

Guidelines

Consensus on the Prevention, Screening, Early Diagnosis and Treatment of Colorectal Tumors in China: Chinese Society of Gastroenterology, October 14–15, 2011, Shanghai, China

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Key Words

Colorectal tumors · Prevention · Screening · Early diagnosis · Treatment

Abstract

Background: Colorectal cancer (CRC) is steadily increasing in China. Colorectal adenoma (CRA) is the most important precancerous disease of CRC. Screening for colorectal tumors can aid early diagnosis. Advances in endoscopic mucosal resection and endoscopic submucosal dissection can aid the early treatment of colorectal tumors. Furthermore, because of high risk of recurrence after removal of adenomas under endoscopy, factors contributing to recurrence, the follow-up mode and the interval established, and the feasibility of application and the time of various chemical preventions should be concerned. However, a relevant consensus on the screening, early diagnosis and treatment, and prevention of colorectal tumors in China is lacking.

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Summary: The consensus recommendations include epidemiology, pathology, screening, early diagnosis, endoscopic treatment, monitoring and follow-up, and chemoprevention of colorectal tumors in China.

Key Message: This is the first consensus on the prevention, screening, early diagnosis and treatment of CRA and CRC in China based on evidence in the literature and on local data.

Practical Implications: Through reviewing the literature, regional data and passing the consensus by an anonymous vote, gastroenterology experts from all over China launch the consensus recommendations in Shanghai. The incidence and mortality of CRC in China has increased, and the incidence or detection rate of CRA has increased rapidly. Screening for colorectal tumors should be performed at age 50–74 years. Preliminary screening should be undertaken to find persons at high risk, followed by colonoscopy. A screening cycle of 3 years is recommended for persistent interventions. Opportunistic screening is a mode suitable for the current healthcare system and national situation. Colonoscopy combined with pathological examination is the standard method for the diagnosis of colorectal tumors. CRA removal under endoscopy can prevent CRC to some extent, but CRA has an obvious recurrence trend. The follow-up interval after the removal or surgery of colorectal tumors should be different with lesions. Primary prevention of CRA includes improved diet with more fiber, supplements containing calcium and vitamin D, supplements containing folic acid for those with low hemoglobin levels, and cessation of tobacco smoking. Non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors have been recognized to prevent recurrence after adenoma removal.

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Colorectal cancer (CRC) is common in China, just as it is in ‘developed’ western countries. With improvements in the standard of living and changes in eating habits, the incidence of CRC has been increasing in China, especially in cities. Colorectal adenoma (CRA) is the most important precancerous disease of CRC [1–3]. Colorectal tumors usually include CRC and CRA.

Scholars have paid considerable attention to the screening for colorectal tumors, which can aid early diagnosis. In general, it mainly includes fecal occult blood test (FOBT), endoscopy (colonoscopy and sigmoidoscopy), imaging tests and laboratory analyses. With technical developments such as confocal laser endoscopy, narrow-band imaging (NBI), magnifying endoscopy and chromoendoscopy, the identification of flat adenomas can be improved. In addition, advances in endoscopic mucosal resection and endoscopic submucosal dissection can aid the early treatment of colorectal tumors. The removal of adenomas under endoscopy can effectively prevent CRC occurrence, but its recurrence after removal has many disadvantages. Therefore, the factors that may cause recurrence should be analyzed, the follow-up mode and the interval established, and the feasibility of application and the time of various chemical preventions discussed.

The international consensus on colorectal tumors includes guidelines formulated by the American Gastroenterological Association/American Society for Gastrointestinal Endoscopy (AGA/ASGE) [4] and by the Asia-Pacific Association for Gynecologic Endoscopy (APAGE) [5, 6]. However, the relevant consensus on the screening, early diagnosis and treatment, and prevention of colorectal tumors in China is lacking. Therefore, the seminar ‘Consensus on the Prevention, Screening, Early Diagnosis and Treatment of Colorectal Tumors in China’ was held in Shanghai on October 14–15, 2011. This seminar was sponsored by the Tumor Cooperative Group, the Chinese Society of Digestive Diseases and the Chinese Medical Association. The seminar was undertaken by Division of Gastroenterology and Hepatology, Renji Hospital, Shanghai Jiaotong University School of Medicine and Shanghai Institute of Digestive Diseases,

all of which are based in Shanghai, China. The experts had repeated discussions and undertook revisions on the draft. They then passed the consensus by secret ballot. The voting options were: (1) totally agree; (2) agree but have some reservations; (3) agree but have greater reservations; (4) disagree but have reservations; (5) totally disagree. If option 1 passed by $>2/3$ or option 1 + option 2 passed by $>85\%$, the term was considered to have been passed. The full text is described below.

I. Epidemic Situation of Colorectal Tumors in China

1. The incidence and mortality of CRC in China has increased.

With changes in diets, the number of new cases of CRC in China has increased. Data have shown that the incidence of CRC (crude rate) of males in cancer registration areas increased from 25.6/100,000 in 2003 to 32.5/100,000 in 2007, whereas that of females increased from 22.7/100,000 to 26.7/100,000. The mortality of males due to CRC increased from 12.3/100,000 in 2003 to 15.6/100,000 in 2007, whereas that of females increased from 11.1/100,000 to 12.7/100,000 [7].

2. The incidence or detection rate of CRA has increased rapidly.

Several scholars have analyzed the epidemics of CRC and CRA. European researchers analyzed 917 cases with an average risk of CRC aged 50–75 years old with colonoscopy. They found the percentages of cases with CRA, advanced adenoma and CRC to be 21.3, 6.7 and 1.2%, respectively, whereas those among 183 cases aged 40–49 years were found to be 9.8, 1.1 and 0%, respectively [8]. A total of 3,121 American patients with abdominal symptoms aged 50–75 years underwent colonoscopy, and the percentage of cases with villous adenomas >1 cm was 7.9%, that of cases with advanced adenoma accompanied by a high level of intra-epithelial neoplasia (IEN; a detailed definition is given below) was 1.6%, and that of cases with invasive CRC was 1% [3, 9]. After a 5.3-year follow-up of 1,256 cases without polyps under colonoscopy, other scholars found that the percentage of cases with CRA, advanced adenoma and CRC was 16, 1.3 and 0%, respectively [10]. A multicenter retrospective study in China confirmed that for urban residents with abdominal symptoms who received colonoscopy within 20 years (157,943, i.e. 26,026 in 1991–2000 and 131,917 in 2001–2010), the number of cases with advanced adenoma increased by 1.88-fold compared to the previous decade ($p < 0.01$), whereas cases with CRC increased by 66% [11]. That study reported that the incidence of adenoma was increased significantly in subjects aged 50 years [11, 12].

Advanced adenomas or high-risk adenomas are more dangerous. Their presence can be confirmed if any one of the following three conditions are met: (i) diameter of polyp or lesion ≥ 10 mm; (ii) villous structure in villous adenoma or mixed adenomas $>25\%$; (iii) the case is associated with high-level IEN [8, 9].

II. Pathology of Colorectal Tumors

3. CRC is a malignant tumor in the mucosal epithelium, including carcinoma in situ, invasive and metastatic carcinoma.

According to the latest definition from the World Health Organization (WHO), CRC is an epithelial tumor of the colon that can penetrate the muscularis mucosa and infiltrate into the submucosa, which emphasizes the fact that a diagnosis of CRC should have anatomical evidence. Although the morphology is malignant, cases in whom the muscularis mucosa is not penetrated cannot be considered to be ‘cancer’ or the term ‘cancer’ should be avoided [13].

Carcinoma in situ is common in the clinic, but it is suggested that this term should be abandoned and gradually replaced by the WHO definition stated above.

4. CRC is divided into five histological subtypes: adenocarcinoma, adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma and undifferentiated carcinoma. A mucosal biopsy specimen is employed to ascertain whether it is a benign or malignant lesion.

CRA has six subtypes: cribriform adenoma, medullary carcinoma, micropapillary carcinoma, mucinous adenoma, serrated adenoma and signet ring cell carcinoma. Other types are very rare, including the papillary adenoma rich in Paneth cells, choriocarcinoma and clear cell carcinoma [13, 14]. One must pay great heed to signs of invasion and metastasis during histopathological observations, i.e. invasion into blood vessels, lymphatic vessels and nerves, as well as the circumferential resection margin. The tumor bud is associated with invasion and should be described [15–18]. The number of lymph glands detected must be ≥ 12 [18, 19].

5. CRC has three grades that can be identified in combination with morphological and molecular properties.

Undifferentiated carcinoma, which belonged to the fourth level in the previous classification, denotes a tumor with epithelioid morphology but without duct formation, mucus production, or squamous differentiation, neuroendocrine differentiation or sarcomatoid differentiation, some of which have a high frequency of microsatellite instability and belong to a low level [13] (online suppl. appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000362585).

6. If qualified, analyses of a relevant indicator of tumor proliferation or relevant proteins as well as microsatellite instability screening can be taken into account as alternatives.

Relevant indicators of tumor proliferation include Ki67, p53, p21^{ras}, the epidermal growth factor receptor, BRAF and phosphatase and tensin homolog (PTEN). Relevant proteins include the immunohistochemical detection of MLH1, MSH2, MSH6 and PMS2. In CRC targeted therapy, the K-ras mutation should be detected in the application of anti-epidermal growth factor receptor monoclonal antibody [13, 19].

7. CRC is classified according to the tumor/regional lymph node/distant metastasis (TNM) staging system of CRC (seventh version, 2009) of the American Joint Committee on Cancer/International Union Against Cancer (AJCC)/UICC (online suppl. appendix 2).

Primary tumor (T): T_x = Primary tumor cannot be evaluated; T₀ = no evidence of primary tumor; T_{is} = carcinoma in situ, confined to the epithelium or invades to the lamina propria; T₁ = tumor invades to the submucosa; T₂ = tumor invades to the muscularis propria; T₃ = tumor penetrates the muscularis propria and reaches the subserosa, or invades the adjacent colorectal tissues without peritoneal covering; T₄ = tumor penetrates the visceral peritoneum, or directly invades or adheres to other organs or structures, where T_{4a} = tumor penetrates the visceral peritoneum and T_{4b} = tumor directly invades or adheres to other organs or structures.

Regional lymph nodes (N): N_x = Regional lymph nodes cannot be evaluated; N₀ = has no regional lymphatic metastasis; N₁ = has 1–3 regions with lymphatic metastasis, where N_{1a} = has one region, N_{1b} = has 2–3 regions, and N_{1c} = has tumor satellite nodules in the subserosa, mesentery, colon/perirectal or the soft tissues around without regional lymphatic metastasis; N₂ = over 4 regions with lymphatic metastasis, where N_{2a} = has 4–6 regions and N_{2b} = has seven or more regions.

Distant metastasis (M): M₀ = Has no distant metastasis; M₁ = has distant metastasis, where M_{1a} = has distant metastasis limited to one organ, and M_{1b} = has over one organ/site or the peritoneum.

8. *Colorectal polyps are divided into neoplastic and non-neoplastic types; the former are called adenomas and classified into IEN.*

Non-neoplastic polyps can be hyperplastic polyps, hamartomatous polyps (including juvenile polyposis and melanin spots-gastrointestinal multiple polyps syndrome, i.e., Peutz-Jeghers polyps or Peutz-Jeghers syndrome), inflammatory polyps, lymphoid polyps and mucosal prolapse polyps.

Adenomas can be early adenoma (abnormal crypt foci), traditional adenoma (including tubular adenoma, villous adenoma and tubular villous adenoma), serrated adenomas (including traditional serrated adenoma, wide-based serrated adenoma polyps and mixed hyperplastic polyp/serrated adenoma) and clubbing-micro duct adenoma.

Intestinal polyposis is a disease in which there are >100 intestinal polyps [20, 21]. These can include familial adenomatous polyposis (FAP), serrated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden syndrome, Cronkhite-Canada syndrome, inflammatory polyposis and lymphoid polyposis.

9. *IEN is an epithelial lesion with morphological changes (including structural and cellular morphological changes) along with abnormal kinetics of proliferation and cellular differentiation.*

This terminology was recorded in the 2000 edition of the WHO document and introduced to describe the preinvasive lesions of the large intestine, which have cloning changes that tend to be associated with invasive diseases [13, 22]. In essence, IEN should be synonymous with the previous epithelial dysplasia, which may be divided into low- and high-grade cervical IEN (CIN) according to the degree of severity.

Low-grade IEN corresponds to grade I–II epithelial dysplasia. High-grade IEN is a mucosal lesion with malignant features in the structure and cell morphology of tissues but lacks invasion of the mesenchyme, including severe (grade III) interstitial dysplasia and carcinoma in situ. Whether or not IEN is present, the specimen should be completely resected to determine the depth of invasion. High-grade IEN cannot be an excuse for diagnostic mistakes and should always be confirmed.

III. Screening for Colorectal Tumors

(I) Strategy and Method for Screening Objects

10. *The recommended target population for the screening for colorectal tumors is 50–74 years old.*

The incidence of colorectal tumors increases significantly after the age of 50 years, is highest for those aged 75–80 years and then gradually decreases. Studies from outside China suggest that those aged 76–85 years should not be included in CRC screening [23]. Therefore, the highest age of screening for CRC in China has been determined to be 74 years.

11. *Due to its large population and the rising incidence of CRC in China, preliminary screening should be undertaken to find persons at high risk, followed by colonoscopy.*

China has a large population, so if all individuals of a certain age need colonoscopy, the number would be huge and a great challenge to healthcare systems. A person at high risk is identified during preliminary screening and then receives additional colonoscopy. Hence, considerable manpower and material resources can be saved.

12. Screening methods include FOBT, a questionnaire on high-risk factors, colonoscopy and sigmoidoscopy.

FOBT is one of the most widely used screening methods with a diagnostic sensitivity of 35.6–79.4% [24, 25]. The common reagents are guaiac, benzidine and quantitative assay antibodies. Immunoassay FOBTs are superior to those with chemical reagents [26]. At least two detection tests or application of the sequential fecal occult blood test are recommended (online suppl. appendix 3).

The questionnaire on high-risk factors is a simple and cost-effective screening method (online suppl. appendix 4) which can be used to find colorectal precancerous lesions based on epidemic case-control studies [27].

Digital rectal examination can help locate neoplasms in the inferior rectal segment, which is recommended in high-risk populations who have not undergone colonoscopy. Colonoscopy is essential for the diagnosis of CRC and should be carried out if necessary. The rate of detection of tumors can be influenced by endoscopy, the skills of the examiners and the time spent examining the patient [28].

Although sigmoidoscopy can only be used to monitor the gut beyond the splenic flexure, it may reduce the overall mortality of CRC populations [29]. Therefore, sigmoidoscopy is recommended if colonoscopy cannot be carried out.

13. A screening cycle of 3 years is recommended for persistent interventions.

Compared with the cumulative mortality of non-screening control regions, that of colorectal tumor screening regions using preliminary screening followed by colonoscopy can be reduced by the third year, reaches the lowest point at the fourth year and then increases gradually to the sixth year, whereas there are no significant differences in mortality between the two regions. Therefore, a 3-year screening interval is appropriate for reducing the mortality of CRC in screening regions [30].

14. Fecal DNA detection and computed tomography simulation colonoscopy can be used only for research and are not suitable for population screening.

Fecal DNA detection is the detection of DNA mutations and/or methylation in the stool samples for the diagnosis of CRC. Computed tomography simulation colonoscopy is used to simulate three-dimensional imaging of the colon with the abdomen after gut cleansing to aid the diagnosis of intestinal tumors. The methods described above are relatively complex and expensive, with the risk of false-positive results or radiation hazards. As such, they are not recommended for current CRC screening [4] but can help in the early diagnosis.

15. Preliminary screening followed by colonoscopy in the early diagnosis and treatment of CRC can be used as a reference for the screening for colorectal tumors.

The objective population for preliminary screening followed by colonoscopy is aged 50–74 years and needs a questionnaire related to high-risk factors (online suppl. appendix 4) [31, 32] and at least two FOBT immunoassays. Populations at a high risk of CRC are those meeting any one of the following items: (i) positive FOBT; (ii) first-degree relatives with the a history of CRC; (iii) history of intestinal adenomas; (iv) history of cancer; (v) meeting any two of the following six items: chronic diarrhea, chronic constipation, bloody mucus, chronic appendicitis or appendectomy, chronic cholecystitis or cholecystectomy, or long-term mental depression. Colonoscopy should be undertaken for populations carrying a high risk of CRC. The biopsy and pathological diagnosis should be carried out for all polypoid lesions. Patients with adenomas, CRC or other lesions associated with high-grade IEN should be treated promptly.

(II) Opportunistic Screening

16. *Opportunistic screening (also known as ‘individual screening’ or ‘case-finding’) is when subjects can seek medical attention or the physician decides the screening methods and strategies based on the danger level of the disease [33].*

Opportunistic screening is clinical-based screening that can be carried out in hospitals, community clinics and town hospitals. Screening methods (direct colonoscopy or positive FOBT + colonoscopy) are chosen based on the characteristics of the individual. These can include healthy subjects actively having physical examinations, patients looking for treatment for other diseases but carrying high-risk factors for CRC, and outpatients without the symptoms associated with colorectal tumors. Such screening is focused on the early detection of colorectal tumors (including precancerous lesions) and improvement of therapeutic effects, but cannot be used to determine whether the incidence of CRC in a certain population or region can be reduced.

Mass screening (also known as ‘natural population screening’ or ‘asymptomatic population screening’) is screening based on the population through a standardized method and is usually launched by the relevant departments or organizations. The overall population (community or units) meeting the screening criteria is urged to take part in the screening in a specified and relatively short time by various means. The purpose is not only to detect early cancer and improve the therapeutic effect, but also to locate precancerous disease and reduce the incidence with appropriate interventions to prevent CRC.

17. *The opportunistic screening for colorectal tumors may improve prognosis and quality of life (QoL) and reduce the huge healthcare burden of the state, and is a screening mode suitable for the current healthcare system and national situation [34, 35].*

Due to the large population of China, the annual national expenditure for CRC screening is about RMB 18.081 billion. This sum is for the lowest-cost FOBT and screening for people >60 years of age. According to the requirements of ‘Guidelines for the Screening and Early Diagnosis and Treatment of Major Cancers in China’ formulated by the China Cancer Foundation, the population aged >40 years should receive CRC screening. However, such screening necessitates funding that is far beyond that available by national financial and medical insurance. In addition, CRC screening is part-time work for clinical staff, but national screening will demand many full-time medical staff and specialized medical facilities, which cannot be met under current national health and human resources.

Opportunistic screening as a type of screening mode for colorectal tumors based on clinics can be carried out in hospitals, community clinics and medical centers due to its simplicity and practicality. Special funding and additional staff are not needed, but patient compliance is. Hence, it is eminently feasible [35–42].

18. *Evidence-based research has confirmed that FOBT can be used for the screening for colorectal tumors and that colonoscopy is an intensive detection.*

Studies on the screening and early diagnosis of CRC began in the 1970s in China. Li and colleagues [43–46] designed the ‘Sequential FOBT Screening Program’ in 1988 and demonstrated it in several large-scale population screenings. Zheng and colleagues [47–49] confirmed the high-risk factors of CRC in China based on research in regions with a high occurrence of CRC, Jiashan and Haining as well as Zhejiang, and created the ‘Quantitative Questionnaire of High-Risk Factors for CRC Screening’ (online suppl. appendix 4).

19. *Opportunistic screening for colorectal tumors involves (i) ensuring that the community, hospital outpatient and health examination centers can implement preliminary screening,*

(ii) knowing that the screening methods and strategies may differ between individuals, and
(iii) ensuring that it can be divided into screening and intensive detection.

There are two screening methods: (i) immunoassay FOBT and (ii) questionnaires (online suppl. appendix 4, 'Quantitative Questionnaire of High-Risk Factors for CRC Screening'). The objects of screening are patients and healthy individuals seeking a physical examination. The object of intensive investigation involves a positive FOBT and individuals at high risk as determined by questionnaire. The intensive method is colonoscopy.

20. The screening objects are divided into 'general' individuals and 'high-risk' individuals in accordance with the risk of CRC (for which different screening strategies are made). All patients undergoing intensive detection need to be registered and filed, and regular follow-up should be arranged according to the specific terms described in online supplementary appendix 5.

(i) General individuals: FOBT (immunochemical method) can be carried out on outpatients and healthy active people having physical examinations; those with a positive response are suggested to have additional colonoscopy. (ii) High-risk individuals: they are the focus of screening and their screening does not have to be bound by FOBT results (immunoassay or chemical method). For this group, colonoscopy is recommended, and tumor marker detection and/or genetic test is carried out if necessary.

For opportunistic screening, the definition of a high-risk individual is someone having one of the following items: (i) gastrointestinal symptoms such as blood/mucus in stools, abdominal pain, and unexplained anemia/weight loss; (ii) history of CRC; (iii) history of colorectal precancerous diseases (e.g. CRAs, ulcerative colitis, Crohn's disease, schistosomiasis); (iv) immediate family members with a history of CRC; (v) immediate family members with a history of colorectal polyps; (vi) history of pelvic radiotherapy.

(III) Screening and Monitoring of Familial Colorectal Tumors

21. Screening strategies for hereditary non-polyposis CRC (HNPCC): screening objects are patients meeting the diagnostic criteria for HNPCC and having family members with HNPCC. Screening is referenced to mutations of the pathogenic gene in the family.

(i) Families in which a pathogenic mutant gene has been detected: the screening objects need mutation analyses of the related genes. For those members without mutation analyses, colonoscopy is needed once every 1–2 years beginning at the age of 20–25 years, or 10 years earlier than the minimum age of onset in the family (the earliest one), and once a year after the age of 35 years [50, 51]. Screening of non-mutation gene carriers can be referenced to that of the average risk of the CRC population. (ii) Families with uncertain pathogenic mutant genes: the screening objects need an immunohistochemical assay and microsatellite instability detection: (a) if both negative, the screening depends on individual circumstances and assessment of family risk; (b) at least one positive (deletion of protein expression as judged by immunohistochemical staining and/or high-degree microsatellite instability), MLH1 and MSH2, or as well as MSH6 and PMS2 genes can also be added to the mutation analyses. If patients with a pathogenic mutation gene or mutation gene carriers are found, or if gene mutation analyses have not been done, the screening can be referenced to item (i) above. If patients with a pathogenic mutant gene are not found, it is recommended that the screening of patients and their first-degree relatives be referenced to that of pathogenic mutation carriers in item (i) above (to avoid missing the diagnosis caused by technical issues), and the screening of other family members depends on individual circumstances and risk assessment for the family.

22. *In the screening of patients with APC gene-associated polyposis (including classical FAP, mild FAP, Gardner syndrome and Turcot syndrome), probands (the first to be found) should be diagnosed first followed by predictive screening.*

(i) Confirmation of probands: (a) if the patient meets the diagnostic criteria for FAP or is suspected to have APC gene-associated polyposis, APC gene sequencing analyses and multiplex ligation-dependent probe amplification analyses should be done; (b) if no APC gene mutation is found, MYH gene molecular genetic testing is needed. (ii) Predictive screening: asymptomatic family members are at risk, so whether they have the familial mutant gene should be confirmed as soon as possible. If the inherited pathogenic APC gene mutation is not found by molecular genetic testing (even with diagnosed family members), CRC screening should be referenced to that of the average-risk population beginning at the age of 50 years. If the APC gene mutation testing is negative but with one or more diagnosed relatives not belonging to the same generation, linkage analyses should be considered with reference to the monitoring methods in item (iii) below and according to individual circumstances and familial risk. (iii) The monitoring methods for patients with APC gene-associated polyposis, pathogenic APC gene mutation carriers without symptoms, and family members who have not had molecular genetic testing: (a) sigmoidoscopy or colonoscopy is needed once every 1–2 years beginning at the age of 10–12 years and, if polyps are found, colonoscopy should be done once a year until colectomy; (b) upper gastrointestinal endoscopy is needed after the age of 25 years or before colectomy, and reviewed once every 1–3 years; (c) examination (endoscopic or radiographic) of the small intestine is necessary once every 1–3 years if a duodenal adenoma is found or before colectomy.

23. *Screening for Peutz-Jeghers syndrome includes confirmation of probands and prospective screening.*

(i) Confirmation of probands: it is recommended that all carriers of Peutz-Jeghers syndrome polyps or patients with typical pigmentation of the oral mucosa should have molecular genetic testing [52]. (ii) Prospective screening: molecular genetic testing is necessary for asymptomatic adults with a family history. (iii) Monitoring methods: (a) stomach: upper gastrointestinal endoscopy is needed once every 2–3 years beginning at the age of 8 years; (b) small intestine: endoscopic or radiographic examination is needed once every 2–3 years from the age of 8 years; (c) large intestine: colonoscopy is needed once every 2–3 years from the age of 18 years.

24. *Monitoring of juvenile polyposis syndrome needs to be carried out aimed at different parts [53].*

Colon: colonoscopy is needed starting before the age of 15 years once a year if polyps are found, and once every 2–3 years if polyps are not found. Stomach: upper gastrointestinal endoscopy is needed starting before the age of 15 years once a year if polyps are found, and once every 2–3 years if polyps are not found.

25. *'Other familial CRC' is defined as CRC or CRA patients having family members (one or more first-degree relatives, or two or more second-degree relatives) suffering from CRC or relevant tumors but who do not conform to any clinical diagnostic criteria for hereditary CRC. Screening depends on the age of onset [53].*

(i) Having CRC patients as first-degree relatives at age 50–60 years: colonoscopy is needed once every 3 years from the age of 40 years. (ii) Having one CRC patient as a first-degree relative aged <50 years, or two or more patients at whatever age: colonoscopy is needed from the age of 40 years or 10 years earlier than the youngest patient, and once every 3–5 years according to family history. (iii) Having one CRC patient as a first-degree relative

aged >60 years, or two or more secondary relatives at whatever age: colonoscopy is needed once every 5 years from the age of 50 years.

(IV) Tumor Screening Associated with Inflammatory Bowel Diseases

26. Inflammatory bowel diseases are high-risk factors for CRC, among which the high-risk factors of ulcerative colitis carcinogenesis include colonic lesions and a course of >10 years. Much more attention should be paid to the colonoscopy screening of such patients.

Colonic lesions and repeated long-term inflammation are the major high-risk factors for the carcinogenesis of ulcerative colitis. In general, the prevalence of cancer is comparatively low for simple ulcerative colitis of the rectum and left colon. Studies have shown that the prevalence of cancer is 2% for ulcerative colitis lasting >10 years, 8% for >20 years and 18% for >30 years [54]; the prevalence is very low for <10 years. Other high-risk factors include sclerosing cholangitis, young patients and a family history of cancer [55, 56].

Based on the high-risk factors of ulcerative colitis, more attention should be paid to the colonoscopy screening of such patients, including colonoscopy screening of the entire colon for patients with a 10-year duration of ulcerative colitis and colonoscopy screening of the left colon for those with a 15–20-year duration of ulcerative colitis [57–59]. The largest screening studies have shown that 5-year screening can lead to benefits in ≤73% of subjects, yet to benefits in only 36% in the group of those who were not screened [60]. This result suggests that targeted screening helps reduce the incidence of cancerous ulcerative colitis. Nevertheless, implementation of a cancer screening program for ulcerative colitis has not been carried out extensively [61].

27. The interval of colonoscopy screening is determined based on the classification of the degree of risk of ulcerative colitis carcinogenesis.

In reference to the 2011 European guidelines [57], the risk of CRC related to ulcerative colitis is divided into three degrees: (i) low-degree risk refers to colonic lesions stabilized or confined to the left colon; (ii) moderate-degree risk refers to colonic lesions confirmed with mild active inflammatory changes by endoscopy, polyps which have formed after inflammation, or CRC patients with first-degree relatives who had disease onset at age >50 years; (iii) high-degree risk refers to colonic lesions confirmed to have moderate-to-severe active inflammatory changes by endoscopy, accompanied by a history of primary sclerosing cholangitis, colonic stenosis or any degree of IEN (dysplasia) during the previous 5 years, and CRC patients having first-degree relatives who had the disease before the age of 50 years. The interval of colonoscopy screening varies with different risks: once every 5 years for low-risk populations, once every 3 years for moderate-risk populations, and annually for high-risk populations. If colonoscopy does not reach the cecum, it should be repeated.

28. The main purpose of colonoscopy screening in patients with ulcerative colitis is to detect mucosal IEN (dysplasia) and its related lesions as early as possible. To this end, multi-point biopsy can be done to improve detection or chromoendoscopy and magnifying endoscopy technology can be adopted.

In general, the intestinal mucosal lesions in ulcerative colitis are flat lesions or hypertrophic polypoid lesions, including dysplasia-associated lesion or mass. With regard to histology they can be (i) adenomatous lesions, (ii) serrated lesions or (iii) villous high-mucus-secreting lesions. At the advanced stage, stenotic lesions may result [62]. Finding flat lesions by endoscopy is very difficult.

29. *The canceration rate of Crohn's disease is similar to that of ulcerative colitis, including CRC and small bowel tumors. Long-term active disease is a high-risk factor for cancer. The screening for Crohn's disease invading the colorectum is similar to that for ulcerative colitis.*

Ulcerative colitis and Crohn's disease can lead to CRC. However, the rate of canceration of Crohn's disease is low [63]. Single-center studies in China have not reported any cancerous cases of Crohn's disease. Lesions invading the colorectum can promote canceration, which is also one of the high-risk factors for tumors of the small intestine. Screening for the invasion of Crohn's disease into the colorectum is similar to that of ulcerative colitis (see the corresponding items above) [64].

IV. Early Diagnosis of Colorectal Tumors

(I) Laboratory Diagnosis

30. *The serological diagnosis of colorectal tumors is hampered by a lack of sensitive and specific methods.*

Conventional serological detection of tumor antigen markers, such as carcinoembryonic antigen, cancer antigen 125 and cancer antigen 19-9, is easy to carry out, but the sensitivity and specificity needs to be improved. Detection of new indicators such as peripheral blood telomerase activity [65], mRNA of human telomerase reverse transcriptase [66] and some miRNAs, is much more complex, and their clinical value needs further evaluation.

31. *A positive result of FOBT suggests only that further examination is needed for the diagnosis. Detection of fecal DNA and transferrin has limited importance for the diagnosis of colorectal tumors, but contributes to their screening.*

DNA can be extracted directly from feces. Detection of the mutations of the K-ras gene [67–69], the p53 gene [70] and the APC gene [71] may aid the early diagnosis of CRC. The detection of DNA in feces has advantages such as convenience and good compliance from patients, but large-scale population-control studies are lacking. The sensitivity and specificity needs to be improved further.

Transferrin is the major iron-containing protein in plasma. It is responsible for the transport of iron absorbed from the digestive tract and released by the degradation of erythrocytes. Transferrin is present at very low levels in the feces of healthy people, but is very high if gastrointestinal bleeding is present. The ratio of hemoglobin to transferrin is 51.2/1 in the blood and 5.4/1 in the feces. Studies have shown that the sensitivity of detection of transferrin in feces is higher than that of FOBT immunoassay for the detection of CRAs and that it can be complementary with FOBT [72].

(II) Imaging Diagnosis

32. *Air-barium double-contrast radiography can be used as an adjunct examination for colorectal tumors, but the diagnostic value is less than that of endoscopy.*

Under air-barium double-contrast radiography, CRC shows destruction of mucosal folds, filling defects, niche shadows, stenosis, wall stiffness, loss of peristalsis as well as oppression/displacement of surrounding organs. Few tumors can be found with high-quality air-barium double-contrast radiography. The rate of detection of flat or prominent lesions (IIa type) is $\leq 70\%$, but that of small lesions in the bending segments and the anterior and posterior walls of the large intestine is low.

33. *Computed tomography colonoscopy is non-invasive and has unique advantages for patients who cannot tolerate colonoscopy, but has limited value for early diagnosis.*

Computed tomography colonoscopy can display colorectal lesions at multiple directions, angles and levels. It can accurately determine the circumference and thickness of the bowel and show the range of invasion of the tumor and surrounding bowel. Intraluminal reconstruction images can clearly show the intestinal mucosal folds for the early detection of colorectal lesions. However, computed tomography colonoscopy cannot biopsy the lesions, has false-negative results for small or flat lesions and false-positive results due to feces [73, 74].

(III) Endoscopic Diagnosis

34. *Colonoscopy combined with pathological examination is the standard method for the diagnosis of colorectal tumors. Adequate bowel preparation and careful observation when withdrawn can improve the rate of detection of colorectal tumors [75–79].*

The size, shape and location of the adenoma, the patient's age and the number of adenomas under initial colonoscopy are risk factors for a missed diagnosis in colonoscopy [78]. Studies have shown that patients with a tumor size <10 mm, a flat tumor, tumor in the left colon, age >60 years or >2 tumors at initial colonoscopy would be missed. Therefore, the diagnosis of small flat lesions should be emphasized and strengthened, especially for lesions in the left colon.

35. *Early CRC has two types under endoscopy: prominent and flat [80]. Biopsy is not recommended for the flat type under endoscopy.*

The prominent type (type I) is a lesion that protrudes significantly in the intestine with a base diameter that is significantly smaller than the maximum diameter of lesions (pedunculated or subpedunculated), or a hemispherical lesion with a base diameter significantly greater than the head diameter. According to the base and pedicle of the lesion, this type is divided into three subtypes: (i) pedunculated, the lesion base has obvious pedicles connected with the intestinal wall; (ii) subpedunculated, the lesion base has subpedicles connected with the intestinal wall; (iii) superficial, the lesion significantly protrudes in the mucosal surface without an obvious pedicle structure in the lesion base, whose diameter is less or greater than the maximum diameter of the head.

The flat type (type II) has a carpet-like shape similar to that of the mucosal surface, slightly prominent or depressed on the mucosal surface, with a base diameter close or equal to the maximum diameter of the surface. This type is divided into four subtypes: (i) IIa, a prominent surface; (ii) IIb, a flat surface; (iii) IIc, a depressed surface; (iv) a laterally spreading tumor whose maximum diameter is >10 mm. For flat lesions, a biopsy at a single location cannot reflect the overall situation of the lesions. Instead it can cause inflammation of the mucous layer and submucosa as well as adhesion with the muscularis propria, resulting in a difficult endoscopic resection.

36. *The colonic mucosal staining method has been shown to significantly improve the rate of detection of small lesions (especially flat lesions) and more clearly shows the boundary and surface structure of the lesions for the initial assessment of the lesions [81–83].*

The content of the endoscopy (colonoscopy) diagnosis is drafted based on the consensus regarding the endoscopic diagnosis and treatment of early CRC by the Endoscopy Professional Committee of the Colorectal Study Group of the Chinese Medical Association in 2008 [84]. A common colorant is 0.2–0.4% indigo carmine solution, which is bright blue and not

absorbed by the mucous membrane. After spraying and staining, it can deposit in the depressed fine structures of the mucosal surface with good contrast to enable observation of the fine structures on the lesion surface and the border of the flat lesions, especially to improve the rate of diagnosis of colorectal flat lesions. Other studies have shown that acetate staining followed by indigo carmine staining can improve the accuracy of the pit pattern analysis [85].

37. Magnifying chromoendoscopy with pit patterns can help determine the nature of the lesions and the depth of the invasion. It can also make the diagnosis consistent with the pathological results to determine the feasibility of endoscopic treatment [86–88].

The Kudo classification from 1996 has been adopted widely to classify colonic mucosal crypts. According to the shape and size of the crypt, it is divided into five types, I–V, where type III is divided into III_L and III_R (the characteristics of different types are shown in online suppl. appendix 6).

38. The vascular classification under NBI can be used to identify intestinal neoplastic and non-neoplastic lesions with high sensitivity and specificity for the appropriate choice of treatments [89–91]. Endoscopic ultrasound can be used to determine the depth of invasion of CRC with higher accuracy for the T stage and determine the suitability of endoscopic therapy [92].

Narrow-band images emphasize the vascular network (CP) and the surface structure of the mucosal surface. The blood vessels on the colonic mucosal surface are brown and the deep veins are green under NBI. The currently common NBI typing has Sano typing [89] and Showna typing [90]. The former, which is simple and practical, is divided into three types: type I – the structure of the mucosal surface is regular and honeycomb-like and CP is not visible; type II – the mucosal surface structure is honeycomb-like, round, and regular, and CP with a uniform diameter can be seen; type III – the blood vessels around the pit are irregular, with interrupted branches and different diameters (online suppl. appendix 7). Sano typing can be used to determine the lesions of colorectal tumors with a sensitivity and specificity of >90%, which is believed to be better than that for chromoendoscopy [89].

In addition, endoscopic techniques such as I-Scan Intelligent Optical Staining[®] [93–95] and confocal laser endomicroscopy [96] have higher accuracy for the identification of intestinal neoplastic and non-neoplastic lesions, whereas determination of the invasion depth needs to be validated further.

V. Endoscopic Treatment of Early CRC and Precancerous Lesions

39. The indications for endoscopic treatment of early CRC are (i) invasion depth limited to cancers in the mucosal layer and (ii) invasion depth limited to cancers in the submucosal layer (sml) [97].

Mucosal cancer is the absolute indication for endoscopic treatment not due to lymphatic and vascular metastasis. The prevalence of lymphatic metastasis of sml is only 3.2%, which can be used as a relative indication. However, the resected specimen should be strictly assessed to determine whether lymphatic or vascular invasion is present and whether additional surgery is needed.

40. Some systemic diseases or pregnancy are contraindications for endoscopic treatment for early CRC.

In this situation, contraindications can be patients (i) with severe heart and lung disease who cannot tolerate endoscopy, (ii) with coagulation disorders, (iii) with unstable vital signs, (iv) with spiritual beliefs or consciousness disorders who cannot cooperate with treatment,

(v) suspected or clearly having intestinal perforation, intestinal necrosis or severe peritonitis, or (vi) with toxic megacolon or fulminating colitis [98].

41. The current endoscopic treatments [97, 99–102] for early CRC include high-frequency electric snare polypectomy, hot biopsy forceps surgery, endoscopic mucosal resection, endoscopic piecemeal mucosal resection and endoscopic submucosal dissection.

These treatments should be carried out according to the lesions, technology and hardware conditions of each unit.

42. For resected specimens under endoscopy, the pathologist should assess whether the tumor invades into the base and surrounding cutting edge and whether lymphatic or vascular invasion is present, and determine whether additional surgery is required according to the pathology results.

The resected specimens under endoscopy should be spread out and fixed with pins, the lesion sizes measured and parallel continuous slices made with 2-mm intervals. The pathologist should assess whether the tumor invades into the base and surrounding cutting edge and whether lymphatic or vascular invasion is present, and determine whether additional surgery is required according to the pathology results [102].

VI. Monitoring and Follow-Up after Endoscopic Treatment of Colorectal Tumors

43. CRA removal under endoscopy (especially advanced adenoma) can prevent CRC to some extent, but CRA has an obvious recurrence trend.

Previously, scholars believed that CRA removal and follow-up under endoscopy could reduce CRC occurrence by >75% [3], which has not been found in recent studies. Martinez et al. [103] surveyed 9,167 patients who underwent CRA resection and found that, with an average follow-up of 4 years, 46.7% had CRA recurrence, 11.2% had advanced adenoma, and in 0.6% CRA developed to CRC. The recurrence was ≤40–50% after CRA removal for 3 years [104]. According to the studies of five medical centers in China, the 1-year recurrence after removal of advanced adenoma was ≤59.46% and that for 5 years was 78.07% [105].

44. The occurrence and diagnosis of interval CRC should be emphasized during screening and follow-up.

An ‘interval cancer’ is a cancer diagnosed between screening and post-screening monitoring [106]. The incidence of interval CRC is 0.3–0.9% due to the fast growth of new tumors [107], incomplete removal of a previous adenoma [108] or a missed diagnosis in the last check (usually the prevalence of a missed diagnosis for adenomas >1 cm in diameter is 2–12%).

45. The follow-up interval after the removal or surgery of colorectal tumors should be different with lesions: (i) the patient with an advanced adenoma should receive colonoscopy for 3–6 months; (ii) CRC should receive colonoscopy within 1 year after surgery and patients with polyps should receive colonoscopy for 1–3 years (online suppl. appendix 8); (iii) adenomatous polyposis receiving anus preservation surgery should receive colonoscopy every 12 months focusing on examination of the rectal stump.

The researchers, headed by Prof. Winawer at the Memorial Sloan-Kettering Cancer Center (New York, N.Y., USA), proposed, in 2006, how to follow-up and monitor after CRA removal. They stated that a high-risk patient (diameter >1 cm/high-grade IEN/≥3 polyps/villous structure) should receive colonoscopy after 3 years; a low-risk patient should receive

colonoscopy after 5–10 years; a patient with hyperplastic polyps should receive colonoscopy after 10 years; a patient with >10 polyps in one check should receive colonoscopy within 3 years according to the clinical situation; a patient with sessile flat polyps should be reviewed after 2–6 months to identify complete removal [4, 109]. According to the recurrence after CRA removal in reports in China and abroad, the follow-up interval after CRA removal in China can refer to the criteria mentioned above with some amendments. If a tumor is not found at the second inspection, the subsequent colonoscopy may be postponed.

46. After endoscopic treatment of early CRC, follow-up colonoscopy should be done at 3, 6 and 12 months. Subjects without residue or recurrence can receive one follow-up each year, those with residue or recurrence can receive additional resection, one follow-up every 3 months (including detection of serum tumor markers and FOBT), and one colonoscopy every year after complete removal.

Early CRC or precancerous lesions receive graded resection and can recur and remain, most of which occurs within 12 months.

VII. Chemoprevention of Colorectal Tumors

47. CRA removal under endoscopy cannot prevent its recurrence [110].

As mentioned above, CRA removal under endoscopy is associated with a higher prevalence of recurrence. Simultaneously, some studies reported that CRA removal was beneficial for the prevention of CRC in the left distal end but not for the right proximal end (and that the latter has more rapid growth [111]), and that more flat polyps which are difficult to identify under colonoscopy can also be malignant [112]. These scholars considered that removal of a right CRA was less beneficial than that of a left CRA.

48. CRC chemoprevention (primary prevention of CRC) contains the primary and secondary prevention for CRA. Primary prevention for CRA is to reduce the incidence of CRA. Secondary prevention for CRA should be aimed at recurrent lesions after adenoma removal under endoscopy [113–115].

Relying entirely on CRA removal under endoscopy to prevent CRC is not sensible due to poor medical conditions in rural areas, poor compliance from the patient, difficult spread of the application, high prevalence of recurrence after removal and difficulty in the identification of some flat polyps. Sporn and colleagues were the first to propose drug-based chemoprevention [116, 117]. These scholars considered prevention of CRA recurrence to be the ultimate goal of CRC chemoprevention.

49. Primary prevention of adenomas includes (i) improved diet with more fiber [118, 119], (ii) supplements containing calcium and vitamin D [120–122], (iii) supplements containing folic acid for those with lower plasma folate concentrations [123,124], and (iv) cessation of tobacco smoking [6].

Some prospective clinical trials have shown that high-fiber foods have a preventive effect. However, two randomized controlled clinical trials [125, 126] classified >1,000 cases with CRA and polyp removal into two groups: a low-fat and high-fiber diet group and a low-fiber diet group. No obvious difference in adenoma recurrence between the two groups was found at 3-year and 5-year follow-up, which showed that high-fiber foods were not associated with CRC prevention. However, recent studies with much larger sample sizes showed that a high-fiber diet was negatively correlated with CRC occurrence. The scientists involved were from several European and American medical centers; 33,971 cases (3,591 cases with adenomas)

and 519,978 patients were involved, respectively, and the decrease in CRC risk by consuming a high-fiber diet was 27% and 40%, respectively [118, 119].

Epidemiological surveys have shown that bioactive food compositions such as folic acid, cellulose, calcium and vitamin D as well as drugs have some CRC preventive features with very few side effects [120–122, 126, 127]. Bioactive food compositions for CRC chemoprevention include folic acid [123, 128]. Despite some controversy [129–131], it is generally believed that early application of folic acid can prevent adenoma, but prevention of recurrence of adenoma (or after adenoma removal) is not known [124, 132].

Recently, the Asia-Pacific CRC Working Group investigated 91 cases with colorectal tumors and 24 cases with advanced adenomas in 395 asymptomatic smokers, and 76 cases with colorectal tumors and 15 patients with advanced adenomas in 452 non-smokers. It is thought that the risk for smokers with colorectal tumors is 1.5 times higher than that for non-smokers, whereas the risk for smokers with advanced adenoma is 1.9 times higher [6].

50. Cases with a high risk of colorectal tumors (aged >50 years, male, with a family history of colorectal tumors or other cancers, smokers, overweight, history of gallbladder surgery or schistosomiasis) may receive non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and selective cyclooxygenase-2 (Cox-2) inhibitors with a special attention to side effects [133–143].

Some observational studies have found that subjects who take aspirin regularly may reduce the occurrence of colorectal tumors. However, the results of randomized studies on aspirin are not consistent. A prospective study carried out by Chan et al. [134] at Massachusetts General Hospital not only confirmed the preventive effect of aspirin on CRC, but also discovered the administration period and dose of aspirin to minimize the risk of CRC: continuous administration for ≥ 6 years at 14 tablets (325 mg/tablet) per week. Therefore, the potential hazard of long-term usage at this dose needs to be considered carefully. Dubé et al. [135] considered the dose of aspirin to prevent CRC to be larger than that used to prevent cardiovascular disease (>10 years) and that the side effects and expenditure-efficacy ratio should be considered carefully. In fact, the preventive effect of low-dose aspirin is controversial [136, 137].

It is widely acknowledged that Cox-2-specific inhibitors can prevent CRC. Cox-2 inhibitors can reduce the incidence of CRA in 72% of subjects. Celecoxib (400 mg b.i.d.) was shown to reduce FAP adenomas in 30% of 81 patients, yet 100 mg reduced FAP adenomas in only 12%. Hence, celecoxib has been approved by the US Food and Drug Administration (FDA) as a drug to prevent FAP [133].

However, non-selective NSAIDs and Cox-2 inhibitors have cardiovascular and gastrointestinal side effects or high costs [139–142]. After careful consideration, both agents are thought to be inappropriate for cases carrying a general risk of CRC [143].

51. NSAIDs and selective Cox-2 inhibitors have been recognized to prevent recurrence after adenoma removal. Supplementation with calcium and vitamin D [122], fiber diets and their intestinal metabolites short-chain fatty acids [144–147] may also aid prevention.

Epidemiological investigations and animal experiments have shown that calcium and vitamin D are related to the incidence of CRC or have preventive effects [120–122, 148, 149]. The preventive effects of calcium is achieved by binding secondary bile acids and fatty acids in the intestine and inhibiting the proliferation of intestinal epithelial cells. Vitamin D may be related to the induction of E-cadherin, inhibition of β -catenin, anti-proliferation and anti-mitosis. Clinical trials have shown that calcium supplementation can reduce CRA recurrence. Several studies showed that daily supplementation with calcium (>700 mg) can effectively prevent CRA recurrence. Calcium and vitamin D may be used together rather than singly to prevent CRC [121, 150].

Many factors that can affect the biological activity of calcium and vitamin D in vivo should be considered. For example, vitamin D can promote the absorption and utilization of calcium, whereas the increased level of phosphorus may affect the bioavailability of calcium. Some ongoing large-scale clinical intervention trials can further evaluate the long-term safety and efficacy of single or combined usage of calcium and vitamin D.

Prevention of CRC or CRA by dietary fiber may be associated with short-chain fatty acids, especially butyrate [144, 145, 151], which can protect the intestinal mucosa through various mechanisms [152] and can be used as an adjunct therapy for ulcerative colitis [153, 154]. Animal experiments have also clarified the preventive effects of butyrate [146, 147]. The healthcare products of butyrate may have certain preventive effects on colorectal tumors, but direct evidence from clinical trials is lacking.

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