CROSSing into New Therapies for Esophageal Cancer

Author links open overlay panelMichael H.BucksteinMD, PhD*Christopher J.AnkerMD†Michael D.ChuongMD‡Maria A.HawkinsMD§JordanKharofaMD‖Jeffrey R.OlsenMD¶

∗Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, New York

†Division of Radiation Oncology, University of Vermont Larner College of Medicine, Burlington, Vermont

‡Department of Radiation Oncology, Miami Cancer Institute, Miami, Florida

§University College London, London, United Kingdom

‖Department of Radiation Oncology, University of Cincinnati College of Medicine, Cincinnati, Ohio

¶Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado

In this issue's Oncology Scan, we would first like to welcome Dr Nina Sanford to the Gastrointestinal Editorial Section. Dr Sanford is a gastrointestinal radiation oncologist at UT Southwestern and was selected based on her disease site expertise and thoughtful critiques as a Red Journal reviewer. We would also like to thank Dr Diana Tait, whose term completed recently, for her commitment and diligence as a gastrointestinal associate editor.

This Oncology Scan takes us on a deep dive into the management of esophageal cancer (EC). The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial, first published in 2012, set a new standard of care for operable EC.[1] We start with the newly published 10-year update of that seminal trial which not only confirms its long-term overall survival (OS) outcome but also provides new insights into the patterns of failure and benefits of that regimen.[2] Although CROSS ushered a new era for resectable EC, the results are still not optimal and the subsequent trials discussed here all try to improve on the CROSS regimen in a variety of different ways: changing radiation dose, positron emission tomography (PET)-driven optimization of chemotherapy, and adjuvant immunotherapy.

The question of whether radiation dose escalation can improve outcomes for unresectable EC has plagued radiation oncologists since the heavily critiqued landmark Intergroup 0123 trial found no benefit to this approach decades ago.[3] The ARTDECO trial adds another randomized attempt at high-quality dose escalation to assess if better results may be achieved with this approach.[4] Also building off the results of early induction chemotherapy trials in EC and data that PET can be used as a prognostic and predictive biomarker, CALGB 80803 reports on whether an early adaptive strategy of changing chemotherapy can improve outcomes in resectable disease.[5] Finally, reporting of Checkmate 577 brings adjuvant immunotherapy as a potential major player in EC.[6]

With this new influx of important data in EC, there are some clear winners and losers. Once and for all, radiation oncologists are going to have to finally admit that increasing radiation dose is not likely to improve outcomes in this disease in unselected patients. Likewise, although there is some hint that changing chemotherapy early in treatment based on PET findings might be helpful, it is not clear the extent to which this strategy is broadly applicable. Immunotherapy, however, demonstrates substantial benefit in the adjuvant setting across histologic types, and we look forward to seeing trials to evaluate the role of immunotherapy in the concurrent and neoadjuvant settings.

Eyck BM et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: The randomized controlled CROSS Trial. *Journal of Clinical Oncology* 2021.[2]

Summary: Eyck et al report 10-year outcomes from the chemoradiotherapy for esophageal cancer followed by surgery study (CROSS) to assess if the previously reported OS benefits, which have defined a standard of care for treatment of esophageal and gastroesophageal junction (GEJ) malignancy, persist after extended follow-up. CROSS was a randomized phase 3 study for patients with cT1N1M0 or cT2-3N0-1M0 esophageal squamous cell carcinoma (ESCC) or adenocarcinoma (EAC) or GEJ. Additional eligibility included being <75 years old, an Eastern Cooperative Oncology Group performance status of ≤2, and <10% weight loss. Patients were randomized to receive either neoadjuvant chemoradiation with concurrent weekly carboplatin and paclitaxel or surgery alone. Radiation therapy was delivered to the primary tumor and involved lymph nodes with margin to a dose of 41.4 Gy at 1.8 Gy per fraction using a 3-dimensional conformal technique. Elective nodal irradiation was not required. In this extended follow-up report, the effect of the study regimen on OS beyond 5 years of follow-up was tested with time-dependent Cox regression and landmark analyses. After median follow-up of 12 1/4 years, the OS benefit from neoadjuvant chemoradiation persisted (10-year OS, 38% vs 25%; *P* = .004), without time dependence (*P* value for interaction = .73). There was no detectable difference between arms in risk of death from other causes (hazard ratio [HR], 1.13; 95% CI 0.68-1.99). The study regimen reduced risk of isolated locoregional recurrence (HR, 0.40; 95% CI, 0.26-0.72) and risk of synchronous locoregional plus distant relapse (HR, 0.43; 95% CI, 0.26-0.72). The overall risk of synchronous locoregional plus distant relapse was reduced for the chemoradiation arm, and appeared driven by reduction in locoregional recurrence, given similar risk of isolated distant recurrence between the surgery (28%) and chemoradiation (27%) arms.

Commentary: These 10-year outcomes confirm that the CROSS regimen prolongs OS by significantly reducing locoregional relapse without affecting distant relapse. However, its applicability remains uncertain for some patients: only 16% had tumors in the upper or middle esophagus and T4 disease was excluded from the trial. Moreover, the study was inadequately powered to compare OS across subgroups including between ESCC and EAC.

Despite the proven OS benefit of preoperative chemoradiation (CRT), there is lack of consensus regarding the optimal treatment regimen, especially for EAC and in the GEJ. The recently published guidelines from the American Society of Clinical Oncology recommend preoperative or definitive CRT for ESCC, although preoperative CRT and perioperative chemotherapy are both endorsed for EAC.[7,8] On the other hand, the National Comprehensive Cancer Network guidelines as well as the American Radium Society Appropriate Use Criteria favor neoadjuvant CRT for both ESCC and EAC.[9] The emergence of perioperative FLOT, which achieved favorable median OS (50 vs 35 months) compared with the MAGIC regimen in the randomized FLOT4-AIO trial, has added to the debate, although only patients with gastric or GEJ cancers were included limiting its applicability to thoracic EC.[10]

So how are we to make treatment recommendations to our EAC patients? Ongoing randomized trials comparing preoperative CRT and perioperative chemotherapy including ESOPEC (NCT02509286), RACE (NCT04375605), and POWERRANGER (NCT01404156) will eventually provide guidance. A preliminary analysis of the phase 3 Neo-AEGIS trial (NCT01726452) for GEJ adenocarcinomas showed no difference in estimated 3-year OS (56% vs 57%; HR, 1.02; 95% CI, 0.74%-1.42%) between the CROSS regimen and perioperative MAGIC/FLOT.[11] Maturing of these data are needed to guide treatment decisions, although in the meantime there are compelling reasons to continue favoring CROSS including its lower toxicity profile (grade 3 neutropenia, 2.8% vs 14.1%), increased pathologic complete response (16% vs 5%), and higher rate of R0 resection (95% vs 82%).[11] Moreover, the ASCO guidelines suggest that CRT should be preferred for especially large tumors and if there are concerns about suboptimal surgery that can increase the risk for a positive margin or inadequate nodal sampling.[7]

Future studies are needed to better understand late adverse effects of CROSS, especially because toxicities were not recorded after the initial 2-year outcomes report. It is expected that the 3-dimensional conformal radiation therapy used in the CROSS trial resulted higher heart and lung doses than would be achieved today with intensity modulated radiation therapy (IMRT) or proton therapy.[12] As such, it is plausible that, had these advanced techniques been used in CROSS, they could have further widened the difference in OS achieved with preoperative CRT compared with surgery alone by reducing late cardiopulmonary mortality.[13,14]

Hulshof MCCM et al. Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO study). *Journal of Clinical Oncology* 2021.[4]

Summary: Hulshof et al report results from the randomized phase 3 ARTDECO trial, which assessed the effect of dose escalation on local progression risk for patients with locally advanced esophageal cancer receiving definitive chemoradiation. Eligibility criteria included medically inoperable or unresectable ESCC or EAC with stage T1-4N0-3M0, or M1 disease on the basis of isolated supraclavicular spread. Patients in the standard dose (SD) arm received 50.4 Gy at 1.8 Gy per fraction to the primary tumor, clinically positive lymph nodes, and elective regional lymph nodes within a 3 cm craniocaudal clinical target volume expansion from the primary gross tumor volume. The planning target volume margin was 1 cm, and, although only weekly setup verification was required, most patients received it daily. In the high dose (HD) arm, a simultaneous integrated boost was given to the primary tumor plus 1-cm planning target volume margin to 61.6 Gy at 2.2 Gy per fraction. All institutions used or adopted IMRT during the study period. Concurrent carboplatin (AUC 2) and paclitaxel (50 mg/m2) was administered once weekly for 6 weeks for all patients. The primary endpoint was defined as local progression-free survival (LPFS) with progression based on histologic confirmation or clear endoscopic/radiographic findings. The study was designed with 80% power to detect a 15% improvement in LPFS, and met planned accrual of 260 patients which were balanced for prognostic factors and histology. A total of 62% of patients had SCC with the remaining 38% having Adenocarcinoma (AC). Radiation therapy was completed by 96% of patients in the SD arm and 92% of patients in the HD arm. The median follow-up time for the current report was 50 months. No significant difference was observed in 3-year LPFS for the entire cohort (70% for SD vs 73% for HD, *P* = nonsignificant [NS]), nor was there any observed LPFS difference for SCC (75% for SD vs 79% for HD, *P* = NS) or AC (61% for SD vs 61% for HD, *P* = NS) subgroups. There was no OS difference observed between arms (3-year OS, 42% vs 39% for SD and HD, respectively). Grade 4 and grade 5 toxicities were observed in 12% and 5% of patients in the SD arm versus 14% and 10% of patients in the HD arm, without significant difference.

Commentary: Over the last 2 decades since the publication of the landmark esophageal cancer study INT 0123, it has been hypothesized that the failure of that trial's high RT dose arm to produce superior results was due to problems including patient selection (eg, inadequate staging due to lack of PET/computed tomography [CT]) and rudimentary treatment techniques.[3,4] Further, concern for a lack of generalizability to AC was noted given that >80% of patients had SCC. Single-armed studies have touted RT dose escalation as the reason for outcomes superior to those seen in INT 0123, leading to definitive doses as high as 64 Gy/32 fractions considered within standard of care in Eastern countries.[15] However, ARTDECO clearly indicates that in an unselected population, RT dose escalation is not expected to provide a clinical benefit, even with IMRT and proper staging. This study is a good reminder that the majority (>2/3) of phase 3 studies do not show a benefit to the investigational treatment, and providers should exercise caution when adopting a more aggressive therapy based on nonrandomized data.[16] In a predominately SCC population (88.4%), early data presented for the phase 3 PRODIGE-26 esophageal cancer study revealed that dose escalation from 50 Gy/25 fractions to 66

Gy/33 fractions involving IMRT also did not increase oncologic control.[17] Although the PRODIGE-26 abstract did not report tumor site location, in ARTDECO only 5% had tumors in the cervical location bringing some question to the generalizability of the results for these patients. The comparability between the ARTDECO arms is particularly remarkable when noting the frequency of tumor assessment, with CT scans only required at 3 planned time points in the first 1.5 years after treatment and endoscopy only performed as needed. Although this might introduce variability and lead time into the detection of a recurrence, it also supports that the 6-month CT scan and 3- to 6-month endoscopy frequency suggested by National Comprehensive Cancer Network guidelines is appropriate for definitively treated patients.[18]

Although the authors of both ARTDECO and PRODIGE-26 do not report worse toxicity with their respective HD arms, it should be clearly noted that this was based on physician assessment, not patient-reported outcomes (PROs). In a secondary analysis of the PRO data from INT 0123 based on the Head and Neck Functional Assessment of Cancer Therapy, total mean quality of life (QOL) declined after CRT most significantly in the HD arm, and it remained decreased long-term, although significance was not retained.[19] The decreased patient compliance with the ARTDECO HD arm is a potential indicator of reduced tolerability and QOL, at least in the short term. Further, although small, the excess number of deaths in the HD arm due to esophageal and bronchopulmonary bleeding and respiratory failure must be recognized. Whereas the phase 3 lung cancer trial RTOG 0617 showed higher toxicity with dose escalation without improved oncologic outcomes, a planned secondary analysis found that the ERCC1/2 SNP indicated a radiation sensitive genotype in the DNA repair pathway.[20] Radiosensitivity was found to apply to both tumor and normal tissue, and therefore dose escalation may have caused worse survival due to increased toxicity without an oncologic benefit. Just as RTOG 0436 did not find a benefit to an EGFR inhibitor in an unselected esophageal cancer population, biomarkers (eg, genomics, radiomics), potentially with artificial intelligence approaches are needed if we are to pursue future RT dose escalation (or de-escalation) approaches for esophageal cancer.[21], [22], [23] In the SCOPE2 trial, early PET response after beginning chemoradiation is being used to stratify patients before randomization standard versus HD treatment arms [NCT02741856]. Similarly, CALGB 80803, as discussed below, also uses PET to help modulate treatment based on early metabolic response.[5] Alternatively, it is encouraging that in selected HPV-positive populations, radiation dose de-escalation is being met with success for head and neck cancer, and clinical trial design is trending toward a stronger focus on PRO such as in the low-risk anal cancer DECREASE trial involving chemotherapy and radiation de-escalation [NCT04166318].[24,25] For resectable esophageal cancer, in patients committed to surgery, data suggests no benefit and a potential detriment to delivering a neoadjuvant dose beyond 40 to 41.4 Gy/20 to 23 fractions.[26] At this time, at least for tumor sites other than the cervical esophagus, ARTDECO offers strong evidence that definitive radiation doses above 50 to 50.4 Gy/25 to 28 fractions are not appropriate outside of a clinical trial. Seizing opportunities to de-escalate or avoid therapies that offer slim to no oncologic benefit are greatly appreciated by patients, and discussing the absolute magnitude of risk/benefit treatment effects are an essential part of the shared decision-making process.

Goodman KA et al. Randomized phase II study of PET response-adapted combined modality therapy for esophageal cancer: Mature results of the CALGB 80803 (Alliance) trial. *Journal of Clinical Oncology* 2021.[5]

Summary: CALGB 80803 is a randomized phase 2 trial that sought to optimize neoadjuvant therapy for resectable EAC by using PET response to make an early change in systemic therapy. The trial hypothesized that making an early change after induction chemotherapy for PET nonresponders would improve pathological complete response (pCR) rates after neoadjuvant chemoradiation.

Primary inclusion criteria was resectable adenocarcinoma of the esophagus or GEJ. After baseline centrally reviewed PET, patients were randomized to receive induction FOLFOX or carboplatin-paclitaxel (CP). PET nonresponders, as defined as <35% reduction in SUV avidity, were then transferred to the alternative chemotherapy while responders continued on the same chemotherapy for chemoradiation. The prescribed radiation dose was 50.4 Gy in 28 fractions. The primary endpoint was to induce a 20% pCR rate in initial PET nonresponders (null hypothesis 5% from the MUNICON II trial.[27] Secondary endpoints included PET response and pCR rates between induction arms as well as OS.

Between 2011 and 2015, 257 patients were enrolled, of which 225 had an interpretable PET after induction chemotherapy. Protocol compliance was overall excellent, and toxicity in both arms was not statistically different. There was no significant difference in PET responders with FOLFOX (64.9%) versus CP (56.1%) (P = .22). For PET nonresponders who crossed from induction FOLFOX to CP, the pCR rate was 18%; for the nonresponders crossing from CP to FOLFOX, the pCR rate 20%. For PET responders who continued on FOLFOX, the pCR rate was 40.3%, whereas responders receiving CP only had a pCR of 14.1% (P = .001). Pathologic node negative rates were higher in the FOLFOX responders (84.1%) and nonresponders (71.4%) compared with CP responders (66.7%) and nonresponders (59.0%). There was no significant difference in OS between responders and nonresponders (HR, 1.34; 0.94-1.92). PET responders who continued on FOLFOX for chemoradation had 5-year survival of 53%.

Commentary: In this report, authors of the CALGB 80803 (Alliance) trial present the initial publication of their results showing the trial met the prespecified endpoint of improving pCR benchmarked to the historic controls. The authors should be congratulated for conducting this adaptive, imaging-based biomarker trial within the context of a multi-institutional setting.

How do these results inform current management of gastroesophageal AC in 2022? An important consideration of the trial design is the central review of PET imaging for all patients. Although PET imaging is commonplace in the setting of esophageal cancer staging, use of PET as an adaptive biomarker requires standardization and expertise. Variability in both adherence to the PET protocol as defined herein or interpretation of results may limit external generalizability of this approach. Cost barriers and access to multiple PETs may also exist in certain regions that could affect broad incorporation. For all patients resected on CALGB 80803 agnostic to PET response, 24% (55/225) were noted to have a pCR. The rate of pCR is similar to patients treated without a PET adapted approach on the CROSS trial (23% pCR in adenocarcinoma; 28/121) recently published RTOG 1010 (chemoradiation arm- 29% pCR, chemoradiation+ trastuzumab– 27% pCR).[1,28] If the proportion of patients with pCR is increased using a PET-adaptive approach, one would expect an increase in the pCR rate in the overall population relative to an unselected approach. With use of historic controls, it is difficult to directly evaluate the magnitude of benefit the adaptive approach provides. Randomization to PET adapted versus nonadapted approaches would more accurately ascertain the added value of this approach but may be more challenging logistically. In addition, it should be noted that improvements in pCR within the radiation therapy treatment field as a consequence of sensitizer selection may not necessarily translate into more meaningful survival endpoints such as disease-free survival (DFS) or OS. Indeed, no survival differences were noted among the arms in this study with similar dropout rates for progression and other toxicities in the responder and nonresponder groups.

The study used induction chemotherapy in both arms, although it was not designed to compare the benefit of induction chemotherapy in the management of esophageal cancer directly. The use of induction chemotherapy in unselected patient populations has been the subject of previous trials without clear benefit of induction chemotherapy before chemoradiation.[29,30] A variety of ongoing trials will continue to shape optimal neoadjuvant regimens for GEJ cancer. The benefit of

chemoradiation after chemotherapy is being assessed in the ongoing TOPGEAR trial.[31] In addition, the CROSS regimen is being directly compared with FLOT chemotherapy in the ongoing ESOPEC trial.[32] As results of these trials are reported, they must be interpreted in the context of Checkmate-577 (see below) which randomized patients with residual disease after esophagectomy to observation or adjuvant nivolumab.[6] Whether adjuvant nivolumab would be similarly efficacious in the absence of preoperative chemoradiation is not clear and this will certainly be debated as the TOPGEAR and ESOPEC trials mature. As additional data are accumulated, the imaging-based adaptive approach used in the CALGB trial may represent one rational platform to further evaluate neoadjuvant regimens with the ultimate goal of tailoring therapy for patient subsets.

Kelly RJ et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. *New England Journal of Medicine*. 2021.[6]

Summary: Recognizing the need for adjuvant therapy for higher risk patients after neoadjuvant CRT for resected esophageal or GEJ cancer, CheckMate 577 was a large randomized trial to explore adjuvant nivolumab versus placebo. Primary inclusion criteria were initial stage II/III EAC or ESCC), completed neoadjuvant CRT (dosing and regimen not specified), R0 resection, with residual disease on pathology. Patients were randomized after resection 2:1 to nivolumab versus placebo and stratified based on PD-L1 expression (>1%), ypN+, and histology. The primary endpoint was DFS. Secondary endpoints included OS and distant-metastasis free survival and QOL. Nivolumab was given every 2 weeks at 240 mg and changed to 480 mg every 4 weeks at week 17.

After enrolling 1085 patients before treatment, 794 were eventually randomized. Seventy-one percent of patients had AC, 60 % had tumors of esophageal location (vs GEJ), 58% were ypN+, and 16% of patients were PD-L1 positive. Median DFS was improved from 11 to 22.4 months with nivolumab (HR, 0.69; 96.4% CI, 0.56-0.86; $P < .0001$). In a posthoc analysis, improved DFS was seen regardless of histologic type, but the greatest benefit appeared to be for SCC where median DFS was 29.7 months. Improved DFS was seen regardless of PDL1 status or neoadjuvant radiation dose. There was also an improvement in distant-metastasis free survival with a 26% reduction in distant recurrence or death with nivolumab (HR, 0.74; 95% CI, 0.60-0.92).

Overall, nivolumab was very well tolerated with equal grade 3 or 4 adverse events in both arms. The majority of immune related toxicity was grade 1 or 2, and grade 3 or 4 immune related events occurred in <1% of nivolumab patients. Neither the nivolumab or placebo arm had a clinically meaningful improvement in the FACT-E total score or the EQ-5D-3L utility index score implying there was no detriment to QOL with the addition of nivolumab over placebo. Thirty percent of the nivolumab patients received subsequent anticancer therapy versus 42% of patients in the placebo arm.

Commentary: That improved therapies for patients with esophageal cancer are needed is an understatement. For 40 years, numerous phase 2 and 3 trials of adjuvant and neoadjuvant chemotherapy, radiation, and CRT failed to consistently improve patient outcomes. As discussed above, the CROSS trial established a new standard of care with neoadjuvant radiation to 41.4 Gy in 23 fractions with concurrent Carboplatin and Paclitaxel improving OS over surgery alone.[1] Nearly a decade later, the landscape is significantly changing. CheckMate 577 emphasizes the value of preoperative CRT as a standard of care, especially as a similar benefit for adjuvant immunotherapy has yet to be established in patients receiving perioperative chemotherapy alone. The majority of patients received standard preoperative radiation doses between 41.4 and 50.4 Gy and only patients who recovered well from surgery were eligible. An important remaining question is whether immune checkpoint blockade will also be effective and safe if used preoperatively concurrent with CRT, a combination that appears feasible in preliminary data.[33] In the PERFECT study (where the CROSS

regimen was combined with Atezolizumab), 83% of patients had surgical resection, lower than historical resection rates of 89% with neoadjuvant CRT or 94% with chemotherapy.[34] For CheckMate 577, the risk of pneumonitis was remarkably low (<1%) despite the fact that both radiation therapy and nivolumab independently carry a risk of pneumonitis. This provides reassurance that RT and nivolumab do not appear to have synergistic toxicity, and it does not suggest a need to curtail or modify existing standard for preoperative chemoradiation in patients planned to receive adjuvant nivolumab. Conversely, serious AEs leading to hospitalization or death were observed in 13 patients (33%) in the PERFECT cohort.[34]

The lack of dependency on PD-L1 expression, HER2 status, and tumor histology increases the applicability of CheckMate 577 to most patients undergoing trimodality therapy (except those with autoimmune disorders and severe organ dysfunction). The importance of this broad applicability cannot be overstated as most EC patients (>70%) have residual disease that would require therapy after induction chemoradiotherapy and surgery.

Nevertheless, it is not yet clear whether the benefit of checkpoint inhibitors is the same for AC and SCC (the HR for benefit in CheckMate 577 was 0.61 for SCC versus 0.75 for EAC). A recurring theme for targeted therapies is that significant benefit is realized only within biomarker-selected subgroups: pathologic responses (TRG1 + TRG2), reaching 37.5%, were noted only in patients with baseline inflamed tumor microenvironment before neoadjuvant CRT, as measured by high PD-L1 combined positivity scores ≥25 and high IFNγ signatures in the PERFECT cohort.

Multiple current studies are evaluating immune checkpoint inhibitor (ICI) therapy pre- and/or postsurgery either as monotherapy or concurrently with chemotherapy, chemoradiotherapy, and/or other ICIs. These include standard of care chemoradiation +/– nivolumab in patients with esophageal and gastroesophageal junction adenocarcinoma who are undergoing surgery (with 2nd randomization to adjuvant nivolumab +/– ipilimumab) in EA2174 (NCT03604991), evaluating the efficacy of pembrolizumab as neoadjuvant or adjuvant treatment in addition to either FLOT or Cisplatin-Floropirimidine in adults with gastric and GEJ adenocarcinoma. KEYNOTE-585 (NCT03221426), and Durvalumab and FLOT Chemotherapy in Resectable Gastric and Gastroesophageal Junction Cancer MATTERHORN (NCT04592913), among others. These studies should be able to confirm further the initial observations of feasibility, safety, and efficacy, but refining biomarkers for selection will be key to identify patients, timing and duration of ICI. The future is likely to change faster for esophageal patients, and we look forward for new treatments to offer to our patients

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