

Clinicopathological predictors of outcome in completely resected stage I lung adenocarcinoma: a retrospective cohort study

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Abstract

Background

Outcomes after complete resection of stage I lung adenocarcinoma vary widely, and anatomical stage alone does not explain this variation. Which clinicopathological factors remain independently prognostic when analysed together is unclear. The extent of resection is particularly contested: randomised trials support limited resection in small peripheral tumours, whereas retrospective series report worse outcomes after sublobar resection in high-risk disease. Competing-risk methods are also rarely applied in single-centre series, although most deaths after resection of stage I disease are not caused by recurrence.

Methods

We retrospectively reviewed 184 patients with pathological stage I lung adenocarcinoma resected between January 2016 and December 2023 at a single centre; 26 were excluded. Overall and disease-free survival were estimated by the Kaplan-Meier method and compared by log-rank test. Cox proportional hazards models were fitted for each endpoint, containing histological grade, lymphovascular invasion, tumour size, extent of resection, age, sex and, for overall survival, adjuvant therapy. Recurrence was additionally analysed with the Aalen-Johansen estimator and a Fine-Gray model, treating death without recurrence as the competing event.

Results

A total of 158 patients were analysed; 118 underwent lobar and 40 sublobar resection. Median follow-up was 84.9 months. Recurrence occurred in 34 patients (21.5%) and 41 (25.9%) died. 5-year overall and disease-free survival were 79.2% and 64.9%. Lymphovascular invasion was independently associated with worse overall survival (hazard ratio 3.24, 95% confidence interval 1.63 to 6.45) and disease-free survival (2.47, 1.42 to 4.29), whereas histological grade and extent of resection were not. Twenty-six of 41 deaths (63.4%) occurred without recurrence. Cumulative incidence of recurrence at five years was 20.3% versus a Kaplan-Meier estimate of 22.6%. Half of all recurrences occurred beyond 24 months.

Conclusions

Analysed together, lymphovascular invasion was the only factor independently associated with both recurrence and death. These data align with the randomised evidence rather than with series favouring lobectomy in high-risk disease. Most deaths occurred without recurrence, which affects how recurrence risk should be estimated, and half of all recurrences occurred beyond two years, arguing against

surveillance limited to the early postoperative period. Confirmation in multicentre cohorts, and prospective collection of cause-of-death and pulmonary function data, are required.

Trial registration

Not applicable.

Background

The proportion of lung cancers diagnosed at stage I has increased substantially with the expansion of low-dose computed tomography screening and incidental detection, and surgical resection remains the standard treatment for these patients [1]. Outcomes after complete resection are nonetheless heterogeneous, with reported 5-year survival in stage I disease ranging from 73% for stage IB to 90% for stage IA1 [2], and a minority of patients experience recurrence despite an apparently curative operation [3]. Identifying which of these patients are at risk remains a practical problem, because anatomical stage alone does not explain this variation.

Several pathological and surgical factors have been proposed to account for it. Lymphovascular invasion has been repeatedly associated with recurrence and death in early-stage disease [3]. The grading system proposed by the International Association for the Study of Lung Cancer, which assigns grade 3 to any tumour containing 20% or more of a high-grade pattern, has been validated as a prognostic classifier [4]. The extent of resection has been the subject of two randomised trials that established the oncological acceptability of limited resection in small peripheral tumours [5, 6]. This is therefore an actively investigated field rather than an unexplored one, and the individual prognostic value of each of these factors has been examined in large cohorts.

Gaps nonetheless remain. These factors are usually studied separately, so their relative contribution when entered into a single model is less well characterised. The evidence base is dominated by cohorts from East Asia, North America and Western Europe, whereas data from Türkiye are limited to a small number of series [7, 8], and the applicability of these estimates to the regional population has not been established. Furthermore, most deaths after resection of stage I disease are not caused by recurrence, yet competing-risk methods have been applied mainly in large institutional databases and less often in single-centre series, where the standard Kaplan-Meier approach may overstate recurrence risk.

We therefore analysed a consecutive single-centre cohort of patients with completely resected pathological stage I lung adenocarcinoma, with the aim of determining which clinicopathological factors are independently associated with overall and disease-free survival when analysed together, and of quantifying recurrence within a competing-risk framework. We hypothesised that lymphovascular invasion, histological grade and the extent of resection would each carry independent prognostic information for both endpoints.

Methods

Study design and patient selection

This retrospective cohort study was conducted at the Department of Thoracic Surgery, Marmara University Pendik Training and Research Hospital, Istanbul, Türkiye. The records of patients who underwent surgical resection for primary lung adenocarcinoma between January 2016 and December 2023 and who had pathological stage I disease were reviewed retrospectively.

Of the 184 patients reviewed, 26 were excluded: invasive mucinous adenocarcinoma (n = 10), neoadjuvant therapy (n = 5), adenocarcinoma in situ (n = 2), synchronous malignancy (n = 5) and incomplete data (n = 4). Patients with M1 disease, R1 resection or 90-day postoperative mortality were likewise not included. Extrathoracic metastases were confirmed by PET-CT and by multidisciplinary oncology board consensus. Pathological staging was performed according to the eighth edition of the TNM classification [2].

After exclusions, 158 patients with pathological stage I disease were included in the analysis (Fig. 1); 118 underwent lobar resection and 40 underwent sublobar resection.

The study was approved by the institutional ethics committee (approval number 09.2024.1008, dated 4 October 2024) and was conducted in accordance with the Declaration of Helsinki. Written informed consent for the use of clinical data in research was obtained from all participants at the time the operative consent was obtained.

Variables and definitions

Clinical, operative and pathological data were retrieved from institutional electronic records and pathology reports. All reported slides were re-reviewed by a pathologist with expertise in thoracic pathology. Comorbidity burden was quantified with the Charlson Comorbidity Index; the index lung adenocarcinoma itself was not scored, whereas previously treated malignancies were included in the score.

Tumours were graded according to the grading system proposed by the International Association for the Study of Lung Cancer Pathology Committee [4] and incorporated into the 2021 World Health Organization classification [9]. In this system, tumours containing 20% or more of a high-grade pattern (solid, micropapillary or complex glandular) are classified as grade 3 even when that pattern is not predominant. For the prognostic analyses, histological grade was treated as a binary variable (grade 3 versus grade 1 to 2) because of the small number of patients in the grade 1 subgroup. The analysis based on the three-level grading is presented in an additional file. The predominant histological pattern was recorded separately and reported descriptively.

Extent of resection was dichotomised as lobar (lobectomy, bilobectomy or pneumonectomy) versus sublobar (anatomical segmentectomy or wedge resection). Segmentectomy and wedge resection were additionally evaluated in a prespecified subgroup analysis.

Because the date of initiation of systemic therapy was not recorded, adjuvant therapy was classified into three mutually exclusive categories: no systemic therapy, systemic therapy given before recurrence, and systemic therapy given after recurrence. As this classification was determined by recurrence status, adjuvant therapy was excluded from all recurrence models and was evaluated only in the overall survival model.

Visceral pleural invasion and perineural invasion were recorded but were not entered into any regression model because of the small number of affected patients ($n = 3$ and $n = 2$, respectively).

Endpoints and follow-up

Overall survival was defined as the interval from the date of surgery to death from any cause. Disease-free survival was defined as the interval from the date of surgery to the first documented recurrence or to death from any cause, whichever occurred first. Patients without an event were censored at the date of last contact. For the competing-risk analysis, the event of interest was recurrence and the competing event was death without recurrence.

Median follow-up was estimated with the reverse Kaplan-Meier method. Recurrence dates were retrieved from clinical records. In most patients the records documented the month or the year of recurrence rather than the exact day; in these cases the midpoint of the documented month or year was used. Cause of death was not available.

Statistical analysis

Sample size was determined by including all consecutive patients who met the eligibility criteria during the study period; no prior power calculation was performed.

The distribution of continuous variables was assessed with the Shapiro-Wilk test. Normally distributed variables are reported as mean with standard deviation, non-normally distributed variables as median with interquartile range, and categorical variables as counts with percentages. Groups were compared with the Mann-Whitney U test, Pearson's chi-squared test or Fisher's exact test, as appropriate.

Survival probabilities were estimated with the Kaplan-Meier method and are reported with 95% confidence intervals at 1, 3 and 5 years; groups were compared with the log-rank test. Associations between covariates and each endpoint were assessed with Cox proportional hazards regression and are reported as hazard ratios with 95% confidence intervals. Univariable models were fitted for each covariate separately. A single multivariable model was then fitted for each endpoint, containing a prespecified set of clinically relevant covariates (histological grade 3, lymphovascular invasion, tumour

size, extent of resection, age, sex, and, for overall survival only, adjuvant therapy); stepwise selection was not used. The proportional hazards assumption was examined by entering a time-dependent covariate constructed as the interaction between each variable and the logarithm of survival time; no significant interaction was observed for any covariate. Model significance was assessed with the omnibus likelihood ratio test and discrimination was summarised with Harrell's concordance index. The number of events per variable was 5.9 for the overall survival model and 10.0 for the disease-free survival model.

Because a substantial proportion of deaths in this cohort occurred without recurrence, recurrence was additionally analysed within a competing-risk framework. Cumulative incidence functions for recurrence and for death without recurrence were estimated with the Aalen-Johansen estimator, and a Fine-Gray subdistribution hazard model was fitted with the same covariates as the cause-specific model. The results of the cause-specific and subdistribution hazard models are reported alongside each other.

All tests were two-sided and a P value below 0.05 was considered statistically significant. Descriptive statistics, Kaplan-Meier estimates, log-rank comparisons and Cox proportional hazards models were performed with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The competing-risk analyses, comprising the Aalen-Johansen cumulative incidence functions and the Fine-Gray subdistribution hazard model, were performed with Python version 3.12 using the lifelines package, as these methods are not available in SPSS. Harrell's concordance index was calculated in Python, as it is not produced by SPSS.

Results

A total of 158 patients were included (Table 1). The mean age was 62.9 years (SD 8.6) and 106 patients (67.1%) were male. The median Charlson Comorbidity Index was 1.0 (IQR 0.0 to 2.0) and the median tumour size was 1.8 cm (IQR 1.2 to 2.5). Pathological stage was IA1 in 20 patients (12.7%), IA2 in 76 (48.1%), IA3 in 45 (28.5%) and IB in 17 (10.8%). The predominant histological pattern was acinar in 69 patients (43.7%), solid in 27 (17.1%), lepidic in 25 (15.8%), papillary in 24 (15.2%) and micropapillary in 10 (6.3%). According to the histological grading system, 26 tumours (16.5%) were grade 1, 66 (41.8%) grade 2 and 66 (41.8%) grade 3. Lobar resection was performed in 118 patients (74.7%) and sublobar resection in 40 (25.3%), comprising 23 segmentectomies (14.6%) and 17 wedge resections (10.8%). Lymphovascular invasion was present in 38 patients (24.1%). Twenty-six patients (16.5%) received systemic therapy before recurrence and 17 (10.8%) after recurrence.

Table 1
Baseline clinicopathological characteristics of the study cohort

Characteristic	n = 158
Age, years, mean (SD)	62.9 (8.6)
Age, years, median (IQR)	63.0 (58.0 to 69.0)
Sex	
Male	106 (67.1)
Female	52 (32.9)
Charlson Comorbidity Index, median (IQR)	1.0 (0.0 to 2.0)
Tumour size, cm, median (IQR)	1.8 (1.2 to 2.5)
<i>Pathological stage</i>	
IA1	20 (12.7)
IA2	76 (48.1)
IA3	45 (28.5)
IB	17 (10.8)
<i>Predominant histological pattern</i>	
Acinar	69 (43.7)
Solid	27 (17.1)
Lepidic	25 (15.8)
Papillary	24 (15.2)
Micropapillary	10 (6.3)
Cribriform	2 (1.3)
Fetal	1 (0.6)
<i>Histological grade</i>	
Grade 1	26 (16.5)
Grade 2	66 (41.8)
Grade 3	66 (41.8)
Data are presented as n (%) unless otherwise stated. IQR, interquartile range; SD, standard deviation; Histological grade was assessed with the International Association for the Study of Lung Cancer grading system. Age was normally distributed (Shapiro-Wilk P = 0.421); tumour size and Charlson Comorbidity Index were not (both P < 0.001).	

Characteristic	n = 158
<i>Extent of resection</i>	
Lobar	118 (74.7)
Sublobar	40 (25.3)
Segmentectomy	23 (14.6)
Wedge resection	17 (10.8)
Lymphovascular invasion, present	38 (24.1)
Visceral pleural invasion, present	3 (1.9)
Perineural invasion, present	2 (1.3)
<i>Systemic therapy</i>	
None	115 (72.8)
Before recurrence	26 (16.5)
After recurrence	17 (10.8)
Recurrence	34 (21.5)
Death from any cause	41 (25.9)
Data are presented as n (%) unless otherwise stated. IQR, interquartile range; SD, standard deviation; Histological grade was assessed with the International Association for the Study of Lung Cancer grading system. Age was normally distributed (Shapiro-Wilk P = 0.421); tumour size and Charlson Comorbidity Index were not (both P < 0.001).	

The median follow-up was 84.9 months (range 4.0 to 128.2). Recurrence occurred in 34 patients (21.5%) and 41 patients (25.9%) died. Neither median overall survival nor median disease-free survival was reached. The 1-, 3- and 5-year overall survival rates were 93.0% (95% CI 87.8 to 96.1), 86.1% (95% CI 79.6 to 90.6) and 79.2% (95% CI 71.7 to 85.0), respectively, and the corresponding disease-free survival rates were 87.3% (95% CI 81.1 to 91.6), 70.2% (95% CI 62.4 to 76.7) and 64.9% (95% CI 56.7 to 71.9) (Table 2, Fig. 2). The median time to recurrence was 24.9 months. Seventeen recurrences (50.0%) occurred within the first 24 months after surgery and 17 (50.0%) thereafter, including 3 recurrences beyond 60 months. Of the 41 deaths, 26 (63.4%) occurred without documented recurrence and 15 (36.6%) after recurrence. The prognostic effect of lymphovascular invasion did not diminish over time: the hazard ratio for disease-free survival was 2.70 (95% CI 1.34 to 5.44, $P = 0.005$) during the first 24 months and 3.25 (95% CI 1.49 to 7.09, $P = 0.003$) in a landmark analysis restricted to the 126 patients who remained event-free at 24 months.

Table 2
Kaplan-Meier estimates of overall and disease-free survival

Outcome	1-year, % (95% CI)	3-year, % (95% CI)	5-year, % (95% CI)
Overall survival	93.0 (87.8 to 96.1)	86.1 (79.6 to 90.6)	79.2 (71.7 to 85.0)
Disease-free survival	87.3 (81.1 to 91.6)	70.2 (62.4 to 76.7)	64.9 (56.7 to 71.9)
Median overall survival and median disease-free survival were not reached. Median follow-up was 84.9 months (range 4.0 to 128.2). CI, confidence interval.			

On univariable Cox regression (Table 3), lymphovascular invasion (HR 3.26, 95% CI 1.75 to 6.06, $P < 0.001$), systemic therapy given before recurrence (HR 2.29, 95% CI 1.15 to 4.58, $P = 0.019$), male sex (HR 2.21, 95% CI 1.02 to 4.78, $P = 0.044$), tumour size (HR 1.54 per cm, 95% CI 1.08 to 2.20, $P = 0.016$) and age (HR 1.05 per year, 95% CI 1.01 to 1.09, $P = 0.007$) were associated with shorter overall survival, whereas histological grade 3 ($P = 0.356$), sublobar resection ($P = 0.207$) and the Charlson Comorbidity Index ($P = 0.622$) were not. For disease-free survival, lymphovascular invasion (HR 2.93, 95% CI 1.74 to 4.95, $P < 0.001$), male sex (HR 2.34, 95% CI 1.24 to 4.40, $P = 0.009$) and tumour size (HR 1.55 per cm, 95% CI 1.16 to 2.07, $P = 0.003$) were significant and histological grade 3 was of borderline significance (HR 1.65, 95% CI 0.99 to 2.74, $P = 0.053$), while sublobar resection ($P = 0.763$), age ($P = 0.093$) and the Charlson Comorbidity Index ($P = 0.896$) were not. Kaplan-Meier curves stratified by lymphovascular invasion, histological grade and extent of resection are shown in Fig. 3.

Table 3
Univariable Cox proportional hazards analysis of overall and disease-free survival

Variable	Overall survival			Disease-free survival		
	HR	95% CI	P	HR	95% CI	P
Age, per year	1.05	1.01 to 1.09	0.007	1.03	1.00 to 1.06	0.093
Male sex (vs female)	2.21	1.02 to 4.78	0.044	2.34	1.24 to 4.40	0.009
Charlson Comorbidity Index	1.06	0.85 to 1.32	0.622	0.99	0.81 to 1.20	0.896
Tumour size, per cm	1.54	1.08 to 2.20	0.016	1.55	1.16 to 2.07	0.003
Histological grade 3 (vs grade 1 to 2)	1.33	0.72 to 2.46	0.356	1.65	0.99 to 2.74	0.053
Lymphovascular invasion	3.26	1.75 to 6.06	< 0.001	2.93	1.74 to 4.95	< 0.001
Sublobar resection (vs lobar)	1.55	0.79 to 3.04	0.207	1.09	0.61 to 1.97	0.763
Adjuvant therapy before recurrence	2.29	1.15 to 4.58	0.019	1.19	0.62 to 2.29	0.598
HR, hazard ratio; CI, confidence interval. Overall survival: 41 events. Disease-free survival: 60 events. Visceral pleural invasion and perineural invasion were not analysed because of low event counts (n = 3 and n = 2, respectively).						

In the multivariable model for overall survival (Table 4, Fig. 4), lymphovascular invasion (HR 3.24, 95% CI 1.63 to 6.45, $P = 0.001$), age (HR 1.06 per year, 95% CI 1.02 to 1.11, $P = 0.002$) and systemic therapy given before recurrence (HR 2.10, 95% CI 1.04 to 4.27, $P = 0.039$) remained independently associated with worse survival, whereas histological grade 3 ($P = 0.467$), tumour size ($P = 0.236$), sublobar resection ($P = 0.169$) and male sex ($P = 0.118$) were not. In the multivariable model for disease-free survival, lymphovascular invasion (HR 2.47, 95% CI 1.42 to 4.29, $P = 0.001$) and male sex (HR 2.05, 95% CI 1.06 to 3.96, $P = 0.032$) were independent predictors, whereas histological grade 3 ($P = 0.879$), tumour size ($P = 0.107$), sublobar resection ($P = 0.661$) and age ($P = 0.099$) were not.

Table 4
Multivariable Cox proportional hazards analysis of overall and disease-free survival

Variable	Overall survival			Disease-free survival		
	HR	95% CI	P	HR	95% CI	P
Histological grade 3 (vs grade 1 to 2)	0.78	0.40 to 1.53	0.467	1.04	0.61 to 1.79	0.879
Lymphovascular invasion	3.24	1.63 to 6.45	0.001	2.47	1.42 to 4.29	0.001
Tumour size, per cm	1.25	0.86 to 1.81	0.236	1.30	0.95 to 1.79	0.107
Sublobar resection (vs lobar)	1.66	0.81 to 3.41	0.169	1.15	0.62 to 2.11	0.661
Adjuvant therapy before recurrence	2.10	1.04 to 4.27	0.039	NE	NE	NE
Age, per year	1.06	1.02 to 1.11	0.002	1.03	1.00 to 1.06	0.099
Male sex (vs female)	1.90	0.85 to 4.24	0.118	2.05	1.06 to 3.96	0.032
HR, hazard ratio; CI, confidence interval; NE, not estimated. Adjuvant therapy was not entered into the disease-free survival model because its classification was determined by recurrence status. Overall survival model: 41 events, 7 covariates, 5.9 events per variable; omnibus likelihood ratio test $P < 0.001$; Harrell C-index 0.737. Disease-free survival model: 60 events, 6 covariates, 10.0 events per variable; omnibus likelihood ratio test $P < 0.001$; Harrell C-index 0.692. The proportional hazards assumption was satisfied for all covariates in both models.						

Patients who underwent sublobar resection were not older than those who underwent lobar resection (median 64.5 versus 63.0 years, $P = 0.906$) and did not have a higher comorbidity burden (median Charlson Comorbidity Index 1.0 in both groups, $P = 0.412$). Their tumours were smaller (median 1.5 versus 1.9 cm, $P = 0.036$) and more often of stage IA1 or IA2 (75.0% versus 55.9%, $P = 0.052$). A complete (R0) resection was achieved in all patients. When segmentectomy and wedge resection were analysed separately, recurrence occurred in 26 of 118 patients after lobar resection (22.0%), in 5 of 23 after segmentectomy (21.7%) and in 3 of 17 after wedge resection (17.6%), whereas death without recurrence occurred in 19 (16.1%), 2 (8.7%) and 5 patients (29.4%), respectively. Overall survival was significantly worse after wedge resection than after lobar resection (log-rank $P = 0.033$), whereas disease-free survival did not differ between these groups (log-rank $P = 0.263$).

Because 26 of the 41 deaths occurred without recurrence, recurrence was additionally analysed in a competing-risk framework. The cumulative incidence of recurrence was 5.7% at 1 year, 16.5% at 3 years and 20.3% at 5 years, whereas the cumulative incidence of death without recurrence was 7.0%, 13.3% and 14.7% at the same time points (Table 5); for comparison, the standard Kaplan-Meier method estimated the 5-year recurrence risk at 22.6%. In the Fine-Gray subdistribution hazard model (Table 6),

lymphovascular invasion was of borderline significance (sHR 1.97, 95% CI 0.95 to 4.06, $P = 0.067$), whereas it remained significant in the corresponding cause-specific model (HR 2.46, 95% CI 1.20 to 5.03, $P = 0.014$). Histological grade 3, tumour size, extent of resection, age and sex were not associated with recurrence in either model.

Table 5
Cumulative incidence of recurrence and of death without recurrence

Time since surgery	Recurrence, %	Death without recurrence, %
1 year	5.7	7.0
3 years	16.5	13.3
5 years	20.3	14.7
7 years	21.5	17.0
Estimated with the Aalen-Johansen estimator. For comparison, the standard Kaplan-Meier estimate of recurrence risk at 5 years was 22.6%, compared with a cumulative incidence of 20.3%.		

Table 6
Competing-risk analysis of recurrence: cause-specific and subdistribution hazard models

Variable	Cause-specific hazard			Subdistribution hazard (Fine-Gray)		
	HR	95% CI	<i>P</i>	sHR	95% CI	<i>P</i>
Histological grade 3 (vs grade 1 to 2)	1.49	0.73 to 3.06	0.273	1.57	0.77 to 3.20	0.216
Lymphovascular invasion	2.46	1.20 to 5.03	0.014	1.97	0.95 to 4.06	0.067
Tumour size, per cm	1.33	0.87 to 2.04	0.191	1.28	0.86 to 1.91	0.218
Sublobar resection (vs lobar)	1.12	0.49 to 2.56	0.797	0.96	0.42 to 2.19	0.921
Age, per year	1.00	0.96 to 1.05	0.854	1.00	0.96 to 1.03	0.875
Male sex (vs female)	1.79	0.76 to 4.24	0.184	1.62	0.70 to 3.76	0.261
The event of interest was recurrence (34 events) and the competing event was death without recurrence (26 events). In the cause-specific model, competing deaths were censored. HR, hazard ratio; sHR, subdistribution hazard ratio; CI, confidence interval.						

Discussion

In this single-centre cohort of 158 patients with completely resected pathological stage I lung adenocarcinoma and a median follow-up of 84.9 months, lymphovascular invasion was the only tumour-related variable independently associated with both overall and disease-free survival. Of the other pathological variables examined, neither histological grade nor the extent of resection retained an independent association with either endpoint after adjustment. A similar hierarchy has been reported in other series of resected stage I disease, in which lymphovascular invasion outperformed visceral pleural invasion, spread through air spaces and the micropapillary pattern as a predictor of recurrence [10].

Evidence from larger cohorts supports this observation. A propensity score-matched analysis of 4622 patients with pathological stage I disease reported hazard ratios of 1.91 for recurrence-free survival and 2.58 for overall survival [11], values close to those observed here (2.47 and 3.24, respectively). A cohort from Türkiye with stage I non-small cell lung cancer likewise identified lymphovascular invasion as an independent predictor of recurrence-free survival [7]. Taken together with our findings, these data support the view that lymphovascular invasion, although not incorporated into the current TNM classification, carries prognostic information beyond anatomical stage in this population [10]. The 5-year overall survival of 79.2% observed in our cohort lies within the range of 73% to 90% reported for pathological stage I disease in the eighth edition TNM database [2], which suggests that the present cohort is not atypical of the wider population with resected stage I disease.

In contrast to lymphovascular invasion, histological grade was not independently associated with either endpoint in our cohort. The grading system classifies as grade 3 any tumour containing 20% or more of a high-grade pattern, even when that pattern is not predominant. In our cohort, this definition identified 66 grade 3 tumours, of which only 37 had a solid or micropapillary predominant pattern. When these two groups were compared, their outcomes were indistinguishable (disease-free survival log-rank $P = 0.974$), which supports the rationale for the 20% threshold. Nevertheless, grade 3 disease as a whole was only borderline associated with disease-free survival in univariable analysis ($P = 0.053$) and lost all association after adjustment ($P = 0.879$). The most likely explanation is that lymphovascular invasion and grade 3 histology identify overlapping groups of patients, and that lymphovascular invasion identifies them more efficiently; whether this reflects genuine biological overlap or insufficient power to separate two correlated variables cannot be determined from a cohort of this size.

Extent of resection was not associated with either endpoint, which is concordant with the two randomised trials that established the oncological acceptability of limited resection in small peripheral tumours [5, 6]. Importantly, the patients who underwent sublobar resection in our cohort were not older and did not carry a greater comorbidity burden than those who underwent lobar resection; their tumours were smaller and more often of stage IA1 or IA2, and a complete resection was achieved in every patient. These observations argue against the interpretation that limited resection was performed predominantly as a compromise procedure.

The subgroup analysis nonetheless revealed a dissociation that deserves comment: patients treated with wedge resection had the lowest recurrence rate of the three surgical groups (17.6%) but the highest

rate of death without recurrence (29.4%) and significantly worse overall survival than the lobar group ($P = 0.033$), while disease-free survival did not differ ($P = 0.263$). The direction of this finding contrasts with that of the post hoc analysis of JCOG0802 restricted to pathologically invasive tumours, in which segmentectomy was associated with a lower, not higher, cumulative incidence of death from other causes than lobectomy [12]. In a randomised setting, where the extent of resection is assigned rather than chosen, limited resection did not increase non-cancer mortality. The opposite pattern in our cohort therefore points to selection rather than to any effect of the operation itself.

This dissociation is unlikely to reflect comorbidity as conventionally measured: the median Charlson Comorbidity Index in the wedge group was 0, the lowest of the three surgical groups, yet these patients had the highest rate of death without recurrence. The index counts chronic diagnoses rather than physiological reserve, and a patient with limited operative tolerance may carry no scored comorbidity at all. In major thoracic surgery, dedicated frailty instruments and comorbidity scores have been compared directly, with the Fried frailty phenotype showing the highest discrimination among the measures tested; that comparison, however, addressed short-term postoperative outcomes rather than mortality during extended follow-up [13]. We consider it likely that the decision to perform a wedge resection was informed by clinical judgement that the recorded data do not reflect. A related question is whether limited resection remains adequate when lymphovascular invasion is present. In a series of 245 patients with stage I tumours of 2 cm or less, the extent of resection had no effect on either overall survival or the cumulative incidence of recurrence within the lymphovascular invasion-positive group [14]. Our cohort was not powered to test this interaction, but the direction of our findings is concordant.

The preponderance of deaths unrelated to recurrence was the most consequential finding for the interpretation of our overall survival analysis. Of 41 deaths, 26 (63.4%) occurred without documented recurrence, and the cumulative incidence of death without recurrence exceeded that of recurrence during the first year of follow-up. This is consistent with registry analyses in which non-cancer causes account for an increasing proportion of deaths with longer follow-up, both among patients with resected stage I disease [15] and in the wider non-small cell lung cancer population [16]. It explains why age emerged as the strongest independent predictor of overall survival in our cohort and why tumour characteristics performed relatively poorly for that endpoint. It also justified the competing-risk analysis: the standard Kaplan-Meier method estimated the 5-year recurrence risk at 22.6%, compared with a cumulative incidence of 20.3%, and the association between lymphovascular invasion and recurrence was attenuated from a cause-specific hazard ratio of 2.46 to a subdistribution hazard ratio of 1.97. This attenuation, although modest, illustrates why competing-risk methods are increasingly preferred in early-stage cohorts [14, 17]. A similar ambiguity applies to sex: male sex was independently associated with worse disease-free survival (hazard ratio 2.05) but not with overall survival, and because cause of death was not recorded we cannot determine whether the excess events observed in men reflected recurrence or competing causes.

Systemic therapy given before recurrence was associated with worse overall survival in both univariable and multivariable analysis. We interpret this as confounding by indication rather than as evidence of

harm: patients selected for adjuvant treatment were more often lymphovascular invasion-positive (38.5% versus 21.2%) and had larger tumours, although neither difference reached significance. This variable is nonetheless informative, because the two bodies of evidence most often cited in this setting handle it differently: the largest institutional analysis of stage I adenocarcinoma excluded all patients who received induction or adjuvant therapy [17], while a single-centre series identified the absence of adjuvant treatment data as a limitation of its own analysis [18]. Our dataset allowed the variable to be retained.

Half of the recurrences in our cohort occurred beyond 24 months, and three occurred more than five years after surgery. This distribution closely parallels that reported in a cohort of 2349 patients, in which 240 of 537 recurrences (44.7%) were classified as late [19]. Our median follow-up of 84.9 months exceeded that of both the cohort in which late recurrence was characterised (71 months) [19] and other single-centre series of resected early-stage adenocarcinoma (60 months) [18], and was therefore long enough to observe these events. The finding argues against limiting structured surveillance to the first five postoperative years. Lymphovascular invasion predicted late events as strongly as early ones in our cohort, which suggests that extended surveillance is most clearly justified in patients with this feature rather than as a uniform recommendation.

Our study has several limitations. It is a retrospective analysis from a single institution, and the findings require external validation; the limitations we describe below, namely single-centre design, retrospective data collection, modest sample size and a limited number of events, are shared with comparable contemporary series [18]. Recurrence dates were documented at the level of the month or the year rather than the exact day in most patients, and the midpoint of the documented interval was used; disease-free survival estimates should therefore be interpreted as approximate to within that interval. Pulmonary function data (forced expiratory volume in one second and diffusing capacity) were not available, so our inference that sublobar resection was selected on tumour rather than physiological grounds cannot be confirmed. The sublobar group was small ($n = 40$), and the segmentectomy and wedge subgroups smaller still ($n = 23$ and $n = 17$), so the subgroup comparisons are exploratory and underpowered. The number of events per variable in the overall survival model was 5.9, below the conventional threshold of ten, and the corresponding estimates should be interpreted with caution. Cause of death was not recorded, which precluded a cancer-specific survival analysis; the competing-risk framework we applied addresses the effect of competing deaths on recurrence estimates but does not substitute for cause-specific mortality data. Finally, the classification of systemic therapy was determined by recurrence status because treatment start dates were unavailable, which is why adjuvant therapy could be evaluated only for overall survival.

Conclusions

In completely resected pathological stage I lung adenocarcinoma, lymphovascular invasion was the only tumour-related factor independently associated with both recurrence and death, whereas histological grade and the extent of resection were not. Two features of this cohort qualify how these results should

be applied. First, most deaths occurred without recurrence, so overall survival in this population reflects competing causes as much as it reflects cancer biology, and this affects how recurrence risk should be estimated in this setting. Second, half of all recurrences occurred beyond two years, which argues against limiting structured surveillance to the early postoperative period. These findings require confirmation in larger and preferably multicentre cohorts.

Abbreviations

CI

confidence interval

HR

hazard ratio

IQR

interquartile range

PET-CT

positron emission tomography-computed tomography

SD

standard deviation

sHR

subdistribution hazard ratio

TNM

tumour, node, metastasis

Declarations

Ethics approval and consent to participate

The study was approved by the Marmara University Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee (approval number 09.2024.1008, dated 4 October 2024) and was conducted in accordance with the Declaration of Helsinki. Written informed consent for the use of clinical data in research was obtained from all participants at the time the operative consent was obtained.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

[Initials] designed the study, collected and analysed the data and drafted the manuscript. [Initials] verified the currency of the dataset and confirmed the recurrence and mortality status of all patients, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Use of large language models

A large language model (Claude, Anthropic) was used to assist with figure generation and language editing. All analyses were performed independently by the authors using IBM SPSS Statistics and were verified with Python. The authors take full responsibility for the accuracy and integrity of the reported results. The large language model does not meet authorship criteria and is not listed as an author.

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Figures

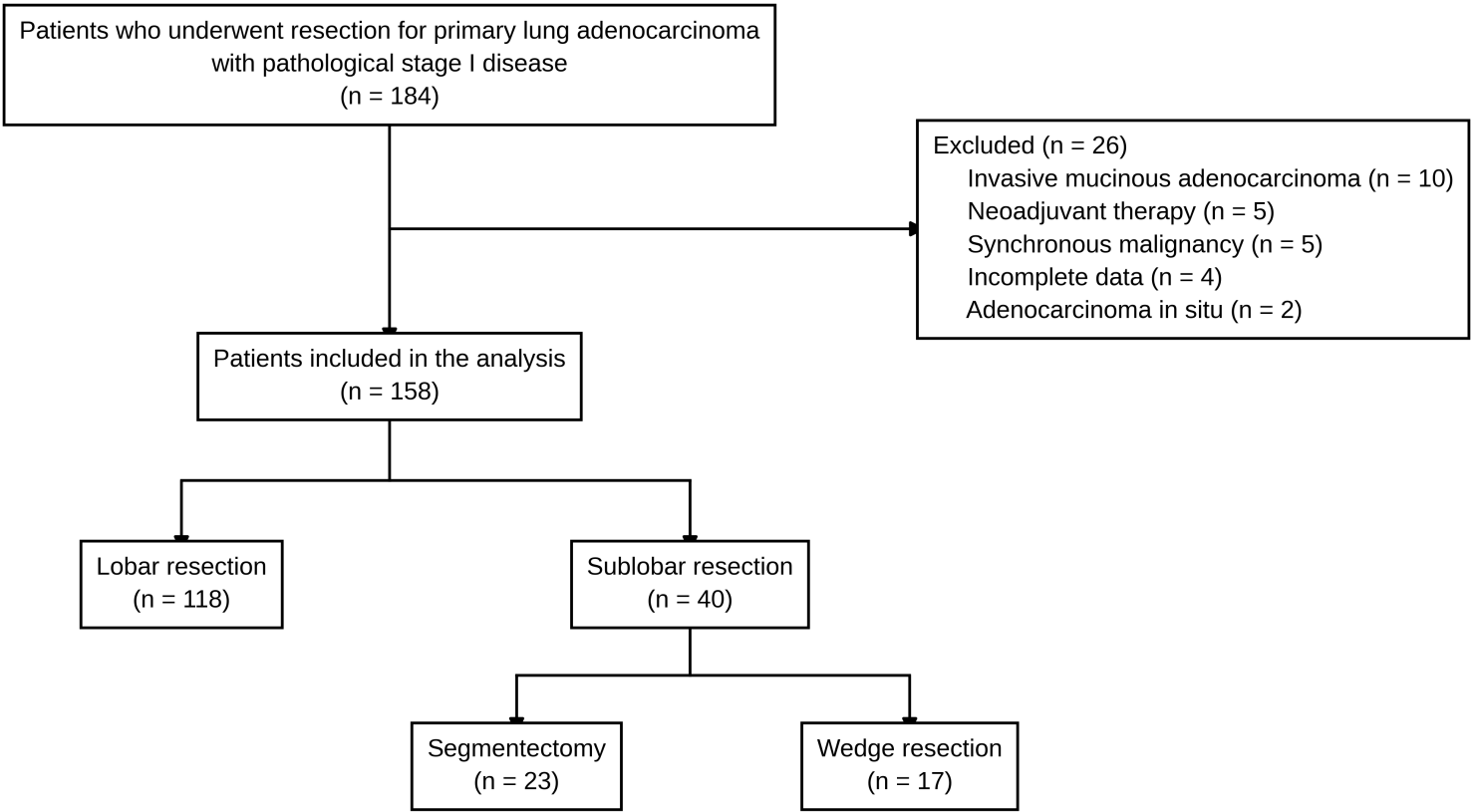


Figure 1

Flow of patients through the study.

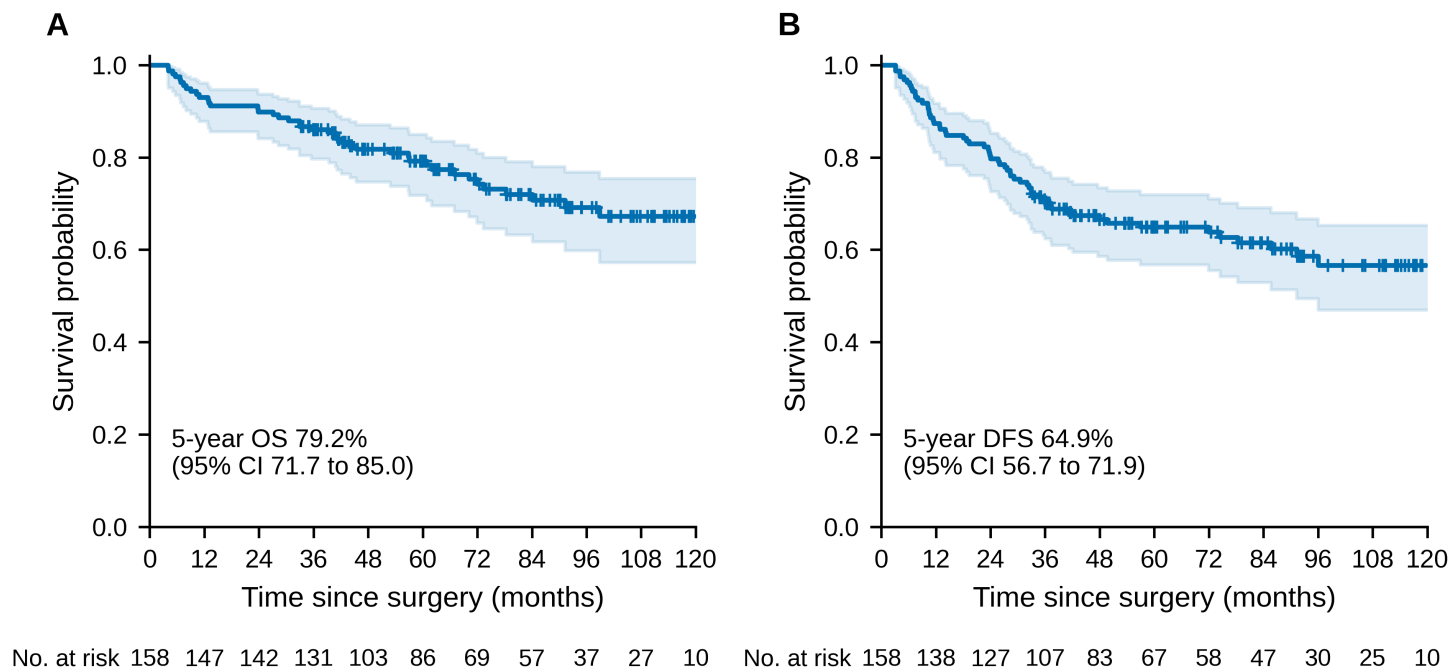


Figure 2

Kaplan-Meier estimates of overall survival (A) and disease-free survival (B) in the whole cohort of 158 patients with resected pathological stage I lung adenocarcinoma. Shaded areas represent 95% confidence intervals and vertical ticks denote censored observations. The number of patients at risk is shown beneath each panel.

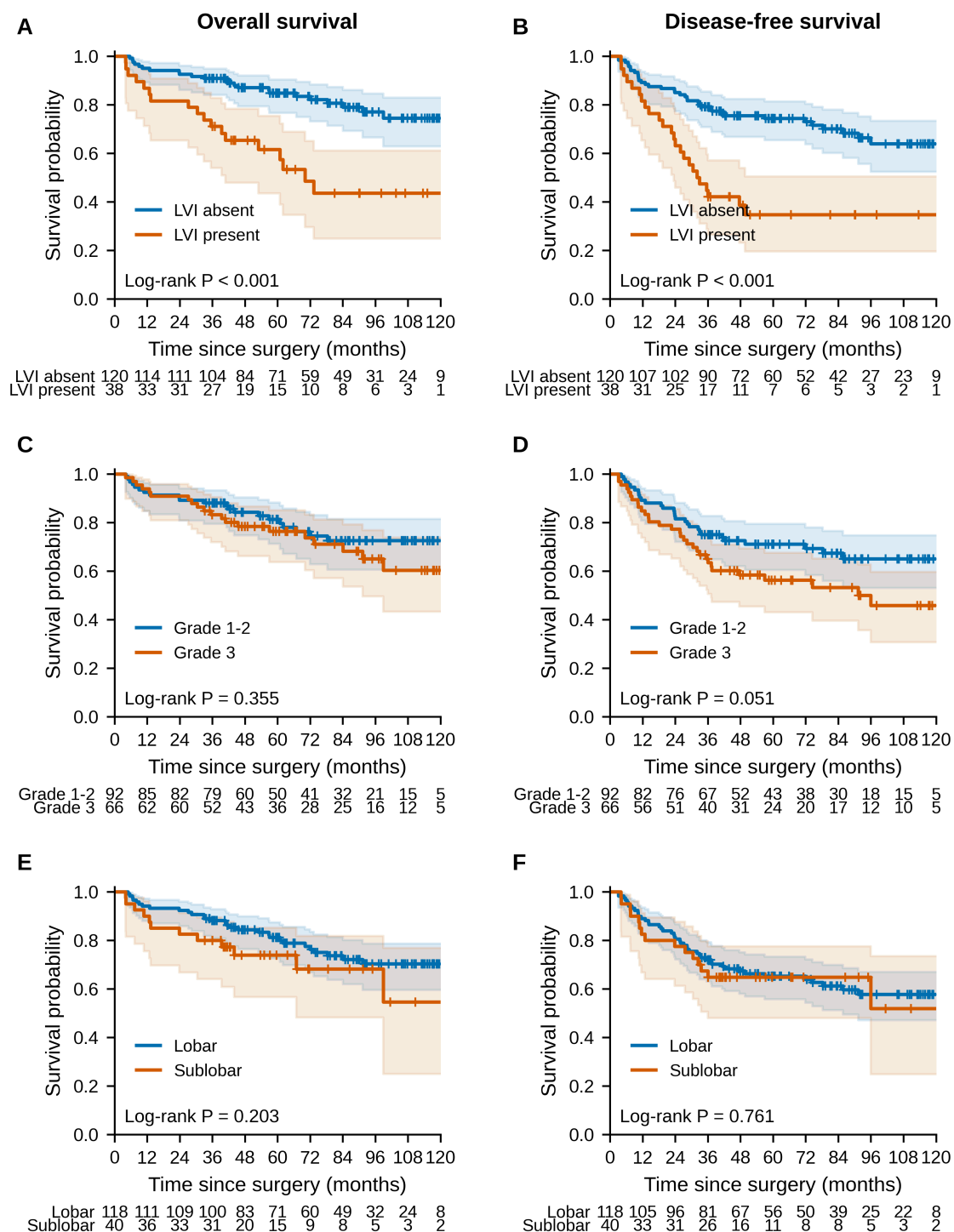


Figure 3

Kaplan-Meier estimates of overall survival (A, C, E) and disease-free survival (B, D, F) stratified by lymphovascular invasion (A, B), histological grade (C, D) and extent of resection (E, F). Shaded areas represent 95% confidence intervals and vertical ticks denote censored observations. Groups were compared with the log-rank test. The number of patients at risk is shown beneath each panel.

Histological grade was assessed with the International Association for the Study of Lung Cancer grading system.

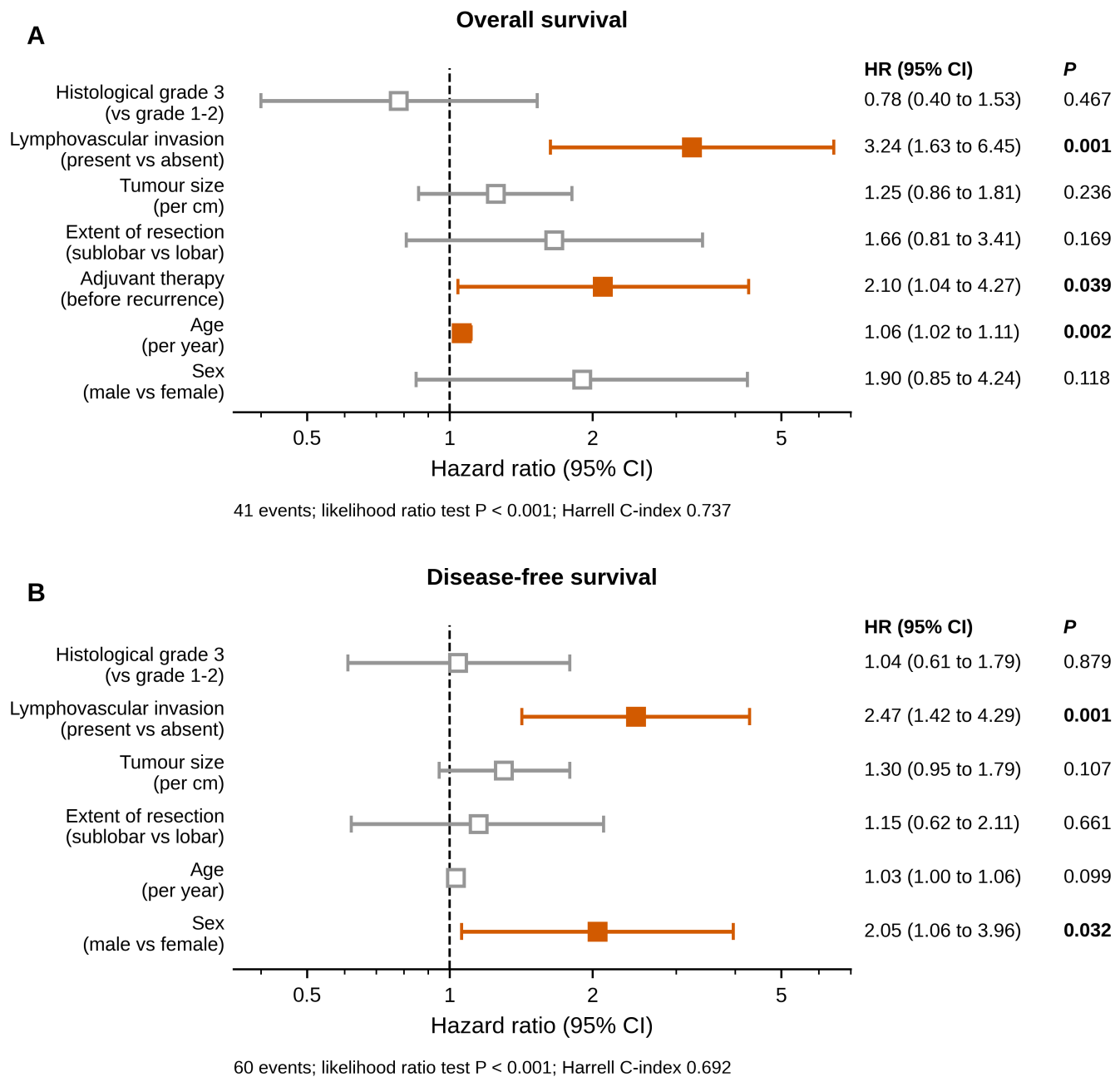


Figure 4

Forest plots of the multivariable Cox proportional hazards models for overall survival (A) and disease-free survival (B). Squares represent hazard ratios and horizontal lines the 95% confidence intervals; filled squares indicate $P < 0.05$. The dashed vertical line marks a hazard ratio of 1 and the x axis is on a logarithmic scale. The number of events, the omnibus likelihood ratio test and Harrell's concordance index are given beneath each panel. CI, confidence interval; HR, hazard ratio.

Supplementary Files

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