1. General guidelines for diagnosis and treatment of colorectal cancer

Attention should be paid to the role of the multidisciplinary team (MDT) in the diagnosis and treatment of colorectal cancer. It is recommended that designated senior attending physicians from colorectal surgery, hepatobiliary surgery, oncology, radiology, imaging, and other relevant departments participate in the MDT, and that the MDT meeting be held at a fixed time and venue. MDT is particularly recommended for patients with liver-limited metastases, late-stage patients with potentially resectable metastases, and patients with middle and low rectal cancers.

2. Diagnostic principles for colorectal cancer

2.1 Colorectal cancer screening of asymptomatic healthy population

High-risk population refers to subjects with history of colorectal adenoma, family history of colorectal cancer, or inflammatory bowel diseases. There are different screening recommendations for average-risk and high-risk populations.
Colorectal screening annually is recommended for high-risk population. The average-risk subjects at the age of 50 to 74 years should also accept colorectal cancer screening (1−2). The screening includes a risk assessment by questionnaire and fecal immunochemical occult blood test (FIT). The subjects tested positive in FIT or risk assessment should undergo colonoscopy examination (3−8). If neoplastic lesions were found under colonoscopy, biopsy and histological examination are required. All polyps and flat neoplastic lesions should be removed. If no lesion was found under colonoscopy, repeated colonoscopy is recommended in 5 years. If advanced colorectal adenoma (adenoma with diameter ≥1 cm, with villous differentiation, or with high-grade dysplasia) were diagnosed, the patient should undergo colonoscopy once every 1−3 years. The interval of follow-up colonoscopy could be extended to 3−5 years if there is no recurrent adenoma in the last colonoscopy. Recommendations of colorectal cancer screening for subjects with family history of colorectal cancer please refer to Section 5 of this guideline. Patients with inflammatory bowel disease should discuss with specialist physician to determine follow-up colonoscopy interval.

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2.2 Basic diagnostic principles

2.2.1 Colorectal cancer diagnosis (Table 1)

2.2.2 Appendix on colorectal cancer imaging staging and diagnosis

Rectal cancer staging (7): T1, Tumor invades submucosa; T2, Tumor invades muscularis propria; T3, Tumor invades subserosa or into non-peritonealised pericolic or perirectal tissues; T4a, Visceral peritoneum invasion (covered by the serosa); and T4b, Surrounding organs and structures invasion. T3 can be further divided into subtypes according to depth of invasion beyond the muscularis propria: T3a (<1 mm), T3b (1−5 mm), T3c (5−15 mm), and T3d (>15 mm). Extramural vascular invasion (EMVI) is defined as: tumor extends beyond the rectal wall and tumor thrombosis is seen within extramural vessels (8). Circumferential resection margin (CRM) is defined as primary tumor, metastatic lymph nodes, and EMVI within 1 mm of the mesorectal fascia, surrounding organs and structures (9,10).

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Table 1 Colorectal cancer diagnosis

| Aim | Class I recommendation | Class II recommendation | Class III recommendation |
|-----|-------------------------|-------------------------|--------------------------|
| Diagnosis | Full colonoscopy + biopsy<sup>a</sup>  
Rectal cancer: digital rectal examination | Barium enema<sup>b</sup>  
Virtual colonoscopy  
Rectal cancer: contrast-enhanced CT/MRI pelvic scan; sigmoidoscopy + biopsy; transrectal biopsy  
Colon cancer: contrast-enhanced abdominal/pelvic CT; exploratory surgery | — |
| Staging-primary tumors (subjects with a confirmed diagnosis by colonoscopy) | Rectal cancer: high resolution pelvic MRI scan<sup>c</sup>  
Endoscopic rectal ultrasound (ERUS)<sup>d</sup>  
Colon cancer: contrast-enhanced chest/abdominal/pelvic CT<sup>e</sup> | Rectal cancer: contrast-enhanced pelvic CT  
Colon cancer: noncontrast chest CT scan and contrast-enhanced abdominal/pelvic MRI | — |
| Staging-distal metastases (subjects with a confirmed diagnosis by colonoscopy) | Contrast-enhanced chest/abdominal/ pelvic CT<sup>e</sup> | Serum carcinoembryonic antigen/CA199  
Noncontrast chest CT scan and contrast-enhanced pelvic MRI | Chest X-rays  
Pelvic ultrasound |
| Staging (ultrasound or CT for patients with suspected liver metastases) | Contrast-enhanced abdominal MRI | Hepatocyte specific contrast-enhanced MRI | Liver ultrasound |
| Staging (suspected metastases according to aforementioned imaging tests but cannot be determined) | PET/CT<sup>f</sup> | — | — |
| Examination before major treatment decisions | — | PET/CT<sup>f</sup>  
Hepatocyte specific contrast-enhanced MRI | Liver ultrasound |

<sup>a</sup> In principle, full colonoscopy is forbidden in patients who are known to have clinical intestinal obstruction.

<sup>b</sup> Patients with intestinal obstruction should not undergo barium enemas.

<sup>c</sup> When liver metastases are suspected by ultrasound (US)/computed tomography (CT) examinations, particularly potentially resectable liver metastases, abdominal magnetic resonance imaging (MRI) scans should be conducted. MRI includes T2 weighted imaging, diffusion-weighted imaging (DWI), multiphase contrast-enhanced MRI, and other imaging markers that can effectively determine the quantity, size, and distribution of liver metastases (1). Patients with certain indications can undergo enhanced MRI with a hepatocyte specific contrast-agent, as this method will aid in detecting more liver lesions less than 1 cm (2).

<sup>d</sup> Pelvic MRI is the most accurate test to define locoregional clinical staging of rectal cancer. ERUS may define the locoregional staging for earliest tumors (3).

<sup>e</sup> CT reconstruction images are used to determine the location, invasion depth, relative relationship with surrounding structures and organs, regional lymph node metastases, and peripheral vascular invasion of colon cancer.

<sup>f</sup> Positron emission tomography (PET)/CT should not be used routinely for initial clinical staging of colorectal cancer (4-6).

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### 2.3 Principles of pathological diagnosis (Table 2)

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2.4 Staging

This guideline uses the 2017 UICC/AJCC TNM staging system (8th edition) (1), which is applicable for primary adenocarcinomas, squamous cell carcinomas, and high-grade neuroendocrine tumors in the colon and rectum. This staging system is not suitable for appendix cancer.

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3. Treatment principles for colon cancer

3.1 Treatment of non-metastatic colon cancer

3.1.1 Treatment of resectable colon cancer

3.1.1.1 Endoscopic treatment

Colon adenomas or some T1 colon adenocarcinomas can

Table 2 Principles of pathological diagnosis

| Type of sample | Class I recommendation | Class II recommendation | Class III recommendation |
|----------------|------------------------|-------------------------|-------------------------|
| Biopsy (Includes endoscopic biopsy or core biopsy) | Macroscopic examination | Microscopic examination | Immunohistochemistry/molecular pathology tests | — |
| | Size and quantity of tissues | Histological identification: Tumor/non-tumor | Immunohistochemical markers used for differential diagnosis^a | — |
| | | Benign/malignant | MMR protein expression^b |
| | | Histological type | |
| | | Histological grade | |
| Polypectomy (Snare resection, endoscopic mucosal resection, endoscopic submucosal dissection) | Tumor size | Subtype of adenoma | Immunohistochemical markers used for differential diagnosis^a | — |
| | Pedunculated/ sessile | Grade of intraepithelial neoplasia (high/low) | MMR protein expression^b |
| | | Accompanied with invasive tumor^c: | |
| | | Histological type^d | |
| | | Histological grade^e | |
| | | Depth of invasion | |
| | | Lateral and deep margins | |
| | | Lymphovascular invasion | |
| Radical surgery sample | Type of specimen | Histological type | Immunohistochemical markers used for differential diagnosis^a | — |
| | Tumor site | Histological grade | MSI^k |
| | Length of intestinal segment | Depth of invasion | |
| | Macroscopic subtype | Lymphovascular invasion | |
| | Tumor size | Perineural invasion | |
| | Distance of tumor from proximal and distal resection margins | Proximal and distal resection margin | |
| | Macroscopic perforation (present/absent) | Circumferential resection margin^h | |
| | Macroscopic intactness of mesorectum for TME specimen | Number of positive lymph nodes/number of total lymph nodes evaluated | |
| | specimen^j | Number of tumor deposits | |
| | Number, size, and anatomical subsite of lymph nodes^g | TNM staging^i | |
| | | TRG^l | MMR protein expression^b |

Table 2 (continued)
be treated by endoscopic removal (Table 3). After resection, postoperative pathology is used to determine the subsequent treatment regimen (Table 4).

### 3.1.1.2 Surgical treatment and postoperative adjuvant treatment (Table 5, 6)

#### 3.1.1.3 Annex: Commonly used adjuvant chemotherapy regimens after colectomy

**5-FU-based monotherapies**

- **Capicitabine**
  - Capicitabine 1,250 mg/m² each time, twice a day, oral administration, Days 1–14
  - Repeat every 3 weeks, for 24 weeks
  - **Simplified two-week 5-FU infusion/LV regimen (sLV5FU2)**

- **LV 400 mg/m² Intravenous infusion for 2 h, Day 1**
  - Followed by 5-FU 400 mg/m² by intravenous bolus and then 1,200 mg/(m²·d)×2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
  - Repeat every 2 weeks, for 24 weeks

**Combined chemotherapy regimens**

- **CapeOx (also known as XELOX)**
  - Oxaliplatin 130 mg/m², intravenous infusion for 2 h, Day 1
  - Capicitabine 1,000 mg/m² each time, twice a day, oral administration, Days 1–14
  - Repeat every 3 weeks, for 24 weeks

- **mFOLFOX6**
  - Oxaliplatin 85 mg/m² by intravenous infusion for 2 h, Day 1
  - LV 400 mg/m² by intravenous infusion for 2 h, Day 1
  - 5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d by continuous intravenous infusion

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### Table 3 Endoscopic treatment strategy

| Stage | Stratification | Class I recommendation | Class II recommendation | Class III recommendation |
|-------|----------------|------------------------|-------------------------|--------------------------|
| Adenomas and T1N0 colon adenocarcinoma<sup>a,b,c,d</sup> | Pedunculated polyps or non-pedunculated polyps with diameters of 5–20 mm | Trapeotomy<sup>a</sup> | EMR | — |
| | 1. Flat lesions with diameters of 5–20 mm, 2. The wide-base lesion >10 mm was suspected to be villous adenoma or sessile serrated adenoma/polyp, 3. Suspicious high-grade intraepithelial neoplasia ≤20 mm, which is expected to be completely resected. | EMR | ESD | — |
| | Mucosa or submucosal adenoma >20 mm | PEMR<sup>e</sup> | ESD | — |
| | 1. Partial T1 (SM <1 mm) colon cancer, 2. Transverse spread tumor ≥20 mm, 3. Colon polyps with fibrosis, Villous adenoma ≥25 mm. | ESD | Operation | — |

**EMR**, endoscopic mucosal resection; **ESD**, endoscopic submucosal dissection.

<sup>a</sup> It is recommended that pathological testing of all non-pedunculated polyps or polyps that are suspected to be cancerous be conducted before determining whether endoscopic removal should be performed.

<sup>b</sup> The risk of cancer accompanied by regional lymph node metastases at the T1 stage is approximately 15%. Local endoscopic excision cannot determine the status of lymph nodes. After endoscopic removal of T1 (SM) cancers, not only should local colonoscopy examination be carried out, but testing of the tumor marker, carcinoembryonic antigen (CEA), abdominal ultrasound, and abdominal CT should also be conducted simultaneously (1).

<sup>c</sup> The histological criteria for confirming curative endoscopic resection of T1 colorectal cancer tissues are as follows: 1) Lesions with submucosal invasion <1 mm; 2) Absence of lymphovascular invasion; 3) Well-differentiated tumors; 4) Absence of tumor budding; and 5) Distance of tumor from resection margin ≥1 mm (2,3).

<sup>d</sup> When it is impossible to determine whether resection margins are negative or positive, it is recommended that follow-up endoscopy be performed in 3–6 months. If resection margins are negative, follow-up can be conducted within 1 year after endoscopic treatment (4,5).

<sup>e</sup> Larger lesions may require piecemeal endoscopic mucosal resection (PEMR). However, the local recurrence rate is high with PEMR and requires increased monitoring (6).

### Table 4 Management strategy after polypectomy

| Pathological staging | Stratification | Class I recommendation | Class II recommendation | Class III recommendation |
|----------------------|----------------|------------------------|-------------------------|--------------------------|
| High-grade intraepithelial neoplasia | NA | Observation | — | — |
| pT1N0M0 Pedunculated polyp with invasive cancer | Good prognosis<sup>a</sup> | Observation | — | — |
| pT1N0M0 Sessile polyp with invasive cancer | — | Observation<sup>c</sup> | Colectomy with enbloc removal of regional lymph nodes | — |
| pT1N0M0 Pedunculated or sessile polyp with invasive cancer | Poor prognosis<sup>b</sup> | Colectomy with enbloc removal of regional lymph nodes | Observation | — |

<sup>a</sup> Patients who fulfilled all the following criteria (7): Specimen was completely excised, with a negative resection margin and good histological characteristics (includes Grade 1 or 2 differentiation and absence of vascular and lymphatic invasion).

<sup>b</sup> Patients who fulfilled one of the following criteria (8): Fragmented specimen, indeterminate or positive resection margin [tumor cells are present within 1 mm from the resection margin or tumor cells can be seen at the electroresection margin (7-9)] or histological characteristics with poor prognosis (Grades 3/4 differentiation and lymphovascular invasion).

<sup>c</sup> The patient should be informed that the probability of poor outcomes will significantly increase with sessile malignant polyps, including disease recurrence, mortality, and blood dissemination, which is highly associated with positive resection margin after endoscopic resection (10).
Table 5 Surgical treatment

| Clinical stage | Stratification | Class I recommendation | Class II recommendation | Class III recommendation |
|----------------|----------------|------------------------|-------------------------|--------------------------|
| cT1−4, N0−2M0 stage I−III | Symptoms that do not require emergency treatment | Colocotomy with en bloc removal of regional lymph nodes<sup>a</sup> | — | — |
| cT1−4, N0−2M0 stage I−III, symptoms requiring emergency treatment | Obstruction | Operation<sup>b</sup> | Stent, two-stage radical resection<sup>c</sup> | — |
| | Perforation | Operation<sup>d</sup> | — | — |
| | Hemorrhage | Colocotomy ± en bloc removal of regional lymph nodes | Endoscopic interventional embolization, selective operation | — |

<sup>a</sup> Radical surgery involves colon resection and regional lymph node dissection. Root lymph nodes at the origin of feeding vessels or suspected lymph nodes outside the dissection area should be removed or biopsied. Only complete resection surgeries can be considered radical surgeries.

<sup>b</sup> Surgery options include one-stage resection and anastomosis; one-stage resection and anastomosis + proximal protective stoma; one-stage tumor resection, proximal stoma, and distal closure; or two-stage resection after ostomy. Laparoscopic surgery is not recommended.

<sup>c</sup> Intestinal stents are usually applicable for lesions at the distal colon as it can result in decompression of the proximal colon, thereby allowing one-stage anastomosis in elective colectomy (11).

<sup>d</sup> Selected according to the degree of peritoneal contamination. Surgical methods similar to b, with sufficient flushing and drainage.

Table 6 Postoperative chemotherapy

| Pathological stage | Stratification | Class I recommendation | Class II recommendation | Class III recommendation |
|--------------------|----------------|------------------------|-------------------------|--------------------------|
| Stage I            | T1−2N0M0       | Observation (Level 1A evidence) | — | — |
| Stage II<sup>a,b,c,d,e</sup> | T3N0M0 with low risk factors | Observation (Level 1A evidence) | — | — |
| | T3N0M0 with medium risk factors | Fluorouracil monotherapy or observation (Level 1A evidence) | — | — |
| | T3 with high risk factors or T4N0M0 | Combined chemotherapy (Level 1A evidence) | Fluorouracil monotherapy (only for pMMR) (Level 1B evidence) | Observation (Level 3 evidence) |
| Stage III<sup>d,e</sup> | TanyN+M0       | Combined chemotherapy (Level 1A evidence) | Fluorouracil monotherapy (Level 1B evidence) | — |

<sup>a</sup> Stage II patients: High-risk factors include T4 (stage IIB or IIC), poor histological differentiation [Grade 3/4, not including patients with high microsatellite instability (MSI-H)], lymphatic/vascular invasion, perineural invasion, preoperative bowel obstruction, or tumor perforation, positive or indeterminate resection margin, insufficient safety resection margin, and less than 12 lymph nodes examined. Low-risk factors refer to MSI-H or deficient mismatch repair (dMMR). Medium risk factors refer to the absence of both high- and low-risk factors.

<sup>b</sup> MMR testing should be considered for all stage II patients. See Section 2.3 Principles of pathological diagnosis for detailed information. Stage II patients with dMMR or MSI-H may have a better prognosis and will not benefit from 5-fluorouracil (5-FU) adjuvant monochemotherapy (12).

<sup>c</sup> The specific regimen for adjuvant chemotherapy should consider the age, physical status, comorbid underlying diseases, etc. of the patient. There is currently no evidence suggesting that addition of oxaliplatin to 5-FU/leucovorin (LV) can benefit patients aged 70 years and above (13).

<sup>d</sup> Adjuvant chemotherapy should be started as soon as the patient recovers after surgery. This usually begins at 3 weeks after surgery and should not occur more than 2 months after surgery. The entire course of adjuvant chemotherapy is 6 months. Three months of CapeOx adjuvant chemotherapy can be considered for low-risk stage III patients (T1−3N1).

<sup>e</sup> Besides clinical trials, it is not recommended that the following drugs be used in adjuvant chemotherapy: irinotecan; S-1 (tegafur/gimeracil/oteracil), TAS-102, and all targeted agents including bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib.
(total amount: 2,400 mg/m², infusion for 46–48 h)
Repeat every 2 weeks for 24 weeks

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3.1.2 Treatment of unresectable colon cancer
Radical resection cannot be achieved in some T4b, M0 patients even after combined organ resection. In these patients, 5-FU-based mono-chemotherapy or combination chemotherapy with oxaliplatin or irinotecan, or even triple drug chemotherapy can be used according to the patient’s condition (1). Clinical trials on advanced colorectal cancer have also shown that chemotherapy can be combined with bevacizumab or cetuximab (2–5). For some T4b patients with local invasion of the sigmoid colon, local radiotherapy can also be performed to increase the response rate of treatment and increase the probability of conversion (6). Endoscopic stent implantation (7,8) or bypass surgery can be carried out to remove obstruction in T4b colon cancer patients with intestinal obstruction.

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3.2 Treatment principles for metastatic colon cancer

3.2.1 Synchronous metastatic colon cancer
3.2.1.1 Treatment of initially resectable metastatic colon cancer
For patients with asymptomatic, resectable synchronous
liver-limited metastases, in which there is the possibility of a potential cure, multimodal therapy including surgery and perioperative chemotherapy is recommended. According to the clinical risk score (CRS), the sequence of neoadjuvant chemotherapy and surgery was determined. If the CRS score shows low risk of recurrence (0–2 points), simultaneous or staged resection of colon cancer and metastatic lesions + postoperative adjuvant chemotherapy is recommended. Neoadjuvant chemotherapy before surgery or resection of the primary lesion + neoadjuvant chemotherapy before local treatment of metastatic lesions can also be considered. If the CRS score shows a high risk of recurrence (3–5 points), neoadjuvant chemotherapy is first recommended, followed by colectomy + simultaneous or staged local treatment of metastatic lesions. Colectomy + neoadjuvant chemotherapy + resection/radiofrequency ablation, other local treatment of metastatic lesions + postoperative adjuvant chemotherapy, simultaneous or staged colectomy and resection/radiofrequency ablation, or other local treatment of metastatic lesions + postoperative adjuvant chemotherapy can also be considered.

For colon cancer patients with symptomatic primary lesions (e.g., obstruction, bleeding, perforation) and synchronous liver metastases only, resection of the primary lesion can be treated first to alleviate symptoms. Stent implantation can also be considered for patients with obstruction. Stratified treatment can then be used based on the CRSs, using the same principles as above.

To reduce drug-induced liver injury, the course of neoadjuvant chemotherapy is usually limited to 2–3 months.

Local management methods for metastatic lesions not only include surgery but also radiofrequency ablation, microwave ablation, and stereotactic radiation therapy.

The CRS contains five parameters: lymph node positivity for primary tumor, synchronous metastases or metachronous metastases that are <12 months from the date of resection of the primary lesion, >1 liver metastases, preoperative carcinoembryonic antigen (CEA) levels >200 ng/mL, and maximum diameter of metastasis >5 cm. Each item scores 1 point. A score of 0–2 points is low while a score of 3–5 points is high. The higher the CRS score, the greater the risk of postoperative recurrence, and the more beneficial the perioperative chemotherapy (1,2).

3.2.1.2 Treatment of initially unresectable metastatic colon cancer
Treatment for initially unresectable metastatic colon cancer can be divided into conversion therapy and palliative treatment based on the resectability of the metastatic lesions. As primary lesions present with symptoms of obstruction, bleeding, and perforation, the primary lesion should be treated first. Comprehensive management and treatment should be used under the guidance of the MDT for these patients.

Patients with potentially resectable tumors should undergo conversion chemotherapy first to shrink metastatic lesions, after that the resectability of these lesions should be re-assessed. Table 7 shows the conversion chemotherapy regimens.

Palliative therapy mainly consists of systemic therapy.

First-line regimens for palliative therapy
Table 8 shows first-line regimens for palliative therapy.

Second-line regimens for palliative therapy
In principle, the regimen of second-line treatment should be changed. The original chemotherapy regimen can be used for stop-and-go patients. Targeted therapy drugs can be used in second-line treatment if they are not used in first-line treatment. If first-line chemotherapy is combined with bevacizumab, the chemotherapy regimen can be changed in second-line treatment while retaining bevacizumab (7). If first-line chemotherapy is combined with cetuximab for palliative treatment, cetuximab is not recommended to be used continuously in second-line therapy. The modified XELIRI (irinotecan + capecitabine regimen, mXELIRI) can be used for second-line chemotherapy (8).

Third-line regimens for palliative therapy
For patients with both wild-type RAS and BRAF genes, cetuximab ± irinotecan (for patients who are cetuximab-naive) regorafenib, or clinical trials are recommended. For patients with RAS or BRAF mutations, regorafenib or clinical trials are recommended.

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Table 7 Conversion chemotherapy for potentially resectable lesions

| Stratification                                      | Class I recommendation                                      | Class II recommendation                                      | Class III recommendation                                      |
|-----------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| Suitable for intensive treatment (both RAS and BRAF wild-type) (Level 2A evidence) | FOLFOX/FOLFIRI ± cetuximab
d (Level 2A evidence) | FOLFOX/CapeOx/FOLFIRI ± bevacizumab (Level 2A evidence); FOLFIRI ± bevacizumab (Level 2A evidence) | Hepatic arterial infusion chemotherapy or other local treatments (Level 2B evidence) |
| Suitable for intensive treatment (both RAS or BRAF mutations) | FOLFOX/CapeOx/FOLFIRI ± bevacizumab (Level 2A evidence) | FOLFIRI ± bevacizumab (Level 2A evidence) | Hepatic arterial infusion chemotherapy or other local treatments (Level 2B evidence) |

a, For potentially resectable patients, 5-fluorouracil (5-FU)/leucovorin (LV) (or capecitabine) combined with oxaliplatin or irinotecan plus molecular targeted therapy should be selected. FOLFIRI ± bevacizumab can be used with caution in patients with a good performance status, who are young, and have a high tumor burden (3). For patients with successful conversion with R0 resection of primary and metastatic lesions, it is generally recommended to continue adjuvant chemotherapy after surgery to complete a total of six months of perioperative treatment. If the preoperative combination of targeted drugs is effective, whether to continue to use targeted drugs postoperatively is still controversial.

b, It is recommended that imaging assessment be conducted every 6–8 weeks during conversion therapy. Surgery is recommended if the metastatic lesions are resectable.

c, If the patient has a responsible or stable disease after 4–6 months of first-line treatment, maintenance therapy can be used or systemic therapy can be temporarily suspended. 5-FU/LV or capecitabine monotherapy ± bevacizumab is recommended for maintenance therapy due to low toxicity (4,5). The use of cetuximab in maintenance therapy has been poorly studied.

d, Recently, many retrospective studies have shown that the prognosis of metastatic colon cancer with right-sided primary lesions (ileocecal junction to splenic flexure) is worse than that of left-sided primary lesions (splenic flexure to the rectum). Retrospective subgroup analysis data of randomized, controlled trials showed that the objective response rate and overall survival of cetuximab are both better than that of bevacizumab for patients with left-sided colorectal cancer. For patients with right-sided colon cancer, cetuximab shows minor advantages over bevacizumab in objective response rate but overall survival is worse than that of bevacizumab (6).

3.2.2 Treatment of postoperative recurrence in metastatic colon cancer

For postoperative patients with resectable recurrence disease, please see “asymptomatic primary lesions” in Section 3.2.1.1 on Treatment of initially resectable metastatic colon cancer, as these patients do not have primary lesions. For postoperative patients with unresectable recurrence disease, please see “asymptomatic primary lesions” in Section 3.2.1.2 on Treatment of initially unresectable metastatic colon cancer.

3.2.3 Annex: Commonly used systemic therapy regimens for metastatic colorectal cancer

mFOLFOX6

Oxaliplatin 85 mg/m² by intravenous infusion for 2 h, Day 1 LV 400 mg/m² by intravenous infusion for 2 h, Day 1 5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)x2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h) Repeat every 2 weeks

mFOLFOX6 + bevacizumab

Oxaliplatin 85 mg/m² by intravenous infusion for 2 h, Day 1 LV 400 mg/m² by intravenous infusion for 2 h, Day 1 LV 200 mg/m² by intravenous infusion for 2 h, Day 1
5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Bevacizumab 5 mg/kg IV, Day 1
Repeat every 2 weeks

**mFOLFOX6 + cetuximab**

Oxaliplatin 85 mg/m² by intravenous infusion for 2 h, Day 1
LV 400 mg/m² by intravenous infusion for 2 h, Day 1
5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Cetuximab 400 mg/m², IV for more than 2 h for first administration followed by 250 mg/m² IV for more than 60 min. Repeat every week
Or cetuximab IV 500 mg/m², Day 1, infusion for more than 2 h, repeat every 2 weeks

**CapeOx**

Oxaliplatin 130 mg/m² IV for more than 2 h, Day 1

Table 8 First-line regimens for palliative therapy

| Stratification | Class I recommendation | Class II recommendation | Class III recommendation |
|----------------|------------------------|-------------------------|--------------------------|
| Suitable for intensive treatment (both RAS and BRAF wild-type) | FOLFOX/FOLFIRI ± cetuximabab (Level 1A evidence); FOLFOX/CapeOx/FOLFIRI ± bevacizumab (Level 1A evidence) | FOLFOXIRI ± bevacizumab (Level 2A evidence) | Hepatic arterial infusion chemotherapy or other local treatments (Level 3 evidence) |
| Not suitable for intensive treatment (both RAS and BRAF wild-type) | Fluorouracil monotherapy ± bevacizumab (Level 1A evidence) | Cetuximab monotherapyab (Level 2A evidence); Dose-reduced dual chemotherapy (FOLFOX/FOLFIRI) ± cetuximab (Level 2A evidence); Dose-reduced dual chemotherapy (FOLFOX/CapeOx/FOLFIRI) ± bevacizumab (Level 2A evidence) | Hepatic arterial infusion chemotherapy or other local treatments (Level 3 evidence) |
| Suitable for intensive treatment (both RAS or BRAF mutations) | FOLFOX/CapeOx/FOLFIRI ± bevacizumab (Level 1A evidence) | FOLFOXIRI ± bevacizumab (Level 2A evidence) | Hepatic arterial infusion chemotherapy or other local treatments (Level 3 evidence) |
| Not suitable for intensive treatment (both RAS or BRAF mutations) | Fluorouracil monotherapy ± bevacizumab (Level 1A evidence) | Dose-reduced dual chemotherapy (FOLFOX/CapeOx/FOLFIRI) ± bevacizumab (Level 2A evidence) | Hepatic arterial infusion chemotherapy or other local treatments (Level 3 evidence) |

a, Recently, many retrospective studies have shown that the prognosis of metastatic colon cancer with right-sided primary lesions (ileocecal junction to splenic flexure) is worse than that of left-sided primary lesions (splenic flexure to the rectum). Retrospective subgroup analysis data of randomized, controlled trials showed that the objective response rate and overall survival of cetuximab are both better than that of bevacizumab for patients with left-sided colorectal cancer. For patients with right-sided colon cancer, cetuximab shows minor advantages over bevacizumab in objective response rate but overall survival is worse than that of bevacizumab (1).

b, Capecitabine combined with cetuximab is not recommended.

5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Bevacizumab 5 mg/kg IV, Day 1
Repeat every 2 weeks

**CapeOx**

Oxaliplatin 130 mg/m² IV for more than 2 h, Day 1

Capecitabine 1,000 mg/m² each time, twice a day, oral administration, Days 1–14 followed by 7 d of rest
Repeat every 3 weeks

**CapeOx + bevacizumab**

Oxaliplatin 130 mg/m² IV for more than 2 h, Day 1
Capecitabine 1,000 mg/m² each time, twice a day, oral administration, Days 1–14 followed by 7 days of rest
Bevacizumab 7.5 mg/kg IV, Day 1
Repeat every 3 weeks

**FOLFIRI**

Irinotecan 180 mg/m² by intravenous infusion for more than 30–90 min, Day 1
LV 400 mg/m² by intravenous infusion for 2 h together with irinotecan infusion, Day 1
5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Repeat every 2 weeks
FOLFIRI + bevacizumab
Irinotecan 180 mg/m² by intravenous infusion for more than 30–90 min, Day 1
LV 400 mg/m² by intravenous infusion for 2 h together with irinotecan infusion, Day 1
5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Bevacizumab 5 mg/kg, intravenous infusion, Day 1
Repeat every 2 weeks

FOLFIRI + cetuximab
Irinotecan 180 mg/m² by intravenous infusion for more than 30–90 min, Day 1
LV 400 mg/m² by intravenous infusion for 2 h together with irinotecan infusion, Day 1
5-FU 400 mg/m² by intravenous bolus on Day 1 followed by 1,200 mg/(m²·d)×2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Repeat every 2 weeks

Cetuximab 400 mg/m², IV for more than 2 h for first administration followed by 250 mg/m² IV for more than 60 min. Repeat every week
Or cetuximab IV 500 mg/m², Day 1, infusion for more than 2 h, repeat every 2 weeks

CapIRI
Irinotecan 180 mg/m² by intravenous infusion for more than 30–90 min, Day 1
Capecitabine: 1,000 mg/m² each time, twice a day, oral administration, Days 1–7
Repeat every 2 weeks

CapIRI + bevacizumab
Irinotecan 180 mg/m² by intravenous infusion for more than 30–90 min, Day 1
Capecitabine: 1,000 mg/m² each time, twice a day, oral administration, Days 1–7
Bevacizumab 5 mg/kg, intravenous infusion, Day 1
Repeat every 2 weeks

mXELIRI
Irinotecan 200 mg/m² by intravenous infusion for more than 30–90 min, Day 1
Capecitabine: 800 mg/m² each time, twice a day, oral administration, Days 1–14
Repeat every 3 weeks

mXELIRI + bevacizumab
Irinotecan 200 mg/m² by intravenous infusion for more than 30–90 min, Day 1
Capecitabine: 800 mg/m² each time, twice a day, oral administration, Days 1–14
Bevacizumab 7.5 mg/kg, intravenous infusion, Day 1
Repeat every 3 weeks

Capecitabine
Capecitabine: 1,250 mg/m² each time, oral administration, twice a day, Days 1–14, repeat every 3 weeks

Capecitabine + bevacizumab
Capecitabine: 1,250 mg/m² each time, oral administration, twice a day, Days 1–14, repeat every 3 weeks
Bevacizumab 7.5 mg/kg, IV, Day 1, repeat every 3 weeks

Simplified two-week 5-FU infusion/LV regimen (sLV5FU2)
LV 400 mg/m² intravenous infusion for 2 h, Day 1
Followed by 5-FU 400 mg/m² intravenous bolus, and then 1,200 mg/(m²·d)×2 d by continuous intravenous infusion (total amount: 2,400 mg/m², infusion for 46–48 h)
Repeat every 2 weeks

FOLFOXIRI + bevacizumab
Irinotecan 165 mg/m², intravenous infusion, Day 1
Oxaliplatin 85 mg/m², intravenous infusion, Day 1
LV 400 mg/m², intravenous infusion, Day 1
Followed by 5-FU 1,600 mg/(m²·d)×2d, continuous intravenous infusion (total amount 3,200 mg/m², 48 h of infusion)
Bevacizumab 5 mg/kg IV, Day 1
Repeat every 2 weeks

Irinotecan
Irinotecan 125 mg/m² by intravenous infusion for more 30–90 min, Day 1, repeat every 3 weeks
Irinotecan 300–350 mg/m² by intravenous infusion for more 30–90 min, Day 1, repeat every 3 weeks

Cetuximab + irinotecan
First dose of cetuximab 400 mg/m² by intravenous infusion, followed by 250 mg/m², once every week
Or cetuximab 500 mg/m², once every 2 weeks
Irinotecan 300–350 mg/m² by intravenous infusion, repeat every 3 weeks
Or irinotecan 180 mg/m² by intravenous infusion, repeat every 2 weeks
Or irinotecan 125 mg/m² by intravenous infusion on Day 1 and 8, repeat every 3 weeks

Cetuximab
First dose of cetuximab 400 mg/m² by intravenous infusion, followed by 250 mg/m², once every week
Or cetuximab 500 mg/m², once every 2 weeks

Regorafenib
Regorafenib 160 mg, oral administration, once a day, Days 1–21, repeat every 28 d
Raltitrexed 3 mg/m² by intravenous infusion in 15 min (+
50–250 mL 0.9% sodium chloride or 5% glucose). Repeat every 3 weeks.

3.3 Colon cancer follow-up

Postoperative follow-up for stage I patients: once every 6 months for 5 years. Postoperative follow-up for stage II/III patients: once every 3 months for 3 years, followed by once every 6 months to 5 years, and then once a year. The follow-up should include: 1) Physical examination with an emphasis on digital rectal examination; 2) Blood CEA levels; 3) Liver ultrasonography for stage I/II patients; 4) Chest, abdominal, and pelvic CT once a year for stage III patients or when there are CEA or ultrasound abnormalities; and 5) Colonoscopy examination within 1 year after surgery. If full colonoscopy was not carried out before surgery due to tumor obstruction, examinations should be carried out in 3–6 months after surgery. If no abnormalities are found, follow-up examinations should be carried within 3 years, followed by once every 5 years (1). Follow-up frequency for R0 resection/ablation for stage IV patients with metastases: once every 3 months for 3 years, followed by once every 6 months until Year 5, and then once a year. Follow-up should include: physical examination; blood CEA levels; and enhanced chest, abdominal, and pelvic CT once every 6–12 months. If the patient’s physical status does not allow him/her to receive anti-neoplastic treatment due to recurrence, it is not advisable to conduct routine tumor follow-up/monitoring for the patient. PET/CT is only recommended for clinically suspected recurrence while routine imaging is negative, such as persistently elevated CEA. PET examination is not recommended as a routine follow-up/monitoring method.

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4. Treatment principles for rectal cancer

4.1 Treatment principles for non-metastatic rectal cancer

4.1.1 Treatment principles for rectal adenoma

Refer to Section 3.1.1.1 Endoscopic treatment for treatment of rectal adenomas. Usually different treatment recommendations are given based on the distance between the lesion and the anal verge in high-grade rectal neoplasia. For patients with a distance of ≤8 cm between the lesion and anal verge, it is primarily recommended that transanal local excision or endoscopic resection be performed, followed by transanal endoscopic microsurgery (TEM), laparoscopic or open rectal resection. For patients with a distance of 8–15 cm, endoscopic resection is the treatment of first choice, followed by TEM, laparoscopic, or open rectal resection.

4.1.2 Treatment principles for cT1–2N0 rectal cancer

The treatment principles for cT1–2N0 rectal cancer is radical surgery. Transanal local excision can be considered in cT1N0 patients when it is difficult to perform sphincter-preserving surgery. Radical surgery should be considered if the following pathological situation occur after local excision: poorly differentiated tumors, vascular invasion, positive resection margin, sm3, or T2. Radiotherapy/chemotherapy is recommended for patients who do not undergo radical surgery (1,2). 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. The next treatment can be selected according to the extent of tumor response: 1) Watch & wait for patients who have complete clinical response (cCR); 2) Transanal local excision for patients with ycT1 tumors; and 3) Radical rectal cancer surgery for patients with ycT2 tumors. The current international consensus for complete clinical remission (cCR) (3) includes: 1) Digital rectal examination: normal; 2) White and flat mucosal scars under the endoscope, accompanied by peripheral capillary telangiectasia, without signs of malignant ulcers or nodules; and 3) High resolution MRI in T2 shows completely dark, without moderate intensity signals and lymph nodes; in DW phase, no tumor signal for B800-B1000 and/or, in ADC shows little or no signal, and intestinal wall linear signals in the tumor area. The watch and wait strategy is currently under exploration. There is a need to fully communicate with the patients, with an emphasis for more frequent follow-up and let them know the results of salvage therapy after tumor recurrence. It is recommended that follow-up visits should be carried out every 1–2 months within 2 years. The assessment methods mainly consist of digital rectal examination, endoluminal ultrasound, and functional MR. There is still controversy over the use of biopsy in the scar region of the primary lesion.
4.1.3 Treatment of cT3/cT4N+ rectal cancer (Table 9)
This section is applicable for midder and lower rectal cancers that were assessed by digital rectal examination and MRI, with a distance from anal verge to the lower edge of tumor <10 cm. Stratified treatment according to risk level should be carried out under the guidance of high-quality MRI imaging and experienced radiologists.

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4.2 Treatment principles for metastatic rectal cancer

4.2.1 Treatment principles for synchronous metastatic rectal cancer (Table 10)

4.2.2 Treatment principles for postoperative recurrence in metastatic rectal cancer
4.2.2.1 Diagnosis and treatment principles for local recurrence after rectal cancer surgery

When local recurrence after rectal cancer surgery is
Table 9 Treatment of cT3/cT4N+ rectal cancer

| Stage | Stratification | Class I recommendation | Class II recommendation | Class III recommendation |
|-------|----------------|------------------------|------------------------|-------------------------|
| cT3N0 | Middle rectal cancers with peritoneum covered | Concurrent radiochemotherapy\(^a\) + transabdominal resection\(^b\) + adjuvant chemotherapy\(^c\) (Level 1A evidence) | Short-course radiotherapy\(^d\) + transabdominal resection\(^b\) + adjuvant chemotherapy\(^c\) (Level 1B evidence) | Transabdominal resection\(^b\) +/- adjuvant therapy\(^c,e,f\) |
|       | Middle rectal cancers without peritoneum covered or lower rectal cancers | Concurrent radiochemotherapy\(^a\) + transabdominal resection\(^b\) + adjuvant chemotherapy\(^c\) (Level 1A evidence) | Short-course radiotherapy\(^d\) + transabdominal resection\(^b\) + adjuvant chemotherapy\(^c\) (Level 1B evidence) | — |
| cT4/any N, cT/N1−2, or locally unresectable | None | Concurrent radiochemotherapy\(^a\) + transabdominal resection\(^b\) + adjuvant chemotherapy\(^c\) (Level 1A evidence) | Chemotherapy\(^g\) + concurrent radiochemotherapy\(^a\) + transabdominal resection\(^b\) +/- chemotherapy\(^h\) (Level 2A evidence) | — |
| cT3,4 or N+ | Medical factors that contraindicate surgical resection are present | Concurrent radiochemotherapy\(^a\) + transabdominal resection\(^b\) + adjuvant chemotherapy\(^c\) (Level 1A evidence) | Chemotherapy\(^g\) + concurrent radiochemotherapy\(^a\) + transabdominal resection\(^b\) +/- chemotherapy\(^h\) (Level 2A evidence) | — |
| cT3,4N0, any T/N+, or patients who did not undergo preoperative radiotherapy due to contraindications for multimodal therapy or other reasons | pT1−2N0 after transabdominal resection | Observation | Re-evaluation:\(^i\): Adjuvant chemotherapy\(^c\) + adjuvant radiochemotherapy\(^a\) + adjuvant chemotherapy\(^c\) (Level 1A evidence) | Re-evaluation:\(^i\): Adjuvant radiochemotherapy\(^a\) + adjuvant chemotherapy\(^c\) (Level 1B evidence) |

\(^a\) Concurrent radiochemotherapy + surgery + adjuvant chemotherapy is the standard treatment for locally advanced top and lower rectal cancers (1-8). Concurrent chemoradiotherapy: capcitabine 825 mg/m\(^2\) bid or 5-FU CIV: 225 mg/(m\(^2\)·d), 5 d every week. Radiotherapy dose is 45.0−50.4 Gy/25−28 fractions. Either 3D-CRT or intensity modulated radiation therapy (IMRT) can be used.

\(^b\) Surgery should be carried out after 5−12 weeks if long-course chemoradiotherapy is used.

\(^c\) Refer to Section 3.1.1.2 postoperative adjuvant treatment as a reference for adjuvant chemotherapy.

\(^d\) Short-course radiotherapy 5 × 5 Gy (9-12) is mainly suitable for low-risk patients. Multidisciplinary team (MDT) discussion should be taken considering the necessity of downstaging and long-term toxicity.

\(^e\) The recommended total adjuvant treatment course is 6 months including neoadjuvant radiochemotherapy and postoperative adjuvant chemotherapy (13). If postoperative pathology after neoadjuvant radiochemotherapy shows the stage is greater than yp stage II, adjuvant fluorouracil monochemotherapy can be considered after communicating with the patient (14).

\(^f\) Surgery + adjuvant chemotherapy can be used on rectal cancer patients with a low risk of local recurrence.

\(^g\) The treatment strategy of preoperative chemotherapy + radiochemotherapy + surgery is based on a small number of phase II or retrospective studies (15,16) and can be an alternative.

\(^h\) Chemotherapy is recommended if surgery contraindications are present. The FOLFOXIRI regimen is not recommended. The recommended total adjuvant treatment course is 6 months (13).

\(^i\) If comprehensive therapy can be carried out on re-evaluation, the total adjuvant treatment course (including chemotherapy and radiotherapy) should not exceed 6 months (13). Postoperative adjuvant therapy should be started as soon as possible (not later than 8 weeks). If poor wound healing in perineum, delayed recovery of intestinal function, or other conditions occur, postoperative adjuvant radiotherapy can be delayed, but no later than 12 weeks.
diagnosed, resectability and history of pelvic radiation should be taken into consideration. For patients with resectable lesions, surgery after radiochemotherapy can be considered in patients without previous radiation, or direct surgery in patients with previous radiation. For unresectable lesions, palliative or conversional chemotherapy and re-evaluation for resectability are recommended.

### 4.2.2.2 Treatment principles for rectal cancer with postoperative metastasis

Refer to Section 3.2.2 Treatment of postoperative recurrence in metastatic colon cancer.

### 4.3 Rectal cancer follow-up

Refer to Section 3.3 Colon cancer follow-up.

### 5. Principles of screening for hereditary colorectal cancer and genetic testing

Management strategy after genetic screening is shown in Table 11. All colorectal cancer patients should be asked on their family history of cancer and their intestinal polyposis status should be determined. Specific disease screening should be carried out for patients who fulfilled the following criteria in regional medical center: 1) Familial adenomatous polyposis (FAP) screening (including colonoscopy examination and FAP genetic screening) is required for individuals with ≥ 20 polyps in the entire colon and rectum or with a confirmed FAP family member (1); 2) Peutz-Jeghers syndrome (PJ) screening is required for individuals with significant melanosis in the oral mucosa, lips, nose, cheeks, periorbital area, reproductive organs, hands and feet, perianal skin, etc. Patients with confirmed PJ family members also should receive screening. STK11 gene mutation test is recommended (2); and 3) Patients excluding FAP and PJ syndrome should receive screening for Lynch syndrome. Individuals who fulfilled the following criteria should be suspected of Lynch syndrome family and detected the relevant genes (mismatch repair genes MLH1, MSH2, MSH6, and PMS2) (3,4). There are at
least two histopathologically diagnosed colorectal cancer patients in the family, and 2 cases of them are first-degree relatives (parents and offspring, or siblings), and meet any one of the following criteria: 1) At least one case with multiple colorectal cancer (including adenomas); 2) At least one with onset of colorectal cancer <50 years; and 3) At least one with Lynch syndrome associated-extracolonic cancers (including gastric cancer, endometrial cancer, small intestine cancer, ureter and renal pelvis cancer, ovarian cancer, and hepatobiliary cancers) (5). After genetic testing, protocols in the following table are used for management and follow-up for those with confirmed pathological germline mutations and mutation carriers. General population screening can be carried out for individuals who are not mutation carriers. For those in which germline mutations cannot be determined, follow-up strategy should be discussed and decided by the doctor and individuals according to family history and clinical presentations.

Table 11: Management strategy after genetic screening

| Clinical assessment                                                                 | Recommendation                                      |
|----------------------------------------------------------------------------------|-----------------------------------------------------|
| 1. Carriers of familial adenomatous polyposis gene mutations:                   | 1) Undergo colonoscopy examinations once every year from 10–15 years old. |
| 2. Carriers of Lynch syndrome gene mutations:                                   | 1) Carriers of MLH1 or MSH2 mutations: Undergo colonoscopy once every 1–2 years from 20–25 years old; Carriers of MSH6 or PMS2 mutations: Undergo colonoscopy once every 1–2 years from 25–30 years old. |
|                                                                                   | 2) Undergo gastroduodenoscopy once every 1–2 years from 30–35 years old. |
|                                                                                   | 3) Prophylactic hysterectomy and bilateral salpingo-oophorectomy can be considered for females who have given birth. For individuals who does not undergo prophylactic surgery, endometrial biopsy once every 1–2 years and regular transvaginal ultrasound as well as serum CA125 test are recommended to monitor endometrial cancer and ovarian cancer. |

CA, carbohydrate antigen.

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