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Neoadjuvant Concurrent Chemoradiotherapy for Locally Advanced Esophageal Cancer in a Single High-Volume Center

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ABSTRACT

Background. Neoadjuvant chemoradiotherapy (CRT) is now considered the standard of care by many centers in the treatment of both squamous cell carcinoma (SCC) and adenocarcinoma of the esophagus. This study evaluates the effectiveness of a neoadjuvant CRT protocol, as regards pathological complete response (pCR) rate and long-term survival.

Methods. From 2003 to 2011, at Upper G.I. Surgery Division of Verona University, 155 consecutive patients with locally advanced esophageal cancers (90 SCC, 65 adenocarcinoma) were treated with a single protocol of neoadjuvant CRT (docetaxel, cisplatin, and 5-fluorouracil with 50.4 Gy of concurrent radiotherapy). Response to CRT was evaluated through percentage of pathological complete response (pCR or ypT0N0), overall (OS) and disease-related survival (DRS), and pattern of relapse.

Results. One hundred thirty-one patients (84.5 %) underwent surgery. Radical resection (R0) was achieved in 123 patients (79.3 %), and pCR in 65 (41.9 %). Postoperative mortality was 0.7 % (one case). Five-year OS and DRS were respectively 43 and 49 % in the entire cohort, 52 and 59 % in R0 cases, and 72 and 81 % in pCR cases. Survival did not significantly differ between SCC and adenocarcinoma, except for pCR cases. Forty-nine patients suffered from relapse, which was mainly systemic in adenocarcinoma. Only three out of 26 pCR patients with previous adenocarcinoma developed relapse, always systemic.

Conclusions. This study suggests that patients treated with the present protocol achieve good survival and high pCR rate. Further research is necessary to evaluate whether surgery on demand is feasible in selected patients, such as pCR patients with adenocarcinoma.

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Despite remarkable improvements in surgical technique, survival with surgery alone in locally advanced esophageal cancer remains poor, with median 5-year overall survival not exceeding 20 %.[1,2]

This prompted the introduction of multimodal approaches: neoadjuvant chemoradiotherapy (CRT) increases local control and improves survival according to recent meta-analyses of randomized trial and the recently published randomized CROSS trial.[3–7]

Responders to treatment have better prognosis than nonresponders.[8] Patients are defined as pathological complete responders (pCR) when residual tumor is detected neither at primary site nor in lymph nodes, representing the best possible response to induction treatment.[8] In an effort to implement a tailored treatment strategy, pCR patients could be considered a group that is probably overtreated, as they might not need surgery. However, surgery is still mandatory even in patients with the best prognosis, as rigorous assessment of clinical response is still lacking.

The present study aims to evaluate the effect of a protocol of concurrent neoadjuvant CRT on overall survival (OS) and disease-related survival (DRS), and on radical resection (R0) and pCR rate. Recurrence rate and pattern of recurrence were also evaluated.

PATIENTS AND METHODS

From 2003 to 2011, at Upper G.I. Surgery Division of Verona University, 155 consecutive patients with locally advanced esophageal cancers (90 SCC, 65 adenocarcinoma

Siewert type I and II) were treated with a single protocol of neoadjuvant concurrent CRT. All patients gave informed consent and met the following inclusion criteria: locally advanced carcinoma [cT2–4 Nx M0, according to the clinical tumor–node–metastasis (cTNM) classification, reclassified according to the seventh edition], no other cancers or chemotherapy/radiotherapy in the previous 5 years, age 75 years or less, and good Eastern Cooperative Oncology Group performance status (ECOG grade 0–2). Clinical stage was evaluated by computed tomography (CT), endoscopy, and endosonography. Positron emission tomography (PET)/CT scans were routinely available since 2008.

The protocol adopted has been fully described previously.[9] Briefly it consisted of 5-fluorouracil (5-FU), cisplatin, and docetaxel (Taxotere; Sanofi-Aventis, Paris, France) along with 50.4 Gy of concurrent radiotherapy. The schedule was: 5-FU 150 mg/m^2 per day on day 1 and 21 by continuous infusion; cisplatin 20 mg/m^2 on day 1, 8, 15, 28, 35, and 42; docetaxel 20 mg/m^2 on day 1, 8, 15, 28, 35, and 42. Radiotherapy started on day 28 along with the second chemotherapy cycle. Patients were treated for 5 days a week with a 1.8 Gy/day dosage for a total radiation dose of 50.4 Gy. Surgery was performed 6–8 weeks after completion of the treatment.

The standard surgical procedure was a modified Ivor–Lewis, consisting of proximal gastrectomy and subtotal esophagectomy with D1+ abdominal and standard mediastinal (two-field) lymphadenectomy. The continuity of the digestive tract was achieved with a right intrathoracic supra-azygotic esophagogastric end-to-end anastomosis with a narrow gastric tube (3 cm wide). Patients with upper thoracic SCC were instead treated with a McKeown procedure with cervical esophagogastric or pharyngogastric anastomosis.

All resected specimens were histopathologically examined. The visible tumor or suspected tumor areas were measured and completely included, and serial 4–5-μm sections were stained with hematoxylin and eosin. Treatment-induced response at the primary tumor site was evaluated according to the size of residual cancer according to Size-based Pathological Response (SPR) classification, which groups tumor regression into four classes: (1) pathological complete response (pCR) (ypT0 N0), (2) minimal residual disease (MRD) (residual foci $\leq$1 cm, ypN0), (3) nonresponse (NR) (foci >1 cm, ypN0), and (4) node-positive cases (ypN+).[8]

Response to CRT was evaluated through percentage of pCR and R0, and overall (OS) and disease-related survival (DRS). R status was defined as absence or presence of infiltrated margins. The circumferential resection margin was considered positive if the gap between the tumor and the margin was <1 mm.

Rate and pattern of relapse were also evaluated. For this purpose, patients were regularly followed up every 6 months. When symptoms were reported, they were immediately investigated. Recurrence was detected by computed tomography, endoscopy, and PET/CT scans.

Locoregional recurrences were defined as recurrences in the surgical bed, at anastomotic level, or more frequently, in locoregional nodes. Systemic recurrence comprised both hematological and distant nodal relapses. When recurrence was simultaneously detected at both systemic and locoregional level, it was classified as mixed.

Statistical Analysis

Significance of differences between SCC and adenocarcinoma groups was computed by Fisher's exact test for qualitative variables and Wilcoxon–Mann–Whitney rank-sum test for quantitative variables.

The life status of individual patients was ascertained on 31 December 2011, no patient being lost to follow-up. Median follow-up in surviving patients was 46 months (range 6–107 months). Overall and disease-related survival were computed; the latter was calculated considering as terminal events both postoperative deaths, defined as deaths occurring within the first 30 days after surgery or in hospital, and deaths from recurrence, while patients dying from other causes were considered as censored observations at the time of death.

Survival curves were estimated by the Kaplan–Meier method and compared by the log-rank test for trend.[10]

RESULTS

Surgery

The demographic and clinical characteristics of the present series are displayed in Table 1. Nearly all patients with adenocarcinoma were male, while females represented about 25 % of patients with SCC ($p = 0.003$). At preoperative workup, the SCC group included a greater proportion of cT4a cases than the adenocarcinoma group, and a lower proportion of cT2 ($p = 0.018$). One hundred thirty-one patients (84.5 % of the entire cohort) underwent surgery; the McKeown procedure was used in 18 SCC patients. Six patients (3.9 %) were not operated on because they had died from treatment toxicity, and 18 (11.6 %) because they had experienced disease progression, which was defined as infiltration of unresectable structures or systemic neoplastic diffusion after CRT, detected with CT, PET/CT, and/or endoscopy. Radical resection (R0) was achieved in 123/155 patients (79.3 %); curative resection was more frequently attained in adenocarcinoma (87.7 %) than in SCC (73.3 %) ($p = 0.043$). When considering only patients undergoing surgery, the R0 rate peaked at 93.8 % (123/131). The median

TABLE 1 Main demographic, clinical, and pathological characteristics of 155 patients undergoing neoadjuvant treatment

	SCC ($n = 90$)	Adenocarcinoma ($n = 65$)	p value
Male/female ratio	66/24 (73/27)	60/5 (92/8)	0.003
Age (years)	60.9 ± 8.1 (60.8, 39.8–75.7)	61.5 ± 7.3 (61.3, 42.2–76.5)	0.667
cT stage			0.018
cT2	12 (13)	17 (26)	
cT3	63 (70)	45 (69)	
cT4a	15 (17)	3 (5)	
cN stage			1.000
cN0	40 (44)	29 (45)	
cN+	50 (56)	36 (55)	
Patients undergoing surgery	73 (81)	58 (89)	0.185
R0	66 (73)	57 (88)	0.043
pCR	39 (43)	26 (40)	0.743

Qualitative variables expressed as number of cases (with percent frequency in parentheses); age expressed as mean ± SD (with median, range in parentheses)

Significance of differences computed by Fisher's exact test for qualitative variables and Wilcoxon–Mann–Whitney rank-sum test for age

TABLE 2 Main clinical and pathological characteristics of 131 patients undergoing surgery

	SCC ($n = 73$)	Adenocarcinoma ($n = 58$)	p value
Size-based pathological response			0.469
pCR	39 (53)	26 (45)	
MRD	12 (16)	7 (12)	
NR	7 (10)	7 (12)	
N+	15 (21)	18 (31)	
Retrieved nodes	22.8 ± 15.6 (18, 3–80)	19.2 ± 7.4 (19, 3–42)	0.704
N+ patients only			
Positive nodes	1.7 ± 1.2 (1, 1–4)	2.7 ± 1.8 (2.5, 1–7)	0.057
N ratio (%)	13 ± 14 (6, 2–50)	19 ± 23 (11, 4–100)	0.164

Qualitative variables expressed as number of cases (with percent frequency in parentheses); quantitative variables expressed as mean ± SD (with median, range in parentheses)

Significance of differences computed by Fisher's exact test for qualitative variables and Wilcoxon–Mann–Whitney rank-sum test for quantitative variables

pCR pathological complete response (ypT0 N0), *MRD* minimal residual disease (residual foci ≤ 1 cm ypN0), *NR* nonresponse (residual foci >1 cm ypN0). *N+* node-positive (ypN+)

number of retrieved nodes was 19 (3–80) (Table 2). One patient (0.7 %) died in the postoperative period.

Pathological Response

Pathological complete response was achieved in 65 cases (41.9 %), and this percentage was not affected by histotype (Table 2). If only the operated on patients were taken into consideration, the percentage of pCR rose to 49.6 %.

Nodal metastases were found in 25 % of cases, with 2.2 ± 1.7 (mean ± standard deviation, SD) (median 1, range 1–7) positive nodes per N+ patient. The frequency of nodal invasion and the number of positive nodes after CRT tended to be higher in adenocarcinoma than in SCC, but the difference did not achieve statistical significance (Table 2).

Survival

Five-year OS and DRS were respectively 43 % [95 % confidence interval (CI) 34–52 %] and 49 % (39–58 %) in the entire cohort of 155 patients. These figures rose to 50 % (40–59 %) and 57 % (46–67 %), respectively, in the 131 operated on patients, and to 52 % (41–62 %) and 59 %

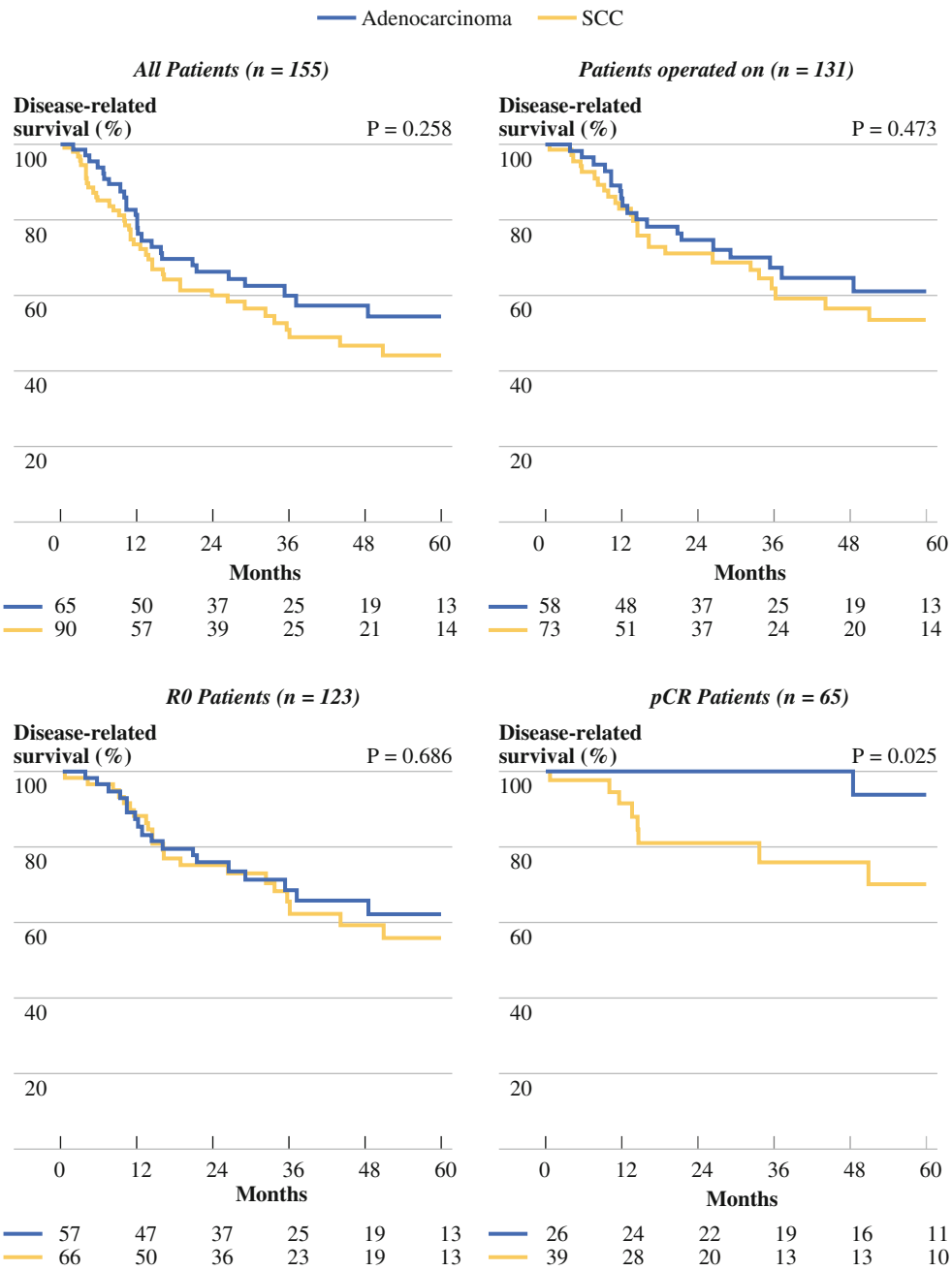

FIG. 1 Disease-related survival, estimated by Kaplan–Meier method, in a series of patients with locally advanced esophageal cancers, as a function of histotype (squamous cell carcinoma vs adenocarcinoma). Significance of differences between survival curves evaluated by log-rank test

(48–69 %) when only R0 resections were considered. Median OS and DRS were 36 and 50 months, respectively, in the entire series. Median OS increased to 51 months in patients operated on and further to 65 months in R0 patients, while median DRS was not reached by the end of the follow-up in these selected groups.

Five-year OS and DRS were particularly high in pCR cases, being respectively 72 % (57–82 %) and 81 % (65–90 %).

Survival did not significantly differ between SCC and adenocarcinoma in the entire cohort, in patients operated on, and in the R0 group, while 5-year DRS was significantly higher in pCR patients affected by adenocarcinoma (94 %, 63–99 %) than in those affected by SCC (70 %, 48–84 %) ($p = 0.025$) (Fig. 1).

Recurrence

Seventy-eight patients died during follow-up: 66 from cancer-related death and 12 from other causes, including other primary malignancy. Among the patients undergoing surgery, one died in the postoperative period and 41 from relapse, while an additional 8 patients suffering from recurrence were still alive at the end of follow-up. Half of

TABLE 3 Pattern of cancer relapse in 131 patients undergoing surgery

	SCC ($n = 73$)	Adenocarcinoma ($n = 58$)	p value
Type of relapse			0.001
Locoregional	9 (12.3)	3 (5.2)	
Mixed	10 (13.7)	2 (3.5)	
Systemic	6 (8.2)	19 (32.8)	

Relapses expressed as number of cases (with percent frequency in parentheses). Significance of differences computed by Fisher's exact test

relapses (25/49 = 51 %) were systemic (mostly liver, lung, and brain), while mixed relapses, meaning both systemic and locoregional, and solo locoregional were equally common, affecting 12 patients (24.5 %) each.

The pattern of recurrence was mainly systemic (19/24) in adenocarcinoma, while locoregional and mixed relapses were more common in SCC (Table 3).

Cancer recurrence was found even in 11 pCR patients (16.9 %), of whom 6 presented systemic relapse. Among relapsing pCR patients, two of the three cases with locoregional recurrence had received suboptimal lymphadenectomy with only four and six harvested nodes, respectively, so that stage migration cannot be excluded. Of note, pCR patients who had suffered from adenocarcinoma less frequently developed relapse (3/26), which was always systemic.

DISCUSSION

According to recent systematic reviews, meta-analyses, and the recent CROSS trial, adoption of neoadjuvant chemotherapy or chemoradiotherapy has led to a 20–35 % decrease in mortality risk as compared with surgery alone in locally advanced esophageal cancer.[3–7,11,12] The advantages of preoperative treatment consist in the downstaging and downsizing of the primary tumor along with clearance of possible circulating neoplastic cells. This translates into an increased rate of radical resection (R0) and a nonnegligible rate of pathological complete response (pCR), achieved in up to 40 % of cases in several studies.[3–6,8,13]

Chemoradiotherapy has been advocated to increase local control, with better survival and higher rate of both R0 resection and pCR than chemotherapy alone.[5,14,15] Hence, CRT is now considered the standard of care by many centers for the treatment of locally advanced esophageal cancer.

In the present study a protocol of concurrent CRT, based on 5-FU, cisplatin, and docetaxel along with 50.4 Gy of concurrent radiotherapy, was found to provide good long-term survival, with 59 % 5-year DRS for R0 patients after median follow-up of 46 months. Also, the R0 rate was notable, amounting to 93.8 % of the operated on cases.

Nonetheless this protocol presented significant toxicity, leading to death in 3.9 % of treated patients, so that its use should be restricted to specialized centers. Surgery instead was not affected by CRT, postoperative mortality being reasonably low (0.7 %). Noteworthily, this study was carried out in a single high-volume center, with >40 esophagectomies performed per year, and mortality is consistent with that reported by other high-volume centers.[16–18]

The present results were compared with those of recent phase II trials with different protocols, but always including cisplatin.[19–23] The present study achieved the highest proportion of patients operated on (85 %) with respect to the other trials (range 69–83 %), while the proportion of pCR (42 %) fell within the range (16–49 %). Overall survival in the present study was either similar to or higher than that reported by the other trials.[19,21–23]

Adenocarcinoma Versus SCC

Adenocarcinoma and SCC, although being different nosological entities, have similar survival after induction chemoradiation.[3,5] This survival similitude was confirmed by the present investigation, except for pCR patients, who presented better OS and DRS when affected by adenocarcinoma than by SCC. Survival was not statistically different between the two histotypes also in a German and a US trial.[24,25] However, both studies found a higher rate of pCR in SCC, while in our experience the pCR rate was similar between the two groups. Furthermore, the US study reported excellent local control in SCC, with only systemic relapses, while adenocarcinoma was burdened with locoregional failure. The opposite was found in the present study, where adenocarcinoma had mainly systemic recurrence, while in SCC also locoregional failure was found.

Relapse

The locoregional relapse rate is reported to be lower after neoadjuvant CRT, accounting for about one-third of the total recurrence rate.[4,26,27] The solo locoregional recurrence rate was only 24.5 % in our experience and even lower (21 %) in a US study.[25]

Other recent studies found a lower recurrence rate after CRT than after surgery alone, particularly in responders to treatment.[27,28] Nevertheless, a nonignorable recurrence rate was found also in pCR patients both in the current literature (18–24 %) and in our experience (16.9 %), and these recurrences were mainly systemic, as in the present investigation.[27–29]

pCR

Responders to therapy, in particular pathological complete responders, have better prognosis than nonresponders, so that in the current literature pCR is deemed a surrogate of treatment efficacy, with prolonged survival.[3–6,8,30–32] We found a very high percentage of pCR in our series, which reached 50 % in operated on patients. A remarkable pCR rate was also reported by the abovementioned phase II trials, ranging between 16 and 49 % with a median of 40 %. In the present study, 5-year OS and DRS in pCR patients were respectively 72 % and 81 %, which is even higher than the 50 % pooled survival computed by a recent review and in line with the best results reported.[30–32]

In the era of tailored treatment development, when two randomized trials on SCC reported that definitive CRT allows achievement of survival comparable to neoadjuvant CRT followed by surgery, it could be hypothesized that a high percentage of patients are overtreated, as they routinely undergo a surgical procedure which could be rather performed only on demand, in case of relapse during follow-up.[33–35]

On the other hand, nonresponders to treatment suffer from the risks related to chemoradiation, without any survival benefit. This is also supported by a very recent trial, where patients treated with upfront surgery presented a survival benefit with respect to nonresponders to neoadjuvant CRT, later operated on.[36] However, it is almost impossible to identify or foresee the responders to treatment, even if molecular biology markers of response are being investigated.[37–40] Until pretreatment markers of response become available, standardized protocols of CRT are needed for all fit patients. We believe that the chance of obtaining downstaging up to complete response is so high that it is better to risk treatment toxicity than to perform upfront surgery.

Hence, the first steps towards tailored treatment could be identifying nonresponders to CRT at an early stage and avoiding surgery for complete responders.

The only study that documented a change in therapeutic strategy during treatment was the MUNICON trial, where PET/CT was employed to distinguish, early during treatment, the patients who probably would not benefit from further chemotherapy.[41] However, the abovementioned study focused on chemotherapy alone in patients with adenocarcinoma, and its findings could not be replicated for CRT and for SCC. Piessen et al. demonstrated a survival benefit only when R0 resection was obtained and proposed aortic contact and tumor height at barium swallow as markers of resectability.[42] Of course, the decision to give up surgery must be taken case by case.

So far the possibility to interrupt induction treatment in selected patients is merely hypothetical, and surgical treatment remains mandatory for all the patients without progression during treatment.

Surgery in clinical complete responders might be considered overtreatment; nonetheless, two main problems exist: first, it is to date impossible to reliably define a clinical complete response and, second, the risk of pCR failure is not negligible, being around 20 % in the current literature and 16.9 % in the present study.

Noteworthily, only three relapses were observed in the 26 pCR cases with adenocarcinoma, which in addition were systemic relapses. These observations suggest that surgery on demand could be first experimentally applied to clinical complete responders in the adenocarcinoma group. However, as long as no staging techniques able to define a clinical complete response exist, surgery on demand remains just hypothetical even in these patients.

In conclusion, a neoadjuvant CRT based on cisplatin, 5-FU, and docetaxel, along with concurrent radiotherapy, can achieve good results in terms both of survival and of radical resection and pCR rate. In our opinion, the benefits of this protocol largely compensate the nonnegligible toxicity. At present, surgery on demand cannot be devised even for patients with lower risk of relapse, as rigorous assessment of clinical response is still lacking.

CONFLICT OF INTEREST The authors declared no conflicts of interest.

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