



Commentary

TNT in rectal cancer may not be the new testament?

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It's often refreshing, when a study questions the current direction of travel and the current growing clinical practice. The present study by Zhu and colleagues published in *EClinicalMedicine* [1] uses retrospective data from the National Cancer Database to compare outcomes after neoadjuvant long course chemoradiation (LCCRT) alone or combined with neoadjuvant systemically active chemotherapy – so called 'total neoadjuvant therapy' (TNT) – in locally advanced rectal cancer (LARC). The authors analysed data from 372 TNT patients and 707 LCCRT patients with cT3/4 or node positive disease using a 2:1 propensity matching. Data for disease free survival (DFS) was not available. Interestingly, despite the use of multivariate and propensity-based matching to minimise the potential biases which retrospective data often entails, the 5-year overall survival (OS) rates for TNT and LCCRT alone were not significantly different – 73.6% vs. 78.5% ($p=0.20$) respectively. TNT was associated with slightly higher pCR and CRM negative rates, which were not statistically significantly different. The high pCR rate possibly reflects additional chemotherapy, but could be explained by the effect of an extended time period from completion of radiation to surgery. There are many limitations to this study, which are acknowledged in the discussion, but almost certainly the strategy of TNT currently overtreats some patients.

Despite all the advances in imaging, surgical technique and the delivery of more precise radiotherapy in LARC, about 20–30% of patients still subsequently develop distant metastases. Hence, induction or consolidation chemotherapy with LCCRT has been investigated and promoted mainly to counter distant metastases [2,3,4]. Many Radiation oncologists have also enthusiastically endorsed TNT because by enhancing CCR rates, it may increase the number of patients eligible for organ preserving strategies [4].

The TNT approach represents a pragmatic solution to the problems of consistently delivering adjuvant chemotherapy postoperatively within a reasonable timeframe and administering appropriate and sufficient doses, which has often compromised adjuvant chemotherapy trials in LARC which use oxaliplatin [5]. Substantial shrinkage in the size of very advanced primary tumours as a result of TNT may also increase the chance of a curative resection and reduce the need for performing multi-visceral resection, which in turn is likely to impact favourably on the rate and severity of Clavien-Dindo surgical morbidity.

In historical studies induction chemotherapy is reported to achieve high levels of down-staging and pCR rates without compromising compliance with chemoradiation. More recent randomised phase II studies suggest induction does to some extent affect compliance to chemoradiation [2,6].

In the USA 4 months of neoadjuvant FOLFOX is now a standard preoperative strategy for patients considered high-risk [7]. This up-front chemotherapy can be assessed in terms of response, and either modify or obviate the need for postoperative adjuvant chemotherapy with its well-recognized poor uptake and woeful compliance rates, which have been consistently reported in randomised trials. Many now consider a 'blanket' TNT tri-modality approach as the standard of care, and indeed this strategy with 8 cycles is used in the NRG-GI002 Clinical Trial Platform NCT02921256.

This rationale for TNT is partly supported by the high pCR rates achieved with increasing sequential courses of FOLFOX following CRT within the Timing of Rectal Cancer Response to Chemoradiation study [8]. But here is the rub. There is no randomised evidence that TNT improves long-term oncological outcomes. Claims from this data for an improvement in DFS should be treated cautiously [9]. This trial was prospective but not randomized. 'Familiarity breeds contempt' – in that the threshold for offering TNT gets lower as experience grows and earlier stage patients are then treated. So this improvement in pCR and DFS may simply reflect the fact that earlier stage patients may have been recruited in later cohorts. Although the pCR increased, earlier assessments of

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this ‘Timing Trial’ did not imply that overall down-staging was enhanced for the whole trial population [10].

Almost all studies on TNT are retrospective from single institutions in highly selected patient populations. Only a single prospective randomised study comparing TNT to LCCRT alone has been published [2], which despite much better compliance for induction chemotherapy compared to postoperative adjuvant chemotherapy, did not demonstrate improvements in DFS or OS.

Yet, patients with stage II rectal cancer, are unlikely to benefit in terms of an improvement in survival from chemotherapy (based on postoperative adjuvant studies in colon cancer. Hence the use of TNT risks a small but unnecessary chemotherapy-related mortality (approximately 0.5%) from FOLFOX or XELOX in these patients as well as the associated burden of potential long-term toxicity effects from oxaliplatin.

Many questions remain. Which component should come first—the chemotherapy or the LCCRT? The CAO/ARO/AIO-12 randomized phase II clinical trial [6] tested two arms with induction followed by LCCRT versus LCCRT followed by consolidation. The aim was to identify the most effective sequence to move to a phase III trial. Their conclusions suggest they are proceeding with a trial investigating consolidation chemotherapy

So, should we adopt a ‘blanket’ use of TNT in patients with LARC? I would agree with the authors perceptive comment “our data suggests awaiting definitive randomized trial results showing a clear benefit for TNT before its routine use in all patients with LARC”

Author Contribution

RGJ is the sole author who performed literature search, figures, study design, data collection, data analysis, data interpretation, and writing.

Declaration of Competing Interest

RGJ has received personal fees for Advisory boards for Servier, Bristol Myers Squibb, Eisai

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