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Prognostic Value of Neural Invasion in Rectal Carcinoma: A Multivariate Analysis on 339 Patients With Curative Resection

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To determine whether neural invasion or other clinico-pathological factors are prognostic, we performed a retrospective study on 339 rectal carcinomas. The overall 5-year survival was 62%. In the multivariate analysis, age over 60 years, a distance from the anal verge of less than 6 cm, the number of positive lymph nodes, neural invasion and tumour penetration were found to be prognostic. A scoring system identified five prognostic groups of patients. Neural invasion is an independent prognostic factor in our scoring system and it is suggested that this parameter should be taken into consideration for postsurgical treatment.

Key words: neural invasion, rectal carcinoma, multivariate analysis, prognostic study
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INTRODUCTION

THE PATHOLOGICAL staging of rectal carcinoma remains the best clinical predictor of outcome. Tumour invasion through the rectal wall and lymph node involvement are currently the most used pathological factors from the staging systems defined by Dukes and Astler-Coller [1]. However, these classifications do not provide enough predictive information. A weakness in the Duke's staging system is that it does not clearly distinguish between the different invasion levels of the rectal wall and, in particular, the penetration of the muscularis propria and involvement of perirectal fat, serosa or extra rectal structures. Survival is worse when the tumour spreads to the mesothelium [2, 3]. Many studies have tried to identify new prognostic factors. Some have suggested using other pathological classifications [4, 5], but only a few have proposed a prognostic scoring system [6–8]. In 1982, we established a classification, modified in 1983 [9] and again in 1988 [10], based on the extent of tumour invasion into the digestive system wall. This classification consists of four parameters which are evaluated independently: tumour extension into the rectal wall, nodal status, absence or presence of vascular and neural invasion. It gives a precise description of the extension of the tumour in the rectal wall, and of vascular and neural invasion.

The aim of this study was to determine whether the histological parameters used in our classification, and especially neural invasion, allow more precise predictive staging.

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PATIENTS AND METHODS

Patients

From 1976 to 1988, 468 patients were treated in the Surgical Department of the Institut Gustave-Roussy (Villejuif, France). The 339 patients who underwent potentially curative resection form the basis of this report. The remaining 129 patients

were excluded for the following reasons: 63 had had palliative resection, 51 had been treated by electrocoagulation, 12 had only had a colostomy, 2 had associated tumours, and 1 patient's pathological review had only been performed outside the Institute. The patients were seen every 3 months during the first 2 years and annually afterwards. Each follow-up visit included a clinical examination, rectoscopy, chest X-ray, and ultrasound liver scan, and from 1982 onwards carcino-embryonic antigen (CEA) determination. All but 76 patients were followed for 5 years or until death. Of the 76 patients, 11 (14.5%) were lost to follow-up during the first 5 years. The median follow-up time was 61 months.

175 patients underwent radical surgery consisting of a total mesorectal excision (abdominal perineal resection); 141 patients had a low rectal anastomosis often with no pelvic lateral lymphadenectomy (low anterieur resection); 23 patients had other procedures. All the tumours which could be reached by digital examination were systematically treated by abdominal perineal resection. 4 patients (1%) died within 30 days of surgery.

161 patients had radiotherapy: 55 preoperative only (35 Gy), 50 postoperative only (45 Gy) and 56 both pre- and postoperative (35 + 25 Gy). Preoperative radiotherapy was used for T3, T4 (TNM clinically infiltrative tumour) in low rectal tumours; postoperative radiotherapy was added for nodal involvement or if the rectal wall was completely invaded. Likewise, postoperative radiotherapy alone was used for large tumours treated by low anterior resection and presenting the same histological features.

Pathological review

One pathologist reviewed the histological slides of all the surgical specimens, without knowledge of the clinical history or outcome. Table 1 gives the pathological classification used in Institut Gustave-Roussy (IGR)[10].

All specimens were fixed by immersion in Bouin's solution for at least 48 h. The tumour was serially sectioned and several representative sections were examined microscopically. Sections from the area where tumour penetration was deepest were always included. All lymph nodes were blocked and labelled separately according to anatomical sites. The median number of lymph nodes examined was 13. The sections were stained with haematoxylin, eosin and saffron (HES). Tumours were of the following histological types: well differentiated adenocarcinoma, moderately well differentiated adenocarcinoma or poorly differentiated adenocarcinoma. Colloid carcinoma was defined as an adenocarcinoma growing largely in a colloid pattern (more than 50%). All slides were carefully screened to identify lymphatic, venous or arterial invasion (vascular invasion, VI), and endoneural or perineural invasion (neural invasion, NI). No special stains were necessary for the detection of neural invasion. VI, however, can be difficult to identify and serial slicing of tissue blocks was necessary to expose vessel structures. Special stains such as orcein were also used to show elastic fibres. The IGR pathological classification was also used for patients who received preoperative radiotherapy, hence the reason why some patients were classified as free of residual tumour (NRT).

Statistical analysis

Univariate analysis. The χ^2 test was used to study the relationship between tumour penetration and nodal status, VI or NI. Five-year overall and disease-free survival rates were estimated by the Kaplan–Meier method and given with their standard deviation. The end-point for disease-free survival was the time of first recurrence or death; for overall survival, the end-point included death following surgery. The prognostic value of each variable was assessed by comparing the survival rates with the log-rank test. Only variables with a P value <0.1 were included in the multivariate analysis.

Table 1. Patients' characteristics (n = 339)

Characteristics	
Male/female	49%/51%
Age (years)	
Mean (range)	61.8 (15–92)
No. of patients with complicated disease	
Bowel occlusion	7
Mural perforation	7
Tumour fixity	22
Tumour penetration (%)	
NRT: No residual tumour*	2
T0: *In situ*	0
T1: Mucosa	3
T2: Submucosa	5
T3: Internal musculatis propria	10
T4: External muscularis propria	18
T5: Partly serosa or perirectal fat	55
T6: Beyond the serosa or into perirectal fat or into adjacent organs	7
Nodal involvement (%)	
N0: None	63
N1: Pararectal nodes	14
N2: Intermediate nodes	21
N3: Pedicular nodes	2
Vascular invasion† (%)	
Yes	34
Neural invasion (%)	
Yes	34

*No residual tumour after preoperative radiotherapy. †114 patients: 55 with lymphatic invasion, 26 with venous invasion, 3 with arterial invasion, 18 with venous and arterial invasion and 12 vascular invasion without other details.

Multivariate analysis. To determine the independent prognostic value of the selected variables, Cox's proportional hazards regression model was used [11]. Two analyses were performed, one for disease-free survival and the other for overall survival. Both analyses were stratified on preoperative radiotherapy as our aim was not to study the role of radiotherapy.

RESULTS

Patients' clinical and pathological characteristics are shown in Table 1. The proportion of positive lymph nodes, VI and NI, increased with T stage (Table 2).

Survival analysis

The overall 3-year survival was 79% (±2%) and 5-year survival 62% (±3%). The 3-year disease-free survival was 60% (±3%) and 5-year survival 51% (±3%). During the first 5 years, 120 patients developed a recurrence: 53 had a regional recurrence, 57 a distant metastasis (17 hepatic, 26 non-hepatic and 14 hepatic and non-hepatic) and 10 had both a regional recurrence and distant metastasis. One hundred and thirty-one (85%) recurrences and deaths occurred during the first 3 years.

In the univariate analysis, the prognostic factors for overall

Table 2. Relationships between histological characteristics

Histological factors	Tumour penetration T0–T1–T2 (n = 33)	T3–T4 (n = 97)	T5–T6 (n = 209)	P
Number of positive nodes				
<3 (n = 279)	33	95	151	$<10^{-4}$
≥3 (n = 60)	0	2	58	
Vascular invasion				
No (n = 225)	30	85	110	$<10^{-4}$
Yes (n = 114)	3	12	99	
Neural invasion				
No (n = 222)	33	88	101	$<10^{-4}$
Yes (n = 117)	0	9	108	

survival were age over 60 years, type of surgery, distance from the anal verge of less than 6 cm, depth of tumour penetration, location of involved lymph nodes, the number of lymph nodes involved, VI and NI. A tumour size exceeding 4 cm was an additional prognostic factor for disease-free survival (Table 3). The other factors studied, which were not prognostic in the univariate analysis, were gender, a complicated disease, macroscopic characteristics (exophitic, infiltrated or ulcerated tumour), associated lesions (polyadenoma, mural perforation or inflammatory bowel disease) and histological differentiation.

The type of surgery (abdomino-perineal amputation) and a distance of less than 6 cm from the anal verge were linked, as expected. Both have a poor prognosis. Because of this association, we decided to exclude the type of surgery from the multivariate analysis. Likewise, nodal status and the number of involved lymph nodes were strongly correlated, consequently only the number of involved lymph nodes was included in the multivariate analysis.

The clinical and pathological factors, which were correlated significantly with the prognosis in the univariate analysis, were included in a multivariate analysis. For overall survival, age over 60 years, distance from the anal verge of less than 6 cm, the number of positive lymph nodes and NI were found to be independently associated with shorter survival (Table 4). For disease-free survival, age, distance from the anal verge, the number of positive lymph nodes, NI and tumour penetration were found to be independently associated with shorter survival (Table 5). As no NI was observed in patients with NRT, T0, T1 and T2 disease (Table 2), we decided to combine tumour penetration and NI in the multivariate analysis.

Prognostic scoring system

In order to design a prognostic scoring system for 5-year disease-free survival, we first discarded age because several authors have shown that, although mortality is related to age in patients with rectal cancer [7, 8], such is not the case for disease-free survival or cancer-related deaths [12, 13]. Table 5 shows the score used for each factor, selected according to the results of the multivariate analysis. The total score was calculated for each patient. With this total score, it was possible to divide the 339 patients into five different prognostic groups according to the number of prognostic factors per patient: group one had no prognostic factor, group two had one prognostic factor, group three had two prognostic factors, group four had three prognostic factors and group five had four prognostic factors. The disease-free survival curves and rates are shown in Figure 1.

Table 3. Univariate analysis of prognostic factors for overall and disease-free 5-year survival

Characteristics	No. of patients (n = 339)	Disease-free 5-year survival Rate (S.D.)	P	Overall 5-year survival Rate (S.D.)	P
Age (years)					
≤60	140	0.64 (0.04)	10^{-4}	0.71 (0.04)	10^{-4}
>60	199	0.43 (0.04)		0.47 (0.04)	
Type of surgery					
Amputation	179	0.44 (0.04)	10^{-2}	0.51 (0.04)	10^{-2}
Other	160	0.61 (0.04)		0.65 (0.04)	
Distance from anal verge					
≤6 cm	152	0.43 (0.04)	10^{-2}	0.49 (0.04)	10^{-2}
>6 cm	187	0.58 (0.04)		0.64 (0.04)	
Circumferential tumour					
No	249	0.51 (0.03)	0.09	0.59 (0.03)	NS
Yes	90	0.43 (0.05)		0.52 (0.06)	
Tumour size*					
≤4 cm	188	0.54 (0.04)	0.09	0.62 (0.04)	0.02
>4 cm	148	0.48 (0.04)		0.51 (0.04)	
Tumour penetration					
NRT-T0-T1-T2	33	0.81 (0.08)	10^{-4}	0.81 (0.08)	10^{-3}
T3–T4	97	0.57 (0.05)		0.64 (0.05)	
T5–T6	209	0.44 (0.04)		0.51 (0.04)	
Location of involved nodes					
N0	214	0.60 (0.04)	10^{-4}	0.66 (0.04)	10^{-4}
N1	46	0.44 (0.08)		0.53 (0.08)	
N2	73	0.30 (0.06)		0.36 (0.06)	
N3	6	0.50 (0.20)		0.50 (0.20)	
Number of positive nodes					
0	214	0.60 (0.04)	10^{-4}	0.66 (0.03)	10^{-4}
1–2	65	0.46 (0.07)		0.48 (0.07)	
≥3	60	0.26 (0.06)		0.35 (0.06)	
Vascular invasion					
No	225	0.59 (0.03)	10^{-4}	0.63 (0.03)	10^{-3}
Yes	114	0.38 (0.05)		0.46 (0.05)	
Neural invasion					
No	222	0.62 (0.03)	10^{-4}	0.66 (0.03)	10^{-4}
Yes	117	0.32 (0.05)		0.46 (0.05)	

NS, not significant. *Data missing for 3 patients.

DISCUSSION

This study on 339 patients who underwent radical resection of rectal cancer confirms the independent prognostic value of histological parameters such as NI, lymph node involvement and tumour extension.

The NI was highly associated with a poor prognosis both in the univariate and multivariate analysis on overall and disease-free survival. This characteristic has been studied by many authors since 1943 [14], but has seldom been evaluated in a multivariate analysis [7, 15–17], and has never been included in a staging system. Our results are in keeping with the findings of these multivariate analyses.

In our study, both the number of involved lymph nodes and the location of involved lymph nodes influenced survival. These two factors were strongly correlated ($P < 10^{-3}$) (data not shown). However, when they were both considered in the multivariate analysis, the number of positive lymph nodes appeared to be

Table 4. Multivariate analysis of prognostic factors for overall survival

Prognostic factors	Relative risk*	95% confidence interval	P†
Age (years)			
≤60	1		$<10^{-3}$
>60	2.6	1.7–3.8	
Distance from anal verge			
>6 cm	1		$<10^{-3}$
≤6 cm	2.2	1.5–3.3	
Neural invasion			
No	1		$<10^{-2}$
Yes	1.6	1.1–2.3	
Number of positive nodes			
0	1		$<10^{-3}$
1 or 2	1.4	0.9–2.3	
≥3	2.8	1.8–4.4	

*Stratified on preoperative radiotherapy. †Likelihood ratio test.

Table 5. Multivariate analysis of prognostic factors for disease-free survival

Prognostic factors	Relative risk*	95% confidence interval	P†	Score
Age (years)				
≤60	1		$<10^{-4}$	0
>60	2.3	1.6–3.3		1
Distance from anal verge				
>6 cm	1		10^{-3}	0
≤6 cm	2.0	1.4–2.9		1.5
Number of positive nodes				
0, 1 or 2	1		$<10^{-4}$	0
≥3	2.5	1.7–3.7		1.5
Combination of T and neural invasion				
NRT-T0-T1-T2, any NI	1		$<10^{-4}$	0
T3-T6 and no NI	2.8	1.1–6.8		1.5
T3-T6 and NI	4.8	1.9–12.0		3

NRT, no residual tumour; NI, neural invasion. *Stratified on preoperative ratiotherapy. †Likelihood ratio test.

more predictive of disease-free survival. The number of positive lymph nodes has often been found to be prognostic [2, 4, 18–20]. It is also important to analyse involved nodal sites as a separate entity, as we did. The pedicular lymph nodes appear to be associated with a low survival rate [5, 19].

Unlike that observed in the univariate analysis, NI was not a prognostic factor in the multivariate analysis. This could be explained by the fact that a relationship exists between VI and the number of positive lymph nodes [21, 22].

This analysis allowed us to highlight the impact of the histological parameters of our classification on the prognosis.

Two other classifications exist and are comparable to that described herein: pTNM [23] and the Australian clinicopathological systems (ACPS) [24]. They are, however, less precise, particularly with respect to the location of involved lymph nodes and the presence of neural invasion. More recently, the prognostic value of other factors, such as DNA ploidy [25], the

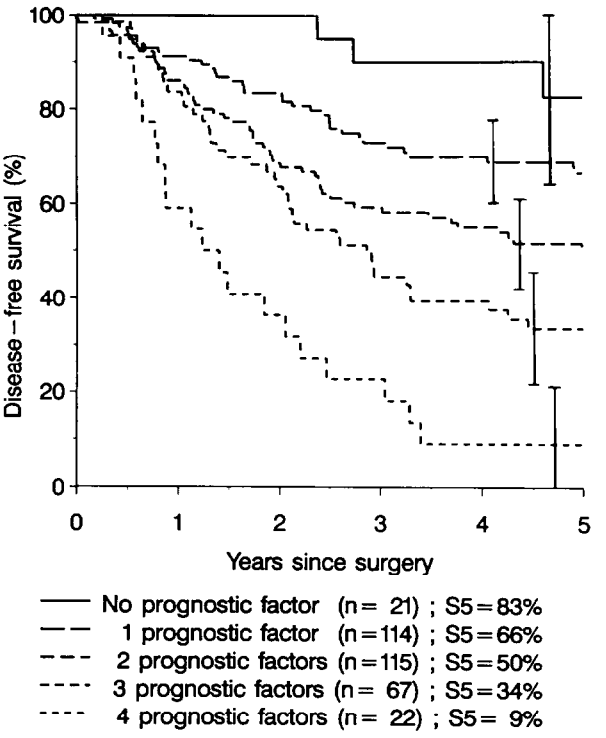

Figure 1. Five-year disease-free survival according to the number of prognostic factors. S5, 5-year disease-free survival rate.

proliferative cell rate and genetic alterations [26, 27], have been studied. However, these factors are difficult to evaluate during routine care in the hospital setting or are still undergoing assessment.

Among the clinical variables, a tumour within 6 cm of the anal verge was associated with a lower probability of survival. Other multivariate analyses, including a previous report from our institution [28], have shown the same results [7, 8]; while other smaller series concluded that this factor was not significant [3, 6]. This finding is probably related to the difficulty in obtaining free margins when tumours are situated close to the anal verge [7]. The anal canal is richly supplied by the dual system of lymphatic and blood vessels; several patterns of metastasis, including lymphatic spread to pelvic or inguinal nodal chains and venous dissemination via caval or portal systems, can occur and account for early distant metastasis [8].

Our scoring system, which associates clinical and pathological variables, was able to identify five prognostic groups of patients: a low-risk group (group one, 6% of the patients) with an 83% 5-year survival rate, three intermediate-risk groups and a high-risk group (group five, 6% of the patients) with a 9% 5-year survival rate. We compared the survival curves of these groups with those established according to the Astler–Coller classification (Figure 2), currently the classification most used for colorectal carcinoma. In our population, the patients with stage B1 and stage B2 disease have a similar disease-free survival rate, and the patients with stage C disease have a 5-year survival rate of about 40%. The proposed scoring system, is simple and allows a better distinction between five groups of patients and identifies a group with a particularly poor prognosis.

As more data are accumulated in favour of adjuvant radiotherapy in rectal carcinoma [29], prognostic studies will need to take into account patients receiving such treatment. To date,

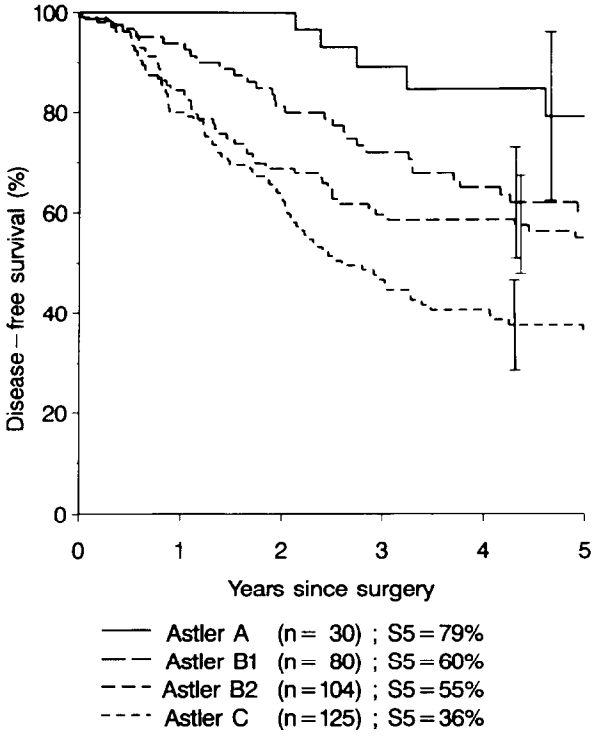

Figure 2. Five-year disease-free survival according to Astler–Coller classification. S5, 5-year disease-free survival rate.

only a few prognostic studies have been performed on patients with rectal carcinoma treated by radiotherapy [16, 22, 30].

CONCLUSION

NI is an independent prognostic factor which adds prognostic information to the well-established pathological factors. As this study confirms previous work, we believe that NI should be meticulously searched for by the pathologist and used as a stratification factor in future controlled trials. Once our scoring system has been validated on an independent population, it will be a very convenient tool for identifying patients that should receive adjuvant treatment and should be included in trials evaluating combination radio-chemotherapy.

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