The Evolving Personalized Landscape of ColorectalCancer Therapies

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We welcome 3 new associate editors to the GI editorial team, all experts in GI oncology and also bringing particular expertise as follows: Dr. Michael Chuong from the Miami Cancer Institute (pancreas, liver and esophagus cancers), Dr. Maria A. Hawkins from the University College London in the UK (hepatobiliary and esophageal cancers as well as treatment-related toxicity), and Dr. Ann Raldow from the UCLA Jonsson Comprehensive Cancer Center (rectal, anal, and pancreatic cancers). They were chosen for proving to be outstanding Red Journal reviewers through their submission of insightful and timely critiques. We are grateful such a collegial and talented group has joined our team.

The selection of manuscripts featured in the current Oncoscan offers hope and an array of options allowing us to further personalize care for colorectal cancer patients. To begin, we report on KEYNOTE-177, a phase 3 randomized trial of pembrolizumab versus chemotherapy in microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) metastatic colorectal cancer(1). Although the trial does not incorporate radiotherapy, results will be highly impactful within GI oncology due to report of both improved oncologic control and tolerability benefits for immunotherapy in this population, which will perhaps one day extend to locoregionally advanced MSI-H-dMMR colorectal cancer.

The remaining articles focus on the increasingly diverse treatment options for rectal cancer. Thankfully, gone are the days where locoregionally advanced rectal patients had a single treatment path of neoadjuvant long-course chemoradiation (nLCRT), surgery and adjuvant chemotherapy. The French Research Group of Rectal Cancer Surgery (GRECCAR)-2 is a phase 3 trial that compared local excision (LE) versus total mesorectal excision (TME) for good responding rectal cancers following nLCRT(2). This trial provides important information regarding when LE may be performed without a need for a completion TME, adding to the data for organ preservation for rectal cancer patients. The Optimized Surgery and MRI-Based Multimodal Therapy (OCUM) group's trial is a prospective, multicenter observational study where lower risk rectal cancer patients received primary surgery, reserving nLCRT for those

with certain high risk clinical features(3). This trial adds to the growing body of literature suggesting that select rectal patients may be able to safely avoid radiation in favor of surgery alone. With the age of diagnosis disconcertingly trending younger, avoiding radiation therapy might help avoid fertility and other more universal late effects concerns. Comparative studies with detailed health-related quality of life (HRQOL) endpoints will be needed to assess relative benefits of omission of radiation, in the context of other evolving paradigms such as nonoperative management (NOM). The Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial is a phase 3 study comparing preoperative short course radiation therapy (SCRT) followed by consolidation chemotherapy versus nLCRT, surgery and adjuvant chemotherapy (4). This study has provided us the best data to date showing that SCRT appears both effective and safe within a total neoadjuvant therapy (TNT) strategy. The current pandemic adds to the numerous reasons including family, transportation, financial and work stresses as to why a patient might prefer just 5 days of radiation over 5-6 week courses.

Maintaining and improving on oncologic outcomes is essential, but the dramatic impact of treatment on patient QOL should not be under-estimated with up to 2/3 of patients undergoing nLCRT and surgery having major GI side effects(5). Survey data indicates that patients may have a higher magnitude of benefit threshold than might be expected before accepting the toxicity of radiation therapy(6), and significant patient interest exists in organ sparing options as well as SCRT as compared to the more traditional nLCRT and surgery(7). Ultimately, the most important endpoints for any patient are overall survival (OS) and quality of life (QOL), and all other endpoints while very important are surrogates for one or both of these. Much progress has been made incorporating HRQOL and specifically patient-reported outcomes (PROs) into clinical trials, and educational resources exist on how to do this optimally(8–10). It is incumbent on us to be rigorous in ascertaining our patients' goals, and we need to remain vigilant not to let longstanding practice patterns or biases interfere with offering patients these novel options during shared decision making. For those involved in clinical trials, optimally integrating patient-oriented outcomes into trial design must be a priority, and we must consider the acquisition of QOL data as important as any other outcome.

Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. André et al. ***NEJM 2020(1).***

Summary

Programmed death 1 (PD-1) blockade has clinical benefit in microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) tumors after previous therapy. The efficacy of PD-1 blockade as compared with chemotherapy as first-line therapy for MSI-H/dMMR advanced or metastatic colorectal cancer is unknown. KEYNOTE-177 is a phase 3, open-label trial, in which 307 patients with metastatic MSI-H–dMMR colorectal cancer who had not previously received treatment were randomly assigned, in a 1:1 ratio, to receive pembrolizumab 200 mg q3 weeks or chemotherapy (5-fluorouracil–based therapy with or without bevacizumab or cetuximab) q2

weeks(1). Cross-over was permitted at progression, and occurred in 59% of the intent-to-treat population assigned first to chemotherapy. The two primary end points were progression-free survival (PFS) and OS. For PFS, the trial had around 95% power to demonstrate that pembrolizumab was superior to standard of care (SOC) at a one-sided 2.5% alpha-level, if the underlying hazard ratio of PFS was 0.55.

After a median follow-up (from randomization to data cutoff for second interim analysis) of 32.4 months (range, 24.0 - 48.3), pembrolizumab was superior to chemotherapy with respect to PFS (median, 16.5 vs. 8.2 months; hazard ratio, 0.60; 95% confidence interval [CI], 0.45 to 0.80; P=0.0002). The estimated restricted mean OS after 24 months of follow-up was 13.7 months (range, 12.0 - 15.4) as compared with 10.8 months (range, 9.4 - 12.2). As of the data cutoff date, data on OS were still evolving, with crude OS at 63% and 55% for the pembrolizumab vs. chemotherapy groups, respectively. An overall response (complete or partial response), as evaluated with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was observed in 43.8% of the patients in the pembrolizumab group and 33.1% in the chemotherapy group. Chemotherapy resulted in 66% grade ≥3 toxicity vs 22% with pembrolizumab.

Commentary

Keynote-177 has been hailed as a potentially practice changing trial. Aside from the dramatic improvement in PFS, overall response rate (ORR), and likely OS (still not fully reported) over standard chemotherapy, this trial brings us one step forward in personalized medicine where therapies are tailored to specific biomarkers. As a very significant added bonus, pembrolizumab was also much better tolerated than standard chemotherapy so it signifies a win on all fronts.

While this is no doubt a very important publication, the results have to be placed in the appropriate context. Only 10-15% of colorectal cancers are dMMR(11). The frequency varies dramatically across other histologies, but is only 3.8% for all cancers(12). Thus, there is unfortunately a very limited number of patients that will benefit from these dramatic results. This data might be even more limited when accounting for BRAF and KRAS status -). There is also some data that dMMR colorectal cancers might have inferior responses to standard chemotherapy so part of the impressive improvement in these results might be from underperformance of the chemotherapy arm(13). It should also be noted that despite the 43.8% ORR, there actually was a higher rate of progressive disease (29.4 v. 12.3%) in the pembrolizumab arm. The PFS and OS is likely being driven by the good responders, as these patients appear to have very durable responses.

Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. Rullier et al. *Lancet Gastroenterol Hepatol 2020* (2).

SUMMARY:

GRECCAR 2 was a multi-institutional phase 3 trial that evaluated patients with T2-3 N0-N1 rectal adenocarcinoma located ≤8 cm from the anal verge who first received nLCRT, and if they achieved a good clinical response were then randomized (1:1) to either TME or LE(2). Good

clinical response was defined as ≤2 cm residual "tumor scar" as seen on pelvic MRI 6-8 weeks after nLCRT; nodal response was not considered for clinical response. Radiation therapy was prescribed to 50 Gy in 25 fractions with concurrent fluorouracil-based chemotherapy. Induction chemotherapy was not given. Patients with >4 cm maximum tumor size, anal sphincter involvement, and prior pelvic radiation therapy were excluded.

Either LE or TME was performed 8 weeks after CRT. For patients undergoing LE, a completion TME was performed 1-4 weeks later if unfavorable pathologic outcomes were present (ypT2-3, positive margin). Adjuvant chemotherapy (FOLFOX) was considered only for patients who underwent TME with positive lymph nodes although was not required; no patient who had only LE were considered for adjuvant chemotherapy. The follow-up schedule included digital rectal examination, pelvic MRI scan, endorectal ultrasound, and CT scans every 4 months for 2 years and then every 6 months up to 5 years.

The primary endpoint was a 2-year composite outcome including death, recurrence, severe toxicity, and adverse effects. These results were previously published in 2017 and included no significant differences between arms(14). Now with longer follow up, the investigators more recently published 5-year outcomes(2).

A total of 186 patients were enrolled and received nLCRT, with 148 being randomized after good clinical response. Three patients randomized to TME were excluded for various reasons, leaving 71 patients in the TME group and 74 in the LE group. Patient, tumor, and neoadjuvant therapy characteristics were well balanced. The median distance of tumor from the anal verge was 4 cm and median tumor size was 3 cm in both groups. There was a modestly higher percentage in both groups of T2 vs. T3 and N0 vs. N1 disease. Approximately one-third of patients who had LE underwent completion TME. Three patients in each arm received adjuvant chemotherapy.

The median follow-up in each arm was 60 months, and there were no significant differences in any oncologic outcome on either modified intention-to-treat (i.e. excluded patients ineligible after randomization or who withdrew consent) or as-treated analyses. Five patients in each arm developed a local recurrence (LR) after a median 12 months, with 80% occurring within 3 years. All LR were endoluminal without nodal recurrence. Seven of the 10 patients with LR were able to have curative intent salvage surgery. For the modified intention-to-treat analyses, 5-year outcomes for the LE vs. TME groups were: local control (7% vs. 7%), distant metastases (18% vs. 19%), disease-free survival (DFS) (70 vs. 72%), OS (84% vs. 82%), and cancer-specific survival (7% vs. 10%).

In post-hoc subgroup analyses of patients with good (ypT0-1) vs. poor pathologic response (ypT2-3) there were no differences in 5-year oncological outcomes. Poor response, however, was associated with a significantly higher incidence of distant metastasis (28% vs. 10%; p=0.02) regardless of the type of surgery.

COMMENTARY:

LE following nLCRT is a relatively controversial option for rectal cancer patients, supported in the recently published ASTRO rectal cancer guidelines(15) but omitted from NCCN guidelines(16). Given that rectal cancer patient-reported survey data highlight organ preservation and avoidance of a permanent stoma as a top priority, it is important to consider

this as a potential option(7). This 5-year update of GRECCAR 2 provides further support for LE, with the authors noting long-term oncologic outcomes as the primary objective of their report(2). It is reassuring that the authors did not find any differences in 5-year LR, metastatic disease, DFS, CSS, or OS for either the modified intent-to-treat or as-treated populations, with the caveat that these were secondary objectives of the original study and thus the trial was not statistically powered to detect differences in these metrics(2, 14). Although the trial was negative regarding its primary composite objective that combined oncologic with QOL outcomes, lessons learned from this longer follow-up can help us understand how to maximize the benefits of LE mainly through avoidance of excessive TME utilization.

Before randomization, it should be noted that 20% of patients were not deemed eligible for LE due to an inadequate response to CRT on restaging MRI. While size as measured by MRI might be more reproducible, poor responders could have been overcalled by MRI. Given that all LRs were endoluminal and since nodal status was not used for decision making, perhaps a "good" response on endoscopic assessment would have been more accurate to detect LE candidates. Further, there are data suggesting a full treatment response might require >3 months following CRT, so deciding on LE eligibility 6-8 weeks following CRT as was done in GRECCAR 2 might have been too soon(17).

Post-randomization, the authors clearly note that they overestimated the frequency of nodal involvement for ypT2 disease at LE, which is what determined their recommendation for completion TME(2, 14). Only 8% of all TME specimens and 8% of those with ypT2 disease had positive lymph nodes at TME. Further, the 86% CSS of the 8 ypT2 patients who declined TME led the authors to conclude that completion TME for ypT2 disease may be overtreatment. These findings are supported by key prospective nLCRT and LE trials including those by ACOSOG Z6041(18) and Lezoche et al.(19), which reported no nodal failures and excellent local control despite not requiring a completion TME for ypT2 patients. However, completion TME is fully appropriate for ypT3 disease which had 40% nodal positivity rate at TME for the GRECCAR 2 patients. These findings led the current authors to develop the ongoing GRECCAR 12. In this study, patients are randomized to plus or minus induction FOLFIRINOX before CRT with the hope of improving the LE eligibility rate and decreasing the unexpectedly high ~20% 5-year distant metastases rate in each arm of GRECCAR 2; completion TME is only recommended for patients found to be ypT3, cN+, or R1 upon LE *(NCT02514278)*. With a nearly 80% incidence of major morbidity/side effects following completion TME for CRT after LE in the initial GRECCAR 2 publication, this treatment sequence should be avoided whenever possible.

QOL metrics have been found superior with a non-operative management (NOM) approach as compared to LE following CRT(20), and with pCR rates of 40-44% in GRECCAR 2 and similar trials it appears NOM could be successful in this population(2, 18, 19, 21). Given that under half of the potential LE patients enrolled in GRECCAR 2 ultimately avoided a TME and most recurrences occur within 3 years, the 3-year organ preservation rate of 58% with CRT and consolidation chemotherapy noted for the organ preservation of rectal adenocarcinoma (OPRA) study conflicts with the authors' supposition that a planned LE approach will result in greater organ preservation than NOM(22). Although organ preservation is expected to be more common with

addition of induction FOLFIRINOX in GRECCAR 12 compared to GRECCAR 2, it should be noted that OPRA's encouraging results are in the setting of more advanced disease without the GRECCAR size and nodal disease burden constraints for eligibility. Perhaps a response-adapted approach would be best to maximize QOL for patients desiring organ preservation, with a plan for NOM in the setting of cCR, reserving LE only for those patients who don't respond fully but may have ypT1-2 disease and also have a very low risk of requiring a completion TME.

Avoidance of Overtreatment of Rectal Cancer by Selective Chemoradiotherapy: Results of the Optimized Surgery and MRI-Based Multimodal Therapy (OCUM) Trial. Ruppert et al. *J Am Coll Surg 2020(3).*

Summary:

The standard treatment for locoregionally advanced rectal cancer involves neoadjuvant radiation and chemotherapy followed by surgery. Although nLCRT has been shown to decrease the risk of LR some patients experience treatment-related side effects and may not benefit from it. The aim of this prospective multicenter observational study(3) was to evaluate the selective omission of nLCRT, based on risk as determined by MRI. The study included patients with cT2-4, any cN, cM0 histologically confirmed rectal adenocarcinoma who were candidates for total mesorectal excision (TME). Work-up included a high-resolution MRI of the pelvis. High-risk patients, defined as those with an involved or threatened (≤1mm) mesorectal fascia (MRF), cT4 disease, or those with cT3 disease of the lower rectum (<6 cm from the anal verge), underwent nLCRT while all others underwent primary surgery. Neoadjuvant LCRT consisted of 50.4 Gy in 28 fractions using 3-D conformal radiation therapy with concurrent fluorouracil administered during weeks 1 and 5 (1000 mg/m2/day). The primary endpoint was 5-year LR rate, and secondary endpoints included circumferential resection margin involvement, quality of TME, frequency of intraoperative local tumor cell dissemination, distant metastasis (DM) rate, OS and DFS, and toxicity.

Of the 1,093 patients included in the study, 878 (80.3%) were treated according to protocol of which 526 (59.9%) underwent primary surgery and 352 (40.1%) underwent nLCRT followed by surgery. With a median follow-up of 61 months (range 0-147 months), the 3-year LR rate was 3.3% (95% CI 2.1-4.5%) for the entire cohort. Among those treated per protocol, the 3-year LR rate was 3.1% (95% CI 1.9-4.3%). The LR rate of patients treated with primary surgery was 2.2%, which was significantly lower than that of higher risk patients treated with nLCRT followed by surgery (4.3%; p=0.045). On multivariate analysis, predictors for LR among those who had undergone primary surgery included disease of the lower rectum and having undergone intersphincteric resection or a Hartmann procedure. Among those who had undergone nLCRT followed by surgery, predictors of LR were pN2 disease, and resection within the muscularis propria plane. The 3-year DM rate among patients treated per protocol was 17.0% (95% CI 14.5-19.5%), and was significantly higher for the higher risk nLCRT cohort (23.7% 95% CI 19.2-28.2%) compared to lower risk patients who had primary surgery (12.5% 95% CI 9.6-15.4%; p<0.001). Of note, in patients who underwent primary surgery, 27.3% of those thought to be Stage II or III were pathologic stage I and were thus overstaged. In patients who had MRI

findings consistent with no MRF involvement, only 2.2% of patients treated with primary surgery had an involved MRF.

Commentary:
MRI is the preferred modality for rectal cancer locoregional staging and to assess features such as threatened MRF that portend increased LR risk(15, 23–25). The OCUM trial supports the paradigm that rectal cancer treatment may be individualized according to MRI assessed risk, and supports omission of nLCRT for select lower risk patients. Although 5-year LR outcomes are not yet reported for the primary study endpoint, the currently reported 3-year LR rate of 2.2% for patients undergoing primary surgery is encouraging and suggests appropriate MRI-based selection for omission of nLCRT. While a significant proportion of patients (31%) in the primary surgery cohort had clinical stage I disease and based on current guidelines would not be recommended for neoadjuvant therapy(15), the 3-year LR rates reported for patients found to have pT3 (2.4%) or pN1 (1.8%) disease after primary surgery were reassuringly low. A primary surgery approach does not appear to be justified for patients with lower-third tumor location (3-year LR 7.7% for patients treated per protocol with primary operation). Although clinical nodal stage was not used for treatment selection, the observed 3-year LR rate of 5.5% for patients with pN2 disease after primary surgery supports consideration of nodal assessment for nLCRT selection. The authors note a significantly higher LR and DM risk for the nLCRT cohort compared to the primary surgery cohort, which consistent with the high risk criteria used to select patients for the nLCRT cohort.

Neoadjuvant rectal cancer therapies have recently become both increasingly risk- and response-adapted. Use of a TNT approach increases tumor downstaging(26) and may improve oncologic outcomes(27) which is of particular importance for patients with risk features portending increased LR risk, and recent studies including RAPIDO(4) and PRODIGE 23(28) demonstrate lower recurrence risk for differing TNT approaches compared to nLCRT. Multiple studies(29) including recently reported data from the organ preservation of rectal adenocarcinoma (OPRA) trial(22) support consideration of NOM for patients who achieve a complete clinical response (cCR). Although neither TNT nor NOM were a component of the OCUM study, it is plausible that a significant proportion of patients in the higher risk nLCRT arm may have derived benefit from TNT. Although the OCUM study results suggest that patients with favorable risk features may avoid nLCRT in favor of primary surgery, results from OPRA suggest that a majority (58%) of patients with MRI stage II/III rectal cancer may preserve their rectum at 3-years with a LCRT and concurrent chemotherapy followed by consolidation chemotherapy TNT approach. Future studies incorporating patient reported outcomes with detailed HRQOL endpoints will be required to determine the relative HRQOL benefit for omission of nLCRT with inclusion of surgery versus possible omission of surgery in the context of NOM. Results of the PROSPECT trial (*NCT01515787*) will provide additional data regarding the role of selective use of nLCRT for lower risk patients.

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. Bahadoer et al. ***Lancet Oncol 2020(4).***

Summary: Patients with locally advanced rectal cancer treated with preoperative chemoradiation and adjuvant chemotherapy are more likely to suffer distant recurrence relative to locoregional failure. There has been emerging interest in delivering full dose, systemic chemotherapy in the neoadjvant setting as part of TNT with hopes of reducing distant metastases. The RAPIDO trial was a multi-center, phase III randomized trial of 920 patients evaluating an experimental arm of SCRT (5 Gy x 5 fractions) followed by FOLFOX/CAPOX chemotherapy prior to surgery compared to the standard arm of nLCRT (50.4 Gy with concurrent flouropyrimidine) followed by surgery and selective adjuvant chemotherapy as indicated by participating centers(4). Investigators have previously reported toxicity analyses which revealed no difference in ≥ grade III Clavien-Dindo postoperative complications between the two arms for all patients or those with a primary anastomosis(30). The current paper reviews the primary efficacy analysis. The primary endpoint was 3-year disease related treatment failure (DrTF) defined as distant metastases, locoregional recurrence, new primary colorectal cancer, or treatment related death. Patients were eligible with at least one high risk feature including T4a/b disease, extramural vascular invasion, N2 disease, mesorectal fascia involvement, or enlarged extra-mesorectal pelvic lymph nodes. In the SCRT/chemotherapy arm, patients received either 6 cycles of CAPOX or 9 cycles of FOLFOX with planned surgery 2-4 weeks following completion of chemotherapy. In the standard arm, patients underwent surgery 8 weeks following neoadjuvant LCRT. The median time from radiation to resection was 25.5 weeks in the SCRT/chemotherapy arm compared to 15.9 weeks in the standard arm. Adjuvant chemotherapy was utilized at the discretion of the treating center and occurred in 41% of those in the standard arm.

Rates of R0 resection were 90.5% in both arms. A greater proportion of patients achieved a pathologic complete response (pCR) in the SCRT/chemotherapy arm compared to the standard arm (28% vs 14%; p<0.0001). There was an absolute reduction of DrTF of ~7% in the SCRT/chemotherapy arm compared to the standard arm (3-year cumulative probability of 30.4% [95% CI: 26.1–34.6] vs 23.7% [95% CI: 19.8–27.6]; p=0·019). The overall difference in DrTF was driven largely by a reduction of distant metastases in the experimental arm. The cumulative incidence of distant metastases was lower in the SCRT/chemotherapy arm relative to the standard arm at 3 years (20.0% [95% CI: 16.4–23.7] vs 26.8%[95% CI 22.7-30.9]; p=0.005). No significant differences in were observed in the SCRT/chemotherapy arm compared to the standard arm for 3 year locoregional failure (8.3% vs 6.0%; p=0.12) or 3 year OS (89.1% vs 88.8%; p=0.59). Serious adverse events occurred in 38% of nSCRT patients, similar to the 34% of nLCRT patients reported regardless of receipt of adjuvant chemotherapy.

COMMENTARY

In rectal cancer, two of the most important oncology questions are 1) the equivalence of SCRT to LCRT in terms of local disease control and toxicity and 2) the value of TNT over standard treatment with neoadjuvant chemoradiotherapy and adjuvant chemotherapy. The RAPIDO trial incorporates both of these issues in an International multicenter randomized trial which

challenges a long-held standard of care for rectal cancer. The trial was designed to see if TNT with SCRT could reduce disease-related treatment failure at 3 years compared with standard chemoradiotherapy prior to surgery. The endpoint was adjusted after one year of trial accrual because of the perceived inappropriateness of using DFS in a population of patients who are not disease free at randomization and some of whom will never achieve this status. The amended endpoint is rather an include-all, and as such may be a rather blunt instrument, which incorporates distant, loco-regional failure as well as new primary colorectal tumor or treatment related death. However, the trial does also report on more specific secondary endpoints, such as distant metastases, pathological complete response rate and R0 resection. Not only did the primary endpoint change during the course of the trial but also, as a result of sequential interim analyses, it became obvious that the required number of events was never going to be reached. Therefore, rather than looking for a decrease in events from 50% to 40%, the newly incorporated levels required a reduction from 30% to 22.5%. The evolution of trial design, although somewhat unusual, was approved by the medical ethics committee and data safety monitoring board at each point.

After 3 years the cumulative probability of disease-related treatment failure was 23.7% in the nSCRT group versus 30.4% in the nLCRT group. Regarding toxicity, although the rate of Grade 3 events is not reported as a percentage of the entirety of each group, the authors did note that severe side effects were comparable between the cohorts regardless of the receipt of adjuvant chemotherapy. On the basis of this, the authors' interpretation is that this reduction is indicative of the increased efficacy and completion rate of preoperative chemotherapy compared to adjuvant chemotherapy, and that therefore the experimental arm can be considered as a new standard of care in high-risk locally advanced rectal cancer.

This is certainly an interesting and potentially practice changing result and is in keeping with current thinking(31, 32). One or two cautions deserve consideration. Staging was allocated on the basis of MR imaging at baseline. However, there was no central review although the protocol specified reporting on complex MR features such as extramural vascular invasion, extramural spread, and nodal involvement. As the authors point out in the discussion, this may have led to either under or over-staging, although the latter is more probable(33). The high level cN1-2 status (91% in the experimental group and 93% in the standard group) is suggestive of such over staging, as is the level of detection of enlarged (presumed involved) lateral lymph nodes. The pathological yield of involved nodes was very much lower (25% experimental arm versus 32% standard arm) and although resolution of nodes can be expected post treatment, the high ypN0 rate seems unlikely with around 75% of nodes having resolved completely. This raises the possibility that the patients included in the trial may not have been as high-risk as expected. This

could lead to an overestimation of the observed pCR rate in true node positive patients, and suggests some caution about applying this approach to other confirmed high risk groups.

The other issue worth noting is the use of adjuvant chemotherapy, particularly for the standard of care group. Adjuvant chemotherapy was given at the discretion of hospital policy, and therefore whereas all nSCRT patients were offered 4.5 months of consolidation chemotherapy as part of TNT, only 41% of the institutions involved typically offered adjuvant chemotherapy. In the experimental arm, 15% of patients stopped chemotherapy prematurely. Although only 10% of the standard patients stopped chemotherapy prematurely during nLCRT, over one third of standard patients discontinued adjuvant chemotherapy. The authors elegantly point out the problems of delivering adjuvant therapy, and this is widely acknowledged. While meta-analyses have failed to show improved OS with adjuvant chemotherapy following nLCRT and surgery (34), there may be subsets of patients (e.g. LMVI) who might benefit(35).

Notwithstanding these issues, RAPIDO found that TNT, incorporating SCRT, is an efficient and effective way to deliver therapy upfront and there was no increase in severe side effects vs. nLCRT. In theory, TNT could result in some patients with little or no response to treatment being disadvantaged by delaying time to surgery, although this has not yet been demonstrated by studies including the recently presented PRODIGE 23 study which also demonstrated a benefit to TNT(28). It is reassuring that most local and distant recurrences occur within the first 5 years and at a median follow-up of 4.6 years for RAPIDO, the current data should reveal most recurrences(36). The comparable efficacy and toxicity of nSCRT vs. nLCRT has been noted in other trials comparing the two modalities, and it is important to note that as the duration of consolidation chemotherapy has increased following nSCRT, so has the pCR rate(37–41). This finding combined with data from OPRA has implications for TNT study design when considering SCRT within the context of NOM, and evaluation of SCRT with consolidation chemotherapy is currently underway in the Non-Operative Management and Early Response Assessment in Rectal Cancer (NOM-ERA) study (*NCT03904043*).

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