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Original Article

The addition of cetuximab to preoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma is associated with high rate of long term survival: Mature results from a prospective phase Ib/II trial ☆

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ABSTRACT

Aim: This phase IB/II study evaluated the safety and efficacy of the addition of cetuximab to standard preoperative chemoradiotherapy (CRT) in locally advanced esophageal cancer (LAEC).
Methods: Patients (pts) with resectable LAEC ($T_{2-3}N_{0-1}M_0$, $T_{1-3}N_1M_0$ or $T_{1-3}N_{0-1}M_{1A)}$ received an induction cycle of cisplatin 100 mg/m^2, day 1, and 5-fluorouracil (5-FU) 1000 mg/m^2/day, days 1–5, followed 4 weeks later by radiotherapy, 50.4 Gy, given with 2 cycles of cisplatin 75 mg/m^2 and escalating doses of 5-FU, days 1–4 and 29–32. Pts received 10 weekly infusions of cetuximab, 250 mg/m^2, with a loading dose, 400 mg/m^2. Surgery was planned 6–8 weeks after CRT.
Results: 64 pts were treated and 60 completed CRT. Median age was 65 years and 66% were males. Adenocarcinoma/squamous ratio was 61%/39%. Tumors were advanced: 95% T_3 and 67% N_1. Grade $\geq$3 toxicities occurred in 72%, with two (3%) toxic deaths. The 5-FU maximal tolerated dose (MTD) was 1000 mg/m^2/day. Clinical complete response rate was 33%. Of the 55 operated pts, R0 resection was achieved in 51 (93%) and pathological complete response (pCR) in 18 (33%), with 8 (14%) postoperative deaths. The 5-year survival rate for all pts was 38%. Pts with squamous histology had higher pCR (55% vs 20%, $p = 0.015$), local control (96% vs. 74%, $p < 0.001$) and 5-year survival (58% vs 25%, $p = 0.011$) rates.
Conclusions: This study suggests that the addition of cetuximab to standard preoperative CRT is feasible. R0, pCR and local control rates are encouraging. Pts with squamous cell tumors benefited more from the addition of cetuximab.
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Esophageal cancer is the 8th most common malignancy and the 6th leading cause of cancer death globally [1]. Despite vigorous efforts to improve treatment, the 5-year survival rates, all stages included, are only about 15–25% [2]. Even in locally advanced esophageal cancer (LAEC), a potentially curable condition, most patients will relapse after treatment and succumb to their disease.

Preoperative (neoadjuvant) chemoradiotherapy (CRT) followed by surgery is a standard approach for LAEC. The most frequently used chemotherapy is the combination of cisplatin and 5-fluorouracil (5-FU), the CF regimen [3], but newer regimens, incorporating other agents such as carboplatin/paclitaxel, are widely used too [4–7]. Still, prognosis remains poor and has only modestly improved over the past two decades; the need to improve current therapies is clear.

The Epidermal Growth Factor Receptor (EGFR) pathway regulates key processes contributing to malignancy, including cell differentiation, proliferation, angiogenesis and apoptosis [8]. Moreover, EGFR over-expression is associated with repopulation of epithelial tumor cells after exposure to radiation and with poor survival [9]. Altogether, EGFR plays an important role in both promotion of cancer and resistance to anti-neoplastic agents and radiotherapy and as such, serves as an attractive target in anti-cancer research.

EGFR over-expression or up-regulation is demonstrated in up to 55% of cases of esophageal cancer [10], suggesting a potential impact of anti-EGFR strategies in this disease. Pre-clinical and

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clinical studies have shown that the anti-EGFR chimeric monoclonal antibody (moAb) cetuximab can overcome radio- and chemoresistance. Indeed, cetuximab has been shown to improve patient outcome when given in combination with both radiotherapy and chemotherapy in several malignancies, including colorectal and head and neck cancers [11–13]. In light of the biological relevance of EGFR in esophageal cancer and the typically non-overlapping toxicity profile of cetuximab with both chemotherapy and radiotherapy, we decided to assess its role in LAEC. We hereby present the mature results of a prospective phase Ib/II study evaluating the efficacy and safety of the addition of cetuximab to standard CF-based preoperative CRT for LAEC.

Patients and methods

Patients

Eligible patients had untreated histologically confirmed squamous cell carcinoma (SqCC) or adenocarcinoma (AC) of the middle or distal esophagus or gastro-esophageal junction (GEJ). Patients had locally advanced tumors, defined as $T_{2\text{-}3}N_{0\text{-}1}M_{0\text{-}1a}$ according to the 1997 American Joint Committee on Cancer criteria (AJCC) 7th edition. The extent of disease was evaluated by physical examination, upper endoscopy, Positron Emission Tomography with Computerized Tomography (PET-CT) scan and Endoscopic Ultrasound (EUS).

Patients had to be surgical candidates, with an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1, intact hematological, cardiovascular, renal and liver functions, no severe comorbidities and no cancer within the preceding 5 years. Patients provided written informed consent prior to study enrollment.

Study design and treatment plan

This trial was a non-randomized single arm prospective study, comprising two phases, Ib and II, of preoperative combined modality treatment of CF chemotherapy and cetuximab prior to and concurrently with radiotherapy. Accordingly, it had two primary objectives. The primary objective of the phase Ib was to determine the Maximal Tolerated Dose (MTD) and the recommended phase II dose of 5-FU during CRT. The primary objective of the phase II was to evaluate the activity of the investigational regimen in terms of pathological and clinical complete response (pCR/cCR). The main secondary objectives were the rates of CRT-related toxicities, perioperative morbidity and mortality (within 30 days from surgery), complete (R0) resection, local control, progression-free survival (PFS) and overall survival (OS). The activity of the study regimen was evaluated in the whole group and by histology.

Treatment included an induction phase and CRT followed by surgery. The 4-week induction phase consisted of one cycle of chemotherapy (cisplatin 100 mg/m^2, day 1 followed by 5-FU 1000 mg/m^2/d as a continuous infusion [CI], days 1–5) and 4 weekly injections of cetuximab (400 mg/m^2 followed by 3 injections of 250 mg/m^2 each). During the phase Ib, CRT included escalating doses of 5-FU, from a starting dose of 800 mg/m^2/d to the standard dose of 1000 mg/m^2/d, unless dose limiting toxicity (DLT), defined as any toxicity-related treatment break greater than two weeks during CRT, occurs. Hence, CRT consisted of cisplatin 75 mg/m^2, days 1 and 29, 5-FU 800–1000 mg/m^2/d CI, days 1–4 and 29–32 of RT, weekly administration of cetuximab, 250 mg/m^2, and concurrent radiotherapy (1.8 Gy/d in 5 weekly fractions, for a total dose of 50.4 Gy). Surgery was planned 6–8 weeks after CRT. Toxicities from treatment were graded using the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTCAEv3.0). Clinical response to treatment, evaluated by repeat PET-CT and EUS 4–6 weeks after CRT, was determined using RECIST criteria version 1.0.

The Phase Ib was designed using a conventional 3 + 3 dose escalation scheme. Only patients who completed the induction phase successfully, i.e. without severe toxicities requiring dose modifications, were eligible for this part of the study. Otherwise, patients were evaluable for all other endpoints but the primary endpoint of the phase Ib. The sample size of phase II was calculated according to the composite primary endpoints of pCR/cCR rates in the whole group and among each of the two histological subgroups, with a power of 80% and alpha error of 0.05. The study protocol was approved by the institutional Ethics Committee.

Radiotherapy planning

CT simulation was performed without contrast. The gross tumor volume (GTV) was defined by the primary tumor and suspicious regional lymph nodes as determined by PET-CT. The clinical target volume (CTV) included the GTV plus a cranial and caudal margin of 3 cm and a radial margin of 0.5–1 cm. Three dimensional (3D) CRT or intensity modulated radiotherapy (IMRT) plans were generated using the Pinnacle Planning System (Phillips Medical Systems), with beam arrangements optimized for each patient. The prescription dose was specified at the ICRU-50 reference point, usually in isocenter.

The constraints for organs at risk are summarized in the Supplementary Appendix. Before treatment, all plans were approved in quality assurance (QA) meetings and weekly portal film verification was performed during treatment.

Results

Patient and tumor characteristics

From June 2006 until December 2015, 64 patients were accrued to the study. Baseline patient and tumor characteristics are shown in Table 1. Median age was 65 years (range, 38–84) and 66% were males. Most tumors were located in the distal esophagus (40%) or GEJ (33%). Patients had relatively advanced disease: 95% had T_3 tumors, 67% had nodal involvement (N_1) and 19% had M_{1a} disease. AC was found in 61% of cases and SqCC in 39%.

Treatment administration

Sixty patients (94%) completed all components of the treatment plan. Of the remaining 4 patients, 2 experienced toxic deaths, 1

Table 1
Patient and tumor characteristics.

Characteristic	Number of pts (N = 64)	Valid %
Age (yrs)		
Median (range)	65 (38–84)	
Gender		
M/F	42/22	66/34
PS		
0/1	12/52	19/81
Location		
Middle/Lower/GEJ	17/26/21	27/40/33
Histology		
AC/SqCC	39/25	61/39
Grade		
I–II/III/Unk	39/21/4	61/33/6
T stage		
$T_1/T_2/T_3$	0/3/61	0/5/95
N stage		
N_0/N_1	21/43	33/67
M Status		
M_0/M_{1a}	52/12	81/19

Abbreviations: PS = Performance Status; GEJ = Gastro-Esophageal Junction; AC = Adenocarcinoma; SqCC = Squamous Cell Carcinoma; Unk = Unknown.

discontinued induction following a cardiac event and 1 refused to complete cetuximab infusions due to grade 3 skin toxicity.

Chemotherapy dose reductions were required in 19 patients (30%) and in 11% of the cycles (21/187). In 26 patients (41%), 38/187 cycles (20%) were delayed more than 3 days. Dose reductions of cetuximab were required in 2 patients (3%) and 95% of the planned infusions were given. Radiotherapy toxicity related interruptions (more than 7 days) took place in 5 patients (8%).

Toxicity

Toxicities were evaluated in all patients. The most common hematological toxicities were leukopenia and neutropenia, in 45% and 41% of patients, respectively; 7 patients (11%) experienced neutropenic fever. The most common non-hematological toxicities were electrolyte imbalances, mostly hyponatremia and hypokalemia, in 30% and 19% of patients, respectively, followed by gastrointestinal (GI) toxicities, esophagitis, stomatitis and diarrhea, in 8% each. The most common cetuximab related toxicity was acneiform rash, observed in 9 patients (14%). Severe (grade $\geq$3) treatment-related toxicities, which were usually manageable, were observed in 72% of patients and were more common during induction, without a significant difference between the phase Ib and phase II parts of CRT (Table 2). Altogether, severe hematological and non-hematological toxicities were recorded in 41 (64%) and 43 (67%) of patients, respectively. There were two treatment-related deaths (3%), including one patient with sudden death during induction and one with fatal neutropenic sepsis during CRT.

Dose escalation

The phase Ib part of the trial included 9 patients. Three of the 6 patients in the first cohort experienced severe toxicities during induction and required a reduced dose during CRT. Therefore, they were not evaluable for the primary endpoint of the phase Ib. After treating the first 3 eligible patients, 5-FU was increased to the standard dose (1000 mg/m^2/d); after treating 3 more patients without any severe toxicity, this was determined the MTD and the recommended phase II dose.

Surgery

Following CRT, 59 patients (92%) were considered eligible for surgery; 5 patients either suffered from progressive disease (2) or toxicity related clinical deterioration (1) and became inoperable, or died from toxicity (2). Four patients refused surgery and 55 (86%) were operated within a median of 64 days (range, 45–154 days) from the end of CRT. Surgeries included trans-hiatal esophagectomy (36 patients), Ivor Lewis esophago-gastrectomy by laparotomy and right thoracotomy (5 patients), minimally invasive three field esophagectomy (11 patients) or exploratory laparoscopy only (3). Complete (R0) resection was achieved in 51 patients (93%). Seventeen patients (31%) experienced major postoperative complications. Of these, 8 (14%) had a fatal outcome: anastomotic leak and sepsis (4), pneumonia (2), gastrointestinal bleeding (1) and sepsis due to pseudomembranous colitis (1). These were probably not treatment-related since all patients completed CRT at least 2 months earlier and were all fit at the time of surgery. Postoperative mortality, which was not associated with any specific surgical procedure, was especially high during the first period of the study, decreasing significantly, to about 7%, during its latter part.

Treatment efficacy

Preoperative staging, using PET-CT and EUS, was compared to the pretreatment clinical stage of the 60 evaluable patients. Four patients (6%) were not evaluable due to fatal toxicities (2), protracted recovery from CRT (1) and refusal (1). Postoperative histopathological staging was available in all 55 operated patients. Data on treatment response and patient outcome are summarized in Table 3. Clinical down-staging was observed in 43 patients (72%), including 20 (33%) with cCR. Stable disease was noted in 10 patients (18%) and 6 (10%) experienced disease progression during treatment. Eighteen of the 55 operated patients (33%) achieved pCR and 8 (14%) had microscopic residual disease (mRD); the major histological response (pCR + mRD) rate was therefore 47%.

At the time of analysis, with a median follow up of 68 months (range, 0.7–136.4), 27 patients (42%) died of disease, 13 (20%) died of other causes and 18 (28%) were alive with no evidence of disease. Disease progression, observed in 32 patients, was distant in 21, loco-regional in 3 and combined in 8. Altogether, 11 of the 64 patients failed locally within the RT field, leading to a local control rate of 83%. Median PFS for all patients was 26.9 months (range, 0.7–136.4) and the 5-year PFS was 39% (Fig. 1a). Median OS was 28.0 months (range, 0.7–136.4) and the 5-year OS was 38% (Fig. 1b).

Table 2
Serious (grade $\geq$3) treatment-related adverse events.

	Induction (n = 64)	Chemo-radiation (n = 62)		Total (n = 64)
		Phase I (n = 6)	Phase II (n = 56)	
Hematological				
WBC	17 (27)	1 (17)	14 (25)	29 (45)
ANC	21 (33)	1 (17)	6 (11)	26 (41)
Neutropenic fever	6 (9)	0 (0)	1 (2)	7 (11)
Hb	3 (5)	1 (17)	1 (2)	4 (6)
PLT	6 (9)	1 (17)	0 (0)	7 (11)
GI				
Esophagitis	0 (0)	0 (0)	5 (9)	5 (8)
Stomatitis	5 (8)	0 (0)	0 (0)	5 (8)
Diarrhea	5 (8)	0 (0)	0 (0)	5 (8)
Electrolytes				
Hypokalemia	8 (13)	1 (17)	6 (11)	12 (19)
Hyponatremia	19 (30)	0 (0)	8 (14)	19 (30)
Hypomagnesemia	1 (2)	0 (0)	1 (2)	2 (3)
Other				
Acne	9 (14)	1 (17)	3 (5)	9 (14)
Fatigue	2 (3)	1 (17)	4 (7)	6 (9)
Cardiac	2 (3)	0 (0)	0 (0)	2 (3)

Abbreviations: WBC = White Blood Cell count; ANC = Absolute Neutrophil Count; Hb = Hemoglobin; PLT = Platelets; GI = Gastrointestinal.

Table 3
Response to Treatment and Patient Outcome.

Clinical response	AC (n = 36)	SqCC (n = 24)	Total (n = 60)	P
Downstaging n (%)	24 (67)	19 (79)	43 (72)	NS
cCR n (%)	10 (28)	10 (42)	20 (33)	NS
NC n (%)	8 (22)	2 (8)	10 (18)	NS
PD n (%)	3 (8)	3 (13)	6 (10)	NS
Pathological response	AC (n = 35)	SqCC (n = 20)	Total (n = 55)	P
Downstaging n (%)	26 (74)	17 (85)	43 (78)	NS
pCR n (%)	7 (20)	11 (55)	18 (33)	0.008
mRD n (%)	6 (17)	2 (10)	8 (14.5)	NS
Patient outcome	AC (n = 39)	SqCC (n = 25)	Total (n = 64)	P
Local Control	74%	96%	83%	<0.001
Median PFS	21.4 mos	NR	26.9 mos	<0.001
2 yr PFS (%)	43	76	56	
3 yr PFS (%)	24	76	45	
5 yr PFS (%)	21	69	39	
Median OS	26.4 mos	NR	28 mos	0.011
2 yr OS (%)	52.8	70.8	59.9	
3 yr OS (%)	38.9	58	46.3	
5 yr OS (%)	25.3	58	37.9	

Abbreviations: cCR = clinical Complete Response; NC = No Change; PD = Progressive Disease; pCR = pathologic Complete Response; mRD = microscopic Residual Disease; PFS = Progression Free Survival; OS = Overall Survival; yr = year; mos = months; NR = Not Reached.

Treatment efficacy by histology

Analysis of treatment efficacy by the two main histological subtypes revealed significantly better outcomes for the SqCC subgroup (Table 3). Of the 20 operated patients with SqCC, 11 (55%) achieved pCR, compared with only 7 of the 35 (20%) with AC ($p = 0.015$). These translated also to long-term outcomes: patients with SqCC had significantly higher local control (96% vs. 74%, $p < 0.001$), 3-year PFS (76% vs. 24%, $p < 0.001$) and 5-year OS (58% vs. 25%, $p = 0.011$) rates (Table 3, Fig. 1). Interestingly, in the only SqCC patient with local failure, biopsy of the recurrence revealed AC, without evidence of SqCC.

Discussion

This study evaluated the addition of cetuximab to standard CF-based preoperative CRT for LAEC. It had two parts and two corresponding primary objectives: to determine the MTD and recommended phase II dose of 5-FU during CRT (phase Ib) and to evaluate the activity of the combined regimen in terms of pCR/cCR rates (phase II). Both objectives were met: the standard 5-FU dose (1000 mg/m^2/d) was indeed feasible, with no unexpected toxicities, and both cCR and pCR rates were 33%. Other findings regarding the study regimen's activity were R0 and local control rates of 93% and 83%, respectively, and median PFS and OS of 26.9 and 28 months, respectively. A pre-planned sub-analysis revealed a clear-cut histology-dependent disparity in activity: patients with SqCC gained substantially more benefit from the addition of cetuximab, with 42%, 55% and 96% rates of cCR, pCR and local control, respectively, and median PFS and OS that had not been reached with a long median follow-up (68 months).

The addition of cetuximab to standard CRT was based on the minimal overlap between the toxicity of the drug and that of chemotherapy or RT. Still, we were initially concerned by the potential increase in GI toxicity with the use of cetuximab, especially with CF-based CRT. Reassuringly, the rates of severe GI

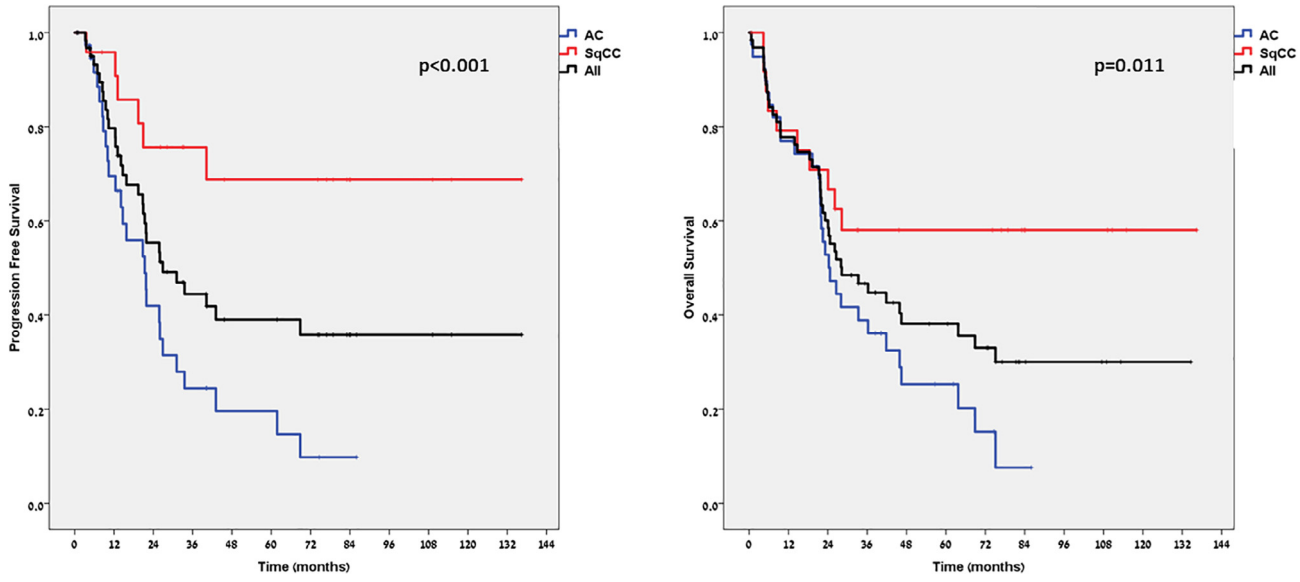

Fig. 1. Kaplan–Meier's curves for progression-free survival and overall survival. *Abbreviations*: AC = Adenocarcinoma; SqCC = Squamous Cell Carcinoma.

Table 4
Trials using anti-EGFR monoclonal antibodies with chemoradiation for resectable esophageal cancer.

Study/Author (Year)	Phase	Setting	No. of Pts.	Histology		Regimen	Response	R0	Local Control	PFS[1]	OS[1]
				AC	SqCC						
Definitive CRT											
Chen (16) (2012)	II	Definit.	31		31	Paclitaxel + Cisplatin + Cetuximab	cCR – 69%	N/A	86%	75 mos	N/A
SCOPE1 Crosby (21) (2013)	II/III	Definit.	258	65	188	Capecitabine + Cisplatin ± Cetuximab	N/A	N/A	N/A	16 mos vs 22 mos	22 mos vs 25 mos
RTOG 0436 Suntharalingam (24) (2017)	III	Definit.	328	203	125	Cisplatin + Paclitaxel ± Cetuximab	cCR – 56% vs. 58%	N/A	3 y LC: 49% vs 49%	N/A	2 yr: AC – 43% vs 41% SqCC – 46% vs 43%
Neoadjuvant CRT											
[2]ECOG 2205 Kleinberg (18) (2010)	II	Neoadj.	22	22	–	Oxaliplatin + 5FU + Cetuximab	pCR – 32%	N/A	N/A	N/A	N/A
De Vita (14) (2011)	II	Neoadj.	41	13	28	FOLFOX + Cetuximab	pCR – 27%	80%	N/A	N/A	17 mos
SAKK 75/06 Ruhstaller (15) (2011)	IB/II	Neoadj.	28	15	13	Cisplatin + Docetaxel + Cetuximab	pCR: AC – 27%, SqCC – 38%	100%	89%	1 yr – 82%	1 yr – 86%
[2]Lee (22) (2013)	II	Neoadj.	19	16	3	Irinotecan + Cisplatin + Cetuximab	pCR: AC – 16%, SqCC – 67%	89%	N/A	AC – 10 mos, SqCC – 38 mos	AC – 31 mos, SqCC – 67 mos
[2]Ubink (17) (2014)	II	Neoadj.	12	12	–	ECX + Cetuximab	pCR – 0%	N/A	N/A	N/A	N/A
ACOSOG Z4051 Lockhart (27) (2014)	II	Neoadj.	70	70	–	Docetaxel + Cisplatin + Panitumumab	pCR – 33%	N/A	N/A	2 yr – 41%	19 mos
SAKK 75/08 (23) Ruhstaller (2017)	III	Neoadj.	300	195	105	Cisplatin + Docetaxel+/- Cetuximab	N/A	95% vs 97%	3 yr - 79% vs 63%	35 mos vs 24 mos	61 mos vs 36 mos
Alsina (28) (2017)	II	Neoadj	50	11	39	Docetaxel + Cisplatin + 5-FU + Cetuximab	pCR – 41%	81%	N/A	12.2 mos	23.4 mos
Current Study Brenner (2018)	IB/II	Neoadj.	64	39	25	Cisplatin + 5FU + Cetuximab	pCR: AC – 20%, SqCC – 55%	93%	83%	AC – 21.4 mos, SqCC – N.R	AC – 25 mos, SqCC – N.R

Abbreviations: Definit. = Definitive; Neoadj. = Neoadjuvant; N/A = Not Available or Not Relevant; yr = year; mos = months; N.R = Not Reached; FOLFOX = Folinic acid, Fluorouracil and Oxaliplatin; ECX = Epirubicin, Cisplatin and Capecitabine.

[1] Median unless otherwise specified.

[2] Closed early due to toxicity or insufficient pCR rate.

toxicities in our study were in the single digit order. Accordingly, adding cetuximab did not preclude the use of optimal doses of CRT. These findings coincide with other reports on combinations of anti-EGFR agents with CRT for LAEC [14–16] or other diseases [11–13]. Similarly to these, while the combined regimen in our study was associated with substantial toxicity, including 3% treatment-related mortality, this rarely required dose reductions, prolonged RT interruption or treatment discontinuation. In other studies, however, the addition of anti-EGFR moAbs did not allow effective administration of CRT, and in some has even led to toxicity-related early study closure [17,18].

We faced high rates of postoperative morbidity and mortality, in the upper range of modern series [19]. The typical complication profile (infections, anastomotic leak and pulmonary insufficiency), the long interval (>2 months) from CRT to surgery and the absence of any apparent clinical sequel from treatment at the time of surgery in any of these patients, suggest that the high operative mortality is unrelated to the addition of cetuximab. Indeed, following an initial learning curve, there was a substantial decrease in the complication rate to figures in line with other series [19].

Despite a strong supportive pre-clinical rational, the contribution of cetuximab to the treatment of LAEC remains controversial [20]. As shown in Table 4, summarizing the overall experience on the use of anti-EGFR moAbs with CRT in this disease, the design of the trials and their results are very heterogeneous. They vary in their developmental phase, clinical setting, patient population, tumor histology, study endpoints and unfortunately, also in their results. This, in addition to the very few mature phase III trials, makes it nearly impossible to draw firm conclusions from existing data. Nevertheless, few observations can still be made. First, the impact of anti-EGFR moAbs in LAEC is probably more significant locoregionally. Contrary to all other endpoints, the data on high R0 (80–100%) and local control (79–89%, with the exception of the SCOPE1 trial [21]) rates across studies are consistent. This may be explained by a rather strong radiosensitizing effect and minimal, if any, systemic effect of anti-EGFR agents in LAEC. Second, as seen in some phase II trials [15,16,22] and in two of the three phase III trials, SAKK 75/08 and RTOG 0436 [23,24], the impact of anti-EGFR moAbs is more substantial in tumors with SqCC histology. This difference may arise from the radiosensitizing effect of these agents, as SqCC tumors are usually more radiosensitive. Lastly, it is impractical to compare the toxicity data from the different trials due to heterogeneous reports, and hence these data are not depicted in Table 4. Still, overall, the addition of anti-EGFR moAbs seems to increase toxicity, but this may depend, as will be discussed below, on the specific regimen and setting. The results of the current trial agree with all three observations: the study regimen lead to promising locoregional outcomes, significant impact in SqCC, and treatment was associated with substantial yet usually manageable toxicity.

The conflicting efficacy results of anti-EGFR moAbs across trials, as shown in Table 4, may derive from the different chemotherapy backbone used, based on data from LAEC and other diseases. The inconsistent data on the combination of cetuximab with oxaliplatin-based but not with irinotecan-based regimens in advanced colorectal cancer (CRC) is one good example [25]. More so, increased toxicity of certain combinations may lead to decreased chemotherapy dose intensity and consequently, to decreased efficacy. Data from SCOPE1, REAL3 and COIN trials, for instance, imply that combining capecitabine with anti-EGFR agents results in undesirable dose reductions in the standard therapy and worse outcome, in esophago-gastric cancer and CRC [21,25,26]. Several studies which are depicted in Table 4, including most of the negative trials and some using capecitabine, also reported substantial toxicities and significant difficulties to administer the standard therapy [17,18,21,22,24,27]. Two of these trials were even closed early due to toxicity, including one with an encouraging pCR rate [17,18]. While the regimens listed in Table 4 included platinum compounds, taxanes, fluoropyrimidines or irinotecan, the current study is the only one to have evaluated the combination of an anti-EGFR moAb with the classical CF-based CRT. If this is the main reason for the manageable toxicity, minimal impairment to CRT administration and encouraging efficacy, at least in SqCC, in this study, is yet to be determined.

Data are conflicting on the potential role for anti-EGFR moABs in the treatment of LAEC. On the one hand, the majority of studies, but not all, are negative, including two of the three randomized trials. On the other hand, the most recent randomized trial, SAKK 75/08, the only randomized trial in the preoperative setting and the only one in which cetuximab did not lead to significant dose reductions, showed a clear trend for superiority, with p values of 0.017, 0.13 and 0.055 for LC, PFS and OS, respectively [23]. In this trial, as in the positive study by Lee and colleagues [22], cetuximab benefit was even larger in SqCC. Clearly, our trial supports the potential contribution of anti-EGFR in LAEC, at least in SqCC, in this as yet unsettled debate.

Finally, our study has several strengths that may somewhat make up for its non-randomized design. First, with 64 patients, it is, to our knowledge, the largest non-randomized study conducted in this setting to date. Second, it has a very long follow-up, with a median of nearly 6 years, allowing reliable evaluation of the long-term treatment results. Third, nearly all patients have been followed by the same team, further enhancing the quality of the follow-up data. Lastly, and maybe most importantly, it is the only study evaluating the addition of an anti-EGFR moAb to the classical RTOG-based CRT in this setting.

In summary, this large phase Ib/II trial showed that combining cetuximab with standard doses of CF-based preoperative CRT for LAEC is feasible. The addition of the drug seems to have enhanced the activity of the regimen, at least locoregionally and more so in patients with SqCC histology. A comprehensive biomarker program is being conducted to define patients who may gain more benefit from the combined regimen. Clearly, its further development seems justified, especially in SqCC.

Conflict of interest statement

All authors declare no conflicts of interests.

Author contributions

BB developed and designed the study protocol. BB, TG and AS wrote the manuscript. BB, NG and TG carried out the data organization and statistical analyses. BB, OP, EI, HK, NM, EF and YK participated in recruiting patients contributing their data and discussing the results. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.013.

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