Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.2708

World J Gastroenterol 2009 June 14; 15(22): 2708-2713
World Journal of Gastroenterology ISSN 1007-9327

ORIGINAL ARTICLES

Size does not determine the grade of malignancy of early invasive colorectal cancer

Takahisa Matsuda, Yutaka Saito, Takahiro Fujii, Toshio Uraoka, Takeshi Nakajima, Nozomu Kobayashi, Fabian Emura, Akiko Ono, Tadakazu Shimoda, Hiroaki Ikematsu, Kuang-I Fu, Yasushi Sano, Takahiro Fujimori

Takahisa Matsuda, Yutaka Saito, Takahiro Fujii, Toshio Uraoka, Takeshi Nakajima, Nozomu Kobayashi, Fabian Emura, Akiko Ono, Endoscopy Division, National Cancer Center Hospital, Tokyo 104-0045, Japan
Tadakazu Shimoda, Clinical Laboratory Division, National Cancer Center Hospital, Tokyo 104-0045, Japan
Hiroaki Ikematsu, Kuang-I Fu, Yasushi Sano, Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa 277-8577, Japan
Takahiro Fujimori, Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine, Shimotsuga, Tochigi 321-0293, Japan
Author contributions: Matsuda T, Saito Y and Fujii T contributed equally to this work; Matsuda T, Uraoka T, Nakajima T and Kobayashi N designed the research; Matsuda T, Ikematsu H, Fu KI and Sano Y performed the research; Shimoda T and Fujimori T performed the histopathology; Matsuda T, Saito Y, Emura F and Ono A wrote the paper.
Correspondence to: Takahisa Matsuda, MD, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. tamatsud@ncc.go.jp
Telephone: +81-3-35422511 Fax: +81-3-35423815
Received: February 24, 2009 Revised: April 15, 2009
Accepted: April 22, 2009
Published online: June 14, 2009

Abstract

AIM: To clarify the clinicopathological characteristics of small and large early invasive colorectal cancers (EI-CRCs), and to determine whether malignancy grade depends on size.

METHODS: A total of 583 consecutive EI-CRCs treated by endoscopic mucosal resection or surgery at the National Cancer Center Hospital between 1980 and 2004 were enrolled in this study. Lesions were classified into two groups based on size: small (≤ 10 mm) and large (> 10 mm). Clinicopathological features, incidence of lymph node metastasis (LNM) and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

RESULTS: There were 120 (21%) small and 463 (79%) large lesions. Histopathological analysis of the small lesion group revealed submucosal deep cancer (sm: ≥ 1000 μm) in 90 (75%) cases, LVI in 26 (22%) cases, and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited submucosal deep cancer in 380 (82%) cases, LVI in 125 (27%) cases, and PDA in 79 (17%) cases. The rate of LNM was 11.2% and 12.1% in the small and large lesion groups, respectively.

CONCLUSION: Small EI-CRC demonstrated the same aggressiveness and malignant potential as large cancer.

Key words: Colorectal cancer; Submucosal invasion; Lymph node metastasis; Endoscopic mucosal resection

Peer reviewers: Peter L Lakatos, MD, PhD, Assistant Professor, 1st Department of Medicine, Semmelweis University, Koranyi S 2A, Budapest H1083, Hungary; Javier San Martín, Chief, Gastroenterology and Endoscopy, Sanatorio Cantegril, Av. Roosevelt y P 13, Punta del Este 20100, Uruguay

Matsuda T, Saito Y, Fujii T, Uraoka T, Nakajima T, Kobayashi N, Emura F, Ono A, Shimoda T, Ikematsu H, Fu KI, Sano Y, Fujimori T. Size does not determine the grade of malignancy of early invasive colorectal cancer. *World J Gastroenterol* 2009; 15(22): 2708-2713 Available from: URL: http://www.wjgnet.com/1007-9327/15/2708.asp DOI: http://dx.doi.org/10.3748/wjg.15.2708

INTRODUCTION

Colorectal cancer (CRC) is the third most important cause of cancer mortality in Japan, and its incidence is gradually increasing. To reduce CRC mortality, early detection and appropriate treatment are required. In general, small lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size[1-3]. Therefore, lesion size is considered to be indicative of the depth of invasion and presence of lymph node metastasis (LNM). In contrast, flat, and in particular depressed lesions, are considered to have a tendency to invade rapidly the submucosal layer, even when small[4-6]. However, clinicopathological features of small EI-CRCs have still

not been studied extensively.

The aim of this retrospective study was to clarify the clinicopathological characteristics of small and large EI-CRCs and their implications for endoscopic treatment.

MATERIALS AND METHODS

Subjects

Five hundred and eighty-three patients (374 male and 209 female) with EI-CRC that had been resected surgically or endoscopically at the National Cancer Center Hospital, between January 1980 and January 2004, were examined retrospectively. In all of these patients, cancer cells invaded through the muscularis mucosa into the submucosal layer but did not extend deeply into the muscularis propria. Eligibility also required the lesions to be macroscopically non-pedunculated (sessile, flat and depressed). Patients with synchronous advanced CRC, multiple EI-CRCs, inflammatory bowel disease, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis were excluded from the study.

Methods

All lesions were classified into two groups according to their endoscopic image size: small (≤ 10 mm) and large (> 10 mm). Furthermore, lesions were classified into three categories (sessile, 0- Ⅰs, Ⅰs+Ⅱa; flat, 0-Ⅱa; and depressed, 0-Ⅱc, Ⅱa+Ⅱc, Ⅰs+Ⅱc) according to the Paris classification[7]. Clinicopathological features, incidence of LNM and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

Histopathology

Resected specimens were fixed in 10% formalin and examined histopathologically following hematoxylin and eosin staining. Histopathological diagnosis was based on the World Health Organization (WHO) criteria[8]. Submucosal invasion was measured from the muscularis mucosa to the deepest portion. When the muscularis mucosa could not be identified because of cancer invasion, the vertical length was measured from the surface of the lesion to the deepest portion according to Kitajima's classification[9]. Tumors with a vertical length of < 1000 μm in the submucosal layer were classified as submucosal superficial invasive cancers (sm-superficial), and lesions with a length ≥ 1000 μm were classified as submucosal deep invasive cancers (sm-deep). The tumor growth patterns were histopathologically divided into polypoid growth (PG) and non-polypoid growth (NPG) types. Shimoda *et al*[10] have reported polyp cancers with protrusions caused by intramucosal proliferation of the carcinoma or coexistent adenoma that behaved as PG type carcinoma, while flat/depressed type carcinoma without polypoid proliferation of intramucosal tumor behaved as NPG type carcinoma.

Statistical analysis

The significance of differences in proportions was assessed by the χ^2 test, Fisher's exact test and the Wilcoxon matched-pairs signed-ranks test using SPSS statistical software (SPSS for Windows , version 16.0J, Tokyo, Japan). Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 583 EI-CRCs were retrospectively evaluated, with 120 (21%) small and 463 (79%) large lesions identified (Table 1). The gender ratio (male/female) was 2.4 and 1.7, and the mean age was 61.5 and 62.4 years in the small and large lesion groups, respectively. Mean size of the small and large lesions was 8.3 and 22.1 mm, respectively.

Macroscopic type, growth type and location

Macroscopic assessment of small lesions identified 51 cases as sessile (42%), 14 as flat (12%), and 55 as depressed (46%). Similarly, large lesion groups comprised 233 sessile (50%), 64 flat (14%), and 166 depressed (36%) type. PG types were identified in 32% (38/120) and 54% (250/463) of small and large lesions, respectively. In contrast, the prevalence of NPG type in the small lesion group was significantly higher than in the large lesion group (68% *vs* 46%, $P < 0.0001$). Regarding tumor location, there were 33 (27%) rectal, 56 (47%) distal colon and 31 (26%) proximal colon cancers in the small lesion group. In contrast, there were 213 (46%) rectal, 139 (30%) distal colon and 111 (24%) proximal cancers in the large lesion group. The incidence of rectal cancer in the large lesion group was significantly higher than in the small lesion group ($P = 0.02$).

LNM

Among the lesions treated surgically, the incidence of LNM was 11.2% (10/89) and 12.1% (46/381) in small and large lesion groups, respectively ($P = 0.85$) (Table 2).

Depth of invasion/LVI/PDA

Histopathological analysis of the small lesion group revealed sm-deep cancer in 90 (75%) cases, LVI in 26 (22%) and PDA in 12 (10%). Similarly, the large lesion group exhibited sm-deep cancer in 380 (82%) cases, LVI in 125 (27%), and PDA in 79 (17%). Therefore, in relation to depth of invasion, LVI and PDA, there were no significant differences between the groups.

Treatment strategy

Among the small lesion group, 62 (52%) cases were initially treated with endoscopic mucosal resection (EMR), while 58 (48%) cases were surgically resected. In contrast, among the large lesion group, 133 (29%) cases were initially treated with EMR, while 330 (71%) cases were surgically resected. Among all lesions treated by EMR, there were no differences in the rate of positive and unknown vertical and/or lateral cut margins in the small (18%, 11/62) and large lesion groups (20%, 26/133). Furthermore, among all positive cut margin cases in the small and large lesion groups, there were 11 (100%) and 18 (69%) positive vertical margin cases (Table 3, Figures 1 and 2).

Table 1 Comparison of clinicopathological and endoscopic characteristics for 583 study cases

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
No. of lesions, *n* (%)	120 (21)	463 (79)	
Gender (M/F)	85/35	289/174	0.09
Age (yr), mean (range)	61.5 (39-84)	62.4 (30-90)	0.86
Macroscopic type, *n* (%)			
Sessile (0-Ⅰs, Ⅰs+Ⅱa)	51 (42)	233 (50)	0.13
Flat (0-Ⅱa)	14 (12)	64 (14)	
Depressed (0-Ⅱc, Ⅱa+Ⅱc, Ⅰs+Ⅱc)	55 (46)	166 (36)	
Size (mm), mean ± SD	8.3 ± 1.6	22.1 ± 9.6	
Growth pattern (PG/NPG)	38/82	250/213	< 0.0001
Location, *n* (%)			
Rectum	33 (27)	213 (46)	0.02
Distal colon[1]	56 (47)	139 (30)	
Proximal colon[2]	31 (26)	111 (24)	

[1]Descending-sigmoid colon; [2]Cecum-transverse colon.

Table 3 Comparison of treatment strategy and positive rate of cut margin *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
Initial treatment			
EMR	62 (52)	133 (29)	< 0.0001
Surgery	58 (48)	330 (71)	
Positive rate of cut margin[1]	11 (18)	26 (20)	0.81
In EMR cases			
Lateral	0 (0)	8 (31)	0.08
Vertical	11 (100)	18 (69)	

[1]Positive and unknown cut margin. EMR: Endoscopic mucosal resection.

According to the initial treatment, there were 134 (69%) and 336 (87%) sm-deep cancers in the EMR and surgery groups, respectively. Furthermore, there were 33 (17%) and 118 (30%) LVI-positive, and 18 (9%) and 73 (19%) PDA-positive cases in the EMR and surgery groups, respectively. There were 37 (19%) positive cut margin cases, including 29 (78%) positive vertical margins in the EMR group. In contrast, there were no positive cut margin cases in the surgery group. In the EMR group, 82 (42%) patients underwent additional surgery with LN dissection after EMR within 6 mo. The incidence of LNM was 11.0% (9/82) and 12.1% (47/388) in the EMR and surgery groups, respectively ($P = 0.79$) (Table 4).

DISCUSSION

Several authors have reported a strong association between lesion size and submucosal invasion or risk of LNM when referring to the grade of malignancy of early CRC. Large lesion size has been considered an indicator of deep submucosal invasion and presence of LNM. However, in this large retrospective study, small EI-CRC demonstrated a similar aggressive behavior and malignant potential to those of large lesions, with a similar risk of LNM , LVI and PDA among both groups.

Intramucosal CRC is thought generally to have no potential for LNM. In contrast, it has been reported that

Table 2 Incidence of LNM and clinicopathological characteristics based on tumor size *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
LNM	10/89 (11.2)	46/381 (12.1)	0.85
Depth of invasion			
sm-superficial (< 1000 μm)	30 (25)	83 (18)	0.08
sm-deep (≥ 1000 μm)	90 (75)	380 (82)	
LVI	26 (22)	125 (27)	0.23
PDA	12 (10)	79 (17)	0.06

LVI: Lymphovascular invasion; PDA: Poorly differentiated adenocarcinoma; LNM: Lymph node metastasis.

Table 4 Comparison of clinicopathological characteristics and incidence of LNM based on the treatment strategy *n* (%)

	EMR (*n* = 195)	Surgery (*n* = 388)	*P* value
Depth of invasion			
sm-superficial (< 1000 μm)	61 (32)	52 (13)	< 0.0001
sm-deep (≥ 1000 μm)	134 (69)	336 (87)	
LVI	33 (17)	118 (30)	0.0006
PDA	18 (9)	73 (19)	0.0006
Positive rate of cut margin[1]	37 (19)	0 (0)	< 0.0001
Lateral	8 (22)	0 (0)	
Vertical	29 (78)	0 (0)	
Additional surgical operation	82 (42)	-	
LNM	9/82 (11.0)	47/388 (12.1)	0.79

[1]Positive and unknown cut margin.

LNM occurs in 6%-13% of patients with submucosal invasive CRC[11-15]. Therefore, radical surgery with LN dissection is recommended strongly in these cases. At present, EMR provides an endoscopic cure of early stage CRC when there is no risk of LNM. Advances in endoscopic instruments and techniques have increased the detection rates of early stage CRC and have expanded the indications for EMR[16].

In the past 20 years, many investigators have proposed the following histopathological criteria when considering additional surgery after EMR of submucosal cancers: massive submucosal invasion (≥ 1000 μm), and/or LVI, and/or PDA[17-22]. Among these factors, LVI and PDA are impossible to predict before resection. At this point, it is crucial to predict the vertical depth of invasion of submucosal cancers prior to EMR. In our center, we use routinely a magnifying colonoscope to decide on the adequate treatment of early stage CRC. Magnifying chromoendoscopy (MCE) is a standardized validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern), in a simple and rapid manner. We have reported previously the efficacy of MCE to diagnose an invasive pattern as a typical finding of sm-deep cancers, and have demonstrated that it provides a good correlation between pit pattern and tumor depth in flat and depressed CRC[23-27].

Many authors have reported that depressed and/or NPG type lesions are considered to have a high malignant potential, compared to the polypoid type lesions of similar

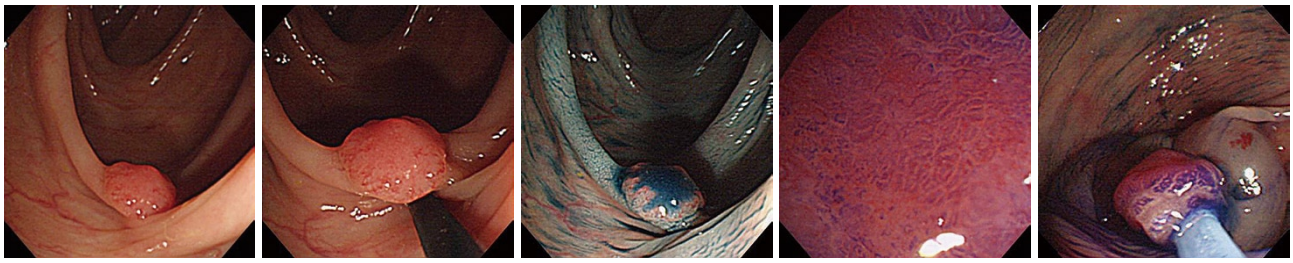

Figure 1 The lesion was located in the transverse colon. Endoscopic examination revealed a flat, elevated lesion with a central depression, which was macroscopically diagnosed as 0-Ⅱa+Ⅱc. The high-magnification view revealed a typical type Ⅵ pit (invasive) pattern on the depressed margin. The final endoscopic diagnosis was a 0-Ⅱa+Ⅱc type early colon cancer with submucosal deep invasion. However, patient strongly hoped EMR as an initial treatment. We performed EMR after injecting normal saline into the submucosa.

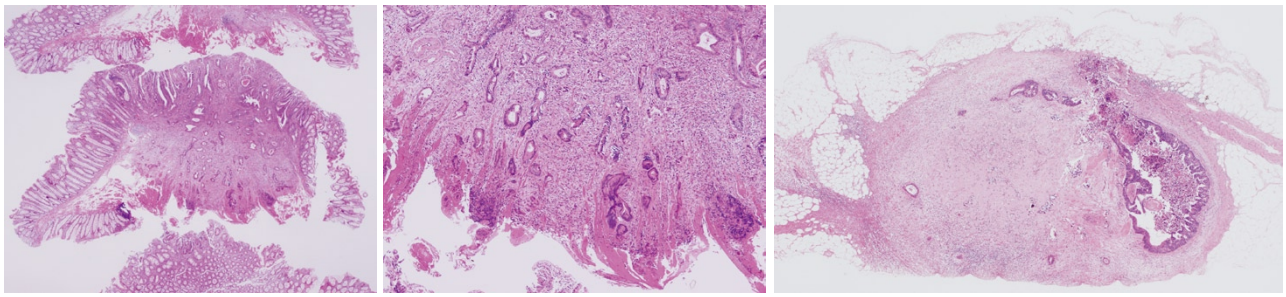

Figure 2 The final histopathological diagnosis was early invasive colon cancer, well-differentiated adenocarcinoma, sm-deep, NPG type, ly (-), v (-), cut end (+) (vertical margin positive). Since cancer was exposed in the vertical cut margin, additional surgical resection was performed and LNM was detected.

size[4,28-31]. Kurisu *et al*[20] have investigated the development and progression of EI-CRC. In that study, NPG lesions were significantly smaller in size (14.2 mm *vs* 24.2 mm) but showed deeper infiltration than PG types. They concluded that tumor development and the degree of invasion differed significantly between the two types of carcinoma. On the other hand, non-polypoid colorectal neoplasms (NP-CRNs) have been reported recently in the United States. Soetikno *et al*[31] have reported the prevalence of NP-CRNs in a veterans' hospital population. The overall prevalence of NP-CRNs and NP-CRNs with in situ or submucosal invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (OR: 9.78) than polypoid lesions, regardless of size. In the present study, small EI-CRCs ≤ 10 mm in diameter showed a significantly higher incidence of NPG type lesions than in the large lesion group ($P < 0.0001$). However, there was no significant difference in proportion of the macroscopic type between the groups ($P = 0.13$). Among the lesions diagnosed as Is type (sessile) in the small lesions group, 47% (14/30) were classified as NPG type histopathologically. From these results, we conclude that further investigation is required to confirm the growth pattern, especially for small sessile lesions diagnosed during colonoscopy.

In contrast, the rate of EMR as an initial treatment was 33% (195/583) in our study. In particular, it was significantly higher in the small lesion than the large lesion group (52% *vs* 29%, $P < 0.0001$). Among the 195 lesions removed by EMR as an initial treatment in both groups, 61 cases (32%) were sm-superficial cancers. On the other hand, there was no significant difference in the positive rate of cut margins between the small and large lesion groups (18% *vs* 20%). This result implies that EMR should not be performed readily for EI-CRC, from the viewpoint of no-touch isolation[32] and EMR complications. Intramucosal lesions (adenoma or intramucosal cancer) are usually well lifted by submucosal injection. In contrast, invasive cancer, especially sm-deep cancer, cannot be lifted because of the presence of submucosal fibrosis or desmoplastic reaction. Uno *et al*[33] have reported this phenomenon as the "non-lifting sign". Kobayashi *et al*[34] have reported, among 271 colorectal neoplastic lesions, that the non-lifting sign of deeper infiltration had a sensitivity of 61.5%, specificity of 98.4%, and accuracy of 94.8%. In contrast, endoscopic diagnosis had a sensitivity of 84.6%, specificity of 98.8%, and accuracy of 97.4%, with statistically significant differences in terms of sensitivity and accuracy. Furthermore, since submucosal injection varies depending on the expertise of the endoscopist, we consider that an endoscopic diagnosis is much more important and accurate when endoscopic resection is considered as the therapeutic option.

There are some limitations to this study. Firstly, this was a single-center study, and although the number of examined EI-CRCs was adequate, a multicenter analysis should be performed to clarify the clinical importance of small EI-CRCs. In addition, this study was carried out retrospectively between 1980 and 2004. In relation to endoscopic treatment for early CRC, endoscopic submucosal dissection (ESD) technique and Glycerol/Sodium hyaluronate as an injected solution during EMR has made progress recently[35,36]. In particular, ESD provides not only an *en bloc* large specimen but also

negative lateral and vertical cut margins.

In conclusion, with regard to the risk of LNM, small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions. Moreover, from the perspective of the concept of no-touch isolation, therapeutic cost, and complications during EMR, special attention must be paid when treating even small early stage lesions, especially NPG type lesions.

COMMENTS

Background

In general, small colorectal lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size.

Research frontiers

The aim of this retrospective study was to clarify the clinicopathological characteristics of small (≤ 10 mm) and large (> 10 mm) EI-CRCs.

Innovations and breakthroughs

A total of 583 EI-CRCs were evaluated retrospectively, with 120 (21%) small and 463 (79%) large lesions identified. With regard to the risk of lymph-node metastasis (LNM), small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions.

Peer review

The authors examined retrospectively a large group of patients with EI-CRCs gathered over 20 years in a national cancer hospital, and demonstrated that small EI-CRCs (≤ 10 mm) had the same aggressiveness and malignant potential as large cancers. Special attention must be paid when treating even small lesions.

REFERENCES

1 **Tanaka S**, Yokota T, Saito D, Okamoto S, Oguro Y, Yoshida S. Clinicopathologic features of early rectal carcinoma and indications for endoscopic treatment. *Dis Colon Rectum* 1995; **38**: 959-963

2 **Saito Y**, Fujii T, Kondo H, Mukai H, Yokota T, Kozu T, Saito D. Endoscopic treatment for laterally spreading tumors in the colon. *Endoscopy* 2001; **33**: 682-686

3 **Uraoka T**, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut* 2006; **55**: 1592-1597

4 **Kudo S**, Kashida H, Tamura T, Kogure E, Imai Y, Yamano H, Hart AR. Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. *World J Surg* 2000; **24**: 1081-1090

5 **Hurlstone DP**, Cross SS, Adam I, Shorthouse AJ, Brown S, Sanders DS, Lobo AJ. A prospective clinicopathological and endoscopic evaluation of flat and depressed colorectal lesions in the United Kingdom. *Am J Gastroenterol* 2003; **98**: 2543-2549

6 **Soetikno R**, Friedland S, Kaltenbach T, Chayama K, Tanaka S. Nonpolypoid (flat and depressed) colorectal neoplasms. *Gastroenterology* 2006; **130**: 566-576; quiz 588-589

7 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-S43

8 **Hamilton SR**, Aaltonen LA, editors. World Health Organization classification of tumours: pathology and genetics of tumours of the digestive system. Lyon: IARC Press, 2000: 104-119

9 **Kitajima K**, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004; **39**: 534-543

10 **Shimoda T**, Ikegami M, Fujisaki J, Matsui T, Aizawa S, Ishikawa E. Early colorectal carcinoma with special reference to its development de novo. *Cancer* 1989; **64**: 1138-1146

11 **Kyzer S**, Bégin LR, Gordon PH, Mitmaker B. The care of patients with colorectal polyps that contain invasive adenocarcinoma. Endoscopic polypectomy or colectomy? *Cancer* 1992; **70**: 2044-2050

12 **Minamoto T**, Mai M, Ogino T, Sawaguchi K, Ohta T, Fujimoto T, Takahashi Y. Early invasive colorectal carcinomas metastatic to the lymph node with attention to their nonpolypoid development. *Am J Gastroenterol* 1993; **88**: 1035-1039

13 **Cooper HS**. Surgical pathology of endoscopically removed malignant polyps of the colon and rectum. *Am J Surg Pathol* 1983; **7**: 613-623

14 **Nusko G**, Mansmann U, Partzsch U, Altendorf-Hofmann A, Groitl H, Wittekind C, Ell C, Hahn EG. Invasive carcinoma in colorectal adenomas: multivariate analysis of patient and adenoma characteristics. *Endoscopy* 1997; **29**: 626-631

15 **Nascimbeni R**, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002; **45**: 200-206

16 **Tanaka S**, Haruma K, Teixeira CR, Tatsuta S, Ohtsu N, Hiraga Y, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F. Endoscopic treatment of submucosal invasive colorectal carcinoma with special reference to risk factors for lymph node metastasis. *J Gastroenterol* 1995; **30**: 710-717

17 **Morson BC**, Whiteway JE, Jones EA, Macrae FA, Williams CB. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. *Gut* 1984; **25**: 437-444

18 **Fujimori T**, Kawamata H, Kashida H. Precancerous lesions of the colorectum. *J Gastroenterol* 2001; **36**: 587-594

19 **Coverlizza S**, Risio M, Ferrari A, Fenoglio-Preiser CM, Rossini FP. Colorectal adenomas containing invasive carcinoma. Pathologic assessment of lymph node metastatic potential. *Cancer* 1989; **64**: 1937-1947

20 **Cranley JP**, Petras RE, Carey WD, Paradis K, Sivak MV. When is endoscopic polypectomy adequate therapy for colonic polyps containing invasive carcinoma? *Gastroenterology* 1986; **91**: 419-427

21 **Nivatvongs S**, Rojanasakul A, Reiman HM, Dozois RR, Wolff BG, Pemberton JH, Beart RW Jr, Jacques LF. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. *Dis Colon Rectum* 1991; **34**: 323-328

22 **Netzer P**, Forster C, Biral R, Ruchti C, Neuweiler J, Stauffer E, Schönegg R, Maurer C, Hüsler J, Halter F, Schmassmann A. Risk factor assessment of endoscopically removed malignant colorectal polyps. *Gut* 1998; **43**: 669-674

23 **Fujii T**, Hasegawa RT, Saitoh Y, Fleischer D, Saito Y, Sano Y, Kato S. Chromoscopy during colonoscopy. *Endoscopy* 2001; **33**: 1036-1041

24 **Kato S**, Fujii T, Koba I, Sano Y, Fu KI, Parra-Blanco A, Tajiri H, Yoshida S, Rembacken B. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? *Endoscopy* 2001; **33**: 306-310

25 **Matsuda T**, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, Ikehara H, Ikematsu H, Fu KI, Emura F, Ono A, Sano Y, Shimoda T, Fujimori T. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. *Am J Gastroenterol* 2008; **103**: 2700-2706

26 **Kato S**, Fu KI, Sano Y, Fujii T, Saito Y, Matsuda T, Koba I, Yoshida S, Fujimori T. Magnifying colonoscopy as a non-biopsy technique for differential diagnosis of non-neoplastic and neoplastic lesions. *World J Gastroenterol* 2006; **12**: 1416-1420

27 **Fu KI**, Kato S, Sano Y, Onuma EK, Saito Y, Matsuda T, Koba I, Yoshida S, Fujii T. Staging of early colorectal cancers: magnifying colonoscopy versus endoscopic ultrasonography for estimation of depth of invasion. *Dig Dis Sci* 2008; **53**:

1886-1892
28 **Kurisu Y**, Shimoda T, Ochiai A, Nakanishi Y, Hirata I, Katsu KI. Histologic and immunohistochemical analysis of early submucosal invasive carcinoma of the colon and rectum. *Pathol Int* 1999; **49**: 608-616
29 **Saitoh Y**, Waxman I, West AB, Popnikolov NK, Gatalica Z, Watari J, Obara T, Kohgo Y, Pasricha PJ. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology* 2001; **120**: 1657-1665
30 **Tsuda S**, Veress B, Tóth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. *Gut* 2002; **51**: 550-555
31 **Soetikno RM**, Kaltenbach T, Rouse RV, Park W, Maheshwari A, Sato T, Matsui S, Friedland S. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *JAMA* 2008; **299**: 1027-1035
32 **Wiggers T**, Jeekel J, Arends JW, Brinkhorst AP, Kluck HM, Luyk CI, Munting JD, Povel JA, Rutten AP, Volovics A. No-touch isolation technique in colon cancer: a controlled prospective trial. *Br J Surg* 1988; **75**: 409-415
33 **Uno Y**, Munakata A. The non-lifting sign of invasive colon cancer. *Gastrointest Endosc* 1994; **40**: 485-489
34 **Kobayashi N**, Saito Y, Sano Y, Uragami N, Michita T, Nasu J, Matsuda T, Fu KI, Fujii T, Fujimori T, Ishikawa T, Saito D. Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non-lifting sign for diagnosing invasion depth? *Endoscopy* 2007; **39**: 701-705
35 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973
36 **Uraoka T**, Fujii T, Saito Y, Sumiyoshi T, Emura F, Bhandari P, Matsuda T, Fu KI, Saito D. Effectiveness of glycerol as a submucosal injection for EMR. *Gastrointest Endosc* 2005; **61**: 736-740

S- Editor Tian L **L- Editor** Kerr C **E- Editor** Lin YP