Radiological aspects of portal vein embolization

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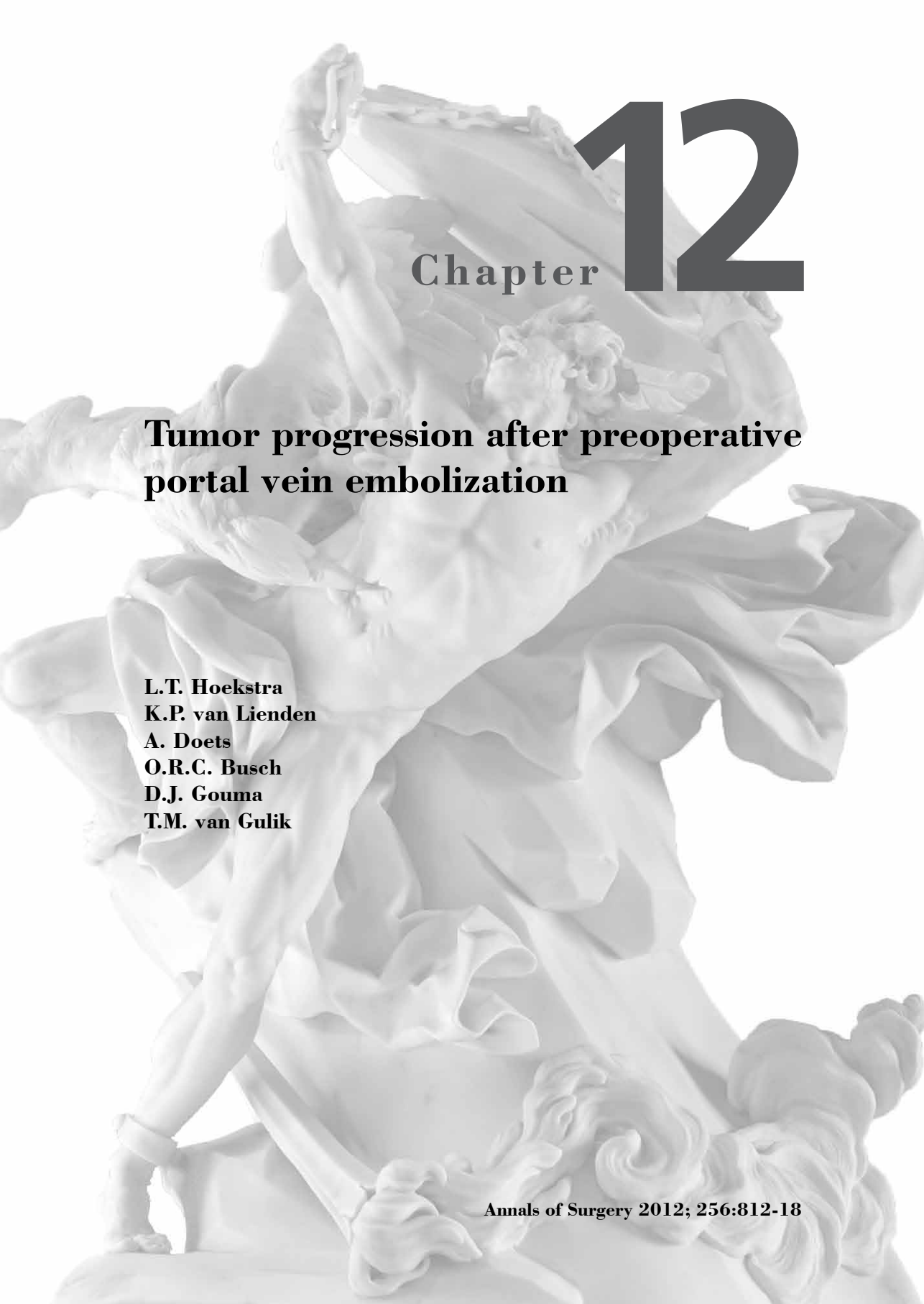

Chapter 12

Tumor progression after preoperative portal vein embolization

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Abstract

Objective: To evaluate tumor growth in a series of patients undergoing liver resection after portal vein embolization (PVE).

Background: The regenerative response after PVE leading to compensatory hypertrophy of the non-embolized liver segments, potentially enhances tumor growth.

Methods: PVE was performed in 28 patients diagnosed with colorectal metastases (CRM) between 2004 and 2011. Tumor volume (TV) was measured by CT volumetry before and after PVE. Tumor growth rate (TGR) was measured by CT volumetry and compared with a non-PVE control group with CRM of whom 30 had two CT-scans preoperatively. Also, newly diagnosed tumors in the future remnant liver (FRL) after PVE and after resection were analyzed.

Results: The median TGR of PVE patients was 0.53 mL/day (IQR 0.02; 1.88) vs 0.09mL/day (IQR -0.04; 0.40; p=0.03) in non-PVE patients. TGR was 0.15 (IQR -0.52; 0.66)mL/day before PVE, and 0.85 (IQR -0.10; 1.62)mL/day after PVE in the same patients (p=0.03). Seven (25%) patients showed new tumor lesions in the FRL after PVE, of whom three patients (11%) were not resectable. Patients after PVE also showed a higher rate (8/19; 42%) of recurrent metastases in the remnant liver at follow-up compared to non-PVE (1/28; 4%). Survival was significantly better for non-PVE patients with a 3-year survival rate of 77% versus 26% in patients undergoing PVE.

Conclusions: PVE is associated with increased TGR and new tumor in the FRL and recurrent tumor after resection. Short intervals as well as interval chemotherapy between PVE and resection are therefore advised.

Introduction

The only curative treatment for malignant liver tumors is (partial) liver resection. Not all tumors are resectable, in many cases because the future remnant liver (FRL) is too small with a high risk of postoperative liver failure which is the major cause of mortality after extended liver resections, especially in patients with compromised liver, such as cirrhosis, steatosis, cholestasis, fibrosis, or after extensive chemotherapy.[1] Portal vein embolization (PVE)[2,3] is an accepted method worldwide, to increase the resectability rate of patients with liver tumors by inducing hypertrophy of the non-embolized FRL. Several studies describe the possibility of enhanced tumor growth after PVE[4-9] as a result of cytokines, growth factors and an increased arterial blood supply, but the exact mechanisms of this phenomenon are still unknown. Growth of tumor may be accelerated, while micrometastases in the non-embolized remnant liver may also develop or progress. The potential boost of tumor proliferation, therefore, creates a dilemma in terms of optimal waiting time until resection. The aim of this study was to examine the consequences of preoperative PVE for tumor growth in a series of patients prepared for resection in our department.

Methods

Study-characteristics

The results of patients with colorectal liver metastases (CRM; n=28) undergoing preoperative PVE (PVE group) from 2004 until 2011 were compared with a series of patients with CRM (n=30) who underwent liver resection without PVE (non-PVE-group), in whom two sequential CT-scans were performed before liver resection. The median follow-up was 6 (IQR 0; 27) months in the PVE-group, and 40 (IQR 26; 52)months in the non-PVE group.

Management policy

The standard diagnostic work-up included a multiphase CT-scan, MR imaging, or dynamic ultrasound of the liver as required. A multidisciplinary team evaluated the imaging studies and came up with a proposal for treatment of patients with CRM. Of all PVE-patients, CT-scans were performed in the portal phase. The volumes of total liver (TLV), tumor (TV) in the embolized liver lobe, and future remnant liver (FRLV) were determined by CT-volumetry in the prePVE and postPVE scans. The percentage of FRL was calculated according to the following formula: FRLV x100/(TLV-TV). Tumor progression was also recorded if presenting in the future remnant liver after PVE. 28 patients with CRM were analyzed in the PVE-group. In all PVE-patients, CT-scans were made before PVE and three weeks later. However, two sequential scans were performed prior to PVE in ten patients. These scans were made to assess tumor response to chemotherapy or to check for new, extra-hepatic disease during therapy. Another reason for an extra CT scan was to perform the CT-volumetry calculations, which can only be determined on our own work-station, indicating that scanning techniques and images were comparable. In these patients, tumor volumes and growth could be

determined before PVE in the same patient group. Follow-up CT scans were made after liver resection to detect recurrent tumor.

In 30 patients of the non-PVE group, CT volumetric data (TLV, TV and FRLV) were assessed in two sequential CT-scans performed before liver resection. Firstly, the volumes were determined, after which the calculations were performed. The results of the volumes measured by CT-volumetry were determined by two independent, experienced investigators, showing no major variations and resulting in reproducible assessments. Calculations were made using established formulas.

To assess tumor volume changes, tumor volumes were determined and the linear tumor growth rate (TGR) per day was calculated by the following formulas:

- For PVE patients: $(TV_{after\ PVE} - TV_{before\ PVE})/days_{between\ scans\ before\ surgery}$ if only one scan was available before PVE, and
  $(TV_{second\ scan\ before\ PVE} - TV_{first\ scan\ before\ PVE})/days_{between\ scans\ before\ PVE}$ for patients in whom two sequential scans were performed prior to PVE (n=10)
- For non-PVE patients: $(TV_{second\ scan\ before\ surgery} - TV_{first\ scan\ before\ surgery})/days_{between\ scans\ before\ surgery}$

Whereas the abovementioned formulas to calculate tumor growth rate implies a linear growth, tumor growth of CRM is likely exponential. Therefore, we also calculated the exponential TGR (ETGR) for characterization of an exponentially growing tumor, by using the formula ETGR=ln(TV2/TV1)/(t2-t1) in which TV=tumor volume, and t=time, described as the "specific growth rate" by Mehrara.[10]

New tumor lesions in the FRL after resection were also reported. Follow-up time was recorded as the period between resection date and the last date of follow-up. Survival was analyzed according to the date of liver resection until the date of death.

Chemotherapy

The administered chemotherapy regimens (number of cycles) varied among patients and groups. In most patients, the combination of Oxaliplatin and/or Capecitabine with or without Bevacuzimab was given. Some patients received Capecitabine, Irinotecan, Panitumumab, or Oxaliplatin with 5-Fluorouracil/leucovorin. In view of the large variation, we only took into account the mere fact that patients received chemotherapy or not.

Statistical analysis

The data were analyzed by statistical software (SPSS for Windows 18.0; SPSS, Chicago, Illinois, USA) and GraphPad Prism (Graph-Pad Software, San Diego, CA). The non-parametric Mann Whitney *U* test was used for comparing unpaired data that was not normally distributed between the PVE-group and non-PVE group. For parametric, paired data the paired T-test was used. Normally distributed data was described as mean±SEM. The Wilcoxon signed rank test was used for comparisons between pre-PVE and post-PVE in the same patients undergoing PVE (n=10), for paired data that was not normally distributed. The chi-square

test was used for comparing binary data for comparisons across the PVE-group and non-PVE group (unpaired). The Spearman correlation coefficient was calculated for the correlation between tumor growth rate or tumor volume increase and increased FRL, and between number of cyclus of chemotherapy and tumor growth rate or tumor size changes. Survival curves were generated by the Kaplan-Meier method. A p-value of <0.05 was considered statistically significant.

Results

PVE was successfully performed in all patients of the present series, without PVE-related complications. Following PVE, liver resection was carried out in the great majority of patients. Characteristics of patients with and without PVE are shown in table 1.

Tumor volume (TV)

In 28 PVE-patients, a mean TV of 131.4±44.3mL pre-PVE versus 180.0±55.2mL after PVE was seen following an overall time-interval of 51.4±5.4days (p=0.011). In this group, an increase of tumor volume after PVE was found in 23 patients, of whom 13 patients (57%) had received chemotherapy before PVE, whereas five patients showed a decrease in tumor size after embolization, in whom chemotherapy was administered in 4 patients (80%). There was a time-interval of 29.1±5.4 days between the first CT scan and PVE, compared to 22.2±0.7 days between PVE and the second scan (three weeks after PVE). In a subgroup of 10 patients two sequential CT scans were made prior to PVE with a time-interval of 44.2±12.1days between scans. These patients showed a stable TV from 176.3±87.3mL to 179.4±87.2mL (p=0.758) before PVE.

In the non-PVE group (n=30), a mean TV of 153.2±54.9mL was seen on the first scan versus 118.2±36.5mL on the second scan. An increase in tumor volume was found in 19 patients (63%), with a mean time-interval of 107.85±19.15 days between the two scans performed prior to liver resection for all patients (n=30). The decrease in tumor size in 11 patients is probably related to the use of chemotherapy. In patients who received chemotherapy preoperatively in the non-PVE group (n=14), a decrease in tumor volume was seen from 267.5±108.8mL to 158.7±68.1mL (p=0.245). Conversely, patients who had no chemotherapy in the non-PVE group (n=16) showed an increase in tumor volume between the initial and second scans (from 53.3±22.9mL to 82.7±33.8mL), although not significantly different (p=0.099).

Tumor growth rate (TGR)

The TGR of the patients (n=28) who underwent PVE was significantly greater before surgery than that of the non-PVE patients, showing median TGR 0.53 (IQR 0.02; 1.88)mL/day and 0.09 (IQR -0.04; 0.40)mL/day, respectively (p=0.03). No significant differences were seen in patients in whom chemotherapy was administered preoperatively (table 1).

Table 1. Patient characteristics of PVE patients and non-PVE patients with CRM. Values are shown in means±SEM or in n(%). PVE = portal vein embolization

	PVE	Non-PVE	p-value
Number of patients	28	30	
Sex (M:F)	20:08	19:11	0.512
Age (years)	62±2	58±2	0.212
Compromised liver	7 (25%)	10 (33%)	ns
CEA-level (median, IQR) in µg/L	16.7 (2.4; 423.0)	6.1 (4.0; 33.3)	0.396
Biggest lesion (median, IQR)	5.4 (2.2; 7.4)	3.1 (1.7; 4.9)	0.037
Number of lesions (median, IQR)	3 (2; 4)	2 (1; 3)	0.003
Synchronous/metachronous tumors	7/21	13/17	0.142
Chemotherapy	17 (61%)	14 (47%)	ns
Cycles of chemotherapy (n)			ns
1-3	2	4	
4-6	11	3	
7-9	3	7	
>10	1		
Type of chemotherapy			ns
Oxaliplatin, Capecitabine, Bevacuzimab	6	3	
Oxaliplatin, Capecitabine	9	8	
Capecitabine, Irinotecan, Panitumumab	1		
Oxaliplatin, 5-Fluorouracil/leucovorin	1	1	
Capecitabine, Bevacuzimab		1	
Irinotecan, Bevacuzimab		1	
Resection type			p<0.05
Right hemihepatectomy	14	6	
Left hemihepatectomy	0	3	
Right extended hemihepatectomy	8	1	
Left extended hemihepatectomy	0	2	
Metastectomy	3	18	
Unresectable	3	0	
Tumor volume pre-PVE/resection (mL)	131±44	153±55	ns

The median TGR in the ten PVE patients in whom two scans were performed before PVE was 0.15 (IQR -0.52; 0.66)mL/day, which increased to 0.85 (IQR -0.10; 1.62)mL/day after PVE in the same patients (p=0.03). Figure 1 summarizes the results of TGR.

Exponential tumor growth rate (ETGR)

In the PVE-patients, a median ETGR of 0.0061 (IQR 0.0023; 0.0244)ln(ml)/day was found, compared to a median of 0.0040 (IQR -0.0039; 0.0099)ln(ml)/day in the non-PVE

group (p=0.269). In the patients undergoing PVE (n=10), the median ETGR was 0.0004 (IQR -0.0073; 0.0143)ln(ml)/day before PVE, and 0.0054 (IQR -0.00900.0186)ln(ml)/day following PVE, showing enhanced tumor proliferation after PVE compared to pre-PVE (p=0.139). These results did not reach statistical significance but are numerically in line with the outcomes of the linear tumor growth rates, showing tumor progression after PVE.

Future remnant liver

The PVE-group (n=28) showed a significant increase in FRL volume after PVE. The mean FRL volume pre-PVE was 480.7±31.9mL versus 716.1±48.7mL post-PVE (p<0.001), which corresponds with a 28.5% FRL prior to PVE and 42.1% after PVE. No significant correlations between tumor volume increase and increased FRL were found (ρ=0.423).

Seven of 28 PVE-patients (25%) showed new tumor lesions in the FRL three weeks after PVE. Three of these patients (11%) were not deemed resectable after PVE for this reason. When examining the first follow-up imaging after resection, PVE-patients showed a higher proportion (8/19; 42%) of recurrent metastases in the remnant liver as compared to the non-PVE patients (1/28; 4%). The median time-interval between resection and first follow-up imaging was 82 (range 6-297) days in the PVE group and 102 (range 5-762) days in the non-PVE group (p=0.011).

Chemotherapy

Chemotherapy before PVE was administered in 17 out of 28 patients (61%), of whom one patient also received chemotherapy after PVE, before resection. Another patient received chemotherapy only in the time period between PVE and surgery (three cycles). No significant correlations were found between the changes in tumor volume after PVE in patients who received chemotherapy or not preceding PVE (*r*=0.262, p=0.178). Also no significant correlations were found between TGR and the number of cycles of chemotherapy (ρ=-0.075, p=0.703). In the non-PVE group (n=30), 14 patients received chemotherapy before

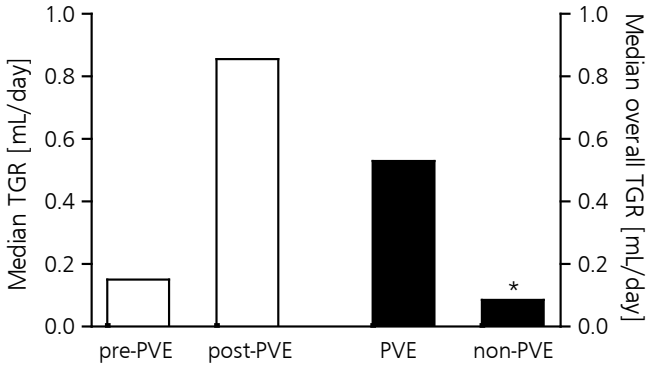

Figure 1. Tumor growth rate (TGR) was 0.15 (range -3.79–1.00)ml before portal vein embolization (PVE), and 0.85 (range -1.46–4.67)mL/day after PVE in the same patients (n=10, p=0.08). The median overall TGR of PVE patients (n=28) was 0.53 mL/day (range -4.24–8.00) vs 0.09mL/day (range -5.01–8.74) in non-PVE patients (n=30, p=0.03).

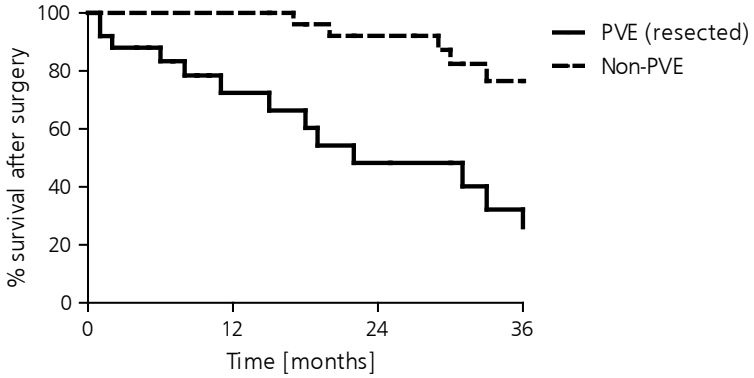

Figure 2. 5-year survival rates of PVE-patients who underwent resection versus PVE-patients who were not resected (p=0.04), and CRM patients who did or did not require preoperative PVE (p=0.02).

surgery. Again, no significant correlations were seen between tumor size changes or TGR and (cycles of) chemotherapy (ρ=-0.081, p=0.782 and ρ=-0.024, p=0.935 respectively).

Survival

We demonstrate a 3-year survival rate of 26% in our series of PVE-patients (figure 2). These patients had otherwise not been resected on the basis of the initial results of CT volumetry. The three patients with CRM (11%) who proved unresectable after PVE survived 5, 10 and 20 months respectively, while palliative chemotherapy was administered. These patients were considered unresectable, due to disease progression. Survival was better for non-PVE patients with a 3-year survival rate of 77% versus 26% in patients undergoing PVE.

Discussion

A schematic overview of the literature results pertinent to PVE and tumor growth is shown in table 2. The literature review suggests that PVE potentially induces tumor proliferation after PVE but there are no solid data to corroborate this notion. An important point is the natural history of tumor growth over time. It has been reported that the mean doubling time of CRM found by the surgeon at laparotomy is 155±34 days, in comparison to 86±12 days for CRM detected by the CT scan post-operatively.[11] We assessed the outcomes of PVE in our department using a large sample size, with the main focus on tumor volume and growth changes after PVE. Furthermore, we paid special attention to potential tumor development in the future remnant liver after PVE, and the effects of chemotherapy. We showed a significant increase in mean tumor volume after PVE, although this increase cannot be ascribed to PVE alone. A control group was therefore included in this study to compare the outcomes with patients who did not undergo PVE. This is the first study comparing patients with and without PVE in which tumor growth before and after PVE are reported, allowing us to compare clinical tumor progression before and after PVE.

Table 2. Summary of literature. Numbers are expressed as median values with range, unless otherwise stated.

Authors	Patients (n)	Diagnosis (n)	Conclusion	Decrease/ Increase
Elias et al Br J Surg 1999	PVE (5)	CRM (3) Carcinoid (1) Sarcoma (1)	Increase TV, NEL (n=4), 60-970% Slightly decrease TV, NEL (n=1), -30%	Increase TV NEL
Azoulay et al Ann Surg 2000	PVE (30) Non-PVE (88)	CRM	10 patients (33%) no resection after PVE because of tumoral extension	Unclear
Kokudo et al Hepatology 2001	PVE (18) Non-PVE (29)	CRM	PVE: TV increase EL (n=15): 20.8% NEL+EL (n=3): NEL: 9.7 (0.5-42.1)% EL: 2.8 (2.5-6.3)%	Increase TV EL
Barbaro et al Acta Radiol 2003	PVE (9)	CRM (6) Carcinoid (3)	TV increase EL (n=6, CRM): 84.4 (62.4-562)% TV unchanged EL (n=3, carcinoid)	Increase TV EL, CRM
Hayashi et al Acta Radiol 2007	PVE (8)	HCC (6) CCC (2)	TGR increase EL: 0.59 (0.22-6.01) to 2.37 (0.29-13.97)cm^3/day	Increase TGR EL, HCC
Ribero et al Br J Surg 2007	PVE (112)	CRM (50) HCC (24) CCC (14) Galbladder carc (6) Other (18)	TV change (n=80): 5.3 (2.2-12.8) to 5.4 (1.9-15.2) cm 10 patients (8.9%) no resection after PVE because of tumoral extension	Unclear
Pamecha et al Br J Cancer 2009	PVE (22) Non-PVE (20)	CRM	TGR increase: PVE: mean 0.36±0.7mL/day Non-PVE: mean 0.05±0.3mL/day	Increase TGR
Mailey et al J Surg Oncol 2009	PVE (20)	CRA (9) HCC (4) CCC (4) Other (3)	Change in max diameter: Unresected: mean 45±63% Resected: mean -6±27% 8 patients (40%) no resection after PVE because of tumoral extension	Increase TV
Treska et al Rozhl Chir 2010	PVE (40)	CRM (35) Breast metast (2) Ovarian metast (1) HCC (2)	11 patients (28%) tumoral extension	Unclear

PVE = portal vein embolization; CRM = colorectal metastases; TV = tumor volume; NEL= non-embolized liver lobe; EL = embolized liver lobe; HCC = hepatocellular carcinoma; CCC = cholangiocarcinoma; TGR = tumor growth rate; CRA = colorectal adenocarcinoma.

The time period between the scans were different within and between groups, therefore, we calculated the TGR and ETGR per day which are better indicators of tumor proliferation. We found a higher TGR after PVE compared to pre-PVE (0.85 vs 0.15mL/day) in the same patients in our series, which is consistent with the results of Hayashi et al.[6] Furthermore, our results show that PVE is associated with larger TGR in comparison to patients that do not require preoperative PVE, a similar finding as found in the study of Pamecha et al.[9]

The effects of PVE on tumor progression are not always clinically relevant since the tumor is commonly located in the part of the liver that will be resected. However, when the tumor is located near the intended resection plane or liver hilum, increase of tumor may become troublesome. Besides that, if PVE also increases tumorigenesis, new tumors may develop in

the FRL endangering resectability of the patient. We assume that PVE can lead to activation of dormant micrometastases in the FRL, while the presence of microtumors is not detectable by imaging studies prior to PVE or to liver resection. These micrometastases are stimulated to grow by the process of liver regeneration triggered by PVE, comprising both cytokines and growth factors. It remains uncertain whether new tumors in the remnant liver are true new tumors or microtumors that were present but not detectable by imaging studies prior to PVE. Either way, PVE does provide a biological test to identify undetectable lesions before undertaking resection, which otherwise would obviously become apparent in the follow-up after resection (under the influence of post-resectional regeneration). In this regard, these new findings are helpful in that they may prevent a futile liver resection.

In literature, survival outcomes have been reported of patients resected after PVE compared to non-PVE patients. In the study of Wicherts et al, non-PVE-patients had a significantly better survival rate compared to PVE patients, with a 3-year survival rate of 61% and 44%, respectively[12], outcomes which compare reasonably well with the 3-year survival rates reported in our series, i.e. 77% and 26%, respectively. Remarkably, of the 99 patients who received PVE in the study of Wicherts et al[12], 32 (32%) patients were not resectable following PVE since tumor had spread (n=27), or an insufficient hypertrophy response had occurred. Of the latter patients, 10 patients survived for one year, 8 patients died within two years and finally, no patients survived longer than 3 years after PVE. In our study, only three patients (10.7%) were not able to undergo resection after PVE, and these patients showed a survival of 10.3±8.4 (range 5-20) months. One of the remaining questions is whether there are other reasons why survival should be different between patients that underwent PVE and non-PVE-patients. Survival could be influenced by chemotherapy, the size of the biggest lesion, the number of lesions, and synchronous or metachronous tumors (table 1). Ideally, independent predictors of poor long-term outcomes are determined by multivariate analysis; however, this was not possible in our study comprising 58 patients in total.

Our study has some limitations. Firstly, a PVE-group was compared with a non-PVE group, although the tumor burden in patients requiring PVE is usually higher and prognosis worse, leading to a bias in selection. Furthermore, the volumes of liver metastases were different between both groups at presentation (i.e., non-PVE: 153.3±54.9, PVE: 131.4±44.3), although not statistically significant (p=0.472). However, this is the first report of a series with a large sample size, primarily focusing on tumor changes in patients after PVE and development of new tumor in the future remnant liver.

Many patients undergo both PVE and chemotherapy. The latter, because of its anti-proliferative effect, may hamper regeneration and influence postoperative complications. In most patients of this study, chemotherapy was administered before PVE. Some studies showed excellent results of the combination of chemotherapy and PVE in relation to the liver hypertrophy response after PVE.[13-15] Chemotherapy pre-PVE did not impair liver regeneration in response to PVE. Also, survival, morbidity and mortality rates were similar for patients undergoing a two-stage hepatectomy (chemotherapy first, then minor hepatectomy, followed by portal vein ligation or PVE if indicated, and finally major hepatectomy), compared

to a single stage hepatectomy.[14] Several studies favor stopping chemoembolization 6 to 8 weeks before any intervention, such as PVE or liver resection.[15,16] Key questions are whether chemotherapy administered post-PVE inhibits tumor progression, and which time interval should be observed between cessation of chemotherapy and resection after PVE. These are important issues to be studied in future research. Recently, de Graaf et al[17] compared the increase in FRL function after PVE as measured by dynamic ^{99m}Tcmebrofenin hepatobiliary scintigraphy, with the increase in FRL volume as measured by CT volumetry. They showed that 23±4.9 days following PVE, the increase in FRL function exceeded the increase in FRL volume. These findings suggest that the recommended waiting time until operation may be shorter than usually indicated by volumetric parameters. Therefore, we assume that a waiting-time of two to three weeks is sufficient between PVE and resection. Furthermore, there seems to be a place for chemotherapy in the waiting time after PVE to control tumor growth. Goéré et al compared 10 patients treated by chemotherapy in the interval between PVE and hepatectomy with 10 patients without chemotherapy.[18] They reported that chemotherapy can be safely continued until liver surgery when the portal vein is embolized without impairment of the hypertrophy of the future remnant volume or the postoperative course after liver resection. In contrast, Beal et al showed that chemotherapy administered in the interval between PVE and liver resection impaired liver hypertrophy.[19] However, the latter authors observed that patients without chemotherapy were more likely to have tumor progression between embolization and liver resection. Concluding from their study, chemotherapy between PVE and hepatectomy did not prevent, but did reduce liver hypertrophy after PVE.[19] Transarterial chemoembolization (TACE) has also been used to prevent tumor progression.[20] The combination of TACE and PVE has a strong anticancer effect[21], and therefore, has a strong potential to suppress tumor growth after PVE.

Although our results support the evidence from literature that PVE increases tumor growth, further research is required to confirm these findings. Ideally, in a clinical trial, patients would be randomized to undergo liver resection for similar tumor burden to receive preoperative PVE or not. Only one prospective clinical trial has been published in which patients were randomized to undergo PVE or not.[22] The authors concluded that in patients with normal livers, there was no benefit of liver regeneration induced by PVE on postoperative outcomes. A criticism on the latter study design is that only standard right hepatectomies were performed, leaving out the extended right liver resections which are the resections prone to insufficient FRL. A randomized controlled trial is unethical to perform in our opinion, since most patients that require preoperative PVE are unresectable without PVE.

In conclusion, there is evidence that PVE increases tumor growth in both the embolized and non-embolized side of the liver. The beneficial effects of preoperative PVE on FRL volume must therefore be weighed against potential enhancement of tumor growth in the tumor bearing lobe, and induction of new tumor in the FRL after PVE, or recurrent tumor after PVE and resection. We therefore advise short intervals (i.e. 2-3 weeks) between PVE and resection as well as interval chemotherapy.

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