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Original Article

A propensity-score matching analysis comparing long-term survival of surgery alone and postoperative treatment for patients in node positive or stage III esophageal squamous cell carcinoma after R0 esophagectomy

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ABSTRACT

Background: Surveillance was recommended for patients after R0 esophagectomy by National Comprehensive Cancer Network (NCCN) guidelines. However, local failure was high in locally advanced patients (48–78%). The present study aimed to determine whether adjuvant treatment improved survival for stage IIb-III thoracic esophageal squamous cell carcinoma (TESCC).

Methods: A retrospective review of patients diagnosed as esophageal carcinoma at the Chinese Academy of Medical Sciences Cancer hospital, between January 2004 and December 2011, was performed. A database compiling 975 patents with node positive or stage III thoracic esophageal carcinoma after R0 surgery with or without postoperative radiation/chemoradiation was created. A 1:1 matched study group was generated by the Greedy method after propensity score matching (PSM) analysis. Survival curves were calculated by the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses were using the Cox proportional hazards regression model.

Results: 975 patients were enrolled in the study, 510 patients (52.3%) did not receive any postoperative treatment after R0 surgery and 465 patients had either postoperative chemoradiation or radiotherapy. Median follow-up was 69.2 months. After PSM, 222 well-balanced patients in each group demonstrated the same results. The 3-year, 5-year survival rates and median survival in surgery group (33.0%, 26.4%, 24.3 months) were inferior to those in postoperative treatment group (48.3%, 37.1% and 34.3 months), ($P = 0.002$). Compared with radiotherapy, postoperative chemoradiation did not improve DFS and OS ($P = 0.692$; $P = 0.368$). N stage and adjuvant treatment are independent prognostic factors.

Conclusions: Adjuvant treatment could improve survival for patients with stage IIb-III TESCC.

In China, esophageal carcinoma is the third prevalent cancer and the fourth leading cause of cancer-related death [1]. Surgery is the mainstay of esophageal carcinoma treatment. Even after radical surgery, the prognosis is still dismal. Recently, it was reported by several prospective clinical trials and retrospective analysis that postoperative radiotherapy or chemoradiotherapy offered survival benefits for patients with stage III or positive lymph node esophageal cancer [2–20]. However, except that Xiao's reports [2,3] were subgroup analysis of large-sampled prospective clinical trial, majority were retrospective analysis and no high-level evidence existed to confirm the clinical value of postoperative radiotherapy, furthermore these reports had more confounding factors such as R1-2 surgery [15]. Given the lack of high-level evidence, adjuvant treatment for thoracic esophageal cancer after R0 surgery was not recommended by National Comprehensive Cancer Network (NCCN) guidelines [21].

A large number of research results have shown that with the increase in advanced stage the survival rates decreased. For instance, according to Rice et al. [22,23] and Ralf Gertler et al. [24] the 5-year survival rate of node negative esophageal cancer patients was about 65%, whereas the 5-year survival rate of node positive patients was

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approximately 20%, resulting in the decrease in survival rate from 32% to 8%. There was also an increase in recurrence and metastasis rate due to an increase in the number of metastatic lymph nodes. Peyre et al. [25] reported that recurrence and metastasis rate of node-negative patients was 16%, which was significantly lower than 93% for the patients with more than 8 positive lymph nodes. Significant differences were observed in the tumor recurrence and metastasis rates according to tumor invasion (T1-4) and lymph node metastases (N0–N3). Therefore, stratified studies for adjuvant therapy are warranted. However, scarcely did prospective clinical study evaluate whether or not the patients with esophageal cancer after R0 resection need adjuvant therapy and which subgroup could benefit from it the most. Therefore, in this study the propensity score-matching method was used to minimize the selection bias of the two cohorts of data. The subgroup of patients with stage III or node-positive esophageal carcinoma after R0 resection were analyzed and the long-term survival outcomes of the patients with surgery alone and adjuvant treatment (radiotherapy or chemoradiotherapy) were compared in order to provide the basis for the prospective stratified randomized controlled study.

Materials and methods

Eligibility

The following are the eligible criteria: (1) the patients with esophageal cancer received R0 resection in Chinese Academy of Medical Sciences from January 2004 to December 2011. (2) Thoracic esophageal squamous cell carcinoma (3) with postoperative pathologic stage III or node-positive according to Union for International Cancer Control 2009 staging system, (4) without neoadjuvant therapy before operation, (5) the KPS (Karnofsky) $\geq$ 70, (6) with postoperative radiotherapy or chemoradiotherapy (radiotherapy using IMRT). (7) No severe drug allergy history. (8) Normal liver and kidney function. (9) Blood tests: WBC $\geq$ 4.0 G/L, HGB $\geq$ 120 g/L, PLT $\geq$ 100 G/L. (Fig. 1). The exclusion criteria: (1) R1 or R2 surgery; (2) received adjuvant chemotherapy only; (3) lost follow-up in 3 months after surgery; (4) perioperative death. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. This study is approved by the ethics committee of our institution.

Operation method

The patients with upper thoracic esophageal carcinoma were undergone the surgery with left neck and right thoracic and middle abdominal incisions; the patients with middle and lower thoracic esophageal cancer were undergone left thoracotomy. The lymph drainage area around esophagus, adjacent to the lesions, subcarinal and perigastric areas including the paracardial, and the left gastric artery for all patients were dissected. The dissection of recurrent laryngeal nerve chain was carried out for the patients with upper thoracic esophageal cancer.

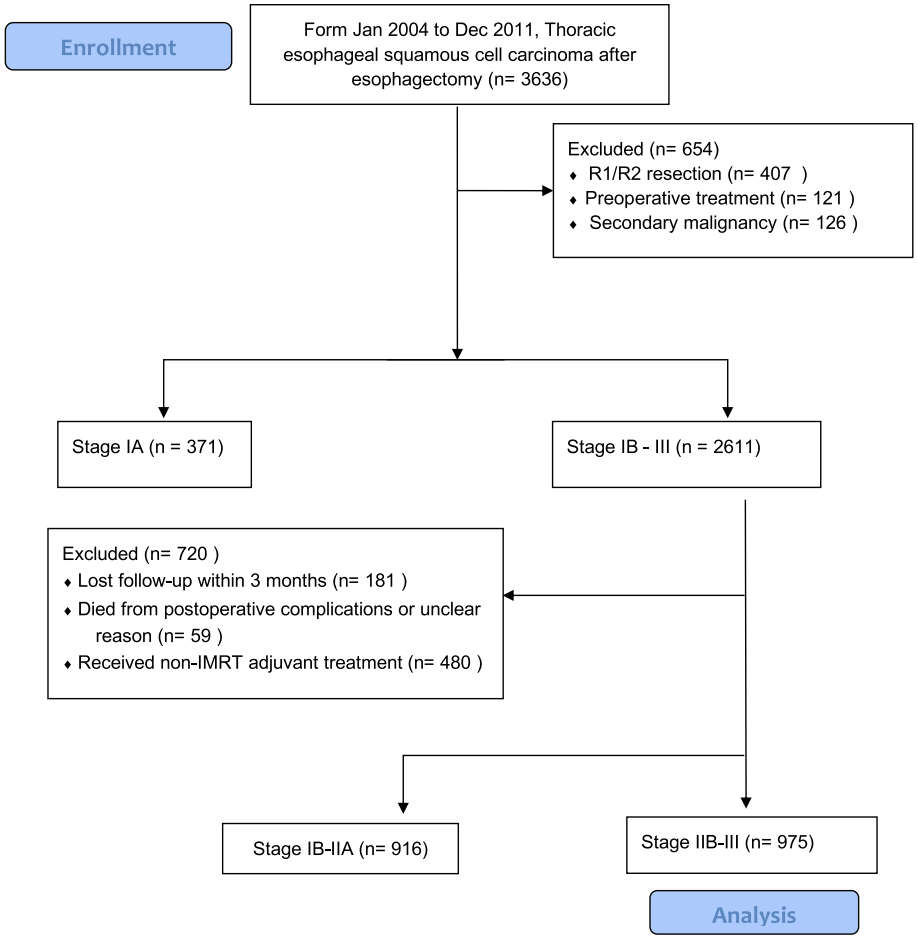

Fig. 1. Flowchart of patients' selection.

Radiotherapy

Before propensity-score matching, 465 patients received the treatment with adjuvant radiotherapy using IMRT (intensity-modulated radiotherapy) with or without chemotherapy, in which 331 patients (71.2%) treated with adjuvant radiotherapy and 134 cases (28.8%) with concurrent chemoradiotherapy. There were 98 patients enrolled in previous prospective clinical trial, half of them did not complete schedule of treatment. The radiotherapy was performed at 5–7 weeks after surgery. A total dose of 50 to 60 Gy was delivered to 95% planning treatment volume (PTV) in 1.8–2.0 Gy per fraction, 30–33 fractions (five fractions per week) over 6–6.5 weeks using 6-Mv photon beams from a linear accelerator.

Statistics

Patients' characteristics of two groups were compared using chi-square test with or without correction for continuity when necessary. The survival rate was calculated by the Kaplan–Meier method and tested by log-rank test. A cox regression model with stepwise selection was used to perform multivariate analyses of the factors obtained from univariate analysis. To adjust unbalanced covariates, a propensity score matching method was used to generate two cohorts in 1:1 between the surgery alone group and the adjuvant radiotherapy or chemoradiotherapy group using Stata 12.0 (Stata Corp LP, College Station, TX) basing on the factors including sex, age, tumor location, upper margin, differentiation, vascular embolism, T stage, N stage. The rest of the statistical analysis was processed using SPSS 20.0 for windows software (SPSS, Chicago, IL). $P < 0.05$ was considered statistically significant.

Follow up

After the surgery, follow-up included the routine inspection for the patients every 3–6 months in the first year and every 6 months in the 2nd year, annually thereafter. The routine examination included upper gastrointestinal contrast, cervical and thoracic abdominal enhanced CT scan, neck and abdomen ultrasonography. Brain MRI and bone scan are optional when necessary such as headache. The overall survival (OS) is defined as the time from surgery to death from any cause or last follow-up. The disease-free survival (DFS) defined as the time from surgery to time of tumor recurrence and distant metastasis, death, or the last follow-up time. Acute and late radiotherapy reactions were evaluated by reference to the CTCAE 4.0.

Table 1
Patients' characteristics.

	Total	Before PSM					Total	After PSM				
	N = 975	Surgery		Surgery + adj		*P*	N = 444	Surgery		Surgery + adj.		*p*
		N = 510	%	N = 465	%			N = 222	%	N = 222	%	
Sex						0.029						1.000
Male	818	415	81.4	403	86.7			202	91·0	202	91.0	
Female	157	95	18.6	62	13.3			20	9.0	20	9.0	
Age						0.000						1.000
≤60	540	249	47.1	300	64.5			131	59.0	131	59.0	
>60	435	270	52.9	165	35.5			91	41.0	91	41.0	
Tumor location (2002)						0.000						1.000
Upper	78	40	7.8	38	8.2			9	4.1	9	4.1	
Middle	468	280	54.9	188	40.4			106	47.7	106	47.7	
Lower	429	190	37.3	239	51.4			107	48.2	107	48.2	
Upper margin						0.002						0.087
≤5.0 cm	631	355	69.6	276	59.3			168	75.7	151	68.0	
>5.1 cm	333	152	29.8	181	38.9			52	23.4	68	30.6	
Unknown	11	3	0.6	8	1.7			2	0.9	3	1.4	
LN resection	12,781			11,397				5608		5518		
LN resection (Median)	23 (3–74)			23 (5–89)				23 (3–74)		23 (5–78)		
Metastatic LN						0.798						1.000
Median (range)		2 (0–37)		2 (0–33)				2 (0–35)		2 (0–33)		
<22	471	244	47.8	227	48.8			104	46.8	104	46.8	
≥22	504	266	52.2	238	51.2			118	53.2	118	53.2	
Differentiation						0.135						1.000
Well	123	71	13.9	52	11.2			22	9.9	22	9.9	
Moderately	524	281	55.1	244	52.5			128	57.7	128	57.7	
Poor	327	157	30.8	169	36.3			72	32.4	72	32.4	
Unknown	1	1	0.2	0	0			0		0		
Vascular embolism						0.388						1.000
Absent	789	418	82.0	371	79.8			195	87.8	195	87.8	
Present	186	92	18.0	94	20.2			27	12.2	27	12.2	
T stage (7th UICC)						0.000						1.000
T1	65	31	5.9	34	7.3			7	3.2	7	3.2	
T2	143	72	14.1	71	15.3			18	8.1	18	8.1	
T3	667	384	75.3	283	60.9			192	86.5	192	86.5	
T4 a	100	23	4.5	77	16.6			5	2.3	5	2.3	
N Stage						0.955						1.000
N0	19	10	2.0	9	1.9			3	1.4	3	1.4	
N1	570	299	58.6	271	58.3			134	60.4	134	60.4	
N2	285	146	28.6	139	29.9			69	31.1	69	31.1	
N3	101	55	10.8	46	9.9			16	7.2	16	7.2	
7thUICC						0.000						1.000
II b	145	66	12.9	79	17·0			21	9.5	21	9.5	
III a	449	263	51.6	186	40.0			118	53.2	117	52.7	
III b	214	117	22.9	97	20.9			65	29.3	66	29.7	
III c	167	65	12.5	103	22.2			18	8.1	18	8.1	

Results

Patients' characteristics

975 patients with stage III or node-positive thoracic esophageal squamous cell carcinoma according to the Union for International Cancer Control (UICC) TNM Cancer Staging 7th were involved in this study after radical operation (R0) in our hospital between January 2004 and December 2011 (Table 1). 510 patients (52.3%) received R0 surgery alone and 465 cases (47.7%) had postoperative adjuvant therapy (including 331 cases with postoperative radiotherapy and 134 cases with postoperative chemoradiotherapy). A total of 11, 126 lymph nodes were removed from 975 patients, and the median number was 23 for each patient (ranging: 3–78). Several clinicopathologic characteristics were statistically significant differences were observed between surgery alone group with that in adjuvant therapy group, such as gender, age, tumor location and TNM stage. After propensity score matching, 222 well-balanced pairs were available for outcome comparison. A total of 1335 lymph nodes were positive, and the median number was two for each patient (ranging: 0–35).

Overall survival rate and disease-free survival rate before and after PSM

Before PSM, the median follow-up time was 69.2 months (95% CI 67.1–71.4 months). The 3-year and 5-year OS were 43.3%, 32.8% respectively, and the median OS (mOS) was 28.9 months. The 3-year and 5-year OS in the surgery alone group were 35.4%, 26.1%, and the mOS was 24.9 months, and those in adjuvant therapy group were 52.3%, 40.3% and 41.8 months (Fig. 2a, $P = 0.000$). The corresponding DFS were 37.7%, 31.7% and 22.5 months, in which those in surgery group were 30.9%, 25.7% and 17.2 months, and those in adjuvant therapy group were 45.1%, 38.2% and 28.6 months (Fig. 2b $P = 0.000$). In matched cohort, the 3-year, 5-year OS and mOS were 40.5%, 31.7% and 27.9 months. The 3-year, 5-year OS and mOS in surgery alone group were 33.0%, 26.4% and 24.3 months, and those in adjuvant treatment group were 48.3%, 37.1% and 34.3 months (Fig. 3a, $P = 0.002$). The corresponding DFS were 35.1%, 29.8% and median DFS (mDFS) was 21.5 months; those in surgery alone group and in postoperative treatment group were 31.0%, 26.5%, 19.2 months and 39.2%, 32.7%, 24.1 months, respectively, the difference is statistically significant (Fig. 3b, $P = 0.035$).

Univariate and multivariate cox analyses

The univariate and multivariate analyses for 11 prognostic factors were done by the Cox regression analysis model in matched patients. The results from univariate analysis showed that not only T and N stage and treatment modality but also the differentiation and intravascular invasion influenced survival. In the multivariate analysis, the independent prognostic factors were the T, N stage and adjuvant therapy (Table 2).

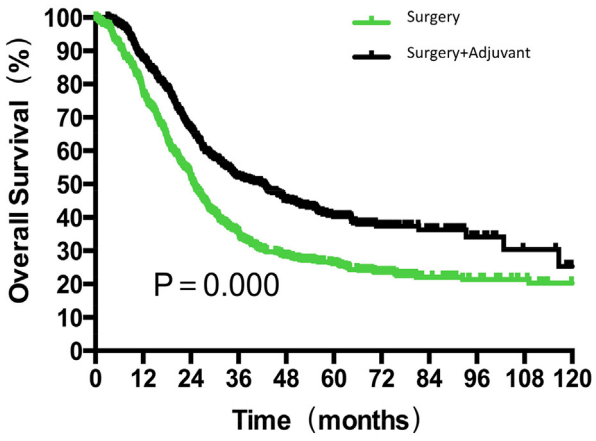

Fig. 2a. There was significant survival improvement between patients with or without adjuvant treatment before PSM.

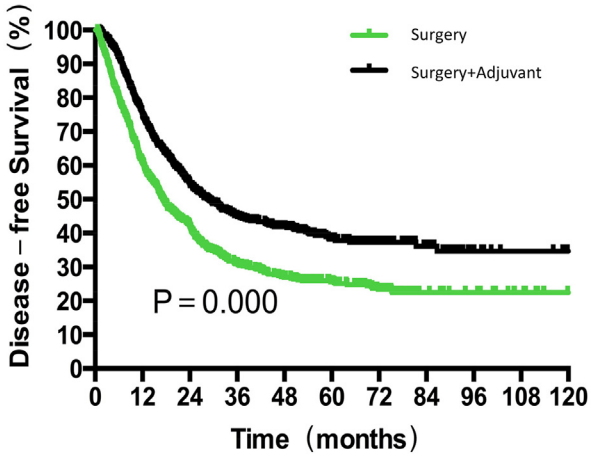

Fig. 2b. There was significant disease-free survival improvement between patients with or without adjuvant treatment before PSM.

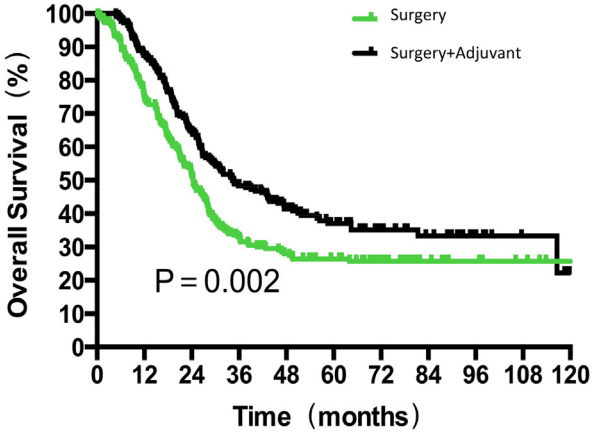

Fig. 3a. There was significant survival improvement between patients with or without adjuvant treatment after PSM.

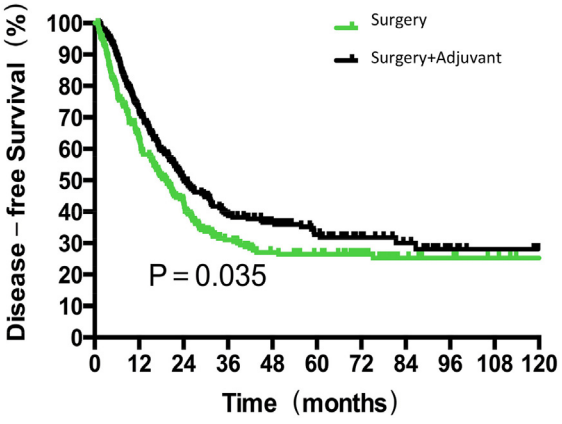

Fig. 3b. There was significant disease-free survival improvement between patients with or without adjuvant treatment after PSM.

Table 2
Univariate and Multivariate Cox Analysis of patients after PSM.

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	p
Sex			0.504			
Male	1					
Female	0.870	0.577–1.311	0.504			
Age			0.918			
≤60	1					
>60	0.988	0.782–1.248				
Tumor site (6th)			0.396			
Upper	1					
Median	0.924	0.513–1.665	0.793			
Lower	0.794	0.439–1.435	0.445			
Proximal margin length			0.749			
≤5 cm	1					
>5 cm	0.958	0.736–1.247				
Number of node harvested			0.385			
<22	1					
≥22	1.108	0.879–1.395				
pT-Stage (09 UICC)			0.013			0.052
T1	1			1		
T2	1.294	0.514–3.262	0.584	1.225	0.483–3.103	0.699
T3	2.391	1.064–5.375	0.035	2.006	0.886–4.538	0.095
T4a	1.733	0.559–5.376	0.341	3.647	0.898–14.811	0.070
p N stage			0.000			0.000
N0	1			1		
N1	1.331	0.424–4.178	0.624	2.274	0.454–11.385	0.318
N2	2.740	0.869–8.642	0.085	0.330	0.887–23.247	0.069
N3	3.423	1.031–11.360	0.044	4.863	0.900–26.272	0.066
Differentiation			0.017			0.185
Well	1			1		
Moderate	1.261	0.828–1.922	0.280	1.092	0.712–1.674	0.687
Poor	1.693	1.092–2.624	0.019	1.363	0.866–2.145	0.180
Intravascular invasion			0.024			0.624
Yes	1			1		
No	1.460	1.052–2.027		1.091	0.770–1.545	
Treatment modality			0.002			0.000
Surgery	1			1		
Surgery + RT	0.690	0.548–0.870		0.635	0.502–0.803	
Weight loss			0.355			
No	1					
Yes	1.156	0.850–1.572				
Tumor length			0.581			
≤3 cm	1					
3–5 cm	1.024	0.670–1.565	0.913			
5–7 cm	1.247	0.788–1.976	0.346			
>7 cm	1.219	0.755–1.967	0.418			

Survival of postoperative chemoradiotherapy and postoperative radiotherapy

In the adjuvant group, 465 patients were enrolled, in which 331 patients (71.2%) received radiotherapy and 134 (28.8%) received chemoradiotherapy. The 3-year and 5-year OS in chemoradiation group and radiotherapy group were 56.1% and 42.4%, and the mOS was 43.5 months (95%CI 31.7–55.2 months). Those in radiotherapy group were 50.6%, 39.6% and 37.7 months (95%CI 29.8–45.7 months) (Fig. 4a $P = 0.692$) respectively. The corresponding 3-year and 5-year DFS and mDFS were 44.6%, 33.3% and 27.5 months in chemoradiation group and those in radiotherapy group were 45.4%, 39.6% and 28.8 months (95%CI 21.8–35.9 months). (Fig. 4b, $P = 0.368$).

Discussion

In the present study, with a median follow-up of 69.2 months, survival benefits were observed in adjuvant radiotherapy or chemoradiation was observed associated with longer survival, and survival benefits maintained in propensity-score matching cohort. T, N stage and adjuvant therapy were independent prognosis factors of overall survival.

Whether adjuvant therapy could improve the survival rate of the patients with esophageal cancer [2–20] remains controversial. At present, the NCCN clinical practice guidelines recommend [21] no adjuvant therapy in patients with clear margin after esophagectomy, regardless of presence of other adverse prognostic factors, such as T3/4, lymph node positive or poor differentiation. The results of prospective randomized study [5–8] failed to show survival benefit of adjuvant radiotherapy for patients with esophageal carcinoma after surgery. A recent meta-analysis showed that surgery along with adjuvant therapies demonstrated no survival advantage when compared with surgery alone (HR 0.87, $P = 0.321$) [25]. However, the results of subgroup analysis of the phase III prospective randomized controlled study reported by Xiao et al. [2,3] showed that postoperative radiotherapy increased the survival rate of patients with stage III and lymph node positive. The same results were also obtained in the literature with a small sample of patients with postoperative radiotherapy and chemotherapy [4,5]. No large-sampled prospective study was reported, although the results of several large-sample retrospective analyses were subsequently published [10–15]. Previous data showed that the survival rate in the patients with adjuvant radiotherapy or chemoradiotherapy was significantly higher than that

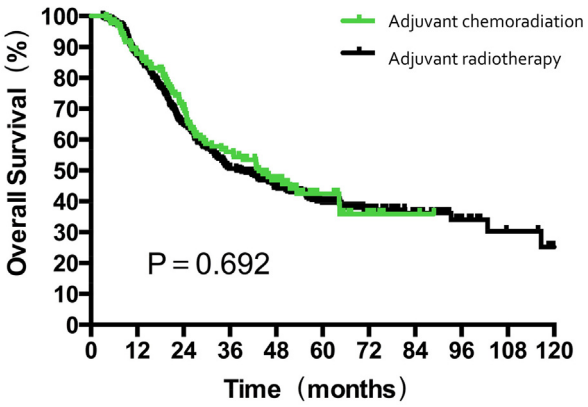

Fig. 4a. No differences were observed in overall survival between patients with adjuvant chemoradiation or adjuvant radiotherapy.

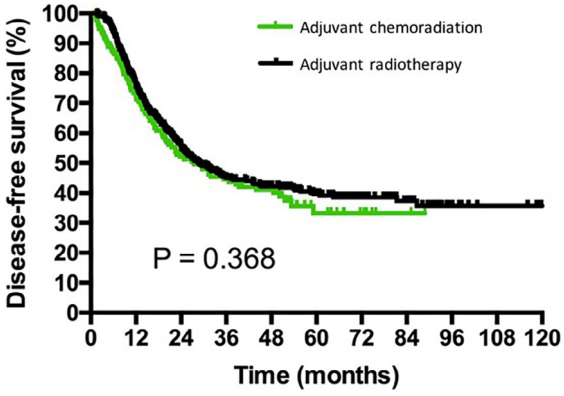

Fig. 4b. No differences were observed in disease-free survival between patients with adjuvant chemoradiation or adjuvant radiotherapy.

with surgery alone; some factors such as R1-2 surgery patients included may confound the results.

Compared with the neoadjuvant therapy, the advantage of adjuvant therapy strategy is the more accurate pathologic staging, avoiding overestimated or underestimated disease. Based on different prognoses including survival rate, failure rate and patterns of recurrence, accuracy of pathological staging reduces the risk of over-treatment or insufficient treatment. However, no prospective large-sampled studies existed to support subgroup analysis.

In order to elucidate the significance of adjuvant therapy for the patients with squamous cell esophageal cancer after R0 surgery, we included only the patients with thoracic esophageal squamous cell carcinoma, who were pathologically diagnosed as stage III or node-positive based on the UICC 7th staging system and received radical surgery in our hospital. The 5-year OS and mOS in the whole group were respectively 32.8% and 28.9 months. These results indicated that survival rate of the patients with esophageal cancer in stage III or node-positive was higher than that in the literature (5-year overall survival approximately 20%). A possible explanation is that only patients with R0 surgery were enrolled, excluding the adverse factors affecting the prognosis of R1-R2 surgery. Another reason may be that 47.7% patients in our cohort received adjuvant therapy. Because the results showed that both overall survival (5-year OS 40.3%, mOS 41.8 months) and DFS (5-year DFS 38.2%, mDFS 28.6 months) in adjuvant therapy group was significantly higher than those in the surgery alone group (5-year OS 26.1%, median 24.9 months, 5-y DFS 25.7%, median 17.2 months, $P = 0.000$). The present result enhances the findings of our previous study [13] and other investigators' reports [10–15,19,20,26] that the adjuvant radiotherapy/chemoradiotherapy has a survival benefit for the patients in this subgroup (stage III and node positive) of esophageal squamous cell cancer.

The patients enrolled in this analysis consist of a retrospective, nonrandomized clinical trial. The propensity score matching method was used to generate a well-balanced cohort, in order to reduce the selecting bias of retrospective analysis. Patients' characteristics are shown in Table 1, the two groups are comparable. 5-year OS and DFS of matched cohort were 31.7% and 29.8%, respectively. The mOS was 27.9 months and mDFS was 21.5 months. The survival rates and median survival time were very close to those before PSM. The matched results still showed that the survival rate of adjuvant therapy (5-year OS 37.1%, DFS 32.7%) was higher than that of the surgery group (5-year OS 26.4%, DFS 26.5%), and the differences were statistically significant ($P = 0.002$, 0.035). This further indicates that adjuvant therapy could improve the survival rate in this subgroup of esophageal cancer patients with R0 surgery. Multivariate analysis of matched group showed that the independent prognostic factors were only adjuvant therapy, T and N stage. However, before PSM the prognostic factors included the cell differentiation, site of the tumor and vascular tumor thrombus in addition to three factors that were consistent with the matched cohort.

It is debatable whether the survival rate of adjuvant therapy increased compared with surgery alone, and the possible reasons were: 1. small-sampled studies, with unselected patients, using conventional 2D technique and old chemotherapy regimens in the prospective studies of early years [4–9]; 2. the presence of confounding factors such as R1-2 surgery, as Rice et al. reported that the 5-year survival rate of patients with R0 surgery was significantly higher than that of R1 surgery and R2 surgery; 3. the different survival rates in the patients in different stage, for example, the discrepant prognoses of stage T1-3N0 and stage T1-4N+ were due to the different rate of recurrence and metastasis, 5y OS in stage IIa, IIb, and III tapering off, from 60% to 18%. Xiao et al. reported [2,3] the 3-year OS of the esophageal cancer patients received postoperative radiotherapy in II a stage according to UICC 6th staging system was increased by 8% (64.0% and 56.0%) compared with the patients in surgery alone group. However, no difference was observed in the 5-year OS (50.3% and 51.3%), although there was a difference in failure modality and failure rate. The retrospective analysis of 1046 patients included in SEER database from MD Anderson Cancer Center in 2010 showed that the 3-year disease-specific survival ($P = 0.010$) and 3-year OS ($P = 0.042$) of the patients with postoperative radiotherapy were significantly improved compared with surgery alone. This especially benefits patients significantly in stage III ($P < 0.001$), but there was no significant difference in the survival rates of patients with II a and II b. Therefore, we conducted a prospective target volume analysis in stratified cohorts (T2-3N0M0 and stage IIb-III) since 2004 and in order to select the patients benefit from postoperative adjuvant radiotherapy. The present study demonstrated that postoperative treatment (radiotherapy or chemoradiation) improved long-term survival of the subgroup of patients (stage IIb-III), providing data for future prospective randomized study.

Zhang et al. [13] reported that hematogenous failure accounted for 30.7% after postoperative radiation, significantly higher than patients who received surgery alone (21%), $P = 0.023$. These data supported the postoperative chemotherapy concurrent or sequential with radiotherapy. To evaluate the merit of postoperative chemoradiation, we compared the chemotherapy with radiotherapy alone and found that postoperative chemoradiation did not improve DFS ($P = 0.368$) or overall survival ($P = 0.692$). The possible explanations are first, patients received both radiotherapy and chemotherapy including paclitaxel and cisplatin (weekly), paclitaxel and cisplatin (3 weeks), cisplatin, capecitabine, S-1. No

consensus on the optimal regimen for postoperative chemotherapy. Moreover, 65 patients were enrolled in a phase I/II clinical trial conducted in our hospital, therefore received insufficient dose intensity of chemotherapy. On the contrary, in 465 patients who received chemoradiotherapy or radiotherapy after esophagectomy, 364 patients were administered radiotherapy in our hospital soundly documented, only twelve patients (3.2%) received a low dose radiotherapy of below 50 Gy. Intolerance to the intensive treatment combined chemotherapy with radiotherapy resulted in limited survival benefits. There were several obstacles stirring the prevalence of chemoradiation: dose of radiation, dose of chemotherapy, target volume, adverse events and completion of regimen. A large-sampled retrospective analysis from Chen et al. [20] demonstrated that adjuvant chemoradiation improved survival, distant metastasis, combined metastasis and recurrence compared with surgery alone. Scarcely did updated evidence support postoperative chemoradiation. Though clinical trials on postoperative radiation dated back to 2001 [5], no validated data supported postoperative radiation as a standard treatment for patients after radical surgery.

This research was a large-sampled, single centered retrospective analysis using propensity score matching to improve the comparability between the surgery alone group and the adjuvant therapy group. As the nature of retrospective study, the bias inevitably exists, patients who were not administered adjuvant treatment had follow ups at local hospitals, thus incomplete KPS were documented. A weakness was no standard target volume and chemotherapy regimen administered. A multi-centered, prospective, randomized study with unique target volume of radiotherapy and dose and regimen of chemotherapy is warranted to validate the results and guide the clinical practice.

Conclusion

The present study showed that the postoperative adjuvant therapy could significantly improve the survival of the patients with TESCC in subgroup (stage IIb-III). It is still necessary to confirm our results by multi-centered, randomized, prospective clinical studies.

Author contributions

Shufei Yu: Data collection, statistics, original draft.

Wencheng Zhang, Wenjie Ni, Qifeng Wang: data collection.

Zefen Xiao: Conceptualization, review and editing the manuscript.

Zongmei Zhou, Zongmei Zhou, Qinfu Feng, Hongxing Zhang, Dongfu Chen, Jun Liang, Jima Lv, Zhouguang Hui: Executed the protocol and data collection.

Xiangyang Liu, Shugeng Gao, Dekang Fang, Kelin Sun, Jie He: Executed esophagectomy.

Yexiong Li: Monitor the clinical trial.

Declaration of Competing Interest

No conflicts of interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.020.

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