Chinese Medical Journal®

Chinese national clinical practice guidelines on prevention, diagnosis and treatment of early colorectal cancer

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Abstract

Background: The incidence and mortality of colorectal cancer (CRC) in China are increasing in recent years. The clarified pathogenesis and detectable precancerous lesions of CRC make it possible to prevent, screen, and diagnose CRC at an early stage. With the development of endoscopic and surgical techniques, the choice of treatment for early CRC is also worth further discussion, and accordingly, a standard follow-up program after treatment needs to be established.

Methods: This clinical practice guideline (CPG) was developed following the recommended process of the World Health Organization, adopting Grading of Recommendations Assessment, Development and Evaluation (GRADE) in assessing evidence quality, and using the Evidence to Decision framework to formulate clinical recommendations, thereby minimizing bias and increasing transparency of the CPG development process. We used the Reporting Items for practice Guidelines in HealThcare (RIGHT) statement and Appraisal of Guidelines for Research and Evaluation II (AGREE II) as reporting and conduct guides to ensure the guideline's completeness and transparency.

Results: This CPG comprises 46 recommendations concerning prevention, screening, diagnosis, treatment, and surveillance of CRC. In these recommendations, we have indicated protective and risk factors for CRC and made recommendations for chemoprevention. We proposed a suitable screening program for CRC based on the Chinese context. We also provided normative statements for the diagnosis, treatment, and surveillance of CRC based on existing clinical evidence and guidelines.

Conclusions: The 46 recommendations in this CPG are formed with consideration for stakeholders' values and preferences, feasibility, and acceptability. Recommendations are generalizable to resource-limited settings with similar CRC epidemiology pattern as China.

Keywords: Colorectal cancer; Early detection of cancer; Prevention; Screening; Diagnosis; Treatment; Follow-up; Guideline

Introduction

The incidence and mortality of colorectal cancer (CRC) in China have increased significantly in recent years.[1] Surpassing gastric cancer, CRC has become one of the main cancers threatening the life and health of Chinese people and causing a serious social burden. According to recent data of the National Cancer Center,[2] there were estimated 388,000 new cases of CRC reported in China in 2015, accounting for 9.9% of all malignant tumors. In the same year, there were estimated 187,000 deaths owing to CRC in China, accounting for 8.0% of all malignant tumor deaths. The incidence and mortality of CRC are at a low level in people younger than 25 years but increase rapidly with older age, reaching a peak in the age group 80–84 years.[1] However, the incidence and mortality of CRC have also shown a significant increase in populations younger than 40 years old.

In recent years, basic and clinical research on CRC has made great progress. Many rigorous conclusions have been drawn from studies on the pathogenesis of CRC, and considerable evidence has also been generated from clinical studies on the prevention, screening, diagnosis,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003253

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Chinese Medical Journal 2024;137(17)
Received: 08-01-2024; **Online:** 06-08-2024 **Edited by:** Yuanyuan Ji

treatment and surveillance of CRC. Considering the disease burden and trend of early-onset CRC, establishing a systematic process for the prevention, screening, diagnosis, treatment, and surveillance of CRC is important. This clinical practice guideline (CPG) integrates the latest clinical evidence and summarizes existing guidelines.

The scope of this CPG is focused on the prevention, screening, diagnosis, treatment, and surveillance of CRC. This CPG is intended to provide whole-process utility for Chinese clinicians and patients to improve patients' health outcomes. This article provides a synopsis of 46 key recommendations, along with summaries of clinical study data supporting each recommendation [Table 1]. We aim to update the current CPG in 2025.

Methods

Guideline development group

A multidisciplinary group of 43 experts on gastroenterology, general surgery, medical imaging, pathology, and methodology from regions across China forms the guideline development group (GDG). Their conflicts

Table 1: Summary and strengths of the recommendations.

No.	Recommendation	Strength of recommendation
Prevention		
1.1	Risk factors and protective factors of colorectal cancer (CRC).	
1.1.1	Diabetes and obesity are risk factors of CRC.	Strong recommendation, high certainty of evidence
1.1.2	Smoking, alcohol intake, and lack of regular physical activity are risk factors of CRC.	Strong recommendation, high certainty of evidence
1.1.3	Intake of red meat and processed meat is a risk factor of CRC; intake of dietary fiber and dairy products can reduce the risk of CRC.	Strong recommendation, high certainty of evidence
1.1.4	Intake of whole grains is a protective factor against CRC.	Strong recommendation, moderate certainty of evidence
1.2	Possible chemoprevention of CRC.	
1.2.1	We do not suggest cyclooxygenase-2 inhibitors for the prevention of CRC considering that cyclooxygenase-2 inhibitors reduce the risk of colorectal adenoma but increase the risk of severe adverse events, such as cardiovascular events.	Weak recommendation, high certainty of evidence
1.2.2	We suggest low-dose aspirin for the prevention of CRC in patients who require treatment with low-dose aspirin for other conditions.	Weak recommendation, high certainty of evidence
1.2.3	We do not suggest calcium, vitamin D, folate, or ursodeoxycholine supplementation for the prevention of CRC.	Weak recommendation, low certainty of evidence
1.2.4	We suggest probiotics for the prevention of colorectal adenoma and cancer.	Weak recommendation, moderate certainty of evidence
Screening		
2.1	The adenoma detection rate (ADR) is an important factor in the screening of CRC.	
2.1.1	We recommend adequate intestinal preparation before colonoscopy to be ensured in screening CRC.	Strong recommendation, moderate certainty of evidence
2.1.2	We suggest that the detection rate of sessile serrated lesions should be increased based on ensuring the ADR.	Weak recommendation, low certainty of evidence
2.1.3	We recommend that endoscopists whose ADR is less than 20% receive professional training.	Strong recommendation, moderate certainty of evidence
2.1.4	We recommend that the cecal intubation rate (CIR) of colonoscopy be more than 95%.	Strong recommendation, low certainty of evidence
2.1.5	We recommend that the withdrawal time of the colonoscopy be more than 6 minutes during screening.	Strong recommendation, low certainty of evidence
2.2	Early screening of CRC includes the fecal immunochemical test (FIT), multi-target stool DNA test, digital rectal examination, and endoscopy.	
2.2.1	We recommend the FIT for screening of CRC in the population with average risk.	Strong recommendation, moderate certainty of evidence
2.2.2	We suggest the multi-target stool DNA (mt-sDNA) test for screening of CRC.	Weak recommendation, low certainty of evidence
2.2.3	We recommend digital rectal examination for screening of CRC in the average-risk population.	Strong recommendation, low certainty of evidence
2.2.4	We recommend colonoscopy for screening of CRC in the average-risk population.	Strong recommendation, high certainty of evidence
2.2.5	We suggest colon capsule endoscopy (CCE) as a supplementary tool for screening of CRC in the average-risk population.	Weak recommendation, low certainty of evidence
2.3	Risk scores obtained on questionnaires play an important role in early screening of CRC.	
2.3	We recommend use of risk scores obtained on the Asia-Pacific Colorectal Screening (APCS) questionnaire for risk stratification in screening of CRC.	Strong recommendation, low certainty of evidence
Diagnosis		
3.1	Definition and endoscopic diagnosis of early CRC.	
3.1.1	We recommend that the definitions of early CRC and precancerous lesions be specified for the diagnosis of CRC.	Strong recommendation, low certainty of evidence
3.1.2	We suggest colonoscopy for the diagnosis of CRC.	Weak recommendation, low certainty of evidence
3.2	Imaging examinations for the diagnosis of early CRC.	
3.2.1	We recommend computed tomography colonography (CTC) and endoscopic ultrasonography (EUS) for the diagnosis and staging of CRC.	Strong recommendation, high certainty of evidence
3.2.2	We suggest 3.0-T magnetic resonance imaging (MRI), including high resolution T2-weighted imaging and diffusion-weighted imaging for the diagnosis of CRC.	Weak recommendation, moderate certainty of evidence
3.3	Serum testing for the diagnosis of CRC.	

(*continued*)

Table 1

(Continued)

No.	Recommendation	Strength of recommendation
3.3	We suggest that carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, CA125, CA242 markers not be used as routine reference for the diagnosis of early CRC. However, for patients with elevated markers at preliminary diagnosis of CRC, we suggest monitoring of dynamic changes for efficacy assessment and surveillance of recurrence after treatment.	Weak recommendation, moderate certainty of evidence
3.4	Advanced imaging technology for the diagnosis of CRC.	
3.4.1	We suggest that dye or virtual chromoendoscopy, as well as add-on devices, can increase the ADR in average-risk populations. However, their routine use must be balanced against costs and practical considerations.	Weak recommendation, high certainty of evidence
3.4.2	We recommend dye-based pancolonic chromoendoscopy or virtual chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing ulcerative colitis in the situation of quiescent disease activity.	Strong recommendation, moderate certainty of evidence
3.4.3	We recommend virtual or dye-based chromoendoscopy in addition to white-light endoscopy for the detection of residual neoplasia at a piecemeal polypectomy scar site.	Strong recommendation, moderate certainty of evidence
Treatment		
4.1	Indication for endoscopic treatment of early CRC.	
4.1.1	We recommend endoscopic treatment as the optimal choice for lesions that are resectable *en bloc* based on size and location, with limited possibility of lymph node metastasis, in early CRC (Tis/T1).	Strong recommendation, low certainty of evidence
4.1.2	Post-operational quality of life is better in patients with early CRC who receive endoscopic resection (super minimally invasive surgery) than those receiving colectomy.	Strong recommendation, moderate certainty of evidence
4.2	Indication for surgical treatment of early colon cancer.	
4.2	Surgical treatment is suggested for pT1 colon cancer and the presence of at least one high-risk factor associated with lymph node metastasis. Risk factors of lymph node metastasis include: (1) Poor histological type (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma); (2) Deep submucosal infiltration (>1 mm); (3) Presence of lymphovascular invasion; and (4) Tumor budding.	Weak recommendation, low certainty of evidence
4.3	Selection of the surgical approach for early colon cancer.	
4.3	Laparoscopic approaches are recommended for early colon cancer surgery.	Strong recommendation, moderate certainty of evidence
4.4	Effect of different radical ranges of surgical operation on the overall survival rate of patients with early colon cancer.	
4.4	Early colon cancer surgery requires a safety margin of at least 5 cm. If no lymph node metastasis is assessed preoperatively, D1 or D2 lymph node dissection is an option. D3 lymph node dissection following the principle of complete mesocolic excision (CME) is recommended if lymph node metastasis is assessed preoperatively.	Strong recommendation, low certainty of evidence
4.5	Indication for transanal local excision of early rectal cancer.	
4.5	The suggested indications for transanal local excision of early rectal cancer are as follows: (1) Tumor diameter <3 cm; (2) Tumor invades rectal circumference <30%; (3) Negative margin >3 mm; (4) Within 8 cm from the anal verge when undergoing traditional local excision, within 15 cm when undergoing transanal endoscopic microsurgery (TEM); (5) No lymph node metastasis on imaging examination; (6) No lymphovascular infiltration (LVI) or perineural invasion; and (7) Well- or moderately differentiated.	Weak recommendation, low certainty of evidence
4.6	Selection of the surgical approach for transanal local excision.	
4.6	Transanal excision (TAE), transanal minimally invasive surgery (TAMIS), and TEM are recommended for transanal local excision.	Strong recommendation, low certainty of evidence
4.7	When is radical surgery needed after endoscopic resection or transanal resection of early rectal cancer?	
4.7	We suggest radical resection for patients with local resection of rectal cancer who are at high risk for recurrence.	Weak recommendation, low certainty of evidence
4.8	Surgical strategy for patients with early-stage CRC.	
4.8	Radical surgery is recommended for patients with early-stage CRC who have unfavorable histologic features.	Strong recommendation, moderate certainty of evidence
4.9	Optimal surgical strategy for familial adenomatous polyposis (FAP) combined with early CRC.	
4.9	Total proctocolectomy (TPC) and ileal pouch–anal anastomosis (IPAA) are suggested for FAP combined with early CRC.	Weak recommendation, very low certainty of evidence
4.10	Optimal surgical strategy for Lynch syndrome combined with early CRC.	
4.10	Total colectomy (TC) or subtotal colectomy (STC) is suggested for Lynch syndrome combined with early CRC.	Weak recommendation, very low certainty of evidence
4.11	Optimal treatment strategy for Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS).	

(*continued*)

Table 1

(Continued)

No.	Recommendation	Strength of recommendation
4.11.1	Endoscopic polypectomy is suggested for patients who have PJS combined with early CRC.	Weak recommendation, very low certainty of evidence
4.11.2	Endoscopic polypectomy is suggested for patients who have JPS combined with early CRC.	Weak recommendation, very low certainty of evidence
Surveillance		
5.1	Post-operative follow-up for early CRC after endoscopic treatment.	
5.1	We recommend that the frequency of follow-up visits and surveillance, including colonoscopy, serum CEA and CA19-9 level measurement, and computed tomography scan, should be decided based upon the characteristics of adenomas/polyps in surveillance after endoscopic treatment.	Strong recommendation, moderate certainty of evidence
5.2	Post-operative follow-up for early CRC after local excision.	
5.2.1	Proctoscopy (with endoscopic ultrasound or pelvic MRI with contrast) every 3–6 months for the first 2 years is suggested for early rectal cancer in patients who receive transanal local excision only, then every 6 months for a total of 5 years.	Weak recommendation, low certainty of evidence
5.2.2	For early CRC, serum CEA and CA19-9 surveillance is suggested every 3–6 months for the first 2 years, and then every 6 months for a total of 5 years.	Weak recommendation, low certainty of evidence
5.2.3	Colonoscopy is suggested in the first and third year post-operatively, and then every 5 years.	Weak recommendation, low certainty of evidence
5.3	Post-operative follow-up for early CRC after curative treatment.	
5.3.1	We suggest scheduled colonoscopy rather than an intensive surveillance strategy for patients with stage I CRC who have a low recurrence risk.	Weak recommendation, low certainty of evidence
5.3.2	We suggest an intensive surveillance strategy for patients with stage I CRC who have a high recurrence risk.	Weak recommendation, low certainty of evidence

of interest were collected and assessed using a standard form constructed under the guidance of principles listed in the Guideline International Network (GIN). All GDG members were free of financial and intellectual conflicts of interest and were permitted full participation. This CPG is registered on the GIN website (https://guidelines.ebmportal.com/node/70399).

Guideline development

This CPG was developed following the process recommended by the World Health Organization (WHO),[3] adopting the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria in assessing evidence quality, and using the Evidence to Decision framework to formulate clinical recommendations, which minimizes bias and increases transparency of the process. The quality of the evidence indicates the degree of certainty of the findings. GRADE categorizes the quality of evidence into high, moderate, low, and very low, through assessing various aspects of the body of evidence, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. These are taken into account to inform the final recommendation, together with the balance of benefit and harm, stakeholders' values and preferences, cost effectiveness, acceptability, and feasibility. The strengths of the recommendations in this CPG are categorized into strong, weak, and conditional. The factors that promote a strong recommendation include high certainty of evidence, similarity in stakeholders' values and preferences, cost-effectiveness, and sharp contrast between benefit and harm.[4]

The GDG identified 23 important clinical questions through discussion, which were later converted into research questions using the PICO format (Population, Intervention, Comparison and Outcomes) in preparation for systematic reviews. The GDG held several meetings between 2022 and 2023 to review the evidence for each PICO question and to reach a consensus on the corresponding recommendations. Consensus was reached in each case through open discussion and voting, where 70% was adopted as the threshold to pass a recommendation.

The full CPG report was sent for review to external guideline methodologists and clinicians with no direct involvement in the current CPG. Their feedback was collected and incorporated, as appropriate. We referenced Appraisal of Guidelines for Research and Evaluation II (AGREE II) before and during development of the CPG to ensure quality and followed the Reporting Items for practice Guidelines in HealThcare (RIGHT) statement for reporting.[5,6]

Evidence synthesis

The systematic review team searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, China Biomedical Database, and WanFang databases between October 2021 and March 2022, with no limits regarding date or language. Additionally, the reviewers manually searched the references of all included articles for further relevant studies and contacted clinicians in potentially relevant studies. Quality of the evidence was appraised using GRADE, as stated in the preceding section.

Recommendations and Evidence Profiles

Part 1. Prevention

Clinical question 1.1: Risk factors and protective factors of CRC.

Recommendation 1.1.1: Diabetes and obesity are risk factors of CRC (strong recommendation, high certainty of evidence).

Recommendation 1.1.2: Smoking, alcohol intake, and lack of regular physical activity are risk factors of CRC (strong recommendation, high certainty of evidence).

Recommendation 1.1.3: Intake of red meat and processed meat is a risk factors of CRC; intake of dietary fiber and dairy products can reduce the risk of CRC (strong recommendation, high certainty of evidence).

Recommendation 1.1.4: Intake of whole grains is a protective factor against CRC (strong recommendation, moderate certainty of evidence).

The etiology of CRC remains unexplained, but a large amount of research evidence indicates that the occurrence and development of CRC are the comprehensive results of many factors that include genetics, environment, and lifestyle. Several risk factors and protective factors have been identified. In 2018, the World Cancer Research Foundation reported that there is high-quality evidence that greater body fatness, alcohol intake, intake of red meat and processed meat, and lack of regular physical activity are all convincing causes of colorectal cancer, whereas intake of dairy products and foods containing dietary fiber and whole grains can reduce the risk of CRC.[7]

The guideline development group performed meta-analyses on the risk factors and protective factors of CRC. The results showed that the risk of CRC in people with diabetes was increased by 33% (risk ratio [RR] 1.33, 95% confidence interval [CI] 1.21–1.47) compared with populations that did not have diabetes. The risk of CRC in obese populations (body mass index [BMI] ≥30.0 kg/m^2) was increased by 33% (RR 1.33, 95% CI 1.19–1.50) compared with normal-weight populations (BMI 18.5–25.0 kg/m^2). Current smokers had a 12% increased risk of CRC compared with never smokers (RR 1.12, 95% CI 1.08–1.18). The risk of CRC was increased by 19% (RR 1.19, 95% CI 1.14–1.25) in individuals who consumed alcohol in comparison with non-drinkers. A reduced risk of CRC (RR 0.74, 95% CI 0.67–0.82) was found in the group with the highest versus the lowest physical activity level. The risk of CRC in people with high intake of dairy products was 13% lower (hazard ratio [HR] 0.87, 95% CI 0.84–0.91) than that in people with low intake of dairy products.

The Chinese guideline for the screening, early detection, and early treatment of CRC (2020, Beijing)[8] suggests that reasonable physical activity is a protective factor against CRC. A meta-analysis of 20 prospective cohort studies or randomised controlled trials (RCTs)[9] showed that the risk of CRC was increased by 10% (RR 1.10, 95% CI 1.03–1.17) in people with high intake of red meat and 18% (RR 1.18, 95% CI 1.13–1.24) in people with high intake of processed meat. Another meta-analysis of 21 cohort studies or case-control studies[10] showed that the risk of CRC in people with high dietary fiber intake was 27% lower (HR 0.73, 95% CI 0.66–0.81) than the risk in their counterparts without high intake of dietary fiber. A meta-analysis of 18 cohort studies or case-control studies[11] showed that the risk of CRC in people with high intake of whole grains was 11% lower than that in people with low whole grain intake (HR 0.89, 95% CI 0.84–0.93).

Clinical question 1.2: Possible chemoprevention of CRC.

Recommendation 1.2.1: We do not suggest cyclooxygenase-2 (COX-2) inhibitors for the prevention of CRC considering that COX-2 inhibitors reduce the risk of colorectal adenoma but increase the risk of severe adverse events, such as cardiovascular events (weak recommendation, high certainty of evidence).

Recommendation 1.2.2: We suggest low-dose aspirin for the prevention of CRC in patients who require treatment with low-dose aspirin for other conditions (weak recommendation, high certainty of evidence).

Recommendation 1.2.3: We do not suggest calcium, vitamin D, folate, or ursodeoxycholine (UDCA) supplementation for the prevention of CRC (weak recommendation, low certainty of evidence).

Recommendation 1.2.4: We suggest probiotics for the prevention of colorectal adenoma and cancer (weak recommendation, moderate certainty of evidence).

Results of a large number of RCTs and meta-analyses have shown that regular use of aspirin and COX-2 inhibitors can reduce the incidence and recurrence rate of colorectal adenoma. However, adverse events, such as gastrointestinal bleeding caused by aspirin and increased risk of cardiovascular events caused by COX-2 inhibitors (e.g., celecoxib) are factors limiting the application of these nonsteroidal anti-inflammatory drugs.[12] Research on calcium, vitamin D, folate, and UDCA supplementation for primary prevention of colorectal adenoma remains controversial. Although some RCTs and cohort studies have shown possible chemopreventive effects of calcium and vitamin D, a meta-analysis of RCTs found non-significant results.[13] Research on probiotics has shown that intake of suitable probiotics might contribute to the prevention of colorectal adenoma and cancer by regulating the intestinal flora and inflammatory pathways, with meta-analyses summarizing such evidence.

The guideline development group performed a network meta-analysis of 29 RCTs with a total sample size of 278,694 participants showed that COX-2 inhibitors significantly lowered the incidence rate of colorectal adenoma (RR 0.59, 95% CI 0.44–0.79) and the recurrence rate of colorectal adenoma (RR 0.58, 95% CI 0.43–0.79) in the general population and high-risk populations, in comparison with placebo. However, COX-2 inhibitors also significantly increased the risk of severe adverse events, defined as cardiovascular events, stroke, and gastrointestinal bleeding (odds ratio [OR] 1.29, 95% CI 1.14–1.47), as compared with placebo.

The network meta-analysis also showed that low-dose aspirin (≤160 mg per day) did not reduce the incidence rate of colorectal adenoma (RR 0.69, 95% CI 0.42–1.13) or the recurrence rate of colorectal adenoma (RR 0.70, 95% CI 0.45–1.11) in the general population and high-risk populations, in comparison with placebo. Additionally, high-dose aspirin (≥300 mg per day) did not reduce the incidence rate of colorectal adenoma (RR 0.88,

95% CI 0.64–1.20) or the recurrence rate of colorectal adenoma (RR 0.91, 95% CI 0.66–1.27) in the general population and high-risk populations, as compared with placebo. No statistically significant difference in the risk of severe adverse events, defined as cardiovascular events, stroke, and gastrointestinal bleeding, was found between the aspirin group and placebo group (RR 0.93, 95% CI 0.73–1.18). Considering the benefit and harm, patients who require low-dose aspirin treatment for other conditions, such as primary prevention of stroke or cardiovascular disease, may benefit from the treatment with respect to the risk of colorectal adenoma, probably enhancing confidence in the aspirin regimen.

The above network meta-analysis also showed that calcium (RR 0.88, 95% CI 0.55–1.41), vitamin D (RR 1.02, 95% CI 0.70–1.50), calcium plus vitamin D (RR 0.93, 95% CI 0.50–1.74), folate (RR 0.90, 95% CI 0.66–1.22), and UDCA (OR 0.89, 95% CI 0.46–1.71) did not reduce the incidence rate of colorectal adenoma in the general population and high-risk populations, in comparison with placebo.

The guideline development group performed another meta-analysis and showed that intake of probiotics could reduce the incidence rate of colorectal adenoma (RR 0.31, 95% CI 0.13–0.72) in high-risk populations. However, probiotics could not reduce the incidence rate of CRC (RR 1.39, 95% CI 0.42–4.64). According to the meta-analysis, probiotics might have beneficial effects in CRC prevention, especially in the adenoma stage. However, more clinical trials with large sample sizes are needed.

Part 2. Screening

Clinical question 2.1: The adenoma detection rate (ADR) is an important factor in the screening of CRC.

Recommendation 2.1.1: We recommend adequate intestinal preparation before colonoscopy to be ensured in screening CRC (strong recommendation, moderate certainty of evidence).

Recommendation 2.1.2: We suggest that the detection rate of sessile serrated lesions should be increased based on ensuring the ADR (weak recommendation, low certainty of evidence).

Recommendation 2.1.3: We recommend that endoscopists whose ADR is less than 20% receive professional training (strong recommendation, moderate certainty of evidence).

Recommendation 2.1.4: We recommend that the cecal intubation rate (CIR) of colonoscopy be more than 95% (strong recommendation, low certainty of evidence).

Recommendation 2.1.5: We recommend that the withdrawal time of the colonoscopy be more than 6 minutes during screening (strong recommendation, low certainty of evidence).

The criteria for adequate intestinal preparation are Boston Bowel Preparation Scale score ≥6, Ottawa Bowel Preparation Scale score <5, and Aronchick Scale score between 1 and 3. Adequate quality intestinal preparation helps in observing intestinal mucosa and avoiding missed diagnosis of adenoma. The serrated pathway is an alternate pathway in which serrated polyps replace traditional adenomas as precursor lesions to CRC.[14] CRCs derived from the serrated pathway account for 20–30% of all CRCs.[15,16] Thus, the detection of serrated lesions may result in an additional reduction in CRC incidence, as compared with the simple detection of adenomas. The detection rate of sessile serrated polyps (SSPs) has been found to be strongly correlated with the ADR. Interval CRCs (I-CRCs), or CRCs detected after testing but before the date of the next recommended exam, are a concern for endoscopists. I-CRCs account for approximately 5% of CRCs. A higher ADR is inversely associated with subsequent I-CRC.[17] Evidence shows that the ADR is associated with the risk of interval cancer after colonoscopy. Considering that colonoscopy reaching the ileocecal part of the colon can ensure observation of the whole intestinal segment,[18] the CIR indirectly reflects the endoscopist's skill level. The current recommendation in the United States is that the overall CIR should be at least 90% at the time of screening.[19] The withdrawal time refers to the actual time for the endoscope to reach the rectum from the cecum during colonoscopy, which does not include the time of staining examination or biopsies of polyps and additional procedures. Adequate withdrawal time can guarantee thorough observation of the intestinal tract.

The guideline development group performed a meta-analysis of eight studies and showed that adequate intestinal preparation resulted in higher detection rates of adenomas than inadequate intestinal preparation (RR 1.54, 95% CI 1.14–2.14). A study in 2017 showed a strict association between a high ADR and the SSP detection rate.[20] Among the 354 endoscopists included in that analysis, those distributed in the two highest quartiles of ADR had a significantly increased rate of SSP detection. The guideline development group performed another meta-analysis of five studies and found a higher incidence of I-CRC among endoscopists with an ADR <20% than among those with higher ADRs (RR 0.22; 95% CI 0.09–0.52). The ADR was also validated as a predictor of I-CRC occurring after colonoscopy in three landmark studies.[18,21,22] There is limited evidence clarifying the relationship between the CIR and ADR. A prospective observational study involving 3129 patients in 2015 showed a positive correlation between the CIR and ADR (RR 1.99, 95% CI 1.24–3.20).[23] Another study in 2011[24] found a significantly lower incidence of interval cancer among patients treated by endoscopists whose CIR was >95% than the incidence among patients treated by endoscopists whose CIR was <80%. Since 2002, the American Multi-Social Working Group on Colorectal Cancer has recommended that the average withdrawal time during colonoscopy should be at least 6–10 minutes, which is recommended as a quality indicator of colonoscopy.[25] A prospective randomized trial in 2017 found that colonoscopy with a 3-minute withdrawal time had a higher rate of missed adenoma detection than a 6-minute withdrawal time (RR 2.78, 95% CI 1.35–5.15).[26] A multicenter RCT in 2021

showed that extending the withdrawal time from 6 minutes to 9 minutes significantly increased the ADR.[27]

Clinical question 2.2: Early screening of CRC includes the fecal immunochemical test (FIT), multi-target stool DNA test, digital rectal examination, and endoscopy.

Recommendation 2.2.1: We recommend the FIT for screening of colorectal cancer in the population with average risk (strong recommendation, moderate certainty of evidence).

Recommendation 2.2.2: We suggest the multi-target stool DNA (mt-sDNA) test for screening of CRC (weak recommendation, low certainty of evidence).

Recommendation 2.2.3: We recommend digital rectal examination for screening of CRC in the average-risk population (strong recommendation, low certainty of evidence).

Recommendation 2.2.4: We recommend colonoscopy for screening of CRC in the average-risk population (strong recommendation, high certainty of evidence).

Recommendation 2.2.5: We suggest colon capsule endoscopy (CCE) as a supplementary tool for screening of CRC in the average-risk population (weak recommendation, low certainty of evidence).

Considering that CRCs are prone to bleeding, FIT screening is an effective supplement when resources for colonoscopy are limited. The main technical principle of the FIT is to detect human hemoglobin in stool samples, which indicate possible intestinal lesions. Patients who are FIT positive require colonoscopy to confirm the diagnosis. The mt-sDNA test was approved by the Food and Drug Administration (FDA) in 2014 for screening CRC in populations with average risk.[28] The mt-sDNA test is an FIT combined with DNA mutation detection in fecal exfoliated cells. Colonoscopy is required with a positive mt-sDNA test result. In the Asia-Pacific population, CRCs often occur in the rectum, and neoplasms can be effectively detected with digital rectal examination. Digital rectal examination is a convenient and quick method for primary screening. Colonoscopy is the gold standard for the screening of CRCs and all classes of precancerous lesions, with high sensitivity and specificity. Endoscopists can examine the entire colorectum and can take a biopsy of suspicious lesions to further clarify the pathological diagnosis. CCE provides an overview of the colon and has several advantages over colonoscopy as a noninvasive test. Capsule colonoscopy has been approved by the FDA for imaging the proximal colon in patients with previous incomplete colonoscopies and, more recently, for patients who require colorectal imaging but who are not candidates for colonoscopy.[29]

In an FIT screening program in Taiwan (China) enrolling 5,417,699 participants, a 10% reduction (RR 0.90, 95% CI 0.84–0.95) in CRC mortality was found in the screened group compared with the unscreened group at a 6-year follow-up.[30] An FIT screening program in Spain yielded an age-standardized mortality reduction of 8.82% (95% CI 3.77–13.86%) after 7 years of screening.[31] The guideline development group performed a meta-analysis of 34 studies systematically evaluating the diagnostic accuracy of FIT compared with colonoscopy for CRC and precancerous lesions. For CRC, the sensitivity and specificity was 0.86 (95% CI 0.75–0.93) and 0.90 (95% CI 0.87–0.92), respectively. For advanced adenoma, the sensitivity and specificity was 0.41 (95% CI 0.33–0.49) and 0.91 (95% CI 0.88–0.94), respectively, with an FIT cutoff value of 10 μg/g. In their updated recommendation on CRC screening, the US Preventive Services Task Force included four studies with 12,424 individuals that evaluated the accuracy of mt-sDNA.[32] The pooled sensitivity was 0.93 (95% CI 0.87–1.00) and the specificity was 0.85 (95% CI 0.84–0.86) for CRC. For advanced adenoma, the pooled sensitivity was 0.43 (95% CI 0.40–0.46) and the specificity was 0.89 (95% CI 0.86–0.92). Few studies have focused on the use of digital rectal examination for screening CRC and no relevant systematic reviews have been published. Several studies have revealed the diagnostic value of digital rectal examination for estimating the size and height of terminal rectal adenomas.[33–35] A meta-analysis of 29 studies conducted in 2020 showed that patients might have a significant reduction in CRC mortality (RR 0.38, 95% CI 0.36–0.40) and incidence (RR 0.48, 95% CI 0.46–0.49) after colonoscopy screening.[36] However, the participation rate in colonoscopy screening in China is still very low owing to its invasiveness and the need for adequate bowel preparation.[37,38] A meta-analysis of 13 studies showed that the sensitivity of CCE ranged between 79% and 96% for polyps >6 mm and between 77% and 97% for polyps >9 mm. The specificity of CCE varied between 66% and 97% for polyps >6 mm and between 91% and 99% for polyps >9 mm.[39] However, limitations to the efficacy of CCE include high requirements for bowel cleanliness, low rates of complete examination, and an inability to perform biopsies.

Clinical question 2.3: Risk scores obtained on questionnaires play an important role in early screening of CRC.

Recommendation 2.3: We recommend use of risk scores obtained on the Asia-Pacific Colorectal Screening (APCS) questionnaire for risk stratification in screening of CRC (strong recommendation, low certainty of evidence).

Risk-adapted assessment models based on CRC-related risk factors can effectively identify people at high risk of CRC, which is of great importance in improving the efficacy of screening. A large number of risk assessment models have been developed, among which the most commonly used risk factors include age, sex, family history of CRC in first-degree relatives, BMI, and smoking history.

A meta-analysis included 22 studies evaluating the efficacy of 17 existing risk scores.[40] The area under the receiver operating characteristic curve (AUC) values of risk scores ranged from 0.62 to 0.77. However, comparability of the diagnostic performance between scores has remained very limited. In the interim analysis of an RCT conducted in China in 2020, the APCS score was used to assess the risk of CRC. The detection rate of colorectal

lesions among high-risk individuals was higher than that in the colonoscopy arm, indicating the effectiveness of risk stratification.[41] A cohort study in 2019 showed that the high-risk tier group had a 3.4-fold (95% CI 1.8–6.4 fold) increased risk for advanced colorectal neoplasia (ACN). The sensitivity of the modified APCS score combined with FIT for screening ACN high-risk cohorts was 76.7%. compared with 36.7% for FIT alone and 70.0% for the modified APCS score alone.[42]

Part 3. Diagnosis

Clinical question 3.1: Definition and endoscopic diagnosis of early CRC.

Recommendation 3.1.1: We recommend that the definitions of early CRC and precancerous lesions be specified for the diagnosis of CRC (strong recommendation, low certainty of evidence).

Recommendation 3.1.2: We suggest colonoscopy for the diagnosis of CRC (weak recommendation, low certainty of evidence).

Early CRC refers to lesions confined within the lamina propria of the mucosa or with submucosal infiltration without involvement of the muscularis propria. Precancerous CRC lesions include adenomatous polyps, serrated polyps, and polyposis (including adenomatous polyposis and non-adenomatous polyposis). Studies have estimated that up to two-thirds of advanced CRC cases can be prevented with early diagnosis and treatment using colonoscopy. The incidence and mortality of CRC have declined in recent years owing to the gradual acceptance of colonoscopy.[43]

The definitions of early CRC and precancerous lesions mainly refer to the WHO classification of tumors of the digestive system (2019 edition); Chinese consensus on screening, diagnosis, and treatment of early CRC and precancerous lesions; and Chinese protocol of the diagnosis and treatment of CRC (2020 edition).[44,45] The guideline development group performed a meta-analysis of 10 studies in 2021 and showed that the accuracy of conventional colonoscopy in the diagnosis of early CRC was 0.80 (95% CI 0.77–0.83). In patients with early CRC, the diagnostic accuracy of conventional colonoscopy was significantly better than that of CT (OR 5.37, 95% CI 2.70–10.69), air-barium double contrast examination (OR 2.49, 95% CI 1.02–6.07), and B-type ultrasonography (OR 27.00, 95% CI 2.34–311.17). Additionally, the diagnostic accuracy of indigo carmine colonoscopy for early CRC was significantly better than that of conventional colonoscopy (OR 4.37, 95% CI 2.86–6.68).

Clinical question 3.2: Imaging examinations for the diagnosis of early CRC.

Recommendation 3.2.1: We recommend computed tomography colonography (CTC) and endoscopic ultrasonography (EUS) for the diagnosis and staging of CRC (strong recommendation, high certainty of evidence).

Recommendation 3.2.2: We suggest 3.0-T magnetic resonance imaging (MRI), including high resolution T2-weighted imaging and diffusion-weighted imaging for the diagnosis of CRC (weak recommendation, moderate certainty of evidence).

CTC has non-invasive advantages and high sensitivity for the detection of CRC and precancerous lesions, but it has disadvantages such as strict requirements for intestinal preparation, limited equipment and professionals for inspection, and radiation risks. In the absence of urgent tumor resection indications, full colonoscopy is recommended for CRC diagnosis, and the combination of limited colonoscopy with CTC is a good alternative.[46] Both EUS and MRI have high accuracy for local staging of early CRC, and EUS can be used to select stage T1 tumors that are suitable for endoscopic treatment by determining whether the lesion is confined to the mucosal layer or the submucosa.[47]

A meta-analysis, including 21 studies, showed that the sensitivity and specificity of CTC in CRC screening were 0.95 (95% CI 0.90–0.98) and 0.98 (95% CI 0.95–0.99), respectively, and the AUC was 0.99 (95% CI 0.97–0.99). The sensitivity and specificity in screening of precancerous lesions were 0.88 (95% CI 0.79–0.94) and 0.95 (95% CI 0.90–0.98), respectively, and the AUC was 0.95 (95% CI 0.90–0.98). In terms of safety, the incidence of bleeding, perforation, and death owing to CTC screening complications was 8.29 (95% CI 1.67–41.07), 2.92 (95% CI 1.32–6.48), and 0.12 (95% CI 0.02–0.60) per 10,000, respectively.[8] A meta-analysis based on six studies of EUS and MRI for CRC staging found that both EUS and MRI had >80% accuracy for early staging (T1 and T2). EUS is superior to MRI for T1 staging (93% *vs.* 77%, $P = 0.06$) and MRI is superior to EUS for T2 staging (92% *vs.* 82%, $P < 0.01$).[48] Positron emission tomography (PET) is rarely used for the assessment of early-stage CRC.

Clinical question 3.3: Serum testing for the diagnosis of CRC.

Recommendation 3.3: We suggest that carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, CA125, CA242 markers not be used as routine reference for the diagnosis of early CRC. However, for patients with elevated markers at preliminary diagnosis of CRC, we suggest monitoring of dynamic changes for efficacy assessment and surveillance of recurrence after treatment (weak recommendation, moderate certainty of evidence).

In recent years, with continued advancements in tumor immunology and related technologies, tumor markers have attracted increasing attention and have been used in the early specific diagnosis of tumor. Increasingly more studies are being conducted on the diagnostic value of CA125, CA19-9, CA242, and CEA in patients with CRC. The guideline development group performed a meta-analysis of 16 studies involving 1742 patients with CRC and healthy participants and found that CEA (20.89, 95% CI 20.41–21.37), CA125 (23.82, 95% CI 23.22–24.42), CA19-9 (78.64, 95% CI 77.78–79.50), and CA242 (25.31, 95% CI 23.27–27.34) levels were higher in the

CRC group than those in the control group. These results indicate that serological methods such as CEA, CA125, CA19-9, CA242 measurement are of great importance in the diagnosis of CRC and have clinical applications. However, a study in 2008 exploring the value of tumor markers in the diagnosis and monitoring of CRC found that tumor protein chip C12 (detection of 12 common serum tumor markers, including CEA, CA125, CA19-9, and CA242) is helpful in the diagnosis of mid- to advanced-stage CRC but has low sensitivity for early CRC.[49]

Clinical question 3.4: Advanced imaging technology for the diagnosis of CRC.

Recommendation 3.4.1: We suggest that dye or virtual chromoendoscopy (CE), as well as add-on devices, can increase the ADR in average-risk populations. However, their routine use must be balanced against costs and practical considerations (weak recommendation, high certainty of evidence).

Recommendation 3.4.2: We recommend dye-based pancolonic chromoendoscopy or virtual chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing ulcerative colitis in the situation of quiescent disease activity (strong recommendation, moderate certainty of evidence).

Recommendation 3.4.3: We recommend virtual or dye-based chromoendoscopy in addition to white-light endoscopy for the detection of residual neoplasia at a piecemeal polypectomy scar site (strong recommendation, moderate certainty of evidence).

Owing to the widespread use of colonoscopy for CRC screening, the cost and practicality of advanced imaging techniques or add-on devices must be taken into consideration to avoid excessive financial or organizational burdens. In general, surveillance of long-standing colitis can only be accurately performed in the absence of disease activity and with adequate bowel preparation. Indeed, all the imaging studies mentioned above only apply to patients with long-standing colitis undergoing surveillance in the setting of quiescent disease activity and adequate bowel preparation. Endoscopic piecemeal polypectomy has emerged as a safe and effective method of removing large sessile or nonpolypoid colorectal lesions. However, because of a relatively high rate of adenoma recurrence, estimated at 15–30%, performing surveillance colonoscopy at 4–6 months after endoscopic resection is recommended.

A meta-analysis, including 11 RCTs, in 2019 showed that high-definition narrow-band imaging (NBI) leads to a significant increase in the unadjusted OR in adenoma detection compared with high-definition white-light endoscopy (HD-WLE) (OR 1.14, 95% CI 1.01–1.29, $P = 0.04$).[50] A recently updated Cochrane systematic review from 2016 analyzed seven RCTs with a total of 2727 patients that assessed the role of dye-based chromoendoscopy in detecting colorectal lesions outside the setting of polyposis or colitis.[51] Pancolonic CE significantly increased the number of patients with at least one polyp detected (OR 1.87, 95% CI 1.51–2.30) and the number of those with at least one neoplastic polyp (adenoma or carcinoma) detected (OR 1.53, 95% CI 1.31–1.79). A multicenter RCT in 2017, including 1065 patients, found an increase in the mean adenoma per patient rate (0.79 *vs.* 0.64, $P = 0.005$), but not in the ADR (40.4% *vs.* 37.5%; OR 1.13, 95% CI 0.87–1.48, $P = 0.35$) or detection rate of sessile serrated lesions, using routine pancolonic CE compared with HD-WLE.[52] Another multicenter RCT in 2019 evaluated the role of a novel pH- and time-dependent per-oral methylene blue formulation (MB-MMX) that is delivered in pill form during the bowel preparation phase. This RCT enrolled 1205 patients undergoing screening or surveillance colonoscopy and found an increased overall ADR in the MB-MMX group compared with the placebo group (56.29% *vs.* 47.81%; OR 1.46, 95% CI 1.09–1.96). The MB-MMX group showed a higher number of patients with adenomas ≤5 mm (37.11% *vs.* 30.90%; OR 1.36, 95% CI 1.01–1.83).[53] A meta-analysis of 10 studies with a total of 494 patients compared dye-based CE with standard-definition white-light endoscopy (SD-WLE) and HD-WLE.[54] The proportion of patients diagnosed with dysplasia using CE was 17% compared with 11% for WLE. When analyzed separately, CE could more effectively identify dysplasia than SD-WLE (RR 2.12, 95% CI 1.15–3.91); however, CE was not as effective in comparison with HD-WLE (RR 1.36, 95% CI 0.84–2.18). Studies have shown that using HD-WLE alone allows for the identification of 69–83% of recurrences, revealed by performing targeted and random biopsies.[55,56] Recent studies have provided new evidence for the efficacy of advanced endoscopic imaging in the detection of post-polypectomy/post-endoscopic mucosal resection (EMR) scars and residual/recurrent colorectal neoplasia. A prospective single-center study that analyzed 183 scars after a median 3.9 months following endoscopic polypectomy found a significantly higher sensitivity for endoscopic residual neoplasia detection with a combination of HD-WLE and NBI in comparison with HD-WLE alone (93.3% *vs.* 66.7%). The negative predictive value for the combination of HD-WLE and NBI was 98.6% (95% CI 95.1–99.8%).[57] Another study comparing the combination of HD-WLE and virtual or dye-based CE against histological verification in recurrence assessment revealed biopsy evidence of residual/recurrent lesions in 16 of 228 (7%) macroscopically inconspicuous polypectomy scars.[58]

Part 4. Treatment

Clinical question 4.1: Indication for endoscopic treatment of early CRC.

Recommendation 4.1.1: We recommend endoscopic treatment as the optimal choice for lesions that are resectable *en bloc* based on size and location, with limited possibility of lymph node metastasis, in early CRC (Tis/T1) (strong recommendation, low certainty of evidence).

Recommendation 4.1.2: Post-operational quality of life is better in patients with early CRC who receive endoscopic resection (super minimally invasive surgery) than those receiving colectomy (strong recommendation, moderate certainty of evidence).

Both endoscopic resection and colectomy are commonly performed for early CRC. However, with development of super minimally invasive surgery (SMIS), such as EMR, endoscopic submucosal dissection (ESD), and digestive endoscopic tunnel technique, more cases of early CRC are resected endoscopically, with effectiveness and safety comparable to that of colectomy.[59,60] The difference is that the anatomy of the colorectum is not changed after resection with SMIS. It is also assumed that post-operational quality of life (QoL) is better for SMIS than colectomy. Nevertheless, few prospective studies have focused on comparisons of post-operational QoL between these two treatments for early CRC.

A meta-analysis, including three cohort studies, with a total of 768 patients who had early CRC undergoing endoscopic resection and 552 patients undergoing surgical resection demonstrated a 7% (95% CI 4–11%) lower risk of complications[61] in the endoscopic group. At present, there are few RCTs or meta-analyses comparing post-operational QoL between SMIS and colectomy for early CRC. A cross-sectional study of 119 patients reported QoL in patients with T1 CRC treated with endoscopic or surgical tumor resection.[62] Compared with the surgery group, perceived time to recovery was, on average, 3 months shorter in endoscopically treated patients after adjustment for confounders (19.9 days *vs*. 111.3 days, $P = 0.001$). The two treatment groups were comparable to global QoL and symptom severity scores.

Clinical question 4.2: Indication for surgical treatment of early colon cancer.

Recommendation 4.2: Surgical treatment is suggested for pT1 colon cancer and the presence of at least one high-risk factor associated with lymph node metastasis. Risk factors of lymph node metastasis include: (1) Poor histological type (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma); (2) Deep submucosal infiltration (>1 mm); (3) Presence of lymphovascular invasion; and (4) Tumor budding (weak recommendation, low certainty of evidence).

Surgery is the main treatment option for early colon cancer and should be performed as quickly as possible. Only cancerised adenomas with well-differentiated cancer, an absence of lymphovascular invasion, and negative margins can be radically treated with endoscopic excision.[63] Oncologic outcomes of laparoscopic resection are equivalent to those of the laparotomy technique, but the former technique has several advantages, such as reduced postoperative pain and early resumption of eating and normal daily activities.[64–67] Laparoscopic colon resection is a safe alternative to open surgery.[68] All lesions highly suspected of being invasive must be treated with total resection. A surgical approach is warranted in certain situations, especially where endoscopic treatment fails or in the presence of high-risk features.[69] At present, systematic evaluation of endoscopy and surgery for early colon cancer is lacking.

According to guidelines of the Italian Society of Colorectal Surgery 2015, early colon cancer (ECC) is defined as a cancer whose invasion is limited to the submucosa, regardless of lymph node status, and is defined as T1NxM0 according to the Royal College of Pathology. The management of ECC is still controversial, ranging from endoscopy to radical resection. Curative endoscopic resection (ER) is applicable to tumor lesions limited to the mucosa or submucosa and that are less than 1 mm (M/SM1), with no lymphatic or vascular invasion (LVI−), well differentiated or moderately differentiated, no ulcer, and no budding.[70]

Clinical question 4.3: Selection of the surgical approach for early colon cancer.

Recommendation 4.3: Laparoscopic approaches are recommended for early colon cancer surgery (strong recommendation, moderate certainty of evidence).

The current high quality of evidence supports the routine use of laparoscopic approaches in patients with ECC. Laparoscopic colectomy is associated with early recovery of gastrointestinal function and shorter length of hospital stay, with no increased morbidity or mortality. Pathological and long-term tumor outcomes are similar to those of open surgery.

The results of the classical COLOR study showed that compared with traditional open surgery, laparoscopic surgery showed no significant difference in long-term efficacy, such as 5-year survival rate, and had advantages of less postoperative pain, shorter recovery time of exhaust and defecation, and shorter hospital stay.[71] The disease-free survival rate was 45.2% in the laparoscopic group and 43.2% in the open group (standardized mean difference [SMD] 2.0%; 95% CI −10.3 to 14.3%, $P = 0.96$). The overall survival rates were 48.4% and 46.7%, respectively (SMD 1.7%, 95% CI −10.6 to 14.0%, $P = 0.83$). During 10-year follow-up, the rates of disease-free survival and overall survival with laparoscopic surgery for non-metastatic colon cancer were similar to those with open surgery.[72] A meta-analysis conducted in 2019, including 13 studies, showed that compared with open surgery, laparoscopic surgery is associated with a shorter total hospital stay (SMD −0.57, 95% CI −1.00 to −0.15, $P = 0.008$), less intraoperative blood loss (SMD −0.68, 95% CI −1.12 to −0.24, $P = 0.002$), shorter incision length (SMD −4.61, 95% CI −5.79 to −3.43, $P < 0.001$), and decreased risk of incision infection (OR 0.30, 95% CI 0.13–0.67, $P = 0.004$).[73]

Clinical question 4.4: Effect of different radical ranges of surgical operation on the overall survival rate of patients with early colon cancer.

Recommendation 4.4: Early colon cancer surgery requires a safety margin of at least 5 cm. If no lymph node metastasis is assessed preoperatively, D1 or D2 lymph node dissection is an option. D3 lymph node dissection following the principle of complete mesocolic excision (CME) is recommended if lymph node metastasis is assessed preoperatively (strong recommendation, low certainty of evidence).

The safety margin should be ensured in the resection range for ECC. A 5-cm proximal and distal margin is safe for routine D1 and D2 surgery. For D3 or CME

surgery, a proximal and distal margin of 10 cm is usually obtained. The extent of lymph node dissection depends on whether the lymph nodes have metastasized and the depth of tumor invasion. D1 lymph node dissection refers to parenteral lymph node dissection. D2 lymph node dissection refers to intermediate lymph node dissection. D3 lymph node dissection refers to central lymph node dissection. The number of lymph nodes in the specimens that must be removed is ≥12; otherwise, regional lymph node infiltration cannot be determined in histopathological examination for correct tumor staging. For hepatic flexure tumor, we recommend dissecting the sub-pyloric lymph nodes (group 6) and the lymph nodes distributed in the retinal vascular arch on the side of the gastric curvature (group 4d). For splenic curvature, we recommend dissecting the subcaudal pancreas lymph nodes. The CME principle of mesenteric resection is applicable to early colon cancer with lymph node metastasis ($T_1N_{1\text{-}2}M_0$).

In 2019, the Japanese Society for Colorectal Cancer Research pointed out that the degree of lymphadenectomy is determined based on preoperative clinical findings, the extent of lymph node metastasis, and the depth of tumor invasion observed during CRC surgery. D3 resection is performed if lymph node metastasis is found or suspected. If no lymph node metastasis is observed in preoperative or interoperative diagnosis, lymph node dissection is performed according to the depth of tumor invasion. D1 resection is recommended for Tis (M), in which no lymph node metastases is usually detected because the depth of tumor invasion diagnosed before surgery may not be sufficiently accurate. D2 resection is necessary for CRC in the T_1 (SM) stage for which the incidence of lymph node metastases is approximately 10%.[63]

Clinical question 4.5: Indication for transanal local excision of early rectal cancer.

Recommendation 4.5: The suggested indications for transanal local excision of early rectal cancer are as follows: (1) Tumor diameter <3 cm; (2) Tumor invades rectal circumference <30%; (3) Negative margin >3 mm; (4) Within 8 cm from the anal verge when undergoing traditional local excision, within 15 cm when undergoing transanal endoscopic microsurgery (TEM); (5) No lymph node metastasis on imaging examination; (6) No lymphovascular infiltration (LVI) or perineural invasion (PNI); and (7) Well- or moderately differentiated (weak recommendation, low certainty of evidence).

Transanal local excision (TAE) has been proven to be a safe and effective technique for the treatment of early rectal cancer. Compared with traditional radical resection surgery, transanal local resection has a shorter operation time, lower postoperative complication rate, faster postoperative recovery, and better preservation of anal function. However, transanal local resection may increase the probability of local recurrence, especially for high-risk early rectal cancer, in which the oncologic outcome of transanal local resection is not ideal, the recurrence rate after surgery is higher, and the 5-year overall survival rate is lower. For low-risk rectal cancer, the oncologic outcomes of these two procedures are similar.

A recent meta-analysis included 12 studies involving 3526 patients with T1 and T2 rectal cancer. The results show that compared with traditional radical surgery, transanal local resection has a shorter operation time, less intraoperative bleeding, lower postoperative complication rate, and better postoperative bowel function. However, the postoperative local recurrence rate among patients in the TEM group was higher, with 12.1% for TEM and 4.1% for radical surgery (RR 2.63, 95% CI 1.60–4.31), and the 5-year survival rate was worse (HR 1.51, 95% CI 1.16–1.96). However, after subgroup analysis, no significant difference was found between the two approaches in patients with negative margins, grade I-II tumor, and no lymph node metastasis.[74]

Clinical question 4.6: Selection of the surgical approach for transanal local excision.

Recommendation 4.6: Transanal excision (TAE), transanal minimally invasive surgery (TAMIS), and TEM are recommended for transanal local excision (strong recommendation, low certainty of evidence).

TAE, TEM, and TAMIS are the main methods used for transanal local resection. Compared with traditional TAE surgery, the TEM system consists of a dedicated platform, rectoscope, and endoscopic instruments for a more precise operation. However, there is limited adoption of TEM because of the cost of this system. The single-incision laparoscopy surgery (SILS) ports and endoscopic instruments used in TAMIS can be an affordable alternative technology to TEM.[75] Because TEM and TAMIS are more minimally invasive and precise methods, postoperative complications, the negative margin rate, and local recurrence are better than those of traditional TAE surgery. However, the longer duration of surgery also means that TAMIS and TEM procedures are technically more demanding and have a longer learning curve.

A meta-analysis, including 16 articles and 2146 patients, showed that TAMIS had the best performance regarding incidence of postoperative complications, followed by TEM and TAE.[76] TAMIS also performed better with respect to perioperative blood loss and hospital stay. TEM is the best option for intact specimen excision, negative margins, and the rate of R0 excision (total excision with negative margin), followed by TAMIS, with no significant difference, and it is superior to TAE. TEM and TAMIS had comparable local recurrence rates (OR 0.90; 95% CI 0.32–2.36), which were lower than that of TAE (OR 0.26, 95% CI 0.15–0.43 and OR 0.23; 95% CI 0.07–0.68, respectively). A meta-analysis, including six retrospective studies with 927 patients, showed that compared with TAE, TEM yielded greater negative margins (OR 5.281, 95% CI 3.201–8.712, P <0.001), as well as less specimen fragmentation (OR 0.096, 95% CI 0.044–0.209, P <0.001) and local recurrence (OR 0.248, 95% CI 0.154–0.401, P <0.001).[77]

Clinical question 4.7: When is radical surgery needed after endoscopic resection or transanal resection of early rectal cancer?

Recommendation 4.7: We suggest radical resection for patients with local resection of rectal cancer who are at high risk for recurrence (weak recommendation, low certainty of evidence).

At present, EMR or ESD via colonoscopy and local resection with the TEM or TAMIS platform are considered good choices for the treatment of early rectal cancer. No significant difference in tumor prognosis has been found between local transanal resection and radical resection of rectal cancer in low-risk early rectal cancer.[78] The former has advantages such as a low complication rate, less trauma, shorter hospital stay, and organ preservation.[79] However, there is still a 20% rate of lymph node metastasis in early rectal cancer.[80] The local recurrence rate in patients with pathological high-risk features after local resection can be up to 25%.[81] Therefore, patients with local excision of rectal cancer with high-risk factors require radical resection of rectal cancer. The timing of the operation remains controversial, however. We recommend that radical resection be carried out once the local resection site has healed; we therefore advocate visualizing this area endoscopically before surgery. Radical resection should be performed before recurrence.

There is little direct evidence to explain the timing of supplementary radical surgery after local resection for early rectal cancer. A recent systematic review[82] included 17 studies with 303 patients having "completion surgery", which means a procedure with curative intent undertaken based on histopathology showing a more advanced cancer than anticipated. The study also included 228 patients having "salvage surgery", meaning a surgical procedure with curative intent following the development of local recurrence. The median 5-year overall survival rate was 83% (67–100%) in the completion surgery group and 52% (31–69%) in the salvage surgery group. The median 5-year disease-specific survival rate was 88% (74–100%) in the completion surgery group and 70% (58–85%) in the salvage surgery group. The median 5-year disease-free survival rate was 94% (85–96%) in the completion surgery group and 46% (35–58%) in the salvage surgery group. Local recurrence after completion surgery was 2.7% (0–6.5%) and repeated local recurrence was 16% (6.2–37%) in the salvage surgery group. The rate of anastomotic leakage was 5.5% (0–15%) in the completion surgery group and 6.7% (2.3–11%) in the salvage surgery group.

Clinical question 4.8: Surgical strategy for patients with early-stage CRC.

Recommendation 4.8: Radical surgery is recommended for patients with early-stage CRC who have unfavorable histologic features (strong recommendation, moderate certainty of evidence).

Screening programs for CRC have resulted in a significant shift toward earlier stages at diagnosis.[83] Therefore, the treatment strategy for early-stage CRC after endoscopic resection requires further consideration by clinicians to balance patients' QoL and recurrence risk. According to clinical studies[84–86] and guidelines[46,63,87–89] recommended in China and other countries, for patients with early-stage CRC who have unfavorable histologic features on pathological examination after local excision, the current standard treatment is radical resection. Unfavorable histologic features include: (1) poor histological differentiation, (2) angiolymphatic invasion, (3) positive margins, (3) depth of tumor invasion more than one-third of the outer submucosal muscularis (SM_3 grade), and (4) submucosal invasion >1 mm and tumor budding. For rectal cancer with difficulties in preserving the anal sphincter, patients after radical surgery can have concomitant organ dysfunction, leading to impaired QoL.[90,91] Local resection of the tumor alone is currently believed to be oncologically unsafe for high-risk pT1 patients with a high risk of recurrence.[92] The available evidence suggests that adjuvant (chemo)radiotherapy following local resection in high-risk pT1 patients is a promising treatment to preserve organs while achieving oncologic safety.[93]

The guideline development group performed a meta-analysis, including 73 studies, and demonstrated that for patients with high-risk pT1 tumors, the rates of local recurrence and weighted distant metastasis in the group without additional treatment after local resection was 13.6% (95% CI 8.0–22.0%) and 3.4% (95% CI 2.5–4.6%), respectively. In the total mesorectal excision group, these rates were 4.1% (95% CI 1.7–9.4%) and 4.9% (95% CI 2.4–9.4%), and in the adjuvant chemoradiotherapy group, these were 3.9% (95% CI 2.0–7.5%) and 5.0% (95% CI 3.0–8.3%), respectively. The meta-analysis is limited by the heterogeneity of the included studies, selection bias in the allocation of treatment, and insufficient reporting of survival data to permit consolidation. For these reasons, we could only describe the scope and could only draw conclusions based upon the existing data.

Clinical question 4.9: Optimal surgical strategy for familial adenomatous polyposis combined with early CRC.

Recommendation 4.9: Total proctocolectomy (TPC) and ileal pouch-anal anastomosis (IPAA) are suggested for familial adenomatous polyposis (FAP) combined with early CRC (weak recommendation, very low certainty of evidence).

FAP is a type of autosomal dominant disease characterized by multiple adenomatous polyposis throughout the colon owing to mutation of the *APC* gene, and the overall risk of CRC is 100% if left untreated.[94] TPC/IPAA and total colectomy/ileorectal anastomosis (TC/IRA) are two major surgical options for patients who have FAP combined with early CRC. The oncologic efficacy, QoL, anal function, as well as patients' intention should be taken into consideration when making surgical decisions.[95] TPC/IPAA are suggested for patients who have FAP combined with early CRC, according to the current guidelines.[95–97]

Relevant studies with high-quality evidence that describe the optimal surgical strategy and oncologic efficacy in patients with FAP are currently limited. In a retrospective study, including a total of 256 patients with FAP, 171

underwent TPC/IPAA and 85 received TC/IRA. The results revealed that ileus was the most common post-operative complication, but no significant difference was observed between the TPC/IPAA and TC/IRA groups in terms of surgical complications.[98] With respect to oncologic efficacy, first, rectal cancer occurring in the remaining rectal stump might compromise survival outcomes.[99,100] A multicenter retrospective analysis, including 659 patients with FAP who underwent IRA, revealed that the total incidence of rectal cancer was 7.1%, and life expectancy was 1.8 years shorter in patients who received IRA than in those who underwent IPAA.[99] Moreover, ileal-pouch adenoma and punch failure should also be considered after IPAA. The cumulative incidence of pouch adenoma was 7%, 35%, and 75% in 5-, 10- and 15-year follow-up of patients with FAP who underwent IPAA.[101] Another study concluded that the total 10-year incidence of pouch adenoma was 64.9%, and 2.8% of adenomas were confirmed as malignancy.[102] Generally, anal function and QoL were better in patients with FAP after IRA than after IPAA.[103] A systemic review and meta-analysis identified a total of 12 retrospective studies and concluded that anal function was better in patients who underwent IRA than in those who received IPAA (OR 2.11, 95% CI 1.02–7.23, P <0.05).[104]

Clinical question 4.10: Optimal surgical strategy for Lynch syndrome combined with early CRC.

Recommendation 4.10: Total colectomy (TC) or subtotal colectomy (STC) is suggested for Lynch syndrome (LS) combined with early CRC (weak recommendation, very low certainty of evidence).

LS is a common hereditary nonpolyposis syndrome caused by mutation of mismatch repair gene, and the lifetime risk of CRC is 60% to 80%.[105] TC/STC and segmental colectomy are the two main surgical options for LS with early CRC. TC/STC is recommended for the management of LS combined with early CRC in the current guidelines.[94–97,105]

Regarding oncologic efficacy, the 10-year cumulative incidence of metachronous CRC (mCRC) is as high as 10% to 45% after STC, and TC can significantly reduce the rate of mCRC.[106–108] A meta-analysis, including a total of six retrospective controlled studies, concluded that the overall incidence of mCRC was higher in SC than that in the TC group (23.5% *vs.* 6.8%, OR 3.68, 95% CI 1.89–7.13, P <0.005), although no significant differences were observed in terms of long-term survival outcomes.[109] With respect to function, TC might have a negative impact on anal function and QoL of patients with LS.[110] Haanstra *et al*[111] studied the impact of STC and TC on anal function and QoL in patients with LS. Their results revealed that the anal function in TC was worse than that in STC, although no significant difference was observed in terms of QoL.

Clinical question 4.11: Optimal treatment strategy for Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS).

Recommendation 4.11.1: Endoscopic polypectomy is suggested for patients who have PJS combined with early CRC (weak recommendation, very low certainty of evidence).

Recommendation 4.11.2: Endoscopic polypectomy is suggested for patients who have JPS combined with early CRC (weak recommendation, very low certainty of evidence).

PJS is a type of autosomal dominant disease characterized by multiple hamartomatous polyps throughout the tract and mucocutaneous pigmentation owing to *STK11* gene mutation.[112,113] In the current study, publications on PJS were limited to case reports and the surgical strategies and efficacy remain uncertain. JPS is a type of rare autosomal dominant disease characterized by multiple hamartomatous polyps throughout the tract (mainly colorectal) owing to *SMAD4/BMPR1A* or *PTEN* gene mutation.[114,115]

A pathologic review of 2500 resected PJS polyps showed that the detection rate of dysplasia was as low as 0.24% (6/2500); thus, the risk of malignancy in PJS is relatively low. However, studies that are focused on the best surgical options and oncologic efficacy of PJS combined with early CRC are limited. We recommend endoscopic polypectomy to remove primary tumor and as many polyps as possible.[116,117] The optimal surgical strategy for JPS combined with early CRC remains uncertain and high-quality evidence is lacking; most studies are case reports.[115] JPS is actually a typical hamartomatous polyp with a relative lower risk of hyperplasia or malignancy. One study retrospectively analyzed the pathologic characteristics of 767 JPS polyps; the results revealed that 8.5% of polyps were mild to moderate dysplasia whereas only 0.3% were malignancy.[118] Therefore, patients who have JPS combined with early CRC can be managed with endoscopic polypectomy under strict surveillance; prophylactic colectomy is not recommended.

Part 5. Surveillance

Clinical question 5.1: Post-operative follow-up for early CRC after endoscopic treatment.

Recommendation 5.1: We recommend that the frequency of follow-up visits and surveillance, including colonoscopy, serum CEA and CA19-9 level measurement, and computed tomography scan, should be decided based upon the characteristics of adenomas/polyps in surveillance after endoscopic treatment (strong recommendation, moderate certainty of evidence).

Considering the tendency of recurrence in colorectal adenoma and CRC (including metachronous adenoma and interval cancer), an appropriate strategy for post-endoscopic follow-up should be established. By summarizing the current guidelines, the optimal post-endoscopic follow-up strategy should be developed considering the combination of number, size, and histopathological type of adenomas or polyps.[8,119]

The survival rate of patients with early CRC and precancerous lesions who undergo intensive follow-up after treatment has been reported to be significantly higher than that of patients who receive average or no follow-up.[120] However, further evidence is needed regarding whether a Western follow-up strategy is suitable for the current situation in China in terms of the preventive effect against interval cancer after endoscopy.[121]

Clinical question 5.2: Post-operative follow-up for early CRC after local excision.

Recommendation 5.2.1: Proctoscopy (with endoscopic ultrasound or pelvic MRI with contrast) every 3–6 months for the first 2 years is suggested for early rectal cancer in patients who receive transanal local excision only, then every 6 months for a total of 5 years (weak recommendation, low certainty of evidence).

Recommendation 5.2.2: For early CRC, serum CEA and CA19-9 surveillance is suggested every 3–6 months for the first 2 years, and then every 6 months for a total of 5 years (weak recommendation, low certainty of evidence).

Recommendation 5.2.3: Colonoscopy is suggested in the first and third year post-operatively, and then every 5 years (weak recommendation, low certainty of evidence).

Post-operative surveillance for CRC patients has been illustrated in the current guidelines. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines also have specific recommendations for early CRC after local excision.[87,122] In comparison with the surveillance for advanced CRC, proctoscopy (with EUS or pelvic MRI) is added in patients with early CRC.

Proctoscopy combined with EUS or pelvic MRI is only recommended for patients with early CRC who received local excision.[123] Regular surveillance of CEA levels is helpful to monitor disease progression. A systemic review and meta-analysis revealed that the specificity and sensitivity were 97% (95% CI: 90–99%) and 68% (95% CI: 53–79%) when choosing a CEA level of 10 ng/ml as the cutoff to predict disease recurrence.[124] For patients with early CRC who received local excision only, colonoscopy is strongly recommended in the first and third year post-operatively (in patients without pre-operative colonoscopy owing to acute obstruction, surveillance should begin at 3–6 months after surgery). Earlier colonoscopy is recommended if advanced adenoma (villous polyp, greater than 1 cm in diameter, and severe dysplasia) is observed.[125,126]

Clinical question 5.3: Post-operative follow-up for early CRC after curative treatment.

Recommendation 5.3.1: We suggest scheduled colonoscopy rather than an intensive surveillance strategy for patients with stage I CRC who have a low recurrence risk (weak recommendation, low certainty of evidence).

Recommendation 5.3.2: We suggest an intensive surveillance strategy for patients with stage I CRC who have a high recurrence risk (weak recommendation, low certainty of evidence).

The recommendations of this consensus should be individually modified according to the type of treatment received and the risk of recurrence. Regular colonoscopy is suggested for the surveillance of most patients with a low risk of stage I CRC. The frequency of examination can be determined according to the patient's willingness, complications, and family history instead of a routine postoperative monitoring program for patients with stage II. Patients with a high risk of stage I CRC include: (1) those with high-risk pathological features: signet ring cell adenocarcinoma (SRCC), lymph node negative but LVI, peripheral nerve infiltration or tumor budding, poorly differentiated tumors or elevated CEA; and (2) patients who received no standardized treatment. Considering that recurrence tends to occur in this type of CRC, an intensive follow-up strategy after surgery may improve clinical outcomes. We recommend establishing an enhanced follow-up strategy for patients with a high risk of stage I CRC after radical resection, which usually follows the postoperative monitoring scheme for stage II patients.

At present, there is little high-quality evidence on the follow-up of patients with a high risk of stage I CRC after radical surgery. According to the guideline released by the Medical Administration of the National Health Committee of China and the Oncology Branch of the Chinese Medical Association in 2020, the enhanced follow-up strategy for patients with a high risk of stage I CRC after radical resection usually follows the postoperative monitoring scheme for stage II patients.[127] The postoperative monitoring strategy of stage II patients includes: (1) physical examination, once every 3 months for 2 years, once every 6 months for 5 years, and then once every year after 5 years; (2) laboratory examination, CEA and CA19-9 monitoring; every 3 months for 2 years, every 6 months for 5 years, and once a year after 5 years; (3) thoracoabdominal and pelvic CT or MRI should be performed every 6 months within the first 2 years and then once a year for 5 years; PET-CT is feasible for patients with recurrence or suspected distant metastasis; (4) colonoscopy should be performed within 1 year after surgery, and colonoscopy shall be reviewed within 1 year if there is any abnormality; colonoscopy is reviewed within 3 years if there is no abnormality, followed by colonoscopy once for 5 years. If no total colon examination was performed before surgery, colonoscopy should be performed again 3–6 months after surgery.

Discussion

A considerable proportion of CRCs can be diagnosed at an early stage, and therefore the detection of early lesions is an important aspect to improving prognosis. There is few definite concepts of early lesions in CRC. According to opinions in the Colorectal Cancer Seminar (Japan, 1975), in China at present, neoplasms confined to the mucosa and submucosa of the colon and rectum are generally defined as early-stage CRC. Among these, neoplasms confined to the mucosa are defined as intramucosal cancer and those infiltrating the submucosa without

invading the musculus propria are defined as submucosal cancer. However, the 2000 edition of the World Health Organization Classification of Neoplasms considers epithelial neoplasms that occur in the colon and rectum malignant only if they penetrate the muscularis mucosa with submucosal infiltration. Precancerous CRC lesions are also defined, referring to pathological changes closely related to colorectal carcinogenesis, including colorectal adenoma and inflammatory bowel disease-related dysplasia. Traditional serrated adenoma (TSA) and sessile serrated adenoma/polyps (SSA/P) are also considered precancerous lesions.

Colorectal adenoma can be divided into tubular adenoma, tubulovillous adenoma, and villous adenoma. Most CRCs develop via the adenoma–adenocarcinoma pathway. Currently, the general consensus is that the definition of advanced adenoma is an adenoma meeting one or more of the following criteria: 1) diameter >10 mm; 2) containing villous components; and 3) severe dysplasia or high-grade intraepithelial neoplasia. Serrated lesions are defined as a group of lesions characterized by more than one serrated epithelial structure, including hyperplastic polyps, SSA/P, and TSA. Hyperplastic polyps are generally believed to have no malignant potential whereas SSA/P and TSA can develop into cancer via the serrated pathway.[128] The serrated pathway has become the focus of recent clinical research. Serrated adenoma, together with traditional adenomas, including tubular adenoma, villous adenoma, and mixed adenoma, constitute generalized colorectal adenomas and account for 85–90% of all precancerous lesions in CRC. Considering the existence of specific precancerous lesions, carcinogenesis pathways, and early stages in CRC, it is feasible to reduce the incidence and mortality of CRC through prevention and screening.

The prevention of CRC can be summarized in three stages. Primary prevention of CRC refers to etiological prevention, including the control of risk factors and the treatment of colorectal adenoma or inflammation to block the carcinogenesis pathway. Secondary prevention refers to early diagnosis and early treatment, that is, timely detection and intervention to prevent early CRC from reaching an advanced stage. Tertiary prevention is aimed at preventing recurrence or metastasis of advanced CRC through surgical treatment and postoperative adjuvant chemotherapy, radiotherapy, targeted therapy, or immunotherapy. Studies have reported that 70% of sporadic CRC is related to lifestyle,[129] and 66–78% of CRCs can be prevented by maintaining a healthy lifestyle.[130] Approximately 75% of CRCs[131] could be prevented by endoscopic treatment (or removal) of adenoma, but the recurrence rate of adenoma (including *in situ* recurrence and metachronous recurrence) after endoscopic treatment is high,[132–134] with the potential need for drugs to prevent recurrence.

Screening contributes to early detection and removal of colon polyps, which is of great importance to reduce the incidence of CRC. The morbidity of CRC in Western developed countries has been declining in recent years, which is attributed to early detection and treatment of early CRC and precancerous lesions through screening.[135,136] The updated guidelines suggest that screening for precancerous lesions, such as polyps, can help prevent the development of CRC.[8] In the 2013 CRC screening guidelines issued by the NCCN in the United States, all adults are assessed for risk and divided into three risk groups: the average-risk group, high-risk group, and hereditary high-risk group.[137] CRC screening is considered at age 40 years for those with a family history of CRC and at age 50 years for those with average risk. Screening is terminated at age 75 years because there was no significant survival benefit from screening in older age groups.[138,139] There are special mechanisms for the development of CRC in the hereditary high-risk group, including LS, FAP, PJS, JPS, and serrated polyposis syndrome. The screening strategy in that guideline is developed for the non-hereditary high-risk population.

Despite these positive results, the Western experience might be not suitable for China from the perspective of cost-effectiveness, considering the huge population base in China. If relevant examinations (such as total colonoscopy) were carried out in the entire population of the target age, the cost and workload of screening would surpass the current medical resources. Therefore, formulating a CRC screening strategy suitable for China's national conditions and identifying high-risk groups at an early stage to reduce the incidence and mortality of CRC are of great importance. A suitable strategy for the Chinese population is a sequential screening strategy based on questionnaires addressing high-risk factors, fecal examination, and colonoscopy. In this strategy, colonoscopy is still the gold standard of CRC screening. Questionnaires to assess high-risk factors and fecal examination, including FIT, are very simple, acceptable, and can be widely promoted in a large population.[42]

At present, there is no single indicator to stratify the risk of CRC. It is current consensus that the population with a high risk of sporadic CRC should be determined according risk factors, including age, sex, BMI, family history of CRC, history of smoking and alcohol consumption, and diabetes mellitus. CRC risk assessment is recommended for people aged 50 years or older, and CRC screening is recommended for people at high risk of CRC aged 40 years or older. People without the following risk factors are defined as the population with average CRC risk: 1) first-degree relative with a history of CRC, including family history of non-hereditary CRC and hereditary CRC; 2) history of CRC; 3) history of colorectal adenoma; d) long-term (8–10 years) history of irritable bowel disease; and e) positive result of fecal occult blood test (FOBT).[140]

Researchers have developed multiple models to assess the individual risk of CRC, which are mainly based on the risk factors mentioned above; however, the efficacy of these models is quite limited.[141,142] Additionally, the participation rate in screening among the general population could be improved based on individualized risk stratification.[41] Most current consensuses recommend the APCS score, a quantitative questionnaire for CRC risk assessment, to improve the efficacy of screening, identify high-risk groups, and guide further screening. Results of RCTs in the Asia-Pacific population suggest that the APCS

score could effectively identify a subset of asymptomatic Chinese individuals at high risk for advanced colorectal neoplasia.[143] Individualized screening programs based on the APCS score combined with FIT screening could ensure a higher rate of screening participation, with a better detection rate than traditional single FIT screening.[41] However, from the perspective of transformational application in the general population, evidence from large-sample prospective studies with CRC risk assessment models is still lacking.

In current research and clinical practice, colonoscopy is the gold standard for CRC screening. High-quality colonoscopy is the key to ensuring the efficacy of screening. At present, the generally accepted criteria of high-quality colonoscopy include: 1) rate of adequate bowel preparation >85%,[144–147] 2) CIR >95%,[24] 3) withdrawal time >6 minutes,[148] and 4) ADR >20% (>25% for men and >15% for women) to reduce the risk of interval cancer.[21] However, considering that the ADR in screening colonoscopy among groups with average risk and age >40 years in China is not well documented, further research evidence is required to help determine the recommended threshold.

As mentioned above, although colonoscopy screening is the gold standard for CRC screening, the participation rate in organized colonoscopy screening is still poor in the general population because it is an invasive method requiring adequate bowel preparation.[37,149] Thus, how to further improve the participation rate in colonoscopy among the general population remains a crucial problem to be solved.

In addition to colonoscopy, noninvasive examinations, including FIT and the multi-target DNA test, are important tools in CRC screening. Patients who are FIT positive tend to be at high risk for CRC and further evaluation with colonoscopy is recommended. Although evidence from randomized controlled studies has shown that screening with traditional guaiac-based FOBT (gFOBT) can help to reduce CRC mortality, the low sensitivity for CRC and precancerous lesions and the influence of diet and drugs on the results limit its widespread use. At present, FIT is suggested to replace gFOBT in screening.[150,151] The participation rate in single-round FIT screening is relatively high in several organized population screening programs in China owing to its low cost and non-invasive technique.[152,153] However, evidence is still lacking regarding the low participation rate in long-term repeated screening. The multi-target stool FIT-DNA test is used to detect DNA mutations in fecal shed cells with laboratory technology combined with FIT to obtain a comprehensive risk score for each individual. Those whose comprehensive score exceeds a preset threshold are defined as having a high CRC risk and are recommended to undergo colonoscopy. Studies have revealed that the capabilities of syndecan-2 (SDC2) and tissue factor pathway inhibitor-2 (TFPI2) alone in detecting left-sided and right-sided CRC showed significant preference.[153] A dual-target stool DNA test (combining SDC2 and TFPI2 methylation) shows high specificity and sensitivity in CRC and advanced adenoma screening.[154] Currently, multi-target FIT-DNA test products have been approved by the National Medical Products Administration in China. However, the application range and long-term screening efficacy of such products in CRC screening need to be confirmed in further large-sample population studies in China. Additionally, considering that the multi-target FIT-DNA test has a high cost and requires central laboratory testing, its application in large-scale CRC screening is not yet feasible. At present, this test is only recommended for eligible individuals who prefer non-invasive screening methods.

With the broad implementation of CRC screening programs worldwide, early-stage cancers are increasingly diagnosed.[155] The surgical treatment of choice for early CRC is surgery with regional lymph node dissection.[156] At present, based on the American Joint Cancer Commission tumor-node-metastasis (TNM) staging system, which is widely used as a guideline for staging and prediction of prognosis, patients with early CRC are grouped as stage I (node-negative tumors within the submucosa) CRC.[157,158]

The main clinical treatment methods for ECC and precancerous lesions are endoscopic treatment and radical surgical resection. Compared with surgery, endoscopic treatment for ECC has a lower complication rate, less trauma, and shorter hospital stay. This approach has obvious benefits for patients' QoL after treatment, although the prognosis is not significantly different from that of surgical treatment.[159,160] Owing to the rate of lymph node metastasis in T1-stage CRC (10–12%), accurately assessing the risk of lymph node metastasis in preoperative examination is difficult. However, regional lymph nodes cannot be removed with endoscopic treatment.[63,161] Therefore, how to accurately assess incomplete resection and the risk of lymph node metastasis to devise an appropriate individualized treatment plan for the patient is the primary issue that clinicians should consider. According to the latest guidelines in China and Japan, high-risk factors for lymph node metastasis among patients with ECC include deep submucosal invasion, LVI, high-grade histological features, and tumor budding.[8,63] For patients with high-risk factors, the risks and benefits of endoscopic treatment and surgical treatment should be weighed, and surgical treatment should be actively considered. For patients with ECC who are pathologically evaluated as high risk after endoscopic treatment, additional surgical treatment should be actively performed. A retrospective study from the United States showed that the 5-year local recurrence rates in patients with low-risk and high-risk ECC after endoscopic resection were 0 and 1.4%, respectively. The American Society of Colon and Rectal Surgeons Colorectal Cancer Treatment Guidelines point out that additional surgery is required in the following cases: (1) positive lateral or basal resection margin; (2) positive submucosal invasion; (3) positive vascular invasion; (4) poorly differentiated adenocarcinoma or undifferentiated carcinoma; and (5) tumor budding grade G2 or above.[162]

The goals of surgical treatment are to resect visible malignant lesions, remove the affected segment of intestine, and remove the corresponding draining lymph nodes with vascular ligation and mesocolon integrity.[163] A planned resection should be based upon the location of the tumor

in the colon and its lymphovascular drainage, with a margin of colon 5–7 cm proximal and distal to the tumor to ensure removal *en bloc*, with the associated mesentery extending to the origin of the named primary blood vessel feeding the segment of bowel.[164] In recent years, primary colon cancers are mainly treated surgically with CME, with arteries and veins ligated as close as possible to the main vascular trunk. This approach is proven to have a lower local recurrence rate and improved survival.[165] As for the range of lymph node dissection (D3 *vs*. D1/2), a systematic review and meta-analysis in 2020 showed that among patients with colon cancer, CME/D3 had an advantage over D1/D2 in the overall 3-year survival rate, 5-year survival rate, and 5-year disease-free survival rate, whereas the overall rate of postoperative complications in CME/D3 and D1/D2 was not statistically significantly different.[166] Controversial questions about whether to narrow the scope of enteral resection and lymph node dissection remain to be confirmed in further research. There is a lack of direct evidence on the scope of radical surgery for ECC. According to the Chinese guideline in 2020, for patients with ECC ($cT_1N_0M_0$) with high-risk characteristics, bowel segment resection plus regional lymph node dissection should be performed; however, the extent of bowel segment resection and lymph node dissection has not been clarified. The 2019 edition of the Guidelines for the Treatment of Colorectal Cancer of the Japanese Society for Colorectal Cancer recommend selecting the extent of lymph node dissection according to the status of intraoperative or preoperative lymph node metastasis.

Rectal cancers can be grouped into four categories: very early (cT_1), early ($cT_{1\text{-}2}$, some cT_3), intermediate (most cT_3, some cT_4), and locally advanced (some cT_3, most cT_4). However, this is a special grouping in cancer staging in that there are several important factors other than T stage, such as distance from the anal verge, circumferential margin (crm), nodal (cN) stage, and vascular and nerve invasion. The choice of surgical approach depends on the location and extent of disease, with the aim to treat primary rectal cancer lesions.[167] The current standard of surgery for mid to low rectal cancer is total mesorectal excision (TME) with radical resection of the rectum. TME in rectal cancer has led to dramatic improvements in the local recurrence rate and anal sphincter preservation.[168] More invasive procedures include transabdominal resection (low anterior resection), proctectomy with TME and coloanal anastomosis, and abdominoperineal resection (APR).[169] In cases of very early rectal cancer, local resection can be considered, using the traditional transanal endoscopic excision or microsurgery (TEM) technique. In early groups, favorable cases ($cT_{1\text{-}2}$, some early cT_3, N_0 [$cT_{3a(\text{-}b)}$ and circumferential resection margin(–) according to MRI]) above the levators, surgery alone—meaning a sharp radical dissection using the TME technique—is appropriate because the risk of local failure is very low. However, because there is a 10–15% risk of lymph node metastasis in T_1 rectal cancer, TAE should be considered only for selected patients who do not have a risk of lymph node metastasis, regardless of anorectal function.[170]

In addition to surgical techniques, the perioperative management of patients with early CRC is important. The recommended protocols for candidate patients are enhanced recovery after surgery and rehabilitation, which have been designed to facilitate the return to functional activity and accelerate convalescence.[171] During the pandemic of coronavirus disease 2019 (COVID-19), perioperative therapy aiming to enhance the immune system requires greater attention.[172] Thymalfasin (thymosin-alpha 1) is an immunomodulating agent that can promote the proliferation, differentiation, and maturation of T cells. Its therapeutic potential has been identified in several infectious diseases, as well as its antitumor effects in CRC.[173] The efficacy and safety of thymosin-alpha 1 in CRC perioperative management are worth verifying.

Screening, early diagnosis, and early treatment clearly contribute to improved prognosis of CRC. However, considering the tendency toward recurrence in colorectal adenoma and CRC (metachronous adenoma and interval cancer), a proper strategy for post-endoscopic follow-up should be established. The survival rate of patients with early CRC and precancerous lesions who receive intensive follow-up after treatment is significantly higher than the rate in patients who receive average follow-up or no follow-up.[120] By summarizing the current guidelines, an optimal post-endoscopic follow-up strategy can be developed considering the combination of number, size, and histopathological type of adenomas or polyps.[8,119] However, whether the Western follow-up strategy is suitable for the current situation in China requires further discussion and evidence regarding the preventive effect against interval cancer after endoscopy.[121]

Patients with early CRC can achieve long-term survival after radical surgery. The 2019 Japanese guideline pointed out that for pTis tumors after radical surgery, only periodic colonoscopy review is needed, without review of other organs. Other organs should be reviewed after radical surgery for stage I–III CRC. The overall follow-up time should be 5 years, and in the first 3 years, follow-up should be more intensive. The rates of liver metastasis and lung metastasis in rectal cancer are higher than those in colon cancer. The NCCN Clinical Practice Guidelines in Oncology, Colon Cancer published in 2021 recommends that colonoscopy should be performed within 1 year after surgery for patients with colon cancer; with postoperative pathological classification of pT_1, colonoscopy should be performed within 1 year for advanced adenoma; and colonoscopy should be performed within 3 years for non-advanced adenoma.[174] Regular postoperative follow-up is of great importance for consolidating the treatment results and improving the long-term prognosis and the QoL of patients. This is also an integral part of the overall surgical treatment plan. For most patients with low-risk CRC, regular colonoscopy is recommended to monitor tumor recurrence after radical surgery. The frequency of examination can be determined according to the patient's wishes, comorbidities, and family history, but patients with high-risk features and those who do not receive standard treatment are classified as high-risk patients.[159] High-quality evidence on the follow-up of patients with high-risk CRC after radical surgery is lacking. In this group of patients, we suggest adoption of

the intensive postoperative surveillance protocol that is generally followed for stage II patients.

Gene mutations and changes in intestinal flora may also have important roles in the pathogenesis of colorectal adenoma and CRC. Relevant studies have not yet reached definitive conclusions; some of the relevant research is covered in this guideline. In terms of the treatment of early CRC, options for endoscopy and surgery are also addressed in this guideline.

In view of the changing epidemiological characteristics of CRC in recent years, this guideline is formulated to provide reference for the prevention, screening, early diagnosis, and early treatment of CRC with the combination of internal medicine and surgery.

Appendix

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Conflicts of interest

None.

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How to cite this article: Li JN, Yao HW, Lu Y, Zhang ST, Zhang ZT; Society of Digestive Endoscopy of the Chinese Medical Association, Colorectal Surgery Group of the Chinese Medical Association, Chinese Association of Gastroenterologist & Hepatologist, National Clinical Research Center for Digestive Diseases, *Chinese Medical Journal* Clinical Practie Guideline Collaborative. Chinese national clinical practice guidelines on prevention, diagnosis and treatment of early colorectal cancer. Chin Med J 2024;137:2017–2039. doi: 10.1097/CM9.0000000000003253