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Dose-escalated neoadjuvant chemoradiotherapy for locally advanced oesophageal or oesophagogastric junctional adenocarcinoma

Victor Duque-Santana[1], Fernando López-Campos[1], Margarita Martin[1], Lira Pelari[1], Antonio Hernandez[1], Mireia Valero[1], Julio Galindo[2], Pablo Priego[2], Marta Cuadrado[2], Federico Longo[3], María Caminoa-Lizarralde[4], Sonsoles Sancho[1]

[1]Radiation Oncology, Ramon y Cajal University Hospital, Madrid, Spain
[2]General and Digestive Surgery, Ramon y Cajal University Hospital, Madrid, Spain
[3]Medical Oncology, Ramon y Cajal University Hospital, Madrid, Spain
[4]Patological Anatomy, Ramon y Cajal University Hospital, Madrid, Spain

ABSTRACT

Background: Neoadjuvant chemoradiotherapy with CROSS-protocol is the standard of care for locally advanced esophageal cancer. The purpose of this study was to demonstrate an improvement in complete pathological response (ypCR) after a dose-escalation neoadjuvant protocol compared to standard treatment. Secondary endpoints were disease-free survival (DFS) and acute gastrointestinal toxicity.

Material and methods: We prospectively evaluated patients with locally advanced esophageal adenocarcinoma who received neoadjuvant chemoradiotherapy. The radiation dose was 41.4 Gy in 23 fractions or 50.4 Gy in 28 fractions with weekly administration of six intravenous cycles of carboplatin AUC 2 mg/mL and intravenous paclitaxel 50 mg/m^2 followed by surgery.

Results: Between December 2015 and July 2020, 21 patients were treated according to the reported radiation schedules. Median age was 61 years (57–67). 20 (95.2%) tumors were located at the esophagogastric junction and 1 (4.8%) in the middle esophagus. Five (23.8%) were stage II and 16 (76.2%) stage III. Twelve (57.1%) patients received 41.4 Gy (standard group) and 9 (42.9%) received 50.4 Gy (intensification group), with 5 (41.67%) and 5 (55.6%) presenting ypCR in the standard and intensification group, respectively (p = 0.67). After a median follow-up of 17 months (8–30), DFS in the standard group was 17.78 months [95% (CI, confidence interval): 12.9–22.6] and 45.5 months (95% CI: 24.4–66.05) in the intensification group (p = 0.299). Grade III acute gastrointestinal toxicity was 16% and 33.33%, respectively (p = 0.552). Postoperative toxicity events ≥ Grade III were 5 (41.7%) and 4 (44.4%), respectively (p = 0.623).

Conclusions: In our study we found a trend towards a higher complete pathological response-rate and disease-free survival in the intensification group compared to the standard group, with no differences in gastrointestinal toxicity. Well-designed randomized and controlled trials are needed to obtain conclusive data.

Key words: chemoradiotherapy; esophagogastric adenocarcinoma; dose-escalated radiotherapy; intensity-modulated radiotherapy

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Address for correspondence: Fernando López Campos, Hospital Universitario Ramón y Cajal, Carretera de Colmenar Viejo Km 9,100 28034 Madrid, Oncologia Radioterápica, tel: 0034663158959; e-mail: Fernando_lopez_campos@hotmail.com

Introduction

Esophageal cancer is the seventh cancer by frequency worldwide, with an approximate annual incidence of 572,034 cases [1]. Adenocarcinoma (ADC) is the most frequent histology in tumors of the gastroesophageal junction (GEJ) and located in the distal third of the esophagus, with a progressive increase in the incidence in the US and Europe in recent years [2].

Currently, 50% of patients with esophageal cancer present locally advanced stages at diagnosis [3] that encompass stages T1–T4, N0–N2, M0 [American Joint Committee on Cancer (AJCC) 8th ed.] [4].

Based on current evidence, the treatment of this entity involves a multimodal approach whose central axis is surgery in combination with neoadjuvant chemoradiotherapy treatment. This approach is supported by both the European clinical practice guidelines of European Society for Medical Oncology (ESMO) [5] and the American clinical practice guidelines of National Comprehensive Cancer Network (NCCN) [6].

The meta-analyses by Gestsbki et al. 2007 [7] and Sjoquist et al. 2011 [8], as well as studies such as the one by Klevebro et al. from 2017 [9], demonstrated an overall survival benefit with neoadjuvant chemoradiotherapy compared to perioperative or neoadjuvant chemotherapy in these patients.

In 2012, the CROSS study [10] was published, which compared neoadjuvant chemoradiotherapy treatment with taxol and carboplatin up to a total dose of 41.4 Gy versus an exclusive surgical treatment. Results favored the neoadjuvant chemoradiotherapy arm with a 29% rate of complete pathological responses. Mature data was published thereafter with a 7-year follow-up, confirming an overall survival of 48.6% compared to 24% in those who underwent surgery [11].

As a result of the publication of these studies, neoadjuvant chemoradiotherapy with the CROSS scheme was established as the standard of treatment in locally advanced resectable esophageal cancer located in the distal third and in the gastroesophageal junction.

In ASCO 2021, the preliminary results of the phase III Neo-AEGIS study were published, which directly compared the neoadjuvant QTRT treatment according to the CROSS scheme *vs* perioperative QT according to the MAGIC scheme [epirubicin, cisplatin (oxaliplatin), 5-FU (capecitabine)] or the FLOT scheme (docetaxel, 5-FU, leucovorin, oxaliplatin), in patients diagnosed with adenocarcinoma of the esophagus or gastroesophageal junction. This study showed that peri-operative chemotherapy is non-inferior to neoadyuvant QTRT. However, higher percentage of R0 (95% *vs.* 84%), higher percentage of grade I and II tumor regression (47.1% *vs.* 12%), higher percentage of complete pathological response (ypCR) (16% *vs.* 5%) and higher percentage of ypN0 (60.1% *vs.* 44.5%) were obtained in the neoadjuvant QTRT arm according to the CROSS scheme [12].

On the other hand, the use of more advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), permits a better conformation of the radiation dose, allowing a higher dose to reached the tumor with lower toxicity in the surrounding tissues. These advanced techniques have been used in other tumor locations efficiently and safely, being correlated with a higher percentage of ypCR and complete resections (R0) as a result of higher radiation doses administered [13–16]. In this line, there are also studies in esophageal cancer that have explored the benefit of IMRT over conventional external radiotherapy techniques with good locoregional tumor control and low toxicity profiles [17].

Based on the above, we consider that the escalation of radiotherapy dose, as part of the neoadjuvant treatment according to the CROSS scheme, would be associated with an increase of ypCR and an increase in disease-free survival, without affecting acute gastrointestinal toxicity.

Material and methods

Study design

This is a prospective, not randomized study that included a total of 21 patients treated in the Radiation Oncology Department of the Ramón y Cajal University Hospital (Madrid) from 2015 to 2020. The inclusion criteria were as follows: patients diagnosed with locally advanced adenocarcinoma of the esophagus or gastro-esophageal junction according to TNM classification, AJCC 8th ed., surgically resectable and medically suitable for treatment with concurrent chemoradiotherapy. Exclusion criteria were as follows: squamous cell carcinoma, esophageal carcinoma stage IV,

unresectable tumors, located at the upper third of the esophagus, patients who did not complete the initially planned therapeutic scheme, medically not suitable for treatment with concurrent radiochemotherapy.

The study selection process is summarized in the Supplementary File — Figure S1.

Diagnosis and Staging

The diagnose and staging work-up was done with a complete blood test, computed tomography (TC) of the thorax, abdomen and pelvis, endoscopy that included a biopsy, and planning positron emission tomography — computed tomography (PET-CT).

Treatment schedule

Patients received 41.4 Gy to the entire PTV in 23 fractions or 50.4 Gy to the entire PTV in 28 fractions according to the clinician's decision based on age, Eastern Cooperative Oncology Group (ECOG), tumor length and comorbidities.

Treatment simulation CT was done with patients immobilized in a supine position with their arms up, and image fusion of the diagnostic PET-CT. All patients were treated using a linear accelerator and intensity-modulated volumetric arc therapy (VMAT). Gross tumor volume (GTV) design was defined as the primary tumor and the affected nodes, based on radiological and endoscopic findings. The clinical target volume (CTV) of the primary tumor was defined as the GTV of the primary tumor plus an upper and lower margin of 3–4 cm along the esophagus and 1 cm radial margin, and the CTV of the affected nodes was defined as GTV plus a 1 cm margin in all directions [18]. The planning target volume (PTV) was defined as the sum of the CTVs plus a margin of 0.5 cm in all directions. 95% of the PTV volume was covered with the 95% prescribed dose. Dose constraints for organs at risk were as follows: Kidney (mean dose < 15 Gy; V20 < 32%), liver (mean dose < 30 Gy; V30 > 30%), small intestine (V45 < 195 cc), heart (mean dose < 26 Gy; V30 > 46%); lungs (V20 < 30%), medulla (D max < 50Gy), duodenum (D max < 55 Gy; V15 < 150 cc). Dose limitations were met in all treated patients (Supplementary File — Fig. S2).

Concurrent chemotherapy scheme was carboplatin with an area under the curve of 2 mg/mL/min, and paclitaxel at 50 mg/m^2 of body surface area administered intravenously on days 1, 8, 15, 22, and 29.

4–6 weeks after neoadjuvant treatment, all patients were revaluated with a CT scan and then surgery was performed between 6–10 weeks after the end of RTQT. Patients underwent a 3-field laparoscopic esophagectomy or open esophagectomy.

Surgical specimens were analyzed by specialists in pathological anatomy of the gastrointestinal area. The pathological report indicated the result of complete pathological response (pCR), partial response or no response to neoadyuvant therapy. In addition, it included the degree of tumor regression according to the modified Ryan classification [19]. TRG 0: no viable tumor cells (complete response). TRG 1: small group of tumor cells (moderate response). TRG 2: residual tumor cells (minimal response). TRG 3: no elimination of tumor cells (no response).

Follow-up

Follow-up included blood tests and CT scans every 3 months during the first year, every 4 months for the second year, and every 6 months thereafter. We also performed endoscopies every 6 months for the first two years and then once a year.

Endpoints and statistical analysis

Disease-free survival (DFS) was defined as the date from the pathological diagnosis to the date of local or distant relapse. Postneoadyuvant complete pathological responses (ypCR) were recorded according to the modified Ryan classification. Gastrointestinal toxicity analysis was performed according to the CTCAE V.4 toxicity scale during treatment with chemoradiotherapy and 30 days after it. In addition, haematological, neurological and skin toxicity analyses were performed during treatment and 30 days afterwards.

Postoperative complication analysis was performed according to the CTCAE V.4 toxicity criteria. This classification considers GIII toxicity as the one that requires reintervention or has an organic dysfunction and requires intensive care.

For the statistical analysis and results, SPSS 20.0 (2011) software was used. To analyze the possible associations between the quantitative variables, we used the Student's T analysis or the Mann-Whitney U analysis, as necessary. For the association between qualitative variables we used the chi-squared test (χ^2) test or Fisher's exact test.

Lastly, the DFS was analyzed using the Kaplan-Meier method for survival analysis and the COX proportional hazard test. We also analyzed the DFS between groups in the 3rd, 6th and 9th months; $p < 0.05$ was considered as statistically significant.

Data collection was carried out by reviewing medical records, pathological anatomy reports, radiotherapy treatment reports, and surgical procedure reports.

Results

Twenty-one consecutively treated patients completed treatment with neoadjuvant chemoradiotherapy and subsequent radical surgery. Out of the excluded (n = 9) patients: 4 did not undergo surgery (2 patients received 50.4 Gy and 2 patients received 41.4 Gy), 1 presented chemotherapy allergy and had it suspended (received 41.4 Gy), 1 patient had induction chemotherapy prior to chemoradiotherapy (received 41.4 Gy), 2 had adjuvant chemotherapy (1 patient received 50.4 Gy and a 1 patient received 41.4 Gy) and 1 refused surgery after finishing neoadjuvant treatment (received 41.4 Gy).

Twenty-one patients with a median age of 61 years (57–67) were analyzed. Fifteen (71.4%) were male and 6 (28.6%) were female. Twenty (95.2%) were adenocarcinomas located in the gastroesophageal junction and 1 (4.8%) was located in the middle third esophagus. Eleven (52.4%) were stage IIIB, 5 (23.8%) IIIA, 2 (9.5%) IIB and 3 (14.3%) stage IIA.

Twelve (57.1%) patients received a radiotherapy dose of 41.4 Gy in 23 fractions and 9 (42.9%) received 50.4 Gy in 28 fractions. All patients received concomitant carboplatin and paclitaxel, except for 1 patient in whom the chemotherapy regimen was replaced due to a hypersensitization reaction after several cycles.

All patients underwent a 3-field laparoscopic esophagectomy surgery, except 1 patient in each group who underwent open esophagectomy, with median time between the end of chemoradiotherapy and surgery being 52 days ($\sigma = 26.31$).

The groups were correctly balanced, with no statistically significant differences in terms of gender ($p = 0.331$), location ($p = 0.429$), age ($p = 0.843$), stage ($p = 0.361$), ECOG, American Society of Anaesthesiology (ASA) ($p = 0.575$), % of weight loss before treatment ($p = 0.523$), tumor length ($p = 0.523$), or time between the end of chemoradiotherapy and surgery ($p = 0.236$) (Tab. 1).

We proceeded to assess both the ypCR rate and the degree of regression in the surgical specimen according to the modified Ryan classification. We found 5 (41.6%) ypCR in the standard group versus 5 (55.6%) in the intensification group (Fisher's exact test, $p = 0.637$). In the standard group we found a GI TRG of 33% and GII of 11% and a GI TRG of 11% and GII of 33% in the intensification group (Fig. 1).

With a median follow-up of 17 months (range 8–30), DFS was 17.78 months [95% confidence interval (CI): 12.9–22.6) in the standard group (median follow up 17 months) and 45.25 months (95% CI: 24.4–66.05) in the intensification group (median follow up 18 months). Mantel-Cox Log-Rank Test 1.079, $p = 0.299$ (Fig. 2).

At 3, 6 and 9 months DFS was 83.3%, 83.3% and 50% respectively in the standard group and was 100%, 83.3% and 83.3%, respectively, in the intensification group (Tab. 2).

In the standard group, 60% of the patients developed distant metastasis (mainly bone and hepatic disease) and 8% local relapse. In the intensification group, 11% developed distant metastasis (peritoneal) and 11% local relapse.

Regarding acute gastrointestinal toxicity, there were no statistically significant differences between the groups (Fisher's exact test, $p = 0.552$). Grade III toxicity was observed in 2 (16%) patients in the standard group and 3 (33.33%) in the intensification group. No statistically significant differences were found in terms of haematological, neurological and skin toxicity during treatment and 30 days after treatment.

The postoperative GIII or higher toxicity was 5 (41.7%) in the standard group and 4 (44.4%) in the intensification group with no statistically significant differences (Fisher's exact test, p = 0,623)

Discussion

Following the results shown by the CROSS study [11, 12], 41.4 Gy was established as the standard of neoadyuvant treatment in oesophageal cancer located in the distal third or GEJ. Despite the results in terms of pathological complete response being of

Table 1. Main characteristics of both treatment groups

	41.4 Gy	50.4 Gy	p
Gender			
Male	10 (83.3%)	5 (55.55%)	0.331
Female	2 (16.7%)	4 (44.44%)	
Age (years)	61 (56–65)	62 (58–67)	0.843
ECOG			
0	4 (33.3%)	3 (33.3%)	–
1	8 (66.7%)	6 (66.7%)	
ASA			
2	6 (50%)	5 (55.6%)	0.575
3	6 (50%)	4 (44.4%)	
Weight loss (%)			
≤ 10%	9 (75%)	6 (66.7%)	0.523
> 10%	3 (25%)	3 (33.3%)	
Tumor length [cm]			
≤ 5	9 (75%)	6 (66.7%)	0.523
> 5	3 (25%)	3 (33.3%)	
Localization			
GEJ	12 (100%)	8 (88,89%)	0.429
Middle esophagus		1 (11.11%)	
Clinical Stage AJCC			
IIIB	6 (50%)	5 (55.5%)	
IIIA	3 (25%)	2 (22.22%)	0.361
IIB	2 (16,7%)	–	
IIA	1 (8.3%)	2 (22.22%)	
Type of surgery			
Laparoscopic radical esophagectomy	11 (91.67%)	8 (88.89%)	–
Open radical esophagectomy	1 (8.33%)	1 (11.11%)	
IMRT	12 (100%)	9 (100%)	–
Time between chemoradiotherapy-surgery (days)	46.75	65.44	0.236
	(39.13–54.36)	(39.64–91.24)	

ECOG — Eastern Cooperative Oncology Group; ASA — American Society of Anaesthesiology; AJCC — American Joint Committee on Cancer; IMRT — as intensity-modulated radiotherapy

around 29% in this study, it is logical to think there is still room for improvement.

Several studies published demonstrate that complete pathological responses in patients undergoing RTQT and subsequent surgery for esophageal cancer, predict decreased local and distant recurrence and improved survival [20, 21].

Clinical trials that have tried to address the role of dose-escalation radiotherapy in patients with esophageal and GEJ cancer have been mostly in the context of treatments with radical intention and, therefore, address a different patient profile from that of our study. The INT 0123 [22] trial that randomized patients to receive 64.8 Gy versus 50.4 Gy with fluorouracil and cisplatin, had its recruitment suspended due to excess mortality in the 64.8 Gy group, with no differences in locoregional control or overall survival. However, the irradiation techniques used in this study are considered suboptimal today, as are the extensive volumes used that affected patient toxicity. In addition, total radiation dose and chemotherapy treatment also differ significantly from our protocol as a result of the treatment intention.

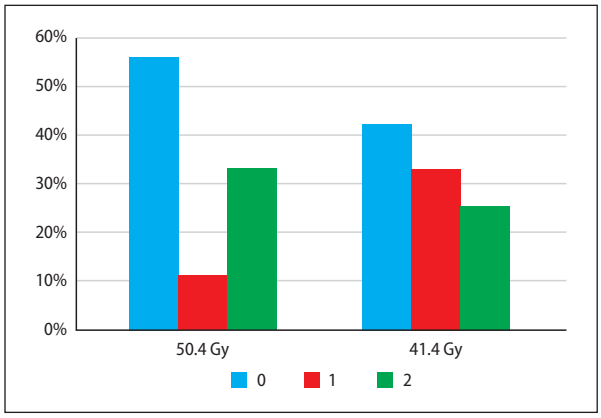

Figure 1. Tumour regression grading in both treatment groups

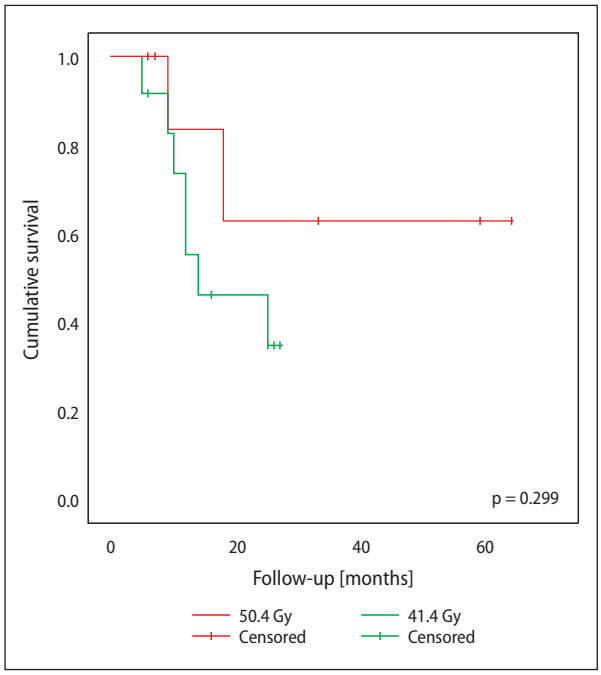

Figure 2. Kaplan-Meier curves of disease-free survival (DFS) in both groups

Table 2. Table comparing disease-free survival (DFS) at 3 time-points in both groups

Disease-free survival	41.4 Gy	50.4 Gy
3 months	83.3%	100%
6 months	83.3%	83.3%
9 months	50%	83.3%

In the later study by Chen et al. [23], more modern radiation techniques were incorporated, where one-year OS and DFS were 86.7% and 72.7%, respectively. In this case, staging procedures did not include PET-CT, unlike our study, and, therefore, are considered obsolete and could influence long-term disease results obtained.

Recently, the ARTDECO [24] study has been published, where 216 patients diagnosed with inoperable esophageal cancer were included, treated either with chemoradiotherapy at 50.4 Gy *vs.* including integrated boost technique up to 61.6 Gy on the primary tumor, both arms with chemotherapy according to the CROSS scheme. Although these are inoperable patients, the chemotherapy regimen used and the radiation dose administered in the 50.4 Gy arm is the same as that administered in the dose escalation arm in our study. The relevance of this study for our analysis lies in the similar volumes and techniques used for radiotherapy treatment, with an equal prescription dose in one of the treatment arms. As in our study, there was no significant grade IV or V toxicity found, an argument in favor of the safety of dose-escalation radiotherapy when treatment is administered with advanced techniques. There were no statistically significant differences in local control.

In this regard, there are several studies that have analyzed the impact of IMRT techniques in this type of treatments compared to the older 3D radiotherapy techniques. The phase II clinical trial by Yu et al. published in 2014 [17] demonstrated that in their 45 patients treated with chemoradiotherapy using IMRT technique and integrated boost with dose-escalation of up to 63Gy compared to conventional 3D radiotherapy, there was an adequate control of the disease without an associated increase in gastrointestinal toxicity. Similar results were published by Zhang et al. in 2018 [25], without finding differences between administering 59.4 Gy and 50.4 Gy with intensity-modulated radiation therapy or 3-dimensional conformal radiotherapy with concurrent platinum-based chemotherapy and taxanes in terms of toxicity, although there were differences in progression-free survival and local control in favor of the 59.4 Gy arm.

At the ESTRO 2021 congress the results of the multicenter phase 2/3 CONCORDE trial by Crehange et al. [26] were published. It analyzed dose-escalation radiotherapy up to 66 Gy (33 fractions) *vs.* 50G y (25 fractions) in unresectable esophageal cancers. 217 patients were included. The study results had no differences in

overall survival between both groups, although a trend towards increased overall survival with IMRT treatment was observed. In addition, there was no significant increase in chronic toxicity in the 66 Gy arm.

Observed complete pathological responses in our study were 41% compared to 29% obtained in the CROSS study [11, 12]. We could argue that IMRT and IGRT applied in our protocol, as well as radiation dose-escalation, were reasons to improve the pCR in our cohort.

Published data on neoadyuvant dose-escalation radiochemotherapy in esophageal cancer is as scarce as they only include one study published by Venkat et al. in 2017 [27], which included 113 patients diagnosed with esophageal or GEJ cancer, treated with neoadjuvant chemoradiotherapy at doses of 50.4 Gy *vs.* 56Gy using the IMRT technique. In this study, a higher proportion of complete pathological responses was observed in the group of patients treated with 56Gy (56.2% *vs.* 30%, p = 0,008), as well as an improvement in local control at 3 years (93.8% *vs.* 78.5%; p = 0.022). They found no significant differences regarding acute grade III or higher gastrointestinal toxicity between both groups. This study shares similar characteristics to our study: recruited patient-profile is similar, mostly adenocarcinomas located in the distal third or GEJ and they also use IMRT techniques for treatment delivery. By contrast, the chemotherapy scheme used was cisplatin and 5-fluorouracil that differs from the scheme used in our study (carboplatin-plaquitaxel). Complete pathological responses in this publication were similar to ours (56% in their study and 55.6% in our study) although higher total dose of radiotherapy was delivered (56 Gy instead of 50.4 Gy).

Finally, we observe a higher rate of distant relapse in the standard group of our study (60%) compared to distant relapse in the intensification group (11%). This finding was unexpected, but could be explained by the elimination of micrometastases in the intensification group. This hypothesis will, nevertheless, need to be studied in future clinical trials.

On the other hand, preliminary results of our study should be taken with caution as they have important limitations. First of all, there is a lack of randomization in the study; therefore, there could be a treatment selection bias. Second, the small number of patients included generates an important limitation in the statistical power, masking the possible differences that could exist in the results. Third, the short follow-up time with a median of 17 months prevents us from analyzing the impact of our treatment in terms of disease-free survival and chronic toxicity.

Bearing in mind these limitations, our study accounts for an homogeneous series of patients with interesting preliminary data. Our data could be used as new hypothesis generating data in the field of dose-escalation neoadyuvant radiotherapy in GEJ and distal oesophageal cancer.

Conclusion

In our study we found a trend towards a higher complete pathological response-rate and disease-free survival in the dose-escalation group compared to the control group, with no differences in gastrointestinal toxicity. Well-designed randomized and controlled trials are needed to obtain conclusive data.

Conflicts of interest

There are no conflicts of interest of any of the authors

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Authors' contribution

All authors have participated in the research and article preparation. Besides, all authors have approved the final article.

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