The Impact of Anastomosis Location in Patients with Lower Thoracic Esophageal Squamous Cell Carcinoma: A Retrospective Observational Study

Wenyu Zhai
Sun Yat-sen University Cancer Center
Shenshen Fu
Guangzhou First People's Hospital
Xiaoqiang Li
Peking University Shenzhen Hospital
Fangfang Duan
Sun Yat-sen University Cancer Center
Hongying Liao
Sun Yat-sen University Sixth Affiliated Hospital
Junye Wang (jywangmed@163.com)
Sun Yat-sen University Cancer Center

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Abstract

Background

Several kinds of anastomoses with varying locations that can be performed after the surgical resection of lower thoracic esophageal squamous cell carcinoma. In this study, we evaluated the prognostic impact of anastomosis locations in these patients who underwent radical esophagectomy.

Methods

Lower thoracic esophageal squamous cell carcinoma patients which underwent radical esophagectomy and confirmed as microscopically complete resection were retrospectively enrolled. Anastomoses below the aortic arch or below the azygos arch were defined as low anastomosis. Other anastomoses were defined as high anastomosis. Overall survival of these two kinds of anastomoses were analyzed using the log-rank test and Cox regression model.

Results

Of the 781 patients enrolled, 196 and 585 were classified as the low anastomosis and high anastomosis groups, respectively. Overall, the survival time in low anastomosis group (median OS, 36.1 versus 65.4; P=0.01) was shorter than high anastomosis group but no statistical difference was observed in multivariate analysis (P=0.195). Again, no significant difference in survival between low anastomosis and high anastomosis group (median OS, 140.9 versus 124.8; P=0.345) were observed in pT1-T2 subgroup. In pT3-T4 subgroups, patients with low anastomosis group had significantly poorer survival that those with high anastomosis (median OS, 27.1 versus 42.9, P=0.003), even after controlling for other confounders (P=0.026). Notably, the impact of anastomosis location on long-term survival in pT3-4 patients was not significantly modified by nodal status. The internal validation of patients undergoing Sweet approach shown that pT3-T4 patients with high anastomosis had survival advantages (adjusted HR=0.711, 95%CI, 0.601 0.990, P=0.041)

Conclusions

For lower thoracic esophageal squamous cell carcinoma with declared T3-4 status, low anastomosis is associated with worse prognosis and should be avoided.

Background

Esophageal cancer (EC) is the sixth most prevalent cancer worldwide and China accounts for more than half of the new cases and death in the world (1–3). EC can be subdivided into two main histological subtypes, namely, squamous cell carcinomas (SCC) and adenocarcinomas (AC). Esophageal squamous cell carcinoma (ESCC) is the major histological subtype in China (4, 5). Although multimodality treatment is the mainstay treatment for operable ESCC, surgery remains the pillar part of the multimodality treatment (6).

The surgical procedures for EC include esophagectomy and lymphadenectomy. An extended esophagectomy with negative margin is critical to guarantee long-term survival after surgery. For ESCC with middle or upper thoracic location, anastomosis in the upper thorax or in the neck is commonly performed to guarantee sufficient margin distance; different to lower thoracic ESCC which has its own characteristics. First, downward lymphatic drainage is more frequent in lower thoracic ESCC (7). Second, the primary tumor of lower thoracic ESCC is relatively further away from the trachea and the available space for performing anastomosis is also larger than those ESCC located at the upper or middle thorax; which reduce the rate of local invasion and make surgery easier. These characteristics allow more anastomosis choices. Anastomosis below the aortic or azygos arch is a lesser invasive approach for limited esophagectomy, which is widely performed in surgical setting (8). However, the prognostic impact of anastomosis location is still unclear. Therefore, to address this unresolved issue we perform this retrospective study.

Methods

Patients

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. In this study, we retrospectively screened for patients with low thoracic ESCC who underwent radical esophagectomy in the thoracic surgery department of Sun Yat-sen University Cancer Center between January 2000 and December 2012. Inclusion criteria included: (1) confirmatory pathological diagnosis as lower thoracic ESCC; (2) pathologic T status of T1, T2, T3, or T4a; (3) absence of distant metastasis; (4) underwent radical esophagectomy with confirmed microscopic clear margins of resection (R0); (5) did not received any form of neoadjuvant therapy. All patients were staged according to the TNM staging criteria of the 8th American joint Committee on cancer (AJCC) staging system.

Surgical Approach And Fellow-up

In this study, esophagectomy was achieved through three thoracic approaches, including the Ivor-Lewis, McKeown, and Sweet approach. Details of surgical procedure have been described previously (9, 10). In this research, we defined anastomosis below the aortic (left thoracotomy) and azygos arch (right thoracotomy) as low anastomosis (LA). Other kinds of anastomoses were defined as high anastomosis (HA). Follow-up were performed every 3 months in the first two years, every 6 months until 5 years and once a year thereafter. Surgeons would choose Upper gastrointestinal contrast or ultrasonography or computed tomography scan as needed.

Statistical analysis

We used t-test to compare quantitative data and Pearson's $\chi 2$ or Fisher's exact test to compare categorical data between two groups. The overall survival was estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression model was constructed to identify prognostic factors and calculate adjusted hazard ratio (HR). Predictors assessed in this study included: age, sex, anastomosis location, pathologic T status, pathologic N status, pathologic G class, operative approach, and number of resected nodes. All factors with $P < 0.1$ in univariate survival analysis were enrolled in multivariate analysis. Statistical significance was reached when P value < 0.05, all hypotheses were two-sided. Statistical analysis to identify risk characteristics were performed using the SPSS 22.0 software package (SPSS, Inc., Chicago, IL).

Results

Patient's characteristics

A total of 781 patients were enrolled, comprising of 667 male and 114 female patients. The average age of the patients was 59 years (range, 32-84 years). Of the 646 patients who underwent left thoracotomy approach, 193 patients had anastomosis below the aortic. 138 patients underwent right thoracotomy of whom 3 had anastomosis below the azygos arch.

Overall, 196 patients were classified in the low anastomosis (LA) group and 585 patients in the high anastomosis (HA) group. The median number of resected lymph nodes of the entire study cohort was 16 (interquartile range, 9 to 25). The baseline characteristics of the patients are shown in Table1. Patients in the HA group had a significantly greater number of resected lymph nodes (median, 13 versus 16; $P<0.001$) and had a notably higher percentage of patients who underwent right thoracotomy approach (22.6% versus1.5%, $P<0.001$). There was no significant difference in age, sex, pathologic T status, pathologic N status and pathologic G class between the two anastomotic groups.

Table 1
Patient Characteristics

Characteristic	HA group n=585	LA group n=196	P value
Age	57.97±9.01	61.37±9.34	0.100
Sex			0.428
Male	503 (86.0)	164 (83.7)	
Female	82 (14.9)	32 (16.3)	
pT stage			0.071
T1	45 (7.6)	14 (7.2)	
T2	146 (25.0)	32 (16.3)	
T3	380 (65.0)	146 (74.5)	
T4a	14 (2.4)	4 (2.0)	
pN stage			0.283
N0	256 (43.8)	94 (48)	
N1	212 (36.2)	73 (37.2)	
N2	85 (14.5)	18 (9.2)	
N3	32 (5.5)	11 (5.6)	
G stage			0.717
G1	134 (22.9)	45 (23.0)	
G2	306 (52.3)	97 (49.5)	
G3	145 (24.8)	54 (27.5)	
Amount of resected nodes	19.23±12.93	13.96±9.65	**<0.001**
Surgical approach			**<0.001**
Left-thoracotomy	453 (77.4)	193 (98.5)	
Right-thoracotomy	132 (22.6)	3 (1.5)	

Survival Analysis

The median overall survival time for the entire cohort was 54.9 months. In HA and LA group, the 1-, 3-, and 5-year OS rate was 84.9%, 59.4%, and 51.4%, respectively and was 84.3%, 50.3%, and 42.8%, respectively.

The median survival time of patients in the HA group was significantly longer than those in the LA group (65.4 versus 36.1; Log Rank P=0.01) (Fig. 1A). However, the prognostic impact of anastomotic location did not show any statistical difference in multivariate analysis after controlling for other confounders identified from univariate analysis (HR=0.860, 95%CI, 0.689 1.078, P = 0.195), while gender, age, pathologic T status, pathologic N status, operative approach, and number of resected nodes were the independent prognostic factors in multivariate analysis. (Table 2).

Table 2
Univariate and multivariate analysis for the entire patients and pT3-4 patients

factors	univariate analysis				multivariate analysis			
	HR	95%CI		*P*	HR	95%CI		*P*
For the entire cohort								
gender	0.618	0.456	0.837	0.002	0.663	0.487	0.904	0.009
age	1.018	1.007	1.029	0.001	1.018	1.007	1.028	0.001
operative approach	0.669	0.505	0.887	0.005	0.726	0.540	0.977	0.034
T								
T1	Ref				Ref			
T2	1.834	1.090	3.088	0.022	1.691	1.001	2.856	0.049
T3	2.837	1.740	4.627	<0.001	2.151	1307	3.543	0.003
T4a	7.710	3.025	15.144	<0.001	3.831	1.905	7.704	<0.001
N								
N0	Ref				Ref			
N1	1.984	1.582	2.489	<0.001	1.783	1.411	2.258	<0.001
N2	3.385	2.566	4.466	<0.001	3.093	2.324	4.117	<0.001
N3	5.385	3.722	7.793	<0.001	4.251	2.872	6.293	<0.001
number of resected nodes	0.989	0,981	0.997	0.01	0.988	0.979	0.997	0.006
For patients with T3-4 status								
age	1.019	1.006	1.031	0.003	1.014	1.002	1.026	0.020
anastomosis location	0.689	0.496	0.956	0.026	0.726	0.597	0.972	0.026
T								
T3	Ref				Ref			
T4a	2.649	1.622	4.326	<0.001	2.018	1.220	3.338	0.006
N								
N0	Ref				Ref			
N1	1.889	1.439	2.480	<0.001	1.910	1.455	2.508	0.000
N2	3.047	2.192	4.235	<0.001	3.148	2.259	4.388	0.000

factors	univariate analysis				multivariate analysis			
	HR	95%CI		*P*	HR	95%CI		*P*
N3	4.475	2.971	6.470	<0.001	4.346	2.845	6.616	0.000
number of resected nodes	0.984	0,975	0.993	0.001	0.984	0.974	0.993	0.001

Then, we calculated the adjusted HR value of anastomosis location at different T stages for HA versus LA. Our findings showed that the HR of LA was higher than that of HA in patients with pT3-4 status (pT3: adjusted HR = 1.459; pT4: adjusted HR = 1.065) but lower than HA in patients with pT1-2 status (pT1: adjusted HR = 0.911; pT2: adjusted HR = 0.802) (Fig. 1B). Therefore, patients from both anatomic groups were then subdivided into two different T-stage subgroups, namely the pT1-T2 group and pT3-T4 group.

For the entire pT1-T2 subgroup, observed median survival time was 140.9 months. The prognosis of patients in the LA group was comparable to those in the HA group (median OS,140.9 versus 124.8; Log Rank P=0.345) (Fig. 1C). Similar results were observed in subgroup stratified by nodal status (N-: HR=1.366, 95%CI, 0.666 2.800, P=0.394; N+: HR=2.294, 95%CI, 0.727 7.242, P=0.157) (Supplementary Fig. 1A and B).

For the pT3-T4 subgroup, the median survival time was 34.7 months. Patients in the HA group had significantly better survival outcomes as compared with patients in the LA group (median OS 42.9 versus 27.1; Log Rank *P*=0.003) (Fig. 1D). This difference remained significant even after controlling for other confounders (adjusted HR=0.726, 95%CI, 0.597 0.972, *P*=0.026) (Table 2). Similar results were observed in subgroup stratified by nodal status (Fig. 1E **and F**) (N-: adjusted HR=0.582, 95%CI, 0.369 0.920, *P*=0.021; N+: adjusted HR=0.567, 95%CI, 0.323 0.995, *P*=0.048).

Taking into account the bias associated with the surgical approach, we performed an internal validation of patients undergoing left thoracotomy approach. As shown in Figure 2, though anastomosis location did not affect the outcome of patients underwent Sweet approach (median OS 51.9 versus 38.0; Log Rank *P*=0.067) (Fig. 2A) as well as patients underwent Sweet approach in pT1-T2 subgroup (median OS 95.1 versus 140.8; Log Rank *P*=0.284) (Fig. 2B), patients underwent Sweet approach in pT3-T4 subgroup with high anastomosis had a better OS compared with patients with low anastomosis (median OS 27.1 versus 25.1; Log Rank *P*=0.024) (Fig. 2C). In multivariate analysis, patients underwent Sweet approach in pT3-T4 subgroup with high anastomosis had survival advantages while controlling for other confounders (adjusted HR=0.711, 95%CI, 0.601 0.990, *P*=0.041) (Table 3)

Table 3
Univariate and multivariate analysis for the entire patients and pT3-4 patients with Sweet approach.

factors	univariate analysis				multivariate analysis			
	HR	95%CI		*P*	HR	95%CI		*P*
For the entire cohort								
gender	0.660	0.482	0.902	0.009	0.709	0.515	0.974	0.034
age	1.019	1.008	1.030	0.001	1.020	1.009	1.032	<0.001
T								
T1	Ref				Ref			
T2	1.712	0.982	2.987	0.058	1.366	0.781	2.391	0.274
T3	2.644	1.570	4.452	<0.001	1.865	1.036	3.005	0.036
T4a	7. 720	3.444	14.520	<0.001	2.800	1.326	5.915	0.007
N								
N0	Ref				Ref			
N1	2.089	1.640	2.661	<0.001	1.911	1.488	2.455	<0.001
N2	3.445	2.544	4.665	<0.001	3.036	2.243	4.178	<0.001
N3	5.566	3.759	8.240	<0.001	4.424	2.918	6.708	<0.001
For patients with T3-4 status								
age	1.020	1.007	1.033	0.002	1.017	1.004	1.030	0.008
anastomosis location	0.755	0.592	0.964	0.024	0.711	0.601	0.990	0.041
T								
T3	Ref				Ref			
T4a	2.632	1.560	4.440	<0.001	1.766	1.029	3.031	0.039
N								
N0	Ref				Ref			
N1	2.053	1.539	2.738	<0.001	2.060	1.544	2.750	<0.001
N2	3.154	2.205	4.511	<0.001	3.102	2.162	4.452	<0.001
N3	4.836	3.128	7.477	<0.001	4.338	2.769	6.797	<0.001

Discussion

Lower thoracic ESCC has its own spread, anatomy, space relation and prognosis characteristics which make it a special type of esophageal cancer. Until now, there has been no consensus on the extent of esophageal resection. Although HA and LA have been widely applied in clinics, comparison between these anastomosis locations on long-term survival is still unclear. Based on our results, LA is associated with poor prognosis in lower thoracic ESCC with pT3-T4 status and should be avoided for this cohort.

In our study, we defined cervical anastomosis and high intrathoracic anastomosis as high anastomosis (HA) and sub-aortic anastomosis and anastomosis below the azygos arch as low anastomosis (LA). The basis of this classification was based on from findings of our pilot study which suggested that the prognosis of cervical anastomosis and high intrathoracic anastomosis was similar both in the entire cohort or subgroup analysis stratified by pT status (data not shown). Manabu Okuyama et al, in their randomized controlled trial reported that patients with cervical anastomosis and high intrathoracic anastomosis had similar surgical outcomes (11).

In this study, we firstly evaluated the impact of anastomosis choice in this entire cohort. Although LA was found to be correlated with shorter survival, it lacked statistical significance after controlling for other confounders. Then, we evaluated the impact of anastomosis choice in subgroup analysis stratified by pT status. We found that for patients with T1-2 status, the prognosis achieved by LA was similar to HA (median OS, 140.9 versus 124.8; P=0.345 by log-rank test), whereas for patients with T3-4 status, HA was associated with better outcome than LA, even after controlling for other confounders adjusted HR=0.726, 95%CI, 0.597 0.972, P=0.026). Furthermore, the survival advantage of HA was not significantly modified by nodal status (N-: adjusted HR=0.582, 95%CI, 0.369 0.920, P=0.021; N+: adjusted HR=0.567, 95%CI, 0.323 0.995, *P*=0.048). Therefore, the detrimental impact of LA might be concentrated on patients with advanced primary tumor stage.

For this issue, although the underlying mechanism is still unclear, it might be associated to two reasons. First, the existence of second multiple primary esophageal squamous cell carcinomas (SMPESCC). According to a previous study, SMPESCC is a common phenomenon in ESCC with the general incidence of 0.1–10% (12–14). A previous study reported that lower esophagus was the most common segment in which SMPESCC occurs (54.7%) (15). In addition, Predrag Pesko et al, in their study found out locally advanced patients were more likely suffered from multiple ESCC (16). This incidence would be even higher when the tumor is low thoracic location and locally advanced. Therefore, lower thoracic ESCC patients with T3-4 status might require a more extended esophagectomy to clear potential SMPESCC. Second, as is well known, lymph vessels exist in all layers of esophageal expect the epithelium and outer membrane (17). When the tumor invades deeper layers, the incidence of lymphatic metastasis or micro-metastasis would increase. Thus, for locally advanced ESCC, it would be beneficial to perform an extended esophagectomy.

Debate between right and left transthoracic approach for resectable ESCC has long been a hot topic for a long time. Recently, a series of studies have shown that the right thoracic approach was superior to left thoracic approach on extensive lymphadenectomy, especially in the upper mediastinum, which was critical for more accurate staging and long-term survival (10, 18). In this study, the proportion of patients undergoing HA was significantly higher in the right-thoracotomy group (97.8% versus 70.1%). The fact that extensive esophagectomy is more common in right thoracic approach might be another explanation for survival advantage of right thoracic approach.

Based on our results, LA for lower thoracic ESCC staged as pT3-4 may not be appropriate. For pT1-2 patients, low anastomosis should still be cautiously adopted due to its potentially detrimental impact on eliminating micrometastasis. Routine EUS examination before operation is greatly help for treatment decision (19).

There are some limitations should be considered in this study. First, this is a single-institution retrospective study. Second, we did not perform an external validation to validate the findings. Third, patients with neoadjuvant treatment were not included. Therefore, further validation from multi-center database is needed and meanwhile, the findings from this study should be cautiously interpreted.

Conclusion

For pT3-4 lower thoracic ESCC, LA was associated with worse prognosis and other alternatives should be considered.

Abbreviations

ESCC
esophageal squamous cell carcinoma
LA
low anastomosis
HA
high anastomosis
OS
overall survival
EC
esophageal cancer
SCC
squamous cell carcinomas
AC
adenocarcinomas
SPSS
Statistical Product and Service Solutions
HR
hazard ratio

N
nodes
SMPESCC
second multiple primary esophageal squamous cell carcinomas

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center.

Consent for publication

All patients enrolled in the study signed the consent for publication

Availability of data and material

The key raw data have been deposited into the Research Data Deposit (http://www.researchdata.org.cn), with the Approval and the datasets used in this study are publicly available.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

JYW and HYL designed the study. WYZ and SSF drafted the manuscript, XQL and FFD collected and interpreted the data. WYZ carried out the statistical analysis. All authors read and approved the final manuscript.

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Figures

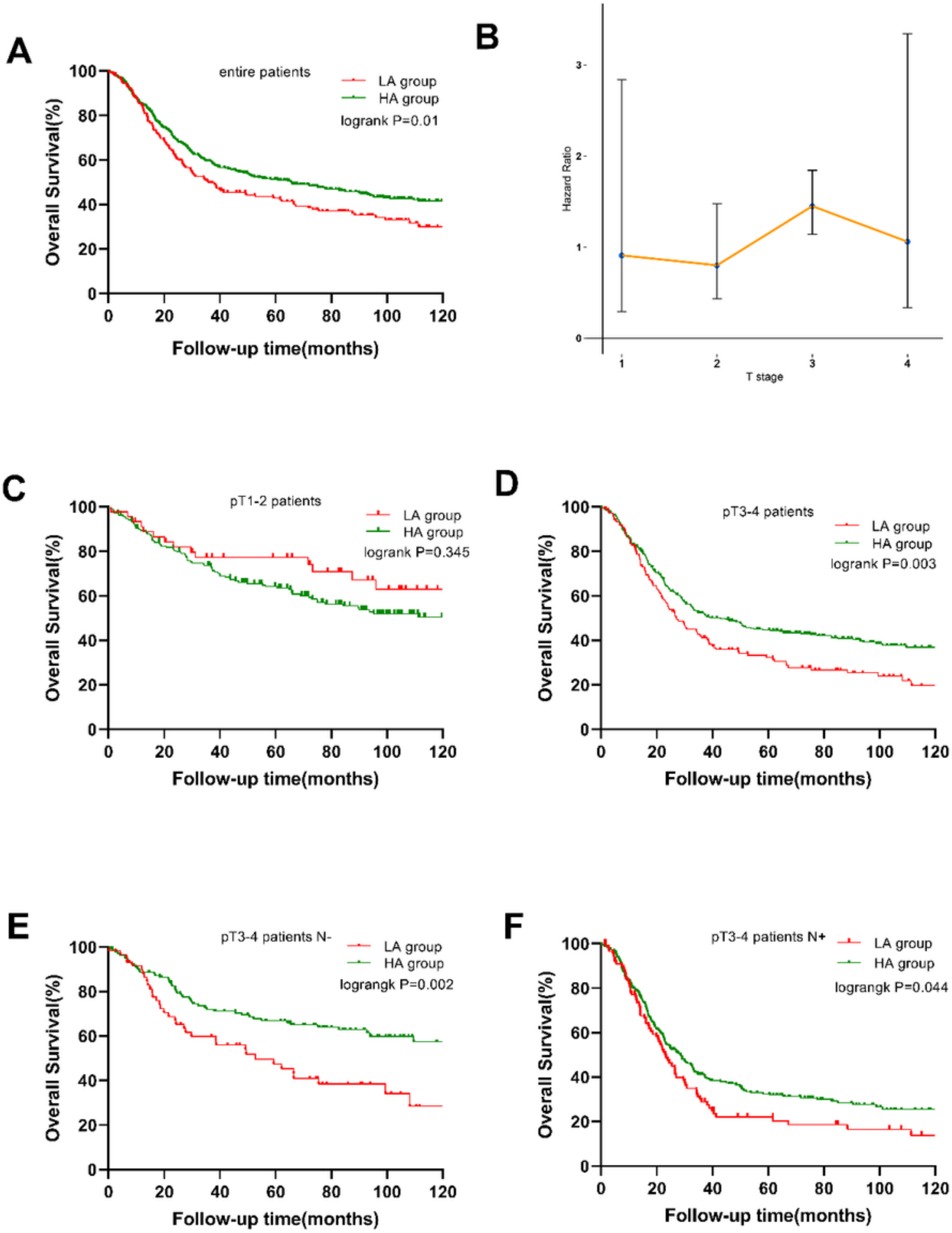

Figure 1

(A) overall survival for entire patients. (B)95%CI of anastomosis location on each pT stage. (C) overall survival for pT1-2 patients. (D) overall survival for pT3-4 patients. (E) overall survival for pT3-4 N-patients. (F) overall survival for pT3-4 N+ patients.

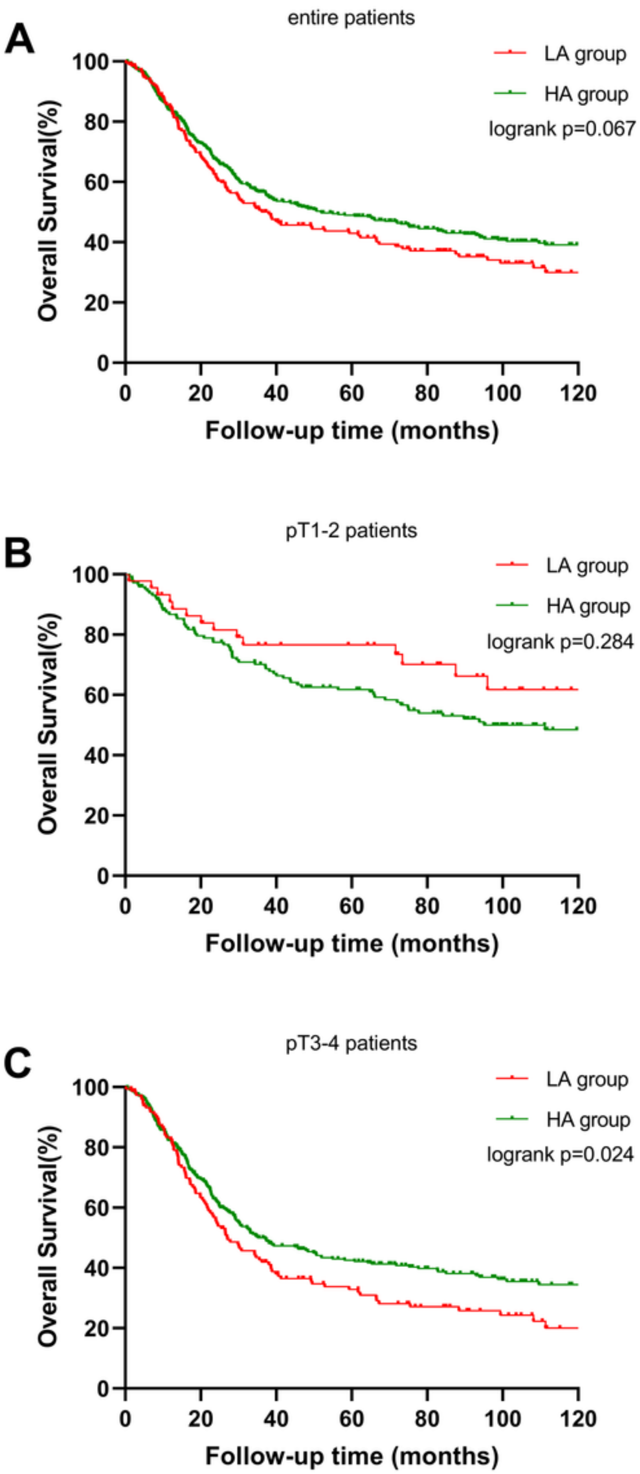

Figure 2

(A) overall survival for entire patients with Sweet approach. (B) overall survival for pT1-2 patients with Sweet approach. (C) overall survival for pT3-4 patients with Sweet approach.