



Is Preoperative Radiotherapy Necessary for Resectable Locally Advanced Squamous Cell Esophageal Carcinoma?

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Based on the guidelines for esophageal and esophagogastric junction cancers, the standard of care for resectable locally advanced (cT2, N0 [high-risk lesions: lymphovascular invasion, ≥ 3 cm, poorly differentiated]; cT1b-T2, N+; cT3-cT4a, anyN) esophageal squamous cell carcinoma (LA-ESCC) is preoperative chemoradiotherapy followed by esophagectomy^[1,2]. However, the administration of radiotherapy in real-world practice faces challenges.

As the publication of the CROSS trial, neoadjuvant chemoradiotherapy followed by surgery has been further confirmed to be the standard of care for patients with LA-ESCC^[3,4]. However, patients in the control group received surgery alone. Notably, mono-surgery is not enough for LA-ESCC. Whether preoperative radiotherapy is necessary for potentially resectable ESCC remains unclear. In the prospective multicenter randomized clinical trial reported by Tan's team^[5], LA-ESCC patients treated with preoperative chemotherapy alone showed comparable survival outcomes compared with preoperative chemoradiotherapy (overall survival: hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.58–1.18; progression-free survival outcome: HR 0.83, 95% CI 0.59–1.16). Based on these results, do patients really need to be treated with radiotherapy?

Another great challenge to radiotherapy is the application of immunotherapy. The addition of immune checkpoint inhibitors to preoperative chemotherapy in patients with LA-ESCC is revolutionizing the therapeutic strategies for LA-ESCC. In LA-ESCC patients treated with chemoimmunotherapy, the pooled rates of major pathological response rate and pathological complete response were 58.3% and 32.9%, respectively; The pooled rates of R0 resection and resection were 92.8% and 81.1%, respectively^[6]. Compared with chemotherapy alone, immunotherapy plus chemotherapy improved the objective response rate (30.4% vs. 9.7%) in patients with ESCC^[7]. More randomized clinical trials are warranted to confirm the long-term survival benefits of combining immunotherapy and chemotherapy.

In addition, esophagectomy after concurrent chemoradiotherapy for resectable LA-ESCC is a complex procedure that can be associated with several potential side effects and complications. Some potential side effects and complications of esophagectomy after concurrent chemoradiotherapy may be critically associated with radiotherapy, including (1) Anastomotic leak: This occurs when the connection between the remaining esophagus and the stomach or intestine (anastomosis) leaks, causing leakage of digestive fluids into the chest or abdominal cavity. This can lead to infection, sepsis, or even death if not treated promptly^[8,9]; (2) Infection: As with any surgery, there is a risk of infection at the surgical site or in other parts of the body^[10]; (3) Pulmonary complications: These can include pneumonia, atelectasis (collapse of part of the lung), and respiratory failure. These complications are more common in patients with poor lung function or a history of smoking^[9]; (4) Gastroesophageal reflux: After esophagectomy, some patients may experience a backflow of stomach acid into the remaining esophagus, causing heartburn and other symptoms^[11]; (5) Nutritional issues: Many patients may experience difficulty swallowing, weight loss, and malnutrition due to changes in the gastrointestinal tract after surgery^[12]; (6) Lymphedema: Swelling caused by a build-up of lymphatic fluid may occur in the arms or legs after lymph nodes are removed during surgery; (7) Long-term side effects of chemoradiotherapy: These may include fatigue, decreased immune function, damage to the heart, lungs, or other organs, and an increased risk of developing a secondary cancer. Although patients who do not receive radiotherapy may also experience similar side effects, it is important to discuss the radiotherapy-related potential serious side effects and risks of esophagectomy after concurrent chemoradiotherapy with a surgeon, as well as strategies to manage and minimize these side effects.

On the other hand, do patients with LA-ESCC benefit from postoperative radiotherapy? According to the results from a prospective randomized study, compared with surgery alone, adjuvant radiotherapy after surgery significantly prolonged disease-free survival instead of overall survival in T2-3N0M0 ESCC patients without neoadjuvant therapy^[13]. Another analysis via the SEER database demonstrated that esophageal cancer patients might not benefit more from adjuvant radiotherapy when they had already been treated with neoadjuvant chemotherapy^[13]. Therefore, we suggest that postoperative radiotherapy may not be necessary for patients who had previously received preoperative

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chemotherapy as well.

Above all, we consider that patients with LA-ESCC could not benefit more from preoperative radiotherapy and suspect to postpone radiotherapy till the time point of recurrence^[14]. More real-world studies are warranted to explore the optimal application of radiotherapy in patients with LA-ESCC.

Abbreviations

HR, hazard ratio; LA-ESCC, locally advanced esophageal squamous cell carcinoma.

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