Editorial

The SCOPE of definitive chemoradiotherapy in locally advanced esophageal cancer: what direction for the future?

Gilles Créhange[1,2], Thierry Conroy[3,4]

[1]Department of Radiation Oncology, Centre Georges François Leclerc, University of Burgundy, Dijon, France; [2]Medical imaging group, IMAC CNRS 6306, University of Burgundy, Esplanade Erasme, Dijon, France; [3]Department of Medical Oncology, Institut de Cancérologie de Lorraine, 6 Avenue de Bourgogne, 54519 Vandoeuvre-lès-Nancy, France; [4]EA 4360, Lorraine University, 9 Avenue de la Forêt de Haye, 54505 Vandœuvre-lès-Nancy, France

Correspondence to: Gilles Créhange, MD, PhD. Department of Radiation Oncology, Georges François Leclerc Cancer Center, 1 rue du Professeur Marion, 21000 Dijon, France. Email: gcrehange@cgfl.fr.

Submitted Mar 05, 2016. Accepted for publication Mar 11, 2016.
doi: 10.21037/jtd.2016.03.74
View this article at: http://dx.doi.org/10.21037/jtd.2016.03.74

Exclusive chemoradiotherapy (CRT) delivering 50 Gy over 5 weeks with cisplatin and fluorouracil-based chemotherapy is a cornerstone in locally advanced esophageal cancer or non-operable patients since the results of the pivotal study of US Intergroup RTOG-8501 (1). This trial has successfully demonstrated that some patients with esophageal carcinoma may be long-term survivors so that this treatment is now definitely accepted as curative (2). Nevertheless the prognosis is still very disappointing with a 5-year overall survival rate of approximately 25%. Attempts to improve overall survival by escalating the dose of radiotherapy with concurrent cisplatin and fluorouracil has been assessed in INT 0123 trial (3). Overall survival rate after 64.8 Gy was not superior or even lower to 50.4 Gy. This result precluded dose escalation in esophageal cancer for more than a decade. However, the results of these two studies established CRT with the 50.4 Gy dose as the standard of care in esophageal cancer.

Given that, several strategies such as upfront chemotherapy or taxane-based definitive CRT have been tested in prospective randomized trials with no improvement in overall outcomes due to harmful or even lethal significant toxicities (4,5).

Crosby *et al.* published in the *Lancet Oncology* the mature results of the SCOPE1 trial which compared 50 Gy CRT with cisplatin and capecitabine with or without cetuximab, a monoclonal antibody targeted toward the Epidermal Growth Factor Receptor (EGFR) (6). The level of EGFR expression in biopsies was not used as an inclusion criterion in the trial. Inclusion criteria included patients with favorable performance status selected to receive potentially curative definitive CRT by a specialist upper gastrointestinal multidisciplinary team. Tumors had to be staged with both endoscopic ultrasound and spiral CT scan to be T1–4 N0–1 M0. Patients should be able to swallow capecitabine, and in case of severe dysphagia, they have received protracted intravenous infusion of fluorouracil 225 mg/m²/d for 84 days.

The control group consists of cisplatin (60 mg/m^2 IV Day 1 of 21 day cycle for 4 cycles) and capecitabine (625 mg/m^2 po bid days 1–84) and, from week 7, radiotherapy (50 Gy in 25 fractions over 5 weeks, 2 Gy per fraction). The experimental group consists of the above plus cetuximab (400 mg/m^2 day 1 of the first week, then 250 mg/m^2 weekly thereafter for a further 11 weeks).

Randomisation was stratified by recruiting hospital, primary reason for not having surgery, tumour stage, and tumour histology. 72% had squamous-cell carcinoma. Tumor length and stage have been well balanced between groups. However, no data are available on weight loss at inclusion which is a major prognostic factor (7,8). 86% of patients had a ^{18}F-fluorodeoxyglucose PET-CT scan to exclude metastatic disease and to identify lymph node involvement before starting radiotherapy.

Surprisingly both study groups received neoadjuvant chemotherapy before definitive chemoradiation. The authors stated that this schedule is the most frequently used regimen in the UK, because it allows time for careful radiotherapy planning, it allows better compliance and a

shrinkage of the tumour before radiotherapy (6,9). However to our best knowledge, this sequence has not been tested in randomized phase III trials versus definitive chemoradiation first which is still the standard of care for non-surgical candidates. Response rate during neoadjuvant phase has not been reported in the paper.

Non-inferiority of capecitabine as compared to infusional fluorouracil has been demonstrated in the REAL-2 study comparing three triplet therapies in advanced esophagogastric cancer (10). In this study, 34.5% of the patients had esophageal cancer, 10.5% had squamous-cell carcinoma and 22.7% had a locally advanced tumour. However all tests for heterogeneity with regard to treatment effect, including the histologic type and the anatomic subsite of the tumor did not reveal any significant heterogeneity. The feasibility of concurrent CRT with capecitabine and cisplatin for patients with esophageal carcinoma was evaluated in small phase II in single-centre series (9,11).

In the SCOPE 1 trial, 258 patients were recruited, 129 in each group. The primary endpoint of the phase 3 trial was overall survival. The CRT plus cetuximab group had a significantly shorter median overall survival [22.1 months (95% CI: 15.1–24.5) *vs.* 25.4 months (20.5–37.9); adjusted HR 1.53 (95% CI: 1.03–2.27); (P=0.035)]. These median survivals are among the best achieved in the literature. Patients randomized to exclusive CRT with cetuximab had a lower compliance to CRT. 19% of the patients in the cetuximab group had no radiotherapy given, versus 8% in the control arm (P=0.006), may be due to progressive disease during neoadjuvant chemotherapy or increased toxicities. Patients who received CRT plus cetuximab had also more grade 3–4 non-haematological toxicity (79% *vs.* 63%; P=0.004) when compared to control group patients. These toxicities were mainly dermatological, biochemical, and cardiac disorders (8 grade 3–4 cardiac events in the cetuximab group versus 2 in the control arm).

In subgroup analyses with respect to baseline characteristics, no subgroup benefit from cetuximab was observed. Evidence of lower local progression-free survival (within the radiotherapy field) was observed in the experimental group (HR 1.38, P=0.051). On multivariate analysis, stage 1–2 *vs.* stage 3, full-dose radiotherapy and higher cisplatin dose intensity (≥75% *vs.* <75%) were associated with improved overall and progression-free survival. Patterns of recurrence were similar in both arms. The proportion of patients with salvage surgery in each arm is unknown.

Patient-reported outcomes were secondary end points in this trial. Quality of life was assessed using the EORTC QLQ-C30, the esophageal module QLQ-OES18 and the dermatology life-quality index (DLQI). Questionnaire compliance was good throughout the study (12). After neoadjuvant chemotherapy, there was no change in the proportion of patients with severe dysphagia, but dysphagia significantly increased after chemoradiation. Significant deterioration in functional scores and more problems with fatigue, dyspnea, appetite loss and troubles with taste were reported during CRT. Patients receiving cetuximab reported was overall higher DLQI scores than those receiving CRT alone, but the difference was not significant.

The findings of the SCOPE1 trial are in line with initial report of RTOG 0436 study which also found no improvement in survival for esophageal cancer patients when adding cetuximab (400 mg/m^2 day 1 then weekly 250 mg/m^2) to weekly concurrent cisplatin (50 mg/m^2), paclitaxel (25 mg/m^2), and radiation 50.4 Gy over five weeks (13).

The addition of cetuximab to CRT has been further explored in head and neck squamous cell cancers in the randomized phase II trial RTOG 0522 which showed no benefit in overall survival and increased grade 3 or higher mucositis and skin toxicities (14). Hence, the remaining question could be whether cetuximab alone combined with radiation may improve outcome with less toxicities and a better compliance? A randomized phase II study has recently compared CRT with cisplatin and 5FU-platinum-based chemotherapy *vs.* cetuximab alone in head and neck squamous cell cancers (15). Although the study was closed prematurely, toxicities were still significantly increased with even more toxic deaths (4 *vs.* 1) with more frequent nutritional support for patients treated with cetuximab monotherapy concomitantly with radiotherapy.

In parallel, another way to increase the therapeutic ratio using an efficient and less toxic chemotherapy scheme has been explored in the PRODIGE 5 trial using a FOLFOX4 regimen (16). In this phase III trial, 267 patients treated with definitive 50 Gy CRT were randomised between the RTOG regimen (four cycles (two concomitant to radiotherapy) of fluorouracil 1,000 mg/m^2 per day for 4 days and cisplatin 75 mg/m^2 on day 1) or the same radiotherapy scheme combined with FOLFOX4 [6 cycles (three concomitant to radiotherapy) of oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, fluorouracil bolus 400 mg/m^2, and infusional fluorouracil 1,600 mg/m^2 over 46 h every 2 weeks]. Although not superior, FOLFOX4 provided similar overall survival than that with the RTOG regimen whereas less toxic deaths occurred with 50

Gy + concomitant FOLFOX4 (1% *vs.* 5%). Hence the American Society of Clinical Oncology (ASCO) advised toward an acceptable treatment option in keeping with the standard RTOG regimen. The widespread use of exclusive chemoradiation with FOLFOX4, a more convenient regimen, is now rapidly growing in some European countries.

From this standpoint, how can we move forward with more long-term survivors and no increased lethal or harmful toxicities with exclusive chemoradiation?

Locoregional control remains the first cause of failure so far with still roughly half of the patients who will have a persistent tumor or who will develop a local and/or regional relapse. In the RTOG 85-01 study, the patients in each arm received elective nodal irradiation from supraclavicular fossa to esogastric junction up to 30 Gy using an outdated 2D technique (1). RTOG 85-01 results (2) showed 37% of persistent disease in the radiotherapy alone group versus 25% and 28% in the CRT randomized and non-randomized group, respectively, and there were 16% of locoregional failure in the radiotherapy-alone group versus 13% and 20% in the CRT randomized and non-randomized groups, respectively (2). The low prophylactic nodal dose used, 30 Gy, might have been too low and the evaluation of nodal status less accurate than today. This hypothesis has been recently verified in the CROSS trial where 188 were randomly assigned to the surgery arm and 178 to the CRT plus surgery arm (17). A total radiation dose of 41.4 Gy was administered in 23 fractions of 1.8 Gy. The locoregional failure rate without distant metastasis was 9.3% in the surgery alone arm versus 3.3% in the CRT plus surgery arm. These results suggest that elective nodal irradiation reduces locoregional failure, which was significantly lower than that observed with surgery alone or with CRT alone. The hypothesis is that CRT plays an important role, probably by sterilizing the microscopic nodal disease, and that the total dose of radiotherapy without surgery may be too low to control macroscopic disease, suggesting that large volumes and high doses are required.

The INT 0123 study was conducted to compare a combined modality treatment with the same scheme of chemotherapy and different doses of radiotherapy (3): the control group received a standard dose (50.4 Gy) and the experimental group received a higher dose of RT (64.8 Gy). Unfortunately, because of 11 treatment-related deaths, only 67% of patients received the high radiation dose compared with 83% in the standard dose group. Despite flaws due to the high mortality of patients, the two-year survival of 31% and 40%, and a cumulative incidence of local failure of 52% and 56% in the standard-dose and high-dose group, respectively. Again, nearly half of the patients had still a locoregional persistent or recurrent disease rates. Several drawbacks surround the interpretation of the results of INT 0123. Firstly, the equivalence in survival between the two groups was influenced by a high number of intercurrent deaths among patients on the dose escalation arm (11 *vs.* 2 deaths). In point of fact, this may not be due to radiation dose escalation as a majority of deaths in the high-dose arm occurred before receiving a cumulative dose greater than 50 Gy. Obviously, most of the causes of deaths were related to chemotherapy. Secondly, no elective nodal irradiation was delivered compared to RTOG 85-01. Lastly, dose escalation was performed on the primary tumor only but not on positive nodes.

Given the above, the differences in local control and survival rates between RTOG 85-01 and INT 0123 were not significant so it was difficult to conclude with evidence that dose escalation could be beneficial. Conversely, the Surveillance Epidemiology and End Results (SEER) program have found a significant correlation between survival and increments of +5 Gy of radiation dose escalation up to 65 Gy in a cohort of more than 5,000 patients treated with exclusive CRT (18). Radiation dose escalation studies showed that nowadays, 60 Gy or higher can be safely delivered in routine practice in most radiotherapy centers (19).

The main problem with esophageal cancer is the close proximity of organs at risk, particularly the heart and lungs. Most of the time, the difficulty is to limit the irradiated volume or the total dose so as not to compromise the benefit/risk ratio. In this context, Intensity-Modulated Radiotherapy (IMRT) (20) or Volumetric Modulated Arctherapy (VMAT) (21) could be used to increase mediastinal irradiated volumes or dose escalation to the primary tumor while effectively protecting healthy tissues. In the MD Anderson Cancer Center retrospective experience on 676 patients with esophageal cancer treated by exclusive CRT (of whom 263 were treated by IMRT), the authors showed that loco-regional control and overall survival were significantly better for IMRT than for three-dimensional radiotherapy (22). These results need to be confirmed in a prospective study. These techniques decrease the volumes of lung and heart (23) that receive a high dose, but at the cost of delivering low doses to a greater volume of lung and normal tissues. The authors found that IMRT provided a significant lower rate of non cancer-related

deaths, including cardiac-related deaths, the second cause of death after cancer in esophageal cancer patients treated with CRT (22). A more accurate approach would be VMAT combined with active breathing control using moderate deep-inspiration breath-hold to reduce doses to the lung and to improve targeting (24).

In line with Crosby *et al.* (6), we strongly believe that dose escalation should be retested with modern radiotherapy techniques, such as IMRT or VMAT with image-guided radiotherapy (IGRT). Accordingly, we recommend a thorough RT Quality Assurance review to make sure this treatment modality is reproducible with an acceptable compliance.

Based on data from SCOPE1 trial, investigators have explored radiobiological modeling of dose escalation for esophageal cancer and found that a +18% increase in tumor control could be achieved with a modest increase in the risk of cardiac and lung toxicities for nearly 75% of patients. The SCOPE trialists have launched a new phase III trial (SCOPE2) that will address the issue of radiation dose escalation up to 60 Gy using modern radiotherapy with an SIB technique.

In France, we are currently investigating dose escalation up to 66 Gy (*vs.* 50 Gy) combined with FOLFOX4 using modern conformal radiation techniques including IMRT and VMAT in a phase II/III trial entitled Cancer of the Oesophagus, Non-resected, treated with Chemoradiotherapy combining Oxaliplatin-based chemotherapy and Radiotherapy delivering Dose Escalation (CONCORDE) (NCT01348217). An elective nodal irradiation to 40 Gy is given in both arms. The CONCORDE study sought to evaluate locoregional control using modern radiotherapy considering improvements in tumor volume definition and tumor staging combined with newer radiation technologies may finally allow delivering "the right dose to the right volume". Patients are stratified by stage, histology, weight loss and center so that the technique of radiotherapy used (IMRT *vs.* 3D conformal) will be assessed on the primary endpoint. An independent review committee (EQUAL-ESTRO) performs a remote RT Quality Assurance Review. We expect in the phase III trial a significant increase in 2-year locoregional progression-free survival from 50% to 65%. The phase II part is ended including 160 patients of whom 80% were treated with IMRT/VMAT (25). Toxicity and efficacy data will be available by fall quarter of 2016.

Unless robust data will be emerging soon, it is hoped that improvements in modern radiotherapy will allow improving the therapeutic ratio in locally advanced esophageal cancer with CRT. In the meantime, 50 Gy with Platinum and fluorouracil-based regimen still remains the gold standard in this setting since more than two decades.

Lastly, the results of the CROSS trial in the preoperative setting showed a significant increased in overall survival with 41.4 Gy outdated 3D conformal radiation therapy combined with Carboplatin (AUC 2) and Paclitaxel (50 mg/m^2 weekly). Locoregional failure rate was 3.3% compared to 9.3% with surgery alone. After the completion of accrual in the CONCORDE study, we plan to move forward by evaluating the CROSS chemotherapy regimen with exclusive CRT 50 or 66 Gy, with respect to the results of the CONCORDE study.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Hongcheng Zhu (Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. 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.
2. 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.
3. 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.
4. 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.

5 Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol 2013;24:2844-9.
6. Crosby T, Hurt CN, Falk S, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol 2013;14:627-37.
7. Thomas CR Jr, Berkey BA, Minsky BD, et al. Recursive partitioning analysis of pretreatment variables of 416 patients with locoregional esophageal cancer treated with definitive concomitant chemoradiotherapy on Intergroup and Radiation Therapy Oncology Group trials. Int J Radiat Oncol Biol Phys 2004;58:1405-10.
8. Crehange G, Maingon P, Peignaux K, et al. Phase III trial of protracted compared with split-course chemoradiation for esophageal carcinoma: Federation Francophone de Cancerologie Digestive 9102. J Clin Oncol 2007;25:4895-901.
9. Crosby TD, Brewster AE, Borley A, et al. Definitive chemoradiation in patients with inoperable oesophageal carcinoma. Br J Cancer 2004;90:70-5.
10 Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.
11. Lee SJ, Ahn BM, Kim JG, et al. Definitive chemoradiotherapy with capecitabine and cisplatin in patients with esophageal cancer: a pilot study. J Korean Med Sci 2009;24:120-5.
12. Rees J, Hurt CN, Gollins S, et al. Patient-reported outcomes during and after definitive chemoradiotherapy for oesophageal cancer. Br J Cancer 2015;113:603-10.
13. Suntharalingam M, Winter K, Ilson DH, et al. The initial report of RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery. The initial report of RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery. J Clin Oncol 2014;32:abstr LBA6.
14. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 2014;32:2940-50.
15. Magrini SM, Buglione M, Corvò R, et al. Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial. J Clin Oncol 2016;34:427-35.
16. 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.
17. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol 2014;32:385-91.
18. Schultheiss TE, Chen Y. Dose Response for Survival in Esophageal Cancer. Int J Radiat Oncol Biol Phys 2007;69:S276.
19. Burmeister BH, Porceddu SV. Targeted therapy and chemoradiotherapy in oesophageal cancer. Lancet Oncol 2013;14:569-70.
20. Roeder F, Nicolay NH, Nguyen T, et al. Intensity modulated radiotherapy (IMRT) with concurrent chemotherapy as definitive treatment of locally advanced esophageal cancer. Radiat Oncol 2014;9:191.
21. Wu Z, Xie C, Hu M, et al. Dosimetric benefits of IMRT and VMAT in the treatment of middle thoracic esophageal cancer: is the conformal radiotherapy still an alternative option? J Appl Clin Med Phys 2014;15:4641.
22. Lin SH, Wang L, Myles B, Thall PF, et al. Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys 2012;84:1078-85.
23. Haj Mohammad N, Kamphuis M, Hulshof MC, et al. Reduction of heart volume during neoadjuvant chemoradiation in patients with resectable esophageal cancer. Radiother Oncol 2015;114:91-5.
24. Gong G, Wang R, Guo Y, et al. Reduced lung dose during radiotherapy for thoracic esophageal carcinoma: VMAT combined with active breathing control for moderate DIBH. Radiat Oncol 2013;8:291.
25. Crehange G, Bonnetain F, Peiffert D, et al. Phase II/III randomized trial of exclusive chemoradiotherapy with or without dose escalation in locally advanced esophageal carcinoma: The CONCORDE study (PRODIGE 26). J Clin Oncol 2016;34:abstr TPS190.

Cite this article as: Créhange G, Conroy T. The SCOPE of definitive chemoradiotherapy in locally advanced esophageal cancer: what direction for the future? J Thorac Dis 2016;8(6):1014-1018. doi: 10.21037/jtd.2016.03.74

