Predictive Value of Serum Biomarkers in Patients After Portal Vein Embolization (PVE): A Pilot Study

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Abstract. *Background/Aim: Insufficient growth of the liver or tumor progression is an important issue of portal vein embolization (PVE) in some patients. This study evaluated the predictive value of serum biomarkers for liver hypertrophy and tumor progression after PVE. Patients and Methods: Serum levels of tumor markers, growth factors and cytokines were determined in 40 patients with malignant liver tumors in the pre- and post-PVE period. The values were compared with contralateral liver hypertrophy and tumor progression. Results: Liver tissue hypertrophy occurred in 26 (65%), tumor progression in 11 (27.5%) and insufficient liver hypertrophy in 3 (7.5%) of the patients. The significant predictive biomarkers of PVE included serum TPA levels, monototal, IGF-BP3, IGF1, TGF-α, EGF, HGF, VEGF, TNFa and IL-10 before PVE; and TK, TPA, monototal, IGF-BP3, TGFa and IL-8 over the course of 28 days after PVE. Conclusion: Certain serum biomarkers have an important predictive value for the result of PVE.*

Patients with primary and secondary liver tumors and insufficient future remnant liver volume (FRLV) are indicated for the stage of liver surgery in which the first step includes portal vein embolization (PVE), which stimulates hypertrophy of the contralateral liver lobe and a sufficient metabolic function of the liver after the resection (1, 2). Hence, PVE enables a significant extension of the operability range in primarily inoparable liver tumors due to insufficient FRLV (3). However, some patients fail to achieve sufficient growth of the liver tissue or experience a progression of the primary or secondary tumor in the liver or body after PVE (4, 5). It is important that a clinician receives early information about insufficient growth of the FRLV or about a possible tumor progression in these patients so that the treatment plan can be modified sufficiently quickly. The aim of this study was to evaluate the predictive value of commonly available and easily determinable serum levels of selected biomarkers for early prognosis of the clinical development of PVE.

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Patients and Methods

This prospective non-randomized study performed PVE in 40 patients with a liver tumor (35 patients with colorectal cancer metastases, two with one breast cancer metastasis, one with ovarian cancer metastasis and two with hepatocellular carcinoma) due to insufficient FRLV. The mean age of the patients was 60.8 years (33.3-70.6 years, Table I). Before PVE, a functional test was performed using the liver clearance of the indocyanine green (ICG test) in each patient. The following serum oncofetal tumor marker levels were determined: alpha-fetoprotein (AFP) and carcinoembryonal antigen (CEA) using the chemiluminescent method with the DXI 800 device (Beckman, USA), proliferative marker of thymidinkinase (TK) using the radioenzymatic method (Immunotech, USA) and cytokeratins of the tissue polypeptide antigen (TPA) and monototal using the immunoradiometric method with DiaSorin and IDL (Biotech, USA). Furthermore, the serum levels of the following growth factors and pro-inflammatory cytokines were evaluated: epidermal growth factor (EGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF-1), insulin-like growth factor-binding protein 3 (IGF-BP3), transforming growth factor (TGFα), vascular-endothelial growth factor (VEGF), interleukin 2, 6, 8, 10 (IL-2, -6, -8, -10) and tumor necrosis factor α (TNFα), using the multiplex analysis (xMAP technology) in a Luminex S device (Millipore, USA) at the time interval of 0-28 days after PVE.

Initially, PVE was performed using embolization coils, but subsequently the procedure was changed to use Histoacryl (B Braun, Germany) with lipidiol (Cedex, France). The change of the FRLV was monitored by high resolution computed tomography (HRCT) volumometry using the Somatom Definition device with

the Syngo Volume Calculation software (both Siemens, Germany) at 14-day intervals until week eight after PVE. Patients were indicated for liver resection once the change in the FRLV achieved sufficient enlargement. If a patient was receiving chemotherapy or biological therapy (often in combination), this therapy was discontinued before PVE and then resumed approximately three weeks after the liver resection. The progression of tumor was also evaluated using the afore-mentioned CT examination. A suitable systemic chemotherapy or a combination of chemotherapy with biological therapy was selected in these patients after the diagnosis of tumor progression based on consultation with the oncologist.

Because this study used a small pilot group, statistical evaluation was performed in three steps using the statistical software Statistica 9.0 (StatSoft, Prague, Czech Republic). This is described in detail in the Results section.

Table I. *Patient characteristics*.

	n (%)
Mean age, years	60.8 (33.3-70.6)
Colorectal cancer metastasis	35
Breast cancer metastasis	2
Ovarian cancer metastasis	1
Hepatocellular carcinoma	2
Liver hypertrophy after PVE	26 (65%)
Tumor progression after the PVE	11 (27.5%)
Insufficient growth of liver parenchyma after PVE	3 (7.5%)

Results

PVE on the tumor side was completed in all patients. Twenty-six patients (65%) (group 1) had liver tissue hypertrophy. A major resection (more than three segments) was performed in 22 patients in an average of 27.6 days (20-52 days) after PVE. A radical resection was not performed in four patients because of the worsening of serious associated, mainly cardiovascular, diseases, and only a radiofrequency ablation was performed in these cases. These patients were not included in the final statistical evaluation. It was not possible to perform a liver resection in 14 (35.0%) patients due to tumor progression in the liver and/or a development of extrahepatic metastases (N=11, group 2) and an insufficient growth of the FRLV (N=3, group 3) (Table I). All the patients who had an insufficient increase of liver tissue volume were diabetics. Diabetes mellitus was present in six patients (15%) out of the whole group (N=40). The result of the ICG test was >14% (14-20%) before PVE in three patients; nevertheless a sufficient growth of FRLV after PVE with subsequent successful liver resection occurred in all three patients.

The serum marker levels were evaluated before PVE in all three groups of patients with regard to liver parenchyma hypertrophy or tumor progression in the body (the first grade of statistical evaluation), Table II. When comparing the results, the following markers seem to be the predictive factors for liver tissue growth or tumor progression: CEA, TPA, monototal, EGF, HGF, IGF-1, IGF-BP3, TGF-α, VEGF, IL-10 and TNF-α. The second step of the statistical evaluation included a correlation of single serum marker levels before PVE with the final PVE result (Table III). The Table shows that based on the statistical evaluation, monotal, HGF, IGF-1, IGF-BP3, TGF-α and IL-10 are predictive markers of the success of PVE. In the third step of the statistical evaluation, the final effect of PVE was compared with the changes of the monitored serum marker levels during the 28-day follow-up after PVE (Table IV). From this point of view, TK, TPA, monototal, IGF-BP3, TGF-α and IL-8 are important for the growth of liver tissue or, in contrast, for tumor progression.

Discussion

There are only a few studies that use biomarkers for the prediction of the effect of embolization therapy in primary liver tumors (6-8). This study is the first that concerns the predictive importance of serum levels of routinely determinable biomarkers with regard to prediction of the result of PVE in patients with primarily non-resecable primary or secondary liver tumors. When selecting the biomarkers, those that are used for the follow-up of patients with liver tumors, or the biomarkers that are typical of cancerogenesis and regenerative processes in the liver parenchyma were chosen.

PVE is a routine method that is indicated as the first step before large liver resection in patients with insufficient FRLV and insufficient liver function. Liver parenchyma hypertrophy after PVE occurs in a number of patients within two to eight weeks by 20-46%, and 70-100% of these patients are able to undergo liver resection within four to six weeks after PVE (9, 10). It is known that in the first three to four weeks after PVE, the regenerative potential of the liver parenchyma is highest. If there is no growth of the liver parenchyma in the contralateral lobe in this time interval, it is less probable that PVE will be successful (11-13).

The liver parenchyma normally has a strong ability to regenerate. After liver resection, a fast hepatocyte replication occurs in the remaining liver parenchyma during the first days and after this growth, an increase of the volume of hepatocytes occurs after several days. Both phases are directly proportionally dependent on the size of the liver parenchyma that was lost. The non-parenchymal cells (Kupffer cells, endothelial cells, cholangiocytes) replicate several days following the replication of hepatocytes. The regeneration process is controlled by a number of mediators. Under normal circumstances hepatocytes are in the so-called

Table II. *Serum biomarker levels before the PVE in correlation with growth of the liver tissue and tumor progression after the PVE.*

Marker	Group 1 (N=26)	Group 2 (N=11)	Group 3 (N=3)	Kruskal–Wallis test
AFP (IU/ml)	4.75±7.06	4.0±6.33	5.34±9.83	$p<0.53$
CEA (ng/ml)	28.96±6.75	18.77±5.0	61.47±12.0	$p<0.09$
TK (IU/l)	10.0±7.25	6.70±5.67	9.27±10.0	$p<0.48$
TPA (IU/l)	221.38±9.38	53.67±8.0	20.0±2.0	$p<0.02$
Monototal (U/l)	251.96±7.75	77.13±6.42	22.27±6.34	$p<0.04$
EGF (pg/ml)	93.12±7.48	261.55±6.61	56.30±6.50	$p<0.02$
HGF (pg/ml)	3556.71±7.75	2926.59±6.51	933.55±6.42	$p<0.01$
IGF-1 (ng/ml)	165.88±10.25	100.67±5.67	61.33±6.41	$p<0.01$
IGF-BP3 (ng/ml)	3380.25±10.38	1851.67±5.0	1056.33±2.33	$p<0.01$
TGFα (pg/ml)	3.89±4.81	5.53±9.67	6.72±12.50	$p<0.01$
VEGF (pg/ml)	126.55±7.74	470.40±6.41	76.16±6.52	$p<0.02$
IL-2 (pg/ml)	5.35±7.64	6.50±5.91	4.63±6.38	$p<0.60$
IL-6 (pg/ml)	3.66±6.64	4.24±5.48	4.24±5.51	$p<0.21$
IL-8 (pg/ml)	16.33±7.71	12.21±5.92	5.86±6.39	$p<0.12$
IL-10 (pg/ml)	3.20±5.0	4.77±5.43	3.40±5.52	$p<0.01$
TNFα (pg/ml)	9.28±7.33	10.23±6.42	4.84±6.24	

Groups: 1, liner hypertrophy; 2, tumor progression/extrahepatic metastasis; 3, insufficient growth of FRLV.

Table III. *Serum biomarker levels before the PVE in correlation with the PVE result.*

Marker	Group 1 (N=26)	Groups 2+3 (N=14)	Will coxon test
AFP (IU/ml)	4.75±7.06	4.67±8.08	$p<0.67$
CEA (ng/ml)	28.96±6.75	40.12±7.75	$p<0.49$
TK (IU/l)	10.0±7.25	7.98±7.83	$p<0.85$
TPA (IU/l)	221.38±9.38	36.83±5.0	$p<0.06$
Monototal (U/l)	251.96±7.75	49.70±7.74	$p<0.02$
EGF (pg/ml)	93.12±7.48	158.92±7.75	$p<0.28$
HGF (pg/ml)	3556.71±7.75	1930.07±7.24	$p<0.03$
IGF-1 (ng/ml)	165.88 ±10.25	81.0±3.83	$p<0.01$
IGF-BP3 (ng/ml)	3380.25 ±10.38	1454.0±3.67	$p<0.01$
TGFα (pg/ml)	3.89±4.81	6.12±7.55	$p<0.01$
VEGF (pg/ml)	126.55±7.74	66.23±6.69	$p<0.33$
IL-2 (pg/ml)	5.35±7.64	5.57±7.71	$p<0.73$
IL-6 (pg/ml)	3.66±6.64	4.24±5.93	$p<0.09$
IL-8 (pg/ml)	16.33±7.71	9.04±7.46	$p<0.57$
IL-10 (pg/ml)	3.20±5.0	4.09±10.83	$p<0.01$
TNFα (pg/ml)	9.28±7.33	7.53±7.74	$p<0.47$

Table IV. *Importance of the postoperative (within 28 days) serum marker levels with regard to the PVE results.*

Marker	Cut-off	95% CI	AUC	SP (%)	SN (%)	Chi-square
TK (IU/l)	8.9	1.01-30.25	0.639	41	89	$p<0.05$
TPA (IU/l)	90	5.53-131.13	0.825	66	93	$p<0.0001$
Monototal (U/l)	130	6.19-148.61	0.852	68	93	$p<0.0001$
IGF-BP3 (mg(ml)	2460	3.34-74.34	0.859	91	78	$p<0.005$
TGF α (pg/ml)	5.1	3.85-38.55	0.773	82	73	$p<0.0001$
IL8 (pg/ml)	10.3	1.66-13.39	0.697	58	83	$p<0.004$

CI: 95% Confidence interval; AUC: evaluated area under the ROC curve for the respective parameter; SP: specificity=probability that growth of the liver parenchyma volume will occur within 28 days after the PVE; SN: sensitivity, probability that no growth of the volume of the liver parenchyma will occur, or that a tumour progression will occur within 28 days after the PVE.

G_0 rest period. After liver resection, the remaining hepatocytes enter into the G_1 phase, which is stimulated by cytokines – TNFα, IL-6 and -8, insulin and prostaglandins. Another step of liver regeneration is the S phase, which is stimulated by the following growth factors: EGF, HGF, VEGF, TGFα, IGF and serotonin (14-16). Termination of liver regeneration is then regulated by another factor, TGFβ (17, 18). It can be assumed that similar metabolic processes are present even after PVE. The very important cells which take part in regeneration (hypertrophy) of the liver parenchyma are the so-called oval (progenitor) cells, which are able to differentiate into hepatocytes and cholangiocytes, and this differentiation is stimulated by the above-stated mediators. Other important cells in the liver parenchyma include stem cells, either hematopoietic or mesenchymal. Their role lies in the fact that they are able supplement the number of progenitor cells and hence increase their proliferation activity, but at the same time they can differentiate themselves into hepatocytes and cholangiocytes (19, 20). The hemodynamic factor plays an important role in the process of regeneration (hypertrophy) of the liver parenchyma. Under physiological conditions, up to 80% of blood comes to the liver from the portal vein and the

remaining 20% comes from arterial circulation. After PVE, the blood flow through the portal vein in the non-embolized lobe is significantly increased and there is also an increase of the arterial flow in the embolized lobe known as 'hepatic arterial buffer response' (21-23).

However, in some patients the appropriate start of the above regenerative processes do not occur, which results in an insufficient growth of the contralateral non-embolized liver lobe. Chronic liver disease, diabetes mellitus or technically insufficient PVE, and portal hypertension with portosystemic shunts are considered as potential factors that negatively affect liver regeneration (24-26). In the patients of the current study, only diabetes mellitus, which was present in all three patients in whom an insufficient hypertrophy of the liver tissue after PVE occurred, was able to be considered. Nevertheless, this is a very small patient number, based on which no conclusions can be made.

The causes of liver tumor progression, which was present in 11 patients in the current study, are not currently clear (27-29). Activation of the metabolic processes of carcinogenesis, in which a number of our monitored factors take part, is one of the causes. An increase of the proliferation activity of the liver metastases is also documented by the tissue proliferation marker Ki-67, which was significantly higher in the metastases after PVE compared to the metastases without PVE (30, 31) A similar finding was described by Hayashi *et al*. (32) in the primary liver tumors in which tumor growth after PVE was 2.37 cm^3 per day compared to 0.59 cm^3 per day before PVE. Of course, the tumor growth (especially micrometastases) at a different location in the body may be a problem because both pro-inflammatory cytokines and growth factors are released into the circulation after PVE (33-35).

It is agreable to find out that a number of markers have predictive features that were presumed in this study. Nevertheless, due to their variable biological activity, it is too early to draw final conclusions based on this pilot study. The pre-operative values of the tumor markers can hardly be evaluated in relation to the regeneration of the liver parenchyma or tumor progression after PVE. Higher serum CEA levels indicated tumor progression in the liver parenchyma, which may be associated with the function of this marker in the Kuppfer cells, as presented recently (36). Some experimental and clinical studies document a stimulation of the Kupffer cells using the CEA to produce TNFα, IL-1β and IL-6, which stimulate endothelial cells of the liver sinusoids to produce the intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin and β2 integrin (37, 38). These adhesive molecules then increase adhesion of the tumor cells in the liver parenchyma. High serum TPA and monototal levels in patients with sufficient regeneration of the liver parenchyma after PVE were probably associated with the high grade of cell division without any relation to the etiology of the process (our repeated findings not yet published). High HGF, IGF and EGF levels after PVE also indicated a sufficient regeneration of the liver parenchyma; however, at the same time high initial serum EGF and VEGF levels were significant for tumor progression in the liver after PVE. These factors possibly play an important role in stimulation of the growth of so-called micrometastases in the liver, which are not visible through the available radiodiagnostic methods before PVE. Nevertheless, the question as to why high serum levels of some growth factors predict a sufficient regeneration of the liver and others predict tumor progression after PVE remains open. High serum IGF-BP3 levels before PVE were a significant predictive marker of the regeneration of the liver parenchyma. It is a marker that is associated mainly with inhibition of angiogenesis and apoptosis, which was indicated by its lower levels in patients with tumor progression and insufficient liver regeneration after PVE (39). It seems that the cytokines (IL-10 and TNFα), which play an important role in the process of carcinogenesis, have a prognostic value, which is in accordance with the study published by Duffy *et al*. (40) When the development of single markers was evaluated before day 28 after PVE with regard to the result of PVE, it was found that the cytokeratins, as well as IGF-BP3, TGFα and IL-8, had a predictive value for regeneration of the liver parenchyma.

This prospective non-randomized pilot study had certain limitations. In particular, it evaluated a heterogeneous group of patients with colorectal cancer metastases and with metastases of non-colorectal cancer in the liver and primary liver tumors. The proliferation activity of the single tumors was not evaluated as an inclusion criterion, which may undoubtedly be important in the progression of tumor after PVE. Nevertheless, all primary and secondary liver tumors were diagnosed before PVE using non-invasive diagnostic methods and a possible tumor biopsy was not acceptable from the ethical point of view, as well as being contraindicated from the oncological point of view. With regard to the small group of patients with insufficient liver hypertrophy after PVE, the study was rather focused on the success (liver hypertrophy) or failure (tumor progression, insufficient liver hypertrophy) after PVE. Nevertheless, this study is ongoing and it would certainly be interesting after some time to present further results with additional data, especially in the group with insufficient regeneration of the liver parenchyma.

However, despite these insufficiencies, it is hypothesized that the monitored serum biomarkers might be important for the prediction of PVE results, which may be very important for the strategy for oncological therapy and oncological surgery in each patient.

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