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ORIGINAL ARTICLE

Prognostic significance of smoking in addition to established risk factors in patients with Dukes B and C colorectal cancer: a retrospective analysis

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Summary

Purpose: To investigate the prognostic significance of smoking in addition to established risk factors in patients with Dukes stage B and C colorectal cancer (CRC).

Methods: 291 consecutive non-selected CRC patients were studied retrospectively. Twenty-three variables were examined using a regression statistical model to identify relevant prognostic factors related to disease free survival (DFS) and overall survival (OS).

Results: On multivariate analysis DFS was found to be negatively affected in patients with a smoking history of ≤10 pack-years vs non-smokers ($p<0.016$). Additionally, performance status (PS)<90 ($p<0.001$), Dukes stage C ($p<0.001$) and elevated tumor markers ($p<0.001$) at the time of diagnosis were found to adversely affect DFS. Smoking also had a significant association with relapse. Patients with a smoking history of ≤10 pack-years had 2.45 ($p<0.018$) higher risk of recurrence compared to patients with no smoking history. OS was influenced by Karnofsky performance status (PS), Dukes stage, and elevated tumor markers. In particular patients with PS< 90 had a 4.69-fold higher risk of death ($p<0.001$) than patients with better PS. Stage C disease was associated with 2.27-fold higher risk of death ($p<0.001$) than stage B disease, and patients with elevated tumor markers at the time of diagnosis had 2.74-fold higher risk of death ($p<0.014$) when compared to those whose tumor markers were normal at presentation.

Conclusion: Our study associates smoking and relapse incidence in non-clinical trial CRC patients and reiterates the prognostic significance of PS, stage and tumor markers at the time of diagnosis.

Key words: colorectal cancer, disease free survival, prognostic factors, recurrence rate, smoking

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Introduction

CRC remains the third more common cancer and the second leading cause of cancer death worldwide despite significant developments in understanding its pathogenesis, advances in earlier diagnosis and improvement in treatment options. It is estimated that a new case of CRC is diagnosed every 3.5 min and a patient dies from it every 9 min [1] . According to the National Cancer Institute (NCI) of the United States 146,970 new cases were diagnosed with and 49,920 patients died of CRC in 2009 [2].

Advances in chemotherapy and better surgical techniques have improved the outcome and quality of life of CRC patients [3,4]. The 5-year relative survival rate for both male and female CRC patients has doubled between the early 1970s and 2000, from 22 to 50% [1,5-7] and the standard use of adjuvant 5-FU-based chemotherapy has decreased tumor recurrence in stage B and C patients from 67% in 5 years, to 55% [8,9]. Further developments in molecular diagnostics and therapeutic approaches have fuelled the interest in clinical and molecular prognostic factors in relation to new therapeutic protocols. Nevertheless the identification of factors that influence the prognosis of CRC in the clinical setting, i.e. without the exclusion criteria of a clinical trial, remains important as clinicians should tailor therapeutic interventions, follow up and out-of-hospital patient care, to the specific needs of the patient.

The purpose of this study was to identify the prognostic value of smoking in addition to established risk factors in CRC patients with Dukes stage B and C receiving standard adjuvant 5-FU treatment within the setting of a single tertiary referral oncology centre.

Methods

Patients

The medical records of 291 patients with histologically proven CRC diagnosed between 1992 and 2007 were retrospectively reviewed. All were non-selected consecutive cases from a single oncology centre and all patients were treated outside clinical trials. Only complete data records (i.e. at least 22 out of 23 investigated parameters) were included in the analysis. All patients had been operated with curative intent and adjuvant chemotherapy based on leucovorin modulated 5-FU [Mayo Clinic or Arbeitsgemeinschaft Internische Onkologie (AIO) regimens] was administered for 6 months. The primary endpoints were DFS, defined as the interval from surgery to either confirmed recurrence or death, and OS defined as the time interval between surgery and death. Patients remained under follow up until the end-date of the study or death.

Prognostic variables

Twenty-three potentially prognostic factors were selected, based on previous studies as well as our own clinical experience. The variables were further categorized into three groups including clinical parameters, tumor-related factors and treatment-related factors. Clinical parameters included gender, age (<60 years, 60-69 years, ≥70 years), pre-treatment Karnofsky PS <90 vs ≥90, body mass index (BMI) grouped as underweight (BMI<20), normal (20-24.9), overweight (25-29.9) and obese or higher grades (>30), presenting complaint (e.g. change of bowel habit, bloody stool), presence of co-morbidities including diabetes mellitus (DM), cardiovascular disease (CVD) and chronic renal failure (CRF) (no vs yes), positive family history for cancer (no vs yes), smoking (no, ≤10 pack/year, >10 pack/year) and alcohol consumption grouped as mild (<10g/d), moderate (10-29g/d) and high (≥30g/d). In particular, the cut-off value of 10 pack/year for smoking was based on other previously published report [10-12].

Tumor-related factors included tumour location (ascending, transverse, descending colon, sigmoid and rectum), histological staging (Dukes B vs C), grading documented as well differentiated (G1), moderately differentiated (G2) and poorly differentiated/undifferentiated; the latter category was jointly grouped as G3. Other tumor-related factors included tumor size (<3, 3-5.9, ≥6cm), total number of lymph nodes harvested (<12 vs ≥12), and number of histologically positive lymph nodes (all negative vs ≤3 or >3).

Additionally, the lymph node ratio (LNR, ratio of positive lymph nodes to total number of lymph nodes examined) was analysed following group

categorisation [0 (LNR 0.0), 1 (LNR 0-0.049), 2 (LNR 0.05 to 0.19), 3 (LNR 0.2 to 0.39), 4 (LNR 0.4 to 1.0)]. Other pathological tumor-related factors included the presence of intratumoral lymphocytic infiltration (no vs yes) and perineural invasion (no vs yes). Tumor markers included carcinoembryonic antigen (CEA): normal ≤5 mg/dl, elevated >5 mg/dL; for cancer antigen 19-9 (CA 19-9): normal ≤30 U/ml, elevated>30 U/ml; If one or both were raised, this was recorded as raised tumor markers.

Treatment-related factors included the type of the hospital where surgical resection of the tumor took place and were grouped into secondary or tertiary-care hospitals including university hospitals; surgeon's experience according to the years of practice and field of expertise categorised as specialised, generally experienced or less experienced; and the patient follow up (systematic, not systematic) and use of growth factors (G-CSF, GM-CSF) during chemotherapy.

Statistics

For descriptive statistics mean, median and standard deviation were calculated for quantitative measurements and counts/percents for discrete factors. OS and DFS were studied using the Kaplan-Meier method. In the Kaplan-Meier plots, actual events at the end of the study were censored.

Changes in OS and DFS between patient groups were recorded with the use of log-rank test. Differences in relapse incidence between patient subgroups were studied using x^2 test. Multivariate Cox regression models were implemented for the study of the parallel effect of any prognostic parameter on OS and DFS. Logistic regression model was used to study the parallel effect on relapse incidence.

The best model was based on forward selection technique moving forward while dropping non-significant variables. Regression results were displayed in Tables. Hazard ratios (HR) of study parameters were calculated for each parameter as well as 95% confidence intervals (95% CI). Categorical parameters were compared with a baseline category group. All analyses were conducted on a predefined significance level of 5% using the statistical software SPSS 12.0.

Results

Patients

A total of 291 patients were included in the study (179; 61.5% men and 112; 38.5% women) giving a ratio 1.59/1, with median age 65 years (mean 61.9 years and standard deviation SD 10.79). The frequencies of the clinical variables are shown in Table 1.

Survival analysis

Survival data were collected for all patients. At the end of the study 193 (66.3%) patients were still alive. The mean OS time was 123.93 months [standard error (SE) 4.54, 95% CI 115.04–132.82] using the Kaplan Meier method, and the median OS 180 months (SE 25.96, 95% CI 129.11-230.89). The 5-year OS rate for stage B patients was 86.1% (95% CI 79.5-92.7) and for stage C 60.7% (95% CI 52.9.9–68.5, p<0.01). Five-year DFS was 82.8% (95% CI 76.5-87.9) for stage B patients and 59.02% (95% CI 52.8–65.2) for stage C patients (p<0.01).

Bivariate analysis

Disease free survival: Factors associated with worse DFS were Dukes stage (p<0.001), pre-treatment PS (p<0.001), number of histologically positive lymph nodes identified (p<0.001), smoking history (p=0.087), raised tumor markers (p<0.001), and LNR (p<0.001) (Table 2).

Relapse rate: Statistically significant bivariate associations were found between Dukes stage (p<0.001), pre-treatment PS (p<0.001), smoking (p=0.02), raised tumor markers (p<0.001), total number of lymph nodes retrieved at surgery (p=0.04), number of histologically positive lymph (p<0.001), and need for growth factors during chemotherapy (p<0.001) (Table 3).

Overall survival: Worse OS was associated with Dukes stage (p<0.001), pre-treatment PS (p<0.001), number of histologically positive lymph nodes (p<0.001), histological grade (p<0.04), raised tumor markers (p<0.01), need for growth factors during chemotherapy (p<0.001), and LNR (p<0.001) (Table 4).

Multivariate analysis: Factors exhibiting strongest associations in bivariate analysis were subjected to multivariate analysis. Forward automated procedures resulted in the final model, which is described in

Table 1. Demographic and clinical variables in the study population (n=291)

Variables	*Parameter*	*N*	*%*	*Variables*	*Parameter*	*N*	*%*
Gender	Female	112	38.5	Total number	<12	143	49.1
	Male	179	61.5	of lymph nodes	≥12	148	50.8
				retrieved at surgery			
Age (years)	<60	100	34.4	Number of positive	All negative	119	40.9
	60-70	111	38.1	lymph nodes	≤ 3	100	34.4
	>70	80	27.5		>3	72	24.7
Body mass index	<20	23	7.9	Lymph node ratio	0	119	40.9
	20-24.9	107	36.8		1 (0-0.05)	11	3.8
	25-29.9	131	45.0		2 (0.05-0.19)	58	19.9
	>30	30	10.3		3 (0.2- 0.39)	42	14.4
					4 (0.4- 1.0)	61	21
Pre-treatment	<90	51	17.5	Tumor size (cm)	< 3	24	8.2
performance	≥90	240	82.5		3-6	181	62.2
status					>6	86	29.6
Family history	Yes	103	35.4	Grade of	High	76	26.1
	No	188	64.6	differentiation	Moderate	196	67.4
					Low	19	6.5
Smoking history	0	167	57.4	Lymphocytic	No	188	64.6
(pack-years)	≤10	69	23.7	infiltration	yes	103	35.4
	>10	55	18.9				
Alcohol con-	<10	246	84.5	Hospital of surgical	Tertiary	187	64.3
sumption (g/d)	10-29	32	11	resection	Other	104	35.7
	≥30	13	4.5				
Co-morbidities	No	110	62.2	Surgical experience	Specialised surgeons	92	31.6
	Yes	181	37.8		Experienced	127	43.6
					Less experienced	72	24.7
Dukes stage	B	119	40.9	Tumor markers	Not raised	141	48.5
	C	172	59.1	(CEA, CA 19-9)	Raised	150	51.5
Presenting	Bloody stool	84	28.9	Growth factors	No	261	89.6
complaint	Change in bowel habit	78	26.8		Yes	30	10.3
	Other	129	44.3				
Location	Ascending colon	94	32.3	Follow-up	Systematic	210	72.1
	Transverse, descending, Sigmoid	127	43.6		Less systematic	81	27.9
	Rectum	70	24.1				

Tables 5-7.

Hazard ratios: PS<90, Dukes stage C and elevated tumor markers expressed a negative effect on DFS (HR 4.93, 95% CI 3.23-7.54, p<0.001; HR 2.52; 95% CI 1.54-4.14, p<0.002; and HR 2.35, 95% CI 1.47-3.72, p<0.001) respectively (Figure 1A-C). In addition, DFS was adversely affected in patients with smoking history of ≤10 pack-years vs non-smokers (HR 1.76, 95% CI 1.11-2.79, p<0.01) (Figure 1D). Similarly, relapse was associated with PS<90 (HR 14.46, 95% CI 6.09-34.34, p<0.001), stage C disease (HR 2.80, 95% CI 1.46-5.38, p<0.002), elevated tumor markers (HR 2.98, 95% CI 1.60-5.56, p<0.001) and use of growth factors (HR 3.43, 95% CI 1.27-9.29, p<0.001). Smoking also had a significant association with relapse. Patients with a smoking history of ≤10 pack-years had

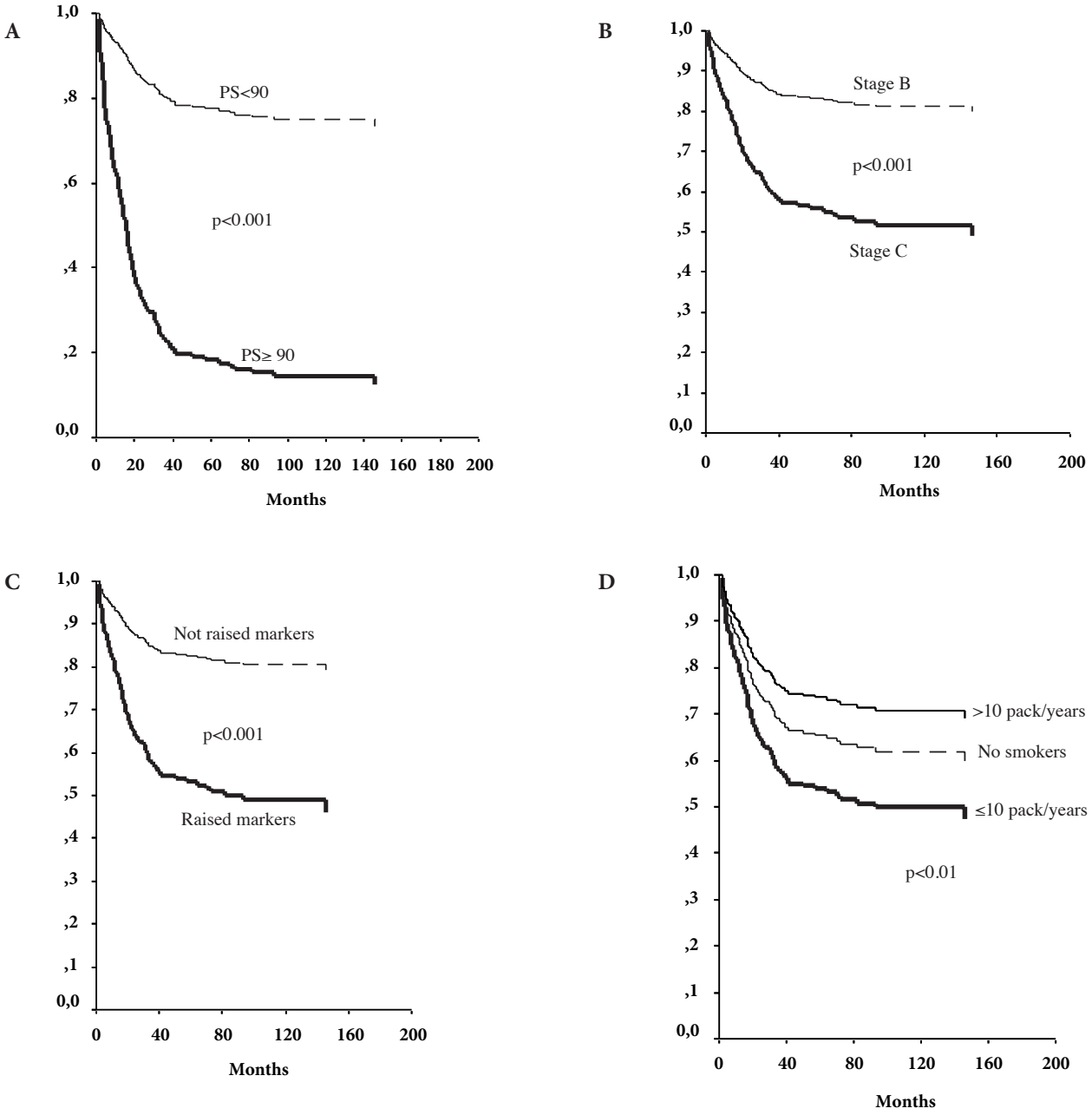

Figure 1. Disease free survival according to performance status **(A)**, Dukes stage **(B)**, tumor markers **(C)** and smoking history **(D)**.

2.45-fold higher risk of relapse compared to patients with no smoking history (HR 2.45, 95% CI 1.16-5.14, p<0.01). Nevertheless, OS was influenced by 3 factors including pre-treatment PS, Dukes stage and elevated tumor markers at diagnosis. In particular, patients with PS < 90 had a 4.69-fold higher risk of death than patients with better PS (HR 4.69, 95% CI 3.08-7.14, p<0.001). Stage C disease was associated with 2.27-fold higher risk of death than stage B disease (HR 2.27, 95% CI 1.42-3.64, p<0.001) (Figure 2A,B). Elevated tumor markers at the time of diagnosis conferred a 2.74-fold higher risk of death (HR 2.74, 95% CI 1.73-4.36, p<0.014) (Figure 2C).

Discussion

Therapeutic planning and overall management of cancer patients requires reliable clinical prediction of survival which in itself is one of the most significant

Table 2. Univariate analysis of disease free survival

Variable	*Groups*	*N*	*Disease free survival (weeks)*		*p-value*
			Mean	*Median*	
Dukes stage	B	119	150	180	
	C	172	100	146	0.001
Pre-treatment performance status	90-100	240	140	180	
	<90	51	39	14	0.001
Number of positive lymph nodes	All negative	119	144	180	
	Positive≤3	100	121	174	0.001
	Positive>3	72	74	33	
Smoking history (pack-years)	0	167	133	180	
	≤10	69	95	169	0.04
	>10	55	116	174	
Tumor markers (CEA, CA 19-9)	Not raised	141	145	174	
	Raised	150	98	82	0.01
Growth factors	No	261	129	180	
	Yes	30	57	13	0.001
Lymph node ratio	0	119	146	180	
	1 & 2	69	134	172	
	3	42	100	174	0.001
	4	61	66	26	

challenges faced by clinicians treating cancer patients [13]. Unanswered questions and controversies still remain despite the existence of several large clinical trials. Specifically, it is still unclear how to optimally identify subgroups benefiting more than others amongst patients receiving adjuvant chemotherapy i.e. the understanding of factors influencing the therapeutic outcome. Furthermore, the use of data from clinical trials in order to establish prognosis for individual patients remains a challenge, as there is often significant heterogeneity among the different clinical trials concerning response and survival rates [8]. Previous experience shows that the external validity or generalization of a trial can be greatly influenced by factors such as inclusion and exclusion criteria, study design and even the enrolment process itself [14,15].

Being able to estimate the prognosis of an individual patient is not important just for the clinician; it is also crucial for the patient. There are several studies emphasizing the need for qualitative and quantitative information to assist when making informed decisions in patients with newly diagnosed cancer regarding the management of their disease [16,17]. We therefore performed our analysis on consecutive non-selected cases with Dukes stage B and C disease from a single centre; all patients were treated outside of clinical trials with standard 5-FU-based adjuvant chemotherapy.

PS has been established as an important prognostic factor especially in patients with advanced disease [18,19]. In a recent study Sargent et al. have shown PS to be a significant prognostic factor irrespectively of therapeutic protocol in patients with advanced CRC. The study demonstrated inferior PFS and OS outcomes for patients with PS 2 compared with those with PS 0/1; PFS was 7.6 months for PS 0/1 vs 4.9 months for PS 2 ($p<0.0001$) and OS was 17.3 months for PS 0/1 vs 8.5 months for PS 2 compared with those with PS 0/1 ($p<0.0001$) [20]. Our findings reiterate the association between PS and OS, DFS and recurrence in Dukes B and C disease and they are in accordance with most previous studies.

As cancer staging using the Dukes classification

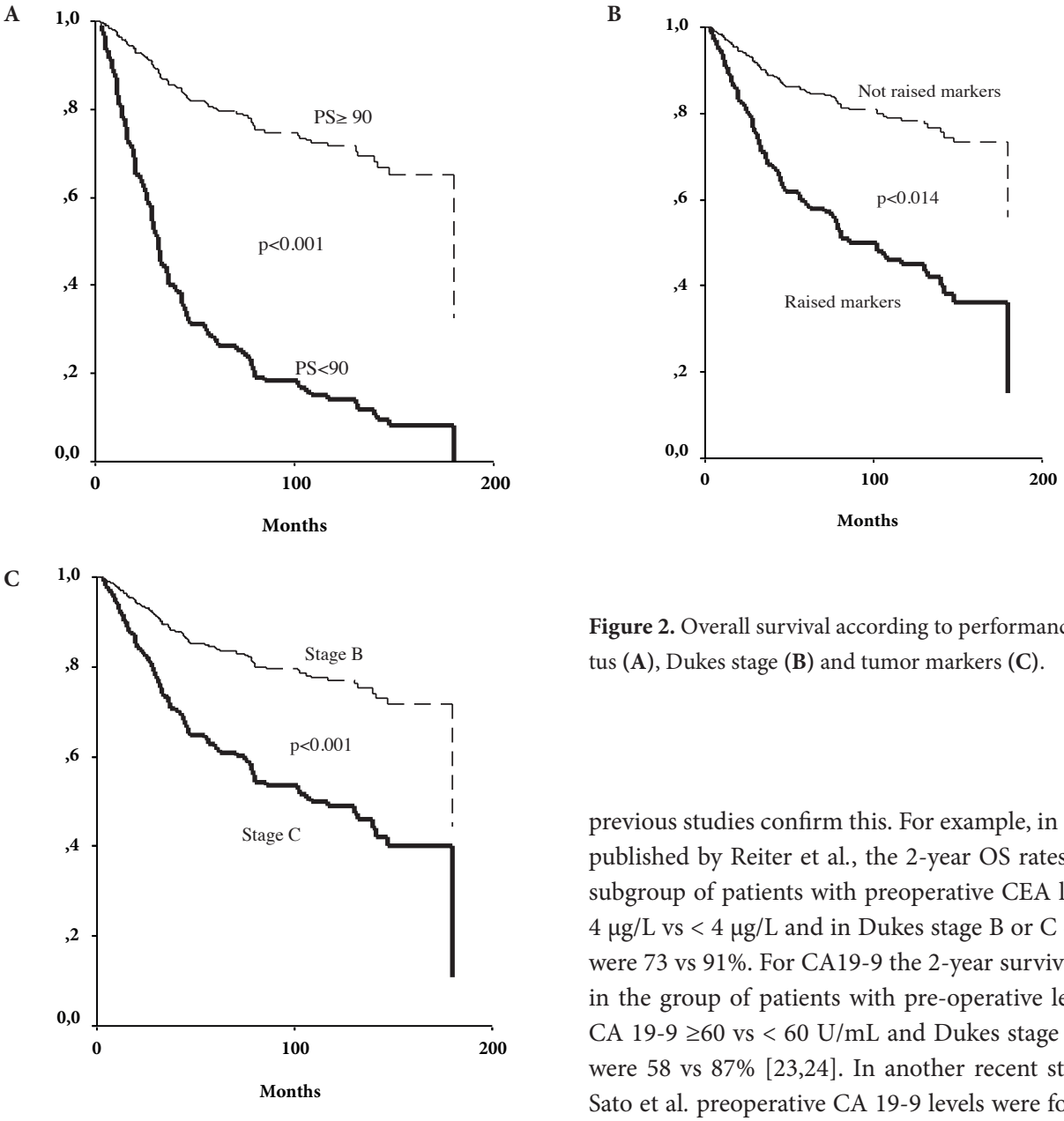

Figure 2. Overall survival according to performance status **(A)**, Dukes stage **(B)** and tumor markers **(C)**.

has been proved to be the most important factor in determining prognosis and decision making with regards to treatment, it is difficult to exclude it from any study of prognostic factors [3]. The survival rates (86.1 and 60.7% for stage B and C, respectively) and the 5-year DFS (82.8 and 59.02% for stage B and C, respectively) reported in our study were comparable with results described in previous studies [8,21,22].

We have also shown that elevated pre-treatment tumor markers CEA and CA 19-9 have significant association with poorer prognosis. Various previous studies confirm this. For example, in a study published by Reiter et al., the 2-year OS rates in the subgroup of patients with preoperative CEA levels > 4 μg/L vs < 4 μg/L and in Dukes stage B or C disease were 73 vs 91%. For CA19-9 the 2-year survival rates in the group of patients with pre-operative levels of CA 19-9 ≥60 vs < 60 U/mL and Dukes stage B or C were 58 vs 87% [23,24]. In another recent study by Sato et al. preoperative CA 19-9 levels were found to be independently associated with poor prognosis in 1476 stage B colon cancer patients [25] . Similarly, higher preoperative CEA levels can be used to identify patients with higher probability of recurrence [26].

The use of growth factors, implicating neutropenia during chemotherapy, was also associated with inferior prognosis in our study. This is not conforming with the results of a retrospective analysis performed by Shitara et al. where chemotherapy-induced neutropenia (both mild and severe) in a cohort of 153 patients with metastatic CRC treated with first-line folinic acid, fluorouracil and oxaliplatin (FOLFOX) was shown to be associated with improved survival

Table 3. Bivariate analysis of relapse

Variables		*Relapse*		*Non relapse*		*p-value*
		N	*%*	*N*	*%*	
Dukes stage	B	22	18.5	97	81.5	<0.001
	C	76	44.2	96	55.8	
Pre-treatment performance status	90-100	56	23.3	184	76.7	<0.001
	<90	42	82.4	9.0	17.6	
Smoking history (pack-years)	0	46	27.5	121	72.5	0.02
	≤10	32	46.4	37	53.6	
	>10	20	36.4	35	63.6	
Tumor markers	Not raised	26	18.4	115	81.6	<0.001
	Raised	72	48.0	78	52.0	
Total number of lymph nodes retrieved at surgery	<12	58	40.5	85	59.5	0.04
	≥12	41	27.7	107	72.3	
Number of positive lymph nodes	All negative	26	21.8	93	78.2	<0.001
	Positive≤3	32	32.0	68	68.0	
	Positive>3	41	56.9	31	43.1	
Growth factors	No	78	29.9	183	70.1	<0.001
	Yes	20	66.7	10	33.3	

Table 4. Univariate analysis of overall survival

Variables	*Groups*	*N*	*Overall survival (weeks)*		*p-value*
			Mean	*Median*	
Dukes stage	B	119	146	180	0.001
	C	172	108	131.8	
Pre-treatment performance status	90-100	240	139	180	0.001
	<90	51	54	26	
Number of positive lymph nodes	All negative	119	140	180	0.001
	Positive< 3	100	130	180	
	Positive>3	72	81	46	
Grade of differentiation	Low	76	138	180	0.04
	Moderate	196	121	180	
	High	19	96	140	
Tumor markers (CEA, CA 19-9)	Not raised	141	150	180	0.01
	Raised	150	100	102	
Growth factors	No	261	129	180	0.001
	Yes	30	70	37	
Lymph node ratio	0	119	141	180	0.001
	1 & 2	69	132	172	
	3	42	107	141	
	4	61	80	43	

(HR 0.55 and 0.35, respectively) by multivariate analysis [27]. Further studies are warranted to clarify these apparent discrepancies.

Smoking and its relation with CRC is under extensive investigation [12,28]. As far as we are aware our study is one of the few studies that shows an adverse effect of smoking on DFS and recurrence rates in non-clinical-trial CRC patients with stage B and C disease. There

Table 5. Final Cox proportional regression model for disease free survival

Variable	*B*	*Standard error*	*Wald*	*p-value*	*Hazard ratio*	*95% confidence interval*	
						Lower	*Upper*
Dukes stage C vs B	0.928	0.253	13.472	<0.001	2.528	1.541	4.149
Smoking history (≤10 pack-years vs none)	0.566	0.235	5.816	<0.016	1.762	1.112	2.792
Tumor markers (raised vs not raised)	0.857	0.240	12.757	<0.001	2.357	1.472	3.722
Pre-treatment performance status (<90 vs ≥90)	1.597	0.216	54.424	<0.001	4.936	3.230	7.544

Table 6. Final Cox proportional regression model for relapse

Variable	*B*	*Standard error*	*Wald*	*p-value*	*Hazard Ratio*	*95% confidence interval*	
						Lower	*Upper*
Dukes stage C vs B	1.031	0.333	9.578	<0.002	2.804	1.460	5.387
Smoking history (≤10 pack-years vs none)	0.896	0.378	5.605	<0.018	2.451	1.167	5.149
Smoking history (>10 pack-years vs none)	0.414	0.401	1.064	<0.302	1.512	0.689	3.318
Tumor markers (raised vs not raised)	1.093	0.317	11.857	<0.001	2.983	1.601	5.567
Pre-treatment performance status (<90 vs ≥90)	2.672	0.441	36.681	<0.001	14.465	6.093	34.341
Growth factors (yes vs no)	1.235	0.507	5.930	<0.014	3.439	1.272	9.296

are other studies that associate smoking with survival including the one by Munro et al. who investigated the impact of active smoking in CRC patients reporting a significant decrease in 5-year survival rates for active smokers 51.3 vs 71.4% for non active smokers (p= 0.0015) [29]. McCleary et al. in a recent study have highlighted that neither the smoking status nor the time period since smoking cessation seemed to have statistically significant impact on DFS, OS or recurrence free survival. However, a dose-response association was noted for smoking intensity, particularly for the risk of death or recurrence in higher quartiles of pack-years smoked before the age of 30 compared to non-smokers [30]. The role of smoking remains controversial with some interesting studies associating smoking with functional changes of natural killer cells and cellular immunity [31,32], with angiogenesis [33,34], or with changes in the metabolism of chemotherapeutic agents [35]. Other studies have attempted to associate smoking with specific mutations in colon cancer carcinogenesis. Diergaarde et al. have noted an overexpression of p53 and the presence of mutations in APC, K-*ras*, in persistent smokers compared with non-smokers [36] and Limsui et al. have highlighted the presence of *BRAF* mutation or CpG island methylation phenotype in older women with smoking history and higher colon cancer risk [37]. In addition, Slattery et al. have identified an increase in the occurrence of microsatellite instability in colon cancers in heavy smokers > 1 pack per day in relation to non-smokers (odds ratio 1.6, 95% CI 1-2.5 for men; odds ratio 2.2, 95% CI 1.4-3.5 for women) [30,38].

The observation that smoking history has an effect on the recurrence rates of CRC patients with Dukes B and C disease is a new, debated and interesting subject with the possibility to offer a new understanding of the pathogenetic mechanisms of this disease. The inclusion in our study of consecutive non-selected patients treated with adjuvant chemotherapy outside clinical trials provides greater reliability and improves the generalization of our results. The limitations our study largely evolve on our reliance on the quality of the data collected retrospectively and the difficulty

Table 7. Final Cox proportional regression model for overall survival

Variable	*B*	*Standard error*	*Wald*	*p-value*	*Hazard ratio*	*95% confidence interval*	
						Lower	*Upper*
Dukes stage C vs B	0.822	0.240	11.701	<0.001	2.275	1.421	3.644
Pre-treatment performance status (<90 vs ≥90)	1.547	0.215	51.814	<0.000	4.695	3.082	7.154
Tumour markers (raised vs not raised)	1.011	0.236	18.316	<0.000	2.749	1.730	4.367

of gathering large number of patients with adequate records. Furthermore, smoking history was based on self-reporting and was recorded at baseline. There were little data for smoking habits over the course of treatment or follow up. These limitations obscured the effect of the intensity of smoking history making it difficult to associate smoking and recurrence rates in a dose-dependent manner. The group of patients with a history of heavier smoking showed a trend towards higher recurrence rates which however did not reach statistical significance, possibly due to confounding factors. It remains an interesting challenge to further clarify the possible role of smoking in the biological behavior of CRC.

In conclusion, this study identified an association between smoking and higher recurrence rates in CRC patients. Furthermore, it stresses the importance of low performance status (PS<90), advanced Dukes stage, and elevated tumor markers as significant prognostic factors in CRC patients, enabling clinicians to decide on their final clinical management and overall care.

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