ORIGINAL ARTICLE

Retrospective Study

Evaluation of prognostic factors and clinicopathological patterns of recurrence after curative surgery for colorectal cancer

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Abstract

BACKGROUND
Colorectal cancer is a common tumor with a quite high-related mortality. Despite the used curative treatments, patients will develop cancer recurrence in up to 50% of the cases and/or other primary neoplasms. Although most of the recurrences are discovered within 3 years from the first treatment, a small percentage is found after 5 years. The early detection of recurrence is crucial to allow further therapies improving patients' survival. Several follow-up programs have been developed but the optimal one is far from being established.

AIM
To evaluation of potential prognostic factors for timing and patterns of recurrence in order to plan tailored follow-up programs.

METHODS
Perioperative and long-term data of all consecutive patients surgically treated with curative intent, from January 2006 to June 2009, for colorectal adenocarcinoma, were retrospectively reviewed to find potential prognostic factors associated with: (1) Recurrence incidence; (2) Incidence of an early (within 3 years from surgery) or late recurrence; and (3) Different sites of recurrence. In addition, the incidence of other primary neoplasms has been evaluated in a cohort of patients with a minimum potential follow-up of 10 years.

RESULTS
Our study included 234 patients. The median follow-up period has been 119 ± 46.2 mo. The recurrence rate has been 25.6%. Patients with a higher chance to develop recurrence had also the following characteristics: Higher levels of preoperative glycemia and carcinoembryonic antigen, highest anaesthesiologists

Score score, occlusion, received a complex operation performed with an open technique, after a longer hospital stay, and showed advanced tumors. The independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1 (multivariate analysis). Younger ages were significantly associated with an early recurrence onset. Patients that received intermediate colectomies or segmental resections, having an N stage 2 or American Joint Committee on Cancer stage 3 tumors were also associated with a higher risk of liver recurrence, while metastatic diseases at diagnosis were linked with local recurrence. Neoadjuvant treatments showed lung recurrence. Finally, bigger tumors and higher lymph node ratio were associated with peritoneal recurrence (marginally significant). Thirty patients developed a second malignancy during the follow-up time.

CONCLUSION
Several prognostic factors should be considered for tailored follow-up programs, eventually, beyond 5 years from the first treatment.

Key Words: Prognostic factors; Recurrence; Recurrence patterns; Colorectal cancer; Long-term follow-up; Follow-up programs

Core Tip: In this retrospective study, several potential prognostic factors for recurrence, timing, and recurrence sites have been evaluated in patients who received curative colorectal surgery for adenocarcinoma with a potential minimum follow-up of 10 years. The independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1. Of note, younger ages were significantly associated with an early onset of recurrence. Some prognostic factors have been found for each site of recurrence: Liver, local, lung, and peritoneum. Thirty patients developed a second malignancy during the follow-up period. These findings may help in providing a tailored follow-up program.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms in the world with an age-standardized worldwide incidence of 19.7 and mortality of 8.9 per 100000 person-year, respectively[1].

Surgical resection is the cornerstone of CRC management. However, according to the clinical and pathological stage, this treatment should be integrated with neoadjuvant and/or adjuvant therapies, where appropriate[2].

Despite the curative-intent of the first treatment, the patients have a considerable risk of developing cancer recurrence and/or other primary tumors[3,4]. Liver is the most frequent site of recurrence and liver metastases are diagnosed in up to 50% of the patients. Lungs are the second site for frequency of recurrence but, unfortunately, only a small percentage of them will develop lungs-only recurrence susceptible to resection[5]. Locoregional and peritoneal recurrences are reported in 4% to 11.5% and 3% to 6%, respectively[5,6]. Finally, the increasing cumulative risk to develop a second colorectal cancer is reported to be 3% every 6 years[7].

Analysis of prognostic factors for recurrence and of the specific recurrence patterns is seldom reported since the great majority of the registries rarely detailed the sites of the development of metastases[8].

About 80% of the recurrences occurs within the first 3 years of primary surgery and about 95% within 5 years with a small percentage of the patients (0.9%-9%) who will

suffer from recurrence 5 years after the treatment[9]. The clinical and pathologic characteristics of early or late recurrence after curative surgery have been rarely described. Therefore, it is unclear whether there is a significant difference between these two groups in terms of prognosis[10,11]. However, the early recurrence detection or the diagnosis of other neoplasms is an important factor to allow radical resection, when technically feasible and oncologically appropriate. Although the relation between early detection of recurrence and prognosis is still under debate[12], many follow-up programs have been developed over the years and in different countries. There are significant variations in the length and strength of follow-up strategies in the different centers, in the type and timing of the examination, in the staff conducting and reviewing the tests, and the optimum follow-up schedule is far from being defined[12,13]. The great majority of the surveillance programs ends in 5 years after the primary colorectal resection[3,9,12] while colonoscopy follow-up programs are recommended to be continued beyond 5 years with the timing established on endoscopic findings[7].

Our study aims to evaluate - in a cohort of patients who received curative surgery and who had a potential minimum of 10-years of follow-up - the clinical, operative, and pathological potential prognostic factors that may influence the recurrence development, the timing and site of disease presentation. This evaluation will allow us to fine-tune a tailored follow-up program.

MATERIALS AND METHODS

Study design

All patients submitted to an elective oncological colorectal surgery at the actually renamed Hepatobiliary Surgery Unit of Careggi Teaching Hospital, Florence, Italy from January 2006 to June 2009 and identified for follow-up of at least 10 years were evaluated for inclusion in this retrospective study.

Exclusion criteria were: Final histopathological diagnosis of benign pathology; other concomitant malignancies; histological report different from adenocarcinoma; previous oncological colorectal surgery; palliative-intent surgery, unavailability of data about recurrence status.

Data concerning demographic aspects, primary lesion, operative and postoperative outcomes, histopathological response, and long-term outcomes were prospectively recorded in a specific database. Standard preoperative work-up included triple-phase contrast-enhanced computed tomography (CT) scan and pancolonoscopy. Other radiological tests, including magnetic resonance imaging and positron emission tomography scan, were performed when required. Every decision about patients' treatments was taken after the weekly Multidisciplinary Team evaluation.

Some definitions: "Right colon" has been defined as the tract between the caecum and middle transverse colon while "left colon" has been defined as the tract between the splenic flexure and sigmoid colon.

The surgical technique was chosen according stage disease, patient conditions, and surgeon's preference and it was reported according to an "intention-to-treat" evaluation. Associated procedures were defined as "minor" including appendicectomy, oophorectomy, or cholecystectomy, and "major" including hepatic resections. Histopathological evaluation was performed following the tumor node metastasis (TNM) classification, 6th edition[14]. The lymph node ratio was defined as the number of positive lymph nodes on the total lymph nodes retrieved. Chemotherapy was considered if administered to the patient despite the interruption of the initially scheduled program due to intolerance or any other reasons. Recurrence was considered in case of high radiological suspicion and/or after the biopsy and it was divided into liver, lung, peritoneal, and "locoregional" metastasis (including tumor recurrence on the previous anastomotic line or in the lymph nodes or soft tissue near the previous surgical site). Recurrence was defined as "early" or "late" if it occurred within or beyond 3 years from surgery, respectively. In case of patient presentation with CRC and synchronous liver metastasis treated with two a 2-step surgery, disease-free survival (DFS) was considered as the time between the second intervention and the time of the first available diagnosis of recurrence or death. Recurrences were treated with surgery, chemotherapy, radiation, palliation of the symptoms including jaundice or best supportive care, as appropriated.

Within the subgroup of patients experiencing recurrence, ananalysis of the potential prognostic factors for each site of recurrence was performed to try to find clinicopathological patterns of recurrence.

Follow-up program

Follow-up was conducted according to a standardized program. The complete follow-up program is reported in Table 1. Follow-up included a physical examination, carcinoembrionyc antigen (CEA) determination, and a routine blood examination, endoscopy, chest radiography, abdominal sonography, and/or a CT scan. If recurrence was suspected or patients developed abdominal symptoms, further examinations were performed (*i.e.* whole-body positron emission tomography or hepatic magnetic resonance imaging). Scheduled tests could have been modified according to the oncologist's indications.

Retrieval of follow-up data was completed with a revision *via* available medical records and phone call interviews.

Analysis

Patients' data were prospectively collected into a database that was retrospectively reviewed. Continuous variables were reported as mean ± SD while categorical variables were reported as frequency and percentage.

To evaluate the association between possible prognostic factors and DFS and overall survival (OS) a Cox model, Kaplan-Meier method, and log-rank test were used.

To estimate possible independent prognostic factors for recurrence a multiple Cox model with a backward selection method was used. To assess the association between each possible prognostic factor and timing to recurrence (< 3 years or ≥ 3 years) a simple logistic regression model was used.

Statistical significance was defined as P value ≤ 0.05.

Data were analyzed using the statistical software SPSS, version 24 (IBM Corp.). The statistical review of the study was performed by the biostatistic Lorenzo Tofani.

RESULTS

During the study period, 360 patients underwent colorectal surgery for neoplasms. According to the exclusion criteria, 234 patients were included in our analysis. Further details are shown in Figure 1.

Analysis of survival and recurrence

The median follow-up time was 119 ± 46.2 mo. Tumor recurrences occurred in 60 patients (25.6%). The OS rate was 86.7%, 78.1%, and 59.9% at 3, 5, and 10 years, respectively. The DFS rate was 75.7%, 71.2%, and 58.3% at 3, 5, and 10 years, respectively, with a median DFS of 150 mo.

Table 2 includes the significant potential prognostic factors for DFS and OS. The American Joint Committee on Cancer (AJCC) stage and the pathological M stage resulted as strong prognostic factors for both DFS and OS. The recurrence timing resulted in a significant prognostic factor for OS but there were no significant differences in post recurrence OS (P = 0.011 and P = 0.991, respectively, Figure 2).

Recurrence characteristics and related treatments are reported in Table 3.

Fifty-one patients (85% of those experiencing recurrence) recurred within 3 years from the first intervention while 9 (15%) of them recurred beyond 3 years. The recurrence rate after 5 years was 1.7% within the entire cohort and 6.7% within the recurrence group. Consequently, 15.3 patients had to be observed between 5 and 10 years from the first treatment in order to detect 1 recurrence beyond 5 years.

Twenty-two out of the 24 patients who received a second surgical curative intervention, with or without subsequent chemotherapy protocols, achieved a status of disease-free. Four of them resulted in disease-free and alive 10 years after surgery while twelve of them developed further recurrence within a mean time from the first intervention of 44.4 mo (11-85 mo). Additional analysis involving recurrence treatments will be no object of the present study.

Fifty patients (83.3% of those experiencing recurrence) presented with the persistence of tumoral disease at death or at the time of the last follow-up.

Actual 10-years survivors were 111 (47.4%), 6 of them had developed a recurrence during the follow-up time and had received a second treatment.

Moreover, during the follow-up period, 30 patients developed a second malignancy: Colorectal (n = 6), breast (n = 4), prostate (n = 2), other urologic cancer (n = 3), intracranial cancer (n = 4), pancreas (n = 4) and other (n = 7). The mean time of second malignancies development was 80 mo (range 8-153). Amongst these patients, 18 developed a second neoplasm beyond 5 years and 6 died because of second neoplasms.

Table 1 Complete follow-up program

Time from surgery	Tests				
	Full blood count, liver function tests, CEA	Abdominal US	Chest X-Ray	Abdominal CT scan	Colonoscopy
3 mo	√				
6 mo	√	√	√		
9 mo	√				
12 mo	√		√	√	√
18 mo	√				
2 yr	√		√	√	√
3 yr	√		√	√	√
4 yr	√	√	√		
5 yr	√		√	√	√

CEA: Carcinoembrionyc antigen; US: Ultrasonography; CT: Computed tomography.

Analysis of the prognostic factors for recurrence and comparison between early and late recurrence

Demographic and patient-related potential prognostic factors for recurrence and evaluation of early *vs* late recurrence are shown in Table 4.

Preoperative glycemia and abnormal CEA values were significantly higher in the recurrence group.

Anaesthesiologists Score (ASA) score grade 4 has a more than 3-fold higher recurrence risk compared to the American Society of ASA grade 1 ($P = 0.045$). Patients presenting with bowel obstruction were 32. Four of them received a transverse loop colostomy before curative surgery. The tumor appearance with occlusive symptoms was higher in the recurrence group ($P = 0.021$).

Younger ages resulted significantly associated with early recurrence ($P = 0.050$).

Table 5 reports the treatment-related potential prognostic factors for recurrence and evaluation of early *vs* late recurrence.

Ten percent of the patients with a rectal cancer location received neoadjuvant chemoradiation and administration of neoadjuvant therapy did not result in a significant prognostic factor although the high rate of missing data has to be taken into account. Patients treated with an associated major procedure have a 3.5-fold higher risk of recurrence when compared to the patients receiving only the colorectal resection ($P = 0.007$). Patients treated with open surgery have a high risk of recurrence ($P < 0.001$) and the open technique showed a marginally significant association ($P = 0.061$) with "early recurrence".

During the hospital stay, 10 patients required reoperations due to complications: Anastomotic leak ($n = 5$), hemoperitoneum ($n = 2$), wound dehiscence ($n = 1$), rectal bleeding not amenable to endoscopic treatments ($n = 1$), acute pancreatitis ($n = 1$). However, reoperation did not result associated with higher recurrence risk. A longer hospital stay resulted significantly associated with recurrence ($P = 0.001$).

Chemotherapy mainly consisted of 5-fluorouracil and folinic acid. Some patients were also treated with capecitabine, irinotecan, and oxaliplatin-based chemotherapy. Administration of adjuvant chemotherapy showed a marginally significant association with recurrence rate and with the early onset of the disease ($P = 0.064$ and $P = 0.057$, respectively).

Pathological-related potential prognostic factors for recurrence and evaluation of early *vs* late recurrence are presented in Table 6.

Each parameter of the TNM classification and the AJCC stage resulted strongly associated with recurrence and the group patients of the AJCC stage 3 showed a marginally significant higher chance to develop an early recurrence when compared to the AJCC stage 1 ($P = 0.053$).

The mean number of lymph nodes retrieved was 19.4 (range 3-133). An incorrect disease stadiation following the retrieval of fewer than 12 nodes did not significantly influence the recurrence ($P = 0.535$). The lymph node ratio was significantly higher in the recurrence group ($P < 0.001$).

Table 2 Potential prognostic factor for disease-free survival and overall survival

	Disease free survival (DFS)			P value	Overall survival (OS)			P value
	3 yr (%)	5 yr (%)	10 y (%)		3 yr (%)	5 yr (%)	10 yr (%)	
CEA				0.095				0.045
< 5 ng/mL	84.4	80.8	73.1		88.3	79.8	69.6	
≥ 5 ng/mL	72.2	61.1	50.0		81.0	66.7	42.9	
AJCC stage				< 0.0001				< 0.0001
1	86.9	82.9	70.6		91.1	83.5	70.4	
2	87.7	76.2	57.9		92.9	82.1	54.3	
3	59.3	57.9	50.6		72.0	61.0	48.5	
4	20.0	-	-		63.6	45.5	18.2	
Pathologic M stage[1]				< 0.0001				0.002
0	77.0	71.2	58.4		85.1	74.4	57.0	
1	20.0	-	-		63.6	45.5	18.2	
Retrieved LN				0.819				0.688
< 12	81.5	75.4	58.1		87.5	76.4	54.7	
≥ 12	73.3	69.3	58.8		83.2	73.8	56.4	
LN ratio				0.068				0.043
< 15	66.8	64.0	55.6		78.0	70.7	56.0	
≥ 15	41.5	41.5	36.2		61.7	44.7	33.8	
Timing of recurrence								0.028
Early (< 3 yr[2])					54.9	33.3	11.8	
Late (≥ 3 yr[2])					100	77.8	22.2	

[1]According to the tumor node metastasis staging system.
[2]Recurrence from the first treatment.
CEA: Carcinoembryonic antigen; AJCC: American Joint Committee on Cancer; LN: Lymph node.

At the multivariate analysis, the only independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1 (Table 7). None of the prognostic factors analyzed remained significant at the multivariate analysis of the comparison between early or late recurrence.

Pattern of recurrence

Two patients were excluded from this analysis because there were no available data about the recurrence site. The most frequent site of recurrence was the liver (41.7%), followed by the locoregional recurrence (28.3%), the lung (26.7%), and the peritoneum (11.7%).

Tables 8-10 reported the results of the univariate analysis of the previously reported potential prognostic factors for liver and lung recurrence.

Patients receiving intermediate colectomies or segmental resections, having an N stage 2 or AJCC stage 3 tumor showed a higher risk of developing a liver recurrence. Patients receiving postoperative blood transfusions and adjuvant chemotherapy had a marginally significant higher chance of suffering from liver recurrence ($P = 0.067$ and $P = 0.055$).

Patients receiving neoadjuvant treatments had a higher rate of lung recurrence ($P = 0.010$).

In Tables 11-13, we have summarized the results of the analysis of the previously reported potential prognostic factors for locoregional and peritoneal recurrence.

Patients with bigger tumors and higher lymph node ratio had a marginally significant probability to develop a peritoneal recurrence ($P = 0.062$ and $P = 0.066$, respectively).

Patients having metastatic disease at diagnosis had a significantly higher probability

Table 3 Recurrence characteristics and related treatment

	Total, *n* = 234	%
Recurrence		
No	174	67.7
Yes	60	23.3
Timing of recurrence[1]		
< 3 yr	51	19.8
≥ 3 yr	9	3.5
Liver recurrence		
No	207	80.5
Yes	25	9.7
Missing	2	9.7
Lung recurrence		
No	216	84.0
Yes	16	6.2
Missing	2	9.7
Local recurrence		
No	215	83.7
Yes	17	6.6
Missing	2	9.7
Peritoneal seeding		
No	225	87.5
Yes	7	2.7
Missing	2	9.7
Treatment of the first recurrence		
Surgery	25	41.7
Chemotherapy	20	33.3
Best supportive care	8	13.3
Palliation	2	3.3
Missing	5	8.3

[1]Recurrence from the first treatment.

to experience a local recurrence while patients receiving a low anterior resection of the rectum or a Miles intervention had a marginally significant higher chance to develop a local recurrence (P = 0.059).

Due to the paucity of significant prognostic factors found for each subgroup, multivariate analysis was not performed.

DISCUSSION

Many known and unknown factors, including patient and tumor characteristics together with surgical technical aspects, take part in the recurrence after curative treatments for colorectal cancer. Therefore, it is rather difficult to investigate every single variable, especially in a cohort with a very long follow-up period.

In agreement with previous reports[3,4,9], we documented that the recurrence rate was 25.6% with 85% during the 3 years from surgery.

In this study, a higher value of preoperative glycemia and abnormal (> 5 ng/mL)

Table 4 Demographic and patient-related preoperative potential prognostic factors for recurrence and evaluation of early *vs* late recurrence (univariate analysis)

| | Recurrence, *n* = 234 | | | | | Timing of recurrence, *n* = 60 | | | |
| | All | No | Yes | HR (95%CI) | *P* value | Early recurrence (< 3 yr) | Late recurrence (≥ 3 yr) | OR (95%CI) | *P* value |
	n (%)	*n* = 174 (67.7%)	*n* = 60 (23.3%)			*n* = 51 (85.0%)	*n* = 9 (15.0%)		
Age, yr; mean ± SD	68 ± 12	68 ± 11	69 ± 12	1.00 (0.98-1.02)	0.868	67 ± 12	77 ± 8	1.10 (1.00-1.21)	0.050
Gender, *n* (%)					0.179				0.421
Male	128 (54.7)	99 (77.3)	29 (22.6)	Reference		25 (86.2)	4 (13.8)	Reference	
Female	106 (45.3)	75 (70.7)	31 (29.2)	1.42 (0.85-2.37)		26 (83.9)	5 (16.1)	1.85 (0.41-8.21)	
Preop Hb, g/dL, mean ± SD	12.3 ± 2.1	12.6 ± 2.1	11.6 ± 2.3	0.84 (0.71-1.01)	0.058	11.9 ± 2.2	9.67 ± 2.3	0.60 (0.31-1.17)	0.136
Preop glycemia, g/dL, mean ± SD	0.99 ± 0.26	0.96 ± 0.24	1.08 ± 0.31	3.44 (1.05-11.24)	0.040	1.10 ± 0.34	0.99 ± 0.19	0.25 (0.00-16.06)	0.518
Preop total proteins, g/dL, mean ± SD	6.8 ± 0.7	6.8 ± 0.6	6.8 ± 1	1.07 (0.54-2.11)	0.839	6.7 ± 1.0	7.3 ± 0.2	2.43 (0.47-12.54)	0.288
Preop CEA, *n* (%)					0.029				0.440
< 5 ng/mL	85 (82.5)	71 (83.5)	14 (16.5)	0.36 (0.15-0.90)		12 (85.7)	2 (14.3)	Reference	
≥ 5 ng/mL	18 (17.5)	11 (61.1)	7 (38.9)	Reference		5 (71.4)	2 (28.6)	2.40 (0.26-22.10)	
Missing	131	131				39			
BMI, mean ± SD	26 ± 4	25 ± 4	27 ± 5	1.06 (0.99-1.14)	0.085	27 ± 5	27 ± 5	0.98 (0.81-1.19)	0.866
ASA, *n* (%)									
1	31 (14.5)	26 (83.9)	5 (16.1)	Reference		5 (100)	0 (0)	Reference	
2	80 (37.4)	61 (76.2)	19 (23.8)	1.50 (0.56-4.02)	0.421	16 (84.2)	3 (15.8)	-	0.951
3	94 (43.9)	72 (76.6)	22 (23.4)	1.51 (0.57-3.40)	0.404	16 (72.7)	6 (27.3)	-	0.948
4	9 (4.2)	5 (55.6)	4 (44.4)	3.85 (1.03-14.41)	0.045	4 (100)	0 (0)	-	1.000
Missing	20	20				10			
Presentation with occlusion, *n* (%)					0.021				0.366
No	42 (59.2)	33 (78.6)	9 (21.4)	Reference		7 (77.8)	2 (22.2)	Reference	
Yes	29 (40.8)	15 (51.7)	14 (48.3)	2.60 (1.15-5.87)		13 (92.9)	1 (7.1)	0.31 (0.02-3.97)	
Missing	163	163				37			
Tumor site, *n* (%)									
Right colon	70 (29.9)	53 (75.7)	17 (24.3)	Reference		13 (76.5)	4 (23.5)	Reference	
Left colon	103 (44)	76 (73.8)	27 (26.2)	0.93 (0.50-1.70)	0.807	24 (88.9)	3 (11.1)	0.41 (0.08-2.10)	0.282
Rectum	61 (26.1)	45 (73.8)	16 (26.2)	0.94 (0.47-1.85)	0.851	14 (87.5)	2 (12.5)	0.46 (0.07-2.98)	0.418

preoperative CEA levels resulted in prognostic recurrence factors. Although there are conflicting results[15,16], a relationship between metabolic syndrome and a higher risk of recurrence has been reported in a large cohort study including more than 1000 patients[17]. The discrepancies between these studies may be explained with the use of non-uniform definitions, however, the insulin role in stimulating cell proliferation *via* mitogen-activated protein kinase pathway is well documented[18]. The role of preoperative CEA as an independent risk factor for both DFS and OS has been already reported, especially in AJCC stage I-III, with the optimal cut off value ranging from 3 ng/mL[19] to 5 ng/mL if associated with positive lymph nodes or 10 ng/mL if in presence of negative lymph nodes[20].

Patients with ASA score grade 4 had a more than 3-fold higher risk of recurrence compared to ASA score grade 1 in our study. Association between ASA score and recurrence has been seldom reported[21,22]. It is reasonable to think that patients with more comorbidity may show a less efficient anti-tumoral response. Similarly, few data are available regarding the relationship between clinical presentation modalities and prognosis after elective surgery. A presentation with perforation, but not with obstruction, was found to be associated with very late (more than 5 years) onset of recurrence[23]. A possible explanation may be related to the presence of an undetectable micro-perforation and/or bacterial translocation with an impairment of the immune response, but it was not demonstrated yet.

Administration of neoadjuvant therapies, especially the combination of radio and chemotherapy for rectal cancer, has been progressively increased during the last decade but in the study period, only a few patients underwent these treatments. Therefore, it was impossible to evaluate this parameter in the present study.

The finding of higher recurrence risk in patients receiving additional major procedures, treated with the open technique, and receiving adjuvant chemotherapy (marginally significant) is easily explainable with more advanced tumor stages diagnosed in each subgroup. Similarly, the interpretation of the length of hospital stay as an independent prognostic factor should take into account that this parameter is actually the result of many other variables including patient's conditions, kind of received operation, and postoperative course.

Our data confirmed the prognostic value of the TNM staging system. Furthermore, the N stage 2 and M stage 1 resulted to be independent prognostic factors for recurrence. Patients with a higher lymph node ratio had significantly higher to develop recurrence. Interestingly, a potential incorrect disease stadiation following the retrieval of fewer than 12 nodes did not significantly influence the recurrence.

Lymph nodes ratio is considered as an effective parameter for stratification, especially because it seems to be independent of the resection length[24], and as a strong predictor for tumor recurrence[25,26]. However, the more recent paper of Jakob *et al*[27] reported the bigger impact of pN than lymph node ratio on recurrence suggesting that the latter parameter could be more helpful in presence of a relatively low number of harvested lymph nodes[27].

Tumor size did not confer a higher risk of recurrence in this analysis. However, previous studies reported a direct correlation between diameter and TNM parameter or, on the contrary, a poorer prognosis of small tumors when associated with advanced T stage[28,29]. These findings could suggest that tumor biology may have a bigger impact on prognosis than tumor size.

Administration of adjuvant chemotherapy and an earlier start of it (within 6 wk from surgery) did not affect the recurrence risk while previously published papers reported opposite results[13]. Administration of chemotherapy in more advanced cancer stages, together with the possible impact of missing data of the present analysis may explain these different findings.

Several factors affecting the timing of recurrence have been proposed and they may differ in subgroups' analysis of different CRC stages[13].

We found that younger ages resulted significantly associated with early recurrence while AJCC stage 3 and administration of adjuvant chemotherapy showed a trend toward higher probability to develop an early recurrence without reaching statistical significance. These findings may be related to more aggressive tumor biology. Advanced T and N stages have been reported to be related to the early onset of recurrence[9,10,13]. It has been reported that adjuvant chemotherapy may or not influence the rate of recurrence[9,13]. These conflicting results may be explained with the use of

Table 5 Treatment-related potential prognostic factors for recurrence and evaluation of early versus late recurrence (univariate analysis)

	Recurrence, *n* = 234					Timing of recurrence, *n* = 60			
	All	**No**	**Yes**	**HR (95%CI)**	**P value**	**Early recurrence (< 3 yr)**	**Late recurrence (≥ 3 yr)**	**OR (95%CI)**	**P value**
	***n*, %**	***n* = 174 (67.7%)**	***n* = 60 (23.3%)**			***n* = 51 (85.0%)**	***n* = 9 (15.0%)**		
Neoadjuvant therapy, *n* (%)					0.921				0.949
No	97 (93.3)	68 (70)	29 (30)	Reference		25 (86.2)	4 (13.8)	Reference	
Yes	7 (6.7)	5 (71)	2 (29)	1.07 (0.26-4.51)		2 (100)	0 (0)	1.13 (0.02-53.57)	
Missing	130	130				29			
Surgery, *n* (%)									
Right emicolectomy	55 (23.5)	42 (76.4)	13 (23.6)	Reference		10 (76.9)	3 (23.1)	Reference	
Extended right emicolectomy	15 (6.4)	12 (80)	3 (20)	1.16 (0.37-3.59)	0.801	2 (66.7)	1 (33.3)	4.20 (0.37-47.64)	0.247
Intermediate colectomy	10 (4.3)	6 (60)	4 (40)	2.16 (0.70-6.71)	0.182	3 (75)	1 (25)	1.80 (0.14-23.6)	0.655
AR/Hartmann	106 (45.3)	80 (75.5)	26 (24.5)	1.09 (0.55-2.17)	0.798	24 (92.3)	2 (7.7)	0.43 (0.06-3.02)	0.395
LAR/Miles	38 (16.2)	28 (73.7)	10 (26.3)	1.16 (0.50-2.68)	0.731	8 (80)	2 (20)	1.23 (0.16-9.69)	0.841
Total/Sub-total Colectomy	6 (2.6)	3 (50)	3 (50)	2.69 (0.76-9.53)	0.126	3 (100)	0 (0.0)	0.60 (0.01-24.50)	0.787
Segmental resection	4 (1.7)	3 (75)	1 (25)	1.12 (0.14-8.68)	0.916	1 (100)	0 (0.0)	1.7 (0.02-162.35)	0.819
Associated procedure, *n* (%)									
No	52 (50.5)	39 (75)	13 (25)	Reference		11 (84.6)	2 (15.4)	Reference	
Minor	40 (38.8)	27 (67.5)	13 (32.5)	1.30 (0.60-2.80)	0.505	11 (84.6)	2 (15.4)	1.00 (0.13-7.44)	1.00
Major	11 (10.7)	4 (36.4)	7 (63.6)	3.56 (1.41-8.96)	0.007	7 (100)	0 (0)	0.31 (0.01-8.95)	0.492
Missing	131	131				27			
Operative technique, *n* (%)					< 0.001				0.061
Open	99 (42.7)	61 (61.6)	38 (38.4)	Reference		35 (92.1)	3 (7.9)	Reference	
Laparoscopy	133 (57.3)	111 (83.5)	22 (16.5)	0.37 (0.22-0.62)		16 (72.7)	6 (27.3)	4.00 (0.94-17.01)	
Missing	2	2				-			
Duration of surgery, min – mean ± SD	232 ± 67	230 ± 61	239 ± 83	1.00 (0.99-1.01)	0.496	238 ± 78	242 ± 112	1.00 (0.99-1.01)	0.808
Postop blood transfusion, *n* (%)					0.123				0.119
No	174 (75.7)	134 (77)	40 (23)	Reference		36 (90)	4 (10)	Reference	
Yes	56 (24.3)	37 (66.1)	19 (33.9)	1.54 (0.89-2.66)		14 (73.7)	5 (26.3)	3.08 (0.75-12.64)	

Missing	4	4				1			
Reoperation, *n* (%)					0.262				0.559
No	82 (91.1)	60 (73.2)	22 (26.8)	Reference		17 (77.3)	5 (22.7)	Reference	
Yes	8 (8.9)	5 (62.5)	3 (37.5)	1.99 (0.60-6.61)		2 (66.7)	1 (33.3)	2.13 (0.17-26.68)	
Missing	144	144				35			
Hospital stay, d, mean ± SD	9.2 ± 6	8.7 ± 3.7	10.9 ± 9.1	1.05 (1.02-1.07)	0.001	10.9 ± 9.8	10.6 ± 4.0	1.01 (0.95-1.08)	0.737
Adjuvant therapy, *n* (%)					0.064				0.057
No	127 (56.4)	103 (81.1)	24 (18.9)	Reference		18 (75)	6 (25)	Reference	
Yes	98 (43.5)	67 (68.4)	31 (31.6)	1.65 (0.97-2.81)		28 (90.3)	3 (9.7)	0.22 (0.04-1.04)	
Missing	9	9				5			
Start of adj CHT, *n* (%)					0.268				0.401
< 6 wk	26 (48.1)	13 (50)	13 (50)	Reference		12 (92.3)	1 (7.7)	Reference	
≥ 6 wk	28 (51.9)	19 (67.9)	9 (32.1)	1.63 (0.69-3.95)		8 (88.9)	1 (11.1)	4.4 (0.14-141.01)	
Missing	180	180				38			

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; AR: Anterior resection of the rectum; LAR: Low anterior resection of the rectum; Adj CHT: Adjuvant chemotherapy.

different chemotherapy protocols and, again, by different aggressiveness of the disease. Although the early or late recurrence is a debate prognostic factor for the OS[13], we observed that the early recurrence onset resulted significantly associated with a shorter OS rate but not with post recurrence overall survival. Similarly, Lan *et al*[13] reported that there was no difference in terms of post-recurrence survival between early or late recurrence[13].

Regarding the recurrence site, we documented that liver was the most frequent site (41.7%) followed by locoregional recurrence, lung, and peritoneal recurrence. In detail, patients receiving intermediate colectomies or segmental resections, having an N stage 2 or AJCC stage 3 tumor had a higher risk of developing a liver recurrence. Patients receiving postoperative blood transfusions and adjuvant chemotherapy had a marginally significant higher chance of suffering from recurrence.

Patients receiving neoadjuvant treatments had a higher rate of lung recurrence suggesting the probable association with the presence of advanced primary tumors located in the lower rectum as a prognostic factor.

Finally, in the present study, patients with bigger tumors and higher lymph node ratio had a marginally significant probability to develop a peritoneal recurrence. Previously reported risk factors for peritoneal carcinomatosis included also mucinous and signet ring adenocarcinomas[8].

Patients having metastatic disease at diagnosis had a significantly higher probability to experience a local recurrence while patients receiving a low anterior resection of the rectum or a Miles intervention had a marginally significant higher chance to develop a local recurrence. These findings may be related to complex technical surgical aspects and to pathological aspects including the circumferential radial margin, which was recently introduced in routine practice as a parameter of correct dissection. While in this analysis anastomotic leak did not result in a higher risk of local recurrence, this association has been previously reported[30,31]. Notably, as we previously reported, the research of a relationship between gut microbiota, anastomotic leak, and local recurrence is a promising field under evaluation[32].

Kind of tests, frequency, and duration of the follow-up is still debated[33,34].

Data from a review of several moderate-high quality randomized controlled trials showed better OS and a higher resectability rate of the recurrence but no differences in cancer-specific mortality rate with a more intensive follow-up program[12].

Most of the follow-up programs end in five years after primary surgery. Only

Table 6 Pathological-related potential prognostic factors for recurrence and evaluation of early versus late recurrence (univariate analysis)

	Recurrence, *n* = 234					Timing of recurrence, *n* = 60			
	All	No	Yes	HR (95%CI)	*P* value	Early recurrence (< 3 yr)	Late recurrence (≥ 3 yr)	OR (95%CI)	*P* value
	n (%)	*n* = 174 (67.7%)	*n* = 60 (23.3%)			*n* = 51 (85.0%)	*n* = 9 (15.0%)		
Major tumor diameter, mm, mean ± SD	43 ± 23	41.6 ± 23	46.8 ± 24.5	1.01 (0.99-1.02)	0.130	47.6 ± 23.5	42.8 ± 29.8	0.99 (0.96-1.02)	0.694
Pathological T stage[1], *n* (%)									
1	46 (19.7)	44 (95.7)	2 (4.3)	Reference		2 (100)	0 (0)	Reference	
2	40 (17.2)	32 (80)	8 (20)	3.44 (0.91-12.99)	0.068	6 (75)	2 (25)	0.64 (0.04-10.57)	0.756
3	141 (60.5)	94 (66.7)	47 (33.3)	6.14 (1.91-19.77)	0.002	40 (85.1)	7 (14.9)	0.27 (0.02-3.20)	0.298
4	6 (2.6)	4 (66.7)	2 (33.3)	6.19 (1.03-37.96)	0.046	2 (100)	0 (0)	0.33 (0.00-24.94)	0.624
Missing	1	1				1			
Pathological N stage[1], *n* (%)									
0	155 (66.5)	129 (83.2)	26 (16.8)	Reference		18 (69.2)	8 (30.8)	Reference	
1	51 (21.9)	36 (70.6)	15 (29.4)	1.95 (1.03-3.69)	0.039	15 (100)	0 (0)	0.07 (0.00-1.44)	0.085
2	27 (11.6)	9 (33.3)	18 (66.7)	6.35 (3.50-11.64)	< 0.001	17 (94.4)	1 (5.6)	0.19 (0.03-1.25)	0.084
Missing	1	1				1			
Pathological M stage[1], *n* (%)					< 0.001				0.408
0	223 (95.6)	171 (76.7)	52 (23.3)	Reference		43 (82.7)	9 (17.3)	Reference	
1	10 (4.3)	2 (20)	8 (80)	5.31 (2.50-11.30)		8 (100)	0 (0)	0.27 (0.01-6.02)	
Missing	1	1				-			
AJCC stage, *n* (%)									
1	77 (32.9)	68 (88.3)	9 (11.7)	Reference		7 (77.8)	2 (22.2)	Reference	
2	75 (32)	59 (78.7)	16 (21.3)	1.65 (0.74-3.67)	0.220	10 (62.5)	6 (37.5)	1.12 (0.20-6.17)	0.894
3	72 (30.8)	45 (62.5)	27 (37.5)	3.59 (1.73-7.42)	< 0.001	26 (96.3)	1 (3.7)	0.12 (0.01-1.03)	0.053
4	10 (4.3)	2 (20)	8 (80)	11.1 (4.35-28.52)	< 0.001	8 (100)	0 (0)	0.13 (0.00-3.43)	0.220
Retrieved LN, *n* (%)					0.535				0.741
< 12	65 (29.3)	53 (81.5)	12 (18.5)	Reference		10 (83.3)	2 (16.7)	Reference	
≥ 12	157 (70.7)	112 (71.3)	45 (28.7)	0.84 (0.47-1.47)		38 (84.4)	7 (15.6)	0.78 (0.18-3.40)	
Missing	12	12				3			
LN ratio, mean ± SD	20 ± 16	16 ± 13	25 ± 19	25.8 (8.22-80.93)	< 0.001	25 ± 19	22	0.00 (0.00-2.20)	0.073

Colloid component, *n* (%)				0.168				0.607
No	63 (60)	49 (77.8)	14 (22.2)	Reference	12 (85.7)	2 (14.3)	Reference	
Yes	42 (40)	27 (64.3)	15 (35.7)	1.68 (0.80-3.53)	13 (86.7)	2 (13.3)	0.55 (0.06-5.22)	
Missing	129	129			31			

[1]According to the tumor node metastasis staging system.

AJCC: American Joint Committee on Cancer; LN: Lymph nodes; HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals.

Table 7 Multivariate analysis of potential prognostic factors for recurrence			
	HR	95%CI	*P* value
Hospital stay, d	1.053	1.023-1.084	< 0.001
Pathological N stage[1]			
0	Reference		
1	1.608	0.773-3.343	0.204
2	6.129	3.070-12.236	< 0.001
Pathological M stage[1]			
0	Reference		
1	5.521	2.113-14.425	< 0.001

[1]According to the tumor node metastasis staging system.

HR: Hazard ratio; CI: Confidential intervals.

routine surveillance is recommended beyond this period but recurrence continues to occur after 5 years. Our data showed a rate of very late first recurrence (> 5 years) of 1.7%, similar to other previously published studies[3,9]. Moreover, a mean time of more than 60 mo for the development of the second recurrence in the patients with lung metastases was observed and the presentation of the second liver recurrence ranged between 24 and 76 mo. Finally, as a collateral finding, 15 patients developed a second neoplasm beyond 5 years from primary colorectal surgery. Perhaps, in these patients, a longer surveillance program could have allowed an earlier diagnosis. Similarly, Chauvenet *et al*[35] estimated the achievement of cure at 9.3 years[35] while Bouvier *et al*[23] reported a recurrence rate of 6.7% between 5 and 10 years after the first treatments, independently from cancer stage[23]. These data could suggest the necessity to extend the actual follow up programs up to 10 years, especially for selected patients. On the other hand, patients may suffer from test-related anxiety and the tests may rarely provoke adverse reactions[12]. No relevant reports about the economic aspect have been found[12]. Consequently, a tailored approach for each patient seems advisable.

Our study has several drawbacks. This has been a retrospective study with an inherent selection bias. Missing data, mostly due to the chosen long follow-up period, may also cause bias throughout the analysis. Patients lost during follow-up and patients who did not undergo radiological imaging after the 5th years of follow-up could have a silent recurrence causing a recurrences' underestimation. On the contrary, not all the patients with a radiological suspicion of metastasis underwent a histological assessment causing a potential overestimation of the recurrence rate. Data concerning chemotherapy are quite simplified and those about molecular biology were almost completely missing, therefore further statistical analysis could not be performed. Similarly, data regarding mesorectal excision were still not available in the histological reports making impossible the analysis of its adequacy. Finally, an accurate cost/benefit evaluation should be considered. Therefore, further analyses, possibly in a larger sample, are needed and could offer stronger evidence.

Table 8 Demographic and patient-related preoperative potential prognostic factors for liver and lung recurrence

	Recurrence, *n* = 58							
	Liver				Lung			
	No, *n* = 33 (55.0%)	Yes, *n* = 25 (41.7%)	HR (95%CI)	*P* value	No, *n* = 42 (70.0%)	Yes, *n* = 16 (26.7%)	HR (95%CI)	*P* value
Age, yr, mean ± SD	67.4 ± 12.3	68.0 ± 12.3	1.00 (0.97-1.03)	0.945	67.3 ± 12.7	68.7 ± 11.0	1.00 (0.96-1.04)	0.837
Gender, *n* (%)				0.702				0.185
Male	16 (55.2)	13 (44.8)	Reference		19 (65.5)	10 (34.5)	Reference	
Female	17 (58.6)	12 (41.4)	0.86 (0.39-1.88)		23 (79.3)	6 (20.7)	0.50 (0.18-1.39)	
Preop Hb, g/dL, mean ± SD	11.28	11.93	1.16 (0.88-1.53)	0.296	11.4 ± 2.3	12.0 ± 2.5	1.14 (0.81-1.61)	0.446
Preop glycemia, g/dL, mean ± SD	1.08 ± 0.36	1.08 ± 0.31	1.72 (0.14-10.00)	0.884	1.06 ± 0.33	1.14 ± 0.35	1.47 (0.12-18.20)	0.764
Preop total proteins, g/dL, mean ± SD	6.7 ± 0.7	7.1 ± 0.8	1.33 (0.56-3.17)	0.514	6.9 ± 0.9	6.9 ± 0.5	0.87 (0.19-3.93)	0.861
Preop CEA, *n* (%)				0.868				0.891
< 5 ng/mL	6 (46.2)	7 (53.8)	Reference		10 (76.9)	3 (23.1)	Reference	
≥ 5 ng/mL	4 (57.1)	3 (42.9)	0.89 (0.23-3.46)		5 (71.4)	2 (28.6)	1.14 (0.18-7.14)	
Missing	23	15			27	11		
BMI, mean ± SD	26.3 ± 4.9	27.8 ± 4.7	1.04 (0.94-1.15)	0.465	27.6 ± 4.8	25.7 ± 4.6	0.96 (0.83-1.13)	0.646
ASA, *n* (%)								
1	3 (60)	2 (40)	Reference		4 (80)	1 (20)	Reference	
2	8 (42.1)	11 (57.9)	0.64 (0.15-2.75)	0.544	14 (73.7)	5 (26.3)	0.46 (0.06-3.38)	0.447
3	13 (61.9)	8 (38.1)	0.34 (0.07-1.55)	0.163	15 (71.4)	6 (28.6)	0.31 (0.04-2.35)	0.258
4	3 (100)	0 (0.0)	0.30 (0.01-7.69)	0.471	2 (66.7)	1 (33.3)	2.09 (0.16-27.56)	0.573
Missing	6	4			7	3		
Presentation with occlusion, *n* (%)				0.465				0.470
No	5 (62.5)	3 (37.5)	Reference		6 (75)	2 (25)	Reference	
Yes	6 (46.2)	7 (53.8)	1.58 (0.46-5.44)		9 (69.2)	4 (30.8)	1.89 (0.34-10.61)	
Missing	23	15			27	11		
Tumour site, *n* (%)								
Right colon	11 (68.7)	5 (31.3)	Reference		13 (81.3)	3 (18.7)	Reference	
Left colon	11 (42.3)	15 (57.7)	2.48 (0.89-6.88)	0.081	20 (76.9)	6 (23.1)	1.73 (0.42-7.04)	0.445
Rectum	11 (68.7)	5 (31.3)	0.98 (0.28-3.41)	0.972	9 (56.3)	7 (43.7)	2.34 (0.59-9.32)	0.226

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Preop: Preoperative value; Hb: Haemoglobin; CEA: Carcinoembryonic antigen; BMI: Body mass index; ASA: American Society of Anaesthesiologists Score.

CONCLUSION

In conclusion, several prognostic factors for recurrence and some specific factors for each site of recurrence have been found and should be taken into account in scheduling a tailored follow-up program for each patient. Since recurrence or other primary tumors may occur even 5 years from the first treatment, an extension of the recommended 5-years follow-up program should be evaluated according to the presence of potential prognostic factors.

Table 9 Treatment-related potential prognostic factors for liver and lung recurrence

	Recurrence, *n* = 58							
	Liver				Lung			
	No, *n* = 33 (55.0%)	Yes, *n* = 25 (41.7%)	HR (95%CI)	*P* value	No, *n* = 42 (70.0%)	Yes, *n* = 16 (26.7%)	HR (95%CI)	*P* value
Neoadjuvant therapy, *n* (%)				0.952				0.010
No	13 (46.4)	15 (53.6)	Reference		21 (75)	7 (25)	Reference	
Yes	2 (100)	0 (0)	0.91 (0.04-18.42)		0 (0)	2 (100)	13.21 (1.86-93.92)	
Missing	18	10			21	7		
Surgery, *n* (%)								
Right emicolectomy	10 (83.3)	2 (16.7)	Reference		10 (83.3)	2 (16.7)	Reference	
Extended right emicolectomy	1 (33.3)	2 (66.7)	2.02 (0.31-13.21)	0.461	2 (66.7)	1 (33.3)	0.81 (0.09-7.66)	0.857
Intermediate colectomy	0 (0)	4 (100)	7.05 (1.34-36.94)	0.021	4 (100)	0 (0)	0.75 (0.03-21.49)	0.864
AR/Hartmann's procedure	11 (44)	14 (56)	2.44 (0.59-10.18)	0.220	19 (76)	6 (24)	1.07 (0.21-5.39)	0.936
Low anterior resection/Miles	9 (90)	1 (10)	0.54 (0.06-4.67)	0.579	3 (30)	7 (70)	2.20 (0.45-10.78)	0.332
Total/Sub-total colectomy	2 (66.7)	1 (33.3)	2.37 (0.27-20.60)	0.433	3 (100)	0 (0)	0.84 (0.03-24.19)	0.920
Segmental resection	0 (0)	1 (100)	110 (5.3-2304.7)	0.002	1 (100)	0 (0)	-	-
Associated procedure, *n* (%)								
No	4 (33.3)	8 (66.7)	Reference		10 (83.3)	2 (16.7)	Reference	
Minor	9 (69.2)	4 (30.8)	0.37 (0.11-1.23)	0.106	10 (76.9)	3 (23.1)	0.92 (0.16-5.43)	0.928
Major	2 (28.6)	5 (71.4)	1.65 (0.53-5.47)	0.377	4 (57.1)	3 (42.9)	3.37 (0.55-20.65)	0.188
Missing	18	8			18	8		
Operative technique, *n* (%)				0.253				0.658
Open	19 (51.4)	18 (48.6)	Reference		27 (73)	10 (27)	Reference	
Laparoscopy	14 (66.7)	7 (33.3)	0.60 (0.25-1.44)		15 (71.4)	6 (28.6)	0.79 (0.28-2.24)	
Duration of surgery, min, mean ± SD	250 ± 90	227 ± 75	1.00 (0.99-1.00)	0.579	231 ± 83	264 ± 86	1.00 (1.00-1.01)	0.221
Hospital stay, d, mean ± SD	10.0 ± 3.9	9.5 ± 2.1	0.97 (0.84-1.11)	0.637	9.8 ± 2.8	9.9 ± 4.3	1.00 (0.86-1.17)	0.980
Postoperative blood transfusion, *n* (%)				0.067				0.992
No	20 (50)	20 (50)	Reference		30 (75)	10 (25)	Reference	
Yes	13 (76.5)	4 (23.5)	0.37 (0.12-1.07)		11 (64.7)	6 (35.3)	0.99 (0.36-2.75)	
Missing	-	1			1	-		
Reoperation due to complications, *n* (%)				0.723				0.705
No	12 (57.1)	9 (42.9)	Reference		18 (85.7)	3 (14.3)	Reference	
Yes	2 (100)	0 (0)	0.58 (0.03-12.07)		1 (50)	1 (50)	1.53 (0.17-13.57)	

Missing	19	16			23	12		
Adjuvant therapy, *n* (%)				0.055				0.703
No	16 (72.7)	6 (27.2)	Reference		15 (68.2)	7 (31.8)	Reference	
Yes	14 (45.2)	17 (54.8)	2.52 (0.98-6.48)		23 (74.2)	8 (25.8)	1.23 (0.42-3.62)	
Missing	3	2			4	1		
Start of adj CHT, *n* (%)				0.913				0.344
< 6 wk from surgery	6 (46.2)	7 (53.8)	Reference		8 (61.5)	5 (38.6)	Reference	
≥ 6 wk from surgery	4 (44.4)	5 (55.6)	1.07 (0.33-3.43)		8 (88.9)	1 (11.1)	0.35 (0.04-1.04)	
Missing	23	13			26	10		

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Adj CHT: Adjuvant chemotherapy.

Table 10 Pathological-related potential prognostic factors for liver and lung recurrence

	Recurrence, *n* = 58							
	Liver				Lung			
	No, *n* = 33 (55.0%)	Yes, *n* = 25 (41.7%)	HR (95%CI)	*P* value	No, *n* = 42 (70.0%)	Yes, *n* = 16 (26.7%)	HR (95%CI)	*P* value
Major tumor diameter, mm, mean ± SD	55.71	42.74	0.99 (0.98-1.01)	0.368	29.09	30.01	0.99 (0.97-1.01)	0.326
Pathological T stage[1], *n* (%)								
1	1 (50)	1 (50)	Reference		1 (50)	1 (50)	Reference	
2	6 (75)	2 (25)	0.68 (0.06-7.50)	0.752	6 (75)	2 (25)	0.77 (0.07-8.58)	0.835
3	25 (55.6)	20 (44.4)	1.66 (0.22-12.44)	0.623	33 (73.3)	12 (26.7)	1.52 (0.19-12.45)	0.695
4	1 (50)	1 (50)	2.18 (0.13-35.75)	0.585	1 (50)	1 (50)	4.28 (0.24-76.14)	0.981
Missing	-	-			1	-		
Pathological N stage[1], *n* (%)								
0	17 (65.4)	9 (34.6)	Reference		18 (69.2)	8 (30.8)	Reference	
1	9 (64.3)	5 (35.7)	1.75 (0.55-5.53)	0.341	10 (71.4)	4 (28.6)	2.31 (0.60-8.88)	0.222
2	7 (41.2)	10 (58.8)	3.48 (1.31-9.27)	0.013	13 (76.5)	4 (23.5)	2.17 (0.57-8.51)	0.264
Missing	-	1			1	-		
Pathological M stage[1], *n* (%)				0.321				0.092
0	29 (58)	21 (42)	Reference		37 (74)	13 (26)	Reference	
1	4 (50)	4 (50)	1.74 (0.58-5.22)		5 (62.5)	3 (37.5)	3.13 (0.83-11.79)	
AJCC stage, *n* (%)								
1	7 (77.8)	2 (22.2)	Reference		6 (66.7)	3 (33.3)	Reference	
2	10 (62.5)	6 (37.5)	2.12 (0.43-10.51)	0.359	11 (68.7)	5 (31.3)	1.45 (0.33-6.33)	0.623
3	12 (48)	13 (52)	5.09 (1.10-23.52)	0.037	20 (80)	5 (20)	2.11 (0.42-10.47)	0.361
4	4 (50)	4 (50)	5.57 (0.96-32.24)	0.055	5 (62.5)	3 (37.5)	3.06 (0.85-30.09)	0.075

Retrieved LN, *n* (%)				0.803				0.961
< 12	6 (54.5)	5 (45.5)	Reference		8 (72.7)	3 (27.3)	Reference	
≥ 12	26 (59.1)	18 (40.9)	0.90 (0.38-2.12)		31 (70.5)	13 (29.5)	0.97 (0.34-2.82)	
Missing	1	2			3	-		
LN ratio, mean ± SD	22 ± 18	28 ± 20	4.21 (0.79-22.42)	0.092	27 ± 21	18 ± 8	1.07 (0.96-18.11)	0.963
Colloid component, *n* (%)				0.367				0.200
No	6 (46.2)	7 (53.8)	Reference		8 (61.5)	5 (38.5)	Reference	
Yes	11 (73.3)	4 (26.7)	0.56 (0.16-1.98)		14 (93.3)	1 (6.7)	0.24 (0.03-2.12)	
Missing	16	14			20	10		

[1]According to the tumor node metastasis staging system. HR: Hazard ratio; CI: Confidential intervals; AJCC: American Joint Committee on Cancer; LN: Lymph nodes.

Table 11 Demographic and patient-related preoperative potential prognostic factors for local and peritoneal recurrence

	Recurrence, *n* = 58							
	Peritoneal				Local			
	No, *n* = 51 (87.9%)	Yes, *n* = 7 (12.1%)	HR (95%CI)	*P* value	No, *n* = 41 (70.7%)	Yes, *n* = 17 (29.3%)	HR (95%CI)	*P* value
Age, yr, mean ± SD	67.6 ± 11.9	66.3 ± 14.9	0.98 (0.92-1.04)	0.489	68.6 ± 11.3	67.5 ± 14.2	0.98 (0.95-1.02)	0.345
Gender, *n* (%)				0.434				0.862
Male	27 (93.1)	2 (6.9)	Reference		21 (72.4)	8 (27.6)	Reference	
Female	24 (82.8)	5 (17.2)	1.97 (0.36-10.77)		20 (69)	9 (31)	0.91 (0.32-2.61)	
Preop Hb, g/dL, mean ± SD	11.7 ± 2.3	11.1 ± 2.7	0.91 (0.55-1.50)	0.712	11.9 ± 2.2	9.9 ± 1.9	0.71 (0.38-1.31)	0.273
Preop glycemia, g/dL, mean ± SD	1.08 ± 0.32	1.08 ± 0.41	2.42 (0.05-123.6)	0.659	1.12 ± 0.33	0.82 ± 0.16	-	0.210
Preop total proteins, g/dL, mean ± SD	7.0 ± 0.7	6.5 ± 1.1	0.17 (0.02-1.23)	0.079	6.9 ± 0.9	7.0 ± 0.4	0.60 (0.02-14.06)	0.750
Preop CEA, *n* (%)				0.727				0.860
< 5 ng/mL	11 (84.6)	2 (15.4)	Reference		12 (92.3)	1 (7.7)	Reference	
≥ 5 ng/mL	6 (85.7)	1 (14.3)	0.52 (0.01-21.28)		5 (71.4)	2 (28.6)	1.32 (0.06-29.55)	
Missing	34	4			24	14		
BMI, mean ± SD	26.7 ± 4.5	30.7 ± 7.2	1.15 (0.91-1.44)	0.238	27.4 ± 5.1	26.0 ± 3.6	0.95 (0.81-1.11)	0.510
ASA, *n* (%)								
1	4 (80)	1 (20)	Reference		4 (80)	1 (20)	Reference	
2	17 (89.5)	2 (10.5)	0.25 (0.02-2.83)	0.264	15 (78.9)	4 (21.1)	0.42 (0.06-3.18)	0.401
3	18 (85.7)	3 (14.3)	0.19 (0.02-2.14)	0.178	14 (66.7)	7 (33.3)	0.35 (0.05-2.61)	0.307
4	3 (100)	0 (0)	0.47 (0.01-23.31)	0.707	1 (33.3)	2 (66.7)	2.32 (0.24-21.92)	0.464
Missing	9	1			7	3		

Presentation with occlusion, *n* (%)				0.674				0.962
No	7 (87.5)	1 (12.5)	Reference		6 (75)	2 (25)	Reference	
Yes	11 (84.6)	2 (15.4)	1.67 (0.15-18.56)		12 (92.3)	1 (7.7)	0.93 (0.06-15.21)	
Missing	33	4			23	14		
Tumour site, *n* (%)								
Right colon	14 (87.5)	2 (12.5)	Reference		9 (56.3)	7 (43.7)	Reference	
Left colon	24 (92.3)	2 (7.7)	0.80 (0.11-5.70)	0.825	19 (73.1)	7 (26.9)	0.79 (0.27-2.30)	0.671
Rectum	13 (81.2)	3 (18.8)	1.36 (0.23-8.17)	0.735	13 (81.3)	3 (18.7)	0.44 (0.11-1.69)	0.232

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Preop: Preoperative value; Hb: Haemoglobin; CEA: Carcinoembryonic antigen; BMI: Body mass index; ASA: American Society of Anaesthesiologists Score.

Table 12 Treatment-related potential prognostic factors for local and peritoneal recurrence

	Recurrence, *n* = 58							
	Peritoneal				Local			
	No, *n* = 51 (87.9%)	Yes, *n* = 7 (12.1%)	HR (95%CI)	*P* value	No, *n* = 41 (70.7)	Yes, *n* = 17 (29.3)	HR (95%CI)	*P* value
Neoadjuvant therapy, *n* (%)				0.569				0.475
No	23 (82.1)	5 (17.9)	Reference		23 (81.1)	5 (17.9)	Reference	
Yes	2 (100)	0 (0)	2.71 (0.09-84.27)		2 (100)	0 (0)	3.88 (0.09-160.22)	
Missing	26	2			16	12		
Surgery, *n* (%)								
Right emicolectomy	10 (83.3)	2 (16.7)	Reference		6 (50)	6 (50)	Reference	
Extended right emicolectomy	3 (100)	0 (0)	0.23 (0.01-11.90)	0.468	2 (66.7)	1 (33.3)	0.20 (0.02-1.68)	0.140
Intermediate colectomy	4 (100)	0 (0)	1.20 (0.03-47.50)	0.923	4 (100)	0 (0)	0.35 (0.01-8.18)	0.511
AR/Hartmann's procedure	23 (92)	2 (8)	0.36 (0.04-3.04)	0.350	17 (68)	8 (32)	0.41 (0.13-1.29)	0.127
Low Anterior resection/Miles	8 (80)	2 (20)	0.68 (0.07-6.27)	0.731	9 (90)	1 (10)	0.15 (0.02-1.07)	0.059
Total/Sub-total colectomy	2 (66.7)	1 (33.3)	2.99 (0.25-35.10)	0.383	2 (66.7)	1 (33.3)	0.98 (0.14-6.95)	0.981
Segmental resection	1 (100)	0 (0)	-	-	1 (100)	0 (0)	-	-
Associated procedure, *n* (%)								
No	11 (91.7)	1 (8.3)	Reference		11 (91.7)	1 (8.3)	Reference	
Minor	11 (84.6)	2 (15.4)	1.16 (0.10-14.11)	0.905	7 (53.8)	6 (46.2)	2.41 (0.33-17.37)	0.384
Major	7 (100)	0 (0)	0.61 (0.01-31.26)	0.808	5 (71.4)	2 (28.6)	3.26 (0.36-29.71)	0.295
Missing	22	4			18	8		
Operative technique, *n* (%)				0.128				0.368
Open	35 (94.6)	2 (5.4)	Reference		25 (67.6)	12 (32.4)	Reference	
Laparoscopy	16 (76.2)	5 (23.8)	3.64 (0.69-		16 (76.2)	5 (23.8)	0.61 (0.21-1.77)	

			19.14)					
Duration of surgery, min, mean ± SD	239 ± 85	249 ± 87	1.00 (0.99-1.01)	0.869	244 ± 81	232 ± 93	1.00 (0.99-1.01)	0.934
Hospital stay, d, mean ± SD	9.8 ± 3.2	10.0 ± 4.1	0.98 (0.76-1.27)	0.907	9.4 ± 3.3	10.7 ± 3.1	1.09 (0.96-1.23)	0.181
Postoperative blood transfusion, *n* (%)				0.272				0.518
No	37 (92.5)	3 (7.5)	Reference		30 (75)	10 (25)	Reference	
Yes	13 (76.5)	4 (23.5)	2.32 (0.52-10.38)		10 (58.8)	7 (41.2)	1.39 (0.51-3.74)	
Missing	1	-			1	-		
Reoperation due to complications, *n* (%)				0.344				0.182
No	17 (81)	4 (19)	Reference		18 (75)	6 (25)	Reference	
Yes	1 (50)	1 (50)	3.00 (0.31-29.24)		1 (50)	1 (50)	4.35 (0.50-37.59)	
Missing	33	2			22	10		
Adjuvant therapy, *n* (%)				0.481				0.852
No	20 (90.9)	2 (9.1)	Reference		14 (63.6)	8 (36.4)	Reference	
Yes	28 (90.3)	3 (9.7)	2.26 (0.23-21.77)		23 (74.2)	8 (25.8)	1.11 (0.38-3.21)	
Missing	3	2			4	1		
Start of adj chemotherapy, *n* (%)				0.648				0.953
< 6 wk from surgery	12 (92.3)	1 (7.7)	Reference		9 (69.2)	4 (30.8)	Reference	
≥ 6 wk from surgery	8 (88.8)	1 (11.1)	1.91 (0.12-30.85)		7 (77.8)	2 (22.2)	0.95 (0.18-5.13)	
Missing	31	5			25	1		

HR: Hazard ratio; OR: Odds ratio; CI: Confidential intervals; Adj: Adjuvant.

Table 13 Pathological-related potential prognostic factors for local and peritoneal recurrence

	Recurrence, *n* = 58							
	Peritoneal				Local			
	No, *n* = 51 (87.9)	Yes, *n* = 7 (12.1)	HR (95%CI)	*P* value	No, *n* = 41 (70.7)	Yes, *n* = 17 (29.3)	HR (95%CI)	*P* value
Major tumor diameter, mm, mean ± SD	46.2 ± 22.4	64.0 ± 35.1	1.02 (0.99-1.05)	0.062	44.2 ± 19	55.8 ± 31.9	1.01 (0.99-1.03)	0.107
Pathological T stage[1], *n* (%)								
1	2 (100)	0 (0)	Reference		2 (100)	0 (0)	Reference	
2	7 (87.5)	1 (12.5)	1.41 (0.03-62.92)	0.858	4 (50)	4 (50)	4.91 (0.19-124)	0.335
3	39 (86.7)	6 (13.3)	3.8 (0.05-270.74)	0.538	33 (73.3)	12 (23.7)	6.29 (0.22-177)	0.281
4	2 (100)	0 (0)	7.03 (0.04-1358)	0.468	1 (50)	1 (50)	21.47 (0.51-897)	0.107
Missing	1	-			1	-		
Pathological N stage[1], *n* (%)				0.196				
0	25 (96.2)	1 (3.8)	Reference		17 (65.4)	9 (34.6)	Reference	
1	11 (78.6)	3 (21.4)	14.5 (0.52-	0.115	8 (57.1)	6 (42.9)	2.41 (0.76-	0.135

			405.2)				7.65)	
2	14 (82.4)	3 (17.6)	15.4 (0.55-428)	0.107	15 (88.2)	2 (11.8)	0.88 (0.19-4.11)	0.874
Missing	1	-			1	-		
Pathological M stage[1], *n* (%)				0.546				0.032
0	44 (88)	6 (12)	Reference		37 (74)	13 (26)	Reference	
1	7 (87.5)	1 (12.5)	1.84 (0.25-13.22)		4 (50)	4 (50)	3.57 (1.12-11.40)	
AJCC Stage, *n* (%)								
1	8 (88.9)	1 (11.1)	Reference		5 (55.6)	4 (44.4)	Reference	
2	16 (100)	0 (0)	0.78 (0.01-73.61)	0.916	12 (75)	4 (25)	1.45 (0.28-7.51)	0.659
3	20 (80)	5 (20)	6.16 (0.21-178)	0.290	20 (80)	5 (20)	1.62 (0.31-8.37)	0.567
4	7 (87.5)	1 (12.5)	5.16 (0.12-215)	0.389	4 (50)	4 (50)	4.64 (0.84-25.69)	0.079
Retrieved LN, *n* (%)				1.000				0.477
< 12	10 (90.9)	1 (11.1)	Reference		8 (72.7)	3 (27.3)	Reference	
≥ 12	38 (86.4)	6 (13.6)			31 (70.5)	13 (29.5)	1.56 (0.46-5.32)	
Missing	3	-						
LN Ratio, mean ± SD	24 ± 17	27 ± 29	12.13 (0.84-174)	0.066	29 ± 20	15 ± 16	0.64 (0.04-11.17)	0.757
Colloid component, *n* (%)				0.106				0.396
No	13 (100)	0 (0)	Reference		9 (69.2)	4 (30.8)	Reference	
Yes	10 (66.7)	5 (33.3)	13.77 (0.57-330)		9 (60)	6 (40)	1.77 (0.47-6.62)	
Missing	28	2			23	7		

[1]According to the tumor node metastasis staging system.

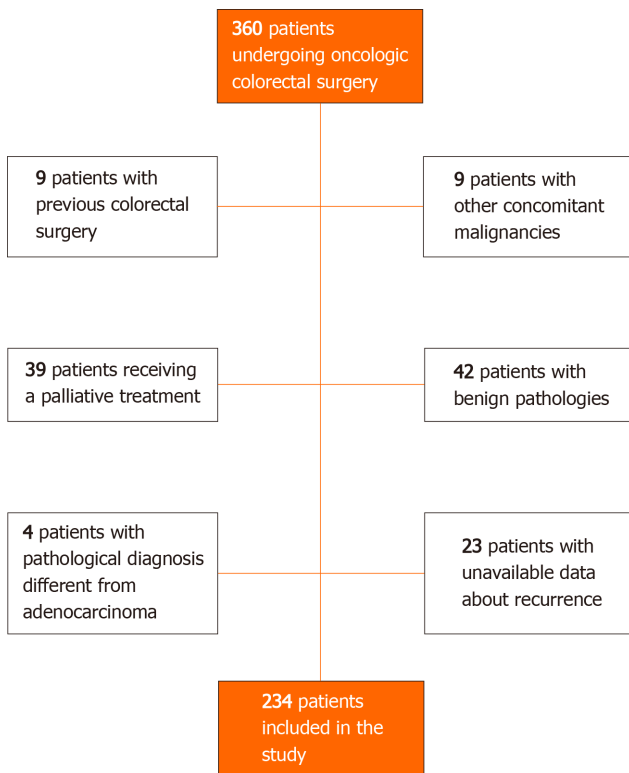HR: Hazard ratio; CI: Confidential intervals; AJCC: American Joint Committee on Cancer; LN: Lymph node.

Figure 1 Inclusion flow-chart. Patients excluded from the study (white boxes) and included in the study.
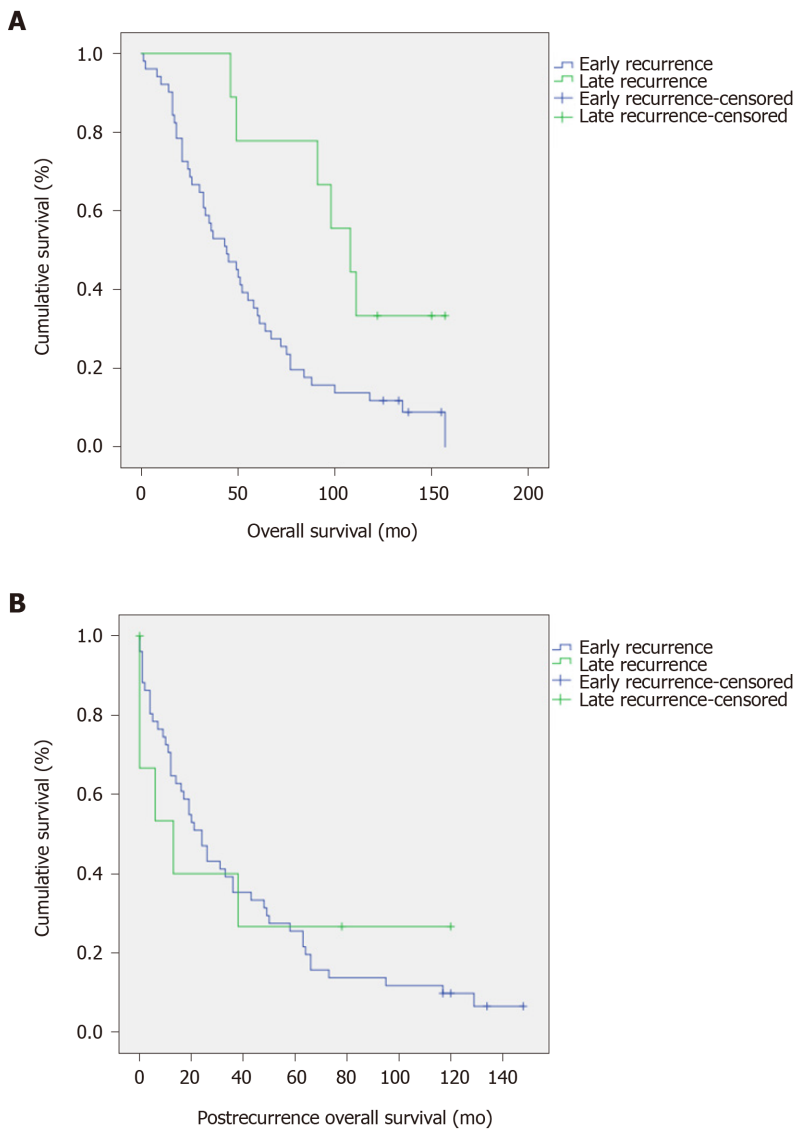
Figure 2 Kaplan-Meier curves for overall survival. A: Kaplan–Meier curve of overall survival (OS) stratified by Timing of Recurrence. Median OS for patients with recurrence < 3 years was 44 mo (95% Confidential interval 29-59 mo) *vs* 108 (95% Confidential interval 79-137 mo) for those with recurrence ≥ 3 years (*P* = 0.011); B: Kaplan Meier curve of post recurrence OS stratified by Timing of Recurrence. Median post recurrence OS for patients with recurrence < 3 years was 24 mo (95% Confidential interval 16-32 mo) *vs* 13 (95% Confidential interval 0-30 mo) for those with recurrence ≥ 3 years (*P* = 0.991).

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer is a common malignancy with a quite high recurrence rate in spite of the curative treatments utilized. Although most of the recurrences occur within the first three years, a percentage of them appear beyond five years after surgery. Early detection of these recurrences is of paramount importance to allow further curative treatments and improve patient prognosis. However, several different follow-up programs have been proposed over the year, mostly ending in 5 years after surgery.

Research motivation

Prognostic factors for recurrence, patterns of recurrence, and different prognostic factors for early or late recurrence are rarely reported in the literature, especially in cohorts of patients with a long follow-up period. Identifications of these parameters may allow a correct allocation of the patients in specific and tailored follow-up programs to improve patient prognosis and to reduce the costs.

Research objectives

The objectives of this study are the research of prognostic factors for overall recurrence, for early or late recurrence, and the analysis of the potential patterns of

recurrence for the most frequent sites of recurrence evaluating patients with a potential minimum follow-up period of 10 years. Clinical, operative, and pathological potential prognostic factors were evaluated and significant results were found for each one of the prospected objectives. These results may help clinicians in predicting patient prognosis and in choosing more cost-effective patient surveillance strategies.

Research methods

All the consecutive patients curatively treated for colorectal adenocarcinoma from January 2006 to June 2009 were prospectively included in a database that was retrospectively reviewed. A standardized follow-up program was applied to all the patients. Several prognostic factors about the patient, the treatment used, and the pathological response were evaluated. To evaluate the association between possible prognostic factors and disease-free survival and overall survival a Cox model, Kaplan-Meier method, and log-rank test were used. To estimate possible independent prognostic factors for recurrence a multiple Cox model with a backward selection method was used. To assess the association between each possible prognostic factor and timing to recurrence (< 3 years or ≥ 3 years) a simple logistic regression model was used.

Research results

Patients with higher levels of preoperative glycemia and carcinoembrionyc antigen, highest anaesthesiologists score score, presenting with occlusion, receiving a complex operation performed with an open technique, after a longer hospital stay, and showing advanced tumors had a higher chance to develop recurrence. At the multivariate analysis, the independent prognostic factors for recurrence were the hospital stay, N stage 2, and M stage 1. Younger ages were significantly associated with an early recurrence onset. Receiving intermediate colectomies or segmental resections, having an N stage 2 or American Joint Committee on Cancer stage 3 tumors was associated with a higher risk of liver recurrence; metastatic disease at diagnosis with local recurrence; receiving neoadjuvant treatments with lung recurrence; bigger tumors and higher lymph node ratio with peritoneal recurrence (marginally significant). However, these results and, in particular, those about the early *vs* late recurrence and the pattern of recurrence should be verified in larger series.

Research conclusions

Several prognostic factors for recurrence and some specific factors for each site of recurrence have been found and should be taken into account to perform a correct allocation of the patient within tailored cost-effective follow-up programs, eventually extended beyond five years after surgery.

Research perspectives

Further studies are needed to confirm these results, possibly prospective studies. The use of the learning machine may offer interesting opportunities in this area. Finally, the analysis of the second malignancies developed during the follow-up, which is marginally mentioned in this study, may represent another potential field of research.

ACKNOWLEDGEMENTS

REFERENCES

1   Cancer Today [accessed on 16 October 2020]. Available from: https://www.cancertodaymag.org/
2   **Watanabe T**, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol* 2018; **23**: 1-34 [PMID: 28349281 DOI: 10.1007/s10147-017-1101-6]
3   **Seo SI**, Lim SB, Yoon YS, Kim CW, Yu CS, Kim TW, Kim JH, Kim JC. Comparison of recurrence

patterns between ≤5 years and >5 years after curative operations in colorectal cancer patients. *J Surg Oncol* 2013; **108**: 9-13 [PMID: 23754582 DOI: 10.1002/jso.23349]

4   **Tjandra JJ**, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. *Dis Colon Rectum* 2007; **50**: 1783-1799 [PMID: 17874269 DOI: 10.1007/s10350-007-9030-5]

5   **Brown KGM**, Koh CE. Surgical management of recurrent colon cancer. *J Gastrointest Oncol* 2020; **11**: 513-525 [PMID: 32655930 DOI: 10.21037/jgo-2019-ccm-09]

6   **Liska D**, Stocchi L, Karagkounis G, Elagili F, Dietz DW, Kalady MF, Kessler H, Remzi FH, Church J. Incidence, Patterns, and Predictors of Locoregional Recurrence in Colon Cancer. *Ann Surg Oncol* 2017; **24**: 1093-1099 [PMID: 27812826 DOI: 10.1245/s10434-016-5643-z]

7   **Renehan AG**, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002; **324**: 813 [PMID: 11934773 DOI: 10.1136/bmj.324.7341.813]

8   **Riihimäki M**, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. *Sci Rep* 2016; **6**: 29765 [PMID: 27416752 DOI: 10.1038/srep29765]

9   **Cho YB**, Chun HK, Yun HR, Lee WS, Yun SH, Lee WY. Clinical and pathologic evaluation of patients with recurrence of colorectal cancer five or more years after curative resection. *Dis Colon Rectum* 2007; **50**: 1204-1210 [PMID: 17566830 DOI: 10.1007/s10350-007-0247-0]

10   **Aghili M**, Izadi S, Madani H, Mortazavi H. Clinical and pathological evaluation of patients with early and late recurrence of colorectal cancer. *Asia Pac J Clin Oncol* 2010; **6**: 35-41 [PMID: 20398036 DOI: 10.1111/j.1743-7563.2010.01275.x]

11   **Sargent D**, Sobrero A, Grothey A, O'Connell MJ, Buyse M, Andre T, Zheng Y, Green E, Labianca R, O'Callaghan C, Seitz JF, Francini G, Haller D, Yothers G, Goldberg R, de Gramont A. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 2009; **27**: 872-877 [PMID: 19124803 DOI: 10.1200/JCO.2008.19.5362]

12   **National Guideline Alliance part of the Royal College of Obstetricians and Gynaecologists (UK)**. Follow-up to detect recurrence after treatment for non-metastatic colorectal cancer: Colorectal cancer (update): Evidence review E1. London: National Institute for Health and Care Excellence (UK); 2020 [PMID: 32730000]

13   **Lan YT**, Chang SC, Yang SH, Lin CC, Wang HS, Jiang JK, Chen WS, Lin TC, Chiou SH, Lin JK. Comparison of clinicopathological characteristics and prognosis between early and late recurrence after curative surgery for colorectal cancer. *Am J Surg* 2014; **207**: 922-930 [PMID: 24355407 DOI: 10.1016/j.amjsurg.2013.08.035]

14   **Greene FL**, Page DL, Fleming ID, Fritz AG.   AJCC Cancer Staging Manual. 6th Ed. Chicago: Springer-Verlag; 2002

15   **Yang Y**, Mauldin PD, Ebeling M, Hulsey TC, Liu B, Thomas MB, Camp ER, Esnaola NF. Effect of metabolic syndrome and its components on recurrence and survival in colon cancer patients. *Cancer* 2013; **119**: 1512-1520 [PMID: 23280333 DOI: 10.1002/cncr.27923]

16   **Colangelo LA**, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 385-391 [PMID: 11927499]

17   **You J**, Liu WY, Zhu GQ, Wang OC, Ma RM, Huang GQ, Shi KQ, Guo GL, Braddock M, Zheng MH. Metabolic syndrome contributes to an increased recurrence risk of non-metastatic colorectal cancer. *Oncotarget* 2015; **6**: 19880-19890 [PMID: 26082438 DOI: 10.18632/oncotarget.4166]

18   **Gunter MJ**, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Howard BV, Wylie-Rosett J, Anderson GL, Ho GY, Kaplan RC, Li J, Xue X, Harris TG, Burk RD, Strickler HD. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res* 2008; **68**: 329-337 [PMID: 18172327 DOI: 10.1158/0008-5472.CAN-07-2946]

19   **Kim CG**, Ahn JB, Jung M, Beom SH, Heo SJ, Kim JH, Kim YJ, Kim NK, Min BS, Koom WS, Kim H, Roh YH, Ma BG, Shin SJ. Preoperative Serum Carcinoembryonic Antigen Level as a Prognostic Factor for Recurrence and Survival After Curative Resection Followed by Adjuvant Chemotherapy in Stage III Colon Cancer. *Ann Surg Oncol* 2017; **24**: 227-235 [PMID: 27699609 DOI: 10.1245/s10434-016-5613-5]

20   **Huang SH**, Tsai WS, You JF, Hung HY, Yeh CY, Hsieh PS, Chiang SF, Lai CC, Chiang JM, Tang R, Chen JS. Preoperative Carcinoembryonic Antigen as a Poor Prognostic Factor in Stage I-III Colorectal Cancer After Curative-Intent Resection: A Propensity Score Matching Analysis. *Ann Surg Oncol* 2019; **26**: 1685-1694 [PMID: 30915591 DOI: 10.1245/s10434-019-07184-3]

21   **Manceau G**, Voron T, Mege D, Bridoux V, Lakkis Z, Venara A, Beyer-Berjot L, Abdalla S, Sielezneff I, Lefèvre JH, Karoui M; AFC (French Surgical Association) Working Group. Prognostic factors and patterns of recurrence after emergency management for obstructing colon cancer: multivariate analysis from a series of 2120 patients. *Langenbecks Arch Surg* 2019; **404**: 717-729 [PMID: 31602503 DOI: 10.1007/s00423-019-01819-5]

22   **Bartolini I**, Ringressi MN, Melli F, Risaliti M, Brugia M, Mini E, Batignani G, Bechi P, Boni L, Taddei A. Analysis of Prognostic Factors for Resected Synchronous and Metachronous Liver Metastases from Colorectal Cancer. *Gastroenterol Res Pract* 2018; **2018**: 5353727 [PMID: 30116264 DOI: 10.1155/2018/5353727]

23   **Bouvier AM**, Launoy G, Bouvier V, Rollot F, Manfredi S, Faivre J, Cottet V, Jooste V. Incidence and patterns of late recurrences in colon cancer patients. *Int J Cancer* 2015; **137**: 2133-2138 [PMID: 25912489 DOI: 10.1002/ijc.29578]

24   **Amri R**, Klos CL, Bordeianou L, Berger DL. The prognostic value of lymph node ratio in colon cancer is independent of resection length. *Am J Surg* 2016; **212**: 251-257 [PMID: 27156798 DOI: 10.1016/j.amjsurg.2015.10.037]

25   **Dedavid e Silva TL**, Damin DC. Lymph node ratio predicts tumor recurrence in stage III colon cancer. *Rev Col Bras Cir* 2013; **40**: 463-470 [PMID: 24573624 DOI: 10.1590/s0100-69912013000600008]

26   **Rosenberg R**, Engel J, Bruns C, Heitland W, Hermes N, Jauch KW, Kopp R, Pütterich E, Ruppert R, Schuster T, Friess H, Hölzel D. The prognostic value of lymph node ratio in a population-based collective of colorectal cancer patients. *Ann Surg* 2010; **251**: 1070-1078 [PMID: 20485149 DOI: 10.1097/SLA.0b013e3181d7789d]

27   **Jakob MO**, Guller U, Ochsner A, Oertli D, Zuber M, Viehl CT. Lymph node ratio is inferior to pN-stage in predicting outcome in colon cancer patients with high numbers of analyzed lymph nodes. *BMC Surg* 2018; **18**: 81 [PMID: 30285691 DOI: 10.1186/s12893-018-0417-0]

28   **Huang B**, Feng Y, Mo SB, Cai SJ, Huang LY. Smaller tumor size is associated with poor survival in T4b colon cancer. *World J Gastroenterol* 2016; **22**: 6726-6735 [PMID: 27547015 DOI: 10.3748/wjg.v22.i29.6726]

29   **Saha S**, Shaik M, Johnston G, Saha SK, Berbiglia L, Hicks M, Gernand J, Grewal S, Arora M, Wiese D. Tumor size predicts long-term survival in colon cancer: an analysis of the National Cancer Data Base. *Am J Surg* 2015; **209**: 570-574 [PMID: 25601557 DOI: 10.1016/j.amjsurg.2014.12.008]

30   **Ramphal W**, Boeding JRE, Gobardhan PD, Rutten HJT, de Winter LJMB, Crolla RMPH, Schreinemakers JMJ. Oncologic outcome and recurrence rate following anastomotic leakage after curative resection for colorectal cancer. *Surg Oncol* 2018; **27**: 730-736 [PMID: 30449500 DOI: 10.1016/j.suronc.2018.10.003]

31   **Ha GW**, Kim JH, Lee MR. Oncologic Impact of Anastomotic Leakage Following Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis. *Ann Surg Oncol* 2017; **24**: 3289-3299 [PMID: 28608118 DOI: 10.1245/s10434-017-5881-8]

32   **Bartolini I**, Risaliti M, Ringressi MN, Melli F, Nannini G, Amedei A, Muiesan P, Taddei A. Role of gut microbiota-immunity axis in patients undergoing surgery for colorectal cancer: Focus on short and long-term outcomes. *World J Gastroenterol* 2020; **26**: 2498-2513 [PMID: 32523307 DOI: 10.3748/wjg.v26.i20.2498]

33   **Zhao Y**, Yi C, Zhang Y, Fang F, Faramand A. Intensive follow-up strategies after radical surgery for nonmetastatic colorectal cancer: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2019; **14**: e0220533 [PMID: 31361784 DOI: 10.1371/journal.pone.0220533]

34   **Pita-Fernández S**, Alhayek-Aí M, González-Martín C, López-Calviño B, Seoane-Pillado T, Pértega-Díaz S. Intensive follow-up strategies improve outcomes in nonmetastatic colorectal cancer patients after curative surgery: a systematic review and meta-analysis. *Ann Oncol* 2015; **26**: 644-656 [PMID: 25411419 DOI: 10.1093/annonc/mdu543]

35   **Chauvenet M**, Lepage C, Jooste V, Cottet V, Faivre J, Bouvier AM. Prevalence of patients with colorectal cancer requiring follow-up or active treatment. *Eur J Cancer* 2009; **45**: 1460-1465 [PMID: 19216071 DOI: 10.1016/j.ejca.2009.01.012]