Adjuvant Therapy for Esophageal Squamous Cell Carcinoma

Jong-Mu Sun, M.D., Ph.D.

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ARTICLE INFO
Received May 12, 2020
Accepted May 20, 2020

Corresponding author
Jong-Mu Sun
Tel 82-2-3410-3459
Fax 82-2-3412-3996
E-mail jongmu.sun@skku.edu
ORCID https://orcid.org/0000-0001-9683-4111

†This article was presented at the 6th Esophageal Cancer Symposium (lecture on November 16th, 2019, Samsung Medical Center, Seoul, Korea).

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-negative, 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/m² for 5 days) and cisplatin (60 mg/m² 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/m² for 5 days or 1,000 mg/m² 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.

**References**

1. Cancer Information Service. Esophageal cancer [Internet]. Goyang: Cancer Information Service; 2019 [cited 2020 Mar 20]. Available from: https://www.cancer.go.kr/lay1/program/S1T211C223/cancer/view.do?cancer_seq=4277&menu_seq=4282.
2. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. Br J Cancer 2009;101:855-9.
3. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.
4. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol 2015;33:3130-6.
5. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study JCOG9204. J Clin Oncol 2003;21:4592-6.
6. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68-74.

7. Van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.

8. National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancers [Internet]. Plymouth Meeting (PA): National Comprehensive Cancer Network [cited 2020 Mar 20]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.

9. Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D; ESMO Guidelines Working Group. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi51-6.

10. ClinicalTriial.gov. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for resectable locally advanced esophageal cancer (HCHTOG1903) [Internet]. Bethesda (MD): ClinicalTriial.gov; 2019 [cited 2020 Mar 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT04138212.

11. Lee J, Lee KE, Im YH, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. Ann Thorac Surg 2005;80:1170-5.

12. Zhao P, Yan W, Fu H, Lin Y, Chen KN. Efficacy of postoperative adjuvant chemotherapy for esophageal squamous cell carcinoma: a meta-analysis. Thorac Cancer 2018;9:1048-55.

13. Li Y, Zhao W, Ni J, et al. Predicting the value of adjuvant therapy in esophageal squamous cell carcinoma by combining the total number of examined lymph nodes with the positive lymph node ratio. Ann Surg Oncol 2019;26:2367-74.

14. Lim SH, Shim YM, Park SH, et al. A randomized phase II study of leucovorin/5-fluorouracil with or without oxaliplatin (LV5FU2 vs. FOLFOX) for curatively-resected, node-positive esophageal squamous cell carcinoma. Cancer Res Treat 2017;49:816-23.

15. Burt BM, Groth SS, Sada YH, et al. Utility of adjuvant chemotherapy after neoadjuvant chemoradiation and esophagectomy for esophageal cancer. Ann Surg 2017;266:297-304.

16. Kudo T, Hamamoto Y, Kato K, et al. Nivolumab treatment for oesophageal squamous-cell carcinoma: an open-label, multicentre, phase 2 trial. Lancet Oncol 2017;18:631-9.

17. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:1506-17.

18. Metges J, Francois E, Shah M, et al. The phase 3 KEYNOTE-181 study: pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Ann Oncol 2019;30(Suppl_4):iv130.

19. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342-50.

20. ClinicalTriial.gov. Adjuvant durvalumab for esophageal cancer [Internet]. Bethesda (MD): ClinicalTriial.gov; 2019 [cited 2020 Mar 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT02520453?term=jong-mu+sun&draw=2&rank=3.

21. ClinicalTriial.gov. An investigational immuno-therapy study of nivolumab or placebo in participants with resected esophageal or gastroesophageal junction cancer (CheckMate 577) [Internet]. Bethesda (MD): ClinicalTriial.gov; 2020 [cited 2020 Mar 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT02743494.