



Contents lists available at ScienceDirect

## The American Journal of Surgery

journal homepage: [www.americanjournalofsurgery.com](http://www.americanjournalofsurgery.com)

## Postoperative serum Vascular Endothelial Growth Factor is an independent prognostic factor of disease free survival and overall survival in patients with non metastatic colon cancer

M. Pascual<sup>a, b, \*</sup>, S. Alonso<sup>a, b</sup>, S. Salvans<sup>a, b</sup>, X. Mayol<sup>b</sup>, S. Mojal<sup>c</sup>, M.J. Gil<sup>a</sup>, L. Grande<sup>a, b</sup>, M. Pera<sup>a, b</sup>

<sup>a</sup> Section of Colon and Rectal Surgery, Department of Surgery, Hospital del Mar, Universitat Autònoma de Barcelona, Spain

<sup>b</sup> Colorectal Cancer Research Group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

<sup>c</sup> Consulting Service on Methodology for Biomedical Research, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

## ARTICLE INFO

## Article history:

Received 22 January 2017

Received in revised form

3 June 2017

Accepted 13 June 2017

Presented as an oral poster at the 7th Annual Meeting of the European Society of Coloproctology, 25–27 September 2012, Vienna, Austria.

## Keywords:

Vascular Endothelial Growth Factor

Colon cancer

Prognostic factor

Surgery

## ABSTRACT

**Background:** Angiogenesis is essential for tumor growth and formation of metastasis. VEGF is the most potent angiogenic cytokine. The aim was to investigate the predictive value of postoperative VEGF serum concentration in patients undergoing surgery for colon cancer.

**Methods:** Consecutive patients with colon cancer undergoing surgery with curative intent were included. VEGF was measured in serum at 48 h and postoperative day 4. Cox proportional hazards model was used to estimate its contribution with prognosis.

**Results:** A total of 94 patients were included. On multivariate analysis VEGF on postoperative day 4 (HR: 1.05;  $p = 0.011$ ) was independent prognostic factor of decreased DFS and OS. Five-year DFS (57.7% vs. 85%;  $p = 0.001$ ) and OS (93% vs. 72%;  $p = 0.005$ ) were significantly lower in patients with postoperative serum VEGF greater than 370 pg/dl.

**Conclusion:** Postoperative VEGF serum concentration was an independent predictor of recurrence. These results must be verified in a prospective independent testing cohort.

© 2017 Published by Elsevier Inc.

### 1. Introduction

The most important prognostic factor in patients with colorectal cancer (CRC) operated on for cure is lymph node involvement,<sup>1</sup> and postoperative chemotherapy is recommended for these patients. However, recurrence occurs in up to 20% of patients with stage II, in which chemotherapy is not routinely given,<sup>2,3</sup> and up to 40% of patients with stage III, despite receiving adjuvant treatment.<sup>4,5</sup> Other tumor-related prognostic factors such as the presence of lymphovascular or perineural invasion, and the degree of differentiation have not improved our ability to predict individual clinical outcome. Therefore, other biological markers are needed in order to identify patients with a higher risk of recurrence that would benefit from adjuvant chemotherapy or targeted therapies.

Angiogenesis is an essential process for tumor growth and

formation of metastases and vascular endothelial growth factor (VEGF) is the most potent angiogenic cytokine.<sup>6</sup> VEGF not only stimulates endothelial cell proliferation but also vascular permeability leading to alterations in the extracellular matrix that favour angiogenesis.<sup>7</sup> Several studies have shown that tumor angiogenesis and VEGF expression assessed by immunohistochemistry are independent prognostic factors in different types of tumors such as prostatic carcinoma,<sup>8</sup> bladder cancer,<sup>9</sup> non-small cell lung,<sup>10</sup> cancer and CRC.<sup>11–14</sup> Furthermore, raised preoperative VEGF serum levels have been shown to be associated with decreased disease-free<sup>15</sup> and overall survival<sup>16</sup> in patients with CRC. However, tumor angiogenesis and preoperative VEGF serum levels are not used in the clinical practice because they have not been able to improve the prognostic value of tumor stage.

The study of factors that may impinge on the oncological outcome during the postoperative period can provide better biological markers in order to practice a more precise treatment. In this regard, there is little information about the influence of a postoperative angiogenic response on the oncological outcome.<sup>17</sup>

\* Corresponding author. Section of Colon and Rectal Surgery, Department of Surgery, Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain.

E-mail address: [mpascual@hospitaldelmar.cat](mailto:mpascual@hospitaldelmar.cat) (M. Pascual).

An early increase in serum VEGF level occurs after several operative procedures and is proportional to surgical trauma.<sup>18,19</sup> Although postoperative activation of angiogenesis should be considered part of the wound healing process, it could have a negative effect in patients with cancer favouring growth of residual tumor cells and occult micrometastasis. The aim of the present study was to investigate the possible predictive value of postoperative VEGF serum concentration in patients undergoing curative surgery for non-metastatic colonic cancer.

## 2. Material and methods

Consecutive patients diagnosed with colon cancer between 2006 and 2008 who underwent surgery, at Hospital del Mar Barcelona, were included in the study. Patients with distant metastases, adjacent organ invasion, concurrent or previous malignant tumor, and those requiring urgent surgery for obstruction or perforation were excluded. Patients included in the present study had been part of a randomized controlled trial comparing the inflammatory and angiogenic response between open and laparoscopic surgery.<sup>20</sup>

Data collected included: age, sex, surgical approach (open or laparoscopic), American Society of Anesthesiologists Physical Status Classification System (ASA classification), operative time, perioperative transfusion, tumor location and stage, histological differentiation, lymphovascular and perineural invasion, number of harvested lymph nodes, length of stay, adjuvant chemotherapy, recurrence and survival. We assessed the postoperative complications according to the Clavien-Dindo classification.<sup>21</sup> Perioperative transfusion was defined as blood transfusion one month previous to or after the index surgery.

### 2.1. Blood sampling, and protein assays

Venous blood was taken before surgery and also at 48 h and on postoperative day (POD) 4. Samples were allowed to clot and were centrifuged for 10 min at 4 °C. The serum collected was stored at –80 °C for cytokine assays. VEGF were measured by enzyme-linked immunosorbent assay with commercially available kits (Quantikine<sup>®</sup> human VEGF kit; R&D Systems, Minneapolis, Minnesota, USA). The VEGF kit used in this study measured the VEGF<sup>165</sup> isoform, which is the predominant one.

### 2.2. Adjuvant treatment and follow-up

Postoperative chemotherapy was administered in stage III patients. Adjuvant chemotherapy in stage II colon cancer is not a routine practice in our institution unless evidence of an increased risk of recurrence exists, such as inadequately sampled nodes, T4 lesions or poorly differentiated histology. Treatment regimens included some of the following regimens: capecitabine, 5-fluorouracil and folinic acid or oxaliplatin, 5-fluorouracil and folinic acid.

Patients received regular follow-up examinations every 3 months during the first 2 years and then every 6 months up to 5 years. Full history, physical examination, blood tests and serum CEA were performed at each follow-up visit. Computed tomography (CT) scan was performed yearly in stage III patients. In stage I and II patients, CT scan would be performed only if recurrences were suspected. Colonoscopic surveillance was performed every 3 years after surgery and also if recurrences were suspected.

Local recurrence was defined as tumor associated with surgical site (anastomosis, tumor bed, mesentery) and confirmed histologically or by imaging. Systemic recurrence was defined as spread of the disease outside the surgical field to organs such as the liver,

lungs, bones, or brain. The study was approved by the Institutional Review Board and all patients provided written informed consent.

### 2.3. Statistical analysis

Categorical data are expressed as frequencies and percentages. Continuous data are expressed as mean and standard deviation or median and interquartile range (IQR). The Cox proportional hazards model was used to investigate the influence of clinicopathological variables on prognosis and to evaluate the independent prognostic effect of VEGF serum concentration by adjusting for confounding factors.

Results of the bivariate and multivariate analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI). Cumulative disease-free survival (DFS) and overall survival (OS) were plotted using the Kaplan-Meier method, with statistical analysis by means of the log rank test.

In order to discover the best cut-off point of VEGF serum concentration on POD4, that maximizes discrimination power, we seek different values and took the one that separates most significantly Kaplan-Meier curves of two resulting groups.

A value of  $p < 0.050$  was used to determine the level of statistical significance. All calculations were carried out with SPSS version 18.0 (SPSS, IL, USA).

## 3. Results

A total of 94 patients undergoing curative surgery for colon cancer were included in the study. Characteristics of patients are shown in Table 1. The most frequent surgical procedure performed was sigmoidectomy in 48 patients, followed by 40 right colectomies. Overall morbidity was 38% and the most common complication was postoperative ileus; there were three intra-abdominal abscesses and two anastomotic dehiscences. According to the Clavien-Dindo classification almost 64% of complications were grade I and II. Two patients **died**, one due to pneumonia and

**Table 1**  
Characteristics of patients and surgical procedures.

	N (%)
Patients	94
Age (years)	68 ± 5
Sex (M/F)	48/46
<b>Approach</b>	
- Open	48 (51)
- Laparoscopic	46 (59)
<b>Surgical Procedure</b>	
- Right hemicolectomy	40 (42)
- Left hemicolectomy	6 (7)
- Sigmoidectomy	48 (51)
Length of hospital stay (days)	8 ± 5
<b>Overall Morbidity</b>	36 (38)
- Ileus	12 (13)
- Intra-abdominal Abscess	3 (3)
- Anastomotic dehiscence	2 (2)
<b>Clavien-Dindo</b>	
- I	8 (8.5)
- II	15 (16)
- III	10 (10.6)
- IV	1 (1.06)
- V	2 (2.12)
<b>Tumor stage (UICC)</b>	
- I	32 (34)
- II	24 (26)
- III	38 (40)
<b>Adjuvant treatment for stage</b>	27 (29)
- II	2 (8)
- III	25 (66)

Download English Version:

<https://daneshyari.com/en/article/8830509>

Download Persian Version:

<https://daneshyari.com/article/8830509>

[Daneshyari.com](https://daneshyari.com)