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Different pathologic types of early stage lung adenocarcinoma have different post-operative recurrence patterns

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Abstract

Objectives: To accurately describe the pattern, timing and predictors of disease recurrence after curative resection for different types of early-stage lung adenocarcinoma (LUAD).

Methods: A total of 1962 patients with early-stage LUAD were included. The presence of micropapillary, solid components or poorly differentiated cancer as a clinical variable was named "high-grade" adenocarcinoma (HGADC), while others were classified as "low-grade" adenocarcinoma (LGADC). Predictive factors for specific recurrence patterns were assessed by univariate and multivariate analyses using Cox-proportional hazard regression models. Event dynamics, based on the hazard rate, were evaluated.

Results: At a median follow-up of 36.0 months, 137 (6.98%) of 1962 patients suffered from recurrence. Multivariable Cox analysis revealed that HGADC was an independent predictor for overall recurrence (hazard ratio [HR] 3.08, 95% confidence interval [CI] 2.09–4.52, $p < 0.001$), local recurrence (HR 2.77, 95% CI 1.38–5.55, $p < 0.001$), distant metastasis (HR 3.22, 95% CI 2.03–5.11, $p < 0.001$), chest recurrence (HR 2.80, 95% CI 1.65–4.75, $p < 0.001$) and brain recurrence (HR 4.11, 95% CI 1.83–9.22, $p < 0.001$). However, HGADC (HR 1.56, 95% CI 0.63–3.86, $p = 0.335$ in univariate analysis) was not a risk factor for bone recurrence. The hazard curve of the whole group presented a double-peaked pattern. Different types of LUAD had different hazard curves. HGADC patients exhibited higher hazard rates than LGADC patients during the whole follow-up. In addition, the recurrence hazard curve in HGADC patients showed a typical "double-peaked" pattern, while the curve in LGADC patients displayed a smooth curve after surgery.

Conclusions: Different postoperative recurrence patterns were seen in HGADC and LGADC. Site-specific recurrence patterns were also different in HGADC and LGADC types.

KEYWORDS
dynamic pattern, lung adenocarcinoma, recurrence, site-specific recurrence

INTRODUCTION

It is very important to identify and understand the postoperative recurrence pattern of non-small-cell lung cancer (NSCLC). The hazard function method[1,2] is applied to

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describe the rate of recurrence at any point time among the "at-risk" patients. The method allows for straightforward visualization of instantaneous risk of recurrence or death over time with no imposed distributional assumptions. The new pathologic classification of lung cancer has resulted in a better stratification of lung adenocarcinoma (LUAD) tumors in more homogeneous morphologic, clinical and biological

types.[3] Several studies[4–6] have highlighted the prognostic impact of LUAD subtyping. But no study to date has demonstrated whether different types of LUAD have different recurrence patterns.

In the present study, we retrospectively investigated the hazard function of tumor recurrence in completely resected early-stage LUAD patients in our institution and generated smoothing curves from the recurrence risk to identify the characteristics of the recurrence pattern of different subtypes of early stage LUAD.

PATIENTS AND METHODS

Patient selection

From January 2000 to December 2018, a total of 3237 patients with LUAD who underwent radical surgical resection in Peking University People's Hospital were collected. These patients satisfied the following inclusion criteria: (1) age > 18 years old, (2) pathologically confirmed T1-2N0M0 stage according to 8th TNM stage system, (3) complete surgical resection (R0) in our thoracic center, (4) no evidence of distant metastatic disease before surgery, and (5) at least 3 months of follow-up information. Exclusion criteria were as follows: (1) pathologically confirmed atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA), (2) patients with malignant tumor history, (3) non-curative resection (R1 or R2), and (4) perioperative death (at the time of hospitalization or within 30 days after surgery). A total of 1962 patients with invasive early-stage LUAD met the inclusion criteria and were included in this study. The study was reviewed and approved by the Institutional Review Board of Peking University People's Hospital. Informed consent was waived because of the retrospective nature of the study.

Histopathological investigation

Surgically resected specimens were routinely fixed with formalin and stained with hematoxylin–eosin. As the IASLC/ATS/ERS classification has been adopted since July 2012 in our center, histological types were recorded as well/moderate/poorly differentiated or undifferentiated for patients before July 2012, and lepidic/papillary/acinar/micropapillary/solid component thereafter. Each histological subtype and the ratio of histological components in 5% increments have been recorded since July 2012. Based on previous reports, we defined any presence of micropapillary component, solid component or poorly differentiated/undifferentiated cancer as a clinical variable named "high-grade" adenocarcinoma (HGADC). Other adenocarcinomas, which did not include any micropapillary component, solid component or poorly/undifferentiated cancer, were classified as "low-grade" adenocarcinoma (LGADC).

Follow-up strategy and definition of recurrence

Patients were examined every 6 months during the first 2 years and annually thereafter. The follow-up protocol included a physical examination, serum tumor marker, chest computed tomography (CT) scan, and abdominal ultrasound. Bone scintigraphy and brain magnetic resonance imaging (MRI) were performed when relative symptoms appeared. For patients who hardly went back to our center to take evaluations, we collected their follow-up information by phone.

Diagnosis of recurrence was made according to physical examination and diagnostic imaging. Pathological examination of biopsy specimens could be performed to confirm the recurrence if necessary. Local recurrence was defined as those at the surgical margins, anastomotic or bronchial stump, ipsilateral chest wall and pleura, ipsilateral lung or in the regional lymph nodes ((levels 1–14, including supraclavicular). Distant metastasis was defined as those in the contralateral lung or lymph nodes (cervical or abdominal lymph node disease) or in a solid organ such as brain, bone, or liver. A combined recurrence was defined as the detection of both local recurrence and distant metastasis either simultaneously or within 30 days. Only first events involving the development of local recurrence, distant metastases or both were considered.

Statistical analysis

Disease free survival (DFS) was defined as the duration from surgery date to first recurrence or death from any cause. DFS was assessed using the Kaplan–Meier method. The log-rank test was used to compare the survival distributions of the two groups. The Cox regression model was used to perform a multivariate survival analysis based on all of the variables that were significant in the univariate analysis. The hazard rate curve was estimated using a Kernel–Epanechnikov smoothing method. Continuous variables were compared using Student's t-test or Mann–Whitney nonparametric test for variables with an abnormal distribution, categorical variables were compared using the chi-square test or Fischer's exact test. $p < 0.05$ was considered statistically significant. All statistical analysis was performed by STATA/MP 16.0 (Stata Corp.).

RESULTS

Patient characteristics

There were 1962 patients included in the final analysis. The clinical characteristics of the whole group and each type are shown in Table 1; the median age was 62 years (range 27–86 years) and 326 (16.6%) patients were included in HGADC type. Compared with the LGADC type, patients in the HGADC type were more male (57.98% vs. 38.75%, $p < 0.001$) and smokers (38.34% vs. 22.13%, $p < 0.001$), with older median age (64 vs. 61, $p < 0.001$) and worse pulmonary function (FEV1% 94.42% vs. 98.73%, $p < 0.001$). Patients with

TABLE 1 Baseline characteristics of all T1-2N0M0 patients (n = 1962), LGADC type and HGADC type

Variable	All patients (n = 1962)	LGADC type (n = 1636)	HGADC type (n = 326)	p value
Male, n (%)	823 (41.95)	634 (38.75)	189 (57.98)	<0.001
Age (years), median(range)	62 (27–86)	61 (27–86)	64 (33–86)	<0.001
Smoking history, n (%)				<0.001
No	1475 (75.18)	1274 (77.87)	201 (61.66)	
Yes	487 (24.82)	362 (22.13)	125 (38.34)	
Tumor history, n (%)	364 (18.55)	313 (19.13)	51 (15.64)	0.139
Family tumor history, n (%)	235 (11.98)	195 (11.92)	40 (12.27)	0.859
Comorbidities, n (%)	1197 (61.01)	997 (60.94)	200 (61.35)	0.89
Tumor size (cm), median (IQR)	1.80 (1.30,2.40)	1.70 (1.20,2.30)	2.10 (1.60,2.90)	<0.001
BMI, mean ± SD	24.25 ± 3.11	24.27 ± 3.16	24.19 ± 2.79	0.696
Pulmonary function test, mean ± SD				
FEV1 (L)	2.49 ± 0.68	2.49 ± 0.67	2.49 ± 0.70	0.986
FEV1%	98.01 ± 17.61	98.73 ± 17.31	94.42 ± 18.66	<0.001
FEV1/FVC%	78.04 ± 7.85	78.49 ± 7.53	75.79 ± 8.95	<0.001
DLCO%	89.06 ± 15.36	89.55 ± 15.20	86.62 ± 15.93	0.002
ASA stage				0.003
I	332	296	36	
II	1551	1279	272	
III/IV	76	58	18	
Unknown	3	3		
Surgical approach				0.458
VATS	1924 (98.06)	1606 (98.17)	318 (97.55)	
Open	38 (1.94)	30 (1.83)	8 (2.45)	
Extent of pulmonary resection, n (%)				0.003
Lobectomy	1488 (75.84)	1220 (74.57)	268 (82.21)	
Sublobectomy	474 (24.16)	416 (25.43)	58 (17.79)	
VPI, n (%)	438 (22.32)	328 (20.05)	110 (33.74)	<0.001
LVI, n (%)	199 (10.14)	80 (4.89)	119 (36.50)	<0.001
T stage, n (%)				<0.001
T1	1372 (69.93)	1202 (73.47)	170 (52.15)	
T2	590 (30.07)	434 (26.53)	156 (47.85)	
8th AJCC stage, n (%)				<0.001
I	1911 (97.4)	1604 (98.04)	307 (94.17)	
II	51 (2.60)	32 (1.96)	19 (5.83)	

Abbreviations: HGADC, high-grade adenocarcinoma; LGADC, low-grade adenocarcinoma; LVI, lymphovascular invasion; Ref, reference; VPI, visceral pleural invasion.

HGADC also had more visceral pleural invasion (VPI) (33.74% vs. 20.05%, $p < 0.001$) and lymphovascular invasion (LVI) (36.50% vs. 4.89%, $p < 0.001$) and larger tumor size (2.10 vs. 1.70 cm, $p < 0.001$). Furthermore, the HGADC type showed more advanced T stage (47.85% vs. 26.53, $p < 0.001$) and American Joint Committee on Cancer (AJCC) stage (5.83% vs. 1.96%, $p < 0.001$).

Survival analysis of different types

At a median follow-up of 36.0 months, a total of 137 (6.98%) of 1962 patients suffered from recurrence.

Figure 1 shows the survival curves of overall recurrence, local recurrence, distant metastasis, and site-specific recurrence by HGADC and LGADC types. Patients with HGADC had significantly poorer DFS than those with LGADC for overall recurrence (hazard ratio [HR] 4.04, 95% confidence interval [CI] 2.52–6.50, $p < 0.001$), local recurrence (HR 3.21, 95% CI 1.29–8.02, $p = 0.0004$), distant metastasis (HR 4.31, 95% CI 2.43–7.64, $p < 0.001$), chest recurrence (HR 3.72, 95% CI 1.93–7.14, $p < 0.001$), and brain recurrence (HR 5.20, 95% CI 1.88–14.38, $p < 0.001$). However, no statistically significant differences were observed between patients with HGADC and those with LGADC type for bone recurrence (HR 1.56, 95% CI 0.55–4.41, $p = 0.331$).
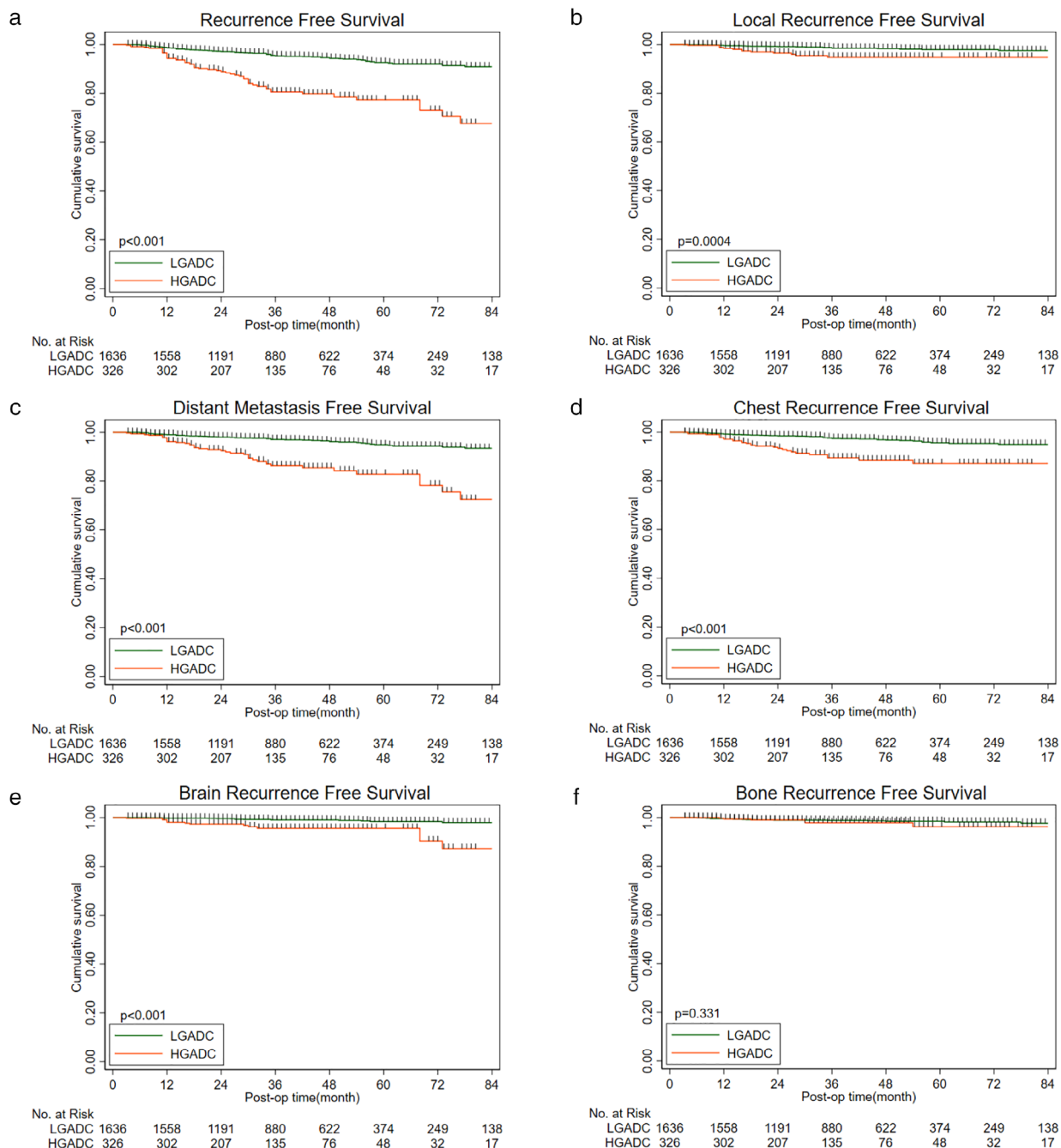
FIGURE 1 Disease-free survival in all patients according to histology for overall recurrence (a), local recurrence (b), distant metastasis (c), chest recurrence (d), brain recurrence (e), and bone recurrence (f)

Cox multivariate survival analysis (Tables 2 and 3) showed that HGADC (HR 3.08, 95% CI 2.09–4.52, $p < 0.001$) and T stage (HR 2.59, 95% CI 1.62–4.15, $p < 0.001$) were independent predictors for overall recurrence. HGADC was an independent predictor for local recurrence (HR 2.77, 95% CI 1.38–5.55, $p < 0.001$), distant metastasis (HR 3.22, 95% CI 2.03–5.11, $p < 0.001$), chest recurrence (HR 2.80, 95% CI 1.65–4.75, $p < 0.001$), and brain recurrence (HR 4.11, 95% CI 1.83–9.22, $p < 0.001$). Otherwise, T stage was an independent risk factor for distant metastasis (HR 3.04, 95% CI 1.76–5.28, $p < 0.001$) and

chest recurrence (HR 1.82, 95% CI 1.13–2.92, $p < 0.001$). However, HGADC (HR 1.56, 95% CI 0.63–3.86, $p = 0.335$ in univariate analysis) was not a risk factor for bone recurrence.

Recurrence hazard rate analysis of all patients

The hazard rate for overall recurrence in all 1962 patients was analyzed. The resulting curve displayed an initial surge in the hazard rate, which peaked about 20–22 months after

TABLE 2 Univariate and multivariate analysis of predictors for overall recurrence, local recurrence and distant metastasis

Variable	Overall recurrence (n = 137)				LR (n = 36)				DM (n = 95)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Sex (male)	1.29 (0.92–1.80)	0.139			2.23 (1.14–4.35)	0.019	1.62 (0.71–3.67)	0.250	1.04 (0.69–1.56)	0.849		
Age	1.03 (1.01–1.04)	0.003	1.02 (1.00–1.03)	0.056	1.02 (0.99–1.05)	0.242			1.02 (1.00–1.04)	0.020	1.01 (0.99–1.03)	0.171
Smoking history	1.69 (1.19–2.39)	0.003	1.31 (0.92–1.87)	0.138	2.16 (1.11–4.19)	0.023	1.39 (0.62–3.13)	0.423	1.54 (1.01–2.36)	0.046	1.17 (0.76–1.81)	0.467
Tumor history	1.06 (0.70–1.62)	0.773			1.24 (0.57–2.72)	0.592			0.94 (0.56–1.59)	0.829		
Family tumor history	0.72 (0.39–1.33)	0.294			1.02 (0.36–2.88)	0.973			0.66 (0.30–1.42)	0.284		
Comorbidity	0.84 (0.60–1.18)	0.320			0.96 (0.50–1.87)	0.916			0.78 (0.52–1.16)	0.221		
Extent of pulmonary resection												
Lobectomy	Ref	-			Ref	-			Ref	-		
Sublobectomy	0.75 (0.48–1.17)	0.204			0.71 (0.30–1.72)	0.450			0.65 (0.37–1.15)	0.141		
Histology												
LGADC	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
HGADC	4.07 (2.89–5.73)	<0.001	3.08 (2.09–4.52)	<0.001	3.22 (1.63–6.37)	0.001	2.77 (1.38–5.55)	0.004	4.35 (2.89–6.54)	<0.001	3.22 (2.03–5.11)	<0.001
VPI	1.59 (1.12–2.27)	0.010	0.64 (0.39–1.03)	0.065	1.35 (0.66–2.74)	0.412			1.62 (1.06–2.47)	0.025	0.58 (0.33–1.01)	0.055
LVI	2.39 (1.56–3.68)	<0.001	1.15 (0.72–1.83)	0.570	1.56 (0.61–4.02)	0.357			2.63 (1.58–4.36)	<0.001	1.21 (0.70–2.11)	0.496
T stage												
T1	Ref	-	Ref	-	Ref	-			Ref	-	Ref	-
T2	2.41 (1.72–3.37)	<0.001	2.59 (1.62–4.15)	<0.001	1.69 (0.87–3.26)	0.119			2.66 (1.77–4.00)	<0.001	3.04 (1.76–5.28)	<0.001

Abbreviations: CI, confidence interval; HGADC, high-grade adenocarcinoma; HR, hazard ratio; LGADC, low-grade adenocarcinoma; LVI, lymphovascular invasion; Ref, reference; VPI, visceral pleural invasion.
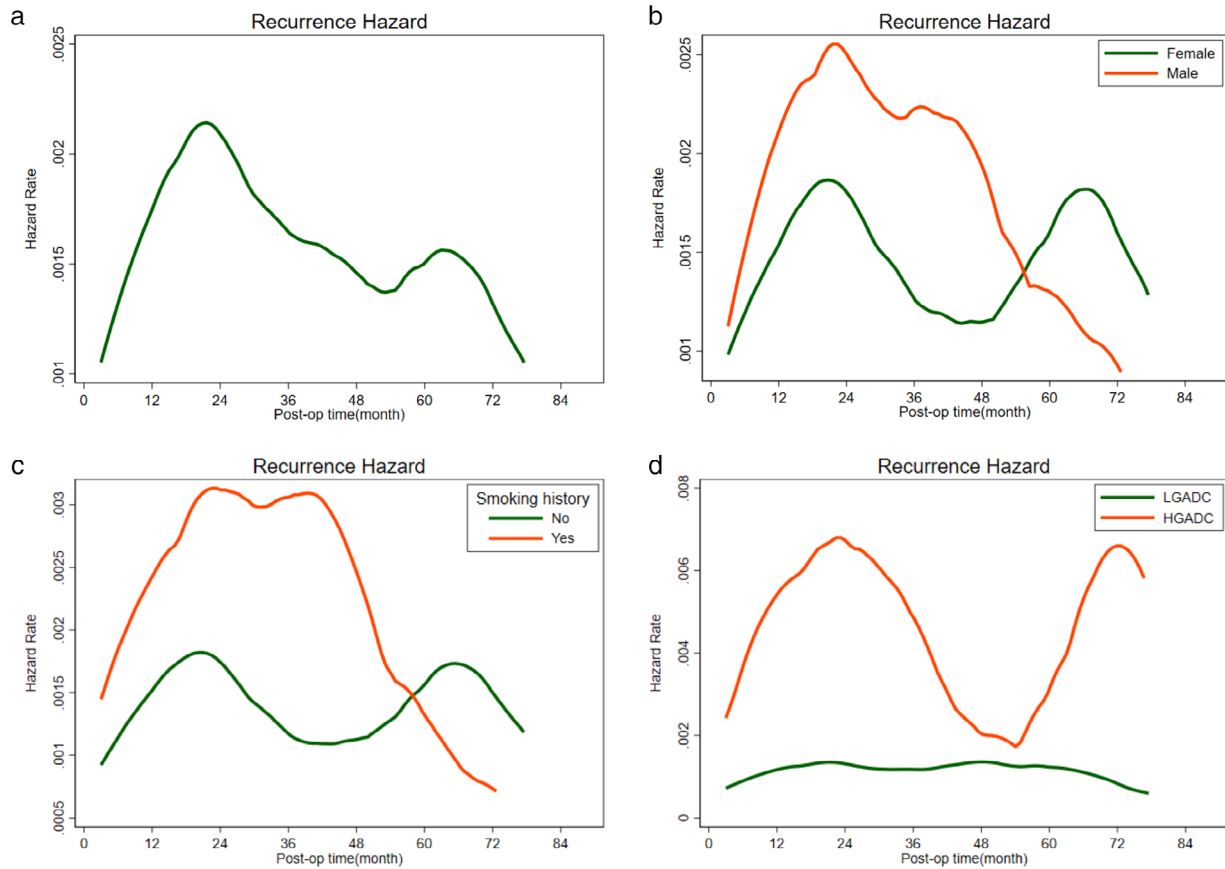
TABLE 3 Univariate and multivariate analysis of predictors for site-specific recurrence

Variable	Chest (n = 72) Univariable analysis HR (95% CI)	p	Multivariable analysis HR (95% CI)	p	Brain (n = 30) Univariable analysis HR (95% CI)	p	Multivariable analysis HR (95% CI)	p	Bone (n = 28) Univariable analysis HR (95% CI)	p
Sex (male)	**2.00 (1.25–3.19)**	**0.004**	1.25 (0.69–2.25)	0.459	0.62 (0.28–1.34)	0.223			0.92 (0.43–1.95)	0.820
Age	**1.04 (1.01–1.06)**	**0.002**	**1.03 (1.01–1.05)**	**0.015**	1.00 (0.97–1.04)	0.813			1.02 (0.98–1.06)	0.303
Smoking history	**2.28 (1.43–3.64)**	**0.001**	1.59 (0.89–2.86)	0.118	0.93 (0.40–2.16)	0.860			1.01 (0.43–2.38)	0.978
Tumor history	0.95 (0.52–1.73)	0.870			0.87 (0.33–2.26)	0.771			1.19 (0.48–2.94)	0.704
Family tumor history	0.89 (0.41–1.94)	0.771			1.29 (0.45–3.69)	0.640			-	1.000
Comorbidity	1.16 (0.72–1.87)	0.539			0.54 (0.26–1.11)	0.095	0.55 (0.27–1.14)	0.107	0.78 (0.37–1.64)	0.516
Extent of pulmonary resection										
Lobectomy	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
Sublobectomy	0.66 (0.35–1.25)	0.203			1.19 (0.51–2.79)	0.691			0.43 (0.13–1.43)	0.170
Histology										
LGADC	Ref	-	Ref	-	Ref	-	Ref	-	Ref	-
HGADC	**3.74 (2.32–6.01)**	**<0.001**	**2.80 (1.65–4.75)**	**<0.001**	**5.24 (2.55–10.77)**	**<0.001**	**4.11 (1.83–9.22)**	**0.001**	1.56 (0.63–3.86)	0.335
VPI	1.40 (0.85–2.30)	0.187			1.42 (0.66–3.05)	0.367			1.70 (0.78–3.70)	0.178
LVI	1.80 (0.95–3.43)	0.073	0.89 (0.45–1.78)	0.745	**3.32 (1.41–7.81)**	**0.006**	1.39 (0.54–3.56)	0.493	0.77 (0.18–3.27)	0.726
T stage										
T1										
T2	**2.31 (1.45–3.68)**	**<0.001**	**1.82 (1.13–2.92)**	**0.014**	**2.27 (1.10–4.66)**	**0.026**	1.72 (0.82–3.61)	0.151	**2.11 (1.00–4.43)**	**0.049**

Note: Values in bold are statistically significant.
Abbreviations: CI, confidence interval; HR, hazard ratio; LGADC, low-grade adenocarcinoma; HGADC, high-grade adenocarcinoma; LVI, lymphovascular invasion; VPI, visceral pleural invasion; Ref, reference; VPI, visceral pleural invasion.

FIGURE 2 (a) Recurrence hazard curve for overall recurrence. Recurrence hazard curves according to clinic-pathological characteristics: (b) sex, (c) smoking history, (d) histology

surgery. A second small peak was noted at about 5–6 years after surgery (Figure 2A). A visual inspection of the hazard curves for histology suggested that the HGADC patients exhibited higher hazard rates than LGADC patients during the whole follow-up. In addition, the recurrence hazard curve in HGADC patients showed a typical "double-peaked" pattern, while the curve in LGADC patients displayed a smooth curve after surgery. In addition, sex affected the temporal distribution of the recurrence risk, with a typical "double-peaked" pattern in females and a "one-peaked" pattern in males. Males reached the highest recurrence hazard at 20–22 months after surgery, while the hazard rate curve of females displayed the first peak at 20–22 months and showed the second peak at about 5–6 years after surgery. Smoking history affected the temporal distribution of the recurrence risk, with higher hazard rate in smokers.

DISCUSSION

In the present study, we analyzed the independent prognostic factors of overall recurrence, local recurrence, distant metastasis, and site-specific recurrence based on a large series of T1-2N0M0 patients with lung invasive adenocarcinoma who underwent complete resection and provide

postoperative monitoring and follow-up strategies for the certain group of patients. In our study, the overall recurrence rate of T1-2N0M0 patients was 6.98% (137/1962). Zhao et al.[7] reported that the presence of an micropapillary and/or solid component in LUAD (HGADC type) is associated with lymph node metastasis and worse recurrence-free survival, even if it is not predominant. Wang et al.[4] found that T1N0M0 invasive adenocarcinoma patients with solid and/or micropapillary components (HGADC type) after lobectomy showed worse clinical recurrence and survival outcome. Our study showed similar results, which were that HGADC was the independent predictor for overall recurrence, local recurrence, and distant metastasis, and the HGADC type displayed significantly worse DFS than the LGADC type in overall recurrence, local recurrence, and distant metastasis. Based on the results of the present and previous studies, it is necessary for us to pay close attention to HGADC-type patients in postoperative follow-up and appropriately increase the review interval of this type.

An important finding in our study was HGADC was not an independent risk factor for bone recurrence, but it was a significantly prognostic factor for chest and brain recurrence. Many previous studies have indicated that the presence of a micropapillary and/or solid component in invasive LUADs (HGADC type) is associated with worse DFS, but

there have been few studies that have analyzed the association between HGADC and site-specific recurrence.

In 994 early-stage (T1a-T2bN0M0) NSCLC patients after complete resection, Zhu et al.[8] found double-peaked recurrence curve, i.e. the time of the first major hazard peak was 1.6 years after surgery and the second peak occurred at 8.8 years. Furthermore, this "double-peaked" pattern was present in several types.[9] Our study also found that the overall recurrence hazard curve for early-stage LUAD showed a "double-peaked" pattern. The first recurrence peak occurred at about 20–22 months after surgery and the second recurrence peak occurred about 5–6 years after surgery, which is a little earlier than Zhu's study. This "bimodal" recurrence hazard curve was consistent with previous studies and supported the tumor dormancy hypothesis.[10,11] The hypothesis indicates that there exists a relatively steady state for micrometastases, most of which will not promote tumor growth, but surgical operation will destroy this steady state, thereby stimulating the proliferation of dormant tumor cells, resulting in accelerated recurrence process and eventually leading to recurrence. This phenomenon may account for the first peak of recurrence after surgery. The second and subsequent peaks of recurrence hazard in our study can be explained by the assumption that after entering the transient state of dormancy, the residual tumor cells will proliferate and gradually develop micro-metastasis. Over time, micro-metastasis eventually leads to recurrence. However, the detailed mechanisms of tumor dormancy remain to be clarified.

Demicheli et al.[12] found that peak timing in NSCLC patients proved to be somehow sex dependent. During follow-up, the timing of the second peak in women was 6 months later than in men. In addition, Watanabe et al.[9] also found the maximum peak in recurrence in men appeared 6–8 months after surgery, while the highest peak occurred 22–24 months after surgery in women. In our study, the recurrence hazard curve was also different between men and women among all patients, which was different from above studies. Male patients reached the highest recurrence hazard at 20–22 months after surgery, then the hazard rate continued to decrease over time. In contrast, female patients showed a "double-peaked" recurrence hazard curve, with the first peak at 20–22 months after surgery and a second peak at 5–6 years after surgery. In addition, male patients had a higher recurrence hazard than female patients during the first 4 years after surgery. One reason may be that those studies included patients with lymph node metastasis, which led to an earlier recurrence peak time and higher recurrence hazard rate. On the other hand, the sex-related inner milieu of the host may have selected tumor cells with different traits and may act differently on men and women.[12] As an alternative, gender or hormone factors might affect tumor behavior to some extent.[13,14] This finding suggests that early-stage adenocarcinoma female patients displayed a unique recurrence pattern, based on which we should use a special follow-up strategy for female patients.

Another finding in our study was that the recurrence hazard of smokers was higher than that of nonsmokers during the first 5 years after surgery. Pathological characteristics of early-stage LUADs showed that tumors in patients with smoking history were significantly more frequently accompanied by LVI or VPI than those in never smokers.[15] These invasive characteristics might be the reason for ever smokers developing more frequent recurrence and experiencing more death than never smokers. In addition, the majority of smokers were male, so the recurrence hazard curve showed similar results with the curve by sex. Moreover, the recurrence hazard of nonsmokers was higher than that in smokers at 5 years after surgery, which means smoking could introduce worse biological behavior in early follow-up.

Our research shows some limitations. First, our study was retrospective, thus there was some selection bias that would be affected by the lead time. Therefore, prospective randomized trials are still needed to explore the dynamic pattern of recurrence after radical resection of LUAD patients to develop a suitable follow-up strategy. Second, the time of failure (recurrence/metastasis) depends largely on the time of imaging examination or hospital visit, and requires a shorter evaluation interval for follow-up and analysis to more accurately estimate the recurrence hazard. Third, the results of our study were established on the basis of Chinese patients, and the universality of the non-Asian population requires external verification and exploration.

CONCLUSIONS

In conclusion, our study showed that different postoperative recurrence patterns were seen in HGADC and LGADC. Site-specific recurrence patterns were also different in HGADC and LGADC types. The postoperative recurrence hazard curve of completely resected early-stage LUAD displays a double-peaked pattern. Different postoperative recurrence patterns were seen in different genders and smoking conditions.

CONFLICT OF INTERESTS
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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