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Original Article

Pathological characteristics and long-term prognosis of submucosal carcinoma of the colon and rectum below 2 cm confirmed by endoscopic submucosal dissection

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Abstract

The purpose of this study was to explore the correlation between additional surgery and the clinicopathological characteristics of colorectal cancer, as well as its impact on patient prognosis. A total of 119 patients with early colorectal cancer were selected and divided into an additional surgery group (28 cases) and a non-additional surgery group (91 cases). According to the tumor size, the patients were further divided into a large diameter group (54 cases, d≥1 cm and <2 cm) and a small diameter group (65 cases, d<1 cm). The clinical and pathological characteristics as well as the prognosis of the patients were statistically analyzed. The results showed that infiltration type, depth of infiltration, and tumor size were correlated with additional surgery (P<0.05). Infiltration type and depth of infiltration were closely related to additional surgery. Differentiation degree, infiltration type, and depth of infiltration were correlated with tumor diameter. Infiltration type was closely related to tumor size. Age, depth of infiltration, and tumor size were correlated with patient survival rates. Infiltration type and depth of infiltration were closely related to patient survival rate (P<0.05). They were independent risk factors affecting patient prognosis. The 5-year disease-free survival rates were 73.33% and 72.5%, respectively, with no statistically significant difference. Infiltration type and depth of infiltration were independent risk factors for recurrence in colorectal cancer patients, while depth of infiltration was an independent risk factor for the 5-year survival rate after surgery. They can be used to predict the prognosis of colorectal cancer and guide clinical treatment as a supplement to the traditional staging of colorectal cancer.

Keywords: Colorectal cancer, Pathological characteristics, Prognosis, Tumor size

1. Introduction

Colorectal cancer, also known as colon cancer, rectal cancer, or colon cancer, is the growth of cancerous cells in the colon or rectum (part of the large intestine). This disease occurs due to the abnormal growth and proliferation of cells. These cells can spread to other tissues of the body (metastasize) or multiply in them. The signs and symptoms of this disease can include things such as blood in the stool (hematochezia), changes in bowel movements and bowel movements, weight loss, and constant fatigue [1].

Most Colorectal cancers are caused by lifestyle factors and aging, and a few cases are caused by inherited genetic disorders. Risk factors include things like diet, obesity, smoking, and lack of physical activity. Dietary factors that increase the risk of this disease include consumption of red meat and processed meats, as well as high alcohol consumption. Another risk factor is inflammatory bowel disease, which includes things like Crohn's disease and ulcerative colitis. Some of the hereditary conditions that cause colon cancer are cases such as familial adenomatous polyps and hereditary non-polyposis colon cancer; But these include less than five percent of cases. This disease usually starts with a benign tumor that turns into cancer over time [1,2].

Colorectal cancer is a common malignant tumor in our country, and in recent years, the incidence and mortality rates of this disease have shown a significant increase trend [1]. Studies have indicated that if colorectal cancer is detected early, patients can achieve a good prognosis, with a 5-year survival rate exceeding 90.00% [2]. Therefore, early detection of early-stage colorectal cancer and the development of more reasonable surgical approaches are crucial for improving the prognosis of patients with colon cancer. This study selected 119 cases of early-stage colorectal cancer patients as the research subjects, aiming to further enhance the clinical efficacy of colorectal cancer through a retrospective analysis of the pathological data after endoscopic resection or additional surgical treatment in our hospital.

2. Materials and methods

2.1. General clinical data

Patients with early-stage colorectal cancer admitted to our hospital from January 2017 to January 2022 were selected.

2.1.1. Inclusion criteria

① Meeting the clinical diagnostic criteria for early-stage colorectal cancer in the "Chinese Consensus on

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Screening, Diagnosis, and Treatment of Early Colorectal Cancer and Precancerous Lesions", confirmed as early-stage colorectal cancer by pathological examination; ② TNM staging is stage I-IIb, with no lymph node or distant metastasis; ③ Lesions are limited to the mucosa or submucosa; ④ Age > 18 years; ⑤ Tumor diameter ≤ 2.0 cm.

2.1.2. Exclusion criteria

① Concurrent other malignant tumors; ② Concurrent liver and kidney dysfunction and coagulation disorders; ③ Lesions invading the muscularis propria; ④ Incomplete medical records.

According to the inclusion and exclusion criteria, a total of 119 patients with early-stage colorectal cancer were included in this study and treated with endoscopic submucosal dissection. According to the above criteria, 72 males and 47 females were included; age ranged from 41 to 73 years with an average of (54.16±6.57) years; tumor diameter ranged from 0.6 to 3.0 cm with an average of (2.35±0.21) cm; lesion locations included rectum (38 cases), sigmoid colon (32 cases), cecum (26 cases), ascending colon (15 cases), descending colon (5 cases), and transverse colon (3 cases). For all patients with recurrence or metastasis, confirmation was made through Doppler ultrasound, CT, MR, colonoscopy, or pathological examination during reoperation. Clinical staging was performed according to the 8th edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) tumor TNM staging criteria published in 2019. This study was approved by the Hospital Ethics Committee, and all patients were properly informed and provided written informed consent.

2.1.3. Grouping criteria

(1) Patients were divided into the additional surgery group (28 cases) and the non-additional surgery group (91 cases) based on whether additional surgery was performed after the initial procedure. (2) Patients were divided into the large diameter group (54 cases, tumor diameter d≥1 cm and <2 cm) and the small diameter group (65 cases, tumor diameter d<1 cm) based on the pathological analysis results of tumor size postoperatively.

2.2. Examination methods

Patients signed informed consent forms for endoscopic examination prior to the procedure. Early diagnosis was performed using endoscopic ultrasonography. Patients fasted for 8 hours before the examination, and bowel preparation was done using a conventional polyethylene glycol electrolyte solution. The patient took the solution until watery stools were passed. Observation was performed after routine insertion of the endoscope, and after identifying the lesion site, the direct contact method, water cushion method, or water insufflation method was used for examination.

2.3. Surgical treatment methods

Preoperative preparation: All patients underwent colonoscopy and histopathological examination, and lymph node and distant organ metastasis were ruled out. Chest X-rays, CT scans of the liver and kidneys, coagulation function tests, electrocardiograms, and other examinations showed no abnormalities. Bowel preparation and examination methods were the same as mentioned above. Surgical procedures: After general anesthesia, the patient underwent marking, submucosal injection, circumferential precutting, en bloc resection of the lesion, and wound closure according to the standard procedure for endoscopic submucosal dissection. The presence of residual tumor tissue at the lateral margin and the basement, lymphovascular invasion, and complete removal of the lesion were observed.

2.4. Postoperative management and follow-up

After surgery, patients received fasting, hemostatic fluid replacement, and preventive measures against infection. The diet was gradually restored based on the patient's condition, and close monitoring of chest and abdominal signs was performed. Patients were followed up for 1 year postoperatively through telephone or outpatient visits. Follow-up included repeat endoscopy, abdominal CT, and chest X-ray to assess lymph node and distant organ metastasis.

2.5. Statistical analysis

SPSS 21.0 was used for statistical analysis of the data. The comparison of clinical and pathological factors between groups was conducted using the chi-square test or Likelihood Ratio correction. Multivariable logistic regression analysis was performed on variables that showed statistical significance. Kaplan-Meier method was used for univariate analysis to calculate and plot survival curves, and differences were assessed using the Log-rank test. Variables with statistically significant differences were included in the Cox proportional hazards regression model. The significance level was set at $\alpha = 0.05$.

3. Results

3.1. Correlation between clinical and pathological factors with additional surgery

The univariate analysis shows that infiltration type, infiltration depth, and tumor size have a correlation with additional surgery, with all $P<0.05$. The results of the multivariate Logistic regression analysis indicate that infiltration type (OR=1.944, 95% CI 1.651-2.289, P=0.048) and infiltration depth (OR=15.37, 95% CI 2.908-23.452, P=0.001) are closely related to additional surgery, both with $P < 0.05$, as shown in Table 1.

3.2. Correlation between clinicopathological factors and tumor size

Univariate analysis showed that the degree of differentiation, infiltration type and infiltration depth were correlated with tumor diameter, all $P<0.05$. The results of multivariate Logistic regression analysis showed that the type of invasion (OR=12.16, 95% CI was 2.671-18.016, P=0.001) was closely related to the tumor size, all $P<0.05$, as shown in Table 2.

3.3. 5-year survival analysis

The results of univariate analysis in Table 3 showed that age, depth of invasion, and tumor size were correlated with patient survival, all $P<0.05$. The results of multivariate Cox regression analysis in Table 4 showed that the type and depth of invasion were closely related to the survival rate of patients, both $P<0.05$; they were independent risk factors affecting the prognosis of patients.

Table 1. Analysis of the correlation between additional surgery in colon cancer and clinical pathological factors.

Clinical pathological features		N	Supplementary group (n=28)	Non-supplementary group (n=91)	χ^2	P
Age	<60	58	13(22.41)	45(77.59)	0.052	0.814
	≥60	61	15(24.59)	46(75.41)		
Gender	Male	72	16(22.22)	56(77.78)	0.237	0.648
	Female	47	12(25.53)	35(74.47)		
General type	Protruding	51	12(23.53)	39(76.47)	0.631	0.371
	Ulcer	62	14(22.58)	48(77.42)		
	Infiltration	6	1(16.67)	5(83.33)		
Differentiation	High + medium differentiation	111	26(23.42)	85(76.58)	0.010	0.919
	low + undifferentiated	8	2(25.00)	6(75.00)		
Histological type	Adenocarcinoma	104	21(23.08)	83(76.92)	3.036	0.081
	Mucinous adenocarcinoma and others	15	7(46.67)	8(53.33)		
Pit type	Vi	76	18(23.68)	58(76.32)	0.014	0.911
	Vn	43	10(23.25)	33(76.75)		
Surgical methods	EMR	30	10(33.33)	20(66.67)	2.347	0.105
	ESD	89	18(20.22)	71(79.78)		
Tumor location	rectum	38	12(31.58)	26(68.42)	0.785	0.249
	ascending colon	15	5(33.33)	10(66.67)		
	Sigmoid colon	32	11(34.38)	21(65.62)		
	descending colon	5	1(20.00)	4(80.00)		
	transverse colon	3	0(0.00)	3(100.00)		
	cecum	26	9(34.62)	17(65.38)		
Tumor size	≥1 cm and <2 cm	54	21(38.89)	33(61.11)	14.921	0.001*
	<1 cm	65	7(3.08)	58(96.92)		
Infiltration depth	pT1+pT2	16	7(343.75)	9(56.25)	4.109	0.040*
Infiltration type	Vascular Infiltration	17	8(47.06)	9(52.94)	6.103	0.014*
	Neural invasion	34	14(31.25)	20(68.75)	2.870	0.004*

Table 2. Correlation analysis between tumor size and clinicopathological factors in colorectal cancer.

Clinical pathological features		N	Large diameter group (n=54)	Small diameter group (n=65)	χ^2	P
Age	<60	58	26(44.82)	32(55.18)	0.117	0.732
	≥60	61	28(45.90)	33(54.10)		
Gender	Male	72	36(50.00)	36(50.00)	1.221	0.168
	Female	47	18(38.29)	29(61.71)		
Types	I	26	12(46.15)	14(53.85)	0.668	0.955
	0-IIa	32	14(43.75)	18(56.25)		
	0-IIb	52	23(44.23)	29(55.77)		
	o-IIc	6	3(50.00)	3(50.00)		
	III	3	2(66.67)	1(33.33)		
Differentiation	High + medium differentiation	111	26(23.42)	85(76.58)	16.31	0.001*
	low + undifferentiated	8	2(25.00)	6(75.00)		
Histological type	Adenocarcinoma	104	47(45.19)	57(54.81)	0.317	0.461
	Mucinous adenocarcinoma and others	15	7(46.67)	8(53.33)		
Pit type	Vi	76	35(46.05)	41(53.95)	0.112	0.783
	Vn	43	19(44.19)	24(55.81)		
Surgical methods	EMR	30	15(50.00)	15(50.00)	0.414	0.320
	ESD	89	39(43.82)	50(56.18)		
Tumor location	rectum	38	18(47.37)	20(52.63)	1.013	0.192
	ascending colon	15	6(40.00)	9(60.00)		
	Sigmoid colon	32	12(37.50)	20(62.50)		
	descending colon	5	2(40.00)	3(60.00)		
	transverse colon	3	1(33.33)	2(66.67)		
	cecum	26	10(38.46)	16(61.54)		
Infiltration depth	pT1+pT2	16	11(68.75)	5(31.25)	4.074	0.043*
Infiltration type	Vascular Infiltration	34	24	10	12.210	0.001*
	Neural invasion	17	13	4	2.747	0.006*

Table 3. Univariate analysis of the 5-year survival rate of patients with colorectal cancer.

Clinical pathological features		N	Non-disease survival	P	Overall survival	P
Age	<60	30	79.31	0.706	82.75	0.029*
	≥60	25	78.69		68.85	
Gender	Male	36	79.31	0.565	86.4	0.784
	Female	19	83.1		88.6	
Types	I	18	85.3	0.751	87.7	0.573
	0-IIa	27	82.6		84.3	
	0-IIb	6	81.4		83.5	
	o-IIc	3	80.6		82.3	
	III	1	79.3		80.9	
Differentiation	High + medium differentiation	50	78.1	0.233	86.5	0.636
	low + undifferentiated	5	76.6		81.4	
Histological type	Adenocarcinoma	47	80.7	0.753	85.3	0.226
	Mucinous adenocarcinoma and others	8	76.6		79.0	
Pit type	Vi	44	83.2	0.552	86.0	0.911
	Vn	11	80.1		83.1	
Surgical methods	EMR	17	82.3	0.249	86.2	0.105
	ESD	38	85.7		87.7	
Tumor location	rectum	14	85.1	0.173	86.2	0.249
	ascending colon	9	82.6		82.6	
	sigmoid colon	18	79.3		81.3	
	descending colon	3	81.5		81.9	
	transverse colon	1	80.7		81.2	
	cecum	10	83.1		83.4	
Tumor size	≥1 cm and <2 cm	25	73.5	0.021*	77.8	0.026*
	<1 cm	30	86.3		87.4	
Infiltration depth	pT1+pT2	5	87.1	0.038*	90.1	0.016*
Infiltration type	Vascular Infiltration	7	42.3	0.001*	54.5	0.001*
	Neural invasion	3	73.7		84.7	

Table 4. Multivariate analysis of the prognosis of patients with rectal cancer.

Clinical pathological		Sig	Exp (β)	95% CI
Age	0.412	0.006	1.565	1.132~2.151
Infiltration depth	0.245	<0.001	1.263	1.101~1.459
Tumor size	0.108	0.477	1.115	0.825~1.508
Infiltration type	0.469	<0.001	1.559	1.006~2.541

3.4. Univariate survival analysis of supplemented and non-supplemented groups

Figure 1 shows that the 5-year overall survival rates of the additional group and the non-additional group were 86.67% and 80.00%, respectively, and the difference was not statistically significant, x^2=0.326, P=0.568. The 5-year disease-free survival rates were 73.33% and 72.50 respectively %, the difference was not statistically significant, x^2=0.004, P=0.951.

4. Discussion

Colorectal cancer is a common malignant tumor in clinical practice, ranking second among malignant tumors of the digestive system, and it is more likely to occur in people over 40 years old. Surgery is an important method for clinical treatment of colorectal cancer [3]. Colorectal cancer should be detected, diagnosed, and treated early, and clinical cure can basically be achieved, and the prognosis of patients is good [4]. The treatment of colorectal cancer has entered the era of surgery-centered multidisciplinary collaborative comprehensive treatment, and standardized treatment has improved the prognosis of patients to a certain extent [5]. The need for additional surgery is the actual manifestation of poor survival-related biological and pathological prognosis, which has guiding significance for formulating a more active adjuvant treatment plan and improving clinical management.

According to reports, the error in judging the prognosis of early colorectal cancer based only on histological typing and TNM grading is as high as 30% [6]. Therefore, we need to further analyze the pathological characteristics of patients with additional surgery to clarify its necessity and importance in clinical treatment. Patients who need additional surgery often suggest that tumor cells may have hematogenous dissemination. Although no clinically visible metastases have been formed in a short period of time, the degree of tumor infiltration is more serious, manifested as nerve/vascular invasion. Cong *et al*. [6] confirmed that

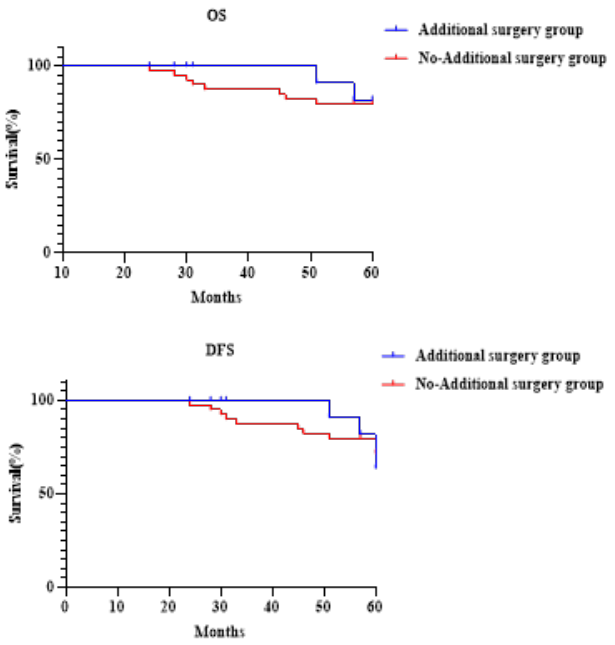

Fig. 1. Comparison of disease-free survival rate and overall survival rate between the additional surgery group and the non-additional group.

neural invasion is an independent factor affecting the prognosis of colorectal cancer. Yang *et al*. [7] found that vascular invasion is a factor that reduces the overall survival rate and disease-free survival rate of colorectal cancer patients. Studies have shown that nerve/vascular invasion is related to tumor invasion depth, size and lymphatic metastasis [8]. In our study, we investigated the association of clinicopathological factors with additional surgery in patients with early-stage colorectal cancer. The results showed that the type of invasion, depth of invasion, and tumor size were correlated with additional surgery. Age, sex, tumor gross type, degree of differentiation, histological type, pit type, surgical method and tumor location were not related. Likewise, a previous report showed that in the case of patients with early-stage colorectal cancer with lymphovascular invasion, additional surgical resection of lymph nodes should be performed after incurable ESD [9]. Another study found that nerve invasion and vascular invasion are important factors for lymph node metastasis of T1 and T2 colorectal cancer, and radical surgery should be performed as soon as possible for T1 and T2 colorectal cancer patients with nerve invasion [10]. These differences may be due in part to differences in patient populations and studies. In this study, the proportion of patients with additional surgery for nerve invasion was 89.28%, which is similar to foreign reports [10, 11].

It is worth noting that since our study adopted two surgical methods, among which EMR surgery was chosen, most of the patients were judged to be benign polyps before surgery, but the pathological examination after surgery revealed submucosal invasive carcinoma. Early diagnosis of colorectal polyps by endoscopy and early intervention of polyps with risk of canceration can provide a theoretical basis for early diagnosis and treatment of colorectal cancer in the clinic. The surface mucosa of colorectal polyps is classified into three types under endoscopy, smooth, rough and lobulated. Among them, polyps with smooth surface mucosa are the most common, and the least is lobulated type. In the distribution of pathological types of villous adenoma, the surface mucosa of villous adenoma was mostly lobulated, and the surface mucosa of tubular villous gland, tubular adenoma and non-adenomatous polyp was mainly smooth. The risk of early cancer in lobulated polyps was about 8 times that of other types, and the risk of early cancer in polyps with smooth mucosa was lower. Therefore, in clinical practice, enough attention should be paid to the changes of the surface mucosa of colorectal polyps under endoscopy, especially the fractal surface mucosa should be excised as much as possible and sent for biopsy in time to prevent the occurrence of cancer.

Tumor size, a common medical parameter calculated from the widest horizontal tumor diameter, has long been studied, but there is no consensus on its prognostic value in colorectal cancer [12]. In many gastrointestinal malignancies, larger tumor level extent is generally regarded as a negative risk factor, while many other studies have shown that tumor size has no prognostic significance in colorectal cancer [13]. Recently, tumor size was again assessed in a large population-based study and was shown to have an impact on overall survival in patients with colorectal cancer [14]. Therefore, our study explored the correlation of clinicopathological factors with tumor size. Univariate analysis showed that the degree of differentiation, type of invasion, and depth of invasion were correlated with tumor diameter. The results of multivariate Logistic regression analysis showed that the type of infiltration was closely related to the size of the tumor. Likewise, previous reports have shown that tumor size is an independent factor affecting disease-free survival in patients with invasive colorectal cancer [15]. When the tumor penetrates the submucosa, the lymphatic vessels are mainly concentrated in this layer. At this time, as the size of the tumor increases, the contact area between the tumor and the lymphatic vessels increases, and the probability of micrometastasis to distant lesions through the lymphatic vessels increases. The possibility of postoperative recurrence increases and the prognosis is poor; in addition, when the tumor penetrates the submucosa, it is more likely to invade blood vessels and nerves in the intestinal wall as the tumor grows larger, causing an increased tendency of blood vessel metastasis, and nerve invasion may provide tumor support. Another route of metastasis leads to a worse prognosis. As the tumor increases, the higher the degree of malignancy and the worse the biological behavior, the stronger the invasion effect of the tumor on the tissues around the colorectal wall; when the tumor involves the serosa layer, the contact area with the abdominal cavity increases with the increase of the tumor, resulting the probability of plant dissemination is increased and the prognosis is poor. In addition, the preoperative measurement of tumor size is not easily affected by factors such as local inflammation, is easy to distinguish from surrounding tissues, and is not affected by micrometastases. The subjective factors are less affected, and the determination accuracy is higher. Therefore, it is important to use tumor size to predict the prognosis of colorectal cancer patients. Second, our study analyzed the 5-year overall survival rate and disease-free survival rate of some patients. Univariate analysis showed that age, depth of invasion, and tumor size were correlated with patient survival. The results of multivariate Cox regression analysis showed that the type and depth of invasion were closely related to the survival rate of patients, and

they were independent risk factors affecting the prognosis of patients. It has been reported that the survival rate of patients aged ≤54 years has been steadily increasing [16], and that advanced age (≥ age (years)) is associated with shorter recurrence-free survival in colorectal cancer patients who underwent surgery [17]. In addition, the type of invasion has been It has been reported to be associated with poor prognosis of various malignant tumors [18]. Zhou *et al*. [19] research analysis showed that the infiltration type has a statistically significant difference in the overall survival rate of cervical cancer. Similarly, van Wyk *et al*. [20] pointed out that neuro Infiltration can be used to assess the prognosis of colorectal cancer patients.

The results of this study also showed that the 5-year overall survival rates of the additional group and the non-supplementary group were 86.67% and 80.00%, respectively, and the 5-year disease-free survival rates were 73.33% and 72.50%, respectively, and the differences were not statistically significant. This is because patients with early colorectal cancer have very few lymph node metastases and thus have a better prognosis. 51 patients with colorectal cancer who received additional surgery had no metastasis or local recurrence during the follow-up period of 59 months. Among them, 3 patients died of other diseases, and no recurrence occurred. Rectal cancer-related death [21].

In summary, this study shows that the type and depth of invasion are independent risk factors for the 5-year survival rate of colorectal cancer patients after surgery, which can be used to judge the prognosis of colorectal cancer and guide clinical treatment. Replenish. However, the sample size of this study is relatively small, and large-scale clinical randomized controlled trials are needed to confirm the impact of these indicators on the prognosis of colorectal cancer.

References

1. Tomonari A, Katanuma A, Matsumori T, Yamazaki H, Sano I, Minami R, et al (2015) Resected tumor seeding in stomach wall due to endoscopic ultrasonography-guided fine needle aspiration of pancreatic adenocarcinoma. World J Gastroenterol 21(27):8458–8461. doi: 10.3748/wjg.v21.i27.8458
2. Hayashi K, Tsuchiya A, Ikarashi S, Takizawa K, Terai S (2018) A case of pancreatic schwannoma diagnosed preoperatively by endoscopic ultrasonography-guided fine needle aspiration and treated with laparoscopic surgery. J Pancreat Cancer 4(1):7–10. doi: 10.1089/pancan.2018.0002
3. Saito S, Tajiri H, Ikegami M (2015) Endoscopic features of submucosal deeply invasive colorectal cancer with NBI characteristics: S Saito et al. Endoscopic images of early colorectal cancer. Clin J Gastroenterol 8(6):353–359. doi: 10.1007/s12328-015-0616-5
4. Stroke Risk in Atrial Fibrillation Working Group (2007) Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 69(6):546–554. doi: 10.1212/01.wnl.0000267275.68538.8d
5. Sun Z, Yu X, Wang H, Ma M, Zhao Z, Wang Q (2015) Factors affecting sphincter-preserving resection treatment for patients with low rectal cancer. Exp Ther Med 10(2):484–490. doi: 10.3892/etm.2015.2552
6. Cong ZJ, Hu LH, Xing JJ, Zhang W, Fu CG, Yu ED, Zhong M (2014) Risk factors associated with sphincter-preserving resection in patients with low rectal cancer. Int Surg 99(4):330–337. doi: 10.9738/INTSURG-D-13-00217.1
7. Yang Y, Huang X, Sun J, Gao P, Song Y, Chen X, et al (2015) Prognostic value of perineural invasion in colorectal cancer: a meta-analysis. J Gastrointest Surg 19(6):1113–1122. doi: 10.1007/s11605-015-2761-z
8. Ozturk MA, Dane F, Karagoz S, Tural D, Selcukbiricik F, Demirelli F, et al (2015) Is perineural invasion (PN) a determinant of disease free survival in early stage colorectal cancer? Hepatogastroenterology 62(137):59–64.
9. Cheng P, Lu Z, Zhang M, Chen H, Guo Z, Zheng Z, Wang X (2021) Is additional surgery necessary after non-curative endoscopic submucosal dissection for early colorectal cancer? J Invest Surg 34(8):889–894. doi: 10.1080/08941939.2019.1697770
10. Adam P, Bonzheim I, Fend F, Quintanilla-Martínez L (2011) Epstein-Barr virus-positive diffuse large B-cell lymphomas of the elderly. Adv Anat Pathol 18(5):349–355. doi: 10.1097/PAP.0b013e318229bf08
11. Hong JY, Ko YH, Kim SJ, Kim WS (2015) Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: a concise review and update. Curr Opin Oncol 27(5):392–398. doi: 10.1097/CCO.0000000000000210
12. Miller W, Ota D, Giacco G, Guinee V, Irimura T, Nicolson G, Cleary K (1985) Absence of a relationship of size of primary colon carcinoma with metastasis and survival. Clin Exp Metastasis 3(3):189–196. doi: 10.1007/BF01786762
13. Kanemitsu Y, Kato T, Hirai T, Yasui K, Morimoto T, Shimizu Y, et al (2003) Survival after curative resection for mucinous adenocarcinoma of the colorectum. Dis Colon Rectum 46(2):160–167. doi: 10.1007/s10350-004-6518-0
14. Saha S, Shaik M, Johnston G, Saha SK, Berbiglia L, Hicks M, et al (2015) Tumor size predicts long-term survival in colon cancer: an analysis of the National Cancer Data Base. Am J Surg 209(3):570–574. doi: 10.1016/j.amjsurg.2014.12.008
15. Dai W, Li Y, Meng X, Cai S, Li Q, Cai G (2017) Does tumor size have its prognostic role in colorectal cancer? Re-evaluating its value in colorectal adenocarcinoma with different macroscopic growth pattern. Int J Surg 45:105–112. doi: 10.1016/j.ijsu.2017.07.100
16. Feng Y, Mo S, Dai W, Li Q, Cai G, Cai S (2020) Increasing age-related survival gap among patients with colorectal cancer: a population-based retrospective study. Int J Clin Oncol 25(1):100–109. doi: 10.1007/s10147-019-01538-3
17. Kosumi K, Mima K, Morito A, Yumoto S, Matsumoto T, Inoue M, et al (2021) Patient age and long-term survival in colorectal cancer patients who undergo emergency surgery. Anticancer Res 41(2):1069–1076. doi: 10.21873/anticanres.14864
18. Stanton SE, Disis ML (2016) Clinical significance of tumor-infiltrating lymphocytes in breast cancer. J Immunother Cancer 4:59. doi: 10.1186/s40425-016-0165-6
19. Zhou Y, Wang H, Gong H, Cao M, Zhang G, Wang Y (2015) Clinical significance of perineural invasion in stages II and III colorectal cancer. Pathol Res Pract 211(11):839–844. doi: 10.1016/j.prp.2015.09.001
20. van Wyk HC, Going J, Horgan P, McMillan DC (2017) The role of perineural invasion in predicting survival in patients with primary operable colorectal cancer: A systematic review. Crit Rev Oncol Hematol 112:11–20. doi: 10.1016/j.critrevonc.2017.02.005
21. Chen T, Zhang YQ, Chen WF, Hou YY, Yao LQ, Zhong YS, et al (2017) Efficacy and safety of additional surgery after non-curative endoscopic submucosal dissection for early colorectal cancer. BMC Gastroenterol 17(1):134. doi: 10.1186/s12876-017-0701-y