Review Article

The frontline of esophageal cancer treatment: questions to be asked and answered

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Abstract: Achieving a good treatment for esophageal cancer is a great challenge. For early stage cancer, endoscopic treatment is considered the first line and a possible curative therapy. Chemotherapy, radiotherapy, and surgery are all used for the treatment of locally advanced esophageal cancer, administered either alone or combined. Some combinations have proven to be feasible, effective, and superior, such as neoadjuvant chemoradiation (CRT) plus surgery in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial. However, other strategies such as perioperative chemotherapy or definitive chemoradiation also have demonstrated substantial effectiveness. The current article addresses the following questions: (I) how can a choice between different multi-modality treatments be made; (II) is there enough evidence to compare the merits of the different strategies; and (III) is there any new evidence to improve the current practice. Moreover, in this article, existing evidence for treatment strategies for locally advanced esophageal cancer have been reviewed.

Keywords: Chemoradiotherapy; chemotherapy; esophageal cancer; esophagectomy; radiotherapy; treatment strategy

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Introduction

Malignant neoplasm of the esophagus is one of the most common tumors in Asian countries, ranked 10th in Taiwan, and 4th among men in China. In the US, approximately 16,910 new cases of esophageal cancer were diagnosed in 2016, and 15,690 deaths were estimated (1-3). Prognosis of esophageal cancer has been dismal regardless of the aggressive treatments, partly owing to the late diagnosis of this disease. Therefore, treatment should be based on tumor stage, patient's physical performance, tolerance of the treatment, as well as the histology.

As per the available guidelines, the treatment strategies for esophageal cancer are based mainly on the stage of the disease. While early stage cancer is a candidate for endoscopic treatment, resectable tumors with deeper involvement generally require surgery with or without additional treatments. For locally advanced esophageal cancer, a much-appreciated concept is that multimodality treatment is warranted. Various treatment strategies have been used for the treatment of esophageal cancers. This article aims to address these questions: (I) how can a choice between different multi-modality treatments be made; (II) is there enough evidence to compare the merits of the different strategies and (III) how can the new evidence improvise the current practice?

Esophageal neoplasm amendable to endoscopic treatment

High-grade dysplasia of the esophageal mucosa is defined as Tis category. This stage of esophageal neoplasm is generally treated with endoscopic resection (ER) and/or ablation (4,5). For T1a or T1bN0 cancer, ER can be performed alone or with ablation, but ablation alone is not recommended (5,6). These treatments are more tolerable compared to esophagectomy or chemoradiation. With the advent of narrow band imaging (NBI) and magnifying endoscopy, a comprehensive and highly accurate diagnostic principle has been established for early esophageal cancer, alongside with early lesions of gastric and colon cancer. Clinical studies (7,8) have demonstrated that certain classifications of mucosal changes correlate well with the invasion depth and prognosis of early esophageal cancer, such as the classification of intrapapillary capillary loops for squamous cell carcinoma. This has made early diagnosis and non-operative curative resection possible. In many circumstances, the initial diagnostic ER has full therapeutic value; no additional therapies are required afterward. In all specimens acquired with ER, the depth of tumor infiltration, vascular or nerve invasion, the presence of tumor cells in the lateral or deep margins should be examined thoroughly. In case a higher stage is unexpectedly detected, further treatment should be considered.

Resectable esophageal neoplasm with muscle or deeper layer invasion

For esophageal cancer of stage T1bN0, direct esophagectomy as a single modality treatment is a valid choice (4). In the Belgian guideline (KCE reports 179A) for tumors beyond the mucosa, surgery with or without neoadjuvant chemoradiotherapy is considered standard (9).

Preoperative (Neoadjuvant) therapies

Preoperative and perioperative chemotherapy

Preoperative chemotherapy plus surgery as a strategy has been studied and compared with surgery alone in more than 10 randomized control trials (RCTs). Most of these trials were carried out before 2012, and only three of them have been published after 2008 (10-20). The trials conducted by Allum *et al.* in 2009 and by Boonstra *et al.* in 2011 are recent trials with adequate power. Allum *et al.* recruited 802 patients with upper, middle or lower third esophageal cancer, as well as cancer of gastric cardia. Histology with squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma were all included. The neoadjuvant group received cisplatin and fluorouracil as the chemotherapy regimen. A hazard ratio (HR) of 0.84 for death [95% confidence interval (CI): 0.72–0.98; P=0.03] was demonstrated. A 5-year overall survival (OS) of 23.0% for the neoadjuvant group was noted, while OS of the surgery alone group was 17.1% (18). Boonstra *et al.* used the regimen of cisplatin and etoposide, for patients with exclusively intra-thoracic esophageal squamous cell carcinoma. The 2-year OS was 42% for the neoadjuvant group, and 30% for the surgery alone group, while the 5-year OS for the two groups were 26% and 17%, respectively (HR for death: 0.71, 95% CI: 0.51–0.98) (19).

Several trials have compared perioperative chemotherapy plus surgery with surgery alone. Major contemporary trials include the RTOG trial 8911 (USA intergroup 113) reported by Kelsen *et al.* in 2007, the MAGIC trial by Cunningham *et al.* in 2006 and a French trial by Ychou *et al.* in 2011 (21-23). The results of the MAGIC trial were debatable since the trial was primarily a "gastric" study, and only 25% of the patients had lower esophageal or gastroesophageal junction (GEJ) tumors. In the RTOG trial, 467 patients were enrolled, of whom 227 had undergone surgery alone. There was no difference in terms of OS between the two groups. Subgroup analysis showed that R0 resection resulted in substantial long-term survival, regardless of chemotherapy. In this study, a significant proportion of the patients had a non-R0 resection (59% of the surgery group and 63% of the perioperative chemotherapy group). In contrast, Ychou *et al.* enrolled 224 patients with esophageal adenocarcinoma, and approximately 60% of them had GEJ tumors. The perioperative chemotherapy group had significantly better OS (HR for death: 0.69; 95% CI: 0.50–0.95; P=0.02) and disease-free survival (DFS, HR for recurrence or death: 0.65; 95% CI: 0.48–0.89; P=0.003) compared to the surgery alone group. In this study, the R0 rate was 87% for the perioperative chemotherapy group and 74% for surgery alone group (23). Another difference was that in the US study, squamous cell carcinoma and adenocarcinoma were both approximately one-half in proportion, while Ychou *et al.* enrolled only adenocarcinoma patients. Both studies used cisplatin and fluorouracil regimen.

Meta-analyses by Kidane *et al.* evaluated 12 RCTs with 2,229 patients, while Xu *et al.* included 16 RCTs with 2,594 patients. Both meta-analyses included the RCTs evaluating

perioperative chemotherapy. The results were similar, and both supported the survival benefit of preoperative chemotherapy. Kidane *et al.* reported an HR of 0.88 for death, 95% CI: 0.80–0.96, P=0.0026 (24). Xu *et al.* stated that the survival benefit would be more pronounced after the first 3 years. In many reviews and meta-analyses, perioperative and preoperative chemotherapies were considered the same and have been discussed together (25). Interestingly, Zhao *et al.* conducted an RCT that enrolled 346 patients with esophageal squamous cell carcinoma, comparing preoperative and perioperative chemotherapies. The results showed that the perioperative chemotherapy group had a better OS and DFS, HR =0.79 (95% CI: 0.59–0.95; P<0.001) and 0.62 (95% CI: 0.49–0.73; P<0.001), respectively. The chemotherapy regimen included paclitaxel, cisplatin, and fluorouracil (26).

Preoperative (neoadjuvant) chemoradiation (CRT)

This treatment option for esophageal cancer that has been validated by many RCTs and meta-analyses, is considered as the standard of care. If we include the studies that are published in Chinese, as many as 18 RCTs and 15 meta-analyses can be found. The results of the RCTs and the meta-analyses were relatively consistent. Not many of the earlier and smaller RCTs such as those published by Nygaard *et al.* in 1992, Urba *et al.* in 2001 and Lee *et al.* in 2004, showed a positive result for preoperative chemoradiation. These studies enrolled around 100 patients, and various chemotherapy regimens were administered; all of them included cisplatin (10,27,28). In the earlier meta-analyses, several of them showed only a trend towards preoperative CRT, while in other studies like those published by Urschel *et al.* in 2003 and Gebski *et al.* in 2007, a significant survival benefit was noted. Gebski *et al.* found a 13% absolute difference in survival (29,30).

The most influential trial would be the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial which was published by van Hagen *et al.* in 2012. This trial enrolled 366 patients, and 75% of them had adenocarcinoma. Patients with T1N1 or T2-3N0-1 disease were included, and they received either surgery alone, or preoperative CRT plus surgery. The CRT regimen consisted of carboplatin and paclitaxel. The authors reported a significant survival benefit in the preoperative CRT group, with an HR of 0.657 (95% CI: 0.495–0.871; P=0.003) (31). After the CROSS trial, most meta-analyses suggested that preoperative CRT group offers a significant OS benefit over surgery alone (29,30,32-45). Wang *et al.* in a 2016 updated analysis reported an increased 3-year survival rate with a risk ratio of 1.26 (95% CI: 1.14–1.39, P<0.001) (42). Sjoquist *et al.* found the HR for death to be 0.78 for the preoperative CRT group (43). Based on these findings, the Cancer Care Ontario's Program in Evidence-Based Care (CCO PEBC), National Comprehensive Cancer Network, and the Belgian Health Care Knowledge Centre recommend in their guidelines that preoperative CRT plus surgery should be the first choice for patients with resectable locoregional diseases, particularly those having the same eligible criteria as seen in the CROSS trial (4,9,46).

Recently, there have been studies utilizing a network meta-analysis in a Bayesian framework (38-40). Montagnani *et al.* and Pasquali *et al.*, both reported that the preoperative CRT group provided the most robust survival benefit (Montagnani *et al.*: HR =0.73; 95% CI: 0.63–0.86; Pasquali *et al.*: HR =0.77, 95% CI: 0.68–0.87) (38,40).

Preoperative (neoadjuvant) radiotherapy (RT)

Preoperative radiotherapy was not an option for resectable esophageal cancer if administered without chemotherapy. Nygaard *et al.* conducted a trial in 1992 with 108 patients, comparing preoperative RT to surgery alone, and reported a survival benefit (10). However, a meta-analysis by Arnott *et al.* did not find any significant difference between the survival rates of the two groups (47). In short, preoperative RT is not recommended to be administered without chemotherapy.

Postoperative (adjuvant) chemotherapy or chemoradiation

The postoperative treatments for completely resected esophageal cancer are different for squamous cell carcinoma and adenocarcinoma. Postoperative CRT or chemotherapy can be administered to patients with resected adenocarcinoma in several conditions, including patients with positive nodes, pT3, 4 with negative nodes, or selected pT2 nodal negative patients (4). However, for esophageal squamous cell carcinoma, there are no current practical guidelines suggesting postoperative treatments, possibly due to the absence of a large randomized trial or meta-analysis demonstrating its survival benefits.

Current evidence for postoperative (adjuvant) therapy of esophageal squamous cell carcinoma

Postoperative chemotherapy administered after curative surgery has been studied. In the JCOG9204 trial, surgery plus adjuvant chemotherapy was compared with only

surgery in patients with pathological stage IIA, IIB, III, or IV due to distant node involvement (M1 lymph node). The 5-year DFS was better in the adjuvant group, with an HR for recurrence of 0.73, 95% CI: 0.51–1.03, P=0.037. The 5-year OS showed a trend towards adjuvant therapy, which was 52% in patients with surgery alone and 61% in patients with surgery plus chemotherapy, but no significant differences were seen. Risk reduction by adjuvant chemotherapy was remarkable in the subgroup with lymph node metastasis (48). However, the same group conducted another trial: JCOG9907, compared neoadjuvant chemotherapy with adjuvant chemotherapy. That study reported that 5-year OS was superior in the neoadjuvant group, with an HR for death of 0.64, 95% CI 0.45–0.91, P=0.01. Both trials used cisplatin and 5-fluorouracil as the chemotherapy regimen (49). Based on the results of these two significant trials, instead of adjuvant chemotherapy, neoadjuvant chemotherapy is the recommended approach for esophageal squamous cell carcinoma.

There were several trials evaluating postoperative RT that focused on patients with squamous cell carcinoma. Zieren *et al.* in 1995 and Xiao *et al.* in 2003 both conducted RCTs comparing postoperative RT with surgery alone. The latter trial comprised of a much larger cohort of patients; 220 patients in the postoperative RT group and 275 in the surgery alone group. However, both these trials revealed a negative effect of postoperative RT on survival. Xiao's trial demonstrated an HR for death of 0.85, 95% CI: 0.51–1.42 (P=0.553). Several RCTs and several meta-analyses were subsequently performed that demonstrated negative results compared to surgery alone (50,51). Other smaller trials and meta-analyses for postoperative RT yielded similar results (38,40).

There are very few trials involving postoperative CRT for squamous cell carcinoma. The SWOG9008/INT-0116 trial showed significant benefits for patients with at least T3 and/or node-positive gastric and GEJ cancer, but the histologic type in this trial was exclusively adenocarcinoma (52). There have been no large trials for squamous cell carcinomas. Lv *et al.* from the Nanjing First Hospital have published a randomized trial, comparing neoadjuvant CRT, adjuvant CRT, and surgery alone. There were approximately 80 patients in each group, from clinical stage II–III, with marginally more patients in stage III than in stage II. The chemotherapy regimen included cisplatin plus paclitaxel. The 1-year DFS was similar in the three groups, the 3-, 5-, and 10-year DFS were similar in the neoadjuvant and adjuvant groups, both being significantly better than the surgery alone group. The 3- and 5-year OS for the neoadjuvant CRT were 63.5% and 43.5% respectively, while the 3- and 5-year OS for the adjuvant CRT group were 62.8% and 42.3% respectively. Both groups were significantly better than the surgery alone group, which had a 3- and 5-year OS of 51.3%, P=0.0453 and 33.8%, P=0.0402, respectively (53).

In nonrandomized studies, Hsu *et al.* compared 104 patients who underwent surgery plus adjuvant CRT to 186 patients who underwent only surgery. The propensity score matching was performed to compare the survival of 56 well-balanced pairs. Both the 3-year OS and the 3-year DFS were better in the adjuvant group. The results were similar in the matched pairs (54). In another large-scale study, survival of esophageal cancer patients from a nationwide database was compared. A total 1,000 patients in the surgical group and 390 patients in the adjuvant CRT group were matched to generate 213 well-balanced pairs. The 3-year OS for the adjuvant therapy and the surgery alone groups were 50% and 38%, respectively, P=0.006. The 3-year DFS was 46% for the adjuvant CRT group and 36% for the surgery alone group, P=0.006 (55).

There have been other retrospective studies that compared different postoperative adjuvant strategies. Chen *et al.* compared 140 patients who underwent postoperative RT, with 164 patients who had postoperative CRT. The 5-year OS for the CRT and RT groups were 47.4% and 38.6%, respectively (P=0.030). The recurrence rate was significantly lower in the CRT group (P<0.05) (56). Tachibana *et al.* compared 23 patients receiving postoperative chemotherapy to 22 patients who underwent postoperative CRT in a randomized trial. The 3- and 5-year OS in the former group were 63% and 38% respectively, and those in the latter group were 58% and 50%, respectively (P=0.97). It is quite difficult to draw any conclusions from the results of these studies.

In the latest network meta-analysis conducted by Montagnani *et al.*, 25 trials were included, neoadjuvant CRT was associated with the most robust survival advantage across different multimodality treatment options, but neoadjuvant CT and adjuvant CRT were associated with a non-significant benefit. In other network meta-analyses, the results for postoperative CRT plus surgery compared to surgery alone was similar (40). Pasquali *et al.* grouped the adjuvant therapies as one group and compared with surgery alone. No significant survival advantage was noted (HR =0.87, 95% CI: 0.67–1.14) (38).

In conclusion, neoadjuvant CRT with surgery is the

standard treatment for patients who can tolerate it. Adjuvant CRT can be administered to patients with an adenocarcinoma histology. In patients with esophageal squamous cell carcinoma, primary surgery plus adjuvant CRT as a strategy seems to be efficient, though the evidence for it is weak. Future large-scale randomized trials are needed to clarify the effectiveness.

Definitive chemoradiation

Most clinical evidence supports curative surgery as the center of standard multimodality treatment and reserves definitive CRT for patients who cannot undergo surgery, or have a neoplasm in the cervical esophagus. However, there are some other guidelines that allow CRT for more clinical indications.

There have been two clinical trials focused mainly on esophageal squamous cell carcinoma, comparing the efficacies of definitive CRT to patients receiving preoperative CRT and surgery. Stahl *et al.* allocated 172 patients with esophageal squamous cell carcinoma to either receive induction chemotherapy followed by chemoradiotherapy (40 Gy) and surgery (arm A, n=86) or the same induction chemotherapy followed by chemoradiotherapy (65 Gy), but not surgery (arm B, n=86). The 2-year OS for arm A was 39.9% (95% CI: 29.4–50.4%), while for arm B it was 35.4% (95% CI: 25.2–45.6%); log-rank test for equivalence with δ=–0.15, P=0.007. The 3-year OS (arm A, 31.3%; arm B, 24.4%; P=0.02) and median OS (arm A, 16.4 months; arm B, 14.9 months) were also equivalent. However, DFS was better in the surgery group. The 2-year DFS for the surgery group was 64.3% (95% CI: 52.1–76.5%), while in the chemoradiotherapy group, it was 40.7% (95% CI: 28.9–52.5%); HR for arm B *vs.* arm A was 2.1 (95% CI: 1.3–3.5; P=0.003) (57). Bedenne *et al.* randomized 259 patients into two arms, with arm A as the surgery group and arm B as the chemoradiation group. Both arms received CRT first, with an either split course or conventional RT. Then the patients were assigned to the different arms, patients in arm A had surgery, and those in arm B had another course of RT as well as chemotherapy. The median survival for arm A and arm B were 17.7 and 19.3 months, respectively. Two-year OS for arms A and B were 33.6%±4.5% and 39.8%±4.5%, respectively, and the survival difference was less than 10%. However, more locoregional relapses were found after definitive chemoradiation (HR for arm B *vs.* arm A =1.63; 95% CI: 1.04–2.55; P=0.03) (58). Both these trials had similar OS for both arms, but the local recurrence rate was higher in the definitive chemoradiation group.

The National Comprehensive Cancer Network guidelines recommend definitive CRT for only medically unfit patients and those with unresectable tumors, as well as those with cervical squamous cell carcinomas. This suggestion conforms to the Belgian guidelines, which limited definitive CRT to patients with unresectable disease, or with a resectable tumor. The European Society for Medical Oncology (ESMO) Guidelines Working Group provided an algorithm, based on which locally advanced esophageal squamous cell carcinoma could be managed with neoadjuvant CRT plus surgery, or definitive CRT with close follow-ups and possible salvage resection. They suggested that if the patient is unwilling to undergo surgery or medically unfit, definitive CRT should be preferred (59). A careful selection of patients should be made, based on the patient's comorbidities, surgical risks, location of the tumor, response to the CRT, surgical volume of the medical facility, and patient's preference, in order to obtain better results.

Conclusions

Three questions to be addressed in this article: (I) how can a choice among different multi-modality treatments be made? (II) Is there enough evidence to tell the difference among those strategies? (III) Is there new evidence to improve the current practice? The first question was answered as follows: for esophageal cancer limited to the mucosa, endoscopic treatments, including ablation and ER are the recommended strategies; while for resectable locally advanced esophageal cancer, neoadjuvant CRT with a platinum-based regimen followed by surgery is the standard of care. For the question (II), there were several choices for neoadjuvant and adjuvant therapies. Perioperative chemotherapy and neoadjuvant chemotherapy combined with surgery are two feasible alternatives for adenocarcinoma in addition to neoadjuvant CRT. However, the recent meta-analyses comparing these strategies indicate that neoadjuvant CRT might be the better option. RT alone with surgery, either given as neoadjuvant or adjuvant therapy, is inferior to other strategies. For the question—definitive CRT is yet another treatment choice with acceptable efficacy for locally advanced disease, but a higher recurrence rate was found, and most guidelines reserve this option for patients who are unsuitable for surgery (III), while adjuvant CRT or chemotherapy can be given in several high-risk conditions for patients with adenocarcinomas, there is limited evidence

for its feasibility and effectiveness in patients with squamous cell carcinoma. However, new evidence supporting postoperative adjuvant CRT were mostly derived from large non-randomized studies. Large-scale RCTs are needed to evaluate adjuvant therapies for esophageal cancer. Multidisciplinary collaboration is paramount for the decision of treatment strategy for the patients.

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Footnote

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