Pergamon

European Journal of Cancer Vol. 31A, No. 6, pp. 888–894, 1995

0959–8049/95 $9.50 + 0.00

0959-8049(94)00520-6

Plasma Tetranectin and Colorectal Cancer

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The prognostic significance of plasma tetranectin (PL-TN) in colorectal cancer was retrospectively examined in 504 patients (80 Dukes' A, 174 Dukes' B, 98 Dukes' C and 152 Dukes' D). Follow-up time was 7–12 years. No significant prognostic variable was found for Dukes' A patients by Cox multivariate analysis. In stage B, PL-TN was the second strongest prognostic variable [relative hazard (RH) = 3.3 for patients with PL-TN ≤ 7.5 mg/l]. The other prognostic variables were perineural invasion (RH = 3.7), tumour distance ≤10 cm from the anal verge (RH = 3.0), postoperative radiotherapy (RH = 2.9) and a high carcinoembryonic antigen (CEA) score (RH = 1.8). In Dukes' C, only CEA score and gender were of prognostic significance. For Dukes' D, PL-TN was the only prognostic variable (RH = 1.7). Testing all patients in one multivariate analysis, Dukes' staging was the strongest and PL-TN the second strongest prognostic variable. The shortened survival for patients with low PL-TN levels is illustrated with lifetables.

Key words: tetranectin, colorectal cancer, tumour markers, survival
Eur J Cancer, Vol. 31A, No. 6, pp. 888–894, 1995

INTRODUCTION

TETRANECTIN (TN) is a plasminogen-kringle-4 binding protein [1], found in mean concentrations from 9.9 to 11.9 mg/l in the plasma or serum of healthy adults [1–3]. Low levels are found in the plasma or serum of patients with primary ovarian cancer [3], patients with residual ovarian tumour at second-look surgery (unpublished data, C. Høgdall) and patients with metastatic breast cancer [4]. Furthermore, patients with a very low concentration of TN in the blood [4, 5], and/or an intense extracellular immunohistochemical staining in tumours for TN [6], have a reduced life expectancy compared to patients with higher concentrations in the blood and no staining [6].

Reduced levels of plasma TN (PL-TN) are found in patients with metastases from colonic cancer, compared to patients with no metastases [7]. By immunohistochemistry, absence of extracellular stromal staining for TN is found in normal colon tissue compared to an intense staining in the extracellular stroma of malignant colon tumours [8] (personal communication, Lise Christensen, Dept. of Pathology, Rigshospitalet, Denmark). This, together with the observation of a strong and distinct signal in stromal cells of colon carcinomas by *in situ* hybridisation [9], suggest that TN also plays a role in the growth and spread of colonic cancer cells.

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Revised 30 Nov. 1994; accepted 8 Dec. 1994.

MATERIALS AND METHODS

The original classification of Dukes' was employed, with A carcinomas defined as carcinomas that have not spread through the bowel wall; group B, defined as those that have penetrated the bowel wall but have not invaded the adjacent lymphatics; and group C, as those that have metastasised to the regional lymph nodes regardless of the degree of bowel wall penetration [10]. Patients with distant metastases that have spread outside the regional lymph nodes were defined as stage D carcinomas.

From 1979 to 1985, a large prospective Danish randomised trial was performed to evaluate the effect of adjuvant postoperative radiotherapy in patients with Dukes' B and Dukes' C carcinoma of the rectum and rectosigmoid [11, 12]. Because the trial was prospective, blood samples from Dukes' carcinoma stage A and D were collected before surgery. From the trial, we randomly selected 504 patients representing all stages. Exclusion criteria were patients bedridden for more than 50% of the day 20–25 days after surgery, postoperative complications, previous cancer within 5 years, previous radiotherapy and complicating disease(s) before surgery.

All the characteristics for patients with Dukes' stage B and C carcinomas collected in the randomised trial have been thoroughly evaluated in previous studies in order to find the variables with an independent prognostic function for survival [12, 13]. These independent prognostic variables have been used for the statistics in the present study (Table 1).

TN ELISA procedure

TN was quantified using an avidin–biotin enzyme-linked immunosorbent assay (ELISA), as described elsewhere [3, 5, 14]. The intra-assay coefficient of variation (CV) was

Table 1. Patients' characteristics

	Dukes' A			Dukes' B			Dukes' C			Dukes' D		
	+	−	(*P* value)	+	−	(*P* value)	+	−	(*P* value)	+	−	(*P* value)
Number	18	62		36	138		60	38		140	12	
Males	12	34	(0.1)	23	77	(0.4)	34	14	(0.1)	86	6	(0.6)
Females	6	28		13	61		26	24		54	6	
Median age (years)	61.5	64.5		69.0	66.0		62.5	64.0		69.0	72.5	
Quartiles	58–73	57–72		62–74	58–71		57–70	59–68		62–75	54–79	
Median tumour size (cm)	—	—		5.0	5.0		6.0	5.0		—	—	
Venous invasion												
Yes	—	—		12	29	(0.2)	24	8	(0.08)	—	—	
No	—	—		24	109		36	30		—	—	
Perineural invasion												
Yes	—	—		11	16	(0.03)	29	13	(0.2)	—	—	
No	—	—		25	122		31	25		—	—	
Resection of neighbouring organs												
Yes	—	—		7	14	(0.5)	5	4	(0.9)	—	—	
No	—	—		29	124		55	34		—	—	
Distance from anal verge												
>10 cm	—	—		17	96	(0.01)	27	23	(0.2)	—	—	
≤10 cm	—	—		19	42		33	15		—	—	
Radiotherapy												
Yes	—	—		23	71	(0.2)	45	27	(0.8)	—	—	
No	—	—		13	67		15	11		—	—	
Median PL-TN (mg/l)	9.8	9.2	(0.1)	8.3	9.1	(0.03)	8.6	9.0	(0.2)	7.2	7.8	(0.1)
Quartiles	8.5–10.7	8.3–10.1		6.8–9.6	7.8–10.4		7.7–9.7	8.0–10.4		5.7–8.4	7.1–8.8	
Median CEA (ng/ml)	1.8	2.3	(0.5)	5.0	2.4	(<0.0001)	5.0	2.4	(0.01)	36.0	16.2	(0.5)
Quartiles	0.5–3.9	1.3–3.4		3.9–8.4	1.4–4.9		2.1–16.6	0.9–4.9		5.4–250	5.7–167	

PL-TN, plasma tetranectin; CEA, carcinoembryonic antigen. +, death from cancer; −, death with no evidence of cancer.

5.1% (n = 123), whereas the interassay CV was 8.8% (n = 25), calculated from a control sample of 10.9 mg/l.

Only pre-operative plasma samples (EDTA) collected in the week before operation were used for the analyses. All analyses for PL-TN were performed without knowledge of patient status.

CEA analysis

For CEA, the Hoffman-La Roche sandwich-enzyme immunoassay was used according to the manufacturer. The intra-assay CV was 9.4% (n = 46) and the interassay CV was 6.9% (n = 23), calculated from a control sample of 6.8 ng/ml.

Statistics

The cumulated survival rate was analysed by the Kaplan–Meier method and tested by the log-rank test. According to previous findings [12], the following variables were included in the multivariate Cox analysis for all Dukes' stages: actual age if ≥60 years and equal to 60 if age <60 years, sex, CEA score (0: 0–3 ng/ml; 1: 3.1–7.0 ng/ml; 2: >7.0 ng/ml). Due to the original study design [12] and definition of Dukes' staging [10], the variables radiotherapy, perineural invasion, venous invasion and resection of other organs could only be included for Dukes' stages B and C, when analyses stratified for stage were performed. Furthermore, the distance of tumour, ≤10 cm or >10 cm from the anal verge, was only recorded for Dukes' stage B and C.

The endpoint used was death from colorectal cancer. Patients still alive at the follow-up (January 1992) and patients dying from intercurrent disease with no evidence of cancer at autopsy were treated as censored observations. All other patients were considered dead of cancer. Life tables and multivariate analysis were based on the full observation time available.

Different set-ups of multivariate Cox analyses were performed. At first, trends were established by using the actual values of PL-TN in the Cox analyses to assure the negative correlation between PL-TN and survival. A separate analysis was performed for each of the Dukes' stages and for all Dukes' stages together (A–D). Hereafter, the same set-up of analyses were performed using PL-TN as a dichotomy variable, dividing the patients into two groups. The first group contained patients with a PL-TN value below or equal to the chosen cut-off level. The second group contained the remaining patients with PL-TN values above the cut-off level. To find the best cut-off level for PL-TN, in order to distinguish between high- and low-risk patients, several Cox analyses were performed in each set-up. These Cox analyses were performed with PL-TN intervals of approximately 0.2 mg/l, beginning at a PL-TN level of 10 mg/l and ending at a PL-TN level of 5.5 mg/l. In the final set-up, including all Dukes' stages (A–D), an analysis was only performed for each of the two best cut-off levels found by the former analyses.

The Spearman rank correlation test was used to test for correlations between variables. Differences between groups were analysed by the Mann–Whitney test and Fisher's exact test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

At the follow-up, 254 patients had died of colorectal cancer (median follow-up 12.5 months, quartiles 5.3–25.2) and 250 were treated as censored patients (median follow-up 96.5 months, quartiles 83.7–115). The distribution in relation to Dukes' stages is given in Table 1. Of the censored patients, 16 Dukes' A, 21 Dukes' B and 6 Dukes' C had died with no evidence of cancer and the remaining 207 censored patients were still alive.

Significant negative correlations were found between PL-TN and the following variables: Dukes' stages (R_s = −0.38, n = 504, $P < 10^{-4}$), maximal tumour diameter (R_s = −0.18, n = 272, P = 0.002) and CEA (R_s = −0.35, n = 504, $P < 10^{-4}$).

For Dukes' stage A, a non-significant, higher PL-TN was found for patients who died from cancer compared to censored patients (Table 1). For Dukes' stage B, the PL-TN was significantly lower for patients dead of cancer compared to censored patients (P = 0.03, Table 1). In Dukes' stages C and D, the median PL-TNs were non-significantly lower for patients who died of cancer compared to censored patients (Table 1). However, for Dukes' stage D, the censored group consisted only of 12 patients.

The survival function for PL-TN and CEA were confirmed by trend analysis, using the actual PL-TN and CEA values in the Cox analyses. By this testing, no significant prognostic factors were found for Dukes' stage A patients. In Dukes' B patients, significant shorter survivals were found for patients with decreasing values of PL-TN [relative hazard (RH) = 0.8, 95% confidence intervals (CI) 0.6–0.9, P = 0.01], while no independent prognostic function was found for CEA. No prognostic function for PL-TN was found for Dukes' stage C patients. For Dukes' D patients, decreasing values of PL-TN were significantly correlated to a shortened survival (RH = 0.8, 95% CI 0.7–0.9, $P < 0.001$), while no other variables were found to have any independent prognostic function. Testing all patients in a single Cox analysis, using stage as a prognostic factor, only decreasing values of PL-TN (RH = 0.87, 95% CI 0.9–0.8, $P < 0.001$) and increasing stage (RH = 3.0, 95% CI 2.6–3.5, $P < 0.001$) were significantly correlated with a shortened survival.

In the set-up of multivariate Cox analyses using PL-TN as a dicotome variable, no independent prognostic variables were found in Dukes' stage A for any of the cut-off limits analysed for PL-TN (Table 2). For patients with Dukes' stage B, a strong independent prognostic function was found for PL-TN in the interval 7.0–8.0 mg/l. At the cut-off limit of 7.5 mg/l, PL-TN was found to be the second strongest independent prognostic variable for survival, with a RH of 3.3 for patients with a PL-TN below the cut-off limit (Table 2). For Dukes' stage C, no independent prognostic significance was found for PL-TN at any cut-off limit tested, and only the variables sex and CEA score were found to have an independent prognostic significance at the cut-off limit of 7.5 for PL-TN (Table 2). In the Cox analyses for Dukes' stage D, PL-TN was found to be the only independent prognostic variable, with an independent prognostic significance in the interval 8.2 to 5.0 mg/l for PL-TN, and a maximal RH of 3.0 for patients with a PL-TN below or equal to 6.3 mg/l. For Dukes' stage D patients with a PL-TN below or equal to 7.5 mg/l, the RH was 1.7 (Table 2).

In the last analysis including all Dukes' stages A–D, the strongest independent prognostic significance for PL-TN was found at a cut-off limit of 6.3 mg/l (RH = 2.6, 95% CI 1.9–3.6, $P < 10^{-4}$). At this cut-off limit, stage was the strongest independent prognostic variable (RH = 3.2, 95% CI 2.7–3.7, $P < 10^{-4}$), and CEA score the third strongest independent variable (RH = 1.4, 95% CI 1.1–1.7, $P < 10^{-4}$). Using the cut-off limit 7.5 mg/l, Dukes' staging was the strongest independent prognostic variable (RH = 3.1, 95% CI 2.6–3.6, $P < 10^{-4}$), PL-TN the second strongest (RH = 1.5, 95% CI 1.2–2.9, $P < 10^{-4}$) and CEA score the third and last independent prognostic variable (RH = 1.4, 95% CI 1.1–1.7, $P < 10^{-4}$).

Table 2. Independent prognostic variables from the Cox multivariate analyses

Variable	Dukes' A RH	Dukes' B RH	Dukes' B 95% CI	Dukes' B *P* value	Dukes' C RH	Dukes' C 95% CI	Dukes' C *P* value	Dukes' D RH	Dukes' D 95% CI	Dukes' D *P* value
PL-TN ≤ 7.5 mg/l	NIP	3.3	1.6–7.1	0.009	NIP	—	—	1.7	1.2–2.3	0.003
CEA score	NIP	1.8	1.2–2.8	0.007	1.6	1.2–2.0	0.001	NIP	—	—
Radiotherapy	NT	2.9	1.4–6.3	0.01	NIP	—	—	NT		
Sex (male)	NIP	NIP	—	—	1.8	1.1–3.0	0.02	NIP	—	—
Age (years)	NIP	NIP	—	—	NIP	—	—	NIP	—	—
Tumour size	NT	NIP	—	—	NIP	—	—	NT		
Perineural invasion	NT	3.7	1.7–7.7	0.004	NIP	—	—	NT		
Venous invasion	NT	NIP	—	—	NIP	—	—	NT		
Resection other organs	NT	NIP	—	—	NIP	—	—	NT		
Tumour localisation	NT	3.0	1.5–6.0	0.01	NIP	—	—	NT		

PL–TN, plasma tetranectin; RH, relative hazard; NIP, no independent prognostic function; NT, variable not tested in the Cox analysis for the Dukes' stage.

The distribution of patients with PL-TN ≤ 7.5 mg/l or PL-TN > 7.5 mg/l in relation to the other variables is illustrated in Table 3.

For Dukes' stage A, the life tables for patients with a high and a low PL-TN concentration, were very similar and intersected with each other (data not shown).

The differences in survival between patients with a PL-TN above the cut-off limit 7.5 mg/l and patients with a PL-TN below or equal 7.5 mg/l are illustrated by life tables for Dukes' stages B–D (Figure 1). In Dukes' stage B, a significant difference in survival was found between patients with PL-TN above 7.5 mg/l (5-year survival 83%) and patients with PL-TN below or equal to 7.5 mg/l (5-year survival 69%) (log-rank test $P = 0.02$). A non-significantly, better survival was found for Dukes' stage C patients with a PL-TN concentration above 7.5 mg/l (5-year survival 38%) compared to patients with a PL-TN concentration below or equal to 7.5 mg/l (5-year survival 22%) (log-rank test $P = 0.2$). For Dukes' stage D patients, a significant increase in survival was found for patients with PL-TN above 7.5 mg/l (5-year survival 12%) compared to patients with PL-TN below or equal to 7.5 mg/l (5-year survival 5%) (log-rank test $P = 0.003$).

DISCUSSION

The present study is the first comprehensive investigation of PL-TN and colorectal cancer. The finding of low PL-TN concentrations compared to healthy controls [2, 3], and a negative correlation between PL-TN and Dukes' stages, support the observation of low PL-TN concentrations in patients with metastases from colorectal cancer [7], and is similar to the negative correlation between PL-TN and FIGO staging found in patients with ovarian cancer [3]. Furthermore, the present finding of an independent prognostic significance of PL-TN is in accordance with the finding of a prognostic significance of TN in patients with ovarian cancer [5] and metastatic breast cancer [4]. However, the prognostic significance of TN in these two forms of cancer were considerably stronger than in the present study.

Dukes' staging is a well-established and very strong prognostic factor for colorectal cancer [10]. However, in many studies, a considerable variation in prognosis has been demonstrated within each stage [15, 16]. In fact, it has been shown that subgroups of Dukes' stage C patients have a better survival than subgroups of Dukes' stage B patients [12]. Therefore, several studies have been performed to find new and stronger prognostic factors for the stratification of patients.

The most frequently used biochemical marker in colorectal cancer is CEA, which correlates pre-operatively with Dukes' staging and is a strong independent prognostic marker for survival in Dukes' stage B and C [12]. Experimental studies have demonstrated that CEA reflects the metastatic potential of the cancer cells [17]. The present finding of a correlation between CEA and PL-TN may indicate that PL-TN also reflects the metastatic potential.

No prognostic factors were found for Dukes' A patients. The reason that we found no prognostic significances for PL-TN and CEA in this localised stage of cancer may be that the tumour mass at this stage was too small to result in any major change in marker status. For PL-TN, this observation is different from the finding for ovarian cancer, where prognostic significance was also found for localised cancer [5]. One explanation may be differences in tumour behaviour between the two forms of cancer. Secondly, the cell number, tumour size and metastatic behaviour of micrometastases [18] may be different between localised ovarian cancer and localised colorectal cancer, resulting in differences in PL-TN and patient survival between the two forms of localised cancer.

In Dukes' stage B, PL-TN was found to be the second strongest prognostic factor at a cut-off limit of 7.5 mg/l (Table 1), with a better survival for patients with high PL-TN values (Figure 1). At this stage, PL-TN may be a valuable prognostic factor in conjunction with the other prognostic factors. In accordance with an earlier report [12], the other prognostic factors associated with a poor prognosis were a high CEA score, postoperative radiotherapy, perineural invasion, venous invasion and a low tumour localisation. The finding of a shortened survival for the patients with postoperative radiotherapy is also in accordance with the earlier reported study, although in that study the finding was reported to be insignificant [12].

Only CEA score and gender were found to have prognostic value in Dukes' stage C. The finding of prognostic significance for CEA and gender is in accordance with an earlier report [12]. Differences in number of patients included a longer follow-up in the present study and inclusion of the new variable PL-TN may explain the lack of prognostic significance for the other variables previously reported to be prognostic factors [12].

In Dukes' stage D, PL-TN was found to be the only prognostic

Table 3. Patients with plasma tetranectin ≤ or >7.5 mg/l and the distribution with regard to the other variables

	Plasma tetranectin ≤7.5 mg/l			Plasma tetranectin >7.5 mg/l		
	+	−	(*P* value)	+	−	(*P* value)
Dukes' A–D						
Number of cases	108	47		146	203	
Males	71	32	(0.9)	84	99	(0.1)
Females	37	15		62	104	
Median age (years)	68	62	(0.01)	67	66	(0.3)
Quartiles	61–75	60–72		60–73	60–71	
Median CEA	36.0	2.5	(<0.001)	5.2	2.4	(<0.001)
Quartiles	5.5–235	1.5–7.8		2.2–22.3	1.2–4.7	
Dukes' B and C only						
Number of cases	27	37		69	139	
Median tumour size (cm)	6.0	6.0	(0.6)	5.0	5.0	(0.5)
Quartiles	4–7	5–8		4–7	4–6	
Venous invasion						
Yes	8	8	(0.7)	28	29	(0.005)
No	19	29		41	110	
Perineural invasion						
Yes	9	4	(0.05)	31	25	(0.0001)
No	18	33		38	114	
Resection of neighbour organs						
Yes	4	5	(0.99)	8	13	(0.8)
No	23	32		61	126	
Distance from anal verge						
>10 cm	16	28	(0.3)	28	91	(0.001)
≤ 10 cm	11	9		41	48	
Radiotherapy						
Yes	18	16	(0.1)	50	82	(0.08)
No	9	21		19	57	

CEA, carcinoembryonic antigen. +, death from cancer; −, death with no evidence of cancer.

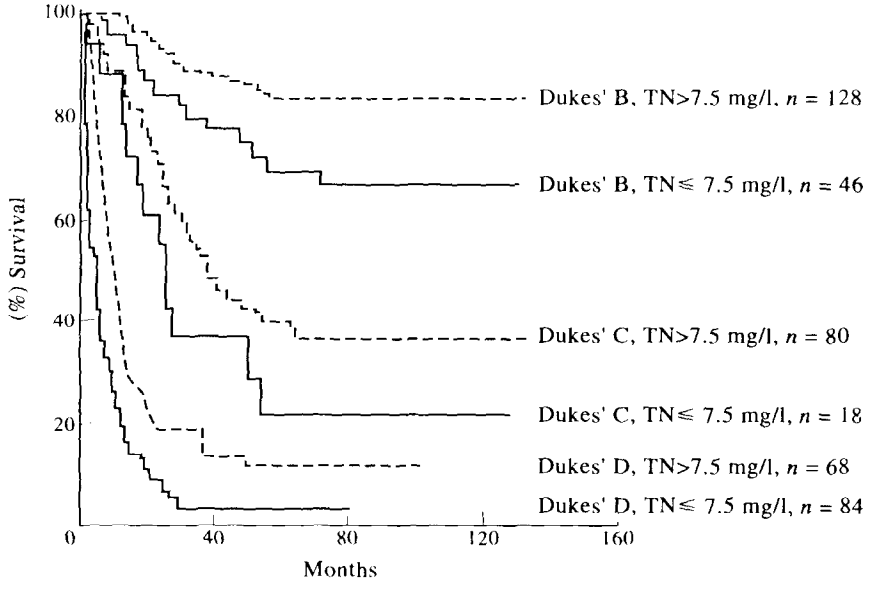

Figure 1. Lifetables of all 424 patients with colorectal cancer in relation to Dukes' stages B–D and plasma tetranectin (TN). The cut-off limit used for TN was 7.5 mg/l.

variable. This finding corresponds to the finding of a powerful prognostic significance of serum TN in patients with advanced ovarian cancer [5] and in patients with metastatic breast cancer [4]. PL-TN seems to be a very strong prognostic factor for a shortened survival in patients with advanced cancers. This is important as few surgical parameters can assist in assessment of prognosis in these patients, where radical surgery is impossible.

By analysing all patients in one multivariate Cox analysis, as in the last set-up, Dukes' staging was consistently found to be the strongest prognostic factor and PL-TN to be the second strongest prognostic factor. A pre-operative low PL-TN may therefore indicate that a careful investigation for possible resectable metastasis should be carried out, including intra-operative ultrasound of the liver [19], and that extended surgery may be required.

To study the prognostic function of PL-TN in the present study group, we performed several Cox analyses and compared the test statistics at different cut-off limits. By this procedure, 7.5 mg/l, which is close to the lower 95% CI (7.6–7.7 mg/l) found earlier for healthy controls [3], (unpublished data, C. Høgdall), was found to be the optimal cut-off limit for distinguishing between different prognostic groups. The optimal cut-off limit and prognostic value found by multiple Cox analyses may vary from one comparable study to another, based on the role of sampling variation [20]. Therefore, the cut-off limits and prognostic findings should be confirmed in other studies. At present, we are preparing a large colorectal cancer study in which these issues will be considered. However, trends established by using actual PL-TN values in the Cox proportional hazards regression analyses assured the prognostic negative correlation between PL-TN and survival.

The precise function of TN in the growth and spread of cancer is still not known, nor is the exact source of the TN in the tumour tissues and blood. From findings using *in situ* hybridisation of normal colon tissues and colon carcinomas [9], the TN found extracellularly in tumours by immunohistochemistry [6, 21], probably partly originates from the stromal cells and not the tumour cells.

In vitro TN has been found to enhance the tissue type plasminogen activator (t-PA) activation of plasminogen to plasmin in the presence of poly-D-lysine [1]. From both model tumour systems and clinical studies, it has been shown that proteases participate in cancer invasion and metastases [22–26]. Most likely, the function of TN is connected with the proteolytic action of the tumour cells because of TN's participation in the *in vitro* activation of plasminogen [1]. One explanation for the lowest TN concentrations found in the serum or plasma from cancer patients with the poorest prognosis may be that more TN is absorbed from the blood by the proteolytically most active and malignant tumours. This hypothesis is supported by the immunohistochemical findings of higher extracellular TN concentrations in more malignant tumours [21] in combination with lower plasma TN values [6].

From the observation that TN binds strongly to sulphated polysaccharides [27], another complementary explanation for the low PL-TN concentrations may be that TN participates in the clearance of sulphated amino sugar-containing polysaccharides (glycosaminoglycans, GAGs), originating from the degradation of the extracellular matrix by the tumours. Thus, PL-TN may bind to the GAGs which are subsequently cleared by the kidneys [28] or taken up and metabolised by the liver endothelial cells [29].

In conclusion, we have demonstrated that PL-TN levels are reduced in patients with colorectal cancer and negatively correlated to Dukes' stages. Furthermore, we found an independent prognostic significance of PL-TN, with a poor prognosis for patients with low PL-TN concentrations. Our findings should encourage future studies of TN in the blood and tissues from patients with colorectal cancer.

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Acknowledgements——This work was supported by the Michaelsen Foundation, the Harboe Foundation, the Danish King Christian, the X Foundation and the Danish Cancer Society.

Pergamon

European Journal of Cancer Vol. 31A, No. 6, pp. 894–898, 1995

0959–8049/95 $9.50 + 0.00

0959-8049(95)00077-1

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

C. Bognel, C. Rekacewicz, H. Mankarios, J.P. Pignon, D. Elias, P. Duvillard, M. Prade, M. Ducreux, J. Kac, P. Rougier, F. Eschwège and P. Lasser

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
Eur J Cancer, Vol. 31A, No. 6, pp. 894–898, 1995

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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Revised 28 Nov. 1994; accepted 7 Feb. 1995.

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