Original Article

Extent of lymph node dissection: common hepatic artery lymph node dissection can be omitted for esophageal squamous cell carcinoma

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Objectives: Controversy persists regarding the adequate extent of lymph node (LN) dissection in thoracic esophageal cancer (EC) surgery. Oncologic efficacy should be balanced with the increased risk of postoperative complications after aggressive radical LN dissection. Here, we evaluate the effectiveness of common hepatic artery LN dissection in surgery for thoracic esophageal squamous cell carcinoma.

Patients and methods: Among a total of 1,563 EC patients who underwent surgery from May 2005 to December 2012 at the Fudan University Shanghai Cancer Center, 1,248 thoracic esophageal squamous cell carcinoma were selected for this study, including 682 patients who underwent esophagectomy with common hepatic artery LN dissection and 566 patients who underwent esophagectomy without common hepatic artery LN dissection. The clinical data of patients were retrospectively analyzed. In addition, the locoregional LN metastasis, relationship between metastatic rates of common hepatic artery LN and clinicopathological factors were analyzed. A propensity score match analysis were performed to control for potential differences in the characteristics of patients with EC cell carcinoma, and postoperative complications were analyzed after propensity score-matching.

Results: The metastatic rate of common hepatic LN was 3.5%. Logistic regression analysis revealed tumor diameter, N classification and pTNM stage were risk factors for common hepatic LN metastasis. Matching based on propensity scores produced 361 patients in each group. The overall incidence of postoperative complications was 32.70% and 35.45%, respectively, no significant difference was found (P=0.432).

Conclusions: The metastatic rate of common hepatic artery LN is low. For patients who undergo resection for Stage I thoracic esophageal squamous cell carcinoma, the dissection of common hepatic artery LN may be safely omitted.

Keywords: Esophageal squamous cell carcinoma; common hepatic artery lymph node (common hepatic artery LN); lymph node dissection (LN dissection); propensity score match

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Introduction

The outcomes for patients with esophageal cancer (EC) remain suboptimal and the incidence of EC has been increasing in recent years. To improve the outcomes of EC, multidisciplinary treatment has been developed and the survival rates have been improving, however, they are still far from satisfactory (1,2). One reason is its high frequency of lymph node (LN) metastasis. In addition, lymphatic

metastasis of EC does not follow a standard pattern (3,4). The latest version of the UICC/AJCC TNM classification (7th edition) emphasizes the importance of LN metastasis for prognosis. However, the Japanese Classification of EC (10th edition) has not incorporated the number of LN metastases into the N factor for its staging system (5,6). Given its frequency and extent of LN metastasis, controlling LN metastasis is a rational therapeutic strategy, and an extended LN dissection may be logical in selected patients. But recent arguments have supported a reduction of unnecessary LN dissection in esophagectomy, which may be associated with increased operative time and postoperative complication (7). Here, we aimed to evaluate the effectiveness of common hepatic artery LN dissection in surgery for thoracic esophageal squamous cell carcinoma.

Methods

Patients

Between 2005 and 2012, 1,563 patients underwent curative intent surgery for EC at the Fudan University Shanghai Cancer Center. The records of all patients with esophageal squamous cell carcinoma were reviewed for the present study. Of these patients, 1,248 patients with esophageal squamous cell carcinoma were enrolled in this study, 682 patients were underwent esophagectomy with common hepatic artery LN dissection and 566 patients were underwent esophagectomy without common hepatic artery LN dissection. The exclusion criteria were as follows: (I) nonsquamous esophageal carcinoma; (II) double primary cancer involving another organ; (III) definite distant metastasis; and (IV) receive neoadjuvant chemotherapy and radiotherapy. All patients were staged according to the TNM classification of the 7th edition of the American Joint Committee for cancer staging manuals (8). The institutional review board of Fudan University Shanghai Cancer Center approved the database of esophageal carcinoma used for the present study.

Preoperative evaluation

Preoperative evaluation at Fudan Universtiy Cancer Center included chest and abdomen computed tomography (CT), barium esophagography, electronic gastroscopy, cervical and abdomen ultrasound, and endoscopic ultrasound (EUS). Through preoperative evaluation, patients with tumors that were confined to the mucosa without nodal metastasis were referred to the endoscopic intervention department for endoscopic mucosal resection (EMR). However, for tumors that were invading the submucosa or for which adequate resection margins were not achieved, EMR was performed at our institution. If a patient had already undergone endoscopy at another hospital, pathology consultation was performed at our insititution. If adequate resection margins were not achieved at another hospital, endoscopy was performed a second time. Integrated positron emission tomography and CT (PET-CT) has not been routinely performed to evaluate nodal metastasis and distant extrathoracic metastasis because of the high price that people cannot afford it. On the basis of the results from those examinations, the patients who were medically suitable, with stage T1-T3 tumors without distant metastases would undergo Surgery.

Surgical approach and lymphadenectomy

Patients was either Ivor Lewis, transhiatal esophagectomy or tri-incisional esophagectomy according to their bodies situation and tumor location, however, the choice of surgical approach also depend on surgeon preference. Middle and lower mediastinal nodes and upper abdominal nodes were routinely removed through a left thoracotomy, however, through a right thoracotomy (Ivor-Lewis procedures), usually the total mediastinal lymphadenectomy was performed. And cervical lymphadenectomy was performed through cervical incision when lymphatic involvement in the neck was indicated by CT scan or ultrasonography.

In our present study, the cervical LNs included the LNs in the supraclavicular and cervical paraesophageal regions. The upper mediastinal nodes included the upper paraesophageal LNs and recurrent laryngeal nerve LNs. The middle mediastinal nodes included the subcarinal, middle paraesophageal, and bilateral hilar LNs. The lower mediastinal nodes included the lower paraesophageal, and diaphragmatic LNs. The upper abdominal nodes included the paracardial LNs, lesser curvature LNs, left gastric artery LNs, common hepatic artery LNs, splenic artery LNs, and celiac artery LNs.

Statistical analysis

Descriptive statistics were used to compare variables between the unmatched groups, using the χ^2 test for categorical variables. Logistic regression analysis was conducted to evaluate the effects of clinical factors. To

Table 1 Distribution of baseline characteristics of the cohorts before and after propensity score matching

	Before matching		P value	After matching		P value
	Cohort one	Cohort two		Cohort one	Cohort two	
Total	682	566		361	361	
Age (years)						
Age >60	308	312	0.92	176	168	0.551
Age ≤60	374	254		185	193	
Sex						
Male	364	477	<0.01	272	277	0.663
Female	318	89		89	84	
Type of surgery						
Ivor Lewis	355	278	<0.01	172	177	0.955
Left transthoracic esophagectomy	22	82		14	14	
Tri-incisional esophagectomy	305	206		175	172	
Tumor location						
Upper	43	37	0.152	27	33	0.482
Middle	425	323		302	303	
Lower	214	206		32	25	
Tumor invasion degree						
T1	85	79	0.442	44	49	0.849
T2	183	163		101	101	
T3	414	324		216	211	
Tumor length (cm)						
≤5	595	488	0.283	314	312	0.826
>5	87	78		47	49	
N classification						
N0	300	285	0.017	160	184	0.106
N1	197	169		104	107	
N2	125	80		68	50	
N3	60	32		29	20	
Tumor differentiation						
Well	63	53	0.938	31	36	0.813
Moderate	457	374		241	238	
Lower	162	139		89	87	
Pathological TNM stage						
I	61	63	0.061	31	39	0.242
II	310	281		165	178	
III	311	222		165	144	

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection.

control for potential differences in the characteristics of patients treated with common hepatic artery LN dissection or without common hepatic artery LN dissection, propensity score methods were used. By using logistic regression model, which included variables such as age, sex, type of surgery, tumor location, tumor invasion degree, tumor length, pathological N stage, tumor differentiation and pathological TNM stage, propensity scores were computed as the conditional probability of receiving either esophagectomy with common hepatic artery LN dissection or esophagectomy without common hepatic artery LN dissection. Using the nearest neighbor match algorithm, we created propensity score-matched pairs without replacement (a 1:1 match). And the caliper definition was set 0.02. The paired patients were extracted from the database. Using this method, 361 of 682 patients who underwent esophagectomy with common hepatic artery LN dissection were matched with 361 of 566 patients who underwent esophagectomy without common hepatic artery LN dissection with similar propensity scores (*Table 1*). A P value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS package (version 19.0).

Results

Patients characteristics

A total of 1,563 EC patients who underwent esophagectomy were enrolled onto the research at the Fudan University Cancer Center from May 2005 to December 2012. The results of the procedure are summarized in *Figure 1*. The enrolled study patients were divided into two cohorts: patients (n=682) who underwent esophagectomy with common hepatic artery LN dissection and patients (n=566) who underwent esophagectomy without common hepatic artery LN dissection. In the first cohort, 364 patients (53.37%) were male and 318 female (46.63%); in the second cohort, 477 patients (84.27%) were male and 89 female (15.73%), all the patients were stage I to III. The baseline characteristics of 1,563 patients are summarized in *Table 2*. Matching based on propensity scores produced 361 patients in each cohort, and the paired cohorts were well balanced (*Table 1*).

Lymph node metastasis (LNMs) before propensity score-matching

A total of 18,277 LNs were dissected (27 LNs per patient),

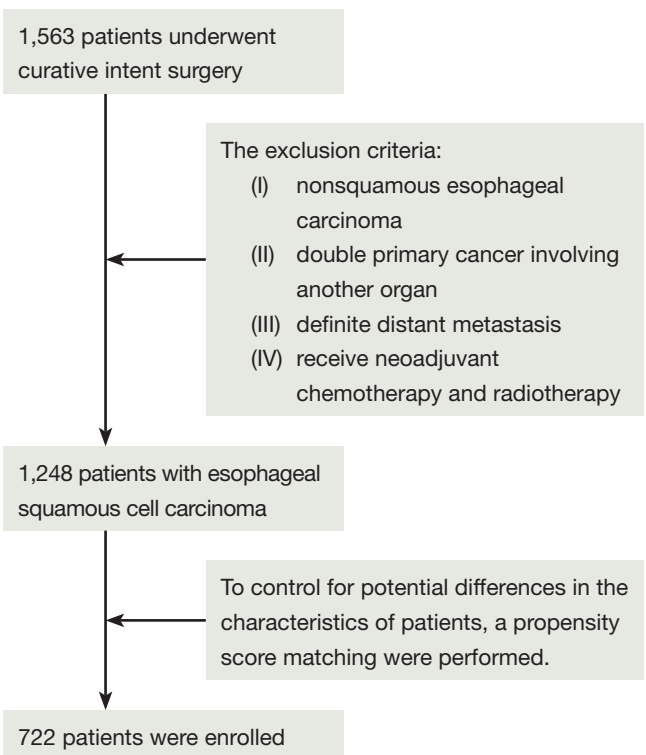

Figure 1 Reliable patients for inclusion.

Table 2 The basic clinical characteristics of patients in two study cohorts

Characteristics	Cohort one	Cohort two	Total
Age (years)	Cases [n]	Cases [n]	
Median [Range]	59 [27-78]	59 [33-80]	59 [27-80]
Sex			
Male	364	477	841 (67.4%)
Female	318	89	407 (32.6%)
Type of surgery			
Ivor Lewis	355	278	633 (50.7%)
Left transthoracic esophagectomy	22	82	104 (8.3%)
Tri-incisional esophagectomy	305	206	511 (41%)
Tumor location			
Upper	43	37	80 (6.4%)
Middle	425	323	748 (60%)
Lower	214	206	420 (33.6%)
Tumor invasion degree			
T1	85	79	164 (13.2%)
T2	183	163	346 (27.7%)
T3	414	324	738 (59.1%)
Tumor length (cm)			
≤5	595	488	1,083 (86.78%)
>5	87	78	165 (13.22%)
N classification			
N0	300	285	585 (46.9%)
N1	197	169	366 (29.3%)
N2	125	80	205 (16.4%)
N3	60	32	92 (7.4%)
Tumor differentiation			
Well	63	53	116 (9.3%)
Moderate	457	374	831 (66.6%)
Lower	162	139	301 (24.1%)
Pathological TNM stage			
I	61	63	124 (9.9%)
II	310	281	591 (47.4%)
III	311	222	533 (42.7%)

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection.

Table 3 The locoregional LN metastatic rates before propensity score-matching

	LN metastasis	Cohort one (n=682)		Cohort two (n=566)		P value
		Cases	Metastasitc rates (%)	Cases	Metastasitc rates (%)	
Neck	Cervival paraesophageal LNs	14	29.79% (14/47)	17	39.53% (17/43)	0.498
	Right supraclavicular LNs	34	16.59% (34/205)	22	22% (22/100)	0.345
	Left supraclavicular LNs	37	21.14% (37/175)	22	22% (22/100)	0.894
Upper mediastinum	Upper esophageal LNs	22	12.22% (22/180)	13	9.29% (13/140)	0.454
	Recurrent laryngeal nerve LNs	125	30.27% (125/413)	73	24.66% (73/296)	0.216
Middle mediastinum	Subcarinal LNs	52	11.71% (52/444)	35	10.12% (35/346)	0.524
	Mid-esophageal LNs	97	23.1% (97/420)	76	24.28% (76/313)	0.769
	Right hilar LNs	12	7.06% (12/170)	11	6.63% (11/166)	0.884
	Left hilar LNs	7	5.26% (7/133)	4	4.71% (4/85)	0.862
Lower mediastinum	Lower-esophageal LNs	79	21.29% (79/371)	66	21.15% (66/312)	0.971
	Diaphragmatic LNs	10	7.94% (10/126)	8	7.41% (8/108)	0.888
Upper abdomen	Lesser curvature LNs	69	28.51% (69/242)	43	23.37% (43/184)	0.360
	Paracardia LNs	84	37.5% (84/224)	59	28.64% (59/206)	0.167
	Left gastric artery LNs	68	27.42% (68/248)	37	27.41% (37/135)	0.998
	Celiac artery LNs	6	22.22% (6/27)	3	27.27% (3/11)	0.796
	Splenic artery LNs	5	9.26% (5/54)	2	11.76% (2/17)	0.786
	Common hepatic artery LNs	24	3.5% (24/682)	0	0	

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection. LN, lymph node.

the LN metastatic rate was 55.87%. Of all the LNMs, the paracardial LNs were the most frequently involved (37.5%), followed by recurrent laryngeal nerve LNs (30.27%) in cohort one. Whatever, only 24 patients had common hepatic artery LN metastasis, with the metastatic rate of 3.5% in cohort one (*Table 3*). Compared with other LNMs, the metastatic rate of common hepatic artery LN is the lowest. In addition, all the common hepatic artery LN metastasis was accompanied with locoregional metastasis.

Risk factors for common hepatic LNMs

In our study, the relationship between metastatic rates of common hepatic artery LN and clinicopathological factors were also analyzed (*Table 4*). Logistic regression analysis identified that tumor length (P=0.014), N classification (P<0.01) and pathological TNM stage (P<0.01) correlated with the occurrence of common hepatic artery LNMs. The common hepatic artery LN metastatic rates of patients with diameter of tumor under or equal 5 cm and 5 cm were 2.86% and 8.05%, with significant difference (P=0.014). The common hepatic artery LN metastatic rates of patients in N0, N1, N2 and N3 stage were 0%, 1.02%, 7.2% and 21.67%, with significant difference (P<0.01). The common hepatic artery LN metastatic rates of patients with stage I, II, III were 0%, 0.65% and 7.07%, significant difference was found (P<0.01).

Postoperative complications after propensity score-matching

After propensity score-matching, the postoperative complications were analyzed in *Table 5*. The percentage of overall complications were 118 patients (32.70%) in cohort one and 128 patients (35.45%) in cohort two (*Table 5*): including anastomotic leakage, infection of incison, gastrointestinal dysfunction, cardiovascular and cerebrovascular disease, chylothorax, pulmonary complication, injury of recurrent laryngeal nerve and atrial fibrillation, no significant difference was found (P=0.432). The overall incidence of anastomotic leakage in the cohort one was lower than that in the cohort two, although this difference was not statistically significant (P=0.054).

Discussion

In EC, the overall 5-year survival rate after surgical

Table 4 clinicopathological factors are associated with common hepatic artery LN metastasis in cohort one before propensity score-matching

Clinical pathologic factor	Cases (n)	Common hepatic artery LN metastasis case (%)	P vaule
Tumor location			
Upper	43	2.33	0.427
Middle	425	4.24	
Lower	214	2.34	
Tumor invasion degree			
T1a	1	0	0.413
T1b	84	2.38	
T2	183	5.46	
T3	414	2.89	
N classification			
N0	300	0	P<0.01
N1	197	1.02	
N2	125	7.2	
N3	60	21.67	
Tumor length (cm)			
≤5	595	2.86	0.014
>5	87	8.05	
Tumor differentiation			
Well	63	0	0.265
Moderate	457	3.72	
Lower	162	4.32	
pTNM stage			
I	61	0	P<0.01
II	310	0.65	
III	311	7.07	

LN, lymph node.

resection is between 70% and 92% for patients without nodal involvement, but only 18-47% for patients with LN metastasis (9-11). However, aggressive radical LN dissection may increase postoperative morbidity and mortality. The latest version of the UICC/AJCC TNM classification (7th edition) emphasizes the importance of LN metastasis for prognosis (12). Therefore, the extent of adequate LN dissection has again become a matter of debate recently (13,14). LN dissection in EC is an old topic, but still requiring discussions.

Chen and colleauges suggested that abdominal LN metastasis is not rare and is associated with poor survival (15). Abdominal LN dissection is a standard surgical procedure in thoracic EC, Shim *et al*. showed that for suitable people after preoperative evaluation, common hepatic artery LN dissection may be safely omitted (16).

In our retrospective study, the metastatic rate of celiac axis node involvement in thoracic EC is 22.2%. Seto *et al*. suggested that celiac axis nodes should be reclassified as regional LNs before the proposal of the new staging system (17). However, common hepatic artery LNs are located more distantly from the esophagus, and the metastatic rate of common hepatic artery LN was less frequent metastasis compared with celiac axis LNs and left gastric artery LNs (18), only 3.5% in our study and the left gastric artery LN metastatic rate is 27.42%. Furthermore, the celiac axis LNs can be dissected together with the left gastric artery LNs during gastric graft preparation. While the dissection of common hepatic artery node requires exposure of an additional surgical plane near the cisterna chyli and can result in complications such as chylous ascites (19,20). However, no case of chylous ascites was experienced in our institute among curative thoracic EC surgeries.

Among the 682 patients with esophageal thoracic squamous cell carcinoma, a total of 18,277 LNs were dissected, 24 had common hepatic artery LN metastasis, and the metastatic rate is the lowest compared with others (*Table 3*). Logistic regression analysis identified that tumor diameter (P=0.014), N classification (P<0.01) and pathological TNM stage (P<0.01) correlated with the occurrence of common hepatic artery LNMs. Rice *et al*. suggested that the depth of tumor invasion was associated with LNMs (21), but no significance difference was found between the tumor invasion and common hepatic artery LN metastasis in our study. For stage T1 tumors, common hepatic artery LN metastasis occurred in 2 (2.38%) of 84 patients with tumor infiltrating the submucosa (stage T1b), only one patient with tumor limited to the mucosa (stage T1a) was found, and no common hepatic artery LN metastasis was occurred (*Table 4*). When it comes to the tumor diameter, more studies are required. In our study, no common hepatic artery LN metastasis was found at stage I, while 2 patients and 22 patients was found at stage II and stage III. What about the postoperative complications between the cohorts? To control for potential differences in the characteristics of patients treated with common hepatic artery LN dissection or without common hepatic artery LN dissection, propensity score methods were used to compare the postoperative complications between the cohorts. The

Table 5 The postoperative complications of patients after propensity score-matching

Postoperative complications	Cohort one (n=361)		Cohort two (n=361)		P vaule
	Cases (n)	Percentage (%)	Cases (n)	Percentage (%)	
Overall complication	118	32.70	128	35.45	0.432
Anastomtic leakage	36	10.00	53	14.68	0.054
Infection of incision	13	3.60	18	4.98	0.359
Gastrintestinal dysfunction	13	3.60	19	5.26	0.278
Cardiovascular and cerebrovascular disease	12	3.32	10	2.77	0.665
Chylothorax	12	3.32	7	1.94	0.245
Pulmonary complication	19	5.26	15	4.16	0.482
Atelectasis or sputurn retention	2	0.55	2	0.55	1
ARDS	5	1.39	4	1.11	0.737
Pneumomitis	10	2.77	6	1.66	0.312
COPD aggravation	2	0.55	3	0.83	0.654
Injury of recurrent laryngeal nerve	3	0.83	1	0.28	0.316
Atrial fibrillation	10	2.77	5	1.39	0.192

Cohort one, esophagectomy with common hepatic artery lymph node dissection; Cohort two, esophagectomy without common hepatic artery lymph node dissection.

overall incidence of anastomotic leakage in the cohort one was lower than that in the cohort two, however, this difference was not statistically significant (P=0.054).

A number of limitations apply to the present study and interpretations should be made with caution. Firstly, this is a retrospective study at our institute; therefore, selection bias was unavoidable. However, propensity score-matching gives the present study the power to represent; Secondly, there were some variability in the experience and skill of individual surgeons.

In conclusion, the metastatic rate of common hepatic artery LN is low. Common hepatic artery LN may be safely omitted in esophagectomy for thoracic esophageal squamous cell carcinoma at stage I. Though LN dissection is an old topic, curtail unnecessary LN dissection is still the most important issues to be resolved for EC, and further accumulation of data and prospective studies are warranted in the future.

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