The evolving radiotherapy landscape for pancreas and rectal cancers: impacting survival, toxicity, and quality of life

Hits & Misses in Novel Pancreatic & Rectal Cancer Treatment Options

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We want to first extend a warm welcome to Drs. Krishnan Jethwa (Mayo Clinic, Rochester), Hyun Kim (Washington University, St. Louis), and Andrzej Wojcieszysnki (Kaiser Permanente, Denver) to the Gastrointestinal Editorial Section. All have provided thoughtful and timely reviews for the Red Journal and bring a wealth of experience treating gastrointestinal cancers. We express our deepest gratitude to Drs. Christopher Anker, Michael Buckstein, and Jordan Kharofa who are rotating off the editorial team. Their contribution to the quality of the gastrointestinal section over the last several years is truly outstanding.

In this Oncology Scan we focus attention on the evolving role of radiation therapy (RT) in the management of pancreas and rectal cancers. RT is controversial for pancreas cancer regardless of resectability, although emerging data are helping us inch closer to understanding which patient subsets benefit. The updated results of the PREOPANC trial show us that, with long-term follow-up, neoadjuvant chemoradiation achieves superior overall survival than up-front surgery for resectable and borderline resectable pancreas cancer(1). The Alliance A021501 trial compared neoadjuvant mFOLFIRINOX +/- 5-fraction RT for borderline resectable pancreas cancer; the early closure of the RT arm has led to increased uncertainty about the role of RT(2). While RT and immunotherapy can have a synergistic effect that results in dramatic responses for some cancers, this strategy has largely been unsuccessful for pancreatic cancer. Therefore, the disappointing results in metastatic pancreas cancer patients from the CheckPAC trial are not surprising(3).

Locally advanced rectal cancer is typically treated with neoadjuvant therapy followed by surgery. Unfortunately, this multi-modality approach is toxic and can negatively impact quality of life well after treatment is completed. Non-operative management has gained increasing traction through the recent publication of prospective studies including the OPRA trial that demonstrate some patients can successfully avoid surgery(4). The exciting response rates of dostarlimab, a

PD-1 inhibitor, indicate that further deintensification of therapy (avoiding chemoradiation or surgery) for mismatch repair-deficient tumors might be possible. Better understanding of which patients will respond to such therapy is needed. Also, our understanding of which rectal cancer patients achieve the greatest benefit from neoadjuvant RT might be enhanced using MRI prognostic factors(5).

Versteijne E et al. Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial. *Journal of Clinical Oncology* 2022.(1)

Summary: The Dutch Pancreatic Cancer Group investigators present long-term results from the PREOPANC randomized trial for patients with resectable or borderline resectable pancreatic cancer (BRPC) who were randomized to up-front surgery or neoadjuvant chemoradiation (CRT) and then surgery. The primary endpoint was overall survival (OS) by intent-to-treat (ITT) and the trial was powered to detect a 6-month improvement in median OS from 11 to 17 months. Secondary endpoints were disease-free survival (DFS), locoregional failure–free interval (LFFI), distant metastasis–free interval (DMFI), resection rate, and R0 resection rate. In the standard arm, patients received 6 cycles gemcitabine following surgery. In the experimental arm, patients underwent laparoscopy prior to initiation of CRT with a radiation prescription dose of 36 Gy in 15 fractions and concurrent gemcitabine 1,000 mg/m2. The gross tumor volume (GTV) included the primary tumor and grossly enlarged lymph nodes although elective coverage of specific nodal or vascular regions was not used. A CTV was created by expanding the GTV by 5 mm and the planning target volume (PTV) was created through a 1 cm expansion of the clinical target volume (CTV).

In the initial publication with a median follow up of 27 months, the median OS was not improved with neoadjuvant CRT compared to up-front surgery (16 months vs. 14.3 months, p=0.096)(6). However, improvements were noted for R0 resection rate (71% vs. 40%; p<0.001), DFS (HR 0.73; 95% CI, 0.55 to 0.96; P = .032), and LFFI (HR, 0.56; 95% CI, 0.38 to 0.83; p=0.0034). With a median follow-up of 59 months in the updated analysis, a modest difference in median OS was found in patients receiving neoadjuvant CRT (15.7 vs. 14.3 months, HR 0.73; 95% CI, 0.56 to 0.96; p=0.025). Notable improvements in 3-year OS (27.7% vs. 16.5%) and 5-year OS (20.5% vs. 6.5%) in the neoadjuvant arm were reported. The HR was 0.79 (0.54 to 1.16, p= 0.23) for resectable patients and 0.67 (0.45 to 0.99, p=0.045) for patients with BRPC.

Commentary: Neoadjuvant therapy for resectable or borderline resectable pancreas cancer has several advantages over upfront surgery: 1) it can be difficult to interpret diagnostic imaging studies to evaluate surgical resectability (~30% of patients on SWOG S1505 with resectable disease were reclassified as being unresectable after central imaging review)(7), 2) >50% of resectable patients may have positive margins(7), and 3) ~20% of patients are found to have more advanced disease at the time of surgical exploration(8).

Long-term outcomes of the PREOPANC trial provides a strong signal that neoadjuvant therapy should be preferred over upfront surgery for resectable and borderline resectable pancreas cancer. These data are consistent with other randomized trials that also demonstrated improved OS with the use of neoadjuvant therapy(9,10). It is noteworthy that a clear OS difference did not emerge until after about 24 months, likely because there was a high incidence of early progression in both arms during at least the first year. The updated PREOPANC analysis reported a statistically significant although modest absolute median OS

difference of 1.4 months; more striking was the absolute 5-year OS improvement of 14% favoring neoadjuvant therapy. This finding should inform future trial designs that incorporate neoadjuvant therapy.

Several study limitations should be noted: 1) there was a high dropout rate (24%) in the neoadjuvant arm (although an OS benefit of neoadjuvant therapy was still observed), 2) CA19-9 level was not considered for study exclusion and was higher in the upfront surgery arm, 3) gemcitabine alone is no longer a preferred chemotherapy regimen. It is unclear whether the results of this trial that used moderate hypofractionation can be extrapolated to other regimens such as stereotactic body radiation therapy (SBRT) or conventional fractionation.

We eagerly await the results of ongoing studies that incorporate contemporary multi-agent chemotherapy regimens and build on the findings of the PREOPANC trial, such as the PREOPANC-2 trial(11) and others (NCT04927780, NCT04340141). Based on current data, neoadjuvant therapy should be considered a standard of care for resectable and borderline resectable pancreas cancer.

Katz MHG et al. Efficacy of Preoperative mFOLFIRINOX vs mFOLFIRINOX Plus Hypofractionated Radiotherapy for Borderline Resectable Adenocarcinoma of the Pancreas: The A021501 Phase 2 Randomized Clinical Trial. JAMA Oncology 2022.(2)

Summary: Katz et al. report outcomes from the Alliance A021501 phase II trial in which 126 BRPC patients were randomized (1:1) to receive either 8 cycles of neoadjuvant mFOLFIRNOX (arm 1) or 7 cycles of preoperative mFOLFIRINOX followed by radiation therapy (RT) (arm 2). Patients without progression after neoadjuvant therapy underwent resection followed by 4 cycles of adjuvant FOLFOX. Diagnostic laparoscopy was not required for study eligibility. SBRT (33-40 Gy in 5 fractions) with fiducial marker guidance and an internal target volume (ITV) approach for motion management was preferred; hypofractionated image-guided RT (HIGRT) prescribed to 25 Gy in 5 fractions was permitted if appropriate image guidance and/or motion management was not available to deliver SBRT. The GTV and tumor-vessel interface (TVI) were treated while specific nodal and/or vascular regions were not targeted. A 3 mm PTV margin was used for SBRT while it was 5-10 mm for HIGRT. Adjuvant chemotherapy was optional in both arms.

In total, 70 patients were registered to arm 1 (54 randomized), and 56 to arm 2. The primary endpoint was OS, with secondary end points of event-free survival (EFS), R0 resection rate, pathologic complete response (pCR) rate, and toxicity. The trial was not powered to compare arms to each other but rather to the historical OS at 18 months. A planned interim analysis was performed to determine futility that was based on R0 resection rate among the first 30 patients in each arm; if 11 or fewer patients in had an R0 resection that arm would be closed early. Arm 2 was closed early because 10/30 patients had an R0 resection compared to 17/30 patients in arm 1. Among evaluable patients, the 18-month OS in arm 1 vs. arm 2 was 66.7% (95% CI 56.1-79.4%) vs. 47.3% (95% CI 35.8-62.5%), respectively. A total of 32/65 (49%) and 19/55 (35%) patients in arms 1 and 2 underwent pancreatectomy; 28/32 (88%) and 14/19 (77%) patients in arms 1 and 2 underwent R0 resection. The authors concluded that neoadjuvant FOLFIRINOX represents a reference regimen for BRPC, and that despite the SBRT trial being closed early in this trial at least a subset of BRPC patients might benefit from SBRT.

Commentary: Advances in perioperative systemic chemotherapy in operable pancreatic cancer have translated into gradual OS improvements(12,13) while neoadjuvant RT has been implemented in hopes of reducing tumor size and nodal disease burden, improving R0 resection rates and OS over upfront surgery. Prior studies of neoadjuvant RT for BRPC have largely reported favorable outcomes, and therefore, the early closure of the RT arm of the A021501 trial came as a surprise to many. A knee-jerk reaction would be to conclude that there is no role for neoadjuvant RT in the management of BRPC, but this was not how the study investigators interpreted the study outcomes that "do not eliminate the possibility that preoperative radiotherapy may benefit a subpopulation of patients or that other delivery approaches may be more effective."

The interim analysis was based on the R0 resection rate, which perhaps was not an optimal measure of treatment efficacy. Details regarding why some patients in the RT arm were not resected remain poorly defined although may be related to the subjectivity behind assessing what is "resectable" according to radiographic response. Although speculative, it is possible that in some centers the post-RT radiographic findings could have influenced confidence in achieving negative margins particularly if centers were not routinely using neoadjuvant RT and accustomed to interpreting post-RT scans. Radiographic "stable disease" is very common after neoadjuvant RT although this does not preclude achieving a high probability of an R0 resection(14). Moreover, radiographic findings are not reflective of the underlying pathologic response for BRPC(15). The interim analysis was performed using a small number of total patients; if only 2 additional patients in arm 2 had an R0 resection the definition of futility would not have been met. Lastly, it is unknown whether arm 2 would have closed early if HIGRT, which delivered a lower dose than SBRT, was not permitted.

Patients in arm 2 had worse OS than those in arm 1, and although the trial was not designed to formally compare OS unless both arms fully accrued, it is hard to ignore the sizeable OS difference. We should be careful to not immediately assume that the shorter OS in arm 2 was due to the inferiority of the delivered treatment. Despite A021501 being a randomized trial there are indications that patients in arm 2 had less favorable baseline characteristics than arm 1: older age (66 vs. 62 years), higher median baseline CA19-9 (260 vs. 167), higher incidence of hepatic artery resections (11 vs. 3%), and a higher incidence of disease progression prior to completion of the assigned study therapy (21.8% vs. 13.8%). In comparison, the median OS in the Alliance A021101 trial that treated BRPC patients with mFOLFIRINOX x 4 cycles and then 50.4 Gy in 28 fractions was noticeably higher than arm 2 of A021501 (22 months vs. 17.1 months); the median baseline CA19-9 was considerably lower in A021101 (122 vs. 260)(14).

It is undisputed that neoadjuvant mFOLFIRINOX should continue to be a standard of care for BRPC, but there is no basis to completely disregard RT. Additional biologic factors may be important considerations for future trials. Patients with BRCA1/2 mutations have higher responses to platinum-based therapy(16) while tumors with low GATA6 expression, basal-like subtype have worse responses to mFOLFIRINOX(17). Alliance A021501, showed that a U.S. multi-institutional study can be performed for BRPC, with appropriate research infrastructure for central imaging, pathology, and radiation treatment review. We eagerly await the results of ongoing trials (NorPACT-1, PANACHE01-PRODIGE48, PREOPANC2, PREOPANC3, ALLIANCE A021806, CONKO-007, PANDAS-PRODIGE44, PIONEER-PANC, STEREOPAC,

MASTERPLAN) in the perioperative setting to refine both the optimal systemic regimen and role of RT.

Chen IM et al. Randomized Phase II Study of Nivolumab With or Without Ipilimumab Combined with Stereotactic Body Radiotherapy for Refractory Metastatic Pancreatic Cancer (CheckPAC). *Journal of Clinical Oncology* 2022.(3)

Summary: CheckPAC is a phase II trial that enrolled metastatic pancreatic cancer (mPC) patients who progressed through first-line systemic therapy and randomized (1:1) to either SBRT (15 Gy x 1) plus nivolumab 3 mg/kg on day 1 and then q2 weeks (arm A) or SBRT (15 Gy x 1) plus nivolumab and ipilimumab 1 mg/kg on day 1 and then q6 weeks (arm B). An initial safety run-in assessment was followed by an expansion phase. Study therapy was continued for a maximum of 52 weeks unless there was progressive disease (PD), unacceptable toxicity, or consent withdrawal.

The primary endpoint was the clinical benefit rate (CBR) as determined by RECIST 1.1 criteria, and included stable disease, partial response, or complete response. Secondary endpoints included overall response rate, duration of response, progression free survival (PFS), OS, and treatment related adverse events (TRAEs). Response assessment using CT scans was performed every 8 weeks or at any time to evaluate potential PD. Adverse events were evaluated every 2 weeks. Blood was collected for translational biomarker analysis at baseline and at various time points after treatment. Core needle biopsies were obtained to evaluate MMR proteins, PD-L1, and tumor microenvironment status (e.g., CD3, CD4, FOXP3).

The study was not designed to formally compare outcomes between arms. Simon's optimal 2-stage design determined that 36 patients were required in each arm. 84 patients who were randomized (41 in arm A, 43 in arm B) and began study therapy were included in the analysis. The most common SBRT target was liver metastasis (77.4%). Median number of nivolumab cycles received was 4 in both arms. Median number of ipilimumab cycles received was 2. The median follow-up was 4.1 months. CBR in arm A vs. arm B was 17.1% vs. 37.2%, respectively. PD-L1 expression was not associated with CBR. Every responder had MMR proficient tumors. The median PFS was 1.7 vs. 1.6 months, respectively, and the median OS was 3.8 months in both arms. The incidence of grade 3-4 TRAEs was 24.4% in arm A and 30.2% in arm B.

Commentary: Little progress has been made in improving the treatment of patients with mPC despite extensive investigation of immune(18) and targeted therapies(19). Increasing evidence on immunomodulatory effects of RT casts new light on a systemic antitumor response. It is hypothesized that RT may be similar to an "accelerant" by means of inducing in situ vaccination by killing tumor cells and triggering a systemic immune response with lung cancer leading the way(20). It is unclear how RT impacts immune cells and induces abscopal regression of tumors and as such abscopal regression is rare(21). The optimal sequence and RT dose and fractionation and optimal tumor targeting coverage are still under investigation. Pancreas cancer is less immunogenic because of multiple factors, including low mutational burden, cancer-cell-intrinsic mechanisms, the immunosuppressive role of peritumoral stroma(22) and autophagy(23).

Data regarding safety of the combination of SBRT and immunotherapy is reassuring in mPC. Unfortunately, the CheckPAC study adds to the body of evidence that the systemic

effects of adding RT to immunotherapy are rather infrequent for patients with pancreatic cancer.(24,25) We need to expand our view of mPC and consider similarities with hematological malignancies. T cell therapies are reaching our horizon(26,27) and perhaps we should further explore using RT as bridging or conditioning therapy for mPC.(28)

Cercek A et al. PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer. *New England Journal of Medicine* 2022.(29)

Summary: While neoadjuvant CRT followed by surgery is a standard of care, the morbidity of surgery and potential for sustained cCR in some patients without surgery has led to growing interest in non-operative management (NOM). Approximately 5% of rectal adenocarcinomas are mismatch-repair deficient, which generally respond poorly to standard chemotherapy. However, programmed death 1 (PD-1) blockade leads to significant and durable responses for patients with metastatic mismatch repair–deficient (dMMR) colorectal cancer (CRC)(30-32). Therefore, the aim of this prospective phase 2 trial was to evaluate outcomes of neoadjuvant dostarlimab, a PD-1 inhibitor, in patients with mismatch repair-deficient stage II-III rectal adenocarcinoma. Mismatch-repair status was determined using a chromogenic immunohistochemical assay that identified loss of expression of MLH1, MSH1, MSH6, and PMS2.

In this phase 2 study, dostarlimab was administered intravenously at a dose of 500 mg every 3 weeks for 6 months (9 cycles). Dostarlimab was to be followed by standard long-course CRT and TME. However, patients who achieved a cCR (defined as absence of residual disease on MRI, endoscopy, and digital rectal examination as well as and no restricted diffusion on T2-weighted MRI) after completion of dostarlimab therapy would pursue NOM. The primary endpoints were to determine the cCR and overall response rates of PD-1 blockade with dostarlimab +/- CRT. At the time of publication, a total of 16 patients had been enrolled. 12 completed dostarlimab with a minimum 6 months of follow-up; all 12 achieved a cCR and therefore did not receive CRT or surgery. None of these 12 patients had experienced progression or recurrence at the time of the analysis. No grade 3 or higher adverse events were reported.

Commentary: This small phase II trial has received a great deal of attention from patients, clinicians, and the media alike, and for good reason: a 100% response rate in oncology is rare, and the potential to avoid surgery, chemotherapy and RT for a subset of patients traditionally requiring all three treatment modalities is highly appealing.

The biologic rationale behind this trial was strong. Immunotherapy has been approved for patients with dMMR metastatic CRC based on the Keynote-177 study(30). Transitioning to non-metastatic CRC, the NICHE trial published in 2020 assessed neoadjuvant ipilimumab and nivolumab in early-stage colon cancer and showed that among dMMR tumors, 95% had major pathologic response and 60% were complete responses(33). Thus, dMMR locally advanced rectal cancer, a curable disease with current standard treatment resulting in significant late toxicity, was a logical population in which to use upfront immunotherapy.

Although the reported trial population was small, the results have been practice changing across many centers. Even if not all patients with dMMR locally advanced rectal cancer respond to immunotherapy and if some who initially have a cCR recur (which will undoubtedly happen with more patients and longer follow-up), many believe that any real

possibility of avoiding trimodality therapy is worth an attempt. As such, many centers have begun to use a similar approach as the dostarlimab study: start patients on immunotherapy and for those who do not respond, transition to total neoadjuvant therapy (TNT) with RT and chemotherapy. The optimal dose, duration and assessment strategy for patients receiving immunotherapy is unknown, although certainly the regimen used in this trial is promising.

What does this mean for the role of RT in rectal cancer? The trial underscores that in locally advanced rectal cancer, one size does not fit all and in the case of dMMR tumors, an entirely new wardrobe may be needed. EA2201 (NCT04751370) is a phase II study of neoadjuvant nivolumab plus ipilimumab with short course RT in dMMR rectal cancer. Initially short course RT was mandated on protocol for all patients regardless of response to immunotherapy; however, after publication of the dostarlimab trial the study is now currently undergoing an amendment to permit WW for patients achieving a cCR to immunotherapy. This trial, among others, will help define the treatment of dMMR locally advanced rectal cancers, for which we suspect RT will have a role in salvage rather than upfront therapy.

Garcia-Aguilar J et al. Organ Preservation in Patients with Rectal Adenocarcinoma Treated with Total Neoadjuvant Therapy. *Journal of Clinical Oncology* 2022.(4)

Summary: Garcia-Aguilar et al. report the results from the randomized phase II OPRA trial, which assessed the sequencing of long course CRT and multi-agent chemotherapy on disease free survival and total mesorectal excision (TME)-free survival in patients with rectal cancer(1). Eligible patients had stage II (T3-T4, N0) or stage III (any T, N1-2) rectal adenocarcinoma. All received TNT with either induction chemotherapy then CRT (INCT-CRT) or CRT then consolidative chemotherapy (CRT-CNCT). Induction/consolidative chemotherapy was either FOLFOX or CapeOX. RT was prescribed to 50-50.4 Gy in 25-28 fractions using 3DCRT or IMRT; an optional 2-6 Gy sequential boost to gross disease was allowed. Concurrent chemotherapy was either 5FU or capecitabine. Tumor restaging was performed 8 +/-4 weeks after completion of TNT via digital rectal examination, endoscopy, and MRI scan. Patients with an incomplete clinical response underwent TME, while patients with either a complete clinical response (cCR) or near-complete response (nCR) were offered watchful waiting (WW) consisting of endoscopy (q4 months) and MRI (q6 months).

The primary endpoint was disease free survival (DFS), for which resectable regrowth was not considered an event. Organ preservation (defined as TME-free survival) was the secondary endpoint, and the intention-to-treat (ITT) analysis included patients who declined TME, had local excision, or had TME withheld due to distant progression. 324 patients were eligible for analysis (158 INCT-CRT, 166 CRT-CNCT). Most had tumors <5 cm from the anal verge and the median RT dose was 54 Gy. After a median follow-up of 3 years, 3-year DFS was the same in both arms (76%). Of the 304 patients restaged at the end of TNT, 225 (74%) were offered WW (76% CRT-CNCT & 72% INCT-CRT, p=NS). Tumor regrowth occurred more frequently among WW patients who had INCT-CRT (40%) versus CRT-CNCT (27%). For the ITT analysis, 3-year organ preservation was higher after CRT-CNCT vs. INCT-CRT (53% vs. 41%; p=.01). Advanced T stage (T3-4 vs. T1-2), nodal metastases, and INCT-CRT were associated with shorter time to TME on multi-variable analysis. DFS was identical for patients undergoing TME after restaging and for patients undergoing TME after regrowth during WW. Adverse events were similar between the two arms.

Commentary: Conventional therapy for rectal cancer is curative, but also toxic. The benefits of WW extend beyond avoidance of an ostomy to include superior rectal, urinary, sexual, and even cognitive function(34). The OPRA trial provides strong rationale for discussing WW as a treatment option with stage II-III rectal cancer patients. Survey data shows that patients prefer WW over surgery due to improved quality of life(35). While the study failed to achieve the primary objective of improved DFS compared to historical control, the observed DFS was similar to other TNT trials in comparable patient populations(36,37). Follow-up was measured from randomization, so although median follow-up exceeds 3 years it is still relatively short. Regardless, over 90% of locoregional recurrences and 80% of distant metastases occur within the first 3 years of WW(38). While additional follow-up is needed to evaluate long-term results from the OPRA trial, meta-analyses have shown no apparent detriment to oncologic outcomes with WW(38).

The 3-year ITT organ preservation rates from the OPRA trial are among the most impressive to date, perhaps because it was permitted for nCR patients to be re-assessed before surgery. Updated OPRA data indicate that over half of nCR patients eventually achieve cCR, and these patients have a prognosis that lies between initial cCR and incomplete response(39). It is reassuring that the organ preservation curve flattened between 2-3 years, and other WW data indicate tumor regrowth past 3 years after CRT-CNRT is rare(40). Nearly 10% who had TME in each arm achieved a pCR, consistent with other WW studies(41). One of the most challenging aspects of WW are the nuances of response assessment and national guidelines (ASTRO, NCCN) appropriately call for WW to be performed at experienced institutions(42). The International WW consensus guidelines provide valuable standardized response assessment definitions(43).

What is the optimal radiation dose to achieve organ preservation? 54 Gy in 30 fractions with CNCT has been used by WW pioneers Habr-Gama et al. since 2006 due to higher organ preservation rates than 50 Gy(44). Boosting gross disease to 54 Gy was also common in the OPRA trial and is reasonable in routine practice. The randomized phase II RECTALBOOST trial showed that nCR/cCR rates were higher after 65 Gy vs. 50 Gy, although there was no difference in sustained cCR(45). While it appears there are potential advantages of radiation dose escalation, additional studies are needed to better define what the optimal dosing strategy should be, balancing potential toxicity risk.

As a phase III non-inferiority trial comparing WW to planned surgery is unlikely to be conducted, the favorable outcomes from OPRA and other WW trials will indicate that WW should be routinely considered by oncologists as a standard of care for appropriate responders. Perhaps RT and chemotherapy for rectal cancer, or even immunotherapy alone for MSI-High patients(29), might eventually be routinely considered definitive therapy rather than neoadjuvant for properly selected patients.

Lord AC et al. Assessment of the 2020 NICE criteria for preoperative radiotherapy in patients with rectal cancer treated by surgery alone in comparison with proven MRI prognostic factors: a retrospective cohort study. *Lancet Oncology* 2022.(5)

Summary: Lord and colleagues report outcomes from a retrospective cohort study of 378 rectal cancer patients who had surgery at 2 centers in the United Kingdom. A primary surgical approach was utilized at both institutions, without RT, for rectal cancer patients without threatening of the circumferential resection margin (CRM). The authors sought to assess implications of risk stratification using the 2020 National Institute for Health and Care Excellence (NICE) guidelines which recommend neoadjuvant RT for any T3-4 or N+ rectal cancer, compared to other MRI prognostic factors that were not included in the NICE guidelines. Patients with T3-4 or N+ disease were classified as NICE-high risk, and those with MRI-detected CRM involvement, extramural venous invasion, or MRI-detected tumor deposits classified as MRI-high risk disease. Patients who did not meet high-risk criteria were considered to have NICE- or MRI-low risk disease.

The median follow-up was 66 months. Local recurrence occurred in 22 (6%) patients, with distant recurrence observed in 68 (18%) patients. A total of 248 (66%) and 121 (32%) patients had NICE-high risk and MRI-high risk disease, respectively. On Kaplan-Meier analysis, NICE-high risk compared to NICE-low risk disease predicted for worse DFS, without statistical difference in OS. MRI-high risk compared to MRI-low risk disease predicted for both 5-year DFS and OS. Among 139 (37%) patients with NICE-high risk but MRI-low risk disease, DFS was similar to that observed for NICE-low risk disease. A total of 12 patients were identified with NICE-low risk but MRI-high risk disease. On multivariate analysis, NICE-risk assessment did not correlate with DFS or OS, although MRI-risk assessment predicted for both DFS and OS. The authors conclude that the 2020 NICE guidelines may result in overtreatment of patients with rectal cancer compared to MRI-based risk stratification.

Commentary: It is always refreshing when a publication comes out that forces the reader to question some of the most basic “oncologic truths” that govern clinical practice. Codified in the NCCN and NICE guidelines, we all know that every stage II or III rectal cancer patient should be treated with neoadjuvant therapy. In the United States we forget that the European Society for Medical Oncology (ESMO) does not universally advocate for neoadjuvant CRT, even for locally advanced disease, if the surgeon believes that an R0 resection can be achieved(46). This article shows that it might be time to rethink our dogmas, especially in the era of high-quality staging MRI, and offer patients individualized risk stratification. We might be overtreating up to 37% percent of patients with RT. This is especially important as the age of onset of rectal cancer decreases, and the late effects of RT on fertility and sexual function become more important(47).

While the methodology of this study was rigorous (independent review by blinded radiologists) and the results of this study are compelling, it is important to appreciate its limitations before it changes clinical practice. First and foremost, the study is retrospective (albeit from prospectively collected databases) from 2 institutions. The authors state that clinicians followed “a general policy” for making decisions, but every case was individualized and potential confounding undoubtably exists. It is also curious that when these patients were treated (2007-2017) these institutions were treating with what is arguably a deviation from standard of care at the time. It makes the data difficult to extrapolate to a broader scale. Even more important is that the investigators are from one of the leading MRI groups for rectal cancer in the world with multiple publications setting the standard for how we use this modality for this disease(48). It is not clear that the recommendations can be universally applied to the community where such expertise might not exist.

Nevertheless, there is clearly a promising signal of how we can improve risk-stratification for rectal cancer. The results support the findings of the previously published QuickSilver, MERCURY, and OCUM trials(46,49,50). One can imagine creating an even more robust model by incorporating histological, biochemical (such as CEA), genetic, and radiographic features of the tumor to give very predictive risk-stratification. To optimize quality of life outcomes, we also do not know if it is better to treat with TNT therapy with the potential of NOM as was done in OPRA, versus surgical resection alone. Future studies are needed to help clarify these important issues, ideally integrating rigorous patient reported outcome measures. Patients might ultimately decide which approach they prefer.

References

1. Versteijne E, van Dam JL, Suker M, et al. Neoadjuvant chemoradiotherapy versus upfront surgery for resectable and borderline resectable pancreatic cancer: Long-term results of the dutch randomized preopanc trial. *J Clin Oncol* 2022;40:1220-1230.
2. Katz MHG, Shi Q, Meyers J, et al. Efficacy of preoperative mfolfirinox vs mfolfirinox plus hypofractionated radiotherapy for borderline resectable adenocarcinoma of the pancreas: The a021501 phase 2 randomized clinical trial. *JAMA Oncol* 2022;8:1263-1270.
3. Chen IM, Johansen JS, Theile S, et al. Randomized phase ii study of nivolumab with or without ipilimumab combined with stereotactic body radiotherapy for refractory metastatic pancreatic cancer (checkpac). *J Clin Oncol* 2022;40:3180-3189.
4. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *J Clin Oncol* 2022;40:2546-2556.
5. Lord AC, Corr A, Chandramohan A, et al. Assessment of the 2020 nice criteria for preoperative radiotherapy in patients with rectal cancer treated by surgery alone in comparison with proven mri prognostic factors: A retrospective cohort study. *Lancet Oncol* 2022;23:793-801.
6. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: Results of the dutch randomized phase iii preopanc trial. *J Clin Oncol* 2020;38:1763-1773.
7. Ahmad SA, Duong M, Sohal DPS, et al. Surgical outcome results from swog s1505: A randomized clinical trial of mfolfirinox versus gemcitabine/nab-paclitaxel for perioperative treatment of resectable pancreatic ductal adenocarcinoma. *Ann Surg* 2020;272:481-486.
8. Versteijne E, Vogel JA, Besselink MG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg* 2018;105:946-958.
9. Jang JY, Han Y, Lee H, et al. Oncological benefits of neoadjuvant chemoradiation with gemcitabine versus upfront surgery in patients with borderline resectable pancreatic cancer: A prospective, randomized, open-label, multicenter phase 2/3 trial. *Ann Surg* 2018;268:215-222.
10. Motoi F, Kosuge T, Ueno H, et al. Randomized phase ii/iii trial of neoadjuvant chemotherapy with gemcitabine and s-1 versus upfront surgery for resectable pancreatic cancer (prep-02/jsap05). *Jpn J Clin Oncol* 2019;49:190-194.
11. Janssen QP, van Dam JL, Bonsing BA, et al. Total neoadjuvant folfirinox versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (preopanc-2 trial): Study protocol for a nationwide multicenter randomized controlled trial. *BMC Cancer* 2021;21:300.

12. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (espac-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017;389:1011-1024.
13. Conroy T, Hammel P, Hebbar M, et al. Folfirinox or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med* 2018;379:2395-2406.
14. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified folfirinox treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for clinical trials in oncology trial a021101. *JAMA Surg* 2016;151:e161137.
15. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 2012;118:5749-56.
16. Uson PLS, Jr., Samadder NJ, Riegert-Johnson D, et al. Clinical impact of pathogenic germline variants in pancreatic cancer: Results from a multicenter, prospective, universal genetic testing study. *Clin Transl Gastroenterol* 2021;12:e00414.
17. O'Kane GM, Grunwald BT, Jang GH, et al. Gata6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer. *Clin Cancer Res* 2020;26:4901-4910.
18. O'Reilly EM, Oh DY, Dhani N, et al. Durvalumab with or without tremelimumab for patients with metastatic pancreatic ductal adenocarcinoma: A phase 2 randomized clinical trial. *JAMA Oncol* 2019;5:1431-1438.
19. Neoptolemos JP, Kleeff J, Michl P, et al. Therapeutic developments in pancreatic cancer: Current and future perspectives. *Nat Rev Gastroenterol Hepatol* 2018;15:333-348.
20. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage iii non-small-cell lung cancer. *N Engl J Med* 2017;377:1919-1929.
21. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer* 2016;40:25-37.
22. Kabacaoglu D, Ciecielski KJ, Ruess DA, et al. Immune checkpoint inhibition for pancreatic ductal adenocarcinoma: Current limitations and future options. *Front Immunol* 2018;9:1878.
23. Yamamoto K, Venida A, Yano J, et al. Autophagy promotes immune evasion of pancreatic cancer by degrading mhc-i. *Nature* 2020;581:100-105.
24. Parikh AR, Szabolcs A, Allen JN, et al. Radiation therapy enhances immunotherapy response in microsatellite stable colorectal and pancreatic adenocarcinoma in a phase ii trial. *Nat Cancer* 2021;2:1124-1135.
25. Xie C, Duffy AG, Brar G, et al. Immune checkpoint blockade in combination with stereotactic body radiotherapy in patients with metastatic pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2020;26:2318-2326.
26. Melief CJM. T-cell immunotherapy against mutant kras for pancreatic cancer. *N Engl J Med* 2022;386:2143-2144.
27. Leidner R, Sanjuan Silva N, Huang H, et al. Neoantigen t-cell receptor gene therapy in pancreatic cancer. *N Engl J Med* 2022;386:2112-2119.
28. Fang PQ, Gunther JR, Wu SY, et al. Radiation and car t-cell therapy in lymphoma: Future frontiers and potential opportunities for synergy. *Front Oncol* 2021;11:648655.
29. Cercek A, Lumish M, Sinopoli J, et al. Pd-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. *N Engl J Med* 2022;386:2363-2376.
30. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med* 2020;383:2207-2218.
31. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to pd-1 blockade. *Science* 2017;357:409-413.

32. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018;36:773-779.
33. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in mmr-proficient and mmr-deficient early-stage colon cancers. *Nat Med* 2020;26:566-576.
34. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of life in rectal cancer patients after chemoradiation: Watch-and-wait policy versus standard resection - a matched-controlled study. *Dis Colon Rectum* 2017;60:1032-1040.
35. Couwenberg AM, Intven MPW, Burbach JPM, et al. Utility scores and preferences for surgical and organ-sparing approaches for treatment of intermediate and high-risk rectal cancer. *Dis Colon Rectum* 2018;61:911-919.
36. Fokas E, Schlenska-Lange A, Polat B, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: Long-term results of the cao/aro/aio-12 randomized clinical trial. *JAMA Oncol* 2022;8:e215445.
37. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (tme) versus preoperative chemoradiotherapy, tme, and optional adjuvant chemotherapy in locally advanced rectal cancer (rapido): A randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:29-42.
38. Dattani M, Heald RJ, Goussous G, et al. Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: A systematic review and pooled analysis. *Ann Surg* 2018;268:955-967.
39. Thompson H, Kim JK, Yuval JB, et al. Survival and organ preservation according to clinical response after total neoadjuvant therapy in locally advanced rectal cancer patients: A secondary analysis from the organ preservation in rectal adenocarcinoma (opra) trial. *Journal of Clinical Oncology* 2021;39:3509-3509.
40. Sao Juliao GP, Karagkounis G, Fernandez LM, et al. Conditional survival in patients with rectal cancer and complete clinical response managed by watch and wait after chemoradiation: Recurrence risk over time. *Ann Surg* 2020;272:138-144.
41. van der Sande ME, Beets GL, Hupkens BJ, et al. Response assessment after (chemo)radiotherapy for rectal cancer: Why are we missing complete responses with mri and endoscopy? *Eur J Surg Oncol* 2019;45:1011-1017.
42. Wo JY, Anker CJ, Ashman JB, et al. Radiation therapy for rectal cancer: Executive summary of an astro clinical practice guideline. *Pract Radiat Oncol* 2021;11:13-25.
43. Fokas E, Appelt A, Glynne-Jones R, et al. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. *Nat Rev Clin Oncol* 2021;18:805-816.
44. Habr-Gama A, Sao Juliao GP, Fernandez LM, et al. Achieving a complete clinical response after neoadjuvant chemoradiation that does not require surgical resection: It may take longer than you think! *Dis Colon Rectum* 2019;62:802-808.
45. Couwenberg AM, Burbach JPM, Berbee M, et al. Efficacy of dose-escalated chemoradiation on complete tumor response in patients with locally advanced rectal cancer (rectal-boost): A phase 2 randomized controlled trial. *Int J Radiat Oncol Biol Phys* 2020;108:1008-1018.
46. Kennedy ED, Simunovic M, Jhaveri K, et al. Safety and feasibility of using magnetic resonance imaging criteria to identify patients with "good prognosis" rectal cancer eligible for primary surgery: The phase 2 nonrandomized quicksilver clinical trial. *JAMA Oncol* 2019;5:961-966.
47. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020;70:145-164.

48. Taylor FG, Swift RI, Blomqvist L, et al. A systematic approach to the interpretation of preoperative staging mri for rectal cancer. *AJR Am J Roentgenol* 2008;191:1827-35.
49. Ruppert R, Kube R, Strassburg J, et al. Avoidance of overtreatment of rectal cancer by selective chemoradiotherapy: Results of the optimized surgery and mri-based multimodal therapy trial. *J Am Coll Surg* 2020;231:413-425 e2.
50. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the mercury study. *J Clin Oncol* 2014;32:34-43.