Editorial Commentary

Definitive chemoradiotherapy with simultaneous integrated boost of radiotherapy dose for T4 esophageal cancer—will it stand for a standard treatment?

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Provenance: This is an invited article commissioned by the Section Editor Xiaozheng Kang (Department of Thoracic Surgery, Beijing Cancer Hospital, Peking University, Beijing, China).

Comment on: Chen D, Menon H, Verma V, *et al.* Results of a Phase 1/2 Trial of Chemoradiotherapy With Simultaneous Integrated Boost of Radiotherapy Dose in Unresectable Locally Advanced Esophageal Cancer. JAMA Oncol 2019. [Epub ahead of print].

Submitted Nov 19, 2019. Accepted for publication Dec 01, 2019.

doi: 10.21037/jtd.2019.12.59

View this article at: http://dx.doi.org/10.21037/jtd.2019.12.59

Esophageal cancer has been recognized as a dismal disease because it metastasizes even in the early stage and invades vital organs, such as the trachea and aorta. Despite advancements in multidisciplinary treatment, consisting of chemotherapy (CT), radiotherapy (RT), and surgery (1), no standard treatment for T4 esophageal cancer has been established. Although definitive chemoradiotherapy (dCRT) has been considered one of the treatment options, a high recurrence rate was observed even after the patients achieved clinical complete response (cCR). Based on previous findings that most local failure occurred within the radiated field (2), Welsh *et al.* planned to evaluate whether intensive local treatment using a simultaneous integrated boost of RT (SIB-RT) could improve local control and survival.

In the current phase 2 study, Chen *et al.* remarkably showed the safety and efficacy of SIB-RT in the primary tumor and lymph node (3). A total boost RT dose of 63 Gy and a standard dose of 50.4 Gy were administered to the subclinical risk area and the clinical targeted volume, respectively. Safety and efficacy evaluated with local control and overall survival (OS) were the endpoints of this trial. As a result, there was no grade 4 or higher toxicity, and the occurrence of grade 3 adverse events was manageable, suggesting the safety of the current protocol. In terms of efficacy, median OS was 21.5 months, and the study group showed significant improvement in local control and prognosis compared with the historical cohorts that received standard-dose dCRT. Although the comparison between the current study cohort and previously treated patients who received standard-dose dCRT needs to be cautiously evaluated because this was not included in the prospective trial, the median OS of 21.5 months was consistent with those in recent trials (4,5) and superior to the OS in the previous study using the classical planning procedure of RT (6).

The Intergroup 0123 study proved that an increase in the local radiation dose did not contribute to survival (6), which was corroborated by the follow-up study (7). However, as the authors mentioned, a number of retrospective trials have suggested the additional efficacy of intensive local treatment (8,9). Therefore, we agree with the motivation of the current study that the longstanding question of whether an increase in local intensity could improve prognosis needs to be revisited at this point. Consequently, this study successfully showed that the dose escalation of RT using an advanced technique potentially improved survival while maintaining the safety. In contrast, the description in the report that the efficacy of treatments for adenocarcinoma and squamous cell carcinoma (SCC) was the same needs to be discussed. Although the authors reported that SCC might be more resistant to RT than adenocarcinoma, it is inconsistent with the result of the CROSS trial, which revealed that the histological response was remarkably better in SCC (10,11). A reasonable explanation could be that an increased dose of RT is capable of eradicating esophageal cancer regardless of histology. The difference

between SIB-RT and standard RT was more evident in adenocarcinoma than SCC, indicating that dose escalation is strikingly required in adenocarcinoma, whereas lower dose could be sufficient in SCC.

Regarding RT technology, 15% of the participants received proton-beam RT. Although several retrospective cohort studies exist (12), there is no concrete evidence that the safety and efficacy of proton beams were the same as those of the photon beams. Generally, proton therapy encourages concentrating the radiation to the targeted lesion, which reduces the adverse effects to the surrounding tissues (13,14). Because the total radiation energy does not differ from that in photon beam, the efficacy is supposed to be the same. However, esophageal cancer could metastasize even in the early stage, and clinically undetectable tumor cells could exist around the primary tumor and lymph node, indicating that radiation to the surrounding tissue would have contributed to local control. To evaluate the efficacy of proton therapy, 15% of the entire cohort is insufficient in this study. Therefore, although SIB-RT can be considered a treatment option, the indication of proton therapy needs be carefully evaluated.

Clinically unresectable esophageal cancer was selected as an indication in the current trial. As summarized in the review article by Makino *et al.*, there are two types of treatment strategies for unresectable esophageal cancer (15). Definitive CRT, including SIB-RT, has been a mainstay, and patients are expected to be cured when they achieve cCR. However, almost half of patients with cCR developed disease recurrence in the advanced stage. Indeed, 33% participants experienced local failure in this study, and 24% eventually underwent salvage esophagectomy. Ultimately, all patients who underwent surgical resection showed distant metastasis, indicating that systemic tumor control is also required to treat unresectable esophageal cancer. Another treatment option for T4 stage disease is induction CT, followed by conversion surgery. Combined with an intensive chemotherapeutic agent, triplet CT, such as 5-fluorouracil, oxaliplatin, and docetaxel (FLOT) and docetaxel, cisplatin, and 5-fluorouracil (DCF), was shown to be tolerable and improve prognosis (16,17). Because intense CT is capable of eradicating systemic micrometastasis and conversion surgery could achieve better local control, induction CT followed by conversion surgery is potentially superior to dCRT. In fact, Yokota *et al.* reported a high rate of conversion surgery after DCF in T4 esophageal cancer, showing 1- and 3-year OS of 100% and 90%, respectively (18). While the inclusion criterion in this trial was T4 esophageal cancer excluding M1 disease, this study aimed to investigate the efficacy of induction CT followed by conversion surgery. Based on the result, the Japan Clinical Oncology Group is currently conducting a multi-institutional phase 3 trial of trimodality therapy with induction DCF versus dCRT for locally advanced unresectable SCC of the thoracic esophagus (JCOG1510: TRIANgLE) (19), which will help establish the standard treatment for T4 esophageal cancer. Because induction CT using FLOT was administered in stage IV or T3/4N+ nonmetastatic cancer in the current trial, this might partially account for the improvement in the local and systemic control of the disease.

The combination of triplet CT and RT can be considered. Higuchi *et al.* conducted a phase 2 trial using definitive dCRT with DCF (DCF-R) for advanced esophageal cancer (KDOG 0501-P2). It showed a 3-year OS of 44%, which was promising, but high incidence of grade 3 or higher leukopenia (71%) and neutropenia (57%), including febrile neutropenia (38%), was observed. Miyazaki *et al.* conducted another phase 2 trial using DCF-R, which also showed high incidence of adverse effects (20). Consequently, despite the high efficacy, triplet CT with concurrent RT should be avoided at this point.

Again, Chen *et al.* should be commended because they successfully suggested that dCRT with SIB-RT can be a valuable strategy for T4 esophageal cancer treatment, regardless of histology. Taking into account the comparison between dCRT and conversion surgery following induction CT, further study is required to establish an ideal multidisciplinary treatment and eradicate local and systemic tumor cells.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Matsuda S, Mayanagi S, Irino T, Kawakubo H, Kitagawa Y. Definitive chemoradiotherapy with simultaneous integrated boost of radiotherapy dose for T4 esophageal cancer—will it stand for a standard treatment? J Thorac Dis 2019;11(12):5682-5684. doi: 10.21037/jtd.2019.12.59

