

High-Risk Clinicopathologic Features for Recurrence in Stage I Lung Adenocarcinoma

Objective: To identify high-risk clinical and pathologic features associated with recurrence in patients with completely resected pathologic stage I lung adenocarcinoma (LUAD).

Methods: A retrospective review of a prospectively maintained institutional database was performed. Patients with pathologic stage I LUAD who underwent surgery from 2010 to 2020 were included. Staging was based on the 8th Edition of the American Joint Committee on Cancer staging system. Patients with a history of lung cancer, neoadjuvant or adjuvant therapy, incomplete resection, or mortality within 90 days were excluded. Other adenocarcinoma pathology including invasive mucinous, minimally invasive, and adenocarcinoma in situ were also excluded. Recurrence was determined by imaging and/or pathology, with molecular testing when necessary. Univariable (UVA) and multivariable (MVA) Fine-Gray models were constructed for recurrence with a competing risk of death without recurrence.

Results: A total of 2,305 patients with a median follow up of 68 months (IQR 66-70 months) were included. Median age at surgery was 69 years (IQR 63-75 years), 66% (1513/2305) were female, and 76% (1748/2305) were ever smokers. Most patients had a minimally invasive surgical approach (83% [1916/2305]) and a lobectomy performed (56% [1300/2305]). Eighty-two percent (1891/2305) of patients had pathologic stage IA disease. EGFR activating mutations (i.e., exon 19 deletions, exon 21 L858R mutation) and ALK fusions were present in 17% (393/2270) and 1.2% (25/2075) of tumors, respectively, and 83% (896/1081) of tumors had PD-L1 <1%. Recurrences were noted in 296 patients. One hundred twenty-four (42%) recurrences were locoregional only, while 172 (58%) were distant. The five-year cumulative incidence of recurrence for patients with pathologic stage IB was 26%, compared to 5.5%, 11%, and 11% for stage IA1, IA2, and IA3, respectively. UVA revealed a higher SUVmax ($p<0.001$), sublobar resection ($p=0.006$), aggressive histologic subtypes ($p<0.001$), poor/undifferentiated grade ($p<0.001$), lymphovascular invasion (LVI) ($p<0.001$), visceral pleural invasion (VPI) ($p<0.001$), spread through air spaces (STAS) ($p<0.001$), larger tumor size ($p<0.001$), and pathologic stage (IB vs. IA) ($p<0.001$) were associated with recurrence (Figure 1). MVA found that recurrence was independently associated with SUVmax (HR=1.05, 95% CI 1.03-1.07, $p<0.001$), sublobar resection (HR=1.41, 95% CI 1.04-1.91, $p=0.025$), LVI (HR=2.11, 95% CI 1.57-2.82, $p<0.001$), and histologic subtype (low v. intermediate: HR=4.53, 95% CI 2.12-9.71; low v. high: HR=4.55, 95% CI 2.01-10.3). Pathologic stage (IB vs. IA) did not remain significantly associated with recurrence in MVA ($p=0.2$).

Conclusions: In stage I LUAD, stratifying patients by pathologic stage (IA vs. IB) for risk of recurrence may be inadequate. Instead, clinicopathologic features such as SUVmax, sublobar resection, LVI, and micropapillary/solid histologic subtypes place patients at a higher risk of recurrence. These features should help identify the high-risk stage I population who may benefit from future investigations into effective screening protocols and/or adjuvant therapies.

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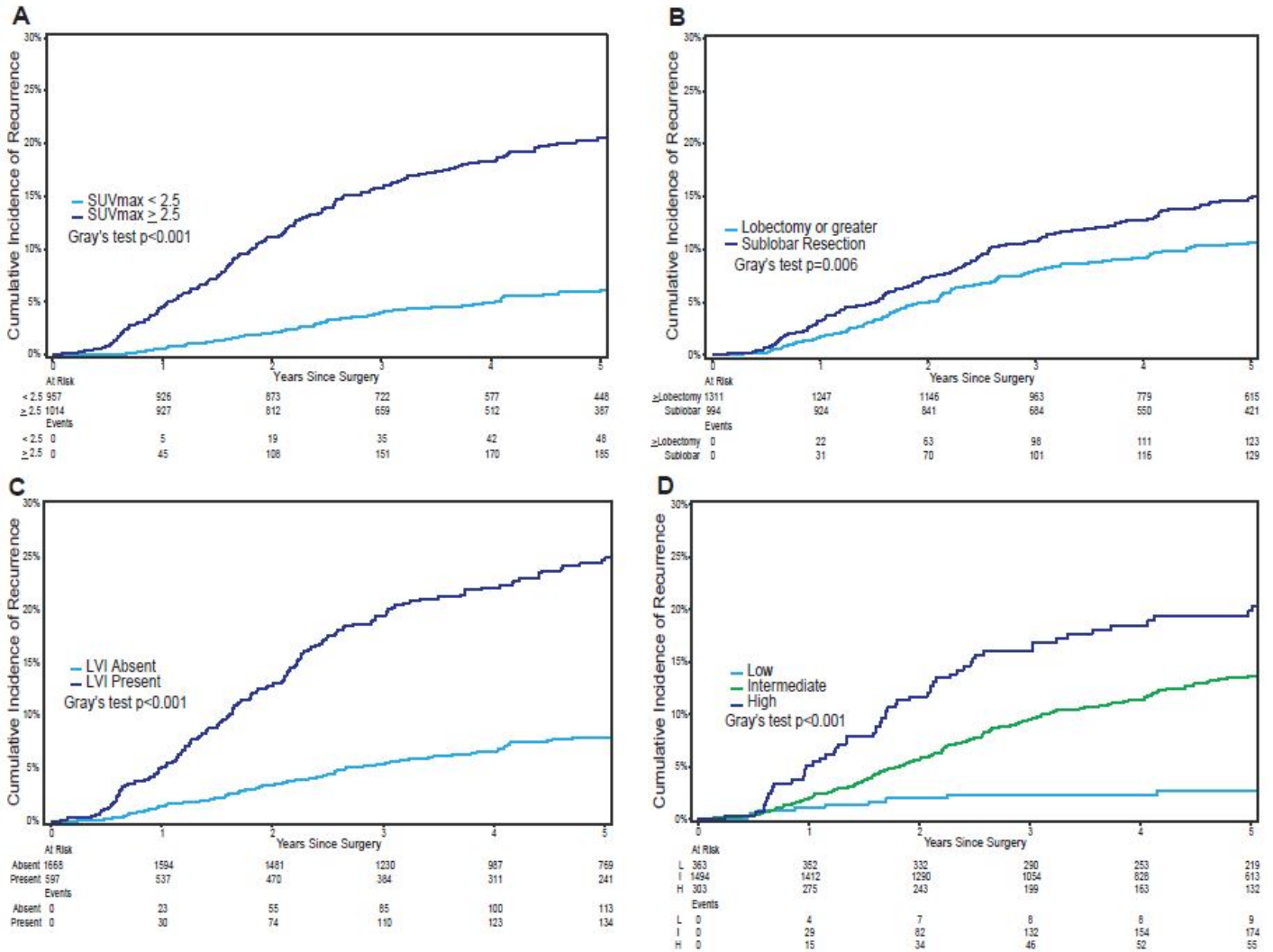


Figure 1. Five-year cumulative incidence of recurrence plots. A, Maximum standardized uptake value (SUVmax). Median SUVmax for entire cohort was 2.5. B, Surgical resection. Sublobar: wedge resection or segmentectomy. C, Lymphovascular Invasion (LVI). D, Predominant histologic subtype. Low (L): lepidic; Intermediate (I): acinar, papillary; High (H): micropapillary, solid.