Factors predictive of prognosis after esophagectomy for squamous cell cancer

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Objective: To evaluate the prognosis after esophagectomy for squamous cell carcinoma of the thoracic esophagus and its prognostic factors.

Methods: Six hundred five patients with primary squamous cell carcinoma of the thoracic esophagus who underwent curative esophagectomy between June 1997 and June 1998 were collected from 3 medical centers. Among them, 26 patients died from the operation and 26 patients did not complete adjuvant treatment owing to toxicity. Univariate and multivariate analysis was performed to identify prognostic factors for survival. The effect of adjuvant treatment on survival was also evaluated.

Results: The 1-, 3-, 5-, and 10-year overall survivals of 605 patients were 90%, 65%, 36%, and 8%, respectively. Multivariate analysis identified the following as independent prognostic factors: number of lymph node metastases ($P < .001$), histologic differentiation ($P < .001$), tumor location ($P = .002$), depth of invasion ($P = .020$), and vascular invasion ($P = .023$).

Conclusions: Several pathologic characteristics of the primary tumor are correlated with the outcome of esophagectomy for squamous carcinoma of the thoracic esophagus. Patients with fewer than 2 metastatic nodes after curative esophagectomy have a better prognosis than those with multiple involved nodes (>2). To stratify patients appropriately for prognosis, it is necessary to refine the current 6th edition TNM staging system.

In China, there is an increased prevalence of esophageal cancer, most of which consists of squamous cell carcinoma (SCC). This is in contrast to the dominant trend toward adenocarcinoma in the Western world. The long-term outcomes for selected patients undergoing multimodality treatment, which combines surgery with chemotherapy and radiation, are promising. In this study, we collected data on 605 patients who had received multimodality therapy for esophageal cancer from 3 regional medical centers and retrospectively evaluated outcomes to identify prognostic factors leading to improved survival.[1]

PATIENTS AND METHODS

From June 1997 to June 1998, 712 patients with primary SCC of the thoracic esophagus were admitted to our regional thoracic surgical centers (Jiangsu Province Tumor Hospital, Jiangsu Province People's Hospital [Nanjing Medical University] and Nanjing Jiangbei People's Hospital [Dongnan University]). Among them, 605 patients underwent en bloc radical esophagectomy through a left thoracotomy, with a 2-field lymph node dissection in the mediastinum and upper abdomen. Reconstruction consisted of a gastric tube placed through the posterior mediastinum, and esophagogastrostomy was performed via a left cervical incision.

Postoperatively, the pathologic status of the resected tumors was evaluated to determine the need for adjuvant treatment. Patients with superficial cancer and no lymph node involvement underwent no further treatment. Those with tumor invading past the submucosa or with lymph node involvement were routinely administered chemotherapy and radiation. Chemotherapy consisted of 2 cycles: a bolus administration of cisplatin (20 mg/m^2 per day) occurred on days 1 to 3, and fluorouracil (500 mg/m^2 per day) was given as a continuous infusion over 24 hours on days 1 to 5. Postoperative radiotherapy was administered by linear accelerators with 10- to 15-MV photons. Radiotherapy was simulated to encompass a tumor volume with 5-cm cephalocaudad margins and 2-cm radial margins. Treatment ports were designed to encompass enlarged regional nodes and metastatic nodal beds based on preoperative computed tomographic evaluation and postoperative pathologic examination. Radiation was delivered in daily fractions of 1.8 Gy with a total dose of 50 to 60 Gy using a multiple-field technique.

Pathologic examination of the resected surgical specimens followed a standardized protocol. First, 4-μm sections of the tumor were stained with hematoxylin and eosin. The total number of lymph nodes resected and the number of lymph nodes involved with tumor were recorded. Vascular invasion was defined as infiltration of vessels or the presence of tumor emboli. Resection was considered microscopically incomplete when tumor cells were present less than 1 mm from the plane of resection (ie, the circumferential margin). The degree of tumor differentiation was classified as well, moderately, and poorly differentiated. Tumor staging occurred according to the pTNM system established by the International Union Against Cancer (UICC) in 2002 (6th edition).[1]

Postoperative patients were surveyed every 3 months by physical examination, every 6 months by imaging (computed tomographic scan and abdominal ultrasound), and every year by esophagoscopy. The study protocol was approved by the regional institutional review board. All patients provided written informed consent.

Statistical Methods

Continuous data were presented as mean values with standard deviations (mean ± SD). Means were compared with the Mann–Whitney test.

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Abbreviations and Acronyms

pM = presence of metastasis
pN = lymph node metastases
pT = depth of tumor invasion
SCC = squamous cell carcinoma
UICC = International Union Against Cancer

Categorical data were compared with a χ^2 test (with the Yates correction) or the Fisher exact test. Follow-up continued until December 2007 or death if earlier. Overall survival was evaluated by the Kaplan–Meier method and included perioperative deaths. Overall survivals were compared by the log–rank test. Multivariate analyses were performed by Cox regression. To evaluate the optimal cutoff point for the number of involved nodes as a predictor for survival, we delineated the relationship between the number of positive nodes and survival using a scatterplot of the variable versus Martingale residuals from a Cox proportional hazards regression model without the variable of interest. A smoothed fit of the scatter was then applied to detect the optimal cutoff point.[2]

All statistical tests were 2-sided. Statistical significance was set at the 5% level. Calculations were performed with SPSS version 12.0.1 (SPSS, Inc, Chicago, Ill).

RESULTS

A total of 605 patients (male/female: 512/93; age: 63.0 ± 9.3 years) underwent en bloc radical esophagectomy. The median length of hospital stay was 15.8 days (range 10–156 days), and 26 (4.3%) patients died as a result of the operation (male/female: 23/3; age: 63.7 ± 11.9 years). Another 26 patients (male/female: 21/5; age: 58.8 ± 12.5 years) did not complete adjuvant therapy owing to nephrotoxicity, gastrointestinal adverse reactions, and myelosuppression. Therefore, the other 553 patients (male/female: 468/85; age: 61.2 ± 10.1 years) completed the proposed chemoradiation treatment.

Overall Survival

Follow-up was complete for all 605 patients. The median follow-up was 47.0 months. At the time of this analysis, the 1-, 3-, 5-, and 10-year overall survivals of the 605 patients were 90%, 65%, 36%, and 8%, respectively, with a median survival of 79.2 months.

The 1-, 3-, 5-, and 10-year disease-specific survivals for stage 0 (n = 30) were 100%, 100%, 90%, and 80%; for stage I (n = 78), 99%, 95%, 85%, and 58%; for stage IIa (n = 111), 99%, 88%, 65%, and 34%; for stage IIb (n = 165), 95%, 73%, 48%, and 18%; for stage III (n = 185), 92%, 67%, 44%, and 9%; and for stage IV (n = 36), 85%, 35%, 19%, and 0 (log–rank test; $P < 0.001$) (Figure 1).

Factors Influencing Survival

Apart from pT (depth of tumor invasion), pN (lymph node metastases), and pM (presence of metastasis), univariate analysis identified the following variables as significant predictors of survival: tumor location, histologic differentiation, vascular invasion, and number of lymph node metastases (Table 1). Age, gender, tumor length, total number of

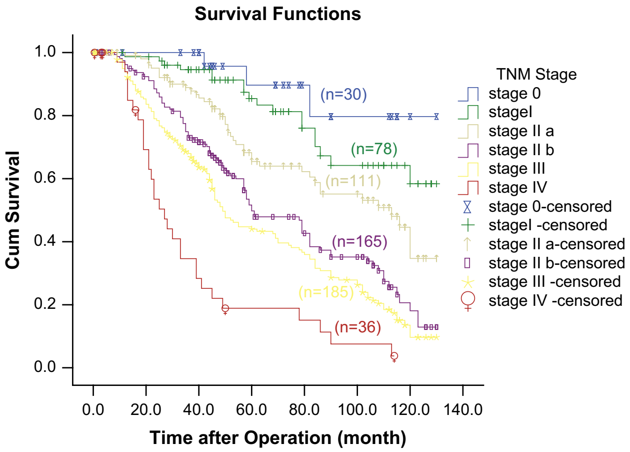

FIGURE 1. Cumulative disease-specific survival curves in terms of tumor pTNM stage. Median survival time for patients with stage 0 (n = 30), stage I (n = 78), stage IIa (n = 111), stage IIb (n = 165), stage III (n = 185), stage IV (n = 36) were 130.0, 130.0, 112.4, 60.8, 49.7, and 26.2 months, respectively (log–rank test, $P < .001$).

TABLE 1. Clinicopathologic features influencing disease-specific survival of 605 patients

Variable	No.	Survival (%) 1 y	3 y	5 y	10 y	P
Depth of invasion*						
pTis	30	100	100	90	80	<.001
pT1	139	98	90	74	51	
pT2	171	96	77	57	29	
pT3	164	94	68	42	8	
pT4	101	88	58	37	8	
Tumor location						
Upper	175	92	59	33	13	<.001
Middle	227	96	78	57	23	
Lower	203	96	86	68	31	
Histologic differentiation						
Well	164	96	88	75	44	<.001
Moderate	159	94	79	62	32	
Poor	189	94	69	41	13	
Undifferentiated	93	94	55	29	0	
Vaso-invasive growth						
Not marked	364	96	79	58	31	<.01
Marked	241	92	69	49	11	
No. of lymph node metastases						
0	156	99	93	77	43	<.001
1~2	239	97	82	63	23	
3	87	91	74	41	0	
>3	123	88	39	12	0	

*Classification of primary tumor and TNM staging according to TMN classification (6th edition, 2002).

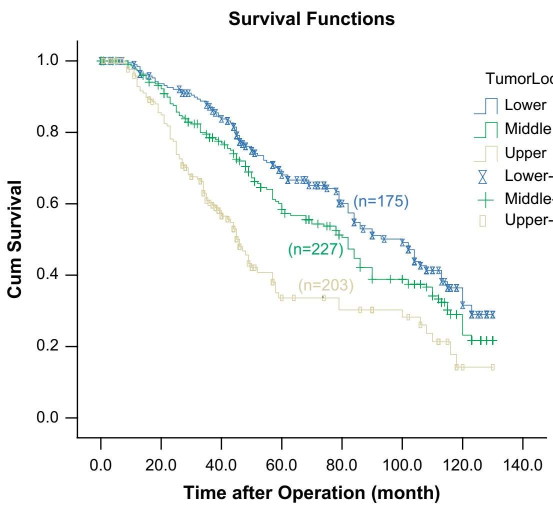

FIGURE 2. Cumulative disease-specific survival curves in terms of tumor location. Median survival time for patients with upper thoracic cancer (n = 175), middle thoracic esophageal cancer (n = 227), and lower thoracic esophageal cancer (n = 203) were 45.9, 82.2, and 93.8 months, respectively (log–rank test, $P < .001$).

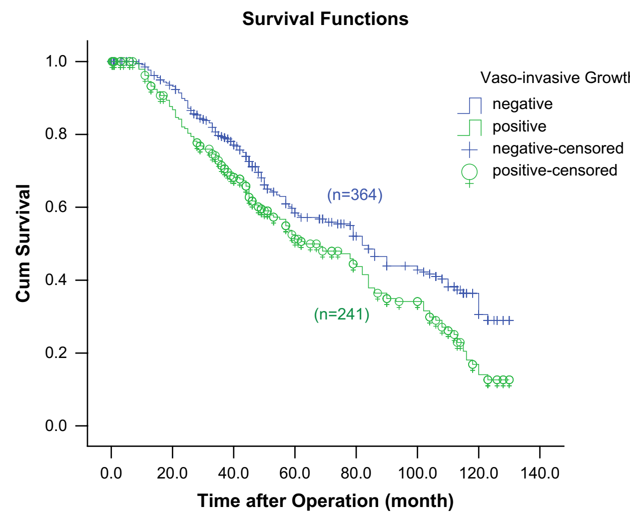

FIGURE 4. Cumulative disease-specific survival curves in terms of vaso-invasive growth of tumor. Median survival time for patients with negative (n = 358) and positive (n = 247) were 84.6 and 61.3 months, respectively (log-rank test; $P < .01$).

dissected lymph nodes, and time of operation did not influence the survival (data not shown).

Cumulative disease-specific survival curves in terms of tumor location, histologic differentiation, and vascular invasion are shown in Figures 2, 3 and 4, respectively. So that the optimal cutoff point for the number of positive lymph nodes could be determined, the Martingale residuals of the Cox model were first calculated and then plotted against the number of positive nodes (not shown). The cutoff value was 3 positive nodes. Subdivision of pN stage into 4 groups based on the number of positive nodes (0, 1–2, 3, and ≥4 nodes positive) showed significant differences in disease-specific survival. For these groups, median survival times were 119.7 (n = 156), 90.4 (n = 239), 51.6 (n = 87), and 32.7 (n = 123) months, respectively (log–rank, $P < .001$). Figure 5 shows that patients with 2 involved lymph nodes or fewer have a longer disease-specific survival than do those with more significant nodal disease (≥3 positive nodes).

Multivariate analysis identified the following as independent prognostic factors: the number of lymph node metastases ($P < .001$), histologic differentiation ($P < 0.001$), tumor location ($P = .002$), depth of invasion ($P = .020$), and vascular invasion ($P = .023$) (Table 2).

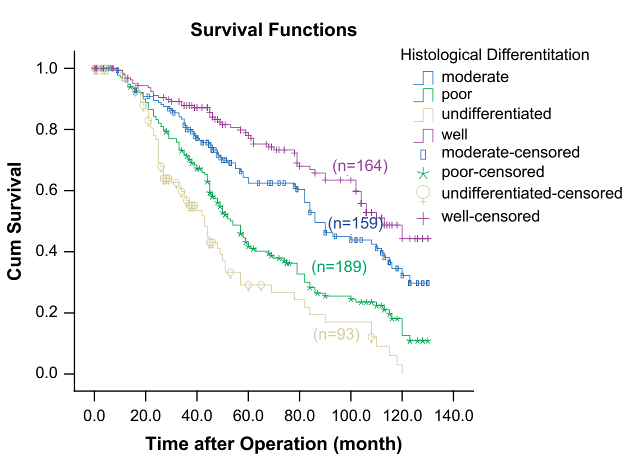

FIGURE 3. Cumulative disease-specific survival curves in terms of histologic differentiation of tumor. Median survival time for patients with well (n = 164), moderate (n = 159), poor (n = 189), and undifferentiated (n = 93) were 111.6, 86.7, 54.0, and 43.1 months, respectively (log–rank test; $P < .001$).

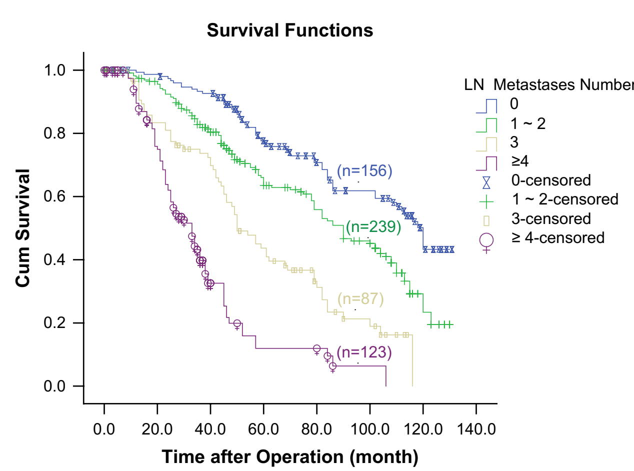

FIGURE 5. Cumulative disease-specific survival curves in terms of number of lymph node *(LN)* metastases (log–rank test; $P < .001$).

TABLE 2. Multivariate analysis of prognostic factors for disease-specific survival by the Cox proportional hazard model

Parameter*	Coefficient	*P*	Hazard	95% CI
Tumor location	–.243	.002	.784	0.674–0.911
Depth invasion	.183	.020	1.201	1.030–1.401
Involved lymph node	.373	<.001	1.453	1.359–1.553
Histologic differentiation	.502	<.001	1.653	1.480–1.845
Vasoactive growth	.261	.023	1.298	1.037–1.625

CI, Confidence interval. *Parameters are categorized in Table 1.

Additional multivariate analysis was performed, including the TNM stage of the disease as a covariate. We excluded the pT factor and the number of involved lymph nodes for a more appropriate analysis of independent prognostic factors. In this additional analysis, vascular invasion no longer appeared as an independent prognostic factor for increased survival ($P = .073$).

To investigate the role of postoperative chemoradiation on survival after esophagectomy, we excluded the 26 patients who died perioperatively. The remaining 579 patients were divided into 3 groups: those who completed adjuvant treatment after surgery (n = 449), those who did not complete adjuvant treatment (n = 26), and those for whom adjuvant treatment was not recommended owing to early disease (n = 104). Figure 6 shows the improved survival in the group who completed adjuvant treatment, in contrast to that in the group who did not complete treatment.

DISCUSSION

Radical esophagectomy has become the standard surgical procedure to achieve an accurate pathologic staging for patients with esophageal cancer,[3,4] but the long-term outcomes are not necessarily satisfactory according to the UICC–TNM staging.[4,5] In this study, we collected a well-defined homogeneous cohort of 605 patients with SCC of the thoracic esophagus and evaluated the long-term outcomes to identify prognostic factors. Given that the data were retrospective, our conclusions are limited. Our findings are interpreted within the context of existing published data.

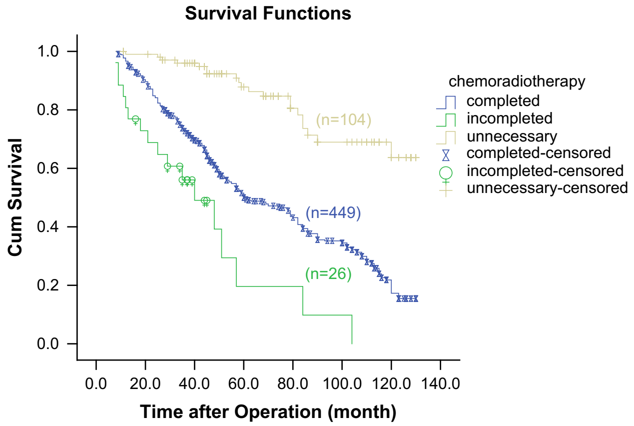

FIGURE 6. Cumulative disease-specific survival curves in terms of postoperative adjuvant radiochemotherapies for the patients with SCC of the thoracic esophagus (n = 579). The 1-, 3-, 5- and 10-year disease-specific survivals for the unnecessary postoperative radiochemotherapy patients (n = 104) were 99%, 96%, 88%, and 63%; for the completed postoperative radiochemotherapy patients (n = 449) were 95%, 72%, 49%, and 17%; and for the incompleted patients (n = 26) were 77%, 56%, 20%, and 0; respectively (log–rank [Mantel–Cox]; $P < .001$).

Esophageal Cancer Located in the Upper Thorax Is an Unfavorable Prognostic Factor

One hundred twenty-nine of 175 patients with upper thoracic cancer who died had locoregional recurrences in the upper mediastinum despite extensive lymphadenectomy. Locoregional recurrence consisted of progression of mediastinal nodal disease, including direct invasion into the tracheobronchial trees. More meticulous lymphadenectomy around the tracheobronchial trees and bilateral recurrent laryngeal nerves may be important to improve the outcomes of these patients.[3]

Patients with Esophageal Cancer Achieved Improved Survival after Multimodality Therapy

All 605 patients underwent left thoracotomy with 2-field lymph node dissection in the mediastinum and upper abdomen. Including those patients who underwent adjuvant chemoradiation, the 3- and 5-year overall survivals were 65% and 36%. Previous studies in the existing literature show excellent results with a surgical approach that includes 3-field lymphadenectomy. Such an approach likely has the highest chance of tumor clearance,[5,6] but this is at the expense of increased morbidity and mortality and poorer postoperative quality of life.[4] Our study suggests that patients who successfully completed adjuvant treatment had an increased survival compared with those who did not complete the treatment. Randomized studies with larger cohorts of patients are needed to further evaluate the effect of adjuvant chemoradiation.

UICC–TNM Staging of Esophageal Cancer Needs to be Refined

The TNM system for classifying the anatomic extent of disease in cancer has been in existence for more than 50 years. In this study, we evaluated additional prognostic factors in a homogeneous group of patients with esophageal cancer treated by multimodality therapy. Our study confirmed that the pT and pN stages according to the 6th edition UICC–TNM staging model are indeed important predictors of survival.

However, there is ongoing debate about the need for revision of the current guidelines, driven by surgeons who believe that the current system does not accurately stratify patients for prognosis.[7-9] Recently, the UICC–TNM committee decided to establish guidelines for the submission and evaluation of proposed changes to the TNM system.[10]

In our study, other pathologic characteristics of the primary tumor, including tumor location, histologic differentiation, and vascular invasion, were shown to correlate with outcome. Such pathologic criteria as histologic differentiation and vascular invasion represent the biological property of the tumor and should be considered in the modified staging system.

Moreover, survival is influenced not only by the presence or absence of involved lymph nodes (pN0 vs pN1) but also by the number of positive nodes. In our study, subdivision of pN1 tumors into pN1∼2, pN3, and pN≥4 had significant differences in survival. These findings are similar to observations made by Rice and associates,[7] who subclassified their node-positive patients as N1 (≤2 metastatic nodes) and N2 (≥3 metastatic nodes) on the basis of significantly different survivals. Generally, patients with more advanced nodal disease had worse survival than those with less nodal disease (eg, 1–3 vs ≥4, 1–4 vs ≥5).[5,11] Published studies thus far differ in the calculations by which the optimal cutoff for the number of positive nodes is determined. By calculating the Martingale residuals, we found that the cutoff should be 3 positive nodes. The patients with fewer than 2 metastatic nodes had improved long-term survival; this was an independent and favorable prognostic factor. Similar data have been reported for adenocarcinoma of the esophagus.[12] Thus, patients with fewer than 2 metastatic nodes after esophagectomy have an improved prognosis compared with those with more advanced nodal disease. This suggests that more aggressive adjuvant therapy may be the key to improve the survival of patients with multiple lymph node metastases.

Within the group of patients with positive locoregional nodes, a further subdivision can be made on the basis of the number of positive nodes divided by the total number of resected nodes, also known as the lymph node ratio.[13,14] Various lymph node ratios have been proposed[13-15] owing to differences in the techniques of lymphadenectomy and the total number of resected nodes.[2] In our patients, lymph node dissection includes the superior, middle, and inferior mediastinum and around the splenic, celiac, and hepatic arteries. About 10 to 17 nodes (a median number of 14) were resected for each patient. The total number of resected nodes was not associated with differences in overall survival. Thus this may suggest that lymph node ratio may not be an independent factor. However, more studies are needed to confirm this finding.

So that patients can be better stratified according to prognosis, the current 6th edition TNM staging system for esophageal cancer must be revised. We would suggest that pathologic criteria such as histologic differentiation and vascular invasion be incorporated into the new staging system inasmuch as our study showed these to be independent prognostic factors in patients who underwent multimodal treatment of esophageal cancer. We look forward to the modification of the UICC–TNM staging system with clinicopathologic variables that are confirmed to be independent prognosticators in further studies and large randomized trials.

CONCLUSION

Several pathologic characteristics of the primary tumor are correlated with differences in long-term outcomes after esophagectomy for SCC of the thoracic esophagus. Patients with fewer than 2 metastatic nodes after radical esophagectomy have a better prognosis than those with multiple involved nodes (>2).

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