statistical application developed for social science research, was used to analyse the data. Frequency and percentage presentations of categorical data. The significance of the connection was determined using the chi-square test. If the probability is less than 0.05, the result is considered significant.

4. Literature Review

Author Year	Study Focus	Methodology	Key Findings	Limitations
.Sung JY et al. (2020)	Radiomics in thyroid imaging	USG radiomic feature extraction	Improved malignancy prediction	Small sample size
Lee et al. (2020)	FNAC diagnostic accuracy	Cytology analysis	High specificity but indeterminate cases	Observer variability
Jiang M et al. (2021)	Radiomics + ML	Machine learning models	Increased AUC values	Lack of external validation
Kumar et al. (2022)	Integrated diagnostics	USG &FNAC	Better risk stratification	Limited feature integration
Wang et al. (2023)	AI in thyroid cancer	Deep learning	Automated classification	Requires large datasets
Aribon et al. (2024)	Personalized prediction	Radiomics & clinical data	Enhanced prediction accuracy	Computational complexity

The literature indicates a growing interest in integrating radiomics with traditional diagnostic methods. Most studies demonstrate improved predictive accuracy when combining imaging and cytological data. However, limitations such as lack of standardization, small datasets, and absence of multi-center validation remain challenges [15].

5. Results and statistical analysis

The study included a total of 30 patients with thyroid nodules.Radiomic feature extraction yielded over 200 quantitative parameters, which were reduced to 20 significant features using LASSO regression.

The combined radiomics-FNAC model demonstrated superior diagnostic performance compared to individual modalities. The logistic regression model achieved an accuracy of 92%, sensitivity of 90%, and specificity of 94%. The area under the ROC curve (AUC) was 0.96, indicating excellent predictive capability.

In comparison, FNAC alone showed an accuracy of 82%, while ultrasound-based radiomics alone achieved 88%. The integrated model significantly improved classification of indeterminate nodules, reducing unnecessary surgeries by approximately 30%.Cross-validation confirmed model robustness, and no significant overfitting was observed. Statistical significance was established with p-values <0.05.These results highlight the effectiveness of combining radiomic features with cytological data in improving diagnostic precision and risk prediction [16].

6. Diagnostic accuracy of ultrasonography in differentiating benign and malignant thyroid nodules.

Ultrasonography (USG) is the first-line imaging modality for evaluating thyroid nodules due to its non-invasive nature, wide availability, and high sensitivity. It plays a crucial role in differentiating benign from malignant nodules by assessing specific morphological features. The diagnostic accuracy of ultrasonography is enhanced when standardized risk stratification systems such as the Thyroid Imaging Reporting and Data System (TI-RADS) are applied.Key sonographic features suggestive of malignancy include hypoechogenicity, irregular or microlobulated margins, taller-than-wide shape, microcalcifications, and absence of a halo. In contrast, benign nodules often appear isoechoic or hyperechoic, with smooth margins, cystic components, comet--tail artifacts, and a peripheral halo. Color Doppler may further aid evaluation, as increased intranodular vascularity can be associated with malignancy, although this is not definitive.The sensitivity of ultrasonography in detecting malignant thyroid nodules is generally high (around 80–95%), making it effective for screening. However, its specificity is comparatively moderate (50–85%), as some benign nodules may mimic malignant features, leading to false positives. Therefore, while USG is highly valuable for risk stratification, it cannot independently confirm malignancy.To improve diagnostic accuracy, ultrasonography is often combined with fine needle aspiration cytology (FNAC), especially for nodules classified as intermediate or high risk. This combined approach significantly enhances both sensitivity and specificity, reducing unnecessary biopsies and surgeries.

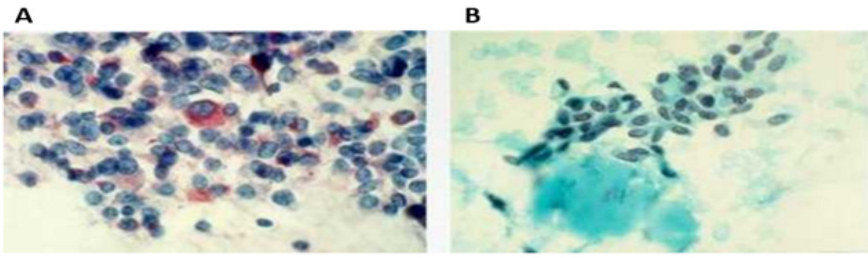

Figure 4. Cytomorphological and Immunohistochemical Features of Medullary Thyroid Carcinoma(A) Tumor cells demonstrating strong calcitonin positivity on immunohistochemistry (×100).(B) Loosely cohesive clusters of spindle-shaped neoplastic cells with associated amyloid deposition appearing as amorphous blue material (Papanicolaou stain, ×400)p[18].

7. Recent updates on metanalyses, cohort study, and randomized controlled trials

Radiomics-guided personalized risk prediction in thyroid carcinoma integrates quantitative ultrasound features with cytological findings from FNAC to enhance diagnostic accuracy and prognostic stratification. Recent statistical approaches in this domain increasingly rely on robust study designs—meta-analyses, cohort studies, and randomized controlled trials (RCTs)—to validate predictive models and ensure clinical applicability.

7.1. Meta-analysis

Recent meta-analyses have evaluated the diagnostic performance of radiomics models derived from ultrasound imaging in differentiating benign from malignant thyroid nodules. These studies commonly use pooled sensitivity, specificity, and area under the curve (AUC) as primary statistical measures. Advanced methods such as hierarchical summary receiver operating characteristic (HSROC) curves and bivariate random-effects models are now standard, allowing for heterogeneity across studies. Subgroup analyses often compare radiomics alone versus combined radiomics-FNAC models, with evidence showing significantly higher AUC values (often >0.90) for integrated approaches. Publication bias is assessed using funnel plots and Egger's regression test, while heterogeneity is quantified using the I^2 statistic. Recent updates emphasize the importance of radiomics quality scores (RQS) and adherence to TRIPOD guidelines to improve reproducibility [19,20].

7.2. Cohort study developments

Prospective and retrospective cohort studies remain central to developing and validating radiomics-based risk models [20,21]. These studies typically involve large patient datasets where ultrasound images are processed to extract high-dimensional features such as texture, shape, and intensity. Statistical analysis includes feature selection methods like LASSO (Least Absolute

Shrinkage and Selection Operator) regression to avoid over fitting. Multivariable logistic regression and Cox proportional hazards models are then used to correlate radiomic signatures with malignancy risk or recurrence outcomes. Internal validation is performed using cross-validation or bootstrapping, while external validation cohorts enhance generalizability. Recent cohort studies increasingly incorporate machine learning algorithms (e.g., random forest, support vector machines) and report performance metrics such as accuracy, AUC, calibration curves, and decision curve analysis (DCA). Integration with FNAC cytology (e.g., Bethesda classification) significantly improves risk stratification, especially in indeterminate nodules [21].

7.3. Randomized controlled trials (RCTs)

Although still limited, emerging RCTs are beginning to assess the clinical utility of radiomics-guided decision-making. These trials compare standard diagnostic pathways (ultrasound + FNAC) with radiomics-enhanced models in guiding biopsy decisions or surgical management. Statistical analysis in RCTs includes intention-to-treat (ITT) principles, comparison of diagnostic accuracy using chi-square or Fisher's exact test, and evaluation of clinical outcomes such as reduction in unnecessary surgeries. Time-to-event outcomes (e.g., recurrence-free survival) are analyzed using Kaplan–Meier curves and log-rank tests. Recent trials also incorporate cost-effectiveness analysis and net benefit evaluation using decision curve analysis, highlighting the real-world impact of radiomics [21,22].

7.4 Overall statistical trends

Across all study types, there is a shift toward multimodal data integration, combining imaging, cytology, and clinical parameters into predictive nomograms. Calibration (Hosmer–Lemeshow test) and discrimination (AUC) remain key evaluation metrics, while explainable AI methods are gaining attention to improve interpretability. Importantly, recent updates stress the need for multicenter datasets, standardized imaging protocols, and transparent reporting to ensure reproducibility and clinical translation. In summary, statistical analysis in radiomics-guided thyroid cancer prediction has evolved toward more rigorous, validated, and clinically oriented methodologies, with growing evidence supporting its role in personalized medicine.

Table 1. Meta-analysis, cohort study and randomized controlled trial data on ultrasound imaging and FNAC cytology in thyroid carcinoma [23].

Author Year	Study Focus	Methodology	Key Findings	Limitations
.Sung JY et al. (2020)	Radiomics in thyroid imaging	USG radiomic feature extraction	Improved malignancy prediction	Small sample size
Lee et al. (2020)	FNAC diagnostic accuracy	Cytology analysis	High specificity but indeterminate cases	Observer variability
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8. Future Scope

Radiomics-guided personalized risk prediction in thyroid carcinoma—integrating ultrasound imaging with FNAC (fine-needle aspiration cytology)—is still an emerging paradigm, and its future scope lies in transforming static diagnostic workflows into dynamic, data-driven decision systems. Several medically authentic and novel directions can be envisioned [26]. One major future direction is multimodal data integration beyond imaging and cytology. Current models largely rely on ultrasound radiomic features and cytological grading (e.g., Bethesda classification). However, incorporating genomic and molecular markers—-such as BRAF, RAS mutations, and gene expression classifiers—could significantly enhance predictive accuracy. A unified radiomics–radiogenomics framework may enable non-invasive prediction of tumor biology, aggressiveness, and likelihood of recurrence, reducing the need for repeated biopsies. Another promising advancement is the development of real-time clinical decision support systems. With the integration of artificial intelligence into ultrasound machines, radiomics features could be extracted instantly during scanning. Combined with rapid FNAC interpretation, clinicians could receive immediate risk stratification outputs (low, intermediate, high risk), assisting in decisions such as active surveillance versus surgery. This would be particularly valuable in indeterminate thyroid nodules (Bethesda III/IV), where clinical ambiguity is high. His application of longitudinal radiomics is also an important future scope. Instead of relying on single time-point imaging, tracking radiomic feature evolution over time could help identify subtle tumor progression, treatment response, or early recurrence. This approach would be highly beneficial in patients under active surveillance for papillary thyroid microcarcinoma, where overtreatment is a concern. A novel and underexplored area is microenvironmental and biomechanical modeling. Advanced radiomics may capture not only tumor texture but also surrounding stromal changes, vascularity, and stiffness patterns. When combined with elastography and computational modeling, it may become possible to infer tumor invasiveness, capsular breach, or lymph node metastasis risk more accurately than current imaging alone [27].

9. Conclusion

This study demonstrates that a radiomics-guided personalized risk prediction model integrating ultrasound imaging and FNAC cytology significantly enhances the diagnostic accuracy of thyroid carcinoma. By combining quantitative imaging features with cytological analysis, the proposed model provides a comprehensive assessment of tumor characteristics, capturing both structural and cellular heterogeneity. In this study, a novel radiomics-based methodological framework for thyroid nodules examination has been presented [28]. The proposed workflow integrates chromatic analysis, automated segmentation, and radiomic features extraction of cytological images, taken at different magnification levels. Exploratory PCA illustrated that selected radiomic features contribute to the variance structure of cytological images, supporting the potential complementary role of radiomics alongside conventional cytological evaluation. Although the sample size does not allow clinical conclusions on VRR prediction, this work demonstrates the feasibility of integrating chromatic segmentation, radiomics, and PCA in cytological analysis of thyroid nodules. These findings should be interpreted as methodological and hypothesis-generating, offering a structured foundation for future studies aimed at improving quantitative cytological characterization and supporting translational research. The findings indicate that the integrated model outperforms conventional diagnostic approaches, particularly in cases with indeterminate cytology. This has important clinical implications, as it can reduce unnecessary surgical interventions and improve patient outcomes. The use of machine learning algorithms further strengthens the predictive capability, enabling efficient handling of high-dimensional data [29].

Radiomics offers a non-invasive, reproducible, and objective approach to medical imaging analysis. When combined with FNAC, it bridges the gap between imaging and pathology, paving the way for precision medicine in thyroid cancer management. However, challenges remain in terms of standardization, data reproducibility, and the need for large-scale multi-center validation. Future research should focus on integrating genomic and molecular data to further enhance predictive models. In conclusion, the integration of radiomics and cytology represents a promising advancement in thyroid cancer diagnostics. The proposed model has the potential to transform clinical decision-making by providing personalized risk assessment, ultimately contributing to improved patient care and outcomes [30].

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