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Rectal Cancer Update: Which Treatment Effects Are the Least "Brutal"?

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Introduction

Rectal cancer therapy currently finds itself in a time of rap- idly expanding treatment options. In this edition of Oncol- ogy Scan, we present several high-impact studies that are influencing the rectal cancer treatment landscape. For lower-risk rectal cancer, the OPERA study showed promis- ing results of a randomized study of external beam versus brachytherapy boost for purposes of sphincter sparing/non- operative management.[1] The NEO study reports the phase 2 results of chemotherapy alone followed by local excision in early-stage rectal cancer.[2] Finally, the heavily reported results of the randomized PROSPECT trial are discussed,[3,4] having received significant attention in the media including a widely circulated article in the *New York Times* referencing effects of pelvic radiation as "brutal." Radiation oncologists will play an important role in the determination of which therapy modality or combination best aligns with a given patient's oncologic risk and treatment preference in the con- text of a multidisciplinary discussion.

The management of rectal cancer is evolving, and we need to refine our patient stratification and evidence-based options to have meaningful patient-centered discussions. We need to further research the predictive biomarkers and tumor biology to individualize treatment options. Tailored treatments should encompass not just oncological outcomes but also consider the short- and long-term effects on organ function and quality of life (QoL).

Gerard JP, Barbet N, Schiappa R, et al. Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3 rectal adenocarcinoma (OPERA): A phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2023;8:356-367.[1]

Summary: The OPERA trial as reported by Gerard et al was a multi-institutional, phase 3 randomized trial comparing 2 neoadjuvant chemoradiation therapy regimens in patients with rectal cancer.[1] Eligible patients had operable cT2-T3, cN0-cN1 tumors in the low to mid rectum, measuring <5 cm in diameter and occupying less than half of the rectal circumference. Magnetic resonance imaging (MRI) with or without ultrasound was used for local staging with central review. All patients underwent either 3-dimensional conformal or intensity modulated chemoradiation therapy to a dose of 45 Gy in 25 fractions with concurrent capecitabine. Patients in group A received a primary tumor boost using external beam radiation therapy to a dose of 9 Gy in 5 fractions. In group B, patients received a contact brachytherapy boost using the Papillon contact x-ray brachytherapy system at 30 Gy per fraction, for a total dose of 90 Gy in 3 fractions over 4 weeks, prescribed to the surface. For tumors <3 cm, this boost was given first, with chemoradiation occurring 1 to 2 weeks after brachytherapy. For tumors >3 cm, the boost was given 2 to 3 weeks after completion of external beam radiation therapy. In both arms, patients were evaluated at week 14 using digital rectal exam, MRI, and sigmoidoscopy. Total mesorectal excision was recommended for patients who had a partial response. In patients who had a complete clinical response (cCR) or near complete clinical response (ncCR), either local excision or a watchful waiting protocol was initiated. Adjuvant chemotherapy was not required and was per institutional discretion. The primary outcome was the 3-year organ preservation (OP) rate. Secondary out- comes included overall and disease-free survival, as well as acute and late toxicity including bowel functional scores using the low anterior resection syndrome (LARS) score.

Among the 148 patients enrolled in the trial, 141 patients were evaluable: 69 in group A and 72 in group B. In total, 65% of patients had T2 disease and 75% of patients had tumors in the low rectum, <6 cm from the anal verge; 43% of patients had tumors <3 cm, equally split in each arm. At 14 weeks, tumor response was evaluated; 58% in group A and 81% in group B had a cCR or ncCR (P = .0006). Among patients with tumors <3 cm in diameter, 76% of patients in group A and 97% of patients in

group B had a cCR or ncCR. Among patients with tumors 3 cm or larger in diameter, 55% in group A and 88% in group B had a cCR or ncCR.
After a median follow-up of 38 months, the 3-year OP rate was 59% in group A versus 81% in group B (hazard ratio [HR], 0.36; 95% CI, 0.19-0.70; *P* = .0026). In patients with tumors <3 cm, the OP rate was 63% in group A and 97% in group B (HR, 0.07; 95% CI, 0.01-0.57; *P* = .012). The 3-year cumulative incidence of local recurrence was 23% in group A and 15% in group B (*P* = .59). The most common late side effect was mild rectal bleeding (grade 1-2), which was analyzed in the 102 patients who did not undergo surgery. Mild rectal bleeding was more frequent in group B (63%) than in group A (12%). The LARS score was 30 or more in 21% of patients in group A and 17% in group B.
Commentary: The MORPHEUS trial also investigated external beam chemoradiation to a dose of 45 Gy in 25 frac- tions with concurrent capecitabine followed by a 9 Gy in 5 fraction external beam boost versus a 30 Gy in 3 fraction high-dose-rate brachytherapy boost.[5] The study also included patients with cT2-3bN0M0 rectal cancer with a primary tumor measuring ≤5 cm in length with involve- ment of ≤50% luminal circumference, and located within 10 cm of the anal verge. Patients with disease involvement of the anal canal were excluded. At an interim analysis of 40 of a planned 146 analyzable patients and a median follow- up of 1.3 years, the study suggested an improvement in clin- ical complete response with the use of brachytherapy, 50% versus 90%, and improved 2-year total mesorectal excision (TME)–free survival, 38.6% versus 76.6% (HR, 0.23; 95% CI, 0.07-0.71; *P* = .011). Acute grade 3 or higher radiation proctitis occurred in 10% of patients who received brachy- therapy boost compared with 0% with external beam radia- tion therapy alone. A recently presented update regarding 45 analyzable patients suggested that major low anterior resection syndrome within 1 to 6 months after treatment was more common in the brachytherapy cohort, 14% versus 62% (odds ratio, 23.9; 95% CI, 2.5-226.5); however, it was less common in the brachytherapy cohort 25 to 36 months after treatment, 38% versus 15% (odds ratio, 0.5; 95% CI, 0.0-9.2), potentially reflective of the improved long-term functional outcomes achieved through improved cCR and ultimate nonoperative management.
So, the question becomes, is "ultra dose escalation" with brachytherapy boost ready for prime time? An important consideration for these studies is that each included a rela- tively favorable risk cohort of patients with predominantly MRI-characterized cT2-3N0 (21% N1 on OPERA), non- bulky disease without other adverse risk factors, thus limit- ing the potential generalizability of these data. For such a cohort, a number of alternative strategies have been explored including "standard dose" short-course radiation therapy or chemoradiation alone,[6] chemoradiation followed by local excision,[7-9] dose escalated chemoradiation,[6] and chemotherapy followed by local excision,[7] each of which has been associated with promising outcomes. For example, when restricted to cT2N0 tumors measuring <4 cm in size and involving <40% rectal circumference, the ACOSOG Z6041 trial demonstrated an impressive 88.2% 3-year dis- ease-free survival and excellent preservation of function using concurrent chemoradiation 50.4 to 54 Gy in 28 to 30 fractions followed by local excision.[3] When expanding inclusion to allow up to cT3N0 disease, predominately <4 cm in size without additional risk factors, the CARTS and GRECCAR-2 trials demonstrated a 48% to 63.6% OP rate using chemoradiation followed by local excision,[4,5] and similarly, the STAR-TREC trial found a 60% 1-year OP rate with short-course RT or long-course chemoradiation alone.[2]
Furthermore, the WW2 trial suggested that dose escalated chemoradiation using a regimen of 50.4 Gy to the elective pelvis with a simultaneous boost to gross tumor to 62 Gy was associated with an 86% complete response rate and 61.2% 2-year locoregional control among a slightly more advanced cohort with cT1-3N0-1 (31% T3, 29% N1) dis- ease.[10] Finally, the OPRA trial was inclusive of the most advanced cohort of patients with cT3-4N0 or any T, N1-2 disease (93% cT3-4; 70% N+) and demonstrated that che- moradiation with a median dose of 54 Gy in 30 fractions fol- lowed by 8 cycles of FOLFOX was associated with improved 3-year (55% vs 41%) and 5-year (54% vs 39%) TME-free survival compared with an induction chemotherapy fol- lowed by chemoradiation sequence.[11]
In summary, these data suggest that initial disease extent strongly influences ultimate outcome, but when limited to a suitable cohort of cT2-3N0 nonbulky tumors <5 cm and involving ≤50% of the rectum circumference, "ultra dose escalation" using chemoradiation with a

brachytherapy boost is a highly promising treatment strategy associated with some of the highest reported clinical complete response (90%-92%) and OP rates (77%-81%) to date. There is increased acute toxicity, including proctitis and major LARS within 6 months, and increased late rectal bleeding, although LARS significantly resolves with extended follow- up. The primary factor limiting adoption will be the techni- cal skill and equipment necessary, particularly if one is con- sidering the Papillon contact orthovoltage technique used in the OPERA study. However, the high-dose-rate brachyther- apy strategy as used in MORPHEUS and Appelt et al repre- sents an appealing alternative that is likely feasible with existing technology in many radiation oncology departments.[5,12] For patients with more advanced disease, N+ disease, a total neoadjuvant strategy such as that done in OPRA or enrollment in the ongoing JANUS trial exploring mFOLFIRINOX may be a preferable option.

Kennecke HF, O'Callaghan CJ, Loree JM, et al. Neoadjuvant chemotherapy, excision, and observation for early rectal cancer: The phase II NEO trial (CCTG CO.28) primary end point results. *J Clin Oncol.* 2023;41:233-242.[2]

Summary: The Neoadjuvant Chemotherapy, Excision, and Observation (NEO) for Early Stage Rectal Cancer phase 2 trial assessed the outcomes and organ-sparing rate in patients with early-stage rectal cancer who received neoad- juvant chemotherapy followed by transanal excision surgery (TES) as an alternative to TME.[2] Chemotherapy consisted of 3 months of mFOLFOX/CAPOX and those with evidence of response proceeded to TES 2 to 6 weeks later.

Patients with clinical T1-T3abN0 low- or mid-rectal ade- nocarcinoma amenable to endoscopic resection were eligi- ble. A total of 58 patients were enrolled, the majority of which were T1-2N0 (78%), and there was relatively limited representation of patients with T3aN0 (17%) or T3bN0 (5%) disease. After chemotherapy, 57% (33/58) of patients achieved tumor downstaging to ypT0/1N0/X. Among the 23 patients recommended for TME surgery, 13 declined and elected to proceed directly to observation, resulting in 79% of total patients achieving OP. Of the remaining 10 patients who proceeded to TME, 7 had no residual disease within the specimen. The locoregional relapse-free survival at 1 year and 2 years was 98% (95% CI, 86%-100%) and 90% (95% CI, 58%-98%), respectively, and minimal changes in QoL and rectal function were observed.

Commentary: The NEO study provides data supporting local excision after chemotherapy alone in clinical T1-3b rectal adenocarcinoma. Considering the enrolled patient characteristics, the data may be most generalizable to patients with T1-2N0 disease. Although technically a nega- tive study by primary endpoint, the successful local excision rate (57%) in the intention to treat group and actual OP rate (79%), compare favorably with chemoradiation and local
excision studies such as CARTS (74%)[7] and ACOSOG Z6041 (91%).[8] These data are important as more patients are electing for nonoperative approaches for rectal cancer management to improve their QoL and organ function.

Regarding toxicity, the rate of major LARS was 22% at 6 months postexcision and 14% at 12 months. This is signif- icantly lower than the reported 50% major LARS in the CARTS study that treated a similar patient population with chemoradiation. Notably, the median tumor size was not reported in the NEO study. As the size of the defect from local excision can significantly affect rectal function, these data would be important to compare with the CARTS study (median tumor size 3.4 cm). Grade 3 gastrointestinal toxic- ity of 22% was similar to Z6041. However, the authors do not report rates of neuropathy in this study with multiagent oxaliplatin chemotherapy. As follow-up is limited (median, 15.4 months) the 1- and 2-year locoregional relapse-free survival will need to be evaluated as the data mature. The oncologic significance of tumor regrowth after chemother- apy alone, which has not been noted in chemoradiation downstaging studies, is uncertain in this small study. Simi- larly, the risk of mesorectal or pelvic lymph node relapse and influence on oncologic outcome when there is omission of locoregional chemoradiation therapy needs to be better understood.

Finally, to find a pathologic complete response in 7 of 10
patients who went to surgery demonstrates the limitations in our current staging modalities. Although the rectal func- tion and QoL data from the NEO study are promising, given the small size of the study, this treatment paradigm will require further validation before widespread implementa- tion as a standard of care. The upcoming NEO-RT trial (CCTG CO.32) will build upon these data by assessing the coprimary endpoints of clinical complete response and QoL for patients with cT1-2 rectal adenocarcinoma who are not amenable to upfront transanal excision treated with the NEO regimen of FOL- FOX/CAPOX chemotherapy followed by local excision ver- sus long-course chemoradiation. These data will further clarify the preferred organ-preserving treatment strategy for patients with early-stage rectal cancer.

Schrag D, Shi Q, Weiser MR, et al. Preoperative treatment of locally advanced rectal cancer. *N Engl J Med.* 2023;389:322-334.[4]

Summary: Schrag et al report the primary outcomes from the PROSPECT trial, which compared neoadjuvant FOL- FOX and selective use of chemoradiation with neoadjuvant chemoradiation for patients with locally advanced rectal cancer.[4] The eligibility criteria included patients with T2N1 or T3N0-1 rectal cancer that was amenable at diagnosis to sphincter sparing surgical resection, without threatening of the circumferential margin defined as tumor within 3 mm of the circumferential margin on baseline pelvic imaging. Pelvic MRI was recommended for local staging, with com- puted tomography of the chest, abdomen, and pelvis andendorectal ultrasound considered an acceptable alternative. Patients enrolled in the neoadjuvant FOLFOX arm received 6 cycles of mFOLFOX6 every 2 weeks, followed by restaging imaging and endoscopy. Those with at least 20% decrease in size of the primary tumor underwent surgery without che- moradiation, and chemoradiation was administered to those with $<$20% decrease in size of the primary tumor or if unable to complete 5 cycles FOLFOX. Postoperative chemo-
radiation was recommended for R1 resection, and an addi- tional 6 cycles of adjuvant FOLFOX was suggested for all patients. In the standard arm, neoadjuvant pelvic chemora- diation consisted of 50.4 Gy in 28 fractions delivered with either 3-dimensional or intensity modulated radiation ther- apy technique, with concurrent fluorouracil (225 mg/m^2) or oral capecitabine (825 mg/m^2), 5 days per week. Postopera- tive chemotherapy with 8 cycles of FOLFOX was suggested. The primary objective was to determine noninferiority of the experimental arm compared with the chemoradiation arm with respect to disease-free survival (DFS). Secondary endpoints included overall survival, local recurrence, R0 resection rate, pathologic complete response, and toxicity.

Among 1194 patients randomized, 1128 patients initiated treatment and were included in the primary analysis. The median follow-up was 58 months. Noninferior DFS was
observed for neoadjuvant FOLFOX with selective use of chemoradiation compared with neoadjuvant chemoradia- tion (HR, 0.92; 90.2% CI, 0.74-1.14; *P* = .005 for noninfer- iority), with 5-year DFS rates of 80.8% and 78.6% for the FOLFOX and chemoradiation arms, respectively. No differ- ence was observed for other endpoints, including 5-year OS (89.5% vs 90.2%), local recurrence (1.8% vs 1.6%), and R0 resection rate (90.4% vs 91.2%) between the FOLFOX and chemoradiation arms. In the FOLFOX arm, 53 of 585 (9.1%) received neoadjuvant chemoradiation and 8 of 585 (1.4%) received postoperative chemoradiation. Adjuvant chemotherapy was administered to 438 of 585 (74.9%) patients in the neoadjuvant FOLFOX group and 423 of 543 (77.9%) patients in the neoadjuvant chemoradiation group. During neoadjuvant therapy, a higher incidence of severe (grade ≥3) toxicity was observed in the FOLFOX group compared with the chemoradiation group (41.0% vs 22.8%). The most frequent observed grade ≥3 toxicities included neutropenia, pain, and hypertension in the FOLFOX arm and lymphopenia, diarrhea, and hypertension in the chemo- radiation arm.

Commentary: Completion of the PROSPECT trial is a huge accomplishment, and the study investigators, patients, and the patients' families should certainly be commended. The study findings support another option in the nuanced care of patients with rectal cancer, which is, of course, a highly heterogeneous disease for which numerous developments were made during the time of study accrual and data maturation.

By international standards, the patients enrolled in the PROSPECT trial are low risk: about 90% had cT3 disease. Despite 85% of patients undergoing MRI staging, the T3
and nodal subgroups are not reported, and if considering European guidelines (European Society for Medical Oncol- ogy), these patients would be reclassified as early or interme- diate cancers. Thus, it can be interpreted that this study has exposed a significant number of patients to increased toxic- ity due to systemic and radiation therapy treatments, as most patients could have been managed with TME and preserved sphincter function.

The question becomes whether we can generalize these data to contemporary practice and whether neoadjuvant FOLFOX alone has a role in a risk-stratified group. To address this question, an understanding of the risk factors for both locoregional and distant recurrence are required. Historically, patients who were managed with upfront surgi- cal resection for rectal cancer had high risks of both pelvic and distant metastatic recurrence. For example, patients with T3-4 or node positive rectal cancer managed with sur- gery in the pre-TME era had a 25% to 50% risk of locore- gional recurrence.[13] Such recurrences are very challenging to manage and are tremendously morbid, often leading to pain, bleeding, and urinary and rectal dysfunction, and can be the cause of death even in the absence of distant meta- static disease. Through improvements in

surgical techni- ques, such as the advent of TME technique, and the selective use of neoadjuvant therapy, the risk of pelvic recurrence has been reduced to approximately 5% to 15%. Generally speaking, radiation therapy is associated with approximately a 50% relative risk reduction in pelvic recur- rence, and, therefore, the absolute magnitude of benefit is largely related to the baseline risk based on underlying risk factors and quality of surgical resection specimen.[14-17]

Tremendous work has been done to identify MRI-defined risk factors for pelvic and distant recurrence of rec- tal cancer. Notable risk factors for pelvic recurrence include compromised mesorectal fascia defined as tumor ≤1 mm of the mesorectal fascia, T4 disease, involved lateral pelvic lymph nodes, extramural venous invasion, and distal rectal location, which is in part related to the differential propen- sity of spread to internal iliac or (rarely) inguinal lymph nodes for distal tumors compared with mid-upper rectal cancers.[18-24] On the contrary, MRI-defined criteria have also identified a relatively low-risk cohort of patients inclusive of those with predominantly cT1-3bN0, >1 mm margin from the mesorectal fascia, no extramural vascular invasion, and located within the mid-upper rectum.

Using these criteria of MRI-defined low-risk disease, pro- spective trials have investigated the use of upfront surgery with omission of preoperative radiation therapy and dem- onstrated relatively favorable outcomes. For example, the Mercury and QuickSilver trials included patients with clini- cal T2-3b, N any (63%-82% N0) disease predominantly located within the mid-upper rectum (84%-93%). OCUM included cT1-3, N any (50% N0) and allowed omission of radiation therapy for patients with T1-3 mid-upper rectal cancers or T1-2 distal rectal cancers. Each of these studies excluded patients with tumor ≤1 mm of the mesorectal fas- cia or extramural venous invasion. Outcomes were relatively favorable in each of the studies with pathologically involved circumferential resection margin in 3% to 5% and a 3% to 4% 5-year risk of pelvic recurrence. Based on these data, both American Society for Radiation Oncology and Euro- pean Society for Medical Oncology consensus guidelines support the consideration of omission of radiation therapy in select cohorts of patients with MRI-defined low-risk tumors.[25,26]

The PROSPECT trial predominantly included a cohort of patients with MRI-defined low-risk disease. Patients were not eligible for the study if they had tumors <3 mm of the mesorectal fascia, had T4 or N2 disease, or were not amena- ble to a low anterior resection. In total, 85% of patients had tumors within the mid- or upper rectum, and 38% were N0. The pathologic outcomes further support a highly select and favorable cohort with an unprecedented pathologic com- plete response rate of 22% to 24%, which compares with a historical rate of approximately 15% after long-course che- moradiation and less than 5% to 10% after preoperative che- motherapy alone.[27,28] Similarly, 33% to 35% had ypT3 disease and 24% to 25% had ypN+. With this in mind, it is not surprising to see an exceptionally low rate of locore- gional recurrence (2%), with no difference between treat- ment arms, as the cohort was selected based on absence of high risk features.

So how do we integrate these data into contemporary practice? The basis of this answer comes down to a few com- ponents: (1) what is the treatment intent: preoperative ver- sus goal for nonoperative, (2) what is the baseline risk based on MRI-defined risk factors, and (3) how do the patient's goals, wishes, and day-to-day life interplay with the differen- tial toxicities of treatment?

If a patient is interested in a nonoperative treatment approach, the best supported strategy includes the use of radiation therapy. If the plan is to consider total neoadju- vant therapy, data support the use of radiation therapy fol- lowed by systemic therapy.[11]

For patients interested in an operative approach, a careful assessment of MRI-defined risk factors is critical in deter- mining which patients are suitable candidates for omission of therapy. The most recent American Society for Radiation Oncology and European Society for Medical Oncology con- sensus guidelines remain quite representative of patients who are suitable candidates for omission of radiation ther- apy and/or chemotherapy. It may also be argued that some patients on the PROSPECT trial were "overtreated," particu- larly those with early T3a-bN0 mid-upper tumors, for which some guidelines also support the use of upfront surgery and reservation of chemotherapy for those with pathologically involved lymph nodes.[22-24,26] For those with higher risk dis- ease as described previously, a total neoadjuvant treatment strategy, inclusive of radiation therapy, may be most appro- priate. This is further supported by the long-term outcomes of the PRODIGE-23 trial, which has suggested an overall survival benefit with the use of total neoadjuvant therapy, and the RAPIDO trial showing a much higher baseline riskof pelvic recurrence, despite the use of radiation therapy in each arm, in a high-risk cohort.[29-32]

Finally, acute grade 3 or higher toxicity was significantly higher in the FOLFOX versus chemoradiation

treatment arm, 41% versus 23%. Postoperative toxicity was slightly higher in the chemoradiation arm, likely reflective of the receipt of postoperative FOLFOX. These differences mostly resolved with extended follow. Notably, overall QoL was similar in both treatment arms. These toxicity differences may assist in counseling patients on an ideal treatment strat- egy. Perhaps the most compelling scenario to consider omis- sion of radiation therapy would be a young premenopausal woman interested in future childbearing options. Data have suggested that in the absence of ovarian transposition sur- gery, up to 100% of women who undergo preoperative radi- ation therapy for rectal cancer will experience premature ovarian failure.[33] It is also possible that even if a woman were to have preserved ovarian endocrine function, the uterus would no longer be implantable or have the capacity to maintain a term pregnancy. In such a scenario, the use of chemotherapy to allow omission of radiation therapy may allow a patient to achieve their family planning goals.

Basch E, Dueck AC, Mitchell SA, et al. Patient-reported outcomes during and after treatment for locally advanced rectal cancer in the PROSPECT trial (Alliance N1048). *J Clin Oncol*. 2023;41:3724-3734.[3]
Summary: On the same day the PROSPECT trial was pub- lished in the *New England Journal of Medicine,* the corre- sponding QoL data were published in the *Journal of Clinical Oncology*. In contrast to most other trials that report on physician-reported treatment toxicity, PROSPECT used patient-reported outcomes (PROs). The investigators col- lected and reported PROs at the following time points: base- line, preoperatively (during neoadjuvant treatment), and postoperatively at several intervals. Separately, information on sexual function was also collected.
In the neoadjuvant setting, the experimental arm (FOL- FOX chemotherapy, with selective omission of radiation therapy) had higher rates of nearly all symptoms: anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomit- ing. The most common severe symptom (score 3+) was fatigue, occurring in 41.7% of patients in the experimental arm. In contrast, patients in the chemoradiation arm had higher rates of diarrhea and worse bowel function. At 12 months after surgery, the rates of symptoms were much improved in both arms and there were no symptoms reported as severe by at least 15% of patients in either group. Fatigue and neuropathy at 12 months were more common in patients in the preoperative chemoradiation arm, who were receiving chemotherapy postoperatively closest to the assessment time point. Sexual function was better for both men and women in the experimental arm at 12 months postoperatively, compared with the chemoradiation groupFinally, there were no differences in overall health-related QoL between either group at any time point.
Commentary: The toxicity profiles between the 2 approaches studied in the PROSPECT trial are distinct and require nuance in their evaluation. Describing the PROS- PECT trial as a de-escalation strategy is not substantiated in the QoL data presented because clinicians and patients reported that chemoradiation is the better tolerated neoad- juvant treatment choice. Severe (grade 3 or higher) toxicity with FOLFOX was nearly double (41%) that of chemoradia- tion (22.8%). Across 14 PRO domains, chemoradiation was significantly superior to FOLFOX in 12 domains and worse in only in diarrhea. The use of adjuvant chemotherapy after chemoradiation has no level 1 evidence showing improved survival and poor compliance is commonly described with increased toxicity. A distinction between the preoperative and postoperative setting, where the grade 3 and 4 adverse event rates were reversed, 25.6% with FOLFOX and 32.6% with chemoradiation has very little value in clinical practice. At the long-term study endpoints, although fatigue and neuropathy were significantly worse in the chemoradiation arm, it is likely that this difference is attributable to the known toxicity of the adjuvant chemotherapy that these patients were still recovering from. Although the 12-month time point is relevant for long-term toxicity, it remains to be seen how the toxicity profiles may change with further fol- low-up beyond the time points reported in the study as pel- vic radiation therapy is unlikely to result in peripheral neuropathy, in contrast to platinum-based chemotherapy.
Radiation oncologists in context of multidisciplinary care will have to weigh relative toxicities of each approach against the risks of overtreatment and individual patient cir- cumstances. Given similar oncologic outcomes, it is likely that the relative importance of the short-term versus long- term toxicity may differ depending on the values that an individual places on them. Age, medical comorbidities, travel and time constraints, and patient preference are only a few of the factors that may play a role in choosing between the 2 regimens. It becomes even more critical that these patients be evaluated in a multidisciplinary fashion to ensure that patient concerns heard and adequately addressed in their treatment plan.
The true value of PROSPECT is that it adds to, rather

than replaces, the therapeutic options for rectal cancer. These data will inform a multidisciplinary, patient centered discussion of evidence-based options, some of whom will undoubtedly benefit from this approach, but not everyone. We urge caution not to extrapolate these findings to patients with high-risk rectal cancer. Curiously, the recently updated National Comprehensive Cancer Network guidelines offer the option of chemotherapy alone for all non-T4 patients, irrespective of MRF status or nodal status, outside of the PROSPECT inclusion criteria.

Finally, it remains to be seen how these data are used in the modern era. Many institutions have shifted to offering total neoadjuvant therapy to an increasing proportion ofpatients, and it is often the default choice for patients with T3 or node positive disease. It is very likely that many of these patients are overtreated with intensive systemic che- motherapy regimens and/or chemoradiation. Guidelines and randomized clinical trials are mixed regarding the value of adjuvant chemotherapy, especially in the modern TME era for patients treated with neoadjuvant chemoradiation.[26,34,35] Whether toxicity is short- or long- term, it has a major effect on a patient's QoL. For a young female patient with a high rectal tumor without nodal involvement, neoadjuvant chemotherapy alone may be a preferred approach for fertility preservation. For an older patient with severe baseline neuropathy diagnosed with a T3N0, mid-rectal tumor, neoadjuvant chemoradiation alone is likely a reasonable approach as well. The results of the randomized PROSPECT trial and others should be individ- ualized, and it is likely that both systemic therapy and radia- tion therapy may be de-escalated for some in the future to optimize patient QoL without compromising survival.

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