Induction Chemotherapy followed by Concurrent Chemotherapy and High-Dose Radiotherapy for Locally Advanced Squamous Cell Carcinoma of the Cervical Oesophagus

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Oesophageal carcinoma · Cervical oesophagus · Radiochemotherapy

Abstract
The efficacy and toxicity of combined radiochemotherapy for locally advanced squamous cell carcinomas of the cervical oesophagus was evaluated retrospectively. Induction chemotherapy consisted of three courses of 5-fluorouracil (5-FU), leucovorin, etoposide and cisplatin (FLEP) or two courses weekly six times of 5-FU and leucovorin combined with biweekly cisplatin. This induction regimen was followed by high-dose external beam radiotherapy up to 60–66 Gy and concurrent chemotherapy with cisplatin and etoposide. Median follow-up of the recruited 17 patients was 37 months (13–73 months). Long-term survival was 24% at 2 and 3 years. The probabilities of locoregional tumour recurrences and distant metastases as sites of first relapse were 67 and 39% at 2 years. Acute and late toxicity of this schedule was moderate. The protocol offers a definitive chance of long-term survival for patients with locally advanced carcinomas of the cervical oesophagus, but local in-field recurrences remain the predominant risk after treatment. Intensification of the regimen seems possible because no dose-limiting late toxicities were observed.

Introduction

Carcinomas of the cervical oesophagus are an uncommon malignancy and comprise only 5–15% of all carcinomas of the oesophagus in Europe or the United States [1, 2]. Radical resection of a cervical oesophageal carcinoma requires in general a laryngopharyngo-oesophagectomy [3, 4]. The postoperative mortality within 30 days of this procedure is about 10–15% [3, 4]. The 5-year survival rates of surgical cohorts range from 10 to 28% [3–5], but the results for the subgroup of locally advanced carcinomas are dismal. A microscopically complete tumour removal, i.e. a R0 resection, is usually not achieved for proximal T3 or T4 oesophageal carcinomas because of their close anatomical neighbourhood to the trachea [6]. According to the overview of Jacobi et al. [3], the 5-year survival rate of patients with cervical carcinomas after surgery alone drops rapidly from 44% in stage I to 8% in stage II.

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Radiotherapy alone offers a small chance of cure for patients with squamous cell carcinomas of the cervical oesophagus. Mendenhall et al. [7] found a surviving fraction of 20% at 5 years in 19 patients with locally advanced carcinomas of the cervical oesophagus after definitive radiotherapy. These authors advocated high-dose radiotherapy up to 70 Gy with 2.0 Gy per daily fraction or hyperfractionated irradiation up to 74.4–76.8 Gy with two fractions of 1.2 Gy per day at 5 days per week. Okawa et al. [8] found 1 long-term survivor among 13 patients with stage III carcinoma of the cervical oesophagus after conventionally fractionated radiotherapy up to 60 Gy. The results of other larger radiotherapy series for carcinomas of the cervical oesophagus were not detailed with respect to the TNM stage. Pearson [2] reported a 5-year survival rate of 25% for their large group of 76 patients with carcinomas of the cervical oesophagus selected for definitive radiotherapy.

In the recent years, combined modality programmes were studied in order to improve the results in locally advanced oesophageal carcinomas of the different anatomical regions. It has been shown that locoregional control after surgery can be improved by pre-operative radiochemotherapy [9–11]. However, there is only one small series on pre-operative radiochemotherapy and resection for locally advanced proximal oesophageal carcinomas with promising results [12]. 4 of 9 patients in this study were tumour-free at the last follow-up more than 20 months from diagnosis. The most effective non-surgical therapy for oesophageal carcinomas seems to be radiochemotherapy according to a randomised intergroup study that compared radiotherapy alone and concurrent radiochemotherapy followed by maintenance chemotherapy [13]. However, this study mainly included patients with T2 tumours of the thoracic oesophagus. Detailed data on the efficacy of definitive radiochemotherapy for squamous cell carcinoma of the cervical oesophagus are almost completely lacking [14].

In the present study, we report long-term survival and the pattern of relapse in patients with locally advanced squamous cell carcinomas of the cervical oesophagus treated by induction chemotherapy followed by concurrent chemotherapy and high-dose radiotherapy.

Materials and Methods

Patient Population

Patients with biopsy-proven squamous cell carcinoma of the cervical oesophagus defined as the segment between the oesophageal-pharyngeal junction at the cricopharyngeal muscle and the thoracic inlet were eligible for induction chemotherapy and concurrent high-dose radiotherapy and chemotherapy. Patients had to have locally advanced tumours, i.e. T3 or T4 tumours according to the International Union against Cancer (UICC) classification [15], or obstructing T2 tumours ≥ 5 cm in length. The latter are known to be T3 or T4 tumours in as much as 88% of cases on histopathological examination [16]. Patients with distant metastases, tracheo-oesophageal fistulas as well as pretreated patients were excluded. The performance status according to the World Health Organisation (WHO) had to be ≤ 2, age between 18 and 70 years, serum bilirubin level < 1.5 mg/dl, serum creatinine < 1.3 mg/dl, leukocyte count $> 4{,}000/\mu l$ and platelet count $> 100{,}000/\mu l$. All patients provided written informed consent. Before treatment, the following examinations were performed: physical examination, complete blood cell counts, serum levels of liver enzymes, bilirubin, creatinine and electrolytes, oesophagoscopy with biopsies, barium oesophagogram, chest radiograph, a computed tomography (CT) of the chest and abdomen, an abdominal ultrasound and a bronchoscopy. After April 1992, endoscopic ultrasound was routinely performed. Dysphagia was scored according to the RTOG/EORTC SOMA scales [21] (grade 1: difficulty eating solid foods; grade 2: difficulty eating soft foods; grade 3: can take liquids only; grade 4: totally unable to swallow).

Patients were treated between March 1991 and December 1996 at the University Hospital in Essen.

Chemotherapy

Induction chemotherapy consisted of 300 mg/m^2 folinic acid administered intravenously (i.v.) over 10 min, followed by 100 mg/m^2 etoposide i.v. over 50 min, 500 mg/m^2 5-fluorouracil (5-FU) i.v. over 10 min, and 30 mg/m^2 cisplatin i.v. over 60 min, all given on days 1–3 (FLEP). A second and third chemotherapy course were started at day 22 of the last course, provided that the patients had recovered from all toxic effects and no tumour progression was observed [17]. In the case of a thrombocytopenia of WHO grade 2–4, leukocytopenia WHO grade 4, or severe infection, the dose of etoposide was reduced to 80% during the subsequent courses. In the case of locoregional tumour progression during the first 2 chemotherapy cycles, induction chemotherapy was terminated immediately and treatment was continued with radiochemotherapy. Since September 1994, another schedule of induction chemotherapy was employed at our institution primarily for patients with locally advanced cancer of the lower thoracic oesophagus [18]. It consisted of folinic acid 500 mg/m^2 over 2 h, followed by 5-FU 2.0 g/m^2 over 24 h, weekly 6 times, combined with cisplatin 50 mg/m^2 over 1 h, week 1, 3, 5 (HD 5-FU/L/P). This course was repeated after a 1-week rest. Treatment was given on an outpatient basis with administration of 5-FU by an implanted port system and a portable pump. This regimen was given to patients with carcinomas of the cervical oesophagus who strongly preferred outpatient treatment. Because of the rareness of carcinomas of the cervical oesophagus, no separate protocol was set up for tumours in this location, but patients were treated according to the protocols for carcinomas of the thoracic oesophagus activated at this institution either with the FLEP or the HD 5-FU/L/P induction chemotherapy.

Concurrent radiochemotherapy started between days 22 and 28 of the last course of induction chemotherapy. At day 2 and 8 of high-dose radiotherapy, 50 mg/m^2 cisplatin was given i.v. over 60 min. In addition, 100 mg/m^2 etoposide was given at days 4, 5, and 6 as a 60-min infusion which was slightly reduced to 80 mg/m^2 on days 4–6 in 1994 during the long recruitment time because of an observed

moderate haematotoxicity in a larger cohort of patients with oesophageal carcinomas in all locations [17].

Radiotherapy

The initial clinical target volume (CTV) contained the gross tumour together with a margin of 5 cm in the proximal and distal direction and of 2 cm to the soft tissues in the transversal directions. It was treated up to a total dose of 50 Gy with conventional fractionation, 2 Gy per daily fraction, 5 fractions per week. The supra- and infraclavicular as well as the cervical lymph nodes up to the level of the hyoid bone were also included into the CTV. The caudal border of the CTV had to be located at or below the level of the tracheal carina. Above 50 Gy, the margins were reduced to 2 cm in the proximal and distal direction and to at least 1 cm in the transversal directions. Since May 1994, this volume was boosted by reduced fields up to a dose of 10 Gy with 2 Gy per daily fraction for non-stenosing T3 tumours located more than 2 cm distal to the cricoid and up to 15 Gy with 2 × 1.5 Gy per day, 6-hour interval, for the other tumour categories. Prior to May 1994, the boost dose was 10 Gy with 2 Gy per daily fraction. Thus, a total external beam dose of 60–65 Gy was given in 6 weeks. Patients were immobilised in a polyurethane body form. Three-dimensional treatment planning was performed which became available in the middle of 1992. 10- to 15-MeV photon beams from a linear accelerator were used. A maximum dose to the spinal cord of 42 Gy was allowed.

Brachytherapy was not recommended by some authors for carcinomas of the cervical oesophagus [19]. In this study, solely patients treated after May 1994 with non-stenosing T3 tumours located more than 2 cm distal to the cricoid cartilage according to the initial staging were selected for a brachytherapy boost after conventionally fractionated external beam irradiation up to 60 Gy. The intracavitary boost was given 5–10 days after the end of the external beam with a high-dose rate iridium-192 source (185–370 GBq) by a remote afterloading system. A dose of 4 Gy in 5-mm tissue depth from the surface of the applicator with a diameter of 10 mm was given twice with a 4- to 8-day interval.

Criteria for Response and Toxicity

During induction chemotherapy, oesophagograms and blood tests were repeated after each course of treatment. CT of the chest and abdomen as well as oesophagoscopies were repeated before and after radiochemotherapy. Response criteria were complete response: normal barium oesophagogram, normal CT, no visible tumour by oesophagoscopy, negative biopsies, if performed; partial response: greater than 50% regression of tumour volume evaluated by CT or greater than 50% reduction of intraoesophageal tumour extension assessed by barium swallow and oesophagoscopy; no change: less than 50% regression of tumour extension and no evidence of tumour progression.

Acute side effects of chemotherapy and radiochemotherapy were classified according to the WHO criteria [20]. Late effects of definitive radiochemotherapy were classified according to the RTOG/EORTC SOMA scales [21].

Follow-Up

All patients were monitored every 3 months during the first 2 years and every 6 months thereafter. Response to definitive radiochemotherapy was assessed 6 weeks after completion of therapy. Barium oesophagograms alternating with oesophagoscopy were routinely performed.

Table 1. Patient characteristics

Characteristic	Patients
Gender	
Female	2
Male	15
WHO performance status	
0	4
1	13
Weight loss >10%	2
Clinical TN categories	
T2 N0	2
T2 N1	1
T3 N0	2
T3 N1	5
T4 N0	4
T4 N1	3
Median age, years	55 (46–68)

Data Analysis

The survival curves were estimated by the product limit method according to Kaplan and Meier [22]. In addition to survival, time-dependent probabilities of locoregional recurrences or distant metastases as one site of first relapse were estimated by the product limit method with intercurrent deaths or competing relapses at other sites as censoring events.

Results

Patient Characteristics

Table 1 shows the characteristics of the patients with carcinoma of the cervical oesophagus treated between March 1991 and December 1996 at the University Hospital in Essen. Reasons for classifying 7 tumours as T4 were paralysis of the recurrent laryngeal nerve in 5, infiltration of the trachea without fistula in 1 and infiltration of the thyroid in a further patient. 3 of the 9 patients with positive lymph nodes had supraclavicular or cervical lymph node metastases which were proven by biopsy in 2 patients, among them 1 patient with the T2 N1 tumour. 16 tumours were well or moderately differentiated squamous cell carcinomas, 1 was an undifferentiated carcinoma. At the start of therapy, 1, 6, 4, 5 and 1 patients had a grade 0, 1, 2, 3 or 4 dysphagia. The median length of the tumours was 5 cm. The median follow-up of the cohort of 17 patients was 37 months (13–73 months).

Compliance with Protocol

11 patients received induction chemotherapy according to the FLEP protocol and 6 received HD 5-FU/L/P.

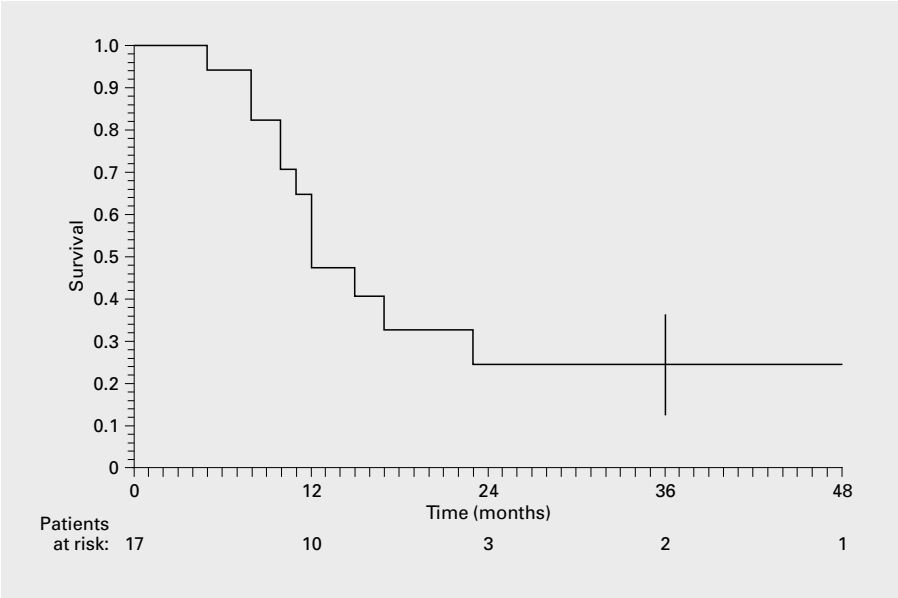

Fig. 1. Overall survival of the patients with locally advanced squamous cell carcinomas of the cervical oesophagus. The error bar indicates the standard error of the survival function.

9 patients were treated with 3 cycles of FLEP induction chemotherapy while 2 non-responders got 1 or 2 cycles before going on to concurrent radiochemotherapy.

All except 2 patients got external beam radiotherapy up to a total dose of ≥60 Gy. In 1 patient radiotherapy was stopped at a cumulative dose of 40 Gy because a hypersensitivity syndrome was suspected because of a brisk erythema and hyperpigmentation observed since a cumulative skin dose of 9 Gy had been given. Skin fibroblasts of this patients were the most sensitive among 25 tested fibroblast lines from different patients in the clonogenic assay after low-dose rate irradiation. Another patient developed bone metastases during induction chemotherapy and radiotherapy was given palliatively up to 50 Gy. 1 patient had a non-stenosing T3 tumour located more than 2 cm distal to the cricoid cartilage and was given a brachytherapy boost. In 3 patients, the intended hyperfractionated accelerated external beam boost was given with conventional fractionation with one 2-Gy fraction per day up to 16 Gy because of the closeness of the dorsal borders of the oblique fields to the spinal cord and the necessary time-consuming patient positioning with frequent portal films analysed before each fraction.

Response to Induction Chemotherapy and Concurrent Radiochemotherapy

A partial and complete response to induction chemotherapy was seen in 8 and 2 patients, respectively, resulting in a response rate of 59%. A no-change or a progressive disease were observed in 5 and 2 patients, respectively. The objective response rates by the induction chemotherapy regimens were 64% for FLEP and 50% for the HD 5-FU/L/P.

8 patients had a complete and 6 had a partial remission after concurrent radiochemotherapy. 1 patient showed no change and 2 others had in-field tumour progression during radiotherapy. The latter 2 were non-responders to induction chemotherapy. At the first follow-up visit after radiochemotherapy, 8, 4, 3, 2 and 0 patients had a grade 0, 1, 2, 3 and 4 dysphagia.

Overall Survival

12 deaths were observed during follow-up, 11 of them due to tumour progression and 1 due to intercurrent disease. Overall survival of all patients was 65 ± 12, 24 ± 11 and 24 ± 11% at 1, 2 and 3 years (fig. 1). There were 3 long-term survivors who survived for more than 30 months without relapse. Their tumour classification was T2 N0, T3 N1, and T4 N1, respectively.

Long-Term Locoregional Control

Locoregional recurrences as a component of first failure were observed in 9 patients. The probability of locoregional recurrences as the site of first failure was 67+14% at 2 and 3 years for the whole group of patients. Figure 2 shows the time-dependent probabilities of locoregional recurrences. 2 of the 9 locoregional recurrences occurred in cervical lymph nodes outside the radiation fields, while

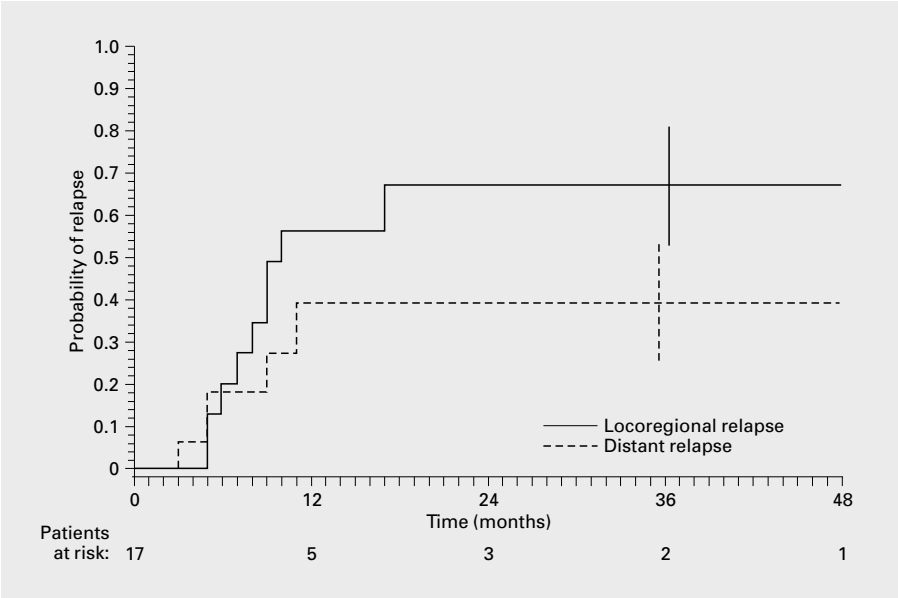

Fig. 2. Probabilities of locoregional and distant relapses as a component of first treatment failure.

the remaining recurrences were in-field. 2 patients had a combined locoregional and distant relapse.

Distant Metastases

Distant metastases as one component of first failure occurred in 5 patients. The probabilities of distant metastases were 39 ± 15% at 2 and 3 years for the whole cohort (fig. 2). Sites of distant metastases were bone, lung, liver and peritoneum in 2, 1, 1 and 1 patients.

Toxicity of Induction Chemotherapy

Grade 3 thrombocytopenia was observed in 36% of patients receiving FLEP chemotherapy during the first or second chemotherapy course. The frequency of grade 3 leukocytopenias was also 36%. Reduction of the etoposide dose reduced the rate of grade 3+ leukocytopenias or thrombocytopenias to 19% in the subsequent chemotherapy courses. No toxic death was observed. Haematotoxicity of HD 5-FU/L/P induction chemotherapy was mild and no grade 3 or 4 leukocytopenias or thrombocytopenias were observed. Hair loss of grade 3 was observed in all patients treated with FLEP but in none of the patients treated with HD 5-FU/L/P.

Acute Side Effects during Concurrent Chemotherapy and High-Dose Radiotherapy

2 patients developed a grade 3 oesophagitis during concurrent radiotherapy/chemotherapy which was reversible within 1 week after the end of radiotherapy. A thrombocytopenia and leukocytopenia of grade 4 was seen in 1 patient during concurrent radiotherapy/chemotherapy. Treatment was stopped at a cumulative dose of 40 Gy for another patient where a hypersensitivity syndrome was suspected because of a brisk skin reaction.

Late Effects after Definitive Radiochemotherapy

The 3 long-term survivors had normal swallowing and no or mild grade I subjective symptoms from the oesophagus. None of the patients developed symptomatic late effects from other thoracic organs.

Palliative Therapy for Locoregional Recurrences

3 patients developed a bilateral paralysis of the recurrent laryngeal nerve during follow-up. 2 of them were treated by tracheotomy, 1 by a bilateral laser chordectomy. The latter patient also received a tracheal stent for stenosing tumour growth in the trachea. 1 additional patient got a laser resection of endotracheal tumour growth. A gastrostomy was performed in 2 patients for restenosing tumours in the oesophagus.

Discussion

The radiochemotherapy schedule for locally advanced carcinomas of the cervical oesophagus was well tolerated and resulted in a 24% chance of long-term survival. Similar survival rates were observed in the other small nonsur-

gical series [7, 14]. However, comparisons between different series are in general difficult because results critically depend on the tumour extension and staging methods were often not very detailed in the past.

An analysis of the pattern of relapse revealed that locoregional recurrences were the predominant site of relapse in the present retrospective study with a risk of 67% at 2 and 3 years. 20% of the locoregional recurrences occurred in cervical lymph nodes outside the radiation fields. Similar high locoregional recurrence rates of 64% were observed by Santoro et al. [14] after definitive radiochemotherapy in 14 patients with locally advanced carcinomas of the cervical oesophagus. However, split dose radiotherapy was given only up to a low total dose of 50 Gy in 78 days. In the radiochemotherapy arm of the land mark RTOG 8501 study for oesophageal carcinomas in all subregions the risk of locoregional recurrences was high with 45% at 2 years [13]. This study recruited predominantly T2 tumours so that the data therefore tended to underestimate the risk of locally advanced carcinomas.

The risk of distant metastases as a site of first failure was 40% at 2 years for patients with locally advanced carcinomas of the cervical oesophagus despite intense induction chemotherapy and may be a reflection of the locoregionally far-advanced tumours selected for this study. Both, the FLEP as well as the HD 5-FU/L/P induction chemotherapy were active with major response rates of 64 and 50% and compare well with the effectiveness of other cisplatin/5-FU-based induction chemotherapy regimens for locally advanced oesophageal carcinomas with a mean response rate of 50% as reviewed by Fink et al. [23]. A high risk of distant metastases was also observed in other studies. Collin and Spiro [24] observed distant or combined distant and locoregional relapses in 42% of patients with carcinoma of the cervical oesophagus after surgery. Mendenhall et al. [7] found a crude distant metastasis rate of 26% after definitive radiotherapy. Most of these patients with distant metastases also had locoregional recurrences. Santoro et al. [14] observed distant metastases in 25% of the patients in complete or partial response after combined radiochemotherapy. The high risk of distant metastases justifies in our opinion the inclusion of chemotherapy schedules with 3 or more cycles in multimodality trials for locally advanced cervical carcinomas aimed to be active against distant metastases. That such schedules can reduce the distant metastasis rate in oesophageal carcinomas has been shown by the randomised RTOG study [13].

Dose-limiting side effects of radiotherapy were not observed in the present study and acute toxicity of radiochemotherapy without 5-FU in the concurrent phase was moderate. The quality of life of long-term survivors was good and no grade 2+ late effects were observed. Therefore, further intensification of the current protocol seems possible in order to improve locoregional control. For selected patients, inclusion of surgery in multimodality programme may be an option to improve locoregional control also in such a difficult region as the cervical oesophagus [12]. According to the latter authors and the experience of this and other groups with carcinomas in thoracic oesophagus [17], surgical resection after neoadjuvant therapy has a potential to reduce the rate of locoregional failures. Adelstein et al. [12] achieved locoregional control in all 9 patients with locoregionally advanced carcinomas of the proximal oesophagus after neoadjuvant concurrent radiochemotherapy and resection. However, due to the pre-operative risk assessment or patient refusal no patient with locally advanced carcinoma of the cervical oesophagus was treated with a trimodality programme at our institution during the recruitment time of the present study. Other strategies for improvement of the locoregional effectiveness of radiochemotherapy programmes are the increase in total radiation dose [7], the use of intensified fractionation schedules such as hyperfractionation [25] or accelerated hyperfractionation [26], and an increase in the intensity of chemotherapy given concurrently to radiotherapy [27]. However, such modifications may increase mucosal toxicity and in addition systemic toxicity that forced some groups to conclude in the past that their definitive radiochemotherapy schedule for oesophageal cancer was too toxic to be continued without modifications [28, 29]. The high risks of locoregional and distant relapse of locally advanced carcinomas of the cervical oesophagus warrants further step by step treatment intensifications.

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