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Research progress on risk factors for recurrence of colorectal adenomas after endoscopic resection and postoperative prevention and treatment

Jing Zuo, Hui Li*

Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, China

*Corresponding Author. Email: jessica20110215@163.com

Abstract. Colorectal Adenoma (CRA) is the main precancerous lesion of Colorectal Cancer (CRC). Its early detection and intervention are of great significance for reducing the incidence of CRC. Currently, endoscopic treatment is the most commonly used and effective method. However, there is still a certain risk of recurrence after adenoma resection, and some may progress to high-grade intraepithelial neoplasia or even CRC. Studies have shown that the recurrence mechanism of CRA is a complex process involving multiple factors, which is closely related to individual patient factors, adenoma characteristics, and factors related to endoscopic operations. Research on the prevention of adenoma recurrence is relatively scarce. In the field of Western medicine, Western drugs are the mainstay, while Traditional Chinese Medicine (TCM) prevents adenoma recurrence through syndrome differentiation using internal and external treatments, but both lack clear mechanism research and support from high-quality evidence-based medical evidence. This article investigates the research progress on the recurrence of CRA at home and abroad in recent years, evaluates some existing recurrence prediction models and monitoring strategies, and finally reviews the existing prevention methods of integrated traditional Chinese and Western medicine, aiming to provide reference for clinical practice, optimize postoperative monitoring strategies and individualized prevention and treatment plans, and ultimately achieve the goal of reducing the risk of CRC.

Keywords: colorectal adenoma, recurrence, prevention

1. Introduction

Colorectal Cancer (CRC) is one of the most common malignant tumors worldwide. It ranks second in the incidence of malignant tumors in China and fourth in cancer-related mortality [1]. Colorectal Adenoma (CRA) is the main precancerous lesion of CRC. Once detected clinically, it needs to be intervened and resected, mainly by endoscopic treatment, such as Cold Snare Polypectomy (CSP), Hot Snare Polypectomy (HSP), Endoscopic Mucosal Resection (EMR), and Endoscopic Submucosal Dissection (ESD) [2]. However, studies have shown that the recurrence rate of CRA can reach 20%-50% within 3-5 years after resection [3]. Regular follow-up monitoring can effectively prevent the occurrence of CRA. However, the recurrence risk varies among different patients, and there is no recognized standard for the postoperative follow-up monitoring time.

In terms of preventing CRA recurrence, there are various clinical methods. Relevant research in the field of Western medicine is insufficient, and there is a lack of drugs and methods with clear mechanisms and definite curative effects. Based on the TCM theory of "treating pre-disease", TCM has unique advantages in individualized prevention, with relatively more research on relevant theories and clinical efficacy, preventing postoperative recurrence of CRA from multiple angles and approaches, but it also lacks sufficient evidence support. Therefore, clarifying the risk factors for CRA recurrence and postoperative preventive measures is crucial for formulating individualized monitoring plans. This article reviews the research progress on risk factors for recurrence of CRA after endoscopic resection and postoperative prevention and treatment.

2. Risk factors for recurrence of colorectal adenoma

2.1. Patient-related factors

2.1.1. Age and gender

The recurrence of CRA is closely related to the patient's age and gender. A clinical study by Zhu Jianwei et al. [4] found that the risk of CRA recurrence was significantly higher in patients aged ≥ 50 years, and the recurrence rate in males was higher than that in females; another randomized controlled clinical study [5] found that the recurrence rate of CRA after resection was significantly higher in patients aged > 70 years than in those aged < 50 years. It can be seen that age is positively correlated with the risk of recurrence after endoscopic resection of CRA, and males have a higher risk of recurrence. This difference in age and gender may be related to changes in hormone levels and differences in metabolic levels.

2.1.2. History of smoking and alcohol consumption

Smoking and alcohol consumption are significantly associated with the recurrence of CRA. Multiple studies have shown [4, 6] that smoking is an independent risk factor for CRA recurrence. A study by Jiang Gui et al. [7] found that the risk of recurrence of advanced adenomatous polyps in smoking patients was 5.222 times that of non-smoking patients. It is speculated that carcinogenic components such as polycyclic aromatic hydrocarbons and nitrosamines in cigarettes bind to the DNA of intestinal epithelial cells, affecting cell replication and DNA repair, thereby causing irreversible damage to rectal mucosal cells and increasing the recurrence rate of CRA [8]. Long-term alcohol consumption also increases the risk of adenoma occurrence, which may be related to alcohol and ethanol altering DNA integrity and stability, as well as the expression of oncogenes and tumor suppressor genes [9].

2.1.3. Metabolic syndrome

Metabolic syndrome, including obesity, diabetes mellitus, hyperlipidemia, and Non-Alcoholic Fatty Liver Disease (NAFLD), is a risk factor for CRA recurrence. Sun Yu [6] found through a retrospective analysis of 220 patients after CRA resection that patients with BMI > 23 kg/m² were more likely to have CRA recurrence than those with normal weight. A further study by Jia Fuhua's team [10] found that diabetes mellitus and metabolic syndrome are independent risk factors for CRA recurrence. Zhuang Jing's [11] clinical observation found that weight loss and strict blood glucose control are beneficial to reducing CRA recurrence. The mechanism may be that the level of insulin-like growth factor in patients increases, and glucose and non-esterified fatty acids in the circulatory system provide energy, increasing the production of reactive oxygen species, inducing gene mutations and triggering inflammatory responses, thereby promoting the proliferation and invasion of intestinal cancer cells [12, 13]. A multivariate logistic regression analysis [7] showed that hypertriglyceridemia is an independent risk factor for recurrence of advanced adenomas after surgery, and it is speculated that high levels of triglycerides in the blood stimulate inflammatory reactions in the large intestinal

mucosa, affecting CRA recurrence. A statistical analysis of studies found that compared with non-NAFLD patients, NAFLD patients have a significantly increased risk of adenoma recurrence [14], which may be related to multiple mechanisms such as abnormal bile acid metabolism, insulin resistance, and chronic inflammatory reactions caused by liver lipid metabolism disorders [15].

2.1.4. Family history

Genetic susceptibility plays an important role in the occurrence and development of CRA. A study by Wang Fei et al. [16] showed that patients with a family history of gastrointestinal polyps or tumors in first-degree relatives have a significantly increased risk of CRA occurrence. This genetic tendency is related to gene expression, chromosomal changes, and malignant cell transformation.

2.2. Adenoma-related factors

2.2.1. Number and size of adenomas

Multiple clinical studies have confirmed that the number and size of CRA are key indicators for predicting postoperative recurrence. Regarding the evaluation of adenoma size, the current mainstream method is based on the maximum diameter of the largest adenoma, and a small number of studies consider the sum of the maximum diameters of all adenomas. Both methods have their own advantages and disadvantages. The former is convenient and fast, while the latter is more comprehensive. A retrospective study involving 163 patients analyzed the 1-year follow-up data of 163 patients after CRA resection. After correction by multivariate logistic regression analysis, it was found that the number of adenomas ≥ 3 and diameter ≥ 2 cm are independent risk factors for CRA recurrence [17]. Another multicenter study indicated that patients with the sum of all adenoma diameters ≥ 10 mm have a higher recurrence risk than those with the sum < 10 mm [18]. Regardless of the calculation method, the more the number and the larger the diameter of CRA, the higher the recurrence risk, which is related to the adenoma residual rate [19].

2.2.2. Location of adenomas

The correlation between the distribution of CRA and its recurrence is still controversial. Current studies believe that CRA is generally located in the distal colon, while sessile serrated polyps are usually found in the proximal colon [20]. Liu Yiwen [21] and Patel A [22] found in their studies that the postoperative recurrence rate of proximal colon adenomas is higher than that of distal colon, and the prognosis is worse; on the contrary, other studies [10, 23] have shown that the recurrence risk of distal colon adenomas is higher; Viel et al. [24] analyzed 1023 community patients and believed that there is no statistical correlation between adenoma recurrence and location. The reasons for these different conclusions may be related to differences in sample size, varying follow-up durations, differences in endoscopic operation techniques, the difficulty in diagnosing some flat adenomas, and the lack of a clear mechanism for adenoma occurrence.

2.2.3. Pathological characteristics

The pathological characteristics of adenomas are very important for postoperative treatment and prognosis of patients. Adenomas with pathological features of villous or tubulovillous adenomas or indicating high-grade intraepithelial neoplasia are high-risk adenomas, which have a higher recurrence rate than non-high-risk adenomas [25]. Tubulovillous adenoma is an independent risk factor for recurrence of colonic adenomas after surgery [13], with a high recurrence rate and malignant transformation rate, which may be due to the high malignancy of villous tissue and the faster rate of tissue cell lysis and growth [26]. Gu Xiumei [27] followed up 160 patients after adenoma surgery for 5 years and found that the recurrence rate of adenomas with villous features (75.9%) was significantly higher than that of simple tubular adenomas (40.0%), and the recurrence time of adenomas containing villous components was shorter than that of tubular adenomas. Similarly, CRA

with high-grade intraepithelial neoplasia is more likely to recur than that with low-grade intraepithelial neoplasia, and the recurrence time is shorter [28, 29]. In addition, sessile serrated polyps or traditional serrated adenomas with intraepithelial neoplasia are also a risk factor for CRA recurrence [30], which is related to the residual tissue that still has the potential to proliferate.

2.3. Factors related to endoscopic operations

The recurrence of CRA is related to the choice of endoscopic treatment methods. Compared with ESD, EMR has a lower en bloc resection rate and a higher local recurrence rate [31]. A Meta-analysis showed that ESD has higher en bloc resection rate (OR = 0.15) and R0 resection rate (OR = 0.35) than EMR, and the postoperative recurrence rate of CRA is also lower [32]. Other treatment methods such as argon plasma coagulation or electrocoagulation resection under snare to ablate the edge of the lesion can reduce the positive rate of adenoma resection edge, thereby reducing the recurrence risk of CRA [33]. However, at the same time, ESD is more difficult to operate, takes longer, and has a higher incidence of postoperative complications. Therefore, the recurrence rate cannot be simply used as a reference for choosing treatment methods, and multiple factors such as the appropriate method for the lesion, the difficulty of the operation, and the patient's tolerance should be considered.

3. Recurrence prediction models and recommended re-examination time

3.1. Prediction models

Zhang Jun et al. [34] established a nomogram model with age (≥ 50 years), number of adenomas (≥ 3), and high-risk pathological classification (villous structure, high-grade intraepithelial neoplasia) as independent risk factors, which can simply and quickly calculate the risk of CRA recurrence in patients and has strong clinical applicability. However, this model considers fewer factors, does not include metabolic syndrome, factors related to endoscopic operations, etc., and lacks time dynamic prediction ability. Zhuang Jing [10] established a nomogram model targeting seven risk factors: age, BMI, adenoma diameter, number of adenomas, adenoma location, adenoma pathological classification, and adenoma atypia, to predict the recurrence rate of CRA every year within 3 years after surgery. Patients with high scores are high-risk patients and need to pay attention to follow-up. The advantage of this model is that it quantitatively evaluates the risk level every year after surgery, which can remind patients of the approximate re-examination time. The disadvantage is that this model is not widely used and lacks recognition.

3.2. Monitoring strategies

Guidelines recommend that CRA should usually be rechecked every 1-2 years after surgery; if the adenoma is accompanied by high-grade intraepithelial neoplasia or has a diameter ≥ 2 cm and is resected en bloc, it should be rechecked at 1 year; if the diameter is ≥ 2 cm but resected in pieces, re-examination within 3-6 months is recommended [2]. Considering the low probability and long time required for developing into advanced adenomas in actual situations, as well as the patient's economic status and personal tolerance, foreign scholars are more inclined to a monitoring window of 5 years or longer [35]. Comprehensive consideration, for high-risk patients with many of the above risk factors, colonoscopy re-examination within 1-2 years is recommended. For patients with fewer risk factors, especially those with CRA with diameter ≤ 1 cm, without high-grade intraepithelial neoplasia or villous components, the re-examination time can be appropriately extended to 3 years [25].

4. Prevention and treatment of colorectal adenoma recurrence

4.1. Western medicine prevention

Multiple studies have shown that prostaglandin E2 (PEG2), as an important digestive hormone, increases blood supply to lesion tissue by dilating blood vessels, promoting the occurrence and development of CRA. Based on this mechanism, the latest guidelines mention that low-dose aspirin can inhibit the expression of PEG2 and reduce the recurrence of CRA [36]. A Meta-analysis pointed out that low-dose aspirin (< 200 mg/d) can not only effectively prevent CRA recurrence but also not increase the risk of adverse events. In contrast, the preventive effect of high-dose aspirin is not obvious [37]. In addition to aspirin, other drugs also have potential preventive value. A clinical study on 146 CRA patients found that the PEG2 content and CRA recurrence rate in patients who took sulfasalazine (SASP) continuously for 6 months after surgery were lower than those in the control group, suggesting that SASP can inhibit CRA recurrence by reducing the production of endogenous PEG2 [38]. In addition, a large number of animal and clinical experiments have confirmed that COX-2 is a target for the prevention and treatment of CRC. Celecoxib, as a selective COX-2 inhibitor, can reduce the recurrence of CRA [39]. Metformin, as a hypoglycemic drug, can inhibit the expression of some inflammatory factors and maintain the secretion of tumor suppressor factors, thereby reducing the risk of CRA occurrence [40, 41]. Other drugs such as folic acid [42], estrogen [43], probiotics [44, 45], vitamin D, and calcium [46, 47] have been reported in relevant studies to have preventive effects on CRA recurrence, but they lack sufficient clinical evidence support. It is also worth noting that long-term use of drugs such as aspirin, SASP, and celecoxib may increase the risk of bleeding and may cause adverse reactions in the gastrointestinal tract, cardiovascular system, and other aspects. Considering the mismatch between benefits and risks, they are not recommended as routine drugs for preventing CRA recurrence. Future studies are still needed to evaluate the effectiveness and safety of different drugs, providing reliable medication plans for clinical prevention of CRA recurrence.

4.2. Traditional Chinese medicine prevention

4.2.1. Etiology and pathogenesis in TCM

In the TCM theoretical system, CRA is classified into categories such as "intestinal mushroom", "intestinal lumps", and "abdominal masses". There is no consensus on the TCM etiology and pathogenesis of CRA recurrence. From the perspective of syndrome factors, Wang Jie et al. [48] proposed that "phlegm-dampness stagnation" is inherently related to lipid metabolism disorders in modern medicine, and phlegm-dampness is an important factor for CRA recurrence. Yang Songlong et al. [49] further proposed that blood stasis and phlegm-dampness are closely related to CRA recurrence. Blood stasis and phlegm pathogens remain in the body, which are difficult to resolve over time and accumulate to cause polyp recurrence. Therefore, prescriptions for promoting blood circulation and resolving phlegm can be used for prevention. From the perspective of zang-fu syndrome differentiation, Zhang Beiping et al. [50] observed the postoperative recurrence of 140 CRA patients and found that the recurrence rate was the lowest in patients with spleen deficiency, dampness, and blood stasis syndrome, and the highest in patients with qi stagnation and blood stasis syndrome. From the perspective of constitution theory, Liu Liting [51] found based on the "Four-Constitution Theory" that CRA is more common in people with yang deficiency and phlegm-dampness constitution, which is often related to their lifestyle and dietary structure, indicating the importance of constitution regulation in preventing CRA recurrence. In short, the etiology of CRA is nothing more than phlegm-dampness, blood stasis, qi stagnation, and yang deficiency. These pathological factors can not only cause diseases independently but also interact with each other, jointly affecting the recurrence of CRA.

4.2.2. Internal treatment of TCM

The general principle of TCM prevention and treatment of CRA is to invigorate spleen qi, resolve turbidity, and detoxify. A study found that "Atractylodes Rhizome-Codonopsis Root-Licorice Root" is the core drug group, and its active components may bind to core targets such as TP53, STAT3, and IL-6, regulating gene expression and cell apoptosis, thereby preventing and treating CRA [52]. Therefore, many prescriptions take this as the core drug group. Yang Ting et al. [53] used Huaijiao Pill, Shenling Baizhu Powder, and Chaihu Shugan Powder to intervene in three syndromes: damp-heat stasis obstruction, spleen deficiency with dampness and blood stasis, and qi stagnation with blood stasis, which effectively reduced the postoperative recurrence rate of CRA. Dai Qiuying [54] treated patients with modified Wumei Pill granules for 3 months and found that the recurrence rate of adenomas in the treatment group (40.00%) was lower than that in the control group (66.67%) after 6 months of follow-up. Another scholar self-formulated Sanzi Decoction for patients to take orally for 12 weeks, and the recurrence rate after 1 year (13.3%) was significantly lower than that in the placebo group (26.6%).

4.2.3. External treatment of TCM

In the clinical practice of TCM in preventing and treating postoperative recurrence of CRA, in addition to oral drugs, various external treatment methods are also a major feature of TCM treatment. Some researchers used acupoint application therapy with Jianpi Lishi Jiedu Ointment (Spleen-invigorating, Dampness-resolving, and Detoxifying Ointment) for acupoint application, which can not only improve the clinical symptoms of CRA patients after surgery but also reduce the recurrence rate [55]. Secondly, moxibustion therapy also has a certain preventive effect on CRA. Dai Meilan et al. [56] performed thunder-fire moxibustion on acupoints such as Shenque (CV8), Zhongwan (CV12), Qihai (CV6), and Guanyuan (CV4) of CRA patients after surgery, and found that fewer patients relapsed than the non-intervention group after 2 years of follow-up. Other researchers found that the use of "enema therapy", i.e., enema with TCM compound prescriptions, can also prevent CRA recurrence. Fan Shiping et al. used Jianpi Sanjie Decoction (Spleen-invigorating and Mass-resolving Decoction) for enema treatment of CRA patients after surgery and found that the recurrence rates in the 1st, 2nd, and 3rd years after treatment were significantly lower than those in the control group.

5. Conclusion

As an important precancerous lesion of CRC, the clinical management of CRA is of great significance. Although endoscopic resection can prevent carcinogenesis, the postoperative recurrence rate of CRA is high. Therefore, a deep understanding of the risk factors for CRA recurrence is crucial for formulating individualized monitoring and prevention strategies for patients. Certain progress has been made in the analysis of risk factors for recurrence of CRA after endoscopic resection. Factors such as the patient's gender, age, history of smoking and alcohol consumption, family history, metabolic syndrome, the number, size, and pathology of adenomas, as well as the choice of endoscopic treatment methods for CRA, are all important factors affecting CRA recurrence. However, most of these studies still lack clear mechanisms, and due to the limitations of sample size, doctor's technology, diverse polyp morphologies, and overlapping multiple factors, the conclusions of the studies may be biased, resulting in no recognized comprehensive and accurate prediction model so far.

Therefore, many scholars have conducted a large number of clinical explorations and studies on postoperative preventive measures for CRA. From the perspective of Western medicine, the prevention of Western medicine has certain effects, but long-term use has many side effects, and the mismatch between benefits and risks limits its clinical application. The internal and external treatments of TCM have shown

unique advantages in the postoperative prevention and treatment of CRA, with good effects and fewer accompanying adverse reactions. However, TCM treatment still faces some challenges, including the lack of a unified syndrome differentiation standard and relatively insufficient high-quality evidence-based research evidence. Therefore, the future research direction can focus on establishing a more comprehensive risk factor assessment system, optimizing the clinical plan of integrated traditional Chinese and Western medicine for preventing CRA recurrence, and conducting large-scale, multicenter clinical studies as evidence-based support to provide individualized, precise, and safe postoperative management plans for patients.

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