Author/s:
Warrier, S;Kong, JC;Waters, P;McCormick, J;Heriot, A

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Kong Joseph (Orcid ID: 0000-0002-1392-2480)
Waters Peadar (Orcid ID: 0000-0003-2947-9206)
Heriot Alexander (Orcid ID: 0000-0001-9846-8776)

Title: Is it time to deliver additional chemotherapy upfront in our rectal cancer patients? A shifting paradigm

Satish Warrier,[1-3] Joseph Cherng Kong,[1-3] Peader Waters,[1-2] Jacob McCormick,[1-2] Alexander Heriot[1-3]

[1]Division of Cancer Surgery, [2]Division of Cancer Research, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

[3] Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia

Correspondence: Dr Joseph Cherng Kong, Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria, 3000, Australia, e-mail: joekong@gmail.com

At the recent American Society of Clinical Oncology (ASCO) meeting, some potentially landmark oncological data were delivered. The three papers of interest were the RAPIDO trial,[1] the PRODIGE 23 trial,[2] and the OPRA study.[3] Whilst these three studies appear to be telling different stories and their study designs appear to vary, the results at least prior to publication seem to deliver a similar narrative. These studies have the potential to shift the oncological landscape for neoadjuvant therapy in rectal cancer.

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Ever since Heald's popularisation and dissemination of TME, in combination with up front chemo-radiation, local recurrence (LR) has been less of an issue for rectal cancer patients. However, despite best attempts at multidisciplinary care a similar impact on disease free survival (DFS), or distant recurrence (DR) has not been seen with the addition of adjuvant therapy. Despite multiple RCTs showing a lack of benefit,[4-6] many international society guidelines recommend adjuvant therapy in patients who have positive lymph nodes, perhaps an extrapolation from studies showing a benefit in adjuvant therapy for colon cancer.[7,8]

The concept of giving neoadjuvant chemotherapy is not completely novel and was born partly from an additional time delay sought to improve pathological response rates following the completion of conventional chemoradiation therapy. In many centres the time delays had been pushed out to 10 to 12 weeks as a result of early oncological publications focused on timing of resection.[9] The attraction of having chemotherapy delivered upfront can make a lot of sense, particularly in an oncological high risk group of rectal cancer patients, that are prone to distant relapse. These patients include advanced T3 or T4 tumours , extramural venous invasion (EMVI), a threatened CRM or a lateral pelvic sidewall node positivity on pre-treatment structural imaging.[1] Such a proactive chemotherapy first strategy in theory was felt to prevent or eradicate micro-metastatic disease, minimise the length of time a patient may have an ileostomy following TME surgery and or potentially select out patients who may be a candidate for an organ preservation approach. The data to support this strategy whilst still maturing and mainly constituting nonrandomised studies has been promising.[10]

The first of the papers to be discussed at the ASCO meeting was the PRODIGE 23 study. The study randomised 2 groups of locally advanced rectal cancer (LARC) cohorts of approximately 230 patients to either standard therapy or the interventional arm (TNT). The standard arm involved long course chemoradiation with capecitabine followed by surgery (TME) and then adjuvant chemotherapy. The TNT arm included chemotherapy upfront (FOLFIRINOX therapy) for 6 cycles and then long course chemoradiation followed by surgery and completion chemotherapy. The TNT arm was surprisingly well tolerated, with clear benefits in pathological response including complete response (27.8 percent versus 12 percent), and 3-year disease-free survival (DFS, 75.7% vs 68.5%). Global QOL scores also seemed to favour the interventional arm of the study.

The second paper, the RAPIDO study again had an interventional arm that had neoadjuvant chemotherapy, but this time with short course radiation therapy. The standard arm included LCCRT and then TME surgery (6-10 weeks), whilst the experimental arm included SCRT and then FOLFOX or CAPOX chemotherapy prior to TME surgery (20-22 weeks). A 3-year DFS rate of 69.6% was seen with conventional therapy whilst a 76.1% DFS was seen in the interventional arm. Again, the complete pathological response rate was doubled (14 to 28%). Local relapse whilst not statistically significant was 8.7% compared with 6% in the standard arm; perhaps possibly food for thought in considering the omission of long course chemoradiation entirely from the protocol in patients that may require downstaging for low coloanal reconstructions.

The third study presented were the preliminary results of the Organ Preservation in Rectal Cancer (OPRA) trial. The hypothesis generated by the research group and led by Memorial Sloan Kettering Surgeon Julio Garcia Aguilar is that a treatment algorithm which includes watch and wait therapy in a TNT program would outperform conventional historical control arms of LCCRT and then TME surgery. Three hundred and twenty-four patients were randomised to either of the interventional arms: induction chemotherapy and then standard LCCRT or alternatively to LCCRT and then consolidation chemotherapy. Like the 2 previous studies, a 3-year DFS of 77 and 78% respectively were seen in the treatment groups. Of note, the consolidation chemotherapy arm appeared to provide a significantly better chance of organ preservation compared with the induction chemotherapy.

For rectal cancer patients each of these studies represented a major shift to our conventional treatment algorithm. These studies potentially provide a compelling story to consider more chemotherapy prior to TME surgery and emphasise the importance of multidisciplinary care in its' management. They do not resolve the issue of whether to give short course radiation therapy or long course chemoradiation therapy, but also seem to say in select centres where a watch and wait strategy exists good DFS data is possible, perhaps with the addition of chemotherapy prior to considering TME surgery. While many multidisciplinary meeting discussions will grapple with the generalisability and how practice changing this data is, it seems at the very least clear that LCCRT followed by a TME approach for high risk rectal cancer patients is potentially selling our patients short. There is a real risk of leaving at least 7 percent of these patients undertreated. Surgeons just like their oncological colleagues will have

to evaluate how and when to integrate this data into a new standard of care, perhaps following the publication of these studies and appropriate scrutiny that they will no doubt receive.

Referral

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