

Intense Therapy in Patients with Locally Advanced Esophageal Cancer beyond Hope for Surgical Cure: A Prospective, Multicenter Phase II Trial of the Swiss Group for Clinical Cancer Research (SAKK 76/02)

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Key Words

Esophageal cancer · Inoperable · Locally very advanced · Chemoradiation

Summary

Background: There is no standard treatment for patients with locally advanced esophageal carcinoma without systemic metastasis in whom surgery is no longer considered a reasonable option. **Patients and Methods:** Patients with cervical esophageal tumors, locally very advanced stage (T4 and/or M1a) or locally advanced (T3 and/or N+) with comorbidities were included. Therapy: 2 cycles of induction chemotherapy (cisplatin and docetaxel, both 75 mg/m² 3-weekly) followed by chemoradiation therapy (CRT) comprising a total radiation dose of 59.4 Gy together with docetaxel 15 mg/m² and cisplatin 25 mg/m² (5 weekly doses). Primary endpoint: Histologically proven freedom from local failure 6 months after CRT completion. **Results:** 21 patients were included: 12 had locally very advanced tumors, 3 had cervical esophagus tumors, and 6 were medically unfit for surgery. 18 patients completed therapy per protocol. Grade 3/4 toxicities during CRT were thrombopenia (10%) and dysphagia (15%). 1 patient died due to herpes simplex infection. The primary endpoint was achieved by 4 patients, 6 were alive after median follow-up of 34 months, and median survival was 16 months. Most patients experienced lasting improvement of dysphagia following induction chemotherapy. **Conclusions:** This regimen is feasible, showed clinically meaningful, long-lasting improvements in quality of life and resulted in long-term survival in 29% of the patients.

Schlüsselwörter

Ösophaguskarzinom · Inoperabel · Lokal sehr weit fortgeschritten · Radiochemotherapie

Zusammenfassung

Hintergrund: Es existiert keine Standardbehandlung für Patienten mit Ösophaguskarzinom ohne systemische Metastasierung, bei denen Chirurgie nicht in Betracht kommt. **Patienten und Methode:** Eingeschlossen wurden Patienten mit zervikalem Ösophaguskarzinom, lokal weit fortgeschrittener Erkrankung (T4 und/oder M1a) oder aus medizinischen Gründen inoperable Patienten mit fortgeschrittener Erkrankung (T3 und/oder N+). Nach 2 Zyklen Induktionstherapie mit Cisplatin und Docetaxel (jeweils 75 mg/m² im Abstand von 3 Wochen) wurde eine Chemoradiotherapie (CRT) mit 59,4 Gy und 15 mg/m² Docetaxel bzw. 25 mg/m² Cisplatin (jeweils 5 Gaben) durchgeführt. Primärer Endpunkt war histologisch bestätigte lokale Tumorfreiheit 6 Monate nach Abschluss der Radiochemotherapie. **Resultate:** Von 21 eingeschlossenen Patienten hatten 12 ein lokal weit fortgeschrittenes Ösophaguskarzinom, 3 hatten ein zervikales Karzinom und 6 waren aus medizinischen Gründen inoperabel. 18 Patienten erhielten die gesamte Therapie gemäß Protokoll. Die häufigsten Grad-3/4-Toxizitäten während der CRT waren Thrombopenie (10%) und Dysphagie (15%). Ein Patient verstarb an einer Herpes-simplex-Hepatitis. 4 Patienten erreichten den primären Endpunkt, nach 34 Monaten Nachbeobachtungszeit waren 6 noch am Leben, das mediane Überleben betrug 16 Monate. Die durch die Patienten erfasste Dysphagie zeigte eine anhaltende Verbesserung nach der Induktionstherapie. **Schlussfolgerungen:** Die geprüfte Therapie war gut durchführbar und zeigte eine klinisch relevante Verbesserung der Lebensqualität sowie ein Langzeitüberleben bei 29% der Patienten.

Introduction

Esophageal cancer ranks sixth among the causes of death from cancer worldwide [1]. Most patients with newly diagnosed carcinoma of the esophagus present with potentially resectable, locally advanced disease. The accepted standard treatment for these patients is potentially curative therapy comprising neoadjuvant chemoradiation (CRT) or chemotherapy followed by surgery and definitive CRT [2–5]. A minority of patients present with systemic metastasis at diagnosis and are usually treated with chemotherapy or only palliative care [6]. However, there is a specific group of patients with locally advanced disease, without systemic metastases, in whom the disease is still regional, but surgery is no longer considered a reasonable option because of tumor location (cervical esophagus), very advanced stage (M1a or T4) or poor performance status and comorbidities. Multidisciplinary team meetings to determine the best treatment strategy for such patients usually focus on the difficult question of how much therapy could or should be given when there is no hope for surgical cure. The range of options includes radiotherapy (external beam or brachytherapy), more intensive CRT, systemic chemotherapy, stenting interventions, or only palliative care. Substantial palliation of dysphagia can be achieved despite the often relatively poor condition of such patients; however, most will experience tumor progression at the primary site. There are few prospective trials focusing on this specific population [7, 8]. Some of these patients deemed to be inoperable have been included in trials of CRT for locally advanced disease [2, 9–11]. These studies provided evidence to suggest improved overall survival for the whole group of patients treated with CRT compared with radiotherapy alone.

Based on these considerations, we initiated a prospective nationwide, multicenter trial to investigate whether an intensive treatment strategy using induction chemotherapy followed by CRT is feasible and beneficial for this specific group of patients with inoperable loco-regional esophageal cancer.

Patients and Methods

This was a prospective, open-label, multicenter phase II study conducted by the Swiss Group for Clinical Cancer Research (SAKK). The protocol was approved by the local ethics committee of each participating institution, and all patients gave their written informed consent before registration.

Major Eligibility Criteria

Previously untreated patients with histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus were eligible if the tumor was: (1) locally very advanced (T4 and/or M1a), (2) located in the cervical esophageal region, or (3) locally advanced (T3 and/or N+) but the patient was medically unfit for surgery. All tumor lesions had to be encompassable in a single radiation port. Patients with distant metastases were excluded. Further selection criteria included age between 18 and 70 years, a World Health Organization (WHO) performance status < 2, and normal organ function.

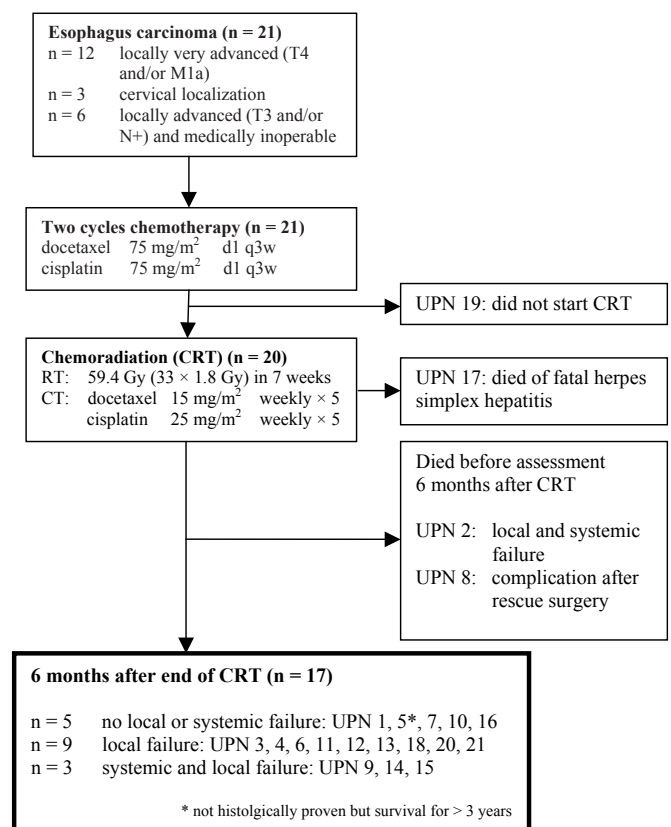


Fig. 1. Treatment plan and outcome.

Treatment Schedule and Evaluation Plan

Pretreatment staging consisted of complete medical history, physical examination, upper endoscopy with biopsy, helical computed tomography (CT) scans of the chest and abdomen (and neck for cervical or upper third thoracic localization), endoscopic ultrasound (EUS), and bronchoscopy for tumors above or at the tracheal bifurcation. A laparoscopy for tumors of the lower third of the esophagus was optional. Positron emission tomography (PET) or PET-CT staging was recommended, but not mandatory.

Treatment consisted of induction chemotherapy followed by CRT (fig. 1). Induction chemotherapy consisted of 2 cycles of intravenous docetaxel and cisplatin, both 75 mg/m² on day 1 of a 3-weekly cycle. CRT was started after completion of the second induction chemotherapy cycle. Three-dimensional (3D) conformal radiotherapy delivering a total dose of 59.4 Gy (33 fractions of 1.8 Gy) was given over 7 weeks with a minimal energy of 6-MV photons. The planned target volume included all known areas of disease with a 5-cm cranial and caudal margin and a 2-cm lateral margin. Concomitant chemotherapy consisted of intravenous docetaxel 15 mg/m² and cisplatin 25 mg/m² administered weekly for 5 weeks on an outpatient basis.

Dose Modifications and Follow-up

Toxicity was graded according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 2.0. In the second induction chemotherapy cycle, cisplatin and docetaxel were both postponed if the absolute neutrophil count (ANC) was < 1500/μl or the platelet count was < 100,000/μl. Patients were required to have an ANC of ≥ 1000/μl and a platelet count of ≥ 75,000/μl prior to starting CRT. During CRT, docetaxel was omitted for 1 week if the ANC was < 1000/μl or the platelet count was < 50,000/μl. Radiotherapy and both drugs were omitted for 1

week if the ANC was < 500/μl and/or the platelet count was < 25,000/μl after weekly reassessment. Docetaxel was omitted if febrile neutropenia occurred during CRT, whereas radiotherapy and cisplatin were continued at the discretion of the local investigator. Early insertion of a feeding tube was recommended for patients developing tumor- or treatment-induced dysphagia. Radiotherapy was continued in patients with grade 3 therapy-induced esophagitis, but the final decision to continue chemotherapy was left to the local investigator. Both chemotherapy and radiation were omitted in patients with grade 4 esophagitis until toxicity resolved to grade 3.

Cisplatin was replaced by carboplatin in patients developing grade 3 peripheral neuropathy, grade 2 hearing impairment, or creatinine clearance < 50 ml/min. Carboplatin was given at a dose of area under the concentration-time curve (AUC) 6 mg · min/ml for the second cycle of induction chemotherapy and AUC 2 mg · min/ml throughout CRT. Dose reduction rules were applied for grade 3 nausea, vomiting or diarrhea.

Follow-up including CT scans, physical examination, evaluation of adverse events, and quality-of-life (QoL) assessment was carried out 3-monthly during the first year following completion of CRT, 6-monthly during the next 3 years, and subsequently on an annual basis unless otherwise clinically indicated. Endoluminal ultrasound and endoscopy with at least 4 biopsies of the previous tumor area were scheduled 6 months after completion of CRT. Further endoscopic examinations were performed only in patients presenting with symptoms raising suspicion of local failure.

Endpoints and Criteria for Response and Survival

The main objective of this trial was to evaluate whether intensive CRT after induction chemotherapy can achieve a high rate of local control with acceptable toxicity and stable QoL in patients with locally advanced esophageal cancer. To test this hypothesis, we selected the primary endpoint 'percentage of patients with histologically proven freedom from local failure 6 months after the last dose of radiotherapy', defined as the absence of primary tumor and any new lesion or recurrence by radiological means within the radiotherapy field. In all patients without signs of tumor, at least 4 biopsies had to be taken from the area of the primary tumor. We defined a feasibility endpoint to evaluate the compliance and toxicity of this treatment. The feasibility endpoint, based on an intention-to-treat analysis, was defined as follows: the proportion of patients alive 30 days after the end of therapy and completing the whole therapeutic regimen comprising 2 cycles of induction therapy and at least 50 Gy of radiotherapy together with at least 4 cycles of weekly concomitant chemotherapy (even if there were dose reductions or only one drug was administered). Overall survival was a secondary endpoint. The pattern of failure was determined by the localization of the tumor at the time of relapse.

Quality of Life

Symptom-specific key aspects of QoL in this situation (i.e. dysphagia and problems with eating) were assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QoL module specific to esophageal cancer (QLQ-OES24) [12, 13]. In addition, two global QoL indicators for physical well-being and coping effort were measured with linear analog self-assessment (LASA) scales [14, 15]. All scales range from 0 to 100, with higher scores representing more symptoms with respect to dysphagia and eating problems, but better physical well-being and less coping effort.

Statistics

To evaluate the primary endpoint 'percentage of patients with histologically proven freedom from local failure 6 months after the last dose of radiotherapy', the sample size was calculated to have a power of 80% and a significance level of 5% to accept an ineffective treatment. This study used a two-stage design based on Herndon's approach, a modification of Simon's 2-stage design that allows continued accrual while waiting for stage-1 results [16]. A ≥ 50% rate of freedom from local failure was con-

sidered promising for further study and a rate of < 30% was considered ineffective. The stage-1 analysis was done after the primary endpoint was evaluable in 15 patients. If ≥ 4/15 patients were failure free, then accrual would continue until a total of 46 patients; otherwise accrual would be suspended and an additional analysis would be carried out on all patients having been enrolled at that time. The results of the additional analysis would determine if the trial should be terminated or continued. Survival analysis was done on an intention-to-treat basis using the Kaplan-Meier method. All QoL scores were reported descriptively. A change of ≥ 8 points on each scale was considered as clinically meaningful [17].

Serious adverse events and response rates were continuously monitored by the SAKK Coordinating Centre. The interim results were presented to the SAKK Executive Committee before a definitive decision about continuation or early stopping was made.

Results

Patient and Tumor Characteristics

The study was stopped prematurely after an interim analysis when 21 patients from 7 Swiss cancer centers were enrolled (table 1). Most patients were men (86%), the median age was 64.3 years (range 45.8–73.1 years), and 11 had the performance status 0. PET-CT was used for staging in 14 (67%) patients. The reasons for inclusion in this trial were as follows: 12 (57%) patients had locally very advanced disease (T4 and/or M1a), 3 (14%) had a tumor in the cervical esophagus (T4 in 1), and 6 (29%) had locally advanced tumors (T3 and/or N+) but were medically unfit for surgery. Histology was squamous cell carcinoma in 10 (48%), adenocarcinoma in 8 (38%) and mixed/undifferentiated carcinoma in the remaining cases.

Feasibility and Toxicity

All 21 patients received 2 full cycles of induction chemotherapy and 18 (86%) received the full course of CRT according to the predefined feasibility endpoint. Peracute fatal herpes simplex hepatitis developed in 1 patient (unique patient number (UPN) 17) 4 weeks after the start of CRT [18]. Another patient (UPN 19) did not start CRT because the tumor volume was too large according to the radiooncologist and, therefore, retrospectively this patient would not have met the trial inclusion criteria. Radiotherapy was stopped early (after 39.6 Gy) in a third patient (UPN 15) because the radiooncologist was concerned about intolerable late sequelae resulting from a very large irradiation volume.

The toxicity profile of induction chemotherapy and CRT is listed in table 2. Toxicities during induction chemotherapy were as expected and manageable. Hematologic toxicity was the most common adverse event occurring to some degree in all patients receiving 2 cycles of docetaxel and cisplatin. Second-cycle chemotherapy dose reductions of 25% were required for docetaxel (1 patient) and both docetaxel and cisplatin (2 patients) as a result of infection, weight loss or stomatitis. CRT was well tolerated by most patients. Grade 3/4 thrombopenia occurred in 2 patients and dysphagia in 3 patients.

Table 1. Baseline characteristics and outcome

UPN	Age, years	Histo	T	N	M	Reason	6 months after CRT	Cause of death	OS
1	55.4	SC	uT3	uNx	M1a	LVA	no failure	alive	45.9
2	62.1	SC	uT4 ^d	uN0	M0	LVA	not alive	tumor	6.6
3	64.6	SC	uT4	uN1	M0	CERV	local failure	tumor	11.6
4	45.9	AC	uT3	uN1	M1a	LVA	local failure	tumor	25.6
5	61.6	SC	uT3	uN1	M1a	LVA	no failure	alive	38.2
6	71.3	ASC	uT3	uN1	M0	MU	local failure	tumor	20.4
7	69.3	AC	uTx	uN1	M1a	LVA	no failure	tumor	24.9
8	49.1	SC	uT3	uN1	M1a	LVA	not alive	other	8.2
9	64.4	AC	uT1	uN1	M0	MU	systemic failure ^f	tumor	9.3
10	73.1 ^a	AC	uT3	uN0	M0	MU	no failure	alive	35.6
11	69.5	undiff	uT4	uN1	M1a	LVA	local failure	other	13.2
12	55.7	AC	uT4	uN1	M0	LVA	local failure	alive	31.7
13	68.5	SC	uT2	uN1	M0	MU	local failure	tumor	14.8
14	62.6	undiff	uT2	uN1	M0	CERV	systemic failure ^f	tumor	9.9
15	68.1	SC	uT3	uN1	M1a	LVA	systemic failure ^f	tumor	19.7
16	50.4	AC	uT2	uN1	M1b ^c	LVA	no failure	alive	28.7
17	68.7	AC	uT3	uN1	M0	LVA ^e	not alive	other	2.3
18	70.5	AC	uT3	uN1	M0	MU	local failure	alive	29.4
19	67.5	SC	Tx ^b	N1	M1a	LVA	no CRT	tumor	15.2
20	59.4	SC	uT3	uN1	M0	MU	local failure	tumor	15.8
21	58.5	SC	Tx ^b	N1	M0	CERV	local failure	tumor	12.3

AC = adenocarcinoma, ASC = adenosquamous, CERV = cervical localization, Histo = histology, LVA = locally very advanced tumor, M = metastasis, MU = medically unfit for surgery, N = node, OS = overall survival, PD = progressive disease, SC = squamous cell carcinoma, T = tumor, undiff = undifferentiated carcinoma, UPN = unique patient number.

^aIncluded with waiver of trial chair.

^bObstructive tumor.

^cTumor located in the lower third of the esophagus with retrojugular lymph node metastasis.

^dMediastinal infiltration.

^eExtensive mediastinal lymphadenopathy.

^fAll patients with systemic failure also had local failure.

Table 2. Adverse events during therapy

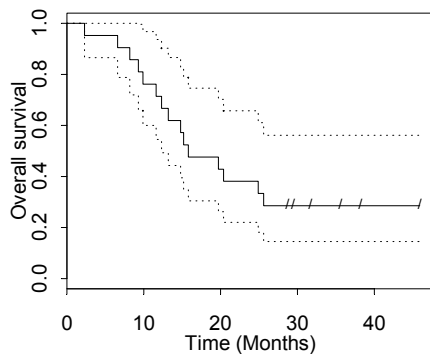
Adverse events	Induction chemotherapy (n = 21)				CRT (n = 20)			
	All grades		Grade 3/4		All grades		Grade 3/4	
	n	%	n	%	n	%	n	%
Anemia	21	100	1	5	20	100	1	5
Leukopenia	12	57	6	29	10	50	1	5
Neutropenia	8	38	6	29	3	15	1	5
Thrombopenia	9	43	1	5	17	85	2	10
Dysphagia	16	76	1	5	18	90	3	15
Stomatitis	3	14	1	5	0	0	0	0
Diarrhea	8	38	1	5	2	10	0	0
Nausea	5	24	1	5	8	38	0	0
Vomiting	3	14	1	5	2	10	0	0
Alopecia	13	62	0	0	17	81	0	0
Asthenia	14	67	0	0	12	57	0	0
Neurosensory	1	5	0	0	2	10	0	0
Other	17	81	4	19	18	90	2	10

Outcome

The predefined primary endpoint (histologically confirmed local control 6 months after end of CRT) was achieved in 4 patients (19%) based on intention to treat. Consequently, the

study was closed prematurely because a rate lower than 30% was considered clinically ineffective, as stated in the sample size calculation. According to the protocol, patients were counted as local failures if they did not have a biopsy 6 months

Fig. 2. Overall survival after a median follow-up of 33.7 months (95% CI: 29.4–38.2 months); median survival 15.8 months (95% CI: 12.3–25.6 months).



after radiotherapy for any reason (e.g. previous dilatation of the esophagus, patient refusal). 1 patient (UPN 5) refusing biopsies remained disease free for more than 3 years after registration. Therefore, it can be assumed that overall 5 of 21 patients (24%) remained free of local and systemic recurrence 6 months after the end of CRT.

Of the other patients, 1 died of herpes simplex hepatitis during CRT (UPN 17), as described above, and 2 died after CRT but before assessment at 6 months, 1 due to local and systemic progression (UPN 2) and 1 due to multiorgan failure after salvage surgery for persistent local tumor (UPN 8). In the remaining 12 patients having finished CRT, there were 9 (43%) local failures and 3 (19%) systemic and local failures (fig. 1). The patient who did not receive CRT (UPN 19) experienced systemic and local failure.

After a median follow-up of 33.7 months (95% confidence interval (CI) 29.4–38.2 months), 6 (29%) patients were still alive, including 2 with proven local residual disease after CRT, 1 of whom (UPN 18) received subsequent salvage surgery. There were 12 (57%) deaths from progressive disease and 3 (14%) from non-disease-related causes (table 1). Median overall survival was 15.8 months (95% CI 12.3–25.6 months). The rates of 1-, 2- and 3-year survival were 71%, 38%, and 29%, respectively (fig. 2). Of the 6 surviving patients, 4 had locally very advanced disease at inclusion and the other 2 had been classified as inoperable for medical reasons. Of note, all of these patients were doing well at the time of writing and 4 had no or only minimal dysphagia 12 months after completion of treatment.

Quality of life

Figure 3 presents the scores for dysphagia, problems with eating, physical well-being, and coping effort at baseline, during therapy, and 3, 6, 9, and 12 months after completion of treatment. At baseline, i.e. before treatment started, all patients (100%) completed the questionnaire. The completion rate remained above 80% throughout the treatment phase. Non-submitted QoL questionnaires were missing due to administrative errors (i.e. questionnaire not presented to the patient). At the 6-month follow-up, 65% of the surviving patients completed the questionnaire. Except in 1 case, all patients who

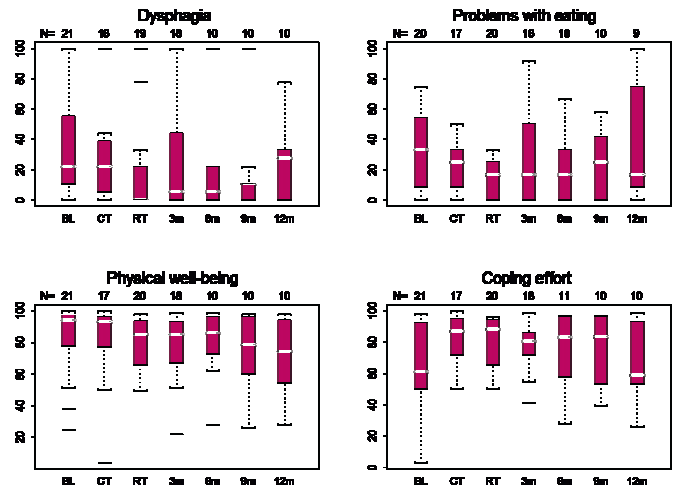


Fig. 3. Quality-of-life scores at baseline, day 1 of cycle 2 of chemotherapy, day 1 of CRT, and 3, 6, 9, and 12 months after completion of treatment. Solid boxes show the 25th to 75th percentiles, with horizontal lines indicating median values; whisker bars represent minimal and maximal values of a standard range.

did not complete a questionnaire had either local or systemic failure at this time point and may have felt too ill to answer the QoL questions. Clinically meaningful improvements were observed for dysphagia (median change –11 points) and problems with eating (median change –8.3) from baseline until the completion of induction chemotherapy. These median scores remained low until the 6-month follow-up, but subsequently scores for both dysphagia and problems with eating deteriorated up to the 12-month follow-up. Subjective improvement of dysphagia and problems with eating during induction chemotherapy may be reflected by the fact that it was not necessary to insert feeding tubes during CRT. Feeding tubes were inserted due to stenosis prior to treatment in 7 patients; however, 1 was not needed because of rapid improvement of dysphagia during induction chemotherapy.

The median scores for physical well-being remained within the highest quartile over the whole observation period, representing a rather good overall physical well-being during treatment and for up to 9 months after treatment, followed by a small decline up to the 12-month follow-up. A clinically meaningful improvement in coping effort was observed during treatment (median change of +19) and the scores remained at this level for 9 months after treatment.

Discussion

We prospectively identified a difficult-to-treat group of patients with esophageal carcinoma and disease status between locally advanced and metastatic for whom there is no standard treatment and therapy is often considered palliative. In this group of patients, we prospectively investigated the value

of an intensified local therapy comprising 2 cycles of induction chemotherapy followed by CRT.

In some centers, patients with M1a disease of the distal esophagus are treated with esophagectomy; however, these patients have a distinctly worse outcome than patients with locally advanced M0 disease [19]. Cervical esophageal cancer is very rare and these patients are usually not included in esophageal cancer trials. Most institutions treat these patients with CRT or radiotherapy alone according to the guidelines for head and neck cancer. The subgroup of patients with locally advanced tumors but medically unfit for surgery is rarely mentioned separately when included in trials of CRT.

In this study, all tumors were staged accurately using CT scan, endosonography and, in most cases, PET scan. The following questions were addressed: How many patients are free of disease as proven by biopsy 6 months after the end of therapy (primary endpoint)? How feasible is such a treatment? And how does it affect the QoL? Formally, the study was negative and was closed prematurely because only 19% of all patients achieved the primary endpoint and therefore missed the predefined threshold of 30% for futility. 1 additional patient (UPN 5) showed long-term disease-free survival, but did not achieve the primary endpoint because endoscopic biopsies were not performed after 6 months. Another patient (UPN 18) remains disease free after receiving salvage surgery to treat local tumor progression more than 1 year after study treatment. With hindsight, both the primary endpoint and the threshold may be judged to be too optimistic considering the low compliance with confirmatory biopsies and a cure rate of 20–40% in operable patients [20–23]. Furthermore, 2 patients died from non-tumor-related causes (herpes simplex hepatitis and complication after rescue surgery) before assessment at 6 months.

Of note, compliance with this intensive treatment regimen was good (86% of all patients completed therapy) and toxicity was manageable. The observed improvement of patient-reported ‘dysphagia’ and ‘problems with eating’ and the lack of necessity for additional feeding tubes during CRT supports the proposition that 2 cycles of induction chemotherapy resulted in increased compliance with subsequent CRT, similar to the finding of a previous study in patients with operable tumors [24].

Patients enrolled in this trial are generally considered to have a dismal prognosis. It is therefore notable that 6 of 21 patients were alive after a median follow-up of 34 months, corresponding to a 3-year survival rate of 29%. Of these patients, 2 were included because of medical contraindications for surgery, while the other 4 had locally very advanced disease. Therefore, these data show that long-term survival can be achieved without surgery even in these poor-risk patients. However, it is difficult to compare our data with the published literature because, in other studies, patients meeting the inclusion criteria for the present trial have been classified using the

broad term ‘inoperable’ [7, 11, 25]. In these studies, there were many diverse reasons for patients being considered inoperable, including older age, comorbidity, advanced stage and the presence of systemic disease. Additionally, not all studies used modern staging methods. The heterogeneity of the inclusion criteria of these studies is reflected by the reported median survival rates widely ranging from 6 to 26 months. However, in one retrospective series [25], about 20% of patients with T4 stages were described as long-term survivors after CRT as well. None of the 3 patients with cervical esophageal tumors included in the present trial were in the group of long-term survivors. Histology did not predict outcome, and long-term survival was achieved in patients with adenocarcinoma or squamous cell carcinoma.

Despite the intense treatment schedule, QoL was impaired only temporarily in the majority of patients. Of note, even patients experiencing relapse had no or minor dysphagia over a period of 9 months after the end of treatment.

We conclude that this intense treatment schedule is feasible in patients with locally advanced esophageal cancer that is not amenable to potentially curative resection. Moreover, some patients in this poor-prognosis group can achieve long-term survival with this intensive therapy. Although the specified primary endpoint of confirmed local control after 6 months was not met, there was evidence of clinical benefit. Specifically, we observed that relapsing patients also benefited from treatment, as shown by improvements in QoL parameters (dysphagia and problems with eating) and the maintenance of good and stable physical well-being for a considerable period after the end of treatment. Induction chemotherapy and CRT may be an option for selected patients with locally very advanced disease. However, the selection of patients for intensive therapy remains difficult. The present data are limited in this regard because patients with both adenocarcinoma and squamous cell carcinoma were among the survivors, whereas patients with cervical cancer were not represented, possibly due to an inadequate number of patients enrolled. Further studies are warranted, particularly to identify predictive factors to justify such an intense therapy in those patients most likely to benefit.

Acknowledgement

We thank Pierluigi Ballabeni for assistance in designing this trial.

Conflict of Interest

The Swiss Group for Clinical Cancer Research (SAKK) sponsored the trial, and it was financially supported by the State Secretariat for Education and Research, Ministry of Internal Affairs of Switzerland and by sanofi-aventis SA, Switzerland.

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