

New Trend of Surgery in Locally Advanced Esophageal Squamous Cell Carcinoma Patients

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Abstract:

The treatment of locally advanced esophageal squamous cell carcinoma is still controversial. Although, preoperative chemoradiation, followed by esophagectomy is the standard treatment, morbidity and patients' quality of life problems after an esophagectomy are still considerable. Since a good pathologic complete response rate in patients after preoperative chemoradiation, a wait and see policy (with active surveillance) has been introduced as a new alternative approach after chemoradiation. Active surveillance involves imaging and biopsy evaluations in patients after chemoradiation to detect residual or recurrent tumors. If there are no residual tumors, observation is considered. Surgery is reserved for patients who present with residual tumors or locoregional recurrence after surveillance to achieve complete resection (salvage esophagectomy). Based on evidence from recent studies, surveillance with salvage esophagectomy is a treatment option for locally advanced esophageal squamous cell carcinoma patients achieving a clinical complete response after chemoradiation.

Keywords: chemotherapy, esophageal cancer, radiation, squamous cell carcinoma, surgery

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Introduction

Esophageal cancer is an aggressive disease. The Global Cancer Observatory reported that in 2018 esophageal cancer ranked 7th in incidence (572,000 new cases), and 6th in mortality overall (509,000 deaths) worldwide.¹ The 2nd most common histologic subtypes are squamous cell carcinoma and adenocarcinoma. There are also geographic variations in esophageal cancer incidence and etiology (Table 1).²

Generally, most esophageal patients present with dysphagia, which implies locally advanced disease. After initial staging, precise tumor, node involvement, metastasis staging is conducted, based on the American Joint Committee on Cancer 8th edition system.³ Locally advanced esophageal squamous cell carcinoma (ESCC) are defined as clinical stage cT2, N0 (high risk lesions), cT1b–cT2, N+ or cT3–cT4a, and any N.⁴

Treatment of locally advanced ESCC is still challenging, due to the normal course of the disease and the complicated anatomy around the disease site. This leads to high morbidity and rates of recurrence, affecting survival and quality of life. Surgery, chemotherapy and radiation therapy are still the current mainstays of treatment.

Overview of ESCC treatment

The National Comprehensive Cancer Network (NCCN) guidelines version 4.2020 for esophageal and

esophagogastric junction cancer recommends the following treatment options in medically fit patients; according to TNM classification:^{3,4}

Early stage:

–pTis: endoscopic resection (with or without ablation–additional ablation if there is multifocal carcinoma in situ) or ablation alone

–pT1a: endoscopic resection with or without additional ablation (for pTis and pT1a, esophagectomy may be indicated if nodular disease)

–pT1b, N0: esophagectomy

–cT1b–cT2, N0: esophagectomy

*cT2, N0 (low risk lesion; tumor <3 cm, well differentiated)

Locally advanced stage:

–cT2, N0 (high risk lesion; lymphovascular invasion, tumorb ≥3 cm, poorly differentiated) or cT1b–cT2, N+ or cT3–cT4a, any N: in this stage, patients with cervical ESCC will proceed to definitive concurrent chemoradiation. Whereas; thoracic ESCC will proceed to preoperative concurrent chemoradiation, followed by esophagectomy.

–cT4b (unresectable) and patients who decline surgery: definitive chemoradiation or chemotherapy alone in the setting of invasion of the trachea, great vessels or heart.

Table 1 Geographic variations between esophageal squamous cell carcinoma and adenocarcinoma

Variable	Squamous cell carcinoma	Adenocarcinoma
Geographic areas	Asia Africa	North America Europe
Risk factors	Smoking Alcohol drinking Betel quid chewing Very hot drinking Low socioeconomic status	Gastroesophageal reflux disease Excess body weight

Advanced stage:

Unresectable locally advanced, recurrent or metastatic disease: systemic therapy or palliative care

Response assessment

The assessment of response should be conducted 5 to 8 weeks after complete preoperative chemoradiation by fluorodeoxyglucose (FDG)-positron emission tomography (PET)-computerized tomography (CT) (preferred) or FDG-PET scans, chest and abdominal CT scanning with contrast along with upper gastrointestinal endoscopy and biopsy.⁴ A recent meta-analysis highlighted the poor accuracy of endoscopic biopsies, CT, and 18F-FDG-PET-CT, when used as lone modalities for assessing residual disease, following preoperative chemoradiation to treat esophageal cancer.^{5,6}

After assessment, patients are classified into 3 groups:

1. No evidence of disease: proceed to esophagectomy or surveillance.
2. Persistent local disease: proceed to esophagectomy.
3. Metastatic or unresectable disease: proceed to palliative management.

Preoperative chemoradiation vs. surgery alone

In the past, esophagectomy alone was the main treatment for ESCC, but this resulted in high surgical morbidity and diminished quality of life. Additionally, this was also associated with higher rates of local recurrence in approximately half of the patients in less than 3 years. The main risk factors of recurrence are invasion depth and lymph node metastasis.^{7,8}

Preoperative chemoradiation has both disease free and overall survival benefits compared with only surgery in patients with locally advanced ESCC. The principles of

this treatment are to treat micrometastases, downstage the disease and facilitate a curative (R0) resection.

In 2010, a meta-analysis found preoperative chemoradiation was superior in terms of survival benefit over only surgery alone in over 4,000 patients with resectable esophageal carcinoma; with a preoperative chemoradiation mortality hazard ratio (HR) being 0.80 (0.68–0.93; p-value=0.004).⁹

The Chemoradiotherapy Oesophageal Cancer followed by Surgery Study (CROSS trial), a large randomized trial in 2012, randomized 368 patients with resectable esophageal or esophagogastric junction cancer (T1, N1, M0 or T2–3, N0–1, M0) into surgery alone and preoperative chemoradiation followed by surgery groups. The majority of patients (75.0%) had an adenocarcinoma. The study found median overall survival rates of 49.4 months in the chemoradiation–surgery group compared with 24.0 months in the surgery only group (p-value=0.003). In subgroup analysis, the study found complete pathological response (pCR) in 18/37 ESCC patients (49.0%). There were no significant differences in 30-day mortality between the groups.¹⁰

A large randomized trial called: the Neoadjuvant Chemoradiotherapy followed by Surgery versus Surgery alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010) study, compared surgery only vs. preoperative chemoradiation in 451 patients with resectable thoracic ESCC (T1–4, N1, M0 or T4, N0, M0). The study found a pathological complete response rate of 43.2%, with a median overall survival of 100.1 vs 66.5 months (p-value=0.025), and disease-free survival of 100.1 versus 41.7 months (p-value<0.001), mortality of 2.2% and 0.4% (p-value=0.212), and a higher R0 resection rate (98.4% vs 91.2%) in the preoperative chemoradiation group than the surgery group (p-value=0.002).¹¹

Currently, the standard treatment for locally advanced squamous cell carcinoma of the esophagus is preoperative

concurrent chemoradiation, followed by esophagectomy.⁴ However, since many studies, as noted above, have found a good response as assessed by pCR for preoperative chemoradiation, this opens the concept of no surgery in patients who achieve clinical complete response.

Definitive chemoradiation vs. preoperative chemoradiation–surgery

No survival benefit was found for further surgery in a study by the Federation Francophone de Cancerologie Digestive (FFCD 9102) trial. This study randomly assigned 259 patients who had responded to preoperative chemoradiation (T3, N0–1, M0 esophageal cancer patients received 2 cycles of fluorouracil and cisplatin and concomitant radiation) continuation of chemoradiation (three cycles of fluorouracil/cisplatin and radiation) and surgery groups. The continuation of definitive chemoradiation was deemed as being the same as preoperative chemoradiation–surgery. After two years, the chemoradiation–surgery group had a 34.0% survival rate (median survival 17.7 months) versus a 40.0% survival rate (median 19.3 months) in the definitive chemoradiation group (p -value=0.440). The mortality rates were 9.3% in the chemoradiation–surgery group vs. 0.8% in the definitive chemoradiation group (p -value=0.002).¹² Thus, with this study showing no benefit for additional surgery, following chemoradiation compared with definitive chemoradiation, in patients with locally advanced squamous cell carcinoma of the esophagus the concept of surveillance alone following definitive chemoradiation alone becomes open.

Wait and see vs surgery

The concept of surveillance is to observe patients, who achieved a clinical complete response after preoperative or definitive chemoradiation, and then move on to surgery if locoregional recurrence later occurs.

A meta-analysis in 2019 showed postoperative salvage esophagectomy complications after definitive chemoradiation; anastomosis leakage in 18.2% of the patients, pulmonary complications in 30.2% and 30-day mortality of 3.2%, figures which are comparable to preoperative chemoradiation–surgery.¹³

Another prospective study (JCOG0909) found clinical complete response after definitive chemoradiation of 59.0%. Salvage surgery was performed in 32.0% of the patients, and the mortality rate was only 4.0%; with the 3-years overall survival being 74.2%. These results show that salvage surgery for locoregional failure patients, after definitive chemoradiation, is a promising option.¹⁴

In the 2019, Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO) trial, 38 (44.2%) patients who had achieved clinical complete response (cCR) after chemoradiation (T3–T4a, Nany, M0 or Tany, N+, M0 ESCC received chemoradiation) were then randomized into surgery and close observation alone groups. Survival was similar in both groups, of whom neither group achieved median overall survival (p -value=0.560); although there was non-significantly, slightly better disease-free survival in the surgery group (p -value=0.262).¹⁵ However, the study did indicate that observation with salvage surgery might be a reasonable choice in achieving cCR in ESCC patients after chemoradiation.

A recent prospective cohort study in esophageal cancer patients treated with preoperative chemoradiation was conducted to examine patients' preferences regarding active surveillance versus esophagectomy. In this discrete-choice experiment, the patients were asked to choose between various treatment strategies, taking into account factors such as short-term/long-term quality of life and survival. Interestingly, they found that many patients were willing to trade off substantial 5-years survival to achieve a reduction in the risk of esophagectomy.¹⁶

Surveillance

Since surveillance is an alternative option in locally advanced ESCC patients who have clinical complete response after chemoradiation, the accuracy of diagnostic tools for surveillance is concerned with residual tumors after chemoradiation which may be missed. The NCCN guidelines recommend clinical follow up every 3–6 months for 2 years. This is then followed by every 6–12 months for 3–5 years, and then annually thereafter.⁴ Although, there is no widely accepted protocol for follow up imaging serial endoscopic with biopsy and CT scan or PET–CT every 3 months × 2, 6 months × 3, then annually is popular.¹³ This is because most locoregional recurrences, after definitive chemoradiation, occur within 12–24 months.¹⁷

Conclusion

Outcomes of locally advanced ESCC could be improved by combined treatments. This is dependent on the location of the cancer; for example in the cervical area definitive chemoradiation, or in the thoracic area preoperative chemoradiation; followed by surgery. Due to good responses of chemoradiation, and the desire to avoid an unnecessary esophagectomy, observation with salvage surgery in patients achieving clinical complete response might become a trend in the future.

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Conflict of interest

None

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