



REVIEW ARTICLE

Current choices and prospects in management of postoperative esophageal cancer patients[☆]



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Summary Locally advanced esophageal cancer is usually dealt with multimodal therapies. The current treatment of choice is neoadjuvant chemoradiation with surgery, but several other choices are also available for adenocarcinoma. For example, adjuvant therapy can be added to the patients received upfront surgery or neoadjuvant therapy in certain conditions. However, squamous cell carcinoma has no such flexibility. This article will address the reason to this remarkable difference, also the current evidence and perspective of adjuvant therapy for esophageal squamous cell carcinoma.

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Esophageal cancer is one of the most lethal malignant diseases, despite of many progress has been made in the treatment modalities.¹ Early esophageal cancer would be treated with surgery alone or endoscopic resection,

however, this disease entity is prone to be detected late in course. Locally advanced esophageal cancer and esophageal cancer with distant metastasis are more frequently encountered. A curative intent could still be planned for locally advanced esophageal cancer, which represented a cT1~T4 esophageal cancer with or without lymph node involvement. However, the survival of patients received surgery alone is generally low if locally advanced disease is encountered.²

For locally advanced esophageal carcinoma, multimodal treatment combining chemotherapy, radiotherapy and surgery is utilized widely. The two main histological types

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of esophageal cancer are adenocarcinoma and squamous cell carcinoma.

1. Adenocarcinoma of esophagus

In most widely accepted guidelines, initial treatment for locally advanced esophageal adenocarcinoma might be chemoradiotherapy (CRT) or chemotherapy (CT). Both treatment choices could be planned as neoadjuvant (preoperative) therapy, and surgery could be given for medically fit patients afterwards. Perioperative chemotherapy is also a viable choice.³ Postoperative treatment such as CT or CRT could be given in various fashions: CT could be given to patients without nodal involvement as part of perioperative chemotherapy, and both CT and CRT for those with positive nodes or R1 resections following either upfront surgery or preoperative chemotherapy, for those with upfront surgery which discovered a pT3-pT4a disease, or patients with pT2 stage with high risk features including perineural invasion or poorly differentiated tumor.⁴ This great variability may be confusing for clinicians to follow. As a matter of fact, more and more doctors would prefer a simpler and straight forward plan for this group of patient, which is trimodal therapy comprised of neoadjuvant CRT and surgery. This trend could be comprehended because this strategy is supported by the by far most powerful single multi-nation trial.⁵ But we could see that all those various strategies are still listed in guidelines, physicians could manage different conditions accordingly. Physicians could follow the protocols with ease, for there are high level and sufficient evidences behind these different strategies.

2. Squamous cell carcinoma of esophagus

The other most common histological type of esophageal cancer: Squamous cell carcinoma, however, has fewer treatment options than adenocarcinoma. The first choice for locally advanced disease is also neoadjuvant CRT followed by surgery, primarily based on the famous CROSS trial, as well as many recent meta-analyses.^{2,6,7} The major differences lied in how physicians treat postoperative patients. Whether for patients with positive or negative nodal involvement, there are no suggestions for adjuvant therapy in guidelines. Adjuvant therapy is only indicated for patients with incomplete resection. This could be attributed to a lacking of high level evidences in adjuvant therapy for esophageal squamous cell carcinoma.⁴

3. Patients received upfront surgery

Similarly, physicians would face two situations that would use adjuvant therapy: in patients received upfront surgery, or those with preoperative treatment but have certain risks that make physicians worry about recurrence. In the first situation, most physicians would agree that surgery alone is far from enough for patients with locally advanced disease. Different forms of adjuvant therapies were studied. Firstly, adjuvant radiotherapy (RT) is not considered effective based on several studies.^{8,9} Adjuvant CT showed some minor benefits or only trends, but after the publishing of

the two hallmark trials by Ando et al, neoadjuvant CT demonstrated a clear benefit over adjuvant CT.^{10,11} Thus, a physician should choose neoadjuvant CT over adjuvant CT, whenever possible. The last possibility is adjuvant CRT. The advantage of this strategy has been studied in one small trial and many retrospective studies. The trial we just mentioned was conducted by Lv et al, he compared three groups: patients received surgery alone, neoadjuvant CRT or adjuvant CRT. Both neoadjuvant and adjuvant CRT group has a survival benefit towards surgery alone group, and the magnitude of survival difference amongst these two groups is similar.¹² A series of retrospective studies also aimed at this strategy, most of the studies showed a significant survival benefits of the postoperative CRT over the surgery alone patients. Hsu et al compared patients received surgery alone and those with adjuvant CRT in a nation-wide database retrospectively, the result was also adjusted with propensity-score matching (PSM). The 5-y OS and 5-year disease free survival (5-y DFS) were both better in the adjuvant group.¹³ However, with only one randomized trial published and the total number of patients compared in randomized trials remain few, a generally accepted suggestion for postoperative treatment of esophageal squamous cell carcinoma with complete resection is yet to be defined.

4. Patients received neoadjuvant treatment and surgery

The other situation that could use an adjuvant therapy would be a patient completed a trimodal therapy, but still have a high risk for recurrence. These patients have already received neoadjuvant therapy, either CT or CRT, then also surgical resection of esophagus. However, how to tell a patient has higher chance of recurrence? Several studies have addressed this question. Most of the author would search the pathological specimen for the answer. For example, some author found tumor response grade would affect recurrence rate.¹⁴ Schoppmann's study showed lymphovascular invasion (LVI) would affect both 5-y OS and 5-y DFS, as Chen and colleagues also reveal the negative effect of perineural invasion (PNI).^{15,16} Tu and colleagues collected the various candidates of pathological prognostic factors after neo-CRT, and stratified patients into low, median and high risk groups with six factors. These factors could be grouped into primary tumor factors, lymph node factors and surgical factors. Primary tumor factors include tumor regression grade (TRG), LVI and PNI, lymph node factors include a positive ypN and extracapsular invasion (ECI), and surgical factor is incomplete resection. This stratification could be powerful adjuncts to the current AJCC system to improve the quality of prognostic prediction.¹⁷ Rice and colleagues break down the details of the 8th edition of the American Joint Committee on Cancer (AJCC) staging of epithelial cancers of the esophagus and esophagogastric junction (EGJ), and highlighted a new addition: postneoadjuvant therapy staging. The main driver of this addition is the pTNM staging lacked the peculiar stage: ypT0N1-3M0, and ypTisN1-3M0, as well as the dissimilar stage group compositions, and markedly different survival profiles. Although the other factors such as LVI and

PNI have not been included into this system yet, a more precise prognostication is now available for post-neoadjuvant cancers.¹⁸

In this subset of patients, a poorer performance status is anticipated, and also they might have slightly higher rate of postoperative complication, the following adjuvant therapy would be hindered. In the other hand, patients classified as high risk group are often those with poorer pathological response to the neoadjuvant therapy. Thus, many physicians would question the effect of adjuvant therapy if similar regimen is given. These factors might explain that there is no consensus regarding the best suggestion for a postneoadjuvant esophageal squamous cell carcinoma, even with high risk of recurrence. Burt et al evaluated 3592 patients from National Cancer Data Base (NCDB) received neoadjuvant CRT and surgery, 335 (9.3%) of them received adjuvant CT. The treatment effect was not seen in patients with squamous cell carcinoma, which comprised of 15.2% of all patients; but adjuvant CT was beneficial for patients with adenocarcinoma, a 30% of lower risk of death in nodal patients was found. Type of chemotherapy regimen was not mentioned, which might not be fully available in a nationwide database. The prevalence of adjuvant CT administration is also low. This would also decrease the power of this study to discover the effectiveness on squamous cell carcinoma.¹⁹ Hsu et al also evaluate the effect of adjuvant CRT on 112 pathological non-responders who had been treated with neoadjuvant CRT and esophagectomy. The comparison of adjuvant treatment to surveillance is done with propensity-score matching. 32 well-matched pairs were compared, and a superior DFS was noted in the adjuvant group. However certain treatment-related mortality was also noted, this may be viewed as why there was only a borderline increase of the 3-y OS rate of adjuvant group. In this study, PF regimen (cisplatin and 5-fluorouracil) or taxanes-platinum regimen were used most frequently.²⁰ In short, we could make a better prediction on patient's fate after neoadjuvant CRT and operation with newly identified prognostic factors, but the best choice of adjuvant treatment are remained to be defined in the future.

5. Conclusion

Treating locally advanced esophageal cancer, whether adenocarcinoma or squamous cell carcinoma, combining surgery with other modalities of treatment became state of art practice. However, a lacking of choices for post-operative patients with squamous cell carcinoma comparing those with adenocarcinoma is notable. The first step would be "Who is to be given the proposed adjuvant therapy?" New staging system, especially aims at post-neoadjuvant therapy emerges and responds the call. But the following question: "Which regimen is clearly beneficial and should be given to them?" is yet to be answered in large clinical trials.

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Conflicts of interest

The authors declare no conflicts of interest.

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