Quantitative Analysis of Vascular Endothelial Growth Factor in Liver Metastases from Pancreatic Carcinoma as a Predictor of Chemotherapeutic Effect and Prognosis

Katsunobu Tawada, Takeshi Ishihara, Akitoshi Kobayashi, Taketo Yamaguchi, Toshio Tsuyuguchi, Masato Matsuyama, and Osamu Yokosuka

Abstract

**Purpose:** In pancreatic carcinoma, vascular endothelial growth factor (VEGF) expression at the primary site has been suggested to be a prognostic parameter. We quantitatively analyzed VEGF expression in liver metastases from pancreatic carcinoma and examined the correlation among VEGF expression in liver metastases, clinicopathologic factors, and clinical outcome.

**Experimental Design:** The subjects consisted of 23 patients with pancreatic adenocarcinoma who had liver metastases and were treated with S-1 and gemcitabine as the first-line treatment. VEGF expression was quantitated by enzyme immunoassay in biopsy specimens of liver metastases and nontumorous liver tissue, and in plasma. In 10 of the 23 patients, VEGF expression was also quantitated in biopsy specimens of the primary pancreatic tumor. All samples were collected before treatment.

**Results:** The VEGF level in nontumorous liver tissue was 36.6 ± 10.0 pg/mg protein versus 376.8 ± 106.1 pg/mg protein in liver metastases (P = 0.0016). Pretreatment VEGF levels in plasma and in primary pancreatic carcinoma did not correlate with VEGF levels in the corresponding liver metastases. The median VEGF level in liver metastases (138.9 pg/mg protein) was used as the cutoff value between high and low VEGF expression in liver metastases. Patients showing high VEGF expression had a significantly longer progression-free survival and overall survival than patients showing low VEGF expression in liver metastases (P = 0.0219 and P = 0.0074, respectively).

**Conclusions:** Evaluation of VEGF levels in liver metastases might be useful in assessing the prognosis of patients with metastatic pancreatic carcinoma who are under systemic chemotherapy.

Pancreatic carcinoma is characterized by its aggressive course, and most patients present with advanced disease at the time of diagnosis (1). The liver is the most common and critical site for distant metastases, further affecting the prognosis of these patients.

Angiogenesis is essential for the growth and metastasis of solid malignancies (2). Where pancreatic carcinoma is concerned, angiogenic factors such as vascular endothelial growth factor (VEGF) are usually investigated in the resected surgical specimen to assess angiogenesis (3–7). In patients with pancreatic carcinoma who underwent surgical resection, it was found that the level of VEGF expression in the primary tumor was of prognostic value.

Angiogenesis is also important for tumor growth at the metastatic site, and VEGF is thought to be closely related to angiogenesis at this site (8). To date, however, few studies have assessed VEGF expression in both the liver metastases and the primary pancreatic tumor in patients with metastatic pancreatic carcinoma. The purpose of this study was to investigate VEGF expression in liver metastases from pancreatic carcinoma obtained by percutaneous fine needle biopsy and its correlation with VEGF expression in the primary tumor, and to clarify its clinical significance.

Materials and Methods

**Patients.** From December 2002 to May 2004, 34 consecutive patients with metastatic pancreatic adenocarcinoma, who received systemic chemotherapy at our institution, were enrolled for this study. Of them, 23 patients fulfilled the following inclusion criteria: (a) Eastern Cooperative Oncology Group performance status of ≤2; (b) no previous chemotherapy or radiotherapy; and (c) presence of metastatic liver tumors assessable for VEGF before chemotherapy. Data were collected through June 2007.

There were 14 men and 9 women, with a mean age of 60 years (range, 36-75 years). The mean primary tumor diameter was 4.1 cm (range, 2.5-6.2 cm): the tumor was located in the head of the pancreas in 12 patients and in the body and/or tail in the other 11.

In all patients the pathologic diagnosis of liver metastases was confirmed by percutaneous needle biopsy, and that of the pancreatic tumor by endoscopic ultrasonography-guided fine-needle aspiration.
Translational Relevance

Vascular endothelial growth factor (VEGF) is mainly examined in the surgical specimen to assess angiogenesis. Several studies have reported that the expression of VEGF in pancreatic carcinoma correlated well with poor prognosis of the patients. In patients with metastatic pancreatic carcinoma, however, few studies have assessed the VEGF expression in both sites of primary pancreatic carcinoma and of liver metastases. This study revealed that VEGF expression was much more in liver metastases than in nontumorous liver tissue, and that VEGF expression in liver metastases was an independent prognostic factor for overall survival in patients with metastatic pancreatic carcinoma who were treated with systemic chemotherapy. The analysis of VEGF expression in liver metastases before systemic chemotherapy may be a valuable tool for prognostic evaluation and treatment planning in patients with metastatic pancreatic carcinoma. Recently, antiangiogenic agents are being used for many malignancies including pancreatic carcinoma. Further studies are needed to clarify whether tissue VEGF expression could be a prognostic predictor of the antiangiogenic therapy for pancreatic carcinoma.

Informed consent for this study was obtained from all the patients, and the study protocol was approved by the institutional review board of Chiba University.

Plasma and tissue sample collection. All plasma and tissue samples were obtained before treatment.

Peripheral blood was taken into glass tubes containing EDTA and immediately centrifuged at 3,000 rpm for 10 min and at 4°C. Plasma samples were removed and stored at -80°C until analysis.

Tumor tissue samples from the liver metastases were obtained under ultrasonographic guidance using a 21-gauge needle (Sonopsy; Hakko). Samples from nontumorous liver tissue were also obtained from the same patients by the same method.

In 10 of the 23 patients, tissue samples from primary pancreatic carcinoma were obtained by endoscopic ultrasonography-guided fine-needle aspiration. The biopsy was done with a linear array (GF-UCT240; Olympus) echoendoscope, using a 22-G manually operated needle device (Echotip; Wilson-Cook). A transgastric approach was used for lesions in the head. Transduodenal approach was used for lesions in the body or tail of the pancreas, and a transduodenal approach was used for lesions in the head. These tissue samples were placed in liquid nitrogen immediately after sampling and stored at -80°C until analysis.

Quantification of VEGF in plasma and tissue. In plasma, VEGF was measured by enzyme-linked immunoassay (Quantikine; R&D Systems). This kit uses a monoclonal antibody, and an enzyme-linked polyclonal antibody for recombinant human VEGF165 was added to the wells. The limit of sensitivity of this kit is 9.0 pg/mL, and the cutoff value for categorical evaluation of plasma VEGF was set at 150 pg/mL as we have previously reported (9).

Tissue specimens were homogenized in 300 μL PBS, centrifuged, and the supernatant was used to measure VEGF by enzyme immunoassay. Briefly, 50 μL of the above mentioned supernatant was added to a microtiter plate coated with solid phase mouse monoclonal antibody for human VEGF165. Then, rabbit anti-human VEGF165 polyclonal antibody was added as the secondary antibody, after which horseradish peroxidase-labeled anti-rabbit IgG was added for colorimetric quantitation. This method of evaluation has previously been applied in other studies in our laboratory (10). The detection sensitivity was 20 pg/mL. In view of the VEGF value in liver metastases, we distributed the patients into a high-VEGF group (n = 12) and a low-VEGF group (n = 11), using the median VEGF value for the 23 patients. Progression-free survival and overall survival were assessed in these two groups.

Chemotherapeutic regimens. All patients were treated with a combination of gemcitabine and S-1, an oral antitumor drug that combines tegafur, 5-chloro-2, 4-dihydroxypridine and potassium oxonate, as part of a phase II trial conducted at our hospital (11). S-1 (60 mg/m2) was given twice daily for 14 d followed by 1 wk rest, and gemcitabine (800-1000 mg/m2) was administered i.v. on day 8 and day 15. Chemotherapy was done every 3 wk as one cycle and continued until disease progression, death, or unacceptable toxicity.

Dynamic computed tomography was done every two cycles, and tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (12).

Follow-up. Follow-up data were available for all 23 patients. At the time of this analysis, the follow-up for the only survivor was 1,148 d, whereas the other 22 patients had died between 66 d and 1,003 d (median, 223 d) after the start of treatment. All deaths were due to disease progression.

Statistical analysis. Data are presented as mean ± SE.

A Wilcoxon’s signed-rank test was used to assess differences in VEGF level between liver metastases and nontumorous liver tissue. The statistical significance of the correlation between VEGF level in liver metastases and clinicopathologic parameters was assessed with the Mann-Whitney U test, Spearman rank correlation test, or Wilcoxon’s rank test. VEGF levels in liver metastases, primary pancreatic carcinoma, and plasma were compared between responders and nonresponders using Mann-Whitney U test. Kaplan-Meier survival analysis was used to estimate progression-free survival and overall survival, and log rank test was used to compare differences between the two groups. Stat View version 5 (Abacus Concepts, Inc.) was used for the above statistical analyses. Statistical significance was set at a P < 0.05.

![Fig. 1. Comparison of VEGF levels in liver metastases and nontumorous liver tissue.](Fig1.png)

**Fig. 1.** Comparison of VEGF levels in liver metastases and nontumorous liver tissue. The VEGF levels in nontumorous liver tissue and liver metastases were 36.8 ± 10.0 pg/mg protein and 376.8 ± 106.1 pg/mg protein, respectively (Wilcoxon’s signed-rank test: P = 0.0016). Circle, each case; bar, mean ± SE.
Results

**VEGF levels in liver metastases and in nontumorous liver tissue.** The VEGF level in nontumorous liver tissue was 36.6 ± 10.0 pg/mg (4.2-239.8 pg/mg) protein versus 376.8 ± 106.1 pg/mg (8.7-1,834.9 pg/mg) protein in liver metastases (Wilcoxon P = 0.0016; Fig. 1).

The results of the univariate analysis of the relationship between VEGF levels in liver metastases and clinicopathologic findings are shown in Table 1. There were no significant correlations between VEGF levels in liver metastases and clinicopathologic factors.

**Correlation between plasma VEGF levels and VEGF levels in liver metastases.** Plasma VEGF levels ranged from 27.0 to 1,580 pg/mL (307.6 ± 78.7 pg/mL) and did not correlate with VEGF levels in liver metastases (P = 0.3281; Fig. 2A).

**Correlation between VEGF levels in liver metastases and in primary pancreatic carcinoma.** In 10 of the 23 patients, tissue samples were obtained from both liver metastases and primary pancreatic carcinoma. In these patients, the VEGF level in primary pancreatic carcinoma was 1,132.0 ± 260.7 pg/mg protein. There was no significant correlation between liver metastases and primary pancreatic carcinoma (P = 0.5730; Fig. 2B). Moreover, there was no significant difference between them (Wilcoxon P = 0.1141).

**VEGF expression in liver metastases and chemotherapy response.** The overall chemotherapy response rate was 43.5% (10 of the 23 patients). Complete response was observed in one patient, partial response in nine, stable disease in five, and progressive disease in eight patients. Patients with complete response or partial response were classified as responders, whereas those with stable disease or progressive disease were classified as nonresponders. The VEGF level in liver metastases was 197.4 ± 75.1 pg/mg protein for nonresponders and 610.1 ± 207.0 pg/mg protein for responders, but the difference did not reach statistical significance (P = 0.0628; Fig. 3A). The plasma VEGF level and that in primary pancreatic tumor did not differ significantly between responders and nonresponders (P = 0.4568 and P = 0.5688, respectively).

**Correlation between VEGF level in liver metastases and patient survival.** The median VEGF level in liver metastases was 138.9 pg/mg protein and was used as the cutoff point between the low and high VEGF level group of patients.

The median progression-free survival was 101 days for patients with low VEGF levels in liver metastases and 175 days for patients with high VEGF levels in liver metastases. The progression-free survival curves are shown in Fig. 3B. There was no significant difference between them (Wilcoxon P = 0.1141).

### Table 1. Univariate analysis of the relationship between VEGF expression and clinicopathologic factors

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Gender</th>
<th>VEGF (pg/mg protein), mean ± SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>14</td>
<td>347 ± 121</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>9</td>
<td>423 ± 204</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td></td>
<td>9</td>
<td>458 ± 201</td>
</tr>
<tr>
<td>≥60</td>
<td></td>
<td>14</td>
<td>325 ± 121</td>
</tr>
<tr>
<td>Primary tumor size (mm)</td>
<td>23</td>
<td>376 ± 106</td>
<td>0.5806 †</td>
</tr>
<tr>
<td>Tumor differentiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate, Well</td>
<td>11</td>
<td>452 ± 183</td>
<td>0.9999*</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>12</td>
<td>308 ± 119</td>
</tr>
<tr>
<td>Plasma VEGF level (pg/mL)</td>
<td>23</td>
<td>376 ± 106</td>
<td>0.3281 †</td>
</tr>
<tr>
<td>Number of liver metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td></td>
<td>8</td>
<td>461 ± 220</td>
</tr>
<tr>
<td>≥5</td>
<td></td>
<td>15</td>
<td>332 ± 118</td>
</tr>
<tr>
<td>Size of the biopsied liver metastasis (mm)</td>
<td>23</td>
<td>376 ± 106</td>
<td>0.5055 †</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test. †Linear regression analysis.

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**Fig. 2.** A, correlation of plasma VEGF level and that in liver metastases. No significant correlation was seen between them (rs = -0.237; P = 0.3281). Circle, each case; rs, Spearman’s rank correlation. B, correlation between VEGF level in liver metastases and that in primary pancreatic carcinoma. In 10 of the 23 patients, tissue samples were obtained from both liver metastases and primary pancreatic carcinoma. In these patients, the VEGF level in primary pancreatic carcinoma was 1,132.0 ± 260.7 pg/mg protein. There was no significant correlation between liver metastases and primary pancreatic carcinoma (P = 0.5730). Circle, each case.
The median overall survival in patients with high VEGF levels and low VEGF levels in liver metastases was 355 days and 180 days, respectively (Fig. 3C; *P* = 0.0074). Univariate analysis (log rank test) showed the number of liver metastases (*P* = 0.0126) and VEGF levels in liver metastases to be significant predictors of a poor prognosis (Table 2). However, on multivariate analysis (stepwise Cox proportional hazards modeling), the VEGF level in liver metastases was the only significant variable associated with a poor prognosis (Table 3).

Discussion

Almost all histologic studies concerning angiogenesis in human pancreatic cancer have been based on tissue sections obtained at surgery. Several researchers have shown that high VEGF expression in primary pancreatic cancer correlates with poor prognosis (3, 4). However, no surgical specimen could be obtained in patients with metastatic advanced pancreatic cancer (13). Thus, there is no information on VEGF expression in liver metastases, nor is there any on a possible correlation between VEGF expression in primary pancreatic carcinoma and liver metastases with the prognosis of patients with metastatic pancreatic cancer. Furthermore, there have been only few studies focusing on tissue VEGF as a predictor of response to systemic chemotherapy and clinical prognosis of patients with a nonresectable malignant tumor.

It is well known that high VEGF expression in the resected specimen is a poor prognostic factor after curative resection in many malignancies including pancreatic cancer (3, 4, 14–19). The reasons for a poor prognosis may be the high rate of local recurrence and distant metastases in case of tumors showing high VEGF expression. In the present study, significantly better prognosis was observed in patients with high VEGF levels in liver metastases than in patients with low VEGF levels. This result might be explained in part as follows: Some investigators have reported that VEGF expression was closely correlated with microvessel density (3, 4, 6, 20) and with tumor vascularity depicted by imaging modalities (10, 21, 22) in pancreatic carcinoma. Increased vascularity suggests increased drug delivery and thereby improved response to chemotherapy. Furthermore, VEGF increases vascular permeability, which might facilitate drug delivery via the circulation (23). Indeed, VEGF expression has been shown to be a marker of favorable response to chemotherapy in unresectable gastric cancers (24, 25). Another study on ovarian cancer, however, found the opposite result (26); thus, the effect of tissue VEGF on chemosensitivity might depend on the type of cancer and remains controversial. Further studies are needed to clarify whether the same result obtained in this study can be expected with different chemotherapeutic regimens for pancreatic cancer as well as for other solid tumors.

As for tissue VEGF expression in primary pancreatic cancer, several investigators have reported an association of tissue VEGF expression with liver metastases (3) and tumor size (20). Other studies, however, have shown no correlation between VEGF expression and clinicopathologic factors (4, 7). In this study, we found no correlation between VEGF level in liver metastases and each of the various clinicopathologic factors. One of the reasons may be that all patients had liver metastases in this series. Another investigator also found no relationship

![Fig. 3. A, relationship between chemotherapeutic response and VEGF level in liver metastases. The VEGF level in liver metastases was 197.4 ± 75.1 pg/mg protein for nonresponders and 610.1 ± 207.0 pg/mg protein for responders (*P* = 0.0628). Circle, each case; bar, mean ± SE. B, progression-free survival curves of patients with high and low VEGF levels in liver metastases. Patients with high VEGF levels had a significantly lower incidence of disease progression compared with patients with low VEGF levels in liver metastases (*P* = 0.0219; log-rank test). C, overall survival curves of patients with high and low VEGF levels in liver metastases. The survival of patients with high VEGF levels was significantly longer than that of those with low VEGF levels in liver metastases (*P* = 0.0074; log-rank test).](www.aacjournals.org)
between VEGF expression in liver metastases and clinicopathologic factors in patients with colorectal cancer (27).

As for other malignancies, several authors investigated the relationship between VEGF expression at the metastatic site and that at the primary site. One study found that there was a significant correlation in VEGF mRNA expression between primary colorectal cancer and the corresponding liver metastases (28), whereas others found that VEGF expression was significantly reduced in the metastatic liver tumor compared with the primary ones (29, 30). In this study, we did not find any correlation or any difference between VEGF expression in liver metastases and that in primary pancreatic carcinoma. One of the reasons, we assumed, is that the organ microenvironment has effects on tumor angiogenesis that can differ between the tumor and its metastases (31, 32).

Concerning the relation between tissue VEGF expression and serum or plasma VEGF level, there have been various reports describing positive (33, 34) or negative (35–37) results. In this study, we did not find any correlation between VEGF expression in liver metastases and plasma VEGF levels. There are numerous reasons for the discrepant findings. First, tumor size will affect the amount of circulating tumor-derived VEGF (38, 39). This means that the amount of VEGF protein in serum or plasma could be high even if each tumor cell expressed a small amount of VEGF. Second, investigators have mainly measured serum (not plasma) VEGF to evaluate circulating VEGF in these studies. However, most VEGF in the serum is derived from platelets during clotting, and VEGF level in serum could be highly variable (40). Thus, VEGF should be measured in plasma and not in serum.

In general, it is necessary to pathologically confirm malignancies before the start of systemic chemotherapy. Some studies have reported that ultrasonically guided percutaneous fine needle biopsy is highly accurate and is rarely associated with fatal complications (41, 42). With regard to biopsy specimens, tumor heterogeneity and unsteady VEGF expression within the same lesion may represent potential biases in our results. The availability of a fully resected metastasis would reduce the risk of analyzing unrepresentative tumor areas in a biopsy. However, laparotomy and surgical resection of pancreatic cancer metastases are difficult to do because they are contraindicated in pancreatic cancer. A previous study found a good correlation between VEGF mRNA expression in the biopsy specimen and the resected specimen in human breast cancer (43). These data suggest that evaluation of VEGF expression using biopsy samples might be useful for assessing VEGF expression in tumor tissue, especially in patients with unresectable cancer.

With regard to the efficacy of treatments against VEGF, the expression of VEGF could be an important predictor of the activity of its inhibitor. Kindler et al., however, reported that pretreatment plasma VEGF levels did not correlate with

### Table 2. Risk factors affecting progression-free and overall survival rates as determined by univariate analysis in 24 patients with pancreatic carcinoma

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>HR (95% CI) P</td>
<td>HR (95% CI) P</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>0.6312 0.2761</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>0.809 (0.340-1.927) 0.620 (0.259-1.484)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>9</td>
<td>1 0.3636 0.1251</td>
</tr>
<tr>
<td>≥60</td>
<td>14</td>
<td>1.506 (0.619-3.667) 2.050 (0.802-5.245)</td>
</tr>
<tr>
<td>Primary tumor size (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>10</td>
<td>0.577 (0.246-1.353) 0.692 (0.293-1.634)</td>
</tr>
<tr>
<td>≥40</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Tumor differentiation</td>
<td></td>
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</tr>
<tr>
<td>Moderate, well</td>
<td>11</td>
<td>1 0.5580 0.5627</td>
</tr>
<tr>
<td>Poor</td>
<td>12</td>
<td>1.289 (0.551-3.012) 1.285 (0.546-3.021)</td>
</tr>
<tr>
<td>Plasma VEGF level (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>9</td>
<td>0.569 (0.238-1.361) 0.861 (0.366-2.025)</td>
</tr>
<tr>
<td>≥150</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>No. liver metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>8</td>
<td>0.013 0.0126</td>
</tr>
<tr>
<td>≥5</td>
<td>15</td>
<td>2.318 (0.825-6.510) 3.479 (1.229-9.849)</td>
</tr>
<tr>
<td>VEGF level in liver metastases (pg/mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;138.9</td>
<td>11</td>
<td>3.125 (1.125-8.696) 3.937 (1.333-11.628) 0.0074</td>
</tr>
<tr>
<td>≥138.9</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

**Abbreviations:** HR, hazard ratio; 95% CI, 95% confidence interval.

### Table 3. Multivariate analysis of prognostic factors of overall survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>No. liver metastases</td>
<td>&lt;5 vs ≥5</td>
<td>2.776 (0.943-8.169)</td>
</tr>
<tr>
<td>VEGF level in liver metastases pg/mg protein</td>
<td>&lt;138.9 vs ≥138.9</td>
<td>3.030 (1.006-9.091)</td>
</tr>
</tbody>
</table>
outcome in a phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer (44). It remains unclear whether tissue VEGF expression in primary pancreatic cancer and liver metastases correlates with the clinical outcome of antiangiogenic therapy. Further clinical studies are needed to evaluate whether tissue VEGF expression serves as a prognostic parameter of survival in patients under antiangiogenic therapy for pancreatic cancer.

In conclusion, the results indicate that the VEGF expression in liver metastases could serve as a useful predictor of the clinical outcome of patients under treatment with gemcitabine and S-1.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


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