Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol.14, Issue 1s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Long Non-Coding RNAs in Thyroid Cancer

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Cite this paper as: Nour El Hoda H. El Emam, Hamdy Sliem, Nearmeen M. Rashad, Mohamed Ahmed Greash, Iman El Sherif (2025) Long Non-Coding RNAs in Thyroid Cancer..Journal of Neonatal Surgery, 14, (1s) 1484-1492

ABSTRACT

Background: Accurate preoperative differentiation between benign and malignant thyroid nodules remains a clinical challenge, particularly in cases with indeterminate cytology. Conventional diagnostic tools such as ultrasound and fine-needle aspiration cytology have limited diagnostic accuracy in a subset of patients. Long non-coding RNAs, including Nuclear Enriched Abundant Transcript 1 (NEAT1), have emerged as potential molecular biomarkers in various malignancies, including thyroid cancer.

Method: This observational cross-sectional study included sixty adult participants divided into three equal groups: patients with malignant thyroid nodules, patients with benign thyroid nodules, and healthy controls. Serum samples were collected from all participants. NEAT1 expression levels were quantified using quantitative real-time polymerase chain reaction and analyzed in serum. Statistical analysis and receiver operating characteristic (ROC) curve analysis were performed to assess the diagnostic performance of NEAT1 expression.

Result: NEAT1 expression levels in serum was significantly higher in patients with malignant thyroid nodules compared with benign nodules and controls ($p < 0.001$). Serum NEAT1 expression showed a strong positive correlation. ROC curve analysis demonstrated high diagnostic accuracy of NEAT1 expression.

Conclusion: NEAT1 is significantly upregulated in malignant thyroid nodules and demonstrates strong diagnostic performance. Circulating NEAT1 may serve as a promising non-invasive molecular biomarker to complement conventional diagnostic tools in the preoperative evaluation of thyroid nodules.

Keywords: Thyroid cancer; NEAT1; Long non-coding RNA; Thyroid nodules; Biomarkers; qRT-PCR..

1. INTRODUCTION

Thyroid cancer is the most common malignancy of the endocrine system and its incidence has shown a steady global increase over recent decades, largely attributed to improved diagnostic imaging and enhanced detection of small and indolent tumors. Despite the generally favorable prognosis of differentiated thyroid cancer, accurate preoperative discrimination between benign and malignant thyroid nodules remains a major clinical challenge (1,2).

Ultrasound-based risk stratification systems and fine-needle aspiration cytology (FNAC) are the cornerstones of thyroid nodule evaluation. However, these approaches are limited by operator dependency and a considerable proportion of indeterminate cytological results, particularly within Bethesda categories III and IV. Consequently, a significant number of patients undergo unnecessary surgical interventions for lesions that are ultimately benign, emphasizing the need for reliable molecular biomarkers to enhance diagnostic accuracy and guide clinical decision-making (3,4).

Long non-coding RNAs (lncRNAs) have emerged as key regulators of gene expression at transcriptional and post-transcriptional levels and have been implicated in cancer initiation, progression, and metastasis (5,6). Unlike protein-based biomarkers, lncRNAs can be readily quantified using standardized molecular techniques and are detectable in both tissue and circulating blood, making them attractive non-invasive diagnostic candidates (7).

Nuclear Enriched Abundant Transcript 1 (NEAT1) is a well-characterized lncRNA involved in paraspeckle formation and cellular stress responses. Accumulating evidence suggests that NEAT1 plays an oncogenic role in multiple malignancies, including thyroid cancer, through modulation of key signaling pathways and interaction with microRNAs (8–11)..

However, data regarding the diagnostic performance of circulating NEAT1 expression remain limited and inconsistent across different populations. Therefore, the present study aimed to evaluate the diagnostic utility of serum NEAT1 expression levels in differentiating benign from malignant thyroid nodules

2. METHODS

This observational cross-sectional study was conducted at the Endocrinology and Surgery outpatient clinics of Suez Canal University Hospital, Ismailia, Egypt, between September 2022 and March 2023. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants prior to enrollment.

A total of sixty adult participants were included and classified into three equal groups (n = 20 each): patients with histopathologically confirmed malignant thyroid nodules, patients with histopathologically confirmed benign thyroid nodules, and healthy controls with no clinical, biochemical, or ultrasonographic evidence of thyroid disease. Inclusion criteria comprised age above 18 years and eligibility for thyroid surgery when indicated. Exclusion criteria included previous chemotherapy or radiotherapy, concurrent malignancies, autoimmune diseases, acute infections, and chronic hepatic or renal failure.

All participants underwent comprehensive clinical evaluation, including demographic data collection, medical history, and physical examination. Thyroid ultrasonography was performed for all patients, and FNAC was obtained when clinically indicated. Laboratory investigations included serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) measurements.

Peripheral venous blood samples were collected from all participants. Total RNA was extracted from serum using standardized commercial extraction kits according to the manufacturer's instructions. Complementary DNA synthesis was subsequently performed, followed by quantitative real-time polymerase chain reaction (qRT-PCR) to assess NEAT1 expression levels. Gene expression was normalized to a housekeeping gene, and relative expression levels were calculated using the $2^{-}\Delta\Delta CT$ method (12). All reactions were performed in triplicate, and mean values were used for analysis.

Statistical analysis was conducted using SPSS software (version 22.0). Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were expressed as frequencies and percentages. Group comparisons were performed using one-way ANOVA or Kruskal–Wallis test for quantitative data and chi-square or Fisher's exact test for qualitative data, as appropriate. Receiver operating characteristic (ROC) curve analysis was applied to evaluate the diagnostic accuracy of serum NEAT1 expression levels. A p-value ≤ 0.05 was considered statistically significant.

Result:

The present study compared the levels of NEAT1 in the peripheral blood collected from subjects with malignant and benign thyroid nodules.

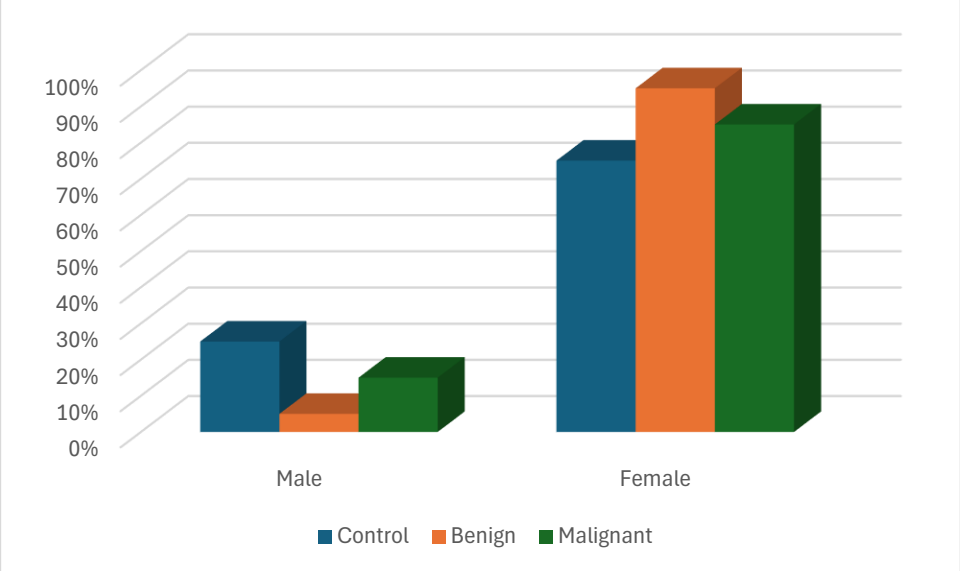


Figure1: Gender distribution of the study population

Figure 1 shows that there was no statistically significant difference between study groups regarding gender distribution.

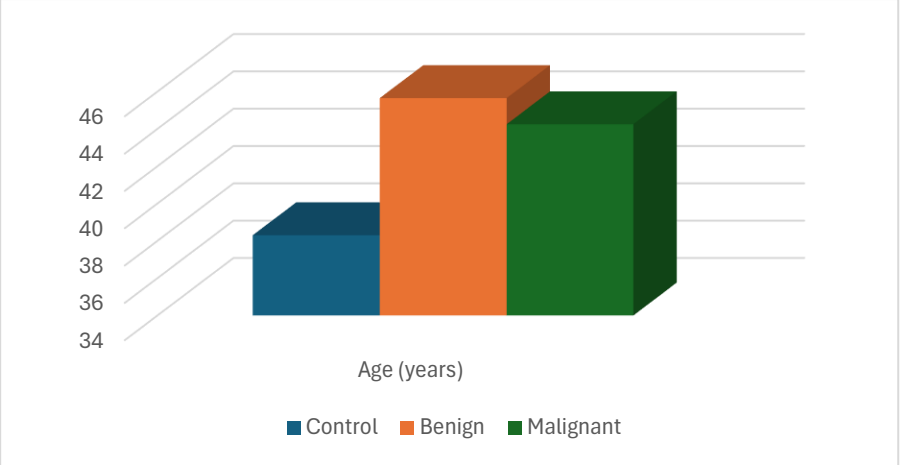


Figure2: Age distribution in the study population

Figure2 show that there was no statistically significant difference between the study's 3 groups regarding age.

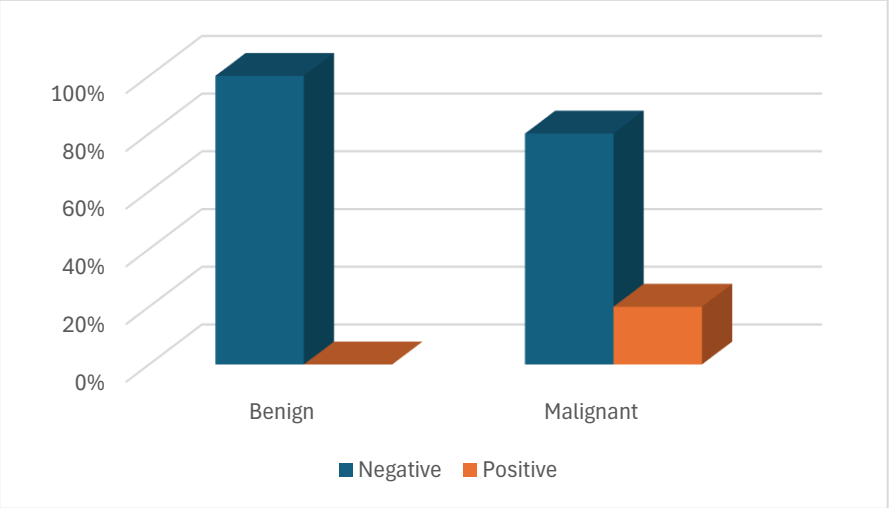


Figure3: family history of thyroid cancer among study population

Figure 3 demonstrates that there was a statistically significant difference between study groups regarding positive family history. The benign group showed negative family history.

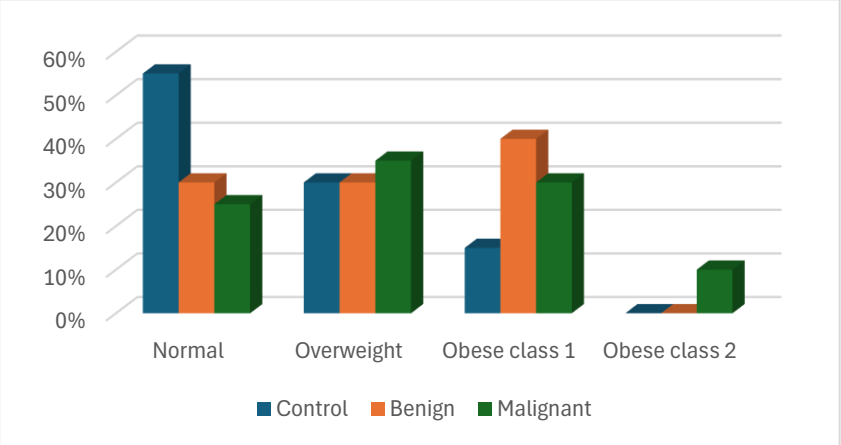


Figure4: Body mass index of the study population

Figure 4 shows that there was no statistically significant difference between study groups regarding body mass index class distribution. The highest frequency shown was for normal control individuals. There was no control or benign lesion individuals of class 2 obesity.

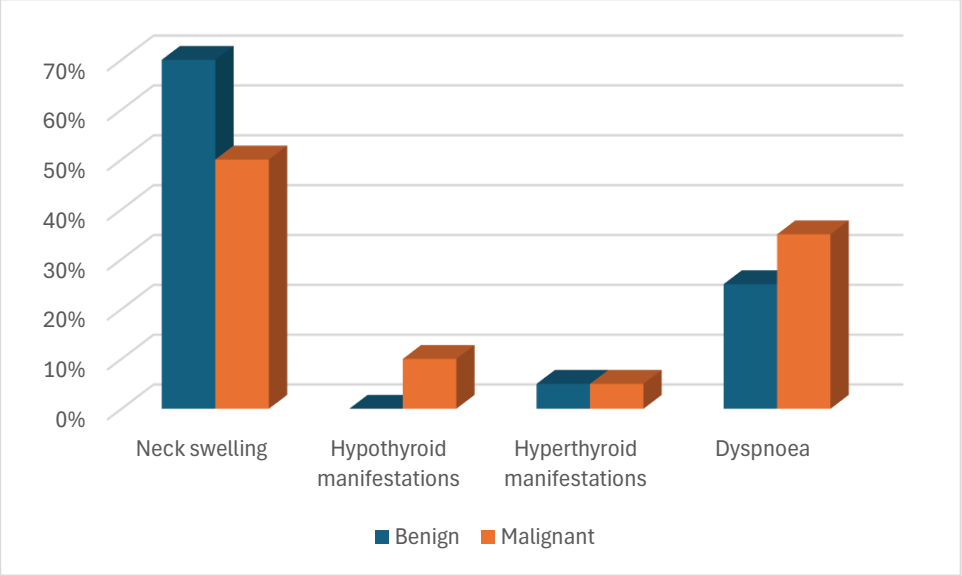


Figure5: Complaints of the study groups

Figure 5 shows that there was no statistically significant difference between benign and malignant groups regarding complaint distribution. The highest frequency in both benign and malignant groups was neck swelling.

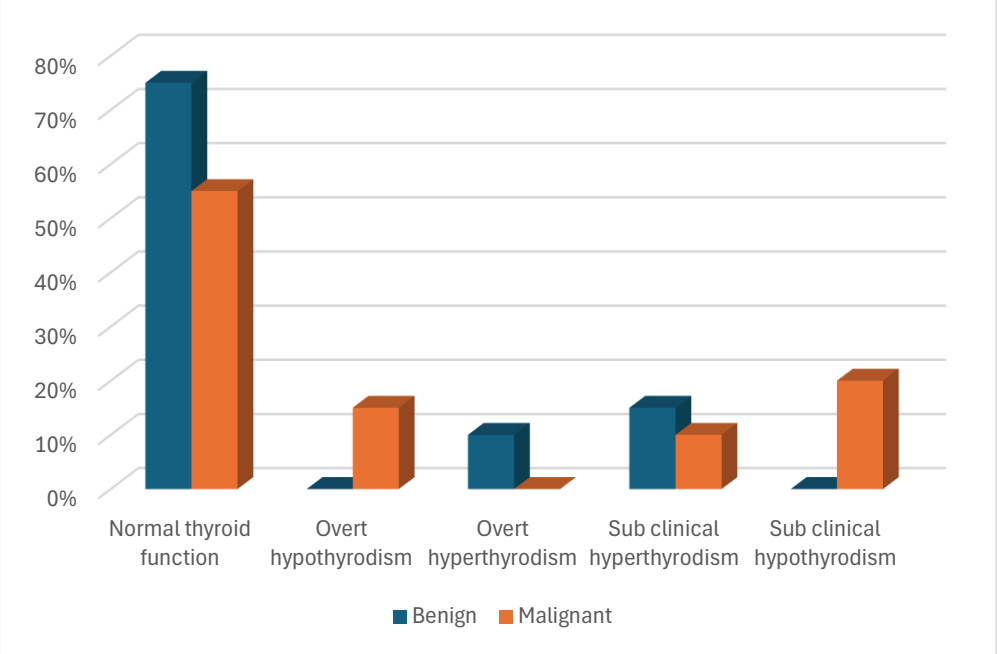


Figure6: Thyroid profiles of benign and malignant groups

Figure 6 shows that there was a statistically significant difference between benign and malignant groups regarding thyroid profile finding distribution. The highest frequency in both groups showed normal thyroid profile. There were no overt hypothyroid or overt hyperthyroid patients in the benign and malignant groups, respectively.

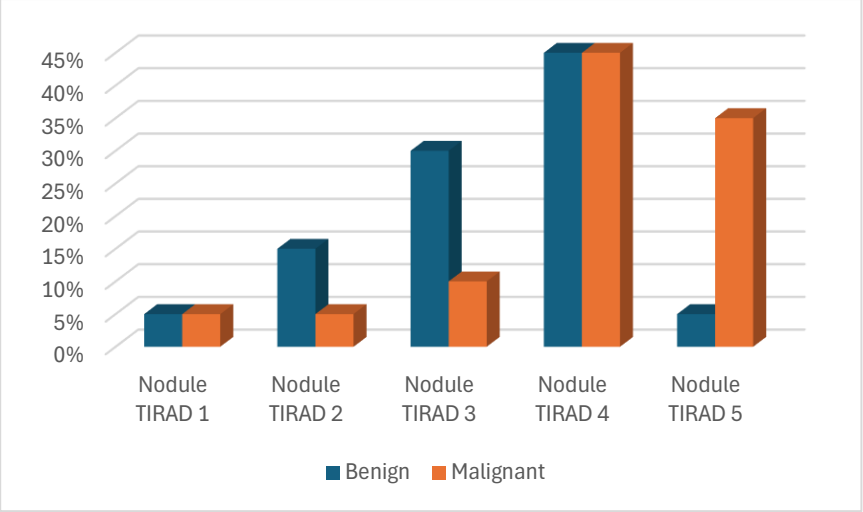


Figure7: Ultrasound findings of benign and malignant groups

Figure 7 shows that there was no statistically significant difference between benign and malignant groups regarding ultrasound examination findings distribution. The highest frequency shown was 9 nodule TIRAD 4 lesions in both groups.

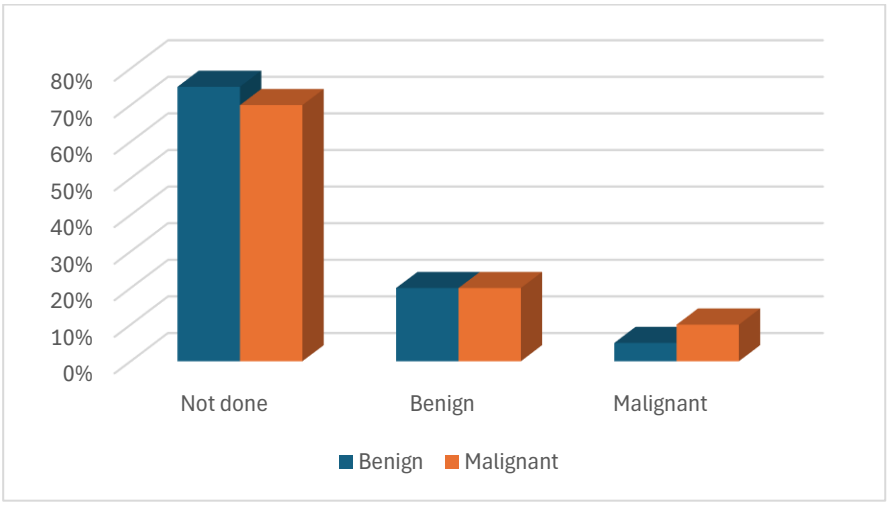


Figure8: FNAC results of benign and malignant groups

Figure 8 demonstrates that there was no statistically significant difference between study groups regarding Fine Needle Aspiration Cytology findings' distribution.

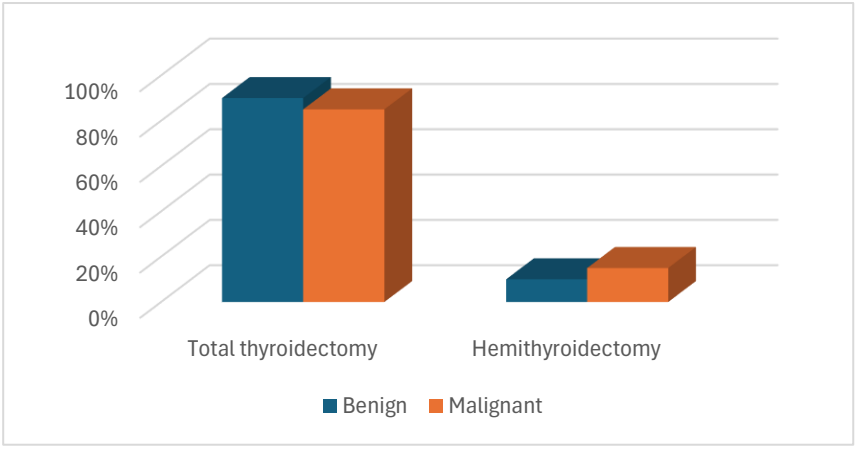


Figure9: Intervention done to benign and malignant groups

Figure 9 shows that there was no statistically significant difference between study groups regarding intervention done to patients.

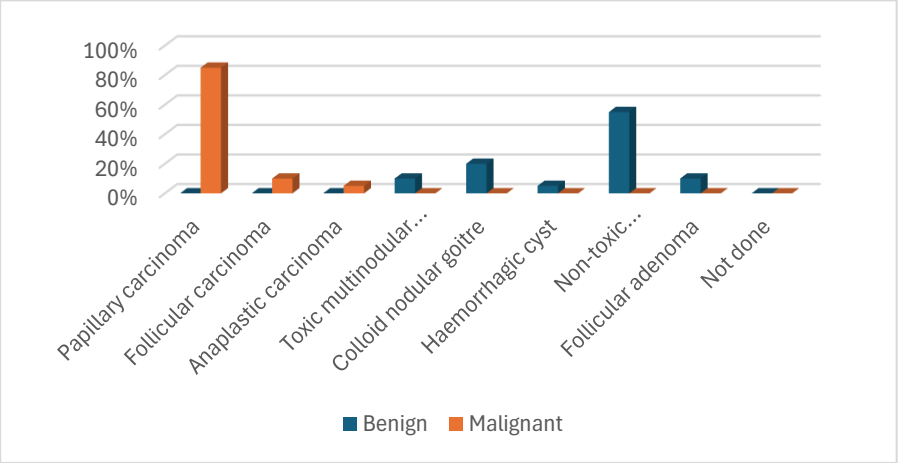


Figure10: Pathology findings

Figure 10 show that there was a statistically significant difference between benign and malignant groups regarding issue pathology findings distribution. The highest frequency shown in the benign group was of Non-toxic multinodular goitre. The highest frequency shown in the malignant group was of papillary thyroid carcinoma.

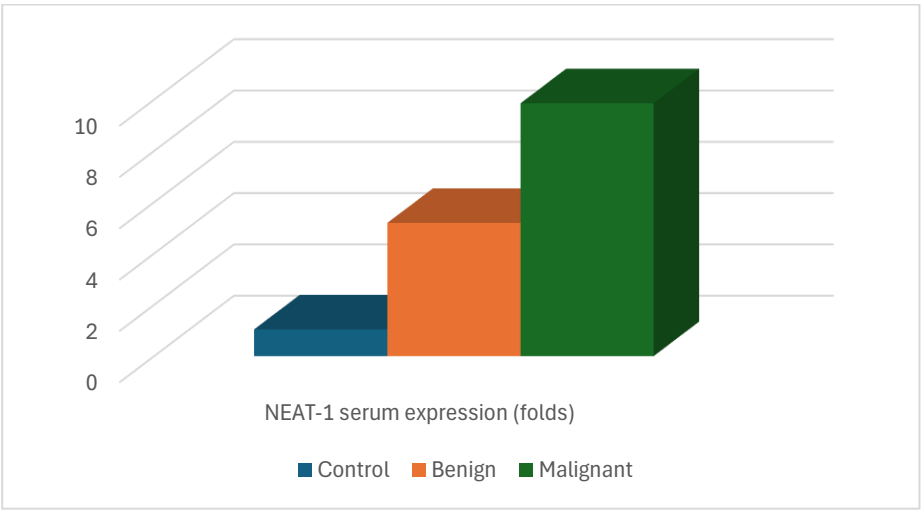
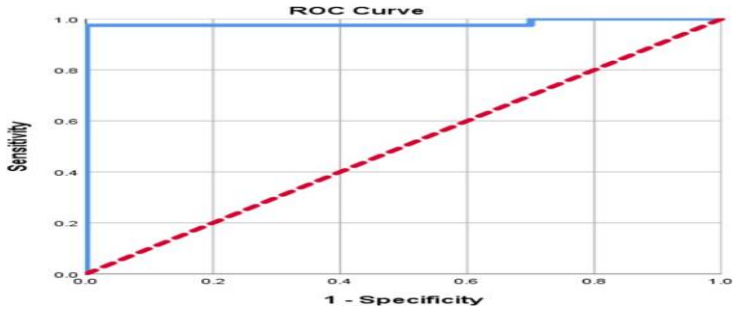


Figure11: NEAT-1 serum in study population (folds)

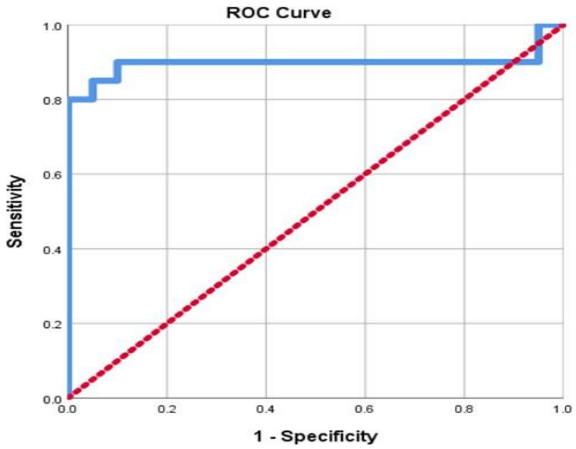
Figure 11 show that NEAT-1 expression in serum was statistically significant between all of the study groups.



p value<0.001

Figure 12: Receiver operating characteristic (ROC) curve of NEAT1 serum expression for distinction of a Benign nodule

ROC curve figure 12 shows that using 1.6177 folds in Serum as a cut-off point in the study population for distinction of a Benign nodule has a sensitivity of 97.5% , a specificity of 90% with a positive statistical significance , AUC 0.982, positive predictive value(PPV)90.7%and negative predictive value(NPV)97.3%.



p value<0.001

Figure 13: Diagnostic accuracy parameters for distinction of malignant nodule using NEAT-1 level in serum

Figure13 demonstrates that using a 7.6766 folds in Serum as a cut-off point in the study population for distinction of a Malignant nodule has a sensitivity of 90%, a specificity of 90% with a positive statistical significance, AUC 0.898, positive predictive value (PPV) 94.2%and negative predictive value (NPV) 90%.

3. DISCUSSION

The present study demonstrated a significant upregulation of NEAT1 expression in serum of patients with malignant thyroid nodules compared with benign nodules and healthy controls. These findings support the potential role of NEAT1 as a diagnostic biomarker for thyroid cancer.

In the current cohort, no statistically significant differences were observed between benign and malignant groups regarding age and gender distribution, indicating appropriate matching of study groups and minimizing potential confounding effects on molecular outcomes (1,13). Although a positive family history of thyroid cancer was more frequently reported among malignant cases, this finding did not reach statistical significance, likely due to the relatively small sample size, and is consistent with previous reports indicating that familial thyroid cancer represents a minority of sporadic cases (13–15).

Body mass index did not differ significantly between study groups. This finding contrasts with some studies reporting an association between higher BMI and increased risk of differentiated thyroid cancer, particularly among women, while aligning with others that failed to demonstrate a consistent relationship, underscoring the influence of geographic and population-related factors (13,14). Similarly, clinical presentation did not significantly differ between benign and malignant groups, with neck swelling being the predominant complaint in both. This observation supports previous evidence that clinical symptoms alone are insufficient for reliable discrimination between benign and malignant thyroid nodules (15).

A statistically significant difference was observed between benign and malignant groups regarding thyroid function profiles, with a higher frequency of thyroid dysfunction among malignant cases. Although thyroid hormone abnormalities lack sufficient specificity to predict malignancy, this finding aligns with previous reports suggesting that thyroid cancer may coexist with altered thyroid function and should be interpreted in conjunction with imaging and molecular data (3,4).

Ultrasound-based risk stratification using the TIRADS system and FNAC findings did not demonstrate statistically significant differences between benign and malignant nodules in the present study. These results highlight the well-recognized limitations of conventional diagnostic tools, particularly in indeterminate cases, and further emphasize the need for adjunctive molecular biomarkers to enhance diagnostic accuracy and reduce unnecessary surgical interventions (3,4).

Histopathological analysis revealed papillary thyroid carcinoma as the predominant malignant subtype, accounting for the majority of cases. This distribution is consistent with global and regional epidemiological data identifying papillary

carcinoma as the most frequent histological variant of thyroid cancer (1,13). Variations in the reported frequencies of other subtypes across studies may be attributed to differences in population size, referral patterns, and geographic variability.

A key finding of this study was the marked elevation of NEAT1 expression in malignant thyroid nodules. ROC curve analysis demonstrated high diagnostic accuracy for NEAT1, yielding excellent sensitivity, specificity, and area under the curve values.

The present results are consistent with several studies reporting an oncogenic role of NEAT1 in thyroid cancer. Xia et al., Zhong et al., and Li et al. demonstrated significant upregulation of NEAT1 in papillary thyroid carcinoma tissues and its involvement in tumor progression through regulation of key microRNAs and signaling pathways (9–11). Conversely, Zhao et al. reported downregulation of NEAT1 in malignant thyroid nodules compared with benign lesions (16). This discrepancy may be explained by differences in ethnicity, sample processing, and experimental methodology.

Overall, the present study provides evidence that NEAT1 is significantly upregulated in malignant thyroid nodules and demonstrates strong diagnostic performance. Larger multicenter studies are warranted to validate these findings and explore the prognostic and therapeutic potential of NEAT1 in thyroid cancer.

4. CONCLUSION

The present study demonstrates that long non-coding RNA Nuclear Enriched Abundant Transcript 1 (NEAT1) is significantly upregulated in patients with malignant thyroid nodules compared with benign nodules and healthy controls. Serum NEAT1 expression levels showed strong diagnostic performance, with high sensitivity, specificity, and area under the curve values. Conventional diagnostic tools, including ultrasound-based risk stratification systems and fine-needle aspiration cytology, showed limited ability to reliably differentiate benign from malignant thyroid nodules in this cohort. In contrast, NEAT1 expression, emerged as a promising non-invasive molecular biomarker that may complement existing diagnostic modalities. Reducing the need for invasive diagnostic procedures in patients with indeterminate thyroid nodules. Collectively, these findings suggest that NEAT1 may represent a valuable adjunctive tool for improving the preoperative evaluation of thyroid nodules. Further large-scale, multicenter studies are warranted to validate these results and to explore the prognostic and therapeutic implications of NEAT1 in thyroid cancer...

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