Adjuvant chemoradiotherapy for patients with pathologic node-positive esophageal cancer following radical resection is associated with improved survival

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Background: Depending on the pathological stage, patients with esophageal squamous cell carcinoma (ESCC) can experience poor prognosis after surgery. This study was designed to analyze the effect of various treatments on prognosis in pathologic node-positive esophageal cancer patients who undergo radical surgery.

Methods: We evaluated 210 pathologic stage IIb–IIIc patients (pT1-4aN + M0) who had undergone esophagectomy for thoracic ESCC from January 2013 to October 2015 at our institute. Surgery alone was applied in 65 patients, postoperative chemotherapy alone was applied in 112 patients, and postoperative adjuvant chemoradiotherapy was applied in 33 patients. Kaplan-Meier and Cox regression analysis were used to compare overall survival (OS) and disease-free survival (DFS). A nomogram was constructed to visualize the multivariate Cox regression analysis model.

Results: The median follow-up period was 49.4 months. The 3- and 5-year OS rates of the patients in the surgery group, postoperative chemotherapy group, postoperative chemoradiotherapy group were 55.4%, 61.6%, and 75.8%, and 30.1%, 44.0%, and 63.0% respectively. The 3- and 5-year DFS rates of the patients in the surgery group, postoperative chemotherapy group, postoperative chemoradiotherapy group were 44.6%, 52.7%, and 72.7%, and 20.0%, 24.1%, and 39.4%, respectively. Both the OS and DFS of the patients in the postoperative chemoradiotherapy group were better than those of the patients in the surgery and postoperative chemotherapy group. Among them, the OS of the postoperative radiotherapy group was longer than that of the surgery group (P=0.011) and the postoperative chemotherapy group (P=0.190), while the DFS of postoperative chemoradiotherapy group was longer than that of the surgery group and postoperative chemotherapy group, but the difference was not statistically significant (P>0.05).

Conclusions: This study showed that postoperative adjuvant chemoradiotherapy could improve 3-year OS and DFS compared with treatment using surgery alone or postoperative chemotherapy alone. However, an evaluation of long-term prognosis requires a longer follow-up.

Keywords: Esophageal squamous cell carcinoma (ESCC); chemoradiotherapy; chemotherapy; esophageal surgery

Submitted Jun 03, 2020. Accepted for publication Oct 22, 2020.
doi: 10.21037/atm-20-4893
View this article at: http://dx.doi.org/10.21037/atm-20-4893

Introduction

Esophageal cancer is a malignant tumor characterized by higher morbidity and mortality, and is responsible for an annual 572,000 new cases and 509,000 deaths worldwide (1). In China, esophageal squamous cell carcinoma (ESCC) is the most common histologic type of esophageal cancer (2). Esophageal squamous cell carcinoma (ESCC) is usually diagnosed at a locally advanced stage. Despite the significant progress in its comprehensive treatment in recent years, its prognosis is still not satisfactory, and the reported 5-year survival rate is between 29.3% and 38.2%, with an even worse rate for patients with tumors involving the lymphatic system (3-5).

Neoadjuvant approaches have become increasingly used for esophageal carcinoma, which proved to improve prognosis (6). However, only a few clinical studies have reported the value of postoperative adjuvant treatment for patients undergoing radical esophagectomy (7-9). Moreover, the patients in those retrospective studies usually did not receive the same chemotherapy or radiotherapy regimen, which might cause bias (5,7,10). Thus far, the most appropriate treatment modality for pathologic node-positive esophageal cancer, especially for squamous cell carcinoma, is still not well established. Therefore, an analysis of the various treatment strategies as potential prognostic factors for survival, including an assessment of operative procedures and postoperative adjuvant treatment, is essential.

The purpose of this clinical study was thus to focus on the prognostic factors which are favorable for survival and to identify the most beneficial adjuvant treatment available.

We present the following article in accordance with the Tripod reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4893).

Methods

Patients

We retrospectively collected the clinical data and follow-up results of 506 thoracic ESCC patients who were admitted to the Thoracic Department of Fujian Medical University Union Hospital and accepted surgical treatment from January 2013 to October 2015. The study's inclusion criteria were the following: (I) patients who received a radical (R0) resection surgery with two- or three-field lymphadenectomy; (II) patients who did not receive any neoadjuvant therapy, such as preoperative radiotherapy or chemoradiotherapy, before the surgery; (III) patients who were ESCC pathological type; (IV) patients who were confirmed to have lymphatic metastasis by postoperative pathology. The study's exclusion criteria were the following: (I) patients who were unanalyzable due to incomplete follow-up information, (II) who had a diagnosis of multiple primary malignant neoplasms, or (III) who had serious basic disease. *Figure 1* provides a flow diagram of the sequential exclusions used to create the cohort. We defined pathological stage according to the seventh edition of the Union for International Cancer Control esophageal cancer staging system (11). This single-institution, retrospective study was approved by the institutional review board of Fujian Medical University Union Hospital (No. 2015KY021) and informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Surgery

Before the operation, patients were intubated with a common single-lumen tube without bronchial blocker, and turned to the semi-prone-position. The majority of patients went through radical minimally invasive esophagectomy which consisted of a right thoracotomy with two-field lymphadenectomy and gastric tube reconstruction. We performed a two-field lymph node dissection of all the patients and added a cervix node dissection depending on the frozen pathological results of lymph nodes along the right recurrent laryngeal nerve or preoperative imaging.

Postoperative treatment and follow-up

The postoperative adjuvant chemotherapy included cisplatin (75 mg/m^2 on day 1, completing at least 4 chemotherapy cycles, with 21 days as 1 cycle). The postoperative adjuvant chemoradiotherapy included: (I) chemotherapy included cisplatin (75 mg/m^2 on day 1, completing at least 4 chemotherapy cycles, with 21 days as 1 cycle); (II) radiotherapy: the clinical target volume contained both tumor area and high-risk lymphatic drainage area. Radiation mode and dose: target area was given a total dose of 50.4 Gy over 5 to 6 weeks by intensity modulated radiation therapy (IMRT). In the postoperative adjuvant chemoradiotherapy group, radiotherapy was performed concurrently with chemotherapy. The first examination was routinely performed 4 weeks after surgery, at 3- to 6-month intervals for 2 years and at 12-month intervals thereafter.

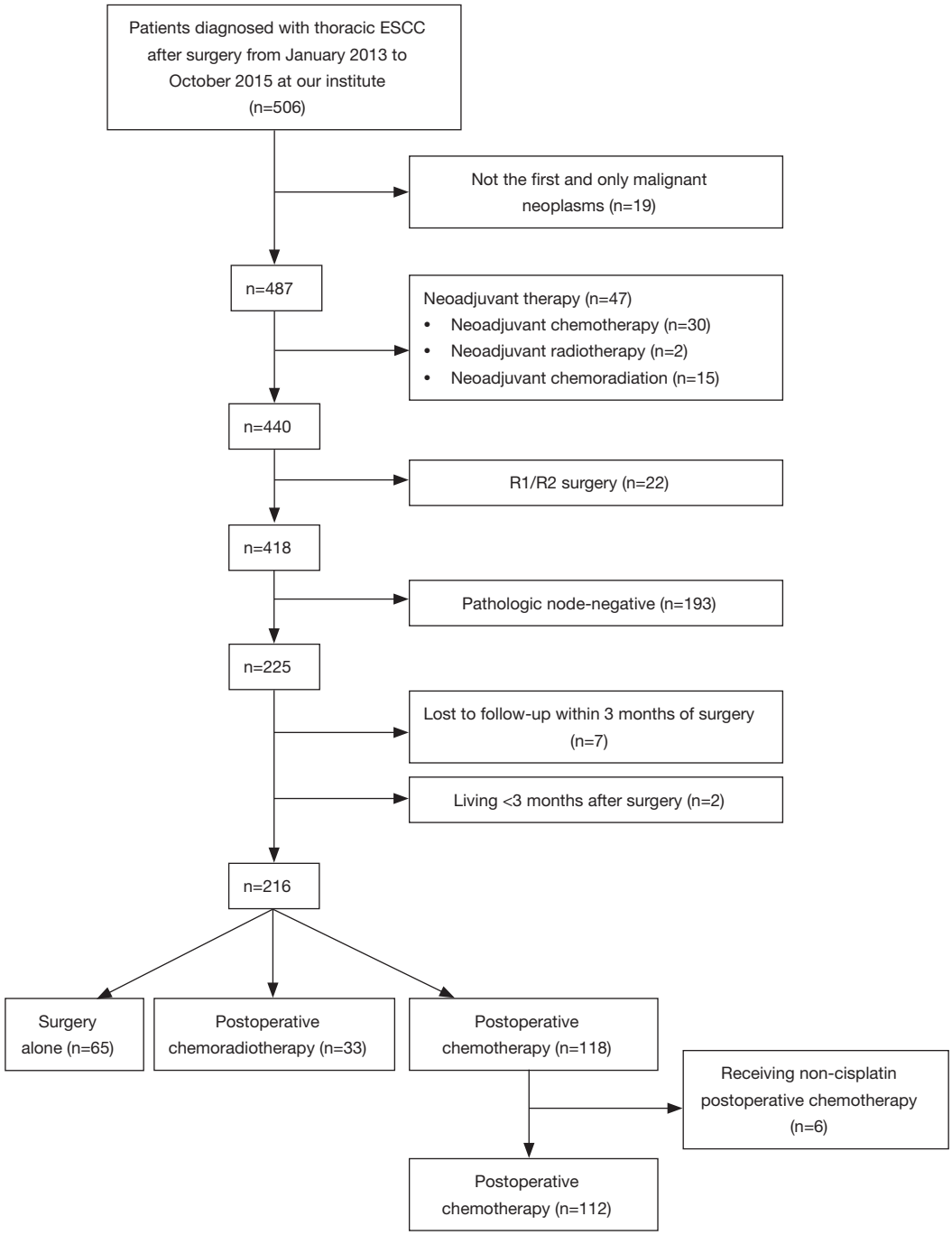

Figure 1 Flow diagram of pathologic node-positive thoracic ESCC patients after radical resection from January 2013 to October 2015. ESCC, esophageal squamous cell carcinoma.

Throughout the follow-up period, the patients underwent examination, including ultrasonography (US) of the neck and abdomen, and computed tomography (CT) of the neck, thorax, and abdomen once a year. Bone scintigraphy, positron emission tomography (PET), and head enhanced magnetic resonance imaging (MRI) were performed on the basis of clinical symptoms, clinical signs, and chemical analysis results. Locoregional, lymph node recurrence was considered tumor recurrence, while organ or hematogenous metastasis was considered tumor metastasis. Overall survival (OS) was defined as the time from the date of surgery to death or to the date of the last follow-up. Disease-free survival (DFS) was defined as the time from the date of surgery to the time of recurrence or to the date of the last follow-up. The patients who could not be contacted were considered lost to follow-up.

Statistical analysis

Baseline patient characteristics and postoperative outcomes were compared using analysis of variance for continuous variables and Chi-square test for discrete variables (12). The primary outcome was OS and DFS which were evaluated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate Cox proportional hazard regression was performed to find the association between the clinicopathologic characteristics and OS, and to identify the prognostic parameters for survival. Statistically significant variables (P<0.05) from the multivariate Cox regression analysis were entered into the nomograms. The scheme of nomogram was drawn using R with the rms package. Calibration curves were plotted to assess the agreement between the actual survival and the predicted survival at 3 years in the primary cohort. All the data obtained from this study were analyzed with the aid of SPSS version 22.0 and R version 2.8.1 (R foundation for Statistical Computing). A P value of <0.05 was considered statistically significant for all procedures.

Results

Patient's characteristics

Table 1 presents the characteristics of 210 patients. The final cohort included 210 patients who underwent esophagectomy without neoadjuvant therapy with pathologic node-positive esophageal cancer. Among them, 65 patients were treated with surgery alone (group S), 112 received postoperative chemotherapy alone following surgery (group CT), and 33 underwent postoperative adjuvant chemoradiotherapy (group CRT). The patient characteristics of the three groups were found to be comparable. In total, 164 (78.1%) patients were male, and the median age of all patients was 58.2 years. A total of 120 (57.1%) patients had a history of smoking, and the same number had a history of alcohol consumption. Almost all patients (97.6%) underwent thoracoscopic surgery, and 155 persons were treated with two-field lymphadenectomy. The median number of harvested lymph nodes of all patients was 35.1, and the median number of positive lymph nodes was 3.38, but neither was statistically significant across the three groups.

Survival

The median follow-up time was 49.4 months. The 1-, 3-, and 5-year OS rates of the patients in the surgery group were 92.3%, 55.4%, and 30.1%, respectively. The 1-, 3-, and 5-year OS rates of the patients in the postoperative chemotherapy group were 92.0%, 61.6%, and 44.0%, respectively. The 1-, 3-, and 5-year OS rates of the patients in the postoperative chemoradiotherapy group were 97.0%, 75.8%, and 63.0%, respectively. The OS of the patients in the postoperative chemoradiotherapy group was significantly better than that of the patients in the surgery-alone and postoperative chemotherapy group (P=0.027, *Figure 2*), with further statistical significance found between group S and group CRT. The 1-, 3-, and 5-year DFS rates of the patients in the surgery group were 81.5%, 44.6%, and 20.0%, respectively. The 1-, 3-, and 5-year DFS rates of the patients in the postoperative chemotherapy group were 81.3%, 52.7%, and 24.1%, respectively. The 1-, 3-, and 5-year DFS rates of the patients in the postoperative chemoradiotherapy group were 93.9%, 72.7%, and 39.4%, respectively. The DFS of the patients in the postoperative chemoradiotherapy group was better than that of the patients in the surgery and postoperative chemotherapy group, but the difference was not statistically significant. (P>0.05, *Figure 3*). In addition, we found no significant difference in OS or DFS between the surgery and postoperative chemotherapy group.

Independent prognostic factors and nomogram model

The univariate Cox regression analyses indicated that age (<60 *vs.* ≥60), history of cigarette smoking, postoperative

Table 1 Characteristics of 210 thoracic ESCC patients included in the study

Variable	Total, n=210	S group, n=65	CT group, N=112	CRT group, N=33	P value
Age, years	58.28±8.30	59.68±8.18	57.59±8.62	57.85±7.23	0.259
<60 years old	118	32	68	18	0.325
≥60 years old	92	33	44	15	
Gender					0.584
Male	164	48	89	27	
Female	46	17	23	6	
Comorbidity					0.667
Yes	44	14	25	5	
No	166	51	87	28	
History of cigarette smoking					0.629
Yes	90	31	46	13	
No	120	34	66	20	
History of alcohol consumption					0.687
Yes	90	25	50	15	
No	120	40	62	18	
Surgery approach					0.849
VATS	205	63	109	33	
Open surgery	5	2	3	0	
Site of the esophagogastric anastomosis					0.341
Thoracic cavity	12	5	4	3	
The left neck	195	58	107	30	
The right neck	3	2	1	0	
The range of lymph node dissection					0.239
Mediastinal + abdominal	155	44	88	23	
Mediastinal + abdominal + cervical	55	21	24	10	
BMI	21.67±3.27	20.99±2.78	22.03±3.63	21.78±2.68	0.123
Tumor location					0.041
Upper one-third	11	4	3	4	
Middle one-third	144	44	84	16	
Lower one-third	55	17	25	13	
Pathologic T category					0.104
1	32	5	22	5	
2	22	3	14	5	
3	145	53	71	21	
4	11	4	5	2	

Table 1 (*continued*)

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Variable	Total, n=210	S group, n=65	CT group, N=112	CRT group, N=33	P value
Pathologic N category					0.242
1	98	32	53	13	
2	90	30	43	17	
3	22	3	16	3	
Pathologic TNM stage					0.206
IIb	30	5	22	3	
IIIa	85	27	43	15	
IIIb	66	26	29	11	
IIIc	29	7	18	4	
Differentiation					0.318
Well (G1)	59	18	36	5	
Moderate (G2)	122	40	59	23	
Poor or undifferentiated (G3 or Gx)	29	7	17	5	
Number of harvested lymph nodes	35.61±12.58	35.51±14.02	34.87±11.85	38.33±11.97	0.380
Number of positive nodes	3.38±2.88	2.98±2.14	3.46±3.03	3.88±3.54	0.317
Postoperative complications					
Anastomotic fistula					0.881
Yes	16	6	8	2	
No	194	59	104	31	
Pulmonary infection					0.524
Yes	61	22	29	10	
No	149	43	83	23	
Chylothorax					0.888
Yes	8	3	4	1	
No	202	62	108	32	
Cardiovascular complications					0.465
Yes	26	10	14	2	
No	184	55	98	31	
Postoperative hospital stay (days)	14.33±7.33	14.98±8.75	14.06±6.94	13.97±5.43	0.690

ESCC, esophageal squamous cell carcinoma; Group S, surgery-only group; group CT, postoperative chemotherapy group; group CRT, postoperative chemoradiotherapy group.

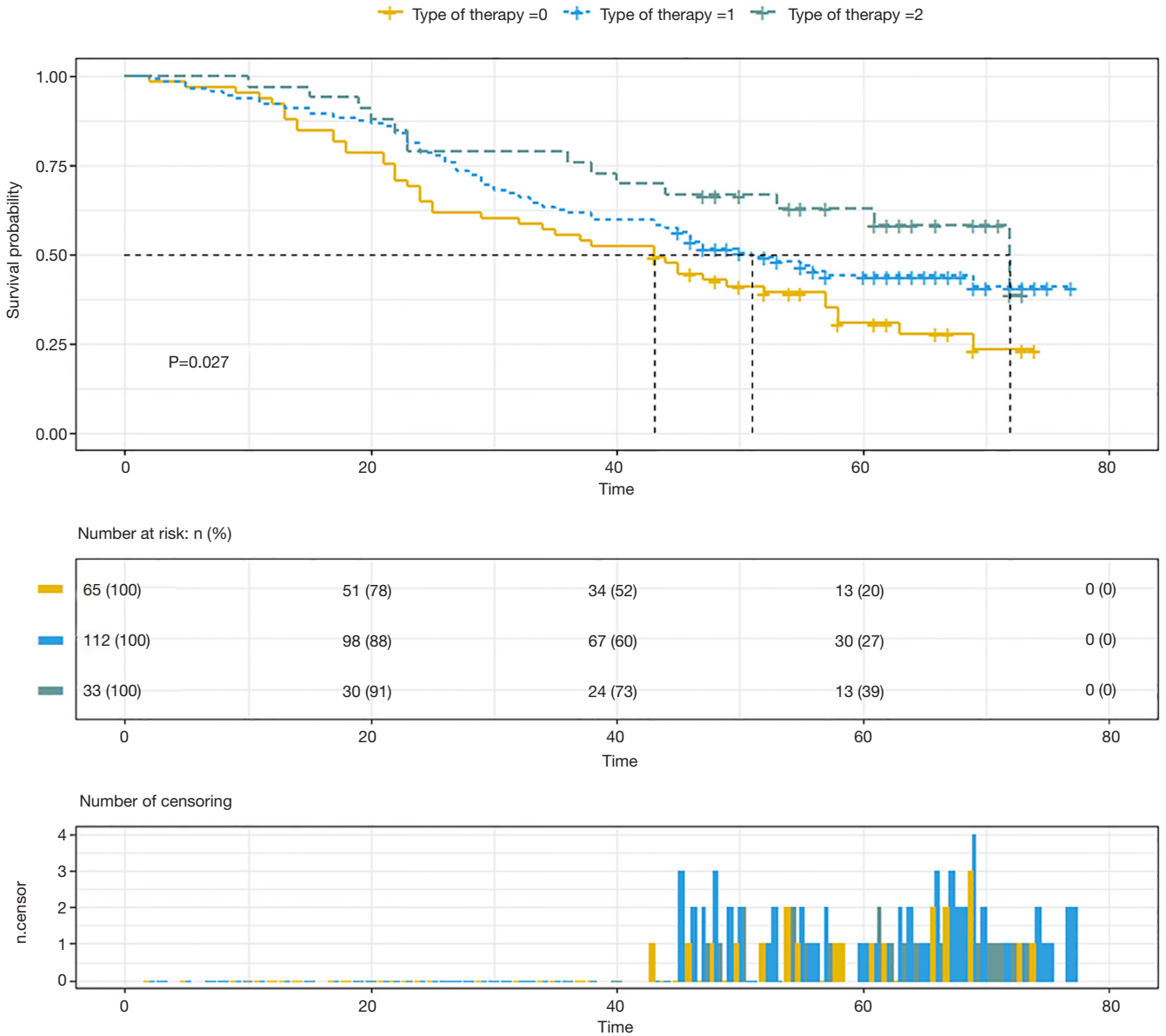

Figure 2 Comparison of OS among the three groups. OS, overall survival.

therapy, pathologic T category, pathologic N category, tumor differentiation, and surgery approach were significantly associated with survival. The results of the univariable analysis are listed in *Table 2*. All significant factors in the univariable analysis were used in the multivariate Cox proportional hazard regression analysis. Age (<60 *vs.* ≥60), a history of cigarette smoking, postoperative therapy, pathologic T category, pathologic N category, and tumor differentiation remained independent prognostic factors in the Cox model (*Table 2*). *Figure 4* is a nomogram derived from this model and depicts the predictive factors for OS; meanwhile, the calibration plots in *Figure 5* show no significant departure from the ideal curve between the nomogram prediction and actual observation for 3-year OS.

Discussion

Radical surgical resection is the standard treatment for

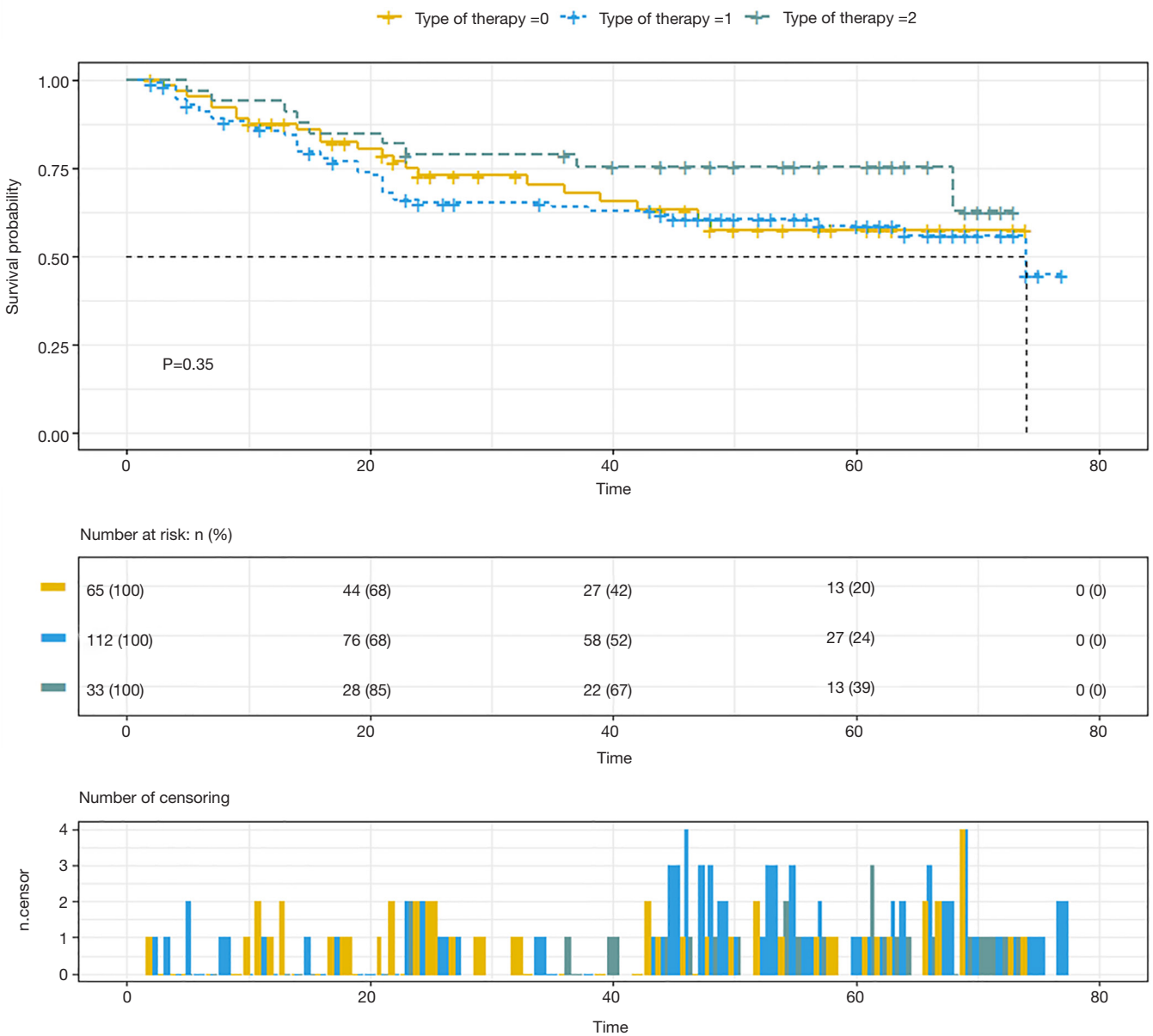

Figure 3 Comparison of DFS among the three groups. DFS, disease-free survival.

resectable thoracic esophageal cancer and has proven effective based on certain results. However, owing to the high rate of recurrence or metastasis, the OS of radical resections still remains poor. The meta-analysis (10) we conducted in 2013 indicated that relatively few studies have analyzed the effectiveness of postoperative CRT for patients with EC in contrast to neoadjuvant CRT. The chief reason for this may be the difficulty faced by the patients in bearing the side effects of postoperative CRT. After surgery, it is not uncommon for postoperative patients to become debilitated and develop postoperative complications. Fortunately, with the advancement in surgical techiques, surgeons can perform operations less invasively than in traditional surgery (13-15). In addition, with the improvement of radiotherapy equipment and the optimization of radiotherapy and chemotherapy, the side effects of postoperative treatment were tolerable and gradually reduced, and only few serious side effects were reported (10,16). Kang *et al.* conducted a

Table 2 Univariable analysis and multivariate Cox proportional hazards regression analysis

Variable	Univariable analysis P	Multivariable analysis		
		Hazard ratio	95% CI	P
Age (<60 *vs.* ≥60)	0.02			
<60		Reference		
≥60		1.460	1.005 to 2.120	0.047
History of cigarette smoking	0.054			
Yes		1.470	1.019 to 2.120	0.039
No		Reference		
Postoperative therapy	0.03			
None		Reference		
Chemotherapy		0.867	0.573 to 1.311	0.499
Chemoradiotherapy		0.446	0.241 to 0.821	0.010
Pathologic T category	0.03			
1		Reference		
2		1.278	0.523 to 3.125	0.591
3		1.914	1.057 to 3.467	0.032
4		1.985	0.810 to 4.861	0.134
Pathologic N category	<0.001			
1		Reference		
2		1.907	1.264 to 2.879	0.002
3		3.263	1.791 to 5.946	<0.001
Differentiation	0.03			
Well (G1)		Reference		
Moderate (G2)		1.489	0.952 to 2.328	0.081
Poor or undifferentiated (G3 or Gx)		2.071	1.157 to 3.707	0.014
Surgery approach	0.09			
Gender	0.2			
BMI (<25 *vs.* ≥25)	0.2			
Comorbidity	0.7			
History of alcohol consumption	0.3			
Site of the esophagogastric anastomosis	0.2			
The range of lymph node dissection	0.6			
Tumor location	0.8			
Anastomotic fistula	0.251			
Pulmonary infection	0.681			
Chylothorax	0.803			
Cardiovascular complications	0.459			

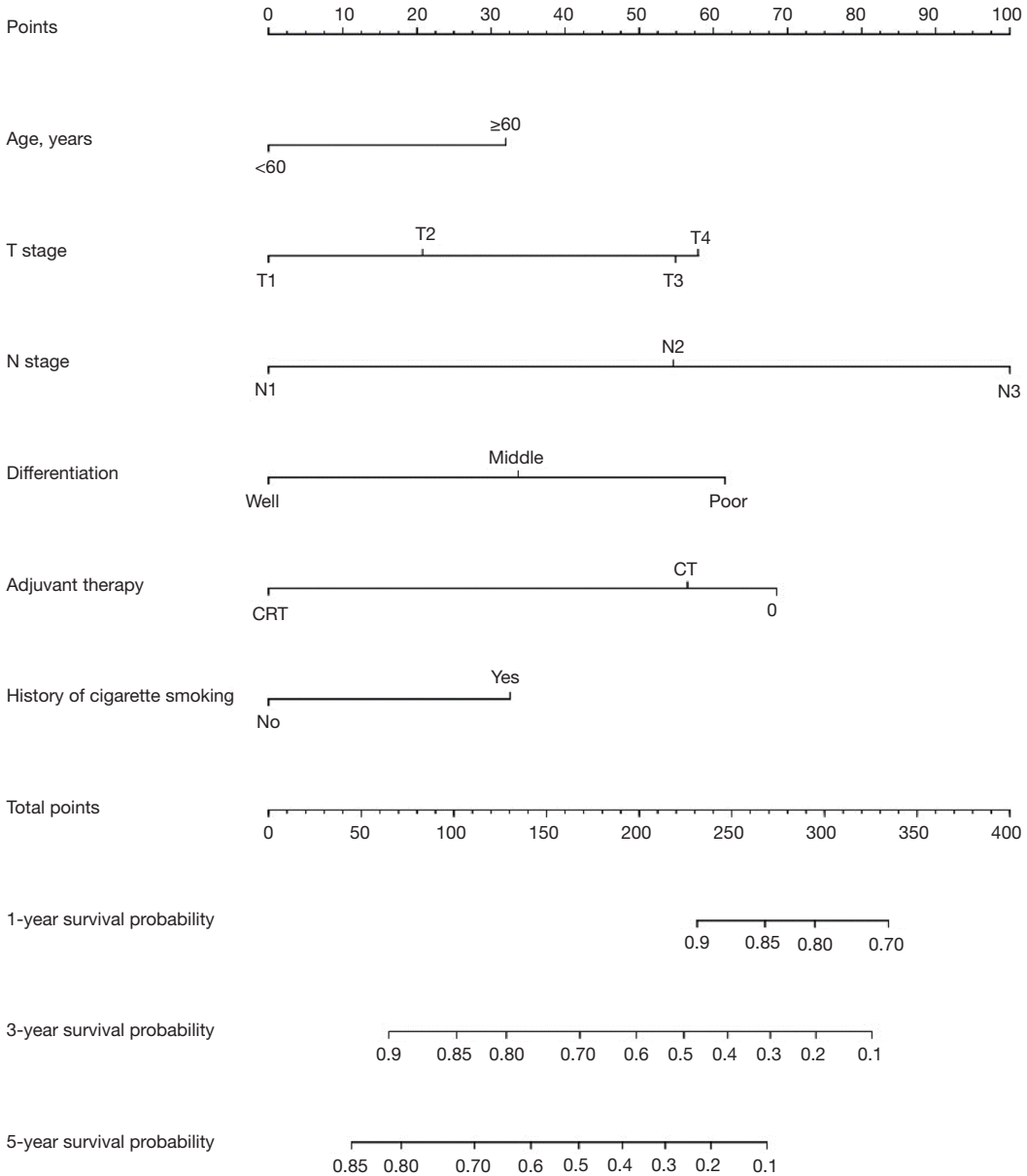

Figure 4 Postoperative prognostic nomogram for patients after radical esophagectomy.

meta-analysis of 2,165 patients and found that postoperative chemoradiotherapy yielded significant survival benefit and improved local-regional control with tolerable toxicity for patients with EC (16). We thus conducted this retrospective study to determine whether postoperative adjuvant chemoradiotherapy and adjuvant chemotherapy can provide meaningful treatment benefit for ESCC patients.

Our results found that postoperative adjuvant chemoradiotherapy was associated with significantly improved OS as compared with the surgery alone and adjuvant chemotherapy groups of pIIb-IIIc ESCC patients. The results are consisted with other reported studies, including a retrospective analysis of patients with ESCC reported in 2014 which found precise chemoradiation treatment to be associated with a significantly higher OS as compared to surgical resection alone (17). Another study of patients with pT3-4Nx-0 disease reported that postoperative CRT increasing the OS rate from

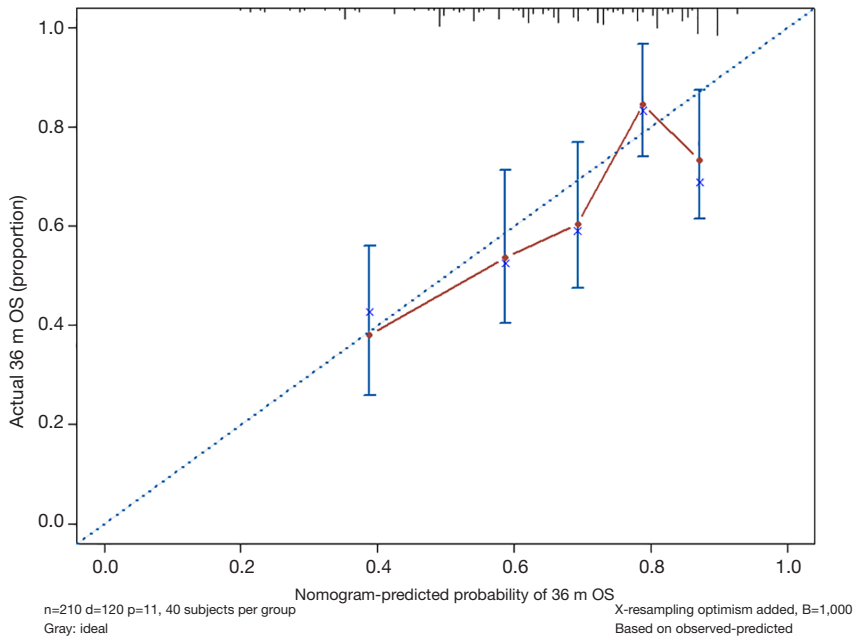

Figure 5 The calibration curve for predicting ESCC patient survival at 3 years in the primary cohort. The X-axis represents the nomogram-predicted survival, and the Y-axis represents actual survival measured by Kaplan-Meier analysis. ESCC, esophageal squamous cell carcinoma.

18% to 36.4% in comparison with surgery alone (P<0.001) (18). Our results also found that postoperative adjuvant chemoradiotherapy improved the OS rate of patients with pIIb-IIIc ESCC as compared to surgery alone, and other research has indicated postoperative adjuvant chemotherapy to be an independent predictor of recurrence (19).

A clinical problem arises when different curative effects occur in ESCC patients who undergo the same treatment. For instance, all patients in a cohort may undergo radical resection, with some surviving for a long time, and others suffering recurrence or metastasis soon after operation. In theory, postoperative adjuvant chemoradiotherapy or postoperative adjuvant chemotherapy can reduce or even eliminate the residual tumor cells via microtransfer. Thus, experts tend to perform postoperative adjuvant treatment throughout the entire therapeutic process. These results show that postoperative adjuvant chemotherapy or chemoradiotherapy can provide increased survival rates for patients with pathologic stage IIb–IIIc (pT1-4aN + M0) ESCC and thus should be considered appropriate treatments.

The current treatment of esophageal cancer in China is mainly based on Western clinical guidelines, but our conclusions differed from those of Western clinical studies. One possible reason for this discrepancy is that the main pathological type of esophageal carcinoma in China is esophageal squamous cell carcinoma, whereas it is esophageal adenocarcinoma in Western countries. This implies differences in histological characteristics, biological behavior, tumor position, sensitivity to chemotherapy drugs, and so on.

Other centers have also examined the suitable treatment for patients with locally advanced ESCC. The results of the study by Lyu *et al.* (20) suggested that paclitaxel- and cisplatin-based adjuvant chemotherapy was associated with a significantly increased OS as compared with surgery alone in lymph node-positive ESCC patients. In addition, the postoperative adjuvant chemotherapy and postoperative adjuvant chemoradiotherapy groups exhibited a substantially lower risk of recurrence or death than did the non-adjuvant group. The study also showed that if patients could tolerate both adjuvant chemotherapy and CRT, they could be spared from later high-dose irradiation for locoregional recurrence without causing an increase in the long-term postoperative complications. Chen *et al.* (21) showed that the effects of postoperative adjuvant CRT in patients with ESCC are not clear. He analyzed the reasons for the shortage of large case-control and prospective clinical studies; the absence of statements concerning the indication for adjuvant

therapy in the guidelines and the consequent variability in application and assessment; and the deficit in esophageal cancer research regarding the mechanisms of metastasis compared to the research in other solid tumors, such as breast and lung cancer.

Some limitations to our study should also be addressed. The sample size in our study was not large. Furthermore, the cause of death was not determined in our study because we lacked the relevant data.

In conclusion, our results show that patients with pIIb-IIIc (pT1-4aN + M0) ESCC can experience improved survival through postoperative adjuvant chemoradiotherapy. We therefore suggest that patients with pIIb-IIIc (pT1-4aN + M0) undergo postoperative chemoradiotherapy.

Acknowledgments

Funding: The study was supported by Climbing project of Science and Technology Department of Fujian Province (2018Y9058), Fujian Provincial Joint Research Project of Health Care and Education (WKJ2016-2-09), Key programs of Science and Technology Department of Fujian Province (2014Y0101), Fujian Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University).

Footnote

Reporting Checklist: The authors have completed the Tripod reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4893

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-4893

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4893). The authors have no conflicts of interest to declare.

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. This single-institution, retrospective study was approved by the institutional review board of Fujian Medical University Union Hospital (No. 2015KY021) and informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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(English Language Editor: J. Gray)

Cite this article as: Zheng B, Chen M, Chen C, Xiao J, Cai B, Zhang S, Liang M, Zeng T, Chen H, Wu W, Xu G, Zheng W, Zhu Y, Chen C. Adjuvant chemoradiotherapy for patients with pathologic node-positive esophageal cancer following radical resection is associated with improved survival. Ann Transl Med 2020;8(24):1633. doi: 10.21037/atm-20-4893

