World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i46.8468

World J Gastroenterol 2013 December 14; 19(46): 8468-8473
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Early stage colon cancer

Hugh James Freeman

Hugh James Freeman, Department of Medicine, University of British Columbia, Vancouver V6T 1W5, Canada
Author contributions: Freeman HJ solely contributed to this paper.
Correspondence to: Hugh James Freeman, MD, CM, FRCPC, FACP, Professor, Department of Medicine, University of British Columbia, 2211 Wesbrook Mall, Vancouver V6T 1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216 Fax: +1-604-8227236
Received: September 29, 2013 Revised: November 6, 2013
Accepted: November 28, 2013
Published online: December 14, 2013

Abstract

Evidence has now accumulated that colonoscopy and removal of polyps, especially during screening and surveillance programs, is effective in overall risk reduction for colon cancer. After resection of malignant pedunculated colon polyps or early stage colon cancers, long-term repeated surveillance programs can also lead to detection and removal of asymptomatic high risk advanced adenomas and new early stage metachronous cancers. Early stage colon cancer can be defined as disease that appears to have been completely resected with no subsequent evidence of involvement of adjacent organs, lymph nodes or distant sites. This differs from the clinical setting of an apparent "curative" resection later pathologically upstaged following detection of malignant cells extending into adjacent organs, peritoneum, lymph nodes or other distant sites, including liver. This highly selected early stage colon cancer group remains at high risk for subsequent colon polyps and metachronous colon cancer. Precise staging is important, not only for assessing the need for adjuvant chemotherapy, but also for patient selection for continued surveillance. With advanced stages of colon cancer and a more guarded outlook, repeated surveillance should be limited. In future, novel imaging technologies (*e.g.*, confocal endomicroscopy), coupled with increased pathological recognition of high risk markers for lymph node involvement (*e.g.*, "tumor budding") should lead to improved staging and clinical care.

Key words: Colon cancer; Node-negative colon cancer; Staging of colon cancer; Nodal micrometastases; Follow-up and surveillance of early colon cancer

Core tip: Evidence has now accumulated that colonoscopy and removal of polyps, especially during screening and surveillance programs, is effective in overall risk reduction for colon cancer. After resection of malignant pedunculated colon polyps or early stage colon cancers, long-term repeated surveillance programs can also lead to detection and removal of asymptomatic high risk advanced adenomas and new early stage metachronous cancers. In future, novel imaging technologies (*e.g.*, confocal endomicroscopy), coupled with increased pathological recognition of high risk markers for lymph node involvement (*e.g.*, "tumor budding") should lead to improved staging and clinical care.

Freeman HJ. Early stage colon cancer. *World J Gastroenterol* 2013; 19(46): 8468-8473 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i46/8468.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i46.8468

INTRODUCTION

Adenocarcinoma of the colon, including rectum, is a major cause of morbidity and mortality among all internal malignant diseases in men and women. When the disease is at an advanced stage with documented metastatic involvement of lymph nodes or other organs, the prognosis is especially dismal. A number of different staging criteria have been used to estimate the depth of cancer penetration in the colon as well as the extent of extracolonic disease involvement. Currently, a commonly used

Table 1 Colon cancer staging

AJCC stage	TNM stage	TNM criteria
Stage 0	Tis N0 M0	Tumor confined to mucosa
Stage Ⅰ	T1 N0 M0	Tumor invades submucosa
Stage Ⅰ	T2 N0 M0	Tumor invades muscularis propria
Stage ⅡA	T3 N0 M0	Tumor invades subserosa
Stage ⅡB	T4 N0 M0	Tumor invades adjacent organs
Stage ⅢA	T1-2 N1 M0	Tumor metastases to 1-3 nodes
Stage ⅢB	T3-4 N1 M0	Tumor metastases to 1-3 nodes
Stage ⅢC	Any T, N2, M0	Tumor metastases to 4 or more nodes
Stage Ⅳ	Any T or N, M1	Metastases to distant sites

AJCC: American Joint Committee on Cancer; TNM: Tumor/Nodes/Metastases. Other classification methods include: Dukes System: A, tumor confined to intestinal wall; B, tumor invading through the intestinal wall; C, tumor with lymph node involvement; D, tumor with distant metastases; and Astler-Coller System: A, Tumor limited to mucosa; B1, Tumor through muscularis mucosa but not muscularis propria; B2, Tumor beyond muscularis propria; C1, B1 with lymph node metastases; C2, B2 with lymph node metastases; D, Distant metastases. Other criteria include: venous and lymphatic invasion and differentiation.

staging method for colon cancer is based on the TNM (tumor/node/metastases) system as delineated by the American Joint Committee on Cancer (AJCC), now with a staging manual and atlas in its 7th edition[1]. These different AJCC stages are summarized in Table 1.

EARLY STAGE COLON CANCER

Early stage colon cancer can be defined as disease that appears to have been completely resected with no subsequent evidence of involvement of adjacent organs, lymph nodes or distant sites. This definition differs from the clinical setting of an apparent "curative" resection later pathologically upstaged following detection of malignant cells extending into adjacent organs, peritoneum, lymph nodes, or other distant sites, including the liver.

This highly-selected group with disease localized in the colon still remains at especially high risk for subsequent development of colon polyps and metachronous colon cancer. Conceptually, this definition of early stage disease reflects increasing use of colonoscopic surveillance as an important tool in an emerging management approach. Precise staging, however, is critical, not only in assessing the need for adjuvant chemotherapy, but also for the selection of patients for continued surveillance. In patients with advanced stages of colon cancer and a more guarded outlook, repeated surveillance should be limited.

IMAGING METHODS

Although imaging methods are important in defining suspected areas of involvement, complete staging currently requires pathological assessment of resected tissue, particularly to define early stage disease. Usually staging has been estimated after surgical removal of the colon cancer, however, experience has shown that complete staging is also possible after endoscopic resection of a malignant pedunculated polyp that has minimal invasion. For these malignant polyps, however, deep histopathological assessment is not possible and lymph nodes are not removed. Further upstaging of colon cancer may result from employment of ultrasound, computed tomography (CT), magnetic resonance imaging or position emission tomography with pathological confirmation. In contrast, studies have already confirmed that methods such as fecal immunochemical testing (FIT) or CT have limited value in the detection of early stage colon cancer. For example, a high rate of false-negative results with FIT for early stage cancers was recently recorded[2] and CT was shown to have a low sensitivity for diagnosis of early T1 or T2 cancers[3].

Studies to explore staging using evolving endoscopic methods have also appeared. For example, a recent report[4] compared new techniques for assessment of the actual depth of colon cancer invasion. Magnification chromoendoscopy and endoscopic ultrasound were found to have similar accuracy in estimating the depth of invasion, but neither procedure was believed to currently have sufficient diagnostic accuracy for use as a reliable or recommended standard[4]. Further investigative efforts are needed to explore novel and emerging imaging developments, particularly endoscope-based or probe-based confocal endomicroscopic methods. These offer the possibility for more rapid (and possibly for economical) differentiation of neoplastic from non-neoplastic colonic disease, earlier diagnosis of colorectal cancer, further evaluation of degree of differentiation and estimation of invasion depth for early colorectal cancer[5-8].

OUTCOME OF STAGING

Evidence has accumulated to show that a more advanced cancer stage is correlated with a worse clinical outcome. In patients with localized and limited disease confined to the submucosa or muscularis propria, the overall 5 year survival is about 70%. With more advanced disease extending beyond the subserosa into adjacent structures, peritoneum, lymph nodes or distant sites, the overall 5 year survival is about 30%. Even in early stage colorectal cancer, bowel perforation from the tumor itself or anastomotic leakage following surgery is associated with increased recurrence rates and an impaired disease-free survival[9].

Early detection of colon cancer has been an important goal for physicians evaluating patients at increased risk for colon cancer. Colonoscopic regimens of surveillance have emerged based on good evidence that morbidity and mortality can be improved[10,11]. A number of guidelines have been developed for endoscopic surveillance of high risk groups to detect colon cancer. Some high risk categories have included a documented personal and family history of colon adenomas and colon cancer as well as inflammatory bowel disease. Among these high risk groups, a prior history of a completely resected colon cancer is a special group that should be considered for regular surveillance, particularly for those with early

stage disease[12]. Most important, recent publications have provided good evidence that colonoscopy is associated with reduced colorectal cancer mortality[13,14]. In addition, persistent and sustained reduction in colorectal cancer mortality has been attributed, in large part, to the effect of polypectomy[14]. For malignant colorectal polyps with localized submucosal invasion, similar long-term results have been recorded, although a risk for new colon polyps, including advanced adenomas, and metachronous colon cancer persists[15].

SURVEILLANCE AFTER COLON CANCER RESECTION

Earlier randomized clinical trials compared intense with less intense surveillance after a "curative" resection[16-20]. Unfortunately, a number of methodological flaws in these studies were noted[21], particularly the inclusion of both early- (*i.e.*, node-negative) and late- (*i.e.*, node-positive) stage disease together in the comparison groups, regardless of the intensity of later surveillance. Perhaps, in these earlier studies, evaluation of more homogeneous populations, particularly with early-stage colon cancer, would have shown a positive effect of surveillance because prognosis for patients with nodal involvement, invasion of other structures and distant metastases would be expected to be much more limited[21]. Moreover, a more recent Cochrane evaluation has suggested a survival benefit for selected patients with more intense follow-up[22]. Finally, long-term studies of symptomatic early stage colon cancer patients followed over more than 10 years[23] demonstrated no locally recurrent disease. However, in the same study[23], there was still an ongoing risk for new and asymptomatic neoplasms, including advanced adenomas and early-stage metachronous colon cancers.

RISK OF LYMPH NODE METASTASES

A number of factors critical to accurate clinical and pathological staging have been explored in recent years, especially definition of high risk factors for lymph node involvement, if only early stage colon cancer with submucosal invasion (or T1) disease appears to be present. These factors include lymphatic invasion, venous invasion, tumor budding, poor tumor differentiation, extent (especially width) of submucosal invasion, complete disruption of muscularis mucosa. Indeed, some studies have suggested that up to 16% with localized submucosal invasive disease may already have lymph node metastases[24-30].

For malignant pedunculated colon polyps, Haggitt *et al*[24] initially proposed a 4-level classification defined by increasing depths of cancer invasion into the submucosa, particularly if deeper than the polyp stalk. Level 4 invasion into the submucosa was thought to represent the highest risk for lymph node metastases. Some have used alternative measures of depth of invasion to ensure complete electrocautery removal of malignant pedunculated polyps. For example, a distance from the leading invasive margin of the cancer to the cautery line of more than 2 mm has been empirically used as a guideline of an adequate resection of a pedunculated lesion with a stalk. If the cautery line is involved with malignant cells after removal of a malignant polyp, colectomy should be done.

For non-polypoid malignant lesions with submucosal invasion, assessment is more difficult. In these, level 4 invasion was traditionally defined[24]. Others have suggested a different classification schema, especially for surgically-resected specimens, defined by submucosal depth of invasion (*i.e.*, specifically, sm1, sm2, sm3) with greatest depth of invasion having greatest risk for lymph node involvement[27,31]. For endoscopic resection, complete removal of the submucosa may be more difficult pathologically to define, although a retrospective evaluation of colorectal cancer initially treated with endoscopic resection suggested that a positive vertical (rather than lateral) resection margin and inadequate lifting sign were positively correlated with risk of residual tumor and lymph node metastases[32]. Other pathological risk factors for node metastases have also been emphasized include venous or lymphatic invasion, moderately or poorly differentiated tumor grade, tumor "budding" at the submucosal invasive front of the cancer, or a completely cancer-disrupted muscularis mucosa[33]. A high CEA value may also be predictive of metastatic disease[34,35]. Because of this increased risk for node involvement after endoscopic resection with these high risk factors, colectomy may be recommended to ensure complete cancer removal and permit more detailed node sampling for metastatic disease.

TUMOR BUDDING AND OTHER RISK FACTORS

"Tumor budding" is an independent prognostic indicator of risk for lymph node involvement, especially in early TNM stage colorectal cancer, as recently emphasized by expert pathologists[36]. This description of "tumor budding" was attributed to Imai who first postulated that this particular pathological feature of an invasive colon cancer represented a sudden or rapid growth of the leading or invasive edge of a carcinoma, in part, related to an interaction between epithelial and mesenchymal elements at the tumor margin[36]. Evidence has accumulated that tumor budding as well as high tumor grade or lymphovascular invasion are independent risk factors for lymph node metastases in patients with submucosally invasive colon cancer[37,38]. Patients with none of these high risk pathological features had only rare lymph node metastases (less than 1%) whereas the risk increased substantially with one (*i.e.*, about 20%) or multiple (*i.e.*, almost 40%) risk factors. In addition, this study showed that absence of extensive, particularly lateral, submucosal invasion (specifically, < 4 mm in width and < 2 mm in depth), had no apparent risk of metastases to lymph nodes (using an-

ti-cytokeratin immunohistochemical staining method for detection of lymph node micrometastases) if other high risk markers were absent. Similar observations have been independently reported[39-42], including a recent evaluation following endoscopic removal of submucosal invasive T1 colorectal cancers[43].

In future, the clinical relevance of other clinical and pathological methods of evaluation for staging, including stage II colon cancer, will need additional evaluation. These include number of lymph nodes surgically harvested[44-47], techniques used for lymph node evaluation (including detection of micrometastases with novel immunohistochemical stains and polymerase chain reaction methods)[48-51] as well as definition of the precise role of sentinel node mapping for node sampling[52-54] and final staging.

CONCLUSION

Colonoscopy screening and surveillance have a documented benefit in reducing the risk of colon cancer. As a result, more early stage colon cancers will be detected in surveillance programs and treated with endoscopic methods. Emerging imaging technologies, such as confocal endomicroscopic methods, may lead to further refinements in definition of patients with early stage disease as well their management. Pathological staging to define early stage disease also continues to evolve, particularly with the increased recognition of risk factors for lymph node disease in early stage colon cancers and immunohistochemical methods for lymph node evaluation, especially detection of lymph node micrometastases.

REFERENCES

1 **Compton CC**, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. Colon and Rectum (Sarcomas, lymphomas, and carcinoid tumors of the large intestine are not included). In: AJCC Cancer Staging Atlas. New York: Springer, 2012: 185-202 [DOI: 10.1007/978-1-4614-2080-4_14]

2 **Chiu HM**, Lee YC, Tu CH, Chen CC, Tseng PH, Liang JT, Shun CT, Lin JT, Wu MS. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. *Clin Gastroenterol Hepatol* 2013; **11**: 832-8.e1-832-8.e2 [PMID: 23376002 DOI: 10.1016/j.cgh.2013.01.013]

3 **Lao IH**, Chao H, Wang YJ, Mak CW, Tzeng WS, Wu RH, Chang ST, Fang JL. Computed tomography has low sensitivity for the diagnosis of early colon cancer. *Colorectal Dis* 2013; **15**: 807-811 [PMID: 23350992 DOI: 10.1111/codi.12140]

4 **Shimura T**, Ebi M, Yamada T, Hirata Y, Nishiwaki H, Mizushima T, Asukai K, Togawa S, Takahashi S, Joh T. Magnifying Chromoendoscopy and Endoscopic Ultrasonography Measure Invasion Depth of Early-Stage Colorectal Cancer with Equal Accuracy, Based on a Prospective Trial. *Clin Gastroenterol Hepatol* 2013; Epub ahead of print [PMID: 23872238 DOI: 10.1016/j.cgh.2013.06.022]

5 **André B**, Vercauteren T, Buchner AM, Krishna M, Ayache N, Wallace MB. Software for automated classification of probe-based confocal laser endomicroscopy videos of colorectal polyps. *World J Gastroenterol* 2012; **18**: 5560-5569 [PMID: 23112548 DOI: 10.3748/wjg.v18.i39.5560]

6 **Liu C**, Li CQ, Zuo XL, Ji R, Xie XJ, Yang YS, Li YQ. Confocal laser endomicroscopy for the diagnosis of colorectal cancer in vivo. *J Dig Dis* 2013; **14**: 259-265 [PMID: 23336610 DOI: 10.111/1751-2980.12039]

7 **Gómez V**, Shahid MW, Krishna M, Heckman MG, Crook JE, Wallace MB. Classification criteria for advanced adenomas of the colon by using probe-based confocal laser endomicroscopy: a preliminary study. *Dis Colon Rectum* 2013; **56**: 967-973 [PMID: 23838865 DOI: 10.1097/DCR.0b013e31829882776]

8 **Dong YY**, Li YQ, Yu YB, Liu J, Li M, Luan XR. Meta-analysis of confocal laser endomicroscopy for the detection of colorectal neoplasia. *Colorectal Dis* 2013; **15**: e488-e495 [PMID: 23810105 DOI: 10.111/codi.12329]

9 **Belt EJ**, Stockmann HB, Abis GS, de Boer JM, de Lange-de Klerk ES, van Egmond M, Meijer GA, Oosterling SJ. Perioperative bowel perforation in early stage colon cancer is associated with an adverse oncological outcome. *J Gastrointest Surg* 2012; **16**: 2260-2266 [PMID: 23093449 DOI: 10.1007/s11605-012-2053-9]

10 **Winawer SJ**, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977-1981 [PMID: 8247072 DOI: 10.1056/NEJM199312303292701]

11 **Zauber AG**, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]

12 **Rex DK**, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, Burt RW, Byers T, Fletcher RH, Hyman N, Johnson D, Kirk L, Lieberman DA, Levin TR, O'Brien MJ, Simmang C, Thorson AG, Winawer SJ. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2006; **130**: 1865-1871 [PMID: 16697749 DOI: 10.1053/j.gastro.2006.03.013]

13 **Nishihara R**, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BA, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013; **369**: 1095-1105 [PMID: 24047059 DOI: 10.1056/NEJMoa1301969]

14 **Shaukat A**, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, Church TR. Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013; **369**: 1106-1114 [PMID: 24047060 DOI: 10.1056/NEJMoa1300720]

15 **Freeman HJ**. Long-term follow-up of patients with malignant pedunculated colon polyps after colonoscopic polypectomy. *Can J Gastroenterol* 2013; **27**: 20-24 [PMID: 23378979]

16 **Pietra N**, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. *Dis Colon Rectum* 1998; **41**: 1127-1133 [PMID: 9749496]

17 **Mäkelä JT**, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. *Arch Surg* 1995; **130**: 1062-1067 [PMID: 7575117 DOI: 10.1001/archsurg.1995.01430100040009]

18 **Ohlsson B**, Breland U, Ekberg H, Graffner H, Tranberg KG. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. *Dis Colon Rectum* 1995; **38**: 619-626 [PMID: 7774474 DOI: 10.1007/BF02054122]

19 **Schoemaker D**, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT, and chest radiography do not influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998; **114**: 7-14 [PMID: 9428212 DOI: 10.1016/S0016-5085(98)70626-2]

20 **Kjeldsen BJ**, Kronborg O, Fenger C, Jørgensen OD. A prospective randomized study of follow-up after radical sur-

gery for colorectal cancer. *Br J Surg* 1997; **84**: 666-669 [PMID: 9171758 DOI: 10.1002/bjs.1800840523]
21 **Meyerhardt JA**, Mayer RJ. Follow-up strategies after curative resection of colorectal cancer. *Semin Oncol* 2003; **30**: 349-360 [PMID: 12870136 DOI: 10.1016/S0093-7754(03)00095-2]
22 **Jeffery M**, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2007; (**1**): CD002200 [PMID: 17253476]
23 **Freeman HJ**. Natural history and long-term outcomes of patients treated for early stage colorectal cancer. *Can J Gastroenterol* 2013; **27**: 409-413 [PMID: 23862173]
24 **Haggitt RC**, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985; **89**: 328-336 [PMID: 4007423]
25 **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 [PMID: 2477139]
26 **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 [PMID: 11852333 DOI: 10.1007/s10350-004-6147-7]
27 **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 [PMID: 15235870 DOI: 10.1007/s00535-004-1339-4]
28 **Okabe S**, Shia J, Nash G, Wong WD, Guillem JG, Weiser MR, Temple L, Sugihara K, Paty PB. Lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastrointest Surg* 2004; **39**: 534-543
29 **Tominaga K**, Nakanishi Y, Nimura S, Yoshimura K, Sakai Y, Shimoda T. Predictive histopathologic factors for lymph node metastasis in patients with nonpedunculated submucosal invasive colorectal carcinoma. *Dis Colon Rectum* 2005; **48**: 92-100 [PMID: 15690664 DOI: 10.1007/s10350-004-0751-4]
30 **Egashira Y**, Yoshida T, Hirata I, Hamamoto N, Akutagawa H, Takeshita A, Noda N, Kurisu Y, Shibayama Y. Analysis of pathological risk factors for lymph node metastasis of submucosal invasive colon cancer. *Mod Pathol* 2004; **17**: 503-511 [PMID: 15001992 DOI: 10.1038/modpathol.3800030]
31 **Kudo S**. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy* 1993; **25**: 455-461 [PMID: 8261988 DOI: 10.1055/s-2007-1010367]
32 **Kim KM**, Eo SJ, Shim SG, Chang DK, Kim YH, Rhee PL, Kim JJ, Kim JY. Risk factors for residual cancer and lymph node metastasis after noncurative endoscopic resection of early colorectal cancer. *Dis Colon Rectum* 2013; **56**: 35-42 [PMID: 23222278 DOI: 10.1097/DCR.0b013e31826942ee]
33 **Tateishi Y**, Nakanishi Y, Taniguchi H, Shimoda T, Umemura S. Pathological prognostic factors predicting lymph node metastasis in submucosal invasive (T1) colorectal carcinoma. *Mod Pathol* 2010; **23**: 1068-1072 [PMID: 20473277 DOI: 10.1038/modpathol.2010.88]
34 **Fang WL**, Chang SC, Lin JK, Wang HS, Yang SH, Jiang JK, Chen WC, Lin TC. Metastatic potential in T1 and T2 colorectal cancer. *Hepatogastroenterology* 2005; **52**: 1688-1691 [PMID: 16334758]
35 **Lou Z**, Meng RG, Zhang W, Yu ED, Fu CG. Preoperative carcinoembryonic antibody is predictive of distant metastasis in pathologically T1 colorectal cancer after radical surgery. *World J Gastroenterol* 2013; **19**: 389-393 [PMID: 23372362 DOI: 10.3748/wjg.v19.i3.389]
36 **Mitrovic B**, Schaeffer DF, Riddell RH, Kirsch R. Tumor budding in colorectal carcinoma: time to take notice. *Mod Pathol* 2012; **25**: 1315-1325 [PMID: 22790014 DOI: 10.1038/modpathol.2012.94]
37 **Ueno H**, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K, Matsukuma S, Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004; **127**: 385-394 [PMID: 15300569 DOI: 10.1053/j.gastro.2004.04.022]
38 **Ueno H**, Murphy J, Jass JR, Mochizuki H, Talbot IC. Tumour 'budding' as an index to estimate the potential of aggressiveness in rectal cancer. *Histopathology* 2002; **40**: 127-132 [PMID: 11952856 DOI: 10.1046/j.1365-2559.2002.01324.x]
39 **Glasgow SC**, Bleier JI, Burgart LJ, Finne CO, Lowry AC. Meta-analysis of histopathological features of primary colorectal cancers that predict lymph node metastases. *J Gastrointest Surg* 2012; **16**: 1019-1028 [PMID: 22258880 DOI: 10.1007/s11605-012-1827-4]
40 **Kye BH**, Jung JH, Kim HJ, Kang SG, Cho HM, Kim JG. Tumor budding as a risk factor of lymph node metastasis in submucosal invasive T1 colorectal carcinoma: a retrospective study. *BMC Surg* 2012; **12**: 16 [PMID: 22866826 DOI: 10.1186/1471-2482-12-16]
41 **Bosch SL**, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. *Endoscopy* 2013; **45**: 827-834 [PMID: 23884793 DOI: 10.1055/s-0033-1344238]
42 **Mou S**, Soetikno R, Shimoda T, Rouse R, Kaltenbach T. Pathologic predictive factors for lymph node metastasis in submucosal invasive (T1) colorectal cancer: a systematic review and meta-analysis. *Surg Endosc* 2013; **27**: 2692-2703 [PMID: 23392988 DOI: 10.1007/s00464-013-2835-5]
43 **Yoshii S**, Nojima M, Nosho K, Omori S, Kusumi T, Okuda H, Tsukagoshi H, Fujita M, Yamamoto H, Hosokawa M. Factors Associated With Risk for Colorectal Cancer Recurrence After Endoscopic Resection of T1 Tumors. *Clin Gastroenterol Hepatol* 2013; Epub ahead of print [PMID: 23962552 DOI: 10.1016/j.cgh.2013.08.008]
44 **Govindarajan A**, Baxter NN. Lymph node evaluation in early-stage colon cancer. *Clin Colorectal Cancer* 2008; **7**: 240-246 [PMID: 18650192 DOI: 10.3816/CCC.2008.n.031]
45 **Chang GJ**, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 2007; **99**: 433-441 [PMID: 17374833 DOI: 10.1093/jnci/djk092]
46 **Leibl S**, Tsybrovskyy O, Denk H. How many lymph nodes are necessary to stage early and advanced adenocarcinoma of the sigmoid colon and upper rectum? *Virchows Arch* 2003; **443**: 133-138 [PMID: 12844262 DOI: 10.1007/s00428-003-0858-3]
47 **Shanmugam C**, Hines RB, Jhala NC, Katkoori VR, Zhang B, Posey JA, Bumpers HL, Grizzle WE, Eltoum IE, Siegal GP, Manne U. Evaluation of lymph node numbers for adequate staging of Stage II and III colon cancer. *J Hematol Oncol* 2011; **4**: 25 [PMID: 21619690 DOI: 10.1186/1756-8722-4-25]
48 **Jeffers MD**, O'Dowd GM, Mulcahy H, Stagg M, O'Donoghue DP, Toner M. The prognostic significance of immunohistochemically detected lymph node micrometastases in colorectal carcinoma. *J Pathol* 1994; **172**: 183-187 [PMID: 7513353 DOI: 10.1002/path.1711720205]
49 **Park SJ**, Lee KY, Kim SY. Clinical significance of lymph node micrometastasis in stage I and II colon cancer. *Cancer Res Treat* 2008; **40**: 75-80 [PMID: 19688052 DOI: 10.4143/crt.2008.40.2.75]
50 **Bilchik AJ**, Hoon DS, Saha S, Turner RR, Wiese D, DiNome M, Koyanagi K, McCarter M, Shen P, Iddings D, Chen SL, Gonzalez M, Elashoff D, Morton DL. Prognostic impact of micrometastases in colon cancer: interim results of a prospective multicenter trial. *Ann Surg* 2007; **246**: 568-75; discussion 575-7 [PMID: 17893493 DOI: 10.1097/SLA.0b013e318155a9c7]
51 **Faerden AE**, Sjo OH, Bukholm IR, Andersen SN, Svindland

A, Nesbakken A, Bakka A. Lymph node micrometastases and isolated tumor cells influence survival in stage I and II colon cancer. *Dis Colon Rectum* 2011; **54**: 200-206 [PMID: 21228669 DOI: 10.1007/DCR.0b013e3181fd4c7c]

52 **Saha S**, Dan AG, Beutler T, Wiese D, Schochet E, Badin J, Branigan T, Ng P, Bassily N, David D. Sentinel lymph node mapping technique in colon cancer. *Semin Oncol* 2004; **31**: 374-381 [PMID: 15190495 DOI: 10.1053/j.seminoncol.2004.03.008]

53 **Bilchik AJ**, DiNome M, Saha S, Turner RR, Wiese D, McCarter M, Hoon DS, Morton DL. Prospective multicenter trial of staging adequacy in colon cancer: preliminary results. *Arch Surg* 2006; **141**: 527-533; discussion 533-534 [PMID: 16785352 DOI: 10.1001/archsurg.141.6.527]

54 **Bembenek AE**, Rosenberg R, Wagler E, Gretschel S, Sendler A, Siewert JR, Nährig J, Witzigmann H, Hauss J, Knorr C, Dimmler A, Gröne J, Buhr HJ, Haier J, Herbst H, Tepel J, Siphos B, Kleespies A, Koenigsrainer A, Stoecklein NH, Horstmann O, Grützmann R, Imdahl A, Svoboda D, Wittekind C, Schneider W, Wernecke KD, Schlag PM. Sentinel lymph node biopsy in colon cancer: a prospective multicenter trial. *Ann Surg* 2007; **245**: 858-863 [PMID: 17522509 DOI: 10.1097/01.sla.0000250428.46656.7e]

P- Reviewers: Gurvits GE, Rodriguez DC **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Zhang DN

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327