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Inflammation and prognosis in colorectal cancer

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Abstract

Aim of the study: Previous work has indicated that quantification of inflammatory cell reaction is of prognostic value in colorectal cancer. We evaluated the prognostic significance of inflammatory cell reaction patterns in colorectal cancer and developed a grading method which could be used in the routine assessment of tumours.
Methods: The intensity of overall inflammatory cell reaction, numbers of neutrophilic and eosinophilic granulocytes, lymphoid cells and macrophages in both the central region and the invasive margin were estimated in 386 colorectal cancer patients. Prognostic significance was analysed by uni- and multivariate analysis.
Results: Our method for classification of inflammatory reaction was reliable. High-grade inflammation at the invasive margin in Dukes' stage A and B cancers (pT1-2N0 and pT3N0, respectively) was associated with better 5-year-survival (87.6%) than low-grade inflammation (47.0%).
Conclusions: Inflammatory cell response at the invasive border is a relevant prognostic indicator and could be easily incorporated into the routine evaluation of histopathological specimens.

Keywords: Colorectal cancer; Inflammation; Prognosis

1. Introduction

Colorectal cancer is the second most common cause of cancer-related death and its incidence is increasing in many Western countries. Over one third of the patients with colorectal cancer will die within five years after diagnosis, and most of fatal outcomes result from liver metastases.

Patients with metastatic colorectal carcinoma benefit from adjuvant chemotherapy [1,2], but it is controversial whether chemotherapy should be offered to patients with Dukes'stage B (pT3N0) colorectal cancer [3,4]. One third to one fourth of the patients with Dukes' stage B colorectal cancer die of the disease despite complete resection of the primary tumour. Numerous reports have focused on ancillary techniques that could be used to determine which Dukes' stage B patients have a poor prognosis, but none of the methods have entered general use so far. To date, the rationale behind the utilization of adjuvant therapy depends largely on the findings given in the pathology report, including WHO histological grade and tumour stage according to pTNM, Astler–Coller or the Turnbull modification of Dukes' classification (see Table 1) [5,6].

The presence of inflammatory cells in human malignant tumours is a common phenomenon. Inflammatory

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Table 1
The relationship of Astler–Coller, Dukes' and TNM (6th edition) classifications

Extent of the tumour	Stage	Astler–Coller	Dukes'	TNM classification		
				T	N	M
Local invasion						
Invasion to submucosa	I	A	A	1	0	0
Invasion to muscularis propria	I	B1	A	2	0	0
Invasion through muscularis propria	IIA	B2	B	3	0	0
Invasion to free peritoneal surface	IIB	B2	B	4	0	0
Invasion to adjacent organs/structures	IIB	B3*	B**	4	0	0
Lymph node metastases						
One to three	IIIA	C1	C	T1-2	1	0
One to three	IIIB	C2***	C	T3-4	1	0
Four or more	IIIC	C1-2***	C	Any T	2	0
Distant metastases	IV	–	D†	Any T	Any N	1

Explanations: * = in modified Astler–Coller classification only; ** = Stage D in Turnbull (1967) modification only; *** = Modified Astler–Coller C3 = B3 plus lymph node metastases; † = Turnbull modification only.

cell reaction within the tumour and at the invasive margin is thought to be a manifestation of the immune response against cancer cells and cancer-associated apoptosis [7,8]. The influence of immune response on the behaviour of colorectal carcinomas has already been established previously. For example, the predictive value of inflammatory cell reaction is a part of the Jass classification [9]. Other prognostic immune-related alterations include the so-called Crohn's-like reaction [10]. There is limited experience of the use of these factors as prognostic indicators. In most studies they have not proven to be better than previous classification systems, hence they are not widely included in routine pathology reports.

New prognostic markers for colorectal cancer, which could be included in routine pathological analysis, are needed to determine optimal therapy. The aim of the present study was to utilize an easy-to-use grading scheme for assessment of the inflammatory reaction, and evaluate the prognostic significance of inflammatory cell reaction in colorectal cancer. In addition to overall prognostic analysis, we focused on the discriminating value of inflammatory cell reaction in Dukes' A and B cancers.

2. Materials and methods

The study material consists of a consecutive series of 466 colorectal carcinoma patients operated in Oulu University Hospital between January 1986 and December 1996. Complete follow-up data could be obtained in 386 patients who were included in the study. The patients were followed up for 60 months or until their death (mean 41 months). Medical histories and clinical details were reviewed from the case records and the outcome of the patients from the cancer registry files (Finnish Cancer Registry). In five curatively operated cases, information of recurrences could not be obtained. All the studies were performed in accordance to the ethical standards of the Ethical Committee of Oulu University Hospital. All histological specimens of the tumours (median = 3, range 1–7) were independently re-evaluated by two pathologists (MJM, TJK) for Turnbull modification of Dukes' stage and WHO histological grade [6]. In cases of disagreement, classification was set up after discussion. A total of 99 cases were previously evaluated for DNA microsatellite instability with five NIH consensus markers, BAT 25, BAT 26, D2S123, D5S346, and D17S250 [11] as previously described to detect MSI-H, MSI-L and MSS tumours [12].

2.1. Estimation of the inflammatory cell reaction

Inflammatory cell reaction was estimated in haematoxylin and eosin stained sections, looking at the central areas of each tumour and at the invasive margin. Invasive margin was defined as an interface between the host stroma and the invading edge area of a tumour. For estimation of the inflammatory cell reaction, areas of deepest invasion were selected.

Overall inflammatory reaction and the amount of lymphoid cells, neutrophilic and eosinophilic granulocytes were assessed by using a four-degree scale. A score of 0 indicated an absence of reaction, 1 weak, 2 moderate, and 3 severe increase of each cell type. A similar scale was used at the invasive margin. A score of 0 was given when there was no increase of inflammatory cells, 1 denoted mild and patchy increase of inflammatory cells at the invasive margin, but no destruction of invading cancer cell islets by the inflammatory cells. A score of 2 was given when inflammatory cells formed a band-like infiltrate at the invasive margin with some destruction of cancer cell islets by inflammatory cells. A score of 3 denoted a very prominent inflammatory reaction, forming a cup-like zone at the invasive margin, and destruction of cancer cell islets was frequent and

invariably present. Fig. 1 shows the spectrum of inflammatory cell reactions at the invasive margin.

Macrophage reaction was graded as either absent (grade 0) or present (grade 1). Macrophage reaction was recorded as being present when collections of foamy macrophages encircling invading tumour islets were observed, and as being absent when such collections of macrophages were not observed after a careful evaluation of all slides of the tumour (Fig. 1). Recognition of macrophages was based on their typical abundant, often foamy cytoplasm and regular nuclear structure. In 20 randomly selected cases, the nature of the foamy cells was confirmed by an immunohistochemical staining for macrophage markers (KP-1 and PGM-1, Dako, Klostrupp, Denmark; Fig. 2).

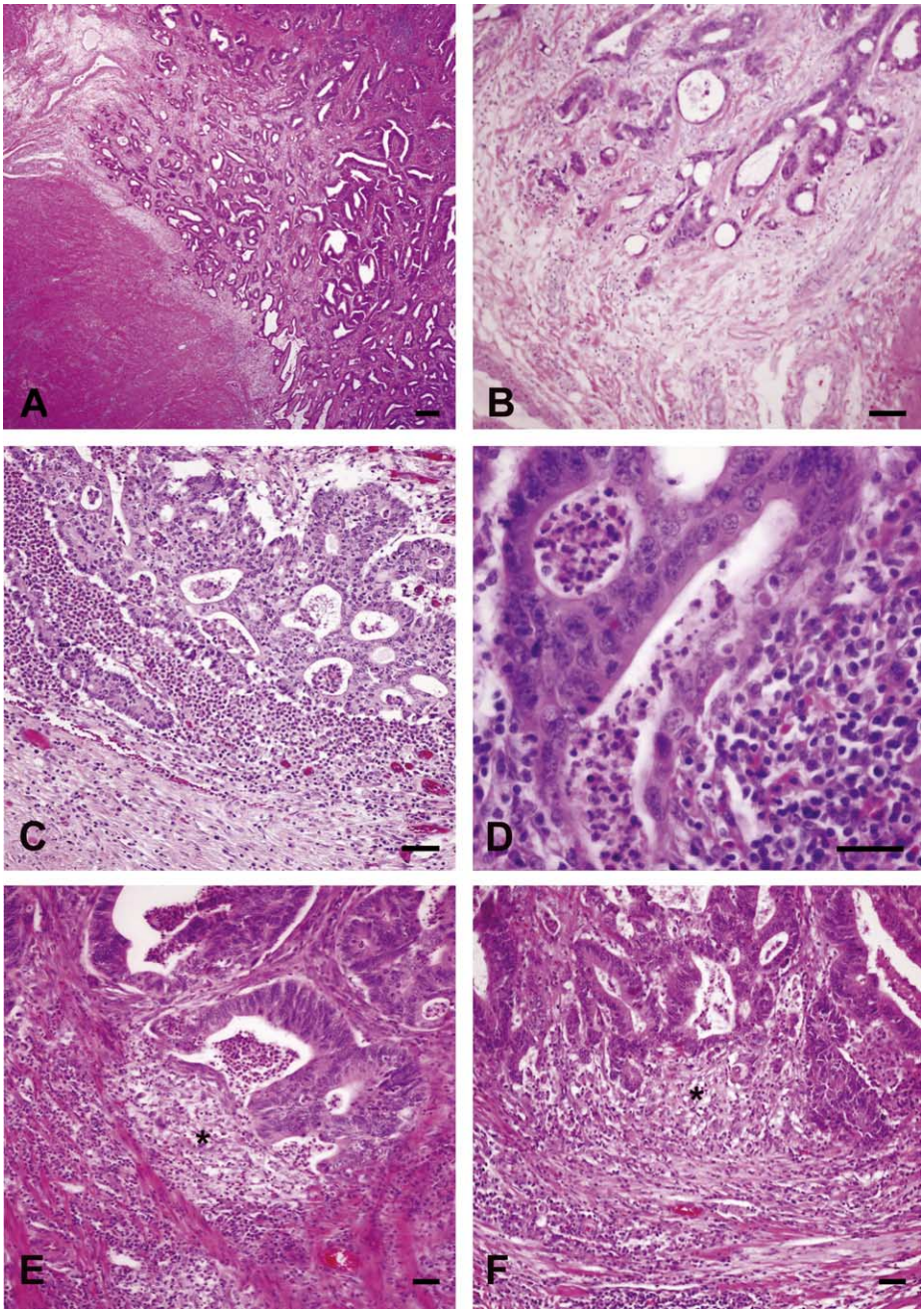

Fig. 1. Spectrum of inflammatory cell reaction at the invasive front area. (A and B) Low grade inflammatory cell infiltration (A, low magnification; B intermediate magnification). (C and D) High grade inflammatory cell infiltration at the invasive edge area; inflammatory cell infiltrate consists of mainly neutrophilic granulocytes, and is destroying the invasive islets of tumour cells (C). Another view of a high grade inflammatory cell reaction, consisting of neutrophilic and eosinophilic granulocytes and lymphoid cells (D). (E and F) High grade macrophage reaction around invasive islets of tumour tissue. Dense collections of foamy macrophages (*) destroy the tumour tissue. Hematoxylin and eosin. A: Bar = 250 μm; B and C: Bar = 100 μm; D–F: Bar = 50 μm.

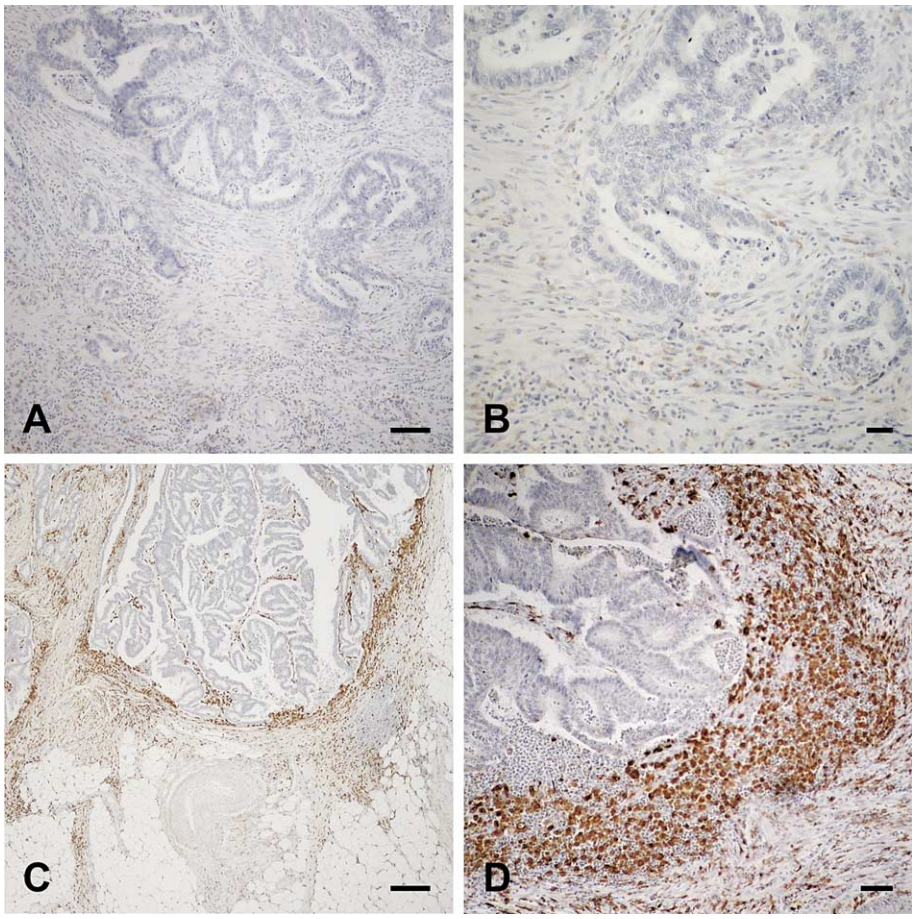

Fig. 2. Macrophage reaction at the invasive front area as detected by immunohistochemical staining for CD68. (A and B) Two cases negative for macrophage reaction according to hematoxylin and eosin stained section. In the first case (A), sharply infiltrating tumour cell islands without any evidence of adjacent CD68 positive macrophages. The overall amount of inflammatory cell infiltrate is very low. In another case (B), a few cells are positive for CD68, but they do not show the abundant cytoplasm of foamy macrophages, and are not located around invasive islets of tumour cells. (C and D) Two cases positive for macrophage reaction according to hematoxylin and eosin stained sections. A low-power magnification shows dense, band-like infiltrate of CD68 positive macrophages around the invasive edge (C). A high-power magnification of another case showing a band-like infiltrate of CD68 positive macrophages with abundant cytoplasm along with abundant infiltration of other types of inflammatory cells. Immunohistochemical staining for CD68. A and C: Bar = 250 μm; B and D: Bar = 50 μm.

2.2. Evaluation of Crohn's-like reaction

All cases were evaluated for the absence or presence of Crohn's-like reaction (CLR) according to the criteria established by Graham and Appelman [10]. However, mild reaction (grade 1) and intense reaction (grade 2) patterns as described in their original report were combined for this study, since we did not observe differences in the preliminary evaluation between mild and intense reaction patterns.

2.3. Assessment of intra- and interobserver variation

A total of 39 randomly selected cases were used to assess the intra- and interobserver variation in inflammatory reaction scoring. Three sets of hematoxylin and eosin stained slides were cut. Six observers, three pathologists (MJM, JM, HT) and three residents (JMM, POV, SK) observed the score of inflammatory reaction independently and without knowing the clinical and pathological information.

2.4. Statistics

The SPSS program (version 12.0, SPSS, IL, USA) was used for statistical analysis. Pearson's Chi-square test was used unless otherwise stated. For the evaluation of survival statistics, Kaplan–Meier and Cox regression models were used.

3. Results

3.1. Inflammatory cells in tumour bulk and invasive margin

We were able to evaluate the invading margin (Figs. 1 and 2) in 374 cases out of 386 cases (96.9%). In 12 cases

the invasive margin was not included in the sections, and these were excluded from further analysis. The mean age of all patients was 67 (SD 13; range 12–93) years. The distribution of Dukes' stage, WHO grading and tumour location in relation to 5-year survival is presented in Table 2. There were no differences between males ($N = 179$) and females in any of these features (data not shown). The prevalence of high-grade inflammation between right-sided (43.7%; $N = 52/119$) and left-sided colorectal cancers (46.3%; $N = 118/255$) did not differ ($p = 0.657$, chi-square). When colon and rectal cancers were evaluated, high-grade inflammatory reaction was observed in 50.7% ($N = 77/152$) of rectal cancers, and in 41.9% of colon cancers ($N = 93/222$), but this difference was not statistically significant ($p = 0.113$, chi-square).

High-level MSI was observed in 10% ($N = 11/99$), low-level MSI in 18.2% ($N = 18$) and 70.7% ($N = 70$) were microsatellite stable. High-grade inflammation was observed in 50.0% of both MSS and MSI-L cancers, and in 72.7% of MSI-H cancers. The higher percentage of high-grade inflammation in MSI-H cancers did not statistically differ from other cancers regardless of whether MSS and MSI-L cancers were analysed separately or together ($p = 0.370$ and 0.206). Neither did we observe any differences in the presence of Crohn's-like reaction in regard to the MSI-status, as Crohn's like reaction was observed in 31.4% ($N = 22/70$)of MSS tumours, in 23.5% ($N = 4/17$) of MSI-L tumours and in 45.5% ($N = 5/11$) of MSI-H–tumours ($p = 0.507$, Fisher's exact test).

Analyses attempting to determine the prognostic significance of inflammation were focused on Dukes' stage A and B cases (pT1-3N0), as Dukes' C (pT1-3N1-2) and D (T1-4N0-2M1 or pT4N0-2M0) cases represent metastatic or advanced disease and therefore the outer margin of tumour is beyond the bowel wall. In univariate analysis, Dukes' stage A cancers showed better survival, but the difference was not statistically significant ($p = 0.109$; Fig. 3). The distribution of inflammatory reaction scores and estimates of the amounts of different inflammatory cell types in the central area and at the invasive margin of Dukes' stage A and B cancers are presented in Table 3. The overall inflammatory reaction score and the scores for neutrophilic granulocytes, lymphocytes and macrophages were higher at the invasive margin than in the central region but this difference was not observed with eosinophilic granulocytes (Table 3). The trends were similar in patients with Dukes' stage C and D cancer (data not shown).

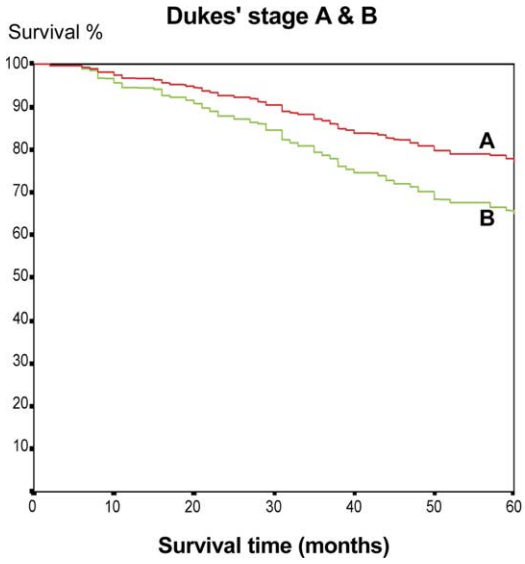

Fig. 3. Kaplan–Meier survival curves for the effect of Dukes' stage A or B on survival. There is no significant difference between Dukes' stage A and B patients ($p = 0.1086$; risk ratio 1.6776; 95% CI 0.8917–3.1561).

Table 2
5-year survival and 5-year recurrence-free survival rates in colorectal cancer in relation to Dukes' stage, histological grade and tumour location

	N	5-year survival (%) All patients	5-year recurrence-free survival (%) Dukes' A, B
Overall survival	374	52.53	
Dukes'stage			
A	84	76.43	72.31
B	145	66.31	65.24
C	87	35.03	–
D	58	13.74	–
WHO grade			
1	87	55.63	67.63
2	217	55.67	69.86
3	70	29.03	66.55
Tumour location			
Proximal	119	58.74	73.87
Distal	118	56.51	74.12
Rectum	137	45.04	58.08

Recurrence-free survival was analysed only in Dukes' A and B patients.

Table 3
Distribution of the inflammatory cell scores in the central region and invasive margin of the Dukes' A and B colorectal carcinomas

Inflammatory cell type	Score				Mean score	Confidence interval (95%)	*N*
	0	1	2	3			
Overall inflammation							
Central region	39	128	53	9	1.14	1.04–1.24	229
Invasive margin	21	80	71	57	1.71	1.59–1.83	229
Eosinophils							
Central region	67	99	55	8	1.01	0.90–1.12	229
Invasive margin	61	86	57	25	1.21	1.09–1.34	229
Neutrophils							
Central region	130	78	10	11	0.57	0.47–0.67	229
Invasive margin	86	78	32	33	1.05	0.91–1.18	229
Lymphocytes							
Central region	5	148	71	5	1.33	1.26–1.40	229
Invasive margin	5	96	100	28	1.66	1.57–1.76	229
Macrophages							
Central region	139	90			0.39	0.33–0.46	229
Invasive margin	54	175			0.76	0.70-0.82	229

3.2. Inflammatory cell reaction and survival: Univariate analysis

The inflammatory score showed an association with the 5-year survival ($p < 0.0001$, log-rank; Fig. 4). In order to make the classification system more reproducible and for ease of analysis, the original four-point scale was reduced to a two-point scale: absent to mild increase (scores 0–1) were combined as low-grade inflammation and moderate to strong (scores 2–3) as high-grade inflammation. In univariate analysis, high-grade inflammation at the invasive margin was a significant predictor of good outcome. This positive correlation with 5-year survival was evident for the overall inflammatory cell grade, neutrophilic granulocyte grade, lymphocyte grade and for the presence of macrophages (Table 4 and Fig. 4). The eosinophilic granulocyte grade in the invasive margin showed some relationship with good prognosis but the effect was not significant ($p = 0.078$).

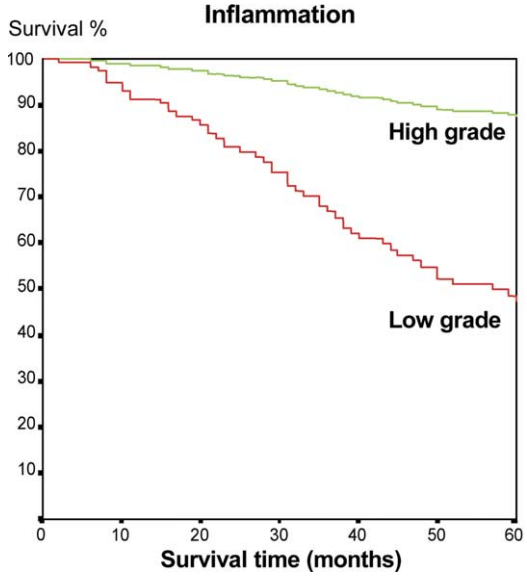

Fig. 4. Kaplan–Meier survival curves for overall inflammatory reaction grade at the invasive front and survival in Dukes' stage A and B patients ($p < 0.00005$; Risk ratio 5.5676; 95% CI 2.8494–10.8789).

In the central region of the tumours, only high overall inflammation grade and a high lymphocyte grade were significantly associated with survival rate, both indicating a good 5-year survival (Table 4). Influence on 5-year recurrence-free survival was similar, the significant prognostic variables being overall inflammation grade (Fig. 5), lymphocyte grade and presence of macrophages in the invasive margin and lymphocyte grade in the centre of the tumour (data not shown).

Since there was a strong correlation between a positive macrophage reaction and the inflammatory response in general ($c = 0.465$, Spearman's correlation, $p < 0.0001$), we excluded cases with positive macrophage reaction to determine the prognostic significance of other inflammatory cells in the absence of a macrophage reaction. The presence of no other inflammatory cell type showed any statistical significance in macrophage-negative tumours. When the cases with high eosinophilic granulocyte, neutrophilic granulocyte or lymphocyte grades were excluded one at a time, macrophage reaction invariably demonstrated a prognostic significance in the cases with low eosinophilic granulocyte grade ($p < 0.0001$, log rank), low neutrophilic granulocyte grade ($p < 0.0001$), and low lymphocyte grade ($p = 0.003$).

Crohn's-like reaction was present in 113/371 cases (30.5%; Dukes' A–D), and it was significantly more prevalent in subjects with heavy inflammation at the tumour margin ($p < 0.001$). The presence of the Crohn's-like reaction did not have any significant

Table 4
Univariate analysis of relationship of intensity of inflammatory reaction in the central region or invasive margin and 5-year cumulative survival rates in patients with Dukes' A or B colorectal cancer

	Central region			Invasive margin		
	5-year survival		Log-rank	5-year survival		Log-rank
	%	N		%	N	
Inflammation						
Low grade	65.9	166	$p = 0.035$	47.0	100	$p < 0.0001$
High grade	77.9	62		87.6	128	
Eosinophils						
Low grade	66.9	165	$p = 0.128$	65.3	146	$p = 0.078$
High grade	75.6	63		75.7	81	
Neutrophils						
Low grade	67.9	207	$p = 0.160$	62.6	162	$p = 0.004$
High grade	81.5	21		84.3	65	
Lymphocytes						
Low grade	62.3	152	$p = 0.001$	55.6	99	$p = 0.0001$
High grade	85.0	76		81.4	128	
Macrophages						
Low grade	70.4	139	$p = 0.674$	50.0	54	$p = 0.0002$
High grade	67.8	89		75.4	174	

prognostic value when all subjects were considered. Since the previously observed strong association with overall inflammation could mask the prognostic value of Crohn's-like reaction, we tested the prognostic significance separately in patients with strong and low overall inflammatory cell reaction at the invasive margin. The influence of Crohn's-like reaction on survival was not significant in the patients with high-grade inflammatory reaction, whereas the presence of Crohn's-like reaction

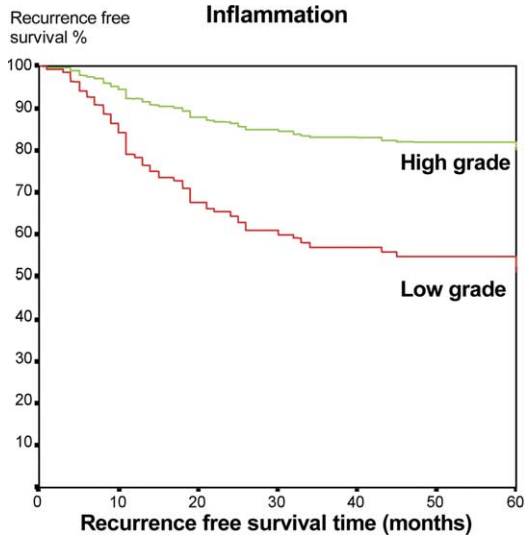

Fig. 5. Kaplan–Meier survival curves for overall inflammatory reaction grade at the invasive front and recurrence-free survival in Dukes' stage A and B patients ($p = 0.0001$; risk ratio 3.0047; 95% CI 1.7511–5.1556).

Table 5
Association of 5-year survival and Crohn's like reaction in patients with Dukes' A–D tumour with mild overall inflammatory reaction

Crohn's-like reaction	5-year survival		CRC cancer death		Total	
	N	%	N	%	N	%
No	45	33.1	93	66.9	138	100.0
Yes	21	52.5	19	47.5	40	100.0
Total	66	100.0	112	100.0	178	100.0

$p = 0.025$ (Chi-square).

in patients with low-grade inflammatory reaction predicted a better survival ($p = 0.025$; Table 5).

3.3. Multivariate survival analysis

For further testing of the independent prognostic significance of inflammatory reaction against known prognostic factors, Cox proportional hazards model with forward selection method (likelihood ratio) was used. High-grade inflammation at the invasive margin was an independent prognostic factor for both 5-year cumulative survival (Table 6) and 5-year recurrence-free survival (data not shown). When Dukes' stage D patients were excluded from the analysis, high-grade inflamma-

Table 6
Assessment of independent prognostic significance of inflammatory reaction in curatively operated Dukes' stage A–C cancers in relation to Dukes' stage and location of the tumour, outcome measure is 5-year survival (Cox stepwise regression analysis)

Prognostic factor	Risk ratio	Confidence interval	p
Inflammation	3.4970	2.0964–5.8333	<0.00005
Dukes' stage			0.0079
A *versus* B*	1.5867	0.8255–3.0498	0.1661
A *versus* C	2.6425	1.3618–5.1279	0.0041
Location			0.0180
Proximal *versus* distal colon*	1.1236	0.5979–2.1116	0.7173
Proximal colon *versus* rectum	1.9662	1.1372–3.3993	0.0155

Explanations: * = no independent prognostic significance; NA = not assessed. Cox stepwise (Forward: likelihood ratio) regression method.

Table 7
Assessment of independent prognostic significance of inflammatory reaction grade at invasive margin in Dukes' A and B cancers in relation to Dukes' stage, location of the tumour, and gender, outcome measure is 5-year survival (Cox stepwise analysis by forward: likelihood ratio)

Prognostic factor	Risk ratio	Confidence interval	p
Inflammation	5.5676	2.8494–10.8789	<0.00005
Location*	NA	NA	0.1078
Gender*	NA	NA	0.2805
Dukes' stage*	NA	NA	0.2906

Explanations: * = no independent prognostic significance; NA = not assessed.

Table 8
κ Values for intra- and interobserver variations for inflammation at invasive margin

	Intraobserver variation	Interobserver variation				
	MJM2	JMM	JM	POV	SK	HT
MJM	0.794	0.794	0.699	0.791	0.741	0.734
JMM		–	0.694	0.588	0.743	0.742
JM			–	0.609	0.504	0.569
POV				–	0.597	0.634
SKA					–	0.645

Explanations: $p < 0.0001$ in between all κ values.

tory reaction at the invasive margin was even a better predictor of 5-year survival and 5-year recurrence-free survival than Dukes' stage. WHO histological grade, gender, mucinous subtype or tumour size did not show any prognostic significance (data not shown).

We then limited the analysis to patients with non-metastatic disease (Dukes' stage A and B cancers). High-grade inflammation at the invasive margin showed independent, positive prognostic influence on both survival and recurrence-free survival (Table 7; $p < 0.0001$; Cox proportional hazards model). In contrast, Dukes' stage, gender, tumour location, WHO grade or mucinous status did not show a statistically significant relationship with survival or recurrence free survival.

3.4. Intra- and interobserver variation

Intra- and interobserver variation was assessed by six observers (MJM, JMM, JM, SK, HT and PV) who were blinded to the clinical and pathological data or the decisions of other observers. Training of the observers was performed on a separate set of cases not belonging to the original series of 466 colorectal cancers. Detailed results are given in Table 8. Estimations of low-grade and high-grade inflammation of 39 cases were very reproducible. The interobserver variation between the principal investigator (MJM) and other observers showed good agreement (mean $\kappa = 0.752$; range 0.699–0.794), and it was almost equal to intraobserver (MJM) variation ($\kappa = 0.794$, $p < 0.0001$). Calculated mean κ for all observers was $\kappa = 0.672$ ($p < 0.0001$, t-test), demonstrating a good agreement between all observers.

4. Discussion

An inflammatory reaction is frequently observed in various cancers, and depending on the cancer type, it has been shown to have either a positive or negative influence on survival. In this study, we developed a simple and reproducible grading scheme for estimation of inflammatory reaction at the invasive margin and analysed the prognostic significance of our classification in a large series of patients with colorectal cancer. We were able to show that high-grade inflammation has an independent prognostic value in colorectal cancer, comparable to Dukes' stage in a multivariate analysis. High-grade inflammation at the invasive margin was even a better predictor than Dukes' stage when Dukes' D patients were excluded from the multivariate analysis. Our classification system provides prognostic information in colorectal cancer independent of cancer stage or grade, and helps to categorize radically operated, lymph node negative patients into two subgroups of differing prognosis (5-year survival of 87.6% *versus* 47.0%). The Dukes' stage A and B patients with low-grade inflammation – and therefore poor prognosis – form a potential target group for adjuvant therapy. Those patients with high-grade inflammation naturally have a very good prognosis and are not likely to benefit from adjuvant therapies.

Most previous studies concerning inflammatory cells as predictive factors in colorectal cancer survival have focused on a selected inflammatory cell type, such as tumour infiltrating lymphocytes and eosinophilic granulocytes or concentrated on inflammatory cell reaction within a tumour [9,13,14]. In rectal cancer, peritumoural inflammatory cell reaction has been shown to have a positive influence on prognosis [15], but in colon cancer, these findings have not been corroborated. The number of tumour-infiltrating lymphocytes has been found to be an independent prognostic factor in colorectal cancer [13]. Jass and colleagues included lymphocytic peritumoural infiltration in their classification [9]. Similarly, the presence of a Crohn's-like reaction has been shown to be an indicator of good prognosis [10]. Both tumour-infiltrating lymphocytes and Crohn's-like reaction have been associated with microsatellite instability [16,17]. In the present study, MSI status was not significantly associated to high-grade inflammation or Crohn's like reaction. MSI-L tumours did not differ from MSS tumours. Slightly more frequent Crohn's like reaction and tumour-destructing inflammatory reaction at the invasive margin in MSI-H tumours did not statistically differ from other tumours, potentially emphasising the prognostic significance of inflammation regardless of MSI status. A lack of correlation between the intensity of inflammatory reaction and location of the tumour could lead to similar conclusion on the significance of inflammatory reaction.

In the present study, we evaluated overall inflammatory cell reaction and the amount of each inflammatory cell type, both at the invasive margin and in the central part of the tumour. We demonstrated a higher intensity of inflammatory reaction at the invasive margin than in the central part of the tumour. Whilst a high-grade inflammatory reaction within the tumour predicted both enhanced survival and recurrence-free survival, the predictive power was significantly improved when inflammatory cell reaction was evaluated from the invasive margin. Inflammatory reaction at the invasive margin

was generally the most significant predictor for both survival and recurrence-free survival; macrophages and lymphocytes were the most valuable individual cell types as predictors. Of the inflammatory reaction patterns in the central part of the tumour, only the lymphocyte grade was of significant prognostic value. At the invasive margin, a high neutrophilic granulocyte grade indicated a good prognosis, and high eosinophilic granulocyte grade showed a non-significant relationship with good prognosis. Besides overall inflammation grade, macrophages were the only cell type with an independent prognostic significance. The important role of macrophages was further evidenced by the absence of any significant prognostic effect of other cell types in macrophage negative tumours, while the presence of macrophages was still a significant prognostic indicator if cases with high scores for other inflammatory cell types were excluded.

In the present study, the presence of Crohn's-like reaction was not significant in patients with high-grade inflammatory reaction, whereas in patients with low-grade inflammatory reaction the Crohn's-like reaction predicted better prognosis. However, patients with low-grade inflammatory reaction and lacking Crohn's-like reaction seemed to have the worst prognosis. This suggests that a Crohn's-like reaction and an inflammatory reaction at the invasive margin do not represent a phenotypic variation of the same immune defence mechanism, but are likely to be independent, both having an effect on prognosis.

The mechanisms linking a strong inflammatory reaction at the invasive margin with a good prognosis are not obvious. The structural features of the invasive margin have been observed to have prognostic significance in various cancers [18–23]. Important aspects of tumour growth including decreased expression of adhesion molecules, increased activity of proteolytic enzymes, increased cell proliferation and angiogenesis are all most dynamic at the tumour–host interface [19,21]. The overall microscopic character of the invasive margin also has prognostic significance in colorectal cancers [9,22]. These observations suggest that the interaction of the mesenchyme investing the tumour and resulting growth regulation are important factors in determining tumour behaviour. On the other hand, immune reaction to tumours plays a central role in the regression of experimental tumours [24]. Macrophages serve as antigen presenting cells in addition to their phagocyte function, and their presence within malignant tumours has been linked to the removal of apoptotic and necrotic tumour cells [25,26]. When macrophages phagocytose a large amount of tumour tissue, it has been shown that these antigen-presenting cells evoke a strong immunologically mediated response [26]. Macrophages are important cells in the orchestration of the inflammatory cell response and also potentially have an influence on tumour cell growth by secreting cytokines and other biologically active substances. Indeed, the macrophage reaction was shown to have a dominant role in the defense against the tumour in the present study.

The current prognostic staging systems (TNM, Astler–Coller, Turnbull modification of Dukes' classification, see Table 1) are satisfactory for routine use. They are simple, reproducible and have significant prognostic value. In comparison, the WHO histological grading has several disadvantages. Approximately nine out of ten colorectal cancers are classed as well to moderately differentiated carcinomas, with limited predictive value [27,28]. Subjective variations in interpretation also decrease its value as a prognostic indicator [28–30]. In recent years, many growth and differentiation-related molecules have been identified, involved in neoplastic transformation, tumour progression, and the development of metastases, and are thought to have a prognostic influence [2]. However, none of the markers studied thus far are in routine clinical use, partly because it is not possible to evaluate them from routinely stained specimens. The availability of immunohistochemistry and molecular genetics is still limited and the usefulness of these markers will require further investigation [2].

In conclusion, the inflammatory reaction at the invasive margin can be reliably analysed in colorectal cancer resection specimens; it does not require special staining methods or additional costs. The grading scheme we used in the present study was reproducible and simple to learn. As the lack of tumour-destructive inflammation is a sign of poor prognosis even in superficially invasive colorectal cancer, we propose that information about the inflammatory reaction at the invasive margin should be given in the pathology report. Further studies are needed to confirm whether patients with non-metastatic colorectal cancer who lack tumour-destructive inflammation will benefit from adjuvant therapy.

Conflict of interest statement

None declared.

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