Editorial Commentary

Dose escalation not improving outcome in esophageal cancer—still far from conclusive

Yun-Hsuan Lin[1,2]^, Shih-Yu Huang[3], Shang-Yu Chou[1,2], Tzu-Ting Huang[1,2], Yu-Ming Wang[1,2,4]^

[1]Department of Radiation Oncology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [2]Department of Proton and Radiation Therapy Center, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [3]Division of Hematology Oncology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [4]School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Taoyuan, Taiwan
Correspondence to: Yu-Min Wang. Department of Radiation Oncology & Proton and Radiation Therapy Center, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan. Email: scorpion@cgmh.org.tw.

Received: 19 Aug 2021; Accepted: 18 March 2022; Published: 30 March 2022.
doi: 10.21037/tro-21-23
View this article at: https://dx.doi.org/10.21037/tro-21-23

The treatment results of definitive chemoradiation for esophageal cancer have long been suboptimal. The standard prescribed radiation dose, 50–50.4 Gy, for esophageal cancer, is much lower than many other common types of cancer (e.g., head and neck cancer, lung cancer). Although there is a dose-response relationship between radiation dose and tumor control in esophageal cancer (1), the only phase III trial focusing on the topic closed prematurely and showed that higher radiation dose did not increase survival or local/regional control (2). Since then, the issue has remained under debate in the field of radiation oncologists for the past two decades.

We appreciated the investigators of the ARTDECO trial for successfully conducting the study to answer the controversial question (3). Unexpectedly, the results were similar to the INT 0123 trial that dose escalation did not result in an outcome improvement. Notably, the completion rate of the planned chemoradiation course was lower in the high dose arm. Fewer patients in the high dose arm (59.3%) completed the full six courses of chemotherapy compared to that in the standard dose arm (69.4%). Cumulative chemotherapy dose may affect the outcomes of chemoradiation. In addition, fewer patients in the high dose arm (91.9%) completed radiotherapy compared to that in the standard dose arm (96%), and the rates of delay completion of radiotherapy were not shown in the report. It is well documented that tumor control is reduced by about 1–2% for each day that overall treatment time is prolonged. Both the less than desirable delivery of chemotherapy and radiotherapy may mask the true efficacy of dose escalation.

To unleash the full potential of dose escalation, several attempts could be made. The optimal scheme of boost is not yet established. The escalated doses to the gross lesion were heterogeneous in different protocols using simultaneous integrated boost technique (range, 2.1–2.5 Gy per fraction). From the perspective of radiobiology, the esophagus consists of rapidly dividing cells and is very sensitive to changes in dose intensity, i.e., fraction size, and overall treatment time. To escalate the total dose but not increase the acute toxicity causing treatment interruption at the same time, dose escalation with sequential boost method using smaller fraction size may be a reasonable choice balancing between tumoricidal effect and tissue repair (4).

Radiotherapy for esophageal cancer is sensitive to inter-fractional and intra-fractional motion (5-7). Although position verifications were executed at least weekly in the trial, more frequent verifications performed daily may be more ideal. Verification with carina-based registration may also increase the precision. Additionally, the use of respiratory gating and active breath control for respiratory motion management may facilitate the precise delivery of the escalated doses. During the treatment course, shrinking of the tumor, edematous changes of the esophagus, and

^ ORCID: Yun-Hsuan Lin, 0000-0002-7352-9955; Yu-Ming Wang, 0000-0002-2441-7551.

significant body weight loss are not uncommon, timely adaptive radiotherapy is crucial to overcome the negative impact of marked anatomic changes on dose distribution.

With the advent of proton beam therapy, particularly intensity-modulated proton therapy, the doses to the critical organs at risk, including lung and heart, and the integral dose, could be substantially reduced. A recent phase IIB trial demonstrated that proton beam therapy reduced the risk and severity of adverse events compared with conventional photon therapy (8). The lower rate of severe lymphopenia after proton beam therapy may theoretically increase the opportunity to complete the full course of chemotherapy, especially when a higher radiation dose is delivered (9). Another recent phase 1/2 trial showed lower local recurrence cumulative incidence by intensity-modulated proton therapy compared to intensity-modulated photon therapy (10). Further investigations are needed to explore the possible benefit of proton beam therapy in dose escalation.

Carcinoma of the cervical or upper thoracic esophagus is distinct from that of the lower esophagus or gastroesophageal junction regarding clinical behavior, treatment response, and outcome. We are wondering whether subgroup analysis of primary tumor location will generate distinct findings. Higher radiation doses may be appropriate for tumors of the cervical esophagus. The experience of Princess Margaret Cancer Centre demonstrated improved overall survival with higher doses (11). A trial focusing on cervical esophageal cancer may better clarify the effect of dose escalation in this group of patients.

There is still a long way to go to confirm the effect of dose escalation in esophageal cancer. Further attempts should be made, including trying different techniques of radiotherapy and combinations of chemotherapeutic and immunotherapy agents (12), to optimize the treatment outcomes of esophageal cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-21-23/coif). 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.

References

1. Zhang Z, Liao Z, Jin J, et al. Dose-response relationship in locoregional control for patients with stage II-III esophageal cancer treated with concurrent chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 2005;61:656-64.
2. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167-74.
3. Hulshof MCCM, Geijsen ED, Rozema T, et al. Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study). J Clin Oncol 2021;39:2816-24.
4. Fan XW, Wang HB, Mao JF, et al. Sequential boost of intensity-modulated radiotherapy with chemotherapy for inoperable esophageal squamous cell carcinoma: A prospective phase II study. Cancer Med 2020;9:2812-9.
5. Machiels M, Jin P, van Gurp CH, et al. Comparison of carina-based versus bony anatomy-based registration for setup verification in esophageal cancer radiotherapy. Radiat Oncol 2018;13:48.
6. Gao H, Kelsey CR, Boyle J, et al. Impact of Esophageal Motion on Dosimetry and Toxicity With Thoracic

Radiation Therapy. Technol Cancer Res Treat 2019;18:1533033819849073.
7. Hoffmann L, Poulsen PR, Ravkilde T, et al. Setup strategies and uncertainties in esophageal radiotherapy based on detailed intra- and interfractional tumor motion mapping. Radiother Oncol 2019;136:161-8.
8. Lin SH, Hobbs BP, Verma V, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. J Clin Oncol 2020;38:1569-79.
9. Shiraishi Y, Fang P, Xu C, et al. Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy. Radiother Oncol 2018;128:154-60.
10. 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;5:1597-604.
11. McDowell LJ, Huang SH, Xu W, et al. Effect of Intensity Modulated Radiation Therapy With Concurrent Chemotherapy on Survival for Patients With Cervical Esophageal Carcinoma. Int J Radiat Oncol Biol Phys 2017;98:186-95.
12. Vivaldi C, Catanese S, Massa V, et al. Immune Checkpoint Inhibitors in Esophageal Cancers: are we Finally Finding the Right Path in the Mist? Int J Mol Sci 2020;21:1658.

doi: 10.21037/tro-21-23
Cite this article as: Lin YH, Huang SY, Chou SY, Huang TT, Wang YM. Dose escalation not improving outcome in esophageal cancer—still far from conclusive. Ther Radiol Oncol 2022;6:1.