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Gastrointestinal Cancers: Fine-Tuning the Management of Rectal, Esophageal, and Pancreas Cancers

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In this edition of the Gastrointestinal (GI) Oncology Scan, the GI Red Journal Editorial Team discusses 6 recent noteworthy studies in GI oncology. These studies continue to hone the management of patients with localized GI cancers.

In the CARTS study on the long-term results of chemoradiation therapy (CRT) followed by organ-sparing transanal endoscopic microsurgery (TEM) (local excision), Stijns et al found that local excision may be feasible in about two-thirds of patients with distal cT1-T3N0 rectal cancers and may result in improved functional outcomes.[1] However, about half of patients treated with TEM as a component of organ preservation will experience significant symptoms similar to a low anterior resection, and one-third of patients will still require radical surgery.

In a retrospective study evaluating a “watch and wait” (WW) approach for patients with rectal cancer who achieved a clinical complete response to neoadjuvant CRT compared with those who had a pathologic complete response to CRT after total mesorectal excision (TME), Smith et al found more favorable results with standard surgery in terms of overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), and rate of distant metastases. However, patients were not matched for baseline characteristics.[2]

In a retrospective study of 1216 patients with cT3 or cT4 rectal cancer, international investigators found that patients with enlarged lateral lymph nodes (LLNs) (obturator and internal iliac) with short axes of at least 7 mm on magnetic resonance imaging (MRI) are more likely to experience subsequent lateral local recurrence in up to 20%, even in the setting of preoperative CRT and TME.[3] For patients with LLNs that underwent additional LLN dissection, LLN recurrence rates were significantly lower at 6%, which raises questions about the optimal management of lymph nodes outside of the mesorectum that are not removed with TME.

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In a large, randomized phase 3 trial comparing CRT followed by surgery to surgery alone for treatment of squamous cell carcinoma of the esophagus, researchers found that trimodality therapy resulted in superior R0 resection, median OS, and median DFS rates and higher rates of postoperative arrhythmias.[4]

A single-arm phase 2 study of FOLFIRINOX followed by individualized CRT for borderline resectable pancreatic cancer resulted in promising rates of R0 resection, 2-year OS of 56%, and 2-year progression-free survival of 43%.[5]

For resected pancreatic ductal adenocarcinoma, the PRODIGE 24 phase 3 randomized trial established modified FOLFIRINOX as a standard of care for adjuvant therapy because this regimen resulted in superior DFS and OS rates compared with gemcitabine alone.[6] However, modified FOLFIRINOX was associated with increased acute toxicities compared with gemcitabine.

Stijns RCH et al. Long-term oncological and functional outcomes of chemoradiotherapy followed by organ-sparing transanal endoscopic microsurgery for distal rectal cancer: The CARTS study. *JAMA Surg*. 2019.[1]

Summary:

In response to the increasing interest in organ preservation after CRT for rectal cancer, the CARTS study investigated the role of TEM as an organ-preserving procedure. This phase 2 study recruited 55 patients with cT1-T3N0 rectal cancer in the Netherlands from February 2011 through September 2012. The primary endpoint was the number of ypT0–1 specimens acquired through TEM. Patients' tumors had to be located within 10 cm of the anal verge and require treatment with abdominoperineal resection or low anterior resection with a coloanal anastomosis, so tumors were generally low, located at a median distance of 3.5 cm from the anal verge. Patients with significant downstaging of the tumor to ycT0-T2 at 8 to 10 weeks after CRT were eligible for TEM surgery consisting of a full-thickness excision of the tumor with a margin of at least 2 mm. The TEM procedure was not only therapeutic but was used for accurate assessment of pathologic responses in patients achieving ycT0-T2 disease after CRT. When there was insufficient downstaging to ypT2-T3 after CRT, patients were advised to undergo completion TME. Secondary endpoints were locoregional recurrence and health-related quality of life. Knowing that 2% to 27% of ypT0 tumors have positive mesorectal lymph nodes (ypN +),[7] the possibility that TEM might be insufficient to achieve long-term control, even in the setting of a clinical and pathologic complete response (pCR), was worthy of investigation.

The initial downstaging outcomes with assessment at 8 to 10 weeks after pelvic CRT (50 Gy-50.4 Gy, 25–28 fractions) with concurrent capecitabine (825 mg/m^2 twice daily during radiation therapy [RT]) were previously reported.[8] The primary endpoint showed that the majority of patients (30 out of 47) undergoing TEM had disease classified as ypT0–1, but 15 out of 47 TEM patients had ypT2, and 1 tumor was classified as ypT3. At a median follow-up of 17 months, 3 of 9 patients with ypT2 tumors who declined TME after TEM developed local recurrence. This initial report concluded that TEM after CRT enabled organ

preservation in half of the patients with rectal cancer but was associated with higher risk of local recurrence in patients with ypT2 disease.[8]

The current publication presents the long-term oncologic and functional outcomes of this study with a median follow-up of 53 (39–57) months.[1] In the TEM group, 4 of 47 patients (9%) developed intraluminal local recurrence (LR). All occurred within 12 months of the local excision procedure, and 3 of 4 patients who developed an LR also developed liver metastases. None of the patients with ypT0 tumors developed LR. One of the 9 patients with a ypT1 tumor developed LR at 9 months, and 3 of the 9 patients with ypT2, all of whom were offered but declined further surgery, developed LR within the first year. Of the 55 patients included in the study, none of the 16 patients who went on to TME developed LR, so the actuarial 5-year LR rate for the entire group was 7.7%. Actuarial 5-year DFS was 81.6%, and OS was 82.8%. The authors concluded that TEM surgery after CRT in early-stage rectal cancer enabled organ preservation in approximately two-thirds of patients.

The other main content of the updated report is functional outcome. The study incorporated European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ) Core 30 and Colorectal 38 questionnaires at 6, 12, 24, and 36 months after surgical interventions. The LARS (low anterior resection syndrome) questionnaire is a validated scoring system that evaluates bowel function after low anterior resection and includes questions on incontinence for flatus and liquid stools and frequency, clustering, and urgency of defecation. The score provides 3 categories: no LARS, minor LARS, and major LARS.[9]

The questionnaire outcomes show an improved emotional functioning score for patients undergoing TEM with a reduction in blood and mucus in the stool but with increased anxiety. These results were based on 33 patients treated with TEM and 10 patients with TME. The LARS data came from 32 of the 35 patients (91%) who had successful organ preservation. Seven patients (22%) had no LARS, 9 (28%) had minor LARS, and 16 (50%) had major LARS.

The conclusion of these updated outcomes is that neoadjuvant CRT followed by full-thickness local excision can lead to preservation of the rectum in two-thirds of patients who present with low-risk distal rectal cancer. This is accompanied by good long-term oncologic outcomes, and health-related quality of life does not seem to be impaired, although incontinence and defecation problems are ambiguous.

Commentary:

The standard of care for patients with stage 2 and 3 rectal cancer remains neoadjuvant CRT followed by TME.[10] This is a successful approach for patients with mid and upper rectal cancers, but patients with lower rectal tumors are faced with the prospect of either a permanent stoma or a low or ultralow anterior resection and the bowel dysfunction that this will incur. These factors have sparked the development of the WW movement[11] and led to the drive to avoid surgery when safely possible, which is a possibility for around 25% of patients who achieve a complete clinical response after neoadjuvant CRT. As a byproduct of this approach, both patients and clinicians have sought to explore modifications, 2 of which form the focus of the CARTS study:

i. The extension of the CRT approach to patients with earlier rectal cancers

ii. The role of the “halfway” surgical procedure of local excision after CRT

Understanding the implications of extending a nonsurgical approach to these 2 circumstances is necessary, and the CARTS study provides longer outcomes in an attempt to report functional performance of the enrolled patients. The report of 2 patients (4%) dying during CRT and 2 patients having to abandon CRT owing to toxicity, although higher than expected for the regimen, provides justification for caution in offering CRT to a population that would have a high chance of cure with surgery (TME) alone. So, is it appropriate to extend this treatment to patients with early-stage disease (cT1–2N0), especially where the distance to anal verge is ≥5 cm? It is of importance that none of the CARTS enrolled patients had tumors with poor prognostic features such as extramural invasion, lymphovascular invasion, or poor differentiation. In addition, 16 of the 55 study patients went on to have TME and arguably could have avoided pelvic CRT and its inherent complications. Clinicians need to be scrupulous in informing patients with a high chance of cure by surgery of the mortality and morbidity risks of pursuing a means of potentially, and only potentially, avoiding surgery that would result in a permanent stoma or low anastomosis.

The other concept tested in the CARTS study was the success of a local excision procedure in an attempt to increase the number of patients who could safely avoid surgical resection. The contribution of TEM is potentially diagnostic, prognostic, and therapeutic. In CARTS, where the TEM specimen was ypT0, the procedure confirmed the appropriateness of avoiding further surgery and pursuing a WW approach. In this group, the procedure’s main role was diagnostic and prognostic. Similarly, for patients with TEM-resected ypT2, the procedure was critically diagnostic and prognostic and indicated the high risk of LR if completion surgery was avoided. However, not all ypT2 tumors went on to have TME, and of those that did not require TME, not all developed tumor regrowth. So for this subset of patients, TEM was also therapeutic. However, the group that gained most therapeutically from the approach was the ypT1 patients; all but 1 of the 9 patients were able to avoid resection without subsequent tumor regrowth. Arguably, however, in all 3 pathologic T stage scenarios, TEM provided useful pathologic data to aid decision-making, either in terms of supporting the safety of a WW approach or indicating the risks and the need to consider further surgery.

Incorporating TEM into the therapeutic pathway is not all positive. Do TEM and avoidance of surgery result in acceptable quality of life and long-term toxicity rates? CARTS set out to address this question by incorporating standard health-related quality of life data (EORTC QLQ Core 30 and Colorectal 38) and LARS data into the study.

The CARTS LARS data warrants attention. Questionnaires were completed by 32 of 35 patients who underwent successful organ preservation. In 16 of these patients (50%), major LARS was reported, and a further 9 (28%) had minor LARS. This is obviously a significant level of bowel dysfunction, but it should be remembered that the LARS system has not been validated in this setting and was not corroborated by the EORTC data. Nevertheless, it indicates the need to acquire more data to recommend this approach to patients and offer informed consent.

Smith JJ et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. 2019.[2]

Summary:

This single-institution study retrospectively evaluated oncologic outcomes for patients with rectal cancer who achieved a complete clinical response (cCR) to neoadjuvant therapy and elected for a WW approach. Outcomes were compared with a separate cohort of patients who underwent TME after neoadjuvant therapy and were found to have a pCR. The rate of local regrowth and success of salvage surgery were described for the WW group, with 5-year OS, DFS, and DSS reported and compared with the pCR group. For the WW group, surveillance included examination and endoscopy every 3 months during the first year, every 4 months during the second year, and every 6 months subsequently for 5 years. Patients with local regrowth were recommended for TME. A total of 113 patients were included in the WW group and 136 patients in the pCR group. There was significant variation in both patient and treatment characteristics between groups. Patients in the WW group were significantly older (median age 67 vs 57 years, $P < .001$) and had lower cancers (5.5 vs 7.0 cm from the anal verge, $P = .003$) than those in the pCR group. Patients in the WW group were also more likely to have received multiagent chemotherapy as a component of neoadjuvant therapy either before or after CRT (80 of 113, 71%), compared with those in the pCR group, who were more likely to have received CRT alone as neoadjuvant therapy (83 of 136, 61%). RT doses ranged from 45 to 54 Gy in 25 to 28 fractions and were given with concurrent 5-fluorouracil (5-FU) continuous infusion or oral capecitabine. The median follow-up was 33 and 55 months for the WW and pCR groups, respectively. In the WW group, 22 of 113 patients (20%) developed local regrowth at a median time of 11.2 months (range, 3.5–74.4) with a 5-year rectal preservation rate of 79%. For patients with local regrowth, pelvic control after salvage surgery was achieved in 20 of 22 patients (91%). The 5-year OS, DFS, and DSS for the WW versus pCR groups were 73% versus 94%, 75% versus 92%, and 90% versus 98%, respectively. Patients in the WW group who developed local regrowth were significantly more likely to develop distant metastases than those without local regrowth (36% vs 1%, $P < .001$).

Commentary:

For patients with rectal cancer who achieve a cCR to neoadjuvant therapy, a WW approach has the potential to improve functional outcomes by avoiding extirpative surgery. Several retrospective series suggest similar oncologic outcomes for WW compared with up-front TME after CRT,[12–14] and as adoption of a total neoadjuvant therapy approach increases, more patients will achieve a cCR, which may facilitate WW.[15] The current study compares outcomes among patients with rectal cancer who achieve a cCR to neoadjuvant therapy and subsequently undergo a WW approach or up-front TME. Consistent with prior studies, a high proportion of patients in the WW group (78%) achieved rectal preservation at 5 years, although there was suggestion of worse OS, DFS, and DSS outcomes for the WW group. As noted by the authors, the reasons for these differences may be multifactorial because the groups were not matched for patient or disease characteristics by propensity score or

other technique. As such, differences in patient and tumor characteristics could have skewed the results. This is particularly significant regarding reported OS outcomes, given a 10-year difference in patient age between groups. It is of note that a recent similar comparison that used a propensity matching technique showed no difference in the rate of extrapelvic recurrence for WW and up-front TME-based approaches.[14]

Knowing the current retrospective body of data, how should patients who are often highly motivated toward the WW approach be counseled regarding such a strategy? Although decisions regarding WW versus TME are highly individualized, the growing body of data allows the choice to be increasingly based on an informed patient's, rather than a physician's, risk tolerance. The 20% rate of local regrowth reported for WW in this series is consistent with other series, and counseling patients regarding this risk (generally 20%–30% across studies) is important. In the current study, the 36% risk of development of distant metastatic disease observed among WW patients with local regrowth is also of particular importance for discussion because such patients will have a significantly lower chance of successful salvage. It is unclear whether this development of distant metastatic disease after tumor regrowth was due to aggressive biology with a similar outcome expected even after TME or if up-front TME may have reduced the risk of distant metastases. Given these uncertainties, prospective data regarding WW outcomes, which will also inform the optimal approach to total neoadjuvant therapy in this population, are eagerly awaited.[16]

Ogura A et al. Neoadjuvant (chemo)radiation therapy with total mesorectal excision only is not sufficient to prevent lateral local recurrence in enlarged nodes: Results of the multicenter lateral node study of patients with low cT3/4 rectal cancer. *J Clin Oncol*. 2019.[3]

Summary:

This retrospective, international (Asia, Europe, US, and Australia), and multi-institutional pooled analysis sought to characterize the lateral local recurrence (LLR) risk posed by enlarged lateral pelvic lymph nodes (LLNs, defined primarily as obturator and internal iliac nodes) for patients presenting with low (within 8 cm of the anal verge on MRI) cT3 or cT4 nonmetastatic rectal cancer. A total of 1216 patients from 12 institutions were included, with reevaluation performed at each center of the initial diagnostic MRI and, when applicable, MRI after neoadjuvant therapy (n = 741). Significant practice variability among institutions regarding use of neoadjuvant therapy and institutional indication for lateral lymph node dissection (LLND, defined as complete resection of lymphatic tissue from the internal iliac and obturator compartments) allowed subset analysis to be performed according to neoadjuvant therapy delivered and local surgical practice. Neoadjuvant therapy, including short-course RT (18%) or long-course CRT (82%), was given in 968 patients (79.6%). LLND was performed in 142 patients (11.7%), with no LLND or sampling performed for 1062 patients (87.3%) according to institutional standard of care. The median follow-up after surgery was 56.5 months. On the initial MRI, at least 1 LLN, including obturator (64%) and internal iliac compartments (28%), was detected in 703 patients (57.8%). LLR was evaluated by stratifying short-axis (SA) LLN size with a threshold value of ≥7 mm

chosen to compare groups. The 5-year risk of LLR among the entire cohort was 5.5%. Patients with LLN short axis size ≥7 mm on the initial MRI had significantly increased 5-year LLR (15.0%) compared with LLN <7 mm ($P < .001$). Among patients with LLN ≥7 mm (SA) who received neoadjuvant therapy, the 5-year risk of LLR was 19.5% for patients who underwent TME surgery without LLND and 5.7% for those who underwent TME with LLND ($P = .042$), suggestive of improvement in LLR risk with inclusion of LLND for these patients. In patients who did not have visible LLNs or with LLNs <7 mm, no differences in LLR were seen between those with and without LLND.

Commentary:

These data highlight the importance of closely evaluating enlarged extramesorectal nodes (LLNs) because this study demonstrates that they are associated with both LR and LLR. LLRs, particularly those that are isolated, are extremely challenging to manage because they often occur in previously irradiated areas. Resection of LLRs is often not feasible; systemic therapy may be considered overtreatment for a local-only problem, and reirradiation often carries a high risk of complications. In US literature, the significance of LLR is surprisingly understated. Internal iliac and obturator nodes are considered regional nodes and are routinely included in standard radiation fields for preoperative treatment. Whereas it is commonplace for LLND to be performed in locally advanced rectal cancers in the East (primarily in Japan), it is an uncommon practice in the US. The reasons for this are not entirely clear but are likely multifactorial and related to training practices of colorectal surgery in the US, the concern for long-term postoperative complications associated with LLND, differences in body habitus between Eastern and Western populations, and the belief that neoadjuvant CRT is sufficient to adequately treat all pelvic nodal disease.

This study clearly raises the concern that standard neoadjuvant (C)RT is not adequate. Neoadjuvant (C)RT can result in shrinkage of enlarged LLNs (77% in those ≥7 mm), which can decrease the risk of pathologic involvement. However, despite neoadjuvant treatment, over 50% of those who underwent LLND had pathologically involved LLNs. Furthermore, in those without LLND, LLR was still seen in 17% of patients who had shrinkage of LLN after neoadjuvant therapy. These findings suggest that post-neoadjuvant therapy imaging is unreliable in determining the complete response of LLNs.

This raises questions and dilemmas regarding how to appropriately manage patients with initially detected LLNs. What is the optimal approach and management of patients with enlarged LLNs? If these LLNs are not to be routinely resected and there is a high risk that they still harbor persistent viable disease after neoadjuvant CRT, should a TME even be attempted? Despite these nodes being considered regional, should these patients instead be treated like patients with limited metastatic disease, using combination systemic therapy first? And if LLND is selectively performed, for which patients should they be performed? Should staging systems differentiate between regional LLNs and mesorectal nodes? This study does not answer these questions but certainly places a concerning spotlight on them.

In addition, other issues are not answered definitively by this study:

First, what is the most accurate nodal size cutoff? The authors justified using 7 mm in SA because LLNs ≥7 mm without LLND were associated with more advanced cT and cN stages, had a higher rate of exhibiting radiographic malignant features, and had an LLR risk greater than 20%. However, the authors do not appear to have performed other analyses, such as an ROC analysis, which perhaps may have elucidated an optimal LLN size cutoff that is most accurately associated with LLR. Furthermore, it should be pointed out that LLN ≥5 mm (SA) without LLND had an LLR risk greater than 15%, which could be argued to be just as clinically relevant. As noted by the authors, however, LLN metastases, regardless of the exact cutoff value, pose a clinically relevant and significant problem. It would also be interesting to determine how useful positron emission tomography with computed tomography (CT) imaging is in this setting and if MRI carries significantly more relevance than endoscopic ultrasound staging beyond determination of circumferential radial margin involvement.

Second, it is unclear whether LLND is the most safe and effective approach to addressing metastatic LLNs. LLND, particularly when combined with RT, can result in significant morbidities. One key piece of missing information in this study is reporting of late complications in patients with and without LLND, particularly those related to LLND such as sexual and urinary dysfunction. It is possible that alternatives to treatment intensification may be substitutes to LLND. A total neoadjuvant therapy approach with neoadjuvant combination systemic therapy followed by CRT may be an effective approach. Perhaps selective radiation dose escalation to enlarged LLNs can be a substitute for LLND. Limited data exists for this approach, and prospective trials will be needed to explore this paradigm.

Yang H et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): A phase III multicenter, randomized, open-label clinical trial. *J Clin Oncol*. 2018.[4]

Summary:

This phase 3 multicenter, open-label clinical trial conducted in China randomized 451 patients with esophageal squamous cell carcinoma (SCC) to neoadjuvant CRT plus surgery (n = 224) versus surgery alone (n = 227) in an effort to compare the safety and survival of preoperative CRT. Eligible patients had histologically confirmed, potentially resectable esophageal SCC clinically staged T1-T4N1M0 or T4N0MO (*AJCC Cancer Staging Manual*, sixth ed) with a Karnofsky performance score of ≥90. Staging workup included CT of the chest, abdomen, and pelvis and esophagogastroduodenoscpy with endoscopic ultrasound, but positron emission tomography scan was optional. Neoadjuvant CRT consisted of vinorelbine and cisplatin starting concurrently with 40 Gy (20 fractions of 2 Gy, 5 days per week) of 3-dimensional conformal RT. Surgery occurred 4 to 6 weeks after completion of neoadjuvant CRT. In the CRT group, 83% of patients were able to fully complete CRT, and 17% of patients (n = 38) did not undergo planned surgery, primarily owing to patient refusal (n = 29 of 38). 54% of patients developed grade 3–4 hematologic toxicity. Any grade of anorexia, vomiting or radiation esophagitis occurred in 56%, 56%, and 38%, respectively,

with the vast majority of these three toxicities as grades 1–2. Postoperative complications and mortality did not differ significantly between the groups, except for arrhythmias, which occurred significantly more frequently in the CRT group (13%) than in the surgery group (4%, $P = .001$). Perioperative mortality was not significantly different (2.2% CRT vs 0.4% surgery). The R0 resection rates were greater in the CRT cohort at 98% compared with 91% in the surgery-alone group. Significant downstaging was seen in lymph nodes dissected, with 33% of patients having positive lymph nodes in the CRT group compared with 65% in the surgery-alone group. Also, stage III disease was found in 11% of the patients undergoing CRT versus 63% of the surgery-alone group. Pathologic complete response was 43% for the trimodality cohort. Median OS and DFS rates were significantly improved in the CRT group at 100 months and 100 months versus 66.5 months and 41.7 months in the surgery group, respectively. Neoadjuvant CRT and lower T stage independently predicted better survival on multivariate analysis.

Commentary:

This study by Yang et al adds to the body of randomized data that defines the utility of trimodality therapy with CRT before surgery compared with surgery alone in esophageal cancer. Including the current study, we now have 3 randomized trials that demonstrate a statistically significant improvement in survival with CRT before surgery,[4,17,18] 1 that found no difference,[19] and 2 that closed early owing to poor accrual.[20,21] The current trial stands apart from the existing literature with its focus on SCC histology, whereas other clinical trials included a mix of adenocarcinoma and SCC or only adenocarcinoma. This study complements the findings of the CROSS study,[17] which found a similar survival benefit among patients receiving CRT before surgery compared with patients receiving surgery alone. The CROSS study included only 23% SCC histology and did not enroll T4 patients. The median survival for all patients in the CROSS study improved with trimodality therapy from 24.0 to 49.4 months, and the survival improvement held for the SCC cohort despite fewer patients. Of note, one criticism of the CROSS study included the relatively low R0 resection rates in the surgery-alone arm (69%). The current study had higher R0 resection rates in the surgery-alone arm (91.2%) than CROSS did, which could be a reflection of different surgical techniques or higher surgeon volume given the high incidence of esophageal cancer in China (current study) compared with the Netherlands (CROSS). Regardless, the findings of the current study support the results of CROSS because of the substantial improvement found in patient outcomes with trimodality therapy compared with surgery alone without an increase in perioperative morbidity or mortality.

The current study does raise a few points about treatment of esophageal cancer worth further discussion. First, the RT doses used (40 Gy in 20 fractions), similar to the CROSS study (41.4 Gy in 23 fractions) and Walsh study (40 Gy in 15 fractions)[18] are lower than doses typically used in the United States. Patterns of care studies in the United States demonstrate that only a very small proportion of patients receive neoadjuvant RT doses on the order of 40 to 41.4 Gy, with the vast majority of patients receiving radiation doses between 45 to 50.4 Gy.[22] We lack prospective data evaluating different radiation doses in the neoadjuvant setting with esophageal cancer, although existing randomized trials in the definitive CRT setting do not support dose escalation in esophageal cancer.[23,24] Together, these trials raise

the question of whether lower doses of RT (40–41.4 Gy) should become the standard of care in the preoperative setting for esophageal cancer. However, one must also consider the counterargument that treatment intensification in the preoperative setting could improve pCR rates, and pCR correlates with improved survival.[25] Retrospective series evaluating the correlation between RT dose and patient outcomes suffer from selection bias; therefore, we need prospective trials to help define the optimal RT dose.

Although this study adds to the evidence supporting trimodality therapy in esophageal cancer, other important questions remain unaddressed. The chemotherapy doublet used in this study (vinorelbine and cisplatin) differs from agents currently used in CRT with esophageal cancer, which typically include a platinum agent combined with a taxane or 5-FU.[26] We lack clear data supporting one concurrent chemotherapy regimen over another, and this study adds another doublet to the list of acceptable agents. Both arms in this study received surgery, although one must consider the question of the overall utility of surgery in patients with SCC of the esophagus. Older randomized trials failed to demonstrate improved survival with surgery,[27] although these trials were associated with perioperative mortality rates much higher than contemporary series. Regardless, the benefits of surgery among patients with SCC of the esophagus remain an important unanswered question. Finally, the current study used conformal radiation techniques, whereas many centers in the US routinely use more advanced treatment modalities including intensity modulated radiation therapy (IMRT).[28] Reduced radiation doses to the heart with IMRT in particular could help spare normal tissues and reduce the risk of cardiovascular toxicity among the increasing number of long-term esophageal cancer survivors.[29] Furthermore, an ongoing NRG randomized study is evaluating the utility of proton therapy in esophageal cancer (NCT03801876), which could help further reduce the risks of toxicity among patients with esophageal cancer treated with radiation.

Murphy J et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: A phase 2 clinical trial. *JAMA Oncol*. 2018.[5]

Summary:

This prospective, single-arm phase 2 study evaluated a regimen of neoadjuvant 5-FU, oxaliplatin, leucovorin, and irinotecan (FOLFIRINOX) followed by CRT at a single institution for patients with borderline resectable pancreatic adenocarcinoma. All patients had borderline resectable disease by consensus multidisciplinary review and Eastern Cooperative Oncology Group performance status 0 or 1. Initially, 4 cycles of FOLFIRINOX were given before CRT with the plan for adjuvant therapy; however, the study was amended after the initial 6 patients were enrolled to apply a total neoadjuvant therapy paradigm in which 8 cycles of FOLFIRINOX were given before CRT. Restaging CT imaging was performed after completion of FOLFIRINOX. For cases where the tumor was converted to resectable, short-course preoperative RT was given using either a 30-Gy (10 fractions) IMRT using photons or a 25-GyE (5 fractions) 3-dimensional passive scatter proton therapy technique with concurrent capecitabine. The RT target included the gross tumor volume

with a 1-cm clinical target volume expansion in addition to elective nodal coverage of the celiac, porta hepatis, superior mesenteric artery and vein, and paraortic regions. For patients with persistent vascular involvement, long-course CRT was given to a dose of 50.4 Gy in 28 fractions with IMRT to the same volume, and the vascular margin abutting the tumor received 58.8 Gy in 28 fractions using a simultaneous integrated boost of either concurrent capecitabine (825 mg/m^2 twice daily) or 5-FU continuous infusion (225 mg/m^2/d). Intraoperative RT was allowed at the surgeon's discretion. Among 50 patients enrolled, a total of 48 were eligible, and 39 (81%) received all planned cycles of FOLFIRINOX. Grade ≥3 preoperative toxicity was observed in 9 out of 48 eligible patients (19%), but only grade 1 and 2 toxicity were observed during CRT. For 43 patients enrolled after adoption of a total neoadjuvant approach, 19 (44%) had a partial response by RECIST criteria, with 22 patients (51%) receiving short-course CRT owing to resolution of vascular involvement. Resection was performed in 32 patients with 31 (97%) achieving a R0 resection. The median progression-free survival among all eligible patients was 14.7 months, with median OS of 37.8 months. Isolated local failure was observed in 3 out of 48 eligible patients (6%), whereas 18 out of 48 patients (38%) developed distant metastases only.

Commentary:

In this phase 2 trial, the Massachusetts General Hospital team developed a novel concept for the treatment of patients with borderline resectable pancreatic cancer. Similar to rectal cancer therapy, the regimen is described as "total neoadjuvant therapy" even if the story is not exactly the same. Indeed, locally advanced rectal cancers have been treated for years with neoadjuvant CRT, and it is only recently that adding systemic chemotherapy before or after radiation therapy has been proposed.[30] For borderline resectable pancreatic cancer, there is not a standard treatment. Up-front surgery, neoadjuvant chemotherapy, and RT are options based on mainly retrospective series. However, with growing evidence of the efficacy of the FOLFIRINOX regimen, neoadjuvant chemotherapy has started to be widely used.[31] Many ongoing trials are assessing the feasibility and efficacy of a combination of neoadjuvant chemotherapy and radiation therapy followed by surgery, the goal being to obtain a R0 resection. The main interest of this monocentric phase 2 trial is the originality of its design. All included patients were treated first with 8 cycles of FOLFIRINOX. After that, if there was a resolution of vascular involvement, they received "short-course" CRT that was either 30 Gy in 10 fractions with photons or 25 Gy in 5 fractions with protons and concurrent capecitabine. Patients with persistent vascular involvement received "long-course" CRT at a dose of 50.4 Gy in 28 fractions with concurrent capecitabine. The clinical target volume encompassed the gross tumor volume and elective lymph node groups such as celiac, porta hepatis, superior mesenteric vessels, and paraortic. It seems that the same volume was treated with the different techniques except on the long-course schedule, where patients had a simultaneous integrated boost to the vascular margin abutting the tumor to a total dose of 58.8 Gy. Intraoperative RT was allowed. The primary endpoint was the rate of R0 resection with a goal to increase the rate from 40% to 60%. Fifty patients were enrolled between 2012 and 2016. Among them 48 were eligible and 34 (79%) were able to complete the 8 planned cycles of FOLFIRINOX. Nineteen patients (44%) had a partial response, 27 (56%) had subsequent short-course CRT, and 17 (35%) had long-course RT. Thirty-nine patients went to have surgery. Among them, 32 had a resection, with negative margins (R0)

in 31 patients (65%) and N1 in 12 (38%). It is important to notice that among the 7 patients who were not resected, 3 received short course and had still vascular involvement, meaning that postchemotherapy assessment was not accurate. The tolerance of the RT within this therapeutic strategy was good, was without treatment-related death, and had only grade 1 to 2 acute toxicities. However, it would have been interesting to know comparative tolerability between the short- and long-course regimens. Moreover, there are few data about treatment with proton therapy for pancreatic cancers.[32] Postoperative morbidity has not been reported, which is a significant omission, especially because intra-operative radiation therapy was allowed with potentially high total doses. In conclusion, individualized radiation therapy for borderline resectable pancreatic cancer is an interesting concept, but it has to be better explored in a larger trial.

Conroy T et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018.[6]

Summary:

This phase 3 multicenter, randomized open-label trial conducted by the Canadian Cancer Trial Group Pancreatic Adenocarcinoma (CCTG PA 6) and the Unicancer-GIePRODIGE Group (PRODIGE 24-ACCORD 24) sought to compare the efficacy and safety of modified FOLFIRINOX versus gemcitabine as adjuvant therapy in resected pancreatic cancer. This modified version of the FOLFIRINOX regimen without bolus 5-FU was used to decrease hematological toxicity and diarrhea without reducing treatment efficacy. The primary endpoint was DFS. Patients were eligible for this study if they had pancreatic ductal adenocarcinoma and had undergone complete macroscopic resection (defined as R0 if no cancer cells were within 1 mm of all margins and as R1 if cancer cells were present within 1 mm of ≥1 margin[s]) within 3 to 12 weeks before randomization, had a carbohydrate antigen 19–9 (CA19–9) level of ≤180 U/mL, and were without evidence of metastatic disease, malignant ascites, or pleural effusion. A central review of surgical reports, CT and MRI scans, and pathology reports was conducted to confirm eligibility and evaluate prognostic factors. A total of 493 patients at 77 centers in Canada and France were randomized to modified FOLFIRINOX (n = 247) or gemcitabine (n = 246). Chemotherapy was planned to be delivered for a total of 24 weeks for both groups, which included 6 cycles of gemcitabine or 12 cycles of modified FOLFIRINOX. Sixty-six percent of patients received all planned cycles of chemotherapy in the modified FOLFIRINOX group compared with 79% in the gemcitabine group. The median DFS was significantly better in the modified FOLFIRINOX group at 21.6 months, compared with 12.8 months in the gemcitabine group. The DFS rates at 1, 2, and 3 years were 69%, 47%, and 40% in the modified FOLFIRINOX group compared with 54%, 31%, and 21% in the gemcitabine group, respectively. On multivariate analysis, tumor grade and portal vein resection were adverse prognostic factors for DFS, and the benefit of modified FOLFIRINOX compared with gemcitabine remained significant after adjusting for these factors. The median OS was significantly better in the modified FOLFIRINOX group at 54 months, compared with 35 months in the gemcitabine group. And the median metastasis-free survival was significantly improved for modified FOLFIRINOX at 30 months, compared with 18 months for gemcitabine. The median cancer-specific survival rate was not reached for modified FOLFIRINOX and significantly

improved compared with gemcitabine, for which it was 36 months. The safety profile of the modified FOLFIRINOX regimen was less favorable than the gemcitabine group: there was a higher incidence of grade 3 to 4 adverse events in the modified FOLFIRINOX group (79%) compared with the gemcitabine group (53%) with grade 4 events accounting for about 12% in both groups. Modified FOLFIRINOX caused increased neuropathy, paresthesia, fatigue, nausea, vomiting, abdominal pain, mucositis, and diarrhea and resulted in increased use of granulocyte colony-stimulating factor compared with gemcitabine.

Commentary:

Although the PRODIGE 24 trial did not involve RT, it is practice changing for management of localized pancreas cancer; thus, radiation oncologists should be aware of the study design, results, limitations, and implications. For patients with resected pancreatic ductal adenocarcinoma, modified FOLFIRINOX was reasonably well tolerated and associated with superior survival compared with gemcitabine, which was the standard-of-care adjuvant regimen for most of the world from 2007 (publication of the CONKO-001 trial results) to 2018 (publication of the ESPAC-4 trial results).[33,34] The impressive 3-year OS rate of 63% for the modified FOLFIRINOX arm far exceeds that reported with any adjuvant therapy regimen to date and demonstrates the promising progress that has been made since the first positive adjuvant therapy trial, which showed that the addition of adjuvant external beam RT and 5-FU improved 3-year survival to 23% versus 7% with surgery alone, was reported by the GITSG in 1985.[35] The favorable outcomes reported with the use of adjuvant modified FOLFIRINOX in the PRODIGE 24 trial should dampen the therapeutic nihilism that has surrounded even the most favorable group of patients with pancreas cancer.

It is important to recognize the limitations of this study. The study was performed using a select population of patients who underwent macroscopically complete resection (R0 or R1) and at 3 to 12 weeks postsurgery had adequate recovery with Eastern Cooperative Oncology Group PS 0 or 1, no evidence of metastatic disease on imaging, and a CA19–9 level <180 U/mL. Therefore, the favorable survival outcomes observed for patients in the modified FOLFIRINOX arm cannot be extrapolated to patients with newly diagnosed localized pancreas cancer before resection, including cohorts treated with neoadjuvant therapy. The median survival for the gemcitabine alone arm is substantially better than that reported for the gemcitabine arm of the CONKO-001 trial (35 vs 22 months, respectively), in spite of fairly similar inclusion criteria.[34] This may reflect selection bias for patients enrolled in the PRODIGE 24 trial or improvements in diagnostic imaging to exclude patients with low-volume metastatic disease (stage migration), improvements in surgical technique, and improvements in salvage chemotherapy options, namely modified FOLFIRINOX and gemcitabine plus nab-paclitaxel. The follow-up duration is still relatively short (median 33.6 months), with <10 patients in total at risk at the 5-year time point. Therefore, estimates of median and 5-year OS for the modified FOLFIRINOX arm are not reliable currently, and mature data will need to be reported in the future.

Reported in the supplemental materials for the current study, the analysis of patterns of first recurrence has implications for the potential role of RT for localized pancreas cancer. Local and regional recurrence and distant metastases as first sites of recurrence

were lower in patients receiving modified FOLFIRINOX (24% and 38%, respectively) versus those receiving gemcitabine alone (35% and 50%, respectively). The rate of local and regional recurrence for the modified FOLFIRINOX arm is similar to that reported for the gemcitabine plus capecitabine arm of the ESPAC-4 trial (30%).[33] Because these numbers represent crude rates and not risk estimates using actuarial or cumulative incidence models treating death as a competing risk, the true risk of local persistence or recurrence is underestimated. Furthermore, autopsy studies demonstrate that imaging and clinical evaluation underestimate the true incidence of local tumor persistence or recurrence after apparent R0 pancreatectomy.[36] Therefore, the risk of local or regional recurrence remains significant even in contemporary studies employing combination chemotherapy. This provides strong rationale for the use of (neo) adjuvant RT to help address local and regional disease, especially in the context of better control of distant metastatic disease. Cure cannot be attained without eradication of local and regional disease.

For patients who undergo up-front resection, we now have 2 combination chemotherapy regimens with proven superiority over gemcitabine alone: gemcitabine plus capecitabine and modified FOLFIRINOX. The APACT trial is assessing the role of adjuvant gemcitabine plus nabpaclitaxel versus gemcitabine, which may end up providing a third adjuvant therapy option. The role of postoperative RT remains unclear, although its use remains reasonable after an initial course of combination chemotherapy in select patients at higher risk for local or regional recurrence, specifically those who had an R1 resection. The recently closed RTOG 0848 study may also provide further information regarding the role of postoperative CRT after an initial course of gemcitabine, although interpretation of results of this trial will be difficult because the standard of care is now combination chemotherapy with gemcitabine plus capecitabine or modified FOLFIRINOX. Furthermore, there has been a shift in practice toward the use of neoadjuvant chemotherapy with or without RT for patients with localized pancreas cancer. Ongoing studies will help determine optimal neoadjuvant therapy regimens, including the role of RT in this context.

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