Variation in diagnosis, treatment and outcome in colon and rectal cancer

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2.3
Prognostic factors for locoregional recurrences in colon cancer

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submitted to Annals of Surgical Oncology

Abstract

Background

There is an increased interest in locoregional recurrences in rectal cancer. Despite comparable locoregional recurrence rates in colon cancer, only a few studies on locoregional recurrences among colon cancer patients have been published. Aim of this study was to identify prognostic factors for locoregional recurrences among patients with colon cancer in the Netherlands.

Methods

The study population was composed of patients who underwent radical surgical resections for invasive colon carcinoma, diagnosed in three regions of the Netherlands from 2000 to 2003. The Kaplan-Meier method was used to calculate 5-year locoregional recurrence rates (LRR). Conditional hazard rates were estimated by the life-table method. Multivariate Cox regression analyses were performed to identify prognostic factors and to calculate a Locoregional Recurrence Risk Score (LRRS).

Results

In total 127 out of 2,282 patients developed locoregional recurrences within 5 years (LRR 6.4%). The risk of developing a locoregional recurrence was highest at 0.5 to 1 year after surgery. Patients with left-sided tumours, T3-T4 tumours and positive lymph nodes and those who did not receive adjuvant chemotherapy were more likely to develop locoregional recurrences. Four risk groups based on the LRRS were defined. Five-year LRR was 2.5% for the very low risk group and 25.1% for the high risk group.

Conclusions

Patients with colon cancer were at highest risk for locoregional recurrence 0.5 to 1 year after surgery. Identifying individual patients who might benefit from adjuvant chemotherapy may reduce the locoregional recurrence rate.

Introduction

Colon cancer is the third most common cancer in the Netherlands. The relatively high incidence is comparable to incidences in other Western countries. In 2008, colon cancer was diagnosed in more than 8,100 new patients in the Netherlands, while 3,750 patients died of this in the same year, making this malignancy the second most frequent cause of cancer-related death.[1;2]

Survival among patients with colon cancer used to be higher compared to survival among patients with rectal cancer.[3] However, several changes in the treatment of rectal cancer have been introduced, including the introduction of the total mesorectal excision (TME) technique and a shift from postoperative to preoperative radiotherapy.[4;5] Due to these changes, survival of all patients with rectal cancer increased more rapidly compared to that of patients with colon cancer. Currently, survival among patients with rectal cancer is higher compared to that among patients with colon cancer.[6]

The changes in treatment also resulted in an increased interest in locoregional recurrences among patients with rectal cancer. In contrast, only a few studies on locoregional recurrences among patients with colon cancer have been published. Two studies comparing the locoregional recurrence rates of colon and rectal tumours revealed that the risk among patients with colon cancer was comparable to that among patients with rectal cancer, and reported rates of 10.2% and 6.0% for rectal cancer and 6.2% and 8.5% for colon cancer, respectively.[7;8]

The overall survival of colon cancer patients who develop locoregional recurrences after their initial treatment is generally poor.[9] Identification of factors which may influence the risk of locoregional recurrences is the next step in the process of prevention. Several factors have already been found to be associated with locoregional recurrence, i.e. emergency surgery, bowel perforation, surgeon's interest in colorectal surgery, poor differentiation of the tumour and advanced stage.[9-13] Most of these studies, however, were performed in a hospital-based setting.

The aim of this population-based study was, therefore, to describe the incidence of locoregional recurrences in a large cohort of patients with colon cancer, to identify prognostic factors and to define risk groups for locoregional recurrences based on the combination of the prognostic factors.

Methods

Cancer registry

All newly diagnosed cancer cases have been registered in the nationwide population-based Netherlands Cancer Registry (NCR) since 1989. Notification is obtained from the automated national pathological archive (PALGA) and from haematology and radiotherapy departments. The National Registry of Hospital Discharge Diagnoses is also an important source, accounting for up to 8% of new cases which were not obtained from PALGA.[14] Data are collected from patient files in the hospital by specially trained registration clerks. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O)[15] and the TNM classification is used for staging of the tumours.[16] The dataset includes patient and tumour characteristics and information about treatment and follow-up. The vital status of all patients is complete up to February 2009 by linking deaths from the municipality registry to the cancer registry.

Patients

Data on recurrences were available for patients who underwent a radical surgical resection for invasive colon carcinoma (ICD-O: C18), diagnosed in the period 2000-2002 in the region of the Comprehensive Cancer Centre Amsterdam, diagnosed in 2003 in the region of the Comprehensive Cancer Centre North Netherlands or diagnosed in 2002-2003 in the region of the Comprehensive Cancer Centre Stedendriehoek Twente. Patients with distant metastases at time of diagnosis, those who died within 30 days after surgery, as well as those with an unknown pathological stage and/or those who had a preceding invasive cancer were excluded from this study.

Information about local recurrences, regional recurrences and distant metastasis is not collected routinely in the NCR. This was obtained by reviewing the medical records of all patients by the registration clerks of the NCR. Locoregional recurrence was defined as any histological or clinical evidence of tumour re-growth in or nearby the primary site after excision of the former tumour, irrespective of the presence or absence of distant metastases. Cases were generally followed for five years after surgery of the primary tumour. Detailed information about the follow-up program of all patients was not available, but most patients were followed at least once or twice per year. In accordance with the Dutch guidelines, follow-up for patients with colon tumours without distant metastases consists of regular clinical checks by a medical specialist, colonoscopy, CEA measurements and ultrasounds of the liver.[17] For the analyses, pathological TNM stage was used. Site of the tumour was categorised into right-sided (C18.0-C18.3), transversum (C18.4), left-sided (C18.4-C18.7) and overlapping lesion of colon or not otherwise specified (C18.8-18.9).

Statistical analyses

The Kaplan-Meier method was used to calculate 5-year locoregional recurrence rates. The life-table method was carried out to estimate conditional hazard rates, defined as the probability of developing locoregional recurrence in a 6-month interval in the case that the patient is free of any recurrence, locoregional recurrence or distant metastases, or second primary colon tumour at the beginning of the interval. The conditional hazard rate at, for example, one year after surgery concerns the interval from 6 months to one year after surgery and is based on all patients who were free of recurrences at 6 months after surgery. To examine differences in patterns of recurrences, separate analyses were performed for patients with stage II and stage III disease. Due to the low number of locoregional recurrences in stage I, this stage was not analysed separately but only included in the overall conditional hazard rates.

Prognostic factors for locoregional recurrences were analysed using Cox regression, including gender, age at diagnosis, year of diagnosis, tumour site, depth of invasion, number of evaluated lymph nodes, number of positive lymph nodes, tumour grade, adjuvant chemotherapy and CCC-region. Time to recurrence was calculated from the date of resection of the primary tumour to the date of diagnosis of the locoregional recurrence. Patients who did not have a locoregional recurrence were censored and the time was calculated from date of resection to date of second primary colon tumour, date of death or date of last follow-up. Separate analyses were conducted to examine differences in prognostic factors for developing a locoregional recurrence only (including diagnosis of a distant metastasis after the diagnosis of a locoregional recurrence) and for developing a locoregional recurrence combined with a distant metastasis diagnosed before or at time of diagnosis of the locoregional recurrence. Risk points for each prognostic factor were defined by multiplying the regression coefficients (β) from the multivariate model with 10 and rounding it to a whole number. For each individual patient, a Locoregional Recurrence Risk Score (LRRS) was calculated by summing the risk points of each prognostic factor. Based on the LRRS, four risk groups were defined using receiver operating characteristics (ROC) analysis. For all analyses STATA version 10.0 was used. A p-value <0.05 was considered to be statistical significant.

Results

In total, 2,282 patients with colon cancer were included in this study. Table 1 shows the characteristics of the study population. Overall, 48% were male and 38% were aged 75 years or older at the time of diagnosis. Almost half of the tumours were stage IIA (T3N0M0). Twenty-three percent of all patients had 1 to 3 positive lymph nodes. Overall, the proportion of patients who received adjuvant chemotherapy was 25%. Median follow-up time was 5.0 years. Locoregional recurrences were diagnosed in 127 patients within five years after surgery of the primary tumour, of which 39 patients (31%) underwent surgical treatment. Almost all patients (97%) who did not underwent surgical treatment died, with a median time between locoregional recurrence and death of 0.4 years (Figure 1).

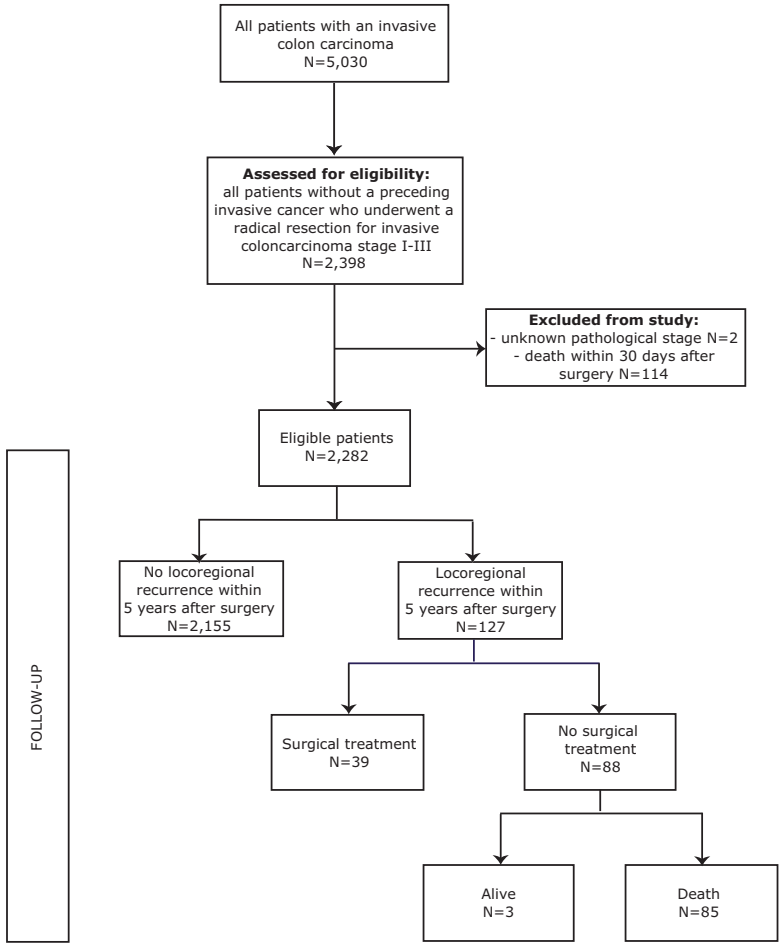

Figure 1 Flow chart

Table 1 Characteristics of the study population and 5-year locoregional recurrences rates (LRR)

Characteristics	N	%	LRR	95% CI	P-value
Total	2,282	100	6.39	5.39-7.56	
Gender					
Male	1,098	48	6.26	4.87-8.04	
Female	1,184	52	6.51	5.17-8.18	0.579
Age at diagnosis					
<50 years	135	6	4.64	2.11-10.05	
50-74 years	1,283	56	6.78	5.47-8.39	
≥75 years	864	38	6.03	4.47-8.10	0.593
Year of diagnosis					
2000	536	23	5.32	3.62-7.80	
2001	515	23	4.65	3.05-7.06	
2002	767	34	7.29	5.55-9.55	
2003	464	20	7.90	5.64-11.01	0.185
Tumour site					
Right-sided	1,031	45	5.18	3.91-6.85	
Transversum	166	7	6.33	3.33-11.88	
Left-sided	1,065	47	7.55	6.01-9.46	
Overlapping lesion of colon and not otherwise specified	20	1	5.26	0.76-31.88	0.321
Stage					
I	385	17	1.74	0.79-3.84	
IIA	1,041	46	4.30	3.16-5.85	
IIB	104	5	9.95	5.28-18.33	
IIIA	59	3	1.72	0.24-11.62	
IIIB	483	21	10.49	7.84-13.97	
IIIC	210	9	17.37	12.39-24.07	<0.001
Depth of invasion					
pT1	134	6	1.76	0.44-6.85	
pT2	319	14	2.06	0.93-4.53	
pT3	1,638	72	6.89	5.67-8.35	
pT4	191	8	13.10	8.79-19.28	<0.001
Number of evaluated lymph nodes					
0	75	3	6.45	2.47-16.32	
1-3	323	14	5.78	3.51-9.45	
4-6	475	21	7.77	5.51-10.90	
7-9	457	20	5.65	3.78-8.40	
10-12	307	13	7.37	4.81-11.22	
13-15	194	9	6.67	3.84-11.46	
16-18	114	5	6.85	3.32-13.88	
≥19	122	5	2.54	0.83-7.67	
Unknown	215	9	6.43	3.69-11.07	0.767

(To be continued on the next page)

Table 1 (part 2)

Characteristics	N	%	LRR	95% CI	P-value
Number of positive lymph nodes					
0	1,451	64	3.92	2.98-5.14	
1-3	532	23	9.51	7.12-12.64	
4-6	139	6	18.55	12.54-26.96	
≥7	57	3	14.02	6.47-28.89	
Unknown	103	5	7.36	3.35-15.76	<0.001
Tumour grade					
Well differentiated	103	5	4.34	1.65-11.18	
Moderately differentiated	1,609	71	6.37	5.19-7.80	
Poorly differentiated/Undifferentiated	324	14	8.55	5.84-12.44	
Unknown	246	11	4.50	2.44-8.22	0.119
Adjuvant chemotherapy					
Yes	569	25	5.48	4.42-6.79	
No	1,713	75	8.96	6.80-11.76	0.004
Region					
CCCA	1,571	69	5.96	4.82-7.37	
CCCN	330	14	8.20	5.56-12.01	
CCCST	381	17	6.54	4.34-9.78	0.337

Of all patients with a locoregional recurrence, 57 patients only had a locoregional recurrence and 30 patients were diagnosed with a distant metastasis after the diagnosis of the locoregional recurrence. In this group the median time between locoregional recurrence and detection of distant metastasis was 108.5 days. Forty patients had a locoregional recurrence combined with a distant metastasis diagnosed before (N=11) or at time (N=29) of the diagnosis of the locoregional recurrence with a median time between distant metastasis and locoregional recurrence of 30 days.

Conditional hazard rate

Locoregional recurrences occurred at a median of 1.5 years after surgery of the primary tumour. Sixty-four percent of all recurrences were diagnosed within two years after surgery and 90% within four years. Figure 2 shows the conditional hazard rates for each 6-month interval for the total study population and for stages II and III separately. Overall, there is one peak at the interval of 0.5 to 1 year after surgery with the highest conditional hazard rate of 0.0269, meaning that the probability of developing a locoregional recurrence in this interval was 2.7%. The same pattern was observed for stages II and III, also with the highest conditional hazard rate at the interval of 0.5 to 1 year after surgery of respectively 0.0153 (1.5%) and 0.0587 (5.9%).

Prognostic factors

Overall, the 5-year LRR was 6.39% (95% CI 5.39-7.56). A significant association was found between the 5-year LRR and pathological stage, depth of invasion, number of positive lymph nodes, and adjuvant chemotherapy (Table 1). Figure 3 shows the locoregional recurrence rate according to stage.

In the multivariate analysis, calculating prognostic factors for the risk of locoregional recurrences irrespective of distant metastases (Table 2), patients with left-sided

Table 2 Prognostic factors for the risk of LR in total, for the risk of LR only at time of diagnosis of the LR and for the risk of LR combined with distant metastasis before or at time of diagnosis of LR (multivariate analyses)

	Total				LR only		LR and DM	
	B	Risk points	HR	95% CI	HR	95% CI	HR	95% CI
Tumour site								
Right-sided		0	1.00	Reference	1.00	Reference		
Transversum	0.126	1	1.13	0.55-2.32	1.94	0.91-4.14		
Left-sided	0.478	5	1.61*	1.11-2.35	1.89*	1.16-3.07		
Overlapping lesion and NOS	0.237	2	1.27	0.17-9.25	2.28	0.31-16.93		
Depth of invasion								
pT1		0	1.00	Reference	1.00	Reference		
pT2	0.417	4	1.52	0.30-7.65	2.39	0.27-20.83		
pT3	1.482	15	4.40*	1.05-18.47	5.04	0.68-37.57		
pT4	2.098	21	8.15*	1.85-35.87	13.17*	1.70-102.12		
No. of positive nodes								
0		0	1.00	Reference	1.00	Reference	1.00	Reference
1-3	1.073	11	2.92*	1.85-4.61	2.90*	1.67-5.03	2.95*	1.44-6.03
4-6	1.846	18	6.34*	3.58-11.23	5.46*	2.61-11.43	8.66*	3.89-19.29
≥7	1.666	17	5.29*	2.12-13.16	5.64*	1.84-17.23	4.87*	1.11-21.34
Unknown	0.796	8	2.22	0.93-5.28	1.52	0.46-5.05	3.04	0.88-10.51
Adjuvant chemotherapy								
Yes		0	1.00	Reference	1.00	Reference		
No	0.478	5	1.61*	1.04-2.49	1.90*	1.09-3.30		

* P<0.05
# Too low numbers to analyse
LR, locoregional recurrence; DM, distant metastasis; HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified
Risk points = B * 10 (rounded to the nearest whole number)

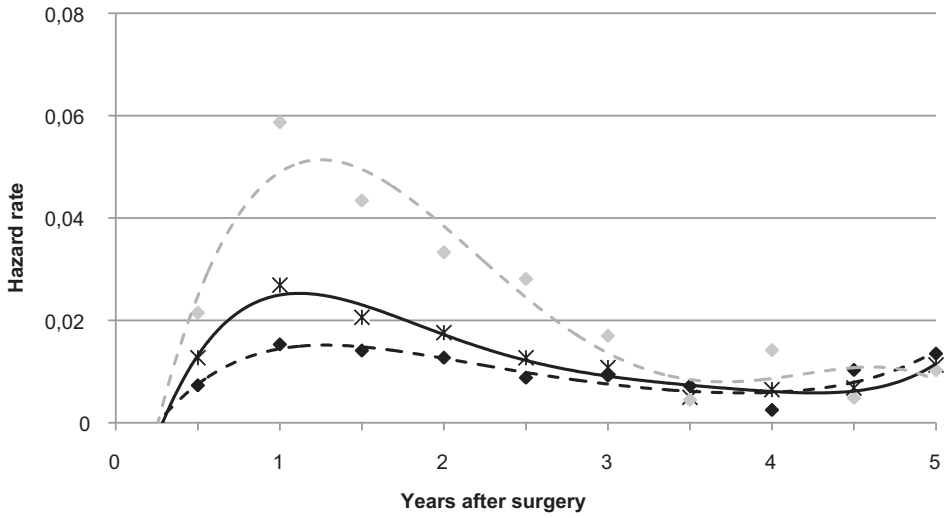

Figure 2 Conditional hazard rates by 6-month interval for the total study population and for stages II and III separately

tumours were more likely to develop locoregional recurrences compared to patients with right-sided tumours (HR 1.61, 95% CI 1.11-2.35). The risk of developing locoregional recurrences increased with increasing T-stage, up to a hazard ratio of 8.15 (95% CI 1.85-35.87) for patients with pT4 tumours. Patients with positive lymph nodes had a higher risk of developing locoregional recurrences compared to patients without positive lymph nodes; patients with 1-3 positive lymph nodes had a hazard ratio of 2.92 (95% CI 1.85-4.61) and patients with more than 6 positive lymph nodes had a hazard ratio of 5.29 (95% CI 2.12-13.16). Patients who did not receive adjuvant chemotherapy had a higher risk of developing locoregional recurrences (HR 1.61, 95% CI 1.04-2.49).

The same prognostic factors were revealed for the risk of locoregional recurrence only at time of diagnosis of the locoregional recurrence (including diagnosis of a distant metastasis after the locoregional recurrence). Only positive lymph nodes was a prognostic factor for the risk of developing a locoregional recurrence combined with a distant metastasis before or at the same time of the locoregional recurrence.

In the subset of patients with pN+ tumours the risk of developing locoregional recurrences was higher among patients with 4-6 positive lymph nodes compared to those with 1-3 positive lymph nodes (HR 2.16, 95% CI 1.28-3.65) (Table 3). No statistical difference in risk of developing locoregional recurrences was found among patients with pN+ tumours and among patients with pN0 tumours who received adjuvant chemotherapy compared to patients who did not receive adjuvant chemotherapy.

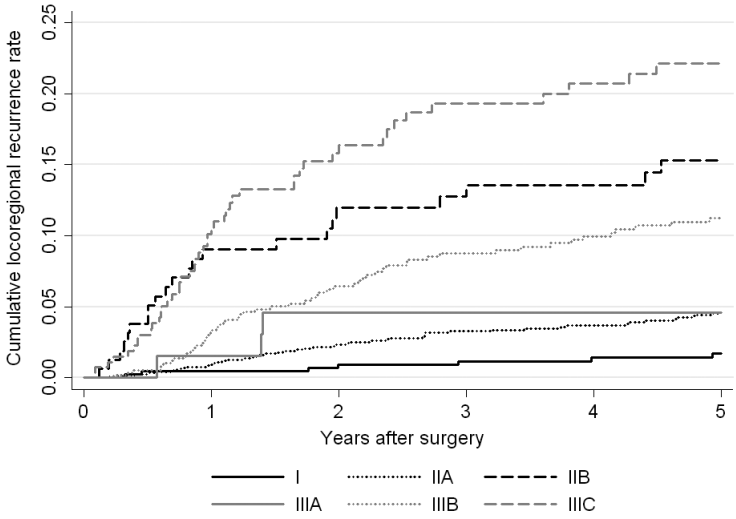

Figure 3 Locoregional recurrence rate according to stage

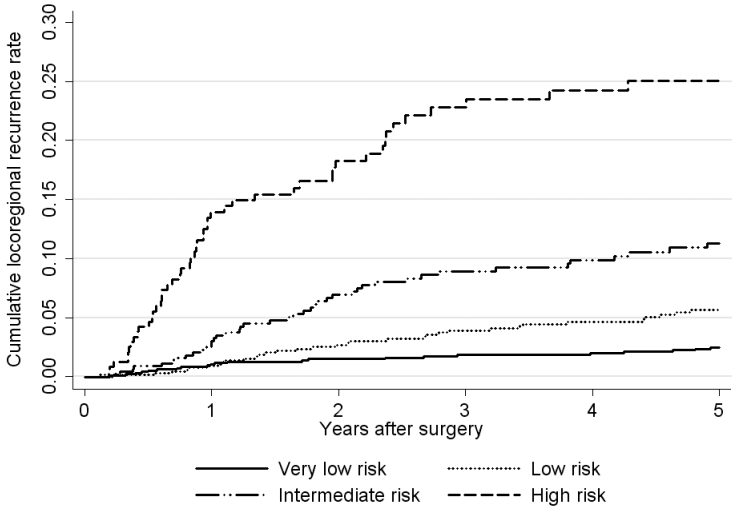

Figure 4 Locoregional recurrence rate according to risk group

Risk groups

The Locoregional Recurrence Risk Score (LRRS) for each patient was calculated by adding all risk points of all prognostic factors (LRRS = risk points (tumour site) + risk points (depth of invasion) + risk points (number of positive lymph nodes) + risk points (adjuvant chemotherapy)) (Table 2). Based on the LRRS, the total population was split into four risk groups: very low, low, intermediate and high risk. Very low risk was defined as a LRRS score of 0-20 points, low risk as a LRRS score of 21-25 points, inter-

Table 3 Prognostic factors for the risk of locoregional recurrence according to nodal involvement (multivariate analyses)

	pN0/pNX		pN+	
	HR	95% CI	HR	95% CI
Tumour site				
Right-sided	1.00	Reference	1.00	Reference
Transversum	1.01	0.29-3.44	1.24	0.51-2.99
Left-sided	1.96*	1.08-3.55	1.40	0.86-2.28
Overlapping lesion of colon and NOS	2.99	0.40-22.59	#	
Depth of invasion				
pT1	0.11*	0.02-0.55	#	
pT2	0.14*	0.04-0.46	0.23	0.05-1.02
pT3	0.39*	0.19-0.82	0.66	0.36-1.21
pT4	1.00	Reference	1.00	Reference
Number of positive nodes				
0	1.00	Reference		
1-3	-		1.00	Reference
4-6	-		2.16*	1.28-3.65
≥7	-		1.72	0.72-4.12
Unknown	1.73	0.60-4.99	1.30	0.31-5.43
Adjuvant chemotherapy				
Yes	1.00	Reference	1.00	Reference
No	2.19	0.67-7.12	1.53	0.94-2.47

* P<0.05
# Too low numbers to analyse
HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified

mediate risk as a LRRS score of 26-32 points and high risk as a LRRS score of >32 points. The 5-year LRR was 2.5% for the very low risk group, 5.7% for the low risk group, 11.3% for the intermediate risk group and 25.1% for the high risk group (Figure 4).

Discussion

The results of this population-based study, analysing the data of 2,282 patients with colon cancer, demonstrated a 5-year locoregional recurrence rate of 6.4%. The risk of developing a locoregional recurrence was highest at 6 months to 1 year after surgery. Several prognostic factors for developing locoregional recurrences were identified, including tumour site, depth of invasion, number of positive lymph nodes and adjuvant chemotherapy. Based on all prognostic factors four risk groups for developing locoregional recurrences could be defined.

One of the prognostic factors was tumour site. Tumours in the transversum had the highest 5-year locoregional recurrence rate. However, the number of patients with a tumour in the transversum was low and in the multivariate analyses only left-sided tumours had a significant higher risk of locoregional recurrence compared to right-sided tumours. One possible explanation is the tendency of left-sided tumours to have more segmental resections without clearance of the central lymph nodes close to the base of the inferior mesenteric artery. Another explanation could be that this is a result of the biological differences between left-sided and right-sided tumors.[18] An American single-institution study did not find an association between tumour site and risk of local recurrence.[11] Similar to other studies,[9;11;12] we found an increased risk of locoregional recurrences in more advanced tumours, i.e. a larger depth of invasion and (more) positive lymph nodes.

In rectal cancer care, the introduction of total mesorectal excision resulted in a decreased local recurrence rate.[19] In the Netherlands, this technique was introduced within the framework of the Dutch TME trial, in which the Dutch Colorectal Cancer Group investigated the effects of preoperative radiotherapy in combination with standardised TME.[20] The technique of TME was translated into colon cancer surgery. Complete mesocolic excision (CME) is still not considered standard surgery in the Netherlands. However, results from a German study demonstrated lower local recurrence rates and better overall survival.[21] A review suggested that the relation between higher lymph node yield and better survival reflects the quality of the surgical resection.[22] An explanation could be that surgeons have carried out a more complete resection with a more extensive lymph node resection, which may subsequently lead to a lower risk of locoregional recurrence. However, our study demonstrated no association between number of evaluated lymph nodes and risk of locoregional recurrence.

Several randomised trials demonstrated the benefit of adjuvant chemotherapy in stage III disease.[23;24] Not all node-positive patients in our population-based study received adjuvant chemotherapy. Explanations could be refusal from patients, older age or comorbidity. In the total study population, patients who received adjuvant chemotherapy had a lower risk of locoregional recurrence. In a subgroup analysis, among node-negative and among node-positive patients the risk of locoregional recurrence was also lower among patients who received adjuvant chemotherapy compared to patients who did not. However, statistical significance was not reached in this subgroup analysis. According to the Dutch guidelines, adjuvant chemotherapy should also be considered for patients with high risk stage II disease, e.g. T4 tumours.[17] With regard to depth of invasion, patients with T4 tumours have the highest risk of developing a locoregional recurrence in our study. The less favourable prognosis of T4 tumours is emphasised by our

result that patients with stage IIB had a higher 5-year locoregional recurrence rate than patients with stages IIA and IIIA. Identifying individual patient who might benefit form adjuvant chemotherapy may improve the locoregional recurrence rate.

Knowledge about patterns of recurrences is important for the follow-up schedule of colon cancer patients. In this study, the median time between surgery of the primary tumour and diagnosis of the locoregional recurrence was 1.5 years and the highest risk of locoregional recurrence was found in the period from 6 months to one year after surgery of the primary tumour, suggesting that approximately the first two years of follow-up are most essential for detecting locoregional recurrences assuming that early detection is important. However, the intensity of follow-up programs after colorectal cancer is still unclear. A Cochrane review revealed an overall survival benefit for a more intensive follow-up program compared to a less intensive follow-up, but the best combination and frequency of visits and diagnostic tests remained unclear due to the large variation in the follow-up programs.[25] However, in only one of the eight studies included in this review, patients were randomly allocated to a specific follow-up program based on their risk of developing a recurrence. The validity of our Locoregional Recurrence Risk Score should be tested in other populations. After that, it could be the base for further studies with different follow-up schedules.

In the present study, the number of evaluated lymph nodes was very low. The Dutch guidelines recommend a minimum of 10 evaluated lymph nodes, meaning that almost 60% of the lymph node evaluations were inadequate. Patients with a low number of evaluated lymph nodes could be wrongly categorised as node-negative which could lead to undertreatment of these patients. This may affect our results, especially the analyses by nodal involvement.

In conclusion, patients with colon cancer had the highest risk of locoregional recurrence at six months to one year after surgery. Patients with left-sided tumours, with a larger depth of invasion and positive lymph nodes and those who did not receive adjuvant chemotherapy were more likely to develop a locoregional recurrence. Adjuvant chemotherapy is a modifiable prognostic factor. Therefore, identifying individual patients who might benefit from adjuvant chemotherapy may reduce the locoregional recurrence rate.

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