Definitive Chemoradiotherapy for Esophageal Cancer

Ailén Martiarena, Mercedes Tamburelli and Javier Castillo

Abstract

Esophagectomy is associated with significant morbidity and mortality, especially in small volume centers. Current data suggest that definitive chemoradiotherapy (dCRT) is at least equivalent to trimodality therapy in terms of long-term survival for patients with esophageal squamous cell carcinoma (ESCC). Frail patients with ESCC who are not fit for surgery should receive dCRT. For those who are considered fit for esophagectomy, decision between dCRT and trimodality therapy should be taken on a case-by-case basis. The use of dCRT in patients with esophageal adenocarcinoma is not supported by data.

Keywords

Esophageal cancer · Definitive chemoradiotherapy · Squamous cell carcinoma

A. Martiarena · M. Tamburelli · J. Castillo (✉)
Department of Medical Oncology, Hospital Alemán of Buenos Aires, Buenos Aires, Argentina
e-mail: jcastillo@hospitalaleman.com

M. Tamburelli
e-mail: mtamburelli@hospitalaleman.com

Introduction

Management of patients with esophageal cancer is challenging and requires a multimodal approach. Endoscopic or surgical treatment is recommended for carcinoma in situ and stage IA esophageal cancer. For locally advanced disease, surgical treatment with perioperative chemotherapy or preoperative chemoradiotherapy is recommended for most patients who are fit for surgery.

Definitive chemoradiotherapy (dCRT) is a reasonable option for poor surgical candidates, and might even have comparable results in those with locally-advanced non-metastatic esophageal squamous cell carcinoma (ESCC), as compared to multimodality therapy. Esophagectomy is associated with significant morbidity (e.g. pulmonary complications, anastomotic dehiscence, cardiac arrhythmias) and mortality, especially in small volume centers. While dCRT also presents toxicity and side effects, this approach is less invasive than surgical resection and might result in reduced mortality and shorter hospital stay. Therefore, current NCCN and ESMO guidelines include dCRT as a treatment option for esophageal cancer patients [1, 2].

Most studies on dCRT for esophageal cancer include ESCC patients. These patients often have many comorbidities, which increase the risk for postoperative complications. Even in experienced centers surgical mortality is high

F. Schlottmann et al. (eds.), *Esophageal Cancer*,
https://doi.org/10.1007/978-3-031-39086-9_9

(1–7%) after an esophagectomy [3]. For this reason, it is important to weigh risks and benefits before deciding therapy.

The RTOG 85-01 trial established dCRT as standard non-operative therapy for localized esophageal cancer [4]. More recent investigations identified prognostic factors for long term survival. For instance, a population-based study showed survival rates at 2 years of 29 and 17% in patients with ESCC and esophageal adenocarcinoma (EAC), respectively, showing histology as an independent prognostic factor after dCRT [5]. In other study, the 3-year survival of ESCC patients dropped down from 42% in stage I to 25 and 16% in stage II and III, respectively [6]. Initial T-category and response to dCRT (evaluated by PET-TC and biopsy) are also prognostic factors for long term survival after dCRT [7, 8].

Definitive CRT Versus RT Alone

The addition of cisplatin-based chemotherapy to RT has significantly improved survival over RT alone [4, 9–11]. Unfortunately, available data are almost exclusively in patients with ESCC, and none of the trials have performed adequate pretreatment staging to reliably correlate outcome with locoregional tumor extent. Based on the results of the phase III RTOG 85-01trial, the standard therapy for patients with localized esophageal cancer selected for non-surgical treatment is dCRT [4]. In this trial (ESCC, n = 106 and EAC, n = 15), patients were randomly assigned to receive four cycles of fluorouracil (5-FU 1000 mg/m^2 per day, days 1–4, weeks 1 and 5] plus cisplatin [75 mg/m^2 day 1 of weeks 1 and 5]) with radiation therapy (50 Gy in 25 fractions over five weeks) delivered concurrently with the first cycle of chemotherapy or to radiation therapy alone (64 Gy in 32 fractions over 6.5 weeks). The study showed a significant survival advantage in patients with the combined modality and was finished prematurely, when an interim analysis showed a significant survival advantage for CRT (5-year overall survival 26% vs. 0%). Despite this benefit, the incidence of local/regional failure was 47% at 12 months.

Subsequent randomized studies confirmed these findings and showed survival rates of 35–40% at 2 years and around 20% at 5 years after dCRT [12–14]. The issue of the unacceptably high locoregional failure rate was addressed in the INT 0123 trial [14]. In this trial, 236 patients with non-metastatic ESCC or EAC who received dCRT (RTOG 85-01-scheme) were randomly assigned to one of two different RT doses: 50.4 Gy (28 fractions over 5.5 weeks) or 64.8 Gy (36 fractions over 7 weeks). After a 2-year follow-up, locoregional control was moderately improved by 52–56% (not significant) in the high-dose group, but there was a trend towards worse overall survival (OS) (31% vs. 40%). High-dose RT was significantly more toxic, and during radiotherapy, 11 deaths were observed in the high-dose arm vs. 2 deaths in the low-dose arm ($p < 0.01$). Interestingly, 7 of the 11 deaths occurred at total doses $\leq$ 50.4 Gy. During subsequent follow-up, 13 non-index cancer-related deaths were observed in the high-dose arm vs. 3 in the low-dose arm ($P < 0.01$). The results of INT 0123 are still inconclusive and do not exclude a benefit of radiation with doses higher than 50.4 Gy in conventional fractionation. In addition, this study was conducted between 1995 and 1999 (i.e. before the era of 3D-CRT).

At present, 50.4 Gy of RT plus concurrent cisplatin and FU remains the standard approach.

In most trials, improved locoregional tumor control was associated with higher total radiation doses, concurrent chemotherapy, lower tumor volume and SCC histology [15, 16]. In locally advanced esophageal cancer, however, improved locoregional tumor control after higher radiation doses does not appear to translate into improved OS. Long-term (5-year) locoregional control rates after radiotherapy and CRT vary between 32 and 75%.

Overall, the optimal radiation dose remains elusive. Investigators in Japan and China consider total doses of 59.4–66 Gy in 30–33 fractions to be standard radiation therapy [17, 18]. Modern

radiation techniques such as intensity-modulated radiation (IMRT) and volumetric modulated arc therapy (VMAT), which use simultaneous integrated boost radiotherapy, have shown to significantly decrease the radiation dose to critical organs such as the heart and lungs [19, 20].

Excellent results have been reported in a phase II trial (n = 60) in which modern technologies were used to deliver 66 Gy in 30 fractions in combination with 2 cycles of cisplatin and 5-FU [21]. A Chinese trial suggested that definitive CRT using the combination of IMRT plus concurrent cisplatin plus docetaxel improves local control and prolongs survival over IMRT alone, but with more prominent side effects [22].

Definitive CRT: Which Chemotherapy?

Several study groups have investigated CRT with different combinations of cisplatin and 5-FU in order to decrease toxicity and improve compliance, and potentially improve treatment efficacy.

The RTOG 85-01 trial established two cycles of cisplatin and 5-FU combined with radiotherapy followed by another two cycles of chemotherapy alone for standard CRT in esophageal cancer. However, the toxicity of this treatment was relatively high. In the study, 20% of patients had life-threatening side effects and 2% died from treatment-related toxicity. In a subsequent RTOG study (94-05, INT 0123) with the same regimen, more than 70% of patients developed side effects of grade 3 or higher [4, 12].

A sequential phase II/III study (PRODIGE 5/ACCORD17) involving 267 patients compared FOLFOX4 chemotherapy scheduled for 6 cycles, 3 of them combined with RT 50 Gy, with the standard RTOG regimen. The relative dose intensity of 5-FU and platinum was comparable in both treatment groups, as well as the percentage of patients with premature discontinuation of chemotherapy and overall toxicity. Similar progression-free survival (median survival 20.2 vs. 17.5 months), OS (3-year survival rate 19.9% vs. 26.9%, HR = 0.94, $P = 0.70$) and clinical complete response rates (44% vs. 43%) were also observed. However, fewer toxic deaths occurred in the FOLFOX4 group compared to dCRT with cisplatin and 5-FU (1% vs. 6%) [17].

In Europe, the CROSS regimen with weekly carboplatin and paclitaxel chemotherapy scheduled in preoperative combined CRT gained wide acceptance due to its very good tolerability and sparked interest in investigating taxane-based chemotherapy for dCRT [23]. A group from the Netherlands reported their experience with the adaptation of the CROSS regimen for dCRT [19]. Patients with locally advanced esophageal or junctional cancer who had received dCRT at a total dose of 46.8–70 Gy combined with four cycles of cisplatin and 5-FU (RTOG 8501 regimen) or with 5–6 weekly applications of carboplatin (AUC 2) and Paclitaxel (50 mg/m^2) were analyzed. Overall survival was similar in both groups (cisplatin/FU: median OS 16.1 months, carboplatin/paclitaxel: median OS 13.8 months, $P = 0.97$). However, the probability of completing planned dCRT was significantly higher in the carboplatin/paclitaxel group (82% vs. 57%, $P = 0.01$) and treatment-related mortality was lower (1.8% vs. 4.3%).

A propensity-matched analysis compared survival of dCRT with either cisplatin/5-fluorouracil (PF group) or docetaxel/cisplatin (DP group). PF group patients received two cycles of cisplatin (60 mg/m^2) and 5-fluorouracil (300 mg/m^2) at 4-week intervals during radiotherapy. DP group patients received a concurrent three-weekly schedule of docetaxel (60 mg/m^2) and cisplatin (80 mg/m^2) or cisplatin (25 mg/m^2) and docetaxel (25 mg/m^2) weekly. A significant improvement in progression-free survival and OS in favor of DP regimen was observed. It is unclear, however, if the results were related to the inclusion of a taxane in the experimental group or to the reduced dose of cisplatin and the unusual dose of 5-FU in the so-called standard group of this analysis [20].

The SCOPE1 study investigated the role of adding the epidermal growth factor receptor (EGFR) inhibitor cetuximab to dCRT in resectable esophageal cancer. Treatment consisted of induction chemotherapy (two cycles of cisplatin

and capecitabine) followed by CRT (50 Gy combined with two cycles of cisplatin and capecitabine) with or without weekly cetuximab. The study was stopped prematurely; OS was significantly worse in the cetuximab group (2-year OS 41.3% vs. 56.0%, HR = 1.45 (1.01–2.09), $P = 0.04$) and subgroup analysis favored CRT alone, particularly in patients with ESCC [24]. Thus, EGFR inhibition combined with dCRT cannot be recommended in unselected patients with esophageal cancer.

Overall, carboplatin/paclitaxel might be an alternative chemotherapy in dCRT. Further studies comparing standard dCRT and dCRT including weekly carboplatin/paclitaxel are needed.

Definitive CRT Versus Surgery Alone

A Japanese study compared results between esophagectomy and dCRT (RT 50–60 Gy with cisplatin and 5-FU) in patients with T1bN0M0 ESCC (n = 173). The 5-year survival was similar in both groups (77.7% vs. 68.6%, $p = 0.12$). Treatment-related mortality was 0%. Progression-free survival, however, was significantly improved in patients undergoing esophagectomy [25].

Another study compared esophageal cancer patients receiving dCRT (n-173), surgery alone (n = 126) or neoadjuvant chemotherapy followed by surgery (n = 118). Patients deemed unsuitable for surgery or with bulky local disease received dCRT. Overall 2-year survival rates were 44.3, 56.2 and 42.4% ($p = 0.42$) [26].

A study from China randomized patients with ESCC of the mid- or lower thoracic esophagus to dCRT (n = 36) or esophagectomy (n = 45). The overall 5-year survival favored dCRT but this was not statiscally significant (50% vs. 29.4%, $p = 0.147$). A trend to improved 5-year survival with dCRT was noted in patients with node-positive disease (47.4% vs. 11.8%, $P = 0.06$) [27].

A previous meta-analysis included 6 randomized studies comparing dCRT with either surgery alone (3 studies) or surgery plus induction therapy (3 studies). Most patients had thoracic ESCC (810/929). Local tumor progression was more common in patients receiving dCRT ($P < 0.001$) and distant metastases were more often in patients undergoing surgery ($P = 0.06$). Overall survival was equivalent between dCRT and surgery. The study suggests that dCRT is equivalent to surgery (with or without preoperative therapy) in patients with locally advanced ESCC [28].

Definitive CRT Versus Trimodality Therapy

The addition of surgery increases morbidity and mortality, but at the same time it might also favor local control of the disease.

A German study included patients with locally advanced ESCC and randomized 172 patients to induction chemotherapy followed by chemoradiotheray (40 Gy) and surgery or induction chemotherapy followed by dCRT (at least 65 Gy). This study reported equivalent OS in both groups with a 2-year survival rate of 39.9% vs. 35.4% ($p = 0.007$), and an updated long-term survival at 10 years of 19.2% vs. 12.2% ($p = 0.36$) [12, 29]. Although the addition of surgery significantly increased treatment-related mortality (12.8% vs. 3.5%, $p = 0.03$), local tumor progression was significantly worse after dCRT (at 2 years 63.3% vs. 40.7%, $p = 0.003$).

The FFCD 9102 trial included resectable T3N0-1M0 esophageal cancer patients (88.8% ESCC) and randomized those who had response to induction CRT (46 Gy/4.5 weeks or 30 Gy/4 weeks combined with cisplatin and 5-FU) to either surgery or further CRT (total radiation dose of 66 Gy or 45 Gy). The rate of early death was significantly higher after surgery (3-month mortality 9.3% vs. 0.8%, $p = 0.002$). Two-year survival rate was similar in both groups (34% vs. 40%, $p = 0.90$) [13]. These results suggested that in patients with locally advanced ESCC who respond to chemoradiation, there is no benefit for the addition of surgery compared to continuing with additional chemoradiation.

A Cochrane database systemic review compared non-surgical versus surgical treatment for esophageal cancer [30]. Long-term mortality was similar between chemoradiotherapy and surgery (HR 0.88, 95% CI 0.76–1.03; 602 participants; four studies; low quality evidence). In addition, there was no difference in long-term recurrence between non-surgical treatment and surgery (HR 0.96, 95% CI 0.80–1.16; 349 participants; two studies; low quality evidence). The study concluded that dCRT is at least equivalent to surgery in short- and long-term survival in patients with ESCC who are fit for surgery and are responsive to induction chemoradiotherapy. There is uncertainty in the comparison of dCRT versus surgery for patients with EAC [30].

Conclusions

Current data suggest that dCRT is at least equivalent to trimodality therapy in terms of long-term survival for patients with ESCC. Frail patients with ESCC who are not fit for surgery should receive dCRT. For those who are considered fit for esophagectomy, decision between dCRT and trimodality therapy should be taken on a case-by-case basis. The use of dCRT in patients with EAC is not supported by data.

References

1. Esophageal and Esophagogastric Junction Cancers. NCCN clinical practice guidelines in oncology version 2. 2023. www.nccn.org.
2. Oesophageal Cancer. ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. 2022.
3. Messager M, de Steur WO, van Sandick JW, et al. Variations among 5 European countries for curative treatment of resectable oesophageal and gastric cancer: a survey from the EURECCA Upper GI Group (European Registration of Cancer Care). Eur J Surg Oncol 2016;42:116–22.
4. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85–01). Radiation Therapy Oncology Group. JAMA. 1999;281:1623.
5. Smit JK, Muijs CT, Burgerhof JG, et al. Survival after definitive (chemo)radiotherapy in esophageal cancer patients: a population-based study in the north-East Netherlands. Ann Surg Oncol. 2013;20:1985–92.
6. Chen HS, Hung WH, Ko JL, et al. Impact of treatment modalities on survival of patients with locoregional esophageal squamous-cell carcinoma in Taiwan. Medicine (Baltimore). 2016;95:e3018.
7. Lin SH, Wang J, Allen PK, et al. A nomogram that predicts pathologic complete response to neoadjuvant chemoradiation also predicts survival outcomes after definitive chemoradiation for esophageal cancer. J Gastrointest Oncol. 2015;6:45–52.
8. Amini A, Ajani J, Komaki R, et al. Factors associated with local-regional failure after definitive chemoradiation for locally advanced esophageal cancer. Ann Surg Oncol. 2014;21:306–14.
9. Chan KKW, Saluja R, Delos Santos K, et al. Neoadjuvant treatments for locally advanced, resectable esophageal cancer: a network meta-analysis. Int J Cancer. 2018;143:430.
10. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593.
11. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. Cochrane Database Syst Rev 2001;CD002092.
12. Stahl M, Wilke H, Lehmann N, et al. Long-term results of a phase III study investigating chemoradiation with and without surgery in locally advanced squamous cell carcinoma (LA-SCC) of the esophagus. J Clin Oncol. 2008;26:431–6. https://doi.org/10.1200/jco.2008.26.15_suppl.4530.
13. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25:1160–8.
14. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (radiation therapy oncology group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20:1167–74.
15. Crehange G, Maingon P, Peignaux K, et al. Phase III trial of protracted compared with split-course chemoradiation for esophageal carcinoma: federation Francophone de Cancerologie Digestive 9102. J Clin Oncol. 2007;25:4895–901. https://doi.org/10.1200/JCO.2007.12.3471.
16. Shridhar R, Almhanna K, Meredith KL, et al. Radiation therapy and esophageal cancer. Cancer Control. 2013;20:97–110.
17. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal

cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol. 2014;15:305–14.
18. Akutsu Y, Matsubara H. Chemoradiotherapy and surgery for T4 esophageal cancer in Japan. Surg Today. 2015;45:1360–5.
19. Honing J, Smit JK, Muijs CT, et al. A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol. 2014;25:638–43.
20. Zhang P, Xi M, Li QQ, et al. Concurrent cisplatin and 5-fluorouracil versus concurrent cisplatin and docetaxel with radiotherapy for esophageal squamous cell carcinoma: a propensity score-matched analysis. Oncotarget. 2016;7:44686–94.
21. Chen J, Guo H, Zhai T, et al. Radiation dose escalation by simultaneous modulated accelerated radiotherapy combined with chemotherapy for esophageal cancer: a phase II study. Oncotarget. 2016;7:22711–9.
22. Ji FZ, Zhu WG, Yu CH, et al. A randomized controlled trial of intensity-modulated radiation therapy plus docetaxel and cisplatin versus simple intensity-modulated radiation therapy in II–III stage esophageal carcinoma. Zhonghua Wei Chang Wai Ke Za Zhi. 2013;16:842.
23. Honing J, Smit JK, Muijs CT, et al. A comparison of carboplatin and paclitaxel with cisplatin and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol. 2014;25:638.
24. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol. 2013;14:627–37.
25. Motoori M, Yano M, Ishihara R, et al. Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. Ann Surg Oncol. 2012;19:2135–41.
26. Morgan MA, Lewis WG, Casbard A, et al. Stage-for-stage comparison of definitive chemoradiotherapy, surgery alone and neoadjuvant chemotherapy for oesophageal carcinoma. Br J Surg. 2009;96:1300–7.
27. Teoh AY, Chiu PW, Yeung WK, et al. Long-term survival outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the esophagus: results from a randomized controlled trial. Ann Oncol. 2013;24:165–71.
28. Pöttgen C, Stuschke M. Radiotherapy versus surgery within multimodality protocols for esophageal cancer—a meta-analysis of the randomized trials. Cancer Treat Rev. 2012;38:599–604.
29. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23:2310–7.
30. Best LM, Mughal M, Gurusamy KS. Non-surgical versus surgical treatment for oesophageal cancer. Cochrane Database Syst Rev. 2016;3:CD011498.