Preoperative therapy in locally advanced esophageal cancer

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Abstract

Esophageal cancer is an aggressive malignancy associated with dismal treatment outcomes. Presence of two distinct histopathological types distinguishes it from other gastrointestinal tract malignancies. Surgery is the cornerstone of treatment in locally advanced esophageal cancer (T2 or greater or node positive); however, a high rate of disease recurrence (systemic and loco-regional) and poor survival justifies a continued search for optimal therapy. Various combinations of multimodality treatment (preoperative/perioperative, or postoperative; radiotherapy, chemotherapy, or chemoradiotherapy) are being explored to lower disease recurrence and improve survival. Preoperative therapy followed by surgery is presently considered the standard of care in resectable locally advanced esophageal cancer as postoperative treatment may not be feasible for all the patients due to the morbidity of esophagectomy and prolonged recovery time limiting the tolerance of patient. There are wide variations in the preoperative therapy practiced across the centres depending upon the institutional practices, availability of facilities and personal experiences. There is paucity of literature to standardize the preoperative therapy. Broadly, chemoradiotherapy is the preferred neo-adjuvant modality in western countries whereas chemotherapy alone is considered optimal in the far East. The present review highlights the significant studies to assist in opting for the best evidence based preoperative therapy (radiotherapy, chemotherapy or chemoradiotherapy) for locally advanced esophageal cancer.

Key words: Esophageal cancer; Preoperative therapy; Multimodality treatment; Chemotherapy; Radiotherapy; Chemoradiotherapy
INTRODUCTION

The eighth most common cancer in the world is esophageal cancer. Esophageal cancer, being the sixth most common cause of death from cancer, has an overall ratio of mortality to incidence of 0.88[1]. Esophageal cancer comprises of two distinct histological entities, i.e. squamous cell carcinoma (SCC) and adenocarcinoma. These two histological types differ in their epidemiology, etiopathogenesis, tumor biology, management and outcomes. SCC is common in Asia and Eastern Europe while adenocarcinoma is prevalent in North America and Western Europe. Unfortunately, majority of the patients present with locally advanced disease in esophageal cancer and survival is dismal regardless of histology.

Traditionally, surgical resection has been the mainstay of treatment with a potential to ensure loco-regional control as well as long-term survival. However, surgery alone fails to contend against the natural history of disease owing to the presence of occult micrometastasis and fatal distant and loco-regional disease relapse is common. Median survival after esophagectomy is 15 to 18 mo with a 5-year survival rate of 20% to 25%[2]. Therefore, clinicians now are inclined towards use of some form of multidisciplinary treatment including surgery as standard of care for locally advanced esophageal cancer. Locally advanced esophageal cancer can be defined as those restricted to the esophagus or resectable periesophageal tissue (T2-T4) and/or lymphnode involvement (N1-N3) in the absence of distant metastasis[3]. The optimal multimodality treatment is still controversial. Potential contentious issues exist regarding the (1) ideal approach-preoperative, perioperative, or postoperative and (2) ideal combination-radiotherapy, chemotherapy or concurrent chemoradiation. Though various randomized and non-randomized trials have been conducted to address these issues, no standard guidelines have been established till date. This review will highlight the significant studies to assist in opting for the best evidence based multimodality management of esophageal cancer. We limit this review to preoperative therapy followed by surgery as it is presently considered the standard of care. The objectives of preoperative treatment are to downstage the tumor to achieve R0 resection, reduce local and distant disease relapses and thus improve survival.

PREOPERATIVE RADIOThERAPY

High rate of local failure after curative resection led to conception of many studies in the '80s and '90s to evaluate the role of preoperative radiotherapy (RT) in esophageal cancer. Preoperative RT was envisaged to increase the resectability rates with negative circumferential margins, to lower the loco-regional recurrences and to improve survival. Five randomized control trials (RCTs) addressed this issue and compared preoperative RT followed by surgery to surgery alone. Table 1 displays the salient features of these RCTs[4-8]. None of the studies reported significantly higher complete resections following preoperative RT. Only two studies reported loco-regional recurrences in the study arms: Wang et al[7] reported no difference whereas Gignoux et al[8] observed significantly lower loco-regional recurrences following preoperative RT and surgery compared to surgery alone (66% vs 76%). None of the RCTs reported significant improvement in survival. Nygaard et al[6] reported improvement in 3-year overall survival (OS) (21% vs 9%) among patients who underwent surgery following preoperative RT compared to patients who were operated upfront. Esophageal Cancer Collaborative Group conducted a quantitative meta-analysis using updated data from these five RCTs comprising 1147 patients to assess whether preoperative radiotherapy improves OS and whether it is differentially effective in patients defined by age, sex and tumour location[9] (Figure 1). In a group of patients with mostly squamous cell carcinoma, who had a median follow up of 9 years, the hazard ratio (HR) was found to be 0.89 (95%CI: 0.78-1.01). This suggested an overall reduction in the risk of death by 11% and an absolute improvement in survival is not expected to be more than 3% to 4%. To detect such an improvement (from
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| Preoperative RT | No preoperative RT |
|-----------------|--------------------|
| Study or subgroup | Events | Total | Events | Total | O-E | Variance | Weight | Hazard ratio [Exp ([O-E]/V), fixed, 95%CI] | Hazard ratio [Exp ([O-E]/V), fixed, 95%CI] |
|------------------|---------|-------|--------|-------|-----|----------|--------|----------------------------------|----------------------------------|
| Launois et al.[8], 1981 | 56 | 61 | 40 | 46 | 0.22 | 22.60 | 9.3% | 1.01 (0.67, 1.53) | 1.01 (0.67, 1.53) |
| Gignoux et al.[9], 1988 | 108 | 116 | 108 | 113 | 1.02 | 53.72 | 22.2% | 1.02 (0.78, 1.33) | 1.02 (0.78, 1.33) |
| Wang et al.[10], 1989 | 131 | 195 | 165 | 223 | -16.67 | 78.83 | 32.6% | 0.81 (0.65, 1.01) | 0.81 (0.65, 1.01) |
| Arnott 1992 | 87 | 90 | 75 | 86 | 6.82 | 40.02 | 16.5% | 1.91 (0.87, 1.62) | 1.91 (0.87, 1.62) |
| Nygaard 1992 (a) | 52 | 58 | 50 | 50 | -11.58 | 22.92 | 9.5% | 0.60 (0.46, 0.19) | 0.60 (0.46, 0.19) |
| Subtotal (95%CI) | 520 | 518 | | | | 90.1% | | 0.91 (0.80, 1.04) | 0.91 (0.80, 1.04) |

Total events: 434 vs 438
Heterogeneity: $\chi^2 = 8.69, df = 4 (P = 0.07); I^2 = 54%$
Test for overall effect: $Z = 1.37 (P = 0.17)$

Table 1 Salient features of randomized controlled trials addressing the role of preoperative radiotherapy followed by surgery versus surgery alone in the management of esophageal cancer

| Ref. | Study period | Treatment | No. of patients | Histology | Complete resection | Local recurrence rate | Operative mortality | 5-yr OS | Conclusion |
|------|--------------|-----------|----------------|-----------|-------------------|----------------------|---------------------|--------|------------|
| Launois et al.[8], 1981 | 1973-1976 | 40 Gy RT + Surgery | 67 | SCC | 74% | NA | 22.6% | 9.5% | No significant benefit |
| Gignoux et al.[9], 1988 | 1976-1982 | 33 Gy RT + Surgery | NA | SCC | 43% | 46% | NA | 11% | No significant benefit |
| Wang et al.[10], 1989 | 1977-1985 | 40 Gy RT + Surgery | 104 | SCC | 74% | 41% | 5% | 5% | Higher pre-op RT dose |
| Arnott et al.[11], 1993 | 1983-1988 | 30 Gy RT + Surgery | 90 | SCC/AC | 76% | NA | NA | 9% | No benefit of low dose |
| Nygaard et al.[12], 1992 | 1983-1988 | 35 Gy RT + Surgery | NA | SCC | 34% | NA | NA | 9% | Beneficial effect of pre-op RT |

SCC: Squamous cell cancer; AC: Adenocarcinoma; RT: Radiotherapy; NA: Not available; OS: Overall survival.

15% to 20%) reliably, trials or a meta-analysis of not less than 2000 patients (90% power, 5% significance level) would be needed([10]).

It can be inferred, based on available RCTs, that preoperative radiation therapy is unlikely to benefit esophageal cancer patients, both in terms of significantly lowering local failure rate and improving survival.

**PREOPERATIVE CHEMOTHERAPY**

Distant recurrence following curative resection in localized esophageal cancer constitutes significant proportion of disease relapse and invariably limits survival. Recurrence pattern analysis of 439 patients who underwent R0 resection highlighted that almost one fifth of the patients developed distant recurrence([11]). Furthermore, autopsy study of 43 curatively resected cases of esophageal cancer revealed that 17 of the 27 patients who had disease recurrence were found to have haematogenous metastasis([12]). Two studies showed that almost 80% of the patients had disseminated tumour cells in the bone marrow samples of ribs resected during esophagectomy for localized esophageal cancer([13,14]). Presence of systemic micro-metastasis in a significant number of esophageal cancer patients and the pattern of higher rates of distant recurrence leading to failure in curatively treated patients led to exploration of role of induction preoperative chemotherapy in esophageal cancer.

The enthusiasm to use preoperative chemotherapy arose due to its potential to exterminate micrometastasis, to down-stage the tumor, thus enhancing resectability, to improve loco-regional control and to provide relief of dysphagia. The downside of giving preoperative chemotherapy is development of chemoresistance and progression of disease in patients who do not respond to it. It is known that almost half of the patients are unresponsive to the presently employed chemotherapy([12]). Moreover, delay in local treatment can further compromise the already marginal nutritional status of the patient when surgery is not the initial treatment.

The role of preoperative/peroperative chemotherapy followed by surgery compared to surgery alone has been addressed by 13 RCTs (Table 2)([6,15-26]). A pooled random-effects meta-analysis of 10 RCTs comprising 2122 participants highlighted the lower risk of mortality among patients who were given preoperative chemotherapy compared to those treated with surgery alone (HR = 0.88, 95%CI: 0.80-0.96, P = 0.003)([27]) (Figure 2). Another updated meta-analysis of 10 RCTs revealed that the risk of all-cause mortality...
Table 2  Salient features of randomized controlled trials addressing the role of preoperative/perioperative chemotherapy followed by surgery versus surgery alone in the management of esophageal cancer

| Trials                        | Study period | Treatment                       | Histology | RO resection | pCR (%) | pN+ (%) | Median follow up | LRR | OS (%) | Conclusions                                      |
|-------------------------------|--------------|---------------------------------|-----------|--------------|---------|---------|-----------------|-----|--------|-------------------------------------------------|
| Roth et al[14, 188]           | 1982-1986    | Periop Cisplatin, bleomycin + S  | SCC       | 35%          | 6%      | NS      | 30 mo           | NS  | 25 (3 yr) | Prolonged OS in responders in perioperative chemotherapy arm with acceptable toxicity and post-op complications. |
| Nygaard et al[15, 192]        | 1983-1988    | Surgery Cisplatin, bleomycin + S | SCC       | 21%          | -       | NS      | 30 mo           | NS  | 05 (3 yr) | No improvement in survival in chemotherapy arm. |
| Schlag et al[16, 192]         | 1990's       | Preop FC + S                    | SCC       | 44%          | 6%      | NA      | NA              | NS  | 09 (3 yr) | No influence on resectability or OS in chemotherapy arm. Rather, it results in increase in side effects and postop mortality rate. |
| Maipang et al[17, 194]        | 1988-1990    | Cisplatin, Vindesine, bleomycin + S | SCC       | NS           | 0%      | NS      | 30 mo           | NS  | 31 (3 yr) | Better OS in control group. Poorly nourished patients may tolerate smaller dosages of chemotherapy. |
| Law et al[18, 197]            | 1989-1995    | Surgery Preop FC + S            | SCC       | 67%          | -       | 70      | NA              | 12  | 44 (2 yr) | Significant downstaging and an increased likelihood of R0 resection in chemotherapy arm. No survival difference but responders fared better. |
| Ancona et al[19, 2001]        | 1992-1997    | Preop FC + S                    | SCC       | 90%          | 13%     | NS      | 30 mo           | 32  | 34 (5 yr) | Significantly improved long term survival in patients with pathologic complete response following perioperative chemotherapy. |
| Cunningham et al[20, 2006]    | 1994-2002    | Peri-op ECF + S                 | AC        | 69.3%        | NA      | NS      | 49              | 14.4 | 36.3 (5 yr) | Preoperative chemotherapy decreased tumor size and stage, and significantly improved PFS, OS. |
| Kelsen et al[21, 1992]        | 1990-1995    | Preop FC + S                    | SCC - 98, | 63%          | 2.5%    | NS      | 8.8 yr          | 23  | 23 (3 yr) | No improvement in OS in chemotherapy arm. Only R0 resection results in long-term survival, regardless of pre-op chemotherapy. |
| MRC OEO2 trial, 2009          | 1992-1998    | Preop FC + S                    | SCC - 123, | 60%          | 4%      | 58      | 5.9 yr          | 11.5| 23 (5 yr) | Preop chemotherapy improves survival and should be considered as a standard of care. |
| Allum et al[22, 2001]         | 1992-1998    | Surgery                         | SCC - 124, | 54%          | -       | 68      | 6.1 yr          | 12.2| 17 (5 yr) | |
| Ychou et al[23, 2011]         | 1995-2003    | Peri-op FC + S                  | AC        | 84%          | 3%      | 67      | 8.8 yr          | 12  | 38 (5 yr) | Peri-op chemotherapy significantly increased R0 reseption rate, DFS, and OS. |
| Boonstra et al[24, 2011]      | 1989-1996    | Surgery                         | SCC       | 73%          | -       | 80      | 15 mo           | 19  | 26 (5 yr) | Significant improvement in OS in chemotherapy arm. |
| Ando et al[25, 2012]          | 2000-2006    | Surgery                         | SCC       | 57%          | -       | 46      | 14 mo           | 25  | 17 (5 yr) | Pre-op chemotherapy can be regarded as standard treatment. |

Periop: Perioperative; SCC: Squamous cell cancer; AC: Adenocarcinoma; RT: Radiotherapy; NA: Not available; OS: Overall survival; NS: Not stated; ECF: Epirubicin, cisplatin, 5-FU; S: Surgery.
was significantly less for preoperative chemotherapy followed by surgery compared to surgery alone (pooled HR = 0.87, 95%CI: 0.79-0.96, \( P = 0.005 \)). The absolute survival difference at 2 years was calculated as 5.1% (number needed to treat = 19). A subgroup analysis by histological type for these studies showed that the preoperative chemotherapy proved beneficial in adenocarcinoma (HR = 0.83, 95%CI: 0.71-0.95, \( P = 0.01 \)) and not in squamous-cell carcinoma (HR = 0.92, 95%CI: 0.81-1.04, \( P = 0.18 \))\(^{[28]}\).

Though the objective of the present review is to analyze the role of preoperative therapy, it is worthwhile to discuss perioperative chemotherapy here as well. The role of perioperative chemotherapy (before and after the surgery) has been evaluated in lower esophageal adenocarcinoma in two RCTs. The British Medical Research Council conducted a phase III trial (MAGIC trial) to evaluate perioperative chemotherapy in the management of resectable gastro-oesophageal adenocarcinoma. Though the proportion of patients with esophageal cancers was less (lower esophagus or junctional adenocarcinoma) in these trials, results of this trial definitely indicated benefit of perioperative chemotherapy. OS significantly improved from 23% to 36%. Only 104 of 250 patients (41.6%) randomized to perioperative chemotherapy arm in this study could complete all six cycles of chemotherapy, due to disease progression or early death, patient choice, postoperative complications, prior toxicity, lack of response to preoperative treatment, and worsening coexisting disease, thus acting as a limitation\(^{[26]}\).

Another recent FNCLCC/FFCD trial reported that perioperative chemotherapy improved 5-year OS from 24% to 38%. It must be noted that 75% of tumors in this trial were lower esophageal or junctional and among the 109 patients who received at least one cycle of preoperative chemotherapy, 54 patients (50%) received postoperative chemotherapy\(^{[23]}\). These two trials suggest that the approach of perioperative chemotherapy may be beneficial for patients with lower esophagus or junctional adenocarcinoma but only half of the patients are able to complete the planned treatment after surgery.

### PREOPERATIVE CHEMORADIATION

High risk of both loco-regional and systemic failures following curative treatment, led to integration of all three treatment modalities namely surgery, chemotherapy and radiation in the management of esophageal cancer. As preoperative RT failed to meet the high expectations of providing additional loco-regional control compared to surgery alone in esophageal cancer; attempts were made to use chemoradiotherapy (CRT) as a double-edged sword. While RT was expected to improve loco-regional control, simultaneously, chemotherapy was thought to eradicate the micrometastases. Chemotherapy adds several benefits with its use along with preoperative RT by (1) containing micrometastasis and lowering systemic failure; (2) providing additive effect to radiation by acting against the different tumor cell populations; and (3) providing assistance to radiotherapy for control of loco-regional disease (spatial cooperation\(^{[29]}\)). Spatial cooperation may exist at different levels: (1) with altered DNA repair or modification of the lesions induced by chemotherapy or radiation at the molecular level; (2) through cytokinetic cooperation arising from differential sensitivity of the various compartments of the cell cycle to the drug or radiation at the cellular level, notably; and (3) including re-oxygenation, increased drug uptake or inhibition of repopulation or angiogenesis at the tissue level\(^{[30]}\).

Table 3 displays the RCTs which compared preoperative CRT followed by surgery to surgery alone\(^{[31-39]}\). The most promising trials which have
| Trial                 | Study period     | Treatment                                                                 | No. of patients | Histology | Completed treatment | RO | pCR | pH+ | LRR | Median survival (mo) | OS | Treatment related mortality | DFS median/ proportions | Conclusion                                                                 |
|----------------------|------------------|---------------------------------------------------------------------------|-----------------|-----------|---------------------|----|-----|-----|-----|----------------------|----|-----------------------|------------------------|--------------------------------------------------------------------------|
| Apinop et al[31], 1994 | 1986-1992        | FC + 40 Gy RT + Surgery                                                 | 35              | SCC       | 26                  | NA | 26.9% | NA | NA | 19.2 (3 yr)          | NS | NS                    | NA                     | No statistically significant difference in OS, complication rate, mortality |
| Le Prise et al[32], 1994 | 1988-1991      | Sequential FC-20 Gy RT-FC + Surgery                                    | 41              | SCC       | 39                  | 51.0% | NA | 17.9% | 10 | 7.6 mo                | No change in operative mortality or survival time                          |
| Walsh et al[33], 1996 | 1990-1995        | FC + 40 Gy RT + Surgery                                                 | 45              | SCC       | 42                  | 36.0% | NA | 21.4% | 10 | 5 mo                  | Multimodal treatment superior to surgery alone                             |
| Le Prise et al[32], 1994 | 1994            | Sequential FC-20 Gy RT-FC + Surgery                                    | 58              | AC        | 53                  | NA | 25%  | 42  | NA | 37 (3 yr)            | 3% | NA                    | CRT induced high clinical and pathological response, but no statistically significant benefit in OS and DFS |
| Walsh et al[33], 1996 | 1996            | FC + 40 Gy RT + Surgery                                                 | 58              | AC        | 54                  | NA | 100% | 37  | 22.8% | 55 (2 yr)           | 8.5% | 51% (2 yr)          | No significant improvement in PFS or OS                                  |
| Lee et al[34], 2004  | 1999-2002        | FC + 45.6 Gy RT + Surgery                                              | 50              | SCC       | 48                  | 87.5% | -   | 10.8% | 27.3 | 57 (2 yr)            | 8.5% | 51% (2 yr)          | No statistically significant benefit in OS and DFS                        |
| Burmeister et al[35], 2005 | 1994-2000    | FC + 35 Gy RT + Surgery                                                | 128             | SCC       | 105                 | 80.0% | 16%  | 43  | 11%  | 22.2 (3 yr)          | NS | 10%                  | No significant improvement in PFS or OS                                  |
| Tepper et al[36], 2008 (CALGB 9781) | 1997-2000     | FC+ 50.4 Gy RT + Surgery                                               | 30              | SCC       | 29                  | 84.6% | 40%  | 12  | 13.7% | 39 (5 yr)            | 28% | 26% (5 yr)          | Long-term survival advantage supports trimodality therapy as a standard of care |
| Lv et al[37], 2010   | 1997-2004        | 2 Cis, Pacli+ 40 Gy + Surgery                                           | 80              | SCC       | 80                  | 97.4% | -   | 11.3% | 33  | 24.5 (10 yr)         | 3.4% | 61.3% (3 yr)        | Rational application of pre-op or post-op CRT can improve PFS, OS         |
| Mariette et al[38], 2014 | 2000-2009       | 2 Cis, 5FU + Surgery                                                   | 98              | SCC       | 84                  | 93.8% | 33.3% | 30.8 | 22.1% | 31.8 (5 yr)          | 11.1% | 35.6% (5 yr)         | No effect on R0 resection rate or survival but enhanced postoperative mortality |

Periop: Perioperative; SCC: Squamous cell cancer; AC: Adenocarcinoma; RT: Radiotherapy; NA: Not available; OS: Overall survival; NS: Not stated; ECF: Epirubicin, cisplatin, 5-FU; S: Surgery.
almost established the role of preoperative CRT are the Dutch chemoradiotherapy in Oesophageal Cancer and the Surgery Study (CROSS) trials[29,38]. The investigators randomly assigned 368 patients with resectable esophageal cancers to either preoperative CRT followed by surgery or to surgery alone. The patients in preoperative CRT arm received weekly carboplatin and paclitaxel for 5 wk and concurrent radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy each, with 5 fractions administered per week, starting on the first day of the first chemotherapy cycle) followed by surgery. The histopathological types were adenocarcinoma (75%), SCC (23%), and large-cell undifferentiated carcinoma (2%). R0 resection rates were significantly better in preoperative CRT arm compared to surgery alone (92% vs 69%, p < 0.001). More than one fourth of patients (29%) achieved pathological complete response following preoperative CRT. Though postoperative complications and inhospital mortality were similar in the two groups, median OS was significantly better in preoperative CRT group (49.4 mo vs 24.0 mo, HR for survival, 0.657, 95%CI: 0.495-0.871, P = 0.003). However, the HR for esophageal adenocarcinoma was only marginally statistically significant (adjusted HR = 0.74, 95%CI: 0.54-1.02, P = 0.07). Long-term results of the study were recently published. These revealed that the survival advantage for preoperative CRT persisted after a median follow up of 84.1 mo for surviving patients (range 61.1-116.8, IQR: 70.7-96.6). Median OS was 48.6 mo (95%CI: 32.1-65.1) in the preoperative chemoradiotherapy plus surgery group and 24.0 mo (14.2-33.7) in the surgery alone group (HR = 0.68, 95%CI: 0.53-0.88, log-rank P = 0.003). The improvement in survival was evident for both histological subtypes - median OS for patients with squamous cell carcinomas and adenocarcinoma were 81.6 mo (95%CI: 47.2-116.0) and 43.2 mo (95%CI: 24.9-61.4) respectively in the preoperative CRT group compared to 21.1 mo (95%CI: 15.4-26.7) and 27.1 mo (95%CI: 13.0-41.2) in the surgery alone group[40]. Preoperative CRT led to significantly lower loco-regional recurrences (14% vs 34%, P < 0.001) and peritoneal carcinomatosis (4% vs 14%, P < 0.001)[41].

In sharp contrast to the findings of the CROSS trial, the French trial (FFCD 9901) could not find any significant benefit of preoperative CRT. FFCD 9901 was a multicentre RCT which was conducted to assess improvement in outcomes for patients with stage I or II esophageal cancer with use of preoperative CRT. The investigators randomized 195 patients (in 30 centres) to either preoperative CRT followed by surgery (n = 98) or surgery alone (n = 97). CRT protocol was 45 Gy in 25 fractions over 5 wk with two courses of concomitant chemotheraphy composed of fluorouracil 800 mg/m2 and cisplatin 75 mg/m2. Preoperative CRT did not improve R0 resection rates (93.8% vs 92.1%, P = 0.749); there was no difference in 3-year OS either (47.5% vs 53.0%, HR = 0.99, 95%CI: 0.69-1.40, P = 0.94). Moreover, significantly higher postoperative mortality was seen in patients who received preoperative CRT (11.1% vs 3.4%, P = 0.049). The authors concluded that preoperative CRT does not improve R0 resection rate or survival but enhances postoperative mortality in patients with stage I or II esophageal cancer[39].

A number of factors can be attributed to these differences in survival outcomes between the French and Dutch studies: (1) small sample size in the FFCD 9901 trial reducing the statistical power of detecting a survival benefit; (2) different histological profiles in two studies (70% of patients in the French study were SCC compared with 23% in the Dutch study); and (3) larger number of patients with early-stage disease (fewer node-positive and T3 patients) in the French study compared to Dutch study[42]. The CROSS trial investigators cautioned against coming to the conclusion that preoperative CRT is not beneficial in early-stage esophageal cancer, as one might, from the results of the FFCD 9901 trial. They highlighted that CROSS trial findings should still be considered for stage II cancers in view of its larger study population, more consistent inclusion rate, less toxic CRT regimen, more sophisticated radiation techniques and lower postoperative mortality rate[43].

A meta-analysis which was designed to compare the role of preoperative CRT for esophageal carcinoma including 14 RCTs (n = 1737) concluded that it has the potential to improve the long-term survival and reduce locoregional cancer recurrence compared to surgery alone. Five-year survival was significantly better in preoperative CRT group compared to the surgery alone group (OR = 1.64, 95%CI: 1.28-2.12). The authors further reported that a complete pathological response to CRT was observed in 10%-45.5% of patients[44].

In a meta-analysis of 12 trials which compared preoperative CRT followed by surgery versus surgery alone (n = 1854), the Australasian gastro-intestinal trials group reported that preoperative CRT led to significant reduction in all-cause mortality (HR = 0.78, 95%CI: 0.70-0.88, P < 0.0001). The beneficial effect was evident in both histological subtypes - the HR for squamous-cell carcinoma was 0.80 (95%CI: 0.68-0.93, P = 0.004) and for adenocarcinoma was 0.75 (95%CI: 0.59-0.95, P = 0.02). They further undertook the pooled analysis of two RCTs and highlighted that the preoperative CRT seemed to lower all-cause mortality compared to preoperative chemotherapy (HR for the overall indirect comparison 0.88, 95%CI: 0.76-1.01, P = 0.07). They concluded that there seemed to be strong evidence for survival benefit with the use of preoperative CRT or chemortherapy followed by surgery versus surgery alone in resectable esophageal cancer[28].

Another meta-analysis which included 13 RCTs (n = 1930, resectable esophageal cancers) addressed the issue of postoperative complications following preoperative CRT compared to surgery alone[45]. The
The standard of care continues to be debated due to difference of opinions and practices across the world and lack of any trial with head-to-head comparison alone to further refine the role of preoperative therapy. The literature suggests that preoperative chemoradiotherapy with chemotherapy radiotherapy followed by surgery results in optimal outcome while managing locally advanced esophageal cancer; however, there is a need to compare preoperative chemoradiotherapy with chemotherapy alone to further refine the role of preoperative therapy. The standard of care continues to be debated due to difference of opinions and practices across the world and lack of any trial with head-to-head comparison between these two established treatment protocols.

**CONCLUSION**

The literature suggests that preoperative chemoradiotherapy followed by surgery results in optimal outcome while managing locally advanced esophageal cancer; however, there is a need to compare preoperative chemoradiotherapy with chemotherapy alone to further refine the role of preoperative therapy. The standard of care continues to be debated due to difference of opinions and practices across the world and lack of any trial with head-to-head comparison between these two established treatment protocols.

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