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ORIGINAL ARTICLE

Safety and efficacy of preoperative right portal vein embolization in patients at risk for postoperative liver failure following major right hepatectomy

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Abstract

Background: Right portal vein embolization (RPVE) has been utilized with or without segment IV (RPVE + IV) prior to hepatectomy to induce hypertrophy and prevent liver insufficiency in patients with a predicted future liver remnant (FLR) of ≤30% or cirrhosis.

Methods: Records of patients who underwent RPVE during 2006–2010 were retrospectively reviewed. Patient demographics, operative outcomes and complications were analysed. Computed tomography-based volumetrics were performed to determine FLR volume and degree of hypertrophy. Patients were stratified by segment IV embolization. Short-term outcomes following RPVE and liver resection are reported.

Results: A total of 23 patients were identified. Ten patients underwent RPVE and 13 underwent RPVE + IV. The RPVE procedure resulted in a 38% increase in FLR volume. Liver volumes, hypertrophy rates and outcomes were similar in both groups. Rates of operative complications in the RPVE and RPVE + IV groups were similar at 50% and 54%, respectively, and most complications were minor. Complication rates as a result of embolization were 30% in the RPVE group and 31% in the RPVE + IV group. One patient underwent modified operative resection as a result of a complication of RPVE.

Conclusions: Right portal vein embolization (±segment IV) is a safe and effective modality to increase FLR volume. Post-embolization complications and short-term outcomes after resection are acceptable and are similar in both RPVE and RPVE + IV.

Keywords

resection, radiological intervention, fluoroscopically guided

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Introduction

Portal vein embolization (PVE) was introduced by Kinoshita *et al.*[1] and Makuuchi *et al.*[2] to induce hypertrophy and prevent postoperative liver insufficiency among patients undergoing major hepatectomy. As originally described, PVE encompassed occlusion of either a left or right second-order portal venous branch. The procedure is now established as a technique to permit hepatectomy in many patients with an otherwise inadequate future liver remnant (FLR). Preoperative PVE is utilized when the FLR is estimated to comprise <20–30% of the total liver volume in a patient with normal hepatic parenchyma or <30–40% in a patient with underlying liver disease.[3–6]

Nagino *et al.* introduced the concept of PVE with extension to segment IV (PVE + IV) in patients undergoing extended right

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hepatectomy.[7] This technique is employed to optimize hypertrophy of segments II and III, but its safety and efficacy are controversial. A single-institution study indicated that it improves the hypertrophy of segments II and III compared with PVE alone without increasing complications.[8] However, others have failed to detect any significant increase in hypertrophy of segments II and III with the addition of segment IV embolization.[9]

Our institution employs a multidisciplinary team to determine the appropriate approach to preoperative PVE and liver resection. Currently, we use PVE in patients with an estimated FLR of ≤30% and normal hepatic parenchyma and in patients with an estimated FLR of ≤40% and underlying liver disease. We employ segment IV embolization when the operative plan includes an extended right hepatectomy. In this study, we sought to analyse our short-term outcomes after right PVE (RPVE) and subsequent operative resection and to assess the risks and benefits associated with segment IV embolization (RPVE + IV).

Materials and methods

Records of patients who underwent RPVE prior to major right hepatic resection during the years 2006–2010 were retrospectively reviewed. Patient clinical characteristics and data on procedural and operative outcomes were obtained via electronic chart review. The study was approved by our institutional review board.

Patients underwent liver resection carried out by one of two surgeons during the study period. Pre-procedure three-phase computed tomography (CT) assessment was performed at 1–71 days prior to embolization. Post-procedure CT scans were obtained at a median of 5.1 weeks (range: 2–18 weeks) following the procedure. In general, a 4-week interval was allowed to elapse between PVE and follow-up CT scan. Earlier scans were obtained in a small subset of patients to rule out disease progression. In others, follow-up scans were delayed for logistical reasons or as a result of complications related to PVE. Future liver remnant volumes and predicted resection volumes were determined by tracing the sections of liver in each transverse 5-mm slice of the patient's pre-procedure CT scan in the portal venous phase.[10] All values obtained were within a 5% standard deviation. The estimated FLR included segment IV as defined by the lateral border of the middle hepatic vein when a right hepatectomy was planned. Values for standardized FLR (sFLR) were obtained according to the following equation: sFLR = FLR volume (mL)/standardized liver volume (mL) × 100%. Values for standardized liver volume (sLV) were calculated by the formula: sLV = −794.41 + 1267.28 × body surface area (m^2).[11] Degree of hypertrophy was defined as [(post-embolization sFLR − pre-embolization sFLR)/pre-embolization sFLR] × 100%.

The PVE technique was performed with ultrasound and fluoroscopic guidance. Ultrasound was used to obtain initial access to the portal vein from a right lateral percutaneous approach in the majority of patients. When access from the right required traversing the tumour burden, contralateral access was obtained. After obtaining stable access to the portal vein, a 5-Fr sheath was placed over the wire, a flush catheter was advanced into the main portal vein, and digital subtraction angiography (DSA) of the portal venous anatomy was obtained. Frequently, oblique magnified projections were required to clearly identify major divisions of the portal vein branching pattern, as well as the portal venous supply to segment IV. After identification, the target vessel was selected with a wire and catheter combination to allow direct access to the vessel. On rare occasions a high-flow microcatheter was required to maintain stable access for both particulate and coil embolization. Once stable access to the target vessel was confirmed, the vessel was embolized to near stasis with small (approximately 100-μm in diameter) complex co-polymer embolic agents. Post-embolization DSA was performed to confirm limited flow. Frequently, additional embolic agents (including platinum coils sized appropriately to the vessel) were required. Using similar techniques, the major branches to the remainder of the targeted liver were catheterized and treated with a combination of embolic particles and additional embolic coils. Post-embolization DSA evaluation of the main portal vein was performed to confirm flow to the left lobe of the liver and minimal flow to the right lobe of the liver (with and without segment IV, respectively). If the right main portal vein was long enough, an Amplatzer plug (AGA Medical Corp., Plymouth, MN, USA) was inserted to embolize it. Effort was made to maintain enough room between the last embolic agent (coil or Amplatzer plug) and the portal vein bifurcation to allow the direct surgical clamp or vascular staple and ligation of the right portal vein at the origin. The catheters and sheath were then pulled back to the entry site of the portal venous system. The intraparenchymal tract was embolized with gel foam slurry and/or platinum microcoils. Completeness of embolization was assessed by a post-procedure CT scan.

Patient clinical characteristics, liver volumes and procedural and operative outcomes were stratified according to whether or not segment IV embolization had been performed and then compared. Postoperative complications were classified as previously described by Dindo *et al.*[12] Complications classified as Grade I or II were considered minor, whereas complications of Grade III or higher were considered major. Postoperative liver insufficiency was defined as a peak serum bilirubin of >7.0 mg/dL.[13] Normally distributed continuous data were expressed as means and standard deviations and were compared using a one-way analysis of variance (ANOVA). All other continuous variables were expressed as medians and interquartile ranges and compared using a Mann–Whitney *U*-test. Categorical data were compared using Fisher's exact test. *P*-values of ≤0.05 were considered to indicate statistical significance for all comparisons.

Results

Clinical characteristics

Twenty-three patients underwent RPVE at our institution during 2006–2010. Patients undergoing RPVE vs. RPVE + IV were similar

Table 1 Clinical characteristics of patients in the right portal vein embolization (RPVE) and RPVE + segment IV groups

Characteristic	RPVE (n = 10)	RPVE + IV (n = 13)	P-value
Age, years, mean ± SD	60.6 ± 9.7	59.4 ± 6.5	0.715
Male gender, *n*	6	8	1.000
ASA score ≥3, *n*	9	9	0.229
Body mass index, kg/m^2, median (IQR)	26.0 (23.3–28.0)	28.1 (23.5–32.7)	0.321
Aetiology, *n*			0.118
Colorectal cancer liver metastases	6	11	
Hepatocellular carcinoma	3	0	
Other	1	2	
Preoperative chemotherapy, *n*	7	11	0.618
Cirrhosis, *n*	1	1	1.000
Operation, *n*			0.068
Right hepatectomy	4	1	
Extended right hepatectomy	4	11	
No resection	2	1	

RPVE, right portal vein embolization; RPVE + IV, right portal vein embolization plus segment IV; SD, standard deviation; IQR, interquartile range; ASA, American Society of Anesthesiologists.

Table 2 Comparison of liver volume in patients undergoing extended right hepatectomy

	RPVE (n = 6)	RPVE + IV (n = 12)	P-value
FLR volume pre-PVE, mL, median (IQR)	532.1 (410.7–614.2)	441.0 (256.9–513.0)	0.396
FLR volume post-PVE, mL, median (IQR)	739.4 (694.9–813.2)	579.6 (420.0–703.3)	0.052
Change in volume, mL, median (IQR)	139.9 (125.3–299.7)	140.9 (119.3–243.8)	1.000
sFLR pre-PVE, %, median (IQR)	26.5 (20.7–37.2)	23.8 (18.9–29.9)	0.777
sFLR post-PVE, %, median (IQR)	37.5 (33.3–57.2)	35.7 (24.8–42.5)	0.697
Degree of hypertrophy, %, median (IQR)	23.8 (20.7–62.3)	38.3 (26.0–87.2)	0.310

RPVE, right portal vein embolization; RPVE + IV, right portal vein embolization plus segment IV; FLR, future liver remnant; PVE, portal vein embolization; sFLR, standardized future liver remnant; IQR, interquartile range.

with respect to age, gender, American Society of Anesthesiologists (ASA) score and body mass index (Table 1). Overall, 74% of these procedures were performed in patients with colorectal cancer metastases. The majority of patients (78%) underwent preoperative chemotherapy. Of those receiving chemotherapy, 94% followed a regimen containing oxaliplatin and completed a median of seven cycles (range: 2–12 cycles). A total of 50% of patients receiving chemotherapy were given bevacizumab (Avastin™). Chemotherapy was withheld for a minimum of 4 weeks prior to liver resection. Regimens including Avastin™ were withheld for 6 weeks preoperatively. One patient received chemotherapy between PVE and liver resection. Only two patients were known to have cirrhosis preoperatively. The majority of patients (87%) underwent definitive operative resection following PVE. Two of the three patients who did not undergo operative resection experienced disease progression that rendered them unresectable. The third patient was found to have macronodular cirrhosis at the time of the planned liver resection and the decision was made to treat the patient with radiofrequency ablation rather than liver resection.

Volumetric assessments

Preoperative sFLR volumes were <20%, 21–30% and >30% in 30%, 40% and 30% of patients, respectively. Preoperative and postoperative volume measurements were compared for patients undergoing extended right hepatectomy. Results are shown in Table 2. Median preoperative sFLR volumes were lower in patients undergoing RPVE + IV (23.8%) compared with patients undergoing RPVE (26.5%), although the difference did not reach statistical significance. The absolute change in FLR volume did not differ between the groups. The median degree of hypertrophy, defined as the percentage increase in the sFLR after PVE, was higher in those undergoing RPVE + IV (38.3%) than in those undergoing RPVE alone (23.8%), although this difference did not reach statistical significance.

Complications and outcomes of PVE

Complication rates after PVE were similar in the two groups (Table 3). No patients had incomplete embolization as evaluated by post-procedure CT scan. Five patients underwent hepatic access via the left portal venous system because of a high right-

Table 3 Short-term outcomes after right portal vein embolization (RPVE) and RPVE + segment IV

Outcome	RPVE (n = 10)	RPVE + IV (n = 13)	P-value
Length of stay, days, median (IQR)	7 (6.25–9)	7 (5–9)	0.350
Operative blood loss, mL, median (IQR)	750 (525–1000)	800 (500–1350)	0.855
Patients requiring transfusion, *n*			
Packed red blood cells	4	6	1.000
Fresh frozen plasma	4	5	0.673
Complications of RPVE, *n*	4	3	0.650
Operative complications, *n*	5	7	1.000

RPVE, right portal vein embolization; RPVE + IV, right portal vein embolization plus segment IV; IQR, interquartile range.

Table 4 Complications from portal vein embolization

Patient no.	Indication	Type of embolization	PVE complication	PVE outcome	Surgical outcome	Disease status at last follow-up
1	Colorectal cancer metastases	RPVE + IV	Pain/nausea	Hospital admission	Complete resection	Alive with disease at 3 months
2	Colorectal cancer metastases	RPVE + IV	Pain/nausea	Hospital admission	Radiofrequency ablation as a result of an intraoperative diagnosis of cirrhosis	Alive with disease at 7 months
3	Colorectal cancer metastases	RPVE	SMV thrombus	Delayed surgical resection by 6 months	Complete resection	No evidence of disease at 42 months
4	Colorectal cancer metastases	RPVE + IV	Subcapsular haematoma	ICU admission, blood transfusion	Complete resection	Alive with disease at 18 months
5	Colorectal cancer metastases	RPVE	Subcapsular haematoma	ICU admission	No resection secondary to disease progression	Died of disease
6	Colorectal cancer metastases	RPVE	Non-target embolization of segment II vessel	Operative plan changed from extended right hepatectomy to right hepatectomy	Complete resection	Alive with disease at 17 months
7	Colorectal cancer metastases	RPVE	Non-target embolization of segment IVa vessel	No change in operative plan	Complete resection	Alive with disease at 6 months

PVE, portal vein embolization; RPVE, right portal vein embolization; RPVE + IV, right portal vein embolization plus segment IV; SMV, superior mesenteric vein; ICU, intensive care unit.

sided tumour burden. Only one of these patients experienced a complication (subcapsular haematoma). Table 4 characterizes in more detail the complications seen after RPVE in our series. Two patients in the RPVE + IV group experienced post-procedure pain and nausea and required hospital admission. One patient had a thrombus in the superior mesenteric vein that delayed definitive operative resection for 6 months. Two patients had subcapsular haematomas and required intensive care unit (ICU) admission. One of these patients needed blood product transfusion, but both patients underwent their planned operative resection without delay. Two patients experienced non-target embolization of a portal vessel. One patient had non-target embolization of a segment IVa vessel that did not impact on the planned operative resection. Another patient had non-target embolization of a segment II vessel that caused the patient to undergo a right hepatectomy rather than the planned extended right hepatectomy. All lesions in this patient were resected with a negative operative margin, but a follow-up CT scan at 8 months demonstrated recurrence in the liver remnant.

Operative outcomes

Twenty (87%) patients underwent definitive operative resection after PVE. Eight (40%) underwent right hepatectomy and 12 (60%) underwent extended right hepatectomy. Short-term operative outcomes are listed in Table 3. There were no differences between the two groups in length of stay, operative blood loss or

requirements for blood product transfusion. The overall postoperative complication rate was 52% ($n = 12$). Nine (75%) of these patients underwent extended right hepatectomy. Most of the complications were minor and included four urinary tract infections, two wound infections, a transfusion reaction and an incisional wound ascitic leak. Four patients (17%), all of whom underwent extended right hepatectomy, experienced more serious complications, including one wound dehiscence, one episode of small bowel ischaemia requiring bowel resection, one case of bacteraemia and one episode of posterior reversible encephalopathy syndrome. There were no episodes of postoperative liver failure or death.

Discussion

Our multidisciplinary team has recently adopted a protocol that mandates the performance of RPVE in patients with normal liver function and a predicted FLR of ≤30% and in patients with impaired liver function and a predicted FLR of ≤40%. In patients who are scheduled for an extended right hepatectomy, we have favoured occlusion of the segment IV portal vein branches. Our results indicate that RPVE is associated with a consistent hypertrophic effect on the FLR. Although the embolic occlusion of the segment IV portal vessels produced a larger fractional hypertrophy of the planned remnant in patients undergoing extended right hepatectomy, this difference did not reach statistical significance compared with embolization of the right main portal vein alone. The lack of statistical significance in this observation is likely to be related to the relatively small numbers in each group. Although few patients in this study had cirrhosis, 78% ($n = 18$) had been treated with preoperative chemotherapy and still benefited from significant hypertrophy. Our findings are consistent with those of Kishi *et al.*, who reported statistically significant improvement in the hypertrophy of segments II and III in a larger series of patients with functionally normal liver after the addition of segment IV embolization to RPVE.[8] Our findings differ from those reported by Capussotti *et al.*, who found no difference in the hypertrophy of segments II and III in patients undergoing RPVE with segment IV embolization vs. RPVE alone.[9] In extended right hepatectomy, we have found that the transection of a small-volume segment IV is technically more favourable than attempting transection in a hypertrophied segment. We believe the potential for increased hypertrophy in segments I, II and III, coupled with the technical advantages provided by the division of an atrophic segment IV, represents sufficient reason to support routine preoperative embolization of segment IV vessels in patients undergoing planned extended right hepatectomy. The limitation of the segment IV embolization relates to the necessity of accessing the left portal vein and the small risk that errant embolic material will compromise one of the vessels in the planned remnant. This occurred in one patient in this series.

We found that although PVE-associated complications were not associated with post-procedural mortality, they did alter patient management. In some instances, the patient required extended hospitalization and in one case of a misplaced coil the patient required a substantive change in the operative plan, which was facilitated by tumour response to chemotherapy. Unfortunately, this patient suffered early disease recurrence in the liver remnant, which might have been avoided if the planned extended hepatectomy had been performed. Other series have reported complication rates in PVE of 2.2–12.8%.[8,14,15] A recent meta-analysis of preoperative PVE reported overall morbidity of 2.2% in 1088 patients and described the most common complications as abdominal pain or discomfort, and fever.[14] A recent article discussing quality improvement for PVE categorized complications after PVE as either minor (abdominal pain, fever, nausea, embolic material displacement without portal thrombosis) or major (liver abscess, cholangitis, main or left portal vein thrombosis, subcapsular haematoma).[16] The authors suggested that rates should not exceed 20–25% for minor and 5% for major complications.[16] In our series, we observed seven complications in 23 procedures, of which four (17% of patients) were minor and three (13% of patients) were major. Although our major complication rate is higher than previously reported rates, there were no episodes of liver insufficiency or death and none of the patients in our series were precluded from operation as a result of a PVE complication. Additionally, patients who underwent RPVE + IV embolization did not require significantly more packed red blood cells, fresh frozen plasma or platelet transfusions compared with those undergoing RPVE alone. This is an important indicator of adequate liver function after resection. Overall, our findings and those of others[8,14,15] underscore the conclusion that although PVE is safe, there is potential for major and minor complications, albeit at an acceptable level. In particular, the errant placement of embolic material may obviate the possibility of resection with curative intent and should be avoided.

Most importantly, our findings indicate that major hepatectomy can be accomplished with a low major complication rate and zero mortality after RPVE ± IV in a select group of chemotherapy-treated patients who would otherwise not have the opportunity to undergo curative liver resection. Although relatively few of our patients had documented cirrhosis, 78% ($n = 18$) had received preoperative chemotherapy for colorectal liver metastases (CLM). In recent years, this group has been shown to be at risk for chemotherapy-associated steatohepatitis (CASH).[17–19] Although the predictors of CASH include obesity, diabetes and irinotecan therapy, most patients are at risk for a non-specific chemotherapy-associated injury to the liver.[17–19] In this group of patients, associated postoperative morbidity and mortality following liver resection are markedly elevated.[17,20] However, we had no episodes of liver failure or death in our series. These results are consistent with those reported by Covey *et al.*, who identified 0% mortality in a cohort of patients who underwent PVE and chemotherapy for resectable CLM.[21] These findings may be explained by the robust hepatic hypertrophic response to PVE seen in our study population. This is supported by the work

of Ribero *et al*., who found an increased risk for postoperative complications and death among patients with a limited response to PVE defined as a post-procedure FLR of ≤20% or hypertrophy of ≤5%.[22] Our results suggest that, even in a group of patients at elevated risk for postoperative liver dysfunction, successful RPVE facilitates major hepatectomy without postoperative liver insufficiency.

Our study has two substantial limitations. Most importantly, it is possible that differences exist between patients undergoing RPVE vs. RPVE + IV that were not detected because our sample size was small. In addition, the performance of CT-based volumetrics is subjective and affects the estimation of the FLR. All measurements were made by the same investigator to decrease inter- and intra-observer variability. To control for image-based volumetrics, we also compared the volumes of our CT-generated estimates of the resection specimen with the measured volume of the surgical pathology specimen. Importantly, we found no statistically significant differences in these measurements.

Our experience indicates that although PVE may be performed with an overall low complication rate, it is not without risk. In fact, some complications may compromise a patient's ability to tolerate surgery or future therapy. These findings underscore the need for the careful selection of patients for the procedure. The selection process should be performed by a multidisciplinary group involving hepatobiliary surgeons, interventional radiologists, hepatologists and oncologists. As is consistent with opinion in the literature on most technically complex procedures, we believe that RPVE (±segment IV) should be performed by multidisciplinary groups capable of maintaining a high-volume clinical practice, the members of which perform PVE frequently. This will ensure that the appropriate patients derive benefit from this procedure and that it is performed as safely as possible.

Conflicts of interest

None declared.

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