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Tatme Combined with IORT for the Treatment of Locally Advanced Rectal Cancer

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Keywords:

TaTME; IORT; Distal resection margin; Local control; Circumferential resection margin; Overall survival

Abbreviations:

TaTME: Transanal total mesorectal excision; IORT: Intraoperative radiotherapy; LC: Local control; OS: Overall survival; CRM: Circumferential resection margin; DRM: Distal resection margin; DFS: Disease-free survival; EBRT: External beam radiotherapy; NOTES: Natural Orifice Transluminal Endoscopic Surgery

1. Abstract

1.1. Background: Colorectal Cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. The surgical method is controversial due to the difficulty in Sphincter-preserved surgery.

1.2. Method and result: Transanal Total Mesorectal Excision (TaTME) is a surgical method that completely passes through the anus and separates the mesentery from the bottom up to the inferior mesenteric arteries and veins. Intraoperative Radiotherapy (IORT), also an emerging treatment method for locally advanced tumors, can lead to the potential for dose escalation, reduce overall treatment time, and increase patient convenience. Therefore, we combine the two and use IORT to make up for the difference in efficacy that may be caused by the operators' technical level in the implementation of taTME surgery, and chose a subject for this purpose. A 65-year-old male patient was diagnosed with rectal adenocarcinoma and the preoperative clinical stage was T2N2bM0 in the Second Hospital of Jilin University. The tumor involved 60 mm rectal wall and was located 30 mm from the anal margin. After the consent form was signed by the patient, taTME and low-energy X-rays IORT were successfully performed.

1.3. Conclusion: TaTME with low-energy X-rays intraoperative radiotherapy not only benefit the circumferential resection margin but also improve the local control for the patient with locally advanced rectal cancer.

2. Statement:

In this article, we proposed a combined procedure: taTME combined with IORT, and included one subject. We took advantage of the advantages of these two methods. The patient's anus was successfully preserved, and no obvious complications such as anastomotic leakage occurred.

3. Introduction

Colorectal adenocarcinoma is the third most common cancer and The Total Mesorectal Excision (TME) rule is the gold standard of surgery to achieve negative Distal Resection Margin (DRM) and Circumferential Resection Margin (CRM) which are closely associated with Local Recurrence (LR) and disease-free survival (DFS) [1, 2]. Medium or lower rectum cancer is often a challenge for surgeons to take the surgical dissection due to the limited width of the distal pelvis and the difficulties in visualization. Abdominoperineal resection (APR) has been the standard surgical method for the treatment of low rectal cancer since it was proposed in 1908 [2]. There are various surgical approaches to locally advanced rectal cancer, but they all build on the two basic surgical approaches of APR and anterior rectal resection, such as columnar APR, intersphincterictesection (ISR) [3], and pull-out surgery.

To overcome these challenges and combine the concept of Natural Orifice Transluminal Endoscopic Surgery (NOTES) and Transanal Endoscopic Microsurgery (TEM), transanal TME (taTME) aiming to achieve more accurately complete resection of distal mesorec-

tum was firstly introduced by Sylla [4] and has been arousing a great deal of attention. TaTME is a surgical method that completely passes through the anus and separates the mesentery from the bottom up to the inferior mesenteric arteries and veins. It has the advantages of good inferior and circumferential margins and is suitable for rectal cancer under peritoneal reflex [5]. Colorectal surgeons around the world have basically reached a consensus on TaTME, that is, for the challenges of pelvic operation and laparoscopically assisted minimally invasive surgery caused by obesity, ensuring adequate distal resection margin of low tumors and maintaining the integrity of mesorectum, the proposal and practice of TaTME provide a new and effective choice for colorectal surgeons. As TaTME uses a transanal rather than a transabdominal approach, it allows for effective TME of the lower and middle rectum and ensures safe distal incisional margins through the manipulation of the transanal platform. There are still doubts and controversies in the technology and function of TaTME, such as a long learning curve and greater difficulty in surgery [6]. It has been reported in the literature that TaTME has an effect on short-term urination and anal function after surgery.

Furthermore, it is of great significance to complete surgical resection and to ensure that the margin is negative and requires multiple methods including surgery, external beam radiation therapy and chemotherapy. Intraoperative Radiotherapy (IORT) can accurately set the irradiation field under direct vision during the operation, and irradiate the tumor or metastasis that cannot be completely resected with an appropriate therapeutic dose [7]. At the same time, with the help of applicators of different shapes and sizes, it can effectively protect the surrounding normal tissues [8]. Compared with external beam radiotherapy, the advantages of IORT include the potential for dose escalation, reduced overall treatment time, and increased patient convenience. Especially, the main advantage of IORT is sterilizing close or positive resection margins.

To overcome the higher positive rate of CRM and improve the Local Control (LC), we take the advantage of taTME and INTRABEAM IORT using low-energy X-rays to provide a new treatment modality in locally advanced patients with the above risk factors. The proper combination can benefit more rectal cancer patients, perform higher-quality TME surgery for patients with "difficult pelvis" and low rectal cancer, and ensure the distal margin of the specimen more effectively. IORT can be used as a supplementary treatment to make up for errors caused by different quality control effects of surgeons [9]. As far as we know, our study is the first report of this novel treatment modality and the purpose of this study is to demonstrate our preliminary experience.

4. Method

The study complied with the "Declaration of Helsinki" and was approved by the Ethics Committee of the Second Hospital of Jilin University, and the patient's informed consent was obtained. And the treatment is jointly participated by surgeons, radiation oncologists, and technicians from the same team.

5. Patient Selection

Based on the early research and consensus, it's confirmed that the ideal candidate for taTME is patients with pelvic stenosis, enlarged prostate, visceral obesity or body mass index (BMI)>30 kg/m2, tumor diameter >4 cm, and distorted tissue makes neoadjuvant radiotherapy difficult to implement [1,10,11]. A proper patient was selected according to the conditions mentioned above.

A 65-year-old male complaint of bloody stools for 1 month to our hospital. The colonoscopy showed a rectal mass located approximately 6 cm from the anal verge and the biopsy revealed rectal adenocarcinoma. No distant metastasis was found by the whole-body Computed Tomography (CT) scan. Magnetic Resonance Image (MRI) showed the tumor involved 60 mm rectal wall (Figure 1A) and located 30 mm from the anal margin (Figure 1B, C). In addition, some suspected lymph nodes were also observed by MRI (Figure 1D). The mesorectum fascia (MRF) and extramural vascular invasion (EMVI) were positive and the preoperative stage was T2N2bM0.

He had no family history and other systemic diseases. The level of carcinoembryonic antigen (CEA) was 1.11 ng/ml (normal, 0-3 ng/ml) and carbohydrate antigen199 (CA199) level is 37.4 U/ml (normal, 0-35 U/ml). In addition, the BMI was 25.43 kg/m2. Due to the exitance of intestinal obstruction, preoperative neoadjuvant radiotherapy and chemotherapy weren't preferred treatments compared with surgery. Based on preoperative evaluation, TaTME surgery combined with IORT using low-energy X-rays was performed for the patient.

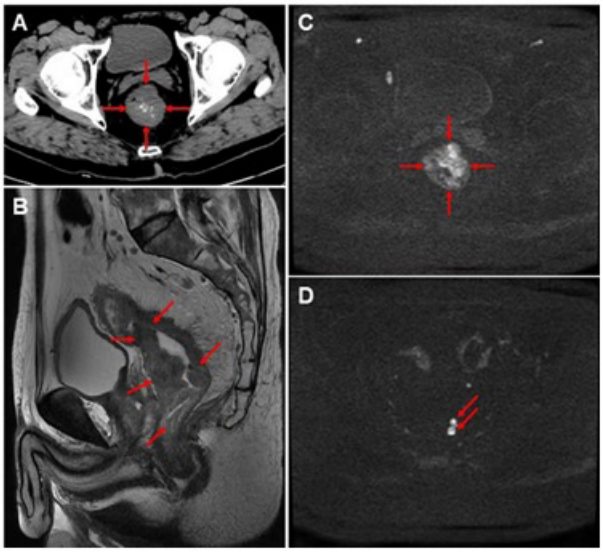

Figure 1: Imageological examination. (A) CT showed the thickening of the rectal wall
(red arrows). (B) MRI showed the tumor involved 60 mm rectal wall and located 30
mm from anal margin. Red arrows indicated the tumor. (C) The high signal mass (red
arrows) under MRI examination showed the tumor. (D) The red arrows indicate the
suspected lymph nodes.

6. Surgical Steps

After general anesthesia was performed, the patient was placed in a lithotomy position to facilitate perineal view and transanal approach. A 10-mm trocar port was inserted through the umbilicus to insufflate the abdomen and a 12-mm trocar port was inserted through the site preoperatively marked for ileostomy. Other three 5-mm trocar ports were routinely inserted following the laparoscopic rectal surgery.

6.1. Transabdominal Approach

- Laparoscopic exploration was performed.
- The origin of the inferior mesenteric artery (IMA) was ligated and lymphadenectomy around IMA was done after the patient was placed in the right-head-ventral position to achieve an optimal view of the left colon. (Figure 2A)
- Dissect the left side colon to the splenic flexure of the colon with the medial-lateral retroperitoneal approach.
- The anterior mesorectum dissection was progressed to the level of seminal vesicles anteriorly (Figure 2B) and the posterior mesorectum dissection was progressed to the level of the 5th sacral or caudal vertebrae. (Figure 2C)
- The transanal approach was operated while the IORT device was modulated.

6.2. Transanal Approach

- The skin around the anus was stretched in six directions by sutures to achieve optimal view.
- Under direct surveillance, a purse-string suture was performed at 1 cm from the lower edge of the tumor to close the rectal cavity and created an operating cavity (Figure 3A).
- Connect the laparoscopic pneumatic machine and the transanal operation platform pushed into the anus to reach a stable pressure of the operating cavity in 13 mmHg. (Figure 3B). In this study, we used the plastic bag to connect the laparoscopic pneumatic machine to the transanal operation platform to obtain stable pressure.
- Under laparoscopic surveillance, dissect the full thickness of the rectal wall circumferentially (Figure 3C) and the mesorectum along the “holy plane” between the visceral and parietal layers of pelvic fascia to meet the transabdominal dissection plane.
- After the rectal mass was dragged up transanally, the proximal sigmoid colon was fixed by the purse-string forceps and cut off by scalpel to remove the rectal specimen (Figure 3D), and the top part of the stapler was inserted into the colon. The dissected rectal specimen was photographed (Figure 3E).
- Based on the width of the anus, 4-cm in diameter applicator was pushed into the tumor bed transanally (Figure 3F, G). Under the transabdominal laparoscopic surveillance, the applicator was pushed closer to the tumor bed and wet gauzes were put to isolate and protect the adjacent structures from radiation (Figure 3H).
- IORT was operated on with a prescribed dose of 18 Gy.
- Purse-string suture was performed at the distal resection site of the intestinal tissue and the digestive continuity was restricted by the circular stapler (Figure 3I).
- Prophylactic ileostomy was performed synchronously.

The whole operative time was approximately 350 min, consisting of 40 min for laparoscopic dissection, 120 min for taTME procedure, 30 min for radiation, 40 min for the connection and prophylactic ileostomy.

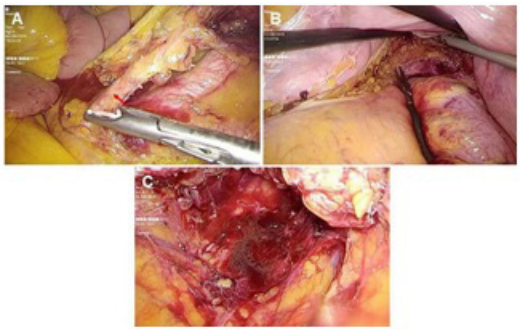

Figure 2: Transabdominal approach. (A) IMA was ligated. (B) The anterior mesorectum dissection was progressed. (C) The posterior mesorectum dissection was progressed.

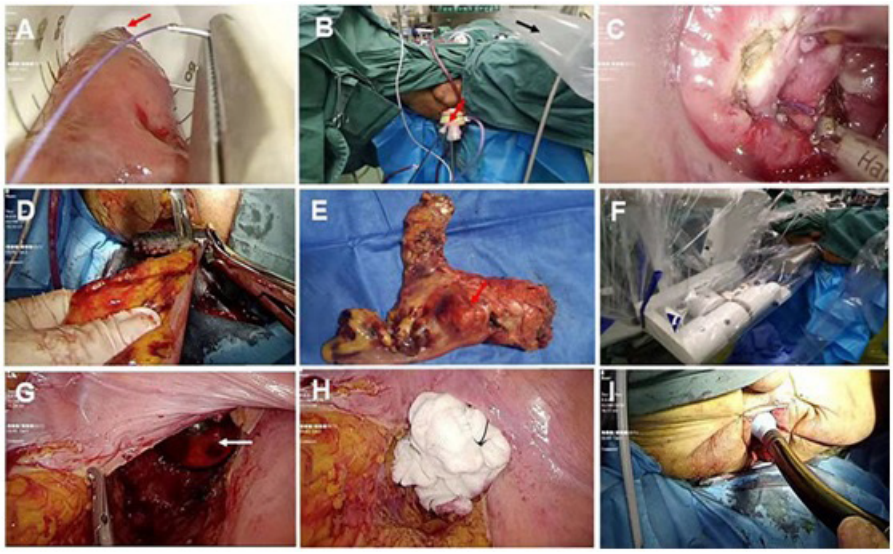

Figure 3: Transanal approach. (A) Purse-string suture was performed at 1 cm from the lower edge of tumor. Red arrow indicates the lower edge of the tumor. (B) Connection of the laparoscopinc pneumatic machine and the transanal operation platform. Red arrow indicates the transanal operation platform. Black arrow indicates the plastic bag which was used to obtain a stable pressure. (C) The full thickness of rectal wall was dissected circumferentially. (D) The rectal mass was dragged up. (E) The dissected rectal mass (red arrow). (F, G) The applicator was pushed into the tumor bed transanally. White arrow indicates the applicator in the pelvic cavity. (H) Wet gauzes were put to isolate and protect the adjacent structures from radiation. (I) The digestive continuity was restructed by the circular stapler.

7. Result

The bowel recovery of patient happened on the 8th day post-surgery. Postoperative pathology revealed the moderately differentiated rectum adenocarcinoma (pT3N2bM0) and the DRM and CRM were negative. To prevent the occurrence of anastomotic or the anal stenosis, dilation of anal canal was done by finger three to five times a day. The patient recovered uneventfully and was discharged to the hospital on the 15th day.

Six to eight cycles of XELOX chemotherapy regimen were suggested to the patient in the next treatment phase. Specifically, it is an intravenous infusion of oxaliplatin at a dose of 130 mg/m2, intravenous injection for more than 3 hours in a single day, combined with capecitabine orally, twice a day for 14 consecutive days, at a dose of 1000 mg/m2. The above chemotherapy was repeated every 3 weeks for a total of 8 cycles. The patient underwent postoperative chemotherapy as recommended. There were no short-term complications after taTME, such as urethral injury and bladder dysfunction, and no long-term complications such as tumor metastasis and recurrence (06, 2021).

8. Discussion

TME, which is a standard surgical approach aiming to achieve complete resection of the rectum and mesorectal lymph nodes, could improve LC and Overall Survival (OS) [12]. And CRM is one of the key prognostic factors that determine LR. The value of CRM involvement is not only concerning for LR or development of distant metastases but also a strong predictor of whether postoperative chemoradiotherapy should be provided. Medium or lower rectum cancer is often a challenge for surgeons to take the surgical dissection due to the limited width of the distal pelvis and the difficulty in visualization. Especially, narrow male pelvis, high Body Mass Index (BMI), bulky tumors, visceral obesity, and locally advanced tumors have been identified as risk factors predicting intraoperative difficulty and potentially leading to a poor oncology specimen. Due to the limited field of vision, laparoscopic or open TME is difficult to identify the resection of DRM, which may lead to the risks of uncomplete TME or positive CRM in patients with the above factors.

TaTME is a surgical method that has been gradually developed in the past 5 years and has received wide attention from colorectal surgeons. TaTME includes the ‘‘push me-pull you’’ and “bottom-to-up” approach, which allows two-team synchronous collaboration to further shorten the operation time [13]. The ‘‘push me-pull you’’ approach can afford the crucial medial retraction of the mesorectum to secure sexual function by providing better visualization of the pillars, plexuses, and neurovascular bundles [14]. The “bottom-to-up” approach makes the dissection more easily and efficiently by overcoming the limitations [15] and also allows for no need for an extra abdominal assist incision. Furthermore, cutting specimens in vitro can avoid multiple stapler firings to reduce the incidence of anastomosis leakage [16].

When the abdominal dissection is completed, based on the transanal approaches of deep pelvic dissection, laparoscopic-assisted taTME can identify the resection plane clearly to achieve better visualization of the distal rectum and more clearly distal resection margin to assure the safety of CRM in these challenging pa-

tients [17]. In an RCT comparing taTME to laparoscopic TME in 100 patients with low rectal cancer, [18] revealed lower positive CRM rates in taTME group (4%) than that in the laparoscopic TME group (18%). TaTME can also reduce the proportion of open surgery with only 0-9.1% in taTME cases, which is much lower compared with that in laparoscopic TME cases in COLOR II [19]. Marks published for the first time the long-term survival results of patients with rectal cancer after TaTME. The single-center study included 373 cases of rectal cancer with TaTME surgery. The quality of TME surgical specimens was evaluated as "complete" and "nearly complete" accounting for 96%, 94% were CRM-negative, 98.6% were specimens with negative distal resection margins, the 5-year local recurrence rate was 7.4%, and the 5-year overall survival rate was 90%, indicating the excellent long-term results of TaTME surgery.

As the standardization of surgical techniques has not yet been achieved, a complete learning curve has not been explored and a systematic training mechanism has not been established, the promotion of taTME has been restricted. Despite advances in the treatment of locally advanced rectal cancer, LR remains a major challenge.

IORT has the irreplaceable advantage of conventional external beam irradiation. Firstly, during the operation, the irradiated area is fully exposed. The doctor can observe with the naked eye and accurately sets the irradiation area through the light limiting tube, which realizes the seamless connection between surgical resection and radiotherapy, eliminates the possibility of regeneration of tumor cells, and greatly reduce the LR rate. Moreover, the radiation dose is determined based on the balanced distribution and the allowable dose of the surrounding normal tissues. High-energy electronic wires and light-limiting tubes of different sizes are used to ensure that the radiation dose drops sharply after reaching the maximum dose depth to protect healthy tissues. Finally, the combination of surgery and IORT is a short-term dual-effect for patients. The biological effect of single high-dose radiation during surgery is 1.5-2.5 times that of conventional external radiation. Therefore, IORT can reduce the systemic response and bone marrow suppression, and the precise irradiation range enables the patient to obtain a high treatment gain ratio. This combined application can reduce the LR rate, improve OS, effectively reduce the postoperative radiotherapy time and reduce the overall treatment cost. IORT has been introduced to multiple treatment modalities [20]. reported a systematic review of 15 studies and revealed the 5- to 6-year LC rates of IORT (> 80%) and the OS of IORT (65%) for primary locally advanced rectal cancer [21]. reported a retrospective review of 42 patients treated with INTRABEAM IORT. The 1-year recurrence rate and distant metastases were 16% and 32% in the whole cohort, respectively [22]. also reported that the recurrence rate was 13% in 68 patients (47 stage II vs 21 patients stage III) treated with INTRABEAM IORT.

The mobile device of INTRABEAM PRS can generate isotropic dose distribution in the applicator with a higher application dose rate of about 10Gy/min, which not only inhibits the potential proliferation or metastasis of residual tumor cells but also shortens the treat time [23]. Furthermore, with the increased distance from the applicator surface, the dose attenuates quickly so that it could lead to better LC and reduce damage to the adjacent critical tissues and surrounding organs. In addition, the applicator with the flexibility at 6 degrees [23] of freedom enables it could be placed into the targeted area by anus easily, which avoids the extra abdominal incision and accords with the concept of “NOTES”.

INTRABEAM PRS could deliver a large radiation dose (10-20 Gy) to the targeted area with rapid dose attenuation. For IORT, the radiation dose (18-20 Gy) is equivalent to the external dose of 50 Gy [24]. In a multi-institutional phase randomized trial of IORT of rectal cancer [25] delivered 18 Gy in the IORT arm and the results revealed that there was no significant superior radiative toxicity [21]. delivered a median safe surface dose of 14.4 Gy and a dose of 5 Gy was prescribed to a depth of 1 cm in locally advanced rectal cancer. In our institution, we have performed INTRABEAM IORT combining Miles, Dixon, laparoscopic ISR (Lap ISR) in locally advanced rectal cancer for more than 5 years. Until now, no obvious radiative toxicity has occurred under the radiation dose of 18 Gy. As a result, 18 Gy radiation dose was recommended in this study. In future studies, more factors will be considered with larger samples and longer follow-up.

In our study, a proper patient was selected according to the conditions mentioned above. Especially, the BMI of the patient is 25.43 kg/m2 which indicates that the pelvis is narrow for the male patient, the maximum diameter of the tumor is about 7 cm, and the lower edge of the tumor locates 3 cm from the anal margin. All of these above may lead to the insufficient space of DRM and positive CRM. Due to the exitance of intestinal obstruction, preoperative neoadjuvant radiotherapy and chemotherapy weren’t preferred treatments compared with surgery. INTRABEAM IORT aims to replace the therapeutic effects of preoperative chemotherapy and radiotherapy in our study. To our knowledge, this is the first time combining taTME with INTRABEAM IORT to improve the LC in locally advanced rectal cancer patients with risk factors predicting difficult manipulation and positive CRM.

There were no symptoms of urinary dysfunction observed and the result of the urinary function questionnaire was satisfactory after surgery, which indicated the good preservation of autonanerve of taTME and dose attenuation effect of INTRABEAM IORT. However, compared to the abdominal approaches for rectal cancer, taTME arises new specific complications, including rectal or vaginal perforation [26], bladder injury, and the injury of the urethra and urethral sphincter [27], which not commonly occurred in laparoscopic TME. Therefore, in future follow-up, more attention

should be paid not only to LC, anastomotic strictures, anorectal measurements and urinary incontinence, but also to LARS and urethral function. Fortunately, this patient did not develop any of these complications.

In our study, importantly, the DRM was negative and there were no signs of anastomotic fistula in this patient. The color of the anal canal tissues near the anastomosis changed to normal gradually which indicated good blood supply. To achieve the satisfactory anastomosis in taTME, the two-steps purse-string suture is vital. The first step of purse-string suture is performed at a distance of 1 cm from the lower edge of the tumor, and only the mucosa and submucosa are sutured. When suturing too many tissues, the purse-string may not be sutured tightly and the isolation of the tumor may not be achieved. For the second step of purse-string suture, a fully sutured intestinal wall should be achieved to obtain the full-thickness anastomosis of the disconnected intestinal tissues.

Whether it is taTME surgery or IORT, attention must be paid to protect anorectal function, especially the frequency of bowel movements and fecal incontinence. TaTME transanal approach may cause damage to the sphincter [28] and the radiotherapy may induce the fibrosis around the rectum affecting the compliance of the rectum [29]. Both of them may lead to the Low Anterior Resection Syndrome (LARS), a complex of symptoms consisting of incontinence for flatus and /or feces, constipation, urgency, and bowel movements [30].

Some tips on the surgery were shared as follows. Due to the lack of a special pneumatic machine to maintain the stable pressure in the transanal procedure, a plastic bag was used to connect the laparoscopic pneumatic machine to the transanal operation platform to obtain a stable pressure. Furthermore, the anus could be exposed by sutures instead of a Longstar retractor to achieve an optimal operation field. To our knowledge, our study is the first to report the taTME with INTRABEAM IORT using low-energy X-rays in locally advanced low rectal cancer, and several advantages of the treatment modality were concluded as follows.

First of all, the procedure of taTME surgery has not yet been standardized, and the requirements for surgeons are relatively high. As a new technique, the learning curve of each research center has not yet been fully defined, and systematic and standardized training has not been carried out. The application of IORT to the tumor bed can partially make up for the difference in expected results due to the different techniques of the operating surgeons. Secondly, it is beneficial to obtain satisfying tumor specimens and reduce the positive rate of CRM in patients with risk factors. The addition of INTRABEM IORT can further improve LC. Thirdly, INTRABEAM IORT has the characteristics of dose attenuation, which can enhance the effect of radiotherapy on the tumor bed while reducing damage to the surrounding normal structures, and can partially replace preoperative neoadjuvant therapy [31]. Fourth, due to the mobility of the equipment, INTRABEAM IORT can be performed in an ordinary operating room, instead of transporting patients to a special isolation room, which not only shortens the time but also reduces the risk of transportation.

Therefore, when faced with male and obese patients with locally advanced rectal cancer and challenging pelvic stenosis, taTME combined with low-energy X-ray IORT may not only benefit CRM, but also improve LC. The main limitation of the study is the small sample size included. More subjects will be included in future studies, and we wish that this combined operation will bring you some new ideas.

9. Conclusion

In this article, we proposed a combined procedure: taTME combined with IORT, and included one subject. We took advantage of the advantages of these two methods. The patient's anus was successfully preserved, and no obvious complications such as anastomotic leakage occurred. Moreover, until now, there is no sign of postoperative recurrence. We believe that our report will provide new treatment ideas and enlightenment.

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