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• REVIEW •

Early diagnosis for colorectal cancer in China

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Abstract

AIM: **To review the present studies on early diagnosis of colorectal cancer.**

METHODS: **The detective rate for early cancer is 1.7%-26.1% based on various statistical data, with much higher detective rate in endoscopy. Since early cancer means invasion involved in the mucosa or submucosa, the diagnosis can only be made when the invasive depth is identified. Pathological tissue materials from both surgical operation or endoscopic resection are suitable for early cancer evaluation.**

RESULTS: **Incidence of polyp malignancy is 1.4%~20.4%. The various constitutive proportion of polyps may explain the different rates. Malignant incidence is higher in adenomatous polyps, that for villous polyps can reach 21.3%-58.3%. Type II early stage of colorectal carcinoma is rarely reported in China. It is shownd that majority of them were not malignant, most of type IIa being adenoma or hyperplasia, and IIb being inflammatory and IIc might be the isolated ulcers. The occurrence of malignancy of type II is far lower than that of polypoid lesion. In China, the qualitative diagnosis and classification of neoplasm generally adopted the WHO standard, including surgical excision or biopsies. There is impersonal evaluation between colorectal pre-malignancy and cancer. The former emphasizes the dysplasia of nuclei and gland, while the latter is marked with cancer invasion. Diagnosis of early stage colorectal cancer in endoscopy is made with too much caution which made the detective rate much lower. Mass screening for asymptomatic subjects and follow-up for high risk population are mainly used to find the early stage colorectal cancer in China. Fecal occult blood test is also widely made as primary screening test, galactose oxygenase test of rectal mucus (T antigen), fecal occult albumin test are also used. The detective rate of colorectal cancer is 24-36.5 per 105 mass population.**

CONCLUSION: **Although carcinoma associated antigen in blood or stool, microsatellite DNA instability for high risk familial history, molecular biology technology for stool oncogene or antioncogene, telomerase activity and exfoliative cytological examination for tumor marker, are utilized, none of them is used in mass screening by now.**

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INTRODUCTION

The colorectal cancer is one of the most common malignant tumors which threatens the people's health[1-3]. The occurrence of colorectal cancer has been rising over the past 3 decades. At present, the colorectal cancer is the second cause of death in western countries, and the forth in China[4,5]. It is clear that the prognosis of colorectal cancer is related to early diagnosis[6-8], For instance, the five-year survival after operation of colorectal cancer, diagnosed in early stage, is over 80%, but in the advanced stage it is lower than 40%. So, it is very important to improve the colorectal cancer's prognosis by means of early diagnosis[9-13]. Recently, much attention has been paid to early detection for colorectal cancer in China. The popularity of the colonoscopy and the mass screening for colorectal cancer in the population who have no symptoms has raised the rate of the early diagnosis of colorectal cancer greatly. However, the study and progress vary among regions in the country, and there are also misdiagnoses. This paper reviews the present study of early diagnosis of colorectal cancer in China.

THE DETECTIVE RATE OF EARLY STAGE COLORECTAL CANCER IN CHINA

At present, the data of detective rate for early stage colorectal cancer are not perfect, and the detective rate is 1.7%-26.1%, based on various reports (Tabel 1)[14-20]. The major reason for the different rate is the various statistical data. In virtue of the endoscopy popularity, the early stage of cancers are detected increasingly. Most of them can be treated by non-surgically. So, there are great differences between the endoscopic and the surgical data. For example, 997 cases of colorectal cancer were treated surgically during 1990-1999 in Nan Fang Hospital, 21 cases are in early stage (2.1%), while 1087 cases of colorectal cancer were found from 20 353 colonoscopied cases during the corresponding period, in which, 146 early stage of cancers were identified (13. 4%). Because most of early cancers are polyps-like and easy to be resected under endoscopy, the percentage of early stage cancer in surgical samples is low.

Table 1 The detective rate for early stage of colorectal cancer in China

Authors	Colorectal cancer		
	Total *n*	Early stage *n* (%)	Year
Lu *et al*[14]	569	85(15.1)	1997
Ni *et al*[15]	132	15(11.4)	1997
Yang *et al*[16]	721	65(22.9)	1997
NI *et al*[17]	296	32(10.8)	1997
Cai *et al*[18]	1058	59(5.6)	1999
Zeng *et al*[19]	300	5(1.7)	1996
Sun *et al*[20]	180	47(26.1)	1998

MORPHOLOGY OF EARLY STAGE COLORECTAL CANCER UNDER ENDOSCOPY

There are two types of early colorectal cancer based on the morphological classification under endoscopy. Type I also called protruded or polyps type, can be further grouped as pedunculated (Ip), subpedunculated (Isp) and sessile (Is) superficial type. Type II can be classified as elevated(IIa), flat(IIb) and depressed (with or without protruded)[6,19]. Since early cancer means invasion involving the mucosa or submucosa, which is not related to the tumor size or special morphology, the diagnosis only can be

made when the invasive depth is identified. Pathological tissues from both surgical operation and endoscopic resection are suitable for early cancer evaluation. It is important that early cancer diagnosis can not be made based on the endoscopic biopsy since invasion is not observed.

Histopathological examination of polyps under endoscopy is a crucial method to detect early cancer in China, and most of them are polyp malignancy[9,14,21,22]. Generally, polyp formation is mostly involved in the proliferation of mucosa and submucosal tissues. As long as cancerous tissues do not touch upon pedicle, they can attribute to early-stage carcinoma. If pedicle of polyp invasion in colorectal cancer can not be observed for incomplete resection or embedded in the wrong direction, diagnosis of early-stage carcinoma can not be made rashly. Incidence of polyp malignant transformation is 1.4%-20.4% (Table 2). Different result may be from various constitutive proportion of polyps. Malignant incidence is high in adenomatous polyps. In villous polyps, it can reach 21.3%-58.3% according to the documents in China [23-31]. Moreover, as some adenomatous ingredient are observed by biopsy,some advanced colorectal cancers are diagnosed as polyp malignancy by pathologists. This kind of lesions can not be included in the early-stage carcinoma. In our previous study, 87/127 (68.6%) advanced colorectal carcinoma had residual of adenoma.

Table 2 The malignant transformation rate of polyps in China

Authors	Area	*n*	Incidence (%)
Zhou *et al*[22]	Guangzhou	539	3.4
Cai *et al*[23]	Guangzhou	216	9.7
Zhang *et al*[24]	Changchun	2000	5.1
Shen *et al*[25]	Kunming	533	6.4
Zhu et *et al*[26]	Beijing	219	1.4
Zhu *et al*[27]	Nanjing	644	5.8
Wang *et al*[28]	Xi'an	548	9.7
Zhang *et al*[29]	Zhejiang	321	14.6
Zhang *et al*[30]	Ha-erbing	494	20.4
Gao *et al*[31]	Shanghai	334	6.6

Type II early stage of colorectal carcinoma is rarely reported in China. Huang *et al* first summarized 6304 patients detected by colonoscopy from 1974 to 1996 in a hospital of Beijing[32], only 36 Type II lesions were discovered, including 31 (86.1%) type IIa,4 (11.1%)type IIb and 1 (7%) type IIc. Thirty-two tubular adenomas, 3 villous adenoma and 1 carcinoid were confirmed by histopathological examination,. Only one case was identified as malignancy by follow-up.

In 137 cases of early stage colorectal cancer detected in Nanfang Hospital from 1990 to 1999, 95.6% were polypoid type, only 6 cases were considered as type II(4.4%)(Table 3). We also analyzed the histopathological features of 186 cases of type II lesions, only 3.2% were diagnosed as early stage carcinoma(Table 4). It indicated that the majority of so-called type II cancer under endoscopy were not real malignancy. Most of type IIa were adenoma or hyperplasia polyps, and most of type IIb were inflammatory changes of mucosa. A large number of type IIc cases might be the isolated ulcers. The occurrence of malignancy of type II is far lower than that of polypoid lesion.

Table 3 Morphology of 137 cases of early stage colorectal cancer under endoscopy

Morphology	Type	*n*	Ratio
Polypoid	I	131	95.6
Elevated	IIa	2	1.4
Flat	IIb	1	0.7
Depressed	IIc or IIc+IIa	3	2.3

Table 4 Histopathology of 186 cases of type II lesion

Morphology	Type	*n* (%)	Histopathologic diagnosis		
			Early cancer	Adenoma	Other
Elevated	IIa	155(83.3)	2(1.3)	86(55.4)	67(43.3)
Flat	IIb	22(11.8)	1(4.5)	2(9.00)	19(86.4)
Depressed	IIc or IIc+IIa	9(4.8)	3(33.3)	4(44.4)	2(22.2)

THE DIAGNOSTIC STANDARD FOR EARLY STAGE OF COLORECTAL CANCER

In China, the qualitative diagnosis and classification of neoplasm generally adopted the WHO standard for both surgical excision and biopsies[17,33]. The evaluation is objective between colorectal pre-malignancy and cancer. The former emphasizes the dysplasia of nuclei and gland, while the latter is marked with cancer invasion[34-37]. Although pathologists hold different opinions about the classification of dysplasia, it could be classified generally into 3 grades. The simpliest classification depends on the ratio of dysplasia karyon in epithelium. Mild dysplasia indicates the crowding nuclei limited within 1/2 depth of epithelium in basement, moderate dysplasia means that atypical nuclei occupied more than 1/2 epithelium, and severe dysplasia refers to the atypical nuclei occupying the whole epithelium with integrated basement. The essential difference between dysplasia and malignancy is invasion. The malignancy is manifested by the destroyed basement, and sporadical dysplasia glands. It is called intra-mucosal cancer if the cancer cell invasion limited within the mucosa. If the cancer destroyed mucosal muscle into submucosa, it is called sub-mucosal cancer. These two types are generally designated as early stage cancer. From the literature reviews, we found that the diagnosis of early stage colorectal cancer in China is made with much cautions under endoscopy. On the one hand, pathologic diagnosis generally adopted the WHO standard, which depends on the invasion, and sometimes it is difficult to observe the invasion on biopsy sections. On the other hand, patients always feel panic to cancer, once the colorectal cancer is diagnosed, they would rather choose surgical operation than endoscopic resection. Besides, they often require consultation of the pathological sections, if diagnostic standard is different, this may cause the psychological pressure to the pathologic doctors in different regions.

In European countries, colorectal cancer is the most common malignant tumor of digestive tract. But the diagnositic rate of early cancer is usually reported less than 9%. In Japan, the diagnostic rate of early stage of cancer detected by endoscopy is 17%-53%. The cases of early stage cancer reported in China is the same as in European countries but far lower than in Japan[14-20]. Schlemper RJ *et al* compared the differences in pathological diagnosis of early carcinoma from strippling or surgically resected specimens of colonic mucosa between Japan and Europe-America[34]. It was found that 4 cancer cases were diagnosed by Japanese pathologists in 11 adenoma with mild dysplasia based on European-American standard. This is because Japanese pathologists emphasize the nuclei dysplasia and gland structural change evaluating malignancy[37], but pathologists in China usually take above changes as markers of pre-malignancy.

DETECTION FOR EARLY STAGE OF COLORECTAL CANCER

Mass screening for asymptomatic subjects and follow-up for high risk population are the major ways to find the early stage of colorectal cancer in China[38-42]. High risk factors are old age, histories of colorectal polyps, familial history of cancer and some colorectal related positive tests[43-51]. Since mass screening for asymptomatic population need a large amount of work, and exact diagnosis must depend on endoscopical and histopathological examination, screening test has been paid much attention. So far, fecal occult blood test is widely used as primary screening test in China[52-55]. Other screening tests include galactose oxygenase

test of rectal mucus(T antigen)[56-60], and fecal occult albumin test[61,62]. If the screening tests appear positive, colonoscopy is then taken. Although carcinoma associated antigen in blood or stool[63-81], microsatellite DNA instability for high risk familial history[82-86], molecular biology technology for stool oncogene or antioncogene[87-99], telomerase activity[100-104] and exfoliative cytological examination[105,107] have been used for tumor marker, none of them is used in mass screening.

There are some excellent work reported in China on mass screening for colorectal cancer. Most of them are based on immune fecal occult blood test(Table 5)[54,55,62]. In mass screening (age above 35 years), the occurrence of colorectal cancer is 24-36 per 10^5 population.

Table 5 Mass screening for colorectal cancer in asymptomatic population

Authors	Region	Age(yrs)	Population	Cancer	Dukers(%) A/B	Detection rate
Li *et al*	North	>35	102 800	25	52.0	$24/10^5$
Zhen *et al*	East	>35	62 667	16	57.2	$25.5/10^5$
Zhou *et al*	Mid-south	>45	24 677	9	55.6	$36.5/10^5$

Tantigen detection in rectal mucus is also used in some mass screenings[57-60,108,109]. In 3820 asymptomatic population, the positive rate of T antigen is 9.1%, among them, 2 cases of early cancer and 28 cases of adenoma were identified. The detective rate of pathologic change is 12.7%. It is shown that T antigen test is not specific for colorectal examination. In 103 cases of T antigen positive subjects, 85 cases were found without any lesion under colonoscopy. The sensitivity is not better than that of feces occult blood examination[110-114].

Since screening tests used so far are not specific for colorectal detection, there are some misdiagnoses either by feces occu1t blood examination or rectal mucous T antigen test. To improve the detective rate of the early stage cancer, it is suggested that combined complementary screening should be taken. Zhejiang University School of Medicine optimized the screening protocol for colorectal cancer among a high-incidence population[113]. Through increasing the cases for colonoscopy follow-up, the detective rate of early cancer was increased. Beijing General Hospital reported that by combined test of sequencial fecal occult blood and albumin in the screening of colorectal neoplasma, 3 cases of carcinoma were found from 883 positive asymptomatic subjects[114]. The Nanfang Hospital recommended the complementary schemes by combining occult blood and T antigen detection. In 5 cases of colorectal cancer, which were found by colonoscopy in 2832 asymtomatic subjects, 3 were positive in feces occult blood examination and 2 in T antigen test. The missed cases will be reduced if complementary screening was taken[13]. Our study showed that the mass screening can reduce the colorectal occurrence(Table 6)[113].

FUTURE STUDY IN EARLY DIAGNOSIS FOR COLORECTAL CANCER

It is definite that asymtomatic mass screening is the important way to identify the early cancer. Because of the poor specificity of screening test, and the high cost, it is difficult to popularize. Target screening will be highlighted. In 1992, Sidransky *et al* first extracted DNA successfully from feces and reported ras gene variation with Southern-Blot[116]. It is considered an effective screening for colorectal cancer in the 21st century. PCR-SSCP technology has a high sensitivity, good specificity and easy manipulation. Gene mutation such as P53, ras, c-erbB-2, APC and MCC was identified in feces (Table 7)[94-96,117,118]. Since no specific gene mutation is found in colorectal cases, the detective rate by molecular technique is low. Though combined genes detection can enhance the screening rate, it is too complex and expensive.

Table 6 The follow-up results in 3,641 cases of asymtomatic population

	Cancer (*n*)	Adenoma		
		n	>1.0 cm	Dysplasia(>II grade)
First screen	4	48	17(35.4%)	12(25.0%)
Two years later	0	18	4(22.2%)	2(11.1%)

Table 7 Gene mutation analysis in colorectal cancer stool (Nanfang Hospital)

Gene	*n*	Tissue DNA		Fecal DNA	
		Positive	%	Positive	%
APC	41	20	48.8	14	34.1
MCC	45	13	28.9	11	24.4
P53	32	32	37.5	10	31.3

Analysis of gene offers possibility and practical significance for detecting high risk population. For example, HNPCC generally represents the microsatellite DNA instability and characteristic DNA mismatch repair gene. Therefore, detecting MIN and DNA mismatch repair gene may identify some high risk population with cancer familial predisposition[119-122]. We analyzed 46 cases of colorectal carcinoma for MIN, and found 14 cases of MIN positive patients, 12 of them with familial predisposition (85.7%). It is suggested that MIN might reflect colorectal carcinoma with familial predisposition in some extent.

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