

Prognostic Value of High-Risk Pathologic Features in Resected Stage I NSCLC Using US SEER Registry Data

Background

- Surgery is the cornerstone of standard-of-care treatment for patients with resectable stage I non–small-cell lung cancer (NSCLC), with additional adjuvant radiation and/or systemic therapy recommended depending on pathologic assessment at the time of of surgery¹
 - Most patients with resectable stage I NSCLC are treated with surgery alone^{2,3}
- The presence of high-risk pathologic features (HRPFs) including larger tumor size, visceral pleural invasion (VPI), high-grade histology, and lymphovascular invasion (LVI) has been associated with worse prognosis in patients with resected early-stage NSCLC^{4,5}
- Contemporary real-world data on the histology-specific prevalence, co-occurrence, and prognostic impact of HRPFs in resected early-stage NSCLC are limited
- This retrospective observational study was conducted to address this data gap by characterizing the epidemiology of HRPFs (larger tumor size [≥2 cm], VPI, and high-grade histology [grade ≥3]) in patients with resected stage I NSCLC in the United States

Objectives

- Estimate the real-world prevalence and co-occurrence of HRPFs in patients with resected stage I NSCLC, stratified by histology
- Identify patient demographic and clinical characteristics associated with the prevalence of HRPFs
- Evaluate prognostic associations between HRPFs and real-world overall survival (rwOS)

Methods

Study design and study population

- The US Surveillance, Epidemiology, and End Results (SEER) 17 database was used to identify patients diagnosed with stage I NSCLC between 2010–2023
- Patients were included in the analysis if they had stage I NSCLC, defined as clinical or pathologic T1a–T2a (≤4 cm) per American Joint Committee on Cancer (AJCC) 8th edition; squamous cell carcinoma (SQ), adenocarcinoma, or NSCLC not otherwise specified (NOS) histology; received curative intent surgical resection; and did not receive pre-operative anticancer therapy (systemic or radiation therapy)
- Patients were excluded if they had rare nonsquamous (NSQ) histologies, including sarcomatoid, neuroendocrine, and large cell, and unknown or positive lymph node status

Study outcomes

- Prevalence of individual HRPFs included larger tumor size (>2 cm), VPI, and high-grade histology (grade ≥3). Although LVI is a recognized HRPF, it is not captured in SEER for lung cancers
- Other metrics used to describe HRPF burden included the presence of any HRPF and total number of HRPFs
- The primary health outcome was rwOS, defined as the time from surgery to death from any cause

Statistical analysis

- Prevalence and co-occurrence of HRPFs were summarized descriptively and compared across patient and clinical characteristics using Chi-square or Fisher’s exact tests
- Kaplan-Meier analysis was used to estimate rwOS from time of surgery, according to the presence or absence of HRPFs
 - Multivariate Cox proportional hazards regression was used to estimate the prognostic effect of HRPFs on rwOS
- Analyses were stratified by histology (SQ vs NSQ) whenever possible

Results

Patients

- Of the 121,962 patients with stage I NSCLC diagnosed between 2010 and 2023, 71,538 (58.7%) met eligibility criteria and were included in the analysis
 - 46,462 patients (64.9%) were alive at the time of data curation (November 2025)
- The median time from diagnosis to surgical resection was 32.0 (IQR, 0.0–58.0) days and from diagnosis to last follow-up was 50.0 (IQR, 22.0–85.0) months
- Most patients were ≥65 years of age (71.2%), female (57.1%), white (82.9%), had NSQ histology (78.4%), stage IA disease (71.9%), and right-sided (59.3%) tumors (**Table 1**)
- 93.1% of patients were treated with surgery alone without post-operative therapy

Table 1. Patient demographics and clinical characteristics

	Total N = 71,538	SQ n = 15,483	NSQ n = 56,055
Age ≥65 y at diagnosis	50,917 (71.2)	12,116 (78.3)	38,801 (69.2)
Female	40,882 (57.1)	6857 (44.3)	34,025 (60.7)
Race			
American Indian/Alaska Native	348 (0.5)	100 (0.6)	248 (0.4)
Asian or Pacific Islander	6026 (8.5)	511 (3.3)	5515 (9.9)
Black/African American	5831 (8.2)	1225 (7.9)	4606 (8.3)
White	59,046 (82.9)	13,610 (88.1)	45,436 (81.4)
Ethnicity			
Not Hispanic/Latino	67,167 (93.9)	14,790 (95.5)	52,377 (93.4)
Hispanic/Latino	4371 (6.1)	693 (4.5)	3678 (6.6)
Stage			
IA	51,431 (71.9)	10,613 (68.5)	40,818 (72.8)
IB	20,107 (28.1)	4870 (31.5)	15,237 (27.2)
Surgery type			
Lobectomy/bilobectomy	50,250 (70.3)	10,758 (69.5)	39,492 (70.5)
Pneumonectomy	409 (0.6)	178 (1.2)	231 (0.4)
Sublobar ^a	20,843 (29.2)	4537 (29.3)	16,306 (29.1)
Surgery and post-operative therapy			
Surgery only	66,585 (93.1)	14,398 (93.0)	52,187 (93.1)
Surgery + CRT	438 (0.6)	123 (0.8)	315 (0.6)
Surgery + RT	1030 (1.4)	354 (2.3)	676 (1.2)
Surgery + SACT	3474 (4.9)	605 (3.9)	2869 (5.1)
Surgery + SACT + RT	11 (0.02)	3 (0.02)	8 (0.01)

CRT, chemoradiotherapy; RT, radiotherapy.
Data are n (%), with percentages out of the numbers of patients with available data for each demographic or characteristic.
^aIncludes segmentectomy, wedge, and other sublobar.

Prevalence and co-occurrence of HRPFs

- 56.7% of patients had ≥1 HRPF (SQ, 69.2%; NSQ, 53.2%)
- The most prevalent HRPF was tumor size >2 cm (41.7%), followed by high-grade histology (24.6%) and VPI (14.8%)
- Multiple co-occurring HRPFs were present in 17.8% of patients and were more common in SQ (26.6%) versus NSQ (15.4%) tumors

Table 2. Prevalence of HRPFs

	Total N = 71,538	SQ n = 15,483	NSQ n = 56,055
Any HRPF ^a	56.7	69.2	53.2
Tumor size >2 cm	41.7	49.4	39.5
VPI ^b	14.8	13.4	15.2
High-grade histology ^c	24.6	40.5	19.9
Number of HRPFs			
1	38.9	42.6	37.8
2	15.6	23.6	13.4
3	2.2	3.0	2.0
Co-occurrence of HRPFs			
Tumor size >2 cm + VPI	7.7	7.7	7.7
Tumor size >2 cm + high-grade histology	11.7	21.6	8.9
VPI + high-grade histology	3.8	4.8	3.6
Tumor size >2 cm + VPI + high-grade histology	2.2	3.0	2.0

Data are the percentages of patients with HRPFs out of the number of patients with available data.
^aAny HRPF included patients with ≥1 individual HRPF as the numerator, with all patients (including those with missing data for individual HRPFs) as the denominator.
^b12.3% of patients had missing data for VPI (SQ: 13.4%; NSQ: 12.0%).
^c10.4% of patients had missing data for high-grade histology (SQ: 6.7%; NSQ: 11.4%).

Table 3. Prevalence of HRPFs across patient characteristics in the total population

	Tumor size >2 cm		VPI		High-grade histology		Any HRPF	
	Yes	P value ^a	Yes	P value ^a	Yes	P value ^a	Yes	P value ^a
Age at diagnosis								
<65 y	38.1		13.9		24.9		53.8	
≥65 y	43.1	< 0.001	15.2	< 0.001	24.4	0.268	57.9	< 0.001
Sex								
Female	39.5	< 0.001	14.4	0.001	21.4	< 0.001	53.6	< 0.001
Male	44.6		15.4		28.7		60.8	
Race								
American Indian/Alaska Native	48.6		14.5		30.7		60.9	
Asian or Pacific Islander	45.7	< 0.001	17.2	< 0.001	17.2	< 0.001	56.8	0.003
Black/African American	42.3		17.3		26.5		58.7	
White	41.2		14.4		25.1		56.5	
Ethnicity								
Hispanic/Latino	44.7		15.5		20.3		56.3	
Not Hispanic/Latino	41.5	< 0.001	14.8	0.235	24.8	< 0.001	56.7	0.595

Data are the percentages of patients with HRPFs out of the total number of patients with each demographic or clinical characteristic.
^aChi-square or Fisher exact test P value comparing the prevalence of each HRPF category (yes/no) across patient characteristics categories.

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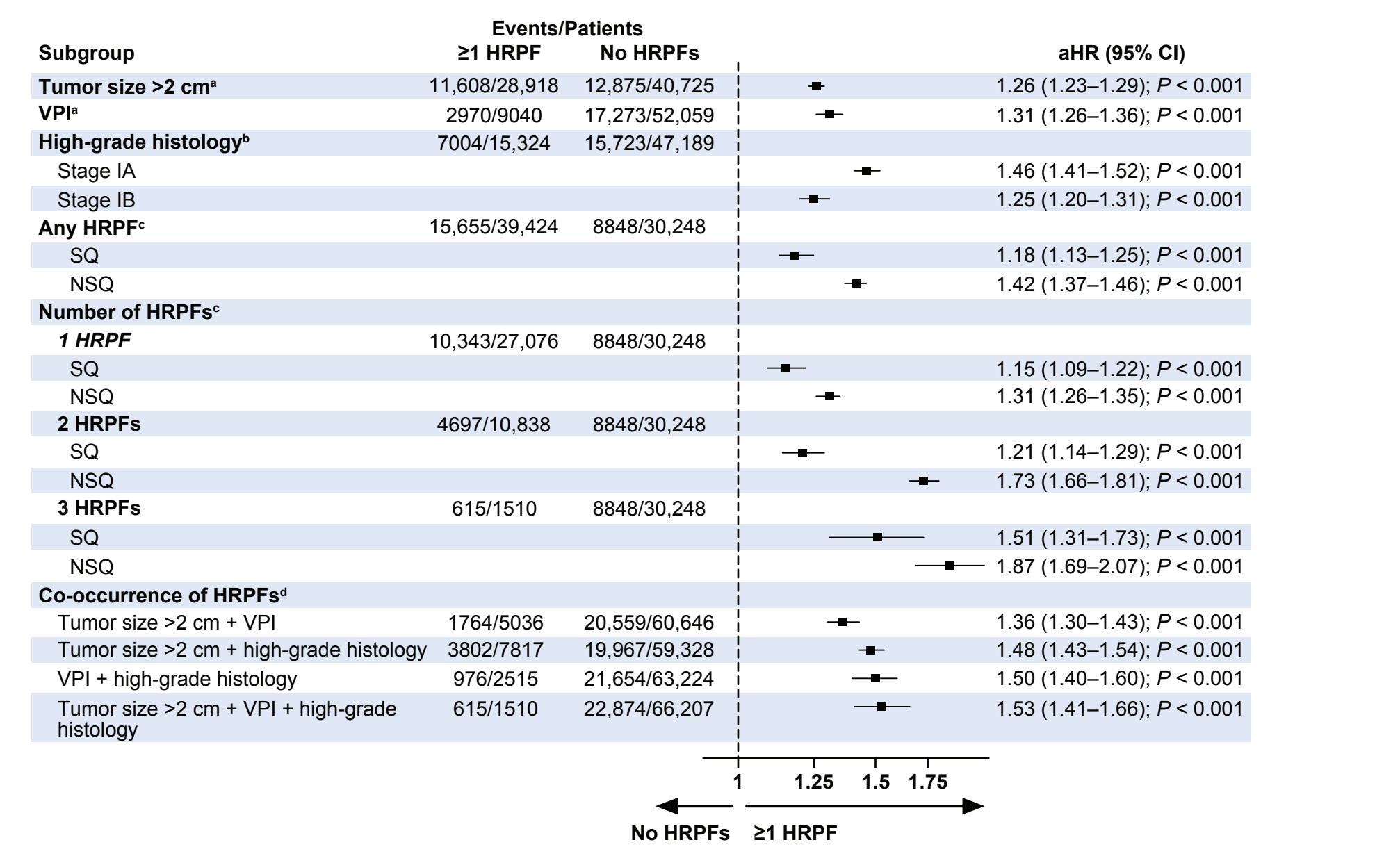
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Association between HRPFs and rwOS

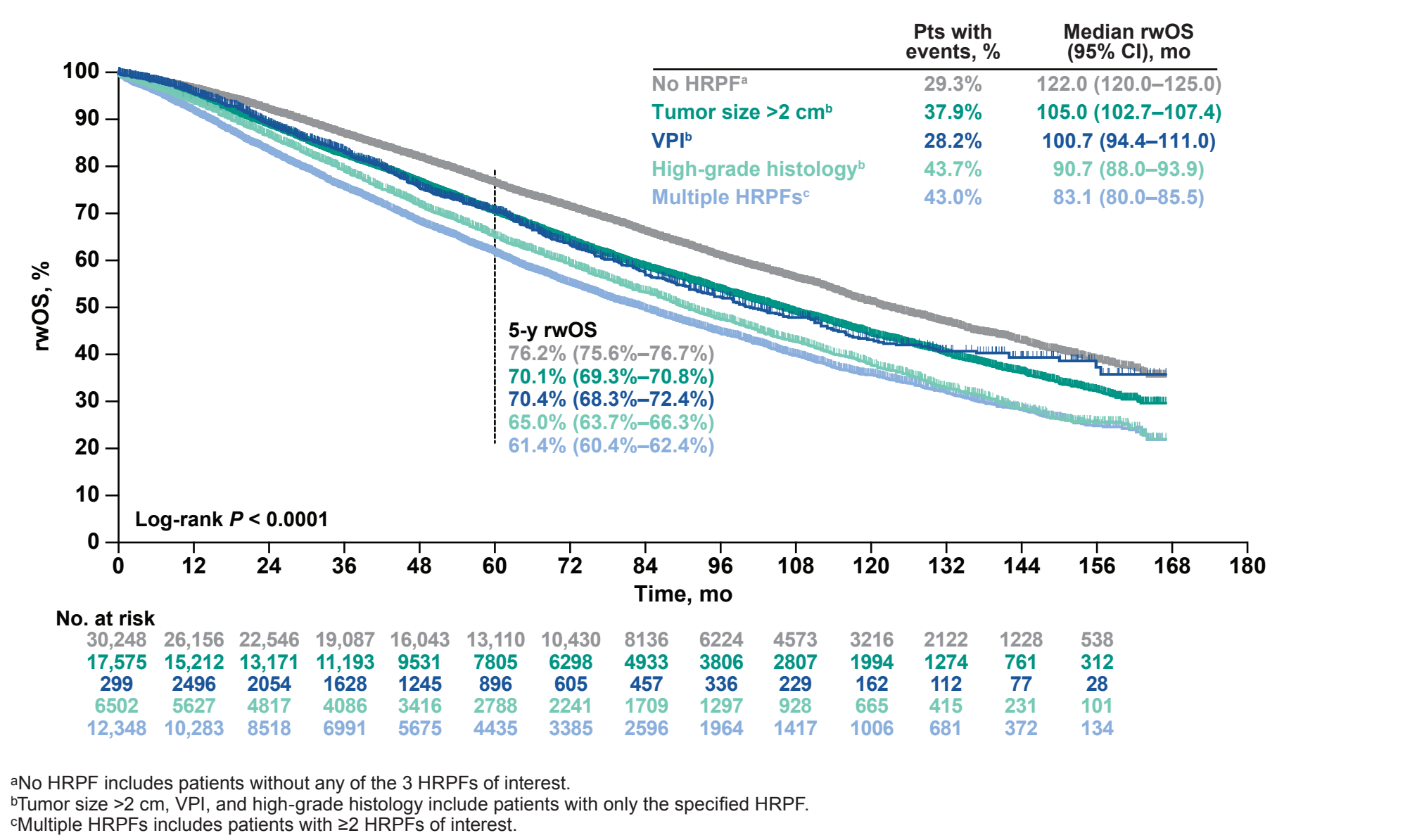
- Among 69,672 patients (97.4%) with available data for survival analysis, the median time from surgery to last follow-up was 49.8 (IQR, 22.0–85.0) months
- 5-year rwOS (95% CI) was 66.5% (66.0%–67.1%) for patients with any HRPFs and 76.2% (75.6%–76.7%) for those with no HRPFs
 - SQ: 57.1% (56.0%–58.2%) vs 63.2% (61.5%–64.7%)
 - Adjusted HR, 1.18 (95% CI, 1.13–1.25); *P* < 0.001
 - NSQ: 70.1% (69.4%–70.7%) vs 78.6% (78.0%–79.2%)
 - Adjusted HR, 1.42 (95% CI, 1.37–1.46); *P* < 0.001
- High-grade histology, tumor size >2 cm, and presence of VPI were independently associated with worse rwOS after adjusting for known prognostic factors (age, sex, race, surgery type, and year of diagnosis)
 - The strength of the association between high-grade histology and rwOS varied by stage, with a stronger association observed for patients with stage IA versus IB tumors
- Presence of any HRPF and a higher number of HRPFs were independently associated with worse rwOS after adjusting for the known prognostic factors
 - The strength of each association varied by histology, with stronger associations observed for patients with NSQ versus SQ tumors
- Presence of co-occurring HRPFs was significantly associated with worse rwOS after adjusting for the known prognostic factors, with the presence of all 3 HRPFs (high-grade histology, tumor size >2 cm, and VPI) associated with the greatest HR (1.53; 95% CI, 1.41–1.66)

Figure 1. Prognostic association of HRPFs and rwOS



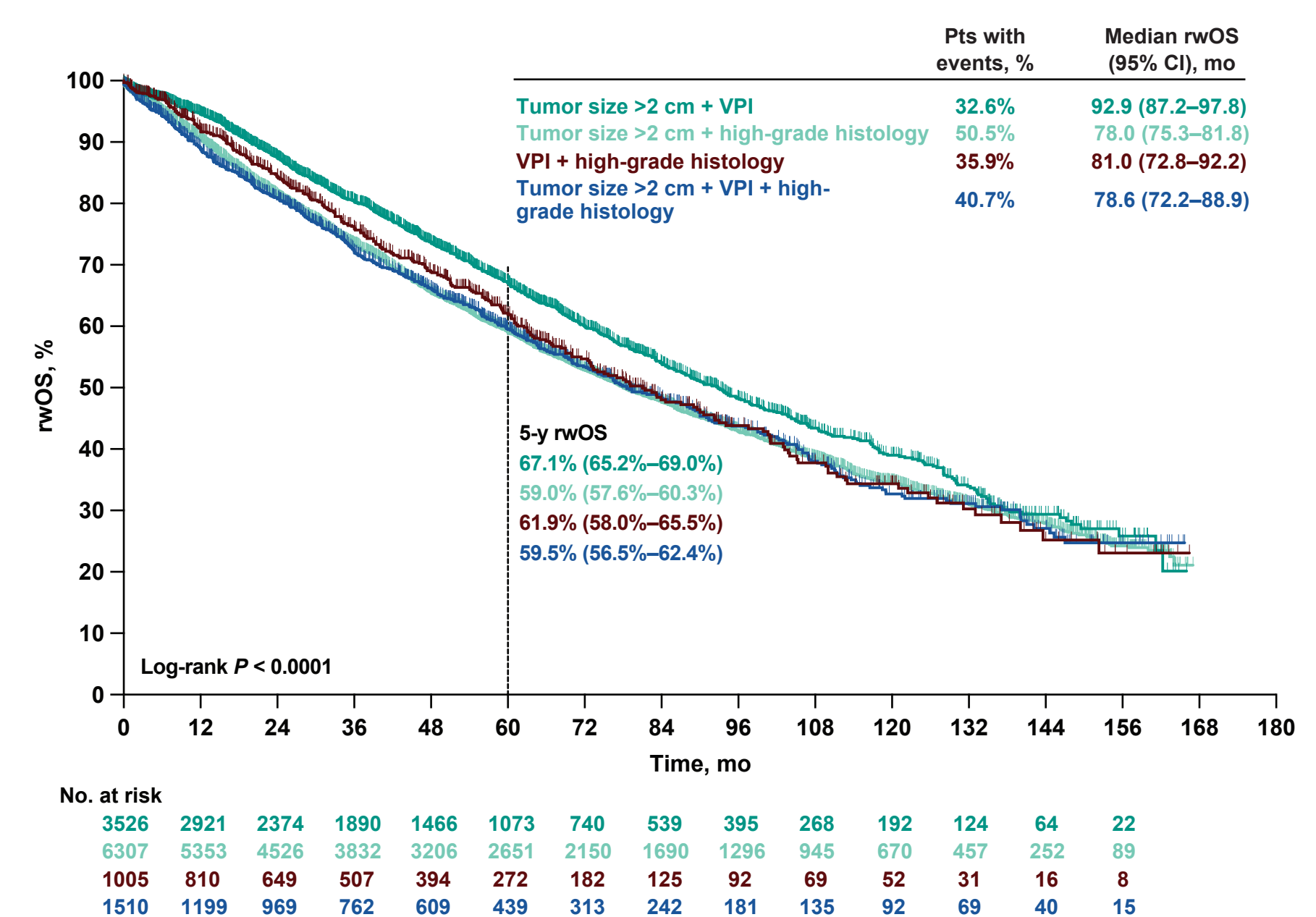
aHR, adjusted hazard ratio.
^aMultivariate Cox proportional hazards regression models adjusted for HRPF, age, sex, race, surgery type, and year, and stratified by histology.
^bStage-specific multivariate Cox proportional hazards regression model adjusted for HRPF, age, sex, race, surgery type, and year.
^cHistology-specific multivariate Cox proportional hazards regression models adjusted for HRPF, age, sex, race, surgery type, and year.
^dMultivariate Cox proportional hazards regression models adjusted for HRPF combination, age, sex, race, surgery type, and year.

Figure 2. rwOS from time of surgery in mutually exclusive HRPF cohorts



^aNo HRPF includes patients without any of the 3 HRPFs of interest.
^bTumor size >2 cm, VPI, and high-grade histology include patients with only the specified HRPF.
^cMultiple HRPFs includes patients with ≥2 HRPFs of interest.

Figure 3. rwOS from time of surgery in mutually exclusive co-occurring HRPF cohorts



Limitations

- Some common variables in real-world oncology analyses, some of which are prognostic factors that can influence rwOS, are not captured in the SEER database or were unavailable (smoking status, comorbidities, performance status, surgical margin status, and disease recurrence)
- Surgical recommendations for stage I NSCLC have changed over time⁶; however, the impact of these changes on long-term rwOS among patients with HRPFs remains to be determined
- In SEER, stage is defined as a combination of clinical and pathologic stage, tumor size is not recorded as either total or invasive component size, data on treatments are only available for ≤6 months post-diagnosis and are limited to the first course of treatment, and LVI is not captured for lung cancers
- The grading system used to categorize high-grade SQ tumors in the SEER database is unclear

Conclusions

- In this large, contemporary real-world analysis of patients with resected stage I NSCLC, HRPFs were present in over half of patients (56.7%)
- After adjustment for known prognostic factors, the presence of any HRPF and total HRPF burden were associated with worse rwOS
 - Tumors with size >2 cm and those with VPI and high-grade histology were independently associated with worse rwOS
 - Distinct patterns were observed across histologies, with the strongest associations observed among patients with NSQ tumors
- These findings add to the evidence supporting the use of HRPFs to identify stage I NSCLC populations at risk of poor prognosis for inclusion in adjuvant therapy trials

Poster presented



<https://bit.ly/45lpSxe>