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Impact of Portal Vein Embolization on Long-Term Outcome in Patients with Colorectal Liver Metastases

Yaacov Goykhman[1#], Saeed Sirhan[2#], Alex Barenboim[2], Isaac Kori[3], Sharon Peles-Avraham[4], Guy Lahat[2], Michal Shimonovich[2], Joseph M Klausner[2], Menahem Ben-Haim[5#] and Nir Lubezky[1#]*

[1]Department of HPB and Transplant Surgery, Tel-Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

[2]Division of Surgery, Tel-Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

[3]Unit of Invasive Radiology, Tel-Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

[4]Institute of Oncology, Tel-Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

[5]Department of Surgery, Shaarey Zedek Medical Center, Israel

[#]These authors contributed equally to this work

Abstract

Background: Portal Vein Embolization (PVE) is used to increase Future Liver Remnant (FLR) volume before major liver resection. There is concern that PVE may stimulate cancer growth and jeopardize long-term outcome in patients with Colorectal Liver Metastases (CRLM). We compared survival outcomes of patients with CRLM who underwent major liver resection without PVE.

Methods: Data of patients undergoing major liver resection for CRLM between 2006 and 2018 were analyzed retrospectively. Clinical characteristics, Overall Survival (OS), and Disease-Free Survival (DFS) were compared between patients who underwent major liver resection w/wo PVE. Groups with comparable oncologic risk factors (Memorial Sloan Kettering Cancer Center [MSKCC] risk score) were compared.

Results: Forty-one of the 53 patients who underwent PVE underwent curative liver resection, and 12 patients did not due to disease progression. Seventy-seven patients underwent major liver resection without preoperative PVE. Subgroup survival analyses based on the MSKCC score (MSCKCC 0-1; 2-3; 4-5) revealed a median DFS for PVE *vs.* non-PVE of 19 *vs.* 34 months (P=0.02), 11 *vs.* 15 (P=ns), and 7 *vs.* 13 (P=ns). The respective median OS of the groups was 90 *vs.* 93 months, 36 *vs.* 46, and 52 *vs.* 33 (P=ns for all). PVE had no influence on DFS or OS (multivariate COX regression analyses).

Conclusion: PVE in patients with inadequate FLR enables safe resection. Multivariable analysis demonstrates that PVE does not result in decreased OS and DFS, thus supporting its long-term oncologic safety.

Keywords: Portal Vein Embolization (PVE); Liver metastases; FLR; CRLM

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Correspondence:
Nir Lubezky, Department of HPB and Transplant Surgery, Tel-Aviv Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, 6 Weizman Street, Tel Aviv 6423906, Israel,
E-mail: nirl@tlvmc.gov.il

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Introduction

Liver resection provides the only chance for cure in patients with Colorectal Liver Metastases (CRLM). Recent series reported 5-year survival rates exceeding 50% following resection of all metastases [1-5]. Current recommendations are to carry out resection in patients in whom complete removal of liver metastases can be achieved with reasonable perioperative morbidity and mortality provided that the tumors demonstrate response or at least stability to preoperative chemotherapy [6]. Similarly, resection is advocated for patients with initially unresectable liver metastases that become resectable after systemic chemotherapy treatment [7]. The main limitation for such extended hepatectomies is insufficient Future Liver Remnants (FLR). Moreover, since most patients who undergo major hepatectomies for CRLM receive preoperative chemotherapy, chemotherapy-associated liver injury may worsen postoperative liver dysfunction in patients with small FLR. First described by Makuuchi et al. in 1990 [8], Portal Vein Embolization (PVE) induces ipsilateral atrophy and contralateral hypertrophy of the FLR. PVE was also shown to decrease perioperative morbidity and liver failure rates in patients undergoing major hepatectomy [9]. Most liver surgeons

recommend PVE in patients receiving chemotherapy who have FLR lower than 30% of the total liver volume [10-12]. However, several authors have raised concerns that the regeneration process following PVE involves activation of regulatory pathways that could potentially increase tumor growth in the embolized as well in the contralateral lobe [13-18]. Such concerns have led to the recommendation that resection of all metastases in the remaining liver should be completed prior to PVE [18-21]. Still, a clear link between PVE and tumor growth has not been demonstrated, and there is controversy as to whether or not PVE negatively affects long-term oncologic outcomes in patients undergoing curative-intent liver resection [22]. The aim of this study was to assess the impact of PVE on Overall Survival (OS) and Disease-Free Survival (DFS) in patients undergoing major hepatectomies for CRLM. This case-controlled study compared outcomes in a matched cohort of patients that underwent major hepatectomies after preoperative PVE with those of patients that underwent major hepatectomies without it.

Patients and Methods

Study design and patients

This is a comparative study based on retrospective data collection. The study was approved by the Tel-Aviv Medical Center (TAMC) Institutional Review Board which waived informed consent. All patients admitted to TAMC for liver surgery for CRLM between 2006 and 2018 were identified in the Department of Surgery - Liver Resection database. All consecutive patients who underwent liver resection of 3 or more segments were included in the study. The PVE group included all patients that underwent PVE before major liver resection, and the non-PVE group (no-PVE) included patients that underwent upfront major liver resection without preoperative PVE. PVE was carried out when the anticipated FLR volume was less than 40% of the total liver volume in patients receiving chemotherapy, and less than 30% in patients planned for up-front liver surgery. FLR is measured by the operating surgeon with the assistance of a radiology technician. The software used for this assessment is Philips IntelliSpace Portal v11 Liver Analysis. Patients were stratified to 3 groups according to a preoperative oncologic scoring system based on the Memorial Sloan Kettering Cancer Center Clinical Score [MSKCC] [21]: Disease-free interval from diagnosis of the primary tumor to metastases development <12 months, Carcinoembryonic Antigen Level (CEA) >200 ng/ml, largest tumor diameter >5 cm, number of liver metastases >1, and node-positive primary tumor.

Initial staging and treatment strategy

Staging included contrast-enhanced chest and abdomen Computer Tomography (CT) or magnetic resonance imaging studies. 5-Fluorodeoxyglucose Positron-Emission Tomography (FDG-PET) scans were included in the initial staging of most of the patients up to 2010, and in all of the patients since 2010. The tumor markers CEA and CA 19-9 were also assessed. Following the initial patient staging, a multidisciplinary team that included liver surgeons, colorectal surgeons, oncologists, and radiologists held discussions for treatment planning. Patients with unresectable metastases and patients with 2 or more clinical prognostic factors were referred for neoadjuvant chemotherapy. Patients with resectable metastases and fewer than 2 clinical risk factors were referred directly for surgery.

Chemotherapy

Patients who underwent preoperative chemotherapy received the standard chemotherapy regimens for first-line metastatic colorectal cancer, FOLFOX/XELOX or FOLFIRI, and a biological agent, either bevacizumab or cetuximab was added at the discretion of the patient's oncologist. Patients with a lower performance status received only 5FU and a biological agent (Table 1). The tumor response to chemotherapy was assessed according to the RECIST criteria [23-36].

Surgery

All resections were initiated with curative intent. Surgical exploration and intraoperative ultrasound were performed in all cases to detect occult metastases and to plan appropriate resections. Resections of all metastatic sites were executed with the goal of maximal parenchymal preservation. A major hepatectomy was defined as the resection of 3 or more liver segments. Patients with bilobar metastases who were planned for PVE underwent 2-stage resections: The first stage included resection of tumors in the FLR followed by PVE, and the second stage included resection of the embolized lobe.

Follow-up

All patients were followed with serum tumor markers and abdominal and chest CT studies every 3 months for the first 2 years, every 6 months for 3 years, and every year thereafter.

Statistical analysis

Based on descriptive tables (max, min, median, mean, standard deviation, and proportions), the original data were checked, anomalous values were excluded, and small categories were combined. Possible relationships between dependent and independent variables were defined with bivariate correlations (Pearson, Spearman). Assessment of the likelihood of PVE (OS and DFS) was done using Kaplan-Meier (log rank test) and COX regression. A P value <0.05 was considered statistically significant for all tests. Statistical analyses were performed with SPSS software package (Release 23.0.0, SPSS Inc., 2014).

Results

A total of 118 patients underwent major liver resection for CRLM at TAMC during the study period, including 41 patients operated after PVE and 77 patients operated up-front without PVE. The demographics, oncologic parameters, tumor characteristics, chemotherapy regimens, and tumor response of both groups of patients are summarized in Table 1. The patients in the PVE group were significantly older (64 *vs.* 59 years, P=0.02). Primary tumor location (rectum versus colon), tumor grade, regional lymph node involvement, liver metastasis with a disease-free interval less than 1 year, tumor marker level, and size of the largest metastasis did not significantly differ between the 2 groups. The number of metastases was significantly higher in the PVE group (2 *vs.* 4, P=0.003). The median MSKCC score was 2 in both groups. More patients in the PVE group received preoperative chemotherapy compared to those in the no-PVE group (100% *vs.* 72.7%, respectively, P=0.01), and they also received more chemotherapy cycles (6 *vs.* 4, P=0.001). There were no significant group differences in tumor response to preoperative chemotherapy.

Portal vein embolization

PVE was performed in 53 patients. The median interval between PVE and the last FLR imaging study was 39.5 (17 to 144) days, and the median period between PVE and liver resection was 59 days. Twelve of the patients that underwent PVE (22.6%) did not subsequently undergo curative resection due to tumor progression found on CT (n=8), tumor progression found on surgical exploration (n=3), and

Table 1: Clinical characteristics.

Characteristic	No PVE *n*=77	PVE *n*=41	*P*
Age, years	59	64	**0.02**
Sex (F)	35 (45.4%)	20 (48.7%)	0.7
Primary tumor			
Colon	58 (75.3%)	29 (70.7%)	0.5
Rectum	19 (24.7%)	12 (29.2%)	
Regional LN positive	42 (54.5%)	16 (39%)	**0.06**
Total lymph nodes	16	16	0.7
Disease-free interval <1 year	41 (53.2%)	28 (68.2%)	0.1
Metastases (median)	2	4	**0.003**
Size of largest metastasis (mm)	45	35	0.2
CEA (median)	17.7	9.8	0.2
CA 19-9 (median)	19.8	16.8	0.2
Grade			
Well-differentiated	4 (5.2%)	6 (14.6)	
Moderately differentiated	37 (48%)	19 (46.4%)	0.5
Poorly differentiated	6 (7.8%)	5 (12.2%)	
Unknown	30 (39%)	11 (26.8%)	
Preoperative chemotherapy			
Yes	56 (72.7%)	41 (100%)	**0.01**
No	21 (27.3%)	0	
Type of preoperative chemotherapy			
5FU + Avastin	4(5.2%)	1 (2.4%)	0.6
Xelox + Avastin	4(5.2%)	5 (12.2%)	0.2
FOLFOX	1 (1.3%)	0	0.3
FOLFOX + Bevacizumab (Avastin)	32 (41.7%)	29 (71%)	**0.03**
FOLFOX+ Cetuximab (Erbitux)	3 (3.8%)	0	0.7
FOLFIRI + Bevacizumab (Avastin)	6 (7.8%)	2(4.8%)	0.9
FOLFIRI + Cetuximab (Erbitux)	2 (2.6%)	1(2.4%)	0.8
FOLFIRI	1 (1.3%)	1(2.4%)	0.8
Unknown	3 (3.8%)	2 (4.8%)	0.1
Number of chemotherapy cycles	4	6	**0.001**
RECIST criteria			
Progressive disease	7(12.5%)	2 (4.8%)	0.1
Stable disease	3 (5.3%)	3 (7.3%)	0.8
Partial response	36 (64.3%)	32 (78%)	0.4
Complete response	3 (5.3%)	3 (7.3%)	0.8
Unknown	7 (12.5%)	1 (2.4%)	0.2
MSKCC score (median)	2	2	0.7
MSKCC1 score 0+1	23	8	0.1
MSKCC2 score 2+3	40	27	0.1
MSKCC3 score 4+5	14	6	0.1

PVE: Portal Vein Embolization
Bold indicates significant

inadequate hypertrophy after PVE and therefore not suitable to undergo curative surgery (n=1).

Surgical procedures

The surgical procedures are listed in Table 2. The PVE group underwent significantly more extended hepatectomies (24.5 *vs.* 2.6%, respectively, P=0.001). The overall morbidity rate was 21.6% (14 patients) in the PVE group, and 29.8% (23 patients) in the up-front resection group. The rate of severe complications (Clavien-Dindo ≥ 3) was 16.8 % (13 and 12 patients, respectively) in each group. The perioperative 90-day mortality rate was 4.8% in the PVE group (2 patients) and 2.6% in the up-front resection group (2 patients).

Survival and recurrence

The operated patients were followed for a median of 46 months (45.5 months for the PVE group and 46 months for the up-front resection group). Recurrence was diagnosed in 32 (78.1%) of the PVE patients after a median of 12 months, and in 49 (63.6%) of the

Table 2: Surgery.

Variable	No PVE *n*=77	PVE *n*=41	*P*
Surgery			
Right hepatectomy			
Left hepatectomy	56 (72.7%)	27 (65.8%)	0.4
Left hepatectomy and single right	14 (18.2%)	3 (7.3%)	0.1
segmentectomy	1 (1.3%)	1 (2.4%)	0.1
Right trisegmentectomy			
3+ different segments resection	2 (2.6%)	10 (24.5%)	**0.001**
Right anterior sector resection + left medial	1 (1.3%)	0	0.2
sectionectomy	2 (2.6%)	0	0.15
Right posterior sector resection + left medial	1 (1.3%)	0	0.8
sectionectomy			
Simultaneous colon/rectum resection	13 (16.8%)/ 64 (83.2%)	3 (7.3%)/ 38 (92.7%)	0.14
Two-stage hepatectomy			
Yes	2 (2.6%)	13 (31.7%)	**0.01**
No	75 (97.4%)	28 (68.3%)	
Hospital stay (days, median)	6	9	0.4
Peak bilirubin (median)	1.8	1.95	0.3
Postoperative complications			
Clavien-Dindo 1-2	10 (13%)	2 (4.8%)	0.1
Clavien-Dindo 3-5	13 (16.8%)	12 (16.8%)	0.1
Length of operation (hours)	5.5	6	0.6
90-day mortality	2 (2.6%)	2 (4.8%)	0.5
Minimum necrosis (%)	40	37.5	0.7
Maximum necrosis (%)	60	50	0.9
Margin			
Involved	12 (15.6%)	8 (19.5%)	0.5
Not involved	65 (84.4%)	33 (80.5%)	

PVE: Portal Vein Embolization
Bold indicates significant

Table 3: Follow-up data.

Variable	No PVE *n*=77	PVE *n*=41	*P*
Follow-up interval (months)	46	45.5	
Recurrence			
Yes	49 (63.6%)	32 (78.1%)	**0.049**
No	24 (31.2%)	6 (14.6%)	
Unknown	5 (6.5%)	3 (7.3%)	
Disease-free interval (months)	17	12	**0.007**
Site of recurrence			
Extrahepatic	16 (20.7%)	7 (17%)	0.6
Intrahepatic	13 (16.8%)	9 (22%)	0.5
Extra + intrahepatic	19 (24.6%)	13 (31.7%)	0.4
Unknown		3 (7.3%)	

PVE: Portal Vein Embolization
Bold indicates significant

Table 4: Median disease free survival by MSKCC subgroups.

	No PVE *n*=77 *n* (range)	PVE *n*=41 *n* (range)	*P*
MSKCC1 score 0+1	34 (5.7-62.2)	19 (10.8-27.1)	**0.02**
MSKCC2 score 2+3	15 (3.4-26.5)	11 (6.3-15.6)	0.3
MSKCC3 score 4+5	13 (9.6-16)	7 (0-14)	0.1

PVE: Portal Vein Embolization
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up-front patients after a median of 17 months. The median DFS survival was significantly higher in the no-PVE group, P=0.01. The sites of initial recurrence are listed in Table 3. The median OS was not significantly different between the PVE and no-PVE groups (56 months and 59 months, respectively, P=0.086). The median survival of patients that did not undergo liver resection after PVE was 28 months. We performed a subgroup survival analysis based on the MSKCC clinical score (MSCKCC 0-1; 2-3; 4-5). The median DFS

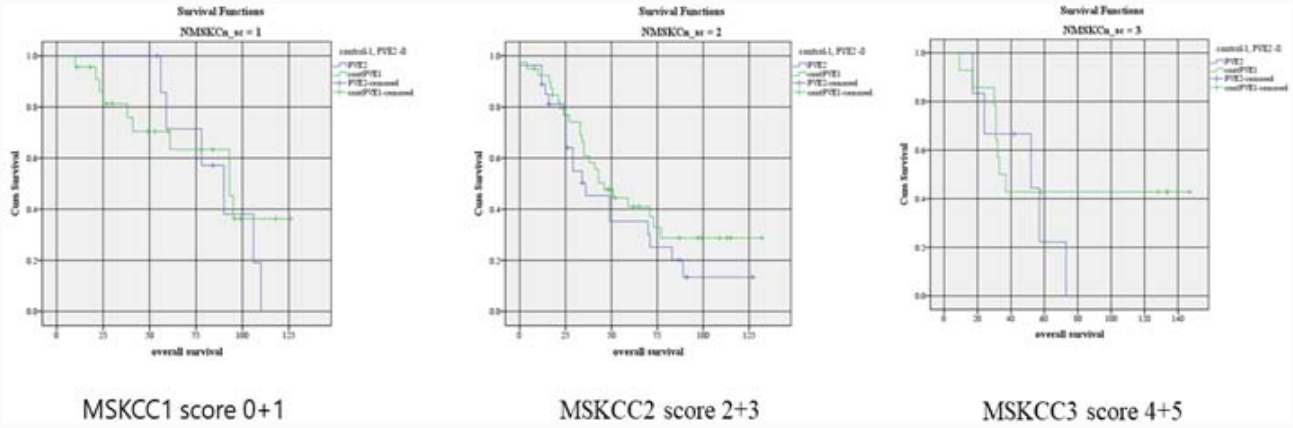

Figure 1: Overall survival by MSKCC subgroups.

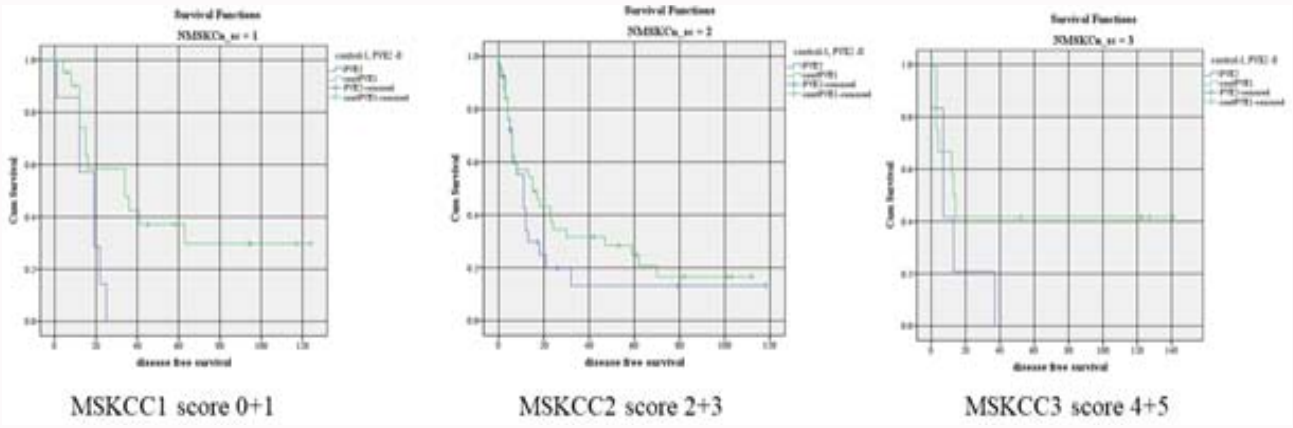

Figure 2: Disease-free survival by MSKCC subgroups.

Table 5: Median overall survival by MSKCC subgroups.

	No PVE *n*=77 *n* (range)	PVE *n*=41 *n* (range)	*P*
MSKCC1 score 0+1	93 (59.8-126.1)	90 (65.3-114.6)	0.6
MSKCC2 score 2+3	46 (31.7-60.2)	36 (18.9-53.08)	0.2
MSKCC3 score 4+5	33 (23.8-42.1)	52 (0-106.8)	0.4

PVE: Portal Vein Embolization

Table 6: Cox model of overall survival.

			95% CI for Exp(B)	
	Exp(B)	Significance	Lower	Upper
Age	1.018	0.06	0.999	1.037
CA 19-9	1	0.001	1	1.001
MSKCC1 score 0+1	0.354	0.048	0.126	0.991
PVE	1.039	0.8	0.598	1.8

of the PVE *vs.* the non-PVE patients in the subgroups was 19 *vs.* 34 months (P=0.02), 11 *vs.* 15, (P=ns), and 7 *vs.* 13 (P=ns). There was a significant difference in DFS only in the first subgroup of a MSKCC score of 0+1 (P=0.02). The median OS between the subgroups was not significantly different among the 3 subgroups: 90 *vs.* 93 months, 36 *vs.* 46, and 52 *vs.* 33 (P=ns for all). We performed a multivariate COX regression analysis which showed that PVE had no influence on median DFS or OS (hazard ratio = -0.4; 95% confidence interval 0.4-1.08; P=0.1).

Discussion

The aim of this retrospective analysis was to assess the impact of PVE on OS and DFS in patients undergoing major hepatectomies for CRLM. Our results demonstrated that PVE in patients with CLRM is associated with significant risk for immediate disease progression, thus precluding curative resection in more than 20% of patients. However, preoperative PVE is not associated with compromised long-term oncologic outcomes in patients that undergo major liver resection compared with patients that undergo major liver resection without it. Our data confirm the safety of extended liver resection in patients operated after PVE. Taken together, these results raise concern about the oncologic benefit of PVE in patients with CRLM and support the search for alternative methods to induce FLR hypertrophy, such as associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) or radioembolization. Several studies reported short-term safety and efficacy of PVE in patients with CRLM as well as other hepatic malignancies, which have insufficient FLR [23,24]. The short-term effect of PVE on the progression of metastases after PVE was first reported by Elias, who described hepatic metastases progression in 80% of patients after PVE [17]. Simoneau et al. [25] reported that following PVE in 141 patients with CRLM, 66% had evidence of intrahepatic tumor progression, including a 12.1% risk for developing new metastases in the FLR. According to their treatment protocol, chemotherapy was stopped between 4 to 6 weeks prior to PVE. Hoekstra et al. [26] reported an

increased tumor growth rate in patients after PVE compared to patients that did not undergo PVE, as well as increased tumor growth rate in PVE patients during the month before they underwent PVE. Additionally, 25% of their patients showed new tumor lesions in the FLR after PVE. Pommier et al [27] observed that the risk for intrahepatic tumor growth after PVE correlated with slow response to induction chemotherapy. Whereas slow responders (more than 6 cycles of chemotherapy) had evidence of tumor progression in 65% of cases, fast responders (fewer than 6 cycles of chemotherapy) showed a decrease in tumor volume after PVE. Short-term tumor progression is clearly associated with reduced long-term survival when it results in the inability to complete curative resection. Several studies have shown that patients who underwent PVE but did not undergo curative resection had poor long-term survival [28,29]. According to our data, 12 patients (22% of our PVE patients) did not undergo curative resection, mostly due to hepatic tumor progression. The median survival of those patients was 15.5 months compared with a median survival of 56 months for patients who underwent curative resection after PVE (P=0.001). The vast majority of our patients did not receive chemotherapy between PVE and surgery. We realize that this practice needs to be changed, and that whenever possible, chemotherapy should be administered between PVE and surgery to minimize risk for disease progression. Another question that needs to be addressed is whether PVE results in compromised long-term oncologic outcomes in patients that undergo curative resection after PVE. Several studies reported conflicting results of the long-term recurrence and survival rates of patients post-PVE compared with up-front surgery [9,30,31]. Ardito et al. [31] reported similar 5-year DFS and 5-year OS rates in patients that underwent right and extended right hepatectomy with or without PVE. A multivariate analysis in their study revealed that PVE was not a prognostic factor for recurrence or survival. Huiskens et al. [30] performed a propensity score matching PVE and non-PVE patients to reduce selection bias and found no differences in DFS and OS rates between the 2 groups. In contrast, other studies demonstrated lower survival outcomes for PVE patients. Wicherts et al. [29] reported inferior long-term outcomes in 67 patients who underwent resection post-PVE compared with 297 patients who underwent major hepatectomies without PVE (5-year DFS 5% *vs.* 21%, respectively, P=0.004). The authors attributed the poorer oncologic outcomes to increased tumor load in the PVE group, although a multivariate analysis found PVE to be an independent prognostic factor for decreased survival. In order to minimize bias, we compared long-term outcomes in patients with similar oncologic risk factors according to the MSKCC clinical risk score. Our data showed that although DFS was shorter for the PVE group and that there was a trend towards shorter OS, PVE was not found on multivariate analysis to be a risk factor for decreased DFS or OS. This is probably the result of the increased tumor load in the PVE groups. Our data therefore support the long-term safety of PVE in patients who achieve curative resection. Alternative modalities to induce liver hypertrophy in patients with insufficient FLR include the use of radioembolization and ALPPS. Radioembolization with glass or resin beads carrying yttrium Y-90 was shown to be effective in both treating CRLM [32] and inducing atrophy [33] in the embolized lobe, with compensatory hypertrophy of the contralateral segments. However, there are currently no reports on either short- or long-term oncologic outcomes in patients with CRLM and insufficient FLR. In contrast, ALPPS is a well-described alternative for patients with CRLM and insufficient FLR. The potential advantage of ALPPS is the reduced interval between ligation of the portal vein and liver resection. A recent prospective randomized study by Sandstrom et al. [34] demonstrated superior short-term oncologic outcomes, significantly higher resection rates, and similar operative morbidity and mortality for patients that require a 2-stage hepatectomy who undergo the ALPPS procedure compared with PVE. It should be noted that long-term oncologic outcomes were not assessed, and that the group included only the patients that required a 2-stage hepatectomy. Limitations of this study include its retrospective nature. There is concern for selection bias since patients who undergo PVE may have a higher tumor load. The facts that more patients in the PVE group underwent extended resection and 2-stage hepatectomies, and that more patients in the non-PVE group underwent combined liver and colonic resections strengthen the concern for bias favoring less tumor load in the non-PVE group. We acknowledge that matching patients according to oncological characteristics, such as number of metastases, amount and type of chemotherapy, and extent of resection, among other factors, would have significantly improved the methodology of this manuscript. Our attempt to perform such a match was unsuccessful because the number of patients in the group that did not undergo PVE was too small, leaving too few patients available for matching. To minimize such bias, we stratified patients to groups according to their MSKCC clinical risk score. Our data demonstrated that PVE resulted in significantly shorter DFS (but not OS) only in patients with 0-1 MSCC risk factors. Indeed, DFS fell from 34 months in the non-PVE group to 19 months in the PVE group. The OS rates in this subgroup were similar for the PVE and the non-PVE patients. Although these data need to be validated in additional studies, they suggest that PVE may have a detrimental effect on DFS in the subgroup of patients with lower disease burden who generally have better survival. It is unclear why this effect is evident only among patients with low tumor load. However, if validated, alternative methods to enhance FLR volume in patients with 0-1 MSKCC risk factors should be preferred. Another limitation of this study is the inability to assess the impact of perioperative chemotherapy upon survival in the two groups. Our strategy with regard to perioperative chemotherapy is to administer a total of 12 cycles. Most patients receive 4 to 8 cycles preoperatively followed by an additional 4 to 8 cycles after recovering from the operation. Unfortunately, it would be very difficult to assess the influence of chemotherapy on survival in such a heterogenous group of patients.

Conclusion

PVE in patients with inadequate FLR who undergo curative-intent liver resection enables safe resection surgery. Multivariable analysis demonstrates that PVE does not result in decreased OS and DFS, thus supporting its long-term oncologic safety.

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