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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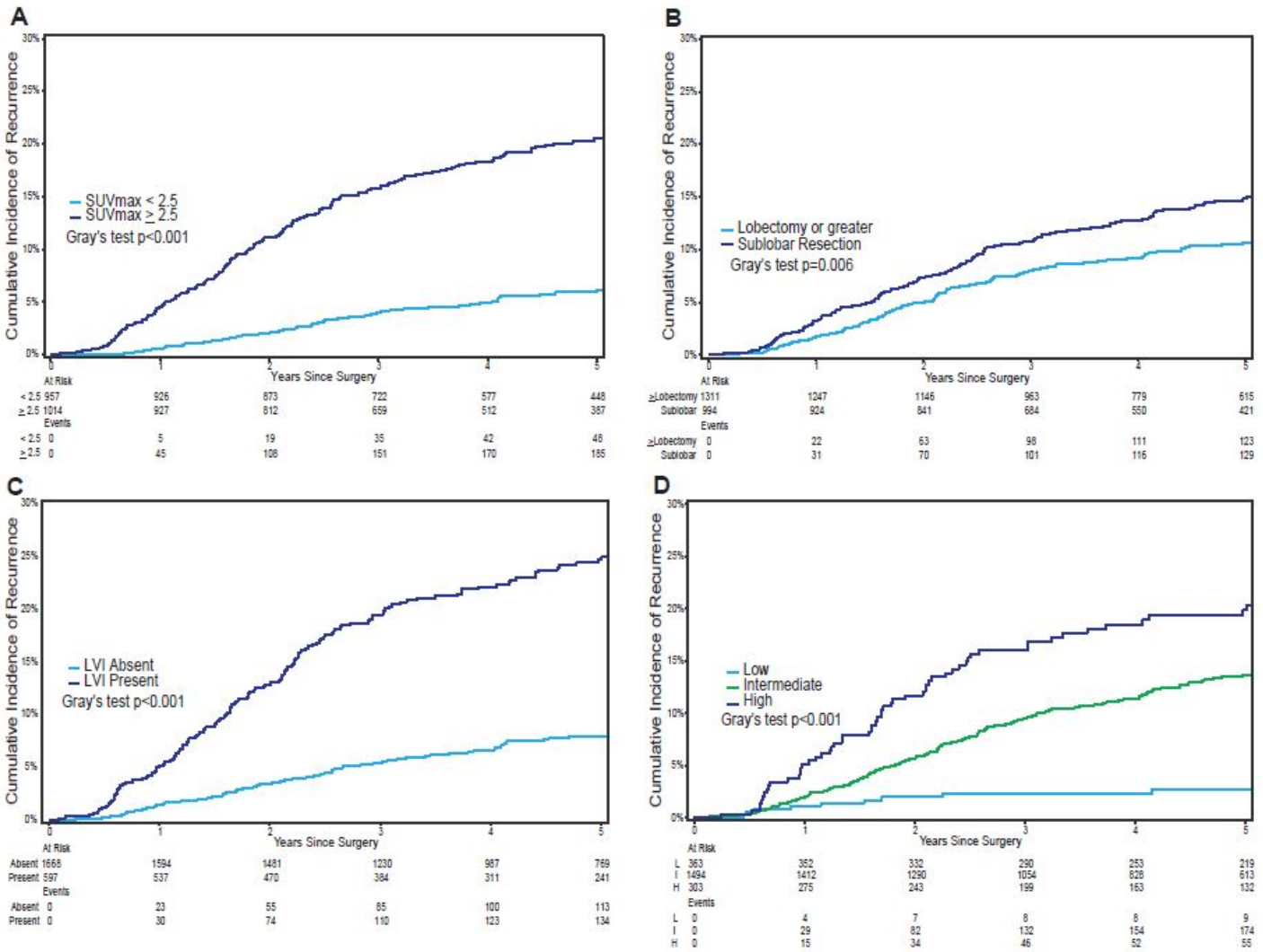

Figure 1. Five-year cumulative incidence of recurrence plots. A, Maximum standardized uptake value (SUVmax). Median SUVmax for entire cohort was 2.5. B, Surgical resection. Sublobar: wedge resection or segmentectomy. C, Lymphovascular Invasion (LVI). D, Predominant histologic subtype. Low (L): lepidic;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