ORIGINAL ARTICLE

Reproducibility of Assessment of Lepidic (Noninvasive) Patterns in Lung Adenocarcinoma With Cytokeratin Immunostain Compared With Hematoxylin and Eosin and the Proposed New International Association for the Study of Lung Cancer (IASLC) Algorithm

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ABSTRACT

Introduction: Lepidic growth is considered noninvasive in lung nonmucinous adenocarcinoma, whereas other patterns are invasive. Considerable interobserver variability in assessing "invasion" has been reported. We assessed the utility of cytokeratin 7 (CK7) stain and recently proposed International Association for the Study of Lung Cancer criteria to improve assessment of noninvasion in lung adenocarcinoma.

Methods: Four pathologists (two staff, two trainees) assessed 158 hematoxylin and eosin (HE)- and CK7-stained slides of 108 pT1N0-2 nonmucinous lung adenocarcinoma cases. Scoring took place in four rounds. First, sections were independently scored for percentage of noninvasive or probable noninvasive and invasive or probable invasive patterns. Second, after a consensus scoring algorithm for CK7 was formulated, the slides were rescored. Subsequent third-round scoring was conducted only on HE slides using the 2023 International Association for the Study of Lung Cancer proposed criteria, and fourth-round scoring on both HE and CK7 slides simultaneously. Intraclass correlation coefficient (ICC) was calculated for each round. Recurrence-free survival was assessed using Cox proportional hazards regression methods.

Results: In the first two rounds, interobserver concordance was consistently higher with CK7 (ICC range = 0.44–0.6) than HE (range = 0.24–0.49) scores. The IASLC proposed algorithm improved ICC of HE scores to 0.60 (95% confidence interval: 0.52–0.67), and round 4 HE and CK7 combined improved ICC to 0.75 (95% confidence interval: 0.70–0.80). Continuous measures of averaged noninvasive and probable noninvasive scores on HE were associated with improved recurrence-free survival (hazard ratio: 0.83–0.86).

Conclusions: CK7 staining consistently increased interobserver concordance in assessment of invasive versus noninvasive patterns than HE. Combining CK7 with the 2023 IASLC criteria for morphologic features of invasion may further improve the interobservers' concordance for the recognition of lepidic growth in nonmucinous lung adenocarcinoma.

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Introduction

In nonmucinous lung adenocarcinoma, lepidic growth is considered a noninvasive/in situ histologic pattern consisting of neoplastic pneumocytes growing in monolayers along the surface of preexisting alveolar septa.[1,2] In contrast, all other histologic growth patterns aside from lepidic, including acinar, papillary, micropapillary, and solid, are considered invasive.[2] The fifth edition of the WHO Classification of Thoracic Tumours further classifies adenocarcinomas with lepidic growth into adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) ($\leq$5 mm invasive focus), and lepidic-predominant adenocarcinoma (>5 mm).[3] The eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM classification specifies that the T category tumor size should include only the invasive component of the primary tumor. Therefore, the distinction between lepidic (noninvasive) and invasive patterns is crucial for the accurate assessment of invasion, and consequently tumor staging and prognostication, particularly when AIS and MIA have 100% 5-year disease-free survival if completely resected.[4]

Previous studies have revealed that despite the reproducibility of the predominant pattern with high interpathologist concordance, the distinction between lepidic and invasive patterns can be challenging with considerable interobserver variability.[5,6] Thunnissen et al.[6] revealed that the kappa for invasion assessment in typical and difficult cases was 0.55 $\pm$ 0.06 and 0.08 $\pm$ 0.02, respectively. Potential explanation of this difficulty included similar histologic features between acinar and papillary patterns with lepidic pattern.[2,3] Architecturally, alveolar wall collapse with variable thickening may raise the concern of invasive (acinar/papillary) pattern, especially when the preexisting alveoli have manifested structural alterations due to chronic lung injury.[7] Tangential sectioning can also mimic similar findings. In the end, much of the interobserver variation was thought to be due to differences in interpretation based on operator experience and opinion.[6] Features to aid in distinguishing lepidic and invasive patterns have been proposed, including absence of myofibroblastic stroma, presence of intra-alveolar macrophages, and preserved alveolar structure.[3] More recently, the International Association for the Study of Lung Cancer (IASLC) Pathology Committee proposed a detailed criteria and algorithm to establish noninvasive and invasive patterns.[8] To address the ongoing need to improve interobserver concordance, we set out to assess the use of cytokeratin 7 (CK7) immunostain as an ancillary aid to improve interobserver concordance in the assessment of invasive versus noninvasive patterns among lepidic- or acinar-predominant lung adenocarcinoma compared with hematoxylin and eosin (HE) stain.

Methods

This study was approved by the Research Ethics Board of University Health Network, Toronto, Canada. A retrospective natural language search of lung resection specimens from 2001 to 2021 with a diagnosis of American Joint Committee on Cancer eighth edition pT1N0-2 lepidic-predominant and acinar-predominant lung adenocarcinoma was performed. A total of 54 lepidic-predominant and 54 acinar-predominant lung adenocarcinomas (104 patients) with available HE slides and CK7 immunostain were retrieved (n = 160) (Supplementary Fig. 1 and Supplementary Table 1). Synchronous tumors from the same patient (n = 4) and multiple sections (range = 1–6 sections, mean = 1.5 sections/tumor) for the same tumor (n = 31) were included. "Training" was conducted before study commencement in a one-hour session at the multiheader microscope. The HE and CK7 slides were independently scored for estimated percentage of noninvasive (NI), probable NI (PNI), invasive (I), and probable I (PI) components. Lepidic pattern was defined as NI, and all other patterns were defined as I, as described in the WHO classification and original IASLC/American Thoracic Society/European Respiratory Society manuscript.[2] The cases (n = 108) were randomized as to the diagnoses, and the entire 108 slides were given to individual pathologists (two staff thoracic pathologists and two fellow/senior residents) for scoring. In terms of the sequence of reading HE and CK7 slides, individual pathologist scored whichever cohort was available without pre-assigned sequence.

Four months after the initial round of scoring, all scorers participated in consensus review. Based on their round 1 experience, an algorithm for the assessment of invasive versus noninvasive features with CK7 stain was formulated (Fig. 1). A second round of scoring was performed subsequently.

In developing the algorithm for assessment of CK-stained sections, the group initially agreed on a multistep approach that begins with assessing the presence of widespread epithelial duplication ($\geq$2 layers) or multilayering (Fig. 2*A*), which we regard as an invasive feature. If epithelial duplication is absent, architectural assessment of disorganized, branching (Fig. 2*B*), budding/single cells (more than expected from tangential sectioning) (Fig. 2*C*) and complex architecture (Fig. 2*D*) are considered invasive features. Organized, streaming, and maintained alveolar architecture is considered noninvasive (Fig. 2*E* and *F*). For cases with

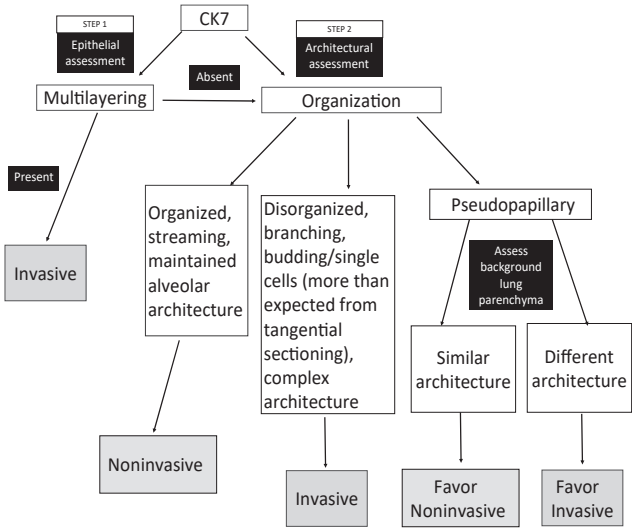

Figure 1. An algorithm developed to assess invasive versus noninvasive features with CK7 stain. CK7, cytokeratin 7.

pseudopapillary architecture, a similar architecture to background lung parenchyma favored noninvasive; a different architecture or an abrupt change to background lung parenchyma favored invasive.

After 14 months from the second round, the latest IASLC proposal on morphologic features of invasion was published. This prompted a third-round scoring on the HE slides.[8]

After seven months from the third round, a fourth round of scoring with both HE and CK7 slides simultaneously available for scoring was performed.

Clinical outcome data (n = 104), including adjuvant treatment, date of diagnosis, date of recurrence/death/last seen in clinic, were retrieved from the electronic patient records.

Statistical Analysis

The percentages of NI, PNI, I, and PI were summarized for HE and CK7 by scorer using the mean/SD, median/range, and I plus PI and NI plus PNI patterns.

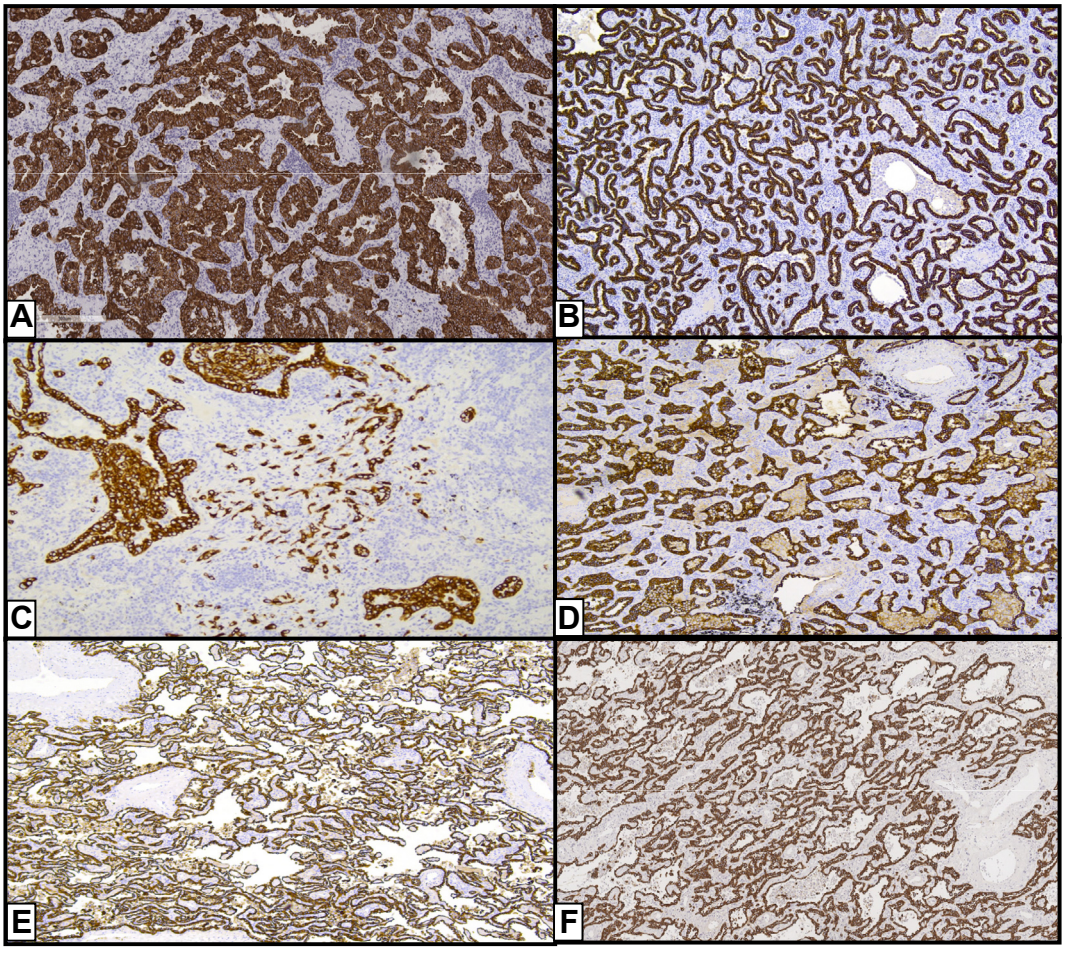

Figure 2. "Invasive" features with CK7 stain: (*A*) multilayering and epithelial duplication; (*B*) disorganized, crowded, and branching architecture; (*C*) budding/single cells; and (*D*) complex architecture. "Noninvasive" features with CK7 stain were characterized by (*E*) organized and streaming architecture and (*F*) maintained alveolar structure. CK7, cytokeratin 7.

Table 1. ICC for Assessment of Lepidic Plus Probable Lepidic for All Tumors and Within Each Diagnostic Group on HE (Rounds 1-3), CK7 (Rounds 1-2), and HE Plus CK7 Combined (Round 4)

	All Tumors (158 Slides)		Lepidic-Predominant (98 Slides)		Acinar-Predominant (60 Slides)	
Round	HE	CK7	HE	CK7	HE	CK7
1	0.36 (0.17-0.52)	0.54 (0.43-0.63)	0.24 (0.08-0.41)	0.44 (0.31-0.55)	0.28 (0.12-0.45)	0.47 (0.32-0.61)
2	0.49 (0.37-0.60)	0.60 (0.53-0.67)	0.38 (0.26-0.49)	0.52 (0.42-0.62)	0.42 (0.23-0.59)	0.59 (0.46-0.70)
3	0.60 (0.52-0.67)	-	0.54 (0.43-0.64)	-	0.47 (0.33-0.60)	-
4 (HE + CK7 combined)	0.75 (0.7-0.8)		0.69 (0.61-0.77)		0.70 (0.6-0.79)	

ICC, intraclass correlation coefficient; HE, hematoxylin and eosin; CK7, cytokeratin 7.

On the tumor section level (n = 158), the intraclass correlation coefficients (ICCs) for the absolute agreement between the raters and the 95% confidence intervals (CIs) were calculated using two-way random effect models for a single rater, as a measurement of interobserver concordance with continuous quantitative variables, for all tumor sections (n = 158) and within each diagnostic group according to the original diagnosis (n = 98 lepidic predominant, n = 60 acinar predominant).[9] ICC was calculated based on scores of HE (rounds 1–3), CK7 (rounds 1–2), and HE and CK combined (round 4). Last, intrarater agreement within the same scorers for all three rounds was computed using ICC with a two-way model, in units of single ratings.

Recurrence-free survival was calculated based on the clinical outcome data on the patient level (n = 104), using the HE and CK7 scores in rounds 2 and 3 (HE only) and round 4 (HE + CK7). For cases with synchronous tumors (n = 8) within the same patient (n = 4), scores for the invasive focus or the larger lepidic focus were used. An average score of NI plus PNI was obtained across all four scorers for HE and CK7 for survival analysis. Cox proportional hazards regression was performed, adjusted for presence of adjuvant treatment and censored after five years.

All tests were two sided, using α less than 0.05 to define statistical significance. All analyses were performed in R statistical software package, version 4.3.0.[10]

Results

Among 54 lepidic-predominant and 54 acinar-predominant lung adenocarcinomas (n = 108), 30 tumors (56%) also have a papillary component, ranging from 5% to 40% of the entire tumor. In addition, 12 tumors (11%) have a micropapillary component (range: 5%–20%), 13 tumors (12%) have a solid component (range: 5%–45%), and three tumors (3%) have a mucinous component (range: focal to 35%).

First and Second Rounds

In both the first and second rounds of scoring, the mean percentages of NI plus PNI and I plus PI for all cases revealed discordance among scorers with both HE and CK7 but less variability with CK7. This is confirmed by the ICC calculations which revealed in rounds 1 and 2 that the ICCs were higher on CK7 than on HE slides and with moderate level of reliability (Table 1). On HE for all slides (n = 158), the ICC for NI plus PNI pattern was 0.36 (95% CI: 0.17–0.52) and 0.49 (95% CI: 0.37–0.60) in round 1 and round 2, respectively. On CK7 for all cases (n = 158), the ICC for NI plus PNI pattern was 0.54 (95% CI: 0.43–0.63) and 0.60 (95% CI: 0.53–0.67) in round 1 and round 2, respectively. Within the lepidic-predominant group, the ICC for NI plus PNI was 0.24 (95% CI: 0.08–0.41) on round 1 HE and 0.44 (95% CI: 0.31–0.55) on round 1 CK7 (Table 1). Concordance with CK7 was increased to 0.52 (95% CI: 0.42–0.62) in round 2. Within the acinar-predominant group, the ICC for NI plus PNI was 0.28 (95% CI: 0.12–0.45) on round 1 HE and 0.47 (95% CI: 0.32–0.61) on round 1 CK7. Concordance with CK7 was increased to 0.59 (95% CI: 0.46–0.70) in round 2. Interestingly, the mean % NI plus PNI across all cases among the four scorers became more comparable after round 2 for CK7 (Fig. 3). There was no bias between trainee and staff pathologists for scoring both the HE and CK7 and images (Fig. 3).

Third Round (HE Only)

The ICC in the third round using the latest IASLC proposal on morphologic features of invasion revealed further improvement in concordance on HE compared with previous rounds (Table 1). For all cases (n = 158), the ICCs for both NI plus PNI and I plus PI patterns were 0.60 (95% CI: 0.52–0.67). The mean percentage of NI plus PNI for all pathologists became comparable only after round 3 HE assessment (Fig. 3).

Fourth Round (HE + CK Combined)

The ICC in the fourth round with HE and CK7 simultaneously available for scoring and the HE based on

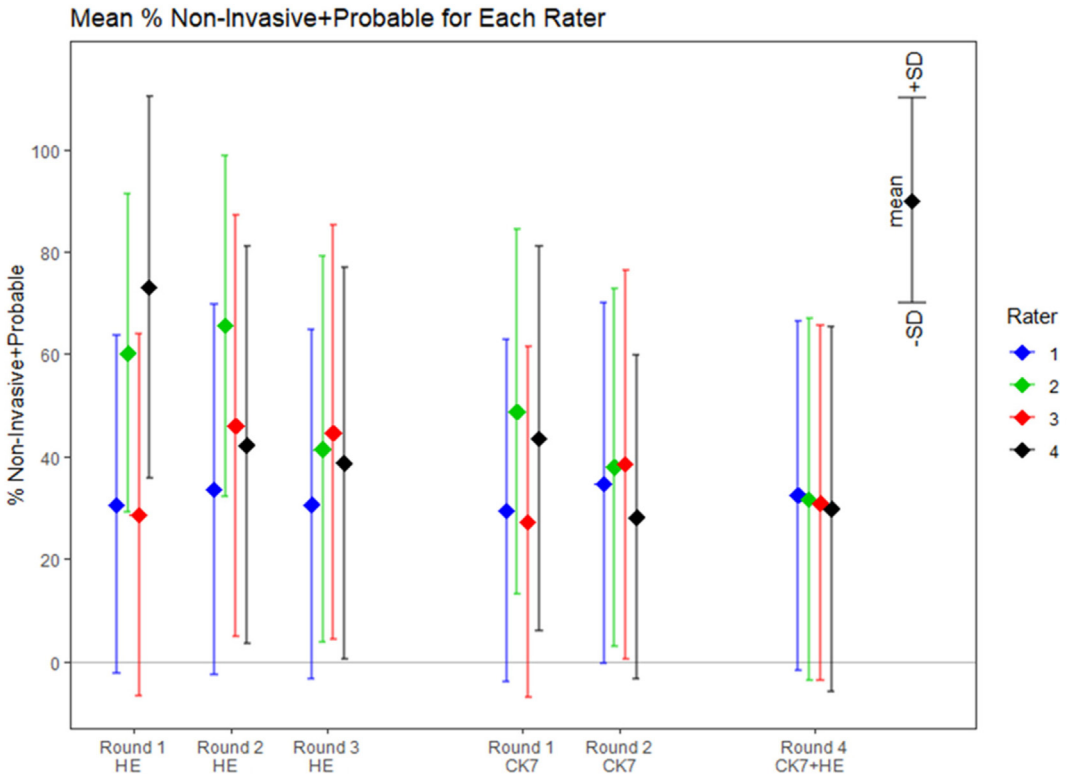

Figure 3. Percentages of sum of noninvasive and probable noninvasive by each scorer for all cases (n = 158), across successive rounds (three rounds for HE and two rounds for CK7 separately and one round for HE and CK7 simultaneously). Raters 1 and 2 are trainee, and raters 3 and 4 are staff pathologists. CK7, cytokeratin 7; HE, hematoxylin and eosin.

the latest IASLC proposal further improved in concordance (Table 1). For all cases (n = 158), the ICCs for both NI plus PNI and I plus PI patterns were 0.75 (95% CI: 0.66–0.77). The mean percentage of NI plus PNI for all pathologists became more comparable in round 4 (Fig. 3).

Clinical Outcome Correlation

The Cox model of recurrence-free survival, using continuous measures of average NI plus PNI scores in rounds 1 and 3 HE (adjusted for treatment), revealed hazard ratio (HR) ranging from 0.83 (95% CI: 0.71–0.96; $p = 0.02$) to 0.86 (95% CI: 0.75–0.99; $p = 0.04$) (Supplementary Table 2). The HR based on combined HE and CK7 in round 4 was comparable at 0.89 (95% CI: 0.76–1.05; $p = 0.16$) (Supplementary Table 2).

Discussion

AIS and MIA are known predictors of better clinical outcome, and improvement of the pathologist's reproducibility in the assessment of invasion has clinical significance.[2] In this study, we assessed the utility of CK7 immunostain as an ancillary tool to improve the assessment of "invasion" among lepidic- or acinar-predominant lung adenocarcinoma. In this cohort of cases, the ICCs on the HE scores among four pathologists in first two rounds of assessment were comparable to previous studies, which reported kappa scores ranging from 0.08 to 0.4 (none to slight, to fair).[6,9,11] Nevertheless, we consistently found in the first two rounds that ICCs with CK7 were higher than HE, with the ICCs ranging from 0.44 to 0.6 (moderate reliability).[7] Equally important, we have validated the recently proposed algorithm by the IASLC committee on morphologic features of invasion and its use to improve the reproducibility of recognizing lepidic versus nonlepidic patterns.[8] For all cases (n = 158), the ICC for NI plus PNI pattern with HE increased from 0.49 (95% CI: 0.37–0.60) in round 2 to 0.6 (95% CI: 0.52–0.67) in round 3 using the IASLC scoring algorithm and further increased to 0.75 (95% CI: 0.70–0.80) in round 4 with HE and CK7 simultaneously available.

Assessment of invasion in lung adenocarcinoma may present various challenges for pathologists, particularly between lepidic and acinar/papillary patterns, as revealed by lower than desired kappa scores in previous studies.[6] Similar reasons for discrepancy were encountered during our study during all rounds, including tangential cutting of lepidic growth along the alveolar surface mimicking acinar or papillary structures.[7] Similarly, alveolar wall collapse (secondary to

poorly inflated gross specimen by formalin) and fibrosis can both add to the mimicry of invasion. It can be further complicated by preexisting lung architectural changes, such as interstitial fibrosis. Ultimately, these issues are not uncommon when assessing complex three-dimensional architectures with two-dimensional histologic sections.

The primary aim of our study is to assess whether the use of CK7 provides better concordance than HE; this is indeed revealed in the first two rounds where CK7 outperformed HE. The consensus review after the first round of scoring identified the differences in interpretation among scorers and allowed for better education of various mimics of invasion, which may explain the slightly improved ICC in round 2 (Table 1). The recently proposed IASLC recommendation as applied in round 3 HE further improved this. Likewise, a consolidation of the differences in operator experience and opinion of the scorers allowed us to develop a step-by-step approach (Fig. 1) for a more consistent way to assess the presence of "invasive" and "noninvasive" patterns on CK7-stained sections. In our study, this strategy seems to have improved the ICC for CK7 slide assessment from 0.54 (95% CI: 0.43–0.63) in round 1 to 0.60 (95% CI: 0.53–0.67) in round 2. Last, when combining the available review of HE and CK7 in round 4, the ICC was further improved to 0.75 (95% CI: 0.70–0.80), suggesting that features found on CK7 could bring clarity to the features found on HE alone.

Although the possibility of the further improved ICC in round 4 due to greater familiarity of scoring cannot be entirely excluded, recall bias was mitigated with case blinding and sufficient time gap between each round (range = 4–14 mo). Particularly, in round 1 without any training, CK7 had higher concordance than HE, which precluded any training bias. This positive trend also reveals the potential of training with CK7 as an ancillary tool of invasion assessment and the application of the recently proposed IASLC recommendation. Our analysis also found no significant difference between trainees and staff pathologists.

Cox proportional hazards regression was performed using continuous measures of invasiveness (Supplementary Table 2) due to the smaller number of patients in our cohort. The HR with averaged NI plus PNI scores on HE in rounds 1 to 3 ranged from 0.83 to 0.86 ($p = 0.02$, $p = 0.04$). This suggests a positive correlation between the presence of lepidic component in lepidic-/acinar-predominant adenocarcinoma and improved recurrence-free survival. This is in line with previous studies that revealed significant correlation between the presence of lepidic growth pattern and improved disease-specific survival and overall survival.[12,13] Radiologically, the ground-glass opacity (GGO) component on chest computed tomography, which has been known to usually represent the lepidic (NI + PNI) component on pathology, was found to have improved prognosis compared with tumors without GGO component.[14–16] Whether this positive correlation is based on the proportion of the GGO of the tumor remains unclear.[14–16] CK7 scores were not included in the recurrence-free survival analysis due to the incomplete availability of all tumor sections (which may contain the aforementioned focal to minor papillary, micropapillary, solid, and mucinous components) that may influence survival outcomes in our retrospective study. This may have contributed to the statistically insignificant, albeit similar HR in round 4 (HE + CK7) (0.89, [95% CI: 0.76–1.05], $p = 0.16$) (Supplementary Table 2).

At consensus review, reasons for discrepancy were raised, including the presence of fibrosis, inflammation, preexisting lung disease (such as usual interstitial pulmonary fibrosis pattern), and reactive atypia; these are similar to those previously reported.[6–8] It is particularly challenging when a combination of factors suggestive of invasion is present, including cytologic atypia, altered lung architecture, and small glands, albeit evidently admixed with NI features such as inflammation and preexisting lung disease. For instance, germinal centers can expand alveolar spaces with altered architecture without raised suspicion for invasion, admixed with surrounding alveolar spaces expanded with small single glands suggestive of invasion.

One of the limitations of our study is that this was a single cohort/center retrospective study with limited pathologists involved, which highlights a need for further validation in a multi-institutional study, particularly with clinical outcome analysis and with larger number of pathologists. The incomplete information on the staging status of the cases has limited our survival analyses. The result of our study suggests that pathologists are capable of capturing features found on CK7 stain that may not be apparent on HE. Nevertheless, the exact features are not yet elucidated and may require artificial intelligence by machine learning to tease out, with the potential to further improve consistency and concordance. Previous studies have used whole side images to investigate concordance for invasion and subtyping of lung adenocarcinoma using a clustering approach.[17,18] Using whole slide images and the application of machine learning is an ongoing direction of our project.

In conclusion, CK7 immunostain reveals "noninvasive" and "invasive" features that may be recognized with greater consistency than HE assessment alone. Further studies to identify these features in conjunction with the recently proposed IASLC recommendation could further improve the accuracy of invasive tumor size measurement in nonmucinous adenocarcinoma.

CRediT Authorship Contribution Statement

Ellen Yang: Conceptualization, Data curation and analysis, Writing—original draft, Writing—review and editing.

Najd Alshamlan: Data curation and analysis, Writing—review and editing.

Katrina Huenien: Data curation and analysis, Writing—original draft, Writing—review and editing.

Jessica Weiss: Data curation and analysis, Writing—review and editing.

Michael Cabanero: Conceptualization, Data generation, Data curation and analysis, Writing—review and editing.

Ming-Sound Tsao: Conceptualization, Data analysis, Funding and supervision, Writing—original draft, Writing—review and editing.

Disclosure

The authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2024.100682].

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