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Preoperative concomitant chemoradiotherapy in esophageal cancer

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Background. *Currently primary treatment options for esophageal cancer are surgery only or concomitant chemoradiotherapy (CRT) and the long-term survival of patients with locally advanced disease is rare. Preoperative concomitant CRT seems to be beneficial, mostly in patients who achieve a complete pathologic response (pCR) after CRT. In this retrospective analysis the efficiency and toxicity of preoperative CRT in patients with locally advanced esophageal cancer was analysed as well as the influence of pCR on the survival.*

Patients and methods *From 1996 to 2002 41 patients with locoregionally confined esophageal cancer were treated with cisplatin 75 mg/m^2 and 5-FU 1000 mg/m^2 as 4 day contonuous infusion starting on days 1. and 22. with concomitant radiotherapy 4500 cGy, 200-300 cGy/day. Esophagectomy followed 4-5 weeks after radiotherapy. After the surgery patients were followed-up regularly at 3-6 months intervals.*

Results. *The pCR was achieved in 26.8% of patients. The overall median survival time was 18 months for all patients, 21.2 months for patients who achieved pCR and 16 months in those with residual disease (p= 0,79). Postoperative mortality rate was 22%. The median dose intensity for cisplatin was 92% and for 5-FU 71.5% of the planned dose. Disease recurred most often locoregionally (31.7%) and the overall recurrence rate was 43.9%.*

Conclusion. *Modern radiation techniques and the adequate dose intensity could further improve the loco-regional control. The selection of patients without comorbid conditions and without already present distant metastases is essential for this combined treatment approach.*

Key words: esophageal neoplasms – drug therapy - radiotherapy

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Introduction

In the last few decades the incidence of esophageal cancer is constantly growing in Western Europe and USA where adenocarcinoma represents 60% of all esophageal carcinomas.[1,2] According to data of the Cancer registry of Slovenia the incidence

of esophageal cancer has risen in recent years (76 patients in 1998, 100 patients in 2002) but adenocarcinoma still represents only 14% of all histological confirmed cancers and most of them are squamous cell carcinomas.[3,4]

Primary treatment modalities include surgery alone or concomitant chemoradiotherapy. The surgical treatment is a standard treatment for stage I, II and III-T3 (www.cancernet.nci.nih.gov) and is feasible in 40-60% of patients.[5,6] In 75% of patients esophageal cancer is diagnosed when already locally advanced (stage IIB, III). The postoperative mortality rate is 10-15%, in experienced centers less than 5%.[7] Postoperatively locoregional recurrence occurs in 30-60%.[8-10] After the only primary surgical treatment, 5-year survival for stage I disease and locally advanced disease is 50-80% and 5-10%, respectively.[11-13] Concomitant chemoradiotherapy was superior when compared to radiotherapy alone in the primary treatment of locally advanced esophageal cancer.[14,15] Preoperative radiotherapy does not improve outcome in comparison to surgery alone.[16-21]

Combined modality therapies (preoperative chemotherapy, preoperative concomitant chemoradiotherapy) are still under the clinical evaluation. According to the results from randomized trials, the role of preoperative chemotherapy is still inconclusive.[9,22-24] In nonrandomized clinical trials with preoperative concomitant chemoradiotherapy (CRT) a pathologic complete response (pCR) was achieved in average in 32% (11%-76%) of patients and predicted a better survival. The survival of patients with pCR at 3-years and 5-years was 29-92% and 20-71%, respectively. The survival of patients who did not achieve pCR at 3-years was 23-33%. The disease recurred in 46% of all patients. In patients with a pCR the disease recurred in 20%, mostly (80%) as distant metastases.[25] In one randomized clinical trial the concomitant preoperative CRT showed some modest survival benefit over surgery alone[26] but there was no benefit in other randomized trials. [10,20,27-29] The inconsistency of these results might be due to heterogeneous patients' population, tumours characteristics and different treatment protocols.

In this retrospective study we analyzed the efficacy and toxicity of preoperative concomitant CRT in our patients with locally advanced esophageal cancer.

Patients and methods

Patients

Medical records of patients with esophageal cancer treated with preoperative concomitant CRT from 1996 to 2002 at the Institute of Oncology Ljubljana and Department of Thoracic Surgery Ljubljana were reviewed. Patients with histological confirmed locoregionally confined esophageal carcinoma (stage II and III), performance status < 2 according to WHO, adequate function of bone marrow, liver and kidney and absence of other malignances in their medical history with the exception of skin carcinoma were eligible. Staging of the tumour was based on the results of physical examination, blood tests, chest radiography, ultrasonography of abdomen, computed tomography of chest and upper abdomen, esophagogastroscopy with biopsy, liquid oral contrast examination of esophagus, endoscopic ultrasound of esophagus and bronchoscopy in patients with tumours in the middle and the upper third of esophagus.

Treatment

Patients were treated with concomitant preoperative chemotherapy (cisplatin 75 mg/m^2 days 1, 22 and 5-FU 1000 mg/m^2 days 1 - 4 and 22 – 25) and concomitant ra-

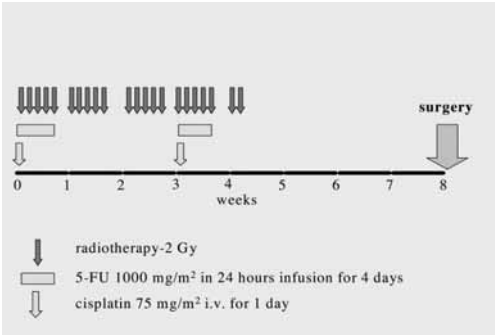

Figure1. Treatment plan with preoperative concomitant chemoradiotherapy.

diotherapy (4500 cGy, 200 – 300 cGy /day, field designs were either two or three-field plans on the linear accelerator, the radiation field included primary tumour with 5-cm superior and inferior margins and 2 cm lateral margins) (Figure 1). Esophagectomy followed 4 to 5 weeks after radiotherapy. After the surgery patients were followed–up regularly at 3-6 months intervals.

Statistical analysis

A statistical analysis with descriptive statistics and survival times and curves was performed using SPSS 10.0 for Windows statistical software. The survival was calculated according to Kaplan-Meier method and compared by a log-rank test between groups. The overall survival was estimated from the date of diagnostic biopsy to death and the relapse-free survival from the date of diagnostic biopsy to the first event of recurrence (local, regional, distant or their combinations).

Results

Forty-one patients (38 men, 3 women) with locoregionally confined esophageal cancer and without other comorbid conditions were treated with preoperative concomitant CRT in the period 1996 to 2002. The median age was 60 years (range 41-74). Squamous cell carcinoma was present in 39 (95.2%) patients and adenocarcinoma and poorly differentiated carcinoma in 2 (4.8%) patients. Tumour was located in the upper third of esophagus in 2 (4.9%) patients, in the middle third in 22 (53.6%) patients and in the lower third in 17 (41.5%) patients (Table 1).

Table 1. Patients and tumors characteristics

CHARACTERISTIC	No. of patients
TOTAL	41
MALES	38 (92,5%)
FEMALES	3 (7,5%)
MEDIAN AGE (min - max)	60 (41-74)
HISTOLOGY	
squamous cell	39 (95,2%)
adenocarcinoma	1 (2,4%)
poorly differentiated carcinoma	1 (2,4%)
TUMOR LOCALIZATION	
upper third	2 (4,9%)
middle third	22 (53,6%)
lower third	17 (41,5%)

Median dose intensity of received cisplatin was 23,2 mg/m^2/week (range, 16-34.2 mg/m^2/week) and of 5-FU 954.1 mg/m^2/week (range, 231.5-1394 mg/m^2/week) comprising 92.8% and 71.5% of the planned dose intensity, respectively. Patients who received in average less than 80% of planned dose intensity of both cisplatin and 5-FU had higher recurrence rate than patients who received 80% or more of the planned dose intensity (50% *vs* 30.8%; difference not statistically significant). Both, distant and locoregional recurrences were more common in patients with lower dose intensity, 28.6% vs. 7.7% and 35.7% vs. 23.1%, respectively (Table2).

Transthoracic esophagectomy (Lewis) and transhiatal esophagectomy were performed in 38 patients and 3 patients, respectively. R0 resection (microscopically free margins) was achieved in 39 patients and R1 resection (microscopically residual

Table 2. Chemotherapy (ChT) dose intensity and recurrence rates

RECURRENCE	No. of patients (%) DOSE INTENSITY OF ChT	
	< 80%	≥80%
LOCOREGIONAL	6/28 (21,4%)	3/13 (23,1%)
DISTANT	4/28 (14,3%)	1/13 (7,7%)
LOCOREGIONAL+DISTANT	4/28 (14,3%)	0
TOTAL	14/28 (50%)	4/13 (30,8%)

disease) in 2 patients. Postoperatively 9 patients (22%) died in 30 days. All patients died in a septic shock with multiorgan failure. Another 10 patient had nonfatal postoperative complications: pneumonia, empyema, necrosis of the stomach wall (fundus), fistula of the anastomosis and hylothorax. In patients with carcinoma located in the upper and middle third of the esophagus both fatal and nonfatal postoperative complications were more common than in patients with their carcinoma in the lower third, 25% vs. 17.6% and 29.2 vs. 17.6%, respectively (Table 3). In 4 out of 5 patients with necrosis of the stomach wall and in 3 out of 4 patients with fistula of anastomosis the tumour was present in the middle third of the esophagus.

A pathologic complete response (pCR) was achieved in 11/41 (26.8%) patients, in the upper two thirds of esophagus in 7/24 patients (29.1%) and in the lower third in 4/17 (23.5%) patients. Postoperatively 2 patients with pCR died. After a thorough lymph nodes examination by the pathologist metastatic disease was found in 9 patients (3 patients M_{1a}, 6 patients M_{1b} disease) and during the follow-up only 5 of these patients relapsed.

The median follow up was 40 months (6-52 months). The overall risk for recurrence was 43.9% (9 recurred locoregionally, 5 distant and 4 locoregionally and distant). Patients with and without pCR had a similar risk for recurrence (45.5% vs. 43.3%).

The median time to relapse was 21.5 months (95% CI: 7.3 – 35.7 months) and the median overall survival time was 18 months (95% CI: 10.8 – 25.1 months). Overall 2-year and 3-year survival was 36% and 28% respectively (Figures 2, 3). Patients with pCR had the median survival time of 21.2, months (95% CI: 2.4-40 months) and patients without a pCR 16 months (95% CI: 7.6-24.4 months, p=0.79).

Discussion

In this retrospective analysis of our patients with locally advanced esophageal cancer treated with preoperative concomitant CRT the pathologic complete response rate (26.8%), recurrence rate (43.9%) and

Table 3. Tumour localization and postoperative complications

POSTOPERATIVE COMPLICATIONS	No. of patients (%) TUMOR LOCALISATION	
	UPPER+MIDDLE THIRD	LOWER THIRD
NONE	11/24 (45,8%)	11/17 (64,7%)
NON-FATAL	7 /24(29,2%)	3/17 (17,6%)
FATAL	6/24 (25%)	3/17 (17,7%)
TOTAL	24	17

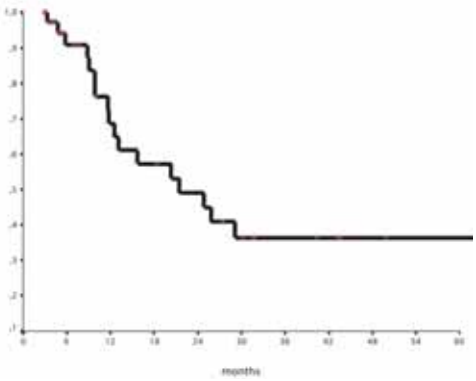

Figure 2. Relapse-free survival (n=41).

median overall survival time (18 months) are comparable with the results of published trials.[25]

In the majority of published clinical trials, the survival of patients who achieved a pCR was significantly better than of those without a pCR. In our study the median survival of patients with a pCR (21.2 months) was also better than in those without a pCR (16 months) but the difference was not statistically significant. The main reason could due to small number of patients included in our study.

We also observe a high postoperative mortality rate and efforts to reduced postoperative mortality could further improve the overall survival. Necrosis of stomach wall occurred in 5 patients and led to death in 2 patients. This treatment complication is not listed among the common in the literature. The postoperative mortality rate was higher in patients with tumours located in the upper two thirds of esophagus in comparison to the lower third (27.3% vs. 17.6%) but the difference was not statistically significant. Altogether, 80% of all stomach wall necrosis and 75% of all fistulas on the anastomoses occurred in patients with tumours in the upper two thirds. Therefore, concomitant CRT without surgery might be a reasonable option for patients with cancer localized in the upper two thirds of the esophagus. Although there are no randomized studies comparing surgery versus concomitant CRT alone, the survival of patients in the concomitant CRT arms (in some randomized clinical trials comparing concomitant CRT versus radiotherapy) is similar to the survival of patients treated in the trials comparing surgery and preoperative concomitant CRT plus surgery. This comparison is speculative and not evidence based, but it might be reasonable to adopt it for the subgroup of patients with high mortality rate after the surgery as are in our case the patients with their cancers in the upper two thirds. Improved surgical techniques and more intense postoperative care are also important options for these patients since the surgery was beneficial in 5 out of 9 our patients with residual carcinoma in the lymphnodes (M_{1a} and M_{1b} disease) after concomitant CRT who are still free of recurrence after the median time of follow up of 40 months. Currently it is also hard to predict who is going to achieve a pCR after concurrent chemoradiotherapy and the achieved pCR rates are relatively low. For these reasons the role of surgery remains an important part of this multimodality treatment approach.

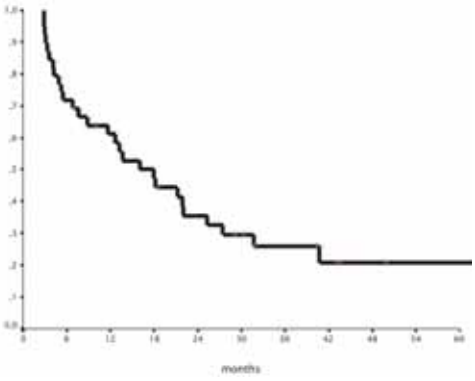

Figure 3. Overall survival (n=41).

The median dose intensity for cisplatin and 5-FU was 92.8% and 71.5% of the

planned dose intensity, respectively. The main reason for the lower dose intensity for 5-FU might be due to well known higher incidence of mucositis in case of concurrent chemoirradiaton. Patients with median dose intensity of less than 80% for both cisplatin and 5-FU had a higher locoregional recurrence rate (35.7% *vs* 21.4%) and increased incidence of distant failure by almost four-fold (28.6% *vs* 7.7,%). Therefore it seems important that the dose intensity is delivered as planned in the schedule. It seems that this is feasible, since in our study the postoperative complication rates (including fatal) were similar regardless of the dose intensity received. Modern three dimensional conformal radiotherapy planning could be of additional benefit for the locoregional control.

An extremely important issue is the selection of patients for this combined modality treatment. We should exclude patients in poor performance status with distant metastases who will not benefit with this kind of treatment.

Conclusion

Preoperative concomitant CRT might be beneficial at least in a subset of patients with locally advanced esophageal cancer in good performance status and without important comorbidity. For tumours originating in the upper two thirds of esophagus the role of surgery should be used in highly selected cases. A multidisciplinary approach of surgeons, radiation oncologists and medical oncologist is essential.

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