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ORIGINAL ARTICLE

Characteristics and risk factors for colorectal cancer recurrence

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Summary

Purpose: *To evaluate the characteristics of recurrence and examine the clinicopathological factors related to disease-free (DFS) and overall survival (OS) of patients with colorectal cancer (CRC) recurrence.*

Methods: *One hundred and sixteen CRC patients with stage II and III disease that had been resected curatively in our clinic between 1999 and 2006 were retrospectively evaluated. The parameters evaluated were gender, age, preoperative CEA levels, tumor localisation, duration of surgery, the units of perioperative blood transfusion, tumor differentiation, TNM stages and adjuvant therapies. The presence of preoperative intestinal obstruction, radical abdominopelvic lymph node (RAPL) dissection and lymphatic, vascular and perineural invasion were also evaluated.*

Results: *With 36.6±2 months follow-up, 49 (42%) patients developed local recurrence and/or distant metastases. Twenty-three (19.8%) patients presented with isolated local recurrence. Thirteen of 49 patients with local recurrence were successfully operated with R0 curative resection. The OS survival rates for those with curatively and palliatively resected recurrences were 29 and 19 months, respectively. In multivariate analysis, the factors related to DFS were tumor localisation and differentiation, neurovascular invasion, blood transfusion and RAPL dissection. Among these factors, only RAPL dissection was not statistically significant for OS.*

Conclusion: *The factors increasing local recurrence rates of CRC should be clearly described. Local and systemic treatment modalities, like preoperative chemoradiotherapy should be planned for patients carrying these risk factors.*

Key words: colorectal cancer, recurrence, risk factors

Introduction

CRC is among the major causes of cancer-related mortality worldwide [1,2]. Five-year OS rates of patients with curative resection for localised disease is 70-90%. In the presence of regional lymph node metastasis this rate decreases to 40-80% [3].

Surgical treatment is the best way to cure CRC, but recurrences occur in a substantial proportion of the patients in relation with the stage of disease. Although new anticancer drugs have improved the survival of patients with unresectable recurrences of CRC, early detection of recurrences at a resectable stage may also lead to curative surgical treatment [4-7]. Despite the new advancements for the treatment of CRC, local recurrence with a 40-50% incidence is still associated with significant morbidity and cancer-related mortality [8]. Nearly 20% of the patients die with locally recurrent disease as the only disease manifestation [9,10].

The aim of the present study was to clarify the characteristics of recurrence and to examine the clinicopathological factors related to DFS and OS of patients with CRC who had been operated with curative intent.

Methods

Patients

One hundred and sixteen CRC patients with stage II and III disease and curative operation carried out at our clinic between 1999 and 2006 were retrospective-

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ly evaluated. All patients had at least 2 cm tumor-free distal surgical margin. Tumors localised 15 cm or more from the anal canal were grouped and evaluated in the colon cancer group.

The study exclusion criteria were distant metastasis at diagnosis, neoadjuvant chemotherapy and/or radiotherapy and palliative surgery. The parameters evaluated were gender, age (<60 vs. ≥ 60 years), preoperative CEA levels (≥ 5 vs. < 5 ng/mL), tumor localisation (colon vs. rectum), duration of surgery, the units of perioperative blood transfusion (<2 vs. ≥ 2 units), differentiation (well vs. poor), TNM stages and adjuvant therapies.

The presence of preoperative intestinal obstruction, RAPL dissection and lymphatic, vascular and perineural invasion were also evaluated.

RAPL dissection technique was defined as high ligation of the inferior mesenteric artery, total mesorectal excision including level I and II lymph nodes and dissection of the area around the external iliac arteries and vena cava inferior. Local recurrence was defined as the recurrence at the anastomotic site, around the peritoneum of the abdominal wall and intraabdominal lymph nodes. All patients were evaluated for DFS and OS, recurrence sites and investigations used for the diagnosis of recurrence.

Statistical analysis

The results were evaluated with multiple logistic regression analysis and SPSS for Windows 10.00 (SPSS Inc. Chicago, Illinois, USA) was used for statistical evaluation. The results are reported as median±standard deviation and defined with odds ratio and 95% confidence intervals (CI). The parameters related with recurrence were evaluated with univariate logistic regression analysis, while backward logistic regression model was used for multivariance analysis. Kaplan-Meier method was used for survival analysis and survival curves were drawn. A p-value of <0.05 was considered as statistically significant.

Results

One hundred and sixteen patients underwent curative surgery during the study period and 49 (42%) of them had local recurrence and/or distant metastases. The patient tumor and treatment characteristics are summarized in Table 1. The average patient age was 58.9±12.6 years (range 25-80). Sixty-seven (57%) patients were male and 49 (43%) female. At initial diagnosis, 46 (39%) patients had colon carcinoma and 70 (61%) had rectal carcinoma.

According to the 6th edition of TNM staging system, 51 (44%) patients had stage II and 65 (56%) stage III disease. Twenty percent of the patients with stage II and 60% with stage III disease recurred (p=0.914). The primary tumor size was T3 in 96 (82.8%) patients and T4 in 20 (17.2%) patients. Fifty-one (44%) patients had N0, 33 (28.4%) N1, 28 (24.1%) N2 and 4 patients had N3 disease. Seventy-six (65.5%) of the tumors were well and the rest (34.5%) were poorly differentiated. The recurrence rates for well and poorly differentiated tumors were 18.4% and 87.5%, respectively (p=0.001). The histopathological evaluation of the tumors showed 33 cases with vascular invasion, 13 with lymphatic invasion and 6 with perineural invasion. Twenty-two (25.8%) out of 30 patients with signs and symptoms of preoperative obstruction recurred. Sixty-nine (60%) patients needed 2 or more units of blood transfusion during the perioperative period. Sixty-one (52%) patients had increased preoperative CEA levels (≥5 ng/mL) and the rest (48%) had normal or minimally elevated levels. Sixty percent of the cases with high preoperative CEA levels recurred during follow-up. The patient characteristics and their impact on survival are summarized in Table 1.

RAPL dissection was carried out on 48 patients and 33 of them had rectal carcinoma. The mean number of lymph nodes dissected with RAPL was 16.2 (range 9-23). The mean number of lymph nodes dissected in patients with RAPL for rectal carcinoma was 22 (range 10-64). Twelve or more lymph nodes were dissected in 79 (68%) patients (Table 2). The ratio of positive lymph nodes to total number of lymph nodes dissected was more than 10% in 42 (36.2%) patients (Table 1).

The average duration of the follow-up was 36.6±2 months. Twenty-three (19.8%) patients had isolated local recurrence and 15 of them were operated for rectal carcinoma. Fifteen (13%) patients had liver metastasis, one patient had an isolated lung metastasis and two patients had both liver and lung metastasis. Eight patients had both local recurrence and liver and/or lung metastasis (Table 2).

Five-year DFS and OS rates were 52% and 61%, respectively. While the 5-year survival rate for colon carcinoma was 87%, it was 46% for rectal carcinoma cases (p=0.015). The time period between curative resection and recurrence was 29±2 months. Thirty-six percent of the recurrences occurred in the first 2 years of follow-up.

The recurrences of the 24 patients were detected during routine follow-up. These patients were asymptomatic. However, the other 25 patients had the diagnosis made after being symptomatic. The major symptoms of recurrent disease were abdominal pain and bowel obstruction. Bleeding, weight loss and urogenital symptoms were also helpful for early diagnosis of recurrence. Medical history, physical examination,

Table 1. Multivariate analysis of patient characteristics and their impact on overall survival

Characteristics	*With recurrence n (%)*	*Without recurrence n (%)*	*Patients, n (total)*	*p-value*	*Odds ratio*	*95% confidence interval*
Patients	49 (42)	67 (58)	116			
Age (years, median)	56.3	60	58	0.065	NSA	NSA
Gender					NSA	NSA
Male	32 (47)	35 (53)	67	0.786		
Female	17 (34)	32 (66)	49			
Tumor localisation						
Colon	15 (32)	31 (68)	46	0.015	7	2-21
Rectum	34 (48.5)	36 (51.5)	70			
Stage					NSA	NSA
II	10 (20)	41 (80)	51	0.914		
III	39 (60)	26 (40)	65			
Preop CEA					NSA	NSA
High	37 (60)	24 (40)	61	0.07		
Normal	12 (21.8)	43 (78.2)	55			
Obstruction					NSA	NSA
Present	22 (73)	8 (27)	30	0.373		
Absent	27 (31)	59 (69)	86			
Transfusion (units)						
<2	14 (30)	33 (70)	47	0.038	7	1-49
≥2	35 (50.7)	34 (49.3)	69			
RAPL dissection					NSA	NSA
Present	5 (10)	43 (90)	48	0.823		
Absent	44 (64)	24 (36)	68			
Adjuvant CT					NSA	NSA
Yes	47 (52)	43 (48)	90			
No	2 (7)	24 (93)	26			
Adjuvant RT					NSA	NSA
Yes	22 (38)	36 (62)	58			
No	27 (46.5)	31 (53.5)	58			
Differentiation						
Well	14 (18.4)	62 (81.6)	76	0.001	261	24-28
Poor	35 (87.5)	5 (12.5)	40			
Lymphatic invasion	7 (53.8)	6 (46.1)	13	0.832	NSA	NSA
Vascular invasion	25 (75.1)	8 (24.2)	33	0.002	12	12-21
Perineural invasion	5 (83.3)	1 (16.6)	6	0.046	6.5	2-21
Nodes						
<12	16 (21.6)	58 (78.4)	74	0.907		
≥12	33 (78.5)	9 (21.5)	42			

CT: chemotherapy, RT: radiotherapy, RAPL: radical abdominopelvic lymph node dissection, NSA: not statistically applicable

elevated tumor markers and ultrasonographic evaluation were additional tools for diagnosis.

The first diagnostic tools for diagnosis were computed tomography (CT) for 27 (55%) patients, ultrasound for 19 (39%) patients and chest X-ray for 3 (6%) patients. Sixteen (70%) of the 23 patients with isolated local recurrence were diagnosed after they had symptoms of recurrence. Fourteen asymptomatic of the 15 patients with liver metastasis were diagnosed during regular follow-up. The diagnosis of liver metastasis was confirmed earlier than the isolated local recurrences (19 vs. 22 months; $p > 0.05$). Curative surgery for recurrences was possible for 6 of 7 patients diagnosed during follow-up. But only 4 of 16 patients with symptomatic local recurrences could have a curative operation.

Thirteen of 49 patients with local recurrence were successfully operated with R0 curative resection and 3 patients were operated for palliation. Ten patients with isolated local recurrence, 2 patients with liver metastasis and one patient with both liver metastasis and local recurrence achieved R0 resection. Seventeen patients with inoperable recurrence were given chemotherapy and/or radiotherapy and 16 patients were followed with supportive care (Table 3).

Table 2. Distribution of patients according to the number of lymph nodes dissected and the features of recurrence and symptoms with regard to the localisation of the primary tumor

	Colon carcinoma n=46 (39.6%) n (%)	*Rectal carcinoma n=70 (60.4%) n (%)*	*Symptomatic cases n=25 (51%) n (%)*	*Diagnosed with routine follow-up n=24 (49%) n (%)*
0-3 lymph nodes	1 (2.1)	1 (1.4)		
4-7 lymph nodes	4 (8.6)	9 (12.8)		
8-11 lymph nodes	12 (26)	10 (14.2)		
≥12 lymph nodes	29 (63)	50 (71.4)		
Isolated local recurrence	8 (17.3)	15 (21.4)	16 (64)	7 (29.1)
Liver metastasis	4 (8.6)	11 (15.7)	1 (4)	14 (58.3)
Local recurrence + liver metastasis	2 (4.2)	4 (5.7)	5 (20)	1 (4.1)
Local recurrence + liver + lung metastasis	–	1 (1.4)	1 (4)	–
Local recurrence + lung metastasis	–	1 (1.4)	1 (4)	–
Lung metastasis	–	1 (1.4)	–	1 (4.1)
Liver and lung metastasis	1 (2.1)	1 (1.4)	1 (4)	1 (4.1)

Table 3. Treatments applied according to the site of recurrence (n=49)

Site of recurrence	*Curative surgery*	*Palliative surgery*	*Chemotherapy and radiotherapy*	*Supportive care*
Local recurrence	10	2	6	5
Liver metastasis	2		5	8
Local recurrence + liver metastasis	1	1	2	2
Local recurrence + liver metastasis + lung metastasis				1
Local recurrence + lung metastasis			1	
Lung metastasis			1	
Liver metastasis + lung metastasis			2	
Total	13	3	17	16

The OS rates for patients with R0 curative resection, palliative surgery, chemotherapy and/or radiotherapy and symptomatic care were 29, 19, 15.5 and 13.3 months, respectively. The only therapeutic method that showed positive impact on OS was R0 resection (p=0.023). Although the statistical difference among palliative surgery, chemotherapy and/or radiotherapy, and symptomatic care was not significant, palliative surgery was effective for symptom control. No patient with R0 resection was given preoperative chemotherapy and/or radiotherapy. Two patients in the palliative surgery group were lost to follow-up with tumor progression and the third one was followed up with stable disease. Multivariate analysis of factors related with DFS is summarized in Table 4.

Table 4. Multivariate analysis of factors related with disease free survival

Factors	*p-value*	*Risk ratio*	*95% confidence interval*
Obstruction	0.621	NSA	NSA
CEA level	0.254	NSA	NSA
Tumor localisation	0.001	5	2-13
Differentiation	0.001	44	9-21
Involved lymph node ratio	0.263	NSA	NSA
Number of lymph nodes dissected	0.704	NSA	NSA
Stage	0.548	NSA	NSA
Vascular invasion	0.014	3	2-7
Perineural invasion	0.018	3.6	2-10
Blood transfusion	0.009	9	17-551
RAPL dissection	0.009	2	1-6

RAPL dissection: radical abdominopelvic lymph node dissection, NSA: not statistically applicable

Discussion

Pelvic recurrence of CRC causes severe pain from nerve involvement, intestinal and urethral obstruction

with hydronephrosis, fistula formation and decreases the quality of life and survival [11,12]. About half of the patients die with locally recurrent disease as the only disease localisation. In this series only 9 of 23 patients with isolated local recurrence died of recurrence.

The morbidity of radical curative surgery after local recurrence is quite high and resectability rates range between 25-50% [11]. To achieve a stable control of local recurrence-related symptoms and to improve survival, complete removal of the tumor (R0 resection) is necessary. The OS rates after R0 resection range between 18-58% [11,12]. In this series, while OS of patients with symptomatic treatment was 11.3 months, the survival of patients with R0 resection was 29 months (p=0.023). Palliative surgical interventions provide short-term symptomatic relief.

One of the most important factors affecting the chance of R0 resection is the diagnosis of recurrence at asymptomatic stage [11,12]. The chance of curative surgery for patients with regular follow-up after CRC surgery was 2.5-fold higher than for patients without regular follow-up [13,14]. Therefore, the diagnosis of asymptomatic local recurrence is of paramount importance in order to successfully perform a curative operation. In this series, most of the patients without regular follow-up were examined at least once a year.

Medical history, physical examination and increased CEA levels were helpful diagnostic tools for patients with asymptomatic recurrences. Curative surgery was possible for 6 out of 7 patients with asymptomatic recurrence. Literature data show that patients being in regular follow-up have better chances for R0 resection compared to those with irregular follow-up [13,14]. It could be said that regular follow-up with detailed history, physical examination and CEA level monitoring are the most important diagnostic tools for the detection of asymptomatic recurrences.

The need for perioperative blood transfusion ranges between 20-75% for patients undergoing CRC surgery [15]. In many other studies, it has been shown that blood transfusion leads to induction of mediators like IL-6, hepatocyte growth factor, VEGF, intracellular and vascular adhesion molecules and immune suppression affecting the long-term prognosis after curative resection of CRC [15-17]. Blood transfusion also increases the risk for infection and morbidity.

In the present study more than 2 units of blood transfusion was an unfavorable parameter for both DFS and OS in univariate and multivariate analysis. This result was expected and predicted.

Adjuvant chemotherapy has been reported to prolong DFS and OS of CRC patients [18-21]. However, in our study there was no significant difference between patients receiving adjuvant chemotherapy or not. This result might be explained by the fact that this study included only patients with stage II and III CRC and therefore the beneficial effect of adjuvant chemotherapy might be masked. Similarly, in some other studies with advanced CRC, the beneficial effect of adjuvant chemotherapy could not be ascertained [22,23].

Many authors have reported that the prognosis of CRC is better for female patients and patients over 60 years of age [22,24-26]. In the present study, no relation between gender, age and prognosis could be demonstrated. It was thought that the decreased beneficial effect of chemotherapy might also mask this difference.

In our series, while preoperative increased CEA level was found to be important for both DFS and OS in univariate analysis, this effect could not be demonstrated in multivariate analysis. The predictive role of preoperatively increased CEA level for early recurrences has been documented in many studies [22,27-31]. In our series the recurrences of the cases with preoperatively increased CEA level occurred at the end of 2nd year of follow-up.

The prognostic significance of the number of lymph nodes dissected has been documented in many studies [32-35], in which it has been shown that the minimum number of lymph nodes that should be dissected for accurate staging should be 12 at least. The positive predictive value of large number of dissected lymph nodes on DFS and OS was also documented in our series where adequate number of dissected lymph nodes (more than 12) has been achieved in 61% of colon cancer and 72% in rectal cancer patients. Hospital characteristics (being reference center and hospital volume) and standardized surgical procedures by the same clinic were thought to be related to this fact.

Advanced lymph node stage is known to increase the risk for recurrence [36-39]. The correlation between advanced nodal stage and risk for recurrence becomes more relevant with the increased number of lymph nodes dissected, allowing better pathological evaluation. The ratio between the number of positive lymph nodes and the total number of lymph nodes dissected might be a more valuable prognostic parameter for recurrence and survival [40]. A ratio above 10% might be regarded as a bad prognostic parameter [24]. In our series, increased ratio was found to be related with worse prognosis, as expected.

The presence of bowel obstruction or perforation at the time of presentation requires adjuvant systemic treatment even for patients without nodal metastasis [39]. Dehydration, sepsis, deterioration of general health status, advanced stage and decreased chance for curative resection are some of the factors related to poor prognosis. Besides major postoperative compli-

cations involving gastrointestinal system (25%), respiratory system (17%), renal system (13%) and cardiac function (3%) are more frequent in these patients. The incidence of obstruction and perforation from CRC is 15-25% and 5-8% respectively [41]. In our investigation, the number of patients presented with obstruction was 30 (25.8%). In univariate analysis, the presence of obstruction was found to be unfavorably related to both DFS and OS.

High grade tumors with lymphovascular and perineural invasion had more aggressive clinical course, as expected.

Some investigators pointed out that RAPL dissection decreased the risk for local recurrence [26,42-45], whilst some others concluded that radical procedures like RAPL dissection were not superior to conventional surgical techniques and were associated with increased morbidity like urinary and sexual dysfunction [46,47]. In a large series from Japan, local recurrence rates were significantly lower after RAPL dissection compared to conventional surgery [45]. In our series, RAPL dissection was applied in 48 patients and both univariate and multivariate analysis showed improved DFS. The risk for local recurrence was 2-fold higher for patients without RAPL dissection. However, no beneficial effect of RAPL dissection on OS could be demonstrated in multivariate analysis.

Literature data shows that 50-80% of local recurrences of CRC occur in the first 2 years after surgery [24]. In this series, 36% of the recurrences were seen in the first 2 years of follow-up. The reason for longer DFS in this series of advanced CRC might be the more frequent use of RAPL dissection. While the duration of surgery in patients operated with RAPL dissection was 4 h and 30 min, it was 4 h and 15 min in patients without RAPL dissection. Following this observation we claim that if the decision to proceed with RAPL dissection is made at the early stages of the operation, the duration of surgery is not prolonged and the patient is not confronted with increased morbidity.

The factors increasing local recurrence rates of CRC should be clearly described. Local and systemic treatment modalities, like preoperative chemoradiotherapy, should be planned for patients with these risk factors.

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