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Personalized total neoadjuvant therapy versus chemotherapy during the 'wait period' versus standard chemoradiotherapy for locally advanced rectal cancer

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Key words

clinical complete response, pathological complete response, preoperative chemotherapy, rectal cancer, total neoadjuvant therapy.

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Abstract

Background: This study aimed to compare current treatment response rates with personalized Total Neoadjuvant Therapy (pTNT), against extended chemotherapy in the 'wait period' (xCRT) and standard chemoradiotherapy (sCRT) with adjuvant chemotherapy for rectal cancer.

Methods: This was a multicentre retrospective cohort analysis. Consecutive patients with rectal cancer treated with pTNT over a 3.9-year period were compared to a historical cohort of patients treated with xCRT or sCRT as part of the published WAIT Trial. pTNT patients received 8 cycles mFOLFOX6 or 6 cycles CAPOX in the neoadjuvant setting (no adjuvant treatment). Patients in the WAIT Trial received either 3 cycles 5-FU/LV during the 10-week wait period after chemoradiotherapy or standard chemoradiotherapy, followed by adjuvant chemotherapy. The primary endpoint was overall complete response (oCR) rate defined as the proportion of patients who achieved either complete clinical response (cCR) or pathological complete response (pCR).

Results: Of 284 patients diagnosed with rectal cancer during the 3.9-year period, 107 received pTNT. Forty of these were matched with 49 patients from the WAIT Trial (25 received xCRT and 24 received sCRT). There was a significant difference in oCR between the groups (pTNT $n = 21$, xCRT $n = 6$, sCRT $n = 7$, $P = 0.043$). Of the patients that underwent surgery, pCR occurred in 13 patients with no significant difference between groups ($P = 0.415$). There were no significant differences in 2-year disease-free survival or overall survival.

Conclusion: Compared with sCRT and xCRT, pTNT results in a significantly higher complete response rate which may facilitate organ preservation.

Introduction

The current standard treatment regimen for patients with locally advanced rectal cancer (LARC) consists of neoadjuvant chemoradiotherapy (sCRT) followed by surgical resection with total mesorectal excision (TME) and adjuvant chemotherapy.[1] While this multimodal approach has significantly reduced local recurrence from 30% to less than 5%, distant recurrence occurs in approximately 30% of patients and remains the leading cause of cancer-related death in LARC patients.[2,3] The role of adjuvant chemotherapy remains controversial, as studies have not demonstrated a significant improvement in disease free survival (DFS) or overall

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survival (OS). This is likely due to poor compliance, delays from time of diagnosis to commencement of adjuvant chemotherapy and suboptimal chemotherapy dosing.[4,5] A 4-week delay in adjuvant treatment has been associated with a 14% decrease in OS.[6,7]

Total Neoadjuvant Therapy (TNT) is a relatively new treatment paradigm, where the chemotherapy is brought forward to the neoadjuvant period, either prior to sCRT (induction) or after sCRT (consolidation), with the aim of treating micrometastasis prior to definitive surgery. This protocol has the potential to increase compliance to systemic chemotherapy and DFS. Recently, two randomized controlled trials (RCT) reported higher pathological complete response (pCR) rates and a lower distant recurrence rate with TNT compared to sCRT.[8,9] Additionally, TNT has been shown to increase the proportion of patients achieving a clinical complete response (cCR) allowing for non-operative management (NOM) and organ preservation.[10,11] Despite the potential advantages of TNT, it remains unclear if TNT benefits all patients with LARC, if it improves overall survival, or whether treatment sequencing should be tailored towards risk for developing local or distant recurrence at presentation.[12]

In 2019, two metropolitan hospitals in Adelaide, South Australia adopted a personalized TNT (pTNT) protocol comprising a risk-adapted treatment strategy based on clinical staging (distant or locally advanced) at presentation whereby those at risk of distant failure (EMVI +ve, cN +ve, M1) underwent induction chemotherapy while those at risk of local failure (cT3/4) underwent consolidation chemotherapy.[13] Prior to this, a locally run randomized control trial (WAIT trial) evaluated the addition of three cycles of 5-fluorouracil/leucovorin during the 10 week wait period after sCRT and reported similar pCR rates to sCRT alone in patients with LARC.[14] Here, we aim to compare current treatment response rates with pTNT versus extended chemoradiotherapy (xCRT) in the 'wait period' or sCRT.

Material and methods

This multicentre retrospective cohort analysis is reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee (HREC Reference number: HREC/15/RAH/186) and St. Andrew's Hospital Research and Ethics Committee (#117). Informed consent was provided by all patients according to the ethical standards of the Helsinki Declaration of 1975.

Patient selection

Prospective data of patients with LARC who underwent pTNT from January 2019 to October 2022 were compared to a historical cohort of patients who received xCRT or sCRT from April 2012 to June 2014 in the WAIT trial.[14,15] Analysis was limited to patients in the pTNT cohort who met the eligibility criteria for the WAIT trial. This included patients diagnosed with LARC located within 12 cm from the anal verge, defined as clinical stage T3/4 or any node positive disease. Local staging was determined based on pelvic magnetic resonance imaging (MRI) and contrast-enhanced chest-abdomen-pelvis computed tomography (CT) evaluated distant disease. Patients were excluded if they were <18 or >80 years old, had metastatic disease (M1) at presentation, or did not undergo neoadjuvant treatment.

Treatment

Groups were determined based on the neoadjuvant treatment regimen received (Fig. 1). From 2019 onwards, pTNT was offered to all rectal cancer patients (induction or consolidation based on risk of locoregional or distant failure) without adjuvant treatment. Patients at risk of distant failure (including those with liver or lung metastases, extramural vascular invasion (EMVI) or abnormal

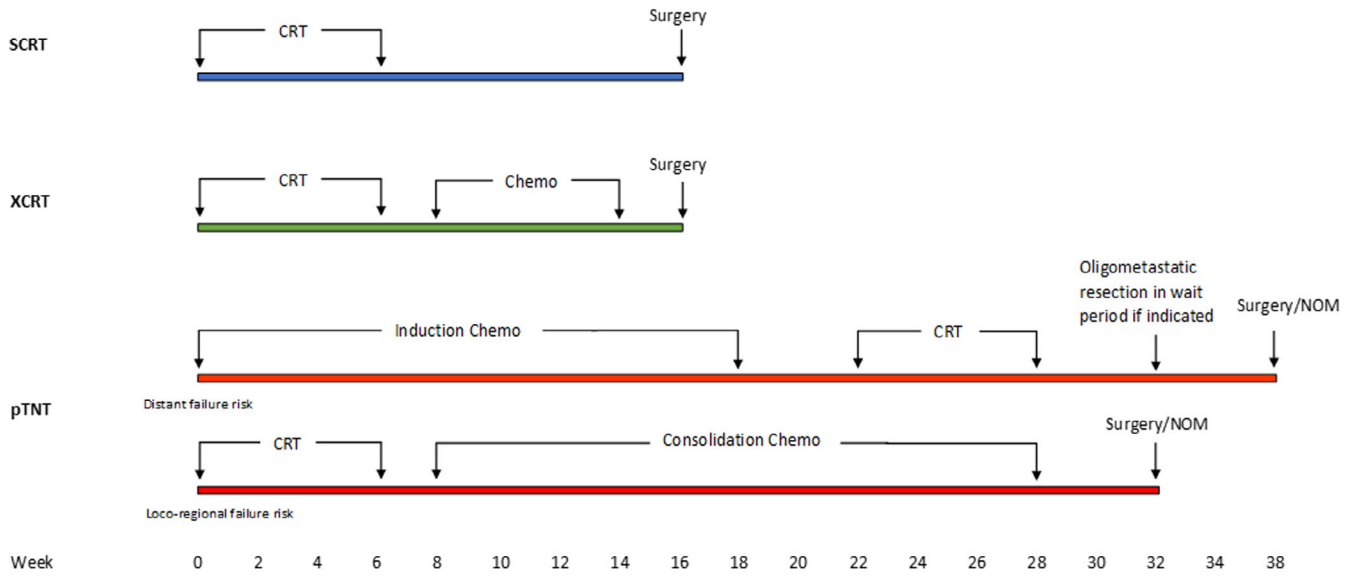

Fig. 1. Schema of the four neoadjuvant therapy approaches. sCRT, standard long-course chemoradiotherapy; xCRT, extended chemotherapy; pTNT, personalized total neoadjuvant therapy.

mesorectal or lateral pelvic lymph nodes) received induction chemotherapy. This consisted of 8 cycles mFOLFOX6 (5-Fluorouracil [5-FU], leucovorin, and oxaliplatin), fortnightly for 16 weeks or 6 cycles of CAPOX (capecitabine and oxaliplatin) for 18 weeks. Following completion of induction chemotherapy and a 2 week wait period, patients received long-course CRT consisting of 50Gy/25 fraction (option for dose escalation 50.4Gy/27 fractions) with concurrent intravenous 5FU or oral capecitabine, over 6 weeks. After completion of CRT, patients underwent a 10-week wait period in which oligometastatic resection was performed if indicated. At the end of the wait period patients were restaged with a CT, MRI, and flexible sigmoidoscopy.

Patients with a high risk of locoregional failure (including bulky local disease, T4 extension and low tumours), received long course CRT over 6 weeks, followed by consolidation chemotherapy over 16 weeks consisting of 8 cycles mFOLFOX6, or 6 cycles CAPOX over 18 weeks. Upon completion of consolidation chemotherapy, patients were restaged with a CT, MRI, and flexible sigmoidoscopy. Patients who achieved a cCR were offered NOM, the remaining proceeded to surgical resection. In cases with both distant and locoregional failure risk, induction chemotherapy was favoured however this was assessed on a case-by-case basis.

Between 2012–2014 as part of the WAIT trial, all patients underwent long-course CRT consisting of 45Gy/25 fractions (option for dose escalation to 50.4Gy/28 fractions) with concurrent intravenous 5-FU, over 5 weeks. For patients in the sCRT group, no further neoadjuvant chemotherapy was administered. Patients in the xCRT group received further chemotherapy comprising of 3 cycles of bolus 5-FU with leucovorin on each of 3 days, 3 weekly. Surgery was scheduled 10 weeks after completion of radiotherapy with the addition of adjuvant chemotherapy if clinically indicated. During this time, NOM was not included in the treatment protocol for patients who achieved a cCR within the participating hospitals.

Endpoints

The primary endpoint was overall complete response (oCR) defined as the proportion of patients who achieved either a cCR or pCR. pCR was defined as no residual tumour cells in the surgical specimen.[16,17] In the pTNT group, cCR was routinely assessed at the end of treatment and defined as the absence of a palpable tumour on digital rectal exam, no visible tumour and the presence of a white scar via flexible sigmoidoscopy, as well as tumour regression grade (TRG) 1 or 2 on restaging MRI without evidence of abnormal lymph nodes or EMVI.[18] In the sCRT and xCRT groups, cCR was assessed if there was absence of macroscopic tumour at the primary tumour site on digital rectal exam and endoscopy. Secondary endpoints included 2-year DFS, 2-year OS, pathological and surgical outcomes as well as 30-day postoperative complications, graded according to the Clavien-Dindo (CD) classification.[19] The quality of mesorectal excision was assessed by pathologists using Quirke's method and Tumour Regression Grade (TRG on pathological assessment) was classified based on the American Joint Committee on Cancer (AJCC).[17,20]

Statistical analysis

Parametricity was determined using the Shapiro–Wilk test. Normally distributed variables were expressed as mean (standard deviation) and nonparametric variables as median (range). Categorical variables were presented as frequencies and percentages. Continuous variables were compared using ANOVA or Kruskal–Wallis test depending on the type of distribution. Categorical variables were compared using χ^2 or Fisher's exact test. DFS and OS were analysed separately using the Kaplan–Meier method and log-rank tests. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, version 28 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Between January 2019 and September 2022, 284 patients presented with rectal cancer and 107 underwent pTNT. Of these, 40 patients fulfilled the inclusion criteria, and were compared with 49 patients from the WAIT Trial (25 received xCRT and 24 received sCRT) (Fig. 2). Baseline patient demographics and tumour characteristics are listed in Table 1. Although baseline patient and tumour characteristics were largely similar, there were some notable differences among the groups. The percentage of patients in the pTNT group with cN0 and American Society of Anaesthesiologists grade 3–4 were significantly higher compared with xCRT and sCRT groups (30.0% versus 0% versus 8.3%, $P < 0.001$; 73.9% versus 28% versus 20.8%, $P = 0.0003$), respectively.

Response to treatment and survival outcomes

The oCR (cCR and/or pCR) rate was significantly higher in the pTNT group compared with xCRT and sCRT (52.5% versus 24.2% versus 29.2%, $P = 0.043$; Table 2). In addition, cCR rate in the pTNT group was significantly increased compared to xCRT and sCRT groups (47.5% versus 12% versus 8.3%, $P < 0.001$). There was no significant difference in pCR rate between the groups (pTNT $n = 3$ (13.0%), xCRT $n = 4$ (16.0%), sCRT $n = 6$ (25.0%), $P = 0.553$). There were no significant differences in 2-year DFS rates between the groups (pTNT $n = 22$ (91.7%), xCRT $n = 19$ (76%), sCRT $n = 19$ (79.2%), $P = 0.249$). The 2-year OS also did not differ between the groups (pTNT n = 23 (95.8%), xCRT $n = 21$ (84.0%), sCRT $n = 23$ (95.8%), $P = 0.182$) (Fig. 3).

Surgical and pathological outcomes

Overall, 23 (57.5%) of 40 patients in the pTNT group, 25 (100%) in the xCRT group and 24 (100%) patients in the sCRT group proceeded to surgery (Table 3). The remaining 17 (42.5%) patients in the pTNT group have so far preserved their rectum. The median (range) interval between completion of radiotherapy and surgery was significantly longer in the pTNT group compared with xCRT and sCRT groups (172 days [76–616] versus 114 days [100–140] versus 112 days [98–134], $P < 0.001$). No differences were noted in operative time ($P = 0.249$), type of surgical approach ($P = 0.080$) or type of resection ($P = 0.173$). The proportion of patients with complete (R0) resection was high (91.7–95.7%) and similar across the three

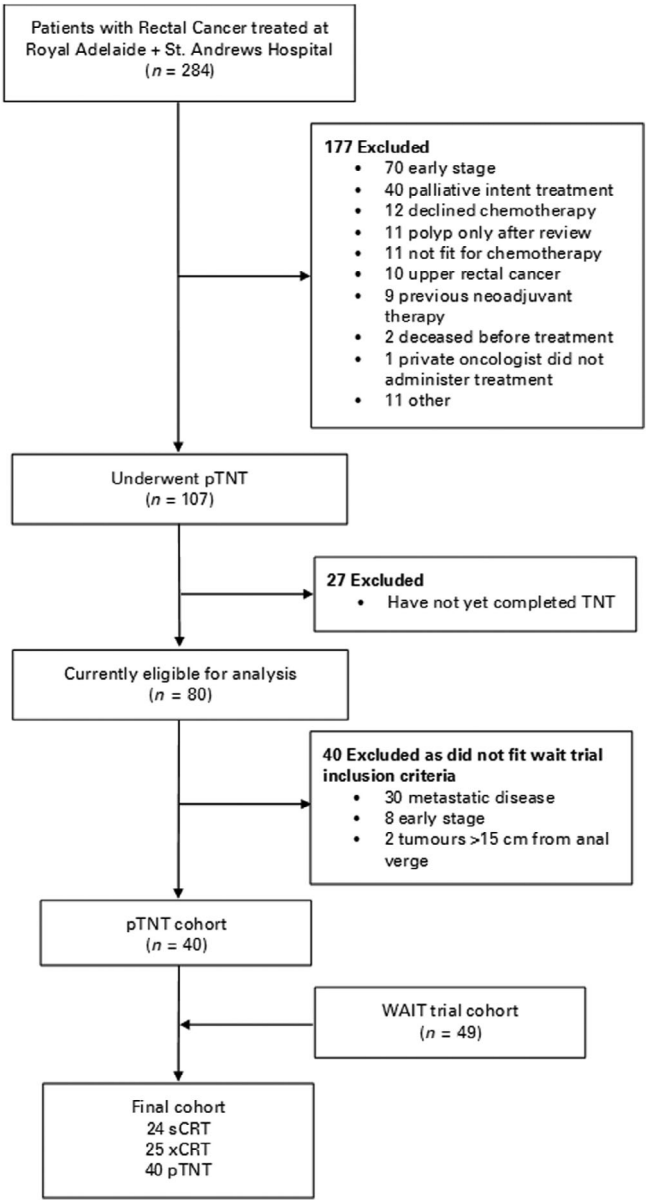

Fig. 2. Patient flowchart.

groups. There were no significant differences in the rate of anastomotic leak, 30-day postoperative complications according to the CD classification and length of hospital stay. There was no mortality within 30-day postoperative period. The quality of mesorectal resection was significantly higher in the pTNT group compared to xCRT and sCRT groups (91.3% versus 60% versus 58.3, $P = 0.049$). There was no significant difference between the groups with respect to pathological T or N stage and TRG.

Discussion

In this study, we found patients with LARC receiving pTNT have a significantly higher rate of oCR compared with those receiving xCRT or sCRT, but no significant difference in DFS and OS. Additionally, in the pTNT group, the cCR rate was approximately double that in the xCRT or sCRT groups, increasing the opportunity for NOM in patients seeking organ preservation. To our knowledge, this is the first multicentred study to compare treatment responses rates in patients with LARC treated with pTNT, xCRT or sCRT.

Previous studies by Habr-Gama *et al.* and Garcia-Aguilar *et al.* showed that sCRT followed by 2–3 cycles of consolidation chemotherapy has the potential to increase in pCR without severe adverse side effects compared to sCRT in patients with LARC.[21,22] Consequently, the WAIT randomized trial proceeded to test this hypothesis and found xCRT does not improve the pCR rate in patients with LARC. The authors of the WAIT trial however, acknowledged that the trial was underpowered to detect small differences in pCR between groups. Furthermore, Garcia-Aguilar *et al.* conducted the TIMING trial and reported a stepwise increase in pCR rates from 25% to 38% with the addition of more chemotherapy cycles.[23] This finding is also consistent with the results of the present study, that demonstrated a higher CR rate in patients who were administered an increased number of chemotherapy cycles and experienced a longer time interval between completion of radiotherapy and surgery (sCRT 112 versus xCRT 114 versus pTNT 172 days). The CAO/ARO/AIO-12 trial, which randomized patients to either induction or consolidation chemotherapy in the form of 3 cycles of FOLFOX before or after oxaliplatin based CRT followed by TME, demonstrated a much lower CR rate when compared with the current study (28% versus 52.5%).[24] Given these results, dose escalation in the form of 6 or more neoadjuvant chemotherapy cycles, and beyond the wait period interval, are expected to increase the CR rate.

Recent evidence suggests that TNT improves the pCR rate and may contribute to better disease-free survival for patients with LARC. Cercek *et al.* observed higher oCR rates and successful NOM with induction chemotherapy followed by CRT in comparison to sCRT.[10] The recently released results of the RAPIDO trial compared neoadjuvant short-course radiotherapy followed by 6 cycles of consolidation CAPOX or 9 cycles of FOLFOX4 followed by TME to sCRT, achieving a pCR rate of 28% and a significant reduction in the probability of distant metastasis in the TNT arm.[9] Additionally, the PRODIGE23 study comparing induction mFOLFIRINOX before CRT and TME followed by adjuvant chemotherapy to sCRT, also achieving a pCR rate of 28% and a significant improvement in DFS.[8] Further, there was no difference in surgical morbidity or compliance of CRT following induction chemotherapy.[8] In our study, no significant improvements were recorded in 2-year DFS or 2-year OS rates between the treatment groups. We attribute this result to the limited number of patients in each group and the short follow-up period. In the recently published OPRA trial, patients with LARC were randomized to receive induction or consolidation chemotherapy in the form of FOLFOX or CAPOX, followed by NOM for patients with cCR or near cCR.[11] Organ preservation at 3-years was achieved in 53% of the patients treated with consolidation TNT without compromising DFS when compared with sCRT. The pTNT group examined in the current study is a closer representation of both arms of the OPRA trial than previous RCTs assessing TNT. The baseline demographics of both studies were similar with clinical tumour and nodal staging together with treatment methodology in terms of chemotherapy agents and dosing and amount of chemoradiotherapy administered. These similarities may explain the similar cCR rates

Table 1 Baseline patient and tumour characteristics

	sCRT $N = 24$	xCRT $N = 25$	pTNT $N = 40$	*P*-value
Age, years (mean ± SD)	60.4 ± 12.5	59.7 ± 10.1	59.2 ± 13.0	0.937
Gender (male:female)	18:6	18:7	26:14	0.970
BMI (kg/m^2)	26.8 ± 4.3	26.0 ± 3.5	28.8 ± 10.3	0.367
Distance from anal verge (cm)	6.0 ± 2.6	6.6 ± 2.6	5.7 ± 3.0	0.435
Clinical stage				
cT2	1 (4.2)	0 (0.0)	2 (5.0)	0.236
cT3	18 (75.0)	24 (96.0)	31 (77.5)	
cT4	5 (20.8)	1 (4.0)	7 (17.5)	
cN0	2 (8.3)	0 (0.0)	12 (30.0)	<0.001
cN1	7 (29.2)	6 (24.0)	23 (57.5)	
cN2	15 (62.5)	19 (76.0)	5 (12.5)	
CRM				0.350
Clear	12 (50.0)	10 (40.0)	15 (37.5)	
Threatened	4 (16.7)	8 (32.0)	6 (15.0)	
Involved	8 (33.3)	7 (28.0)	19 (47.5)	
EMVI				0.676
Positive	8 (33.3)	11 (44.0)	22 (55.0)	
Negative	16 (66.7)	14 (56.0)	18 (45.0)	
ASA score[†]				0.0003
1–2	19 (79.2)	18 (72.0)	6 (26.1)	
3–4	5 (20.8)	7 (28.0)	17 (73.9)	

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; CRM, circumferential radial margin; EMVI, extramural vascular invasion.

[†]23 out of 33 patients underwent surgery in the pTNT group.

$P < 0.05$.

Table 2 Response to treatment

	sCRT $N = 24$	xCRT $N = 25$	pTNT $N = 40$	*P*-value
oCR (pCR and/or cCR)	7 (29.2)	6 (24.2)	21 (52.5)	0.043
cCR	2 (8.3)	3 (12.0)	19 (47.5)	<0.001
pCR[†]	6 (25.0)	4 (16.0)	3 (13.0)	0.553

Abbreviations: cCR, complete clinical response; oCR, overall complete response; pCR, pathological complete response.

[†]23 out of 40 patients underwent surgery in the pTNT group.

$P < 0.05$.

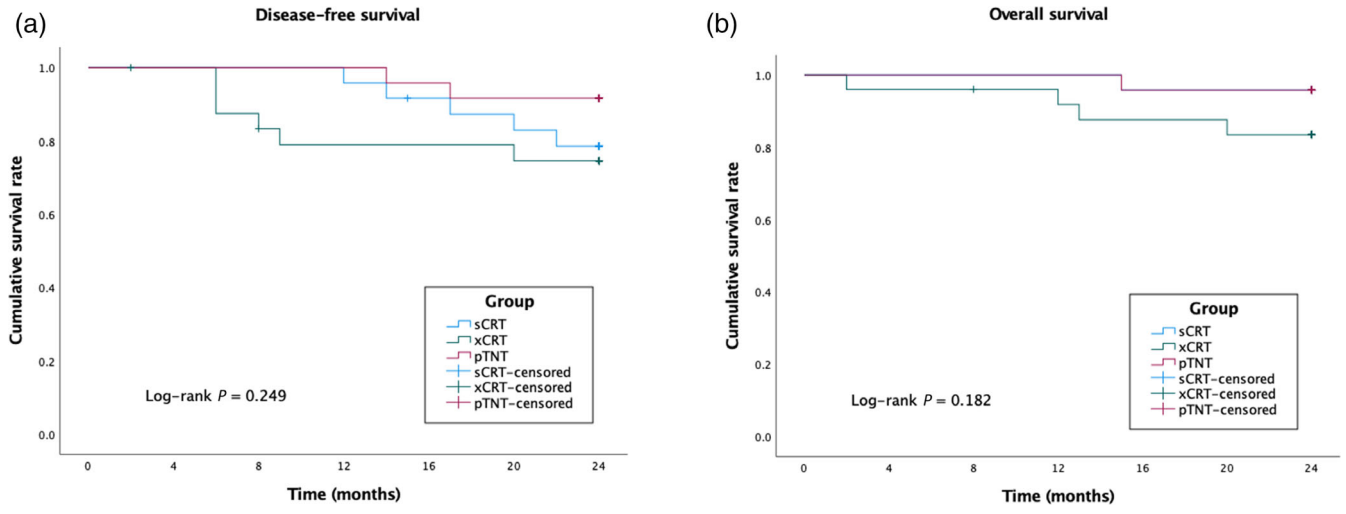

Fig. 3. Kaplan–Meier estimates of (a) disease-free survival and (b) overall survival in different study groups.

(47.5% versus 42.2%) between the OPRA trial and the present data. Whether a risk-adapted treatment strategy based on clinical staging at presentation (induction for distant failure risk and consolidation for local control), or a one size fits all approach (either induction or consolidation for everyone) is better remains to be clarified with data on this question still pending.

It is noteworthy that diagnostic criteria for cCR differed between the patient group undergoing pTNT and those in the WAIT trial. Strict

Table 3 Surgical and pathological outcomes

	sCRT $N = 24$	xCRT $N = 25$	pTNT $N = 23$	*P*-value
Days from completion of radiotherapy to surgery	112 (98–134)	114 (100–140)	172 (76–616)	<0.001
Operative time, mins	274 (191–393)	246 (180–400)	246 (112–540)	0.249
Type of surgical approach				0.080
Laparoscopic	8 (33.3)	4 (16.0)	11 (47.8)	
Laparoscopic converted	2 (8.3)	1 (4.0)	0 (0.0)	
Open	14 (58.3)	20 (80.0)	12 (52.2)	
Type of resection[†]				0.173
Restorative	12 (50.0)	18 (72.0)	11 (47.8)	
Non-restorative	12 (50.0)	7 (28.0)	12 (52.2)	
Anastomotic leak[‡]	1 (8.3)	0 (0.0)	0 (0.0)	0.363
30-day postoperative complications (Clavien-Dindo grade)				0.675
None	14 (58.3)	12 (48.0)	14 (60.9)	
1 and 2	6 (25.0)	7 (28.0)	8 (34.8)	
3	3 (12.5)	5 (20.0)	1 (4.3)	
4	1 (4.2)	1 (4.0)	0 (0.0)	
Length of stay	8 (4–42)	9 (5–39)	7 (4–27)	0.295
Mesorectal grade				0.049
1	2 (8.3)	3 (12.0)	1 (4.3)	
2	8 (33.3)	7 (28.0)	1 (4.3)	
3	14 (58.3)	15 (60.0)	21 (91.3)	
Resection status				1.000
R0 > 1 mm	22 (91.7)	23 (92.0)	22 (95.7)	
R1 ≤ 1 mm	2 (8.3)	2 (8.0)	1 (4.3)	
ypT stage				0.985
ypT0	6 (25.0)	5 (20.0)	3 (13.0)	
ypT1	2 (8.3)	1 (4.0)	1 (4.3)	
ypT2	4 (16.7)	5 (20.0)	6 (26.1)	
ypT3	11 (45.8)	13 (52.0)	12 (52.2)	
ypT4	1 (4.2)	1 (4.0)	1 (4.3)	
ypN stage				0.207
ypN0	19 (79.2)	16 (64.0)	20 (87.0)	
ypN1	2 (8.3)	5 (20.0)	3 (13.0)	
ypN2	3 (12.5)	4 (16.0)	0 (0.0)	
TRG				0.874
0	6 (25.0)	4 (16.0)	3 (13.0)	
1	10 (41.7)	11 (44.0)	8 (34.8)	
2	5 (20.8)	5 (20.0)	7 (30.4)	
3	3 (12.5)	5 (20.0)	5 (21.7)	

Abbreviation: TRG, tumour regression grade.

[†]Restorative procedures consisted of ultra-low or low anterior resections and non-restorative procedures consisted of abdominoperineal resections, Hartmann's, proctocolectomies and pelvic exenterations.

[‡]Anastomotic leak was calculated including only patients with an anastomosis in the denominator.

$P < 0.05$.

criteria currently define cCR, and this mandates formation provided by three assessment modalities: clinical examination, endoscopic, and MRI.[25] However, radiological confirmation of cCR after CRT was not required during the WAIT trial, since surgery was mandated regardless of response. Therefore, although some patients in the WAIT trial were macroscopically diagnosed as having had cCR, for a subset of these patients, clinically undetectable residual tumour could have been present at the time of restaging. Thus, we speculate that the cCR rate may have been overestimated in the WAIT trial and suggest that the difference in response with pTNT could have been even more pronounced.

The current study has several other limitations. The small sample size which was limited through matching current prospective data (pTNT) to that of the WAIT Trial. Secondly, the period of time expired from completion of the WAIT trial to the adoption of pTNT may have introduced confounding bias, although other aspects of clinical care for LARC have not altered much in that time. Additionally, a common concern of TNT is acute toxicity to chemotherapy. While prospective toxicity data for the pTNT patients are available, they were not recorded as part of the WAIT trial, making comparisons difficult.[15] Lastly, variations in tumour response between the groups could be attributed to differences in treatment plans, patient characteristics and time intervals from completion of radiotherapy to surgery.

Conclusion

Compared with sCRT and xCRT, pTNT results in a significantly higher complete response rate which may facilitate organ preservation. No difference was noted in the 2-year DFS rates or 2-year OS rates between the three treatment groups. Long-term follow-up is required to determine whether pTNT impacts DFS or OS outcomes.

Author contributions

Luke Traeger: Data curation; formal analysis; methodology; validation; visualization; writing – review and editing. **Tracy Fitzsimmons:** Data curation; formal analysis; investigation; project administration;

validation; writing – review and editing. **Joanne Perry:** Data curation; formal analysis; investigation; project administration; resources; validation; writing – review and editing. **Ryash Vather:** Conceptualization; data curation; methodology; supervision; writing – review and editing. **James W. Moore:** Conceptualization; data curation; methodology; supervision; writing – review and editing. **Tarik Sammour:** Conceptualization; data curation; funding acquisition; methodology; supervision; writing – review and editing.

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Conflicts of interest

None declared.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1: STROBE_checklist_cohort.