

ORIGINAL ARTICLE

Curative intent for unresectable advanced squamous cell esophageal cancer: Overall survival after chemoradiation

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Summary

Purpose: To analyse the overall survival (OS) of patients with locally advanced, unresectable esophageal cancer treated with chemoradiation (CRT) with or without surgery.

Methods: CRT was administered to 63 patients with locally advanced (T3-4, N0-1), initially unresectable squamous cell esophageal cancer. After the assessment of tumor response to treatment, medically fit patients converted to operable stage were subjected to surgery. Regular follow-up was performed every 3 months during first 2 years, and then every 6 months.

Results: All 63 patients completed the whole radiotherapy course. Forty patients (63%) received complete 4 cycles of chemotherapy. In the remaining 23 patients (37%) chemotherapy was interrupted due to toxicity. Clinical response to CRT was: complete response (CR) in 4 patients (6%), partial response (PR) in 27 (43%), stable disease (SD) in

22 (35%) patients, and 10 patients (16%) had disease progression (PD). After reevaluation, 23 patients (15 PR and 8 SD after CRT) underwent surgery (37%), all with R0 resection. OS in the whole group was 53% at one year, and 36% at two years. OS was significantly better in the operated group of patients than in the non-operated group. No statistically significant difference in OS was observed comparing operated to CR patients with no surgery (70 vs 50%). In the non-operated group of patients there was no difference in OS between CR, PR, and SD patients.

Conclusions: With appropriate selection, patients with advanced squamous cell esophageal cancer should be considered for potentially effective treatment.

Key words: chemoradiation, esophageal cancer, surgery, survival

Introduction

More than 50% of squamous cell esophageal cancer patients at the time of diagnosis have either unresectable tumor or metastases [1]. When treated, the OS of these patients remains poor, with median ranging from 12 to 14 months. During their oncological journey, most of them will receive no more than palliative treatment or best supportive care, leading to even worse survival of 4 to 6 months [2,3].

Both chemotherapy and radiotherapy have modest results given as a single modality for palliative intent, with mostly symptom relief but no impact on survival [4-10]. For the small number of potentially curable patients with (non)metastatic advanced esophageal cancer, radiotherapy with concurrent chemotherapy (CRT) is recommended [11]. The superiority of CRT is demonstrated in both survival and local control. Still, long-term

survival does not exceed 25-35%. The highest percentage (50-60%) in 5-year survival rate is noted in patients with histological complete response (pCR) to CRT [12-16]. More advanced disease is associated with lower survival rates and higher risk for relapse, even in complete responders to CRT [17]. Radiation dose escalation as well as additional chemotherapy failed to demonstrate superior results with significant treatment-related morbidity and mortality [18,19].

Adding surgery to operable and fit patients after CRT is often suggested. Several large trials demonstrated better local control after trimodality treatment, but the impact on survival is controversial. It seems that if CR to CRT is reached, adding surgery has no significant impact on survival. However, surgery can be offered to PR patients in which cases the survival approaches the one of complete responders [20-22].

Nevertheless, most of esophageal cancer trials include patients with local or locally advanced but resectable esophageal cancer (T1-T3, N0-1, M0) [23]. There is no consensus yet on the treatment of patients with advanced unresectable esophageal cancer.

In our study, we analysed OS of patients with locally advanced unresectable esophageal cancer treated with CRT with or without surgery. This group of patients was previously analysed for response to treatment regarding molecular markers [24].

Methods

Patients

All procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained from all the participants of the study.

This prospective, multicentric, non-randomized phase II study was performed at the Institute for Oncology and Radiology of Serbia and the First Surgery University Clinic from 2006 to 2010. Sixty-three patients with biopsy proven locally advanced (T3-4, N0-1) unresectable squamous cell esophageal cancer were enrolled in this study. Patients were estimated as unresectable due to T4, N stage, comorbidity or performance. Patients with poor performance status (ECOG 3), acute and chronic uncontrolled severe physical and mental disorders were excluded, as well as patients previously treated for esophageal cancer with chemo or radiotherapy, laser or photodynamic therapy, or any other antitumor method, patients with esophageal stent, tracheobronchial fistula and/or second malignancy.

Pretreatment evaluation included complete physical examination, complete blood count and serum biochemistry (liver and kidney function), barium esophagography, computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and upper abdomen, esophagoscopy or esophagogastroduodenoscopy (if esophagus allowed endoscope passage) with biopsy. Endoscopic ultrasound (EUS) and whole body ^{18}F -fluorodeoxyglucose-positron emission tomography (^{18}F -FDG-PET) were performed in selected cases. Staging was determined based on 7th AJCC TNM staging system [25].

Treatment plan

After the diagnostic work out, all patients were presented to the multidisciplinary team and treatment plan decision was made. CRT consisted of radiotherapy to a total dose of 45-50.4Gy (with 1.8Gy per fraction given over 5-6 weeks) concurrent with chemotherapy with cisplatin, leucovorin and 5-Fluorouracil (5-FU) (4 cycles every 14 days). Each cycle of chemotherapy was administered in two days: 50 mg/m² of cisplatin on days 1, 15, 29 and 43 with adequate hydration; 20mg/m² of leucovorin (LV) iv infusion for 2 hrs, 5-FU 400 mg/m² iv infusion and 600 mg/m² as 22-hr iv infusion on days 1, 2, 15, 16, 29, 30, 43, and 44. Radiotherapy began on the third day of the first chemotherapy cycle. The treatment plan was made according to ICRU 50/62 using 2D or 3D planning system (based on 5 mm CT images of the chest and upper abdomen). The gross tumor volume (GTV) was defined as the volume of visible esophageal tumor and involved lymph nodes. Clinical target volume (CTV) included GTV plus areas of microscopic risk i.e. 5 cm longitudinal and 2cm circumferential margin for esophageal tumor and 0.5-1 cm for lymph nodes. Planning target volume (PTV) encompassed CTV plus 1 cm margin in all directions. Radiotherapy was delivered using high energy photons on linear accelerators through 3 or 4 fields. CRT was performed at the Institute for Oncology and Radiology of Serbia.

Treatment toxicity was evaluated according to NCI-CTC criteria [26].

Five to 6 weeks after CRT, tumor response to treatment was assessed using RECIST criteria [27] with the same examination done at baseline, and operability was estimated again for each patient. Medically fit patients converted to operable stage were subjected to surgery. Surgical approach was individually tailored and included resection of esophagus and proximal stomach by transthoracic or transhiatal approach with regional lymph nodes (mediastinal, paraesophageal, pericardial, left gastric and celiac lymph nodes) with esophagogastric anastomosis (Ivor-Lewis). Both techniques were performed based on the tumor localization and the judgement of the operator. The resected specimen was pathologically evaluated for tumor extension (ypTNM), residual status and tumor regression grade (TRG) according to Mandard criteria [28]. All surgical and pathological evaluations were performed at the First Surgery University Clinic, in Belgrade.

Patients not eligible for surgery continued with chemotherapy and/or best supportive care.

Regular follow-up was performed every 3 months during first 2 years, and then every 6 months. Follow-up consisted of physical examination, tumor assessment (esophagoscopy, CT of the chest and upper abdomen every 6 months, EUS and PET if indicated) and evaluation of treatment toxicity according to NCI-CTC criteria.

OS was defined as the time from the beginning of treatment to the death.

Statistics

For statistical analysis the R package was utilized (version 2.8.1 (2008-12-22); Copyright (C) 2008 The R Foundation for Statistical Computing; ISBN 3-900051-07-0). Basic patient characteristics were summarized. Frequency Tables were formed for categorical variables, and for continuous variables descriptive statistics were used (mean, median, range and standard deviation-SD). The overall rate of clinical response was presented with 95% confidence interval for percentage. Methods of the survival analysis were used for the investigation of different parameters impact on OS (Kaplan-Meier product limit method, median of survival analysis with corresponding 95% confidence interval, and log-rank test). The results were presented on Tables and Figures.

Results

Sixty-three patients met the inclusion criteria and were enrolled in the study. Baseline characteristics of our patients are presented on Table 1.

Most of the patients were male, with locally advanced (stage III) unresectable squamous cell esophageal cancer. More than half of the included patients had T4 esophageal cancer with dysphagia and weight loss up to 10kg. Performance status was ECOG 1 in almost 80% of enrolled patients. The upper and middle part of the esophagus predominated (86%). Five patients with IV clinical stage had lung metastases.

Concurrent CRT with cisplatin/5FU/LV and radiotherapy with a total dose of 45-50.4Gy was administered to all patients. All 63 patients completed the whole radiotherapy course, and 40 patients (63%) received complete 4 cycles of chemotherapy. In the remaining 23 patients (37%) chemotherapy was stopped due to toxicity (in 10 patients after 3 cycles, and in 13 after 2 cycles of chemotherapy).

Out of 63 enrolled patients clinical CR was noted in 4 patients (6%). Twenty-seven (43%) achieved PR, and 22 (35%) SD. Immediately after CRT 10 patients (16%) developed disease progression (Table 2).

After the reevaluation, 23 patients (37%) underwent surgery, all with R0 resection. Out of 23 operated patients, 15 were partial responders to CRT and 8 had SD.

Patients not suitable for surgery were treated with further chemotherapy or best supportive care.

Table 1. Patient and disease characteristics

Characteristics		n	%
Age (years)	50-59	29	46
Mean 56	60-69	21	33
Range 34-74	70-79	1	2
Gender	Female	8	13
	Male	55	87
Performance status (ECOG)	2	2	3
	1	49	78
	0	12	19
Dysphagia	No dysphagia	0	0
	Grade I	38	60
	Grade II	15	24
	Grade III	6	10
	Grade IV	4	6
Weight loss	No weight loss	8	13
	1-5 kg	16	25
	5-10 kg	22	35
	>10 kg	17	27
Tumor differentiation	Grade 1	25	40
Squamous cell carcinoma	Grade 2	24	38
	Grade 3	6	9
	Unknown	8	13
Clinical stage group (CS)	T3 N0 M0 CS II	13	21
	T3 N1 M0 CS III	17	27
	T4 N0 M0 CS III	9	14
	T4 N1 M0 CS III	19	30
	T4 N1 M1 CS IV	5	8
Localization	Cervical esophagus	4	6
	Upper third	28	45
	Middle third	26	41
	Lower third	5	8

Table 2. Clinical response to chemoradiation

Response	n=63		95% confidence interval
	n	%	
Complete response	4	6	2.52-19.43
Partial response	27	43	23.59-51.88
Stable disease	22	35	23.59-51.88
Progressive disease	10	16	10.23-34.01

The mean follow-up time was 9 months (range 2-31). By the end of the study, 28 patients (44%) had died (tumor recurrence or progression 23 patients (82%), postoperative complications 4 patients and stroke one patient).

One-year OS of the whole group was 53%, and 2-year OS was 36% (Figure 1).

In two groups of patients, with and without surgery, one and 2-year OS was significantly better in the operated group (72 vs 44% in one year, and 72 vs 21.5% in 2 years) (Figure 2).

Comparing the group of complete responders to CRT who were not operated with the operated group of patients, no statistically significant difference in OS was noted (Figure 3). Still, one-year OS in the operated group was 70% compared to 50% in patients with definitive CRT.

Analysis of OS in the group without surgery has shown no statistical difference between complete responders and patients with PR or SD after CRT (50-60% in one year). The only subgroup with statistically significant poor OS were patients estimated as PD, without survivors after 9 months (Figure 4).

Due to their relatively good performance, 5 patients initially presented with lung metastases were treated in the same fashion as non-metastatic patients. Clinical response was SD in 3 patients and PD in 2.

One of the PD patients was presented with locoregional progression, and the other had distant progression with bone metastases. Both died in a month.

Out of the 3 SD patients, two were operated with lung resection at the same time. They were alive by the end of the study. The third patient died in one month due to locoregional progression.

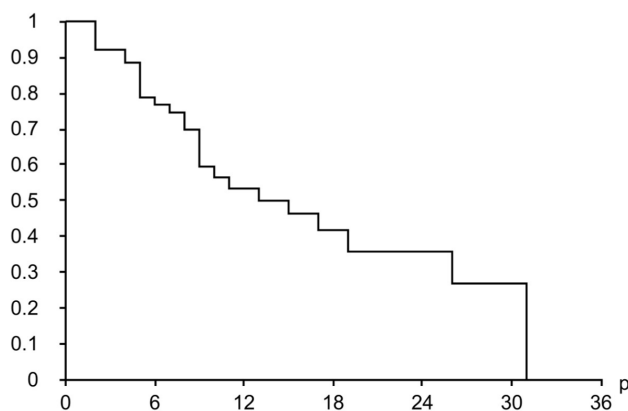


Figure 1. Overall survival in the whole group of patients.

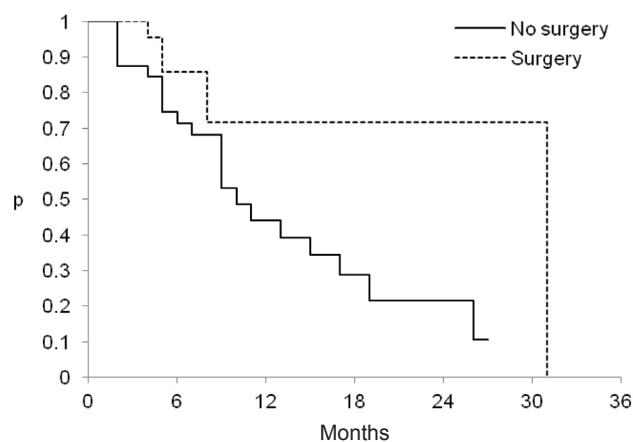


Figure 2. Overall survival regarding operation. Log rank test, $p=0.02$.

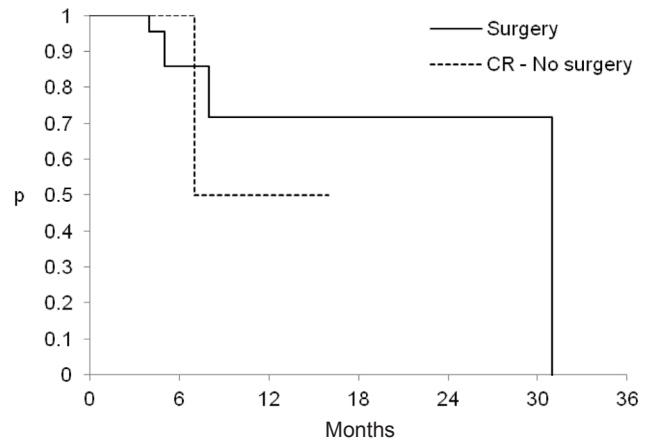


Figure 3. Overall survival of CR non-operated patients vs operated patients. Log rank test, $p=0.518$. CR: complete response to chemoradiation.

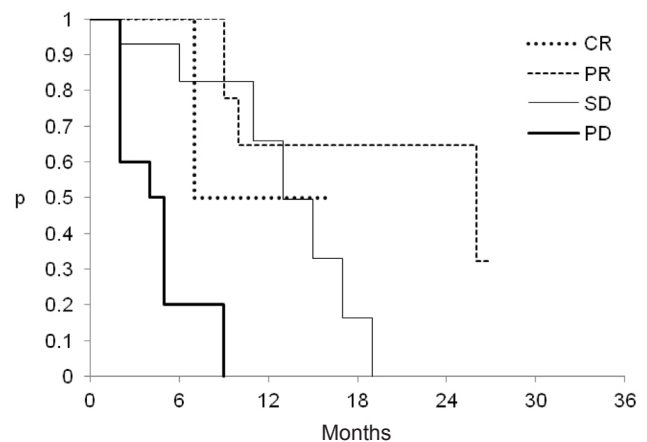


Figure 4. Overall survival in non-operated group of patients. Log rank test, $p=0.0083$.

CR: Complete response to chemoradiation
PR: Partial response to chemoradiation
SD: Stable disease to chemoradiation
PD: Progression of disease to chemoradiation

Discussion

Although many esophageal cancer trials report significant results both in local control and survival, it is noticeable that they include mostly initially resectable patients as well as those with esophageal cancer in the distal esophagus or esophago-gastric junction. For patients with more advanced disease, nonresectable, poorer performance status, or those with esophageal cancer in the upper or middle third of the esophagus the best treatment regimen remains to be defined.

All patients enrolled in our study were initially unresectable, with one third having T4N1 disease. More than 80% of patients had cancer in the upper or middle third of the esophagus with significant weight loss and dysphagia. Five of our patients were diagnosed in stage IV with lung metastases. It can be said that most of these patients would be considered as having poor prognosis and suitable

for palliative treatment only.

The response rate in our group of patients was satisfactory, with CR of 6% and PR of 43%. Still, the literature data present even better response rate with 20-30% of complete responders [29-31].

The importance of complete surgical resection in OS is well known. The resection rate in our study was 37% including two patients initially presented in metastatic stage who were subjected to lung resection simultaneously. All patients had R0 resection. None of the operated patients in our study had CR to CRT, 15 had PR and 8 had SD. The literature data report R0 resection rate in about 80%, but mostly for initially resectable cancer. Berger et al. [32] performed surgical resection in 157 out of 179 patients after CRT. More than half of the patients had IIA stage, and 4 stage IV patients were operated too. In this study, 34 patients underwent R1 resection. Ancona et al. [33] also included IIA stage esophageal cancer patients and performed R1-2 resection in 9 out of 47 patients after CRT. Kahn et al. [34] reported 20% R+ resections even in early esophageal cancer where curative esophagectomy is performed.

The mean follow-up time in this study was 9 months (range 2-31), which is close to the mean follow-up time stated in the literature for this category of patients where it is no more than 12-14 months [2, 35, 36].

Comparing our OS results to well-known trials one can be optimistic. One-year OS was 53% in the whole group, and 2-year OS was 36%. We also noticed, statistically significant, better OS in patients who were operated after CRT versus those with CRT alone (72 vs 44%, respectively). One-year OS in the operated group was 70% compared to 50% in CR patients who had no surgery. Namely, operated non CR patients had OS comparable to complete CRT responders, although no statistical significance was reached. The literature data support this stand. In the study of Stahl and colleagues [20] with locally advanced (T3-4, N0-1, M0) esophageal cancer treated trimodally, 2-year OS was similar to ours (40%). But, no difference in OS between surgery and non-surgery group was noticed. The results of this study showed that complete responders to CRT had 50% 3-year OS, regardless of surgery, which can improve OS in non-responders up to 30% in 3 years. A large French trial by Bedenne et al. [21] with trimodality treatment showed OS of 16 months in the whole group, with 2-year OS of 33%. No difference in OS was noticed between

surgery and non-surgery group, but with higher locoregional relapse rate in the non-surgery group (43 vs 34%). This study, also, concluded that if CR to CRT is achieved, subsequent surgery does not bring improvement in OS. The patients with incomplete response to CRT, operated with R0 resection, had OS comparable to complete responders. The Japanese study of Noguchi et al. [36] included only T4 patients treated with CRT with or without surgery. Mean follow-up time was 11 months (range 1-96). OS was statistically significantly better in the surgery group (13.3 vs 3.3 months for definitive CRT) with 2-year OS of 8.3% and 0% for surgery and non-surgery group, respectively. Hennequin et al. [37] also enrolled patients with T3/T4, N0/+ esophageal cancer, and noted better OS in the surgery than in the non-surgery group (63% in 2 years after CRT).

Analysis of OS in our patients with no surgery after CRT showed no difference regarding response to CRT. One-year OS in the whole non-operated group was 50%, except patients with early progression where there were no survivors after 9 months. In the literature, mean OS of patients with definitive CRT is no more than 25 months, with significantly lower OS in T4 patients [38, 39].

The results of our study correlate very strongly with the literature data. But, as it was mentioned, most of these studies included less advanced disease and inhomogeneous group of patients (stages I to IV). Further studies are needed to bring up closer the best treatment option for advanced esophageal cancer patients.

Conclusion

Despite adverse prognosis of advanced, initially inoperable, esophageal cancer, the results of this study suggest that, with appropriate selection, these patients should be considered for potentially effective, trimodality treatment.

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Conflict of interests

The authors declare no conflict of interests.

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