

The efficacy of preoperative cisplatin and 5-fluorouracil combination in patients with stage III squamous cell carcinoma of the esophagus

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SUMMARY

We aimed to assess the efficacy of neoadjuvant cisplatin and 5-fluorouracil (CF) combination chemotherapy in patients with potentially resectable squamous cell carcinoma of the esophagus. Thirteen consecutive patients with clinically stage III esophagus carcinoma were included in this study. Median age was 55 years (range:27-70 years). All patients were treated by 2 cycles of neoadjuvant chemotherapy (CF) with cisplatin 20 mg/m²/d, iv, and 5-fluorouracil 1000 mg/m²/d, continuous infusion, days 1-5. The objective response rate was 41.6%. Total resection rate was 61.5%. No pathologic complete response was observed. Two patients who underwent curative surgery died on early postoperative period. Five out of 6 resected patients had relapsed disease. Median relapse-free survival was 24 months in patients who had complete resection and the overall survival of all the patients included was 17 months. The results of preoperative chemotherapy with CF combination are not encouraging in patients with squamous cell carcinoma of the esophagus. [Turk J Cancer 2005;35(1):26-31].

KEY WORDS:

Neoadjuvant, chemotherapy, cisplatin, 5-fluorouracil, esophageal carcinoma

INTRODUCTION

Surgery is the treatment of choice for the patients with potentially resectable squamous cell carcinoma of the esophagus (SCCE) (1,2). However, 5-year survival rate remains poor, which is ranging between 5-30%, following surgical treatment (2-4). Addition of radiotherapy, chemotherapy or both to surgery has not been reported to improve survival (3,4). The role of adjuvant chemotherapy or radiotherapy still remains unclear. The asymptomatic patients with small tumors confined to the esophageal mucosa or submucosa have the best results for surgery. However, once symptoms are present, the tumor has usually invaded the muscularis propria or beyond with or without lymph node metastases. Therefore, the resectability of the tumor is an important issue for this group of patients. The resection rate of the esophageal cancer is not so high. The preoperative use of chemotherapy or radiotherapy, have been reported to increase the resection rate in patients with potentially resectable esophagus cancer. Despite many studies, there is no definitive proof that any one approach is superior.

In this prospective study we have evaluated the efficacy of preoperative cisplatin and 5-fluorouracil in patients with squamous cell carcinoma of the esophagus (SCCE).

PATIENTS AND METHODS

Eligibility criteria included the followings: 1) histologically confirmed diagnosis of squamous cell carcinoma of the esophagus or gastro esophageal junction; 2) having clinically stage III disease; 3) no previous treatment; 4) no medical contraindication to surgery; 5) performance status less than 3; 6) age younger than 75 years; 7) creatinine clearance greater than 60 mL/min; 8) a white blood cell count greater than 4000 cells per micro liter and a platelet count greater than 150,000 cells per micro liter; 9) no previous malignancy or previous malignancy only if the patient was considered to be cured; 10) no serious medical conditions that would preclude safe administration of treatment; and 11) ability to give informed consent. The patients with only the mucosal or submucosal tumor invasion or with distant metastases were not included.

The staging procedures included the upper endoscopy and biopsy, barium swallow, endoscopic ultrasonography (EU), and a computed tomography (CT) scan of the chest

and abdomen. Staging was done according to the UICC classification (5).

Patients were planned to administer two courses of a combination of cisplatin and 5-fluorouracil before surgery. The schedule of chemotherapy was cisplatin 20 mg/m²/d, i.v., and 5-fluorouracil 1000 mg/m²/d, continuous infusion, days 1-5, every 3 weeks.

Response to chemotherapy was evaluated by CT, EU, and barium swallow following the second cycle, according to WHO Criteria (6). Surgery, either transthoracic or transhiatal subtotal esophagectomy, was planned for 3-4 weeks after the completion of the second cycle of chemotherapy or after the hematological recovery from the second cycle was achieved.

RESULTS

Thirteen consecutive patients with squamous cell carcinoma of the esophagus were enrolled within a 3-year period.

Table 1
Patient Characteristics

	No. of Patients (%)
No. included in study	13 (100)
Gender	
Female	4 (30.7)
Male	9 (69.3)
Median age (Range)	55 (27-70)
Performance status (ECOG)	
0	1
1	5
2	7
Tumor stage at diagnosis	
T3N1	5 (38)
T4N0	5 (38)
T4N1	3 (24)
Position of primary tumor	
Upper esophagus	3 (23)
Middle esophagus	6 (47)
Lower esophagus	4 (30)
Histologic grade	
Good differentiated	1 (8)
Middle differentiated	6 (46)
Poor differentiated	6 (46)

The characteristics of the patients are given in table 1. Male/female ratio was 6/4. Median age was 55 years. All the patients had tumors invaded the adventitia or beyond or had enlarged lymph nodes at the time of inclusion.

Responses to chemotherapy were assessed in 12 patients, because of one patient died due to neutropenic sepsis after the second cycle of chemotherapy. Five out of 12 patients (41.6%) had partial response and 2 (16.6%) had minimal response after 2 cycles of chemotherapy. None of eight patients who underwent resection determined pathologic complete response.

Grade 3-4 neutropenia was observed in 7 (53.8%) patients. One patient (7.6%) died of sepsis secondary to febrile neutropenia after the second cycle of chemotherapy. Grade 3 thrombocytopenia was observed in 1 (7.6%) patient. Grade 3 emesis was occurred in 3 (23%) patients.

Eight patients (61.5%) underwent curative resection surgery after neoadjuvant chemotherapy. One patient (7.6%) having partial response refused surgical resection and he was given chemoradiotherapy then after. Another patient (7.6%) having stable disease after 2 cycles of chemotherapy was found to be unresectable during surgical procedure. Two nonresponding patients died from progressive disease. Two of the patients who underwent curative surgery, a 61 years old man and a 70 years old woman, were died on days 3 and 14 of the postoperative period, respectively. The study was stopped after the second postoperative mortality which might probably attributable to the surgical procedure after chemotherapy.

Reconstruction of the intestinal route was re-established by interposition of the stomach with a cervical anastomosis in patients having complete resection.

Resected specimens were opened longitudinally, pinned out on a cork board, mapped before processing. Sufficient full-thickness blocks were taken to sample tumor or to include entirely a volume previously occupied by tumor. The consultant histopathologists sought diligently to isolate the maximum number of nodes from the resected specimens. Blocks were fixed routinely in formol saline and processed to paraffin wax. Sections were reported by a consultant histopathologist and graded and staged according to the International Union Against Cancer System (5). No patho-

logic complete response was observed. The down staging was achieved in 4 out of 8 patients having complete resection.

After surgery, all patients were monitored extensively to obtain the accurate information regarding the patterns of failure every 3 months during the first year, every 6 months during the next 2 years. None of the patients with complete resection were given adjuvant treatment. Recurrence at the primary site or at distant metastases were detected by chest x-ray, barium swallow, CT, ultrasonography, or endoscopy and confirmed by biopsy.

Two of the patients (25%) who had total resection died at early postoperative period. Five out of 6 remaining operated-patients had relapsed disease. The sixth patient without relapse died of a non-tumor related cause at the third year of follow-up. Median relapse-free survival in patients who had complete resection was 24.0 ± 5.4 months (95% Confidence Interval: 13.4-34.6) (Figure 1). However, the overall survival of all the patients included was 17.0 ± 4.7 months (95% Confidence interval: 7.7-26.3) (Figure 2).

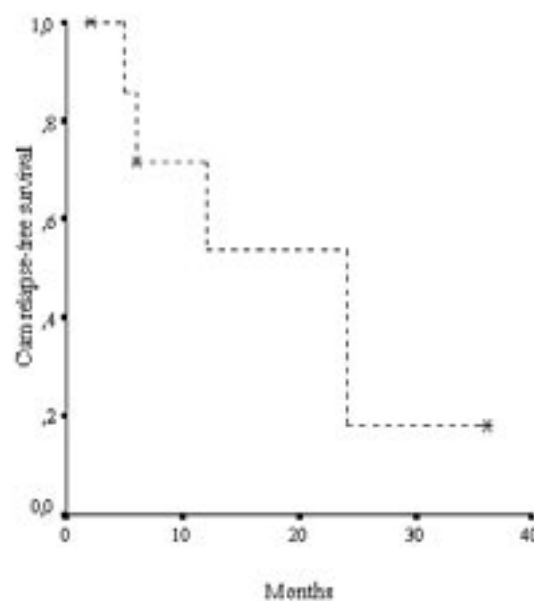


Fig 1. The relapse-free survival curve of the patients according to the Kaplan-Meier method (X: Censored patients)

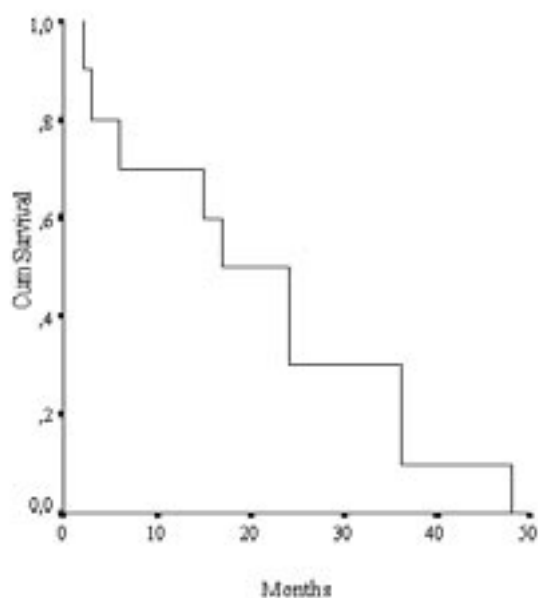


Fig 2. The overall survival curve of the patients according to the Kaplan-Meier method (X: Alive patients)

DISCUSSION

Surgery has been the treatment of choice for localized esophageal cancer. However the prognosis of the patients with SCCE treated by surgery alone is still poor. The locally invasive nature of the disease and anatomic limitations are both the major obstacles for a curative resection. In unselected patient cohorts, the 5-year survival rates for potentially resectable patients are low as 10-15% (1,7,8). A number of studies have investigated whether preoperative chemotherapy followed by surgery leads to an improvement in cure rates, but the individual reports have been conflicting.

In early studies using different chemotherapy regimens with or without radiotherapy preoperatively, the rate of resectability was found as 35-86% (4, 8-12). Also the rate of pathologic response in those studies was ranging between 0 and 10% and median survivals were between 10 and 18 months. Cisplatin and 5-FU combination with different schedules has been the most widely used regimen preoperatively. In this small group of patients with locally advanced disease (stage III), we achieved a 60% complete resection rate. However, early mortality rate following the surgical procedure was 20%, which is highly unfavorable when

compared to the previous reports (8-16). It might be due to the preoperative chemotherapy that caused very frequent side effects being mainly the grade 3-4 myelosuppression. Although the higher response rate achieved in the current study, lack of the pathological response following chemotherapy is another unfavorable result. Further cycles of chemotherapy would possibly result in pathological responses. However, the complete pathological response rates seen in nonrandomized trials reported so far are ranging between 0 and 10% (17,18).

In the vast majority of the previous studies no survival advantage has been reported with the use of neoadjuvant chemotherapy. In a randomized trial studying the efficacy of 3 cycles of preoperative cisplatin and 5-FU combination chemotherapy and 2 additional cycles of the same regimen after surgery, no survival advantage over surgery alone arm has been reported (14.9 months v.s. 16.1 months) (19). However, The Medical Research Council Esophageal Cancer Working Party has reported a slight survival advantage in the patients administering 2 cycles of preoperative cisplatin and 5-FU combination compared to surgery alone group (16.8 v.s. 13.3 months, respectively) (20). In the current study, we observed a median survival of 17 months, which is comparable to those achieved in previous both randomized and nonrandomized trials. However, it could be noticed from the previous reports that, there is a trend of increased survival rates in the subgroup of patients achieving pathological complete response (21-23).

Recently, results of some phase II and randomized neoadjuvant chemoradiotherapy trials have raised the hopes for increasing the survival in SCCE, although some of them failed to show survival benefit (14-16, 24,25). In Nygaard study (14), the comparison between the chemoradiation plus surgery arm with the surgery-alone arm showed a statistically insignificant improvement in 3-year disease-free survival from 9% to 17% ($p=0.03$). In the same study, the rate of curative resection was lower than compared with similar studies. In the Michigan University study, median survival was approximately 17 months in both arms; 3-year survival was compared in the chemoradiation plus surgery arm (32% v.s. 15%) but of borderline statistical significance. The rate of loco regional recurrence was 19% for the chemoradiation plus surgery arm v.s. 39% for the

surgery-alone arm ($p=0.039$) (24). Also the use of the combination of new drugs is reported to yield better results in terms of response and survival (21,26). However, along with the non-clear survival benefit, the increased morbidity of the surgery following chemoradiotherapy seems to be an important limitation for this multimodal therapeutic approach.

The question of which therapeutic approach yields the best survival benefit in patients with potentially resectable

stage III SCCE remains unanswered. Although the majority of the previous reports show a minor benefit from the preoperative chemoradiotherapy in patients with locally advanced SCCE, the interpretation of the results of those trials are challenging. To clarify the role of neoadjuvant treatment, either chemotherapy or chemoradiotherapy, in the treatment of patients with potentially resectable SCCE, further studies are needed.

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