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ORIGINAL ARTICLE

Procalcitonin in patients with colorectal cancer

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Summary

Purpose: *Bacterial translocation (BT) is common in colon cancer patients and may be associated with increased occurrence of septic complications as well as with adverse oncologic outcomes. The aim of the present study was to correlate the BT detectable through peritoneal lavage culture or identified by abnormal inflammatory parameters with the clinicopathologic parameters and the short-term prognosis in a prospective series of patients.*

Methods: *Fifty-four consecutive patients with histologically proven colorectal cancer were included in this prospective study. White blood cells (WBC), erythrocyte sedimentation rate (ESR) and serum levels of procalcitonin (PCT) and C-reactive protein (CRP) were determined and cultures from peritoneal lavage were collected immediately after laparotomy.*

Results: *Positive PCT was detected in 31 (55.3%) patients while positive cultures were obtained in 6 (11%) patients. Significant positive correlation of PCT with inflammation markers was noticed. Patients with distant metastases had higher serum PCT levels than patients without distant metastases (p=0.01). Borderline statistical significance was found between PCT and tumor grade (p=0.09). PCT was not correlated with the cultures of the lavage or the outcome.*

Conclusion: *PCT is an adequate inflammatory marker, able to preoperatively discriminate patients with bacterial systemic inflammatory reaction due to BT. However, the clinical consequence of BT may be minimal as is shown by the lack of association of PCT or positive peritoneal lavage cultures with time to discharge, complications and short-term survival.*

Key words: *bacterial translocation, colorectal cancer, procalcitonin*

Introduction

BT is defined as the phenomenon by which live organisms or their products escape from the intestinal tract to extra-luminal sites [1]. The presence of BT in colorectal cancer patients is well established and is attributed to the destruction of the normal gut barrier, but its significance is a matter of debate. There are studies that failed to find a correlation between BT and the development of systemic inflammatory response syndrome (SIRS) or other infectious complications, characterizing it as a phenomenon lacking clinical significance in colorectal cancer patients [2]. On the other hand, there are reports claiming that the impaired immune function of colorectal cancer patients results in BT, dissemination of cancer cells and establishment of distant dormant micrometastases, which affect negatively the long-term survival [3].

PCT is a 116 amino acid protein most commonly deriving from neuroendocrine cells. Despite its unclear primary action, PCT is considered to be one of the earliest and most specific markers of bacterial infection. Moreover, it is also a useful marker in monitoring the host response to an infection and the efficiency of its treatment [4,5]. As a marker of infection, PCT seems to have a significant role in cases of colorectal surgery. The postoperative estimation of PCT in colorectal cancer patients could reduce the morbidity and mortality associated with infectious complications by two ways. Firstly, PCT is more sensitive in detecting patients in SIRS after colorectal surgery than other markers (CRP, WBC, IL-6) [6]. Secondly, PCT has a high negative predictive value for systemic

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infectious complications after colorectal surgery and could guide preemptive antibiotic treatment in cases with elevated PCT levels [7].

Given the fact that PCT does not rise following inflammation of non infectious origin [8], there are studies which support that PCT might be more suitable than other markers (e.g. CRP) for the perioperative monitoring of infectious complications in gastrointestinal cancer patients [9].

The aim of the present study was to correlate the BT detectable through peritoneal lavage culture or identified by abnormal inflammatory markers with the clinicopathologic parameters and the time to discharge, complications and short-term survival in a prospective series of patients.

Methods

Fifty-four consecutive patients with histologically proven colorectal cancer were included in this prospective study. All patients were operated on between January 2008 and May 2009 by the same operative team at a University Hospital setting. The study protocol was approved by the Ethics Committee of our institution. All patients received written information about the study and gave their approval to participate.

After informed consent had been received the patient demographics and disease characteristics were documented. Patient data are summarized in Table 1. Exclusion criteria were: 1) Active bacterial inflammation during admission; 2) Prior history of cancer with perioperative chemotherapy or radiotherapy; and 3) Preoperative antibiotic therapy.

After the medical history was documented and the physical examination was completed, 10 ml of blood were drawn and PCT, WBC, ECR and CRP levels were determined. PCT serum levels were determined by immunoluminometric assay, which measures PCT within 18 min (ECLIA, BRAHMS PCT, Roche Diagnostics, GmbH, Mannheim, Germany). The calculation range of the assay was 0.02 – 100 ng/ml. The normal value was set at 0.046 ng/ml and the clinical cut–off values were <0.5 ng/ml (low possibility of septic shock) and >2 ng/ml (high possibility of septic shock).

In the operating room, immediately before the incision, all patients received cefuroxim and metronidazole as antibiotic prophylaxis. After laparotomy and before any manipulation, a lavage of the peritoneal cavity with 100 cc N/S 0.9% was performed. The lavage fluid was suctioned and sent for culture in order to identify the presence of bacteria in the abdominal cavity.

Postoperatively, patients were followed–up for 60 days, during which all postoperative complications were recorded.

Statistics

Statistical analysis was carried out using the SPSS software release 13.00 (SPSS Inc. Chicago. IL). Normal distribution assessment of different factors was done using the Kolmogorov–Smirnov test. Normally distributed data (age, maximum tumor diameter, WBC count, ESR) were expressed as mean ± SD, while abnormally distributed data (CRP, PCT, duration of hospital stay) were expressed as median and interquartile ranges with 25% and 75% percentiles. The correlation of PCT with other values of the study was done using Spearman's correlation test, Kruskal–Wallis test and Mann – Whitney test. Further data evaluation was done in statistically significant correlations with multivariate linear analysis. A p value <0.05 was considered as statistically significant.

Table 1. Patient demographic and clinical characteristics

Characteristics	*N (%)*
Gender	
Female	22 (40.7)
Male	32 (59.3)
Age, years±SD	71±11.02
TNM stage	
I	2 (3.7)
II	15 (27.8)
IIIa	2 (3.7)
IIIb	15 (27.8)
IIIc	7 (13.0)
IV	13 (24.1)
Complications	19 (35.2)
Hospitalization (days; median/interquartile range)	11(9-14)
Outcome	
Discharge	52 (96.3)
Death	2 (3.7)

SD: standard deviation

Results

The tumor location was in the colon in 67% of the patients and in the rectum in the remaining 33%. The distribution of the patients according to the TNM staging system is shown in Table 1. The pathologic characteristics of the tumors are presented in Table 2.

Table 3 demonstrates the preoperative serum levels of inflammation markers and PCT.

The linear regression analysis between PCT and the others quantitative variables of the study showed a statistically significant positive relation between PCT and inflammation markers (WBC: p= 0.01, CRP: p=0,03, ESR p=0.02) (Table 4). On the contrary, there was no correlation of PCT regarding age, tumor size and the duration of hospi-

Table 2. Macroscopic and microscopic characteristics of the tumors

Characteristics	*N (%)*
Location	
Colon	36 (66.7)
Rectum	18 (33.3)
Length (cm), mean±SD	5±2.04
Ulceration	39 (75.0)
Grade	
II	48 (88.9)
III	6 (11.1)
Lymphocytic infiltration	46 (86.8)
Fibroblastic reaction	50 (94.3)
Lymph node metastasis	
Yes	37 (68.5)
No	17 (31.5)
Distant metastasis	
Yes	13 (24.1)
No	41 (75.9)

SD: standard deviation

tal stay. In multivariate regression analysis, PCT still had a statistically significant correlation with WBC count (p=0.01) and ESR (p=0.01), but not with CRP (p=0.12) (Table 5).

PCT and tumor characteristics demonstrated that patients with distant metastases had higher PCT serum levels than those who had not (p=0.01; Table 6, Figure 1). High grade tumors had higher serum PCT levels (0.073 ng/ml) than low grade tumors (0.045 ng/ml; p=0.09; Figure 2). No correlation of PCT with other tumor characteristics

Table 3. Inflammation markers and CEA values

Markers	*Values*
WBC cells/mm^3*	8205±2400
CRP mg/L§	0.90 (0.20,2.700)
ESR mm/h*	43±28.8
PCT µg/L§	0.046 (0.027,0.075)
CEA µg/L§	3.25 (1.40,19.10)

WBC: white blood cells, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, PCT: procalcitonin, CEA: carcinoembryonic antigen
*mean±SD, §median/interquartile range

(location, ulceration, fibroblastic reaction, nodal involvement) was detected (Table 6).

Multivariate analysis showed that tumor grade had no significant correlation between PCT and distant metastases. Moreover, there was no significant correlation of PCT with gender, complications and outcome (Table 7).

Finally, no statistically significant correlation was found between PCT and the results of the cultures of the peritoneal lavage fluid (p=0.52; Table 8).

Discussion

BT is considered as a major contributing factor for the development of postoperative septic complications [10]. Although the lymphatics are probably the most important route of dissemination of bacteria from the gut lumen, some bacteria may also enter the vascular network, or translocate through the muscularis propria into the peri-

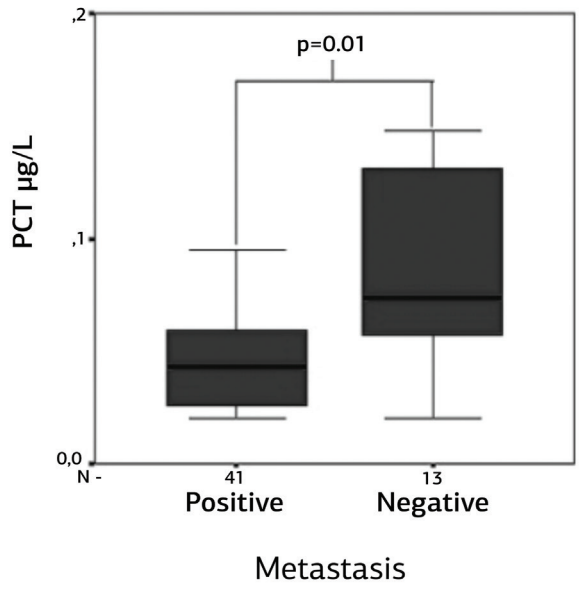

Figure 1. Boxplot graph showing statistically significant difference in PCT values in patients with distant metastasis.

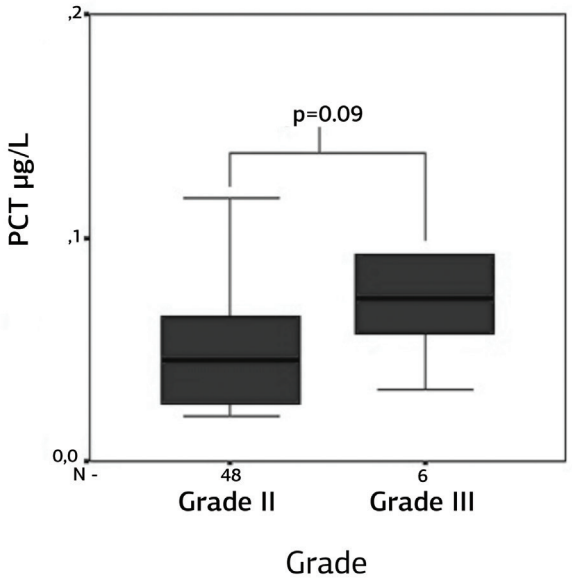

Figure 2. Boxplot graph showing that PCT values were higher in patients with high-grade tumors.

Table 4. Linear regression analysis of PCT with quantitative variables

Variables	*PCT μg/L*	
	r	*p-value*
Age (years)	-0.03	0.85
Size (cm)	0.13	0.38
WBC cells/mm^3	0.35	0.01
CRP mg/L	0.30	0.03
ESR mm/h	0.31	0.02
CEA μg/L	0.30	0.03
Hospitalization (days)	- 0.05	0.73

For abbreviations see footnote of Table 3

Table 5. Multivariate analysis of PCT with TNM, WBC, CRP, ESR, CEA, grade and metastasis

Variables	*B*	*SE*	*p-value*
TNM	0.009	0.008	0.28
WBC/mm^3	0.0000202	0.000	0.01
TNM	0.014	0.008	0.09
CRP (mg/L)	0.004	0.002	0.12
TNM	0.014	0.008	0.09
ESR (mm/h)	0.001	0.001	0.01
TNM	0.015	0.009	0.09
CEA (μg/L)	0.000095	0.000	0.53
Distant metastasis	0.114	0.040	0.01
Grade	-0.051	0.055	0.35

For abbreviations see footnote of Table 3

toneal cavity [11-13]. In patients with colonic cancer, disruption of the intestinal barrier is explained through increased gut permeability caused by the disorganization of the bowel architecture by the malignant tissue [14]. Other parameters that may influence the amount of bacteria that translocate are the altered gut flora and suppressed immune mechanisms of the submucosa [15,16].

In our study increased values of PCT were detected in 31 (55.3%) patients while positive cultures were obtained in 6 (11%) patients. Several studies have reported that BT rates to regional draining nodes ranged from 17 to 70% [17-21], whereas in a study positive cultures of ileal serosa and mesenteric nodes in 448 patients were 15.4% [22]. Our data, along with other studies, show that BT is a fairly common event and causes systemic inflammatory reactions. Relevant studies showed that BT is common in septic patients, patients with superior mesenteric artery occlusion, in inflammatory bowel disease, in patients who had undergone chemotherapy for advanced colon cancer, in obstructive jaundice, in patients with gastrointestinal malignancy as well as in patients receiving total parenteral nutrition [23,24]. Another study showed that the presence of distal intestinal obstruction at laparotomy was the strongest predictor of BT [22].

A number of studies showed that BT is associated with a significant increase in the development of postoperative sepsis in patients undergoing abdominal surgery [10,23]. Several inflammatory markers have been studied for the diagnosis of postoperative infection. Among them, CRP is frequently used and is a good marker of infection but it rarely distinguishes between bacterial and viral infection. PCT is a prohormone of calcitonin secreted from the C-cells of the thyroid, and has been proposed as a candidate marker for diagnosis of active bacterial infections. Serum PCT concentration in healthy individuals is low, but raises during septic conditions, especially when related to bacterial infections [25,26]. A cut-off value of serum PCT≥0.5 ng/mL to document bacteremia was adopted in this study as proposed previously [27,28]. Our results showed statistically significant correlation between PCT and inflammation markers (WBC: p= 0.01, CRP: p=0.03, ESR: p=0.02). These findings suggest that PCT is a useful marker to detect bacteremia in colon cancer patients and it may be of better value than CRP as implied in the multivariate analysis. Furthermore, PCT was statistically correlated with CEA but this finding was not sustained in the multivariate analysis similarly to age, tumor characteristics or T stage.

Our study showed that PCT was significantly higher in patients with metastasis and marginally significant with tumor grade. A study examining PCT levels in solid tumors suggested that higher values of serum inflammatory markers may imply a higher risk for hepatic metastatic potential [29]. Moreover, these findings imply that BT more probably occurs when the protective function of the bowel mucosa is more disorganized and this occurs in advanced tumors or in tumors with lower differentiation as. Schoeffel et al. similarly concluded based on their results [14]. These data are also in concordance with the study of Chin et al. who concluded that the defense function of the bowel wall is itself a prognostic indicator in colorectal cancer patients.

The results of the cultures of the peritoneal lavage was not correlated with the patient demo-

Table 6. Association of tumor characteristics with PCT

Characteristics	*Serum PCT values (mg/L) [Median/interquartile range]*	*p-value*
Location		0.30
Colon	0.046 [0.027,0.091]	
Rectum	0.046 [0.027,0.058]	
Ulceration		0.36
No	0.057 [0.028,0.083]	
Yes	0.045 [0.026,0.063]	
Lymphocytic infiltration		0.92
Yes	0.046 [0.027,0.075]	
No	0.057 [0.026,0.086]	
Fibroblastic reaction		0.12
Yes	0.045 [0.026,0.068]	
No	0.086 [0.059,0.093]	
Grade		0.09
II	0.045 [0.026,0.063]	
III	0.073 [0.050,0.106]	
Lymph node metastasis		0.47
Yes	0.057 [0.026,0.089]	
No	0.045 [0.028,0.056]	
Distant metastasis		0.01
Yes	0.074 [0.048,0.139]	
No	0.043 [0.026,0.060]	

Table 7. Associations of PCT with gender, complications and outcome

	PCT μg/L [Median/interquartile range]	*p-value*
Gender		0.75
Female	0.044 [0.029,0.085]	
Male	0.051 [0.026,0.072]	
Complications		0.98
Yes	0.045 [0.032,0.067]	
No	0.046 [0.026,0.080]	
Outcome		0.74
Discharge	0.046 [0.028,0.074]	
Death	0.056 [0.020,0.093]	

graphics, characteristics of tumor, clinical course and the levels of WBC, ESR, CRP, PCT and CEA, showing that the peritoneal route of the BT is not as important as the lymphatic route. These results are in agreement with the study of Schoeffel et al. [14] who reported no association of the systemic response with the bacteriological findings in cultures from regional nodes. Furthermore, bacterial contamination of the samples by the skin flora cannot be excluded even if we collected samples immediately after laparotomy and before any bowel manipulation.

Although previous studies have shown that BT was associated with increased incidence of septic complications [10,23], our data failed to show any correlation of abnormal PCT or positive cultures with increase of postoperative complications, increase hospital stay or outcome.

Whether BT is associated with the oncologic outcome in terms of recurrence or survival of colorectal cancer patients is to be elucidated when long-term follow up of our cohort of patients will be completed.

In conclusion, this study showed that PCT is an adequate inflammatory marker, able to preoperatively discriminate patients with bacterial systemic inflammatory reaction due to BT. However, the clinical consequence of BT may be minimal as shown by the lack of association of PCT or positive peritoneal lavage cultures with short-term outcome.

Table 8. Association of the cultures of the peritoneal lavage with inflammation markers, PCT and CEA

	Peritoneal lavage cultures		
	Negative	*Positive*	*p-value*
WBC mm^3*	8241±2483	7916±1728	0.75
CRP mg/L§	0.9 [0.2,1.9]	2.2 [0.4,10.6]	0.22
ESR mm/h*	42±29.86	45±20.23	0.85
PCT μg/L§	0.045 [0.026,0.076]	0.058 [0.047,0.078]	0.52
CEA μg/L§	2.9 [1.3,17.5]	7.7 [3.5,157.1]	0.12

*mean±SD, §median/interquartile range

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