RAPIDO: Sprint ahead with short course radiotherapy or not so fast?

Since the early 2000's, the standard of care management for patients with locally advanced rectal cancer included either pre-operative long-course chemoradiation (LCCRT) or short-course radiotherapy (SCRT) followed by surgery with the delivery of post-operative chemotherapy based upon clinical and pathologic risk factors. Such an approach was associated with favorable rates of R0 resection and locoregional recurrence (LRR) of approximately 5-10%. Multiple trials have compared pre-operative LCCRT vs. SCRT [1, 2]. The Trans-Tasman Radiation Oncology Group (TROG) 01.04 trial and the Polish Trial compared 50.4 Gy in 28 fractions with concurrent 5-fluoruracil (5-FU) followed by surgery 4-6 weeks later vs. 25 Gy in 5 fractions with immediate surgery. Each study demonstrated comparable rates of LRR, disease-free survival, and overall survival for each radiotherapy regimen. Despite favorable pelvic control, the competing risk of distant metastasis by 3-5 years has remained approximately 25-30%, thus suggesting the need for novel strategies targeted at reducing this risk. One such approach has been to intensify the pre-operative regimen with the delivery of total neoadjuvant therapy (TNT) including both radiotherapy and systemic therapy prior to surgery [3, 4].

The RAPIDO Trial included 920 patients with rectal cancer and high-risk features of cT4, extra-mural venous invasion (EMVI), cN2, compromised mesorectal fascia (MRF), or extra-mesorectal/lateral pelvic lymph nodes and compared pre-operative LCCRT with post-operative chemotherapy delivered to 42% at investigator discretion vs. a SCRT-TNT regimen of SCRT followed by either 9 cycles of FOLFOX or 6 cycles of capecitabine and oxaliplatin (CAPOX) [3, 5]. SCRT-TNT was associated with improvement in pathologic complete response (28% vs. 14%) and the primary endpoint of 3-year disease-related treatment failure (DrTF), a composite end-point of rectal cancer recurrence, treatment-related death, or new colon primary cancer, primarily through a reduction in risk of distant metastasis, 20% vs. 27%. There was no difference in overall survival, and per the initial report, no difference in LRR, 8% vs. 6% (p=0.12) for the TNT and LCCRT arms, respectively.

A recently published 5-year update of the RAPIDO trial evaluated the planned secondary endpoint of locoregional failure (LRF) incorporating both early locoregional failure (eLRF) amongst patients who either did not have surgery or underwent R2 resection (3% of patients) and LRR amongst those who underwent R0 or R1 resection (97% of patients) [5]. Amongst the overall cohort as analyzed per intent-to-treat, there was not a significant difference in LRF, 11.7% vs. 8.1% (p=0.07) for SCRT-TNT vs. LCCRT, respectively. Amongst the subset of patients who underwent R0 or R1 resection, SCRT-TNT was associated with a higher rate of LRR, 10.2% vs. 6.1% (p=0.027). In addition to treatment allocation (SCRT-TNT vs. LCCRT), involved lateral pelvic lymph nodes were also associated with LRR on multivariate analysis.

It is not immediately clear why there were more LRR in the SCRT-TNT arm than the LCCRT arm, which has both statistical and clinical implications. Although LRF amongst the overall cohort was a planned secondary end-point, LRR amongst the R0 or R1 subset was an unplanned post-hoc subset analysis. Additionally, there were changes in the study primary

endpoint (from disease free survival to DrTF) and sample size calculations prior to completion of accrual and it is unclear if or how the changes affected power to evaluate LRR. Finally, some may propose that a 4% difference in LRR is of marginal clinical significance against a backdrop of lower rate of distant metastasis , equivalent overall survival, significant increase in convenience, and reduced financial toxicity for SCRT-TNT.

What could explain the difference in LRR? From a clinical perspective, baseline disease characteristics including cT4, cN2, enlarged lateral pelvic lymph nodes, EMVI, involved MRF, and proportion with tumors less than 5 cm from the anal verge were similar between treatment arms. Most metrics of local tumor response were improved with SCRT-TNT, including "good response" radiographically (80.1% vs. 70.1%) and pathologically (93.0% vs 87.3%), factors which were associated with lower LRR (6.8% vs. 12% and 6.9% vs. 16.9%, respectively). There were no significant differences in type of operation with LAR (48.6% vs. 47.5%) and APR (35.0% vs. 40.0%) in the SCRT-TNT and LCCRT arms, respectively. However, amongst those who had LRR, there was both a greater proportion who underwent LAR and a higher proportion of anastomotic recurrence in the SCRT-TNT vs. LCCRT arm suggesting the possibility that the use of sphincter-sparing operations tailored per tumor response may have increased the risk of microscopic residual disease.

SCRT-TNT was associated with a higher risk of mesorectum breach compared with LCCRT (11% vs. 6%, p=0.022), and amongst the subset with a breached mesorectum, LRR was more common in the SCRT-TNT group (21% vs. 4%, p=0.053). These data are consistent with prior studies suggesting that total mesorectal excision (TME) quality is associated with LRR [6, 7]. The question becomes- was this a surgical quality issue unrelated to pre-operative intervention or is it possible that SCRT-TNT with both heightened dose per fraction and a longer interval after SCRT was associated with tissue fibrosis that made surgical resection more challenging thus increasing the risk of mesorectum breach?

The authors also suggest an association between LRR and treatment with 3D conformal radiotherapy (3D-CRT) vs. intensity modulated radiotherapy (IMRT). The use of 3D-CRT (68.6% vs. 73.7%) and IMRT (31.2% vs. 26.3%) were similar between the LCCRT and SCRT-TNT cohorts. Amongst the subset treated with 3D-CRT, LRR was more common in the SCRT-TNT vs. LCCRT cohorts, 11.6% vs. 6.0%, p=0.016. In contrast, amongst the subset treated with IMRT, LRR rates were similar in each treatment group (6.3% vs. 6.2%). Notably, this analysis was performed assuming time-independence with a chi-square analysis rathan than with survival methodology. Because the authors made these assumptions and reported sufficient detail of patient characteristics to reconstruct a limited data set, we performed additional exploratory multivariate logistic regression analyses to assess the association between treatment allocation and radiotherapy technique (3D vs. IMRT) with LRR. Our exploratory analysis suggested that SCRT-TNT was associated with LRR (OR: 1.73, 95% CI: 1.05-2.87, p=0.033). However, in contrast to the published chi-square analysis, the use of 3DCRT was not associated with LRR (OR: 1.43, 95% CI: 0.79-2.59, p=0.238) nor was there a significant interaction between treatment cohort and RT technique (p=0.264).

The authors findings, however, do call for additional consideration. At first glance, a geographic miss or increased risk of marginal recurrence may be more likely with IMRT versus 3DCRT as IMRT requires careful target delineation and planning as it delivers radiation more conformally to the target. The study finds the opposite, however, with patients who underwent 3DCRT having significantly higher rates of LRR and in particular, anastomotic recurrence centrally in the target. If accepting RT technique as correlated with LRR, one possible explanation may have been the use of fixed anatomic landmarks for 3CRT planning, making the risk of a geographic miss higher. Further RT quality analysis is needed to help clarify this finding.

Although the authors offer several hypotheses for the higher LRR in the SCRT-TNT arm, one possibility not explicitly discussed is the lower radiation dose with SCRT. Using an alpha/beta ratio of 10 Gy for tumor, the biologically effective dose of SCRT is 37.5 Gy, more than 20% lower than that of long course chemoradiation (50 Gy). Could the lower dose have translated into more LRR despite a higher rate of pathologic complete response? Critics of this explanation would point to the pre-TNT era randomized studies comparing LCCRT vs. SCRT that showed no difference in LRR between the two strategies [1, 2]. However, in looking at the details of the Polish and TROG trials, there did appear to be local endpoints that were worse with SCRT. In the Polish trial, the SCRT group had higher rates of R1 resection (13% vs. 4%), non-reversed stomas (20% vs. 11%), and late stoma creation due to worse anorectal function or morbidity (9% vs. 4%) as compared to LCCRT. In the TROG study, a subgroup analysis showed higher rates of LRR for distal tumors with SCRT (13% vs. 3%). Although these were unplanned subset analyses that were not statistically significant, they raise a concern for a potential detriment with SCRT that could potentially be detected in a larger sample size and/or a higher risk rectal cancer subgroup. With that background in mind, the RAPIDO trial, with close to 1000 patients (3 times the number of the POLISH and TROG studies) each with high-risk disease, further supports the signals of worse LRR rates associated with SCRT in select patient subsets, acknowledging it is not possible to uncouple possible impact of SCRT with that of a TNT approach.

Should this update to the RAPIDO trial lead to refinement of patient selection for SCRT in the context of TNT? Acknowledging that DrTF was lower in the SCRT-TNT group even accounting for LRR, and with multiple trials that pre-dated the TNT era showing similar rates of LRR between SCRT and LCCRT, we can not be sure that LCCRT would have reduced the LRR rate in the RAPIDO SCRT-TNT arm [1, 2]. As our field moves towards greater use of risk stratification for neoadjuvant therapy choice, including possible omission of RT for MR-low risk disease, SCRT remains an important consideration. We encourage practitioners to consider multiple risk factors in assessing LRR (presence of T4 disease, threatened MRF, lateral or extramesorectal lymph nodes, low tumor <5cm from anal verge) when deciding between SCRT or LCCRT [8-12]. One such strategy for total neoadjuvant therapy that balances risk factors for local versus distant recurrence in use at University of Colorado is shown in Table 1, with other risk adapted strategies having recently been proposed [13, 14]. Given the results of the RAPIDO trial, for patients with multiple high risk features for LRR, LCCRT may be preferred. Finally, it is important to delineate at treatment outset if the goal is watch and wait (W&W); W&W was not addressed by RAPIDO which evaluated TNT with operative management. For patients under

consideration for W&W, a greater volume of evidence currently exists for LCCRT, with SCRT not yet having been directly compared to LCCRT in this setting. The currently accruing ACO/ARO/AIO-18 trial, which randomizes patients to TNT regimens of SCRT vs. LCCRT followed by chemotherapy will hopefully bring much needed clarity to this decision.

Figure 1: Risk-adapted total neoadjuvant therapy approach for patients with cT3+ or N+ Rectal Cancer per University of Colorado

Local Risk Features present	Distant Risk Features Present	Watch and Wait Motivated	Treatment
Any	Yes	Any	SCRT→ chemotherapy
Yes	No	Any	LCCRT→ chemotherapy
No	No	Yes	LCCRT→ chemotherapy
No	No	No	SCRT→ chemotherapy
Local Risk Features: T4, EMVI+, MRF threatened, < 5 cm from anal verage, extramesorectal or lateral pelvic lymph nodes			
Distant Risk Factors: T4, N2, extramesorectal or lateral pelvic lymph nodes or high/common iliac lymph nodes, non-specific M1 imaging			

References

1. Bujko, K., et al., *Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer.* Br J Surg, 2006. **93**(10): p. 1215-23.
2. Ngan, S.Y., et al., *Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04.* J Clin Oncol, 2012. **30**(31): p. 3827-33.
3. Bahadoer, R.R., 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**(1): p. 29-42.
4. Conroy, T., et al., *Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial.* Lancet Oncol, 2021. **22**(5): p. 702-715.
5. Dijkstra, E.A., et al., *Locoregional Failure During and After Short-course Radiotherapy followed by Chemotherapy and Surgery Compared to Long-course Chemoradiotherapy and Surgery - A Five-year Follow-up of the RAPIDO Trial.* Ann Surg, 2023.

6. Kitz, J., et al., *Association of Plane of Total Mesorectal Excision With Prognosis of Rectal Cancer: Secondary Analysis of the CAO/ARO/AIO-04 Phase 3 Randomized Clinical Trial.* JAMA Surg, 2018. **153**(8): p. e181607.
7. Quirke, P., et al., *Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial.* Lancet, 2009. **373**(9666): p. 821-8.
8. Battersby, N.J., et al., *Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study.* Ann Surg, 2016. **263**(4): p. 751-60.
9. Bhoday, J., et al., *How Should Imaging Direct/Orient Management of Rectal Cancer?* Clin Colon Rectal Surg, 2017. **30**(5): p. 297-312.
10. Lord, A.C., 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**(6): p. 793-801.
11. Ruppert, R., et al., *Oncological outcome after MRI-based selection for neoadjuvant chemoradiotherapy in the OCUM Rectal Cancer Trial.* Br J Surg, 2018. **105**(11): p. 1519-1529.
12. Siddiqui, M.R.S., et al., *A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases.* Br J Cancer, 2017. **116**(12): p. 1513-1519.
13. Bedrikovetski, S., et al., *Personalized total neoadjuvant therapy versus chemotherapy during the 'wait period' versus standard chemoradiotherapy for locally advanced rectal cancer.* ANZ J Surg, 2022.
14. Hui, C., et al., *Neoadjuvant Therapy in the Post-German Rectal Trial Era: Making Sense in the Absence of Consensus.* Pract Radiat Oncol, 2023. **13**(1): p. e54-e60.