A Swedish Study of Chemoradiation in Squamous Cell Carcinoma of the Esophagus

Dag Stockeld, Jan Tennvall, Gunnar Wagenius, Maria Albertsson, Lars Backman, Ola Brodin, Magdalena Cwikiel, Lars Granström, Gunnar Gustafsson, Sven Gustavsson, Göran Hambraeus, Rolf Lewensohn, Svante Sjöstedt, Hans Strander, Bengt Åberg and Jan Fagerberg

From the Department of Surgery, Danderyd Hospital, Stockholm (D. Stockeld, L. Backman, L. Granström), the Departments of Oncology (J. Tennvall, M. Albertsson, M. Cwikiel), and Thoracic Surgery (G. Hambraeus), Lund University Hospital, Departments of Oncology (G. Wagenius, O. Brodin), Thoracic Surgery (G. Gustafsson), and General Surgery (S. Gustavsson), Akademiska Hospital, Uppsala, the Departments of Oncology, Radiumhemmet (R. Lewensohn, H. Strander, J. Fagerberg), and Thoracic Surgery (B. Åberg), Karolinska Hospital, Stockholm and the Department of General Surgery, Huddinge University Hospital, Stockholm (S. Sjöstedt), Sweden

Correspondence to: Dag Stockeld, Department of Surgery, Danderyd Hospital, SE-182 88 Danderyd, Sweden. Fax: +46 8 6557766. E-mail: stockeld@ebox.tninet.se

Acta Oncologica Vol. 40, No. 5, pp. 566–573, 2001

This multicenter study describes the development of a chemoradiation protocol for the treatment of non-metastatic squamous cell carcinoma of the esophagus. Eighty patients were treated with three courses of chemotherapy (cisplatinum and 5-fluorouracil) with concomitant radiotherapy (40 Gy) during the last two courses of chemotherapy. Esophagectomy was performed, when feasible. If no operation was performed, patients were planned to receive a target dose of 64 Gy. Toxicity was mainly attributable to hematological impairment and led to two adjustments of the treatment protocol (addition of filgrastim and lowering of the 5-fluorouracil dose). These changes made it possible to administer the planned treatment in a gradually higher proportion of patients (13/23 [57%] before changes of treatment compared with 30/36 [83%] after changes). Treatment-related mortality was 3.75% (3 patients, associated with leucopenic septicemia after chemotherapy). Fifty-four patients were resected. No per- or postoperative mortality was encountered. The complete response (pathological CR) rate in operated patients was 46% (27/59 patients) after chemoradiation. In the whole series the CR rate (including clinical CR for non-resected patients) was 44%. With a minimum follow-up of 37 months, the 3-year survival for the whole group was 31% compared with 57% for the CR patients. Total 5-year survival thus far (July 1999) is 26%.

Received 5 June 2000
Accepted 6 December 2000

Squamous cell carcinoma of the esophagus is a dreaded disease with severe symptoms and a poor prognosis. In large historical series the 5-year survival is in the order of 5–10% (1–3). Newer surgical procedures claim a better 5-year survival because of more radical techniques, but this may be an effect of selection of patients (4–6). It is well established that most patients present late, with a disease that is no longer locoregional. With this background, the stage is set for the development of new therapeutic strategies.

New surgical procedures and endoscopic treatments of early tumors have been developed (7) as has the use of intraluminal brachytherapy (8). However, with early dissemination, it seems rational to use systemic treatment modalities such as chemotherapy and not just the locoregional techniques of surgery and/or radiation. With cisplatinum-containing regimens good partial response rates (around 50%) can be obtained in patients with locoregional disease (9). The rationale for combining radio- and chemotherapy is that, as the toxicities of these modalities are not entirely overlapping, an enhanced tumoricidal effect might be obtained (10, 11). In studies where concomitant radiation is added, a high frequency (exceeding 40%) of complete responses has been observed (12–15).

This was the base for this multicenter study where the antitumoral effect of a combination of cisplatinum and 5-fluorouracil administered simultaneously with radiotherapy was studied as well as the associated implications for surgery.

MATERIAL AND METHODS

Patient selection

Eligibility criteria for the study included histologically confirmed squamous cell carcinoma of the esophagus without signs of distant metastases, i.e. tumor stage T1-4,

 ISSN 0284-186X

N0-1, M0 according to the International Union against Cancer (16). The patients had to have a functional performance status of ≤ 2 according to the WHO classification and they should not suffer from any other condition that could be worsened by the planned treatment, such as serious heart (i.e. heart failure or angina) or kidney disorders. Hematological and renal function test parameters had to be normal (leucocytes $\geq 3.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, cr-EDTA clearance > 65 mL/min). There should not be a history of other squamous cell malignancy prior to entry nor should there be any history of any type of malignant tumor during the last five years before inclusion. Before entry into the study, the patients were investigated with spirometry, EKG, barium esophagogram, chest x-ray, CT scan of the chest and upper abdomen, abdominal and endoscopic ultrasound (42 patients), esophagoscopy with biopsies and, finally, bronchoscopy, if the tumor was located at or above the carina. Patients with intraluminal airway growth were excluded. The results of these pretreatment investigations were evaluated by a surgeon and an oncologist to determine whether the patients were fit for the planned treatment.

Criteria for resectability

Before starting the treatment the patients were stratified as primarily resectable or unresectable by the surgeon and the oncologist. The criteria for initial unresectability were: 1) medical conditions contraindicating thoracotomy, 2) tumor overgrowth of the tracheobronchial tree or of the mediastinal vascular structures, and finally 3) tumors in the cervical esophagus. This stratification was repeated after the primary chemoradiation treatment, when a new CT scan and EUS (if available) were performed.

Study design

The treatment schedule is presented in Fig. 1. The objective of the study was to administer three courses of chemotherapy within 7 weeks where the last two courses were given with concomitant radiotherapy of 40 Gy. After chemoradiation the patients were re-evaluated. Cases considered resectable were operated on while the other patients, if possible, received further radiotherapy up to a total of 64 Gy.

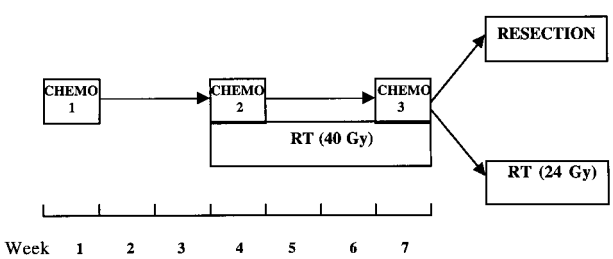

Fig. 1. Planned treatment with three courses of chemotherapy (CHEMO) with concomitant radiotherapy (RT) during the last two courses of chemotherapy.

Surgery was planned 2 to 4 weeks after the end of oncological therapy.

Ethics considerations

All patients gave their informed consent prior to therapy. The study protocol passed the evaluation of the ethics committees of the participating centers according to the World Medical Association's Declaration of Helsinki 1964 and the Amendment of Tokyo in 1975.

Treatment modalities

Chemotherapy. Cisplatinum (100 mg/m^2) was administered on day 1 by an intravenous 1-h infusion with hydration and diuresis carefully monitored. 5-fluorouracil was delivered by a 120-h continuous infusion. Initially 1 000 mg/m^2/day for 5 days was given, but that dose was later (after treatment of 44 patients) reduced to 750 mg/m^2/day because of the toxicity that was encountered. The procedures were repeated twice, starting on days 22 and 43, respectively. Owing to hematological toxicity the G-CSF analogue filgrastim was introduced into the protocol after the treatment of 23 patients. Filgrastim was administered subcutaneously daily (0.3 mg) for 10 days after chemotherapy cycles 2 and 3, starting on days 28 and 49, respectively.

Three different treatment groups (A, B and C) were thus identified, where the 23 patients in group A received a 'full dose regimen' including 1 000 mg 5-FU/m^2/day without filgrastim. The 21 patients in group B also received 1 000 mg 5-FU/m^2/day but filgrastim was added after chemotherapy cycles 2 and 3. Finally, the 36 patients in group C received a lower dose of 5-FU with 750 mg/m^2/day. This latter group was also treated with filgrastim.

A dose reduction scheme was applied when significant hematologic or nephrologic toxicity was encountered (i.e. leukocytes ≤ 1.0, platelets ≤ 75, serum creatinine > 130 μmol/l).

Radiotherapy. Radiotherapy, which was started on day 22, was either given as a preoperative treatment of 40 Gy or as a full-dose therapy of 64 Gy. Longitudinally, the target volume was calculated as the length of the tumor craniocaudally plus 5 cm in both directions. The areas of the supraclavicular lymphatic glands were included in the target volume for patients with most of the tumor above the level of the carina. The lymphatic glands of the coeliac truncus were included in the target volume for patients with the bulk of the tumor below the level of the carina. Laterally, the target volume was calculated as the volume of the tumor plus 2 cm in either direction, including periesophageal lymph node stations. The treatment was given with a two-field technique with a daily fractionation of 2 Gy 5 days a week up to 40 Gy. Further radiotherapy was given with a three- or four-field technique after 2 weeks' rest. Before these last 24 Gy, the target volume was

recalculated as the tumor volume plus 2 cm in any direction.

Surgery. If the patient was considered resectable at the re-evaluation after 40 Gy, surgery was performed. The standard technique was an Ivor Lewis procedure with a gastric pull-up or with a colon interponate as the esophageal substitute.

Evaluation of toxicity and response to chemoradiation

During treatment the patients were closely followed with hematological and serum tests, audiograms and EKGs. Toxicity was classified according to the WHO criteria. After 40 Gy of radiotherapy and surgery, the patients were evaluated based primarily on findings at the operation. Patients not operated on were evaluated by clinical methods (x-ray of the esophagus, endoscopy, CT scans and, when available, endoscopic ultrasound). Responses were classified as complete responses (CR), when no manifestations of malignancy could be found with clinical techniques. When no tumors were found postoperatively after histopathological examination, the responses were classified as pathologic complete responses (p-CR). Partial remission (PR) was found when there was a reduction in tumor volume of $\geq 50\%$ without any new tumor manifestations. If the tumors showed a $< 50\%$ reduction, or an increase of $< 25\%$, the responses were classified as stable disease (SD). Finally, any increase in tumor volume of $\geq 25\%$ or the appearance of any new tumor manifestations was considered as progressive disease (PD).

Follow-up

After completion of therapy the patients were followed on an outpatient basis every 3 months during the first year and thereafter on an individual basis every 3–6 months. Investigations such as radiologic or endoscopic procedures were undertaken when clinically indicated.

Statistical considerations

The disease-free interval was recorded as the time from the first day with no evidence of disease until the time of relapse, while survival time was calculated from the first day of treatment using the Kaplan-Meier method. Comparisons between different survival curves were made with the log-rank test. Other comparisons between groups were made with the χ^2 test.

RESULTS

Demographic data

During a 5-year period (March 1991–February 1996) 80 consecutive eligible patients with squamous cell carcinoma of the esophagus were included into the study. Chemoradiation was administered at three oncological centers (S, L and U) and surgery was performed in six surgical departments. Thirty-eight patients (48%) were found to belong to stage IIA and 37 patients (46%) were classified as stage III disease. Endoscopic ultrasound was used for classification in 42 patients. Based on other investigations, the T-stage in 19 of the remaining 38 patients could only be settled to T2–T3. Five patients (6%), where no endoscopic ultrasound was performed, belonged either to stage IIB or stage III. Thirteen patients with T4 tumours were included, but no patients with airway invasion (as determined by bronchoscopy) were admitted to the study. Further details regarding the patients are given in Table 1.

Table 1

Patient characteristics (percentage of total in each group in parentheses)

No. of patients entered	80
No. of women	34 (42)
No. of patients evaluated	80 (100)
WHO performance status	
0	28 (35)
1	44 (55)
2	8 (10)
Grade of dysphagia pretreatment	
Can eat solids	24 (30)
Minced food	24 (30)
Liquids	29 (36)
Unable to swallow liquids	3 (4)
Unknown	0 (0)
Pretreatment weight loss (kg)	
No weight loss	14 (18)
≤ 10	49 (61)
> 10	15 (19)
Unknown	2 (3)
Grade of differentiation	
High	11 (14)
Moderate	22 (28)
Low	42 (53)
Unknown	5 (6)
Tumor location in the esophagus	
Upper	17 (21)
Middle	34 (43)
Lower	29 (36)
Unknown	0 (0)
Tumor length (cm)	
< 5	19 (24)
≥ 5–≤ 10	54 (68)
> 10	7 (9)
Unknown	0 (0)
T-stage (UICC)	
II	6 (8)
II–III	19 (24)
III	42 (52)
IV	13 (16)
Tumor stage (UICC)	
IIA	38 (48)
IIB or III	5 (6)
III	37 (46)

Table 2

Treatment compliance—radiotherapy (percentage of group in parentheses)

Planned treatment	40 Gy	64 Gy
No. of patients in group	69	11
Received treatment (Gy)		
0	4 (6)	–
12	2 (3)	–
40	59 (86)	2 (18)
50	–	1 (9)
64	4 (6)	8 (73)

Treatment compliance

Sixty patients (75%) received three courses of treatment, 11 patients (14%) two courses and 9 patients (11%) only one course of chemotherapy. Reasons for interruption of chemotherapy are given in Table 4. Over time and with the instituted changes to the chemotherapy protocol (inclusion of filgrastim and lowering of the 5-fluorouracil dose) the possibility to administer three courses of chemotherapy increased (group A 13/23 patients [57%], group B 17/21 patients [81%] and group C 30/36 patients [83%]). Individually reduced doses of chemotherapy were administered to 14 patients (16%) because of toxicity (12 cases) or pretreatment morbidity (one case with stenosis of the aortic outlet and one patient with initial pathologic audiogram).

Sixty-nine patients were planned to receive 40 Gy of radiation. Of these, 59 (86%) were actually treated according to the initial plan. The corresponding compliance figure among the 11 patients who were planned to receive 64 Gy was 8 (73%) (Table 2).

Four patients included in the preoperative treatment group received full-dose radiation (64 Gy). Two of these patients had advanced disease at the time of re-evaluation while the other two cases were regarded as inoperable at the time of operation because of poor general condition. Four other patients in the same group were not started on radiotherapy owing to toxicity from chemotherapy and another two patients stopped radiotherapy before 40 Gy, also because of chemotherapy side effects. Radiotherapy was stopped after 40 Gy in one patient initially planned for full-dose radiation since it was believed that the patient had developed pulmonary metastases. This later proved to be wrong and the patient was resected 5 months after the chemoradiation. Another two patients stopped radiotherapy before 64 Gy because of toxicity, judged to be mainly secondary to chemotherapy.

Toxicity at chemoradiation

A total of 211 courses of chemotherapy were administered. Three patients (3.75%), one from each treatment group, died of toxic complications related to chemotherapy. The first patient died of multiorgan failure after leucopenic septicemia with Klebsiella and thrombocytopenia after the first cycle of chemotherapy. The second patient suffered terminal heart failure and pulmonary infarction following thrombocytopenia and leucopenic septicemia after the third cycle of chemotherapy. An autopsy showed no signs of tumor. The third death was also caused by leucopenic septicemia after the third cycle of chemotherapy. The incidence of grade 3–4 side effects is recorded in Table 3. The number of leucopenic episodes is lower in the groups treated with filgrastim during cycles 2 and 3 but this difference is not statistically significant ($p < 0.07$). The figures for significant (WHO ≥ 3) infections did not show any advantage for the filgrastrim-treated patients but the reduction of the 5-fluorouracil dose in group C had an influence on leukopenia. Group C showed significant toxicity ($\geq$ grade 3) in only 2% of the courses compared with 19% in the otherwise equally treated group B ($p < 0.002$). There was also a difference, although not a significant one, in platelet toxicity (16 vs. 7%, $p > 0.09$) between groups B and C.

Toxicity caused the interruption of chemotherapy in 18 cases and the reduction of planned doses in 12 cases. Two other patients interrupted chemotherapy due to progress of disease and a general poor performance status, respectively (see Table 4).

Table 3

Toxicity grade ≥ 3 according to WHO during chemotherapy, number of affected cycles (percentage of total number of cycles in the group in parentheses)

	Total	Group A	*Group B*	*Group C*
No. of chemotherapy cycles	211	55	57	99
Leukopenia	32 (15.1)	19 (34.5)	11 (19.2)	2 (2.0)
Thrombocytopenia	19 (9.0)	4 (7.2)	8 (14.0)	7 (7.0)
Infection	7 (3.3)	1 (1.8)	4 (7.0)	2 (2.0)
Cardiac toxicity	5 (2.4)	2 (3.6)	2 (3.5)	1 (1.0)
Renal toxicity	1 (0.4)	–	–	1 (1.0)
Otological toxicity	2 (0.9)	–	2 (3.5)	1 (1.0)
Nausea, vomiting	6 (2.8)	1 (1.8)	3 (5.3)	2 (2.0)
Diarrhea	3 (1.4)	1 (1.8)	1 (1.8)	1 (1.0)
Mucositis	10 (4.7)	2 (3.6)	5 (8.8)	3 (3.0)

Table 4

Reasons for interruption of chemotherapy (percentage of total in each group in parentheses)

	Total	Group A	Group B	Group C
No. of patients	80	23	21	36
Cardiotoxicity	7 (8.8)	3	1	3
Nephrotoxicity	2 (2.5)	2	–	–
Haemotoxicity	4 (5.0)	2	1	1
Ototoxicity	1 (1.3)	–	–	1
Mucositis	1 (1.3)	–	1	–
Combined toxicity [1]	3 (3.7)	2	1	–
Progress of disease	1 (1.3)	–	–	1
Poor performance status	1 (1.3)	1	–	–
Sum:	20 (25.0)	10 (43.5)	4 (19.0)	6 (16.7)

[1] One patient with significant cardio-, hemo- and nephrotoxicity and 2 patients with significant hemo- and nephrotoxicity.

Surgery

In five of the 59 patients investigated, unrecognized advanced disease was noted intraoperatively and no resection was performed. In four of these cases unrecognized metastases were found (three pulmonary and one in the liver), while one patient had local overgrowth of the trachea causing irresectability, leaving 54 patients who were resected. Fifty-one of these patients were among the 69 patients initially planned for surgery, giving a resectability rate of 74% in this group. Three of the 11 patients initially planned for non-surgical treatment were finally resected (27%). Gastric pull-ups were performed in 51 patients, while the colon was used as the esophageal substitute in the remaining 3 patients. The median time from the last day of oncological treatment to day of operation was 25 days (range 1–136 days). Two patients were resected after 64 Gy of radiotherapy. All other resections were performed after 40 Gy.

No 30-day postoperative mortality was registered among the operated patients. Two cases of anastomotic leaks were recognized, but both were successfully treated conservatively. Neither of these cases was treated with full-dose radiotherapy. One case of chylothorax required a reoperation, as did two patients with postoperative bleeding. Four patients experienced a prolonged postoperative recovery, defined as a stay in the intensive care unit exceeding 7 days. One of these cases had received 64 Gy preoperatively. Postoperative complications are listed in Table 5.

Response to chemoradiation

In the 59 operated patients histopathological evaluation showed a pathologic complete response (p-CR) in 27 patients (46%). Four of the non-CR operated patients had no signs of tumor in the resected specimens but other manifestations of disease were found. Thirteen of the operated patients (22%) had only microscopic evidence of disease in the resected specimens and no other signs of disease. The remaining 18 non-explored patients were re-evaluated by means of radiological and endoscopical investigations. Eight clinically complete responders (44%) were thus found.

Out of the whole series, 34 CR patients (44%) were hence found (Table 6). After complete treatment, 51 cases (64%) were considered as being tumor free, i.e. with no evidence of disease (NED). No fistulas to the tracheobronchial tree or to other hollow organs developed during treatment.

Of the patients in the CR group, 65% (22/34) were initially classified as stage IIA patients compared with 35% (15/43) of the non-CR cases ($p < 0.01$).

Responses for the different treatment groups showed a total CR of 32% (7/22) in group A, 55% (11/20) in group B and, finally, 46% (16/35) in group C (n.s.). No significant differences were found, regarding response rates, between the three participating centers.

Survival and relapse-free survival

For all patients followed until death or for a minimum of 37 months, the 3- and 5-year survival figures were 31% and 26%, respectively (Fig. 2). The median survival for the whole

Table 5

Surgical complications in resected patients

No. of patients	54
Anastomotic leaks	2
Serious infection	1
Cardiac insufficiency	2
Respiratory insufficiency	3
Left-sided pneumothorax	1
Bleeding causing reoperation	2
Chylothorax causing reoperation	1
Prolonged stay in the ICU	4
30-day mortality	0

Table 6

Response to chemoradiation—treatment groups. (Percentage of group in parentheses)

	Total	Group A	Group B	Group C
No. of patients [1]	77	22	20	35
Total CR	34 (44.2)	7 (31.8)	11 (55.0)	16 (45.7)
Clinical CR	7 (9.1)	3 (13.6)	1 (5.0)	3 (8.6)
Pathological CR	27 (35.1)	4 (18.2)	10 (50.0)	13 (37.1)
PR microscopic disease	13 (16.9)	3	3	7
PR macroscopic disease	10 (13.0)	3	2	5
SD	7 (9.1)	4	1	2
PD	13 (16.9)	5	3	5

[1] Responses in patients who died of treatment-related toxicity are not included in the table. Abbreviations: CR = complete response; PR = partial remission; PD = progressive disease; SD = stable disease.

group was 16.1 (range 1.0–91.7+) months with 19.1 months for women and 15.5 months for men. The median survival among patients in tumor stage IIA (38 patients) according to the IUCC classification was 21.4 months compared with 12.1 months for patients in stage III (37 patients) and 12.3 months for the five T2-3N1M0 patients belonging to stage IIB or III ($p < 0.12$ stage IIA vs. IIB / III). The median survival for operated patients was 21.1 months and for non-operated patients 10.3 months corresponding to a 3-year survival of 36% vs. 19% ($p < 0.05$). All patients with a CR had a median survival of 41.7+ months in comparison with 10.7 months for patients without a CR after chemoradiation ($p < 0.0001$) (Fig. 3). The median survival for operated patients with only microscopic evidence of disease after chemoradiation (13 patients), where surgery may have an important potential, was only 17.5 months as compared with 41.2+ months for resected patients with a p-CR after chemoradiation. Of the 13 resected patients with only microscopic disease left after chemoradiation, only 4 survived more than 3 years. The median disease-free survival for the 51 patients with no evidence of disease after treatment was 27.1 months while the median survival among the resected patients was 22.3 months. The 3-year survival rate for these patients was 39%.

Failure pattern

Eighteen of the 51 patients with no evidence of disease (NED) after the primary treatment had relapses during follow-up. In the present study only 17% (3/18) of the relapses affected the remaining part of the esophagus. Two of these relapse patients had been resected earlier. Six of the relapses have been registered within regions treated with radiation while 11 patients showed relapses in non irradiated areas. One case demonstrated relapses in both irradiated and non-irradiated regions.

DISCUSSION

The survival of patients with esophageal cancer after locoregional therapy, such as surgery and radiotherapy alone, or combined, is disappointing (1–3). A number of chemotherapy regimens have been studied either as single drug therapies or in different combinations, mostly in the form of cisplatinum-based regimens. A relatively high response rate has been found, usually in the form of partial responses, but complete responses and hence potential cure are rare (9).

However, concomitant radiotherapy and chemotherapy seem to increase response rates (13–15). Pathological complete response rates of up to 51% have been reported (17) as well as a correlation between complete responses after chemoradiation and survival (18, 19). Randomized studies have shown a survival benefit for patients treated with chemoradiotherapy as compared with patients treated with

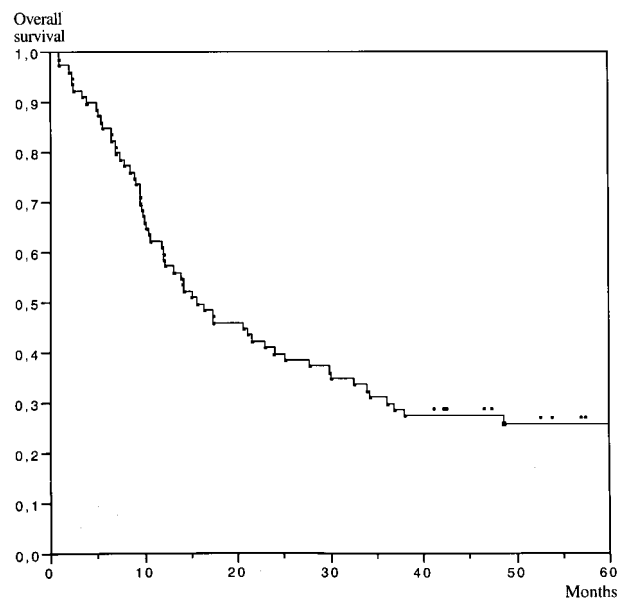

Fig. 2. Total survival among all patients in the series according to Kaplan-Meier.

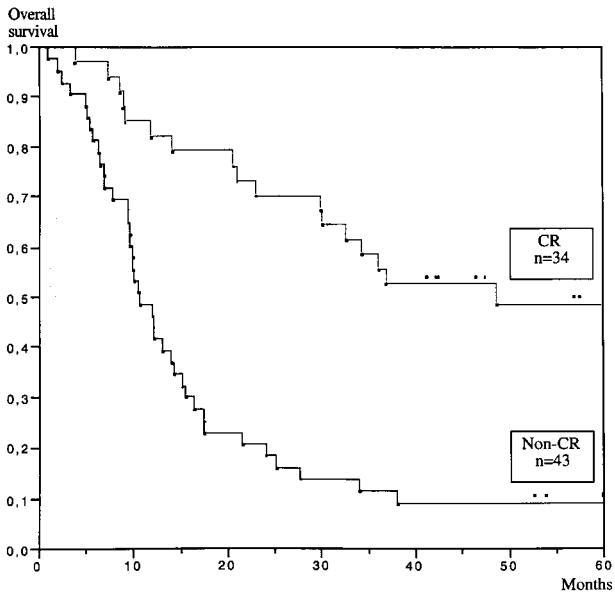

Fig. 3. Survival for patients with a total CR (n = 34) after chemoradiation as compared with patients without such a response. The difference in survival is significant ($p < 0.001$) according to the log-rank test.

radiotherapy alone (20–22). This picture of a survival benefit is less clear in the randomized studies where preoperative chemoradiation is compared with surgery alone. Some trials suggest a survival benefit for neoadjuvant chemoradiation (18, 23) while others have not been able to show this effect (24, 25). In the study by Bosset et al. (24) (two one-week courses of cisplatin 80 mg/m^2 followed by 18.5 Gy in five fractions of 3.7 Gy each) a longer disease-free survival and a higher frequency of curative resections have been found in the combined treatment group, but these advantages were not manifested in a prolonged survival as compared with the surgical group. This may be due to an increased postoperative mortality in the neoadjuvant group (12.3% vs. 3.6%). The high postoperative mortality may reflect the high fractions of radiotherapy that were applied. In our study we found complete responses in 44% of the patients compared with 26% in the Bosset study. This frequency of complete responses in the French series may also have influenced survival in the multimodal group of patients.

In the study by Walsh et al. (23) a significant downstaging of tumors was found after multimodal therapy (two courses of fluorouracil 15 mg/kg and cisplatin 75 mg/m^2 week 1 and 6 with 40 Gy of radiation therapy weeks 1–3) as compared with surgery alone. A survival benefit for the combined treatment reached significance at three years (32% vs. 6% survival). The 3-year survival after surgery alone in the Walsh study (6%) is, however, rather poor in comparison with other series. On the other hand, the fraction of complete responses in the Irish chemoradiation group was 25% compared with our 44%. This may also have influenced survival.

The study by Urba et al. (18) shows that a long follow-up may be crucial. In their first report in 1995 no survival differences were found between the surgical and the neoadjuvantly treated groups (26), but in a report two years later a survival benefit was found for the chemoradiation group (18). The investigators concluded that the survival difference supported the view of a combined modality therapy being a superior treatment for esophageal cancer.

The present investigation was not a randomized trial but a study with the aim of developing a manageable and safe chemoradiation protocol for esophageal cancer patients. As noticed in other studies, preoperative chemoradiation is not without its hazards. Treatment-related mortality of 12.5% has been reported (27). We noted three treatment-related deaths among the 80 patients (3.75%). Hematological toxicity with leukopenia and septicemia was the common factor among these three patients. Toxicity in other patients also indicated that mainly the hematological side effects interfered with the possibility to administer the planned treatment. Based on this the protocol was modified twice, by addition of filgrastim and by lowering the 5-fluorouracil dose. An increasing proportion of patients were able to receive the planned treatment (57% before and 83% after adjustments). In the present study we did not find that these modifications had a significant influence on treatment outcome.

Among surgeons there is widespread caution concerning an increased number of perioperative complications following neoadjuvant therapy. A higher incidence of perioperative complications following preoperative oncology has been reported (24, 28), but a number of studies are unable to verify this (18, 25). Postoperative complications were found in our study, but the numbers and types do not seem to justify the exclusion of preoperative neoadjuvant chemoradiation. No postoperative 30-day mortality was encountered.

The prognosis even for only microscopically positive resected patients was poor, as was the survival for all other non-CR patients including those with no evidence of disease after surgery, where the operation should be potentially curative. It is of interest that the CR patients had a larger proportion of less advanced tumor stages (i.e. stage IIA) than the non-CR patients (65% vs. 35%, $p < 0.01$) illustrating the influence of tumor stage on response rates, and finally survival.

The overall 3-year and 5-year survival rates for all patients in the present study were 31% and 26%, respectively, according to Kaplan-Meier.

The recurrence pattern among the patients with no evidence of remaining malignancy after treatment showed a high proportion of distant disease where more radical locoregional therapy such as more extensive surgery or

more intensive radiotherapy would not have been of any survival benefit. The relapse pattern may also have implications for quality of life, since only 3 of 18 relapses affected the remaining esophagus and hence the majority of relapsing NED patients avoided the severe symptoms of dysphagia.

In conclusion, after protocol adjustments, a high proportion of complete responses combined with a good compliance was found in the study. As in other studies, the CR patients had a significantly longer survival rate than the non-CR patients. This study indicated that neoadjuvant treatment in the study setting did not increase the incidence of surgical complications. The relapse pattern showed that further development of the systemic part, i.e. chemotherapy, of the protocol might be beneficial. However, in our opinion the results of the final schedule in this trial are promising enough to be tested in a randomized setting.

REFERENCES

1. Earlam R, Cunha-Melo JR. Esophageal squamous cell carcinoma I. A critical review of surgery. Br J Surg 1980; 67: 381–90.
2. Earlam R, Cunha-Melo JR. Esophageal squamous cell carcinoma: II. A critical review of radiotherapy. Br J Surg 1980; 67: 451–61.
3. Müller JM, Erasmi H, Steltzner M, Zieren U, Pichlmaier H. Surgical therapy of esophageal carcinoma. Br J Surg 1990; 77: 845–57.
4. Skinner DB. En bloc resection for neoplasms of the esophagus and the cardia. J Thorac Cardiovasc Surg 1983; 85: 59–71.
5. Lerut T, DeLeyn P, Coosemans W, Van Raemdonck D, Scheys I, Le Saffre E. Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. Ann Surg 1992; 216: 583–90.
6. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994; 220: 364–72.
7. Soehendra N, Binmoeller KF, Bohnacker S, et al. Endoscopic snare mucosectomy in the esophagus without any additional equipment; a simple technique for resection of flat early cancer. Endoscopy 1997; 29: 380–3.
8. Gaspar LE, Nag S, Herskovic A, Mantravadi R, Speiser B. American brachytherapy society consensus guidelines for brachytherapy of esophageal cancer. Int J Radiat Biol Phys 1997; 38: 127–32.
9. Kelsen D. Chemotherapy of esophageal cancer. Semin Oncol 1984; 11: 59–168.
10. Wendt TG, Chucholowski M, Hartenstein R, Rohloff R, Willich N. Sequential chemo-radiotherapy in locally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1985; 12: 397–9.
11. Mercke C, Albertsson M, Hambraeus G, et al. Cisplatin and 5-FU combined with radiotherapy and surgery in the treatment of squamous cell carcinoma of the esophagus. Acta Oncol 1991; 30: 617–22.
12. Stahl M, Wilke H, Fink U, et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer: interim analysis of a phase II trial. J Clin Oncol 1996; 14: 829–37.
13. Forastiere A, Heitmiller R, Lee D-J, et al. Intensive chemoradiation followed by esophagectomy for squamous cell and adenocarcinoma of the esophagus. Cancer J Sci Am 1997; 3: 144–52.
14. Forastiere AA, Orringer MB, Perez-Tamayo C, et al. Concurrent chemotherapy and radiation therapy followed by transhiatal esophagectomy for local-regional cancer of the esophagus. J Clin Oncol 1990; 8: 119–27.
15. Fagerberg J, Stockeld D, Lewensohn R. Combined treatment modalities in esophageal cancer. Should chemotherapy be included? Acta Oncol 1994; 33: 439–50.
16. Hermanek D, Sokni LH, eds. International Union Against Cancer (UICC): TNM-classification of malignant tumors. 4th ed. Heidelberg: Springer, 1987.
17. Bates BA, Detterbeck FC, Bernard SA, Qaqish BF, Tepper JE. Concurrent radiation therapy and chemotherapy followed by esophagectomy for localized esophageal carcinoma. J Clin Oncol 1996; 14: 156–63.
18. Urba S, Orringer M, Turrisi A, et al. A randomized trial comparing surgery to preoperative concomitant chemoradiation plus surgery in patients with resectable esophageal cancer: updated analysis. Proc Am Soc Clin Oncol 1997; 16: 983.
19. Forastiere AA, Heitmiller RF, Lee DJ, et al. Intensive chemoradiation followed by esophagectomy for squamous cell carcinoma of the esophagus. Cancer J Sci Am 1997; 3: 144–52.
20. Herskovic A, Martz K, Al-Sarraf M, 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.
21. Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 1997; 15: 277–84.
22. Cooper J, Guo M, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer. JAMA 1999; 281: 1623–7.
23. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996; 335: 462–7.
24. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997; 337: 161–7.
25. Le Prise E, Etienne P, Meunier B, et al. A randomized study of chemotherapy, radiation therapy and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 1994; 73: 1779–84.
26. Urba S, Orringer M, Turrisi A, et al. A randomized trial comparing transhiatal esophagectomy to preoperative concurrent chemoradiation followed by esophagectomy in loco regional esophageal carcinoma. Proc Am Soc Clin Oncol 1995; 14: 475 (abstr).
27. Ganem G, Dubray B, Raoul Y, et al. Concomitant chemoradiotherapy followed, where feasible, by surgery for cancer of the esophagus. J Clin Oncol 1997; 15: 701–11.
28. Schlag P. Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. Arch Surg 1992; 127: 1446–50.