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Postoperative radiotherapy for the young–old patients with thoracic esophageal squamous cell carcinoma

A 2-center experience

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Abstract

This study aimed to retrospectively analyze the efficacy and safety of esophagectomy and postoperative radiotherapy (PORT) for patients with thoracic esophageal squamous cell carcinoma (TESCC) in the young–old (aged between 65 and 75 years).

The clinical data of 166 young–old patients with esophageal cancer who underwent esophagectomy and PORT from May 2004 to May 2018 in The First Affiliated Hospital of Nanjing Medical University and The PLA Cancer Center, Jinling Hospital were analyzed. The Kaplan–Meier method was used to calculate overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS). The log-rank method was used to test the differences. The Cox regression model was used for the multivariate prognostic analysis.

The follow-up rate was 98.5%, and the median follow-up time was 41.2 months. The whole 1-, 3-, and 5-year OS rates were 92.0%, 69.3%, and 58.3%, respectively, and the median OS was 64.7 months (95% CI, 58.3–71.1). The median DFS was 57.9 months (95% CI, 47.4–68.4), and the 1-, 3-, and 5-year DFS rates were 84.8%, 61.5%, and 44.6%, respectively. The median LRFS was 60.8 months (95% CI, 50.5–71.0), and the 1-, 3-, and 5-year LRFS rates were 85.8%, 64.94%, and 53.9%, respectively. The median DMFS was 65.0 months (95% CI, 60.6–69.6), and the 1-, 3-, and 5-year DMFS rates were 91.9%, 77.0%, and 67.5%, respectively. Pathological T staging, lymph node metastasis, pathologic staging, and Karnofsk Performance Status (KPS) were the main factors affecting prognosis. In addition, T staging, lymph node metastasis are also independent prognostic factors. Little severe toxicity was observed.

The result indicates that PORT for TESCC patients who can tolerate surgery is safe in the young–old. The efficacy is similar to that of previous patients including younger populations. Pathological T and N stage are major factors that affect prognosis. Concurrent chemotherapy may not improve the survival of the young–old patients undergoing postoperative radiotherapy.

Abbreviations: 3D-CRT = 3-dimension conformal radiotherapy, AJCC = the American Joint Committee on Cancer, CCRT = concurrent chemoradiotherapy, DFS = disease-free survival, DMFS = distant metastasis-free survival, IMRT = intensity modulated radiotherapy, KPS = Karnofsk performance status, LRFS = local recurrence-free survival, MOS = median overall survival, OS = overall survival, PORT = postoperative radiotherapy, TESCC = thoracic esophageal squamous cell carcinoma.

Keywords: esophageal cancer, postoperative, radiotherapy, squamous cell carcinoma, the young–old

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1. Introduction

Esophageal cancer is one of the most common malignancies and the seventh leading cause of cancer-related death.[1] New cases of esophageal cancer in China account for about 49.0% of the total cases worldwide.[2] The most important treatment for esophageal cancer is surgery. However, the effect of surgery alone is poor, and its 5-year overall survival rate was 10% to 66%.[3] The postoperative local recurrence rate is still as high as 41.5% to 49%. Postoperative radiotherapy (PORT) alone or combined with chemotherapy can improve the local regional control rate, thereby enhancing the patient's overall survival (OS). Therefore, PORT is widely used in the treatment and clinical study of esophageal cancer.

The number of elderly patients with esophageal cancer has also increased significantly over the recent decades due to the increased life expectancy. The cutoff for a definition of elderly patients varies from 65 to 70 years of age, world health organization (WHO) regulations 60 to 74 years old for the elderly. Elderly patients with esophageal cancer tend to receive relatively low intensity treatment. But defining elderly patients based on functional status is more accurate than the actual age. Elderly patients compared with younger ones frequently have ≥1 comorbidities and are often "frail"; they are at greater risk of morbidity and mortality. Optimizing a care pathway during the perioperative period, promoting and improving enhanced recovery programs, may be fundamental.

Several studies and a meta-analysis demonstrated that, compared with younger patients, patients >70 years of age undergoing surgical resection for esophageal cancer had lower survival rates. However, no significant differences were observed in survival between elderly and younger patients after esophageal resection in some studies.[4,5] Age did not result a significant predictor for postoperative complications.[6] So, age is not an absolute contraindication for surgery. Patients with esophageal cancer who undergo esophagectomy have significantly improved 5-year survival.[7,8] But it is not yet clear whether elderly patients who are in good condition can benefit from PORT. It is more and more important to discuss the best treatment mode for esophageal cancer in the elderly. Therefore, the aim of this study was to review the 2-center experience on the young–old patients with esophageal cancer who were treated with PORT so as to better understand the efficacy of this approach and potentially severe toxicities and also to provide a reference basis for the young–old patients with esophagectomy.

2. Patients and methods

2.1. Clinical data

The outcomes of all patients undergoing curative treatment with esophagectomy and PORT in the 2 hospitals from May 2004 to May 2018 were retrospectively examined. Initially, 201 patients were identified. Patients who had incomplete records (n = 13) or who did not complete planned radiation for various reasons (n = 5) or whose Karnofsk Performance Status (KPS) <70 (n = 17) were excluded. Ultimately, 166 patients with thoracic esophageal squamous cell carcinoma (TESCC), aged 65 years or older, treated with esophagectomy and PORT were included in this study. All patients were staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) esophageal cancer staging system.

2.2. Treatment delivery

Due to the long time period covered by this study, target delineation, radiation technique, and dose prescription varied to some extent. The target volume included postoperative tumor bed and high-risk lymphatic drainage area, and the total dose was 50 to 66 Gy, 1.8 to 2.0 Gy/fraction. The high dose of radiation in some patients was due to the detection of suspicious lymph nodes on medical images before radiotherapy. The patients were treated with 3-dimension conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT) technique. None of the patients had serious postoperative complications. Among them, 55 underwent concurrent chemoradiotherapy (CCRT), and 111 received postoperative radiotherapy alone. The chemotherapy regimens consisted mainly of 5-fluorouracil 1000 mg/m^2, days 1–3 and 29–31, or single-agent S-1 (Tegafur, Gimeracil, and Oteracil) 40 mg bid orally, or capecitabine tablets 1.5 g qd orally. 3D-CRTor IMRT was used for the patients (detailed in Table 1). The patient's eating status, body weight changes, blood routine examination, and liver and kidney function were monitored.

2.3. Follow-up

The first follow-up was generally scheduled 6 to 8 weeks after PORT. The follow-ups were scheduled every 3 to 4 months for the first year, every 4 to 6 months for the second year, every 6 months for the third year, and annually thereafter, during which the abnormalities were reviewed at any time. Local recurrence, regional lymph node metastasis, and distant metastasis were all defined as treatment failures during the follow-up.

2.4. Data collection and statistical methods

Data on clinical characteristics, histopathology results, toxicity, complications and comorbidities, recurrence, and survival status were obtained from patient records. The observations of survival time included overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS). The starting point for all survival times was the date of surgery. The end point of OS referred to the last follow-up or any cause of death. DFS was defined as the progression or recurrence of disease, the last follow-up, or any cause of death. LRFS was the time from the beginning of surgical treatment to the time at which the patient's death occurred due to local or regional lymph node recurrence, last follow-up, or any other cause of the primary lesion. The end point of DMFS defined as distant metastasis, last follow-up, or any cause of death. Failure time and survival time were calculated in units of months. The Kaplan–Meier method was used to calculate OS, DFS, LRFS, and DMFS. The log-rank test was used for the univariate analysis. Factors with $P < .05$ were included in the Cox regression model for the multivariate analysis. A P value $<.05$ was considered statistically significant. The statistical analysis was performed using IBM SPSS (IBM company, Chicago. Statistical Product and Service Solutions) Statistics 24 software.

3. Results

3.1. Patients' characteristics

Total of 166 patients were identified. The median age at diagnosis was 68 years (ranges, 65–78 years). All patients had no previous history of malignant tumors and had not received any

Table 1

Characteristics of 166 young–old patients with TESCC undergoing PORT.

Variable	No.	(%)	Variable	No.	(%)
Gender			Stage		
Male	125	75.3	I	3	1.8
Female	41	24.7	IIa	46	27.7
Age, yr	68 (66–71)		IIb	26	15.7
Tumor location			IIIa	12	7.2
Upper	14	8.4	IIIb	76	45.8
Middle	83	50	IVa	3	1.8
Distal	69	41.6	T Stage		
KPS			1	7	4.2
≥80	123	74.1	2	29	17.5
<80	43	25.9	3	111	66.9
Smoking			4	19	11.4
Yes	85	51.2	Pathological N		
No	81	48.8	N+	88	53
Alcohol abuse			N0	78	47
Yes	56	33.7	Differentiation		
No	110	66.3	Poorly	65	39.2
Weight loss			Medium/Well	101	60.8
Yes	47	28.3	Dose of radiation (Gy)	50 (50–54)	
No	119	71.7	>50.4	47	28.3
CCRT			≤50.4	119	71.7
Yes	55	33.1	The interval between RT and S (d)	61 (31–85)	
No	111	66.9	>60	94	56.6
Technique			≤60	72	43.4
3D-CRT	118	71.1			
IMRT	48	28.9			

3D-CRT = 3-D conformal radiation therapy, CCRT = concurrent chemoradiation therapy, KPS = Karnofsk performance status, IMRT = intensity-modulated radiation therapy, PORT = postoperative radiotherapy, RT = radiotherapy, S = surgery, TESCC = thoracic esophageal squamous cell carcinoma.

radiotherapy before surgery (KPS ≥70). After the surgery, the patients were staged according to the eighth edition of the AJCC esophageal cancer staging system (detailed in Table 1).

3.2. Survival

The follow-up deadline was May 15, 2018. The follow-up time was 4.6 to 133.37 months, the median follow-up time was 41.2 months. The follow-up rate was 98.5%. The whole 1-, 3-, and 5-year OS rates were 92.0%, 69.3%, and 58.3%, respectively, and the median OS was 64.7 months (95% CI, 58.3–71.1). The median DFS was 57.9 months (95% CI, 47.4–68.4), and the 1-, 3-, and 5-year DFS rates were 84.8%, 61.5%, and 44.6%, respectively. The median LRFS was 60.8 months (95% CI, 50.5–71.0), and the 1-, 3-, and 5-year LRFS rates were 85.8%, 64.94%, and 53.9%, respectively. The median DMFS was 65.0 months (95% CI, 60.6–69.6), and the 1-, 3-, and 5-year DMFS rates were 91.9%, 77.0%, and 67.5%, respectively (Fig. 1).

3.3. Analysis of prognostic factors

The prognostic factors including age, sex, KPS, radiotherapy, weight changes in perioperative period, T stage, N stage, postoperative staging, tumor differentiation, the interval between surgery and radiotherapy, dose of radiation, and concurrent chemotherapy were analyzed. The univariate analysis showed that postoperative T stage ($\chi^2=2$; $P=.04$), lymph node metastasis ($\chi^2=12.132$; $P=.000$), postoperative staging ($\chi^2=16.528$; $P=.000$), KPS <80 ($\chi^2=4.715$; $P=.03$) were the main prognostic factor for overall survival. The multivariate analysis showed lymph node metastasis ($P=.003$) and T stage ($P=.041$) as independent prognostic factors (Fig. 2 and Tables 2 and 3).

Complications: Of the 166 patients, 12 had pulmonary complications, including emphysema, tuberculosis, and pleurisy; 3 had diabetes; 3 had cardiac insufficiency; and 19 had hypertension.

Adverse reactions: Grade 3 radiation pneumonitis occurred in 8 patients (4.82%), late third-degree stenosis occurred in 10 patients (6.02%), and unexplained hemorrhage occurred in 4 patients (2.41%); others had below grade 2 adverse reactions (Table 4).

Failure analysis: At the end of the follow-up, 64 of 166 (38.6%) patients died. Fourty two patients died of tumor, of which 23 had a local recurrence, 19 had distant metastases, and 10 had a local recurrence and distant metastasis. Twenty two died of nontumor causes. Four patients died of undiagnosed gastrointestinal bleeding, 9 died of infection, 3 died of malnutrition, 2 died of cardiopulmonary insufficiency, and 1 died of sudden death. The 3 other causes of death were unknown.

4. Discussion

The rapid aging of the population has led to a rapid increase in the incidence of esophageal cancer in elderly patients. However, many clinical studies excluded elderly patients. Therefore, the treatment of elderly patients with esophageal cancer lacks evidence-based support. According to previous studies, patients with esophageal cancer in the elderly can benefit from anti-tumor therapy without increasing apparent toxicities. Some authors think that elder patients showed relatively poor prognosis

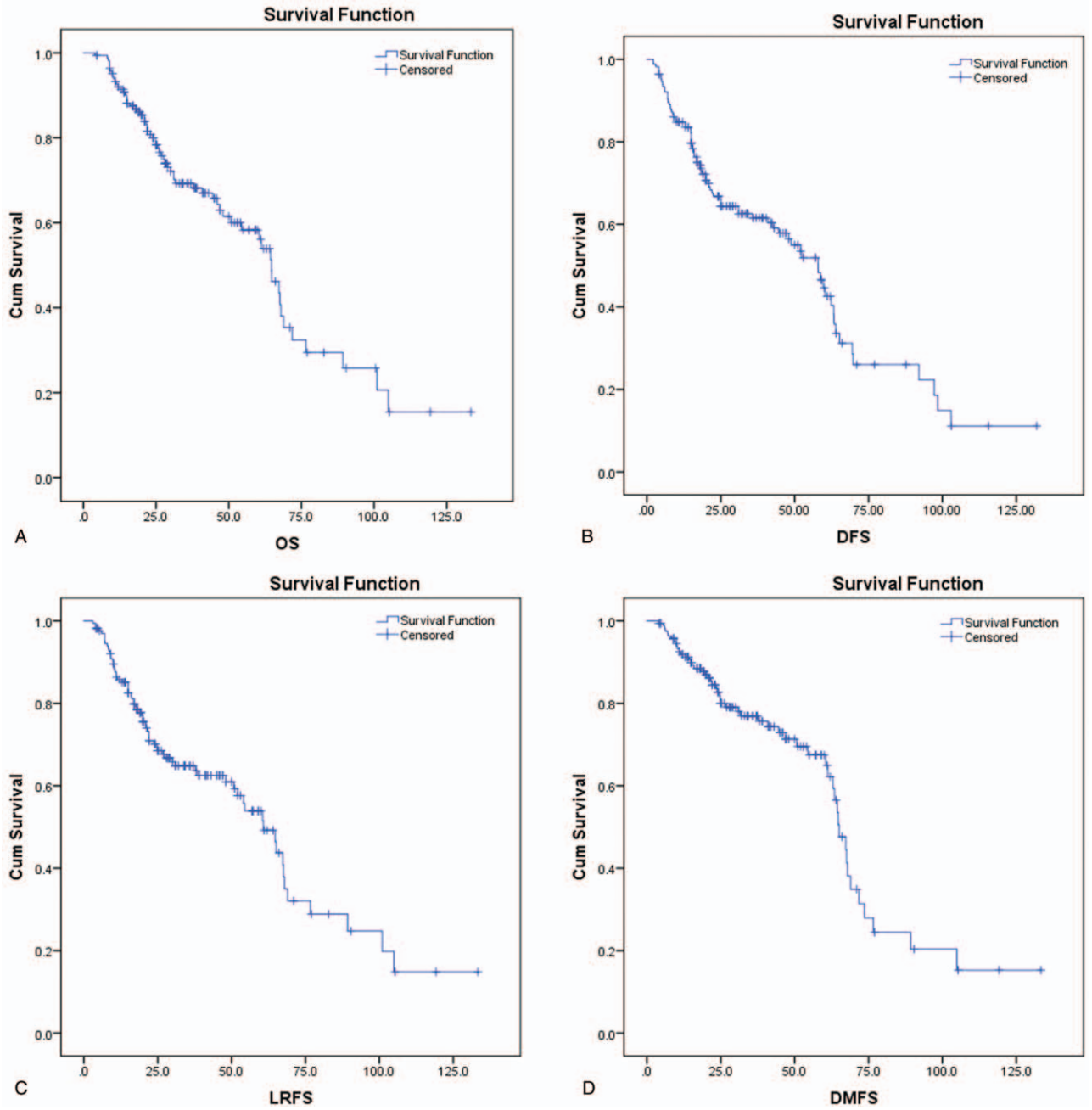

Figure 1. Kaplan–Meier curves of overall survival (OS, A), disease-free survival (DFS, B), local recurrence-free survival (LRFS, C) and distance metastasis-free survival (DMFS, D) in 166 patients with stage II /III TESCC in the young-old after PORT.

compared with younger patients partly because they less often received active therapy.[9,10] Under current surgical conditions, the risk of resection of esophageal cancer in the patients >80 years is controllable.[4] Tapias et al[5] reported the survival results of radical surgery in 474 elderly patients over 70 years old with esophageal cancer. The overall 5-year survival rate was 58.1%, and 5-year cancer-specific survival was 66.8%. The hospital length of stay was only 1 day longer in the elder than in the patients <70 years. The patients <80 years had good treatment tolerance. Except for non-tumorigenic causes, its long-term survival is similar to that of young patients. Jing et al[8] also believed that advanced age should not be the cause for elderly patients to avoid aggressive regimens. Esophageal cancer resection can be recommended cautiously and individually for esophageal cancer patients aged 70 to 80. For patients exceeding 80 years old, considering esophagectomy should be recognized as a high-risk cohort, and these patients must be carefully risk-stratified, counseled, and selected for surgical intervention to prevent unnecessary hospitalization and mortality. In view of the above reasons, we selected the young–old patients aged 65 to 75 years to study the long outcomes of postoperative radiotherapy in the treatment of esophageal cancer.

Multimodality treatment has become increasingly used for esophageal cancer, which proved to have good outcomes.

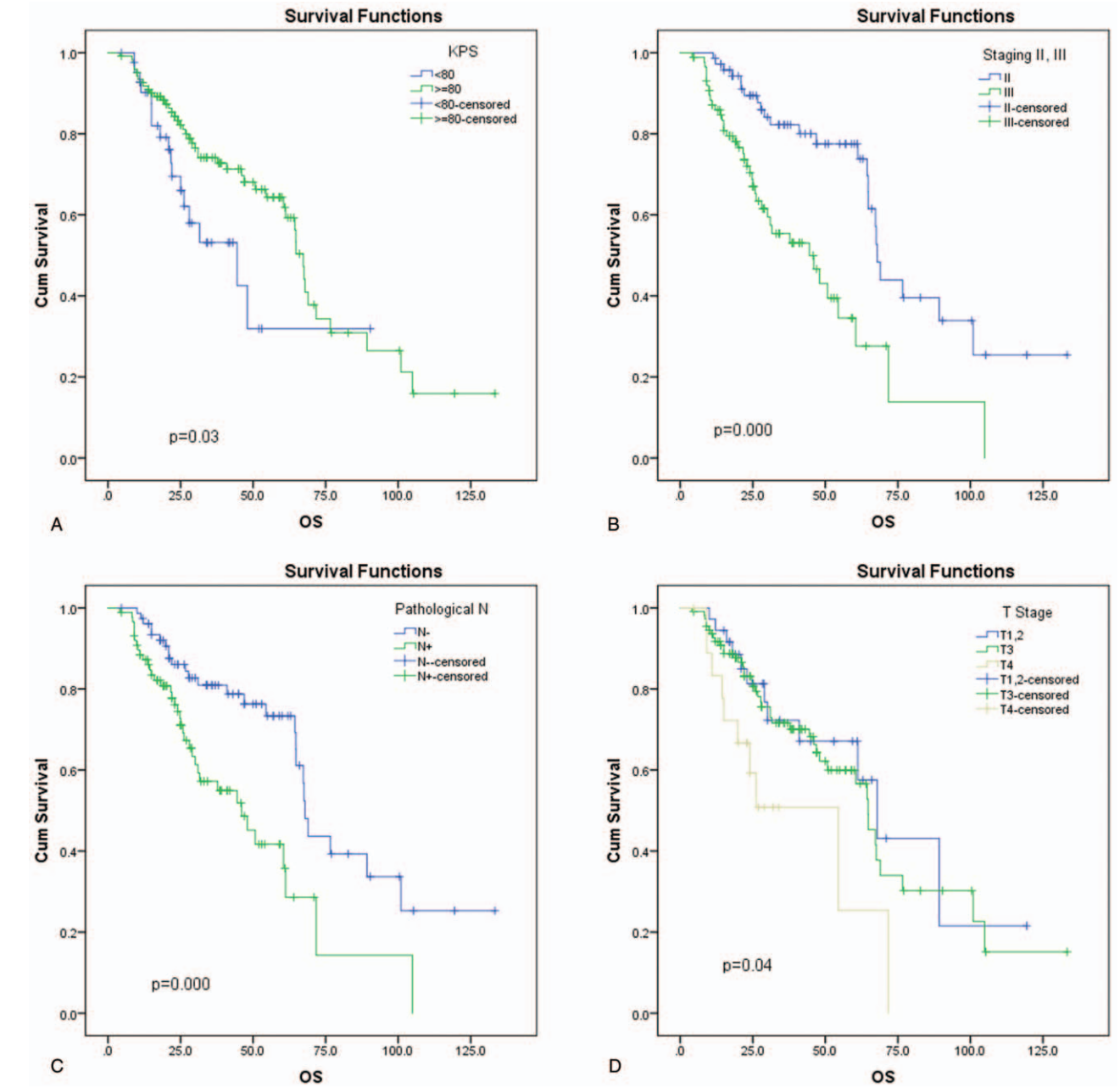

Figure 2. Comparison of overall survival in patients with different groups. (A) Overall survival in patients with KPS ≥ 80 or <70; (B) overall survival in patients with Pathologic Stage II, III; (C) overall survival in patients with N negative or N positive; (D) Overall survival in patients with T (1, 2), T3 or T4.

Neoadjuvant chemoradiotherapy was proved to be a better strategy for local advanced patients. PORT was only recommended for positive margin patients in NCCN guidelines. However, in most area of China, surgery was still the first choice of esophageal cancer patients by now. PORT was controversial and had been studied for many years. Several meta analyses concluded that PORT significantly decreased postoperative mortality, local recurrence, and distant metastasis rates, with no increased postoperative complications for patients with resectable esophageal carcinoma.[11–13] A series of large-scale retrospective analysis showed that postoperative radiotherapy can significantly improve the OS of patients with lymph node positive and stage III esophageal cancer. The addition of adjuvant radiotherapy significantly increased the rate of local control and significantly reduced the recurrence rate in supraclavicular and upper and middle mediastinum regions. PORT was the most important predictor of good prognosis.[14–16]

In our study we analyzed 166 patients treated with esophagectomy and PORT, which is the most common treatment for patients including younger populations in China. Our study showed that the overall 1-, 3-, and 5-year overall survival rates for all patients were 92.0%, 69.3%, and 58.3% months, these results are similar with those of non-elderly patients, suggesting that the young–old esophageal cancer patients who can tolerate

Table 2

Log-rank univariate analysis of the clinical characteristics and therapeutic factors on young–old patients with TESCC.

Variable	No.	MOS	1-year	3-year	5-year	χ^2	*P*
Gender							
Male	125	64.4	91.8	65.6	53.8	1.137	.286
Female	41	67.9	92.5	79.4	70		
Age, yr							
≥70	60	64.4	91.6	61.4	55.2	0.016	.898
<70	106	64.7	93.3	74.3	55.5		
Tumor location							
Upper	14	67.9	100	63.5	50.8	1.322	.724
Middle	83	61.2	87.5	68	55.3		
Distal	69	67.3	95.7	71.2	62.6		
KPS							
≥80	123	67.3	92.6	74.1	64.3	4.715	.030
<80	43	44.5	90.2	53.1	31.9		
Stage							
I	3					16.528	.000
II	72	67.9	98.6	82.2	77.5		
III	88	44.5	85.9	55.4	34.5		
IV	3						
T Stage							
1–2	36	67.9	97.2	72.3	67.1	2	.040
3	111	64.7	91.7	71.6	60		
4	19	54.3	83.3	50.8	25.4		
Pathological N							
N+	88	46.0	87.2	57.2	41.7	12.132	.000
N0	78	67.9	97.4	80.9	73.4		
CCRT							
Yes	55	48.0	96.3	63.7	49.6	0.041	.840
No	111	64.8	89.9	71.6	61.1		
Differentiation							
Poorly	65	61.2	92.1	64.7	52.8	0.83	.362
Medium/Well	101	64.7	91.9	71.5	58.2		
Dose of radiation, Gy							
>50.4	47	60.8	83.0	67.6	50.1	1.566	.211
≤50.4	119	67.9	95.7	80.2	63.6		
The interval between RT and S, d							
>60	94	64.4	95.7	84.4	67.3	0.035	.853
≤60	72	64.7	87.3	70.8	60.3		

3D-CRT = 3-D conformal radiation therapy, CCRT = concurrent chemoradiation therapy, IMRT = intensity-modulated radiation therapy, KPS = Karnofsk performance status, MOS = median overall survival, RT = radiotherapy, S = surgery, TESCC = thoracic esophageal squamous cell carcinoma.

esophagectomy can benefit from PORT in the basis of active symptomatic supportive care. Age is not an absolute effect factor on the efficacy of postoperative radiotherapy.

The univariate analysis results of the present study showed that age, sex, tumor location, concurrent chemoradiation therapy (CCRT), dose of radiation, tumor differentiation, and the interval between surgery and radiation were not associated with prognosis.

It is worth noting that CCRT did not improve OS in our study. Some authors believe that CCRT can improve the survival of patients over 70 years old with inoperable esophageal squamous cell carcinoma compared with radiotherapy alone. One thousand twenty four patients were enrolled in the study for retrospective analysis.[17] The results showed 3 months of survival benefit (17 months vs 14 months), and the 2 regimens were well-tolerated and there were no therapy-associated mortalities. This seems to suggest that the tolerance of elderly patients with esophageal cancer to aggressive treatment is acceptable, and it is possible to improve the prognosis of patients. For patients who are in better physical condition and can tolerate surgery, there is a similar conclusion. A meta-analysis of 2165 patients included 13 studies showed that postoperative CCRT significantly improved OS in

Table 3

Cox analysis of survival after PORT in young–old patients with TESCC.

Factor	β	SE	Wald	Exp(β)	*P*	95% CI
KPS	−0.581	0.299	3.767	0.559	.052	0.311–1.006
N+ vs N–	0.799	0.273	8.559	2.224	.003	1.302–3.799
T1,2 vs T3,4	0.887	0.435	4.164	2.428	.041	1.036–5.692

PORT = postoperative radiotherapy, TESCC = thoracic esophageal squamous cell carcinoma.

Table 4

Adverse reactions in 166 young–old patients with esophageal carcinoma after PORT.

Adverse reactions	0	1	2	3	4
Radiation pneumonia	54	75	29	8	0
Myelosuppression	63	76	24	3	0
Mucosal response	17	79	70	0	0
Fatigue	78	76	12	0	0
Stricture	58	87	11	10	0

PORT = postoperative radiotherapy.

patients with esophageal cancer.[18] We believe that this difference is due to the different ages of the basic research population and the relatively small number of samples in our study. Of course, there are also some studies that suggest that simultaneous radiotherapy and chemotherapy does not benefit patients, which is similar to our conclusion. In another study, the clinical data of radiotherapy and radiotherapy plus concurrent chemotherapy in 185 elderly patients with esophageal cancer were analyzed. The results show that concurrent chemotherapy with radiotherapy for esophageal cancer in patients aged 80 years or older did not have significant OS benefit over radiotherapy alone.[19] As for specific chemotherapeutic regimens, we used fluorouracil-based chemotherapy, which is similar to other studies.[16,20] Most of the studies are retrospective. In the future, a randomized controlled study of elderly patients with esophageal cancer should be considered carrying out to find out whether postoperative radiotherapy and concurrent chemotherapy is beneficial to the patients.

The log-rank test showed that KPS, T staging, lymph node metastasis, and pathologic staging were the main factors affecting prognosis. Further Cox regression model shows that T staging, lymph node metastasis were independent prognostic factors. This is consistent with the results of most previous studies.[15] Gulben et al[21] reported a group of patients and the prognostic role of age, sex, tumor location, cell type, pathological lymph node status, number of metastatic lymph nodes (<3 vs >/=3), metastatic lymph node ratio, type of resection, local recurrence, and distant metastasis on overall survival were examined by univariate and multivariate analyses. The results showed that the patients with ≥3 metastatic lymph nodes and distant metastasis have a poor OS. We believe that the treatment of these patients needs to be more aggressive, and the optimal treatment approaches need to be further studied.

The comorbidity in the aforementioned group was mainly hypertension, and also included diabetes, emphysema, insufficiency, cardiac, and tuberculosis. Radiotherapy did not increase the degree of comorbidity. The adverse effects of these patients were similar to the results of previous studies on nonelderly patients. In general, the side effects of the treatment model of these patients are acceptable.

In the aforementioned group of patients, 22 patients died of non-tumor reasons. The cause of these deaths might be summarized as lower organ function, increased cardiopulmonary complications, and low nutritional immunity in elderly patients, suggesting that the best supportive treatment for elderly patients should be strengthened. At the same time, these causes of death cannot rule out the toxic and side effects of treatment. Appropriate treatment approaches should be taken to balance the risks and potential benefits of treatment for elderly patients. In clinical practice, it is necessary to observe the treatment response of elderly patients more carefully, especially those who have received concurrent chemotherapy.

There were some limitations in this study. First, some patients did not have postoperative radiotherapy because of postoperative complications and other reasons, so there is a certain select bias. Second, this was a retrospective study that was not particularly large in sample size. Furthermore, some potential prognostic factors were not involved in this study due to some potential confounding factors. Therefore, well-designed prospective researches need to be conducted to further explore the potential prognostic factors in more detail.

In conclusion, PORT for TESCC who can tolerate surgery is safe in the young–old. The efficacy is similar to the younger populations. Postoperative T staging, lymph node metastasis are major factors that affect prognosis. Concurrent chemotherapy may not improve the survival of the young–old patients undergoing postoperative radiotherapy. This study requires a large sample of prospective trials to confirm.

Author contributions

Min Yang and Xinchen Sun were major contributors in designing the study. Wei Ding and Wanrong Jiang performed the data analysis. Wei Ding was a major contributor in writing the manuscript. Xiaolin Ge, Xiangdong Sun, Bin Zhou, Feng Liu, Kai Jiang, and Fangcheng Shen contributed to data collection and data analysis. All authors read and approved the final manuscript.

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