Original Article

Predictive value of perioperative carcinoembryonic antigen changes for recurrence in non-small cell lung cancer

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Background: Despite surgical resection, the prognosis for patients with non-small cell lung cancer (NSCLC) remains unsatisfactory. The objective of this study was to investigate the impact of serum carcinoembryonic antigen (CEA) levels on recurrence in patients with NSCLC before and after surgical resection. In addition, for patients with invasive lung adenocarcinoma (IAC), which constitutes the majority of cases, we further explored the effect of pathological subtype on recurrence.

Methods: A total of 349 patients were included in the study. The correlation between clinicopathological factors and post□surgery survival outcomes was analyzed. Kaplan-Meier curves were constructed based on the pertinent data and analyzed using the Cox regression model. Recurrence risk curves were plotted according to the time to recurrence for each CEA subgroup and pathological subtype to explore the change in recurrent rate over time in each group.

Results: A total of 9 (81.82%) patients in the low preoperative CEA but higher than normal postoperative CEA levels group experienced recurrence, with a median recurrence-free survival (RFS) of only 24 months and a median overall survival (OS) of 57 months. These outcomes demonstrated poorer RFS and OS than those observed in the other three groups. Multivariate analysis of RFS revealed postoperative CEA level (P<0.001), histological type (P=0.01), tumour size (P=0.048), tumor-node-metastasis (TNM) stage (P<0.001) and pN stage (P=0.04) as independent poor prognostic factors. postoperative CEA level (P=0.003), histological type (P=0.02), tumor size (P=0.03), TNM stage (P=0.004) and pN stage (P=0.049) were independent poor prognostic factors for OS. Among the pathological subtypes, patients with Grade 3 (high-grade patterns ≥20%) exhibited a higher risk of recurrence after surgery.

Conclusions: Elevated CEA levels in the postoperative period, as well as pathological subtypes of Grade 3, have been identified as risk factors for early recurrence in NSCLC patients after surgery.

Keywords: Carcinoembryonic antigen (CEA); non-small cell lung cancer (NSCLC); pathological subtypes; recurrence

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Introduction

Worldwide, the incidence of lung cancer is increasing every year. At the same time, current epidemiology shows that lung cancer continues to be the leading cause of death in humans around the world (1). Lung cancer prognosis varies widely, with 5-year survival rates ranging from 90% to 10% for stage I–IV lung cancer (2). Surgical resection is the most effective treatment for stage I and II lung cancer, and tumor node metastasis (TNM) staging is currently the most commonly used staging system for non-small cell lung cancer (NSCLC) patients and the best predictor. However, even patients with a low TNM stage are at risk of relapse after surgery.

Risk factors for lung cancer recurrence include the patient's pathological type, stage, treatment modality, and individual characteristics. Treatment for lung cancer recurrence needs to be individualized according to the patient's specific situation and may include chemotherapy, targeted therapy, immunotherapy, and other methods. However, treatment after lung cancer recurrence is often more complex and challenging, and patients usually have a poorer prognosis. In addition, serological markers in lung cancer patients may serve as predictors of recurrence (3,4). Serum tumor markers can be used as a basis for diagnosis and assessment of recurrence, like carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 19-9 (CA19-9), etc. Research on various tumor markers is ongoing and continues in the areas of diagnosis, treatment, and prognosis of lung cancer.

CEA, a tumor-associated antigen first isolated from colon cancer and embryonic tissue, is an acidic protein with human embryonic antigenic properties. In adults, it is produced at low levels in the gastrointestinal tract, pancreas, and liver. It has been hypothesized that the elevation of CEA in cancer is due to reduced inhibition of the gene encoding CEA (5). As many different types of cancer can cause elevated CEA levels, testing serum CEA levels can help monitor cancer recurrence or evaluate the effectiveness of treatment. In many colorectal cancer studies, changes in CEA levels can be a good predictor of tumor recurrence (6-8).

Lung adenocarcinoma is the largest histological type of lung cancer, and invasive lung adenocarcinoma (IAC) is one of the most common types with a poorer prognosis. Even among invasive adenocarcinomas, the prognosis of patients still varies widely. According to the 2011 histological classification system published by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS), IAC can be divided into five different histological types (lepidic, acinar, papillary, micropapillary, and solid subtypes), with micropapillary/solid being classified as a high-grade pathological pattern due to its worse prognosis (9). In 2020, the IASLC proposed a new classification system. The IASLC grading system was classified as follows: Grade 1 (well-differentiated, W/D), lepidic-predominant tumors with no or less than 20% high-grade patterns; Grade 2 (moderately differentiated, M/D), acinar or papillary-predominant tumors with no or less than 20% high-grade pattern; and Grade 3 (poorly differentiated, P/D), any tumor with a high-grade pattern of 20% or more (10). Studies have confirmed the prognostic value of this classification (11,12).

Inspired by this, we investigated whether pre- and post-operative CEA levels are predictive of NSCLC recurrence and further explored the impact of different pathological subtypes on lung adenocarcinoma recurrence. We conducted a retrospective study to investigate the risk factors for postoperative recurrence and survival in patients with NSCLC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-776/rc).

Highlight box

Key findings

- Elevated carcinoembryonic antigen (CEA) levels in the postoperative period, as well as pathological subtypes of Grade 3, have been identified as risk factors for early recurrence in non-small cell lung cancer (NSCLC) patients following surgery.

What is known and what is new?

- In many colorectal cancer studies, changes in CEA levels can be a good predictor of tumor recurrence.
- High perioperative CEA can be used as a predictor of poor survival in NSCLC patients. In early-stage NSCLC, high perioperative CEA levels are also associated with more aggressive tumor behavior and poorer clinical outcomes.

What is the implication, and what should change now?

- Our study demonstrates that high CEA levels, especially after surgery, could indicate NSCLC recurrence. High-grade invasive lung adenocarcinoma (IAC) (Grade 3, ≥20%) is also a risk factor for postoperative recurrence or metastasis.

Methods

Patient selection

The study was conducted in accordance with the

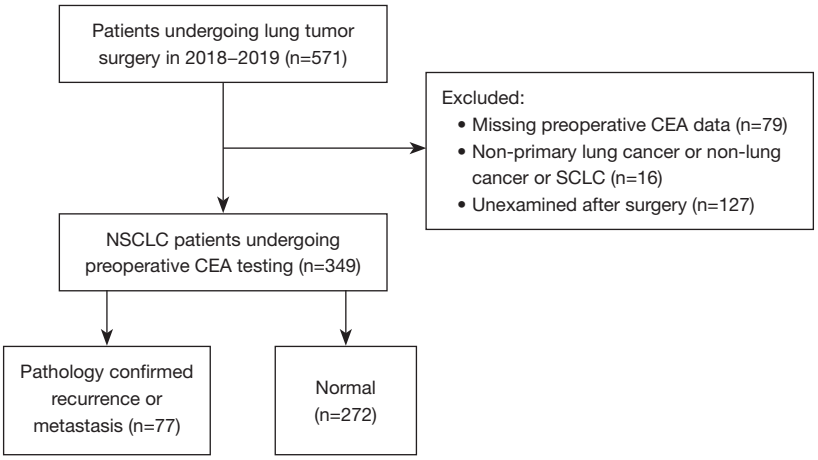

Figure 1 Flow chart of the study cohort characteristics. CEA, carcinoembryonic antigen; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Review Committee of Taizhou Hospital, Zhejiang Province (No. K20240660). The requirement for informed consent was waived in this retrospective study. A total of 571 patients were included in the trial. All patients underwent surgical treatment between 4 January 2018 and 8 January 2019. Of these, 555 (97.2%) were ultimately diagnosed with primary NSCLC and staged according to the 8th edition of the International Lung Cancer TNM Staging. The patients underwent pre-surgical serum CEA collection and at least one serum CEA collection at the 6-month follow-up after surgery. Those who lacked pre-surgical CEA data and those who did not undergo post-surgical review or who had missing CEA data at review were excluded. The total number of patients ultimately included in the trial was 349 (*Figure 1*).

CEA concentrations were quantified utilizing Abbott kits. The upper percentile limit for healthy individuals for CEA is 5 ng/mL, according to the criteria. This data was therefore used in this study to differentiate CEA levels.

In this study, patients were divided into four groups based on serum CEA levels: patients with preoperative and postoperative CEA levels below normal (LL group), patients with low preoperative CEA but higher than normal postoperative CEA levels (LH group), patients with preoperative and postoperative CEA levels above normal (HH group), and patients with high preoperative CEA but lower than normal postoperative CEA levels (HL group).

Two experienced pathologists reassessed the primary tumor pathology sections of each patient using the grading system recommended by the 2020 IASLC Pathology Committee. The percentage of each histological pattern (lepidic, acinar, papillary, micropapillary, solid, and complex glandular) was also recorded to explore whether pathological subtypes are of research value for recurrence. Since the majority of lung adenocarcinoma pathology was of mixed subtypes, the subtype occupying the largest area was the predominant subtype and was further categorized into a new grading system. The pathological subtypes were classified into three groups according to the IASLC criteria: Grade 1 tumors have <20% high-grade components and are predominantly lepidic-dominant tumors, whereas Grade 2 tumors have <20% high-grade components and are predominantly acinar- or papillary-dominant tumors, and Grade 3 tumors have ≥20% high-grade components (solid, micropapillary, or complex gland) in any combination.

Recurrence

Recurrence or metastasis is determined based on radiological findings. The gold standard is pathological findings. For patients undergoing lung cancer surgery, surgeons will perform chest computed tomography (CT) plain scanning at 3 months, 6 months, and 1 year after surgery. Patients are advised to undergo chest and head CT scanning at 1-year intervals thereafter. The majority of patients will receive information about disease progression in the follow-up CT. Some patients will discover disease progression, including recurrence in the lungs and metastasis to other sites when they are admitted to the

respiratory medicine department for symptoms such as cough, sputum, and hemoptysis before the next standard follow-up. These patients will be diagnosed with recurrence or metastasis by bronchoscopy or local puncture biopsy, and by a multidisciplinary consultation. If reoperation is required, surgery is performed following a multidisciplinary consultation. Intraoperative cryo-fast biopsy and postoperative routine pathology serve as the basis for confirming the diagnosis in these patients.

In instances where recurrence or metastasis was identified, the site of recurrence was divided into five relatively independent categories. The categories were as follows: "local", "bone", "brain", "multiple-sites", and "other". The designation "multiple-sites" signifies the occurrence of recurrence or metastasis in at least two distinct locations, including local and distant metastases. The category "other" encompasses mediastinal lymph node metastases and other less common metastatic sites.

The data about each patient was collected in the medical record management system of our hospital. The data included the patient's age, gender, smoking history, CEA level, tumor characteristics, recurrence and survival, and follow-up treatment characteristics. Pre- and postoperative serum CEA levels were recorded for each patient, and the presence of recurrence or metastasis was determined for each patient through follow-up, and the earliest time at which recurrence or metastasis was detected on imaging was recorded at their outpatient follow-up visits.

Statistical analysis

Descriptive statistics were employed. Measures that exhibited a normal distribution were expressed as the mean ± standard deviation (mean ± SD). One-way analysis of variance (ANOVA) was employed for the comparison between groups. Measures that did not exhibit a normal distribution were expressed as the median and interquartile spacing [M (interquartile range, IQR)]. The Kruskal-Wallis *H* test was used for the comparison between groups. Furthermore, the data were expressed as the number of cases, and the unordered categorical data was analyzed using Fisher's exact probability method for comparison between groups, while the Kruskal-Wallis *H* test was employed for comparison between groups of ordered categorical data. Recurrence-free survival (RFS) was defined as the time interval between the date of surgery and the date of recurrence, or as the date of the last follow-up. Overall survival (OS) was defined as the time interval between the commencement of treatment, the initiation of neoadjuvant therapy, the date of surgery, and the date of death or the date of the last follow-up visit. Kaplan-Meier curves were employed to generate survival curves, and the statistical significance of observed differences in survival was evaluated using log-rank tests. A Cox regression analysis model was employed for statistical analysis. For preoperative and postoperative CEA levels, the data were divided into four groups according to the cut-off value of <5 ng/mL. Univariate and multivariate analyses were then performed to assess the independent prognostic effects of these levels on RFS and OS. A P value of less than 0.05 was considered statistically significant. The statistical analyses were conducted using SPSS software (version 27.0.1.0), while the charting was generated by GraphPad Prism 10.0.3 software and R software (version 4.3.3).

Results

Patient characteristics

A total of 571 patients underwent surgical treatment during the study period. Of these patients, 206 were missing pre- or postoperative CEA data, and 16 were excluded as their tumor pathology was reported as non-NSCLC (*Figure 1*). Subsequently, 349 patients (61.12%) met the inclusion criteria and were included in the study. These patients were stratified according to serum CEA levels.

We counted the demographic and tumor characteristics of the patients (Table S1). A comparison of the cohorts revealed that the distributions of age, preoperative CEA, postoperative CEA, RFS, OS, smoking history, pathological subtype, tumor size, pN stage and TNM stage were significantly different. In the entire cohort, the number of female patients was higher (54.41%), the median age of the patients was 58.19±10.64 years, the median size of the resected tumor was 1.30 cm (IQR, 0.80–2.20 cm), and 294 (84.24%) were identified as stage I NSCLC according to the eighth edition of TNM staging. The histological type of these tumors was predominantly adenocarcinoma (82.81%), with other histological types including squamous carcinoma, large cell lung cancer, and sarcoma. Among the patients, 87 (24.93%) had a history of previous or current smoking. In the smoking population, their median preoperative and postoperative CEAs were higher than the overall. During the follow-up period, 77 (22.06%) patients experienced a recurrence, while the remaining 272 (77.94%) patients did not. The highest number of sites of

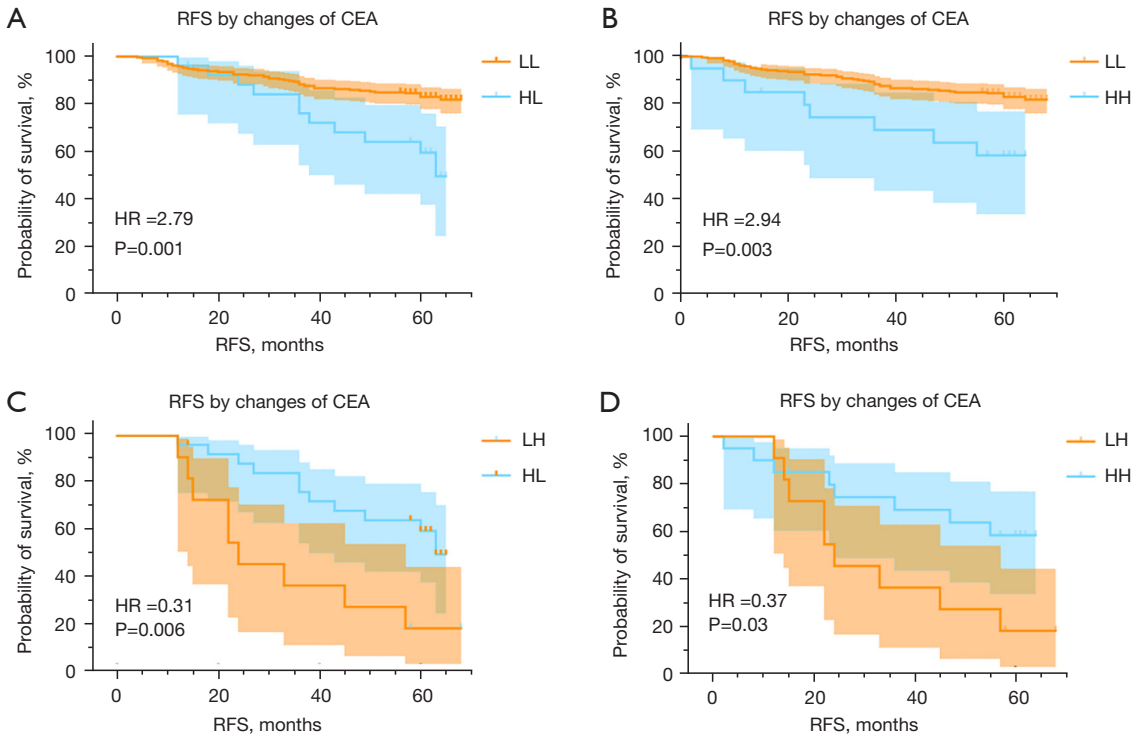

Figure 2 Survival curves for RFS stratified by CEA level comparing patients with each CEA level (A-D). RFS, recurrence-free survival; CEA, carcinoembryonic antigen; HR, hazard ratio; LL group, normal preoperatively and postoperatively; HL group, elevated preoperatively and normal postoperatively; HH group, elevated preoperatively and postoperatively; LH group, normal preoperatively and elevated postoperatively.

recurrence was local recurrence only, which was present in 39 (11.17%) cases, followed by the presence of multiple site metastases, which was present in 14 (4.01%) cases. The remaining recurrences included 8 cases of bone metastasis, 6 cases of brain metastasis, and 10 cases of recurrence at other sites. The median RFS was 60 months (IQR, 57.00–63.00 months) and the median OS was 60 months (IQR, 58.00–63.00 months).

The patients were divided into groups according to their CEA level. The median age (57.08±10.76 years) and tumor size [1.20 (0.80–2.00) cm] of the patients in the LL group were significantly smaller than those of the remaining three groups. There was a gradual increase in the proportion of male patients with increasing serum CEA levels, as well as an increase in the number of patients who were smokers or previous smokers. Concerning the location of the tumors, right-sided lung cancer was the predominant form in all four groups. Stage I lung cancer, adenocarcinoma, alveolar subtype, pN0 stage, lobectomy and local recurrence were the highest in all four groups. The median RFS in the LH group was 24 months (IQR, 18.50–51.00 months), which was significantly lower than that in the remaining three groups.

Recurrence and survival analysis

A total of 77 patients experienced recurrence during the follow-up period, with both local recurrence and distant metastasis observed. Among the patients, 38 (13.01%) in the LL group, 9 (81.82%) in the LH group, 11 (42.31%) in the HL group, and 8 (40.00%) in the HH group experienced recurrence. The RFS of the HH and HL groups was comparable, but both had worse RFS than that of the LL group (*Figure 2A*,*2B*). The RFS of the LH group was significantly worse than that of the remaining three groups, indicating the presence of early recurrence in the LH group (*Figure 2C*,*2D*).

With regard to OS, the LL and HL groups exhibited superior outcomes, whereas the HH group demonstrated relatively inferior outcomes (*Figure 3A*,*3B*). However, when considering the LH group, its prognosis was found to be inferior to that of the HH group (P=0.11) (*Figure 3C*,*3D*).

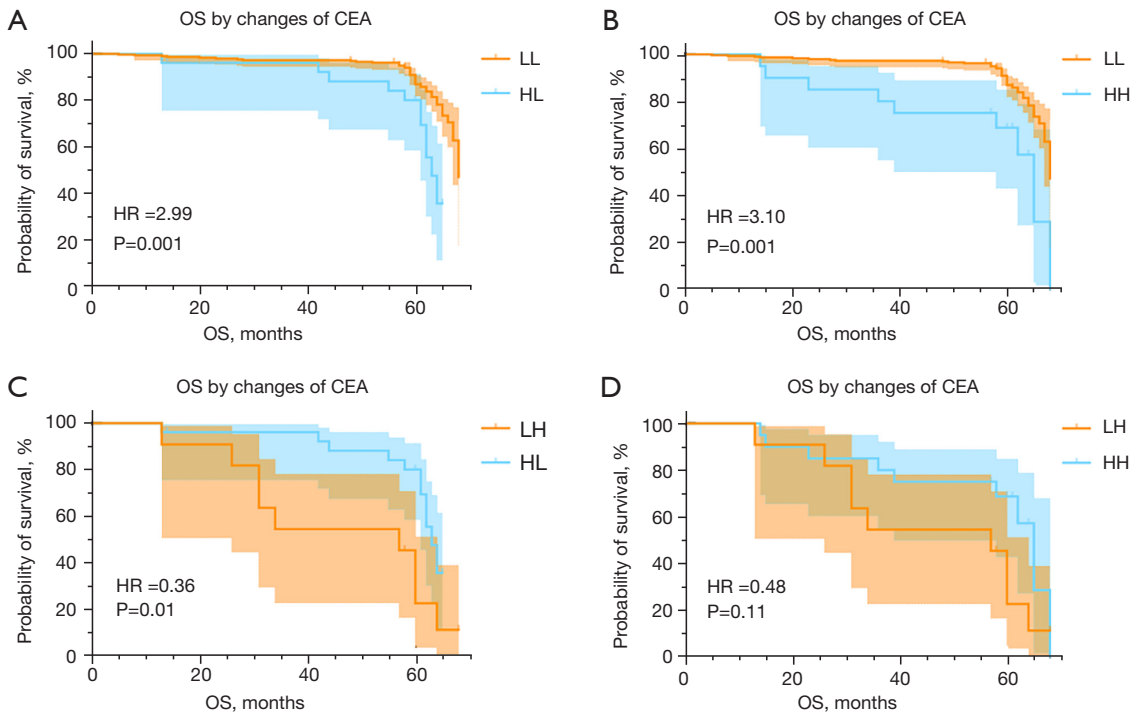

Figure 3 Survival curves for OS stratified by CEA level comparing patients with each CEA level (A-D). OS, overall survival; CEA, carcinoembryonic antigen; HR, hazard ratio; LL group, normal preoperatively and postoperatively; HL group, elevated preoperatively and normal postoperatively; HH group, elevated preoperatively and postoperatively; LH group, normal preoperatively and elevated postoperatively.

This indicates that elevated postoperative CEA levels are associated with poorer RFS and OS.

Risk factors for RFS and OS

We performed univariate and multivariate analyses of potential risk factors associated with RFS (*Table 1*). The univariate analysis revealed that age (P=0.02), gender (P<0.001), preoperative CEA (P<0.001), postoperative CEA level (P<0.001), pathological type (P<0.001), tumor size (P<0.001), TNM stage (P<0.001), pN stage (P=0.002) and surgical procedure (P=0.046) were risk factors for RFS in NSCLC patients. In the context of multivariate analysis, postoperative CEA level [hazard ratio (HR) =3.54; 95% confidence interval (CI): 1.85–6.78; P<0.001], histological type (HR =2.25; 95% CI: 1.21–4.19; P=0.01), tumor size (HR =1.81; 95% CI: 1.01–3.28; P=0.048), TNM stage (HR =1.79; 95% CI: 1.30–2.46; P<0.001) and pN stage (HR =3.59; 95% CI: 3.39–11.24; P=0.04) were identified as independent risk factors for recurrence following surgery.

We performed univariate and multivariate analyses of potential risk factors associated with OS (*Table 2*). Univariate analysis showed that age (P=0.02), gender (P=0.001), preoperative CEA (P<0.001), postoperative CEA level (P<0.001), histological type (P<0.001), tumor size (P<0.001), TNM stage (P<0.001) and pN stage (P=0.045) were risk factors for OS in patients with NSCLC. In multivariate analysis, postoperative CEA level (HR =2.86; 95% CI: 1.43–5.72; P=0.003), histological type (HR =2.20; 95% CI: 1.16–4.17; P=0.02), tumor size (HR =1.92; 95% CI: 1.06–3.46; P=0.03), TNM stage (HR =1.62, 95% CI: 1.17–2.25, P=0.004) and pN stage (HR =3.20; 95% CI: 1.73–6.67; P=0.049) were the independent risk factors affecting survival after surgery.

Dynamic effects of CEA levels and pathological subtypes on recurrence events

A comparison of the recurrence risk rates between the four CEA groups revealed that the LL group had a significantly lower risk of recurrence than the remaining three groups throughout the study period. The LH group experienced a

Table 1 Univariate and multivariate analysis of predictors of RFS

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≤70 *vs.* >70 years)	2.03	1.14–3.62	0.02*	1.15	0.63–2.11	0.65
Gender (female *vs.* male)	2.21	1.39–3.50	<0.001*	0.96	0.54–1.71	0.90
Pre CEA (≤5 *vs.* >5 ng/mL)	2.61	1.57–4.35	<0.001*	0.94	0.51–1.75	0.85
Post CEA (≤5 *vs.* >5 ng/mL)	4.20	2.47–7.13	<0.001*	3.54	1.85–6.78	<0.001*
Location (right *vs.* left)	0.82	0.51–1.31	0.41	–	–	–
Smoking history (no *vs.* yes)	1.20	0.73–1.96	0.47	–	–	–
Histological type (adeno *vs.* others)	4.68	2.98–7.36	<0.001*	2.25	1.21–4.19	0.01*
Tumor size (≤2 *vs.* >2 cm)	4.62	2.95–7.25	<0.001*	1.81	1.01–3.28	0.048*
TNM stage (I *vs.* II–III)	2.62	2.05–3.35	<0.001*	1.79	1.30–2.46	<0.001*
pN stage (pN0 *vs.* pN1–3)	3.83	3.34–12.14	0.002*	3.59	3.39–11.24	0.04*
Surgical procedure (lobectomy *vs.* others)	8.72	5.27–19.62	0.046*	3.29	0.01–6.57	0.05

*, P<0.05. RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; TNM, tumor node metastasis.

Table 2 Univariate and multivariate analysis of predictors of OS

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≤70 *vs.* >70 years)	2.06	1.15–3.68	0.02*	0.91	0.51–1.62	0.76
Gender (female *vs.* male)	2.14	1.35–3.40	0.001*	1.49	0.82–2.70	0.19
Pre CEA (≤5 *vs.* >5 ng/mL)	2.70	1.62–4.49	<0.001*	0.76	0.38–1.49	0.42
Post CEA (≤5 *vs.* >5 ng/mL)	3.94	2.30–6.73	<0.001*	2.86	1.43–5.72	0.003*
Location (right *vs.* left)	0.83	0.52–1.33	0.43	–	–	–
Smoking history (no *vs.* yes)	1.26	0.77–2.06	0.36	–	–	–
Histological type (adeno *vs.* others)	4.69	2.98–7.36	<0.001*	2.20	1.16–4.17	0.02*
Tumor size ≤(2 *vs.* >2 cm)	4.26	2.71–6.69	<0.001*	1.92	1.06–3.46	0.03*
TNM stage (I *vs.* II–III)	2.57	2.01–3.28	<0.001*	1.62	1.17–2.25	0.004*
pN stage (pN0 *vs.* pN1–3)	8.52	4.69–12.35	0.045*	3.20	1.73–6.67	0.049*
Surgical procedure (lobectomy *vs.* others)	0.27	0.09–0.32	0.30	–	–	–

*, P<0.05. OS, overall survival; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; TNM, tumor node metastasis.

surge in recurrence around 24 months after surgery, which was then maintained at a relatively high level of recurrence. The HL group exhibited a high recurrence rate at 36 months post-surgery. The HH group's risk of recurrence decreased over time, but with a peak at 60 months after surgery (*Figure 4A*).

As the majority of the included population were adenocarcinomas, to explore the influence of other factors on recurrence, we further analyzed the lung adenocarcinoma patients in the study subjects according to pathological subtypes and investigated the recurrence rate of each group. It can be found that the recurrence rate of the Grade 1 group was consistently lower than that of the remaining two groups throughout the study period. In contrast, the risk of recurrence was consistently high in the Grade 3 group. The Grade 2 group showed a peak of one recurrence at 24 months after surgery, and the Grade 3 group exhibited a peak of one recurrence at 36 months after

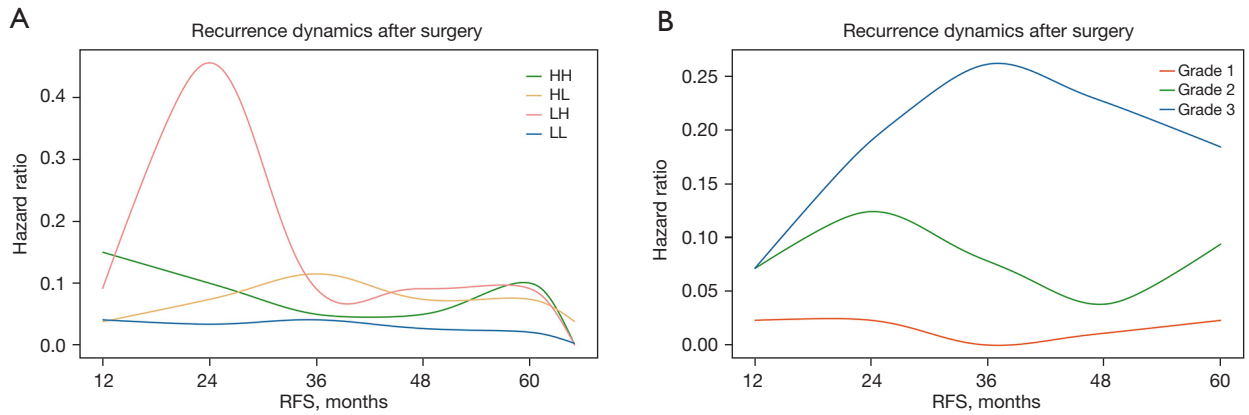

Figure 4 Recurrence dynamics (time hazard) after surgery. (A) CEA level. (B) Pathological subtypes. RFS, recurrence-free survival; HH group, elevated preoperatively and postoperatively; HL group, elevated preoperatively and normal postoperatively; LH group, normal preoperatively and elevated postoperatively; LL group, normal preoperatively and postoperatively; CEA, carcinoembryonic antigen.

surgery (*Figure 4B*). In conclusion, patients in the Grade 3 group were at greater risk of postoperative recurrence.

Discussion

In this study, we investigated the role of preoperative and postoperative serum CEA levels in detecting early recurrence in postoperative NSCLC surveillance. Our analysis showed that patients with normal preoperative CEA levels and elevated postoperative CEA levels had a significantly worse prognosis and were more likely to experience postoperative recurrence. For the majority of patients with invasive adenocarcinoma cancer (IAC), those with Grade 3 (high-grade patterns ≥20%) of the pathological structure were also more likely to have early recurrence than other subtypes.

The effect of CEA levels on cancer recurrence and prognosis has been studied for a long time, mainly in colorectal cancer (13-16). Another prognostic example of tumor marker is CA19-9 level for pancreatic cancer (17). In colorectal cancer, CEA is the only serological indicator used as a diagnostic, treatment monitoring, and prognostic indicator (8). Preoperative CEA levels not only affect the treatment of the tumor but also have an impact on tumor size and staging, with patients with high preoperative CEA levels having poorer RFS and OS. Pre- and postoperative serum CEA ratios are also associated with colon cancer prognosis (6). In early-stage NSCLC, high perioperative CEA levels are also associated with more aggressive tumor behavior and poorer clinical outcomes. Regarding the predictive effect of postoperative CEA, elevated serum CEA is an important determinant of worse prognosis in stage I NSCLC. For example, Yoshiki Kozu *et al.* (4) reported that high serum CEA levels (>5.0 ng/mL) were an independent factor for recurrence and poor survival. Another study showed that when stratifying CEA levels and examining prognosis, patients with elevated CEA at 1–3 months postoperatively had a significantly worse prognosis than those with normal CEA (5-year RFS: 66% *vs.* 36%, OS: 77% *vs.* 39%) (18). In conclusion, high perioperative CEA can be used as a predictor of poor survival in NSCLC patients.

The understanding of the pathological subtypes of IAC also developed early, with Fukutomi *et al.* (19) suggesting that the progression from a poorly differentiated adherent subtype to a papillary subtype to a micropapillary subtype may represent different stages in the progression of IAC from a precancerous lesion to a tumor. The clinical features of the different pathological subtypes vary, so a subtle grading of their pathological structures may have a predictive effect on prognosis. One example is the micropapillary subtype, which is now thought to be prone to early metastasis (20,21). As for the solid subtype, it has been shown that this subtype is more likely to have significant lymph node metastasis, lymphovascular infiltration, and a poorer prognosis (22). In addition, a previous study has shown that once the micropapillary/solid subtype is present, it has a worse prognosis, regardless of whether the ratio is dominant or not (23). In the present study, Grade 3 (high-grade patterns ≥20%) showed high recurrence and early metastasis among all pathological subtypes, which is consistent with other studies. However, it is worth

mentioning that Grade 2 also showed a high recurrence peak in this study, which may be because most IAC are mixed subtypes and therefore the determination of the dominant subtype is inaccurate. Interestingly, using targeted next-generation sequencing, the genomic alterations of *CDKN2A*, *FAS*, *SUFU* and *SMARCA4* in early-stage NSCLC are found to be associated with recurrence (24).

In the present study, two factors were found to influence prognosis: perioperative CEA levels, especially normal preoperative CEA levels and elevated postoperative CEA levels (LH group), and lung adenocarcinoma patients with Grade 3 (high-grade patterns ≥20%). Interestingly, Grade 3 (high-grade patterns ≥20%) were rare in the LH group. Therefore, abnormally elevated CEA levels after surgery may be a more important factor contributing to postoperative recurrence.

However, there are a few limitations in this study. Firstly, it is a single-centre retrospective study with limited sample size and unavoidable selection bias. A prospective multicentre study is needed for further validation before it is further applied to clinical practice. Secondly, we focused on the use of CEA as a recurrence detector. We did not study the ability of CEA to assess its therapeutic efficacy. Thirdly, pathological subtypes assessment may be inconsistent when multiple subtypes co-exist. Finally, smoking will increase the serum CEA level of NSCLC patients, so that it cannot reflect the tumour load accurately. And comorbidities which may cause elevated serum CEA levels, such as chronic obstructive pulmonary disease and lung fibrosis, were not controlled in this study.

Conclusions

In conclusion, high CEA levels in the perioperative period, especially elevated CEA levels after surgery, could be used as a serological marker to predict NSCLC recurrence. IAC, Grade 3 (high-grade patterns ≥20%) are also high-risk factors for postoperative recurrence or metastasis.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-776/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-776/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Review Committee of Taizhou Hospital, Zhejiang Province (No. K20240660). The requirement for informed consent was waived in this retrospective study.

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