International Journal of Colorectal Disease (2018) 33:719–726
https://doi.org/10.1007/s00384-018-3031-9

ORIGINAL ARTICLE

The prognostic implications of primary tumor location on recurrence in early-stage colorectal cancer with no associated risk factors

Sung Il Kang[1] · Duck-Woo Kim[1] · Yoonjin Kwak[2] · Hye-Seung Lee[2] · Min Hyun Kim[1] · Myung Jo Kim[1] · Heung-Kwon Oh[1] · Sung-Bum Kang[1]

Accepted: 14 March 2018 / Published online: 28 March 2018

Abstract

Purpose Recently, several reports have suggested that tumor location serves as a prognostic biomarker in advanced colorectal cancer. However, the prognostic implication of tumor location in patients with early-stage colorectal cancer remains unclear. This study was aimed to examine the prognostic implication of tumor location in patients with early-stage colorectal cancer.

Methods Patients with stage I and low-risk stage II colorectal cancer, treated with radical surgery in a hospital setting between May 2003 and September 2014, were retrospectively reviewed. Patients who underwent (neo) adjuvant chemotherapy and/or radiotherapy and whose microsatellite instability (MSI) status was lacked were excluded. Distal colon cancer was defined as tumors located from the splenic flexure colon to the sigmoid colon.

Results A total of 712 patients were included in this study. Of these patients, 23 (3.2%) had a recurrence at a median follow-up time of 46 months. The tumor recurrence rate was significantly low in patients with proximal colon cancer. In the multivariate analysis, tumors located in the distal colon or rectum (distal colon, hazard ratio [HR] 9.213, $P = 0.035$; rectum, HR 15.366, $P = 0.009$) and T3 tumors (HR 4.590, $P = 0.017$) were related to tumor recurrence. A higher prevalence of tumor recurrence was found in patients with two recurrence factors than those who had only one factor or none ($P < 0.001$).

Conclusions Tumor location, as well as T stage, had prognostic implication in patients with early-stage colorectal cancer. Validation of our results is needed in a large cohort with genetic characterization.

Keywords Early colorectal cancer · Tumor location · Tumor recurrence · Risk factors

Introduction

The incidence of colorectal cancer (CRC) has been rapidly increasing in several Asian countries, including Korea, China, Japan, and Singapore [1–3]. In Korea especially, the age-adjusted CRC incidence ranked the highest among other Asian countries, with CRC being the second most common cancer in males and the third most common cancer in females presently in this country [1]. Despite this sharply increasing trend of CRC incidence, the survival rate of CRC patients in Korea has increased from 50% before 2000 to 70% between 2004 and 2008 [4]. This increase in survival might be due to the high rates of screening and early detection by the nationwide CRC screening and detection program, as well as the development of more advanced therapeutic chemo-agents.

Surgical R0 resection is the only curative treatment for early-stage (I–II) CRC, although multimodal treatment including surgery, chemotherapy, and radiotherapy is the main therapeutic choice for advanced CRC. The 5-year overall survival rate has been reported to be as high as 90% after R0 resection of the primary tumor in patients with localized CRC [5]. However, tumor recurrence can occur after curative resection. The cumulative local recurrence rate in patients with early-stage CRC was reported to be up to 11% and the cumulative rate of distant metastasis was as high as 21% [6]. Several guidelines recommend adjuvant chemotherapy for reducing tumor recurrence after curative surgery when patients have stage II CRC with well-known poor prognostic factors such as a T4 tumor, poorly differentiated histology, lymphatic/

✉ Duck-Woo Kim
kdw@snubh.org

[1] Department of Surgery, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do 463-707, South Korea

[2] Department of Pathology, Seoul National University Bundang Hospital, Seongnam, South Korea

vascular/perineural invasion, obstruction, perforation, and suboptimal lymph node sampling [7, 8]. However, there is no level I evidence regarding the use of adjuvant therapy for stage II CRC patients with these clinicopathologic risk factors. In addition, other factors associated with prognosis in patients with early-stage CRC remain unclear.

Recently, several reports suggested that tumor location, analyzed from the different embryological origins, may serve as a prognostic biomarker [9–13]. However, these studies mainly investigated patients with advanced stage CRC and there is paucity in the literature on the prognostic implications of tumor location in patients with early-stage CRC. In this study, we aimed to investigate primary tumor location as a prognostic factor in patients with early-stage CRC and without the clinicopathologic risk factors commonly associated with tumor recurrence.

Patients and methods

Patients

We retrospectively reviewed the records of consecutive patients who underwent curative resection for final stage I–II CRC between May 2003 and September 2014 at Seoul National University Bundang Hospital, a tertiary-referral hospital in Korea. The inclusion criteria for this study were as follows: (i) patients who underwent radical surgery including D2 or D3 lymphadenectomy for CRC and (ii) the tumor was pathologically confirmed as adenocarcinoma with stage I, or stage II with no risk factors for recurrence according to the National Cancer Comprehensive Network (NCCN) guidelines [7]. Patients who underwent (neo) adjuvant chemotherapy and/or radiotherapy, as well as those without a clear microsatellite instability (MSI) status, were excluded. Surgery for CRC was performed with curative intent by qualified, experienced colorectal surgeons (D-W Kim, H-K Oh, and S-B Kang).

Clinicopathologic data

Tumor recurrence was determined by histologic or radiologic findings. Recurrence-free survival was determined from the date of radical surgery to the date of detection of the local recurrence or distant metastasis, the last follow-up, or death. All patients were routinely followed up according to our postoperative surveillance protocol for CRC, which was described in one of our previous reports [14].

Patients were classified into three groups according to the embryological origin of the tumor location, based on previous reports [9, 11]. Proximal colon cancer (PCC) was defined as the tumor located from the cecum to the transverse colon, and distal colon cancer (DCC) was defined as tumors located from the splenic flexure colon to the sigmoid colon. Rectal cancer was defined as tumors located within 15 cm from the anal verge.

The MSI status was determined from tumor specimens after surgical resection with five markers (BAT 25, BAT 26, D2S123, D5s346, and D17S250), which were recommended by a National Cancer Institute workshop on MSI [15]. MSI-high was determined as when MSI was present in two or more of the five markers, whereas MSI-low was only if one marker showed instability. Microsatellite status-stable (MSS) was determined if no marker showed evidence of MSI.

Statistics

Categorical variables were analyzed using either the chi-square test or Fisher's exact test. Continuous and non-normally distributed data are presented as the median values (with the interquartile range, IQR) and were analyzed using the Mann-Whitney *U* test. Analysis of the variables affecting tumor recurrence was conducted using both univariate and multivariate Cox proportional-hazard regression analysis. Recurrence-free survival was compared using the Kaplan-Meier survival curve and the log-rank test. A *P* value less than 0.05 was considered indicating a statistically significant difference. Statistical analyses were performed using SPSS software (ver. 21.0) for Windows (IBM Corporation, Armonk, NY, USA). This retrospective study was approved by the Ethics Review Board at our institution (SNUBH IRB No. B-1709-420-110).

Results

Baseline characteristics

A total of 3809 patients were confirmed as having colorectal adenocarcinoma between May 2003 and September 2014 at Seoul National University Bundang Hospital. Of those, 1685 patients were confirmed as having adenocarcinoma with pathologic stage I or II after radical surgery. Among these patients, 712 were included in this study after excluding patients who underwent preoperative chemoradiotherapy ($n = 757$), those who had stage II cancer with one or more risk factors ($n = 53$), and those who lacked a defined MSI status ($n = 163$).

The rate of tumor recurrence was 3.2% (23/712) with a median follow-up time of 46 months (interquartile range, 28–74 months). Among the study patients, 29.8% ($n = 212$) had PCC, 33.7% ($n = 240$) had DCC, and 36.5% ($n = 260$) had rectal cancer (Table 1). The median tumor size was larger in the recurrence group than in the non-recurrence group (2.9 cm [IQR 2.0–4.5 cm] vs. 4.0 cm [2.5–6.0 cm], $P = 0.026$). Tumor recurrence occurred in 2.4 and 5.4% of patients with stages I and II, respectively, but there was no statistically significance in this difference ($P = 0.056$). There was no colonic

Table 1 Patient baseline characteristics

	No recurrence ($n = 689$)	Recurrence ($n = 23$)	P value
Age, median (IQR), year	67 (58–74)	64 (51–74)	0.396
Sex			0.084
Men	410 (95.8)	18 (4.2)	
Women	279 (98.2)	5 (1.8)	
BMI, median (IQR), kg/m^2	23.5 (21.8–25.5)	23.9 (21.8–26.5)	0.292
Preoperative CEA, ng/dL			0.677
≤ 5	640 (96.8)	21 (3.2)	
> 5	49 (96.1)	2 (3.9)	
Preoperative EMR			0.402
No	637 (96.5)	23 (3.5)	
Yes	52 (100)	0 (0)	
Tumor location			0.019
Proximal colon (A–T)	211 (99.5)	1 (0.5)	
Distal colon (SF–S)	231 (96.3)	9 (3.8)	
Rectum	247 (95.0)	13 (5.0)	
Operation method			0.293
Laparoscopy	548 (97.2)	16 (2.8)	
Open	141 (95.3)	7 (4.7)	
Tumor size, median (IQR), cm	2.9 (2.0–4.5)	4.0 (2.5–6.0)	0.026
Stage			0.056
1	498 (97.6)	12 (2.4)	
2	191 (94.6)	11 (5.4)	
T stage			0.069
1	275 (98.2)	5 (1.8)	
2	223 (97.0)	7 (3.0)	
3	191 (94.6)	11 (5.4)	
MSI status			0.156
MSS/MSI-low	623 (96.4)	23 (3.6)	
MSI-high	66 (100)	0 (0)	

Continuous variables presented as median (IQR) and analyzed by means of Mann-Whitney *U* test. Categorical variables presented as number (%) and analyzed by means of Chi-square test or Fisher's exact test

A, ascending colon; *BMI*, body mass index; *CEA*, carcinoembryonic antigen; *EMR*, endoscopic mucosal resection; *IQR*, interquartile range; *MSI*, microsatellite instability; *MSS*, microsatellite stable; *T*, tumor; *S*, sigmoid colon; *SF*, splenic flexure colon; *SD*, standard deviation

obstruction, perforation, or insufficient lymph nodes found in patients with stage I cancer.

Factors associated with tumor recurrence

In the univariate Cox regression analysis, distal colon cancer, rectal cancer, and T3 stage were associated with tumor recurrence. In the multivariate Cox regression analysis using factors with P values ≤ 0.1 from the univariate analysis, tumor location (DCC, hazard ratio [HR] = 9.213, 95% confidence interval [CI] = 1.167–72.995, $P = 0.035$; rectal cancer, HR = 15.366, 95% CI = 1.960–120.473, $P = 0.009$), as well as T3 stage (HR = 4.590, 95% CI = 1.409–14.954, $P = 0.017$), was independently associated with tumor recurrence (Table 2). Recurrence-free survival was significantly longer in patients with PCC than in those with either DCC or rectal cancer (log-rank, $P = 0.026$). T3 tumor status had a significantly higher tumor recurrence rate than T1 and T2 tumors (log-rank, $P = 0.044$) (Fig. 1). Moreover, patients with two recurrence-associated factors had more frequent tumor recurrence than those who had only one or no factor ($P < 0.001$) (Fig. 2). Patients with PCC and either T1 or T2 cancer had no tumor recurrence, in contrast to patients with one risk factor such as DCC, rectal cancer, or T3 tumor having tumor recurrence rates of 2.7% (13/461), as well as patients with two risk factors, who had a tumor recurrence rate of 8.8% (10/104).

MSI status of the study patients revealed MSS in 592 patients (83.1%), MSI-low in 54 patients (7.6%), and

Table 2 Univariate and multivariate Cox regression analyses of the study patients for tumor recurrence factors after curative resection

		Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age, year	< 70	Ref.	0.603		
	≥ 70	1.245 (0.545–2.840)			
Sex	Women	Ref.	0.089	Ref.	0.115
	Men	2.363 (0.877–6.365)		2.242 (0.823–6.109)	
BMI, kg/m^2	< 25	Ref.	0.618		
	≥ 25	1.244 (0.527–2.937)			
Preoperative CEA, ng/dL	< 5	Ref.	0.698		
	≥ 5	1.332 (0.312–5.687)			
Tumor size, cm	< 3	Ref.	0.080	Ref.	0.690
	≥ 3	2.211 (0.910–5.376)		1.216 (0.466–3.174)	
Tumor location	Proximal colon (A–T)	Ref.	0.084	Ref.	0.028
	Distal colon (SF–S)	8.238 (1.044–65.028)	0.045	9.213 (1.167–72.995)	0.035
	Rectum	10.077 (1.317–77.094)	0.026	15.366 (1.960–120.473)	0.009
T stage	1	Ref.	0.055	Ref.	0.035
	2	1.751 (0.556–5.518)	0.339	1.820 (0.572–5.784)	0.310
	3	3.454 (1.199–9.951)	0.022	4.590 (1.409–14.954)	0.017
MSI status	MSI-high	Ref.	0.317		
	MSS/MSI-low	23.349 (0.049–11,129.116)			

Factors with a *P* value of 0.1 or less in the univariate analysis were included in the multivariate analysis

A, ascending colon; *BMI*, body mass index; *CEA*, carcinoembryonic antigen; *MSI*, microsatellite instability; *MSS*, microsatellite stable; *T*, tumor; *S*, sigmoid colon; *SF*, splenic flexure colon

MSI-high in 66 patients (9.3%). PCC had a significantly higher rate of MSI-high tumors (PCC vs. DCC vs. rectal cancer; 22.6 vs. 4.2 vs. 3.1%, respectively, $P < 0.001$). All patients with MSI-high did not have tumor recurrence, in contrast to a tumor recurrence rate of 3.6% (23/647) in patients with MSI-low/MSS tumor, although this difference was not statistically significant ($P = 0.156$).

Characteristics and clinical course of the patients who had tumor recurrence

All recurrences were distant metastases, except for one male patient, who experienced local tumor recurrence after lower anterior laparoscopic resection for rectal cancer, located 4 cm from the anal verge (Table 3). In this patient, pathologic examination of the surgical specimen showed pT2N0 stage, with moderate differentiated histology, and no lymphatic/perineural/vascular invasion. Resection margin was clear (distal resection margin 8 mm, circumferential resection margin 2 mm). Recurrence in a pelvic lateral lymph node was found 17 months post-surgery on abdomen and pelvis computed tomography, without elevation of carcinoembryonic antigen (CEA) levels. This patient underwent surgery for the metastatic pelvic nodule and was administered postoperative chemoradiotherapy, followed by adjuvant chemotherapy. He has been recurrence-free for 58 months after adjuvant

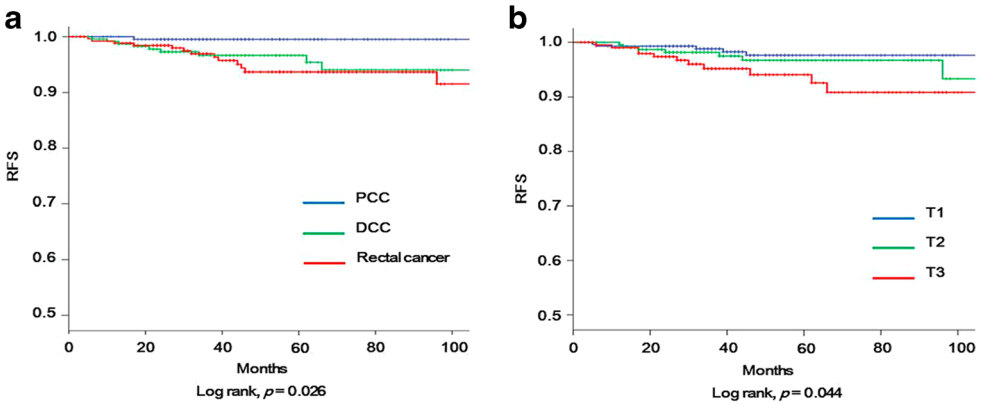

Fig. 1 Recurrence-free survival curve according to tumor location (**a**) and T stage (**b**). RFS, recurrence-free survival; PCC, proximal colon cancer; DCC, distal colon cancer

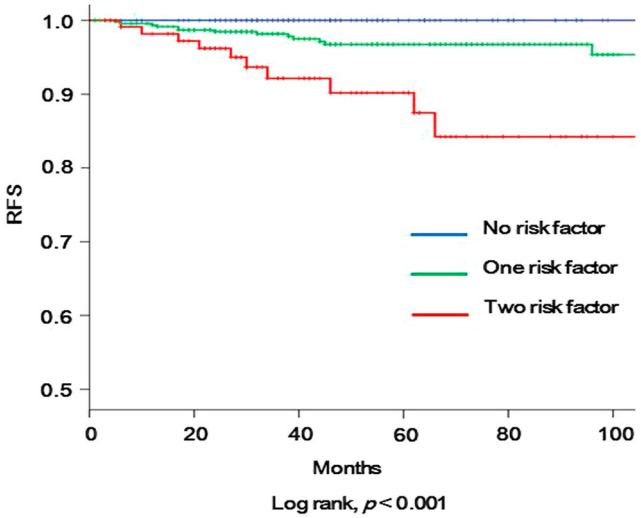

Fig. 2 Recurrence-free survival curve according to the number of patient-associated risk factors

chemotherapy. For patients with distant tumor recurrence, the main recurring site was the lung, followed by the liver. Of the 22 patients with distant tumor recurrence, 13 patients (59.1%) were eligible for treatment with surgical resection.

Discussion

Tumor location has recently been investigated as a marker of treatment response and prognosis among patients with CRC [16]. PCCs have been more frequent in older people and women, with the initial diagnosis typically occurring at a more advanced disease stage when compared to DCC [9, 17–19]. PCC arises from the midgut, in contrast with DCC, and rectal cancer arises from the hindgut [9, 11]. These differences result in a discrepancy of molecular biology and genetic patterns of the tumor. Therefore, tumor location may represent the differences in tumor characteristics, such as etiology, embryology, molecular biology, and genetic patterns between PCC and DCC.

However, conflicting results regarding tumor location and prognosis have been reported in the literature. Sasaki et al. [12] reported that right-sided colon cancer has longer relapse-free survival in patients with colorectal liver metastasis, which contrasts with Benedix et al. [9], who reported that right-sided colon cancer has a worse prognosis. Lee et al. [20] reported that the prognosis of rectal cancer was not worse than that of colon cancer. A recent propensity-matched study by Ishihara et al. [10] reported that the proximal tumor location of non-metastatic colon cancer had a good prognosis in terms of tumor recurrence, but had low cancer-specific survival if there was a tumor recurrence, when compared with left-sided colon cancer. Other previous studies have reported conflicting results about survival and prognosis according to tumor location [11, 21, 22]. These previous studies were very heterogenous among study populations such as tumor stage, treatment modality, and other oncologic risk factors. To overcome these limitations in the present study, we included patients with early-stage CRC without clinicopathologic risk factors that may affect oncologic prognosis, as well as showed that tumor location and T stage affected prognosis; patients with PCC and T1 or T2 cancer had no tumor recurrence. To the best of our knowledge, this is the first study to show tumor location as a prognostic marker for stage I and low-risk stage II CRC.

In addition, we collected and analyzed patient MSI status to investigate if this was a possible risk factor of tumor recurrence. MSI status is a representative genomic carcinogenic pathway, which differs between PCC and DCC, with many previous studies revealing that MSI status is associated with tumor recurrence, overall survival, and treatment response for adjuvant chemotherapy in patients with advanced CRC [23–25]. However, the prognostic impact of MSI status in patients with early-stage CRC was not previously investigated. A previous study reported that lymph node metastasis was not detected in patients with T1 CRC and MSI-high although the association of MSI status and lymph node metastasis was not statistically significant because of small sample size [26]. Tumor recurrence also did not occur in our patients with MSI-high cancer, although there was no statistical difference between MSI-high cancer and MSS/MSI-low cancer. This finding suggests that MSI-high status may serve as a good prognostic factor, even in patients with early-stage CRC and with no risk factors after curative resection.

The lung was the most common tumor recurrence site followed by the liver in this study. It might be due to that the rectum was the most common primary tumor site in patients who had tumor recurrence (13/23, 56.3%). Advanced rectal cancers have more chance to metastasize to the lung than colon cancers because of the inferior rectal vein; venous drainage among the trimodal potential spreading systems drains into systemic venous circulation via the inferior vena cava rather than portal circulation [27, 28]. Our result revealed that patients with early-stage rectal cancer also had more chance to metastasize to the lung same as in patients with advanced staged rectal cancer.

This study had certain limitations. First, the retrospective design of the study could have led to some selection bias. Second, only a small portion of this cohort had tumor recurrence since this study was limited to patients with early-stage CRC. For this reason, we could not compare the overall and cancer-specific survival in the study population. Third, other molecular and genetic characteristics of tumors, which may affect prognosis, were not available for analysis.

The survival benefit of adjuvant chemotherapy for stage II patients with one or more risk factors is no more than 5% [7]. Therefore, the controversy whether to require adjuvant therapy in these patients is still under debate, with consideration for

Table 3 Baseline characteristics and clinical course of patients with tumor recurrence

No.	Tumor location		Age at diagnosis (years)	Sex	T stage	Period from surgery to recurrence (months)	Recur site	Risk factor	Treatment of recurrence	Prognosis after recurrence treatment
	Segment	Specific location[a]								
1	Proximal colon	Transverse colon	72	F	3	17	Liver	–	RFA	No recurrence for 23 months
2	Distal colon	Descending colon	88	M	3	17	Liver	–	RFA	Residual tumor and tumor regrowth
3	Distal colon	Descending colon	73	M	3	66	Lung	–	No treatment[b]	Lost to follow-up
4	Distal colon	Sigmoid	53	M	2	13	Liver	–	Surgery + CapeOX	Lost to follow-up
5	Distal colon	Sigmoid	36	M	3	10	Liver	–	Surgery + CapeOX	No recurrence for 14 months
6	Distal colon	Sigmoid	48	F	2	24	Liver	–	Surgery + CapeOX	No recurrence for 58 months
7	Distal colon	Sigmoid	40	F	3	8	Liver	–	Surgery + FOLFOX	No recurrence for 44 months
8	Distal colon	Sigmoid	67	M	3	21	Liver	–	No treatment[b]	Lost to follow-up
9	Distal colon	Sigmoid	84	M	3	67	Lung	–	No treatment[b]	Lost to follow-up
10	Distal colon	Sigmoid	75	M	3	12	Liver	–	Surgery + FOLFOX	Recurrence to lung 23 months after metastasectomy
11	Rectum	15 cm	53	M	1	38	Lung	LI	Surgery + CapeOX	No recurrence for 70 months
12	Rectum	15 cm	74	F	1	32	Lung	LI	No treatment[b]	Expired
13	Rectum	13 cm	60	M	2	12	Lung	–	Surgery + FOLFOX	No recurrence for 37 months
14	Rectum	12 cm	58	M	2	44	Lung	–	Surgery + CapeOX	No recurrence for 60 months
15	Rectum	10 cm	84	M	3	30	Lung	–	Capecitabine	Expired
16	Rectum	6 cm	51	M	1	6	Liver	–	Surgery + bevacizumab + FOLFOX	No recurrence for 89 months
17	Rectum	6 cm	64	F	2	96	Lung/ Multiple LNs	–	FOLFOX followed by FOLFIRI	Expired
18	Rectum	5 cm	70	M	1	5	Lung/Bone	PNI	Surgery, RFA	Lost to follow-up
19	Rectum	4 cm	80	M	3	27	Lung	–	No treatment[b]	Lost to follow-up
20	Rectum	4 cm	39	M	2	38	Liver	–	Surgery	No recurrence for 71 months
21	Rectum	4 cm	38	M	2	17	Pelvic LN	–	Surgery + CCRT + CapeOX	No recurrence for 58 months
22	Rectum	2 cm	74	M	3	46	Lung	–	Surgery + capecitabine	No recurrence for 41 months
23	Rectum	2 cm	53	M	1	45	Lung/Bone	LI	No treatment[b]	Lost to follow-up

LN, lymph node; *LI*, lymphatic invasion; *PNI*, perineural invasion; *RFA*, radiofrequency ablation

[a] Tumor locations in rectal cancer patients are described as the distance of the low margin from the anal verge

[b] Six patients had no treatment for the tumor recurrence because of underlying medical illness (heart failure, renal failure, and liver cirrhosis), old age, or patient's refusal of further treatment

side effects and toxicity of the chemotherapeutic agents. The results of the present study should not change the current treatment strategy, since tumor recurrence rates are too low in early-stage CRC patients. However, it is important to identify factors for recurrence in these patients who had been regarded as contraindicated for adjuvant chemotherapy. Well-designed, large-scale prospective future studies with tumor molecular and genetic characteristics are required to clarify the possibility of tumor location as a prognostic biomarker in patients with early-stage CRC.

In conclusion, tumor location, as well as T stage, shows prognostic implications for patients with early-stage CRC after curative resection. PCC had a better prognosis in terms of tumor recurrence compared with DCC and rectal cancer. MSI-high status may also be a favorable factor in patients with early-stage and low-risk CRC.

Compliance with ethical standards

This retrospective study was approved by the Ethics Review Board at our institution (SNUBH IRB No. B-1709-420-110).

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Kim DH (2013) Colorectal cancer epidemic in Korea. Ann Coloproctol 29(1):1–4
2. Kuriki K, Tajima K (2006) The increasing incidence of colorectal cancer and the preventive strategy in Japan. Asian Pac J Cancer Prev 7(3):495–501
3. Yee YK, Tan VP, Chan P, Hung IF, Pang R, Wong BC (2009) Epidemiology of colorectal cancer in Asia. J Gastroenterol Hepatol 24(12):1810–1816
4. Lee BI, Hong SP, Kim SE, Kim SH, Kim HS, Hong SN, Yang DH, Shin SJ, Lee SH, Park DI, Kim YH, Kim HJ, Yang SK, Kim HJ, Jeon HJ, Multi-Society Task Force for Development of Guidelines for Colorectal Polyp Screening, Surveillance and Management (2012) Korean guidelines for colorectal cancer screening and polyp detection. Clin Endosc 45(1):25–43
5. Moghimi-Dehkordi B, Safaee A (2012) An overview of colorectal cancer survival rates and prognosis in Asia. World J Gastrointest Oncol 4(4):71–75
6. Manfredi S, Bouvier AM, Lepage C, Hatem C, Dancourt V, Faivre J (2006) Incidence and patterns of recurrence after resection for cure of colonic cancer in a well defined population. Br J Surg 93:1115–1122
7. National Comprehensive Cancer Network. Colon cancer (Version 2. 2017). Accessed March 13, 2017. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
8. Schmoll HJ, Van Cutsem E, Stein A et al (2012) ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 23(10):2479–2516
9. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H (2010) Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 53(1):57–64
10. Ishihara S, Murono K, Sasaki K et al (2017) Impact of primary tumor location on postoperative recurrence and subsequent prognosis in nonmetastatic colon cancers: a multicenter retrospective study using a propensity score analysis. [Epub ahead of print] Ann Surg. https://doi.org/10.1097/SLA.0000000000002206
11. Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N (2008) Is there a difference in survival between right- versus left-sided colon cancers? Ann Surg Oncol 15(9):2388–2394
12. Sasaki K, Andreatos N, Margonis GA, He J, Weiss M, Johnston F, Wolfgang C, Antoniou E, Pikoulis E, Pawlik TM (2016) The prognostic implications of primary colorectal tumor location on recurrence and overall survival in patients undergoing resection for colorectal liver metastasis. J Surg Oncol 114(7):803–809
13. Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M, Kitagawa Y (2016) The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. J Gastrointest Surg 20(3):648–655
14. Kang SI, Kim DW, Cho JY, Park J, Lee KH, Son IT, Oh HK, Kang SB (2017) Is MRI of the liver needed during routine preoperative workup for colorectal cancer? Dis *Colon rectum* 60(9):936–944
15. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S (1998) A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 58(22):5248–5257
16. Chang GJ, Gonen M (2017) Prognostic and predictive ability of tumor sidedness: another vexing difference between localized and advanced colon cancer. JAMA Oncol 3(10):1314–1315
17. Saltzstein SL, Behling CA (2007) Age and time as factors in the left-to-right shift of the subsite of colorectal adenocarcinoma: a study of 213,383 cases from the California Cancer Registry. J Clin Gastroenterol 41(2):173–177
18. Nawa T, Kato J, Kawamoto H, Okada H, Yamamoto H, Kohno H, Endo H, Shiratori Y (2008) Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. J Gastroenterol Hepatol 23(3):418–423
19. Maruta M, Kotake K, Maeda K (2007) Colorectal cancer in Japan. Rozhl Chir 86(11):618–621
20. Lee YC, Lee YL, Chuang JP, Lee JC (2013) Differences in survival between colon and rectal cancer from SEER data. PLoS One 8(11):e78709. https://doi.org/10.1371/journal.pone.0078709
21. Loupakis F, Yang D, Yau L et al (2015) Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 107(3):dju427. https://doi.org/10.1093/jnci/dju427
22. Karim S, Brennan K, Nanji S, Berry SR, Booth CM (2017) Association between prognosis and tumor laterality in early-stage colon cancer. JAMA Oncol 3(10):1386–1392
23. Malesci A, Laghi L, Bianchi P, Delconte G, Randolph A, Torri V, Carnaghi C, Doci R, Rosati R, Montorsi M, Roncalli M, Gennari L, Santoro A (2007) Reduced likelihood of metastases in patients with microsatellite-unstable colorectal cancer. Clin Cancer Res 13(13):3831–3839
24. Liang JT, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM (2003) Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg 90(2):205–214
25. Gryfe R, Kim H, Hsieh ET et al (2000) Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med 342(2):69–77

26. Kang J, Lee HW, Kim IK, Sohn SK, Lee KY (2015) Clinical implications of microsatellite instability in T1 colorectal cancer. Yonsei Med J 56(1):175–181
27. Chiang JM, Hsieh PS, Chen JS, Tang R, You JF, Yeh CY (2014) Rectal cancer level significantly affects rates and patterns of distant metastases among rectal cancer patients post curative-intent surgery without neoadjuvant therapy. World J Surg Oncol 30(12):197. https://doi.org/10.1186/1477-7819-12-197
28. Lee JL, Yu CS, Kim TW, Kim JH, Kim JC (2015) Rate of pulmonary metastasis varies with location of rectal cancer in the patients undergoing curative resection. World J Surg 39(3):759–768