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The impact of short-course total neoadjuvant therapy, long-course chemoradiotherapy, and upfront surgery on the technical difficulty of total mesorectal excision: an observational study with an intraoperative perspective

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Purpose: Total neoadjuvant therapy (TNT) is becoming the standard of care for locally advanced rectal cancer. However, surgery is deferred for months after completion, which may lead to fibrosis and increased surgical difficulty. The aim of this study was to assess whether TNT (TNT-RAPIDO) is associated with increased difficulty of total mesorectal excision (TME) compared with long-course chemoradiotherapy (LCRT) and upfront surgery.

Methods: Twelve laparoscopic videos of low anterior resection with TME for rectal cancer were prospectively collected from January 2020 to October 2021, with 4 videos in each arm. Seven colorectal surgeons assessed the videos independently, graded the difficulty of TME using a visual analog scale and attempted to identify which category the videos belonged to.

Results: The median age was 67 years, and 10 patients were male. The median interval to surgery from radiotherapy was 13 weeks in the LCRT group and 24 weeks in the TNT-RAPIDO group. There was no significant difference in the visual analog scale for difficulty in TME between the 3 groups (LCRT, 3.2; TNT-RAPIDO, 4.6; upfront, 4.1; P = 0.12). A subgroup analysis showed similar difficulty between groups (LCRT 3.2 vs. TNT-RAPIDO 4.6, P = 0.05; TNT-RAPIDO 4.6 vs. upfront 4.1, P = 0.54). During video assessments, surgeons correctly identified the prior treatment modality in 42% of the cases. TNT-RAPIDO videos had the highest recognition rate (71%), significantly outperforming both LCRT (29%) and upfront surgery (25%, P = 0.01).

Conclusion: TNT does not appear to increase the surgical difficulty of TME.

Keywords: Rectal neoplasms; Neoadjuvant therapy; Surgical difficulty; Minimally invasive surgical procedures; Radiotherapy

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with rectal cancer accounting for 1/3 of these cancers [1]. The mainstay of treatment of rectal cancer is proctectomy with total mesorectal excision (TME) [2], and to improve oncological outcomes for locally advanced rectal cancer, multimodal approaches combining chemotherapy, radiotherapy, and surgery have been

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used with increasing frequency over the years. These regimens have demonstrated lower rates of local recurrence and improved patient survival [3–5].

Common treatment regimens for locally advanced rectal cancer include long-course chemoradiotherapy (LCRT) [6] or short-course radiotherapy [7], followed by proctectomy with or without adjuvant therapy [8]. Many randomized controlled trials have been performed to determine the optimal treatment regimen [9]. However, issues with patient compliance to adjuvant therapy have resulted in suboptimal oncological outcomes. Studies have reported compliance rates ranging from 30% [10] to 70% [11], with associated poorer overall survival due to higher rates of distant metastasis. This has provided an impetus for the adoption of total neoadjuvant therapy (TNT) for locally advanced rectal cancer. An improved rate of clinical complete response with TNT has also prompted some to adopt it as the first-line therapy for all rectal cancers in an attempt to pursue organ preservation and avoid the morbidity associated with proctectomy [12].

In recent years, TNT has begun to gain ground as the new standard for locally advanced rectal cancer, with regimens such as the RAPIDO (Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation) trial [13] and PRODIGE 23 (Partenariat de Recherche en Oncologie Digestive 23) trial [14] becoming popular because of improved patient compliance and oncological outcomes [15, 16]. However, these regimens inevitably entail deferring proctectomy till months after the completion of radiation therapy, which may increase surgical complexity due to tissue inflammation, oedema, or fibrosis. These physiological changes can reduce the visibility of anatomical planes, increasing the technical difficulty of dissection. Studies assessing perioperative morbidity rates after an extended interval from the end of radiotherapy to surgery have also yielded mixed findings [8, 17–20]. These concerns have hampered the widespread adoption of TNT by the surgical community.

To date, there remains a dearth of evidence addressing the technical difficulty of proctectomy after TNT. Since the publication of the RAPIDO study groups' results, an increasing number of our center's patients are undergoing TNT with the RAPIDO protocol (Fig. 1) followed by curative laparoscopic proctectomy with TME [13]. This results in surgery approximately 24 weeks from completion of radiotherapy. The aim of this study is to determine whether the 24-week interval after completion of radiotherapy impacts the surgical difficulty of proctectomy.

METHODS

Ethics statement

This study was approved by the Singapore Healthcare Centralised Institutional Review Board (No. 2020/2525). Written informed consents for publication of the research details and clinical images were obtained from the patients.

Study design

After ethical approval was obtained, we prospectively collected consecutive full-length laparoscopic videos of TME for rectal cancers from January 2020 to October 2021 at Sengkang General Hospital (Singapore), a tertiary institution. All the rectal cancers were histologically proven adenocarcinoma, with complete staging by magnetic resonance imaging (MRI) of the rectum and computed topography of the thorax, abdomen, and pelvis (CT-TAP). Patients who underwent upfront surgery did not require any neoadjuvant therapy based on international guidelines. Patients identified to require neoadjuvant therapy prior to resection were presented at a multidisciplinary tumor board including medical oncologists, radiation oncologists, radiologists, and surgeons to determine the neoadjuvant regimen they would undergo.

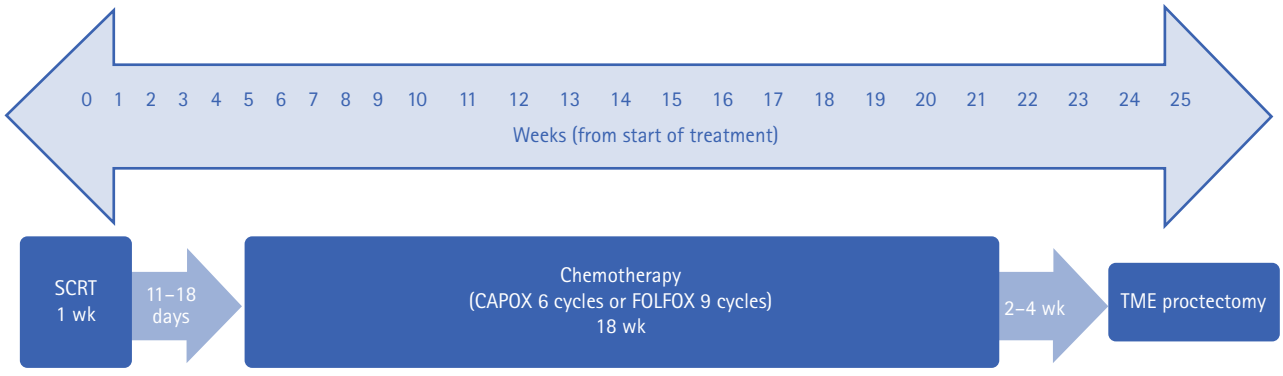

Fig. 1. The RAPIDO (Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation) protocol. SCRT, short-course radiotherapy; CAPOX, capecitabine and oxaliplatin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; TME, total mesorectal excision.

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Patients recommended for long-course chemoradiation received 25 fractions of 1.8 Gy radiotherapy. Concurrent chemotherapy consisted of either capecitabine or 5-fluorouracil. Patients who received TNT underwent the RAPIDO protocol, which included short-course radiotherapy consisting of 5 fractions of 5 Gy radiotherapy, followed by 6 cycles of oral capecitabine and intravenous oxaliplatin doublet chemotherapy. All patients who received neoadjuvant therapy had their cancers re-staged with a repeat MRI and CTTAP before undergoing curative resection.

The operations were performed at our institution by 6 consultant-grade colorectal surgeons via a laparoscopic approach. The procedure undertaken (abdominoperineal excision or sphincter-preserving surgery–anterior resection) was at the discretion of the participating surgeons. All patients received TME. The surgeons included have performed a minimum of 50 laparoscopic rectal cancer resections and participate in a regular audit of their practice in our institution. In our unit, the laparoscopic approach is the default option for all rectal cancers, barring multivisceral resections or pelvic exenterations, and our institutional rate of conversion to open surgery is 5.2%.

All videos were recorded in high definition. The videos were categorized into 3 groups: LCRT, TNT-RAPIDO, and upfront surgery. The first 4 videos (total 12) in each category during the study duration were included for analysis in this study.

The videos were edited by a colorectal surgeon who was not involved in the review process. All 12 videos were assessed using the Laparoscopic Surgery Video Educational Guidelines (LAP-VEGaS) video assessment tool [21], and the checklist is in Supplementary Table 1. However, due to the intention of the videos—namely, to evaluate a certain step in surgery in a blinded fashion to determine surgical difficulty—certain items in the tool were not present in the final videos, as detailed in Supplementary Table 1. The videos were edited to incorporate specifically the full duration of the following steps: mobilization of the rectum with TME, distal transection, and formation of an end-to-end colorectal anastomosis with Knight-Griffen's double stapler technique [22]. The videos were deidentified and arranged in a random order, labeled A to L. An encrypted USB storage device containing all 12 videos (A to L) was distributed to all 7 consultant-grade colorectal surgeons to assess the videos independently. They were blinded to the type of neoadjuvant treatment (if any) received.

Assessors made their assessment using a standardized form (Supplementary Fig. 1), grading the difficulty of TME using a visual analog scale (VAS) [23–25], which has been used in several studies on surgeon-assessed operative difficulty of cases. The form was created in Microsoft Excel (Microsoft Corp), with a sliding scale for each video, where assessors could slide the dark grey marker from 0 to 100 (the individual values were hidden and only visible to the author). Assessors were also tasked with identifying which treatment arm the patient in each video belonged to (LCRT, TNT-RAPIDO, upfront).

Perioperative clinical parameters were also collected, including demographics, tumor characteristics before and after neoadjuvant treatment, operative parameters, and short-term postoperative outcomes. In particular, operative duration and duration of hospital stay were used as adjuncts to surgical difficulty.

Statistical analysis

The statistical analysis was performed using IBM SPSS ver. 25.0 (IBM Corp). Categorical variables were presented as proportions, and comparisons were performed using the chi-square test or the Fisher exact test. Continuous data were presented as medians with the corresponding range and compared using the Kruskal-Wallis test for 3-group comparison, while the Mann-Whitney U-test was performed for 2-group comparison where applicable. The VAS was continuous; each reviewer's score was externally validated across all reviewers to determine inter-reviewer variability, and the Pearson coefficient was employed. A P-value of <0.05 was considered statistically significant.

RESULTS

Demographics

The median age was 67 years (range, 45–76 years), and 10 patients (83.3%) were male. The median body mass index was 22.2 kg/m^2 (range, 16.6–31.3 kg/m^2). The median interval from completion of radiation therapy to surgery was 13 weeks (range, 10–16 weeks) for the LCRT group and 24 weeks (range, 23–25 weeks) for the TNT-RAPIDO group. The patient demographics and tumor characteristics (preoperative radiological and postoperative histopathology) are summarized in Table 1. All tumors were completely resected (R0 resection) on final histopathology. In the LCRT group, 1 patient with MRI-based tumor regression grade 3 had a close circumferential margin of <1 mm. In the LCRT group, there was 1 patient with pathological complete response (pCR). The radiological characteristics generally concurred with final histopathology results.

Surgical complexity

Primary observations (assessment of videos)

There was no significant difference in the VAS for difficulty in TME dissection between the 3 groups (LCRT, 3.2; TNT-RAPIDO, 4.6; upfront, 4.1; $P=0.12$) (Table 2). The subgroup analysis demonstrated the graded difficulty of surgery was similar between

Table 1. Demographics and tumor characteristics (n = 12)

Characteristic	LCRT group (n = 4)	TNT-RAPIDO group (n = 4)	Upfront group (n = 4)	P-value
Demographic				
Age (yr)	67 (59–76)	59 (45–71)	70 (54–74)	0.16
Sex				> 0.99
Male	4	3	3	
Female	0	1	1	
Body mass index (kg/m^2)	20.0 (16.6–23.7)	24.1 (19.9–31.3)	23.6 (21.8–26.5)	0.26
Interval from radiotherapy to surgery (wk)	13 (10–16)	24 (23–25)	NA	0.29
Preoperative tumor characteristic (radiological)				
Endoscopic distance of tumor from the anal verge (cm)	3.9 (1.0–6.0)	9.8 (6.0–15.0)	8.8 (4.0–15.0)	0.13
Clinical T category[a]				0.14
T0	1	0	0	
T1	0	0	0	
T2	2	1	0	
T3	0	3	4	
T4	1	0	0	
Clinical N category[a]				0.59
N0	1	2	1	
N1	2	2	3	
N2	1	0	0	
Circumferential resection margin status[a]				0.34
> 1 mm	3	4	4	
≤ 1 mm	1	0	0	
mrTRG[a]			NA	0.45
mrTRG1	1	0		
mrTRG2	1	0		
mrTRG3	1	2		
mrTRG4	1	2		
mrTRG5	0	0		
Postoperative tumor characteristic (histopathological)				
Resection margin status				> 0.99
R0	4	4	4	
R1	0	0	0	
R2	0	0	0	
Circumferential resection margin status				0.34
> 1 mm or complete response	4	3	4	
≤ 1 mm or involved	0	1	0	
Tumor regression (modified Ryan scheme)			NA	0.36
0 (Complete response)	1	0		
1 (Near complete response)	0	1		
2 (Partial response)	3	2		
3 (Poor or no response)	0	1		
Pathological complete response (ypT0, ypTN0)	1	0	NA	0.29

Values are presented as median (range) or number only.
LCRT, long-course chemoradiotherapy; TNT, total neoadjuvant therapy; RAPIDO, Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation; NA, not applicable; mrTRG, magnetic resonance imaging–based tumor regression grade.
[a]Post-neoadjuvant for LCRT and TNT RAPDIO groups.

LCRT and TNT-RAPIDO (3.2 vs. 4.6, P = 0.05) and between TNT-RAPIDO and upfront (4.6 vs. 4.1, P = 0.54). There was an overall good correlation of responses between assessors for 9 out of 12 of the videos (Supplementary Table 2), with a P-value of ≥ 0.05 showing no significant differences in the observations.

The assessors were only able to correctly identify the neoadjuvant treatment from the videos 42% of the time. Patients who underwent TNT-RAPIDO were easiest to identify compared to the

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Table 2. Differences in primary and secondary observations between groups (n = 12)

Variable	LCRT group (n = 4)	TNT-RAPIDO group (n = 4)	Upfront group (n = 4)	P-value
Primary observation (assessment of videos)				
Visual analog score (cm)	3.2 (1.7–5.1)	4.6 (3.6–8.0)	4.1 (1.2–6.1)	0.12
Proportion of surgeons who correctly identified treatment category (%)	29	71	25	0.01
Secondary observation (objective measure)				
Operative time (min)	278 (286–365)	350 (283–520)	283 (206–335)	0.33
Duration of hospitalization (day)	5 (4–8)	5 (4–5)	6 (5–7)	0.27
30-day Morbidity	1[a]	0	0	0.34
30-day Mortality	0	0	0	> 0.99

Values are presented as median (range) or number only.
LCRT, long-course chemoradiotherapy; TNT, total neoadjuvant therapy; RAPIDO, Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation.
[a]Blood transfusion; morbidity rate, 25%.

LCRT and upfront surgery groups (71% vs. 29% vs. 25%, P = 0.01).

Secondary observations (objective measures)

Secondary observations used as adjuncts to surgical difficulty, including operative time in minutes (LCRT, 278 minutes; TNT-RAPIDO, 350 minutes; upfront, 283 minutes; P = 0.33) and the duration of hospitalization in days (LCRT, 5 days; TNT-RAPIDO, 5 days; upfront, 6 days; P = 0.27) were similar. Morbidity occurred in 1 out of 12 patients (Clavien-Dindo classification, grade II; a blood transfusion was required), and the 30-day mortality rate was 0% (Table 2).

DISCUSSION

TNT has been gaining traction in the treatment of locally advanced rectal cancers, with improved oncological outcomes [12]. It also maximizes the rates of complete clinical response after neoadjuvant treatment, so that appropriate patients may be entered into a "watch and wait" trial protocol [26, 27].

In the setting of the recent COVID-19 pandemic [28], TNT has allowed for shorter time spent in hospital for radiation treatment, which reduces the risk of exposure to COVID-19. These reasons have increased the adoption of TNT in the management of rectal cancer.

While TNT has gained popularity, concerns remain regarding its impact on the technical difficulty of proctectomy. The increased interval from radiotherapy to surgery—up to 24 weeks—with increased pelvic fibrosis has been postulated to increase surgical difficulty with increased perioperative morbidity. This prompted us to perform this study to assess and compare the technical difficulty of surgery after TNT, LCRT, and upfront surgery.

In our study, the difficulty of TME dissection appeared to be similar amongst the 3 groups with comparable VAS scores. In the subgroup analysis, there was also no significant difference in the difficulty of dissection between the LCRT and TNT-RAPIDO groups. These findings are congruent with the existing literature on perioperative outcomes and interval to surgery from non-TNT neoadjuvant chemoradiation regimens. Numerous studies have been performed to determine the optimal interval of surgery from the end of radiotherapy, balancing pCR with the surgical challenge and perioperative morbidity. Garcia-Aguilar et al. [29] compared surgery at 6 weeks and another group with a longer interval, concluding that a longer interval did not increase surgical morbidity and, in turn, increased pCR rates. A systematic review published by Du et al. [30] in 2018 similarly concluded that there was no significant difference in outcomes between operating < 8 and > 8 weeks from the end of radiotherapy, with the longest interval included in the analysis being 12 weeks. The STARRCAT trial demonstrated no increase in surgical difficulty and morbidity despite waiting 12 weeks after completion of radiotherapy [31]. It is important to emphasize that none of the above studies included patients who underwent surgery beyond 12 weeks from completion of radiotherapy. In contrast, our study demonstrated similar surgical difficulty despite the interval of surgery from end of radiotherapy being 13 weeks in the LCRT group and a staggering 24 weeks in the TNT-RAPIDO group. This may provide some reassurance to surgeons that TNT may not significantly increase the technical difficulty of proctectomy.

The assessors correctly identified 42% of the videos in the study. Amongst the 3 groups, patients who underwent TNT-RAPIDO appeared to be most distinct and were correctly identified 71% of the time. This suggests that either TNT or an extended interval beyond 12 weeks after the completion of radiation treatment may indeed have an impact on tissue quality, allowing the assessors to

identify the TNT-RAPIDO cases with greater accuracy. We postulate that this could be related to either fibrosis or the extent of tissue oedema, as described in a prior study on radiation effects on tissue in colorectal cancer surgery [32]. In the trial published by the Timing of Rectal Cancer Response to Chemoradiation Consortium, pelvic fibrosis was noted to be increased when surgery was delayed beyond 12 weeks of chemoradiation completion [33]. Despite increased pelvic fibrosis, the technical difficulty of surgery remained similar, a finding that our study appears to have validated.

The secondary observations from our study further suggest that TNT did not increase the surgical complexity, as the operative time was not significantly longer in the TNT-RAPIDO group than in the other 2 groups. Postoperative outcomes, such as complication rates and length of stay, were also largely similar amongst all 3 groups. This has been replicated by other studies investigating perioperative outcomes and a prolonged interval from the end of neoadjuvant therapy [19, 21]. A phase 3 trial that enrolled patients who underwent the RAPIDO protocol compared to LCRT did not show any significant increase in perioperative morbidity [13]. These results are congruent with our earlier findings that operative difficulty did not increase after TNT-RAPIDO.

The authors postulate a few reasons why the study did not demonstrate an increase in difficulty despite increased fibrosis and oedema: there may truly have been no difference in operative difficulty, or surgeons may have been aware of the pretreatment regimens received by the patients, meaning that the cases of LCRT and TNT-RAPIDO involved more preoperative planning, preparation of relevant equipment, and personnel, which mitigated the difficulties faced during the cases. Lastly, this study was performed at a single institution, and the authors recognize the limitation of this study is its small sample size. We acknowledge the possibility of type II error in view of the small sample size, which restricted the statistical power to differentiate the characteristics and outcomes between the groups. While we could have included more cases for analysis, we expected a reduction in the compliance of assessor surgeons and potentially reduced reliability of observations due to observer fatigue if the number of videos had been increased. A larger series of videos could be accrued with fewer reviewers to increase inter-rater reliability and make the conclusions more robust. Nonetheless, this is one of the few studies to date that has attempted to compare the technical difficulty of surgery after TNT with that of LCRT and upfront surgery and will be an invaluable addition to the existing literature.

Another limitation is that the cases presented may have also come from some of the 7 consultant-grade colorectal surgeons; however, the chance of bias was minimized by deidentifying the videos, only presenting the TME portion of the case, and asking the surgeons to review the videos independently. Future studies may have surgeons from another institution watch the same videos, which could provide a more objective assessment of the TME. One may also point out that the decision to include upfront surgery may add a degree of selection bias, as only locally advanced rectal cancers would be subjected to neoadjuvant treatment (TNT-RAPIDO, LCRT). This would include the presence of a threatened mesorectal fascia, presence of mesorectal lymph nodes, or a locally invasive tumor (cT3 or more). The decision to include upfront surgery in the series was made because most rectal tumors and mesorectal nodes would have shrunk from the neoadjuvant treatment, their intraoperative appearance would have been similar, and that would not have been a useful characteristic for the reviewer. This observation was justified by the posttreatment, preoperative tumor staging on MRI, which did not yield any significant difference amongst the 3 groups, leaving the mesorectal dissection, fibrosis, oedema, and bleeding as potential reasons for the difference in the evaluated operative difficulty. Regardless, our findings could provide the foundation for larger scale studies to investigate the pertinent issue of surgical difficulty after TNT.

In conclusion, proctectomy after TNT does not appear to be associated with increased technical difficulty by experienced colorectal surgeons. The short-term surgical outcomes are also similar to those of LCRT and upfront surgery. Further studies are required to investigate and quantify the impact of TNT on the technical difficulty of proctectomy.

ARTICLE INFORMATION

Conflict of interest

Frederick H. Koh is an Editorial Board member of *Annals of Coloproctology*, but was not involved in the reviewing or decision process of this manuscript. No other potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: CXZC, FHK, WJT; Data curation: CXZC,

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HLT, SSS, JLN, LMLH, DKLA, WHK, SH, SLK, CSPY, FQW, FJF; Formal analysis: CXZC, FHK; Investigation: CXZC; Methodology: CXZC, FHK, WJT; Supervision: FJF, WJT; Writing–original draft: CXZC; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Supplementary materials

Supplementary Table 1. LAP-VEGaS video assessment tool

Supplementary Table 2. Correlation of visual analog scale for videos

Supplementary Fig. 1. Assessor form.

Supplementary materials are available from https://doi.org/10.3393/ac.2023.00899.0128.

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