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GI Cancers—Modulating the Modern Management of Gastrointestinal Malignancies: A Look at Liver Metastases, Rectal Cancer, Esophagogastric Cancer, and Anal Cancer

By Salma K. Jabbour, MD, *Senior Editor*, Smith Apisarnthanarax, MD, *Associate Editor*, Christopher L. Hallemeier, MD, *Associate Editor*, Florence Huguet, MD, PhD, *Associate Editor*, James D. Murphy, MD, *Associate Editor*, Jeffrey R. Olsen, MD, *Associate Editor*

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In this edition of the GI Oncology Scan, we would like to express our deepest gratitude to Daniel Chang, MD, who has served as the Senior Editor for the GI Red Journal Editorial Team for the past 4 years and recently retired from this role. As a leader in the field of gastrointestinal (GI) oncology, Dan is a highly accomplished radiation oncologist who has headed the efforts in developing stereotactic body radiation therapy (RT) for pancreatic cancer and innovative concepts in GI radiation oncology. Thank you for your solid yet elegant leadership!

Also, we would like to welcome Florence Huguet, MD, PhD, of Paris, France, who is the Chair of the Department of Radiation Oncology of Tenon Hospital, University of Paris VI, Paris, France. Dr Huguet is an international expert in pancreatic cancer and is co-author of the LAP07 trial. We are very enthusiastic and honored to have Dr Huguet's expertise in GI cancers on our Team.

It is also a great pleasure to have Christopher Hallemeier, MD, of the Department of Radiation Oncology at Mayo Clinic, join the Red Journal GI Team. After completing his residency at Mayo Clinic, he was recruited to join the faculty there as an attending physician. Dr Hallemeier's interests include esophageal and liver cancers. We welcome his detailed and analytical approach to our group.

In this edition of the Oncology Scan, we discuss 6 important studies in GI radiation oncology. The first is the global FOXFIRE/SIRFLOX trial evaluating FOLFOX (5-fluorouracil, oxaliplatin, leucovorin) chemotherapy alone versus FOLFOX with yttrium-90 radioembolization in chemotherapy-naive patients with liver-dominant metastatic colorectal cancer (mCRC) (1). Although the study demonstrated no survival benefit to the combination regimen of chemotherapy and radioembolization, benefit was seen for liver control and response rate, with possibly greater benefit for right-sided colon cancer. These findings leave us with questions regarding how and when to best incorporate liver-directed therapy for colorectal cancer metastases.

In the next report, the GRECCAR-2 trial evaluated local excision (LE) compared with standard total mesorectal excision for stage T2 to T3 rectal adenocarcinoma with a favorable response to neoadjuvant chemoradiation therapy (CRT) (2). The investigators found that organ preservation and LE could occur in 61% of patients who achieved a good clinical response (ypT0-T1). Also, a post hoc analysis of the American College of Surgeon Oncology Group trial Z6041 study evaluating quality of life (QoL) measures for cT2N0 rectal cancer patients treated with preoperative CRT followed by LE demonstrated preservation of anorectal function with overall stable QoL 12 months after surgery (3). These results suggest that less invasive surgery might help to maintain patients' QoL.

Next, the POET (PreOperative therapy in Esophagogastric adenocarcinoma Trial) trial, comparing preoperative chemotherapy to preoperative CRT for gastroesophageal junction (GEJ) carcinoma, demonstrated an improvement in pathologic complete response and local control with CRT preoperatively and borderline improvement in survival compared with chemotherapy preoperatively (4). Also, a study evaluating the National Cancer Database (NCDB) comparing perioperative chemotherapy (PECT) to postoperative CRT in GEJ and gastric cancer patients concluded that PECT is superior to postoperative radiotherapy.

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However, that study is difficult to interpret owing to the multiple methodologic flaws and confounders (5). Our choice to include the study was to caution readers about the potential shortcomings of these analyses.

Finally, in a large analysis of anal cancer nodal staging, Sekhar et al (6) proposed that the Will Rogers phenomenon is applicable in anal cancer lymph node staging because of improved imaging technologies. They concluded that staging misclassification occurs in anal cancer and can result in the possible risk of overtreatment (6).

Wasan et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): A combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 2017;18:1159-1171. (1)

Summary: This report details the pooled findings of 3 separately conducted, international randomized trials (FOXFIRE, SIRFLOX, and FOXIRE-Global) evaluating the combination of ^{90}Y radioembolization (selective internal RT [SIRT]) that aimed to clearly define the role of SIRT combined with FOLFOX (Folinic acid, fluorouracil, and oxaliplatin chemotherapy) versus FOLFOX alone for first-line treatment of colorectal liver metastases. In aggregate, from 2006 to 2014, the 3 trials enrolled 1103 patients, with 549 in the FOLFOX-alone arm and 554 in the FOLFOX + SIRT arm. The chemotherapy regimens varied slightly. FOXFIRE required chemotherapy to consist of the oxaliplatin modified de Gramont chemotherapy (85 mg/m^2 oxaliplatin infusion over 2 hours, L-leucovorin 175 mg or D,L-leucovorin 350 mg infusion over 2 hours, and 400 mg/m^2 bolus 5-fluorouracil, followed by a 2400-mg/m^2 continuous infusion 5-fluorouracil over 46 hours); the protocol therapy continued for 12 cycles. In the SIRFLOX and FOXIRE-Global trials, the chemotherapy regimen modified the leucovorin dose to 200 mg, and chemotherapy could continue until disease progression. Also, for the combined modality arms, the timing of anti-vascular endothelial growth factor therapy and anti-epidermal growth factor receptor therapy began at cycle 7 (FOXFIRE) or cycle 4 (SIRFLOX and FOXFIRE-Global).

With a median follow-up of 43.3 months, no differences were found in overall survival (OS) between the FOLFOX + SIRT (22.6 months) and the FOLFOX (23.3 months) groups. In the post hoc unplanned subgroup comparisons, right-sided colon cancer benefited from FOLFOX + SIRT, with a hazard ratio (HR) of 0.67 (range 0.48-0.92), and left-sided cancer appeared to have more favorable results with chemotherapy alone (HR 1.13, range 0.93-1.38). In the combined modality arm, fewer first progression events were radiologically observed in the liver at 1 year (22%) compared with FOLFOX alone (39%) (HR 0.51; $P < .0001$). In contrast, the incidence of first extrahepatic progression was more pronounced in the FOLFOX + SIRT group (54%) than in the FOLFOX group (36%; HR 1.76; $P < .0001$). Also, the odds of achieving an objective response in the liver were significantly greater in the FOLFOX + SIRT group than in the FOLFOX-alone group. Approximately 16.5% of patients were able to subsequently undergo hepatic resection. Serious adverse events were more common in the FOLFOX + SIRT group than in the chemotherapy-alone group.

Comment: This combined analysis of 3 international, randomized, phase III trials sought to clarify the role of first-line liver-directed therapy in patients with liver-dominant mCRC. In all 3 trials, patients were randomized to receive either FOLFOX alone or with the addition of SIRT as first-line metastatic treatment. Although the addition of SIRT resulted in a greater objective response rate (72% vs 63%), no improvement was observed in progression-free survival or OS. From results of their combined analysis, SIRT cannot be recommended outside of a clinical trial as a component of first-line mCRC treatment.

The role of liver-directed therapy for unresectable mCRC remains controversial. Long-term follow-up data from the phase II EORTC CLOCC 4004 study (7) suggest a survival benefit for the addition of liver radiofrequency ablation to systemic treatment for mCRC. Additional mature follow-up data from patients undergoing liver stereotactic body RT in prospective clinical trials suggest an association between improved local control of targeted liver disease and OS, emphasizing the importance of an observed dose response (8). An important underlying consideration in evaluating liver-directed therapy is distinguishing the goal of ablation, such as in radiofrequency ablation or stereotactic body RT, versus provision of regional treatment in the setting of SIRT or other transarterial-based therapies.

A greater rate of nonliver progression was observed in the study for SIRT with FOLFOX compared with FOLFOX alone, although the reasons for this difference are unclear. In the SIRT arm of the analysis, fewer patients received full-protocol dose chemotherapy, fewer received bevacizumab as a component of treatment, and fewer received irinotecan, fluoropyrimidine, anti-vascular endothelial growth factor, or anti-epidermal growth factor receptor therapies on progression compared with the FOLFOX-alone arm. This reduction in the intensity of systemic treatment could have contributed to the differential pattern of progression but could have also been a consequence of the experimental treatment, given the increased toxicities noted in the SIRT arm. Although not reported in the their study, the investigators noted that molecular subtyping analysis is under way and could help to clarify the subgroup analysis, suggesting a possible survival benefit with SIRT among patients with right-sided primary tumors.

For patients undergoing SIRT as regionally directed therapy, variability in the extent of the tumor-absorbed dose among treated lesions has been described according to the positron emission tomography (PET) findings after radioembolization ^{90}Y, with correlation of the dose

response (9, 10). Such assessments are not yet available on a widespread basis and thus were not available for their study but could provide a route toward individualized treatment considerations in future studies, with "postimplant" quality metrics similar to those that are standard for other brachytherapy procedures.

Although their study demonstrated an absence of benefit to SIRT as a component of first-line therapy for mCRC, the role of nonsurgical liver-directed therapies, with an important distinction between ablative and regionally directed treatments, continues to evolve. Although not recommended in an unselected first-line setting, SIRT remains a consideration based on available evidence for carefully selected patients with liver-dominant disease in whom previous systemic therapy has failed.

Rullier et al. Organ preservation for rectal cancer (GRECCAR 2): A prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet* 2017;390:469-479. (2)

Summary: This French, multicenter, phase III randomized trial compared LE versus total mesorectal excision (TME) in patients with a good clinical response after CRT for patients with stage T2-T3N0-N1 low-lying rectal cancer (≤8 cm from the anal verge) not involving the anal sphincter, ≤4 cm in diameter, to evaluate both oncologic and nononcologic outcomes. Staging consisted of colonoscopy with biopsy, pelvic magnetic resonance imaging (MRI), and abdominal and thoracic computed tomography (CT) scan. CRT consisted of 50 Gy of 3-dimensional conformal pelvic RT (18 MV) in 2 Gy daily for 5 weeks with capecitabine 1600 mg/m^2 and oxaliplatin 50 mg/m^2 weekly during CRT (oxaliplatin was stopped in 2009). Restaging was performed 6 to 8 weeks after CRT using pelvic MRI.

Patients could be included before or after neoadjuvant CRT and were randomized before surgery. The surgeon determined whether the patient had a good clinical response (tumor ≤2 cm, no vegetative component, no significant hollow or deep infiltration into the muscle layer), and patients were then randomized to LE or TME. If at LE, the patients were found to have ypT0-T1 disease, they underwent follow-up. If, however, the patients had a poor clinical response on LE (ypT2-T3 or R1), they underwent completion TME. The primary endpoint was a composite outcome of operative death, local recurrence, major morbidity, and severe side effects at 2 years after surgery to show superiority of LE over TME in the modified intention-to-treat analysis. From 2007 to 2012, 186 patients were enrolled. A total of 148 patients were randomized. Of the 148 patients, the data from 145 were analyzed, and 74 were assigned to LE and 71 to TME. Of the 74 patients assigned to LE, 73 received LE, and 39 were found to have ypT0-T1 R0 rectal cancer (53%) versus 34 with ypT2-T3 or R1 (47%). Also, of the 71 assigned to TME, 60 underwent TME, 8 received LE, and 3 received no surgery.

In the modified intention-to-treat analysis, no significant differences were found between LE and TME with regard to operative death, tumor recurrence, disease-free survival, OS, and major morbidity. Local recurrence developed in 5% to 6% of all patients with an 89% (LE) and 95% (TME) OS rate at 3 years. No superiority of LE was found owing to the high number of completion TMEs performed. Also, the TMEs increased the morbidity and side effects at 2 years. However, the large number of nodal responses suggests that completion TME was not often necessary; only 8% of lymph nodes occurred in small, irradiated tumors. Given this small rate of lymph node positivity (LNP), the investigators thought that completion surgery could be limited to <10% of patients with ypT2/N1 and ypT3 tumors. Their results suggest that organ preservation approaches are feasible and require methods to more optimally select the most appropriate patients for these limited operative approaches.

Comment: Multimodality therapy has become the standard of care for patients with locally advanced rectal cancer using preoperative CRT, followed by TME. With this strategy, the rate of local recurrence at 5 years has been very low (<10%). Most of the relapses are distant metastasis (18% at 1 year, 28% at 2 years, 35% at 5 years). However, these results after TME are at the cost of significant postoperative morbidity, including long-term urinary, sexual, and fecal continence dysfunction. After CRT, ~20% of patients will have a pathologic complete response (pCR), defined as no residual viable tumor cells in the specimen (ypT0N0). For the patients with a good clinical response to CRT, alternative treatment strategies have been suggested to avoid major postoperative complications, including no immediate surgery (also known as the watch and wait strategy or nonoperative management [NOM]) and LE (11, 12). The main issue with these new strategies is the ability to identify the optimal candidates for surgical deflation. A clinical complete response is not easy to affirm. Moreover, these criteria alone are probably not robust enough to identify the patients without residual tumor cells.

In their prospective phase III trial, patients with T2 or T3 and N0-N1 rectal carcinoma <4 cm in diameter underwent preoperative CRT at the standard dose. Patients with a good clinical response as assessed by MRI were then randomized between TME and LE. In the LE arm, patients with ypT2-T3 tumors or R1 resection underwent TME 1 to 4 weeks after. The rate of clinical good response was 75%. Of these patients, 61% had a good pathologic response (ypT0-T1).

First, it is important to underline that 47% of patients treated with LE underwent secondary TME, much greater than expected (10%-20%). The rationale was that the rate of lymph node involvement was expected to be ~25% for ypT2 tumors and 55% for ypT3 tumors. In their study, the rate of lymph node involvement was much lower, 8% for ypT2 tumors and 40% for ypT3 tumors. We agree with the investigators' conclusion that TME could have been avoided for ypT2 patients.

Second, patients undergoing TME after LE presented with a high rate of major morbidity or side effects (78% vs 38% after TME only). Taken together, these 2 facts have contributed to the absence of a benefit of LE over TME. In a post hoc exploratory analysis, the investigators compared the outcomes of the population divided into 3 groups: LE, TME, and LE + TME. The rate of major morbidity or side effects was significantly lower in the LE group, with similar survival. This analysis demonstrated that LE is a good alternative for patients who are well selected for more limited surgical approaches.

The main question raised by their trial was how to better select patients who could benefit from LE. The question is the same for the watch and wait strategy. We should perhaps limit these strategies to patients with T2 tumors. However, these patients do not always require preoperative treatment, and the risk of overtreatment is significant. Another question is the best method to assess the tumor response after preoperative CRT. Clinical examination, endoscopy, and MRI seem to be insufficient. An urgent need exists to identify biomarkers that can be used to predict the pathologic tumor response after neoadjuvant treatment. To conclude, the high rate of severe complications after secondary TME is in favor of LE or a watch and wait strategy.

Lynn et al. Anorectal function and quality of life in patients with early stage rectal cancer treated with chemoradiation and local excision. *Dis Colon Rectum* 2017;60:459-468. (3)

Summary: This study reports the outcomes from the anorectal function (AF) and health-related QoL (HRQoL) assessments from patients with cT2N0 rectal adenocarcinoma who underwent preoperative CRT followed by LE in the American College of Surgeon Oncology group trial Z6041. AF and QoL were assessed at enrollment and 1 year postoperatively. Patients treated in the study had rectal cancer located within 8 cm of the anal verge, <4 cm in diameter, and occupied <40% of the rectal circumference. Patients initially enrolled in this study received CRT, including capecitabine, oxaliplatin, and 50.4 to 54 Gy. However, owing to an unfavorable toxicity profile, the neoadjuvant treatment was amended to capecitabine with 50.4 Gy. Either conventional transanal excision or transanal endoscopic microsurgery (TEM) occurred 4 to 8 weeks after CRT completion.

AF was evaluated using the Fecal Incontinence Severity Index, which addresses the frequency of leakage of gas, mucus, liquid, and/or solid stool, with higher scores indicating worse function. HRQoL was evaluated using 2 scales. The first was the Functional Assessment of Cancer Therapy-Colorectal (FACT-C), a validated questionnaire that contains subscales of physical, emotional, social/family, and functional well-being and a colorectal cancer subscale (CCS), with a higher score indicating better HRQoL and overall function. Physical well-being, social/family well-being, and the CCS score are used to calculate the Trial Outcome Index, which better reflects the true effect of the treatment intervention. The second was the Fecal Incontinence Quality-of-Life Scale (FIQL), which is composed of 29 items evaluating subscales that include lifestyle, coping/behavior, depression/self-perception, and embarrassment.

The 72 patients who underwent CRT and LE constituted the eligible study cohort. Of these 72 patients, 71 completed the baseline evaluations, and 66 completed the 12-month evaluations. At the 12-month postoperative evaluation, no significant change was observed in the overall Fecal Incontinence Severity Index score and its subdomains compared with the baseline scores. The FIQL showed significantly worse outcomes in the lifestyle, coping/behavior, and embarrassment scales; however, the depression scale values had not changed significantly. At 1 year postoperatively, the FACT-C scores were not significantly different from those at baseline; however, waterfall plot analyses showed that one half of the patients had experienced improvement, and one half had experienced deterioration, and this was true in regard to the subscales of CCS and Trial Outcome Index. Also in the FACT-C, the social/family and functional well-being and CCS subdomains showed no statistically significant difference. However, in the physical well-being domain, significant deterioration was found at 1 year compared with improvement in the emotional well-being domain. On multivariate analysis, treatment with the capecitabine/oxaliplatin CRT regimen was associated with worse outcomes of depression/self-perception and embarrassment in the FIQL, and men fared worse in the FACT-C assessment. Overall, CRT, followed by LE, had minimal influence on AF after surgery, with stable overall QoL but mixed effects in the subscales.

Comment: For cT2N0 rectal cancer undergoing CRT followed by LE, the data presented in their study are valuable in understanding a patient's perspective for AF and QoL. The study found that AF was not significantly different from baseline after curative treatment for early-stage rectal cancer. Although overall QoL was reasonable after CRT and LE, both of these therapies can still negatively affect patients' lifestyles at the 1-year mark after surgical resection, especially in the realms of lifestyle, coping/behavior, and physical and emotional well-being. Although the study answered some questions about AF and HRQoL, it also left some questions unanswered.

It is likely that the patients' symptoms worsened in the postoperative period and might have gradually improved until the 1-year assessment; however, the trajectory at 3, 6, or 9 months remains unknown. A study of rectal cancer patients that compared QoL after neoadjuvant CRT before TEM demonstrated an immediate decline at 1 month postoperatively in overall health status, physical functioning, fatigue, pain, and defecation. However, the

symptoms and QoL had reversed at 6 and 12 months postoperatively compared with preoperatively. These findings are in contrast to the study by Lynn et al (13), which suggested a significant persistence of symptoms at 1 year postoperatively. These differences could have resulted from the use of different QoL assessments between these studies. Similar results evaluating TEM alone have shown that TEM has a temporary and reversible effect on QoL (14) and that symptoms of therapy continue to improve at least to the 1-year evaluation.

In a study from Italy comparing the QoL of patients with T2 to T3 rectal cancer who had undergone TEM (n = 15) or laparoscopic TME (n = 15), at 6 months postoperatively, the TEM group fared better for emotional functioning, insomnia, appetite, and body image. At 12 months, the TEM patients had improved body image, defecation, and less weight loss compared with the TME group (15). Furthermore, after CRT, QoL has also been more favorable in NOM cases compared with TME cases. NOM patients demonstrate improved defecation, sexual, and urinary tract function and better physical, emotional, and global health scores (16). In comparing the QoL with TEM to the QoL with NOM approaches after neoadjuvant CRT, NOM for those with a clinical complete response resulted in better AF compared with that in those with a near complete response followed by TEM. The investigators found that TEM patients had worse rectal capacity, resting/squeezing pressure, incontinence scores, and QoL compared with the NOM patients (17). Therefore, for QoL and AF, it does appear that less invasive approaches result in better QoL, since NOM appears to provide the most promising QoL, followed by LE, and, finally, TME. Both the GRECCAR-2 study and these data about QoL lend support to the notion that reducing the extent of surgery can afford patients improved QoL.

Stahl et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. *Eur J Cancer* 2017;81:183-190. (4)

Summary: The POET was originally designed when preoperative chemotherapy was considered the most appropriate therapy for adenocarcinoma of the esophagogastric junction in Europe. This randomized phase III study aimed to determine whether preoperative CRT was superior to preoperative chemotherapy. A total of 126 patients with Siewert type I to II, International Union Against Cancer stage T3/T4 tumors were enrolled from 2000 to 2005, with a median follow-up of 46 months. The study closed early after 119 patients were randomized and eligible. After a planned interim analysis in 2015, it was calculated that another 163 patients per treatment group would be necessary to determine the OS endpoint. Owing to the slow accrual, the study coordinators decided to close the trial in 2005. For the chemotherapy-alone arm (arm A), patients received 5-fluorouracil, folinic acid, and cisplatin for 14 weeks, followed by an additional 3-week course of these agents. The CRT arm (arm B) received the same 14-week chemotherapy regimen. However, instead of receiving additional chemotherapy, they received CRT to 30 Gy in 15 fractions with concurrent cisplatin and etoposide. Surgery was performed 3 to 6 weeks after the end of preoperative therapy.

The results included a greater rate of pCR in arm B (14%) compared with arm A (2%, $P = .03$). In the pCR group, the 5-year OS rate was 88%. Those with complete resection but residual tumor in the surgical specimen had a 5-year survival rate of 39%. After preoperative treatment, resection with positive margins (R1 resection) was more often observed after chemotherapy (15.4%) than after CRT (4.1%). Progression-free survival was significantly better for those receiving CRT. The survival differences between the groups demonstrated a trend toward statistical significance with a 5-year OS for arm A of 24% compared with 40% in arm B ($P = .055$). Local progression-free survival was significantly improved in the CRT arm. Likewise, fewer locoregional recurrences developed in the CRT arm (21% vs 38%). However, 4 and 6 patients died of treatment-related causes in arm A and arm B, and the postoperative in-hospital mortality was 3.8% and 10.2%, respectively.

Comment: This update of the POET study reports on the long-term outcomes of GEJ cancer patients treated with either preoperative chemotherapy or CRT. The initial report in 2009 reported on the 3-year results with a trend toward improved OS in the CRT group (28% vs 47%; $P = .07$) (18). The relative improvement in OS with this update was maintained at 5 years, with a greater trend toward statistical significance. Although the study was underpowered owing to the early closure from poor accrual and not meeting its primary endpoint, its importance should not be minimized. The study is the only phase III study that addresses specifically only GEJ cancers and is the only study that has shown a clinically relevant OS benefit to CRT over chemotherapy alone in this disease. Although one might argue that the OS benefit is not statistically meaningful, it is difficult to ignore the 1.6-fold improvement in OS and a P value of .055 with locoregional treatment.

The improved OS with CRT can be explained by other pertinent positive findings in the study. CRT was able to reduce the positive resection margins by nearly fourfold—an important finding because surgical margin positivity is a known important prognostic factor associated with decreased OS (19). Moreover, patients in the CRT group had a decrease in locoregional recurrence without differences in distant metastatic failure rates. This finding argues strongly that for esophageal cancers, locoregional control translates into improved OS, a finding uncommon in our field, in particular, for cancers with high distant metastatic failure rates.

However, one could question the relevance of the study to modern approaches to trimodality therapy. Most conventional trimodality treatment approaches do not involve induction chemotherapy before CRT. In addition, with the encouraging survival outcomes and toxicity profile of patients treated in the CROSS trial with concurrent carboplatin/paclitaxel (20), the use of concurrent cisplatin/etoposide might be less generalizable to current trend in trimodality therapy. It is also noteworthy that the pCR rate with CRT was low in the study at 14% compared with that in the CALGB and CROSS studies (pCR 23%-38%) (20, 21). This is likely explained by the relatively low doses of RT used in the POET study (30 Gy) compared with 50.4 and 41.4 Gy used in the CALGB and CROSS studies, respectively. However, despite these differences in pCR rates, the locoregional control and OS rates were remarkably similar (~80% and ~40%, respectively) among these studies. One possible explanation for this observation is that the addition of induction chemotherapy to CRT patients in the POET study might have contributed to the locoregional control (in the absence of pCR) and "made up" for the lower RT doses.

The most significant concern regarding preoperative CRT is the increased cardiopulmonary toxicity with irradiation of the heart and lungs compared with chemotherapy alone. Although not statistically significant, more patients died in the hospital after surgery in the CRT group than in the chemotherapy-alone group in the POET study. In addition, a slight narrowing of the OS benefit was seen with CRT over time, with 1.8-fold improvement at 3 years that had decreased to 1.6-fold at 5 years. It is unclear whether accumulation of morbidity from cardiopulmonary toxicity occurred over time in these patients. Because the POET study only used 3-dimensional CRT planning techniques, it is possible that the differential benefit of preoperative CRT might be further magnified with the usage of modern RT techniques. Recent data have suggested that advanced radiation delivery techniques with intensity modulated RT or proton therapy that reduce the heart and lung dose might play a pivotal role in mitigating postoperative complications in esophageal patients (22).

Finally, the data from the POET study are primarily applicable only to Siewert type I and II tumors. The treatment of tumors involving the GEJ junction with predominant stomach involvement (Siewert type III) was not addressed by the study, and the optimal treatment approach remains to be clearly defined regarding whether a gastric cancer regimen (in which chemotherapy alone is commonly given as neoadjuvant and adjuvant therapy) or an esophageal cancer regimen (trimodality treatment) is superior.

In summary, although the results of the study might not completely end the debate of CRT versus chemotherapy for preoperative treatment of GEJ cancer, it certainly adds to the mounting data of preoperative CRT as a preferred approach in this disease.

Fitzgerald et al. Perioperative chemotherapy versus postoperative chemoradiotherapy in patients with resectable gastric/gastroesophageal junction adenocarcinomas: A survival analysis of 5058 patients. *Cancer* 2017;123:2909-2917. (5)

Summary: Fitzgerald et al (5) analyzed cases of clinical stage II to III GEJ and gastric cancer from the NCDB from 2004 to 2013 to determine the comparative survival advantage of PECT versus postoperative CRT (POCRT). Patients were classified as having been treated with PECT if they had received both preoperative and postoperative chemotherapy. Patients were considered to have undergone POCRT if they had received a total radiation dose of 4000 to 6000 cGy. A total of 536 patients were included in the PECT group compared with 4522 in the POCRT group. PECT was more frequently used for malignancies of the GEJ (42% vs 22%), and POCRT was more often used for stomach cancer, cancer of an unknown anatomic site (37% vs 27%), and cancer of the distal stomach (30% vs 19%; $P < .0001$). Patients receiving POCRT were more likely to have larger tumors (>4 cm; 63%) and positive surgical margins (18%) compared with those receiving PECT (55% [$P = .0004$] and 10% [$P < .0001$], respectively).

The authors reported that PECT was associated with a 42% decreased risk of death compared with POCRT (HR, 0.58; $P < .0001$). Accounting for the total radiation dose did not change the overall findings. Both PECT and POCRT conferred a survival advantage compared with surgery alone ($P < .001$). A survival advantage was seen for PECT compared with neoadjuvant chemotherapy alone (adjusted HR 0.74; $P = .0004$). More lymph nodes were harvested in the PECT group (median 18 lymph nodes) than in the POCRT group (median 15 lymph nodes; $P < .0001$). The magnitude of the survival advantage for PECT (vs POCRT) was greater among patients with clinical lymph node-positive disease (adjusted HR 0.52; $P < .001$) than for those with clinical lymph node-negative disease (adjusted HR 0.90; $P < .5$). For those with clinical lymph node-positive disease, those receiving PECT were 4.6-to 4.8-fold more likely to experience clearance and downstaging than those receiving POCRT. The 3- and 5-year actuarial survival rates were 62% and 44% for PECT compared with 52% and 38% for POCRT, respectively.

Comment: The current treatment paradigms in gastric cancer stem from 2 large randomized clinical trials: the Intergroup study and the MAGIC trial. The Intergroup study, reported in 2001, found that 5-fluorouracil–based CRT improved OS when given adjuvantly after margin-negative surgery compared with surgery alone for gastric and gastroesophageal cancer patients (23). The MAGIC study, reported in 2006, found that PECT with epirubicin, cisplatin, and 5-fluorouracil improved survival compared with surgery alone for gastric, gastroesophageal, and esophageal cancer patients (24). Adjuvant CRT per the Intergroup study and PECT per the MAGIC trial have not been compared in a prospective

randomized clinical trial. The study by Fitzgerald et al (5), highlighted here in OncoScan, attempted to address this question in a retrospective study using data from the NCDB.

The central finding of the study by Fitzgerald et al (5) relates to the observation of a 42% decreased risk of death among the PECT group compared with the POCRT group (adjusted HR 0.58). This magnitude of a survival difference stands somewhat at odds with the existing data. PECT in the MAGIC trial reduced the risk of death by 25% compared with surgery alone (HR 0.75). Similarly, adjuvant CRT in the Intergroup study reduced the risk of death by 24% compared with surgery alone (HR 0.76). Comparing the results from different randomized trials comes with risk, although given the similar survival improvement with PECT in the MAGIC trial and adjuvant CRT in the Intergroup study, one might anticipate similar survival in a head-to-head comparison between PECT and adjuvant CRT. The notable difference in survival between the prospective randomized clinical trial findings and the retrospective analysis of the NCDB raises some important questions about study methodology with observational studies.

The first issue to consider with retrospective database analyses relates to the potential for "selection bias" to skew the findings toward 1 treatment arm or another. With gastric cancer, in particular, the inherent difficulty in completing treatment leads to the potential for bias in that one could accidentally exclude patients with a poor outcome from the analysis. For instance, with the original MAGIC trial, only a small fraction of patients completed PECT. Also, 12% of the patients in the MAGIC trial who had started preoperative chemotherapy never underwent surgery. Only 41.6% of patients altogether ultimately completed all of both preoperative and postoperative chemotherapy regimens. The NCDB has defined PECT as the completion of $\geq$2 cycles of systemic therapy before surgery and completion of 2 cycles after surgery. Therefore, when using the NCDB definition of PECT, a substantial number of patients who were treated with the "intent" of PECT will be excluded because of failure to complete therapy. In the MAGIC trial, the reasons for failing to complete therapy included disease progression or death, complications from surgery, toxicity, lack of a treatment response, or worsening coexisting disease (24). The study by Fitzgerald et al (5) by nature excluded this large and important subgroup of poor prognosis patients—which would dramatically sway the survival analyses in favor of the PECT arm. This same selection bias problem of preferentially excluding "unhealthy" patients would influence the adjuvant CRT group as well—although likely to a lesser degree, given that more patients finished adjuvant CRT after surgery (64% in the Intergroup study) than those completing PECT (41.6% in the MAGIC trial). Overall, this bias will skew survival analysis results toward the PECT group.

A second methodologic issue to consider relates to the concept of "immortal time bias." This important, yet often overlooked, source of bias has been previously described in a well-written Red Journal piece by Park et al (25). Immortal time bias is most easily explained by example. In this study, patients in the PECT group, by definition, must have survived from diagnosis, through preoperative chemotherapy, surgery, and postoperative chemotherapy (5). Similarly, those in the adjuvant CRT group must have survived from diagnosis through the end of postoperative CRT. The potential for an immortal time bias arises in situations in which this "immortal time," or the time during which a patient cannot die, differs between study groups. In this study (5), it takes longer for a patient to complete PECT than to complete CRT, which leads to an immortal time bias that tends to favor the PECT group. Statistical techniques exist to quantify immortal time bias, including landmark analyses (25) and time-dependent analyses (26), although these were not used in the study by Fitzgerald (5).

Comparative effectiveness research with large databases often suffers from biases such as those discussed that can cloud results, obscure conclusions, and, in general, raise questions about internal validity. Other potential concerns are the inclusion of positive-margin resection in their analyses when only margin-negative patients were studied in the Intergroup study. Also, the use of RT doses $\leq$6000 cGy in the postoperative setting raises the concern of misclassification of the primary tumor or situations in which gross disease might have been present. The study by Fitzgerald et al (5) had limitations, although it did attempt to address the important question about the utility of RT in GEJ cancer. This question is less controversial in esophageal and gastroesophageal cancer, as discussed in the POET study. However, 2 recent randomized trials in gastric cancer call into question the role of RT in this disease. First, the ARTIST study found no benefit for adjuvant CRT compared with adjuvant chemotherapy after gastrectomy (27). Second, the CRITICS study evaluated patients with gastric or GEJ cancer treated with preoperative chemotherapy and surgery, followed by randomization to adjuvant CRT or adjuvant chemotherapy alone. The preliminary results of the CRITICS study found no survival benefit for CRT compared with chemotherapy alone (28). Ongoing randomized trials include the ARTIST II trial, which will evaluate the effect of adjuvant CRT in a more select subgroup of gastric cancer patients (ClinicalTrials.gov identifier, NCT01761461). Additionally, the TOPGEAR study will evaluate the addition of preoperative CRT to PECT (ClinicalTrials.gov identifier NCT01924819). Altogether, these forthcoming prospective randomized studies will help to define the utility of RT in gastric cancer.

Sekhar et al. Nodal stage migration and prognosis in anal cancer: A systematic review, meta-regression, and simulation study. *Lancet Oncol* 2017;18:1348-1359. (6)

Summary: In the report by Sekhar et al (6) on anal cancer lymph node stage migration or the increase in the

proportion of patients with nodal positivity, they evaluated the influence of the Will Rogers phenomenon, in which after the introduction of a new diagnostic technology or staging system, some patients are reclassified from 1 tumor stage to another, resulting in a paradoxical improvement in survival for patients in both stages without a change in OS for the individual patients. Therefore, Sekhar et al (6) hypothesized that LNP in squamous cell carcinoma of the anal canal (SCCA) had increased owing to enhanced detection using newer imaging modalities (nodal stage migration) but that the T stage distribution had remained constant, resulting in the Will Rogers phenomenon such that no increase in OS would be realized for any patient. The investigators performed a systematic review and meta-regression to quantify the changes in LNP over time and the effect of this change on survival and prognostic discrimination with the primary outcome of 5-year OS. They amassed studies with >50 patients for whom CRT was used as the primary treatment (6). They simulated varying true LNP proportions and true OS and compared these results with the expected observed outcomes for varying levels of misclassification of true nodal state.

In the meta-regression analysis of the complete data set of 62 studies, most of which were reported after 2000, a significant increase in observed LNP was found over time. The proportion of LNP patients increased 6.8% per decade. In 1980, the predicted mean LNP was 15.3% compared with 37.1% in 2012. However, the combined T3 and T4 stages remained constant over time, with 41.3% in 1980 and 38.9% in 2012. Furthermore, the 5-year OS increased in both lymph node-positive and lymph node-negative patients with the increasing observed LNP. Despite these improvements in survival rates with the increasing LNP, the 5-year OS estimates were not significantly different in 1980 (64%) compared with 2010 (72%; $P = .39$). Across a range of LNP proportions from 15% to 40%, the HRs for OS for LN-positive versus LN-negative patients decreased significantly from 2.5% at 15% LNP to 1.3% at 40% LNP. In summary, the investigators suggested that staging misclassification occurs in anal cancer, resulting in reduced prognostic discrimination. They found that the LNP of >30% was greater than the true LNP proportions, which might misclassify the disease stage and result in the possible risk of overtreatment.

Comment: For SCCA, clinical lymph node involvement is a well-established prognostic factor for outcomes (29) and currently guides the radiation therapy dose and volume (30). Sekhar et al (6) have presented data supporting a phenomenon of lymph node stage migration and resultant "reduced prognostic discrimination" of clinical lymph node status. This observation has broad-reaching implications regarding the choice of imaging modalities for staging, treatment decisions (specifically, prescribed radiation dose to lymph nodes), prognostication of outcomes for patients, interpretation of results from the published data, and design of future clinical trials. Lymph node stage migration is entirely plausible when one considers the significant changes in staging techniques that have occurred during the past 40 years for SCCA. In the 1980s to 1990s, lymph node stage was assigned on the basis of the clinical examination and low-resolution CT findings. At present, staging involves high-resolution CT and often an advanced imaging modality, typically fludeoxyglucose-PET and/or MRI.

The analysis had several limitations that warrant comment. They performed a systematic review of mostly retrospective observational series; thus, many sources of bias could be at play. Even when considering data from randomized controlled trials, the heterogeneity in the inclusion criteria between trials can affect the LNP rates. For example, RTOG (Radiation Therapy Oncology Group) 87-04 allowed patients with T1 tumors (15% of the patients enrolled) but RTOG 98-11 excluded patients with T1 tumors (29, 31). Population-based data from national cancer registries might be less prone to biases. An analysis of the US Surveillance, Epidemiology, and End Results Program database demonstrated that the proportion of patients with newly diagnosed SCCA with regional disease (defined as spread to adjacent organs or regional lymphatics) actually decreased from 40% during 1973 to 1996 to 32% during 1997 to 2009 (32). The proportion of patients with localized disease increased from 50% to 57%, which the investigators attributed to increased screening of high-risk populations, and the proportion with distant disease remained constant at 11%. Additionally, available data suggest that advanced imaging modalities might be equally likely to upstage versus downstage the nodal status. In a recent systematic review and meta-analysis evaluating the utility of fludeoxyglucose-PET/CT compared with CT alone for initial staging of SCCA, PET/CT led to lymph node upstaging in 15% and downstaging in 15% (33).

It remains unclear whether and how these findings should affect the current clinical management of SCCA. For example, how should one treat the patient with a T2 primary tumor and a 9-mm PET-avid lymph node? Such a patient might have been staged as having T2N0 in the RTOG 87-04 or ACT I trial, and the lymph node would have been treated with a prophylactic radiation dose of 30.6 to 45 Gy (31, 34). However, the current guidelines recommend boosting a clinically involved lymph node to ≥50 Gy (30). A higher radiation dose might increase the risk of treatment-related adverse effects. Although some data have suggested that an increased dose to the primary tumor is associated with better local control (35), such data regarding the dose response of lymph nodes are lacking. Isolated lymph node recurrence is rare (36), suggesting that perhaps doses as low as 30 Gy, such as used with the original Nigro regimen, might be sufficient for eradicating low-volume lymph node disease (37). Clinical lymph node status determines the eligibility for the recently opened UK ACT 4 and 5 trials, in which patients with T1-T2N0 SCCA are randomized to standard versus reduced-dose RT (ACT 4). In ACT 5, patients with lymph node-positive SCCA are randomized to standard versus escalated-dose

RT. Data from the ACT trials will inform evidence-based recommendations on the optimal radiation dose to lymph nodes for SCCA.

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