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ORIGINAL ARTICLE

Definitive chemoradiation therapy or surgery for clinical T1-3N0-1M0 thoracic esophageal squamous cell carcinoma: A propensity score matching analysis

Xu-Yuan Li [a,d], He-San Luo [b,d], Sheng-Xi Wu [b], Ze-Sen Du [c], Chun-Peng Zheng [c,*], Zhi-Yong Wu [c]

[a] *Department of Medical Oncology, Shantou Central Hospital, Shantou, Guangdong, China*
[b] *Department of Radiation Oncology, Shantou Central Hospital, Shantou, Guangdong, China*
[c] *Department of Surgical Oncology, Shantou Central Hospital, Shantou, Guangdong, China*

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Summary *Background:* To compare overall survival in patients with clinical T1-3N0-1 thoracic esophageal squamous cell carcinoma treated with surgery or definitive chemoradiation therapy (CRT).
Methods: We used propensity-score matching to derive 1:1 cohorts of surgery versus definitive CRT. Statistical analysis was performed using χ^2 or Fisher's exact tests. Survival functions were estimated using Kaplan–Meier survival plots, and survival distributions were compared using log-rank tests. Cox proportional hazards modeling was used to analyze the factors affecting overall survival.
Results: A total of 334 patients treated with surgery and 252 treated with definitive CRT were included. 129 (38.6%) of 334 patients had recurrence after surgery versus 118 (46.8%) of 252 after definitive CRT. Before matching, the median overall survival were 39.5 months (95% CI, 28.8–50.2) and 23.5 months (95% CI, 18.5–28.5) ($P < 0.001$) in the surgery and definitive CRT group, respectively. After matching (112 patients in each treatment group), median overall survival was 43.6 months (95% CI, 28.1–59.1) with surgery versus 19.3 months (95% CI, 14.4–24.2) with CRT ($P < 0.001$).
Conclusions: In this retrospective analysis, surgery was associated with better overall survival compared with definitive CRT.

* *Corresponding author.* Waima Road 114, Shantou, China. Fax-number: +86-0754-88550540.
E-mail address: 185694719@qq.com (C.-P. Zheng).
[d] These two authors contributed equally.

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1. Introduction

Esophageal cancer is the fifth most common cause of cancer-related mortality in China.[1] The Chao—Shan region in southern China is noted for its high incidence of esophageal cancer, and squamous cell carcinoma accounts for over 90% of all cases of esophageal cancer in our hospital. There is currently no clear consensus regarding the optimal management modality for localized esophageal squamous cell carcinoma.[2] The results of the CROSS study suggested that surgery combined with neoadjuvant chemoradiation therapy (CRT) should be regarded as the standard treatment for patients with resectable, locally advanced esophageal cancer.[3] However, squamous cell carcinoma only comprised 23% (84/359) of all cases in the CROSS study, which does not reflect the routine practice in our region.

Definitive CRT demonstrated acceptable survival outcomes compared with surgery for the potential curative treatment of esophageal cancer in some clinical reports,[4—9] with positive impacts on some aspects of quality of life assessments.[10] However, this evidence was based on small prospective clinical trials or retrospective analyses. The low incidence of esophageal squamous cell carcinoma in western countries makes it difficult to perform randomized clinical trials of surgery versus non-surgical treatments,[11] and inadequate resources and funding also make such prospective studies unfeasible in our region. However, we established a database at the Oncology Treatment Center at Shantou Central Hospital, Shantou, China, between 2009 and 2011, and have included data on patients who have received radical surgery or definitive CRT at our institution since then. Herein, we report on the recurrence and survival patterns of patients with clinical T1-3N0-1M0 thoracic esophageal squamous cell carcinoma treated with surgery or definitive CRT.

2. Methods

2.1. Patient population

This was a retrospective cohort study. Data were analyzed anonymously. For the use of these clinical materials for research purposes, approval from the Ethics Committees of the Shantou Central Hospital was obtained. All protocols were approved by the committee. The methods were carried out in accordance with the approved guidelines.

Between January 2009 and December 2011, patients with esophageal squamous cell carcinoma who underwent radical surgery were registered in the surgery database, and patients who received definitive CRT were included in the CRT database. All the data in this study were obtained from these databases. Patients in the database with clinical T1-3N0-1M0 were eligible for inclusion, while patients with T4 stage, or evidence of metastatic cancer were not eligible. Patients with cervical esophageal cancer were also excluded. A total of 586 consecutive patients were finally included in this study, including 252 treated with definitive CRT and 334 with surgery. Endoscopic ultrasonography was unavailable at the time in our hospital; therefore patients were diagnosed by computed tomography (CT). Each esophageal carcinoma was staged according to the American Joint Committee on Cancer TNM clinical stage classification (2002). The last follow-up was performed in October 2015.

2.2. Esophagectomy

All esophagectomy procedures were performed by experienced thoracic surgeons. The most frequently used procedure was esophagectomy with two-field lymphadenectomy via right thoracotomy. Lymphadenectomy included the mediastinal and abdominal lymph nodes. Esophagectomy and lymphadenectomy were followed by esophageal reconstruction using a gastric tube.

2.3. Definitive CRT

Each treatment field encompassed the tumor bed with 3 cm proximal and distal margins and 1 cm lateral margins. Patients received a total of at least 50.4 Gy irradiation. All patients received 5-fluorouracil (5-FU) and cisplatin-based chemotherapy concurrently with irradiation. The most frequently used chemotherapy protocol consisted of two cycles of 5-FU (750 mg/m^2, days 1—4) and cisplatin (65—75 mg/m^2, day 1) every 21 days.

2.4. Pattern of recurrence and follow-up evaluation

Patterns of recurrence were defined by the first site of recurrence. Locoregional sites included the mediastinum, perigastric region, and celiac trunk region. Distant disease included cervical and para-aortic lymph node dissemination below the level of the pancreas, malignant pleural effusions, peritoneal carcinomatosis, and further organ dissemination. All patients received follow-up at 1 month after their initial treatment (CRT or surgery) and then every 3—6 months, for 5 years. The first follow-up evaluation included a physical examination, blood test, endoscopy of the esophagus, and CT scan of the neck, chest, and abdomen. Following evaluations included a physical examination, blood test, and barium-meal examination. Endoscopy and CT scans were performed if indicated.

2.5. Statistical analysis

We used propensity score matching to address imbalance between groups. Cases for matching were restricted in patients who received treatment between January 2009 and December 2011. The propensity-score model included age, gender, tumor location, clinical T stage, clinical nodal status, and stage, using a one-to-one nearest neighbor caliper of width 0.1. R software (version i386 3.3.2) was applied for treatment groups matching.

Survival periods were calculated from the date of surgery or start of CRT. Time to treatment failure included time to death from all causes and all recurrences. Statistical analysis was performed using χ^2 or Fisher's exact tests. Survival functions were estimated using Kaplan—Meier survival plots, and survival distributions were compared using log-rank tests. Cox proportional hazards modeling was used to analyze the factors affecting overall survival. A *P* value < 0.05 indicated a significant difference. All P values were two-sided. Analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 334 patients who underwent surgery and 252 who received definitive CRT were eligible for this study. All patients were documented good performance status (ECOG 0 or 1). CRT was well tolerated. Three patients developed esophageal fistulas, and three suffered bleeding caused by tumor necrosis. Of the 252 patients who received definitive CRT, 128 showed disappearance of esophageal cancer by CT scan, and 73 received two cycles of 5-FU or cisplatin-based chemotherapy after definitive CRT.

Esophagectomy was performed successfully in all patients, with a R0 resection rate of 61%. The operative mortality was as low as 1.19% (4/334). Sixty-one patients received postoperative adjuvant therapy, 17 with four cycles of 5-FU or cisplatin-based chemotherapy, 37 with adjuvant radiation, and seven with adjuvant CRT. There was no discrepancy of T status in the surgery group.

The baseline characteristics of the two groups are summarized in Table 1. Before matching, imbalance was existed in age, location, T stage, nodal status, and disease stage. After matching, baseline characteristics were balanced. Fig. 1 showed the distribution of propensity scores.

Twenty-one and two patients were lost to follow-up in the surgery and CRT groups, respectively. The median follow-up times (range) were 60.7 months (1.2—79.1) and 48.6 months (1.6—81.3) in the surgery and CRT groups, respectively.

The recurrence patterns differed between the two groups, with more locoregional recurrence in the CRT group but more distant recurrence in the surgery group (Table 2). Locoregional recurrence accounted for 73% of all 118 events in the CRT group, whereas distant recurrence accounted for 72% of all 129 recurrences in the surgery group. The median times to treatment failure were 31.3 months (95% confidence interval [CI], 22.3—40.3) and 16.4 months (95% CI, 20.6—27.0) in the surgery and the CRT groups ($P < 0.001$), respectively.

There were 185 deaths in the surgery group and 169 in the CRT group during the follow-up period. The median overall survival times were 39.5 months (95% CI, 28.8—50.2) and 23.5 months (95% CI, 18.5—28.5) in the surgery and CRT groups ($P < 0.001$), respectively (Fig. 2). The 1-, 2- and 3-year overall survival rates were 86.5%, 69.5%, and 54.5%, respectively, in the surgery group and 76.2%, 49.6%, and 40.5% in the CRT group. Cox proportional hazards modeling showed that surgery, T stage, and nodal status were prognostic factors for overall survival (Table 3). Among 128 patients in the CRT group who showed disappearance of the tumor after initial treatment, the 90 were with tumor length $\leq$6 cm, and only 7 were with T1 or T2 disease. Of the 128 patients who had complete response, 27 developed recurrence, consisting of 6 distant metastasis and 21 locoregional relapse. The recurrence pattern was in line with the whole group. The median overall survival time was 48.5 months (95% CI, 36.6—60.4), which was comparable with the surgery group ($P = 0.809$).

After matching (112 patients in each treatment group), median overall survival was 43.6 months (95% CI, 28.1—59.1) with surgery versus 19.3 months (95% CI, 14.4—24.2) with CRT ($P < 0.001$) (Fig. 3). There was about 48% (54/112) of patients who were complete responders in the match group.

4. Discussion

Long-term survival of patients with esophageal squamous cell carcinoma is poor. Surgery is traditionally the mainstay of treatment but has been challenged by definitive CRT. Previous randomized studies compared definitive CRT and CRT with surgery for the treatment of squamous esophageal carcinoma,[12,13] and showed no overall survival benefit when incorporating surgery. Furthermore, complete tumor response was frequently observed after neoadjuvant CRT, thus prompting investigations into definitive CRT as an alternative to surgery.

In the retrospective study, we aimed to investigate the recurrence pattern and survival in patients under dCRT or surgery. More patients underwent surgery suffered from distant recurrences, while those received dCRT had more local relapse. However, it should be noted that more patients with stage III disease in the surgery group. In our study, 33% of patients in the surgery group had cervical and para-aortic lymph node metastasis, compared with about 20% of patients in the CROSS trial.[14] Therefore, insufficient lymph node dissection might contribute to such a high incidence of lymph node metastasis.

Survival data from all cases in this study indicated that surgery was associated with remarkably better survival outcomes than definitive CRT, in contrast to the results of some previous reports. Before propensity-score matching, patients from the two departments who received surgery or definitive CRT were all included, and the results could therefore be subject to imbalances in terms of patient characteristics such as age, T staging, nodal status, and disease stage.

A propensity score matching method was widely used in retrospective studies to adjust for confounders thus to enhance comparability,[15—17] which was adopted in this

Table 1 Patient characteristics.

	Before matching		*P*	After matching		*P*
	Surgery N = 334 (%)	Definitive CRT N = 252 (%)		Surgery N = 112 (%)	Definitive CRT N = 112 (%)	
Age, years			<0.01			0.54
Mean	58.5	64.4		58.9	60.1	
Range	33–81	40–95		33–81	43–95	
Gender			0.24			0.11
Male	249 (74.6)	177 (70.2)		83 (74.1)	72 (64.3)	
Female	85 (25.4)	75 (29.8)		29 (25.9)	40 (36.7)	
Location			<0.01			1.00
Upper	29 (8.7)	72 (28.6)		29 (25.9)	29 (25.9)	
Middle	217 (65.0)	134 (53.2)		70 (62.5)	70 (62.5)	
Lower	88 (26.3)	46 (18.2)		13 (11.6)	13 (11.6)	
Nodes			<0.01			1.00
Negative	53 (15.9)	101 (40.1)		39 (34.8)	39 (34.8)	
Positive	281 (84.1)	151 (59.9)		73 (65.2)	73 (65.2)	
T			0.04			1.00
1	29 (8.7)	9 (3.6)		5 (4.5)	5 (4.5)	
2	42 (12.6)	35 (13.9)		16 (14.3)	16 (14.3)	
3	263 (78.7)	208 (82.5)		91 (81.2)	91 (81.2)	
Stage			<0.01			1.00
I	9 (2.7)	6 (2.4)		2 (1.9)	2 (1.9)	
IIA	44 (13.2)	94 (37.3)		37 (33.0)	37 (33.0)	
IIB	53 (15.9)	16 (6.3)		10 (8.9)	10 (8.9)	
III	228 (68.2)	136 (54.0)		63 (56.2)	63 (56.2)	

study. After matching, all the clinical parameters which were considered prognostic were well balanced such as T stage, nodal status, and disease stage. Because the pathological T and N stage was not defined in the definitive CRT group, we included clinical stage to be balanced in the propensity score matching process. As for nodal status, the accurate number of positive lymph nodes could not be determined in the CRT group, therefore, the 6th edition of American Joint Committee on Cancer stage was applied. The results from the matching cohorts again confirmed the superiority of surgery over dCRT with regard to overall survival.

The median overall survival in the definitive CRT group in our study was similar to those in previous prospective trials.[12,13] The median overall survival for surgery in the

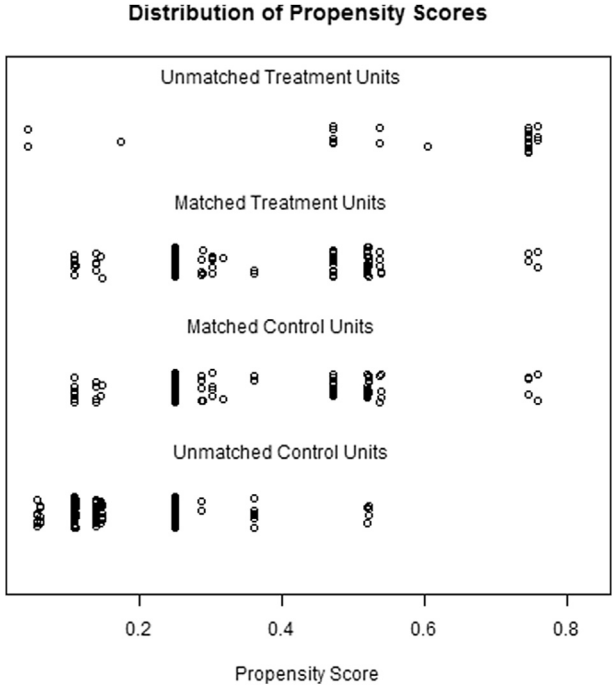

Fig. 1 The distribution of propensity scores.

Table 2 Site of first recurrence.

Recurrence	CRT	Surgery
Locoregional	**79**	**36**
Esophagus	61	4
Mediastinal LN	13	21
Perigastric LN	5	11
Distant	**39**	**93**
Lung	14	19
Liver	6	15
Bone	8	13
Brain	0	2
Cervical LN	3	18
Para-aortic LN	4	13
MPE	1	2
PC	1	1
Mixed	2	10

LN, lymph nodes; MPE, malignant pleural effusion; PC, peritoneal carcinomatosis.

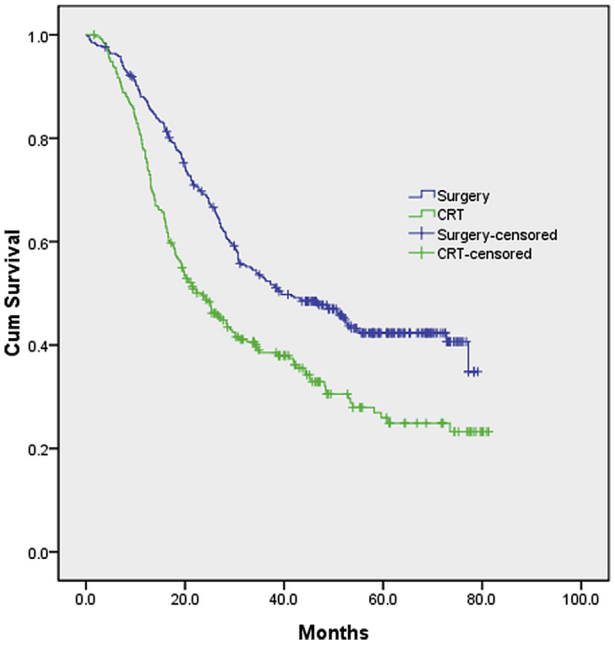

Fig. 2 Overall survival curve of the surgery and dCRT groups before matching.

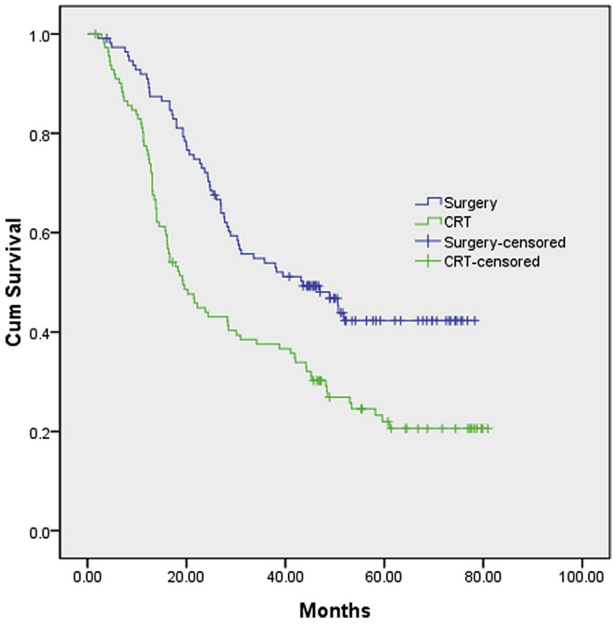

Fig. 3 Overall survival curve of the surgery and dCRT groups after matching.

present cohort was better than most previous reports; however, a recent large prospective study reported a median overall survival of 81.6 months for patients with squamous cell carcinomas under neoadjuvant chemoradiotherapy.[3] Approximately 20% of patients in the surgery group have received adjuvant therapy, which may contribute to survival.

Notably, overall survival of the 128 patients who showed complete tumor response by CT scan after definitive CRT was similar to that of patients in the surgery group. In the previous small prospective trial[9] that demonstrated identical survival outcomes of surgery and CRT, definitive CRT achieved a complete tumor response in 92% (33/36) of all patients. This supports the idea that surgery may be omitted in patients who show a complete response after neoadjuvant CRT.[12,13]

There are several limitations in this study. First, assignment to the CRT and surgery groups was not randomized, reflecting the nature of the current study and representing an important limitation. Second, the CRT group included some patients considered medically unfit for surgery, and the unfavorable survival of this population could have compromised the survival of the group as a whole. Third, post-recurrence treatment was not regularly recorded in the database, and this might have had an impact on the survival analysis. Fourth, even the propensity score matching method may introduce bias.

In conclusion, this retrospective study indicated that patients in our institution with thoracic esophageal squamous cancer who underwent radical surgery had longer overall survival than those who received definitive CRT. The results of this study warrant further large, prospective randomized studies to compare the outcomes of surgery and CRT in patients with locally advanced esophageal squamous cancer.

Table 3 Multivariate analysis using Enter or Forward Stepwise Method.

	HR (95% CI)	*P* value
Enter		
Treatment (surgery, CRT)	1.77 (1.41–2.23)	<0.001
N (N0, N1)	1.48 (1.14–1.94)	<0.01
T (T1, T2, T3)	1.56 (1.24–1.96)	<0.001
Stage (I, IIA, IIB, III)	1.24 (1.10–1.41)	<0.001
Age (≤60, >60 years)	1.18 (0.96–1.47)	0.12
Location (upper, middle, lower)	1.15 (0.98–1.33)	0.07
Sex (male, female)	0.97 (0.76–1.23)	0.78
Forward Stepwise		
Treatment (surgery, CRT)	1.65 (1.27–2.12)	<0.001
T (T1, T2, T3)	1.60 (1.26–2.04)	<0.001
N (N0, N1)	1.54 (1.13–2.10)	0.005

Conflicts of interest

None.

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.04.009.

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