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Adjuvant Therapy for Esophageal Squamous Cell Carcinoma

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Adjuvant therapy for completely resected esophageal squamous cell carcinoma is less commonly applied in clinical practice than neoadjuvant therapy, but it plays a substantial role in improving survival for esophageal cancer patients. This article presents a concise review of the evidence regarding adjuvant therapy for esophageal squamous cell carcinoma and future directions, particularly immunotherapy.

Keywords: Adjuvant therapy, Esophageal neoplasms, Neoadjuvant therapy, Immunotherapy

Introduction

Esophageal cancer is the eighth most common cancer in Korea and has the sixth highest cancer mortality rate worldwide. In Korea, 2,483 new esophageal cancer cases were diagnosed in men and women in 2017, comprising 1.1% of all newly diagnosed cancers in Korea that year [1]. Despite its low incidence, esophageal cancer has a high mortality rate. This suggests that, though more early-stage esophageal cancers are being detected due to regular universal screening, which has led to higher cure rates, esophageal cancer remains a difficult disease to overcome.

Adjuvant therapy after complete resection is associated with improved survival for most cancer types. Adjuvant chemotherapy as a treatment for esophageal cancer has been well investigated, but histologic differences among esophageal cancer cases are known to exist according to race and geography [2]. Therefore, cautious interpretation of larger studies is required.

Most esophageal cancers in Korea are squamous cell carcinomas, as in other East Asian countries such as Japan and China, whereas more than half of esophageal cancers in Caucasians or Western populations are adenocarcinomas [2]. Among 2,362 esophageal cancers diagnosed in Korea in 2017, 2,255 (95.5%) were squamous cell carcinomas [1]. Meanwhile, large randomized studies of adjuvant chemotherapy in gastroesophageal cancer patients have mostly included gastric cancers or gastroesophageal junctional adenocarcinomas, with very few squamous cell carcinomas analyzed [3,4].

Adjuvant chemotherapy (JCOG9204)

The Japan Clinical Oncology Group trial (JCOG9204) compared adjuvant chemotherapy (2 cycles of 5-fluorouracil [5FU] and cisplatin) with observation in 242 patients with completely resected pathologic stage IIA–IV esophageal squamous cell carcinoma [5]. The difference in disease-free survival, the primary endpoint, was statistically significant between the 2 arms (p=0.037). However, an exploratory subgroup analysis revealed that the benefit of adjuvant chemotherapy was limited to node-positive (pN1) cases, while there was no difference in disease-free survival between the adjuvant chemotherapy and observation arms among node-negative (pN0) cases. Furthermore, there was no difference in overall survival between the 2 arms for the whole study population (p=0.13). Several interpretations can be derived from this study. First, although it failed to

show an overall survival benefit of adjuvant chemotherapy, we should bear in mind that the primary endpoint was disease-free survival, not overall survival. Nonetheless, this study cannot be interpreted as providing confirmatory findings supporting the recommendation of adjuvant therapy in patients with esophageal squamous cell carcinoma. However, it is the largest randomized study to strongly suggest a benefit from adjuvant chemotherapy for completely resected esophageal squamous cell carcinoma, especially in pathologically node-positive cases.

Neoadjuvant chemotherapy or chemoradiotherapy

Since the JCO9204 trial was published, many oncologists have begun to suspect that neoadjuvant chemotherapy may be superior to adjuvant chemotherapy. The JCOG9907 trial randomized 330 patients with clinical stage II or III esophageal squamous cell carcinoma into 2 arms: surgery followed by adjuvant chemotherapy (2 cycles of 5FU and cisplatin) or the same (neoadjuvant) chemotherapy followed by surgery [6]. Interestingly, the neoadjuvant chemotherapy arm showed statistically superior overall survival compared with the adjuvant chemotherapy arm (p=0.04). Based on this study, all patients with locally advanced esophageal squamous cell carcinoma are recommended to receive chemotherapy prior to surgery, not after surgery.

Meanwhile, a larger randomized study (N=368) showed that concurrent neoadjuvant chemoradiotherapy with surgery was associated with significantly improved overall survival compared with surgery alone [7]. Accordingly, many guidelines began recommending neoadjuvant concurrent chemoradiotherapy for esophageal cancer along with a histologic examination to determine whether the underlying cancer is adenocarcinoma or squamous cell carcinoma [8,9]. However, some have criticized that study for being performed across too many institutions with a small number of participants enrolled at each institution during a relatively long-term study period (2004–2008). Another concern raised by physicians working with Asian patient populations is that markedly fewer squamous cell carcinoma cases (n=84) were included than adenocarcinoma cases (n=275).

No report has yet compared neoadjuvant chemotherapy to chemoradiotherapy. Recently, a highly anticipated phase III trial was initiated to investigate this issue [10].

Studies of adjuvant chemotherapy

Based on the JCOG9907 trial, neoadjuvant therapy has been preferred to adjuvant therapy in patients with locally advanced esophageal cancer, especially for patients with clinically identified lymph-node-positive disease. In clinical practice, however, many patients receive surgery without prior neoadjuvant chemotherapy or chemoradiotherapy and are subsequently found to have locally advanced or node-positive esophageal cancer. For these patients, adjuvant chemotherapy is universally performed in clinical practice. Within this context, several retrospective studies have investigated the role of adjuvant chemotherapy in real-world clinical settings. Lee et al. [11] reviewed data from 40 patients who received adjuvant chemotherapy for node-positive, completely resected esophageal squamous cell carcinoma and compared them with a matched control arm with a history of surgery alone. There was a statistically significant difference in disease-free survival, favoring adjuvant chemotherapy. A meta-analysis also demonstrated that adjuvant chemotherapy played an effective role in patients with completely resected, node-positive esophageal squamous cell carcinoma [12].

Some subgroups benefit more from adjuvant chemotherapy than others

Previous studies showed that adjuvant chemotherapy was more effective for patients with lymph-node-positive esophageal cancer than for patients with node-negative esophageal cancer [5,11]. A retrospective study aimed to further identify the subgroup that could benefit most from adjuvant therapy [13]. The researchers grouped 298 patients who underwent esophagectomy for esophageal squamous cell carcinoma according to the total number of resected lymph nodes and the ratio of cancer-involved lymph nodes divided by all resected lymph nodes. In a subgroup with a low number of resected lymph nodes (<28) and a high lymph-node ratio (>4.17%), survival was significantly superior in patients who received adjuvant therapy compared with those who received no adjuvant therapy.

Adjuvant chemotherapy regimens

Based on the JCOG9204 and JCOG9907 trials, the standard regimen of adjuvant chemotherapy is 2 cycles of 5FU (800 mg/m^2 for 5 days) and cisplatin (60 mg/m^2 for day 1). In clinical practice, however, many patients receive a maximum of 4 cycles of 5FU and cisplatin with variable doses

and infusion times for 5FU (800 mg/m^2 for 5 days or 1,000 mg/m^2 for 4 days).

Given the neurotoxicity and renal toxicity of cisplatin, new platinum regimens have been applied, such as the FOLFOX regimen, which is a combination of 5FU, oxaliplatin, and leucovorin. Currently, no data support any regimen as the superior option [14].

Adjuvant therapy after neoadjuvant chemoradiotherapy and surgery

Among patients who undergo surgery after neoadjuvant chemoradiotherapy, many are subsequently found to have a high tumor burden based on the removed tumor specimens and are at a high risk of esophageal cancer recurrence and death. Therefore, many physicians have come to recognize the need for further therapy after concurrent neoadjuvant chemoradiotherapy and surgery.

One retrospective study reviewed all esophageal cancer patients who received neoadjuvant concurrent chemoradiotherapy and esophagectomy [15]. Some patients received further adjuvant chemotherapy, while others did not. No survival difference was found according to adjuvant chemotherapy history across the study population, but in a subgroup with residual node-positive disease, patients who received adjuvant chemotherapy lived much longer than those who did not. However, these data should be interpreted cautiously because the patients who received adjuvant chemotherapy after neoadjuvant therapy and surgery were likely to be in a better overall condition and to have had fewer complications from their previous therapy.

Adjuvant immune checkpoint inhibitor therapy

Patients who received neoadjuvant chemoradiotherapy followed by esophagectomy are generally likely to experience a deterioration of their condition, and therefore would not easily withstand further adjuvant chemotherapy, despite the possibility that they may have a high risk of recurrence. Immune checkpoint inhibitors have demonstrated anti-tumor efficacy against many tumor types, including esophageal cancer [16-18]. The synergistic effect of immune checkpoint inhibitors and radiotherapy has been well documented in patients with non-small-cell lung cancer [19]. Furthermore, these agents are relatively tolerable compared with chemotherapy, making them a good adjuvant therapy option for esophageal cancer patients who have received concurrent neoadjuvant chemoradiotherapy and surgery.

In an ongoing study, we are evaluating the role of adjuvant durvalumab in patients whose esophageal squamous cell carcinoma was completely resected after concurrent chemoradiotherapy [20]. We have completed enrollment (N=86) in a placebo-controlled randomized study, with publishable results expected within a few years. A phase III study (CheckMate 577) with a similar design to evaluate nivolumab also recently completed enrollment of 794 patients [21].

Conclusion

Although the standard practice for clinical stage II–III esophageal squamous cell carcinoma is neoadjuvant chemotherapy or chemoradiotherapy based on reliable guidelines, adjuvant chemotherapy plays a particularly beneficial role in terms of disease-free survival in patients who did not receive neoadjuvant therapy. Adjuvant chemotherapy yields greater benefits for patients with pathologic lymph-node-positive disease. Future research in this field will focus on adjuvant immunotherapies.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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