Optimal radiation dosing in concurrent neoadjuvant chemoradiation for resectable esophageal cancer: a meta-analysis

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Background: This is the first meta-analysis to study optimal radiation dose in the setting of concurrent neoadjuvant chemoradiotherapy (cnCRT) for esophageal cancer (EC). We sought to compare outcomes between high dose radiotherapy (HDRT) [>48.85 Gy biologically effective dose (BED)] group and low dose radiotherapy (LDRT) (≤48.85 Gy BED) for patients with EC receiving cnCRT.

Methods: Medline, Embase, and Cochrane databases were searched independently by two members of our team on August 07, 2017. Articles were screened using Covidence. Study quality was assessed via CONSORT. Eligible studies had to be randomized controlled trials (RCT) comparing cnCRT *vs.* surgery alone in full-text English. Those with induction or sequential chemoradiotherapy were excluded. We captured data points including radiation dose, hazard ratios (HRs) for overall survival (OS), and treatment-related mortality (TRM). We analyzed HRs for OS and risk ratio (RR) for TRM and corresponding 95% confidence interval (CI) as the summary statistic. We used both fixed- and random-effects models in the presence of heterogeneity. The primary outcome was OS; secondary endpoint was treatment related mortality (TRM). We compared outcomes by HDRT *vs.* LDRT. To minimize chemotherapy heterogeneity, we performed a pre-planned analysis excluding the CROSS trial.

Results: The eleven included studies contained a total of 1,697 patients. Eight hundred forty-eight were randomized into the cnCRT. Of these 848 patients, 287 received HDRT and 561 received LDRT. HR for OS was not statistically different between LDRT (HR 0.67; 95% CI, 0.55–0.8) and HDRT (HR 0.68; 95% CI, 0.45–0.91). Excluding the CROSS trial, there was still no difference in outcomes between LDRT and HDRT. TRM was similar between LDRT and HDRT.

Conclusions: With no difference in OS or TRM between LDRT and HDRT, 48.85 Gy BED cnCRT may be a sufficient radiation dose for cnCRT for patients with EC fit for surgery.

Keywords: Esophageal; carcinoma; neoadjuvant; chemoradiation

Introduction

Esophageal cancer (EC) is the eighth most prevalent cancer worldwide, and the sixth leading cause of cancer death (1). Historically, patients diagnosed with EC were treated with surgery alone but survival outcomes rarely exceeded 20% (2). In an attempt to improve outcomes, researchers in the 1980s began introducing chemotherapy, radiation, or both in addition to resection for locally advanced EC. Adjuvant chemotherapy (3), radiotherapy (4), and chemoradiotherapy (5) strategies were abandoned after poor trial outcomes. Most recent trials have focused on neoadjuvant treatment intensification, with studies comparing neoadjuvant chemotherapy (nCT) and surgery (6), neoadjuvant chemoradiotherapy (nCRT) and surgery (6-21), nCRT and nCT (6,18,22,23), and even nCRT and definitive chemoradiotherapy (24).

The recently updated CROSS trial data (20) provides the strongest evidence for cnCRT over surgery as well as the best outcomes of any treatment for locally advanced EC in a large randomized study. In this trial, patients received neoadjuvant carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions) or surgery alone. Median overall survival (OS) was 48.6 months in the nCRT arm compared to 24 months with surgery alone. Several meta-analysis have confirmed improved survival with nCRT compared to surgery (25-30). Greer et al. (31) was the only negative meta-analysis, but even this study showed a trend for increased survival in patients who received nCRT. Five meta-analyses (25,27-29,32) showed increased survival in nCRT compared to nCT. Therefore, nCRT has become the standard of care as evidenced by its utilization in current trials, including both arms of the PROTECT-1402 trial (33) and on one arm of the Neo-AEGIS trial (34).

Nearly all published meta-analyses (25-29,31,32) contained heterogeneous studies with nCRT that included induction chemotherapy (22,23,35) and sequential chemoradiotherapy (6,8,10). Liu et al. (30) was the sole study to include only concurrent nCRT (cnCRT) trials, albeit including retrospective data. However, the optimal radiation dose which should be used in the setting of cnCRT has not been clearly established. Prescribed doses have ranged from 30 Gy (22) to as high as 50.4 Gy (14). To our knowledge this is the first meta-analysis evaluating outcomes by radiation dose in the setting of prospective RCT using cnCRT for resectable EC. The primary outcome of our study was OS, and the secondary outcome was treatment-related mortality (TRM). We hypothesized that LDRT would have similar OS and TRM to HDRT.

Methods

In this meta-analysis, we sought to compare survival in patients with resectable EC based on radiation dose received as part of a cnCRT protocol, we first conducted a systematic review of current literature and selected studies to be included in our analysis based on a set of eligibility criteria. To be eligible, reviewed studies had to be randomized controlled trials (RCT) which compared cnCRT followed by surgery vs. surgery alone in the initial treatment of esophageal or gastro-esophageal junction carcinomas. Studies were only included if the protocol offered cnCRT in one treatment arm; trials which utilized a sequential chemotherapy and radiotherapy or induction chemotherapy were excluded. Only full-text articles published in English were included in the final analysis. Studies were not excluded on the basis of histology (squamous cell vs. adenocarcinoma) or chemotherapy agents used. Studies were excluded if gastro-esophageal junction (GEJ) was the only sub-site treated in the trial. If the study combined cancers of the GEJ along with cancers of the esophagus proper, then they were included in our analysis.

For our initial literature search, we utilized three databases: Medline, Embase, and the Cochrane clinical trials database. The searches were conducted independently by two members of the research team on August 07, 2017. Studies since 1994 were included. Search strategy began with two broad searches. The first search, using the search terms "('esophageal' OR 'esophagus' OR 'gastroesophageal') AND ('neoplasm,' OR 'carcinoma,' OR 'cancer')" yielded 96,536 citations. The second search, using the terms "'chemotherapy,' OR 'radiotherapy,' OR 'chemoradiotherapy,' OR 'combined modality therapy'" yielded 166,068 citations. In addition, members of the team manually reviewed reference lists of other meta-analyses; this identified 39 potential studies which were then entered into the final review process.

The citations from the online searches and the manual review were combined to form a common pool of 262,643 citations. These results were subsequently refined to exclude any citation that was redundant, not a RCT or not a full-length article. Refinement yielded 572 citations, which underwent subsequent abstract and full-text screening. During this review process, articles were individually selected for inclusion or exclusion based on the criteria described above; eleven studies were included in the
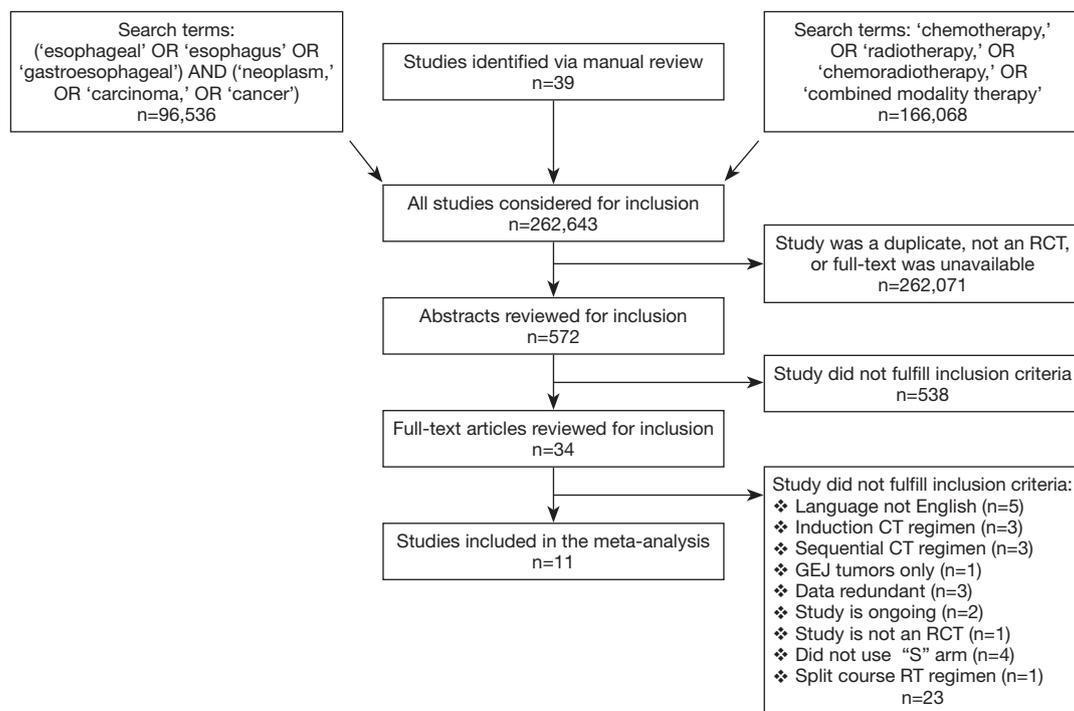
Figure 1 PRISMA flow diagram.

final analysis. The literature review process is summarized in the PRISMA flow diagram in *Figure 1*.

Articles were screened using Covidence, a web-based platform made for improving healthcare evidence synthesis. Two authors performed both an abstract screening and a subsequent full-text screening to evaluate studies for inclusion into our meta-analysis. Any disagreements regarding abstract or full-text screens were settled by a senior researcher on the team. Study quality was assessed via the CONSORT checklist. We captured data points including follow-up time, radiation dose, OS, stage, performance score (PS), sex, and TRM. Age and comorbidities were not included due to heterogeneity in the reporting.

Radiation doses were converted to biologically effective dose (BED) to make comparisons across fractionation schemes. Forty-eight point eighty-five Gy BED was selected as a cutoff as this is the BED of 41.4 Gy in 23 fractions as delivered in the CROSS trial (20). BED >48.85 Gy was considered high dose radiotherapy (HDRT) and BED ≤48.85 Gy was low dose radiotherapy (LDRT).

Statistics

We used reported hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI) for comparing OS between cnCRT and surgery alone. Standard error (SE) of HR was calculated from 95% CI. When these two quantities were not reported, we calculated HR and corresponding SE based on either reported Kaplan-Meier plot or using the methods of Parmar and Tierney. TRM was analyzed by the risk ratio (RR) and corresponding 95% CI. For the meta-analysis, we used random-effects models based on the DerSimonian and Laird method. Study heterogeneity due to study characteristics between studies was examined by using meta-regression analysis. We conducted meta-regression with publication year, the percentage of female, the percentage of stage III or higher, the percentage of performance status 1, radiation dose, and median follow-up. Statistical heterogeneity across studies was quantified using the Cochran Q statistic and I^2 statistic. A pre-planned subgroup analyses was performed for OS excluding the CROSS trial (20) to account for heterogeneity in chemotherapy. All P values of <0.05 (two-tailed) were considered statistically significant. Consort scores for dose groups were compared using Mann-Whitney test. We selected studies which scores were equal to or higher than median (27) and compared scores by dose groups using Mann-Whitney test as well.

All statistical analyses were performed using Stata 13 (StataCorp LP, College Station, TX, USA) and RStudio (RStudio, Inc. Boston, MA, USA).

Results

Eleven studies met our inclusion criteria and were entered in the final analysis. Our analysis included one study (15) which did not populate in our initial database search but was identified via manual reference review. One study identified via database search was part of the author's thesis statement (12), but the full text was not available. Attempts were made to contact the author; however, no response was received. Therefore, the study was not included in the final analysis.

Studies that passed abstract review but not full-text review were not included for the following reasons. Five of the studies were published in a language other than English (36-40); three studies, utilized induction chemotherapy (22,23,35); three studies utilized sequential instead of concurrent CRT (6,8,10); one study looked solely at carcinomas of the GEJ (41); three of the studies featured redundant data (21,42,43); two of the studies remained ongoing (33,34); one of the studies was not an RCT (44); four of the studies did not utilize a "surgery alone" arm (45-48); one study utilized a split course, sequential radiation protocol and did not compare with a "surgery alone" arm (24).

The eleven included studies contained a total of 1,697 patients, 848 randomized to cnCRT and 849 to surgery alone. Of the 848 patients randomized into the cnCRT group, 287 received HDRT and 561 received LDRT. Further details, including radiotherapy and chemotherapy schedules pertaining to each individual study, can be found in *Table 1*.

OS was not statistically different between LDRT (HR 0.67; 95% CI, 0.55–0.8) and HDRT (HR 0.68; 95% CI, 0.45–0.91). OS was improved with cnCRT compared to surgery alone (HR 0.67; 95% CI, 0.55–0.79). There was no significant heterogeneity among studies (P=0.10, Q=16, I^2=42.4%). The forest plot for HR of death may be seen in *Figure 2*. A meta-regression was performed to assess whether certain variables may have affected the OS outcomes. All variables studied were non-significant, including median follow-up (P=0.8206), stage III or IV (P=0.5284), female sex (P=0.5968), performance status 1 (P=0.7165), radiation dose in BED (P=0.4840), total sample size (P=0.7434), or year of publication (P=0.9979).

OS outcomes were re-analyzed excluding the CROSS (20) trial to minimize chemotherapy heterogeneity. Still, there was no significant difference between LDRT (HR 0.67; 95% CI, 0.49–0.86) and HDRT (HR 0.68; 95% CI, 0.45–0.91).

TRM was not statistically different between cnCRT and surgery alone (RR 2.97; 95% CI, 0.83–10.64). There was no significant heterogeneity (P=0.90, Q=4.87, I^2=0%) among studies. In the cnCRT group, there was no statistical difference in TRM between LDRT (RR 1.2; 95% CI, 0.66–2.16) and HDRT (HR 1.77; 95% CI, 0.83–3.77).

For both OS and TRM outcomes, there was no obvious publication bias among studies included in our analysis. The funnel plot for cnCRT *vs.* surgery alone showed a symmetrical distribution pattern, as seen in *Figure 3*.

The overall study quality was assessed by the CONSORT checklist. This showed that most of the studies were of relatively good quality with a median score of 27 and a range of 14–34. There was no statistical difference between the CONSORT scores of LDRT and HDRT (P=0.3142). Stratified analysis of higher quality studies demonstrated the same trend seen in the overall analysis denoting that lesser quality studies did not skew the overall analysis results (P=0.1002).

Discussion

The results of this meta-analysis showed that LDRT (≤48.85 BED) has similar OS and TRM outcomes as HDRT (>48.85 BED) when used as cnCRT in resectable EC.

Multiple previous meta-analyses demonstrated a survival benefit of nCRT when compared to surgery alone (25-30). Only one meta-analysis showed no statistically significant survival advantage for nCRT, but there was a trend towards increased survival compared to surgery (31). Our results fall in line with published literature and showed a statistically significant decreased hazard for death with cnCRT.

The CROSS trial (20) provided the most robust data regarding cnCRT in the treatment of locally advanced EC. This study accrued a large number of patients, 366, along with a long-term follow-up time of 84.4 months. Patients with T2-3N0-1M0 EC received neoadjuvant carboplatin and placlitaxel for five cycles with concurrent radiotherapy of 41.4 Gy in 23 fractions before surgery or surgery alone. Compared to surgery alone, cnCRT increased R0 resections from 69% to 92% (P<0.001), decreased positive pathological nodes from 75% to 31% (P<0.001), and resulted in a complete pathologic response (pCR) rate of 29% (42). Median OS was 48.6 months in the nCRT arm compared to 24 months with S (20). Only Natsugoe

Table 1 Characteristics of included studies

Author	Year started	Year of publication	Radiotherapy schedule	Biological effective dose (Gy)	Chemotherapy schedule	Tumor histology	Tumor location	Sample size	Median follow-up (months)	CONSORT checklist rating
Apinop	1986	1994	40 Gy in 20 fractions over 4 weeks	48	Two cycles cisplatin 100 mg/m² days 1 and 29; fluorouracil 1,000 mg/m² days 1–4, 29–32	SCC	Middle and lower third + GEJ	69	12	14
Walsh	1990	1996	40 Gy in 15 fractions over 3 weeks	58.5	Two cycles cisplatin 75 mg/m² days 7, 42; fluorouracil 15 mg/kg days 1–5, 36–40	Adenocarcinoma	Esophagus excluding cervical esophagus	113	10	24
Urba	1989	2001	45 Gy in 30 fractions over 3 weeks	51.75	Two cycles cisplatin 20 mg/m² days 1–5, 17–21; fluorouracil 300 mg/m² days 1–21, vinblastine 1 mg/m² days 1–4, 17–20	Adeno + SCC + mixed	Esophagus + GEJ	100	98	27
Lee	1999	2004	45.6 Gy in 38 fractions over 4 weeks	51.07	Two cycles cisplatin 60 mg/m² days 1 and 21; fluorouracil 1,000 mg/m² days 2–5	SCC	Esophagus excluding cervical esophagus	101	25	29
Burmeister	1994	2005	35 Gy in 15 fractions over 3 weeks	42.44	One cycle cisplatin 80 mg/m² day 1; fluorouracil 800 mg/m² days 1–4	Adeno + SCC + mixed	Esophagus + GEJ excluding cervical esophagus	256	65	33
Natsugoe	1997	2006	40 Gy in 20 fractions over 4 weeks	48	One cycle cisplatin 7 mg over 2 hours; fluorouracil 350 mg over 24 hours	SCC	Esophagus	45	24	21
Tepper	1997	2008	50.4 Gy in 28 fractions over 6 weeks	59.47	Two cycles cisplatin 100 mg/m² days 1 and 29; fluorouracil 1,000 mg/m² days 1–4, 29–32	Adeno + SCC	Thoracic esophagus + GEJ	56	72	32
Cao	1991	2009	40 Gy in 20 fractions over 4 weeks	48	One cycle cisplatin 20 mg/m² days 1–5; fluorouracil 500 mg/m² days 1–5; mitomycin 10 mg/m² day 1	SCC	Esophagus	236	Unavailable	17
Lv	1997	2010	40 Gy in 20 fractions over 4 weeks	48	Two cycles cisplatin 20 mg/m² days 1–3 and 22–24; paclitaxel 135 mg/m² days 1 and 22	SCC	Thoracic esophagus	160*	45	20
Mariette	2000	2014	45 Gy in 25 fractions over 5 weeks	53.1	Two cycles cisplatin 75 mg/m² days 1 or 2 and 29 or 30; fluorouracil 800 mg/m² days 1–4, 29–32	Adeno + SCC + undifferentiated	Thoracic esophagus	195	94	33
Shapiro	2004	2015	41.4 Gy in 23 fractions over 5 weeks	48.85	Five cycles carboplatin AUC 2 mg/mL/min; days 1, 8, 15, 22, 29; paclitaxel 50 mg/m² days 1, 8, 15, 22, 29	Adeno + SCC + undifferentiated	Esophagus + GEJ	368	84	34

*, does not include 78 patients who received postoperative chemoradiotherapy. GEJ, gastro-esophageal junction; AUC, area under curve; SCC, squamous cell carcinoma.
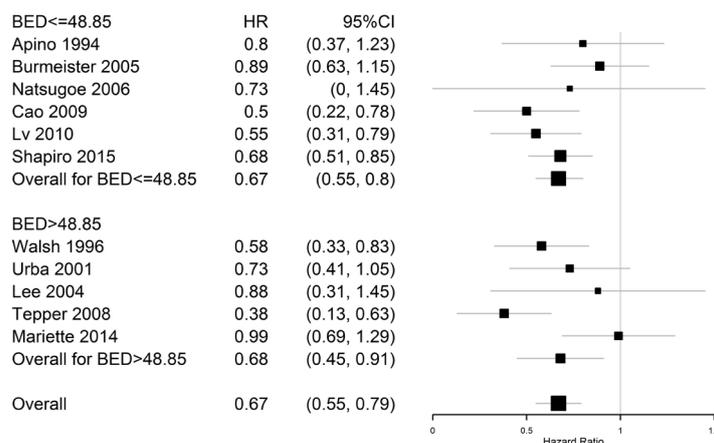
BED<=48.85	HR	95%CI
Apino 1994	0.8	(0.37, 1.23)
Burmeister 2005	0.89	(0.63, 1.15)
Natsugoe 2006	0.73	(0, 1.45)
Cao 2009	0.5	(0.22, 0.78)
Lv 2010	0.55	(0.31, 0.79)
Shapiro 2015	0.68	(0.51, 0.85)
Overall for BED<=48.85	0.67	(0.55, 0.8)
BED>48.85		
Walsh 1996	0.58	(0.33, 0.83)
Urba 2001	0.73	(0.41, 1.05)
Lee 2004	0.88	(0.31, 1.45)
Tepper 2008	0.38	(0.13, 0.63)
Mariette 2014	0.99	(0.69, 1.29)
Overall for BED>48.85	0.68	(0.45, 0.91)
Overall	0.67	(0.55, 0.79)

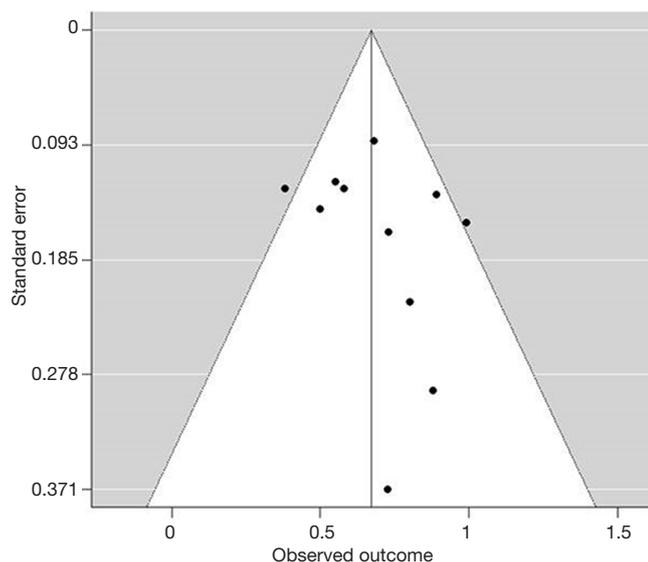**Figure 2** Overall survival outcomes.

Figure 3 Publication bias funnel plot, cnCRT *vs*. surgery. cnCRT, concurrent neoadjuvant chemoradiotherapy.

et al. showed a superior 5-year OS with cnCRT, but this trial only included 45 patients with only 24 months of follow-up (17).

Two ongoing clinical trials investigating optimal treatment for locally advanced EC include cnCRT (33,34). PROTECT-1402 is a phase II study that compares cnCRT including oxaliplatin and fluorouracil (FOLFOX) with carboplatin and fluorouracil (5-FU) in EC; patients in both arms will receive 41.4 Gy in 23 fractions concurrently (33). Neo-AEGIS (34) is a phase III trial which compares CROSS

trial cnCRT with neoadjuvant etoposide, cisplatin, and 5-FU, which was found to improve survival compared to surgery alone in gastro-EC (49). Given the implementation of cnCRT in the design of current clinical trials (33,34), in addition to the results of the CROSS trial (20), cnCRT has established itself as the current standard of care in the treatment of EC.

One of the strengths of our study is that it only includes prospective, pure cnCRT trials. The majority of previous meta-analyses (25-29,31) contained heterogeneous studies with nCRT that included induction chemotherapy (22,23,35) and sequential chemoradiotherapy (6,8,10). Liu *et al.* (30) is the only other meta-analysis to our knowledge that included only cnCRT. It too showed a survival advantage of cnCRT compared to surgery.

While ongoing RCT are trying to establish the ideal chemotherapy regimen for cnCRT, one of the major questions which remain unanswered regarding cnCRT is the appropriate radiation dose. NCCN guidelines advocate for 41.4 to 50.4 Gy, stating that patients who are at risk of not undergoing surgery should receive higher doses as a lower dose would not be adequate for definitive treatment (50). With varying radiation doses in the prospective trials, previously published meta-analyses did not address this question. Our study is the first to look at survival outcomes by radiation dose, aiming to define whether a CROSS trial radiation dose of 48.85 BED is sufficient. We found that both OS and TRM were not statistically different between cnCRT with LDRT and HDRT.

OS outcomes are affected by the balance between oncologic response rates and toxicity. Determining the

appropriate dose for the optimal therapeutic gain has been difficult due to inconsistency in the literature. Ordu *et al.* found that increasing neoadjuvant radiotherapy dose results in higher rates of pCR but also in higher grade 3 or 4 non-hematologic acute toxicity (51). However, a recent National Cancer Data Base study found that OS, 30-day re-admission, 30-day mortality, or length of postoperative hospital stay did not vary with radiotherapy dose (52). This is in line with the results of our meta-analysis.

The limitations of this study include small sample sizes as well as heterogeneity of tumor types, staging techniques, surgical techniques, radiation doses, and chemotherapy regimens. The meta-regression demonstrated that there were no significant differences between the groups that were predictive of OS including median follow-up, advanced stage disease, sex, performance status, radiation dose in BED, sample size, and year of publication.

One might hypothesize that the LDRT group's survival outcomes were improved by the CROSS trial (20), whose OS results exceed the rest. This is the only study to use a chemotherapy regimen of carboplatin and paclitaxel; the remainder of the studies in our analysis utilized cisplatin-based chemotherapy. We therefore excluded the CROSS trial (20) in a pre-planned analysis by dose to minimize chemotherapy heterogeneity. On this analysis including only cisplatin-based chemotherapies, there was still no difference in OS between LDRT and HDRT. Therefore, 48.85 Gy BED may be adequate in the cnCRT setting regardless of chemotherapy used.

Conclusions

In conclusion, this meta-analysis shows that 48.85 Gy BED, or 41.4 Gy in 23 fractions, may be an adequate dose for cnCRT treatment of resectable EC; this dose has equivalent OS and TRM to HDRT (>48.85 Gy BED). We suggest creating treatment plans to 50.4 Gy with an intent to deliver 41.4 Gy. If at that point, the performance score is adequate, then the patient should proceed to surgery without completing the prescription to 50.4 Gy. If clinical or radiographic evaluation indicates that the patient is not fit for surgery, then chemoradiation should continue to 50.4 Gy to deliver a definitive dose.

Acknowledgements

Footnote

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