Prognostic impact of primary tumor location after curative resection in stage I-III colorectal cancer: a single-center retrospective study

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Running head: Tumor location in stage I-III CRC

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Abstract

Objective: The relationship of tumor site with post-recurrence course and outcome after primary surgery in resectable colorectal cancer (CRC) is unclear. This study investigated the prognostic impact of primary tumor location following radical resection without preoperative treatment in stage I-III CRC.

Methods: We analyzed 3770 patients with stage I-III CRC who underwent curative resection at our hospital during 2000-2015. We defined the right-sided colon as the cecum, ascending colon, and transverse colon, and the left-sided colon as the descending colon, sigmoid, and rectosigmoid junction. Patients were divided into three groups according to tumor site: right-sided colon, left-sided colon, and rectum. Endpoints were overall survival (OS), recurrence-free survival (RFS) by stage and survival after recurrence, respectively.

Results:

The 5-year OS rates of patients with stage I left-sided colon cancer (LCC), right-sided colon cancer (RCC), and rectal cancer (RC) were 98.2%, 97.3%, and 97.2%, respectively (p=0.488). The 5-year OS rates of patients with stage II LCC, RCC, and RC were 96.2%, 88.7%, and 83.0, respectively (p=0.070). The 5-year OS rates of patients with stage III LCC, RCC, and RC were 88.7%, 83.0%, and 80.2, respectively (p=0.001). The 5-year RFS rates of patients with stage I LCC, RCC, and RC were 95.1%, 94.5%, and 90.6% (p=0.027). The 5-year RFS rates of patients with stage II LCC, RCC, and RC were 85.2%, 90.2%, and 76.1%, respectively (p<0.001). The 5-year RFS rates of patients with stage III LCC, RCC, and RC were 75.3%, 75.3%, and 59.8%, respectively (p<0.001). RCC was significantly associated with better RFS compared with LCC (HR 1.29, 95% CI 1.04–1.62; p=0.023) and RC (HR 1.95, 95% CI 1.57–2.44; p<0.001) after adjusting for clinical factors. Among patients with recurrence, RCC was significantly associated with poorer survival after recurrence compared with LCC (HR 0.68, 95% CI 0.48–0.97; p=0.036), and showed a tendency toward poorer

survival after recurrence compared with RC (HR 0.79, 95% CI 0.57–1.10; p=0.164).

Conclusions: In stage I-III CRC without preoperative treatment, our results suggest that the three tumor sites (right-sided colon, left-sided colon, or rectum) may have prognostic significance for RFS and survival after recurrence, rather than sidedness alone.

Brief abstract:

Not only sidedness but also three tumor sites in stage I-III CRC without preoperative treatment may have prognostic significance in terms of RFS and survival after recurrence.

Keywords

right-sided colon cancer; left-sided colon cancer; rectal cancer; primary tumor location; curative resection

Introduction

The prognostic impact of primary tumor location in colorectal cancer (CRC) has recently received considerable attention. The right colon (cecum, ascending colon, and transverse colon) and left colorectum (descending colon, sigmoid colon, sigmoid rectum, and rectum) differ in terms of their embryological origin and microbiota,[1] with the former originating from the midgut and the latter from the hindgut, and they are reported to have physiological differences.

In unresectable advanced or recurrent CRC, sidedness is considered a prognostic factor and a predictor of the efficacy of chemotherapy. Several epidemiological studies and meta-analyses have reported that prognosis is poorer for right-sided colon cancer (RCC) compared with left-sided CRC (LCRC) in unresectable or recurrent CRC.[2-5]

In resectable CRC, on the other hand, the relationship between the primary tumor location and the disease course after primary surgery is not clear. Several epidemiological studies overseas have reported that stage II left-sided colon cancer (LCC) and stage III RCC have poor prognosis.[6-8] Subgroup analyses of RCTs of postoperative adjuvant chemotherapy conducted in Europe and the United States also support those results,[9-11] and a meta-analysis also showed poor prognosis for stage II LCC and stage III RCC.[12] However, some epidemiological studies have produced conflicting results, and consensus is still lacking on the association between primary tumor location and prognosis after primary surgery in resectable CRC.[13,14] One reason for this may be variation in the quality of surgical procedures, which is directly related to treatment outcomes in resectable CRC, and variation in postoperative treatment, which may have led to differing results among the studies. In addition, the prognosis of rectal cancer (RC) is generally poorer than that of colon cancer. To more accurately compare prognosis between RC and colon cancer, RCC, which has an embryological origin different from that of RC, needs to be studied separately from LCC,

which has a common origin. However, there have been no such reports yet.

The relationship between the primary tumor location and the disease course after recurrence in initially resectable CRC is also unclear. In a large retrospective Japanese study of patients with stage II-III disease, disease-specific and survival after recurrence were poor in RCC.[15,16] These results indicate that the prognosis of RCC is also poor in recurrent CRC and that differences in the biological grade of the primary tumor may affect the prognosis after recurrence.

In Japan, surgical resection with D2 and D3 dissection is the main principle of treatment for both RC and colon cancer: they have the same standard treatment and same indications for adjuvant chemotherapy. In a setting of high-quality surgery and postoperative adjuvant therapy for CRC, we believe that there is a need to examine the true significance of primary tumor location in RC and colon cancer.

The purpose of this study was to investigate the prognostic impact of primary tumor location after primary surgery and recurrence in patients with stage I-III CRC who underwent radical resection without preoperative treatment.

Methods

Study population and design

A total of 5516 Japanese patients with pathologically diagnosed stage I-III CRC who underwent curative surgery between January 2000 and December 2015 were included. For all patients, the recommended follow-up period was at least 5 years after primary surgery and observation was continued until any event or January 31, 2021. Patients meeting the following criteria were excluded from the analysis: multiple primary tumors, multiple CRCs, preoperative adjuvant therapy, histology other than adenocarcinoma, unknown follow-up information, and unknown stage information. After exclusions, 3770 patients with stage I-III

CRC were included in the analysis. Of these 3770 patients, 598 (15.9%) had recurrence (Fig. 1).

The Institutional Review Board (IRB) of the National Cancer Center Hospital approved this retrospective study (IRB code: 2017-437)

Characteristics of the study cohort

A total of 3770 patients of CRC were included in the analysis: 944 (25.0%) with RCC, 1547 (41.0%) with LCC, and 1279 (34.0%) with RC. Lower rectal cancer was present in 796 of the 1279 RC patients (62.4%). Lateral lymph node dissection was performed in 39.2% (312/796) of stage I-III RC patients, of whom 9.3% (29/312) had lateral node metastases. Postoperative adjuvant chemotherapy was administered to 23% (866/3770) of the patients. The clinicopathological features of these groups are summarized in Table 1. There were significant differences in age, sex, tumor differentiation, pT stage, pN stage, adjuvant therapy, recurrence after surgery, and stage among the three groups (all $p<0.05$). During the study period, 378/3770 (10.0%) patients died of CRC recurrence. After primary surgery, 598 patients relapsed, including 98 (16.9%) with RCC, 211 (35.3%) with LCC, and 289 (48.3%) with RC. Recurrence rates were 10.4% (98/944) in RCC, 13.6% (211/1547) in LCC, and 22.6% (289/1279) in RC.

Follow-up

Postoperative follow-up consisted of physical examination and serum carcinoembryonic antigen (CEA) and CA19-9 measurements every 3 months for the first 2 years, then every 6 months for 3 years; computed tomography (CT) every 6 months for 5 years; and colonoscopy at 1 and 3 years, as described in Japanese treatment guidelines.[17] Follow-up data were analyzed until an event occurred or until the study cutoff date of January 31, 2021. The mean

follow-up time was 2142 days (standard deviation = 2015 days, range 5 to 6396 days). This study is a retrospective cohort study.

Data selection

Patients were divided into three groups according to tumor site: right-sided colon, left-sided colon, and rectum. We defined the right-sided colon as the cecum, ascending colon, and transverse colon; and the left-sided colon as the descending colon, sigmoid, and rectosigmoid junction. The following parameters were retrospectively reviewed from medical records: year of treatment, age, sex, tumor differentiation, CEA at recurrence, adjuvant therapy, tumor location, pathological stage according to the TNM classification (8th edition),[18] preoperative CEA levels, and adjuvant chemotherapy.

Outcome measures

Clinical and pathological features were compared among RCC, LCC, and RC. OS and RFS after surgery were investigated separately in stage I, II, and III. OS was defined as the time from primary surgery to death from any cause. RFS was defined as the time from primary surgery until first recurrence or death from any cause. Survival after recurrence was defined as the time from date of recurrence to death from any cause. The prognostic impact of primary tumor location was examined after adjusting for important clinical factors. To investigate factors related to prognosis after recurrence, we examined metastatic sites and the resection rate for recurrent disease after curative resection.

Statistical analysis

Categorical variables were analyzed using Pearson's chi-square test and Fisher's exact test, and continuous variables were analyzed using one-way analysis of variance in order to

examine various factors in the three groups. Continuous variables are presented as the mean ± standard deviation (SD) or median (interquartile range) as appropriate. Survival curves were calculated using the Kaplan–Meier method to estimate RFS and OS and compared using the log-rank tests. Patients who were alive at the end of the follow-up period were censored. Multivariable Cox proportional-hazards regression models were subsequently fitted to evaluate factors independently associated with recurrence and death. All p values were one-sided, and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using JMP statistical software version 14 (SAS Institute Inc., Cary, NC).

Results

Long-term outcomes: RCC vs LCC vs RC (OS)

OS curves for patients with stage I-III CRC are shown in Figure 2A to 2C. The 3- and 5-year OS rates of patients with stage I LCC (n= 512) were 99.0% and 98.2% respectively, while those of patients with stage I RCC (n=338) were 98.4% and 97.3%, and those of patients with stage I RC (n=486) were 98.5% and 97.2% (p=0.488) (Figure 2A). The 3- and 5-year OS rates of patients with stage II LCC (n= 459) were 97.9% and 96.2% respectively, while those of patients with stage II RCC (n=272) were 96.1% and 93.8%, and those of patients with stage II RC (n=276) were 94.7% and 91.8% (p=0.070) (Figure 2B). The 3- and 5-year OS rates of patients with stage III LCC (n= 578) were 92.7% and 88.7% respectively, while those of patients with stage III RCC (n= 329) were 89.3% and 83.0%, and those of patients with stage III RC (n=520) were 89.9% and 80.2% (p=0.001) (Figure 2C).

Long-term outcomes: RCC vs LCC vs RC (RFS)

RFS curves for patients with stage I-III CRC are shown in Figure 2D to 2F. The 3- and 5-year

RFS rates of patients with stage I LCC (n=512) were 96.6% and 95.1% respectively, while those of patients with stage I RCC (n= 338) were 96.9% and 94.5% and those of patients with stage I RC (n= 486) were 94.9% and 90.6% (p=0.027) (Figure 2D). The 3- and 5-year RFS rates of patients with stage II LCC (n= 459) were 87.2% and 85.2% respectively, while those of patients with stage II RCC (n=272) were 92.1% and 90.2%, and those of patients with stage II RC (n=276) were 80.7% and 76.1% (p<0.001) (Figure 2E). RFS rates of patients with stage III LCC (n= 578) were 77.0% and 75.3% respectively, while those of patients with stage III RCC (n= 272) were 77.8% and 75.3%, and those of patients with stage III RC (n=520) were 65.9% and 59.8% (p<0.001) (Figure 2F).

OS curves after primary surgery for patients with recurrent CRC

Figure 3 shows survival after recurrence was significantly poorer in the patients with recurrent stage I-III RCC compared with recurrent stage I-III LCC and RC. Figure 3 shows survival after recurrence stratified by tumor location. The 3- and 5-year survival rates were respectively 48.6% and 35.0% in patients with recurrent RCC (n= 98) 68.5% and 49.7% in patients with recurrent LCC (n= 211), and 60.3% and 44.5% in those with recurrent RC (n= 289) (p=0.042). The median survival time was 34.6 months, 49.1 months, and 60.6 months, respectively.

Factors affecting RFS in Stage I-III CRC

Table 2A shows the univariable and multivariable analyses of factors affecting RFS in patients with stage I-III CRC. According to univariable analysis, Poorer RFS after recurrence was significantly associated with age (≥75), sex, adjuvant therapy, pT stage (T4), pN stage (N2), lymphatic invasion, vascular invasion, and tumor location. According to multivariable analysis, poorer OS was significantly associated with age (≥75) (HR 1.72, 95% CI 1.37–2.13;

p<0.001), sex (HR 1.32, 95% CI 1.12–1.55; p<0.001), adjuvant therapy (HR 0.97, 95% CI 0.79–1.17; p=0.726), pT stage (T4) (HR 2.31, 95% CI 1.87–2.83; p<0.001), pN stage (N2) (HR 2.75, 95% CI 2.24–3.38; p<0.001), lymphatic invasion (HR 1.76, 95% CI 1.49–2.09; p<0.001), vascular invasion (HR 1.47, 95% CI 1.24–1.76; p<0.001), and tumor location. RCC was significantly associated with better RFS compared with LCC (HR 1.29, 95% CI 1.04–1.62; p=0.023) and RC (HR 1.95, 95% CI 1.57–2.44; p<0.001).

Factors affecting prognosis after recurrence

Table 2B shows the univariable and multivariable analyses of factors affecting survival after recurrence in patients with recurrent stage I-III CRC. According to univariable analysis, poorer survival after recurrence was significantly associated with age (≥75), tumor differentiation, CEA at recurrence, pN stage (N2), lymphatic invasion, and tumor location. According to multivariable analysis, poorer survival after recurrence was significantly associated with age (≥75) (HR 2.19, 95% CI 1.51–3.10; p<0.001), tumor differentiation (HR 2.10, 95% CI 1.02–3.82; p=0.043), CEA at recurrence (HR 2.05, 95% CI 1.60–2.62; p<0.001), pN stage (N2) (HR 1.75, 95% CI 1.36–2.26; p<0.001), and tumor location. RCC was significantly associated with poorer survival after recurrence compared with LCC (HR 0.68, 95% CI 0.48–0.97; p=0.036) and showed a tendency toward poorer survival after recurrence compared with RC (HR 0.79, 95% CI 0.57–1.10; p=0.164).

Recurrence sites and resection rate after curative surgery

Table 3 shows the recurrence sites and resection rate after curative surgery for stage I-III CRC. Including patients with metastasis at the initial detection of recurrence, the sites of recurrence were liver only (n=180), lung only (n=180), peritoneal dissemination only (n=17), locoregional only (n=127), and multiple organs or sites (n=94). Liver only metastasis was

significantly more common in RCC and LCC than in RC ($p<0.001$). Lung only metastasis was significantly more common in RC and RCC than in LCC ($p=0.017$). Peritoneal dissemination was significantly more common in RCC and LCC than in RC ($p<0.001$). On the other hand, local recurrence was significantly more common in RC ($p<0.001$). Resection after recurrence was performed in 52% (51/98) of patients with recurrent RCC, 60.7% (128/211) with recurrent LCC, and 51.9% (150/289) with recurrent RC, showing no significant difference in the resection rate according to tumor location.

Discussion

In unresectable advanced or recurrent CRC, sidedness affects the treatment strategy and the prognosis of RCC is poorer than that of LCRC. [3,6] Does sidedness have the same impact in resectable CRC? A major barrier to answering this question is that the relationship between tumor site and outcome after primary surgery in resectable CRC varies due to the quality of surgical procedures and pre- and postoperative treatments, which are directly related to treatment outcomes. This variability is particularly evident in RC, where treatment strategies differ between Japan and other countries. In several previous studies in Japan, the three tumor sites (LCC, RCC, and RC) had different prognostic significance for recurrence and overall mortality after curative resection in 9194 patients with stage III CRC, indicating that tumor site can serve as a prognostic biomarker for stage III CRC.[20] In another study with 820 patients who had stage I-III colon cancer, no significant difference was found in 5-year disease-free survival.[21] These studies may have been affected by selection bias in terms of tumor site and stage. However, in Japan, surgical resection is the treatment of first choice not only for colon cancer but also for RC, with the aim of improving local control by surgical resection. In Japan, the standard treatment strategy is the same for colon cancer and RC, suggesting that it is appropriate to consider RC together with colon cancer.[17]

In previous studies overseas comparison of prognosis was difficult because of differences in preoperative treatments. In Japan, however, the treatment strategy for RC allows for comparison between RC and colon cancer without any influence of preoperative therapy. Accordingly, this retrospective study was able to clarify the prognostic impact of the three tumor locations on recurrence and subsequent survival in patients with stage I-III CRC. In other words, in resectable stage I-III CRC, sidedness was not associated with recurrence and the poor prognosis of LCRC was due to RC, suggesting that different treatment strategies should be considered for "colon cancer" and "rectal cancer". Another important finding of this study was that survival after recurrence was significantly poorer in RCC when the analysis was limited to patients who relapsed. As previously reported, compared with other sites in resectable CRC, RCC may have different prognostic implications in terms of the recurrence rate after curative resection and cancer-specific survival after recurrence.[15] These differences are associated with sidedness and support the results of previous studies of recurrent lesions in resectable stage I-III CRC.[22]

The embryological origin of normal tissue could be one reason why the location of the primary lesion may be a prognostic factor. RCCs originate from the midgut, whereas LCCs and RCs originate from the hindgut. Because of this difference in embryological origin, heterogeneity in the primary site is also important; RCC is characterized by a higher incidence of mucinous carcinoma and poorly differentiated adenocarcinoma in older women compared to LCC. These differences may explain why the location of the primary tumor is associated with different prognoses. Another possibility identified in the present study is differences in the site of recurrence. The peritoneal dissemination rate of RCC was low but was otherwise similar to previous reports. Regardless of the location of the primary tumor, survival after recurrence was more favorable for lung and liver metastases, followed by local recurrence and then peritoneal dissemination. Taken together, these results suggest that the

longer survival after recurrence in the order of left colon, rectum, and right colon for the primary tumor may be explained by differences in the distribution of recurrence sites. We also examined the resection rate of the recurrent tumor as another possible reason why the location of the primary tumor could be a prognostic factor, but no significant difference was found.

This study has some limitations that must be kept in mind. First, the study period was more than 20 years. Treatment strategies for CRC have changed significantly during that time, including postoperative chemotherapy regimens and standardized surgical techniques. The presence or absence of postoperative adjuvant chemotherapy may have altered the prognosis. In addition, only 23% of all patients in this cohort received postoperative chemotherapy, which does not reflect the current use of postoperative adjuvant chemotherapy in Japan. Second, genetic information was not available. Prognostic differences in RCC have been characterized by a higher frequency of MSI and the presence of BRAF mutations. Such information would have aided in the examination of prognostic factors in this study. Other limitations are inherent to the study's single-center retrospective design. Despite these limitations, RCC was significantly associated with better RFS compared with LCC.

In conclusion, in this single-center retrospective study, three tumor sites (right-sided colon, left-sided colon, and rectum) were found to have different prognostic significance for recurrence and all-cause mortality after curative resection without preoperative treatment. RFS before recurrence was worse in RC than in RCC and LCC, indicating that the tumor site should be considered as "colon cancer" vs. "rectal cancer". The difference in survival after recurrence according to tumor site may be due to differences in the distribution of recurrence sites, which impacts prognosis, and tumor site should be considered as a stratification parameter in metastatic CRC. RCC, LCC, and RC can be considered as separate entities and may serve as prognostic biomarkers in resectable stage I-III CRC without preoperative

treatment.

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Figure legends

Figure 1. Flowchart of patients in this study.

The clinicopathological data of 5516 patients with pathologigcally diagnosed stage I-III colorectal cacer who underwent curative surgery during 2000-2015 at the National Cancer Center Hospital. After exclusions, 3770 patients with colorectal cancer were included in the final study population.

Figure 2. Survival outcomes in all patients.

(A) Overall survival in patients with stage I colorectal cancer: right-sided colon cancer vs left-sided colon cancer vs rectal cancer. (B) Overall survival in patients with stage II colorectal cancer: right-sided colon cancer vs left-sided colon cancer vs rectal cancer. (C) Overall survival in patients with stage III colorectal cancer: right-sided colon cancer vs left-sided colon cancer vs rectal cancer. (D) Relapse-free survival in patients with stage I colorectal cancer: right-sided colon cancer vs left-sided colon cancer vs rectal cancer. (E) Overall survival in patients with stage II colorectal cancer: right-sided colon cancer vs left-sided colon cancer vs rectal cancer. (F) Relapse-free survival in patients with stage III colorectal cancer: right-sided colon cancer vs left-sided colon cancer vs rectal cancer.

Figure 3. Survival after recurrence in patients with recurrent CRC.

Survival after recurrence in patients with recurrent CRC: right-sided colon cancer vs left-sided colon cancer vs rectal cancer.

Table 1. Clinicopathological characteristics of patients with stage I-III colorectal cancers

	All, n=3770	RCC, n=944 (25.0%)	LCC, n=1547 (41.0%)	RC, n=1279 (34.0%)	p-value
Age, years					
<75	3268 (86.7)	744 (78.8)	1355 (87.6)	1169(91.4)	<0.001
≥75	502 (13.3)	200 (21.2)	192 (12.4)	110(8.6)	
Sex					
Male	2120 (55.8)	476 (50.4)	798 (51.6)	846 (66.1)	<0.001
Female	1650 (44.2)	468 (49.6)	749 (48.4)	433 (33.9)	
Tumor differentiation					
Differentiated	3656 (97.0)	898 (95.1)	1515 (97.9)	1243 (97.2)	0.104
Others	114 (3.0)	46 (4.9)	32 (2.1)	36 (2.8)	
Preoperative CEA, ng/ml					
≤5	2920 (77.5)	756 (80.1)	1212 (78.3)	952 (74.4)	0.006
>5	850 (22.5)	188 (19.9)	335 (21.7)	327 (25.6)	
pT stage					
T1	940 (24.9)	250 (26.5)	390 (25.2)	300 (23.5)	<0.001
T2	660 (17.5)	132 (14.0)	221 (14.3)	307 (24.0)	
T3	1770 (46.9)	429 (45.4)	769 (49.7)	572 (44.7)	
T4	334 (8.6)	120 (12.7)	146 (9.4)	68 (5.3)	
pN stage					
N0	2343 (62.2)	614 (65.1)	969 (62.6)	760 (59.4)	<0.001
N1	993 (26.3)	241 (25.5)	430 (27.8)	322 (25.2)	
N2	434 (11.5)	89 (9.4)	148 (9.6)	197 (15.4)	
Adjuvant therapy					
Yes	866 (23.0)	177 (18.8)	372 (24.0)	317 (24.8)	0.002
No	2904 (77.0)	767 (81.2)	1175 (76.0)	962 (75.2)	
Recurrence after surgery					
Yes	598 (15.9)	98 (16.4)	211 (13.6)	289 (22.6)	<0.001
No	3172 (84.1)	845 (89.5)	1336 (86.4)	991 (77.5)	
pStage					
pStage I	1336 (35.4)	338 (35.8)	512 (33.1)	486 (38.0)	<0.001
pStage II	1007 (26.7)	272 (28.8)	459 (29.7)	276 (21.6)	
pStage III	1427 (37.9)	329 (34.9)	578 (37.4)	520 (40.7)	

Table 2A. Univariable and multivariable analyses of factors affecting relapse-free survival in patients with stage I-III colorectal cancers

Variable	Category	Univariable analysis p-value	Multivariable analysis		
			Hazard ratio	95% CI	p-value
Age, years	<75	0.036	Reference		
	≥75		1.72	1.37-2.15	<0.001
Sex	Male	<0.001	Reference		
	Female		0.73	0.62-0.87	<0.001
Tumor differentiation	Differentiated	0.386			
	Others				
CEA, ng/ml	≤5	<0.001	Reference		
	>5		1.54	1.29-1.82	<0.001
Adjuvant therapy	Yes	<0.001	Reference		
	No		1.11	0.91-1.36	0.298
pT stage	T1/T2/T3	<0.001	Reference		
	T4		2.09	1.68-2.58	<0.001
pN stage	N0/N1	<0.001	Reference		
	N2		2.86	2.32-3.53	<0.001
Lymphatic invasion	-	<0.001	Reference		
	+		1.74	1.46-2.07	<0.001
Vascular invasion	-	<0.001	Reference		
	+		1.44	1.21-1.73	<0.001
Tumor location	RCC	<0.001	Reference		
	LCC		1.29	1.03-1.63	0.025
	RC		1.89	1.51-2.38	<0.001

Table 2B. Univariable and multivariable analyses of factors affecting survival after recurrence in patients with recurrent stage I-III colorectal cancers

Variable	Category	Median overall survival (months)	Univariable analysis p-value	Multivariable analysis		
				Hazard ratio	95% CI	p-value
Age, years	<75	55.7	<0.001	Reference		
	≥75	24.1		2.19	1.51-3.10	<0.001
Sex	Male	58.5	0.158			
	Female	46.5				
Tumor differentiation	Differentiated	52.0	0.003	Reference		
	Others	11.8		2.10	1.02-3.82	0.043
CEA at recurrence, ng/ml	≤5	82.1	<0.001	Reference		
	>5	33.9		2.05	1.60-2.62	<0.001
Adjuvant therapy	Yes	38.7	0.173			
	No	55.9				
pT stage	T1/T2/T3	54.0	0.058			
	T4	35.7				
pN stage	N0/N1	67.1	<0.001	Reference		
	N2	34.3		1.75	1.36-2.26	<0.001
Lymphatic invasion	-	41.8	0.003	Reference		
	+	67.3		1.19	0.93-1.53	0.176
Vascular invasion	-	67.3	0.719			
	+	41.8				
Tumor location	RCC	34.6	0.049	Reference		
	LCC	61.0		0.68	0.48-0.97	0.036
	RC	49.1		0.79	0.57-1.10	0.164

Table 3. Site of recurrence and resection rate of recurrent colorectal cancer after curative surgery

Site	RCC, n=98 (16.4%)	LCC, n=211 (35.3%)	RC, n=289 (48.3%)	Univariable analysis p-value
Single organ or site				
Liver only (n=180)	38 (38.8)	91 (43.1)	51 (17.6)	< 0.001
Lung only (n=180)	24 (24.5)	53 (25.1)	103 (35.6)	0.017
Peritoneal dissemination (n=17)	3 (3.1)	13 (6.2)	1 (0.3)	< 0.001
Locoregional only (n=127)	18 (18.4)	19 (9.0)	90 (31.1)	< 0.001
Multiple organs or sites (n=94)	15 (15.3)	35 (16.6)	44 (15.2)	0.911
Resection after recurrence				
+ (n=329)	51 (52.0)	128 (60.7)	150 (51.9)	0.121
- (n=269)	47 (48.0)	83 (39.3)	139 (48.1)	

Figure 1

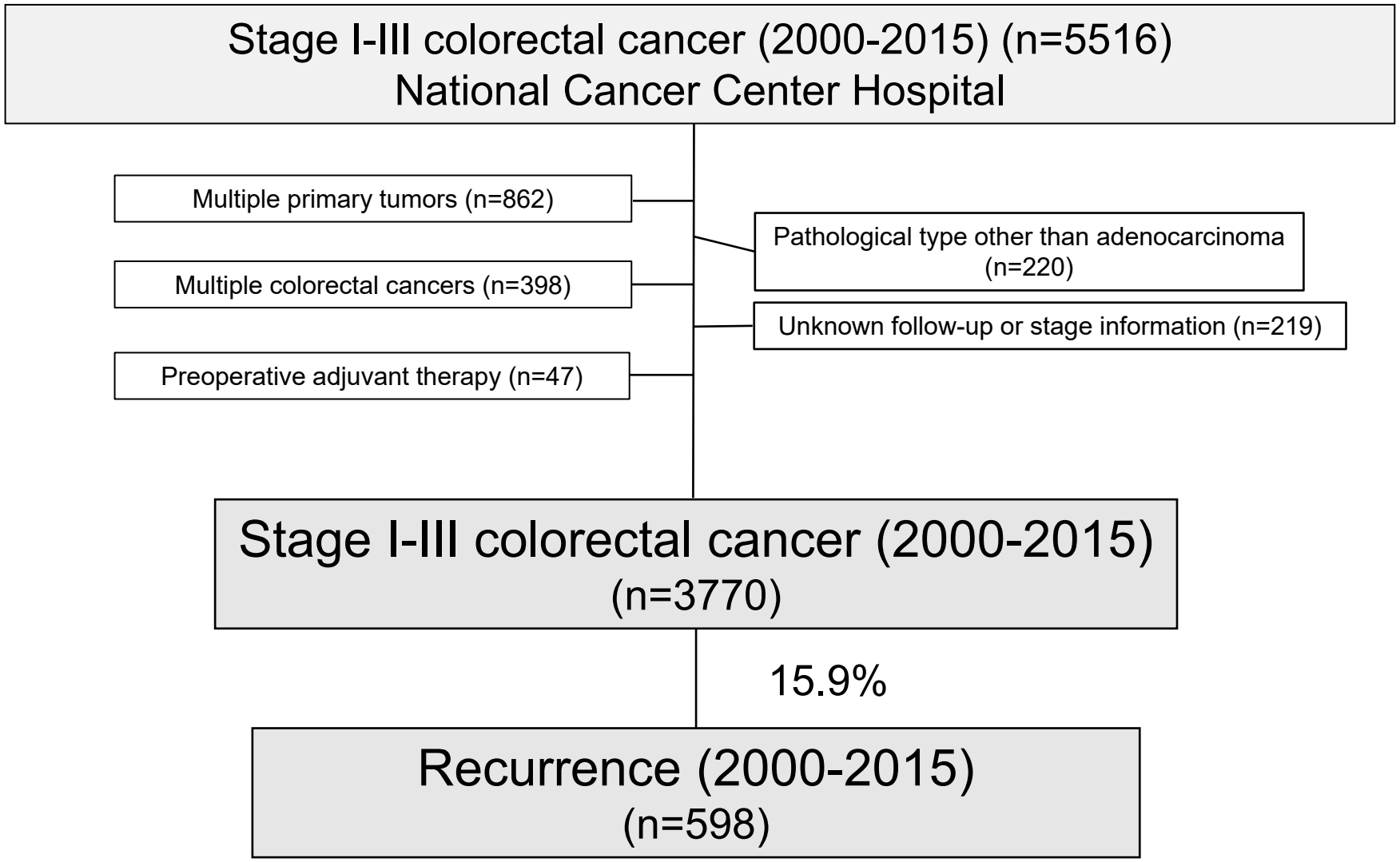
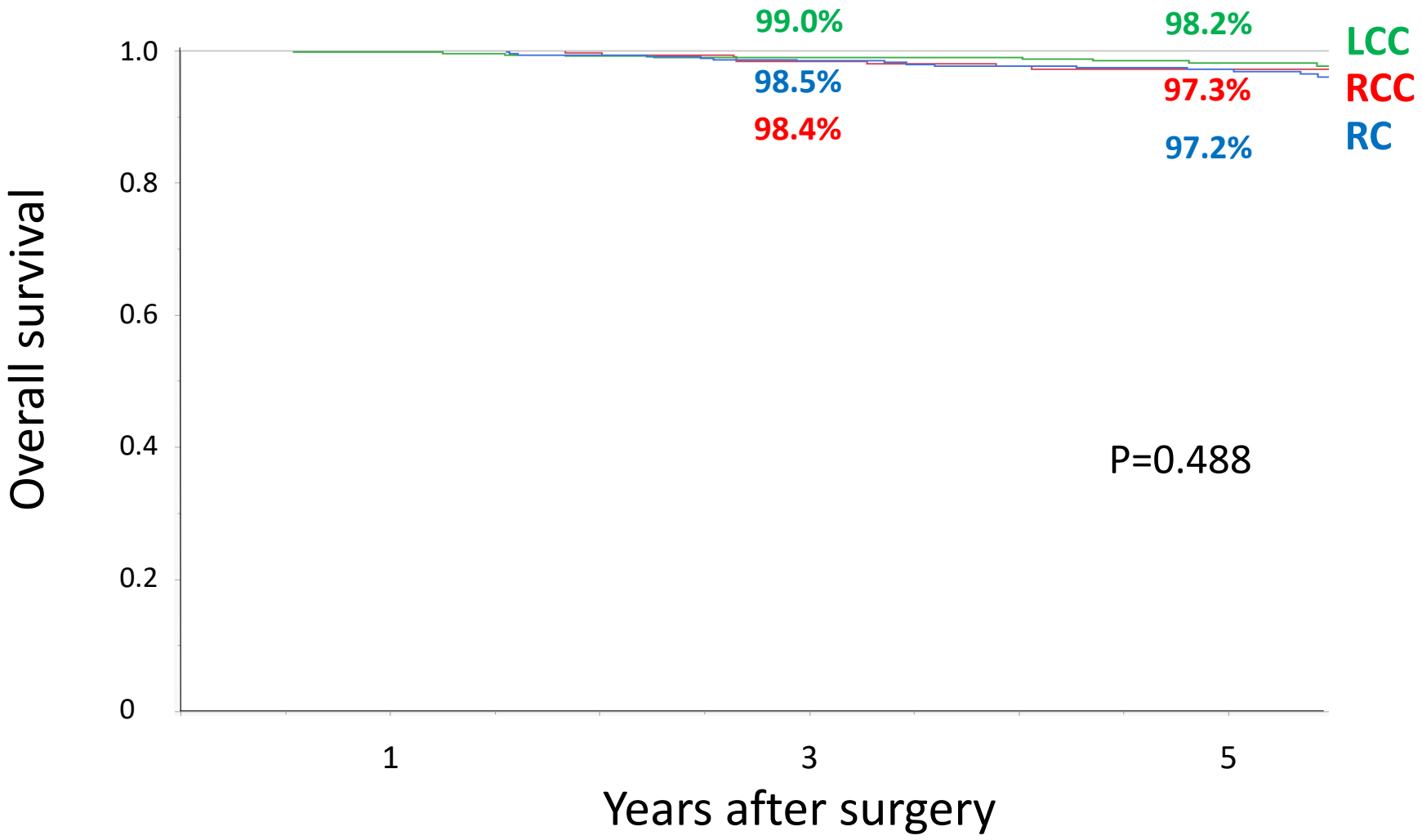

Stage I-III colorectal cancer (2000-2015) (n=5516)
National Cancer Center Hospital
Multiple primary tumors (n=862)
Multiple colorectal cancers (n=398)
Preoperative adjuvant therapy (n=47)
Pathological type other than adenocarcinoma (n=220)
Unknown follow-up or stage information (n=219)
Stage I-III colorectal cancer (2000-2015) (n=3770)
15.9%
Recurrence (2000-2015) (n=598)

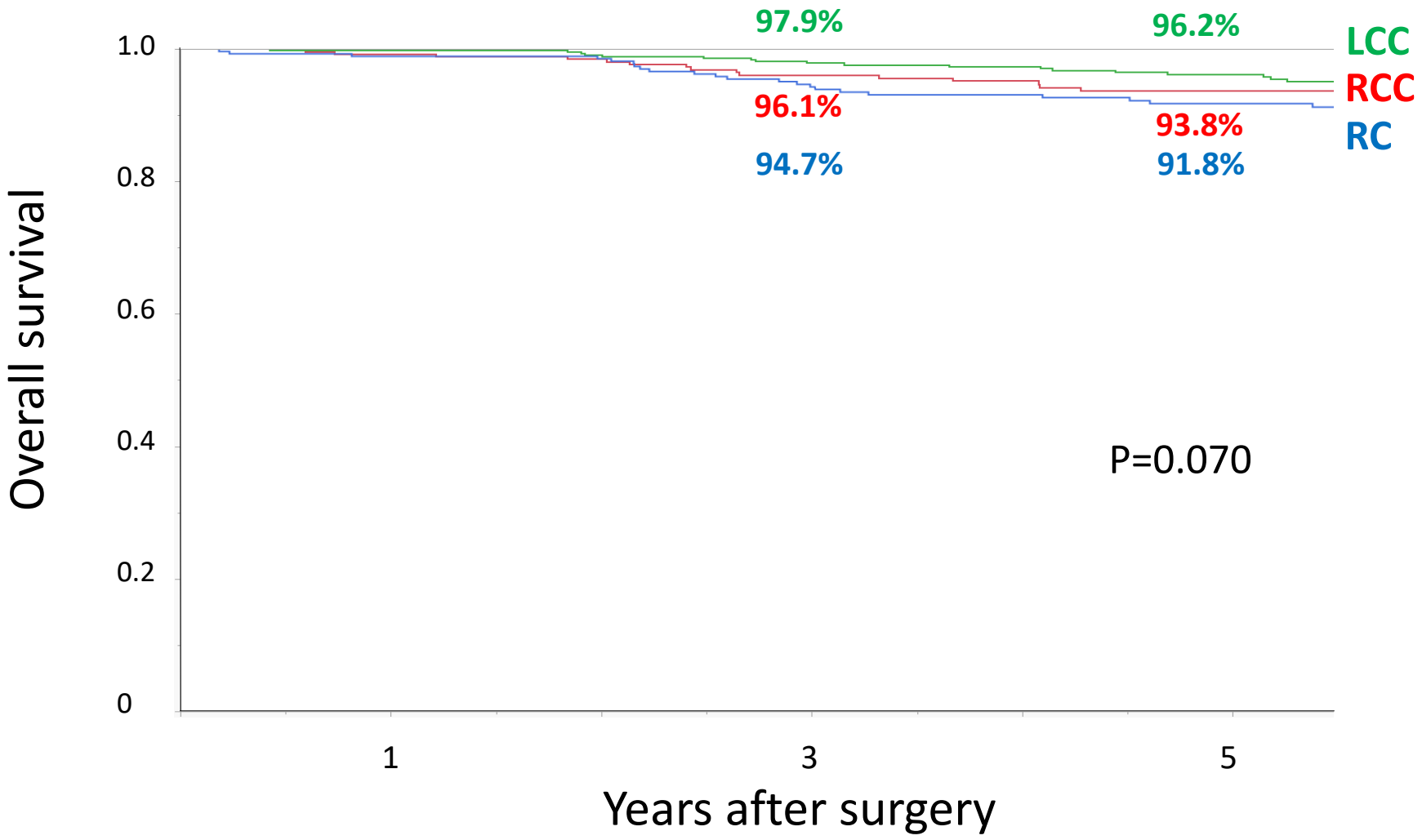
Figure 2A. Overall survival in patients with stage I colorectal cancer.



No. at risk

RCC	338	333	326	293	262	215
LCC	512	504	488	446	399	352
RC	486	482	467	437	396	334

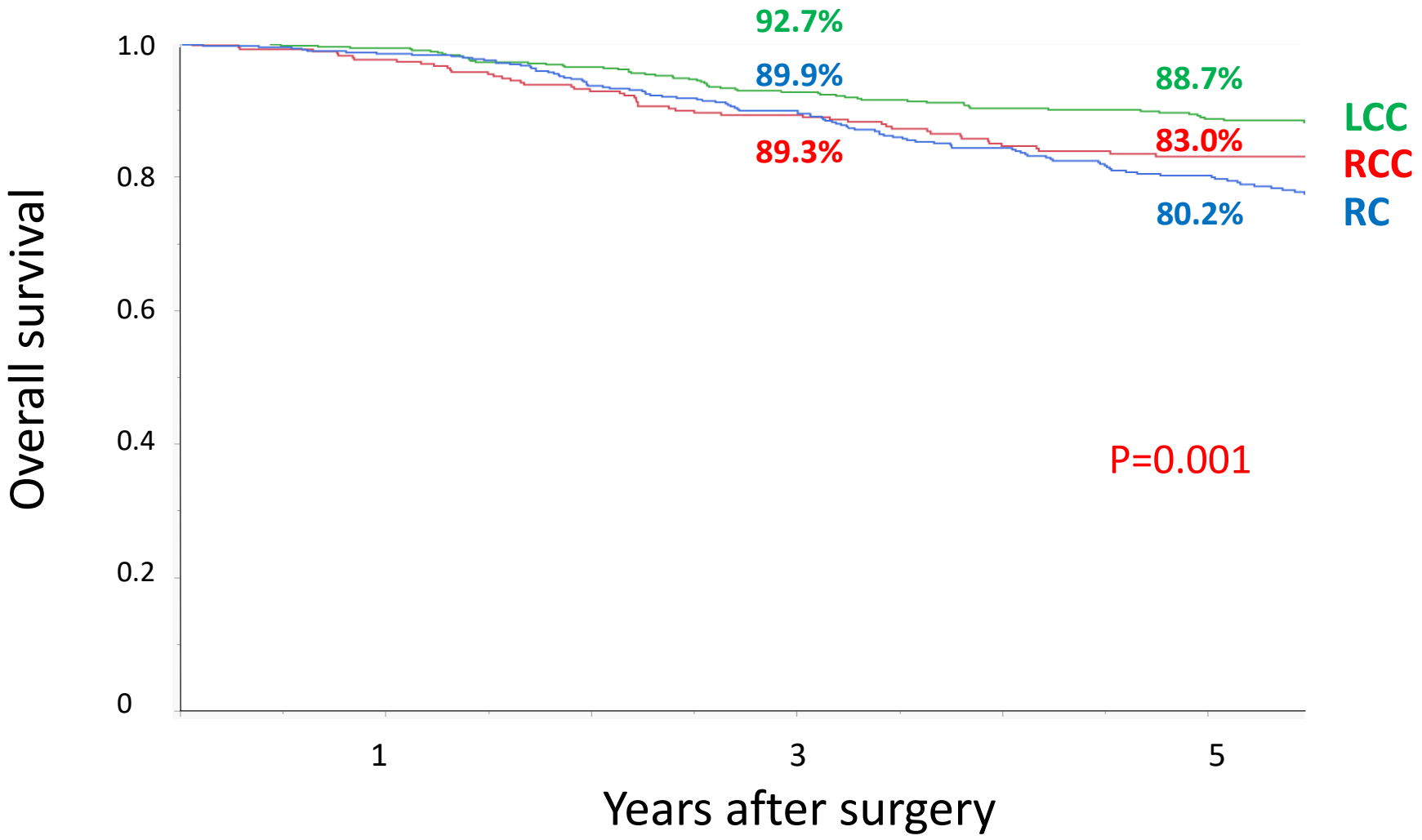
Figure 2B. Overall survival in patients with stage II colorectal cancer.



No. at risk

RCC	272	266	255	230	203	178
LCC	459	450	436	392	354	307
RC	276	271	261	241	219	194

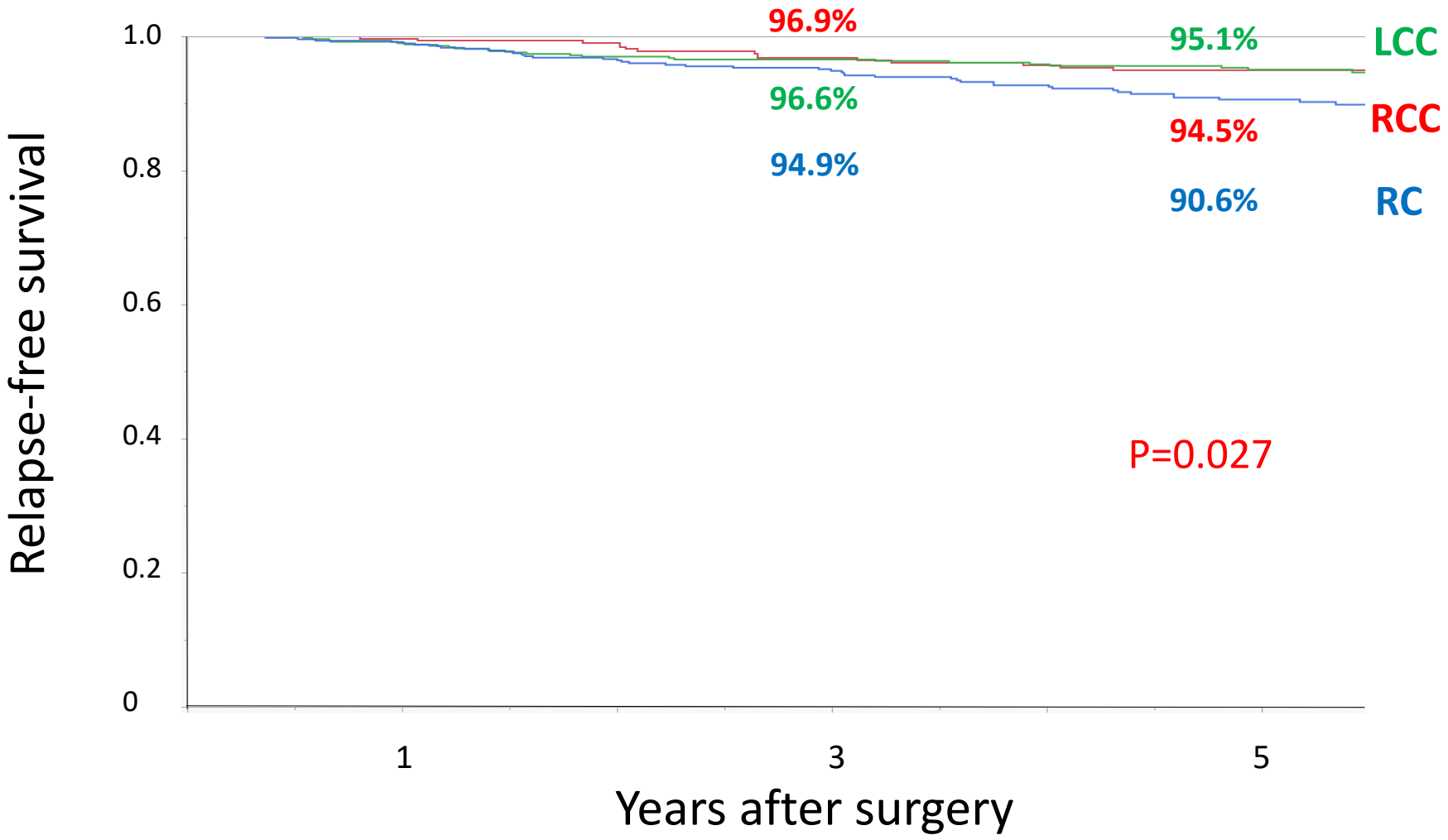
Figure 2C. Overall survival in patients with stage III colorectal cancer.



No. at risk

RCC	329	315	292	268	229	192
LCC	578	563	533	476	430	387
RC	520	502	463	419	359	315

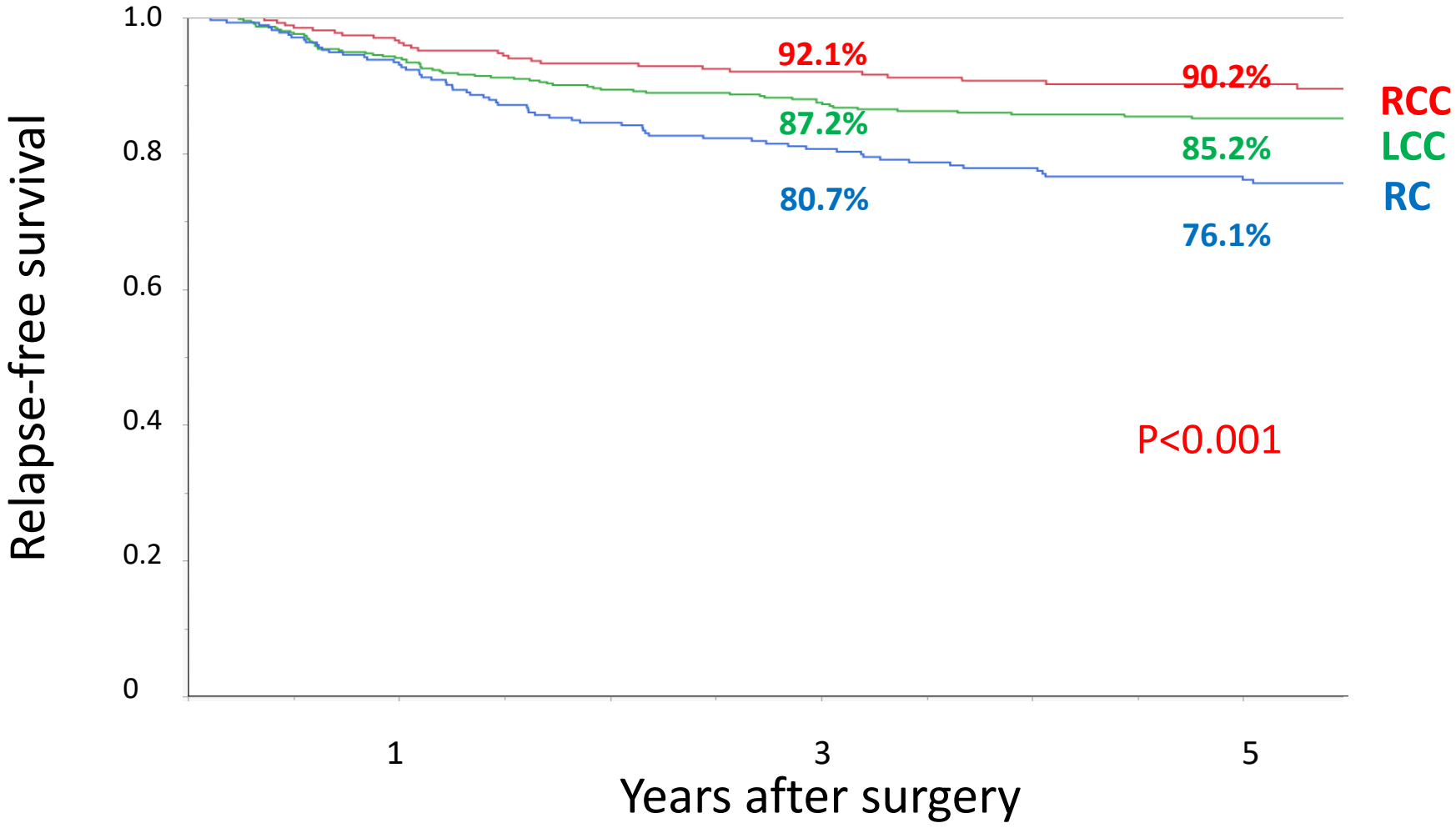
Figure 2D. Relapse-free survival in patients with stage I colorectal cancer.



No. at risk

RCC	338	333	324	288	257	210
LCC	512	500	478	437	389	342
RC	486	477	454	422	378	313

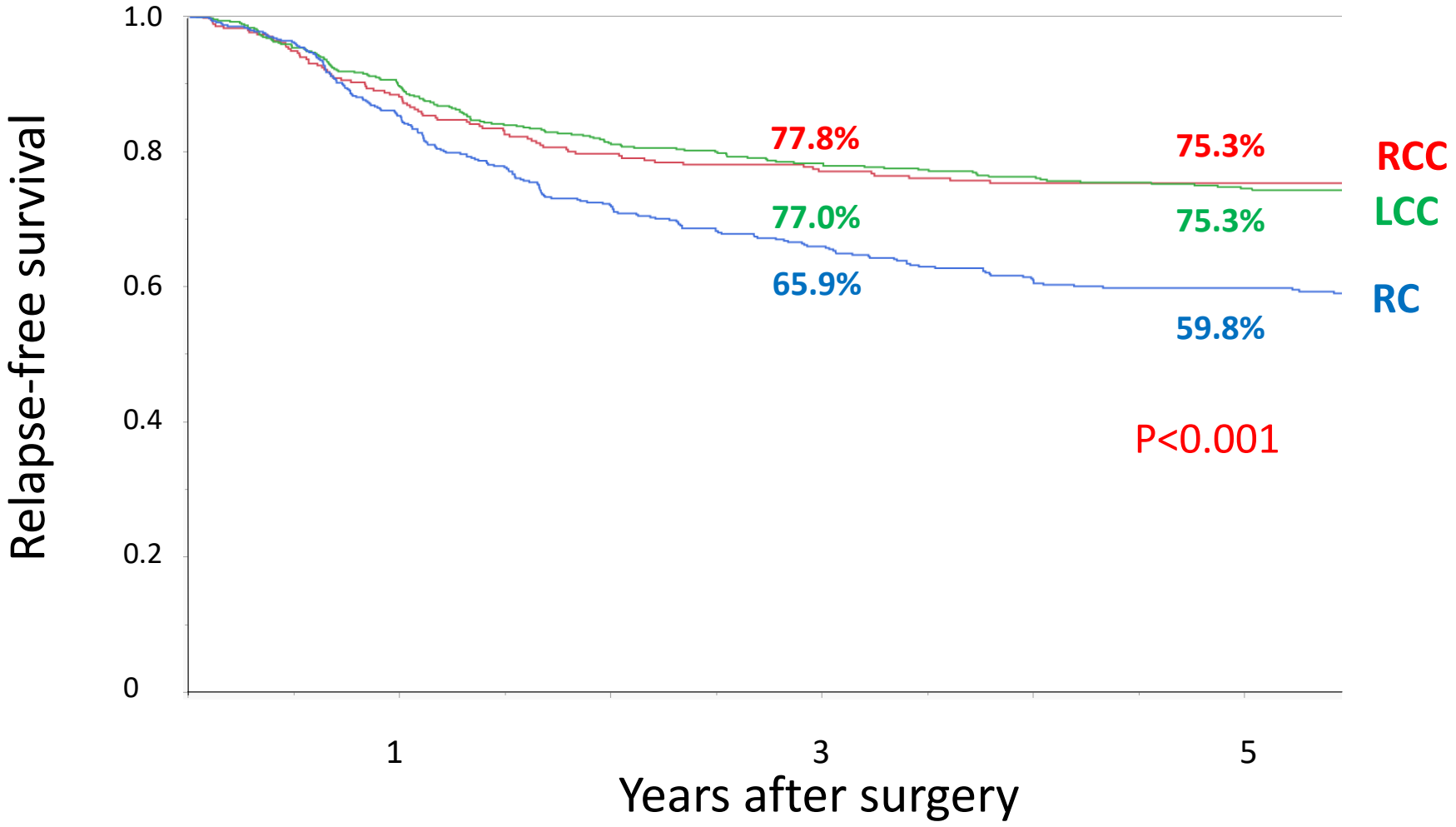
Figure 2E. Relapse-free survival in patients with stage II colorectal cancer.



No. at risk

RCC	272	259	242	220	193	170
LCC	459	426	398	358	324	282
RC	276	256	224	206	185	164

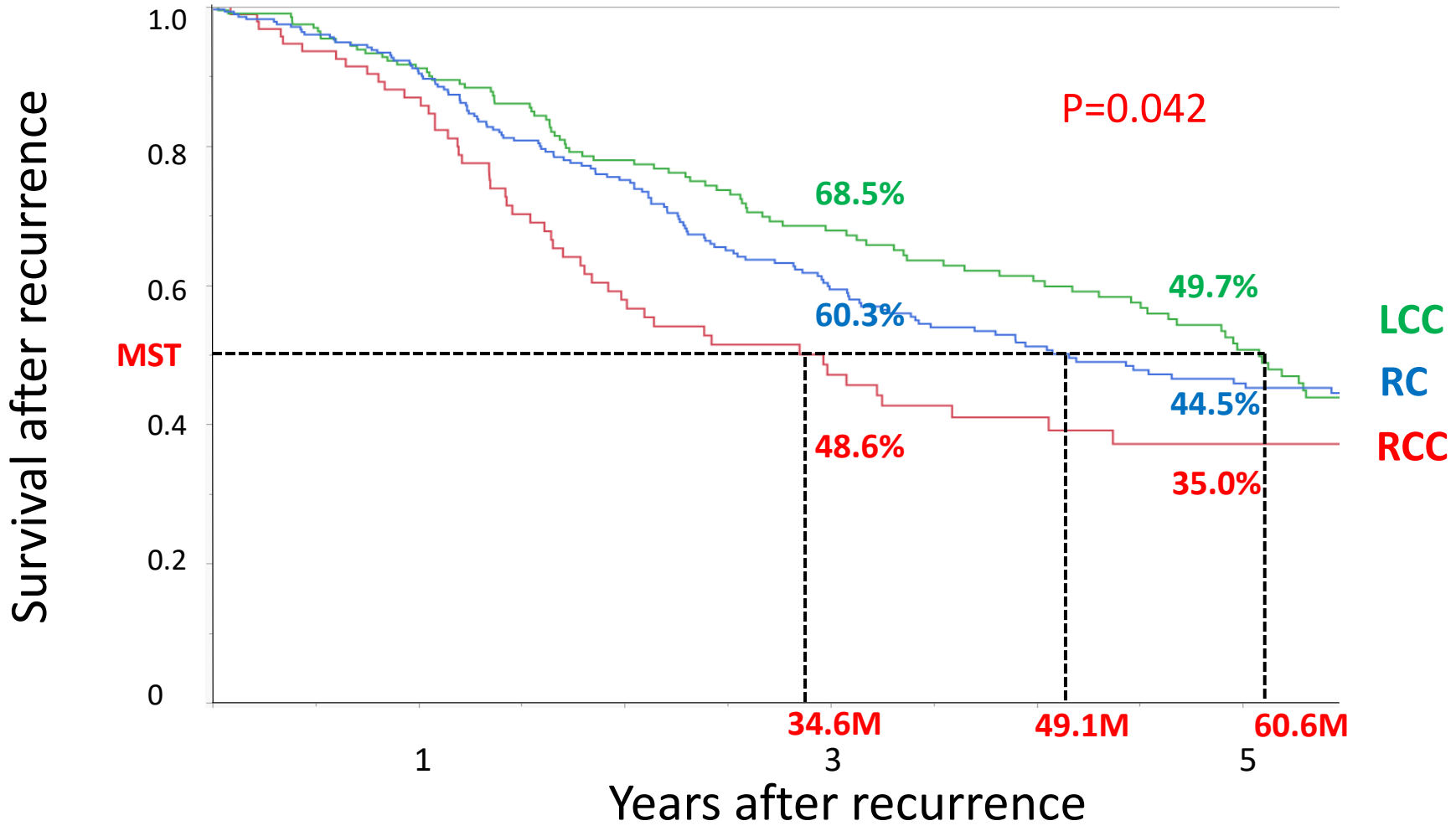
Figure 2F. Relapse-free survival in patients with stage III colorectal cancer.



No. at risk

RCC	329	286	251	234	209	182
LCC	578	511	453	407	366	327
RC	520	437	360	318	270	243

Figure 3. Survival after recurrence in patients with recurrent CRC.



No. at risk

RCC	98	76	47	34	24	17
LCC	211	165	133	103	81	58
RC	289	240	180	127	94	70