

Possible refinement of the standard treatment of esophageal cancer

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Mattiucci and colleagues made exquisite comments on the study published by Hwang *et al.* (1), summarized on the role of adjuvant chemoradiation (CRT) in treatment of esophageal cancer (2). The essential features of the referring article and the challenges of research in the topic were pointed out. Hwang and colleagues compared survival between patients with esophageal squamous cell carcinoma (ESCC) receiving either surgery alone (group 1) and adjuvant CRT (group 2). Propensity-score matching (PSM) as a supplementary statistic tool, has excellent performance in reducing the selection bias of a retrospective study, though it still has some major drawbacks. In Hwang's study, the patient demographics were significantly different in the two groups initially. The majority of patients in the surgery alone group had a pT1 stage (47%), while 61% of patients in the adjuvant group had a pT3 tumor. The characteristics of the patients became less different after matching. The matching omitted large number of patients with less advanced tumor. The post-matching T stage distribution was not an average between groups 1 and 2, but became T3-predominant in both group instead. Thus, the result reflected the treatment effect on a more advanced disease. As previous studies showed, in ESCC patients with relatively advanced stage disease, surgery alone is insufficient, trimodal therapy is better suited for locally advanced esophageal patients (3,4). Assuming the matching did its job, the result was not very surprising.

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for locally advanced ESCC, there were no enough randomized control trials (RCTs) to support a clear survival benefit of adjuvant CRT. A randomized trial conducted by Lv *et al.* enrolled 238 patients and divided them into three groups, received either surgery alone, neoadjuvant CRT or adjuvant CRT. This study discovered similar survival benefit of neoadjuvant and adjuvant CRT over surgery alone (5). A smaller trial conducted by Tachibana *et al.* compared 23 patients receiving postoperative chemotherapy to 22 patients who underwent postoperative CRT. The 5-year OS in the former group was 38%, which in the latter group was 50%, but statistical significance was not reached (6). Besides of these trials, there were mostly retrospective studies. Thus, the role of adjuvant CRT in locally advanced ESCC with complete resection (R0) was not defined or suggested in the National Comprehensive Cancer Network (NCCN) guideline (7). Although there were many retrospective studies have shown strong survival benefits of adjuvant CRT over surgery alone, the level of evidence should be always respected. For the first issue mentioned by Mattiucci in the commentary, "May we potentially reconsider the general indication of upfront preference for preoperative CRT?" The answer is: the preference for preoperative CRT would still be strong, because the evidences supporting postoperative treatment are still not enough.

Therefore, what is the true value of these discoveries from the retrospective studies about adjuvant CRT? One interpretation is: they might point out some possible

direction of future study. Hsu *et al.* used PSM method on a nation-wide database in Taiwan, compared 286 well-balanced pairs of patients received either neoadjuvant CRT or adjuvant CRT. The survival was similar (8). This retrospective study added another support for adjuvant CRT to the pool of lower level evidences. However, in the editorial commentary to this article, Ahmad *et al.* stated “*we like to think that there is a perfect order for everything*”, and “*why must the simple, hierarchic ordering system become so inconsistent and impossible to remember when it comes to the management of locally advanced ESCC?*” (9) The thing is: a system with a perfect order is nothing more than someone’s wish, not necessarily be the truth. Every person in the modern society must remember various things with complex arrangement and orders, such as passwords, driving manuals or antibiotic treatment for tuberculosis. What people really care would be “does it work?” rather than “is it simple?” If a regimen works for a certain disease, then medical doctors would be required to know it whether it is complicate or not. In the other hand, we should respect the scientific truth of medicine. We agree adjuvant CRT for locally advanced ESCC should not be a formal recommendation as neoadjuvant CRT by now, but if the survival benefit of adjuvant CRT is backed by future large-scale RCTs, we should also agree this option to be included in the practical guidelines. Adjuvant CRT is gaining more momentum than adjuvant chemotherapy or radiotherapy alone, as the second issue asked by Mattiuci, “*Should we offer postoperative CRT to a wider population of patients?*” The answer would be: it could be considered if proven with large RCT.

For the third issue, “*Is there room for further integration of postoperative CRT as an intensification of multimodal treatment?*” Since many patients still fare poorly after trimodality therapy, additional treatment is eagerly wanted. In the other hand, tolerance for such treatment is also increased to more than 70%, it might attribute to the use of minimally invasive esophagectomy (10). Thus, the answer would be yes, there is room for integration.

To understand and treat patients following the practical guidelines is one of the basic requirements of medical professionals. But to see beyond the guidelines and discover new possibilities are the ability of leaders. The available knowledge formed an imaged model of the real world. Those who usually try infrequent paths might not give forth the answer all the time, but they have bigger chance to shape this model rather than followers. One way to peek into the maze is through studies with lower level of evidences, such as retrospective studies. These researches

aren’t going to give the final judgment, but may help us to know which new ground is more promising, and decide how the new trials be arranged. Large RCTs are still required to define the role of adjuvant CRT for locally advanced ESCC, and it will certainly reward us with a more precise model of esophageal cancer treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Mattiucci GC, Cellini F. Role of the modern radiotherapy in the postoperative setting for esophageal cancer. *J Thorac Dis* 2017;9:4212-5.
2. Hwang JY, Chen HS, Hsu PK, et al. A Propensity-matched Analysis Comparing Survival After Esophagectomy Followed by Adjuvant Chemoradiation to Surgery Alone for Esophageal Squamous Cell Carcinoma. *Ann Surg* 2016;264:100-6.
3. 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.
4. Hsu PK, Huang CS, Wang BY, et al. Survival benefits of postoperative chemoradiation for lymph node-positive esophageal squamous cell carcinoma. *Ann Thorac Surg* 2014;97:1734-41.
5. Lv J, Cao XF, Zhu B, et al. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. *World J Gastroenterol* 2010;16:1649-54.
6. Tachibana M, Yoshimura H, Kinugasa S, et al. Postoperative chemotherapy vs chemoradiotherapy for thoracic esophageal cancer: a prospective randomized clinical trial. *Eur J Surg Oncol* 2003;29:580-7.
7. Ajani JA, D’Amico TA, Almhanna K, et al. Esophageal and esophagogastric junction cancers, version 1.2015. *J Natl Compr Canc Netw* 2015;13:194-227.
8. Hsu PK, Chen HS, Liu CC, et al. Pre- versus postoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg* 2017;154:732-40.e2.
9. Ahmad U, Murthy SC, Raja S. Trimodality therapy for

- esophageal squamous cell carcinoma: Is it really a medical
palindrome? *J Thorac Cardiovasc Surg* 2017;154:741-2.
10. Tu CC, Hsu PK, Chien LI, et al. Prognostic histological

factors in patients with esophageal squamous cell
carcinoma after preoperative chemoradiation followed by
surgery. *BMC Cancer* 2017;17:62.

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