Clinicopathological and Molecular Characterization of Papillary Thyroid Carcinoma in a Saudi Arabian Cohort: An Integrated Analysis

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Abstract

Background: The rising incidence of Papillary Thyroid Carcinoma (PTC) in Saudi Arabia necessitates a deeper understanding of the factors driving aggressive disease. This study aimed to evaluate the prognostic significance of KRAS mutations and a standard immunohistochemical (IHC) panel in PTC within a Saudi cohort.

Methods: A retrospective cohort study of 150 PTC cases from a major Saudi tertiary care center was performed. Associations between clinicopathological parameters, IHC expression profiles (CK19, HBME-1, Galectin-3, TTF-1, Ki67), and KRAS mutational status with lymph node metastasis (LNM) and extrathyroidal extension (ETE) were analyzed using Chi-square tests, Fisher's exact tests, t-tests, and multivariate logistic regression.

Results: The cohort demonstrated high rates of LNM (46.0%) and ETE (36.0%). KRAS mutations were identified in 11.3% of cases. No statistically significant association was found between KRAS status and LNM (p=1.000) or ETE (p=0.460). The evaluated IHC markers did not correlate significantly with LNM. A non-significant trend linked aggressive variants (Tall Cell and Solid) with higher LNM frequency compared to non-aggressive variants (58.8% vs. 42.3%; p=0.117). Multivariate logistic regression identified aggressive variant morphology as the strongest trend toward predicting LNM (OR=2.08, 95% CI: 0.93–4.69, p=0.076), without reaching significance.

Conclusions: In this Saudi cohort, KRAS mutations and the evaluated IHC panel did not serve as significant predictors of aggressive PTC behavior. Morphological assessment remains paramount for risk stratification, and larger population-specific studies are needed to identify robust prognostic biomarkers.

Keywords: Thyroid Cancer, Papillary; Mutation; Immunohistochemistry; Lymphatic Metastasis; Saudi Arabia

Introduction

Papillary Thyroid Carcinoma (PTC) is the most prevalent endocrine malignancy globally, accounting for the vast majority of thyroid cancers. Its incidence has shown a significant and sustained upward trend in the Kingdom of Saudi Arabia (KSA) over the past two decades [1]. While most PTCs follow an indolent clinical course with excellent long-term survival rates, a clinically significant subset presents with aggressive features such as extrathyroidal extension (ETE), extensive lymph node metastasis (LNM), and distant spread. Furthermore, aggressive histological variants, particularly the Tall Cell and Solid subtypes, are associated with adverse outcomes, including higher rates of recurrence, radioiodine refractoriness, and disease-specific mortality [2]. Consequently, accurate risk stratification at the time of initial diagnosis is critical for guiding appropriate surgical extent and adjuvant clinical management.

The prognostic paradigm for PTC is progressively evolving from a purely morphological assessment to an integrated model that incorporates ancillary diagnostic tools. Immunohistochemical (IHC) markers, including Cytokeratin 19 (CK19), Hector Battifora Mesothelial-1 (HBME-1), Galectin-3, and Thyroid Transcription Factor-1 (TTF-1), have been widely investigated for their potential diagnostic utility in distinguishing PTC from benign mimics, as well as their prognostic value [3]. Furthermore, the molecular landscape of PTC is increasingly recognized as a key determinant of tumor biology and behavior. While BRAF V600E is the most common mutation, the mutational status of other oncogenes such as KRAS plays a significant role in thyroid tumorigenesis and has been implicated in determining tumor aggressiveness [4].

Despite the high prevalence of PTC in KSA, there is a notable paucity of comprehensive studies that integrate detailed histopathology, extensive IHC profiling, and molecular data within a single, well-characterized cohort from this region. Understanding the unique clinicopathological and molecular signature of PTC in the Saudi population is essential for optimizing patient care. This study was therefore undertaken to address this knowledge gap by performing a detailed, integrated analysis of PTC in a representative Saudi Arabian population, with a specific focus on evaluating the predictive value of KRAS mutations and IHC markers for aggressive disease phenotypes.

Materials and Methods

Study Design and Cohort

This retrospective cohort study included 150 patients diagnosed with PTC who underwent surgical resection (total thyroidectomy or lobectomy, with or without lymph node dissection) at a major tertiary care center in Saudi Arabia. The inclusion criteria required the availability of complete clinicopathological data, archived formalin-fixed paraffin-embedded (FFPE) tissue blocks sufficient for IHC analysis, and conclusive results from KRAS mutational testing. The study protocol was reviewed and received ethical approval from the Institutional Review Board at King Abdulaziz Specialist Hospital (KAASH) (Reference No.: 2026-THC-17E). All patient tissue samples were handled anonymously in accordance with the Declaration of Helsinki, and informed consent was obtained from participants where required by institutional guidelines.

Data Collection and Pathological Review

A comprehensive dataset encompassing demographic, clinical, and pathological variables was systematically extracted from electronic medical records and pathology reports for each case. The variables included patient age, sex, tumor size, multifocality, presence of ETE, presence of LNM, and AJCC staging. To ensure diagnostic consistency and rigor, two senior pathologists performed a blinded consensus review of all original hematoxylin and eosin (H&E)-stained slides. Tumors were classified into specific histological variants according to the criteria established by the latest World Health Organization (WHO) Classification of Endocrine Tumors.

Immunohistochemical staining was performed on representative FFPE tissue sections using standardized, automated laboratory protocols. The primary antibodies utilized included CK19, HBME-1, Galectin-3, TTF-1, and the proliferation marker Ki67. Staining intensity and distribution were evaluated semiquantitatively. For the purpose of statistical analysis, marker expression was dichotomized into Positive and Negative based on established cutoff values. The Ki67 proliferation index was recorded as a continuous percentage representing the fraction of positively stained tumor nuclei.

Molecular Analysis

DNA extraction from FFPE tumor tissue and subsequent molecular testing for KRAS mutations were performed using standard laboratory procedures. The specific mutation types (e.g., G12D, G12V, G13D) were recorded when available.

Statistical Analysis

Statistical analysis was performed using Python (version 3.9) utilizing the pandas, scipy, and statsmodels libraries. Descriptive statistics were generated for all variables. Associations between categorical variables and aggressive features (LNM, ETE) were assessed using the Chi-square test or Fisher's exact test, as appropriate based on expected cell counts. Continuous variables were compared between groups using independent sample t-tests. To control for potential confounding variables and identify independent predictors of LNM, a multivariate logistic regression model was constructed. Variables entered into the model included Age, Sex, Tumor Size, KRAS status, Ki67 index, ETE, Multifocality, and Aggressive Histological Variant. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A two-sided p-value of <0.05 was considered statistically significant for all analyses.

Results

Cohort Demographics and Clinicopathological Characteristics

The study cohort comprised 150 patients with a mean age of 44.06 ± 17.7 years (range: 18-79 years). A significant female predominance was observed, with 96 female patients (64.0%) compared to 54 males (36.0%). The mean tumor size was 3.14 ± 1.83 cm. Histological review classified the tumors into five variants. The Classic variant was the most frequent diagnosis, accounting for nearly half the cases (49.3%, n=74), followed by the Follicular variant (22.7%, n=34), Solid variant (12.0%, n=18), Tall Cell variant (10.7%, n=16), and Diffuse Sclerosing variant (5.3%, n=8) (Fig. 1A). The cohort exhibited a substantial burden of aggressive disease features; lymph node metastasis (LNM) was present in 46.0% (n=69) of cases, and extrathyroidal extension (ETE) was identified in 36.0% (n=54) of cases. Multifocality was noted in 38.0% of the tumors. According to AJCC staging, the majority of patients presented with Stage I disease (58.7%), followed by Stage II (22.0%), Stage III (10.7%), and Stage IV (8.7%) (Fig. 1D). A comprehensive summary of clinicopathological features across histological variants is presented in Table 1.

Molecular and Immunohistochemical Profiles

Molecular testing revealed KRAS mutations in 11.3% (n=17) of the cohort (Fig. 1C). Among the specified mutations, G12D and G13D were the most frequently identified alterations (Fig. 4A). The tumors demonstrated high overall positivity rates for the evaluated IHC diagnostic panel: CK19 (83.3%), HBME-1 (82.7%), Galectin-3 (76.7%), and TTF-1 (86.7%). The mean Ki67 proliferation index across the cohort was 19.5% ± 10.8%. When analyzing IHC expression across the different histological variants, the Tall Cell and Solid variants consistently showed high positivity rates for CK19 (>88%) and HBME-1 (>81%) (Fig. 2A). The Ki67 index showed considerable overlap between the different variants, with the Diffuse Sclerosing and Classic variants exhibiting the highest mean values (22.5% and 20.5%, respectively) (Fig. 2B). A detailed breakdown of IHC expression and molecular features across histological variants is presented in Table 2.

Correlation of Molecular and IHC Markers with Aggressive Features

We systematically evaluated the association between the molecular/IHC profiles and aggressive clinicopathological behavior. Our analysis failed to demonstrate a statistically significant association between KRAS mutational status and the presence of LNM (OR=1.02, 95% CI: 0.35-2.98, p=1.000) or ETE (p=0.460) (Fig. 4B). Similarly, the expression status of the individual IHC markers (CK19, HBME-1, Galectin-3, TTF-1) did not show any statistically significant correlation with the presence of LNM ($p>0.05$ for all comparisons). Furthermore, the Ki67 proliferation index did not differ significantly between tumors with and without LNM (mean 19.9% vs. 19.1%, p=0.686). A comprehensive correlation matrix illustrating the relationships between all evaluated IHC markers and clinicopathological features is presented in Fig. 5, demonstrating generally weak correlations between these biomarkers and aggressive clinical parameters. The univariate analysis results are summarized in Table 3.

Histological Subtype and Clinical Behavior

To assess the prognostic value of morphology, we stratified the cohort by histological subtype. We categorized the Tall Cell and Solid variants as "Aggressive Variants" (n=34) and compared them to the "Non-Aggressive Variants" (Classic, Follicular, Diffuse Sclerosing; n=116). A trend was observed indicating a higher frequency of LNM in the aggressive variant group compared to the non-aggressive group (58.8% vs. 42.3%), although this difference did not reach statistical significance (OR=0.51, p=0.117) (Fig. 3C). A similar non-significant trend was observed for ETE (50.0% vs. 32.8%, p=0.156).

Multivariate Analysis for Predictors of LNM

To control for confounding variables and identify independent predictors of lymph node metastasis, a multivariate logistic regression analysis was performed. The model incorporated Age, Sex, Tumor Size, KRAS status, Ki67%, ETE, Multifocality, and Aggressive Variant status. Consistent with the univariate analyses, the multivariate model did not identify any of these variables as statistically significant independent predictors of LNM in this cohort (Fig. 3D, Table 4). The Aggressive Variant status showed the strongest trend toward predicting LNM (OR=2.08, 95% CI: 0.93-4.69, p=0.076), while Multifocality showed a borderline protective trend (OR=0.54, 95% CI: 0.27-1.08, p=0.083).

Discussion

This study provides a comprehensive, integrated analysis of the clinicopathological, immunohistochemical, and molecular landscape of Papillary Thyroid Carcinoma in a Saudi Arabian cohort. The most salient finding of our investigation is the lack of a significant association between KRAS mutations, a standard panel of IHC markers, and aggressive clinicopathological features, specifically lymph node metastasis and extrathyroidal extension.

The prevalence of KRAS mutations in our cohort (11.3%) is consistent with some reports in the literature, although lower than the rates typically observed for BRAF V600E mutations in PTC. The prognostic significance of RAS mutations in thyroid cancer remains a subject of ongoing debate. While some previous studies have suggested that RAS mutations, particularly in the context of follicular-patterned tumors, may portend a higher risk of distant metastasis or aggressive behavior [4], our data did not support KRAS mutational status as a reliable predictor of LNM or ETE. This discrepancy may be attributable to several factors, including differences in cohort size, ethnic background, environmental exposures, or the specific distribution of mutation subtypes. It is plausible that in the Saudi population, alternative molecular drivers or complex epigenetic alterations play a more dominant role in dictating the aggressive phenotype of PTC.

Similarly, the evaluated IHC markers (CK19, HBME-1, Galectin-3, TTF-1), while demonstrating high sensitivity for the diagnosis of PTC, did not exhibit significant prognostic utility in our cohort. These markers are invaluable tools in the differential diagnosis of thyroid nodules, particularly in distinguishing PTC from benign follicular lesions [3]. However, their expression levels did not reliably discriminate between tumors with and without aggressive clinical features. This suggests that while these proteins are fundamentally involved in the pathogenesis of PTC, their mere presence or absence is insufficient to predict the biological trajectory of the established tumor.

The observed trend linking aggressive morphological variants (Tall Cell and Solid) with a higher rate of LNM, while not reaching strict statistical significance (p=0.117), aligns with the well-established principle that tumor histology is a powerful indicator of biological potential [2]. The lack of statistical significance in our multivariate model is likely a consequence of the relatively small number of aggressive variant cases (n=34) within our cohort, which limits statistical power. Nonetheless, the trend (OR=2.08) reinforces the clinical imperative to carefully identify and report these specific histological subtypes, as they may warrant closer surveillance and potentially more aggressive initial management.

This study has several inherent limitations that must be acknowledged. Its retrospective design and single-center origin may introduce selection bias and limit the generalizability of the findings to the broader Saudi population. Furthermore, the relatively low absolute number of cases with KRAS mutations restricted our ability to perform highly powered subgroup analyses based on specific mutation types. Future prospective, multi-center studies with larger sample sizes are necessary to validate our findings.

In conclusion, within the context of this Saudi cohort, KRAS mutations and the standard evaluated IHC panel did not function as significant independent predictors of aggressive behavior in PTC. Morphological assessment, particularly the identification of aggressive histological variants, remains a cornerstone of risk stratification. These findings emphasize the critical necessity of conducting larger, population-specific genomic and transcriptomic studies to

elucidate the unique molecular drivers of PTC in Middle Eastern populations and to develop more effective, personalized prognostic tools.

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Author Contributions
Each author listed on this manuscript has made substantial contributions to the study, including the conceptualization, methodological design, data acquisition, statistical analysis, and interpretation of findings. All authors have critically reviewed the manuscript for intellectual content and have given their final approval for the submitted version.

Conflicts of Interest
The authors confirm that no conflicts of interest exist in connection with this research.

Ethics Statement
This research was performed in compliance with the ethical standards outlined in the Declaration of Helsinki. The study protocol received approval from the Institutional Review Board at King Abdulaziz Specialist Hospital (KAASH) (Reference No.: 2026-THC-17E). All patient tissue samples were handled anonymously, and informed consent was obtained from participants where required by institutional guidelines.

Author Contributions
Conceptualization: TAA, EMAJ. Data curation: TAA, AHE. Formal analysis: TAA, AHE. Funding acquisition: Not applicable. Investigation: TAA, EMAJ, AHE, KEH. Methodology: TAA, EMAJ, AHE. Project administration: TAA. Resources: TAA, KEH. Software: AHE. Supervision: EMAJ, KEH. Validation: EMAJ, AHE, KEH. Visualization: TAA, AHE. Writing - original draft: TAA. Writing - review & editing: EMAJ, AHE, KEH.
Approval of final manuscript: all authors.
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Table 1. Clinicopathological characteristics of the study cohort stratified by histological variant.

Feature	Total (n=150)	Classic (n=74)	Follicular (n=34)	Tall Cell (n=16)	Solid (n=18)	Diff. Scler. (n=8)
Age, mean ± SD	44.1 ± 17.7	44.1 ± 17.7	47.3 ± 20.9	46.8 ± 19.3	38.7 ± 12.8	36.2 ± 15.3
Female, n (%)	96 (64.0)	48 (64.9)	23 (67.6)	10 (62.5)	11 (61.1)	4 (50.0)
Tumor size, cm	3.14 ± 1.83	3.15 ± 1.87	3.04 ± 1.57	3.01 ± 2.11	3.41 ± 1.73	3.17 ± 2.25
Multifocality, n (%)	57 (38.0)	26 (35.1)	12 (35.3)	7 (43.8)	9 (50.0)	3 (37.5)
ETE, n (%)	54 (36.0)	24 (32.4)	12 (35.3)	8 (50.0)	8 (44.4)	2 (25.0)
LNM, n (%)	69 (46.0)	32 (43.2)	14 (41.2)	10 (62.5)	10 (55.6)	3 (37.5)
AJCC Stage I, n (%)	88 (58.7)	44 (59.5)	18 (52.9)	8 (50.0)	11 (61.1)	7 (87.5)
AJCC Stage II, n (%)	33 (22.0)	16 (21.6)	9 (26.5)	4 (25.0)	4 (22.2)	0 (0.0)
AJCC Stage III, n (%)	16 (10.7)	8 (10.8)	5 (14.7)	2 (12.5)	1 (5.6)	0 (0.0)
AJCC Stage IV, n (%)	13 (8.7)	6 (8.1)	2 (5.9)	2 (12.5)	2 (11.1)	1 (12.5)

ETE, extrathyroidal extension; LNM, lymph node metastasis; AJCC, American Joint Committee on Cancer; SD, standard deviation.

Table 2. Immunohistochemical and molecular features across histological variants.

Feature	Total (n=150)	Classic (n=74)	Follicular (n=34)	Tall Cell (n=16)	Solid (n=18)	Diff. Scler. (n=8)
CK19 Positive, n (%)	125 (83.3)	62 (83.8)	26 (76.5)	15 (93.8)	16 (88.9)	6 (75.0)
HBME-1 Positive, n (%)	124 (82.7)	59 (79.7)	29 (85.3)	13 (81.2)	16 (88.9)	7 (87.5)
Galectin-3 Positive, n (%)	115 (76.7)	60 (81.1)	26 (76.5)	11 (68.8)	13 (72.2)	5 (62.5)
TTF-1 Positive, n (%)	130 (86.7)	66 (89.2)	30 (88.2)	12 (75.0)	15 (83.3)	7 (87.5)
Ki67%, mean ± SD	19.5 ± 10.8	20.5 ± 10.6	18.9 ± 11.9	19.4 ± 9.0	16.5 ± 11.1	22.5 ± 10.8
KRAS Mutated, n (%)	17 (11.3)	11 (14.9)	2 (5.9)	2 (12.5)	1 (5.6)	1 (12.5)

CK19, Cytokeratin 19; HBME-1, Hector Battifora Mesothelial-1; TTF-1, Thyroid Transcription Factor-1; SD, standard deviation.

Table 3. Univariate analysis of clinicopathological and molecular variables associated with lymph node metastasis.

Variable	LNM+ (n=69)	LNM- (n=81)	OR (95% CI)	p-value
Age, mean ± SD	44.5 ± 17.7	43.7 ± 17.8	-	0.686
Male sex, n (%)	26 (37.7)	28 (34.6)	1.15 (0.59-2.22)	0.735
Tumor size, cm	3.07 ± 1.88	3.21 ± 1.77	-	0.635
KRAS Mutated, n (%)	8 (11.6)	9 (11.1)	1.05 (0.38-2.87)	1.000
CK19 Positive, n (%)	58 (84.1)	67 (82.7)	1.10 (0.47-2.60)	0.826
HBME-1 Positive, n (%)	59 (85.5)	65 (80.2)	1.45 (0.59-3.55)	0.502
Galectin-3 Positive, n (%)	54 (78.3)	61 (75.3)	1.18 (0.55-2.52)	0.698
TTF-1 Positive, n (%)	59 (85.5)	71 (87.7)	0.83 (0.33-2.12)	0.808
Ki67%, mean ± SD	19.9 ± 10.9	19.1 ± 10.8	-	0.686
ETE, n (%)	29 (42.0)	25 (30.9)	1.62 (0.80-3.28)	0.175
Multifocality, n (%)	22 (31.9)	35 (43.2)	0.62 (0.31-1.21)	0.179
Aggressive variant, n (%)	20 (29.0)	14 (17.3)	1.95 (0.90-4.24)	0.117

LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; ETE, extrathyroidal extension.

Table 4. Multivariate logistic regression analysis for independent predictors of lymph node metastasis.

Variable	Adjusted OR	95% CI	p-value
Age	1.005	0.987-1.024	0.601
Sex (Male)	1.190	0.595-2.379	0.622
Tumor Size (cm)	0.942	0.782-1.134	0.529
KRAS Mutated	1.025	0.352-2.981	0.964
Ki67 (%)	1.011	0.980-1.043	0.487
ETE	1.621	0.802-3.277	0.178
Multifocality	0.538	0.267-1.084	0.083
Aggressive Variant	2.084	0.927-4.688	0.076

OR, odds ratio; CI, confidence interval; ETE, extrathyroidal extension. Model pseudo $R^2 = 0.041$; LLR p-value = 0.388.

Fig. 1

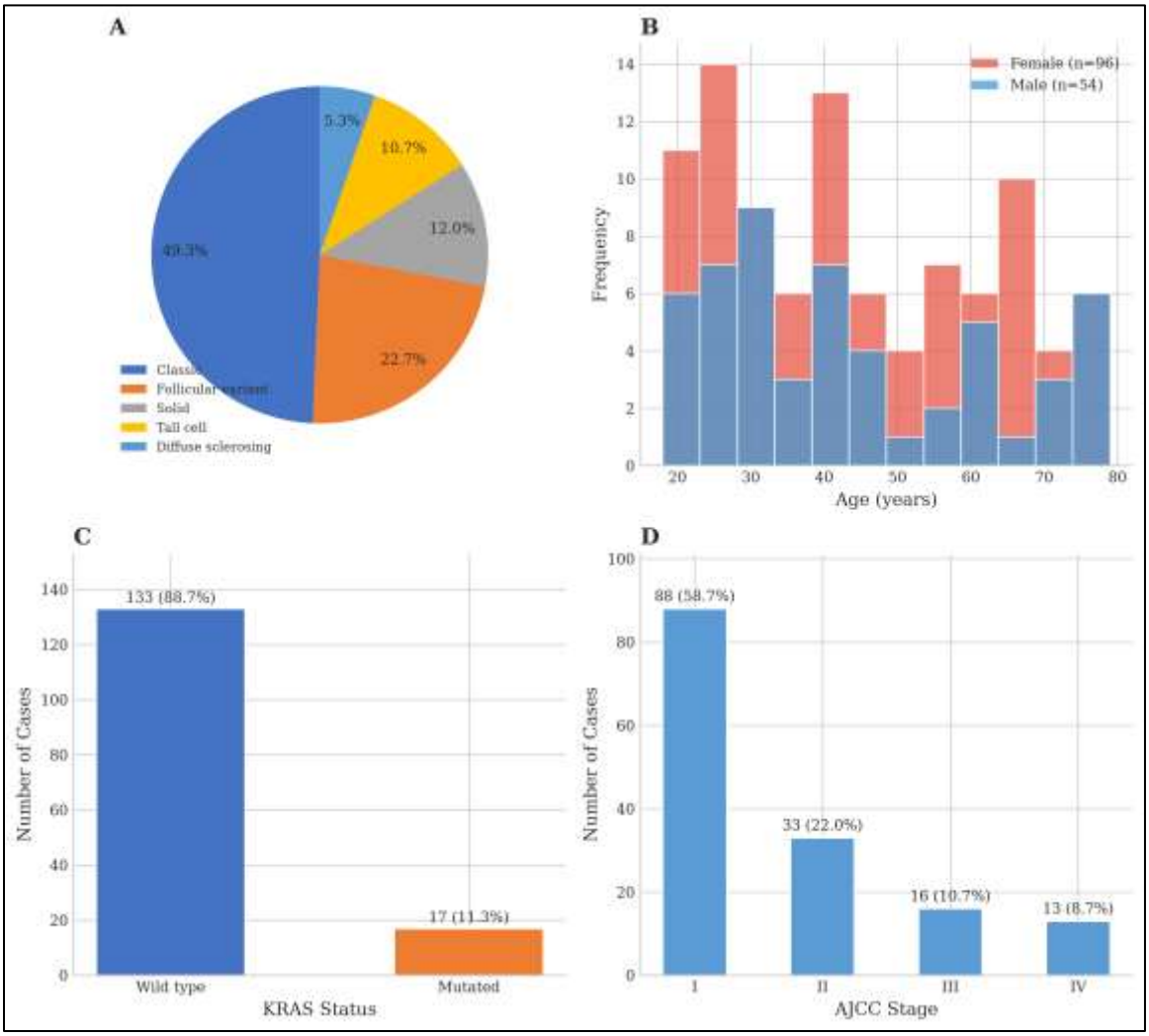

A
5.3%
10.7%
12.0%
49.3%
22.7%
Classic
Follicular variant
Solid
Tall cell
Diffuse sclerosing
B
Female (n=96)
Male (n=54)
Frequency
Age (years)
C
133 (88.7%)
17 (11.3%)
Number of Cases
Wild type
Mutated
KRAS Status
D
88 (58.7%)
33 (22.0%)
16 (10.7%)
13 (8.7%)
Number of Cases
I
II
III
IV
AJCC Stage

Fig. 2

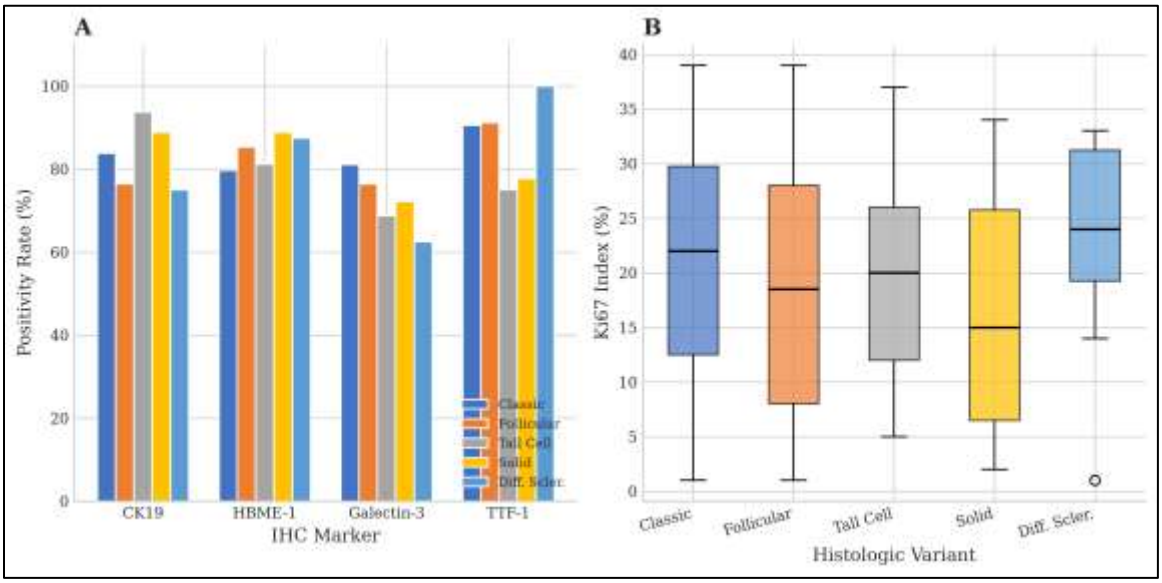

A
Positivity Rate (%)
CK19
HBME-1
Galectin-3
TTF-1
IHC Marker
Classic
Follicular
Tall Cell
Solid
Diff. Scler.
B
Ki67 Index (%)
Classic
Follicular
Tall Cell
Solid
Diff. Scler.
Histologic Variant

Fig. 3

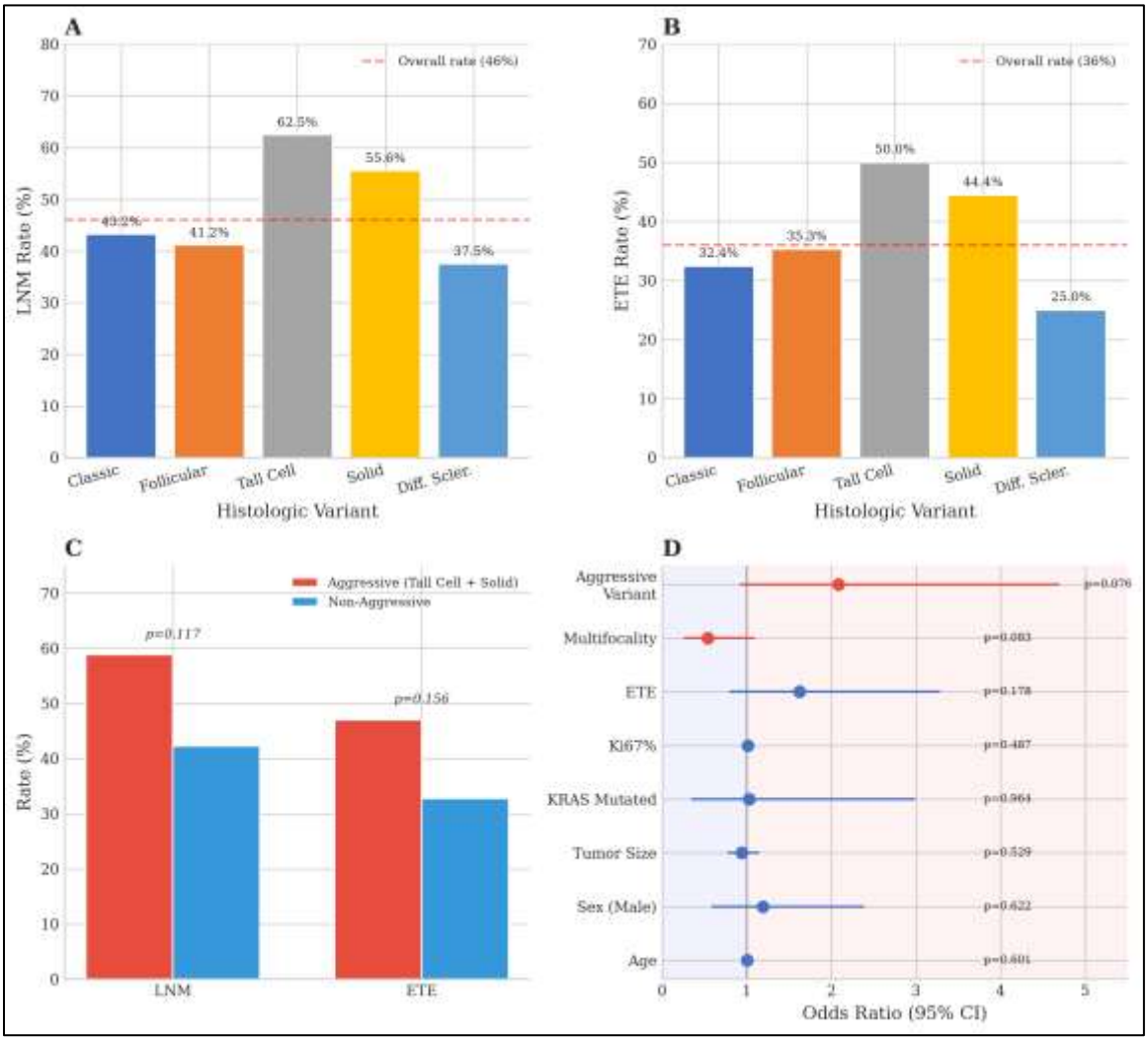

A
Overall rate (46%)
LNM Rate (%)
43.2%
41.2%
62.5%
55.6%
37.5%
Classic
Follicular
Tall Cell
Solid
Diff. Scler.
Histologic Variant
B
Overall rate (36%)
ETE Rate (%)
32.4%
35.3%
50.0%
44.4%
25.0%
Classic
Follicular
Tall Cell
Solid
Diff. Scler.
Histologic Variant
C
Aggressive (Tall Cell + Solid)
Non-Aggressive
Rate (%)
p=0.117
p=0.156
LNM
ETE
D
Aggressive Variant
Multifocality
ETE
Ki67%
KRAS Mutated
Tumor Size
Sex (Male)
Age
p=0.076
p=0.083
p=0.178
p=0.487
p=0.964
p=0.529
p=0.622
p=0.601
Odds Ratio (95% CI)

Fig. 4

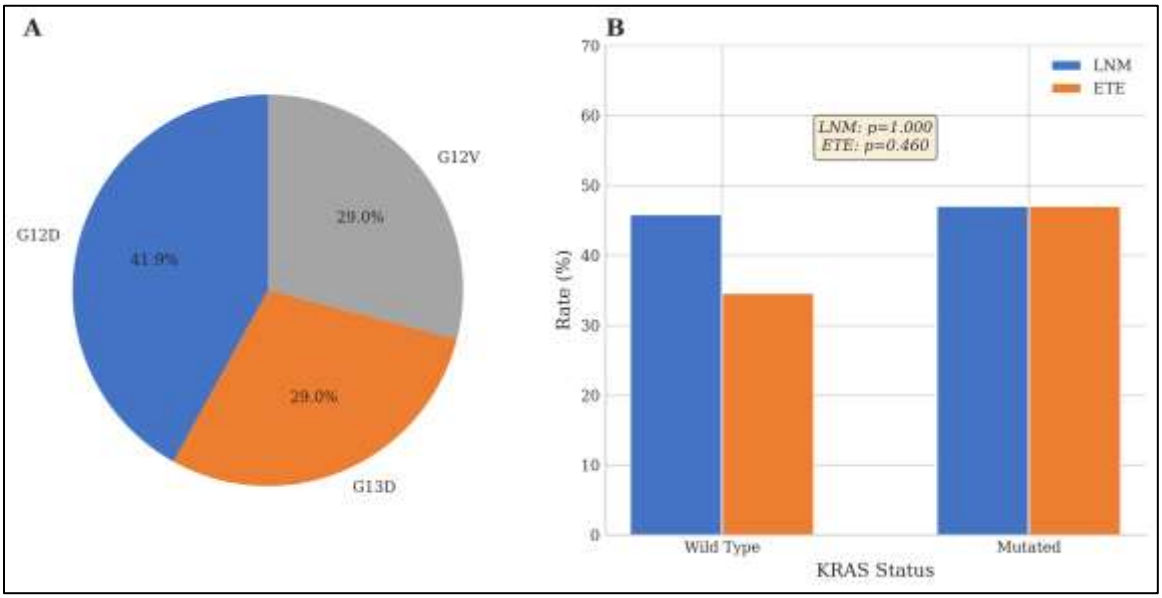

A
G12V
29.0%
G12D
41.9%
29.0%
G13D
B
LNM
ETE
LNM: p=1.000
ETE: p=0.460
Rate (%)
Wild Type
Mutated
KRAS Status

Fig. 5

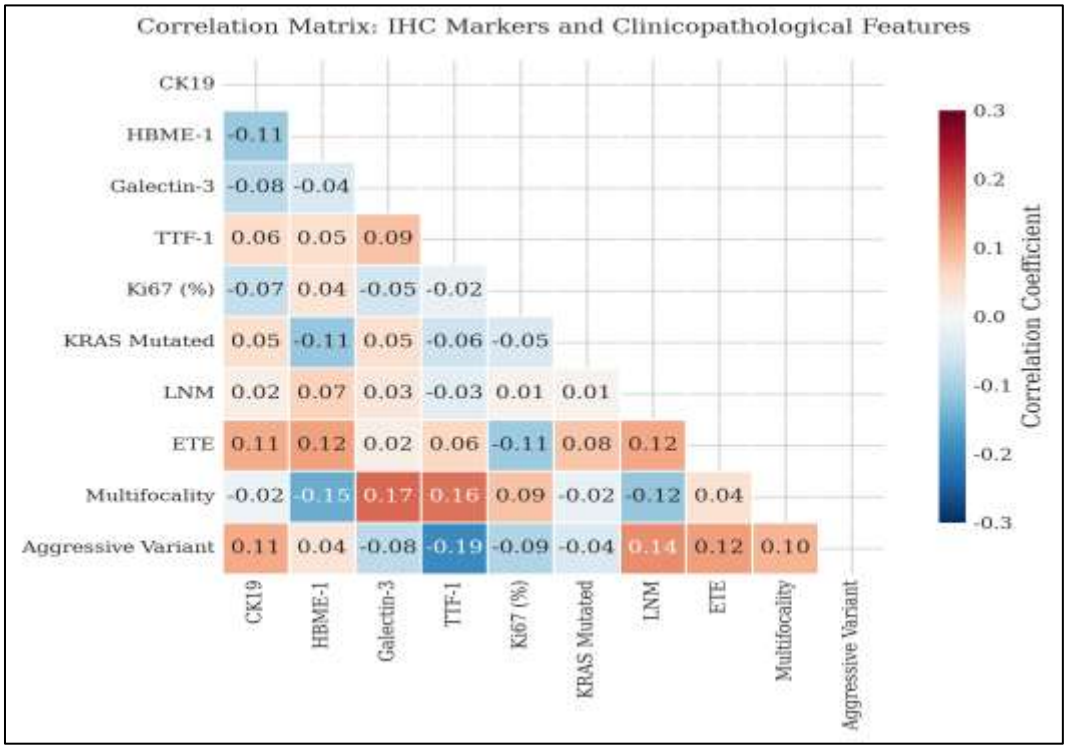
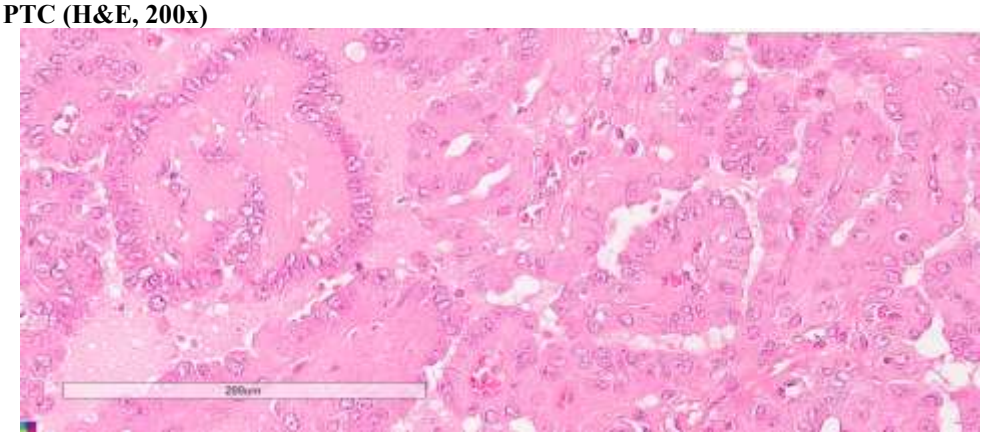
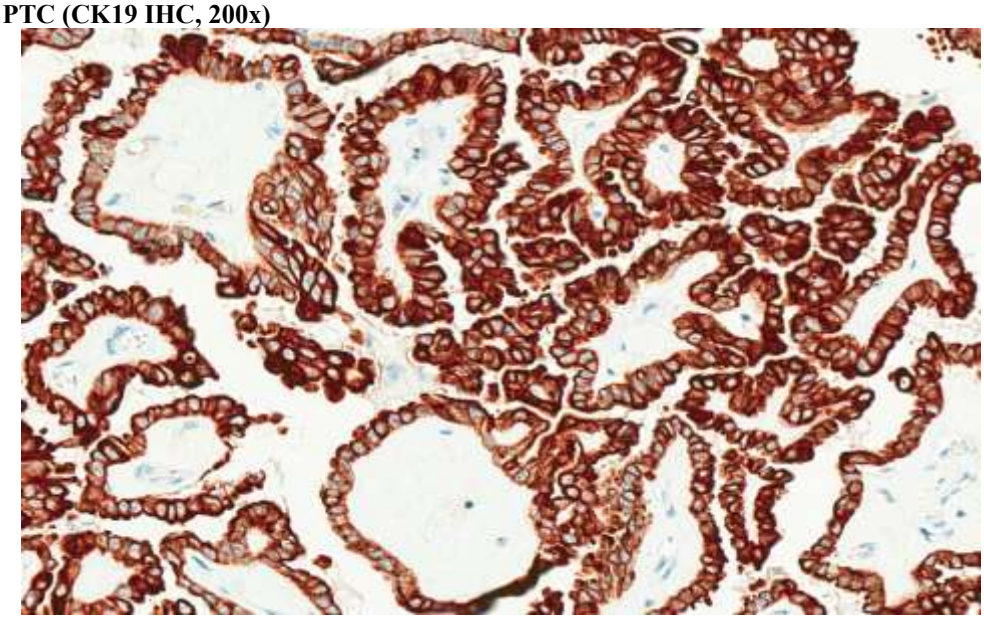


Fig. 6

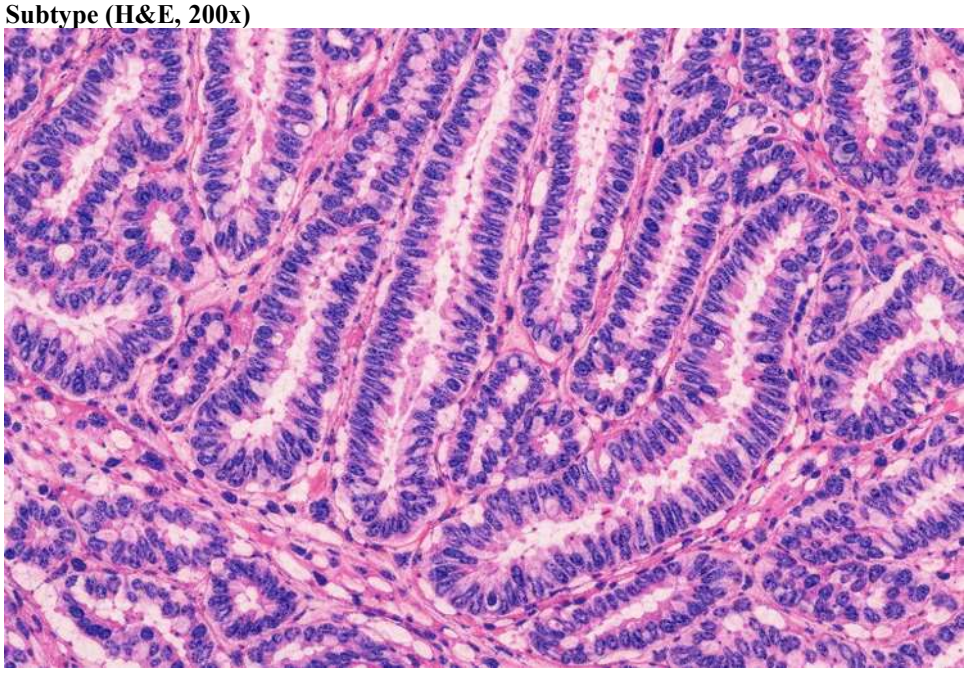
(A) Classic PTC (H&E, 200x)



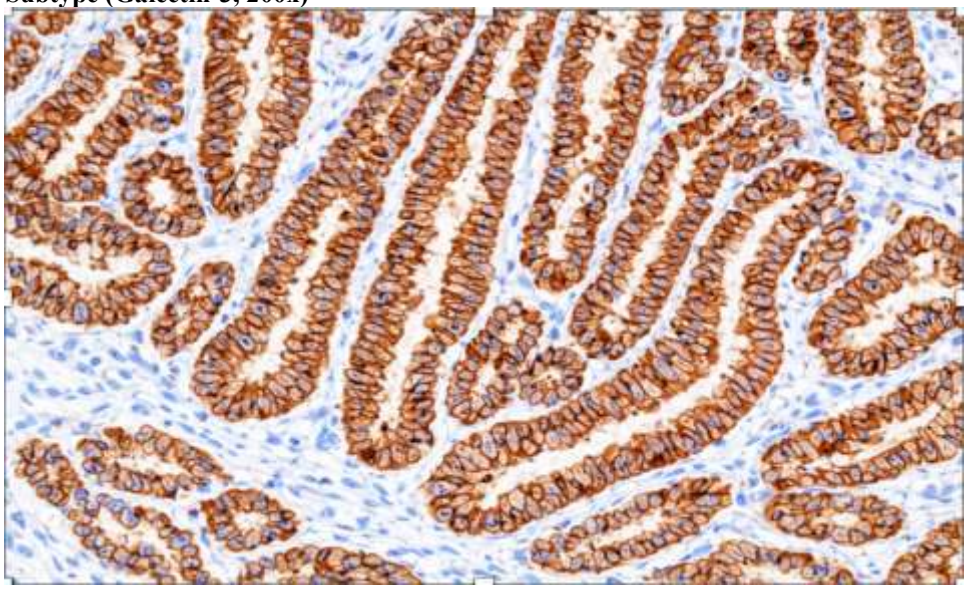
(B) Classic PTC (CK19 IHC, 200x)



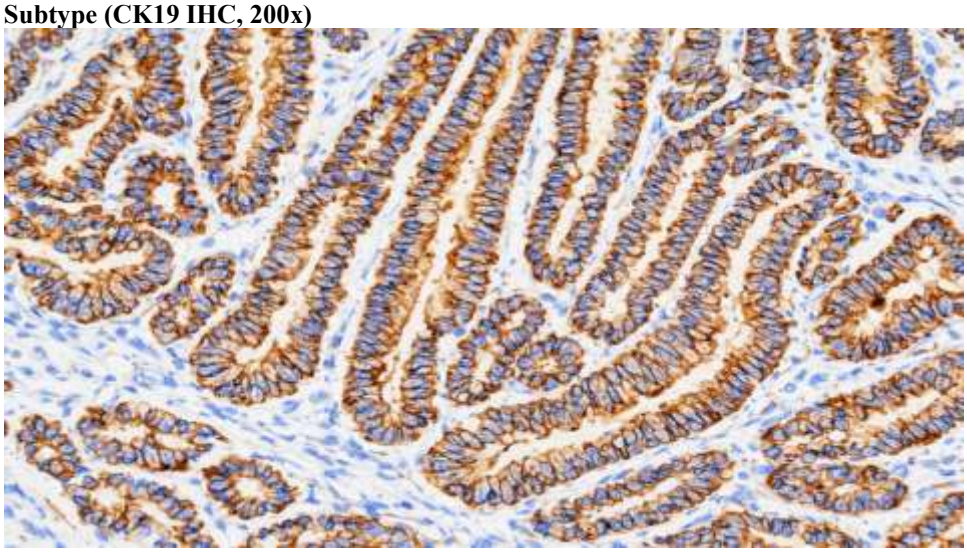
(C) Tall Cell Subtype (H&E, 200x)



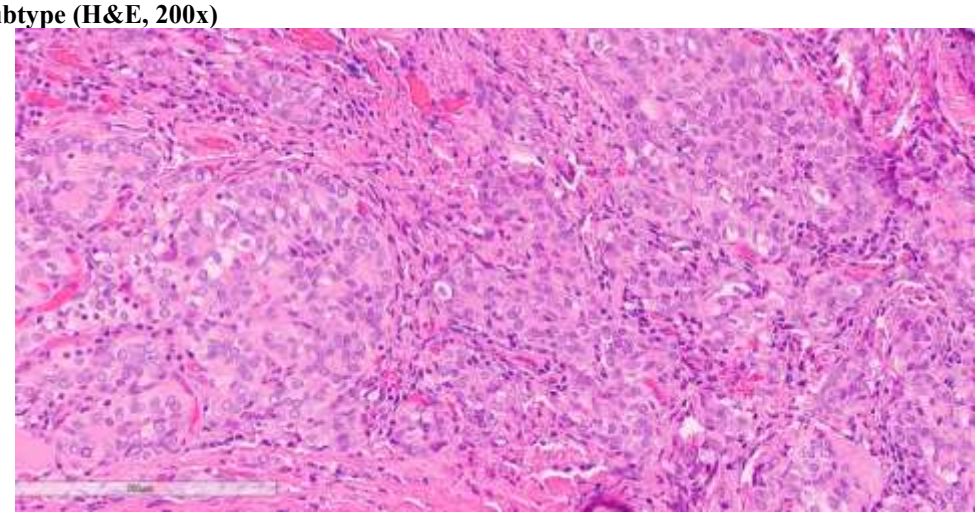
(D) Tall Cell Subtype (Galectin-3, 200x)



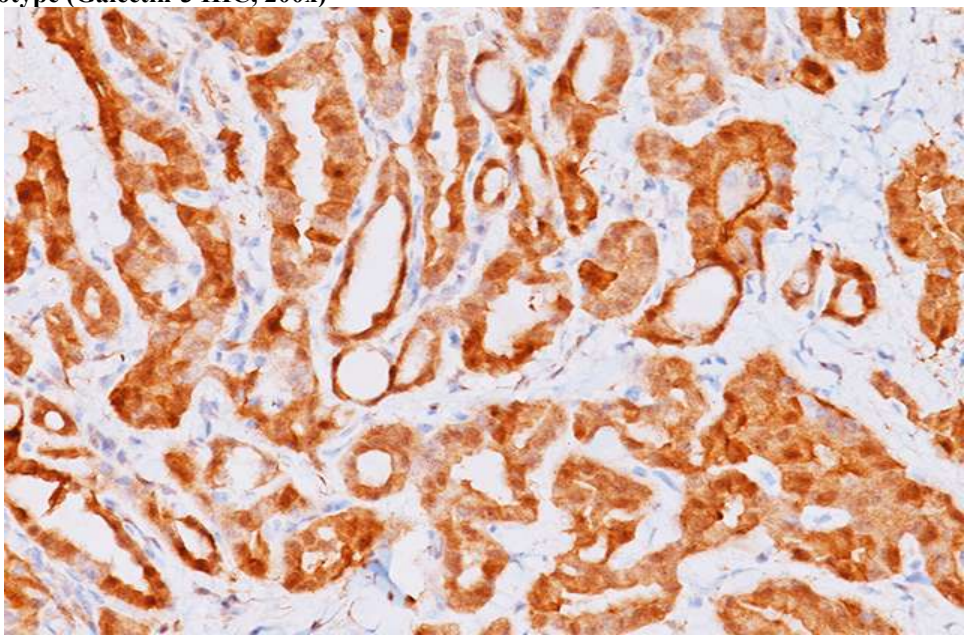
(E) Tall Cell Subtype (CK19 IHC, 200x)



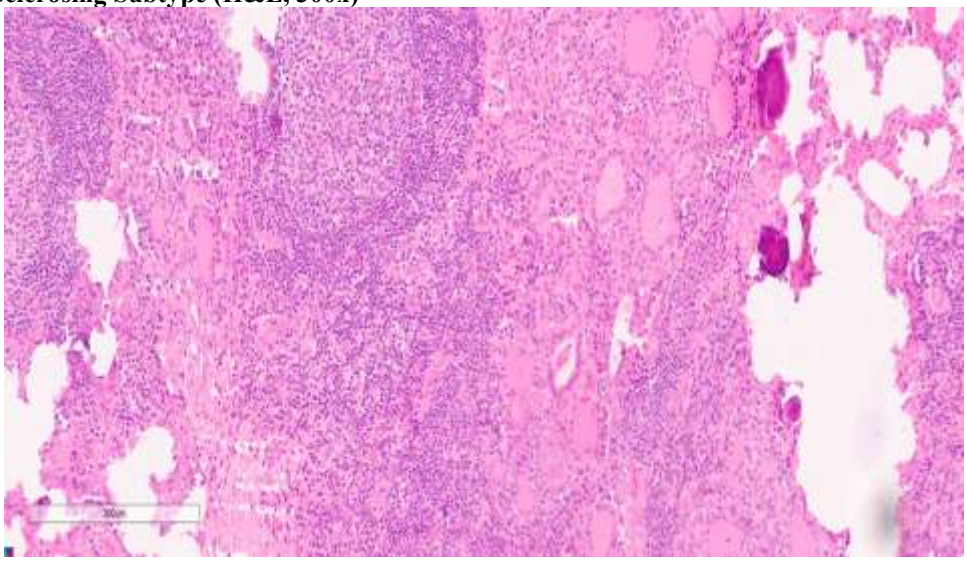
(F) Solid Subtype (H&E, 200x)



(G) Solid Subtype (Galectin-3 IHC, 200x)



(H) Diffuse Sclerosing Subtype (H&E, 300x)



(I) Follicular Subtype (H&E, 200x)