Radiation Oncology

RESEARCH

Open Access

Preoperative chemoradiotherapy for esophageal or gastroesophageal junction cancer: results from a retrospective study using extended CROSS regimen

Tobias Haltmeier[1], Jennifer Brazerol[2,3], Yves Borbely[1], Elena Riggenbach[2], Anna Stenger-Weisser[2,4], Burim Sermaxhaj[2,5], Martin D. Berger[3] and Hossein Hemmatazad[2*]

Abstract

Background The standard of care for locally advanced esophageal cancer includes perioperative chemotherapy or neo-adjuvant chemo-radiotherapy (CRT), followed by surgery. At our institution, a modified neo-adjuvant regimen combining elements from CROSS and CALGB 9781 trials was adopted. This study aimed to assess the impact of our modified regimen on oncological outcomes, toxicity profile and pathological complete response rates compared to the CROSS trial.

Methods This observational study included patients with esophageal cancer who underwent neo-adjuvant CRT followed by tumor resection at a tertiary care university hospital between 2014 and 2018. The modified radiation therapy consisted of 28 fractions of 1.8 Gy (50.4 Gy in total) with weekly carboplatin/paclitaxel. We assessed mortality over time using the median survival time. The impact of pathological complete response and radiation intensity on mortality was assessed in multivariable Cox regression analysis, adjusting for clinically relevant variables, including sex, age, American Society of Anesthesiologists (ASA) physical status classification system score, tumor and nodal stage, and the histological tumor type.

Results A total of 46 patients were included. Median age was 67 years (IQR 9), 36 patients (78.3%) were male. An ASA score ≥ 3 was reported in 90.7% of the patients. Among the patients, 38 (82.6%) had a clinical tumor stage (cT) of ≥ 3, and 42 (91.3%) showed a positive endo-sonographic nodal stage (uN+). Pathological complete response was found in 7/42 patients (16.7%). Median survival time was 2.7 years (95% CI 1.340–4.084). In multivariable Cox regression analysis, pathological complete response was associated with significantly lower mortality over time (OR 0.152, 95%CI 0.049–0.989, $p = 0.048$). For larger radiation volumes, a trend towards increased mortality was shown, although not statistically significant (radiation volume/100: OR 1.172, 95%CI 0.987–1.392).

Conclusions In patients with esophageal cancer undergoing trimodal therapy, the radiation dose escalation to 50.4 Gy was not associated with higher rates of pathological complete response or a survival benefit compared

*Correspondence:
Hossein Hemmatazad
hossein.hemmatazad@insel.ch

Full list of author information is available at the end of the article

to the results of the CROSS trial. However, multivariable analysis revealed a trend toward increased mortality with larger radiation volumes. Based on these results, using modern radiotherapy techniques such as online adaptive radiotherapy might be more beneficial instead of escalating the radiation dose.

Keywords Esophageal cancer, Neo-adjuvant treatment, Chemo-radiotherapy, Esophagectomy, Pathologic complete response, Survival

Introduction

Worldwide, esophageal cancer (EC) has been reported as the sixth leading cause of cancer-related mortality [1]. Both the incidence of EC and related mortality are expected to increase in the coming years [2]. Despite advances in oncological treatment, the 5-year overall survival rates for locally advanced EC remain poor [3].

Treatment for non-metastatic EC typically consists of multimodality therapy, including perioperative chemotherapy or neo-adjuvant CRT followed by surgery [2]. Neo-adjuvant therapies have the potential to improve oncological outcomes by downsizing the primary tumor and reducing the incidence of distant metastases [4]. The CROSS trial reported an increased overall survival with neo-adjuvant CRT using 41.4 Gy in 23 fractions with concurrent weekly carboplatin and paclitaxel compared to surgery alone [5]. On the other hand, the CALGB 9781 trial utilized 50.4 Gy in 28 fractions with concurrent cisplatin/5-FU and revealed a long-term survival benefit for this neo-adjuvant treatment regimen compared to surgery alone [6].

At our institution, we have adopted a neo-adjuvant treatment regimen combining elements from these two trials. Patients with esophageal or gastroesophageal junction cancer received CRT with 50.4 Gy over 5.6 weeks and weekly carboplatin/paclitaxel. We avoided using simultaneous integrated boost (SIB) for dose escalation since most studies applying the SIB concept focused on patients with inoperable EC undergoing definitive CRT. The rationale for the increased radiation dose was to account for cases initially selected for a multimodal treatment approach but later deemed inoperable due to associated side effects. The aim of the current study was, therefore, to investigate the radiation toxicity of the modified neo-adjuvant CRT and to compare its effect on clinical outcomes with the results of previous studies, namely the CROSS trial. In other words, we aimed to determine whether the extended CROSS regimen with 50.4 Gy offers comparable toxicity and either equivalent or potentially enhanced clinical efficacy compared to the standard 41.4 Gy in neo-adjuvant setting.

Materials and methods

Study design

This is a retrospective single-center study performed at a tertiary care university hospital in Switzerland. The study included patients with EC who underwent neo-adjuvant CRT followed by surgical tumor resection between 2014 and 2018. The competent ethics committee (ID 2018 – 01937) approved the study.

The aim of this study was to (1) investigate the radiation toxicity of the modified preoperative treatment regimen, as well as (2) its effect on the pathological response and overall mortality in comparison to the CROSS trial.

Patient selection and data collection

Patients with histopathologically confirmed resectable adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction (Siewert type 1 and 2) undergoing multimodal therapy were retrospectively included. The homogenous multimodal treatment consisted of neo-adjuvant CRT followed by esophagostomy. We excluded patients with distant metastases, tumors located in the cervical esophagus, or the distal gastroesophageal junction (Siewert type 3), as these cases required different treatment regimens.

We retrieved patient and tumor characteristics, along with treatment modalities, from electronic medical records. We obtained radiotherapy data from the Eclipse treatment planning system.

Staging and oncologic treatment

For initial staging and workup, patients underwent esophagogastroduodenoscopy with biopsy, contrast-enhanced computed tomography (CT), positron emission tomography (PET), and endoscopic ultrasound (EUS). Following this, a multidisciplinary gastrointestinal tumor board, including medical oncologists, radiation oncologists, pathologists, radiologists, and surgeons, reviewed all cases. A dedicated upper GI surgical team evaluated the eligibility of patients for oncological tumor resection after neo-adjuvant CRT based on clinical examinations and re-staging with EUS and CT.

Our team administered neo-adjuvant CRT using a modified CROSS protocol, which included 28 fractions of 1.8 Gy (totaling 50.4 Gy) and weekly chemotherapy with carboplatin (AUC 2) and paclitaxel (50 mg per square meter of body surface area). For all patients, we used volumetric modulated arc therapy for radiotherapy application. The team defined target delineation for the primary tumor, positive lymph nodes, and elective volumes according to international contouring guidelines [7]. Four to six weeks after completing preoperative treatment, the team performed re-staging using

esophagogastroduodenoscopy and PET/CT scans. If no signs of distant metastasis appeared, the patients proceeded to surgical tumor resection.

Radiotherapy parameters

We evaluated radiation-induced toxicity using the following parameters: the whole radiation volume in cubic centimeters (cc), the mean radiation dose to the heart and lungs in Gray, and the lung volumes receiving 10 Gy (V10Gy), 20 Gy (V20Gy), and 30 Gy (V30Gy).

Statistical analysis

Normality of distribution was assessed using histograms, skewness, and the Shapiro-Wilk test. Categorical variables were reported as numbers and percentages, continuous variables as medians and interquartile ranges (IQR).

Survival over time, as well as survival in patients with or without histopathological complete response was plotted using Kaplan-Meier curves. To visualize the effect of the radiation volume on survival over time, the volume was dichotomized at the median. Survival over time was then plotted for patients with a radiation smaller or greater than the median radiation volume.

The effect of the radiation dose and pathological complete response on mortality over time was assessed in univariable and multivariable Cox regression analysis. Variables that were significantly associated with mortality in univariable analysis were further assessed in multivariable analysis. In multivariable analysis, the effect of the radiation dose and pathological complete response and was adjusted for clinically important variables, including sex, age, ASA physical status classification system score, tumor and nodal stage, as well as the histological tumor type. Collinearity between the covariates of the regression model was assessed using the variance inflation factor (VIF). A VIF < 5 was assumed to exclude significant collinearity.

P-values of 0.05 or less were considered statistically significant. Analysis was performed using SPSS Statistics (IBM Corporation, Armonk, NY, USA) and STATA (StataCorp, College Station, TX) software.

Results

Patient characteristics

A total of 46 patients with EC undergoing multimodal therapy were included in the current study. The majority of included patients were male ($n = 36$, 78.3%) and of older age (median age 67.0 years, IQR 9.0). Median BMI was 25.5 kg/m2 (IQR 4.7) and pretreatment median weight loss 2.0 kg (IQR 7.0). Comorbid conditions were frequent with an ASA score ≥ 3 in 74.4% of the patients (Table 1).

Table 1 Patient and tumor characteristics

	N **= 46**		***N*** **= 46**
Male sex	36 (78.3)	Endosonographic nodal stage	
Age (years) [a]	67.0 (9.0)[a]	uN0	4 (8.7)
Body mass index (kg/m^2) [a]	25.5 (4.7)[a]	uN1	22 (47.8)
Weight loss (kg) [a]	2.0 (7.0)	uN2	14 (30.4)
ASA score		uN3	6 (13.0)
2	7/43 (16.3)	Clinical metastatic stage (cM)	
3	32/43 (74.4)	M0	46 (100.0)
4	3/43 (7.0)	Histopathological tumor stage	
Cardiac disease	27 (58.7)	ypT0	8/42 (17.4)
Pulmonary disease	8 (17.4)	ypT 1	6/42 (13.0)
Diabetes	10 (21.7)	ypT 2	8/42 (17.4)
Liver disease	7 (15.2)	ypT 3	19/42 (41.3)
Adenocarcinoma	39 (84.8)	ypT 4	2/42 (2.2)
Squamous cell carcinoma	7 (15.2)	Histopathological nodal stage	
Endosonographic tumor stage		ypN0	25 (59.5)
uT1	3/40 (7.5)	ypN 1	6 (14.3)
uT2	4/40 (10.0)	ypN 2	10 (23.8)
uT3	30/40 (75.0)	ypN 3	1 (2.4)
uT4	3/40 (7.5)	Number of resected lymph nodes	30.0 (14.0)[a]
Clinical tumor stage		Percentage of positive lymph nodes	8.6 (6.5)[a]
cT1	4 (8.7)	Pathological complete response	7/42 (16.7)
cT2	4 (8.7)		
cT3	35 (76.1)		
cT4	3 (6.5)		

Values are numbers, unless indicated otherwise. [a]Median (interquartile range)

ASA: American Society of Anesthesiology

Tumor characteristics

Tumor characteristics are outlined in Table 1. Thirty-nine patients (84.8%) suffered from adenocarcinoma, while 7 patients (15.2%) had squamous cell carcinoma. A clinical tumor stage (cT) ≥ 3 was found in 38 patients (86.2%). Endosonographically, nodal positive disease (uN+) was detected in 42 patients (91.3%). On histopathological examination, viable tumor cells (ypT1-4) were found in 34 of 42 patients (81.0%). Twenty-one patients (45.7%) had histopathologically confirmed nodal tumor metastasis (ypN1-3). The median number of resected lymph nodes was 30.0 (IQR 14.0). Pathological complete response was found in 7 patients (16.7%).

Radiation

The median radiation volume was 786.5 cc (IQR 423). The median heart and lung dose was 23.0 Gy (IQR 5.0) and 10.0 Gy (IQR 6.0), respectively. The median lung V10 Gy, V20 Gy and V30 Gy were 46.0% (IRQ 33.0), 12.0% (IQR 0.0), and 3.5% (IQR 2.0), respectively.

Survival

Following a standardized follow-up protocol, we scheduled patient visits every 3 months during the first year after therapy, every 6 months in the second year, and annually from the third year onward. Each visit included clinical examination and CT scan. Patients underwent esophagogastroduodenoscopy if they experienced dysphagia, odynophagia, or if imaging modalities indicated a suspicious tumor. Median follow-up was 2.653 years (4.045). Overall survival over time is shown in Fig. 1. Median survival time was 2.712 years (95% CI 1.340–4.084).

In univariable analysis, higher radiation volumes were associated with significantly higher mortality over time (OR 1.184, 95% CI 1.070–1.311, $p = 0.001$), whereas pathological complete response was associated with significantly lower mortality over time (OR 0.221, 95% CI 0.049–0.989, $p = 0.048$). The mean heart and lung dose, as well as the lung V10 Gy, V20 Gy und V30 Gy were not significantly associated with mortality in univariable analysis.

Multivariable analysis, adjusting for sex and age, together with the ASA score, clinical tumor stage, endosonographic nodal stage, and histological tumor type, revealed histopathological complete response as an independent predictor for lower mortality over time (OR 0.152, 95% CI 0.020–1.155, $p = 0.017$). For the radiation volume, a trend towards higher mortality in association with higher radiation volumes was visible, although not statistically significant (OR 1.172, 95% CI 0.987–1.392, $p = 0.071$) (Table 2; Figs. 2 and 3). No significant collinearity was detected between the covariates of the regression analysis. The VIF was smaller than 1.508 for all variables included in regression analysis.

Discussion

The current study investigated a modified neo-adjuvant CRT approach in patients with resectable esophageal cancer, using 28 fractions of 1.8 Gy (50.4 Gy in total) with weekly carboplatin/paclitaxel. The median survival time was 2.7 years. In addition to following our institutional protocols that favor extending fractions over the

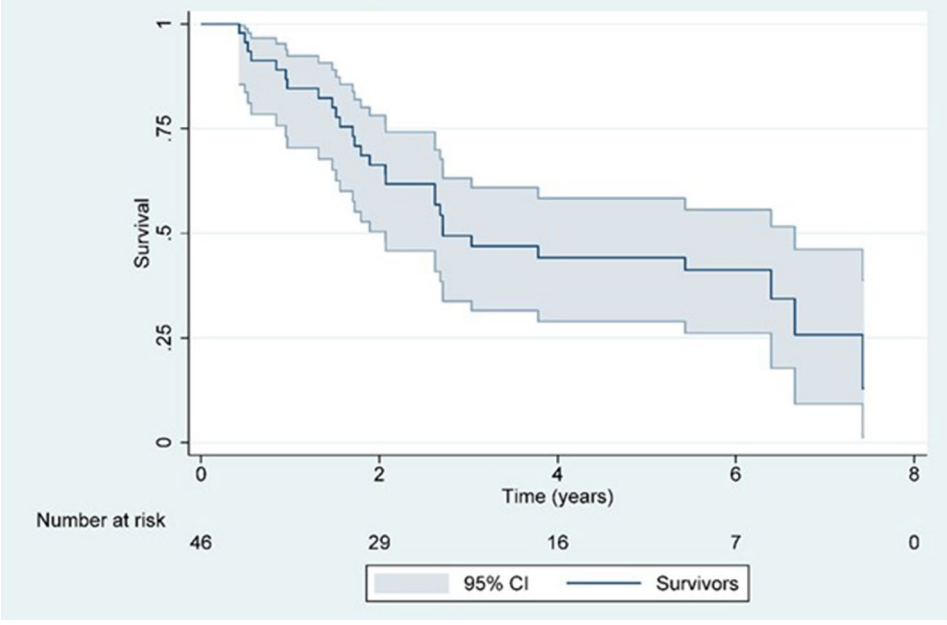

Fig. 1 Overall survival estimate

Table 2 Effect of pathological response and radiation on mortality over time

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Path. complete response	0.221	0.049–0.989	0.048	0.152	0.020–1.155	0.017
Radiation volume (cc/100)[a]	1.184	1.070–1.311	0.001	1.172	0.987–1.392	0.071
Mean heart dose (Gy)	1.073	0.974–1.181	0.153			
Mean lung dose (Gy)	1.014	0.906–1.135	0.805			
LV10 (%)[b]	1.002	0.983–1.021	0.858			
LV20 (%)[b]	1.010	0.936–1.090	0.800			
LV30 (%)[b]	1.068	0.870–1.312	0.527			

Uni- and multivariable Cox regression analysis

Multivariable analysis: Effect of radiation volume and pathological complete response adjusted for sex, age, ASA score, cT and uN stage, and histological tumor type

[a]For ease of interpretation, the radiation volume was divided by 100

[b]LV10/20/30: Lung volume receiving > 10 Gy, 20 Gy, or 30 Gy

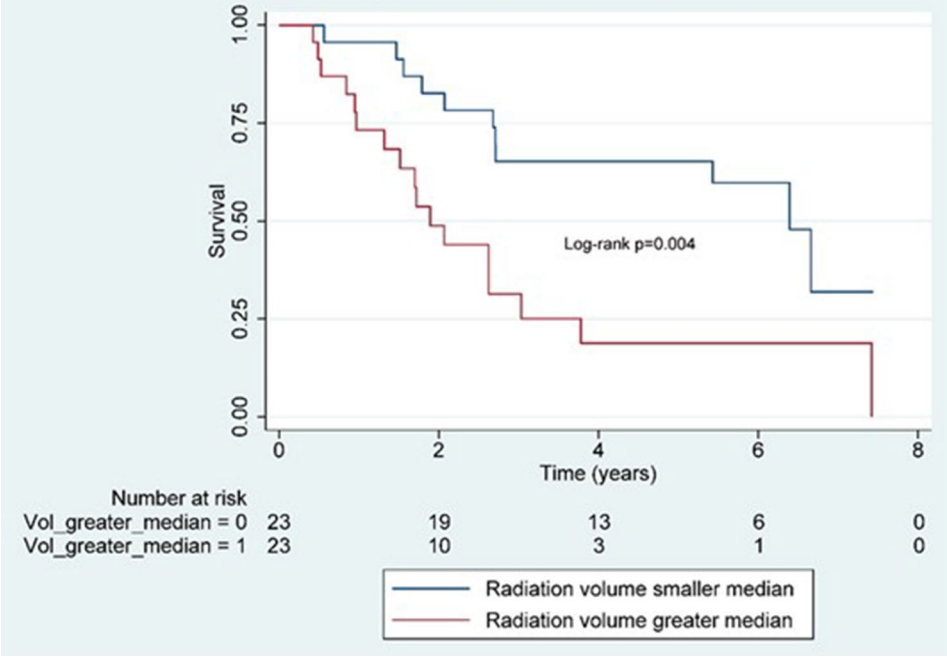

Fig. 2 Survival estimates for radiation volume

SIB concept, most studies applying SIB in this context have used higher doses than 50.4 Gy [8]. Moreover, more data exist on using the SIB concept for esophageal SCC as part of definitive CRT [9, 10]. We deliberately avoided applying a boost, as our goal was to compare our results primarily with data from the CROSS trial, which also did not employ the SIB technique. Pathological complete response was found in 16.7% of the patients. Multivariable Cox regression analysis identified pathologic complete response as an independent predictor for lower overall mortality over time.

For the radiation volume, a trend towards higher mortality over time was observed, although not statistically significant. In univariable analysis, higher radiation volumes were associated with significantly higher mortality over time, whereas in multivariable analysis, a trend towards higher mortality was visible (Table 1; Fig. 2). The trend, but not statistically significant association between the radiation volume and mortality in multivariable analysis may be explained by the relatively small sample size. These results must be interpreted with care, as higher radiation volumes are required for larger tumors and pathological lymph nodes. It is therefore important to note that in the current analysis, the effect of radiation volume was adjusted for the tumor and nodal stage. Although in the current study with a small number of cases the radiation volume was not significantly associated with mortality in multivariable analysis, it seems reasonable to keep the radiation volume as limited as possible. Decreasing the size of irradiated volume could not only be beneficial in terms of better survival, but also may reduce radiation toxicity to adjacent

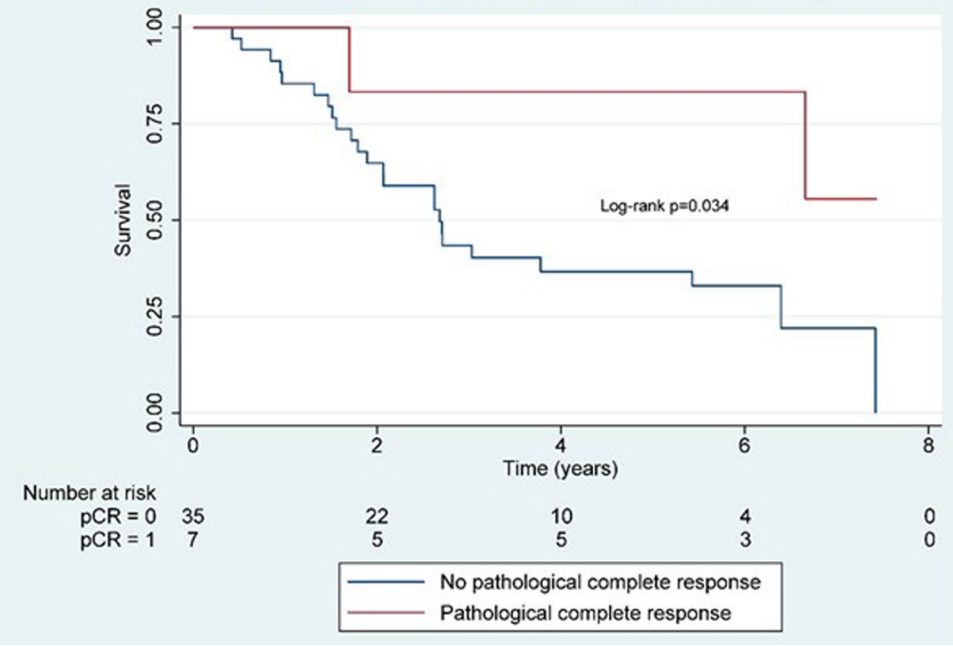

Fig. 3 Survival estimates for pathological complete response

organs, namely heart and lungs. According to the literature, radiation-induced toxicity following radiotherapy for esophageal cancer may lead to pulmonary and cardiac complications with a corresponding increase in mortality [11–14]. Modern radiation techniques that limit the irradiation volume are therefore highly desirable. Online adaptive radiotherapy may be an option for radiotherapy in patients with esophageal cancer. This technique allows for daily re-planning of radiotherapy, offering the potential to reduce radiation exposure to adjacent organs while ensuring better coverage of the target volumes [15]. Our group recently demonstrated the feasibility of online adaptive radiotherapy in patients with locally advanced esophageal adenocarcinoma [16]. However, the current study excludes patients treated with online adaptive therapy, as our clinic only started implementing this technique in 2021.

The CROSS trial compared preoperative CRT with 41.4 Gy in 23 fractions and weekly carboplatin/paclitaxel, followed by surgery, to surgery alone in patients with esophageal or junctional cancer [5]. In the NA treatment group, the rate of pathologic complete response was 29% and the median 5-year overall survival 4.1 years. Thus, both the rate of pathologic complete response and median overall survival were lower in the current study compared to the CROSS trial. However, when comparing these results, the different patient and tumor characteristics in the current study and the CROSS trial must be taken into account. Patients in the NA treatment arm of the CROSS trial were younger (median 60 vs. 67 years) and suffered less frequently from adenocarcinoma (75% vs. 86%). Furthermore, no patients with a clinical tumor stage four (cT4) were included in the NA treatment arm, whereas in the current study, a cT4 stage was detected in 6.5% of the patients. Regarding the histologic subtype, radio-sensitivity and the complete response rate to neo-adjuvant CRT has been reported to be lower in adenocarcinoma than squamous cell carcinoma of the esophagus [17, 18]. Considering the higher age, more advanced tumor stage, and higher rate of adenocarcinoma in the current study compared to the CROSS trial, the difference in pathologic complete response and median overall survival time may have been less pronounced, if these patients and tumor characteristic had been balanced in the two cohorts. Recently, Van Laarhoven et al. reported real-world outcomes of the CROSS regimen in neo-adjuvant setting for EC [19]. They reported the median OS of 33.7 months with a 3-year OS rate of 48.1%. Furthermore, 20.5% of patients in real-world analysis achieved pCR; this aligns closely to our data with pCR rate of 17%.

In the current study, the radiation dose escalation to 50.4 Gy did not lead to better outcomes compared to the current standard of care for neo-adjuvant CRT, i.e. the CROSS regimen. In a post-hoc analysis of data from the CROSS trial it has been shown, that only 5% of recurrences occurred within the radiation field [20]. A retrospective cohort study including patients with esophageal cancer undergoing neo-adjuvant CRT followed by esophagectomy revealed that recurrent disease most frequently occurred distantly with dismal prognosis. Post-recurrence survival was superior for patients with loco-regional compared to distant and combined

locoregional and distant recurrence [21]. These results support the use of preoperative CRT to reduce the risk of loco-regional treatment failure. However, increasing the radiation dose beyond 41.4 Gy may have a minimal effect on loco-regional recurrence.

Multivariable analysis revealed pathologic complete response as an independent predictor for lower mortality over time (Table 2; Fig. 3). This is in line with the findings of previous studies that reported significantly higher rates of overall and disease-free survival, as well as lower recurrence rates in patients with pathologic complete response after NA therapy and surgical tumor resection [22–24].

Aside from the usual restrictions of a retrospective analysis, the current study has a number of limitations. First, radiation therapy was performed at the same tertiary care university hospital in all patients included. However, surgical tumor resection and the oncologic follow-up were also performed in other hospitals. Thus, a more extensive data collection regarding long-term outcomes was not feasible in the scope of this retrospective study. Furthermore, the treatment at other institutions has led to missing data for some variables, as outlined in Table 1. Second, different surgical techniques for oncologic tumor resection may have been applied but were not accounted for in multivariable analysis. Third, the number of covariates in the regression models was relatively high compared to the number of patients included, which may have led to overfitting of the model. Fourth, the number of patients included in the current analysis is relatively small, limiting generalizability of the results.

Conclusion

In conclusion, in patients with resectable esophageal cancer undergoing trimodal therapy, radiation therapy dose escalation (50.4 Gy in total) was not associated with a higher rate of pathological complete response or a survival benefit compared to the results of the CROSS trial. However, multivariable analysis revealed a trend towards increased mortality in association with higher radiation volumes. Based on these results, utilizing modern radiotherapy techniques, such as online adaptive radiotherapy that accounts for anatomical and tumoral changes, may be more advantageous than merely escalating the radiation dose.

Abbreviations

EC	Esophageal Cancer
CRT	Chemo-Radiotherapy
CT	Computer Tomography
PET	Positron Emission Tomography
EUS	Endoscopic UltraSound
Gy	Gray
AC	Adenocarcinoma
SCC	Squamous Cell Carcinoma
SIB	Simultaneous Integrated Boost

Acknowledgements

Not applicable.

Author contributions

T. H.: literature review, study design, data management, statistical analysis, data interpretation, drafting of articleJ. B.: literature review, data collection, data management, drafting of articleY. B.: Critical revision of articleE. R.: Data collection (A) S.: Data collectionB. S.: Data Collection M. (B): Study design, supervision, critical revision of articleH. H.: literature review, study design, data management, drafting of article, supervision.

Funding

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical committee in canton Bern has reviewed and approved this study protocol (approval number: 2018 – 01937). We obtained the written informed consent from all participants in this study.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[2]Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[3]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[4]Department of Radiation Oncology , Kantonsspital Luzern, Lucerne , Switzerland
[5]Department of Radiation Oncology , Stadtspital Zürich, Zurich , Switzerland

Received: 28 January 2025 / Accepted: 9 April 2025
Published online: 08 May 2025

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Morgan E, Soerjomataram I, Rumgay H, Coleman HG, Thrift AP, Vignat J et al. The Global Landscape of Esophageal Squamous Cell Carcinoma and Esophageal Adenocarcinoma Incidence and Mortality in 2020 and Projections to 2040: New Estimates From GLOBOCAN 2020. Gastroenterology [Internet]. 2022;163(3):649–658.e2. Available from: https://doi.org/10.1053/j.gastro.2022.05.054
3. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.
4. Lewis S, Lukovic J. Neoadjuvant Therapy in Esophageal Cancer. Thorac Surg Clin [Internet]. 2022;32(4):447–56. Available from: https://doi.org/10.1016/j.thorsurg.2022.06.003
5. van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, Henegouwen MI, van Wijnhoven B. Preoperative chemoradiotherapy for esophageal or junctional Cancer. N Engl J Med. 2012;366(22):2074–84.
6. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R et al. J OURNAL OF C LINICAL O NCOLOGY Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB 9781. 2016;26(7).
7. Wu AJ, Bosch WR, Chang DT, Hong TS, Jabbour SK, Kleinberg LR et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and. Gastroesophageal Junction Cancer. 2015;92(4).

8. Zeng M, Fernando NA, Taral P, Knapp M, Zhu XQ, Chen XL, et al. Intensity modulated radiation therapy with simultaneous integrated boost based dose escalation on neoadjuvant chemoradiation therapy for locally advanced distal esophageal adenocarcinoma. World J Gastrointest Oncol. 2016;8(5):474–80.
9. Welsh JW, Seyedin SN, Allen PK, Hofstetter WL, Ajani JA, Chang JY et al. Local Control and Toxicity of a Simultaneous Integrated Boost for Dose Escalation in Locally Advanced Esophageal Cancer: Interim Results from a Prospective Phase I/II Trial. J Thorac Oncol [Internet]. 2017;12(2):375–82. Available from: https://doi.org/10.1016/j.jtho.2016.10.013
10. Ristau J, Thiel M, Katayama S, Schlampp I, Lang K, Häfner MF et al. Simultaneous integrated boost concepts in definitive radiation therapy for esophageal cancer: outcomes and toxicity. Radiat Oncol [Internet]. 2021;16(1):1–9. Available from: https://doi.org/10.1186/s13014-021-01749-x
11. Frandsen J, Boothe D, Gaffney DK, Wilson BD, Lloyd S. Increased risk of death due to heart disease after radiotherapy for esophageal cancer. 2015;6(5):516–23.
12. Kowalchuk RO, Spears GM, Morris LK, Owen D, Yoon HH, Jethwa K, et al. Risk stratification of postoperative cardiopulmonary toxicity after trimodality therapy for esophageal cancer. Front Oncol. 2023;13(February):1–8.
13. Witt JS, Jagodinsky JC, Liu Y, Yadav P, Kuczmarska-haas A, Yu M et al. Cardiac toxicity in operable esophageal Cancer patients treated with or without chemoradiation. 2019;42(8):662–7.
14. Xu C, Guo L, Liao Z, Wang Y, Liu X, Zhao S et al. Heart and lung doses are independent predictors of overall survival in esophageal cancer after chemoradiotherapy. Clin Transl Radiat Oncol [Internet]. 2019;17:17–23. Available from: https://doi.org/10.1016/j.ctro.2019.04.016
15. Lim-reinders S, Keller BM, Al-ward S, Sahgal A, Kim A. Online Adaptive Radiation Therapy. Radiat Oncol Biol [Internet]. 2017;99(4):994–1003. Available from: https://doi.org/10.1016/j.ijrobp.2017.04.023
16. Bachmann N, Schmidhalter D, Corminboeuf F, Berger MD, Borbély Y, Ermiş E et al. Cone beam computed Tomography-Based online adaptive radiation therapy of esophageal cancer: first clinical experience and dosimetric benefits. Adv Radiat Oncol. 2025;10(1).
17. Tougeron D, Richer JP, Silvain C. Management of esophageal adenocarcinoma. J Visc Surg [Internet]. 2011;148(3):e161–70. Available from: https://doi.org/10.1016/j.jviscsurg.2011.05.008
18. Cools-Lartigue J, Ferri L. Should Multidisciplinary Treatment Differ for Esophageal Adenocarcinoma Versus Esophageal Squamous Cell Cancer? Ann Surg Oncol [Internet]. 2019;26(4):1014–27. Available from: https://doi.org/10.1245/s10434-019-07162-9
19. van Laarhoven H, Verhoeven R, van Berge Henegouwen M, Mohammad NH, van Hillegersberg R, Slingerland M et al. Real-world outcomes of the CROSS regimen in patients with resectable esophageal or gastro-esophageal junction adenocarcinoma: a nationwide cohort study in the Netherlands. eClinicalMedicine [Internet]. 2025;80:103067. Available from: https://doi.org/10.1016/j.eclinm.2024.103067
20. Oppedijk V, Van Der Gaast A, Van Lanschot JJB, Van Hagen P, Van Os R, Van Rij CM, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014;32(5):385–91.
21. Schuring N, Stam WT, Plat VD, Kalff MC, Hulshof MCCM, van Laarhoven HWM et al. Patterns of recurrent disease after neoadjuvant chemoradiotherapy and esophageal cancer surgery with curative intent in a tertiary referral center. Eur J Surg Oncol [Internet]. 2023;49(10):106947. Available from: https://doi.org/10.1016/j.ejso.2023.05.022
22. Blum Murphy M, Xiao L, Patel VR, Maru DM, Correa AM, Amlashi G. Pathological complete response in patients with esophageal cancer after the trimodality approach: the association with baseline variables and survival—The university of Texas MD Anderson Cancer center experience. Cancer. 2017;123(21):4106–13.
23. Hipp J, Kuvendjiska J, Hillebrecht HC, Herrmann S, Timme-Bronsert S, Fichtner-Feigl S et al. Oncological recurrence following pathological complete response after neoadjuvant treatment in patients with esophageal cancer — a retrospective cohort study. Langenbeck's Arch Surg [Internet]. 2023;408(1):1–10. Available from: https://doi.org/10.1007/s00423-023-03100-2
24. Soror T, Kho G, Zhao K, Le, Ismail M, Badakhshi H. Impact of pathological complete response following neoadjuvant chemoradiotherapy in esophageal cancer. J Thorac Dis. 2018;10(7):4069–76.

Publisher's note