

Definitive, Preoperative, and Palliative Radiation Therapy of Esophageal Cancer

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Keywords

Radiotherapy · Esophageal cancer · Chemotherapy · Brachytherapy imaging methods

Summary

Background: Long-term survival in patients with esophageal cancer remains dismal despite the recent improvements in surgery, the advances in radiotherapy (RT) technology, and the refinement of systemic treatments, including the advent of targeted therapies. Although surgery constitutes the treatment of choice for early-stage disease (stage I), a multimodal approach, including preoperative or definitive chemoradiotherapy (CRT) and perioperative chemotherapy, is commonly pursued in patients with locally advanced disease. **Methods:** A review of the literature was performed to assess the role of RT, alone or in combination with chemotherapy, in the management of esophageal cancer. **Results:** Evidence from large, randomized phase III trials and meta-analyses supports the application of perioperative chemotherapy alone or preoperative concurrent CRT in patients with lower esophageal and esophagogastric junction adenocarcinomas. Preoperative CRT but not preoperative chemotherapy alone is now routinely used in patients with locally advanced squamous cell carcinoma (SCC). Additionally, definitive CRT without surgery has also emerged as a valuable approach in the management of resectable esophageal SCC to avoid surgery-related morbidity and mortality, whereas salvage surgery is reserved for those with persistent disease. Furthermore, brachytherapy offers a valuable option in the palliative treatment of patients with locally advanced, unresponsive disease. Fluorodeoxyglucose-positron emission tomography (FDG-PET) can facilitate a more accurate treatment response assessment and patient selection. Finally, the development of modern RT techniques, such as in-

tensity-modulated and image-guided RT as well as FDG-PET-based RT planning, could further increase the therapeutic ratio of CRT. **Conclusion:** Altogether, CRT constitutes an important tool in the treatment armamentarium for esophageal cancer. Further optimization of CRT using modern technology and imaging, targeted therapies, and newer chemotherapeutic agents is a major challenge and should be the goal of future research and clinical trials.

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Introduction

For decades, surgical resection constituted the main treatment option in the management of esophageal cancer. Despite advances in surgical methodology, the long-term survival after surgery alone remained poor. The implementation of preoperative chemoradiotherapy (CRT) has improved the rates of complete (R0) resection in those patients responding. Large meta-analyses have demonstrated that the outcome of patients after definitive CRT is comparable to surgery, at least in a subset of patients with advanced disease. In the present work, we review the role of radiotherapy in the management of esophageal cancer and discuss future challenges and perspectives.

Surgery for Esophageal Cancer

The role of surgical resection in patients with esophageal cancer has been a subject of controversy [1]. Prospective randomized trials have demonstrated complete surgical resection in up to 80% of patients, although high variability has been noticed (range 67–95%) [2–5]. However, patients are often diagnosed at late disease

Table 1. Summary of the CROSS phase III trial

Parameter	41.4 Gy and paclitaxel/carboplatin followed by surgery	Surgery alone	p-value
Number (Adeno/SCC)	178 (134/41)	188 (141/43)	59
Complete resection R0, %	92	69	<0.001
pCR, %	29	–	
ypN+, %	31	75	<0.001
Postoperative complications			
Pulmonary	46	44	
Anastomotic leakage	22	30	
Death, in hospital, 30 days, %	4/2	4/3	
OS, months, median	49.4	24	0.003

Adeno = Adenocarcinoma; SCC = squamous cell carcinoma; pCR = pathological complete response; OS = overall survival.

stages which make complete surgical resection impossible due to the close proximity of the tumor to the trachea and/or the main stem bronchi [6]. Indeed, for tumors of the upper thoracic esophagus and/or bulky tumors (T3–T4), the rate of R0 resection remains low, whereas localization of the tumor above the carina represents an independent adverse prognostic factor [7]. A decrease in the mortality rates after transthoracic esophagectomy from 5–10% to less than 5% has been achieved due to the improvements in anesthesia, surgical techniques, and postoperative intensive care therapy [8]. Nevertheless, meta-analyses have revealed worse outcomes in patients with squamous cell carcinomas (SCC) compared to adenocarcinomas following surgery [1, 9].

Preoperative Chemoradiotherapy Followed by Surgery versus Surgery Alone

Accumulating evidence supports a beneficial role of preoperative CRT in improving resectability and survival in patients with locally advanced esophageal cancer. In the recent landmark CROSS trial (table 1), van Hagen et al. [10] recruited 366 patients with esophageal cancer (25% SCC, 75% adenocarcinoma) into either preoperative CRT using carboplatin with paclitaxel, followed by surgery (n = 178) or surgery alone (n = 188). Preoperative CRT resulted in a significant improvement in overall survival (OS) (median: 49 vs. 24 months). Importantly, the survival advantage conferred by preoperative CRT remained consistent across the histological subgroups (SCC and adenocarcinoma). Of note, the number of patients receiving tumor resection in the two arms was equivalent, which underlines the clear benefit of preoperative CRT [10]. Several studies have previously demonstrated a beneficial role of preoperative CRT (table 2).

Following the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) [11] and the FNCLCC and FFCD [12] multicenter phase III trials, preoperative or perioperative chemotherapy is often used in patients with esophageal or esophago-gastric junction cancer. However, both trials included gastric

tumors in addition to esophageal tumors, making an interpretation of the results challenging. Two recent studies directly compared the survival after preoperative chemotherapy versus preoperative CRT [13, 14] (table 3). Although a trend towards improved survival was observed after CRT, there was no significant difference in survival between the two arms in either of the clinical studies. Preoperative CRT was associated with better complete pathological response rates compared to the chemotherapy arm [13, 14], while less patients had a positive microscopic resection margin (R1) after surgery [14].

The effect of preoperative CRT in patients with early-stage esophageal cancer has been investigated in three previous studies [15–17]. Two of the studies only included SCC [15, 17], while patients with both SCC and adenocarcinomas were recruited in the third trial [16]. Notably, in contrast to patients with advanced disease, the addition of preoperative CRT to surgery failed to improve survival compared to surgery alone [15–17]. Although these trials were heterogeneous with regard to the radiotherapy schedules and staging systems, they indicate that preoperative CRT is unlikely to be beneficial in patients with early-stage disease.

Even though increased postoperative mortality following addition of preoperative CRT has been previously reported in some studies, this was most likely due to the high fractionation doses used in the combination arm (up to 3.7 Gy) [17]. Indeed, no significant increase in postoperative mortality was observed in trials that used conventional (1.8–2 Gy per fraction) fractionation doses during the preoperative treatment [15, 18, 19].

Definitive Chemoradiation versus Surgery

Several trials have examined the role of definitive CRT versus surgery in the management of patients with potentially resectable esophageal cancer (table 4). These studies included patients with potentially resectable esophageal tumors located above the carina [2, 3, 5, 20], except for the study by Gray et al. [4] which included lesions located at the gastroesophageal junction. Furthermore, in

Table 2. Comparison of neoadjuvant chemoradiotherapy plus surgery versus surgery alone

Clinical study	Patients, n	Histology	Stadium	RT dose	Chemotherapy	Follow-up, months	Treatment	Median survival, months	3-year survival, %	p-value
Nygaard et al., 1983/1988	88	SCC	T1–2 N0–1 M0	35 Gy 1.75 Gy/fraction, 4 weeks	cisplatin bleomycin, 2 cycles sequentially	18	CRT+S S	NA NA	17 9	ns
Le Prise et al., 1988/1991	86	SCC	T1–3 N0 M0	20 Gy 2 Gy/fraction, 12 days	cisplatin 5-FU, 2 cycles sequentially	12	CRT+S S	10 10	19 14	ns
Apinop et al., 1986/1992	69	SCC	–	40 Gy 2 Gy/fraction, 4 weeks	cisplatin 5-FU, 2 cycles concurrently	12	CRT+S S	10 7	26 20	ns
Bosset et al., 1989/1995	282	SCC	T1–3 N0–1 M0	37 Gy 3.7 Gy/fraction, 2 weeks	cisplatin, 2 cycles sequentially	55	CRT+S S	19 19	39 37	ns
Urba et al., 1989/1994	100	SCC Adeno	T1–3 N0–1 M0	45 Gy 1.5 Gy/fraction, 3 weeks	cisplatin vinblastine 5-FU, 2 cycles concurrently	98	CRT+S S	17 18	30 16	0.15
Walsh, 1990/1995	61	SCC	T1–3 N0–1 M0	40 Gy 2.7 Gy/fraction, 3 weeks	cisplatin 5-FU, 2 cycles concurrently	10	CRT+S S	16 11	32 6	<0.01
Cao et al., 1991/2000 ^a	236	SCC	T1–4 N0–1 M0	40 Gy 2 Gy/fraction, 4 weeks	cisplatin 5-FU mitomycin C, 2 cycles concurrently	60	CRT+S S	NA NA	73.3 ^a 53.4 ^a	<0.005
Burmeister et al., 1994/2000	256	SCC Adeno	T1–3 N0–1 M0	35 Gy 2.3 Gy/fraction, 3 weeks	cisplatin 5-FU, concurrently	65	CRT+S S	19 22	NA NA	0.38
Lee et al., 1993/1996	101	SCC	T1–3 N0–1 M0	45.6 Gy 1.2 Gy/fraction, 28 days	cisplatin 5-FU, concurrently	25	CRT+S S	28.2 27.3	NA NA	0.69
Tepper et al., 1997/2000	56	SCC Adeno	T1–3 N0–1 M0	50.4 Gy 1.8 Gy/fraction, 5–6 weeks	cisplatin 5-FU, 2 cycles concurrently	60	CRT+S S	54 21	NA NA	0.002
Natsugoe et al., 1997/2001 ^a	45	SCC	T2–3 N0–1 M0–1	40 Gy 2 Gy/fraction, 4 weeks	cisplatin 5-FU	24	CRT+S S	NA NA	57 41	0.58

^aSurvival measured in percentage (%) instead of months.

Adeno = Adenocarcinoma; SCC = squamous cell carcinoma; 5-FU = 5-fluorouracil; CRT+S = chemoradiotherapy plus surgery; S = surgery; NA = not available.

some of the studies only patients with SCC were recruited [2, 5], while the rest included adenocarcinomas as well. Some used surgery without induction therapy (n = 440) [5, 20, 21], whereas in three other studies preoperative CRT was administered (30–46 Gy; 489 patients) [2–4]. Histologically, the majority of the tumors in the above studies were SCC (n = 810), and only 119 patients with adenocarcinoma were treated as part of the trials. Importantly, more patients with large, advanced esophageal tumors (T3/T4 and/or stage III) received preoperative CRT (mean 79.3%, range 38–100%) compared to surgery alone (mean 49.8%, range 30–70.5%).

Regarding the radiotherapy schedule, in the majority of the trials, three-dimensional conventional radiotherapy with a fraction dose of 1.5–3.0 Gy and a total dose of 45–71 Gy was used. The only exception was the German trial by Stahl et al. [2] that also used brachytherapy (single dose: 4 Gy; total dose: 8 Gy) as a boost for T3 tumors. Chemotherapy consisted of 5-fluorouracil (5-FU), administered as bolus injection [2] or continuous infusion [3–5, 20], in combination with leucovorin and/or cisplatin or carboplatin or paclitaxel [4]. In the FFCO 9102 trial, patients received induction chemotherapy (5-FU plus cisplatin) followed by either conven-

Table 3. Comparison of chemoradiotherapy followed by surgery versus chemotherapy followed by surgery

Clinical study	Histology	Stadium	Patients, n	Treatment	Follow-up, months	3-year survival, %	5-year survival, %
Stahl	Adeno	T3–4, N0–1, M0	59	PLF × 2.5 cycles followed by surgery	46	27.7	–
			60	PLF × 2 cycles followed by 30 Gy with cisplatin and etoposide followed by surgery		47.4	–
Burmeister	Adeno	T2–3, N0–1	36	cisplatin, 5-FU × 2 cycles followed by surgery	94	49	36
			39	cisplatin, 5-FU × 1 cycle followed by 35 Gy with cisplatin, 5-FU followed by surgery		52	45

Adeno = Adenocarcinoma; 5-FU = 5-fluorouracil; PLF = cisplatin, 5-FU, and leucovorin.

Table 4. Comparison of definitive chemoradiotherapy versus neoadjuvant treatment followed by surgery or surgery alone

Clinical study	Histology	Stadium	Patients, n	Treatment	R0, %	Survival, months	2-year survival	3-year survival	p
Bedenne et al., 1993/2000	SCC	T1–3 N0–1 M0	129	cisplatin, 5-FU, 46 Gy + esophagectomy	75	18	34	–	NS
			130	cisplatin, 5-FU, 66 Gy	–	19	40	–	
Stahl et al., 1994/2002	SCC	T3–4 N0–1 M0	86	cisplatin, 5-FU, leucovorin, etoposide, 40 Gy + esophagectomy	82	16	40	31	NS
			86	cisplatin, 5-FU, leucovorin, etoposide, 65 Gy	–	15	35	24	NS
Chiu et al., 2000/2004	SCC	T2–3 N1 M0	45	esophagectomy		24	55	–	NS
			36	cisplatin, 5-FU, 50–60 Gy		21	58	–	

Adeno = Adenocarcinoma; SCC = squamous cell carcinoma; 5-FU = 5-fluorouracil. Only published articles were included.

tional fractionated radiotherapy (23 fractions of 2 Gy/fraction) or split-course radiotherapy (5 fractions of 3 Gy/fraction on week 1 and 3), and only randomized patients that showed response to induction therapy (58% of 444 patients) were eligible for the study [3]. Similar survival rates were observed in the two arms. Of note, this study was criticized for including only responders to preoperative therapy [3]. In the trial by Yu et al. [21], patients received definitive radiotherapy without chemotherapy (28 fractions of 1.8 Gy/fraction) followed by an accelerated, hyperfractionated irradiation (1.5 Gy/fraction twice daily, up to a total dose of 68 Gy). The median survival in both arms was comparable (28.5 vs. 30.5 months; $p = 0.58$). Locoregional failure in the radiotherapy and surgery group occurred in 57.3 and 27.8% of patients, respectively ($p = 0.001$), but higher mortality rates were noticed in the surgery group ($p = 0.02$) [21].

Crucially, the survival rates of patients treated with definitive CRT or surgery alone appear to be comparable. Indeed, OS at 2 and 4 years was 35–58% and 20–51% in the CRT arm and 40–65%

and 24–49% in the surgery arm, respectively [2, 4, 5]. Importantly, in the FFD9102 trial, 58% of patients presented an objective tumor response [3]. Moreover, the German study demonstrated an objective response in 34% of patients that received induction chemotherapy; however, no survival benefit was detected after surgery compared to definitive CRT [2]. Indeed, a survival rate of more than 55% at 3 years was found, regardless of whether surgery was performed or not. Local control was improved in patients that received surgery after induction chemotherapy/CRT compared to definitive CRT (2-year progression-free survival (PFS): 40.7 vs. 28.9%, respectively). However, surgery was associated with a significant increase in mortality rates (12.8 vs. 3.5%) [2].

Altogether, these findings indicate that patients with esophageal cancer have similar survival rates after treatment with either surgery or definitive CRT. However, despite the improvements in preoperative risk assessment and patient selection, surgery is characterized by a higher treatment-related mortality compared to definitive CRT [1, 8, 22]. This inevitably leads to the critical question as

to which approach is the treatment of choice in this patient cohort. Currently, clear-cut selection criteria are lacking, and hence it is essential to establish a consensus with regard to the management of these patients.

Palliative Brachytherapy

Accumulating evidence supports the use of intraluminal brachytherapy in the palliative treatment of patients with advanced incurable esophageal cancer [23–26]. The main indications of esophageal brachytherapy in the palliative setting are persistent dysphagia and bleeding. It is commonly preferred to external beam radiotherapy in the palliative treatment as it enables safe local administration of large radiation doses. Brachytherapy offers better control of tumor-associated symptoms compared to stent insertion of coagulation using argon plasma. Indeed, two large randomized studies reported a significantly better lasting effect of health-related quality of life and dysphagia scores with lower complication rates after brachytherapy as compared with stent insertion [23, 24].

EGFR Targeting in Combination with (Chemo-)Radiotherapy

Epidermal growth factor receptor (EGFR) overexpression occurs in 27–55% of esophageal cancer and correlates with poor prognosis [27]. Previous phase I/II clinical studies showed that addition of the anti-EGFR antibody cetuximab to preoperative radiotherapy/CRT was tolerated with acceptable toxicity and was associated with complete pathological response and resection (R0) rates [28, 29]. In a similar fashion, addition of erlotinib, a tyrosine kinase inhibitor, to definitive CRT was associated with a satisfactory 2-year OS and locoregional control and was well-tolerated [30]. However, the SCOPE-1 phase II/III clinical trial failed to demonstrate a survival benefit for the addition of cetuximab to definitive CRT in patients with localized esophageal SCC and adenocarcinomas [31]. Notably, the use of cetuximab in combination with CRT was associated with a significantly worse OS (22.1 vs. 25.4 months; $p = 0.035$) and higher non-hematologic grade 3 or 4 toxicity rates (70 vs. 63%; $p = 0.004$) compared to CRT alone [31]. Hence, the addition of anti-EGFR agents to standard CRT cannot be recommended.

Future Challenges and Perspectives

It is important to use appropriate selection criteria since patients with good performance status with potentially resectable tumors are the most likely to benefit from surgical resection with regard to local control [8]. Currently, it remains unclear to which extent surgery benefits those patients that showed a poor response to induction therapy. Furthermore, salvage surgery in this patient subgroup is associated with increased postoperative complication

rates compared to surgery alone, or even surgery following preoperative CRT [32]. Nevertheless, long-term survival has been reported for surgery in this patient cohort.

Additionally, we should intensify our efforts to identify markers predicting response to CRT as this is expected to facilitate appropriate patient selection and will avoid unnecessary delays in patients at high risk of local failure upon CRT. In that context, Wieder et al. [33] assessed the role of fluorodeoxyglucose-positron emission tomography (FDG-PET) in patients with esophageal SCC treated with preoperative CRT. Interestingly, tumor response and patient survival closely correlated with the changes in tumor metabolic activity 2 weeks after initiation of preoperative therapy [33]. Suzuki et al. [34] reported a close association between higher initial standardized uptake value in PET and worse survival in patients with esophageal or gastroesophageal cancer after definitive CRT. Hence, FDG-PET could be used to identify nonresponders early during treatment to allow for early modifications in the treatment protocol. More studies are needed to elucidate this issue [35].

Could radiotherapy dose escalation lead to improved clinical outcome in patients with esophageal cancer? The implementation of modern radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy could improve the response of patients to CRT. In a systematic review, Geh et al. [36] showed a strong correlation between radiation dose and tumor response, thus supporting dose escalation in order to enhance locoregional control. Welsh et al. [37, 38] showed that IMRT with simultaneously integrated boost achieves a selective increase of the dose to the gross tumor volume (GTV), the area at highest risk of failure, with simultaneous reduction of the dose distribution to the heart and the lung. However, in the INT 0123 phase III clinical trial, Minsky et al. [39] failed to detect an increase in survival or locoregional control following dose escalation of radiotherapy from 50.4 to 64.8 Gy. Of note, this trial was conducted before the development of modern radiotherapy methods. Proton radiotherapy represents another promising method aiming at radiotherapy dose escalation while sparing normal tissues [40].

The advent of new imaging modalities, such as FDG-PET, could also contribute to improve radiotherapy planning by enabling contouring of tumor areas otherwise undetectable when using conventional imaging [35]. In a recent study, Welsh et al. [41] examined the radiotherapy treatment volumes of 239 patients that received definitive CRT in conjunction with the follow-up FDG-PET scans that provided information on the failure patterns. In total, 119 patients (50%) presented local failure, 114 (48%) had distant failure, and 74 (31%) had no evidence of failure. Of all local failures, 90% were found within the GTV, while failures within the clinical target volume and planning target volume were only found in 23 and 12%, respectively [41].

Last but not least, recent studies have investigated the efficacy of alternative chemotherapy regimens, such as cisplatin/docetaxel or carboplatin/paclitaxel, for CRT of patients with SCC of the esophagus and have reported a satisfactory outcome as well as acceptable toxicity rates [42]. Conroy et al. [43] randomized patients to CRT (50 Gy) with either cisplatin plus 5-FU ($n = 47$) or FOLFOX4

(n = 53). The complete response rate was 30 and 44.7%, respectively. PFS/OS rates were 9.2/15.1 and 15.2/22.7 months, respectively [43]. The PRODIGE 5/ACCORD 17 phase III trial compared 5-FU/cisplatin with FOLFOX4-based CRT [44]. After a median follow-up of 25.3 months, PFS was 9.7 and 9.4 months in the FOLFOX and the 5-FU/cisplatin groups, respectively (p = 0.64), and no significant differences were observed regarding high-grade toxicities between the two arms [44].

Conclusion

In summary, preoperative CRT constitutes a valuable therapeutic approach for patients with inoperable esophageal cancer and results in superior survival rates than radiotherapy alone. Defini-

tive CRT should be considered in the treatment of morbid patients with locally advanced disease located above the tracheal bifurcation as complete surgical resection is often impossible in this patient cohort and is associated with high rates of postoperative morbidity. The implementation of modern imaging and radiotherapy methods is expected to further improve local control and treatment protocol adaptation after CRT. The potential of novel targeted agents to improve the response of tumors to radiotherapy and CRT should be further explored for the benefit of patients with esophageal cancer.

Disclosure Statement

The authors hereby confirm that they have no conflict of interest relevant to this work.

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