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Original Paper

Survival for Colon and Rectal Cancer in a Population-based Cancer Registry

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Dukes' stage is the most powerful indicator of patient outcome for colorectal cancer. Several cancer survival studies have considered other prognostic variables, but results are often conflicting. We sought to assess the independent value of several clinical and morphological variables in defining colorectal cancer specific survival. 397 colorectal cancer patients diagnosed from 1984 to 1986, and registered in a large bowel cancer registry instituted in a local health district of Northern Italy, were actively followed-up until 31 December 1991. Univariate and multivariate survival analyses were carried out in colon and rectal cancer cases, separately, using the actuarial life-table method and Cox proportional hazard regressions. Crude and specific 5-year survival rates were 37.5 and 41.4%. In univariate analysis, TNM (tumour, nodes and metastases) stage was the strongest predictor of prognosis in both sites. Other variables significantly related to survival were age of patient at diagnosis and pattern of tumour growth in colon cancer, type of differentiation and pattern of tumour growth in rectal cancer. In multivariate analyses, after adjusting for stage, age had a weak but significant negative effect on colon cancer survival, whereas rectal tumours with the infiltrating type of growth had a significantly worse prognosis than those with the expanding type. Colorectal cancer survival should be analysed in the main large bowel subsites in order to define high-risk groups within each TNM stage category.

Key words: large bowel, cancer, registry, survival
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INTRODUCTION

IN RECENT years, much effort has been paid to improve survival after colorectal cancer diagnosis. In fact, despite recent advances in the knowledge of tumour biology, in devising new strategies for prevention in high risk individuals, and in the management and therapy, cancer of the large bowel remains a major health concern in most developed countries. Little is known about colorectal cancer aetiology. It is believed that both environmental [1] and genetic [2] factors are involved.

Several clinical, biological and histological variables have been tested in survival studies, and many have been shown to be related to prognosis. Moreover, in recent years, the development of multivariate models for analysing survival data has enabled the evaluation of an independent effect of each variable on prognosis [3]. However, the clinical meaning of those factors has not been clearly established, and tumour stage remains the most powerful indicator of clinical outcome [4, 5].

When considering survival data, cancer registries provide a unique opportunity to evaluate the impact of health measures on the general population. Here we report the results of survival analysis of a population-based study of patients with diagnosis of colorectal cancer, made from 1984 to 1986 in the Health Care District of Modena, Northern Italy. Patients were followed-up until 31 December 1991, when 5-year survival for the last registered patient could be assessed.

The aims of the present study were to evaluate some clinical and pathological variables of the tumour in relation to 5-year survival after diagnosis of colon or rectal cancer, and to assess the independent value of variables in defining prognosis, separately for colon and rectal cancer.

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PATIENTS AND METHODS

Patients

From 1 January 1984 to 31 December 1986, 406 patients were registered with colorectal cancer in the Health Care District 16 of Modena, Northern Italy. Whenever possible, each case was contacted during hospitalisation where demographic and clinical data were recorded; furthermore, the genealogy of the patients was traced with special attention to family history of cancer. For 397 subjects (190 women and 207 men), the clinical status could be established on 31 December 1991, at least 5 years from diagnosis. 9 patients (2.2%) were lost to follow-up. During the period under study, 255 died, 22 from causes other than cancer of the large bowel. The cause of death was reported on death certificates computerised in the local Health Service. Moreover, an active follow-up was pursued: endoscopic and pathological reports were periodically reviewed, in some cases surgeons were directly interviewed, as well as family physicians and close relatives of the registered patients. This approach was necessary when the cause of death was uncertain, based only on death certificate or clinical charts.

Survival analysis: clinical variables

The following clinical variables were evaluated in the 397 patients suitable for the analysis (238 with colon and 159 with rectal cancer): (1) Age of patient at diagnosis. Three age-groups were considered: <60, 60–74 and >74 years. (2) Sex of patient. (3) Site of tumour. Large bowel was divided into two main sites: colon (from caecum to sigmoid colon) and rectum (rectosigmoid junction, rectum and anus). (4) Tumour stage. TNM (tumour, nodes and metastases) classification was adopted [6, 7]. This classification in four groups is closely related to the original Dukes' of rectal cancer [4], supplemented with a further group (stage D) which included patients with distant metastases or who were not operated on due to poor clinical status [8] (Table 1). Furthermore, in 38 resected specimens, no lymph node was found for pathological examination. We feel that these cases should be included in survival analysis as a separate group, because they could not be accurately staged.

Table 1. *TNM stage of colorectal cancer: correlation with Dukes' classification*

TNM group	TNM stage	Dukes' stage
Tis, N0, M0 T1, N0, M0 T2, N0, M0	I	A
T3, N0, M0 T4, N0, M0	II	B
Every T, Nx, M0	Not Staged	
Every T, N1, M0 Every T, N2–N3, M0	III	C
Every T, every N, M1	IV	D

Tis, carcinoma *in situ*; T1, tumour not beyond submucosa; T2, tumour not beyond subserosa in the colon, and muscularis propria in the distal rectum; T3, tumour invades serosa; T4, tumour invades adjacent tissues; N0, no regional lymph node metastasis; Nx, regional lymph nodes cannot be assessed; N1, metastasis in 1–3 pericolic or perirectal lymph nodes; N2, metastasis in four or more pericolic or perirectal lymph nodes; N3, metastasis in any lymph node along the course of a named vascular trunk; M0, no distant metastasis; M1, distant metastasis.

Survival analysis: morphological variables

Morphological variables could be evaluated in 275 tumours (69% of the total), 169 from the colon and 106 from the rectum. Tumour slides were independently examined by two pathologists who were unaware of the clinical outcome. When more than one tumour was present in a patient, only the tumour with the most advanced stage was considered in the analysis. For each case, at least three histological sections were stained with haematoxylin and eosin and evaluated for the following parameters: (1) Pattern of tumour differentiation. This was based on the general characteristics of the tumour rather than the worst area. Two main features were considered: (a) glandular configuration at the histological level, and (b) nuclear polarity at the epithelial cell level. In poorly differentiated or completely undifferentiated tumours, glandular configuration and nuclear polarity were almost completely lost. (2) Amount of mucin. Tumours were classified into five groups, according to the amount of mucin, although in survival analysis only two were considered: (a) absence or little mucinous component, or (b) extensive mucinous component (50% or more of the tumour section). (3) Pattern of tumour growth. Tumours were defined as expanding or infiltrating [9], as previously suggested for gastric carcinoma [10]. Expanding tumours had a well delineated and circumscribed border of growth, while infiltrating tumours had cluster or single cells leaving the tumour mass and spreading into the bowel wall. (4) Lymphocytic infiltration. Presence and quantification of the lymphocytes was evaluated at the advancing front of the tumour. Absence or little infiltration was found when no or few lymphocytes were observed, as opposed to moderate or extensive infiltration, in which lymphocytes were progressively more abundant in the inflammatory aggregates. The two latter aspects were grouped in the analysis. (5) Extent of fibrosis. Two categories were considered, evaluating the fibrotic component at the advancing front of the tumour: absent or little fibrosis, and moderate or extensive. (6) Size of tumour. This parameter was defined by the largest diameter of the tumour. Two groups were considered, fixing the cut-off value at 40 mm: (a) 40 mm or smaller (b) > than 40 mm.

Statistical analysis

Crude and colorectal cancer specific survival rates were obtained using the actuarial life-table method [11]. Crude survival rate was calculated only on the overall data, whereas both univariate and multivariate analyses were carried out using specific survival data. Deaths unrelated to colorectal cancer were censored at the time of death. All univariate analyses were also carried out with the actuarial life-table method, separately in colon and rectal cancer. Differences between the numbers were tested by the log-rank test [12]. Furthermore, Bonferroni tests were used in order to adjust for multiple comparisons and thus to identify variables for the subsequent multivariate analysis. In univariate analyses, differences were considered significant when $P < 0.001$. The independent value of the variables in predicting survival, separately in colon and rectal cancer cases, was evaluated using Cox proportional hazard regression models [13]. We decided to carry out separate analyses in the two main cancer sites because of the different biological features of cancer at

these sites (for example, mucinous histology, nuclear diploidy) [14, 15]. Furthermore, in our series, the pattern of survival was dependent on the site of tumour (see Figure 1), so that the proportionality assumption of the Cox model was not met. Dummy variables (categories) were created for nominal and ordinal variables. Age of patient and stage at diagnosis were considered *a priori* the known variables with a possible predictive value [5, 16]. The first step was to verify the independent role of these two variables. The variable which showed such a significant independent effect was considered in the other models with the morphological variables in order to identify the independent value of these. However, a putative interaction effect of age of patients and tumour stage in influencing the role of morphological variables was excluded by specific analyses (data not presented). At the beginning of each multivariate analysis, the variables were forced into the model, then those having the highest P value (>0.05) were removed stepwise from the model, until only those which independently influenced survival remained. All survival analyses were carried out using the BMDP statistical software.

RESULTS

Colorectal cancer specific survival rates were 69.7, 48.7 and 41.4% at 1, 3 and 5 years from diagnosis, respectively, whereas crude survival rates were 68.3, 46.1 and 37.5%.

Clinical variables

When survival data were examined separately for colon and rectal cancer cases, an interesting tumour site effect was observed. In particular, patients with rectal cancer seem to have a lower risk of death in the first 2 years from diagnosis (Figure 1), but subsequently, survival became worse than that of colon cancer patients, although there was no statistical difference in survival between the two groups, both in the first 2 years and in the subsequent follow-up period. This tumour site-related difference in survival could produce a distortion in the analysis. This observation, along with other biological and epidemiological considerations, prompted us to evaluate the impact of each variable separately in the two main cancer site categories. The results of such analysis for clinical variables is shown in Table 2. The effect of gender on prognosis was negligible in both cancer sites. Age of patient at diagnosis significantly influenced survival only of colon cancer cases,

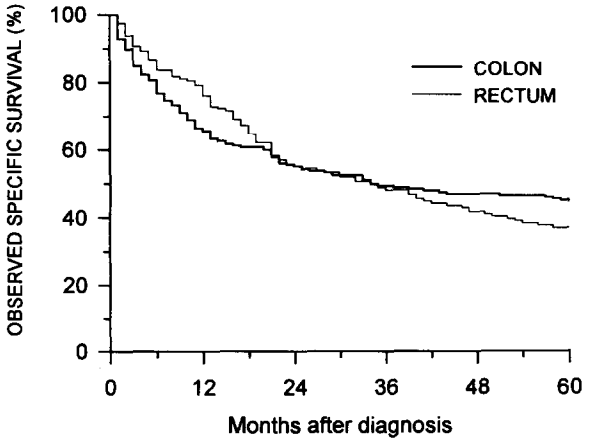

Figure 1. Specific survival rates (%) of patients with colon (n = 238) and rectal (n = 159) cancer. Health Care District of Modena, Northern Italy, 1984–1986.

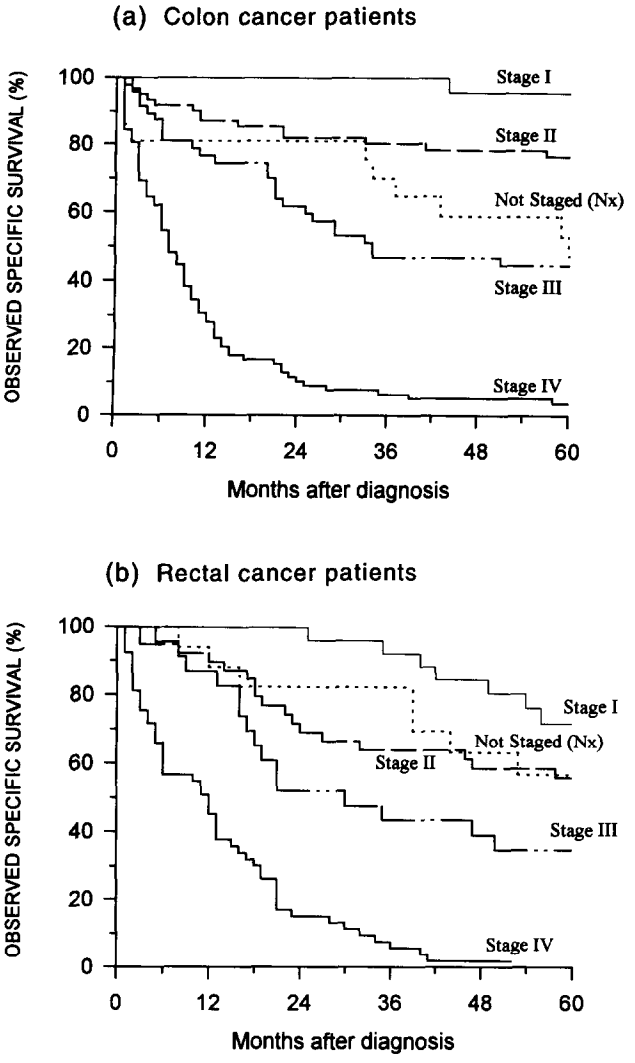

Figure 2. Specific survival rates (%) of patients with colon or rectal cancer according to TNM stage at diagnosis. Health Care District of Modena, Northern Italy, 1984–1986.

and in particular, of right-sided colon cancer ones (data not shown). The prognostic value of TNM stage was remarkable in each tumour site group, although survival for rectal cancer was worse than for colon cancer in all stage categories, except for not staged cases. Survival curves according to TNM stages for colon and rectal cancer patients are shown in Figure 2.

Morphological variables

Five-year survival rates, by tumour site, for morphological parameters, are presented in Table 3. Pattern of tumour differentiation significantly influenced survival only in rectal cancer cases. Pattern of tumour growth was strongly related to survival in both tumour site groups. No significant tumour site-related difference in prognosis was observed for the other morphological parameters.

Multivariate analyses

Variables significantly related to colorectal cancer specific survival were entered into multivariate models. First, we created several models, in which the independent effects of TNM stage and age of patient at diagnosis could be evaluated in colon and rectal cancer (Table 4). The effect of age of patient

Table 2. Five-year specific survival (non-cancer deaths censored), by tumour site, according to clinical variables of patients with colorectal cancer (univariate analyses). Health Care District of Modena, Northern Italy, 1984–1986

Variable	Colon			Rectum and rectosigmoid junction		
	No. of subjects	% Survival	*P* value	No. of subjects	% Survival	*P* value
Sex						
Men	112	44.3		95	36.6	
Women	126	44.9	N.S.	64	37.4	N.S.
Age at diagnosis (years)						
<60	48	58.3		39	41.0	
60–74	113	48.1		79	40.7	
>74	77	30.3	<0.001	41	25.6	N.S.
TNM stage						
I	26	95.6		26	71.9	
II	62	76.6		39	56.1	
III	47	44.5		24	34.8	
IV	82	3.6		53	0.0	
Not staged	21	47.1	<0.001	17	57.0	<0.001

N.S., not significant.

Table 3. Five-year specific survival (non-cancer deaths censored), by tumour site, according to morphological variables of the tumour (univariate analyses). Health Care District of Modena, Northern Italy, 1984–1986

Variable	Colon			Rectum and rectosigmoid junction		
	No. of subjects	% Survival	*P* value	No. of subjects	% Survival	*P* value
Pattern of differentiation						
Well	31	73.3		25	72.0	
Moderately	102	51.1		72	47.5	
Poorly	36	60.5	N.S.	9	25.4	<0.001
Amount of mucin						
Absent or little	145	55.3		97	52.4	N.S.
50% or more	24	69.0	N.S.	9	44.4	
Pattern of tumour growth						
Expanding	93	70.9		73	63.6	
Infiltrating	76	40.9	<0.001	33	25.1	<0.001
Lymphocytic infiltration						
Absent or little	92	54.3		41	36.4	
Moderate or extensive	77	60.5	N.S.	65	61.6	N.S.
Fibrosis						
Absent or little	60	64.7		36	62.1	
Moderate or extensive	109	53.2	N.S.	70	46.5	N.S.
Size of tumour (mm)						
≤40	97	57.0		54	50.1	
>40	72	57.6	N.S.	52	43.4	N.S.

N.S., not significant.

was evaluated both as categorical and continuous variable in separate models. Tumours which were not staged were excluded from multivariate analyses. TNM stage was confirmed as the factor with the strongest independent effect on survival. For both tumour sites the prognostic value of age disappeared after adjusting for stage, except in colon cancer patients, where age, considered as continuous variable, maintained a marginal but significant independent effect, mainly due to older patients.

As far as morphological variables are concerned, multivariate models for colon and rectal cancer are shown in Table 5. Each variable was singularly tested against TNM stage. In

Table 4. Cox regression models for colon and rectal cancer specific survival: prognostic value of TNM stage and age at diagnosis. For each tumour site, two models were created, one with TNM stage and age at diagnosis as categorical variables (Model a), the other with TNM stage categorical, and age at diagnosis as continuous variable (Model b)

Model	Variable	β coefficient	Crude RR	*P* value	Adjusted RR*	*P* value
Colon cancer (n = 217)						
a,b	TNM stage					
	I (reference)	—	1.0	—	1.0	—
	II	2.12	8.3	<0.01	8.2	<0.01
	III	3.00	20.0	<0.01	19.3	<0.01
	IV	4.48	88.2	<0.01	85.1	<0.01
a	Age at diagnosis (years)					
	<60 (reference)	—	1.0	—	1.0	—
	60–74	0.25	1.3	N.S.	1.0	N.S.
	>74	0.81	2.2	<0.01	1.6	N.S.
b	Age at diagnosis (continuous)	0.03	1.03	< 0.01	1.02	<0.05
Rectal cancer (n = 142)						
a,b	TNM stage					
	I (reference)	—	1.0	—	1.0	—
	II	0.77	2.1	N.S.	2.2	N.S.
	III	1.40	4.1	<0.01	4.3	<0.01
	IV	2.79	16.3	<0.01	21.0	<0.01
a	Age at diagnosis (years)					
	<60 (reference)	—	1.0	—	1.0	—
	60–74	0.15	1.2	N.S.	1.0	N.S.
	>74	0.57	1.8	<0.05	0.6	N.S.
b	Age at diagnosis (continuous)	0.02	1.02	<0.05	0.99	N.S.

* TNM stage adjusted by age at diagnosis (categorical); age at diagnosis (categorical and continuous) adjusted by stage.

colon cancer, the effect of pattern of tumour growth on survival was no longer significant after adjusting for stage, whereas in rectal cancer this maintained an independent value in predicting clinical outcome. The effects of pattern of tumour differentiation disappeared after controlling for stage. In rectal cancer, the independent effect of TNM stage was weaker than for colon cancer; indeed, even the risk of death for stage III tumour decreased and was not significant after adjusting for pattern of tumour growth.

DISCUSSION

The present study reports univariate and multivariate survival analyses for patients affected by colon or rectal cancer, and registered in a local colorectal cancer registry of Northern Italy. Our population-based approach allowed the definition of survival probability 5 years after diagnosis of the entire population affected by cancer of the large intestine in our health care district, during the period 1984–1986. The cause of death was accurately identified, thereby excluding problems in analysing survival data due to background mortality (caused by diseases other than colorectal cancer) [17]. Nevertheless, relative risk of death from causes other than cancer rapidly decreases with time [18]. Crude survival was 37.5%, but rose to over 41% when colorectal cancer unrelated deaths were excluded. These figures are in good agreement with most recently published population-based studies [19–21]. Moreover, the clinical value of cancer registries is of utmost importance in this regard, since they provide updated information on cancer incidence and mortality, and thus help in planning prevention strategies and reducing social costs for health.

By univariate analysis, we examined survival according to clinical variables. As expected, TNM stage was the strongest predictor of clinical outcome. We decided to group separately tumours which were not staged. Indeed, it was a heterogeneous group, comprising both stage II and stage III neoplasms. This group should disappear when more lymph nodes are systematically removed at surgery and carefully isolated at pathology, using new techniques to detect small lymph nodes.

Age of patient at diagnosis was inversely related to survival in patients with colon cancer. Younger age groups had more favourable prognosis. This is not a new finding [22, 23], although other studies reported no relationship [24] or conflicting results [25]. As opposed to other studies, gender had no appreciable effect on survival.

When we considered survival according to tumour site (colon and rectum), we observed a non-significant worse prognosis for rectal cancer, but, more importantly, survival curves followed markedly different profiles. It is also worth noting that the survival curve for left-sided colon cancer patients was more similar to that of rectal cancer patients (Figure 3). This trend could be accounted for by a lead-time bias for rectal cancer cases (and probably in part for left-sided colon cancer), whose diagnosis was made approximately 6 months earlier than colon cancer (especially proximal to the splenic flexure). This fact can be deduced by comparing the patterns of survival curves, according to tumour site, during

Table 5. Cox regression models for colon and rectal cancer specific survival: prognostic value of TNM stage and morphological variables

Variable	β coefficient	Crude RR	*P* value	Adjusted RR*	*P* value
Colon cancer (n = 151)‡					
TNM stage					
I (reference)	—	1.0	—	1.0*	—
II	1.99	7.3	<0.01	6.3*	<0.05
III	2.78	16.0	<0.01	12.7*	<0.01
IV	3.93	50.9	<0.01	38.1*	<0.01
Pattern of tumour growth					
Expanding (reference)	—	1.0	—	1.0*	—
Infiltrating	1.04	2.8	<0.01	1.5*	N.S.
Rectal cancer (n = 90)‡					
TNM stage					
I (reference)	—	1.0	—	1.0†	—
II	0.62	1.8	N.S.	1.6†	N.S.
III	1.50	4.5	<0.01	2.5†	N.S.
IV	2.90	18.2	<0.01	10.8†	<0.01
Pattern of differentiation					
Well differentiated (reference)	—	1.0	—	1.0†	—
Moderately differentiated	0.89	2.4	<0.05	1.7†	N.S.
Poorly differentiated	2.24	9.4	<0.01	3.5†	N.S.
Pattern of growth					
Expanding (reference)	—	1.0	—	1.0†	—
Infiltrating	1.52	4.6	<0.01	2.5†	<0.01

*TNM stage adjusted by pattern of growth; pattern of growth adjusted by TNM stage. † TNM stage adjusted by pattern of growth; pattern of differentiation adjusted by TNM stage, pattern of growth adjusted by TNM stage. ‡ The number of colon and rectal cancer cases is lower than that in Table 4 because morphological variables could be evaluated only in a subset of tumours.

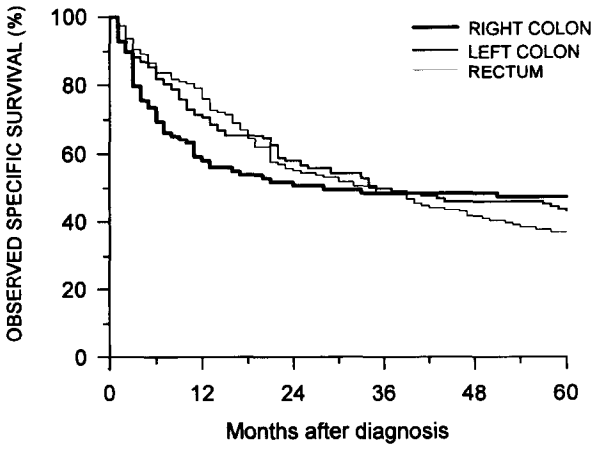

Figure 3. Specific survival rates (%) of patients with right colon (n = 99), left colon (n = 139) and rectal (n = 159) cancer. Right colon includes caecum, ascending and transverse colon, and flexures; left colon includes descending and sigmoid colon; rectum includes rectosigmoid junction, rectum and anus. Health Care District of Modena, Northern Italy, 1984–1986.

the first 18 months of follow-up (Figure 1). Indeed, in our series and in others [26], higher percentages of early-stage rectal tumours (stage I and II) and lower percentages of late-stage tumours (stage III and IV) suggest earlier diagnosis of rectal cancer, probably due to easier access for examinations [16]. However, long-term survival of rectal cancer patients was slightly worse than that of colon cancer patients. Biological and anatomical factors are probably more important in determining prognosis than preclinical or early diagnosis of rectal cancer. The different patterns of survival of colon and rectal cancer patients have already been observed on a larger number of cases [27], and the possible influence on cancer survival analyses discussed [28, 29]. Furthermore, several lines of evidence suggest that colorectal cancer is not a unique entity. Different aetiological factors may be important in the development of cancer at different sites along the large bowel [14, 30], and this is also supported by studies on genetic alterations in colorectal tumours [31]. Thus, we considered it mandatory to evaluate clinical and morphological variables within each tumour site.

TNM stage was the main determinant of prognosis in both cancer sites (colon and rectum), in agreement with most published studies since Dukes' [4]. However, 5-year survival rates were higher for colon cancer in each stage category (except in tumours which were not staged). Anatomical and biological factors could render rectal cancer more aggressive than colon cancer, independently of stage. Indeed, higher rates of locoregional and distant recurrence have been reported for rectal than for colon cancer [32, 33]. Moreover, a higher proportion of rectal cancer were aneuploid in a recent study [34], and aneuploidy seems to correlate with lower survival rates than diploidy [35].

Young patients with colon cancer had more favourable prognosis. In fact, in a multivariate analysis, age of patient, as a continuous variable, maintained a slight but significant independent effect on colon cancer survival, after adjusting for stage. The effect of age was also evident in patients with rectal cancer in univariate analysis, although the study was not

large enough to show significant results. Furthermore, age had no independent influence on survival. Indeed, after adjusting for stage, age was even protective. In spite of the small number of cases, this might be accounted for by a better prognosis for older patients with late stage tumours (stage III and IV). Five-year survival rates were almost the same for the older group of colon and rectal cancer patients. However, patients younger than 60 years with rectal cancer had a 5-year survival rate of only 41%, as opposed to 58% in patients younger than 60 years with colon cancer. One of the possible explanations is that the "youngest group" with colon cancer includes patients with hereditary tumours. Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is a genetic disease inherited as an autosomal dominant trait. Two of the main features of that disease are the early onset of large bowel cancer (usually <50 years) and the frequent localisation of tumours in the right colon (proximal to the splenic flexure). Better prognosis has been reported by some authors for hereditary colon cancer [36], although not confirmed by others [37]. Thus, better survival in colon cancer patients could be accounted for by better survival of hereditary colon cancer patients. Indeed, in our series, 16 of 397 patients with colon cancer were members of HNPCC families, and the 5-year specific survival rate in these patients was over 56% as opposed to 41% in the whole series. 6 of these 16 patients were younger than 60 years and all had colon cancer.

In terms of morphological variables, we observed that, in colon cancer, only pattern of tumour growth was significantly related to survival, whereas, in rectal cancer, tumour growth as well as tumour differentiation were important determinants of prognosis. In multivariate analyses, in addition to TNM stage, pattern of tumour growth remained an independent variable related to prognosis only in rectal cancer. Colon cancer is probably more influenced by host than by tumour characteristics, whereas the opposite is true for rectal cancer. Grinnell found that, among grade-related parameters, tumour invasiveness had the greatest prognostic value [38]. This observation remained somewhat unnoticed until Jass and associates [9] and Carlon [39] reported that the expanding type of tumour has a better prognosis than the infiltrative type. This morphological feature probably accounts for the higher frequency of local recurrence in rectal cancer.

Pattern of tumour differentiation did not show appreciable effect on survival. In fact, it is strictly related to TNM stage, as shown by multivariate analysis in rectal cancer cases. Histological grading is frequently influenced by subjective judgement, therefore, as in our earlier experience [5], this marker is not useful in further defining prognosis.

In summary, the main findings of the present study are: a different pattern of survival between colon and rectal cancer cases, suggesting that cancers at those sites have different biological features and should be considered different nosologic entities; a strong impact of TNM stage on survival in both cancer sites, though weaker for rectal cancer; a slightly negative effect of age of patient at diagnosis, after controlling for TNM stage, on colon cancer survival; and an independent prognostic value of pattern of tumour growth in rectal cancer.

These results are consistent with the hypothesis of different aetiologies between colon and rectal cancer, as also suggested by recent population-based, age–period–cohort analyses of colorectal cancer incidence [40].

The independent prognostic variables identified through the present analysis could be introduced in a unified prognostic system, in order to increase accuracy in prediction of clinical outcome within each TNM stage category and tumour site [41]. Moreover, these results warrant further analysis, when more cases are available.

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