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Study protocol

STUDY PROTOCOL

Transanal vs laparoscopic total mesorectal excision for rectal cancer: a multicenter randomized phase III clinical trial (TaLaR trial) protocol

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Abstract

Background: Total mesorectum excision (TME) is considered the standard surgical procedure for rectal-cancer treatment. Transanal TME (taTME) is a new procedure to treat low rectal cancer. Some published studies have proven that taTME can provide a better-quality resected specimen in low-rectal-cancer patients in comparison to the transabdominal procedure, yet long-term outcomes must be investigated. We designed this non-inferiority trial (TaLaR trial) to compare short-term and long-term outcomes between taTME and laparoscopic TME (lapTME) for rectal cancer.

Methods: The TaLaR trial is a phase III open-labeled multicenter randomized–controlled trial. Patients who are diagnosed with rectal cancer with no more than T3N2 stage, and with the tumor location below the peritoneal reflection by magnetic resonance imaging scan, digital rectal examination, or colonoscopy, qualify for this study. After calculating, a total of 1,114 patients (557 per group) will be randomly allocated to either the taTME or the lapTME group. Primary endpoints are the 3-year disease-free survival (DFS) rate and the 5-year overall survival (OS) rate. Secondary endpoints include specimen quality, perioperative results, pelvic and anal function, and quality of life.

Discussion: The TaLaR trial is expected to clarify whether taTME can achieve comparable oncological outcomes, as well as improve specimen quality and recovery conditions in rectal-cancer patients compared with lapTME.

Key words: transanal total mesorectal excision; total mesorectal excision; laparoscopic; rectal cancer; surgery

Introduction

About 704,000 patients per year are diagnosed with rectal cancer globally [1]. Total mesorectal excision (TME) was first highlighted in the 1980s by Heald and Ryall [2, 3] due to its significant contribution to reducing local recurrence. The procedure has been considered the standard surgical technique for rectal cancer since then.

Along with the development of minimally invasive techniques, laparoscopy has become common practice in colorectal surgery for decades. Even though controversy still exists, laparoscopic TME (lapTME) has been proven to achieve similar resection quality and oncological outcomes compared with open TME (opTME) in several clinical trials. Laparoscopic surgery proved feasible and safe in the COREAN trial; moreover, this procedure has some short-term benefits for patients compared with open surgery, especially those with middle or low rectal cancer who have been treated with neoadjuvant chemoradiotherapy [4]. In addition, the COLOR II trial reported no statistically significant differences for treating high- or middle-rectal-cancer patients with either lapTME or opTME, but lapTME had advantages for low-rectal-cancer patients [5]. It is also worth noting that, when comparing lapTME with opTME, the former can reduce the operative wound, enhance patient recovery, and reduce wound-related complications [6]. As a result, lapTME has become common over the past few decades.

However, it remains difficult to acquire complete TME with a safe surgical margin by conventional transabdominal methods in obese male patients with low rectal cancer have undergone neoadjuvant treatment and have a narrow pelvic floor, etc. [4, 6, 7]. In order to tackle these issues, transanal total mesorectal excision (taTME) was introduced by Sylla *et al.* [8]. The feasibility, safety, and advantages of this method have been verified by more recent studies, and it has become a hot topic for rectal cancer both in the literature and at conferences [8–10]. Theoretically, taTME could achieve better pathological outcomes than lapTME, as it provides better vision to mobilize the distal rectum. Thus, taTME may result in a better oncological outcome for patients [11]. However, taTME is still in the early stages of development and the desired or expected oncological outcomes have yet to be achieved before it can become the standard technique for rectal-cancer treatment. Thus, the aim of this study is to establish a multicenter randomized clinical trial comparing taTME with lapTME for low rectal cancer to prove the hypothesis that taTME can achieve non-inferior results with regard to oncological outcomes as well as obtain better short-term outcomes and resection quality.

Methods

The TaLaR trial is a prospective open-label multicenter randomized parallel-group phase III trial with 10 major medical institutions involved (The Sixth Affiliated Hospital of Sun Yat-sen University, the Peking Union Medical College Hospital, the Daping Hospital of Army Medical University, The First Hospital of Jilin University, the Shengjing Hospital of China Medical University, the Renji Hospital of Shanghai Jiao Tong University, the Affiliated Nanchong Central Hospital of North Sichuan Medical College, the Second People's Hospital of Yibin, the Peking University Cancer Hospital, and the First Affiliated Hospital of Guangzhou Medical University). These facilities are the most famous Grade-A Tertiary referral centers in China. The study scheme is described in Figure 1.

Patient criteria

The eligibility of patients for the study is based on several criteria including the presence of a rectal carcinoma proved by biopsy; clinical stages no more than T3N2 rectal cancer; cases in which TME is determined to be suitable for elective resection; an age of >18 but <75 years; tumor location below the level of the peritoneal reflection by magnetic resonance imaging (MRI) scan, digital rectal examination, or colonoscopy; and cases in which computed tomography (CT) examination of the abdomen and thorax excludes distant metastases. Patients with stages cT4N0 or T1-4N1-2 disease will be recommended for neoadjuvant radio-chemotherapy. Patients with a body mass index of $<30\,kg/m^2$ and having undergone abdominal or pelvic surgery; those without threatened mesorectal fascia (MRF); those without contraindications of laparoscopic surgery; and those without a history of other malignancies are also eligible. Patients will be given an informed consent form to confirm their consent to participate in the clinical study.

Types of cancers excluded from the study are T1 cancers that can be locally resected, T3 cancers with margins of <1 mm (MRF+) to the endopelvic fascia and tumors with ingrowth in the internal sphincter or levator ani. Conditions in which the tumor is staged as T4 confirmed through MRI after neoadjuvant therapy are also excluded. Other reasons for elimination include

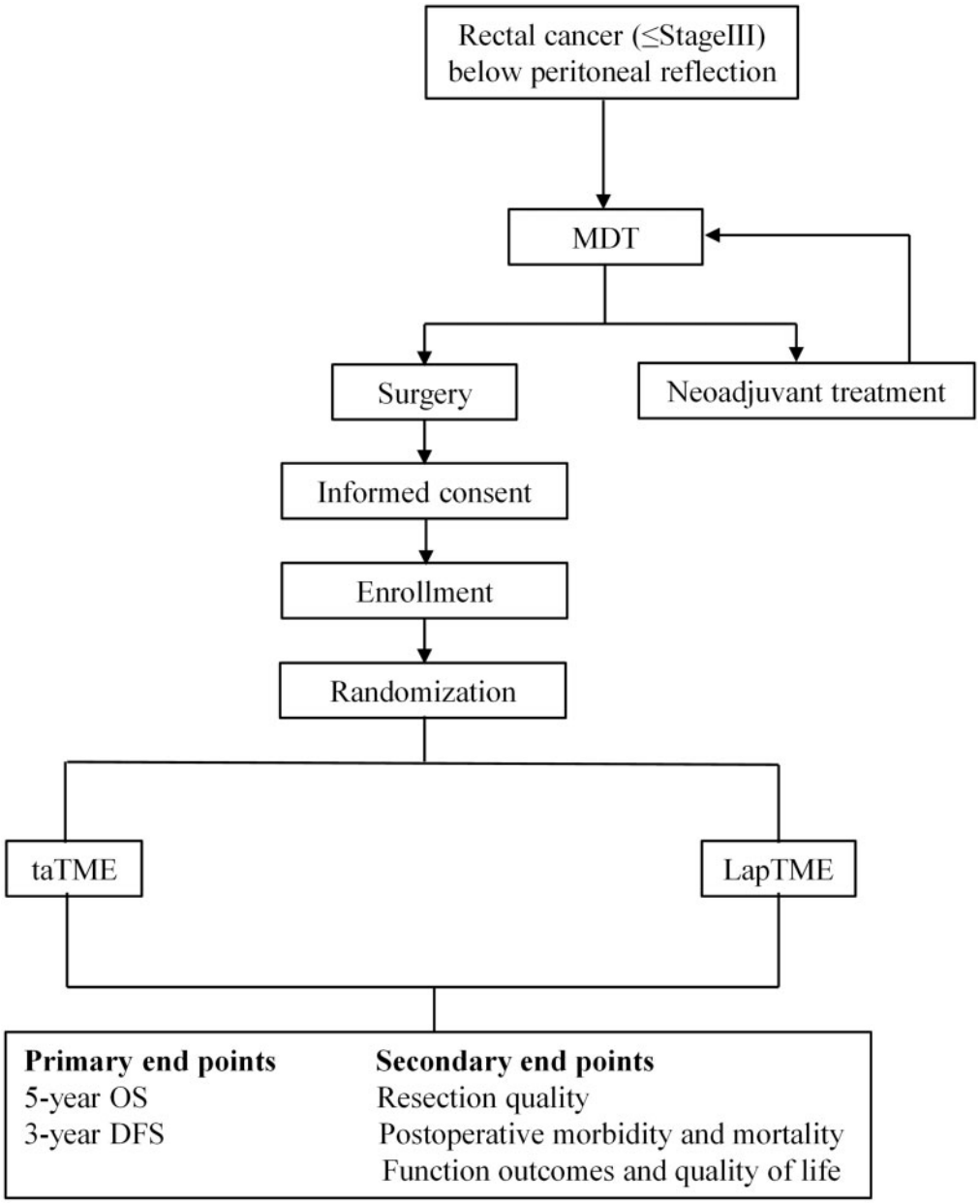

Figure 1. Study scheme of the TaLaR trial. taTME, transanal total mesorectum excision; lapTME, laparoscopic total mesorectum excision; OS, overall survival; DFS, disease-free survival.

a history of rectal surgery, pregnancy, absolute contraindications to general anesthesia or prolonged pneumoperitoneum, and signs of acute intestinal obstruction or synchronous abdominal surgery. Furthermore, patients are also excluded from this trial if they have a medical history of familial adenomatous polyposis coli, hereditary non-polyposis colorectal cancer, active Crohn's disease, ulcerous colitis, adequately treated basocellular skin carcinoma, *in situ* cervix uteri carcinoma, and/or refuse neoadjuvant therapy.

Randomization

Once the eligibility of the case has been affirmed, patient details will be recorded and preoperative files will be reviewed by the corresponding medical center. All patients will be allocated randomly to either taTME group or lapTME group, subsequently. Randomization will be executed by computer through the internet and stratified for different institutions. Patients will be randomized in a 1:1 ratio. Data will be analysed on an intention-to-treat basis in case patients are not subjected to the randomized treatment modality.

Surgical procedures

Experimental group

In patients of the taTME group, the rectum is mobilized transanally according to rules of TME. The corresponding procedure is considered a resection to the level of the peritoneal reflection from 'down to up'. The procedures applied are as follows. The patient is placed in an extended lithotomy position and prepared for a combined transabdominal and transanal surgery in

case laparoscopic assistance or conversion to open surgery is necessary. After digital anal dilation and perineal disinfection, a lone-star retractor or a metal circular retractor with six radiating sutures is applied to fully expose the anorectum. Two 2/0 Prolene purse strings are placed to tightly occlude the rectal lumen. Depending on the tumor height, it is either placed under direct vision or after introducing the transanal platform but it has to be $\geq$1 cm away from the tumor. A full-thickness circumferential dissection or extension of the intersphincteric plane (if intersphincter resection had been done) towards the perirectal plane is then performed. The dissection is started posteriorly first to provide access to the presacral plane, as this cotton-like avascular plane is easier to identify, which is consistent with the 'holy plane' of TME. The embryological plane is then extended either laterally or anteriorly in a sequence depending on the specific situation, while the whole procedure progressed proximally. If the transanal procedure showed difficulty in ligating the inferior mesenteric vein and mobilizing the proximal colon requiring mobilization of the splenic flexure to obtain adequate colonic length, standard laparoscopic assistance is introduced. After a resection of the rectum and the mesorectum, a hand-sewn or stapled anastomosis is created according to the preference of the performing surgeon, as well as a diversion ileostomy and drainage of the surgical field [12, 13].

Control group

Cases of lapTME in which transitional laparoscopic low anterior resection (LAR) with colorectal or coloanal anastomosis is the procedure constitute the control group. Extralevator abdominoperineal excision (ELAP; indicated in patients with tumor in growth in the anal-sphincter complex or levator ani) and abdominoperineal resection are excluded. A complete laparoscopic excision of the total mesorectum is considered mandatory for the procedure to qualify as 'laparoscopic TME'. The level of transection of the inferior mesenteric artery is up to the surgeon's preference. The splenic flexure have to be mobilized when undue tension at the anastomosis is likely. Other aspects of the surgical procedure such as type of anastomosis, use of diverting ileostomy, and drainage of surgical field are up to the discretion of the surgeon.

Conversion is decided by the surgeon either to provide additional safety for the patient or to complete the TME procedure adequately if technical difficulties arise that result in the inability continue or associated conditions requiring treatment occur. Multiport laparoscopy is allowed for the abdominal part of the procedure in both treatment arms as well as single-port. Robotic TME is not allowed, since it results in different primary and secondary endpoint compared with laparoscopic TME. In laparoscopic TME, conversion is determined when the completion of the dissection of the mesorectum is performed through a traditional open abdominal or transanal approach. In taTME, conversion (to either laparoscopic or open TME) is defined as the interruption of transanal TME due to technical difficulties or complications during transanal dissection, requiring the completion of the majority of TME using the abdominal approach.

Post-operative follow-up schedule

Follow-up (according to ESMO guidelines) will be carried out for a period of 5 years following surgery [14]. An enhanced CT examination of the thorax, abdomen, and pelvic cavity will be given to evaluate the development of any local recurrence and distant metastases. Recurrences and deaths should be reported to the coordinating center within 2 weeks of detection. Patients with local recurrence or distant metastases will continue follow-up procedures for at least 3 years after detection or until death. Functional surgery outcome and quality of life will be evaluated at 3, 6, 9, 12, 24, 36, 48 and 60 months post operation (measured by low anterior resection syndrome and Wexner questionnaires, and EORTC QLQ-CR38 and C).

Assessment of outcome

Primary endpoints

Primary endpoints of this clinical trial are a 3-year disease-free survival (DFS) rate and a 5-year overall survival (OS) rate. DFS is defined as the length of time following primary cancer treatment while the patient survives without any signs or symptoms of that cancer. For the aim of DFS evaluation in this clinical trial, standard events to consider include primary tumor recurrence at resection margins, metachronous cancer development at the remnant colon, histologically proven or radiologically apparent recurrence in the peritoneal cavity including intra-abdominal lymph nodes, distant metastasis, newly developed malignancy in other organs, and other causes of death. The OS rate is defined as the percentage of patients included in the study who are still alive for a certain period following surgical treatment.

Secondary endpoints

These include the quality of the mesorectum or TME specimen [15], resection number of retrieved lymph nodes, morbidity, mortality, functional outcome, and quality of life.

Sample-size calculation

All subjects were expected to take part in the trial for 5 years, with an average follow-up time of 5 years. According to existing results for our hospital, the 5-year survival rate of patients undergoing traditional abdominal TME for stage I–III rectal cancer was 77.4%. We introduced the non-inferiority test formula by applying a 1:1 ratio between the experimental group and the control group to calculate the total sample size. The non-inferiority margin is set as 10%. Based on a log-rank test in which alpha = 0.05 and beta = 0.2 (efficacy = 80%), 557 patients are needed for each group considering ~20% of the shedding rate.

Data analysis

Survival status will be described using the Cox proportional-hazards model, whereas survival-curve estimation will be carried out using Kaplan–Meier curves. Categorical variables will be tested using a Pearson's chi-squared test or Fisher's exact test, while continuous variables will be tested using a Student's *t*-test or an appropriate non-parametric method. Any difference will be considered statistically significant if $P < 0.05$.

Quality assurance

Based on our previous learning-curve study [16], each center should finish at least 35 cases applying the procedure, as taTME is still a new technology. Before the trial entry, each surgeon from the participating subcenter will need to provide two unedited videos for both lapTME and taTME. Members of the Quality Control Group will assess the videos independently before

voting for approval. Every surgical video will need to be recorded and saved during the trial period. Videos will be reviewed by the Quality Control Group every 3 months.

Trial registration

The clinical trial has been registered at http://clinicaltrials.gov (NCT 02966483).

Status of enrollment

We enrolled the first patient in April 2016 and 600 patients were enrolled by February 2020. We expect to complete the enrollment in September 2021.

Discussion

Colorectal cancer is the third most common cancer globally [1]. In the USA, more than one-third of people developing colorectal cancer die of the disease [17]. Radical resection surgery remains the primary strategy to cure the illness so far. Rectal-cancer surgery is usually recognized to be technically more difficult than colon surgery, mainly due to limited working space and vision in the pelvic cavity. Particularly in low rectal cancer, whether applying laparoscopy or laparotomy, the distal margin of the resection is usually very difficult to confirm for the visualization from 'up to down', leading to an increased risk of positive circumferential resection margin or insufficient distal margin and the risk of recurrence [18, 19].

For this reason, a new approach to execute TME from 'down to up' was proposed, which is also known as taTME or transanal endoscopic surgery. It was first reported by Sylla *et al.* in 2010 [8]. Since the procedure is started from the distal margin of the resection, theoretically, it could achieve better TME completeness and circumferential resection margin (CRM) in low rectal cancer [20]. Many authors have reported its safety and feasibility. A large-scale study on taTME in terms of sample size was recently reported by Penna *et al.* [21]. In this study, 720 patients were registered internationally, including 634 patients with rectal cancer and 86 patients with benign diseases. Perineal and abdominal conversion rates were 2.8% and 6.3%, respectively. An R0 resection was achieved in 97.3% of patients. In addition, post-operative mortality and morbidity rates were 0.5% and 32.6%, respectively. Another report included 140 cases gathered from three centers [10]; in this study, 97.1% and 2.1% of patients underwent complete and nearly complete TME, respectively. Minor complications (Clavien-Dindo I and II) occurred in 24.2% of patients, whereas serious complications (Clavien-Dindo III and IV) occurred in 10% of patients. However, no patient died within the post-operative period of 30 days. Furthermore, with a median follow-up of 15 months, a local recurrence rate of 2.3, and a systemic recurrence rate of 7.6% were identified. Thus, these results have proved the safety and feasibility of taTME.

In comparison to the traditional laparoscopic approach, taTME also exhibited its potential advantages in certain aspects of rectal cancer. Fernández-Hevia *et al.* [22] compared rectal-cancer patients with identical characteristics in taTME and lapTME, and found that the surgical time was shorter in the taTME group (215 ± 60 min) than in the lapTME group (252 ± 50 min) ($P < 0.01$). Moreover, coloanal anastomosis was performed more frequently (43% vs 16%, respectively; $P = 0.01$) and the distal margin was longer (2.7 ± 1.7 mm vs 1.8 ± 1.2 mm, respectively; $P = 0.05$) in the taTME group than in the lapTME group. There was no significant difference in the 30-day post-operative complication rate between the two groups, but early readmissions were more frequent in the lapTME group than in the taTME group (22% vs 6%; $P = 0.03$). A further matched case–control study involved 50 patients with middle or low rectal cancer after neoadjuvant chemoradiation therapy who underwent taTME thereafter, as well as 100 matched patients who received LapTME [23]. The results showed a longer distal margin in the taTME group than in the lapTME group. Otherwise, a meta-analysis recently showed that taTME was a feasible and safe method compared with lapTME for mid- and low-rectal-cancer patients, as the patients undergoing taTME had longer and lower positive CRM, a higher quality of resected TME, and shorter post-operative hospital stays [24]. Nonetheless, multicenter randomized–controlled trials are needed to further assess the safety and efficiency of taTME.

This TaLaR study is the first prospective multicenter study to investigate long-term outcomes of taTME for rectal cancer. The primary study endpoints including DFS and OS are based on oncological results, whereas the secondary endpoints focus on safety, morbidity, and functional outcomes. Our presumed result is that taTME is superior to laparoscopic surgery for patients with low rectal cancer in aspects of post-operative recovery, resection quality, functional outcomes, and quality of life without impaired long-term survival. Our study objectives were set based on previous knowledge of taTME for rectal cancer in practice. Treatment strategies for all study objectives were referred to standard National Comprehensive Cancer Network guideline recommendations for rectal cancer to eliminate the influence of other factors, ensuring that the only variable remains the surgical procedure. Another multicenter study concerning taTME (COLORIII), hypothesizing that taTME has a lower involved CRM rate than lapTME in patients with middle and low rectal cancer, was designed as a superior study with the primary endpoint of CRM status and secondary endpoints including quality of resected mesorectum, morbidity and mortality, percentage of sphincter-saving techniques, functional outcome, quality of life, local recurrence, DFS, and OS [25]. Study objectives involve all patients with stage I–III rectal cancer for whom TME is indicated, who are suitable for elective resection, and who have rectal carcinoma observed at colonoscopy and histologically confirmed through biopsy. The length between the distal border of the tumor and the anal verge must be within 10 cm on an MRI scan. The COLOR III study started in May 2016 and was extended for 4 years to enroll 1,098 patients in total.

Conclusion

Evaluation is indispensable for all surgical innovation [26]. As a developing technique, taTME still needs to be validated repeatedly in many prospective trials before its wider adoption or acceptance as standard surgical therapy for rectal cancer. We expect all these prospective trials to provide more powerful evidence for the application of taTME.

Authors' contributions

Z.W.Z. and S.L.L.: conceptualization, date curation, methodology, validation, visualization, and writing of the original draft. H.Z., Q.W., M.Y.R., M.W., W.D.T., Q.X., and Y.X.M.: validation, formal analysis, resources, review of the writing, and editing. A.W.W., Y.G.C., B.F., Z.L.S., L.H., and X.W.Z.: writing of the original draft, review of the writing, and editing. M.H.Z., L.K., and J.P.W.: conceptualization, writing of the original draft, review of

the writing, editing, funding acquisition, and supervision. All authors read and approved the final manuscript.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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