Annals of Clinical Case Reports

Research Article
Published: 03 Jan, 2018

Trimodality versus Chemo Radiation Therapy Alone: The Role of Surgery in Treatment of Locally Advanced Squamous Cell Carcinoma of the Esophagus

Yaping Xu[1], Chenxue Jiang[1], Gang Lin[1], Xiang Zhu[2], Shuiyun Han[2], Xiaojiang Sun[2], Jinshi Liu[3], Qixun Chen[3] and Weimin Mao[3]*

[1]Department of Radiation Oncology, Zhejiang Cancer Hospital, China

[2]First Clinical Medical School, Wenzhou Medical University, China

[3]Department of Thoracic Surgery, Zhejiang Cancer Hospital, China

Abstract

Background and Purpose: The current practice varies in treatments of locally advanced Squamous Cell Carcinoma (SCC) of esophagus in different countries. This study aimed to compare the results of trimodality therapy with CRT alone in patients with locally advanced resectable SCC.

Patients and Methods: Patients with locally advanced resectable SCC of esophagus were eligible. For trimodality, patients received surgery and preoperative/postoperative chemoradiation. In CRT alone group, patients only received radiation and chemotherapy. Local tumor control, 3-year survival and treatment-related mortality were assessed.

Results: 184 consecutive patients were analyzed. 109 were treated with trimodality therapy, 75 received CRT alone depended on patients' willing. 17.4% of the resected patients in trimodality group had locoreginal recurrent disease versus 30.7% in the CRT alone group (P= 0.036). The 3-year progression-free survival (PFS) was 53.8% versus 33.5% (P= 0.019), and the overall survival (OS) was 51.2% versus 39.8% (P= 0.011), for patients received trimodality and CRT alone, respectively. Treatment-related mortality was 3.7% in trimodality group compared with 1.3% in definitive CRT group (P= 0.650). There was no significant difference in the 3-year OS in patients receiving a 50.4 Gy radiation dose compared with >50.4 Gy radiation dose in CRT alone group (45.3% vs. 36.4%, P = 0.927).

Conclusions: Compared with CRT alone, trimodality therapy appeared to have superior local control, PFS and OS, with similar treatment-related mortality for the treatment of patients with SCC of esophagus. The role of surgery could not be replaced by CRT alone, even with increased radiation dose.

Keywords: Oesophageal squamous cell carcinoma; Trimodality therapy; Preoperative chemoradiotherapy; Postoperative chemoradiotherapy; Definitive chemoradiotherapy

OPEN ACCESS

Correspondence:
Yaping Xu, Department of Radiation Oncology, Zhejiang Cancer Hospital, No.1 Banshan East Road, Hangzhou, China,
E-mail: xuyp@zjcc.org.cn

Received Date: 25 *Sep 2017*
Accepted Date: *28 Dec 2017*
Published Date: *03 Jan 2018*

Citation:
Xu Y, Jiang C, Lin G, Zhu X, Han S, Sun X, et al. Trimodality versus Chemo Radiation Therapy Alone: The Role of Surgery in Treatment of Locally Advanced Squamous Cell Carcinoma of the Esophagus. Ann Clin Case Rep. 2018; 3: 1490.

ISSN: 2474-1655

Introduction

Esophageal cancer is the sixth most common cause of cancer deaths worldwide and is more common in the developing nations[1]. Esophageal cancers are histologically classified as Squamous Cell Carcinoma (SCC) or adenocarcinoma. SCC is the major histology in Eastern Europe and Asia, and 95% of esophageal cancer is pathologically diagnosed as SCC in China[2]. Radiochemotherapy and surgical resection are standard therapies for patients with locally advanced resectable SCC of the esophagus.

Numerous randomized trials have investigated the impact of radiotherapy dose modifications, combined-modality therapy, and preoperative/postoperative administration of adjuvant therapy in an effort to improve effectiveness without compromising safety, reducing the incidence of local recurrence, and prolonging survival [3-7]. For example, results from the multicenter phase III randomized trial (CROSS study), the largest trial in its class, showed that preoperative chemoradiotherapy (CRT) with carboplatin and paclitaxel significantly improved overall survival (OS) and disease-free survival (DFS) compared to surgery alone in patients with resectable (T2-3, N0-1, M0) esophageal or esophagogastric junction (EGJ) cancers[8]. Similarly, the results of

two meta-analyses have shown that preoperative CRT combined with surgery significantly reduced 3-year mortality and locoregional recurrence when compared with surgery alone[9,10]. On the other hand, the efficacy of postoperative CRT compared to surgery alone has not been demonstrated in a randomized trial in patients with esophageal cancer. However, in retrospective analyses, the addition of postoperative CRT has been associated with survival benefit in patients with locally advanced esophageal cancer, such as those that are lymph node-positive and with deeper primary tumor invasion (pT3, pT4), compared with surgery alone[11-13]. Finally, two randomized trials comparing trimodality therapy with definitive CRT demonstrated no OS benefit with the addition of esophagectomy to CRT[14,15], especially in patients with locally advanced SCC of the esophagus who experience response to initial CRT[15]. Therefore, the optimal multimodality therapy for locally advanced SCC of the esophagus is still unclear.

This retrospective study was designed to determine the best approach to administer multimodality therapy to patients with locally advanced SCC of the esophagus. The primary aim was to determine if the addition of surgical resection to CRT decreases local recurrence and prolongs in survival compared with CRT alone. Furthermore, we sought to assess the factors that may affect survival and recurrence in patients with locally advanced SCC of the esophagus.

Materials and Methods

Patient population

Patients with locally advanced resectable (cT3, potentially resectable cT4 or N+) SCC of the esophagus who were treated with preoperative CRT or postoperative CRT plus esophagectomy (trimodality therapy group), or only radiation with chemotherapy (CRT alone group), between April 2011 and November 2015 were included. Patients were included if they were aged 18 to 75 years, with an ECOG/WHO performance score <2, and showed <10% weight loss. Patients were excluded if their esophageal cancer was located in the cervical esophagus, if this was their second malignancy, if they were identified as receiving irradiation to a site other than the esophagus, or if they received radiotherapy without concurrent chemotherapy. The patient population consisted partially of patients enrolled in the ZTOG1201 trial, a randomized controlled trial in which eligible patients were randomly assigned to receive preoperative CRT plus surgery or surgery plus postoperative CRT (NCT01463501)[16].

Chemoradiotherapy

Chemotherapy consisted of concurrent paclitaxel (50 mg/m^2 of body-surface area) and carboplatin (intravenous carboplatin [AUC 2 mg/ml per min]) targeted at an area under the curve of two, starting on days 1, 8, 15, 22, 29, and 36 during the first and sixth weeks of radiotherapy in the preoperative CRT group and the CRT alone group. Patients in the postoperative CRT group mostly underwent postoperative CRT at 4–6 weeks after surgery. Chemotherapy in the postoperative CRT group consisted of two cycles of sequential paclitaxel (150 mg/m^2 of body-surface area) and carboplatin (intravenous carboplatin [AUC 5 mg/mL per min]) targeted at an area under the curve of five, starting on week 3, and week 6 after radiotherapy.

All patients were treated with external-beam radiation using an intensity-modulated radiation therapy technique. Gross tumor volume was drawn on each relevant slice of the planning CT and was defined by the primary tumor and any enlarged regional lymph nodes. The planning target volume (PTV) provided a proximal and distal margin of 4 cm and a radial margin of 1.3 cm around the gross tumor volume. Individually shaped beams were used in each field by multileaf collimators to ensure optimal sparing of normal tissue. The daily prescription dose of 1.8 to 2.0 Gy was specified by the International Commission on Radiation Units and Measurement 50/62 reference point, and the 95% isodose had to encompass the entire PTV. The maximum dose to the PTV was not to exceed the prescription dose by <7%. Tissue density inhomogeneity correction was used.

Patients were required to have complete information regarding the total radiation planning, as well as the chemotherapy regimen. We limited our analysis to patients who received radiation doses of 41.4 to 50.4 Gy in the preoperative CRT group, 45 to 50.4 Gy in the postoperative CRT group, and 50 to 64.8 Gy in the definitive CRT group, as these represent the expected ranges for preoperative/postoperative to definitive radiation doses. All patients received the same chemotherapy regimen with paclitaxel and carboplatin. The delivery of concurrent CRT was determined by only including patients who were identified as receiving their chemotherapy within a 1-week window before or after the initiation of radiotherapy.

Surgery

Patients in the trimodality therapy group preferably underwent surgery at 4-6 weeks after completion of preoperative CRT, or as soon as possible after randomization in postoperative subgroup. The final choice of surgical procedure including minimally invasive oesophagectomy (MIE) or open oesophagectomy (OE) with a intrathoracic gastric tube reconstruction (Ivor Lewis procedure) or neck anastomosis (Mckeown procedure) was at the surgeon's discretion, depending on tumor localization, patient characteristics. Gastric-tube reconstruction with a cervical anastomosis was the preferred technique. A wide local excision of the N1 lymph nodes, including standard excision of the celiac nodes, was carried out.

Assessment of recurrence

Relapses were classified as locoregional or distant. Locoregional relapses were defined as recurrences at the site of the primary tumor or locoregional lymph nodes. Lymph node recurrences at the celiac trunk or in the supraclavicular region were also considered to be locoregional. Distant recurrences were defined as non-regional lymph node recurrences, systemic metastases, malignant pleural effusions, or peritoneal metastases. Most patients suspected of experiencing recurrence underwent a CT scan of the thorax and abdomen or an endoscopy. If necessary, cytology or histology was obtained. If a second recurrence was detected within 4 weeks after the first occurrence, it was considered to be synchronous. Localization and date of identification of all locoregional and distant recurrences were recorded.

Statistical analysis

Demographic details were compared between patients who received trimodality treatment or CRT alone using the $\chi 2$ test, the Fisher exact test, and the Mann-Whitney test, where appropriate. Multivariate Cox regression of OS and tumor recurrence was performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) using these same covariates, excluding age, gender, WHO/ECOG score, tumor location, tumor length, T staging, N staging, radiation dose, and treatment approach. Kaplan-Meier analyses of OS were performed comparing patients who received

Table 1: Patient Characteristics (n = 184).

Characteristic	Trimodality therapy (n = 109)		CRT alone (n = 75)		*P* value
	No.	%	No.	%	
Age, years					
Median	59		61		0.010
Range	42–74		41–75		
Gender					
Male	104	95.4	62	82.7	0.004
Female	5	4.6	13	17.3	
WHO performance status score					
0	5	4.6	6	8	0.672
1	104	95.4	69	92.0	
Tumor location					
Proximal third	4	3.7	20	26.7	0.037
Middle third	58	53.2	34	45.3	(Proximal and Middle vs. Distal)
Distal third	47	43.1	21	28.0	
Tumor length (cm)					
<5	36	33	47	62.7	<0.001
≥5	73	67.0	28	37.3	
Clinical T category					
T1 or T2	25	22.9	13	17.3	0.356
T3 or T4	84	77.1	62	82.7	
Clinical N category					
N0	20	18.3	8	10.7	0.154
N1	89	81.7	67	89.3	
Radiation dose (Gy)					
<50.4	30	27.5			
50.4	79	72.5			
50–50.4			28	37.3	
>50.4			47	62.7	

CRT – Chemoradiation Therapy; WHO – World Health Organization

definitive radiation to a dose of 50 to 50.4 Gy with those who received >50.4 Gy. Survival analyses were also performed comparing those who received definitive CRT with those who received trimodality therapy after stratification by treatment sequence (preoperative CRT or postoperative CRT). Significant values were defined as those with a P-value of <0.05.

Results

Study population

The analysis included 184 patients: 109 (59.2%) underwent trimodality therapy, including 57 (31.0%) who underwent preoperative CRT followed by oesophagectomy and 52 (28.2%) who underwent oesophagectomy followed by postoperative CRT, and 75 (40.8%) underwent CRT alone. The median age was 60 years old (range, 41 to 75 years). Patients undergoing trimodality therapy were more likely to be younger, male gender, have a longer tumor length, and a tumor location in the distal third of the esophagus. Additional details on patient characteristics are listed in Table 1.

Analysis of recurrence

After a median follow-up of 36 months (range, 6 to 53 months) and a median survival time of 31 months (95% CI: 20.2–41.8 months), 33.9% (37/109) of the resected patients in the trimodality therapy group had recurrent disease versus 50.7% (38/75) in the CRT alone group. There was a significant difference between the two treatment groups in terms of tumor recurrence (P = 0.023). Only 17.4% (19/109) of the resected patients in the trimodality arm had locoregional recurrent disease versus 30.7% (23/75) in the definitive CRT arm (P = 0.036). Moreover, fewer patients (16.5%, 18/109) in the trimodality arm had distant failure compared to those in the CRT alone arm (18.7%, 14/75), although this difference was not significant (P = 0.705).

Table 2 lists the univariate and multivariate Cox Regression Analyses for tumor recurrence. Prognostic factors predicting locoregional relapses in univariate analysis were younger age and CRT alone. In the multivariate analysis, the backward method showed that patients with younger age who received CRT alone had a significantly increased risk of developing a locoregional relapse.

Survival outcomes

A significant difference in the 3-year progression-free survival (PFS) was observed between the trimodality group and the CRT alone group (53.8%, 95% CI: 42.8-64.8% vs. 33.5%, 95% CI: 20.6-46.4%, respectively; P = 0.019). Figures 1A, 1B, and 1Cshow the differences

Table 2: Univariate and Multivariate Cox Regression Analyses for Tumor Recurrence (n = 184).

	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (≥60 vs. <60 years)	1.718	1.087–2.717	0.021	2.283	1.412–3.690	0.001
Gender (female vs. male)	1.099	0.528–2.289	0.800			
WHO performance status score (0 vs. 1)	3.645	0.507–26.228	0.199	3.228	0.445–23.401	0.246
Tumor location (proximal vs. middle vs. distal)	1.077	0.770–1.507	0.663			
Tumor length (≤5 cm vs. ≥5 cm)	0.814	0.499–1.331	0.413			
T staging (T1 vs. T2 vs. T3 vs. T4)	1.377	0.943–2.010	0.098	1.240	0.837–1.836	0.284
N staging (N0 vs. N1)	0.853	0.513–1.418	0.540			
Treatment approach (CRT alone vs. Trimodality)	0.657	0.496–0.869	0.003	0.563	0.418–0.759	<0.001

HR– Hazard ratio; CI – Confidence interval; WHO – World Health Organization; CRT – Chemoradiation Therapy

Table 3: Multivariate Cox Regression Analyses for Overall Survival in the Trimodality Therapy and CRT alone Groups (n = 184).

	Trimodality therapy (n = 109)		***P* value**	**CRT alone (n = 75)**		***P* value**
Factor	**HR**	**95% CI**		**HR**	**95% CI**	
Age (≥60 vs. <60 years)	1.534	0.705–3.344	0.281	2.083	1.089–3.984	0.027
Gender (female vs. male)	1.018	0.198–5.231	0.983	1.280	0.476–3.441	0.624
WHO performance status score (0 vs. 1)	0.362	0.085–1.542	0.17	1.653	0.207–13.212	0.653
Tumor location (proximal vs. middle vs. distal)	0.801	0.444–1.443	0.46	1.404	0.908–2.170	0.127
Tumor length (<5 cm vs. ≥ 5 cm)	1.354	0.503–3.641	0.548	0.888	0.423–1.865	0.754
T staging (T1 vs. T2 vs. T3 vs. T4)	1.399	0.71–2.754	0.332	1.238	0.701–2.187	0.461
N staging (N0 vs. N1)	1.396	0.489–3.983	0.533	1.167	0.688–1.978	0.566
Radiation dose (<50.4 Gy vs. 50.4 Gy in trimodality group)	0.681	0.284–1.635	0.39			
Radiation dose (50–50.4 Gy vs. >50.4 Gy in the CRT alone group)				0.761	0.353–1.643	0.487

CRT – Chemoradiation Therapy; HR– Hazard ratio; CI – Confidence interval; WHO – World Health Organization.

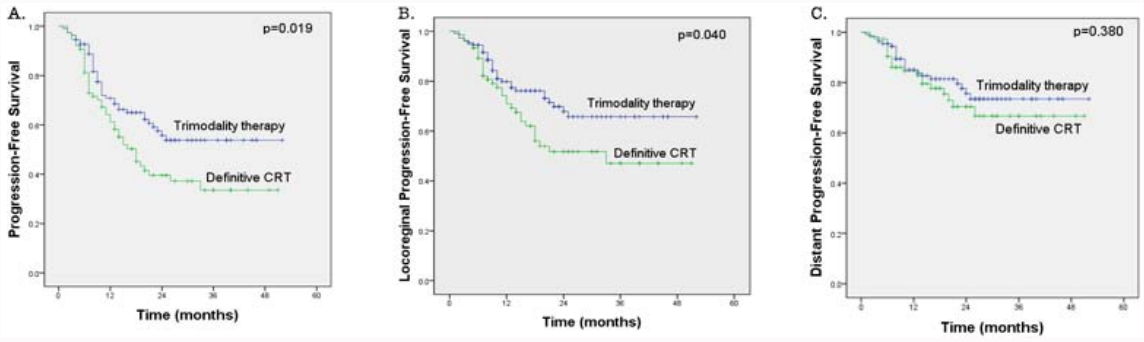

Figure 1: Kaplan-Meier survival curves for patients receiving trimodality therapy or CRT alone: A. There was significant difference between the groups in the 3-year progression-free survival (53.8%, 95% CI: 42.8–60.8% vs. 33.5%, 95% CI: 20.6–46.4%; P = 0.019); B. There was significant difference between the groups in the 3-year locoregional progression-free survival (65.7%, 95% CI: 54.9–76.5% vs. 47.0%, 95% CI: 32.3–61.7%; P = 0.040); C. There was no significant difference between the groups in the 3-year distant progression-free survival (73.5%, 95% CI: 63.3–83.7% vs. 66.7%, 95% CI: 53.2–80.2%; P = 0.380).

between the trimodality therapy group and CRT alone group for PFS(53.8%, 95% CI: 42.8-60.8% vs. 33.5%, 95% CI: 20.6-46.4%; P = 0.019),locoregional PFS(65.7%, 95% CI: 54.9-76.5% vs. 47.0%, 95% CI: 32.3-61.7%; P= 0.040), and distant PFS (73.5%, 95% CI: 63.3-83.7% vs. 66.7%, 95% CI: 53.2-80.2%; P = 0.380), respectively.

Trimodality treatment was also associated with superior OS outcomes. In the trimodality treatment group, the 3-year OS rate was 51.2% (95% CI: 36.1-66.3%) and the median survival time was not reached; while in the CRT alone group, the 3-year OS rate was 39.8% (95% CI: 26.7-52.9%) with a median survival time of 22.0 months (95%: CI 17.1 to 26.9 months; P = 0.011, (Figure 2)). Furthermore, treatment related mortality was 3.7% in the trimodality group compared with 1.3% in the definitive CRT group (P = 0.650).

A total of 37.3% (28/75) of patients received a radiation dose of 50 to 50.4 Gy, and 62.7% (47/75) received >50.4 Gy radiation dose in CRT alone group. These who received 50 to 50.4 Gy had a median OS of 26.0 months (95% CI: not reached) and a 3-year OS of 45.3% (95% CI: 24.7-65.9%). However, the survival was not significantly

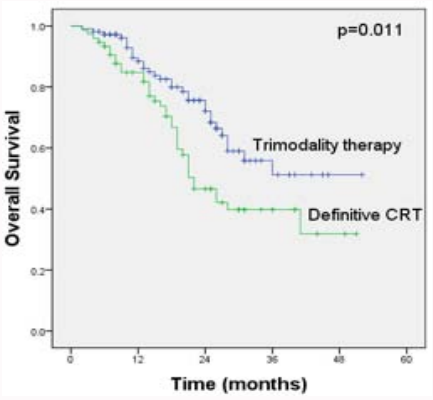

Figure 2: Kaplan-Meier survival curves for patients receiving trimodality therapy or CRT alone. There was significant difference between the groups in the 3-year overall survival (51.2%, 95% CI: 36.1–66.3% vs. 39.8%, 95% CI: 26.7–52.9%; P = 0.011).

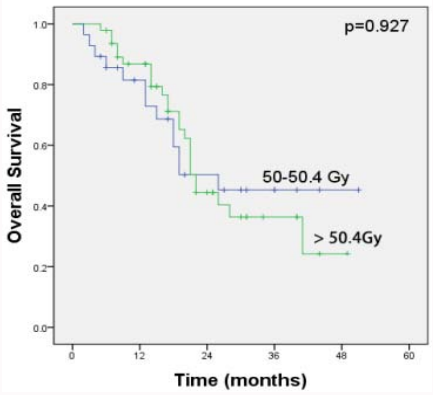

Figure 3: Kaplan-Meier survival curves for patients receiving a 50.4 Gy radiation dose or >50.4 Gy radiation dose in CRT alone group. There was no significant difference in the 3-year overall survival (45.3%, 95% CI: 24.7–65.9% vs. 36.4%, 95% CI: 19.4–53.1%; P = 0.927).

different (P= 0.927) to those receiving radiation doses >50.4 Gy, who had a median survival of 22.0 months (95% CI: 20.2-23.8 months) and a 3-year OS of 36.4% (95% CI: 19.4-53.1%). Figure 3 depicts the Kaplan-Meier survival curves for patients who received CRT alone by doses. In multivariate analysis, an increased radiation dose was not associated with OS: only younger age was associated with inferior survival (HR= 2.941; 95% CI: 1.441-5.988; P = 0.003). Further details of the multivariate analysis are shown in Table 3.

Discussion

The present study indicated that adding surgery to CRT for the treatment of clinical resectable, locally advanced SCC of the esophagus significantly decreased the local recurrence rates, prolonged PFS and OS, with similar treatment-related mortality for the treatment compared with CRT alone. In the trimodality treatment group, the 3-year OS was 51.2% (95% CI: 36.1-66.3%) similar to the result achieved for preoperative CRT in the CROSS trial (51%)[8], which were better than that achieved in the CRT alone group (39.8%, 95% CI: 26.7-52.9%).

Surgery is a major component of treatment for resectable disease. Based on data from the National Cancer Database of America, trimodality therapy was associated with improved OS (P < 0.001), with a median OS of 35.6 months and 3-year OS of 49.6%, compared to patients receiving CRT (median and 3-year OS were 16.8 months and 26.8%, respectively)[17]. The effect of adding surgery to CRT in patients with locally advanced SCC of esophagus has also been evaluated in two randomized trials[14,15]. Stahl et al. randomized 172 patients to either induction chemotherapy followed by CRT and surgery or induction chemotherapy followed by CRT[14]. The 2-year PFS rate was better in the surgery group (64.3%) than in the CRT group (40.7%), without significantly affecting 3-year OS (31% vs. 24%, respectively). However, this study was prematurely terminated due to lack of accrual. On the other hand, Bedenne et al. (FFCD 9102 trial) showed that adding surgery to CRT provided no benefit compared with treatment with additional CRT, especially in patients with locally advanced SCC of the esophagus who responded to initial CRT[15]. However, this trial suffered from suboptimal study design, indeed, the results of non-randomized patients in the FFCD 9102 phase III trial indicated that OS did not differ between responders to induction CRT and patients having salvage surgery after clinical failure of CRT[18]. Moreover, in a recent prospective study that compared the outcomes of surveillance versus surgical resection in patients with esophageal cancer achieving complete clinical response after preoperative CRT, surgical resection was independently associated with less recurrence (32.7% vs. 50.8%; P= 0.021) and better median survival (83 months vs. 31 months; P = 0.001)[19]. Similarly, Patients who completed TMT (chemoradiotherapy [CRT] and surgery)had the best local control in a Single-Institution Experience conducted by [20]Sio TT et al. 5-year local control was 82% for TMT, while 60% for CRT and 40% for PTMT patients who began treatment with trimodality intent but did not undergo surgery groups (P<0.001).

Regarding if the role of adding surgery could be replaced by escalated radiation dose in the CRT alone group. The current National Comprehensive Cancer Network (NCCN) recommended ranges for preoperative, postoperative and definitive radiation are 41.4 to 50.4 Gy, 45 to 50.4 Gy, and 50 to 50.4 Gy, respectively [21]. Despite the lack of significant evidence supporting radiation dose escalation, we found that radiation doses exceeding 50.4 Gy were used in 58.7% of patients in the CRT alone group in this retrospective study due to the historical situation in China. However, we found no survival benefit to a dose escalation of >50.4 Gy compared with those receiving a 50 to 50.4 Gy radiation dose. A previous study on the use of definitive CRT (the RTOG 8501 trial) showed that the 5-year OS was 26% in patients receiving chemotherapy with radiotherapy (to a total dose of 50 Gy) and 0% when radiotherapy (to total dose of 64 Gy) was used alone[3]. Owing to the low OS and high local failure rate with definitive CRT, the Intergroup 0123 trial subsequently randomized patients to receiving the same chemotherapy with either 50.4 Gy or 64.8 Gy of radiation[4]. However, the trial was stopped early after an interim analysis showed the 2-year median survival (13 vs. 18.1 months) and locoregional failure rates (56% vs. 52%) were not significantly different between the high-dose and standard-dose arms. Similarly, our multivariate analysis indicated no differences in OS and recurrence based on the radiation dose delivered in both the trimodality and CRT alone groups. As no subsequent studies have revealed a significant benefit to dose escalation exceeding 50.4 Gy in CRT alone group, our study indicated that the role of surgery could not be replaced by CRT alone, even with increased radiation dose for locally advanced SCC of the esophagus.

The current study does have some limitations. For example, as this was a retrospective study and only esophageal SCC patients in China were recruited, we may have introduced selection bias and we lack a

proper intent-to-treat analysis. Furthermore, while the incidence of esophageal adenocarcinoma is dramatically increasing in Western countries, the results of our study should not be generalized to apply to North American and European patients until a randomized study including esophageal adenocarcinoma patients confirms our results. Moreover, based on our study, its unclear what is the potential value of additional locoregional therapy with surgery in patients with clinical complete response to CRT.We also had no idea about the timing and necessity of oesophagectomy in (all) patients. In the future, molecular biology techniques probably may enable to improve prognostic stratification, thereby allowing us to determine the types of patients who benefit from surgical therapy and show improved OS[22-25]. In addition, we did not analyze whether patients received salvage therapies, such as salvage esophagectomy, in the CRT alone group, which may have affected survival outcomes. Further investigation of the innovative multidisciplinary management (i.e., preoperative CRT followed by salvage esophagectomy) for patients with locally advanced esophageal cancer is warranted. Indeed, this approach is currently being explored in Netherlands by investigators of the preSANO trial, clinical response evaluation after neoadjuvantchemoradiotherapy in esophageal cancer (NTR4834)[26].

In conclusion, adding surgery to CRT appears to have superior local control, PFS and OS, with similar treatment-related mortality for the treatment of patients with SCC of esophagus. The role of surgery could not be replaced by CRT alone, even with increased radiation dose.

Acknowledgement

This work was supported by the Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents (to YapingXu). This paper has been accepted for oral presentation at the 15th World Congress of International Society for Diseases of the Esophagus, taking place on September 19-21, 2016 in Singapore (Abstract ID: 1942).

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.
2. Guo M, Zhao YD, Yang HJ, Yan XF. Analysis of clinicopathological characteristics for 5406 cases of esophageal neoplasm. Chin J Cancer Prev Treat. 2008;15:54-6.
3. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326:1593-8.
4. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20:1167-74.
5. Oppedijk V, van der Gaast A, van Lanschot JJ, van Hagen P, van Os R, van Rij CM, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014;32:385-91.
6. Christophe Mariette, Laetitia Dahan, Françoise Mornex, Emilie Maillard, Pascal-Alexandre Thomas, Bernard Meunier, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32:2416-22.
7. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol. 2012;30:2327-33.
8. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074-2084.
9. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg. 2003;185:538-43.
10. Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. Gut. 2004;53:925-30.
11. Bédard EL, Inculet RI, Malthaner RA, Brecevic E, Vincent M, Dar R. The role of surgery and postoperative chemoradiation therapy in patients with lymph node positive esophageal carcinoma. Cancer. 2001;91:2423-30.
12. Rice TW, Adelstein DJ, Chidel MA, Rybicki LA, DeCamp MM, Murthy SC, et al. Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma. J Thorac Cardiovasc Surg. 2003;126:1590-96.
13. Xu Y, Chen Q, Yu X, Zhou X, Zheng X, Mao W. Factors influencing the risk of recurrence in patients with esophageal carcinoma treated with surgery: A single institution analysis consisting of 1002 cases. Oncol Lett. 2013;5:185-90.
14. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23:2310-7.
15. Bedenne L, Michel P, Bouché O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25:1160-8.
16. Neoadjuvant versus adjuvant therapy in treating resectable thoracic esophageal cancer. 2011.
17. Shao MS, Wong AT, Schwartz D, Weiner JP, Schreiber D. Definitive or Preoperative Chemoradiation Therapy for Esophageal Cancer: Patterns of Care and Survival Outcomes. Ann Thorac Surg. 2016;101:2148-54.
18. Vincent J, Mariette C, Pezet D, Huet E, Bonnetain F, Bouché O, et al. Early surgery for failure after chemoradiation in operable thoracic oesophageal cancer. Analysis of the non-randomised patients in FFCD 9102 phase III trial: Chemoradiation followed by surgery versus chemoradiation alone. Eur J Cancer. 2015;51:1683-93.
19. Piessen G, Messager M, Mirabel X, Briez N, Robb WB, Adenis A, et al. Is there a role for surgery for patients with a completeclinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. Ann Surg. 2013;258:793-9.
20. Sio TT, Wilson ZC, Stauder MC,Bhatia Sumita,Martenson James A,Quevedo J Fernando, et al. Long-term Treatment Outcomes for Locally Advanced Esophageal Cancer: A Single-Institution Experience. Am J Clin Oncol. 2016;39:448-52.
21. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Besh S, Chao J, et al. Esophageal and esophagogastric junction cancers, version 1.2015. J Natl Compr Canc Netw. 2015;13:194-227.
22. Cheng-Che Tu, Po-Kuei Hsu, Ling-I Chien, Wan-Chen Liu, Chien-Sheng Huang,Chih-Cheng Hsieh, et al. Prognostic histological factors in patients with esophageal squamous cell carcinoma after preoperative chemoradiation followed by surgery. BMC Cancer. 2017;17:62.
23. Chang-Juan Tao, Gang Lin, Ya-Ping Xu, Wei-Min Mao. Predicting the Response of Neoadjuvant Therapy for Patients with Esophageal Carcinoma: an In-depth Literature Review. J Cancer. 2015;6:1179-86.
24. Hamai Y, Hihara J, Emi M, Furukawa T, Yamakita I, Kurokawa T, et al.

Ability of Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography to Predict Outcomes of Neoadjuvant Chemoradiotherapy Followed by Surgical Treatment for Esophageal Squamous Cell Carcinoma. Ann Thorac Surg. 2016; 102:1132-9.

25. Shen LY, Wang H, Dong B, Yan WP, Lin Y, Shi Q, et al. Possible prediction of the response of esophageal squamous cell carcinoma to neoadjuvant chemotherapy based on gene expression profiling. Oncotarget. 2016;7:4531-41.

26. Clinical response evaluation after neoadjuvant chemoradiotherapy in esophageal cancer. NTR4834. 2014.