Definitive chemoradiation for resectable carcinoma of the cervical esophagus: do we need more evidence?

Antoine Adenis[1,2,3,4], Guillaume Piessen[3,5], David Azria[2,6]

[1]Department of Medical Oncology, Montpellier Cancer Institute (ICM), Montpellier, France; [2]INSERM, Montpellier Cancer Institute (ICM), Montpellier Cancer Research Institute (IRCM), University of Montpellier, Montpellier, France; [3]FREGAT Network, Lille, France; [4]Lille Catholic University, Lille, France; [5]Department of Digestive and Oncological Surgery, Claude Huriez University Hospital, University of Lille, Lille, France; [6]Department of Radiation Therapy, Montpellier Cancer Institute (ICM), Montpellier, France

Correspondence to: Antoine Adenis. Department of Medical Oncology, Montpellier Cancer Institute (ICM), Montpellier, France. Email: Antoine.Adenis@icm.unicancer.fr.

Provenance: This is an invited Editorial commissioned by the Section Editor Hongcheng Zhu, MD, PhD. (Department of Radiation Oncology, the First Affiliated Hospital, Nanjing Medical University, Nanjing, China).

Comment on: Zenda S, Kojima T, Kato K, *et al.* Multicenter Phase 2 Study of Cisplatin and 5-Fluorouracil With Concurrent Radiation Therapy as an Organ Preservation Approach in Patients With Squamous Cell Carcinoma of the Cervical Esophagus. Int J Radiat Oncol Biol Phys 2016;96:976-84.

Submitted Oct 19, 2017. Accepted for publication Oct 26, 2017.
doi: 10.21037/atm.2017.10.27
View this article at: http://dx.doi.org/10.21037/atm.2017.10.27

Esophageal cancer (EC) is the 8th most common cancer worldwide, with striking differences in incidence in different regions of the world. Incidence rates range from 1 per 100,000 in Western Africa to 20 per 100,000 in Eastern Asia, with intermediate rates reported in Europe (about 10 per 100,000) (1). EC is also a devastating malignancy, which ranks 6th on the list of cancer-mortality causes (1). Surgery is the mainstay of treatment for patients with localized or locally advanced EC (2), although some patients may be cured with chemoradiation (CRT) only [definitive CRT (dCRT)] (3,4). Over the past 2 decades, the management of resectable EC has dramatically changed with the advent of neoadjuvant chemotherapy (CT) and neoadjuvant CRT (NCRT). NCRT provides a 23% reduction of the risk of death, as reported in a meta-analysis by Sjoquist *et al.* (5). The benefit of NCRT over surgery alone has been also strengthened by the results of the so-called CROSS trial, which demonstrated a dramatic 35% reduction in the risk of death with the use of NCRT (6). Of note, dCRT appears to be at least equivalent to surgery in terms of survival in patients with squamous cell carcinoma EC who are fit for surgery and are responsive to induction CRT, as reported in a recent Cochrane review (7). For patients who do not undergo surgery for some reason (patients not suitable for surgery due to the local extent of disease or as a result of comorbidities), dCRT has represented a standard of care (8,9) since the pioneering RTOG 85-01 trial was reported in 1992 (10). A significant survival benefit was reported favoring dCRT over radiation therapy (RT) only for patients with localized EC. Together with concurrent RT (50 Gy, 25 fractions), patients received 2 cycles of fluorouracil and cisplatin, which were given at 4-week intervals. Two additional cycles are given 3 weeks apart after the end of dCRT. Briefly, this regimen provides an actual 26% 5-year survival rate versus 0% with RT only (11). Up to now, RT dose escalation (11), paclitaxel-based regimens with induction CT preceding CRT (12), addition of cetuximab to standard dCRT (13,14), and the substitution of cisplatin by oxaliplatin (4) have not produced a significant survival benefit over the RTOG 85-01 regimen.

Cervical EC (CEC) is rare and accounted for about 4% of patients with EC in a nationwide survey conducted in Japan (15), as well as in a recently reported randomized trial conducted in Europe (4). The cervical esophagus is the most proximal part of the esophagus, extending from the pharyngoesophageal junction to the suprasternal notch. Most, if not all, CEC are squamous cell cancers. Conversely to what is recommended for EC in general, European and American guidelines recommend dCRT as the preferred primary treatment option for CEC (8,9).

Japanese recommendations are more balanced between dCRT and radical surgery. They acknowledge that the role of surgery must be discussed after due consideration given the balance between the curative intent of the surgical procedure and the postoperative quality of life in patients in whom vocal function will be irrevocably compromised in case of concurrent laryngectomy (15). Of note, all these guidelines are low-evidence recommendations based on retrospective series.

Zenda *et al.* (16) recently reported the results of a Japanese, multicenter, phase 2 trial of dCRT in patients with operable CEC. The CT consisted of intravenous fluorouracil 700 mg/m^2 on days 1–4 and intravenous cisplatin 70 mg/m^2 on day 1, which was repeated every 4 weeks for 2 cycles. RT consisted of 60 Gy given in 30 fractions. After completing CRT, patients received 2 additional cycles of CT with fluorouracil (800 mg/m^2, days 1–5) and cisplatin (80 mg/m^2, day 1), which were repeated at 4-week intervals. The primary endpoint was 3-year overall survival. All but 1 of 30 patients included in the trial completed RT, 28/30 patients received the full dose of CT during RT, 23/30 patients received at least 1 course of additional CT, and 19/30 patients received 2 courses of additional CT per protocol. Toxicities reported were mild during both the CRT or CT phases, with 4% to 13% severe mucositis, 7% to 30% severe neutropenia, 13% dysphagia, and no reported acute radiation-induced esophagitis. A complete response was documented in 22/30 patients (73%), and nine patients (including six patients with residual disease after CRT) underwent salvage surgery after CRT. The 3-year local failure-free survival rate was 43.3%, and 3-year overall and laryngectomy-free survival were 66.5% and 52.5%, respectively.

Prospective studies are so rare in this setting of CEC that Zenda *et al.* (16) should be commended for conducting this prospective, multicenter, phase 2 trial. What makes this study very special is that the authors selected CEC patients who were candidates for radical surgery (i.e., total pharyngo-laryngo-esophagectomy). Although there is weak evidence that dCRT is at least equivalent to surgery in terms of survival in patients with squamous cell-type EC (7), all international guidelines recommend surgery-based therapy for patients fit for surgery and who present with locally-advanced EC (8,9,15). However, it has always been unclear whether or not these recommendations also apply to CEC. With this recent report from Zenda *et al.* (16), do we need more evidence in order to accept dCRT as the main therapeutic option for operable patients with CEC?

Although it is hazardous to make indirect comparisons among different studies, continents, periods of time, and tumor stages or nutritional status and, obviously, different treatment modalities, it is worth noting that a 3-year survival rate of 67% (95% confidence interval, 41–77%) is a pretty good outcome, especially because patients who presented with T1 disease who could have been treated with endoscopic resection or who were not candidates for laryngectomy were not included in that trial. Actually, survival results from Zenda's trial (16) compare favorably to those from retrospective series with mature enough survival data (17-22). In these studies, 3-year survival rates ranged from 15% to 45%, and from 13% to 48% in CEC patients treated with dCRT (17-19) and radical surgery (20-22), respectively. Quality of live also matters. Providing larynx preservation in half of the patients (3-year laryngectomy-free survival: 52.5%) is a very important result. At this point, we do not know what makes this CRT regimen so efficient. It should not be related to the use and dosing of cisplatin and fluorouracil because these compounds have already been used for years, or with the use of high-dose radiation (60 Gy) because the latter issue is still under investigation (23) after initially negative experiences (11). Actually, we cannot rule out that these results are related to the patients who were included in the trial; i.e., patients with good performance status and fit for radical surgery, and definitively fit for dCRT. The tolerance of Zenda's regimen (16) was good, with few severe adverse events. The doses of fluorouracil are usually lower in Japan (and Asia) than in the western world, and Zenda *et al.* (16) were keen enough to deliver a lower fluorouracil dose than that given in the RTOG 85-01 regimen in order to avoid the anticipated risk of severe mucositis/esophagitis related to concurrent RT. The late toxicity profile reported by Zenda *et al.* seemed good, too, with only four patients free from disease who needed endoscopic dilatations because of esophageal strictures (16).

Finally, the report from Zenda *et al.* (16) definitely supports dCRT as an alternative to radical surgery in patients with locally-advanced CEC. Whether this recommendation also applies to the rare subset of CEC patients who are eligible for surgery without laryngectomy is not elucidated here. The survival results of this trial, together with the rarity of CEC and the obvious organ preservation challenges, are reasons for not supporting a need for more evidence in this setting. Of note, a similar story could be told for squamous cell-type anal cancer. It

is a rare malignancy that has been treated since the 1970s with dCRT as an organ preserving approach in the locally-advanced setting, without more evidence than phase 2 trial results in a few patients who could have been operated on with abdominoperineal resection, with obvious loss of their anal-sphincter function (24).

Acknowledgements

None.

Footnote

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

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. Lancet Oncol 2007;8:545-53.
3. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623-7.
4. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol 2014;15:305-14.
5. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 2011;12:681-92.
6. 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.
7. Best LM, Mughal M, Gurusamy KS. Non-surgical versus surgical treatment for oesophageal cancer. Cochrane Database Syst Rev 2016;3:CD011498.
8. Ajani JA, Barthel JS, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers. J Natl Compr Canc Netw 2011;9:830-87.
9. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v50-7.
10. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992;326:1593-8.
11. 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.
12. Ajani JA, Winter K, Komaki R, et al. Phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus: RTOG 0113. J Clin Oncol 2008;26:4551-6.
13. Crosby T, Hurt CN, Falk S, et al. Long-term results and recurrence patterns from SCOPE-1: a phase II/III randomised trial of definitive chemoradiotherapy +/- cetuximab in oesophageal cancer. Br J Cancer 2017;116:709-16.
14. Suntharalingam M, Winter K, Ilson D, et al. Effect of the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation Therapy for Patients With Esophageal Cancer: The NRG Oncology RTOG 0436 Phase 3 Randomized Clinical Trial. JAMA Oncol 2017;3:1520-8.
15. Kuwano H, Nishimura Y, Oyama T, et al. Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. Esophagus 2015;12:1-30.
16. Zenda S, Kojima T, Kato K, et al. Multicenter Phase 2 Study of Cisplatin and 5-Fluorouracil With Concurrent Radiation Therapy as an Organ Preservation Approach in Patients With Squamous Cell Carcinoma of the Cervical Esophagus. Int J Radiat Oncol Biol Phys 2016;96:976-84.
17. Gkika E, Gauler T, Eberhardt W, et al. Long-term results of definitive radiochemotherapy in locally advanced cancers of the cervical esophagus. Dis Esophagus 2014;27:678-84.
18. Zhang P, Xi M, Zhao L, et al. Clinical efficacy and failure pattern in patients with cervical esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol 2015;116:257-61.
19. 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.
20. Triboulet JP, Mariette C, Chevalier D, et al. Surgical management of carcinoma of the hypopharynx and cervical esophagus: analysis of 209 cases. Arch Surg 2001;136:1164-70.
21. Daiko H, Hayashi R, Saikawa M, et al. Surgical management of carcinoma of the cervical esophagus. J Surg Oncol 2007;96:166-72.
22. Ott K, Lordick F, Molls M, et al. Limited resection and free jejunal graft interposition for squamous cell carcinoma of the cervical oesophagus. Br J Surg 2009;96:258-66.
23. Crehange G, Bertaut A, Peiffert D, et al. Exclusive chemoradiotherapy with or without dose escalation in locally advanced esophageal carcinoma: The CONCORDE study (PRODIGE 26). J Clin Oncol 2017;35:4037
24. Nigro ND, Seydel HG, Considine B, et al. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. Cancer 1983;51:1826-9.

Cite this article as: Adenis A, Piessen G, Azria D. Definitive chemoradiation for resectable carcinoma of the cervical esophagus: do we need more evidence? Ann Transl Med 2017;5(24):503. doi: 10.21037/atm.2017.10.27

