Radiotherapy guidelines for rectal cancer in China (2020 Edition)

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Abstract
Rectal cancer is one of the most common malignant tumors. In China, rectal cancer has been the third most frequently diagnosed cancer and the fifth leading cause of cancer death, with changes of residents’ lifestyle factors and diets. The best treatment for rectal cancer depends on many factors. Multidisciplinary Treatment has become the basis for improving the therapeutic effect, in which radiology is increasingly necessary for treating patients with rectal cancer. For patients who have extensive, fixed, bulky tumors or obvious nodal disease, radiotherapy and chemotherapy combined with surgery has emerged as the standard of care. For patients with metastatic disease, the reasonable combination of local and systemic therapy might be an alternative. Improvements in imaging, pathological diagnosis and radiation techniques provide a solid foundation for promoting the level of clinical practice in rectal cancer. High-quality magnetic resonance imaging distinguishing risk stratification, molecular markers predicting therapeutic effect and prognosis, magnetic resonance imaging in delineating target volumes drawn, intensity-modulated radiation therapy, and image-guides radiation therapy for precision treatment delivery are all being widely applied in multiple centers. Furthermore, as the role of targeted therapy and immune therapy has become increasingly prominent, the attempt of combined radiotherapy is also ongoing. In view of the characteristics and current situation of diagnosis and treatment of rectal cancer in China, the guidelines will present the basis and reference for combined treatment and standardized treatments. Meanwhile, there may be continuous new advances in clinical practice, and that will be a new basis to update the guidelines, directly benefiting all rectal cancer patients and facilitating discipline developments.

KEYWORDS
guidelines, radiotherapy, rectal cancer

1 | INTRODUCTION

Rectal cancer is one of the most common malignant tumors. In China, rectal cancer is the third most frequently diagnosed cancers and the fifth leading cause of cancer death, with changes in residents’ lifestyles and diets. The best treatment for rectal cancer depends on many factors. Multidisciplinary treatment (MDT) has become the basis for improving the therapeutic effect, whereas radiology is increasingly necessary for treating patients with rectal cancer. For patients who have extensive, fixed, bulky tumors, or obvious nodal disease,
radiotherapy and chemotherapy combined with surgery have emerged as the standard of care. For patients with metastatic disease, it may be an alternative to reasonably combine local and systemic therapy. Improvements in imaging, pathological diagnosis, and radiation techniques provide a solid foundation for promoting the level of clinical practice in rectal cancer. High-quality magnetic resonance imaging (MRI) distinguishing risk stratification, molecular markers predicting therapeutic effect and prognosis, MRI in delineating target volumes, intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy for precision treatment delivery, are all being widely applied in multiple centers. Furthermore, as the role of targeted therapy and immune therapy has become increasingly prominent, the attempt of combined radiotherapy is also ongoing. In view of the characteristics and current situation of diagnosis and treatment of rectal cancer in China, the guideline will present the basis and reference for combined treatment and standardized treatments. Meanwhile, with the increasing emergence of new advances in clinical practice, the guideline will keep being updated, directly benefiting all rectal cancer patients and facilitating developments in this discipline.

2 | CLINICAL PRESENTATION

2.1 | Symptoms

Rectal cancer in the early stage often presents minimal or no symptoms, so most patients are diagnosed when they are showing symptoms. Patients with symptomatic rectal cancer commonly experience changes in bowel habits, hematochezia, or pain, often accompanied by tenesmus and stool thinning. Less common presenting symptoms include iron deficiency anemia, which may be indicative of more blood loss or longer course of disease. Nausea and vomiting may be the signs of tumor-related obstruction. In severe cases, local infiltration or encapsulated perforation of a rectal tumor may lead to the formation of a malignant fistula. For example, male patients may have difficulty urinating and have fever with unknown origin when the symptoms are serious, which are caused by the tumor invasion in the prostate or the bladder; for female patients, if feces are found in vaginal secretions, they indicate a rectovaginal fistula. Even worse, patients may also be diagnosed by symptoms of metastatic lesions, such as liver masses and pelvic effusion.

The majority of rectal cancer are sporadic cases, occasionally originating from several specific genetic disorders. Familial adenomatous polyposis and Lynch syndrome are the most common disorders in the familial colorectal cancer (CRC) syndromes, but they only account for approximately 5% of CRC cases when adding up these two conditions.2–4

2.2 | Physical signs

Digital rectal examination (DRE) can often aid in finding rectal masses, especially for the tumors in the lower rectum. While a DRE is being carried out, it is recommended by the panel to pay attention to the patient’s position, check the tightness of the anal sphincter, determine whether there are masses in or around the rectal wall, and whether there is stenosis in the rectum. If patients present with a palpable mass, the doctors should note the size, shape, texture, and mobility of the mass, and observe whether there is any pus, blood stool, or mucus after the finger is removed. There are no evident signs for patients with a negative DRE. Only a small percentage of patients may develop abdominal distention and masses in the left lower abdomen. Therefore, it is necessary to notice the signs of distant metastases, such as liver masses and pelvic effusion.

3 | WORK-UP

3.1 | Laboratory tests

3.1.1 | General examination

Blood counts, liver and kidney function tests, virus serum, blood sugar, blood coagulation, and urine and stool routine tests are carried out. Some patients with rectal cancer present with iron deficiency anemia. However, the liver function test lacks sensitivity for the detection of liver metastases.

3.1.2 | Tumor marker

The common tumor markers include carcinoembryonic antigen (CEA), CA199, and CA242, whereas CA724, CA50, and CA195 are less used. CEA, with a higher specificity of 89%, is highly effective for the diagnosis of CRC, which plays a great role in treatment strategies, prognosis assessment, and follow up.5

3.2 | Endoscopy

3.2.1 | Colonoscopy

Colonoscopy, as an important method in the diagnosis of rectal cancer, can not only be used to directly observe the size, shape, color, and location of lesions, but also to obtain tissue samples for pathological examination, so as to make a clear diagnosis. Colonoscopy can be used for the treatment of early colorectal cancer, which is limited to the mucosa or submucosa and without lymph node metastases.

3.2.2 | Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) can be performed in patients with early and advanced rectal cancer without evident lumen stenosis. EUS can evaluate the shape, size, depth of invasion, degree of extraintestinal diffusion, lymph node metastasis, and adjacent tissue involvement, and provide an effective basis for accurate staging.6,7
3.3 | Imaging examination

3.3.1 | Routine examination

For locally advanced rectal cancer, pelvic MRI is the preferred imaging method for clinical staging and risk factor stratification. Computed tomography (CT) scan or contrast-enhanced scan of the chest, abdomen, and pelvis is used to search for possible pelvic or extrapelvic metastases. If the diagnosis of CT is questionable or the treatment decision needs to be changed, it is recommended that liver cell-specific contrast enhanced MRI be used to assess the liver metastasis of rectal cancer.

As the soft tissue resolution of CT scan is inferior to that of MRI, CT scan is not recommended as the preferred imaging method for clinical staging and risk factors stratification of locally advanced rectal cancer. However, if patients have MRI contraindications, CT scan is an alternative and multiplanar reconstruction should be used.

3.3.2 | Special inspection

1. Bone scan is the method for the diagnosis of malignant bone lesions. Positive bone scan findings require X-ray, CT, MRI, single-photon emission computed tomography/CT, positron emission tomography/computed tomography (PET/CT) radiological confirmation.
2. PET/CT is not routinely indicated. For patients with metastatic diseases other than liver metastasis, or with local rectal tumor recurrence, PET/CT can be used for confirmation.

3.3.3 | Clinical stage and risk stratification of rectal cancer assessed by medical imaging

The extent of the rectal cancer is measured from the most caudal aspect of the raised rolled edge of the tumor to the anal verge. The broken line distance between the lower edge of a rectal tumor and the connecting line of the external anal sphincter is recommended by the Chinese Society of Clinical Oncology as the tumor localization standard. High resolution pelvic MRI is suggested to detect extramural depth of rectal cancer invasion, metastatic lymph nodes, and extramural vascular invasion. Positive circumferential resection margin (CRM) is defined as tumor deposits, main tumor extension, extramural vascular invasion (EMVI), or suspicious lymph nodes lying within 1 mm of the mesorectal fascia. The structured report templates can improve the quality of MRI reporting for rectal cancer staging compared with free-text formats, and lead to higher risk satisfaction levels (see Appendix 1). The items should include the extent of tumor, extramural depth of tumor invasion, lymph node, EMVI, and CRM. If the short axial length of the pelvic sidewall lymph node is between 5 and 10 mm, it can be defined as involvement suspected on MRI; it is defined as metastatic lymph nodes if the short axial length of the pelvic sidewall lymph node is ≥ 10 mm.

3.3.4 | Response of rectal cancer to neoadjuvant chemoradiotherapy assessed by imaging

Whether delayed surgery after radiotherapy for rectal cancer can improve the pathological complete remission rate and whether it increases the difficulty of surgery is still controversial. It is recommended to perform MRI imaging evaluation 6–8 weeks after the end of radiotherapy for rectal cancer. It is suggested to deploy the structured report template in the evaluation of the response of rectal cancer, with assessment generally in the sixth to eighth week after neoadjuvant chemoradiotherapy. Any changes regarding clinical stage and risk factors should be clarified in the report. The most important point is to show clinical complete response (CR). The common imaging modalities, such as EUS, MRI, and PET/CT, are helpful in diagnosing clinical CR. If the clinical CR is detected, the strategy of watch and wait can be considered.

4 | DIAGNOSIS

4.1 | Clinical diagnosis

Patients with the aforementioned symptoms (e.g., hematochezia, stool frequency, and stool deformation), and patients in line with one of the following clinical situations, should be highly suspected of rectal cancer.

1. Masses are found at DRE. The mass is hard, brittle, and easy to bleed on touch; rectal stenosis and fixation when palpating in the late stage.
2. Pelvic CT, MRI, and PET/CT examinations can reveal a rectal mass, thickening and stenosis of the rectal wall, or high uptake of fluoro-deoxyglucose by PET/CT.
3. Colonoscopy is recommended. Early lesions present with local mucosal erosion, ulcers, nodules, and polypoid masses. In the middle stage, there is a cauliflower-like tumor or concave ulcer surface. The surface of the tumor is dirty, the texture is stiff, and it is bleeds easily when touched. In the late stage, it can show rectal stenosis.

It needs to be emphasized that clinical diagnosis of rectal cancer should be further confirmed by histopathological examination.

4.2 | Laparotomy or laparoscopic exploration

If the diagnosis is still not definite and rectal tumors are highly suspected after a variety of diagnostic methods, or the distant metastasis of rectal cancer cannot be determined by other auxiliary examinations, such as abdominal metastasis, laparotomy or laparoscopic exploration is recommended. Laparoscopic exploration has the advantages of less trauma and quick recovery, and has little impact on the subsequent regimens, such as radiotherapy and chemotherapy. Although, laparotomy
can be carried out on patients who have a history of abdominal surgery or abdominal adhesions. If the laparoscopic method is chosen, doctors can try to avoid the original surgical or adhesive area as much as possible by combining preoperative images, and insert the trocar with the help of a small abdominal incision.

4.3 Histopathological examination

4.3.1 Biopsy specimens

1. All biopsy tissues should be taken, and it is recommended that they should be embedded in at least two wax blocks for immunohistochemical and molecular pathological detection.

2. Pathological report content should involve histological classification and grading.

4.3.2 Radical specimens

1. It is recommended that the residual or suspected residual tumor area and the intestinal tube within 2 cm above and below the area should be sampled. Pathologists are recommended to evaluate the integrity of mesorectum and circumferential margin.

2. Pathological report contents are as follows. Basic information of patients; location, size, and gross type of tumor; histological classification and grading of tumor (refer to the World Health Organization Standard Version 5); depth of tumor invasion (pT stage); proximal, distal, and CRM; the evaluation of tumor margin, sm3, or pT2 (class I recommendation). If there is no difficulty in performing sphincter-preserving surgery, radical surgery should be considered if the following pathological situations occur after local excision: poorly differentiated tumors, vascular invasion, positive resection margin, sm3, or pT2 (class I recommendation). Chemoradiotherapy is recommended for patients who do not undergo radical surgery (class II recommendation). Concurrent chemoradiation can be considered if it is difficult to carry out an organ-preservation operation in cT1N0 patients who have a strong intention for organ preservation. The subsequent treatment can be selected according to the extent of the tumor response: (i) watch and wait for patients with clinical CR; (ii) transanal local excision for patients with ycT1 tumors; and (iii) radical rectal cancer surgery for patients with ycT2 tumors (class II recommendation). Radical surgery (class I recommendation) and transanal local excision (class II recommendation) can be considered in cT1N0 patients if there is no difficulty in performing sphincter-preserving surgery. Radical surgery should be considered if the following pathological situations occur after local excision: poorly differentiated tumors, vascular invasion, positive resection margin, sm3, or pT2 (class I recommendation).

Radical surgery should be recommended in cT2N0 patients (class I recommendation). Concurrent chemoradiation can be considered if it is difficult to carry out organ preservation operation in cT2N0 patients, but the patient has a strong intention for organ preservation (class II recommendation). The following treatment can be selected according to the extent of tumor response: (i) watch and wait for patients who have clinical CR; (ii) transanal local excision for patients with ycT1 tumors; and (iii) radical rectal cancer surgery for patients with ycT2 tumors. Concurrent chemoradiation can be considered if cT1-2N0 patients are medically unfit for surgery (class II recommendation).

Concurrent chemoradiation + radical surgery + adjuvant chemotherapy (class IA recommendation) or chemotherapy + concurrent chemoradiation + radical surgery + adjuvant chemotherapy (class II recommendation) is recommended for cT3–4 or N+ patients. Short course radiotherapy in combination with radical surgery and adjuvant chemotherapy is recommended for cT3N0 patients (class II recommendation). If the patients do not receive preoperative radiotherapy for various reasons, and pathologically show pT1–2N0 after radical operation, it is recommended to observe and follow up (class I recommendation); if the pathology after radical operation is pT3–4 and/or N+, adjuvant chemotherapy in combination of adjuvant chemoradiotherapy and adjuvant chemotherapy is recommended (class I recommendation). The watch and wait strategy can be used when patients achieve complete clinical response after neoadjuvant chemoradiation (class II recommendation).19,22,23

For stage IV rectal cancer, the primary tumor and distant metastasis should be considered comprehensively, and the sequence of local treatment and systemic treatment should be discussed under the framework of MDT.24,25 For local recurrence without distant metastasis (resectable, without previous chemoradiotherapy), a combination of preoperative concurrent chemoradiotherapy and surgery is the preferred treatment (class I recommendation); if radiotherapy and chemotherapy are not tolerated, direct surgery is recommended (class I recommendation); if surgery is
intolerable, chemotherapy and radiotherapy alone are recommended (class I recommendation).

For patients with resectable local recurrence and a history of previous chemoradiotherapy, but no distant metastasis, direct surgery is appropriate (class I recommended). If surgery is not tolerated, re-radiotherapy and chemotherapy are recommended (class I recommendation). For unresectable local recurrence without distant metastasis, chemoradiotherapy is recommended for those who have not received previous chemoradiotherapy (class I recommendation); whereas for those who have received previous radiotherapy and chemotherapy, they are recommended to undergo re-radiotherapy and chemotherapy (class I is recommended). All patients should evaluate the possibility of re-resection after treatment.26,27

For local recurrence with distant metastasis, we should consider both distant metastasis and local recurrence. It is suggested to choose the best treatment after MDT discussion.

5.2 | Surgical treatment

The surgical treatment regimens are mainly determined by both clinical stage and CRM in rectal cancer.

For stage I rectal cancer, immediate surgical treatment is highly recommended and the total mesorectal excision (TME) principle should be followed, except for some T1N0M0 tumors, for which local excision is also acceptable. When the pathology findings show low differentiation, vessel invasion, positive margin, up to 1000 µm submucosal infiltration or T2/T3 staging of tumor specimens, further radical surgery (class I is recommended) or chemoradiotherapy (class II is recommended) should be implemented.28

For stage II or III rectal cancer with negative CRM, the neoadjuvant chemoradiotherapy is recommended followed by TME-guided rectal surgery.

For stage II or III rectal cancer with positive or suspicious positive CRM, a reassessment of CRM is essential after initial neoadjuvant chemoradiotherapy. If the CRM becomes negative, subsequent surgical interventions can be carried out. If the CRM is still positive, multidisciplinary discussions are necessary and systemic chemotherapy or combined multiple organs resection should be considered for en bloc R0 resection.

For stage IV rectal cancer, chemoradiotherapy and multidisciplinary discussions are the cornerstone of further surgical treatment. However, some emergency conditions, such as intestinal obstruction and hemorrhage, are the indications of operation in rectal cancer patients.

5.3 | Medical therapy

5.3.1 | Preoperative neoadjuvant

5-Fluorouracil + leucovorin (5FU/LV) serves as the preferred treatment recommendation for simultaneous preoperative neoadjuvant or postoperative adjuvant chemoradiotherapy.28,29 A number of recent studies have shown that capecitabine is not inferior to 5FU/LV in efficacy, so that it can replace 5FU/LV in radiotherapy,30 whereas some other studies have shown that raltitrexed is well tolerated by elderly patients in preoperative chemoradiotherapy.31 5FU/LV or capecitabine-based therapy combined with oxaliplatin is not able to improve the survival of patients. Instead, compared with a single drug, the adverse events of treatment are increased.32,33 In addition, neoadjuvant chemoradiotherapy targeted therapy has limited efficacy. Therefore, both of them are not recommended as routine treatments.

5.3.2 | Induction chemotherapy or total neoadjuvant therapy

Phase II studies have shown that induction chemotherapy or total neoadjuvant therapy has yielded great benefits, including early prevention and elimination of micrometastasis; a higher pathological CR rate, a short period of ileostomy, an increase of resection rate, and an improvement in the tolerance and the completion rate of chemotherapy (class III recommendation).34

5.3.3 | Preoperative chemotherapy

Some phase II/III studies have shown that the combination of the three drugs in neoadjuvant chemotherapy FOLFOXIRI alone or with targeted drugs has a higher pathological response rate, effectively avoiding radiation-related damage.35,36

5.3.4 | Adjuvant chemotherapy

Adjuvant chemotherapy is recommended as the standard treatment after stage II and III rectal surgery, with the FOLFOX or CAPOX regimen being commonly used. Adjuvant treatment with 5FU/LV or capecitabine monotherapy is recommended for patients with significant efficacy of monotherapy in advanced age or preoperative neoadjuvant chemotherapy. Adjuvant chemotherapy follows the principle of the earlier the better, with treatment duration of 6 months. For example, adjuvant chemotherapy can be administered after 4 months for patients receiving preoperative or postoperative chemoradiotherapy.

5.3.5 | Systemic therapy for patients with advanced metastasis

Combining chemotherapy with targeted therapy or chemotherapy alone is selectable according to the physical conditions of patients with advanced colorectal cancer. The commonly used drugs include: 5FU/LV, capecitabine, irinotecan, oxaliplatin, raltitrexed, bevacizumab, cetuximab, pertuzumab, vemurafenib, regorafenib, fruquintinib, pembrolizumab, nivolumab, ipilimumab, and so forth. For patients with deficient mismatch repair/microsatellite instability-high, pembrolizumab...
or nivolumab alone or in combination with ipilimumab can be recommended as an option of the first-line treatment.

5.4 | Radiotherapy

5.4.1 | Indications of radiotherapy

The main modes of radiotherapy or chemoradiotherapy for rectal cancer include neoadjuvant/adjuvant therapy, radical therapy, transformational therapy, and palliative therapy. The indications of neoadjuvant radiotherapy are mainly for the rectal cancer at the stage II–III. After long-range concurrent chemoradiotherapy (CRT), it is recommended to accept radical therapy after the interval of 5–12 weeks. Short-term CRT (SCRT) combined with immediate radical therapy (surgery within 1–2 weeks after radiotherapy) is recommended for resectable T3 rectal cancer diagnosed by MRI or EUS. The SCRT was combined with delayed radical therapy, whereas adding neoadjuvant radiotherapy during the waiting period can be recommended for rectal cancer at stage II–III containing high-risk factors of recurrence. Adjuvant radiotherapy is recommended for rectal cancer patients at the postoperative pathological stage of II–III and without preoperative radiation therapy.

For rectal cancer patients with low sensitivity to radiotherapy and with a strong desire to preserve the anus, radical radiotherapy is recommended to achieve cCR status after tumor chemotherapy. Transformational radiotherapy is recommended for rectal cancer patients with recurrence/metastasis who have a chance of radical treatment. The indications of palliative radiotherapy for rectal cancer are local tumor recurrence and/or distant metastasis, or some patients cannot tolerate surgery and cannot be cured by radiotherapy and comprehensive treatment.

Preoperative radiotherapy layering of rectal cancer is recommended

For clinical diagnosis of stage II–III rectal cancer, based on the location of the tumor in the rectum, the layered therapy in conjunction with recurrence risk shown by MRI is recommended. First, for patients with mesorectal fascia (MRF)(–) and EMVI(–) low cT3a/b, or medium-high cT3a/b and cN0-2, direct TME surgery is a priority and the quality of TME surgery is evaluated. Whether postoperative adjuvant therapy is required depends on postoperative pathology. If high-quality TME surgery cannot be guaranteed, preoperative CRT combined with delayed surgery/SCRT and immediate surgery are recommended. Second, for MRF(–) with any of the following conditions: (i) cT3c/d; (ii) extremely low lesions; (iii) cN1-2 (cancerous nodules); and (iv) EMVI(+), preoperative CRT combined with delayed surgery or SCRT combined with immediate surgery is recommended. Third, for cT3 with MRF (+); cT4; invaded levator ani; and lateral lymph nodes (+), preoperative CRT combined with delayed surgery or SCRT sequential neoadjuvant chemotherapy followed by delayed surgery is preferred. Fourth, SCRT combined with delayed surgery is recommended for weak and elderly patients, or patients with severe complications who cannot tolerate CRT.

Postoperative radiotherapy in primary rectal cancer without metastases

Postoperative radiotherapy was recommended to primary rectal cancer patients with the following conditions:

1. Without transabdominal resection, pathological findings after transanal local excision are pT1Nx with adverse histopathological features or pT2Nx. Adverse histopathological features include lymphovascular invasion, positive margins, poorly differentiated tumors, sm3, or submucosal invasion to the lower third of the submucosal level.

2. Pathological stage after transabdominal resection is pT3–4 and/or pN+ for middle or lower rectal cancer without preoperative chemoradiotherapy.

3. In addition to the aforementioned, postoperative radiotherapy could be selectively used in patients with poor histopathological features after surgery for example, positive CRM, perforation in the tumor area, incomplete mesorectal resection, extranodal deposits, or nodal deposits with extracapsular spread close to the MRF, or in other cases with a high risk of local recurrence if without preoperative chemoradiotherapy.

Management of low rectal cancer with difficulty in preservation of the anal sphincter

For patients with low rectal cancer (cT1N0, cT2N0, cT3–4 or N+) who have difficulty in preservation of the anal sphincter and have a strong desire to maintain sphincter function, preoperative concurrent CRT is recommended. If the tumor achieves clinical complete remission (cCR) after CRT, the strategy of watch and wait is feasible. The evaluation for cCR should be arranged during 8–12 weeks after CRT. cCR evaluation items, including DRE, colonoscopy, rectal MRI, and blood CEA levels, are highly recommended, and all the items should meet the cCR evaluation criteria (cCR criteria, see attachment).  Local transanal resection is feasible for ycT1N0 after CRT. Radical resection is still recommended for ypT2 or higher or node-positive.

5.4.2 | Radiotherapy standard

Radiotherapy technology

1. Choose different radiotherapy technologies according to the radiotherapy equipment in the hospital, such as conventional radiotherapy, three-dimensional (3-D) conformal radiotherapy (3D-CRT), IMRT, volumetric arc intensity modulated radiotherapy (VMAT), and so forth.

2. 3-D conformal and intensity-modulated radiotherapy technology are recommended. Compared with two-dimensional (2-D) radiotherapy, they have obvious physical dosimetry advantages, which can reduce the damage to normal tissues, while achieving precise tumor treatment.

3. If IMRT is used, then treatment plan verification is mandatory. Image-guided radiation therapy is recommended to collect relevant imaging information during treatment, to determine the treatment target area and reduce positioning errors.
4. Intraoperative radiotherapy, brachytherapy, or external irradiation techniques can be used for local intensive treatment.

5. Radioactive seed implantation is not routinely recommended.

Positioning technical specifications
CT simulation of 3D-CRT and IMRT techniques.

1. Empty the bladder and rectum 1 h before CT simulation, then drink 600–800 mL water, which contains 20 mL iodine contrast agent to visualize the small intestine, and hold back the bladder to reduce the irradiated volume of the small intestine; repeat this process, but stop drinking iodine contrast agent for every fraction of radiotherapy.

2. The body position can be selected according to the treatment techniques during CT simulation. The application of a belly board in the prone position can effectively reduce the radiation dose of the small intestine compared with the dose delivered in the supine position by conventional radiotherapy and 3D-CRT. IMRT, VMAT, and spiral tomography techniques have no significant difference in the irradiation dose of the organ-at-risk in the supine or prone positions, with better reproducibility in the supine position, so the supine position can be used. During postoperative radiotherapy, the small intestine easily falls into the pelvic cavity due to the removal of pelvic organs. A prone position is recommended to reduce small intestinal radiation damage.

3. For rectal cancer patients undergoing preoperative radiotherapy or postoperative radiotherapy after low anterior resection, a lead point marker can be placed on the anus to clarify the position of the anal margin; for rectal cancer patients after abdominal and perineal resection, a thin lead wire is used to mark the perineal scar.

4. Thermoplastic abdominal film is used for fixation during CT simulation and radiotherapy.

5. CT scan range: the upper boundary is the upper edge of the second lumbar vertebrae, and the lower boundary is the level of the middle femur, with a thickness of 5 mm. CT scanning images should be obtained layer by layer. Enhanced CT simulation is recommended to combine with iodine contrast agent if the patients do not have a history of allergy to clearly distinguish the tumor and the blood vessels.

6. For patients who need to receive preoperative radiotherapy, it is recommended to use MRI simulation simultaneously. CT/MRI image fusion can help radiation oncologists identify the scope of the tumor, so as to delineate the gross tumor volume (GTV) accurately. PET/CT simulation is not recommended for routine applications due to its low tissue resolution and high cost.

2-D radiotherapy simulation. See 2-D irradiation.

Target definition and delineation
2-D irradiation. Preoperative or postoperative radiotherapy for rectal cancer must include the primary tumor or tumor bed, lymphatic drainage areas, and a high-risk recurrence area. It is usually recommended to use isocentric three-field irradiation technology, consisting of one “posterior field” and two “lateral fields”. Two “lateral fields” should be adjusted with 30° wedge-shaped plates. For reference boundaries of two-dimensional irradiation see Table 1. The irradiation field must be determined by referring to the tumor condition, surgical records and pathology, and so forth. The dose ratio of one “posterior” and two “lateral fields” is 2:1:1. The irradiation volume of the small bowel could be determined depending on diagnostic CT or referring to drinking water containing meglumine diatrizoate before positioning.

Reference boundaries of two-dimensional irradiation

| Cranial | Caudal | Lateral |
|---------|--------|---------|
| “Posterior fields” | Caudal border of L5 | Middle or upper carcinoma: Caudal of obturator |
|            | 1-cm expansion to pelvic | Lower carcinoma: Anal edge |

| Cranial | Caudal | Anterior | Posterior |
|---------|--------|----------|-----------|
| “Lateral fields” | The same as “Posterior fields” | The same as “Posterior fields” | Posterior 1/3-1/2 of femoral head |
|          |        |          | Half of sacrum |

Notes: Caudal boundary for post-“Dixon” operation: caudal of obturator. Caudal boundary for post-“Miles” operation: perineal scar.

3D-CRT and IMRT.

1. Target volume definition before operation

GTV: gross tumors refer to endoscopy, MRI, and pelvic CT imaging information.

GTVnd: metastatic lymph nodes and tumor deposits of lymphatic drainage area, include the mesorectum, the presacral, the common iliac, the internal iliac, the obturator, and the external iliac.

Clinical target volume (CTV): it is typically defined as the high-risk lymph nodes and the recurrence region. It is recommended to distinguish different high-risk areas according to the following Table 1, and include corresponding subareas according to the situations. Considering the various filling degree of the bladder, CTV should expand 1–2 cm outside the bladder.

CTVp: it is typically defined as the CTV of the primary tumor, including a 2-cm expansion of GTV from cranial to caudal. When a primary tumor invades the surrounding organs, it is recommended to include a 1–2 cm expansion of the infiltrated area, of which the motion and deformation should be fully considered.

CTVf: it is suggested to include the bladder, the vagina, and the ipsilateral ischiorectal fossa, when a T4b tumor is combined with rectovesical fistula or invades from external anal sphincter into the ischiorectal fossa.

PTV: it is recommended to expand 0.5–1.0 cm in the left and right, ventral and dorsal direction, 1 cm in the head and foot direction from CTVp and CTV, and 3-D expansion is recommended.

Appendix 3: Cases atlases of preoperative radiotherapy for upper rectal cancer

Appendix 4: Cases atlases of preoperative radiotherapy for lower rectal cancer
**TABLE 1** Clinical target volume delineation of preoperative radiotherapy based on T/N stage and location of rectal cancer

|                      | Pelvic presacral area | Mesorectum | Internal iliac lymph area | Obturator lymph area | External iliac lymph area | Sphincter complex | Ischiorectal fossa | Inguinal lymph area |
|----------------------|-----------------------|------------|---------------------------|----------------------|--------------------------|-------------------|-------------------|-------------------|
| cT3N0, upper disease | +                     | +          | +                         | +                    |                          |                   |                   |                   |
| cT3N0, middle or lower disease* | + | + | + | + | + | (Anal canal infiltration) |
| Any T stage, mesorectum/presacral lymph node metastasis | + | + | + | + | + | (Anal canal infiltration) |
| Any T stage, internal iliac lymph node metastasis | + | + | + | + | + | (Anal canal infiltration) |
| Any T stage, obturator lymph node metastasis | + | + | + | + | + | (Anal canal infiltration) |
| cT4 invading an anterior organ or structure** | + | + | + | + | + | (Anal canal infiltration) |

*For both mesorectal fascia (-) and N0 based on accurate imaging, the cranial border of clinical target volume may be lowered at the level of the bifurcation of superior rectal artery or at the S1–S2 interspace. **The external iliac lymph area may be included when T4b tumors invade anterior organs or structures, but except levator ani muscle infiltration or T4a. ***Ischiorectal fossa should be included when ischiorectal fossa, external anal sphincter, or levator ani muscles are infiltrated. Clinical target volume is suggested to include the infiltrated part of the ischiorectal fossa (gross tumor volume extended 1 cm) and the unaffected contralateral ischiorectal fossa may not be included. ****Inguinal lymph area is not routinely irradiated for prophylactic purpose when tumors invade the anal canal/levator ani muscle/ischiorectal fossa/semenal vesicle gland/prostate/bladder/uterus. If the skin around the anus or the lower one-third of the vagina is invaded, prophylactic irradiation of inguinal lymph area should be considered.

2. Target volume definition after operation

CTV: CTV is suggested to include the tumor bed, anastomose (Dixon), perineal scar (Miles), lymphatic drainage area, and high-risk recurrence area. It is recommended to include the corresponding sub-areas according to the following Table 2.43

PTV: It is recommended to expand 0.5–1.0 cm in the left and right, ventral and dorsal direction, 1 cm in the head and foot direction from CTV, and 3-D expansion is recommended.

Appendix 5: Cases atlases for rectal cancer after "Miles"42
Appendix 6: Cases atlases for rectal cancer after "Dixon"42

3. Exception

For patients with tumor and/or residual disease, it is recommended to treat with a sequential boost after pelvic radiation, meanwhile the dose of the small bowel should be considered with caution.

Radiotherapy for recurrent pelvic lesion.

1. For patients without radiation history, the panel recommends radiotherapy for the pelvic area and an irradiation boost for recurrence regions.
2. For patients with pelvic radiation history, the panel recommends that a decision whether to receive radiotherapy should be in accordance with the situations.

**TABLE 2** Clinical tumor volume delineation of postoperative radiotherapy based on different surgical methods and different positions

|                      | Post-Dixon operation | Post-Miles operation |
|----------------------|----------------------|----------------------|
| Anastomose/perineal scar | + (Anastomose)       | + (Perineal scar)    |
| Tumor bed            | +                    | +                    |
| Presacral space + mesorectum + internal iliac lymph area* | + | + |
| Obturator lymph area | +                    | +                    |
| External iliac lymph area | -              | -                    |
| Inguinal lymph area  | -                    | -                    |
| Ischiorectal fossa   | +                    | (The center of tumor is within 6 cm from the anal edge) |

*ptT3N0 if middle or lower disease, the cranial boundary of clinical tumor volume could be lowered to the S1–S2 interspace.

**Radiation dose and fractionation**

*Adjuvant radiotherapy.* Adjuvant radiotherapy is recommended to be performed within 1 month after surgery. A dose of 45–50 Gy in 25
fractions (1.8–2.0 Gy per fraction) is required for irradiation of the tumor bed and lymph node drainage areas. Furthermore, a boost irradiation to sites of residual tumor is recommended when a non-R0 resection is found by post-surgical pathological examination, with an additional dose of 10–20 Gy in 5–10 fractions given, making the total dose of 60–70 Gy. Yet, irradiation doses of important normal organs should be controlled within the safe and tolerable range. Short-course radiotherapy is not recommended.

Adjuvant CRT. Schemes and indications are similar to that of adjuvant radiotherapy. Also, short-course radiotherapy is not recommended.

Neoadjuvant radiotherapy.

1. Short-course radiotherapy

The commonly used fractionation is 25 Gy in five fractions. It is recommended to conduct surgery within 1 week after radiotherapy. This scheme is mainly performed when it is unnecessary to obtain an obvious downstage or R0 resection through neoadjuvant radiotherapy. It is also performed in locally advanced rectal cancer with serious distant metastases, for controlling local lesions before systemic chemotherapy and targeted therapy.

2. Long-course radiotherapy

The commonly used fractionation is 45–50.4 Gy in 25–28 fractions. Surgery is recommended to be conducted at 6–12 weeks after radiotherapy. This scheme is suitable for nearly all rectal cancer patients in need of neoadjuvant radiotherapy.

Neoadjuvant CRT. Long-course radiotherapy is more frequently used. There are different modes to combine radiotherapy and chemotherapy: (i) standard concurrent CRT; (ii) induction chemotherapy + concurrent CRT; (iii) concurrent CRT + consolidated chemotherapy; (iv) induction chemotherapy + concurrent CRT + consolidated chemotherapy (also called “sandwich: mode45”); and (v) total neoadjuvant therapy mode.

Certainly, short-course radiotherapy could also be feasible. Neoadjuvant chemotherapy is often followed 1–2 weeks after short-course radiotherapy.

Radical CRT. Radical CRT is mainly carried out in patients unsuitable or unwilling to receive surgery. Radiation dose and fractionation depend on therapeutic effects after neoadjuvant CRT.

1. When a cCR is obtained, a “watch and wait” strategy could be applied, instead of a boost irradiation.
2. When a cCR is not obtained, a boost irradiation could be considered, according to the interval between two courses of radiotherapy, irradiated doses of normal organs, and so forth.
3. In patients treated with long-course neoadjuvant radiotherapy, the dose of a boost irradiation is recommended as 10–20 Gy in 5–10 fractions (external beam radiotherapy) or 5 Gy (brachytherapy), to make the total dose be 60–70 Gy.

Palliative radiotherapy. Palliative radiotherapy is often performed in patients who are unsuitable for chemotherapy or surgery, due to their advanced age or systemic diseases. Radiation doses, fractionation, and techniques depend on clinical stages and therapeutic aims.

Delineation of organs at risk and dose constraints

The organs at risk for rectal cancer radiotherapy mainly include the small bowel, colon, bladder, femoral heads, perineum, and other unspecified tissues. Considering the problems that may be encountered in clinical practice, we divide the constraints of organs at risk into two types: (i) the recommended constraints; and (ii) the maximum constraints (taking the calculation–accuracy limitation of the treatment planning system into account. $D_{\text{max}}$ is defined as the dose received by the volume of 0.03 cc).

Small bowel. Defined as all the small bowel loops below the upper limit of the fifth lumbar spine (LS), or all the small bowel loops contoured down from 1 cm above the upper limit of the PTV.

| Recommended constraints | Maximum constraints |
|-------------------------|---------------------|
| $D_{180\, \text{cc}} \leq 35\, \text{Gy}$ | $D_{230\, \text{cc}} \leq 35\, \text{Gy}$ |
| $D_{100\, \text{cc}} \leq 40\, \text{Gy}$ | $D_{130\, \text{cc}} \leq 40\, \text{Gy}$ |
| $D_{60\, \text{cc}} \leq 45\, \text{Gy}$ | $D_{90\, \text{cc}} \leq 45\, \text{Gy}$ |
| $D_{\text{max}} \leq 50\, \text{Gy}$ | $D_{\text{max}} \leq 50\, \text{Gy}$ |

Colon. Defined as the colon above the sigmoid colon, it includes the ascending colon, transverse colon, descending colon, and sigmoid colon. Starting from 1 cm above the upper boundary of the PTV, it can include the colon tissue within the range of the CTV, but the intestinal tissue at the junction between the straight and the second must be excluded (the constraints refer to the small intestine).

| Recommended constraints | Maximum constraints |
|-------------------------|---------------------|
| $D_{40\%} \leq 40\, \text{Gy}$ | $D_{55\%} \leq 40\, \text{Gy}$ |
| $D_{15\%} \leq 45\, \text{Gy}$ | $D_{30\%} \leq 45\, \text{Gy}$ |
| $D_{\text{max}} \leq 50\, \text{Gy}$ | $D_{5\%} \leq 50\, \text{Gy}$ |

Femoral heads. Defined as bilateral femoral heads and proximal femurs, contouring the femoral head, femoral neck, greater
trochanter, and lesser trochanter under the condition of the bone window.

| Recommended constraints | Maximum constraints |
|--------------------------|---------------------|
| $D_{40\%} \leq 40\text{ Gy}$ | $D_{65\%} \leq 40\text{ Gy}$ |
| $D_{25\%} \leq 45\text{ Gy}$ | $D_{40\%} \leq 45\text{ Gy}$ |
| $D_{\text{max}} \leq 50\text{ Gy}$ | $D_{5\%} \leq 50\text{ Gy}$ |

Perineum. Defined as the skin and adipose tissue of the penis, scrotum, and pubic symphysis in men, and the skin and adipose tissue of the clitoris, labia, and minor symphysis in women.

| Recommended constraints | Maximum constraints |
|--------------------------|---------------------|
| $D_{40\%} \leq 20\text{ Gy}$ | $D_{50\%} \leq 20\text{ Gy}$ |
| $D_{25\%} \leq 30\text{ Gy}$ | $D_{35\%} \leq 30\text{ Gy}$ |
| $D_{\text{max}} \leq 40\text{ Gy}$ | $D_{5\%} \leq 40\text{ Gy}$ |

Unspecified tissues. It is defined as the upper limit of L5 below, referring to all the normal tissues except PTV and organs at risk mentioned above. The upper constraints of this tissue shall not exceed 105% of the prescribed dose. That is, the radiotherapy treatment plan should avoid the generation of dose hot spots in other undefined normal tissues.

5.4.3 Radiotherapy plan design

Preparation before planning
1. Inspection before planning: Check coordinate origin (user origin) and reference mark points.
2. Add the treatment couch structure: The pink outline of the structure in Figure 1 is the inserted linear accelerator treatment couch.\(^{53,54}\)
3. Determination of the isocenter: Add the geometric center point of the target area generated by the radiation field, and compare the relative position of this point with the reference mark point. The position of the isocenter is shown in Figure 2-1, 2-2.

Plan design
Adding auxiliary structures before optimization.

| Structure name | Purpose |
|---------------|---------|
| Ring 1 (the pink area in Figure 1) | Increase CI |
| Ring 2 (the orange area in Figure 1) | Increase CI |
| B-P (the blue area in Figure 1) | Control low-dose |

CI = $\frac{TVPV_2}{TV \times PV}$, TVPV represents the volume of the PTV wrapped by the prescription dose, the TV represents the volume of the PTV, and the PV represents the total volume wrapped by the prescription dose. Larger CI values indicate the better conformity of the target.

IMRT plan.

1. Field setting:

   IMRT plan for rectal cancer generally uses five to seven fields according to the size and complexity of the target area. The angle distribution of the field can be divided equally or patients can be treated in the prone position, avoiding 180° and focusing the beam on the back, so as to better protect the small intestine.\(^{55}\) The schematic diagram of the field is shown in Figure 3.

2. Parameter optimization:

   The optimization conditions suggest that the dose–volume physical optimization parameters should be combined with the generalized equivalent uniform dose biological optimization parameters. When the basic plan optimization is completed, select “using the current plan as the intermediate dose for optimization” to optimize again.

3. Plan evaluation:

1. Dose distribution evaluation: view the dose distribution layer by layer, sketch or automatically generate the dose structure for the high-dose area (hot spot) and the low-dose area (cold point) in the target, and then iteratively optimize the dose distribution, as shown in Figure 3-1, 3-2, 3-3.

   (2) Dose–volume histogram (DVH): The DVH is shown in Figure 4. The target and organs are evaluated in detail according to the DVH diagram. If the result is not satisfactory, iterative optimization can be repeated to ensure the coverage of the prescription dose to the target area while keeping a high dose drop steepness of the target area as far as possible.

VMAT plan.

1. Field setting:

   Two arcs are generally recommended for rectal cancer, because double arcs have stronger modulation ability than a single arc, which can improve the uniformity and conformability of the target, and the dose control ability of the target and organs is better. The schematic diagram of the field is shown in Figure 5.
2. Normal tissue objective design: The normal tissue objective design method is shown in Figure 6.

Optimize parameters and optimize control (optimize parameters and optimize control is shown in Figure 7)

There are four levels in the VMAT (Varian Eclipse version 13.5; Palo Alto, CA, USA) optimization process. There is a different step in each level. In practice, it is recommended that each step be paused, with particular attention to the third step in the first level, and the first step in the third level. The penalty function curve is flat and then goes to the next step or level. If the intermediate dose is calculated and at least two iterations are carried out in the process of plan optimization, a more realistic dose distribution will be obtained at the optimization interface.

3. Plan evaluation:

(1) Dose distribution evaluation: The dose distribution is shown in Figure 8-1, 8-2, 8-3, 8-4, 8-5.

(2) DVH: The dose volume histogram is shown in Figure 9. The radiation dose of each organ and target is evaluated in detail according to the DVH diagram to ensure that the corresponding prescription dose is obtained in the target and to control the dose gradient of the target as far as possible. Compared with IMRT, VMAT has stronger modulation ability and produces a better target dose distribution while protecting the organs. In addition, it can also shorten treatment time, accelerate dose delivery, and reduce the discomfort caused by patients' staying in a fixed position for a long time, thus avoiding the dose offset due to involuntary movement brought about by patients' discomfort. However, the disadvantage is that it has to take a long time to optimize its rotational intensity modulation, which can be somewhat cumbersome. Therefore, it is suggested that conditional treatment institutions should choose VMAT as one of the radiotherapy planning methods for rectal cancer.

5.4.4 Recommendation of preoperative radiotherapy and operation interval

The immediate operation mode of short-course (5 × 5) was within 1–2 weeks after radiotherapy, whereas the delayed operation mode was within 6–8 weeks. Surgical treatment is recommended 5–12 weeks after long-course CRT.
5.4.5 Principle of combined radiotherapy and chemotherapy for rectal cancer

**Concurrent chemoradiotherapy**

See Section 5.3.1

**Concurrent chemoradiotherapy or short-course radiotherapy combine with neoadjuvant chemotherapy before surgery**

1. Concurrent chemoradiotherapy or short-course radiotherapy combines chemotherapy before surgery, and the chemotherapy regimens include FOLFOX, CAPEOX, 5-FU/CF, or capecitabine alone.\(^{58}\)
2. Induction chemotherapy is followed by concurrent CRT or short-course radiotherapy before surgery. Chemotherapy regimens could use FOLFOX, CAPEOX, 5-FU/CF, or capecitabine alone. However, more phase III clinical trials are required to support this approach.\(^{59}\)

**Sequencing of postoperative radiotherapy and chemotherapy (for patients who did not receive neoadjuvant RT or concurrent chemotherapy/RT)**

1. For patients with pT3N0M0 disease, postoperative concurrent chemotherapy/RT, followed by chemotherapy (5-FU/LV or capecitabine) or observation is recommended. For patients with negative margins, but adjacent to the tumor, concurrent chemotherapy/RT followed by chemotherapy (FOLFOX or CAPEOX) is recommended.
2. For patients with pT4N0M0 or pT1–4N1–2M0 disease, chemotherapy (FOLFOX or CAPEOX or 5-FU/LV or capecitabine) followed by concurrent chemotherapy/RT, and then followed by chemotherapy (FOLFOX or CAPOX or 5-FU/LV or capecitabine) is recommended. Adjuvant concurrent chemotherapy/RT followed by chemotherapy is also recommended.
**FIGURE 6**  Normal tissue objective design

**FIGURE 7**  Optimization of parameters control

**FIGURE 8**  Dose distribution evaluation
Traditional Chinese medicine can effectively alleviate side-effects caused by radiotherapy and chemotherapy, promote appetite, and improve performance status of patients. The common administration methods of traditional Chinese medicine include oral medication, retention enema, external application on perineum, and others. Retention enema with Chinese herbs plays an important role in the prevention and treatment of radiation-induced enteritis.\(^60,61\) External application of radix scutellariae ointment can attenuate the perianal skin injury caused by ionizing radiation.\(^62\)

### 5.6 | Local treatment of metastatic lesions

#### 5.6.1 | Treatment principles

**Liver metastases**

All patients with liver metastases are recommended for MDT (category 1A). Local therapies include local surgery, radiofrequency ablation (RFA), and stereotactic body radiotherapy (SBRT).

**Treatment of pulmonary metastases**

Surgery for pulmonary metastases in rectal cancer can be performed based on imaging diagnosis without histopathological diagnosis or the evidence of percutaneous needle biopsy. However, under certain conditions, such as atypical image features of pulmonary metastases, the metastases should be confirmed by histopathology or close observation. Local therapies for pulmonary metastases in rectal cancer include local surgery, RFA, and SBRT.

**Brain metastases**

The treatment of rectal cancer brain metastasis includes surgical resection, stereotactic radiotherapy, and whole brain radiotherapy. The treatment plan is based on the number and location of brain metastases, whether there are extracranial metastases, and the general condition of the patient.\(^63\)

#### 5.6.2 | Surgical resection

Surgical resection is the best way to achieve long-term survival for patients with liver metastases from rectal cancer. At present, the premises of resection for liver metastases include: (a) the primary tumor of rectal cancer could be resected radically; (b) liver metastases could be completely resected (R0) by imaging evaluation, and enough functional liver volume could be reserved (residual liver volume is greater than 30–40% of the standard liver volume); (c) the patient’s general condition is acceptable; and (d) no unresectable extrahepatic metastasis. It is suggested that intraoperative ultrasound whole liver exploration should be used to detect the occult lesions not found by preoperative imaging examination.

For multiple liver metastases or poorly located liver metastases, surgery combined with RFA or SBRT can achieve the goal of R0 resection. If liver metastases are combined with resectable extrahepatic metastases, it may be considered simultaneous or metachronous resection of liver metastases and extrahepatic metastases according to the guidance of MDT.

For unresectable liver metastases, conversion therapy could be tried, and if the liver metastases could be reduced to resectable disease, surgery should be performed as soon as possible.

#### 5.6.3 | Stereotactic radiotherapy

**Liver metastases**

The indications of SBRT for liver metastases are as follows (3A evidence):

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**FIGURE 9** Dose volume histogram of volumetric modulated arc therapy plan

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1. The number of liver metastases up to three, the maximum diameter of liver metastasis $\leq 5$ cm;
2. The primary lesion was controllable, and there was no extrahepatic metastases or with small extrahepatic metastases.
3. The expected survival time is $\geq 3$ months;
4. The liver has not received radiotherapy and the volume of normal liver tissue $> 700$ mL;
5. The general condition of the patient is good, the level of serum liver enzyme is normal or $< 200\%$ of the upper limit of normal value; the blood coagulation function is normal; Child–Pugh grade is A or B.

It is recommended that for most liver metastases, especially those with diameter $\leq 3$ cm, the effective biological dose should be $\geq 100$ Gy on the premise of safety. Sixty-five

SBRT is not suitable for liver metastasis, which is closely adjacent to important organs, such as the small intestine, stomach, duodenum, and kidney.

It is not recommended to carry out SBRT for liver metastasis in hospitals without image guidance or respiratory control technology.

**Lung metastases**

The indications of SBRT for lung metastases are as follows (3B evidence):

1. The number of lung metastases is one to three; the maximum number of small lesions is no more than five; and the maximum diameter is $\leq 5$ cm.
2. The distribution of lung metastasis is relatively limited, and it is the best in the same side of the lung; the peripheral lung metastases are more suitable for SBRT.
3. The primary lesion was under control, and no extrapulmonary metastasis or extrapulmonary metastasis was controlled.
4. The general condition of the patient is good and the lung function is normal.
5. Expected survival time is $\geq 6$ months.

It is recommended that the BED $\geq 100$ Gy on the premise of safety. It is recommended that different techniques be used to limit or track the motion of lung metastasis, and the exact location of lung metastases can be confirmed by image guidance system before each SBRT. It is not recommended to carry out SBRT for lung metastasis in hospitals without image guidance or respiratory control technology.

**Brain metastases**

Stereotactic radiotherapy for brain metastases from rectal cancer includes stereotactic radiosurgery, fractionated stereotactic radiotherapy, and hypofractionated stereotactic radiotherapy.

It is recommended that fractionated stereotactic radiotherapy is used for large lesions (usually with its diameter $> 3$ cm), with a single dose of 3.5–4 Gy and a total dose of 52.5–60 Gy.

For huge lesions, the mode of segmented radiotherapy can be used. After giving 40°50 Gy, rest for 1–2 months, and then replenish the volume after the tumor shrinks.

**Spinal metastases**

The indications of SBRT for spinal metastases: up to two vertebral bodies are involved, and there is a distance of 3–5 mm between the metastatic tumor and spinal cord.

At present, the main segmentation modes are single segmentation and multiple segmentation. The single segmentation has a relatively low local control rate, but a relatively high recurrence rate.

**5.6.4 Ablation and radiofrequency therapy**

The most studied techniques for metastatic colorectal cancer (mCRC) in the lungs and liver are RFA, microwave ablation, I-125 brachytherapy ablation therapy, and cryoablation in China.

Lung metastases from CRC: The local ablation therapy was suitable for up to three metastatic sites and lesion size $< 3$ cm. Simultaneous treatment is not recommended in left and right lung lesions.

Liver metastases from CRC: The local ablation therapy was suitable for up to five metastatic sites and lesion size $< 3$ cm. A treatment option is up to the lesions’ location, size, number, and doctor’s experience.

**5.7 Local treatment of locally recurrent rectal cancer**

**5.7.1 Principles of treatment**

Evaluate the conditions of patients and lesions. For patients with resectable or potentially resectable recurrence, strive for surgical resection of recurrence, in combination with preoperative or postoperative radiotherapy and chemotherapy, intraoperative radiotherapy, and so forth. Sixty-seven Comprehensive treatment of radiotherapy and chemotherapy is recommended for unresectable patients.

**5.7.2 Surgical treatment**

**Preoperative evaluation**

According to the scope of recurrence, the resectability should be evaluated to decide whether to use preoperative chemoradiotherapy.

**Surgical methods**

The mode of operation is recommended according to the classification of local recurrence.

**5.7.3 Radiotherapy**

**Principles of radiotherapy**

For patients who have not received pelvic radiotherapy before, concurrent preoperative chemoradiotherapy is recommended (if it is possible, confirm the pathological diagnosis of recurrent lesions before treatment). For patients with resectable local lesions, surgical resection can
also be received first, and then decide whether to receive postoperative chemoradiotherapy. Capecitabine is recommended for concurrent chemoradiotherapy. For patients who have previously received pelvic radiotherapy, radiotherapy is no longer performed in principle, and no clear consensus has been made on the use of re-irradiation. A multidisciplinary team evaluation is recommended to make a reasonable treatment plan. The treatment effect of surgical patients after neoadjuvant radiotherapy was significantly better than that of non-operative patients.68

**Irradiation scope and dose**

3-D conformal or intensity modulated radiotherapy is recommended. For patients who have not received pelvic radiotherapy before, irradiation of recurrent lesions or the tumor bed and pelvic lymphatic drainage area should be considered pre- or postoperation, with the irradiation dose of 50 Gy. For patients who have previously received pelvic radiotherapy and who require re-irradiation, only the area of the recurrent tumor should be irradiated. The re-irradiation dose is determined according to the first radiation dose, which is generally 30–40 Gy. Hyperfractionation radiotherapy is recommended, 1.2–1.5 Gy per fraction, twice daily with an interval of >6 h.69 The operation is performed 6–12 weeks after the end of concurrent chemoradiotherapy. If possible, intraoperative radiotherapy can be added. Choose the electron beam of 6–18 MeV and irradiate 12–15 Gy.

**6 | PREVENTION AND TREATMENT OF RADIOTHERAPY COMPLICATIONS**

The most common complications of pelvic radiotherapy for rectal cancer occur in the hematopoietic system, digestive system, and genitourinary system.

**6.1 | Hematopoietic system**

The main responses are leukopenia and thrombocytopenia, which are more obvious during concurrent chemotherapy. Check the blood cell analysis every week during the treatment. If it occurs ≥ Grade 3 leukopenia and thrombocytopenia, patients should be treated quickly with granulocyte colony-stimulating factor and macrophage colony-stimulating factor.

**6.2 | Digestive system**

**6.2.1 | Gastrointestinal complications**

Gastrointestinal complications are manifested as loss of appetite, nausea, even vomiting, abdominal pain and diarrhea, and so forth. In mild cases, patients can be treated symptomatically by supplementing vitamins, and antiemetic and antispasmodic drugs, whereas in severe cases, doctors have to stop radiotherapy, turning to intravenous fluids, or even adjust the radiotherapy plan.

**6.2.2 | Rectal complications**

The main related factors of rectal complications are the dose, volume, and dose rate of rectal radiation. The most important factor is the radiation dose.

1. Early rectal complications are mainly manifested as tenesmus, painful stools, and even mucus in the stools. Those with a rectal reaction should reduce the irritation to the rectum, avoid constipation, and ensure adequate supply of nutrients and water. Oral administration of compound glutamine capsules and injection of amifostine can prevent and treat acute radiation proctitis. Aluminum hydroxide latex combined with dexamethasone needles are administered via an enema within 1 h after the end of radiotherapy, and kept for >2 h to protect and repair the intestinal mucosa. If there is no obvious improvement after active treatment, radiotherapy should be suspended and the radiotherapy plan should be modified if necessary.

2. Late complications are difficult to treat and often occur at 3–6 months after the end of radiotherapy, including chronic radiation proctitis, bleeding, rectal or anal stricture, and pain.

**6.3 | Urogenital system**

Radiation cystitis is common. The early reactions are urethritis, cystitis, and painful urination. Most of the symptoms are mild. After drinking more water, if necessary, one is quickly relieved or healed with hormone therapy. The long-term complications are mainly hemorrhagic cystitis, bladder contracture, urethral stricture, and obesity contracture. Some patients have sexual dysfunction after radiotherapy, which is related to the damage of blood vessels and nerves caused by radiotherapy and surgery.

**7 | EVALUATION OF THERAPEUTIC EFFECTS**

The evaluation of therapeutic efficacy of rectal cancer is divided into two parts, namely, preoperative and postoperative evaluation. The evaluation methods mainly include the following examinations: DRE, CT examination (chest/whole abdomen/pelvic enhanced CT scan is recommended), ultrasound, proctoscopy, MRI, and PET-CT.

**7.1 | Evaluation of the therapeutic effect of preoperative radiotherapy (chemotherapy)**

DRE, proctoscopy, and MR examination are mainly used to evaluate the preoperative therapeutic effects of patients. Relevant results
can assist to formulate appropriate surgical strategies, select the expected surgical type, and decide whether it is suitable for the "watch and wait" strategy. Generally, the evaluation of therapeutic effect is performed 12 weeks after the initiation of radiotherapy (chemotherapy).

### 7.2 Evaluation of the postoperative therapeutic effect

See follow up in Section 8.

### 8 FOLLOW UP

A post-treatment surveillance program should be recommended for patients with rectal cancer as their following treatment. During the surveillance, the recurrence and metastasis of cancer should be closely monitored; the resolution of acute toxicities, long-term effects of treatment, possible late sequelae of treatment, and their impacts on patients’ function should be carefully observed. The recommended surveillance program is as follows.

Medical history and physical examination, monitoring of cancer biomarkers, such as CEA and CA199, chest and abdominal CT scan, pelvic CT, or MRI scan: Once every 3–6 months for 2 years, then once every 6 months, and once a year after 5 years.

Colonoscopy: Once a year after surgical operation, then once every 3 years if it shows a normal examination.

PET/CT study: Should not be recommended as a routine examination; it might be helpful to detect or verify recurrence and/or metastasis for those patients who are in suspicion of it.

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APPENDIX 1: BASELINE MRI REPORT FORM FOR RECTAL CANCER

1. The date of primary MRI scan: □□□□/□□/□□
2. Good image quality for primary staging: □Yes □No
3. Tumor height from anal verge: ______ cm
4. Tumor above/below puboretalis sling:
   □Above □Below
   Tumor height from puboretalis sling: ______ cm
5. Relationship between tumor and peritoneal reflection: □Below □Above □Straddle
6. Tumor location on the axial image (Take pubic symphysis as 12 o’clock and evaluate clockwise): ______ to ______ o’clock
7. Craniocaudal length of tumor: ______ cm
8. Tumor thickness: ______ cm
9. Average ADC value: ______ × 10⁻³ mm²/s
10. Tumor invades beyond muscularis propria: □Yes □No
    Extramural depth of tumor invasion (EMD): ______ mm
11. Post-treatment tumor stage:
    □Tumor above puboretalis sling:
       □ymrT0 (Without residual tumor)
       □ymrT1 (Tumor invades submucosa, but does not extend into the muscularis propria)
       □ymrT2 (Tumor invades, but does not penetrate the muscularis propria)
       □ymrT3a (EMD: <1 mm) □ymrT3b (EMD: 1-5 mm)
       □ymrT3c (EMD: 5-15 mm) □ymrT3d (EMD >15 mm)
       □T4a (Invasion of visceral peritoneum)
       □T4b (Tumor invades adjacent organs)
    □Tumor below puboretalis sling:
       □mLrL1 (Tumor confined to internal sphincter)
       □mLrL2 (Tumor replaces the muscle coat, but does not extend into the intersphincteric plane)
       □mLrL3 (Tumor invades the intersphincteric plane and lies within 1 mm of levator muscle)
       □mLrL4 (Tumor invades external anal sphincter, and is within 1 mm and beyond levators with or without invading adjacent organs)
12. Extramural venous invasion: □Yes □No
    If yes, score:
    □0 Pattern of tumor extension through the muscle coat is not nodular, and there are no vessels adjacent to areas of tumor penetration
    □1 Minimal extramural stranding/nodular extension, but not in the vicinity of any vascular structure
    □2 Stranding demonstrated in the vicinity of extramural vessels, but these vessels are of normal caliber, and there is no definite tumor signal within the vessel
    □3 Intermediate signal intensity apparent within vessels, although the contour and caliber of these vessels is only slightly expanded
    □4 Obvious irregular vessel contour or nodular expansion of vessel by definite tumor signal
2) Name of the vessel:
   □Inferior rectal □Middle rectal branch
   □Superior rectal vein branch □Non-anatomical vein
13 Lymph node status
   (1) Number of suspicious malignant lymph nodes:
       □Inside the mesorectal fascia: ______
       □Peripheral to the superior rectal artery: ______
       □Peripheral to the internal iliac vessels: ______
   (2) N stage:
       □N0 No nodes/only high-signal nodes
       □N1a One node with either irregular border or mixed signal
       □N1b Two or three nodes with either irregular border or mixed signal
       □N1c Presence of tumor deposits, without suspicious malignant lymph nodes
       □N2a Four to six nodes with either irregular border or mixed signal
       □N2b Seven nodes with either irregular border or mixed signal
   (3) Non-regional lymph nodes:
Location: □ Peripheral to the external iliac vessels □ Left/□ Right □ Inguinal region □ Left/□ Right □ Other regions (Note: _____), number of suspicious malignant nodes: ____

14. Presence of tumor deposits: □ Yes (Number: ___) □ No

15. Circumferential resection margin □ Involved □ Not involved
   □ Distance of tumor edge to mesorectal fascia < 1 mm
   □ Distance of tumor edge to intersphincteric plane < 1 mm
   Closest CRM relates to: □ Tumor □ EMVI □ Lymph node □ Tumor deposit
   Closest CRM at ______ o’clock

16. MRI staging: [High/Middle/Low] rectal cancer, T[ ], N[ ], CRM [Not involved/Involved], EMVI [Negative/Positive], Non-regional lymph node [Negative/Positive], [With/Without] tumor deposit

APPENDIX 2: RESTAGING MRI REPORT FORM FOR RECTAL CANCER

1. The date of restaging MRI scan: □□□□ / □□□□ / □□□□

2. Good image quality for tumor restaging: □ Yes □ No

3. Tumor height from anal verge: _____ cm

4. Tumor above/below puborectalis sling:
   □ Above □ Below
   Tumor height from puborectalis sling: _____ cm

5. Relationship between tumor and peritoneal reflection:
   □ Below □ Above □ Straddle

6. Tumor location on the axial image: (Take pubic symphysis as 12 o’clock and evaluate clockwise)
   _____ to _____ o’clock

7. Craniocaudal length of tumor: _____ cm

8. Tumor thickness: _____ cm

9. Average ADC value: _____ × 10⁻³ mm²/s

10. Tumor invades beyond muscularis propria: □ Yes □ No
    Extramural depth of tumor invasion (EMD): _____ mm

11. Tumor stage:
   □ Tumor above puborectalis sling:
       □ ymrT0 (Absence of residual tumor)
       □ ymrT1 (Tumor invades submucosa but does not extend into muscularis propria)
       □ ymrT2 (Tumor invades but does not penetrate muscularis propria)
       □ ymrT3a (EMD: < 1 mm) □ ymrT3b (EMD: 1–5 mm)
       □ ymrT3c (EMD: 5–15 mm) □ ymrT3d (EMD: > 15 mm)
       □ ymrT4a (Invasion of visceral peritoneum)
       □ ymrT4b (Tumor invades adjacent organs)
   □ Tumor below puborectalis sling:
       □ ymrLR1 (Tumor confined to internal sphincter)
       □ ymrLR2 (Tumor replaces the muscle coat, but does not extend into the intersphincteric plane)
       □ ymrLR3 (Tumor invades the intersphincteric plane and lies within 1 mm of the levator muscle)
       □ ymrLR4 (Tumor invades external anal sphincter, and is within 1 mm and beyond levators with or without invading adjacent organs)

12. Post-treatment EMVI status: □ Yes □ No
    If yes, score:
    □ 0 Pattern of tumor extension through the muscle coat is not nodular, and there are no vessels adjacent to areas of tumor penetration
    □ 1 Minimal extramural stranding/nodular extension, but not in the vicinity of any vascular structure
    □ 2 Stranding demonstrated in the vicinity of extramural vessels, but these vessels are of normal caliber, and there is no definite tumor signal within the vessel
    □ 3 Intermediate signal intensity apparent within vessels, although the contour and caliber of these vessels is only slightly expanded
    □ 4 Obvious irregular vessel contour or nodular expansion of vessel by definite tumor signal

2) Name of the vessel:
   □ Inferior rectal □ Middle rectal branch
   □ Superior rectal vein branch □ Non-anatomical vein

13. Post-treatment lymph node status
   (1) Number of suspicious malignant lymph nodes:
Inside the mesorectal fascia:____
Peripheral to the superior rectal artery:____
Peripheral to the internal iliac vessels:____

(2) N stage:
□ N0 No nodes/only high signal nodes
□ N1a One node with either irregular border or mixed signal
□ N1b Two or three nodes with either irregular border or mixed signal
□ N1c Presence of tumor deposits, without suspicious malignant lymph nodes
□ N2a Four to six nodes with either irregular border or mixed signal
□ N2b Seven nodes with either irregular border or mixed signal

(3) Non-regional lymph nodes:
Location: □ Peripheral to the external iliac vessels (□ Left/□ Right) □ Inguinal region (□ Left/□ Right) □ Other regions (Note:____), number of suspicious malignant nodes:
14. Presence of tumor deposits: □ Yes (Number: ) □ No
15. Post-treatment CRM status: □ Involved □ Not involved
□ Distance of tumor edge to mesorectal fascia <1 mm
□ Distance of tumor edge to intersphicteric plane <1 mm
Closest CRM relates to: □ Tumor □ EMVI □ Lymph node □ Tumor deposit
Closest CRM at_____o’clock

16. Tumor regression grade:
□ mrTRG 1 Absence of tumor signal
□ mrTRG 2 Small amounts of residual tumor visible but with predominantly fibrotic low signal intensity
□ mrTRG 3 Low signal intensity fibrosis predominates but there are obvious areas of intermediate signal intensity
□ mrTRG 4 Little areas of low signal intensity fibrosis or mucin but mostly tumor
□ mrTRG 5 No regression (intermediate signal intensity, same appearances as original tumor)
17. MRI restaging:[High/Middle/Low]rectal cancer, ymrT [], ymrN [], ymrCRM [Not involved/Involved], ymrEMVI [Negative/Positive], post-treatment Non-regional lymph node[Negative/Positive], [With/Without]tumor deposit , mrTRG []

APPENDIX 3: CCR CRITERIA

| Evaluation project | CCR criteria |
|--------------------|--------------|
| Digital rectal examination | No definite tumor was touched and the intestinal wall was soft |
| Enteroscope | There was no clear residual tumor, and only mucosal leukoplakia and/or telangiectasia could be seen in the original tumor area |
| MRI | There was only fibrosis, no residual tumor or lymph node |
| Serum CEA level | Normal |

APPENDIX 4: AMERICAN JOINT COMMITTEE ON CANCER (AJCC) TNM STAGING (8TH EDITION) CLASSIFICATION FOR RECTAL CANCER

T—Primary tumor
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1 Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2 Tumor invades the muscularis propria
T3 Tumor invades through the muscularis propria into pericolorectal tissues
T4 Tumor invades * * the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b Tumor directly invades* or adheres** to adjacent organs or structures

N—Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  One to three regional lymph nodes are positive (tumor or lymph nodes measuring \( \geq 0.2 \) mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a One regional lymph node is positive
N1b Two or three regional lymph nodes are positive
N1c No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2  Four or more regional lymph nodes are positive
N2a Four to six regional lymph nodes are positive
N2b Seven or more regional lymph nodes are positive

**M—Distant metastasis**
M0  No distant metastasis by imaging, etc; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
M1  Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a Metastasis to one site or organ is identified without peritoneal metastases
M1b Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

*Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina). ** Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.
APPENDIX 5: FLOWCHART FOR DIAGNOSIS OF RECTAL CANCER

Clinical symptoms
  ▼
  Complete medical history
    ▼
    Physical examination (Rectal palpation)
      ▼
      Touchable lump
        ▼
        Un touchable lump
          ▼
          Colonoscopy + histopathological examination
            ▼
            Pathology confirmed
              ▼
              Colonic air-barium double contrast examination
                ▼
                Pelvic MRI/CT/ERUS
                  ▼
                  Chest CT/Chest DR
                    ▼
                    Abdominal US/CT
                      ▼
                      Laboratory tests
                        ▼
                        Diagnosis and staging confirmation of rectal cancer
                          ▼
                          Access to therapeutic process

MRI: magnetic resonance imaging
CT: computed tomography
ERUS: endorectal ultrasound
DR: digital radiography
US: ultrasound
APPENDIX 6: PREOPERATIVE TARGET DELINEATION OF UPPER RECTAL CANCER (THE FOLLOWING EXAMPLES ARE PRONE POSITION, RED: GTV; PINK: GTVND; BLUE: CTV; GREEN: PTV)

*68 years-of-age, male, upper rectal cancer, cT4aN2M0.
APPENDIX 7: PREOPERATIVE TARGET DELINEATION OF LOWER RECTAL CANCER

*64 years-of-age, male, lower rectal cancer, cT3N2M0.
APPENDIX 8: DELINEATION OF RADIOTHERAPY TARGET AFTER ABDOMINAL AND PERINEAL RESECTION FOR RECTAL CANCER

*53 years-of-age, male, postoperative of abdominal and perineal resection for lower rectal cancer, pT3N1aM0.
APPENDIX 9: DELINEATION OF RADIOTHERAPY TARGET AFTER DIXON FOR RECTAL CANCER

*63 years-of-age, female, after DIXON operation for middle and upper rectal cancer, pT3N2bM0.