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CISPLATIN AND 5-FU COMBINED WITH RADIOTHERAPY AND SURGERY IN THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

Palliative effects and tumor response

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Abstract

The combination of cisplatin (90–120 mg/m^2) and 5-fluorouracil (5-FU) (1 000 mg/m^2/day in continuous infusion for five days) was given for 2–3 cycles, prior to combined radiotherapy and surgery, to 73 patients with esophageal squamous cell carcinoma, 60 with limited disease (LD), and 13 with extensive disease (ED) (i.e. with metastasis) of whom 3 had recurrent disease. Before preoperative radiotherapy among 60 LD patients, 12 (20%) had complete response, 21 (35%) partial response, 25 (42%) had stable disease, and 2 (3%) progressive disease. Swallowing was improved in 35/73 (48%) of the cases. In the resected specimens, no tumor was found in 8/53 (15%) of the cases, microscopic tumor in 18/53 (34%) and macroscopic tumor in 27/53 (51%). In the ED group, complete response of distant metastases was obtained in 6/13 (48%) of the patients, one of whom is still alive with no evidence of disease 62 months after the start of treatment.

Key words: Esophagus, squamous cell carcinoma, cisplatin, 5-FU, radiotherapy, surgery.

Squamous cell carcinoma of the esophagus carries a gloomy prognosis. Approximately 50% of patients with newly diagnosed disease will present with distant metastases or local disease too advanced for curative surgery or radiotherapy to be considered. Even in patients given such therapy the 5-year survival is usually less than 10% (1, 2). Similar survival rates have been reported after combination of surgery and radiotherapy (1–5). With regard to dysphagia the beneficial effect of resection, when it can be performed, is often immediate and enduring, while the effect of irradiation is less predictable. Combination of radiotherapy and surgery has been tried in an effort to improve the results. Some workers have reported improved resectability and subsequent palliation with this approach, though long-term survival is still disappointing. Even after an aggressive approach, including high-dose radiotherapy and surgery, local recurrence was seen in 30/53 (57%) of the patients (5). Chemotherapy is therefore studied both in cases with early dissemination of the disease and in cases with loco-regional disease, often in combination with subsequent radiotherapy and/or surgery.

Both cisplatin and 5-FU have, as single drugs, been reported to have modest effect on squamous cell cancer of the esophagus. Used in combination, the two drugs have been found to have a synergistic effect on animal tumors (6), and to achieve a high response rate in humans with squamous cell cancer of the head and neck (7, 8).

Since 1983, patients with squamous cell carcinoma of the esophagus referred for treatment to the Department of Oncology or Department of Thoracic Surgery Hospital, Lund, have been entered into a treatment program including 3 courses of induction chemotherapy (cisplatin and 5-FU) followed by irradiation and, depending on tumor stage, surgery. Preliminary treatment results are now reported with special emphasis on palliative effects and tumor response to the chemotherapy component of the regimen.

Material and Methods

The patients included in this study had biopsy-verified, untreated metastatic (ED) or loco-regional (LD)

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Table 1

Carcinoma of the esophagus. Consecutive cases. Patient data

	n
Patients	73
Men, mean age 65 y (48–80)	56
Women, mean age 63 y (48–72)	17
Limited disease	60
Extensive disease	13
Metastatic site	
Lung	5
Coeliac nodes	5
Supraclavicular nodes	1
Liver	1
Trachea	1

squamous cell carcinoma of the esophagus and were referred to the treatment center between May 1st, 1983 and May 1st, 1987. There were 73 patients, 56 men with a mean age of 65 years, and 17 women with a mean age of 63 years (Table 1).

Pretherapy staging was based on clinical history and examination, barium radiography of esophagus, esophagoscopy, chest radiography, liver scintigraphy, CT of thorax and upper abdomen, blood count, and serum tests of liver function. Thirteen patients were found to have extensive disease and 60 to have limited disease (LD) (Table 1).

The tumor was located in the upper third of the esophagus in 12 patients (17%), in the mid-third in 38 patients (54%), and in the distal third in 20 patients (29%). Three patients had recurrent disease (pulmonary metastasis) but no esophageal tumor. Tumors were well differentiated in 10 patients (14%), moderately differentiated in 40 patients (55%), and poorly differentiated in 23 patients (31%).

The treatment plan consisted of three courses of chemotherapy followed by radiotherapy and surgery (Fig. 1). In the most recent cases included, 20 patients with limited disease, peroperative radiotherapy was given concomitantly with the third chemotherapy cycle. Cases with extensive disease were only considered for radiotherapy and/or surgery if chemotherapy produced complete response (4 patients). Twelve patients had preoperative radiotherapy only, and two patients only postoperative radiotherapy (the reasons for this are given in Table 2).

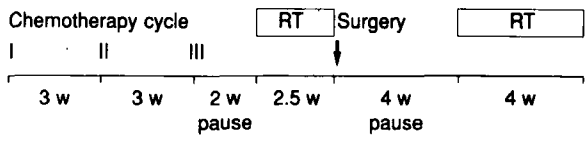

Fig. 1. Treatment schedule.

Table 2

Reasons for only preoperative or only postoperative radiotherapy

	n
Preoperative radiotherapy	
40 Gy preoperatively	3
Metastases at surgery	2
Histopathology: no tumor	4
Early death	3
Postoperative radiotherapy	
Esophageal fistula during chemotherapy	2

Chemotherapy. The patients were given cisplatin, 90–120 mg/m^2 BSA on day 1, and 5-FU 1 000 mg/m^2 BSA daily as a continuous infusion on days 1–5 inclusive (Fig. 1).

Before cisplatin administration, the patients were prehydrated with 1 000 ml 0.9% saline given as a 2-h infusion. Cisplatin was dissolved in 2 000 ml 0.9% saline and given together with 500 ml 15% mannitol as an intravenous infusion over four hours. Uresis was measured every fourth hour, and diuretics given if it was less than 400 ml/4 h. The 5-FU treatment started immediately after the completion of cisplatin infusion. 5-FU was dissolved in 2 000 ml 0.9% saline and given as continuous infusion over 24 h for 5 consecutive days. Allopurinol (300 mg) was given every treatment day in order to reduce kidney toxicity. According to the treatment plan 3 courses of induction chemotherapy should be given.

Radiotherapy. For limited-disease patients an absorbed dose of 64 Gy in the esophageal tumor (target volume I) was planned in two series as pre- and postoperative radiotherapy. In all cases radiation therapy was given with 6 MV or 8 MV photons from a linear accelerator. Target volume I was defined as the tumor demonstrated by chest radiography or CT. For tumors located at or above the level of the tracheal carina, the caudal border of target volume I was located 5 cm below the lower limit of the diagnosed tumor while the cranial border included the supraclavicular nodes. For these upper tumors, a 3-field technique was used both pre- and postoperatively. For tumors located mainly below the carina level, the cranial border of target volume I included 5 cm of radiographically uninvolved esophagus while the celiac lymph nodes were included in target volume as target volume II, and also defined the caudal border of target volume I. Any nodes in the celiac region were resected at surgery. If histopathologic examination showed viable cancer cells, the total absorbed dose in target volume II was 40 Gy, otherwise only 24 Gy (i.e., only the preoperative radiotherapy was given). In the case of tumors below the tracheal carina, AP-PA fields were used preoperatively (target volumes I and II); and postoperatively a 3-field technique was used for target volume I together with AP-PA fields for target volume II with a specified dose of 40 Gy. The

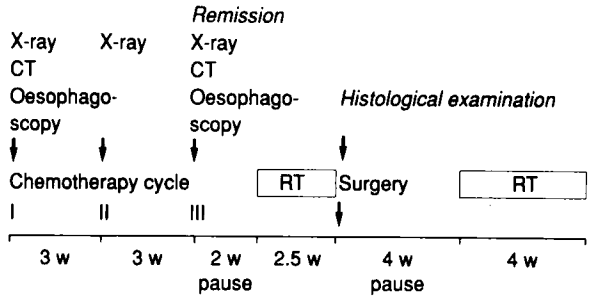

Fig. 2. Follow-up schedule.

target-absorbed dose was specified according to minimum absorbed dose. Daily fractionated irradiation was given with a target dose of 2.0 Gy.

Surgery. Surgery included laparotomy for inspection of liver and coeliac nodes, the latter being resected if cancer was suspected. The stomach and the duodenum were mobilized and pyloromyotomy performed. The esophagus was resected through a right-sided thoracotomy, the stomach being pulled up into the chest and an anastomosis performed between the fundus and the proximal esophagus. Colonic interposition was used in three patients. Tumors were found to be non-resectable in 6 cases, in two of which esophageal bypass was performed with gastric intubation and colonic interposition. Two patients with mild dysphagia were only explored and resutured.

Follow-up. The patients were evaluated prospectively by means of a special questionnaire and with staging procedures (Fig. 2). Dysphagia, chest pain, weight, Karnofsky index, chemotherapy and radiotherapy-related toxicity (neuropathy, impairment of hearing, mucositis, vomiting, kidney toxicity, infections, heart toxicity, hematologic toxicity) and tumor volume were recorded with regular intervals (Fig. 2). Response to chemotherapy was assessed immediately after the 3 cycles of treatment (i.e., before radiotherapy). In 20 cases, the response was assessed very soon after the start of radiotherapy (Fig. 1). The following criteria were adopted; Complete response (CR) required normal clinical examination findings supported by normal barium esophagogram or CT of the esophagus; in ED cases, metastatic sites were to be normalized as evaluated with the same procedures as before treatment. For partial response (PR) reduction of the tumor site by more than 50% as assessed with the same procedures as before treatment was required. Tumor growth was defined as progressive disease (PD), and stable disease (SD) as a reduction less than 50% or no increase of 25% or more in any indicated lesion.

Results

Quality of life. At the start of chemotherapy 70 patients (96%) had dysphagia; ten patients could eat normal food, 29 patients minced or mashed food, and 34 patients could ingest liquids only. After three courses of chemotherapy, 35 patients still had dysphagia; 42 patients were able to eat normally, 19 minced and mashed food, and 12 liquids only. Pain was eliminated in 34 out of 39 patients; weight increased in 26 patients, was stable for 23, and decreased in 24. The Karnofsky index increased in 7 patients, was stable in 65, and deteriorated in one patient.

Tumor response. Six ED patients had CR (6/13 = 46%) and one of these (with pulmonary metastases before chemotherapy) is living with no evidence of disease after 62 months (Table 3). Three patients had PR and four SD. In the group of LD patients (n = 60), 12 (20%) had CR after three courses of chemotherapy, 21 PR, 25 SD and 2 PD (Table 3). Thus, the overall response rate to the chemotherapy regimen (CR + PR) was 33/60 (55%) among LD patients, and 9/13 (69%) among ED patients. The complete response rate for LD and ED patients was 18/73 (25%). The response rate was compared to the findings at surgery (24 Gy having been given), and at histologic examinations of the resected specimens (for results see Table 3). In 8 cases no tumor was seen in the resected specimen; in 18 patient cases histologic examination showed only microscopic residual disese, while in 27 cases tumor could be identified macroscopically.

Side-effects. Although the regimen outlined above was well tolerated, about one-third of the patients (32%) had mucositis between the chemotherapy courses, which healed in a few days. If serum hemoglobin was below 100% after 3 courses of chemotherapy, erythrocyte transfusion was given with the intention to reduce the risk of hypoxic tumor components appearing during radiotherapy. Almost half of the patients had such transfusion. Renal or cardiac toxicity, neurotoxicity or infections were rare (Table 4), and side-effects of radiotherapy few. There was one case of pericarditis and 5 of pneumonitis, all of which responded to medical treatment. Postoperative complications were very few and are listed in Table 4.

Table 3

Esophageal cancer. Treatment response

Extensive disease (n = 13)	
CR 6 (46%)	(lungs 4, coeliac nodes 2)
PR 3 (23%)	(trachea 1, supraclav. nodes 1, liver 1)
SD 4 (31%)	(lungs 1, coeliac nodes 3)
Limited disease, response before preop. RT (n = 60)	
CR 12 (20%)	
PR 21 (35%)	
SD 25 (42%)	
PD 2 (3%)	
Histological exam. of resected specimens (n = 53)	
No tumor remnant	8 (15%)
Micr. tumor	18 (34%)
Macr. tumor	27 (51%)

Table 4

Side-effects

	n (%)
Side-effects of chemotherapy	
Anemia-blood transfusion	36 (49)
Mucositis	23 (32)
Peripheral neuropathy	5 (7)
Impairment of hearing	6 (8)
Kidney toxicity with a rise of S-kreatinin (>30% reversible)	5 (7)
Kidney toxicity not reversible	1 (1)
Infection with need of hospitalization	2 (3)
Presumed serious heart toxicity	2 (3)
Vomiting	9 (12)
Alopecia	2 (3)
Complications to surgery	
Anastomosis leakage	3 (6)
Extended postoperative course > 6 weeks	2 (4)
Life-threatening infection	2 (4)
Pulmonary embolism	1 (2)

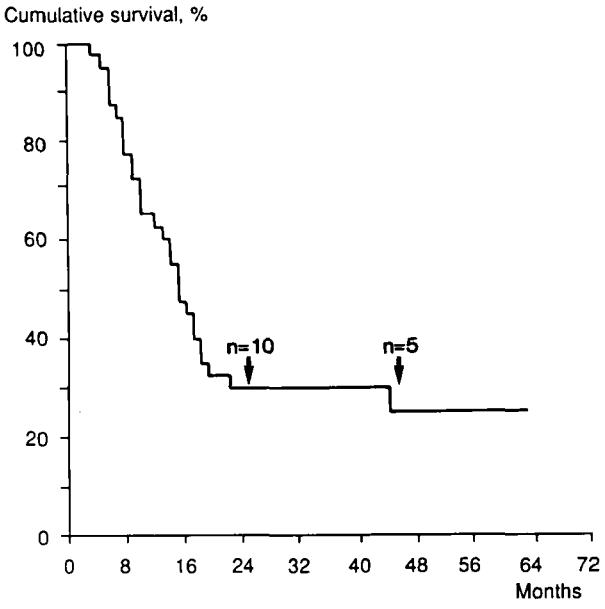

Fig. 3. Survival curve, all patients.

Table 5

Causes of death in 50 patients (autopsy in 15, clinical assessment in 35)

	n (%)
Local recurrence	10 (14)
Peripheral metastasis	11 (15)
Local recurrence + peripheral metastasis	5 (7)
Intercurrent disease	9 (12)
Treatment complications	7 (10)
Unknown cause	8 (11)

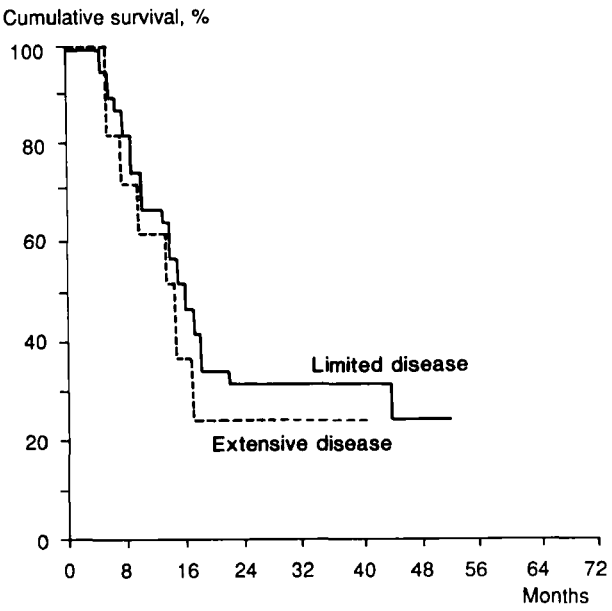

Fig. 4. Survival curves for LD and ED groups.

Survival. The duration of follow-up was at least 1 year. The actual one-year survival rate was 68% for LD patients and 56% for ED patients. The actuarial survival curve for all patients is shown in Fig. 3 and for the LD and ED group respectively in Fig. 4. Complete responders and patients with no tumor left in the resected specimen had a longer survival than patients with PR and SD.

Causes of death are listed in Table 5. Three patients died before surgery, one of pneumonia, one of pulmonary embolism and one of acute myocardial infarction. These cases were interpreted as complications related to chemotherapy. Four deaths were interpreted as related to surgery as they occurred shortly after the operation. Two cases of septicemia, one of pulmonary embolism and one of anastomosis leakage and pulmonary edema; autopsy was performed in all four cases. In 10 cases, the cause of death seemed to be related to local disease, although most of these patients had non-resectable tumors or were so improved by chemotherapy and radiotherapy that they refused surgery.

Discussion

Since overall treatment results for esophageal squamous cell carcinoma are poor, with a 5-year survival rate of about 5% for radiotherapy and surgery, it has been discussed whether the aim of treatment should be cure or palliation (9–13).

Although combined treatment with radiotherapy and surgery has been reported to result in better palliation and restitution of swallowing function (5), most of the patients so treated die of disseminated disease within two years after the start of treatment. Consequently new treatment

methods are needed. Cisplatin or cisplatin-based regimens have been found effective in cases of squamous cell carcinoma, both in the head and neck region and in the esophagus, and especially good response has been reported after combination of cisplatin with high-dose 5-fluorouracil (7, 14, 15).

In the present investigation this regimen has been found to have a palliative effect with a relief of the main symptom, dysphagia, in almost 50% of cases. Pain relief was obtained in almost all patients, and weight gain in 30%. This palliative effect is in good agreement with a response rate of 55% (CR + PR), as verified by esophagogram and computerized tomography, and with the findings in the resected specimens where no tumor or only microscopic disease was observed in 58% of patients. Moreover, the chemotherapy was rather well tolerated. The mucositis observed in almost one-third of the cases healed in a few days with adequate medical treatment. The frequency of serious toxicity with adverse cardiac effects and sudden death was fortunately very low (2%). The etiology of such toxicity may be multifactorial, and include hydration, increased blood vascular volume, angina pectoris with a coronary artery spasm caused by 5-FU (16–18), and possibly an effect of cisplatin on the sino-atrial node (19–21). The adverse cardiac effects were investigated separately and are reported elsewhere (22). The frequency of complications in conjunction with the other treatment modalities, radiotherapy and surgery, was similarly low (Table 4). This combined regimen is thus well tolerated, has few side-effects, and provides good palliation. Moreover, with combined treatment for squamous cell carcinoma of the esophagus comprising chemotherapy, radiotherapy and surgery, it would seem that a subgroup of patients can be completely relieved from their symptoms and eventually cured. Fourteen patients now live NED > 2 years, and one patient with bilaterally pulmonary metastases at the start of treatment lives NED > 62 months. Similar results have been reported by others (23, 24) using similar regimens. It is, however, too early to know whether response to this chemotherapy regimen for esophageal cancer will lead to marked improvement in survival.

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