Gastroenterology Report, 2024, **12**, goae062
https://doi.org/10.1093/gastro/goae062
Original Article

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Changes to circulating tumor cells in the central vein during laparoscopic versus transanal endoscopic surgeries for rectal cancer: can surgical approach make a difference?

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Abstract

Background: The oncological safety of transanal total mesorectal excision (taTME) remains uncertain, and its special surgical approach may contribute to tumor cell dissemination. Thus, we conducted a study to investigate the impact of surgical approach on circulating tumor cell (CTC) counts and phenotypes in rectal cancer.

Methods: This is a prospective randomized controlled study (ClinicalTrials: NCT05109130). The patients were randomized to either the taTME ($n = 49$) or laparoscopic TME (laTME) ($n = 48$) groups. Blood samples were collected from the central vein to measure CTC counts and phenotypes at three time points: preoperative (t1), immediately post-tumor removal (t2), and one week post-surgery (t3). The effect of surgical procedure on CTCs at each time point was analyzed, with the primary endpoint being the change in CTC counts from t1 to t3 for each surgical approach. This study adheres to Consolidated Standards of Reporting Trials Guidelines.

Results: The baseline clinicopathologic characteristics of the laTME and taTME groups were balanced. The change in CTC count from t1 to t3 was 1.81 ± 5.66 in the laTME group and 2.18 ± 5.53 in the taTME group. The taTME surgery was non-inferior to laTME in terms of changing CTC counts (mean difference [MD]: −0.371; 95% confidence interval [CI]: −2.626 to 1.883, upper-sided 95% CI of $1.883 < 2$, non-inferiority boundary value). Compared with that at t1, the CTC count at t2 did not change significantly. However, higher CTC counts were detected at t3 than at t2 in the taTME ($P = 0.032$) and laTME ($P = 0.003$) groups. From t1 to t3, CTC counts significantly increased in both the taTME ($P = 0.008$) and laTME ($P = 0.031$) groups. There were no significant differences in CTC phenotype changes between the two groups from t1 to t3.

Conclusions: Compared with laTME, taTME did not affect CTC counts and phenotypes. Our findings indicate that taTME is not inferior to laTME in terms of CTC changes from an oncological perspective.

Keywords: circulating tumor cells; transanal total mesorectal excision; safe

Introduction

In recent years, significant advancements in treatment modalities have significantly improved the survival rates of colorectal cancer (CRC) patients following surgical resection, 30%–50% of CRC patients still exhibit recurrence at some point [1, 2]. One important cause of recurrence is micrometastasis, wherein circulating tumor cells (CTCs) with intact, viable nuclei detach from the primary tumor and enter the bloodstream. Studies have linked CTCs to hematogenous micrometastases, where they travel through the bloodstream, eventually leading to distant metastases [3]. Furthermore, CTCs promote invasiveness, immune escape, and metastasis by enhancing epithelial-mesenchymal transition [4, 5]. The increase of biphenotypic and mesenchymal CTCs is more likely to be associated with a poorer prognosis, highlighting the importance of monitoring changes in CTC counts and phenotypes.

Research by Fisher and Turnbull [6] has shown that surgical procedures can lead to the shedding of tumor cells into the

Received: 10 December 2023. **Revised:** 22 March 2024. **Accepted:** 24 May 2024

bloodstream. Surgeons generally aim to minimize micrometastases by avoiding excessive tumor manipulation, leading to the development of the "no-touch isolation" technique [7]. However, the impact of this technique on CTCs has not been extensively studied. Laparoscopic total mesorectal excision (laTME), the standard surgical approach for middle-low rectal cancer, has been supported by high-quality evidence [8, 9]. Nonetheless, its use in low rectal cancer patients with narrow pelvises is associated with a high conversion rate and positive resection margins. To address these limitations, Sylla *et al.* [10] introduced a new approach: transanal total mesorectal excision (taTME). However, a Norwegian study raised concerns about taTME's oncological safety, leading to its suspension in Norway due to high local recurrence rates and unusual multifocal recurrence patterns [11]. Aiming at the oncological safety of taTME, our team has carried out the TaLaR trial and reported short-term outcomes [12]. However, comprehensive evidence requires a multifaceted approach. Unlike the traditional transperitoneal approach, taTME surgery adopts a "bottom-up" approach from the distal to the proximal mesorectal plane [13, 14]. It remains unclear whether the close proximity of taTME to the tumor violates the "no-touch" principle and promotes tumor cell spread. However, there is currently no research investigating whether taTME affects CTC counts or phenotypes.

The process of cancer metastasis was eloquently described in the 1830s by Steven Padgett's "seed and soil" hypothesis [15]. Previous research has explored the influence of taTME and laTME on inflammatory indexes, which is partial "soil" [16]. However, there is a gap in our understanding of their effects on CTCs, which is "seed." Therefore, we conducted this prospective randomized controlled study to assess the impact of laTME and taTME on tumor cell spread using central venous CTCs as biomarkers.

Methods

Patients

This prospective randomized controlled study enrolled rectal cancer patients (Clinical stage: T2-3N0-1) who exhibited no distant metastasis and planned to undergo radical resection at The Sixth Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). Patients with multiple primary CRC and/or histories of malignant tumors were excluded. Additionally, patients who received neoadjuvant treatment or underwent local resection and those who experienced massive hemorrhage during operation or required a change in surgical method were excluded. Patients were randomly assigned to either the taTME or laTME treatment groups (1:1) by using Random V1.0 software. Patient clinicopathological information and related data were recorded according to the established research plan. This study was conducted in accordance with the Helsinki Declaration. It was reviewed and approved by the Institutional Review Board of the Independent Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (E2021114) and registered at ClinicalTrials (No. NCT05109130). This work has been reported following the Consolidated Standards of Reporting Trials Guidelines.

Blood sample collection

Following the established research plan, 5 mL of blood samples were collected at three different time points, as depicted in Figure 1A. Blood samples were obtained through jugular vein cannulation (Figure 1B). Considering the potential impact of the operation on the release of CTCs, the first blood sample was collected before surgery (t1), with subsequent samples taken after tumor resection (t2). Based on the model suggesting that CTCs increase after the operation but gradually decrease during circulation [17], a third blood sample was collected one week post-surgery (t3) to more accurately reflect CTC changes during the perioperative period. CTCs were detected immediately following blood sample collection.

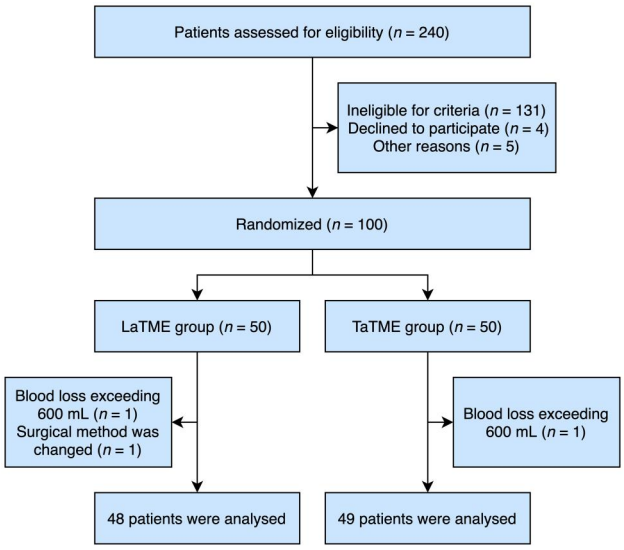

Figure 1. Group flow chart and blood collection time points. (A) Timeline displaying the different time points at which blood was collected. The first sample was collected before surgery (t1), immediately after tumor removal (t2), and one week post-surgery (t3). (B) Diagram illustrating blood specimen collection. (C) Detection of epithelial-mesenchymal transition phenotypes of circulating tumor cells by RNA *in situ* hybridization in rectal cancer patients.

Enumeration of CTCs

CTC detection was conducted by using the semiautomated Food and Drug Administration-approved CellSearch® system, as described in previous studies [18]. In brief, CTC enumeration involved immunomagnetic enrichment targeting the epithelial cell adhesion molecule (EpCAM). CTCs automatically pre-selected by the CellSearch® system as cytokeratin- or EpCAM-positive nucleated cells lacking CD45 and larger than 15 μm in size were independently reviewed by two investigators to confirm CTC status. Epithelial CTCs and biphenotypic CTCs were distinguished based on an EpCAM signal intensity threshold established by the CellSearch® system, while mesenchymal CTCs displayed an EpCAM-negative phenotype. The three CTC phenotypes are illustrated in Figure 1C.

Sample size

The main hypothesis of this research was the non-inferiority of taTME compared with laTME in patients with rectal cancer. The primary endpoint of this study was determined by the CTC counts at t3 minus that at t1 for two surgical approaches. Based on previous test data from our hospital, we assumed that the difference between t1 and t3 in the laTME group was 3, with a standard deviation (SD) of 3.4. We also assumed that the difference and SD of the taTME group were the same as those of the laTME group. The non-inferiority boundary value was set at 2 after discussions with clinical experts, meaning the difference in the taTME group could not exceed 5. According to calculations by using PASS, version 11 (NCSS, LLC), with 80% power and a one-sided type I error of 0.025, 47 cases in each group were required.

Accounting for an expected 5% dropout rate, the final sample size was set at 50 cases in each group, for a total of 100 cases.

Statistical analysis

The primary analysis was conducted on the primary analysis set, which was defined as the cohort of participants who were randomized, excluding those who experienced massive hemorrhage during the operation. For participants with missing third CTCs data, the last observation carried forward method was utilized to impute missing values. Continuous variables were compared by using the Mann–Whitney *U* test and Student's *t*-test. Categorical variables are expressed as numbers and percentages and were analyzed by using the chi-square test. Additionally, Kruskal–Wallis *H* and chi-squared tests were employed for categorical variables. The impact of laTME and taTME on the change in CTCs was assessed by using unpaired non-parametric testing. Interaction terms were tested for the type of surgery and measurement time point. A *P* value of < 0.05 (two-sided) was considered statistically significant.

Results

Study population and clinicopathologic characteristics

Ninety-seven patients participated in this prospective clinical study (Figure 2), with a median age of 59 years (range, 23–89 years), including 58 male patients (59.8%). Table 1 presents the clinicopathologic characteristics of the patients. Baseline characteristics were well-balanced between the laTME and taTME groups, with no significant differences in T stage, N stage, tumor circumference, tumor size, blood loss, operation time, or other factors.

Relationship between CTCs and clinicopathologic characteristics

To evaluate the association between the presence of CTCs and clinicopathologic features, we analyzed the following characteristics: age, sex, T stage, N stage, carcinoembryonic antigen (CEA) level, carbohydrate antigen 19–9 (CA19–9) level, distance from the anal verge, presence of vascular/nervous invasion, tumor circumference, gross type, tumor diameter, and tumor differentiation grade. Our results showed a significant association between preoperative CTC count and tumor circumference > 50% ($P = 0.017$) and poor tumor differentiation grade ($P = 0.031$) (Supplementary Figure S1). Moreover, a higher proportion of mesenchymal CTCs was observed in cases with tumor circumference > 50% ($P = 0.035$), and poorly differentiated rectal cancer ($P = 0.020$) (Supplementary Figure S2). No significant associations were found between CTC counts or phenotypes and other clinical characteristics.

Enumeration of CTCs

Ninety-five patients (97.9%) had CTCs at t1. The CTC numbers exhibited similar trends for both taTME and laTME groups across

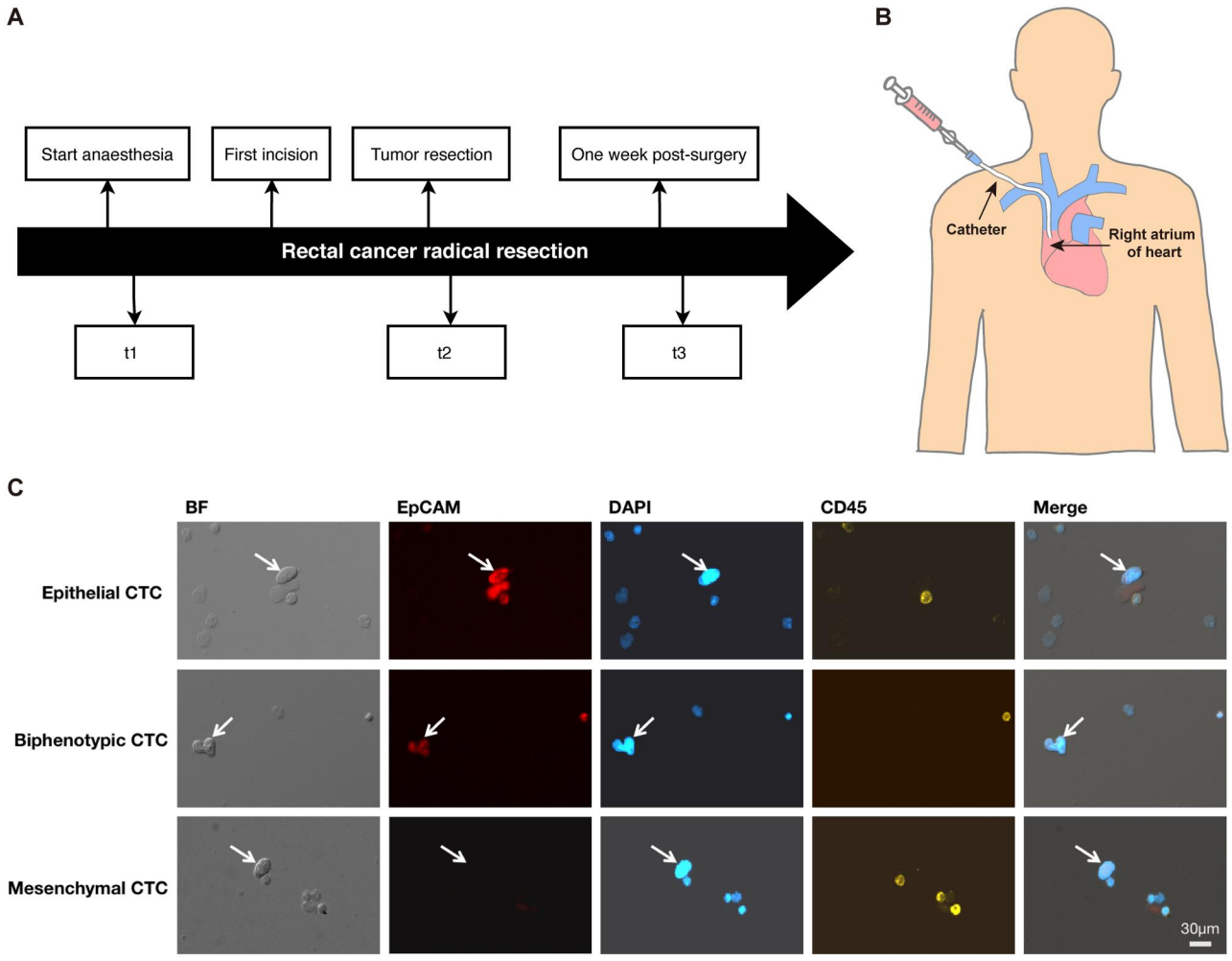

Figure 2. Group flow chart and blood collection time points.

Table 1. Comparison of clinicopathologic characteristics and treatment measures between patients subjected to different surgeries

Variable	laTME-group ($n = 48$)	taTME-group ($n = 49$)	*P*-value
Age (years)			
<65	30 (62.5)	35 (71.4)	0.350
≥65	18 (37.5)	14 (28.6)	
Sex			
Male	27 (56.3)	31 (63.3)	0.481
Female	21 (43.7)	18 (36.7)	
Pathological T stage			
2	21 (43.7)	23 (46.9)	0.752
3	27 (56.3)	26 (53.1)	
Pathological N stage			
0	31 (64.6)	37 (75.5)	0.240
1	17 (35.4)	12 (24.5)	
Tumor differentiation			
Poor	5 (10.4)	7 (14.3)	0.563
Moderate/Well	43 (89.6)	42 (85.7)	
Tumor circumference			
<50%	18 (37.5)	19 (38.8)	0.897
≥50%	30 (62.5)	30 (61.2)	
Gross type			
Ulcerative type	17 (35.4)	11 (22.4)	0.159
Elevated type	31 (64.6)	38 (77.6)	
CEA (ng/mL)			
<5	31 (64.6)	33 (67.3)	0.774
≥5	17 (35.4)	16 (32.7)	
CA19-9 (ng/mL)			
<37	42 (87.5)	45 (91.8)	0.483
≥37	6 (12.5)	4 (8.2)	
Vascular/Nervous invasion			
−	41 (85.4)	43 (87.8)	0.735
+	7 (14.6)	6 (12.2)	
Tumor diameter (cm)			
<3	25 (52.1)	31 (63.3)	0.265
≥3	23 (47.9)	18 (36.7)	
Location from anal verge (cm)			
<5	22 (45.8)	24 (49.0)	0.756
≥5	26 (54.2)	25 (51.0)	
Operating time[a] (mean ± SD, min)	171.25 ± 43.12	174.82 ± 46.78	0.170
Blood loss[a] (mean ± SD, mL)	64.48 ± 51.65	61.22 ± 42.11	0.233

[a] Except for the two values, the others are presented as number of patients followed by percentage in the parentheses.
CEA = carcinoembryonic antigen, CA19-9 = carbohydrate antigen 19-9, SD = standard deviation.

all three time points (Figure 3). However, the proportion of epithelial CTCs showed divergent trends between the two surgical approaches at t2 and t3. There were no significant changes in CTC numbers between t1 and t2 for either group. However, from t2 to t3, there was a significant increase in CTC numbers in both the laTME group ($P = 0.003$) and the taTME group ($P = 0.032$). From t1 to t3, both the laTME ($P = 0.031$) and taTME ($P = 0.008$) groups showed a significant increase in CTC counts. There were no statistical differences in CTC changes between the two surgical methods at any of the tested time points (Figure 4). The mean difference (MD) of the primary endpoints between the taTME and laTME groups was −0.371 and 95% confidence interval (CI) was −2.626 to 1.883. Given a non-inferiority threshold of 2, it can be considered that the influence of taTME on CTC changes was not inferior to that of laTME, as the upper-sided 95% CI of 1.883 was less than 2. Only the taTME group exhibited an increase in the proportion of epithelial CTCs between t2 and t3 ($P = 0.033$), but there were no significant differences in CTC phenotypes changes between the taTME and laTME groups from t1 to t3.

Discussion

This study represents the first investigation into the impact of taTME compared with that of laTME on CTC changes. Our results indicated that taTME did not elevate CTC dissemination and was as safe and feasible as laTME from an oncological standpoint.

Surgical procedures are often implicated as potential factors in tumor dissemination [19]. The numbers of CTCs detected in post-operative or post-dissection blood samples of CRC patients were significantly higher than those detected in pre-operative or pre-dissection samples [20, 21]. Additionally, intraoperative CTC spread during resection of colorectal liver metastases is a key predictor of intrahepatic or extrahepatic tumor recurrence [22, 23]. These findings suggest that surgical procedures may contribute to the dissemination of cancer cells into circulation, leading to poorer outcomes. Consequently, several studies have compared the effects of different surgical methods on CTC changes. For example, Tamminga *et al.* [17] compared the effects of video-assisted thoracic surgery and open surgery on CTC changes in lung cancer. Gall *et al.* [24] compared the effects of standard pancreaticoduodenectomy and no-touch isolation pancreaticoduodenectomy on CTCs in pancreatic cancer. In addition, Wind *et al.* [25] compared the effects of laparoscopic surgery and open surgery on CTCs in colon cancer. These studies provide a foundation for exploring changes in CTCs induced by different surgical methods and using CTCs count as a reference for the informed selection of surgical cancer treatments.

In 2010, Sylla *et al.* [10] first reported the feasibility of taTME for rectal cancer treatment. As a "bottom-to-top" and

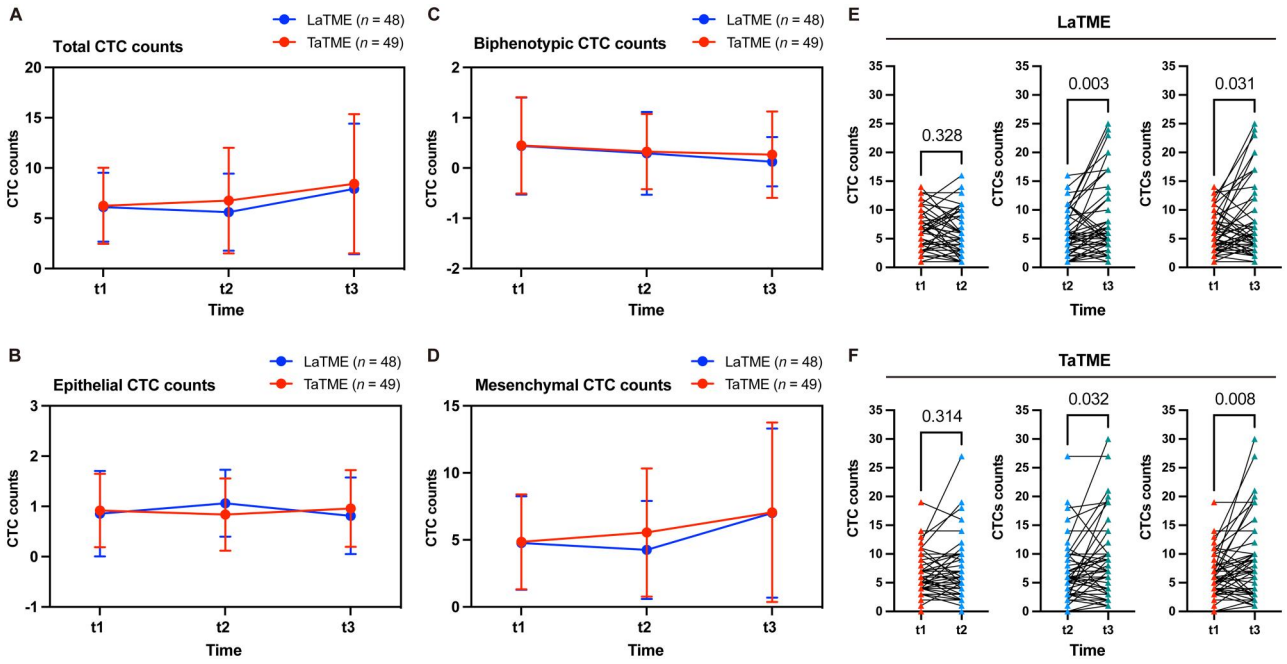

Figure 3. Average number of circulating tumor cells (CTCs) detected in samples from patients who underwent laparoscopic or transanal endoscopic surgery at different time points. (A) Total CTC counts. (B) Epithelial CTC counts. (C) Biphenotypic CTC counts. (D) Mesenchymal CTC counts. (E) Changes in CTCs at all three time points for laparoscopic total mesorectal excision patients. (F) Changes in CTCs at all three time points for transanal total mesorectal excision patients.

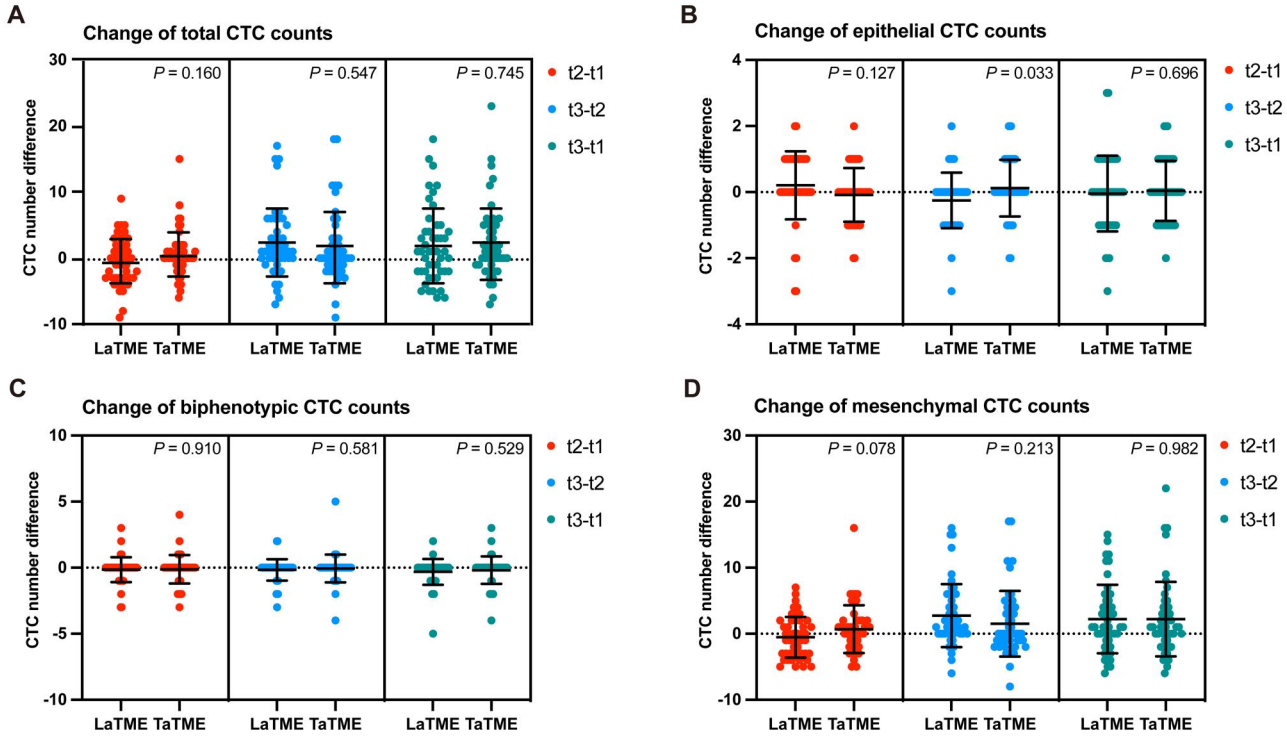

Figure 4. Changes in circulating tumor cell (CTC) counts at different time points. (A) Changes in total CTC counts. (B) Changes in epithelial CTC counts. (C) Changes in biphenotypic CTC counts. (D) Changes in mesenchymal CTC counts.

"inside-to-outside" technique, taTME solves some of the challenges inherent to laTME. Previous findings have indicated that taTME yielded favorable short-term oncological outcomes [26, 27], showing promise for rectal cancer patients. However, robust high-level evidence on the long-term oncological outcomes of taTME is still lacking. More importantly, a Norwegian study of 110 cases treated with taTME revealed a high rate of multifocal local recurrence, leading to controversy regarding the safety of taTME [11]. The primary shortcomings of transanal dissection in oncological setting include tumor exposure before purse-string closure of the tumor-bearing segment with the rectal lumen and the necessity for a tight suture to seal the rectum preventing gas

or liquid contaminated with cancer cells from leaking [28]. Surgical manipulation and gas pressure might compress the suture, increasing the risk of cancer cell leakage into the pelvic cavity [29]. Additionally, it is unclear whether this procedure has an impact on CTCs. It has been proven in animal models that injury sites are preferential areas for tumor growth, and surgical trauma enhances local regional metastasis [30]. Several experimental studies have demonstrated accelerated local and distant tumor growth following tumor resection [31, 32]. Therefore, evaluating whether the specialized surgical approach of taTME influences CTC changes is crucial for assessing the safety of taTME surgery.

Our results indicated that there were no statistically significant differences between the laTME and taTME groups regarding CTC changes and taTME was not inferior to laTME. Therefore, the specialized surgical procedure of taTME did not impact the release of CTCs or lead to adverse effects. Theoretically, CTCs must traverse the microcirculation of the liver, lungs, and other tissues before entering systemic venous circulation. Thus, detecting CTCs in central venous blood, rather than peripheral venous blood, better reflects the influence of surgical intervention on CTCs.

Certain limitations should be noted. The biological process of cancer metastasis is exceedingly complex [33]. CTCs entering the bloodstream due to a surgical procedure do not necessarily instigate metastasis, as they can be deactivated by immune cells such as natural killer cells and macrophages [34]. However, CTC changes can somewhat indicate the safety of an operation. Additionally, surgeon proficiency may be a significant confounding factor in the reported CTC changes, particularly for patients undergoing taTME. Moreover, this is a single-center study and may lack external validity. In the early-stage development of taTME, the primary concern was the oncological safety of the surgery due to the potential expansion of the laparoscopic area. Encouraging results from the TaLaR trial have demonstrated a reliable short-term safety profile for taTME [12]. In the future, the ongoing multicenter randomized controlled trials, such as TaLaR, COLOR III and ETAP-GRECCAR, will provide more robust evidence for the safety of taTME [35, 36].

Conclusions

This trial addressed the knowledge gap regarding the influence of taTME on CTC release. Our findings demonstrated that taTME did not impact CTC counts compared with laTME. From an oncological standpoint regarding CTC changes, the specialized surgical approach of taTME is as effective as laTME.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

L.H. and L.K. contributed to conception of the study and supervision. M.C., F.J.Y., and W.W.Z. contributed to data collection, quality assessment and manuscript draft. L.X., Z.X.L., and H.S.L. contributed to statistical analysis and interpretation of data. X.B.Z. and W.X.L. contributed to interpretation of data and revision of the manuscript draft. All authors have approved the final draft of the manuscript.

Funding

None declared.

Acknowledgements

This study was supported by National Key Clinical Discipline, The Program of Guangdong Provincial Clinical Research Center for Digestive Diseases [2020B1111170004], Science and Technology Key Research and Development Plan Project of Guangzhou (China) [202103000072], Natural Science Foundation of Guangdong Province (China) [2018A030313621], Science and Technology Projects in Guangzhou [202206010062], Sun Yat-sen University Clinical Research 5010 Program [2016005], Shenzhen "San Ming Projects" Research [Grant No. lc202002].

Conflicts of Interest

None declared.

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Gastroenterology Report, 2024, 12, –
https://doi.org/10.1093/gastro/goae062
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