Radiology

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BestFLR Trial: Liver Regeneration at CT before Major Hepatectomies for Liver Cancer—A Randomized Controlled Trial Comparing Portal Vein Embolization with *N*-Butyl-Cyanoacrylate Plus Iodized Oil versus Polyvinyl Alcohol Particles Plus Coils

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Conflicts of interest are listed at the end of this article.

See also the editorial by Arellano in this issue.

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Background: In patients with liver cancer, portal vein embolization (PVE) is recommended to promote liver growth before major hepatectomies. However, the optimal embolization strategy has not been established.

Purpose: To compare liver regeneration as seen at CT in participants with liver cancer, before major hepatectomies, with *N*-butyl-cyanoacrylate (NBCA) plus iodized oil versus standard polyvinyl alcohol (PVA) particles plus coils, for PVE.

Materials and Methods: In this single-center, prospective, randomized controlled trial (Best Future Liver Remnant, or BestFLR, trial; International Standard Randomized Controlled Trial Number 16062796), PVE with NBCA plus iodized oil was compared with standard PVE with PVA particles plus coils in participants with liver cancer. Participant recruitment started in November 2017 and ended in March 2020. Participants were randomly assigned to undergo PVE with PVA particles plus coils or PVE with NBCA plus iodized oil. The primary end point was liver growth assessed with CT 14 days and 28 days after PVE. Secondary outcomes included posthepatectomy liver failure, surgical complications, and length of intensive care treatment and hospital stay. The Mann-Whitney *U* test was used to compare continuous outcomes according to PVE material, whereas the χ^2 test or Fisher exact test was used for categoric variables.

Results: Sixty participants (mean age, 61 years ± 11 [standard deviation]; 32 men) were assigned to the PVA particles plus coils group ($n = 30$) or to the NBCA plus iodized oil group ($n = 30$). Interim analysis revealed faster and superior liver hypertrophy for the NBCA plus iodized oil group versus the PVA particles plus coils group 14 days and 28 days after PVE (absolute hypertrophy of 46% vs 30% [$P < .001$] and 57% vs 37% [$P < .001$], respectively). Liver growth for the proposed hepatectomy was achieved in 87% of participants (26 of 30) in the NBCA plus iodized oil group versus 53% of participants (16 of 30) in the PVA particles plus coils group ($P = .008$) 14 days after PVE. Liver failure occurred in 13% of participants (three of 24) in the NBCA plus iodized oil group and in 27% of participants (six of 22) in the PVA particles plus coils group ($P = .27$).

Conclusion: Portal vein embolization with *N*-butyl-cyanoacrylate plus iodized oil produced greater and faster liver growth as seen at CT in participants with liver cancer, compared with portal vein embolization with polyvinyl alcohol particles plus coils, allowing for earlier surgical intervention.

Online supplemental material is available for this article.

Liver resection offers the best survival rate for malignant hepatic tumors (1,2). Indications for hepatectomies have changed from being based mainly on tumor characteristics, such as tumor size and number of tumors, to focus on volume and function of the future liver remnant (FLR) (3). The contemporary paradigms of liver resection focus on what will remain with the patient, the FLR, instead of what will be removed, and its capacity to maintain appropriate liver functions (4). In that sense, liver regeneration strategies are pivotal in enabling patients to undergo major hepatic resections. Throughout the past decades, portal vein embolization (PVE) has been accepted as the standard of practice (5). Occlusion of portal vein branches in one side of the liver to promote contralateral hypertrophy is the

Abbreviations

FLR = future liver remnant, NBCA = *N*-butyl-cyanoacrylate, PHLF = posthepatectomy liver failure, PVA = polyvinyl alcohol, PVE = portal vein embolization

Summary

Portal vein embolization with *N*-butyl-cyanoacrylate plus iodized oil generates greater and faster liver regeneration as seen at CT compared with standard polyvinyl alcohol particles plus coils, allowing for earlier surgical intervention for liver cancer.

Key Results

- In this randomized controlled trial of 60 participants with liver cancer, portal vein embolization (PVE) with *N*-butyl-cyanoacrylate (NBCA) plus iodized oil produced greater absolute liver hypertrophy at CT compared with polyvinyl alcohol (PVA) particles plus coils (absolute hypertrophy of 46% vs 30% at 14 days [$P < .001$] and 57% vs 37% at 28 days [$P < .001$], respectively).
- More participants in the NBCA plus iodized oil group presented sufficient liver hypertrophy for surgery 2 weeks after PVE compared with the PVA particles plus coils group (87% vs 53%, respectively; $P = .008$).

technical rationale of PVE (6), but the optimal embolic material for PVE is not yet established. However, it is suggested that *N*-butyl-cyanoacrylate (NBCA) might generate superior liver hypertrophy (7). This liquid embolic material has also been associated with faster hypertrophy and less use of contrast material and radiation than other commonly used materials (8,9). Our study assessed through the Best Future Liver Remnant, or BestFLR, trial, which had a randomized trial design, the liver regenerative results for PVE when using NBCA plus iodized oil versus PVA particles plus coils as the embolic materials.

Materials and Methods

Trial Design and Oversight

This prospective trial, registered at *https://www.isrctn.com* (International Standard Randomized Controlled Trial Number 16062796), was conducted according to the published protocol, followed Consolidated Standards of Reporting Trials guidelines, and complied with International Committee of Medical Journal Editors requirements. This was an investigator-initiated, single-blinded, single-center superiority trial where participants assigned to undergo PVE were randomly allocated to one of two embolic strategies—PVA particles plus coils or NBCA plus iodized oil. Approval for the trial was obtained from the National Ethics Committee for Clinical Research. The trial was supported by the local university hospital center, without funding sources, supervised by a study conductance committee and monitored by an external independent group. Data generated or analyzed during the study are available from the corresponding author by request. All participants obtained oral and written information before signing the informed consent form.

Participant Characteristics

Between November 2017 and March 2020, 76 patients were admitted to the interventional radiology unit of Curry Cabral Hospital (Central Lisbon University Hospital Center) for PVE after a hepatobiliary multidisciplinary team discussion. Eligible participants needed to meet the following inclusion criteria: *(a)* diagnosis of a primary or secondary malignant liver tumor, documented with CT, MRI, or tumor biopsy; *(b)* indication for liver or extended liver resection (four or more segments); and *(c)* an estimated FLR of less than 25% in participants with a healthy liver or an estimated FLR of less than 40% in participants with a diseased liver (1,10). Exclusion criteria included portal vein thrombosis or tumor invasion, previous hepatic segmentectomy, and prohibitive coagulative disorders. The randomization list was generated by one of the authors (P.M.L., an epidemiologist and statistician with 15 years of experience) in August 2017 using a random allocation rule (11). Eligible participants were randomly allocated in a 1:1 ratio to undergo PVE with PVA particles plus coils or PVE with NBCA plus iodized oil. Participants were blinded to the embolic material adopted.

CT Volumetry

Axial contrast-enhanced CT was performed with 1.5-mm collimation in the portal-venous phase with a 16–detector row multisection CT scanner (Brilliance, Philips Medical Systems) before and 14 and 28 days after PVE. Hospital-integrated software (syngo.via VB20A; Siemens Healthcare) was used.

PVE Procedure

PVE was performed by interventional radiologists (J.H.M.L, N.V.C., F.V.G., E.C., and T.B., with 5–20 years of experience) as described previously (12–14). Portal branches were accessed through a US-guided transhepatic percutaneous puncture. Use of an ipsilateral approach was preferred for PVE with PVA particles plus coils. For PVE with NBCA plus iodized oil, ipsilateral puncture was used if the left portal vein branch puncture was not straightforward for the contralateral approach (ie, very small left liver segments). The contralateral approach has the advantages of using shorter catheters, easier catheterization, and performing embolization in the direction of flow (15). After initial portography, embolization of non-FLR portal branches was achieved, as follows: *(a)* with increasing-size PVA particles (Bearing Calibrated PVA; Merit Medical) followed by central deposition of coils (IMWCE; Cook Medical) or *(b)* with a mixture of iodized oil (Lipiodol Ultra Fluid; Guerbet) and NBCA (Glubran 2; GEM). The NBCA plus iodized oil proportion varied from 1:3 to 1:5, administered in aliquots, followed by dextrose flushing. Control portography was performed to confirm occlusion of the targeted vessels followed by transhepatic track embolization with gelatin sponge sludge (Spongostan; Ethicon). PVE with PVA particles and coils has been the standard approach in our interventional radiology unit for 15 years. The portal segments targeted during the BestFLR trial were the right portal vein or the left portal vein plus segment V and VIII branches. Right portal vein plus segment IV embolization was not performed. One of the three performing interventional radiologists (J.H.M.L., F.V.G., and N.V.C.) evaluated pain intensity experienced during the procedure in accordance with the visual analog scale.

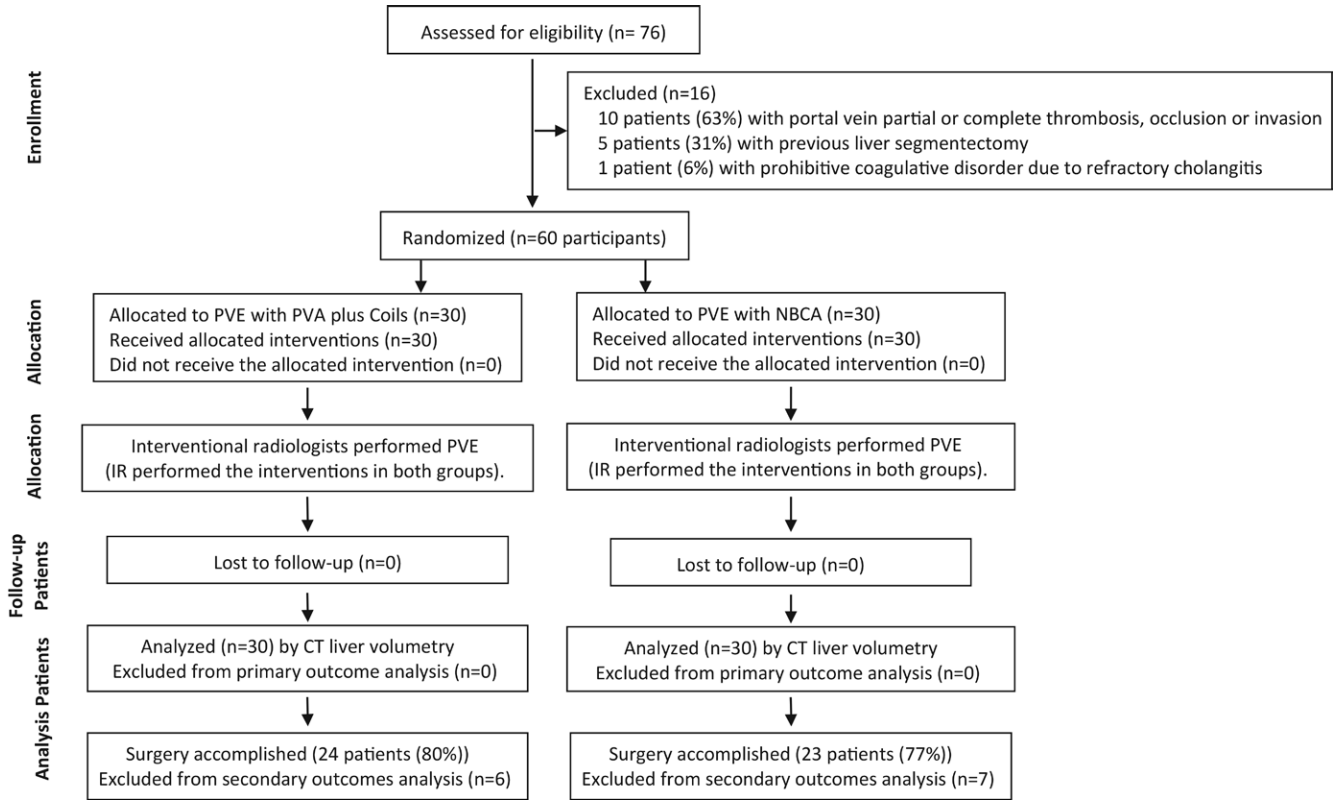


Figure 1: Participant flowchart for Best Future Liver Remnant, or BestFLR, trial. IR = interventional radiologists, NBCA = *N*-butyl-cyanoacrylate, PVA = polyvinyl alcohol, PVE = portal vein embolization.

Liver Surgery

All hepatectomies were performed by liver surgeons with experience in liver surgery ranging from 10–25 years (H.P.M., J.S.C., R.M.A.M., V.N.T.V.R., J.T.R.d.C.L., M.M.d.S.N.e.S., S.R.G.d.S., A.S.d.T.C., and S.C.C.R.). Surgical technique and intraoperative management have been described in detail previously (16). Concomitant procedures performed at the time of a major hepatectomy were allowed and recorded (ie, major extrahepatic procedures). Right and left hepatectomy and extended right and left hepatectomy were defined previously (17).

Primary Outcome

The primary end point was FLR absolute hypertrophy at 14 days and 28 days after PVE. FLR absolute hypertrophy was calculated as (FLR volume after PVE−FLR volume before PVE) × 100/(FLR volume before PVE) (18). All volumetric measurements were performed by a body radiologist not involved in the study protocol and trial execution.

Secondary Outcome

Secondary outcomes included results from PVE procedures and from the accomplished hepatectomies. Comparison between PVE groups included additional volumetric liver growth variables (degree of hypertrophy and kinetic growth rate [19]), total contrast material volume used, pain intensity according to visual analog scale (range, 0–10), total fluoroscopy and procedure time, minor and major complications (20), and hospital stay.

From the accomplished hepatectomies, data included intraoperative transfusions, type of hepatectomy performed, necessity of vascular resection during surgery, intensive care unit and postoperative hospital stay, surgical complications (Clavien-Dindo classification) (21), and posthepatectomy liver failure (PHLF), which was defined as increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5 (22).

Histologic Evaluation

Resection specimens (embolized liver) and liver biopsy specimens of the FLR were fixed in a 10% formalin solution and stained with hematoxylin-eosin, Masson trichrome, and Gordon and Sweet. The slides were assessed by two pathologists (A.A.F.P.d.F., with 8 years of experience in liver pathology, and M.V.S., with 2 years of experience in liver pathology) in consensus. Liver parenchyma was evaluated for trabecular atrophy, sinusoidal dilatation, centrolobular congestion, central necrosis, and granuloma formation.

Statistical Analysis

The primary end point of the trial was FLR absolute hypertrophy after PVE. We a priori designed the trial to have 80% power to detect, using a Z test, a significant difference in the mean FLR absolute hypertrophy between the two groups, with a two-sided significance of $P = .05$. Previous publications had shown that FLR absolute hypertrophy varied from 48% (standard deviation, 73%) (23) to 74% (standard deviation, 69%) (8) for PVE with NBCA plus iodized oil and from 23% (standard deviation,

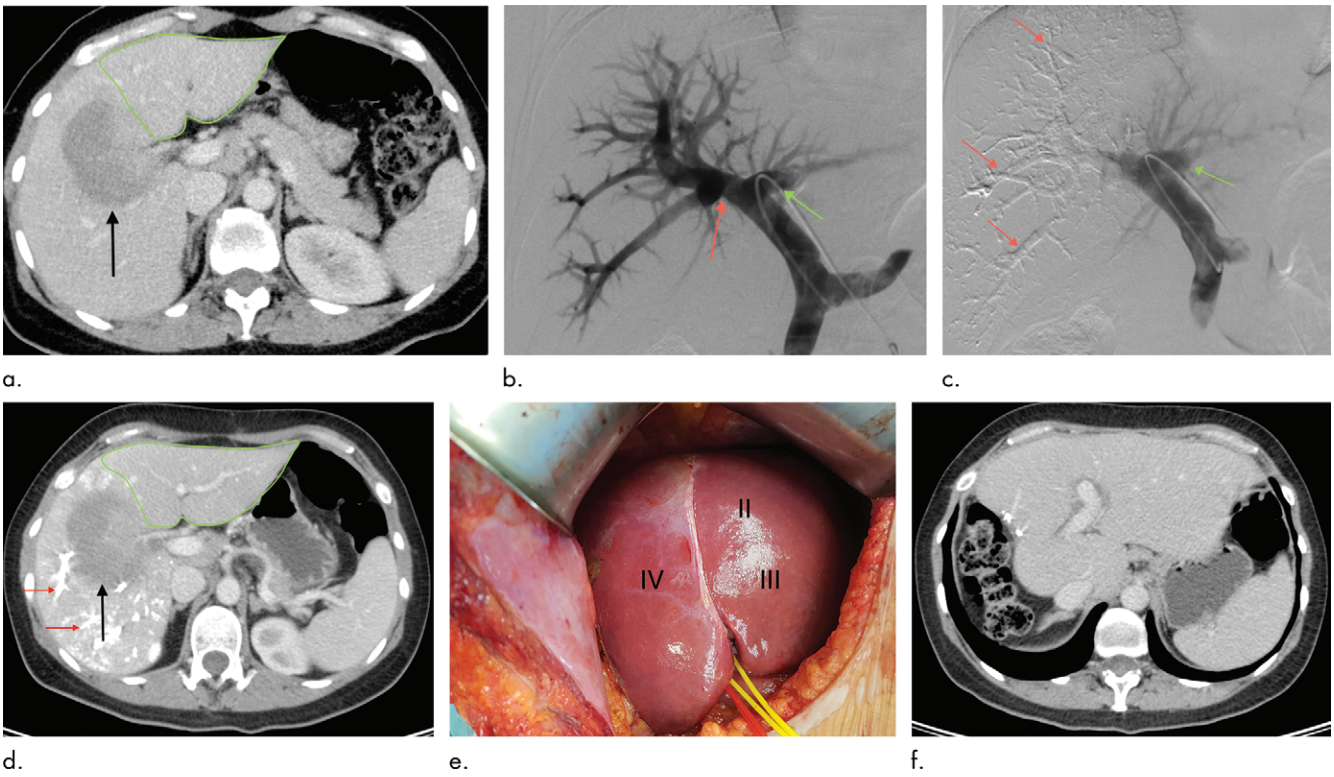


Figure 2: Main stages of a participant in the Best Future Liver Remnant, or BestFLR, trial, a 41-year-old woman with single large right liver metastasis from adenoid cystic carcinoma. **(a)** Contrast-enhanced portal venous phase CT scan in axial plane shows right liver metastases (arrow) and left liver (future liver remnant [FLR] outlined in green) before right portal vein embolization (PVE). **(b)** Portography immediately before PVE shows normal portal vein anatomy. Red arrow indicates right portal vein, and green arrow indicates left portal vein. **(c)** Final portography shows occlusion of right portal vein branches with *N*-butyl-cyanoacrylate (NBCA) plus iodized oil (red arrows) and patent left portal vein (green arrow). **(d)** Contrast-enhanced CT scan in axial plane 14 days after PVE shows FLR hypertrophy (outlined in green). Notice hyperattenuated NBCA plus iodized oil inside right portal vein branches (red arrows) and right liver tumor (black arrow). **(e)** Intraoperative aspect of left liver after right hepatectomy (liver segments II, III, and IV). **(f)** Axial contrast-enhanced CT scan 1 year after right hepatectomy shows no tumor recurrence.

12%) (8) to 44% (standard deviation, 7%) (24) for PVE with PVA particles plus coils. These and other results were combined using a meta-analytical approach for continuous outcomes to inform on the expected mean FLR absolute hypertrophy in each group. We estimated that FLR absolute hypertrophy would be 59.7% (standard deviation, 50.2%) for PVE with NBCA plus iodized oil and 35.4% (standard deviation, 11.4%) for PVE with PVA particles plus coils. Using the expected mean difference in hypertrophy and the preset significance level and power, we estimated the sample size requirement for the study to be 72 patients, 36 in each intervention group. It was estimated that 2 years would be sufficient for participant recruitment.

An interim analysis for the primary outcome after enrollment of 75% of the participants was anticipated in the trial protocol. Given this additional hypothesis testing of the same data set, we corrected the significance level. The Bonferroni-corrected *P* value for evaluating the statistical significance of the primary end point was .025.

Descriptive statistics of continuous variables were provided by estimates of the mean (standard deviation) and median (interquartile range) and compared with the more conservative Mann-Whitney *U* test because of the sample size at the point of the interim analysis. Categoric variables were described with absolute and relative frequencies and compared using the χ^2 test or Fisher exact test. All statistical tests were performed with R software (version 4.0.2; the R Foundation for Statistical Computing).

Results

Participant Characteristics

Among 76 patients, 16 met exclusion criteria, as follows: *(a)* 10 patients (63%) had portal vein partial or complete thrombosis, occlusion, or invasion; *(b)* five patients (31%) had previously undergone liver segmentectomy; and *(c)* one patient (6%) had prohibitive coagulative disorder because of refractory cholangitis. Sixty participants in total (mean age, 61 years ± 11 [standard deviation]; 32 men) were included in the study and randomly assigned to the PVE with PVA plus coils group ($n = 30$) or to the PVE with NBCA plus iodized oil group ($n = 30$). The study was stopped for benefit when the interim analysis showed superior primary outcomes for participants submitted to the PVE with NBCA plus iodized oil. No participant was lost to follow-up (Figs 1, 2; Fig E1 [online]).

Participant characteristics are shown in Table 1. The two groups had similar baseline characteristics, including age, sex, weight, height, body mass index, hypertension, diabetes, American Society of Anesthesiologists physical status classification system grade, liver background laboratory values, presence of liver

Table 1: Participant Characteristics

Characteristic	PVA Particles Plus Coils Group (n = 30)	NBCA Plus Iodized Oil Group (n = 30)	All Participants (n = 60)	P Value
Age (y)*	61 ± 12	62 ± 10	61 ± 11	.87
Sex				>.99
Women	14 (47)	14 (47)	28 (47)	
Men	16 (53)	16 (53)	32 (53)	
Hypertension				.12
No	10 (33)	16 (53)	26 (43)	
Yes	20 (67)	14 (47)	34 (57)	
Diabetes				.12
No	21 (70)	26 (87)	47 (78)	
Yes	9 (30)	4 (13)	13 (22)	
Weight (kg)†	69 (65–76)	68 (63–73)	69 (65–75)	.73
Height (cm)*	165 ± 8	166 ± 9	166 ± 8	.86
Body mass index (kg/m^2)*	26.2 ± 4.4	25.7 ± 3.4	25.9 ± 3.9	.88
ASA physical status classification grade				>.99
II	17 (57)	17 (57)	34 (57)	
III	13 (43)	13 (43)	26 (43)	
Liver cirrhosis				.61
No	29 (97)	27 (90)	56 (93)	
Yes	1 (3)	3 (10)	4 (7)	
Tumor type				.58
Cholangiocarcinoma	13 (43)	8 (27)	21 (35)	
Colorectal liver metastases	14 (47)	13 (43)	27 (45)	
Hepatocarcinoma	2 (7)	3 (10)	5 (8)	
Hepatocholangiocarcinoma	0 (0)	1 (3)	1 (2)	
Hepatic cystadenoma	0 (0)	1 (3)	1 (2)	
Gallbladder adenocarcinoma	0 (0)	1 (3)	1 (2)	
Hepatic adenoma	1 (3)	0 (0)	1 (2)	
Other liver metastases	0 (0)	3 (10)	3 (5)	
Chemotherapy before PVE				.80
No	15 (50)	14 (47)	29 (48)	
Yes	15 (50)	16 (53)	31 (52)	
FLR volume before PVE (cm^3)†	457 (403–534)	431 (383–498)	442 (398–512)	.59

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. ASA = American Society of Anesthesiologists, FLR = future liver remnant, NBCA = *N*-butyl-cyanoacrylate, PVA = polyvinyl alcohol, PVE = portal vein embolization.

* Data are means ± standard deviations.

† Data are medians, with interquartile ranges in parentheses.

cirrhosis, type and number of cycles of systemic chemotherapy, cause of liver tumors, and FLR volumes and ratios.

PVE Procedures

Technical success was obtained in 59 of the 60 participants (98%). One participant had a patent segment VII portal branch identified at the 14-day CT examination and required an additional embolization procedure. Fluoroscopy time, total PVE time, and intravenous contrast material usage were higher in the PVE with PVA particles plus coils group than in the NBCA plus iodized oil group—24.7 minutes versus 17.7 minutes, 80 minutes versus 60 minutes, and 250 mL versus 110 mL, respectively ($P < .001$). Pain observed immediately after PVE was at level 5 for participants in the NBCA plus iodized oil group and at level 1 for participants in the PVA particles plus coils group ($P < .001$), although major complications and hospital stay were similar in both groups. A nontarget coil to the left portal vein was retracted using a snare device (Amplatz Goose Neck EV3; Medtronic), and a portion of the NBCA plus iodized oil cast, extending to the main portal vein, was also repositioned, pulling it with a catheter (Simmons; Cordis) and a guide wire to the right portal vein. Both complications occurred once in each group and were resolved in the same procedure, leaving no sequela (Fig 2). Detailed procedures are described in Table 2 and Table E1 (online).

Primary Outcome

PVE with NBCA plus iodized oil promoted higher FLR absolute hypertrophy than PVE with PVA particles plus coils after 14 days and 28 days (46% vs 30% [$P < .001$] at 14 days and 57% vs 37% [$P < .001$] at 28 days, respectively). Additional volumetric liver growth variables were also superior, such as degree of hypertrophy (12% vs 9% at 14

Table 2: Portal Vein Embolization Procedures Performed

Parameter	PVA Particles Plus Coils Group (n = 30)	NBCA Plus Iodized Oil (n = 30)	All Participants (n = 60)	P Value
PVE technical success	30 (100)	29 (97)	59 (98)	>.99
Portal vein segments targeted				>.99
Right portal vein	26 (87)	26 (87)	52 (87)	
Left portal vein plus segments V and VIII	4 (13)	4 (13)	8 (13)	
PVE percutaneous approach				<.001
Ipsilateral	28 (93)	12 (40)	40 (67)	
Contralateral	2 (7)	17 (57)	19 (32)	
Ipsilateral and contralateral	0 (0)	1 (3)	1 (2)	
Fluoroscopy time (min)*	24.7 (20–31)	17.7 (15–23)	22.1 (16–27)	.002
Total PVE time (min)*	80 (60–90)	60 (40–70)	68 (55–84)	.002
Pain after PVE (VAS)*	1 (0–2)	5 (2–7)	2 (0.75–5)	<.001
Contrast material volume usage (mL)*	250 (230–290)	110 (100–133)	159 (110–250)	<.001
Hospital stay (d)†	2.8 ± 2.6	2 ± 0	2.4 ± 1.9	.042
Minor complications	8 (27)	7 (23)	15 (25)	.50
Major complications				>.99
None	28 (93)	28 (93)	56 (93)	
Cholangitis	1 (3)	0 (0)	1 (2)	
Liver abscess	1 (3)	0 (0)	1 (2)	
Portal vein branch thrombosis	0 (0)	1 (3)	1 (2)	
Liver subcapsular hematoma	0 (0)	1 (3)	1 (2)	

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. NBCA = *N*-butyl-cyanoacrylate, PVA = polyvinyl alcohol, PVE = portal vein embolization, VAS = visual analog scale.

* Data are medians, with interquartile ranges in parentheses.

† Data are means ± standard deviations.

Table 3: Liver Growth at CT

Parameter	PVA Particles Plus Coils Group (n = 30)	NBCA Plus Iodized Oil Group (n = 30)	All Participants (n = 60)	P Value
Primary outcome				
FLR absolute hypertrophy 14 days after PVE (%)	30 ± 15	46 ± 19	38 ± 19	<.001
FLR absolute hypertrophy 28 days after PVE (%)	37 ± 17	57 ± 23	47 ± 22	<.001
Other volumetric parameters				
DH 14 days after PVE (%)	9 ± 3	12 ± 4	11 ± 4	<.001
DH 28 days after PVE (%)	12 ± 4	16 ± 5	14 ± 5	<.001
KGR 14 days after PVE (percentage per week)	4 ± 2	6 ± 2	5 ± 2	<.001
KGR 28 days after PVE (percentage per week)	3 ± 1	4 ± 1	3 ± 1	<.001
FLR sufficiency 14 days after PVE				.008
Yes*	16 (53)	26 (87)	42 (70)	
No*	14 (47)	4 (13)	8 (30)	

Note.—Except where indicated, data are means ± standard deviations. DH = degree of hypertrophy, FLR = future liver remnant, KGR = kinetic growth rate, NBCA = *N*-butyl-cyanoacrylate. PVA = polyvinyl alcohol, PVE = portal vein embolization.

* Data are numbers of participants, with percentages in parentheses.

days [$P < .001$] and 16% vs 12% at 28 days [$P < .001$], respectively) and kinetic growth rate (6% per week vs 4% per week at 14 days [$P < .001$] and 4% per week vs 3% per week at 28 days [$P < .001$], respectively), after 14 and 28 days (Table 3, Fig 3).

Surgical Outcome

After PVE, 47 of the 60 participants (78%) underwent surgery, 24 of the 30 participants (80%) in the NBCA plus iodized oil group and 23 of the 30 participants (77%) in the PVA particles plus coils group (P = .75). The most common reason for not proceeding to

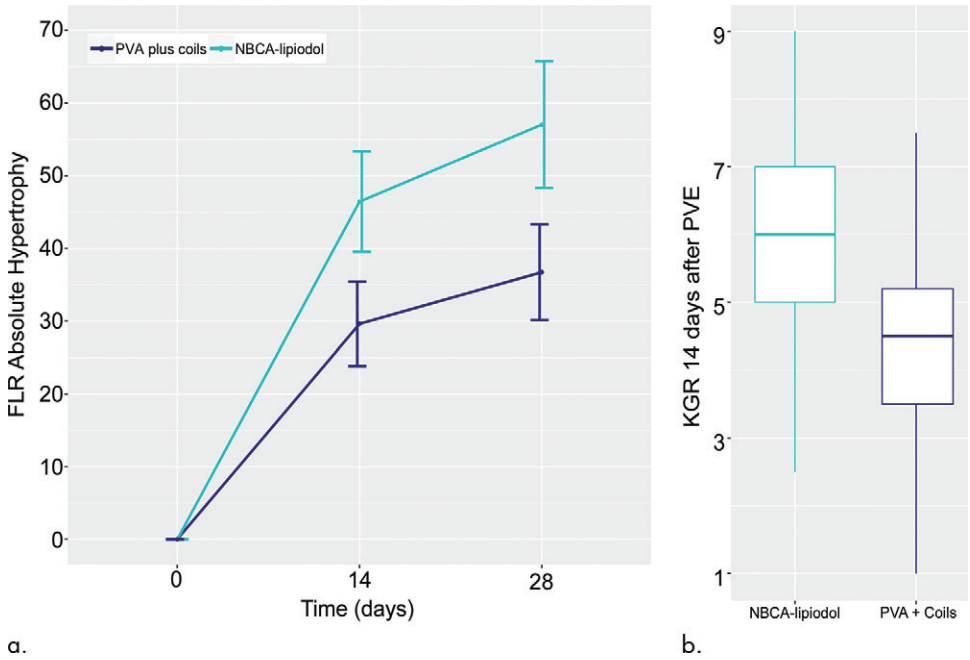


Figure 3: Liver hypertrophy after portal vein embolization (PVE). **(a)** Graph depicts future liver remnant (FLR) absolute hypertrophy (mean ± standard deviation) after PVE. *N*-butyl-cyanoacrylate (NBCA) plus iodized oil promoted faster and superior liver hypertrophy at both 14 days and 28 days after PVE ($P < .001$) when compared with polyvinyl alcohol (PVA) particles plus coils. **(b)** Box plot shows superior kinetic growth rate (KGR) percentage per week (mean ± standard deviation) 14 days after PVE with NBCA plus iodized oil versus PVE with PVA particles plus coils ($P < .001$).

surgery was disease progression in 10 participants. Right hepatectomy, the most common surgery, was performed in 21 of the 47 participants (46%), followed by right hepatectomy plus segment I in 11 of the participants (24%). Clavien-Dindo grade III or higher surgical complications occurred in 10 of the 47 participants (21%) and did not differ between groups. Posthepatectomy 60-day mortality was 4% (two of the 47 participants), both in the NBCA plus iodized oil group. One participant died 27 days after an extended right hepatectomy because of a small bowel perforation and refractory sepsis. Another participant presented with uncontrollable bleeding during her 10-hour long extended left hepatectomy and died 24 days later. Neither of these deaths were directly related to liver failure nor to factors attributable to the PVE procedure (Table 4, Table E2 [online], and Table E3 [online]).

Liver Failure

Clinically relevant PHLF (grades B and C) was detected in 13% (three of 24) and 27% (six of 22) of participants in NBCA plus iodized oil and PVA particles plus coils groups ($P = .27$), respectively. PHLF grades B and C were more frequent after extended right hepatectomies ($n = 5$) when compared with right hepatectomies ($n = 1$) (25% and 5%, respectively; $P = .03$). Participants with PHLF ($n = 9$), when compared with participants with no PHLF ($n = 37$), showed longer intensive care unit stay (8 days vs 1 day, respectively; $P < .001$) and total hospital stay (33 days vs 11 days, respectively; $P < .001$), more Clavien-Dindo grade III and higher complications (55% [$n = 5$] vs 19% [$n = 7$], respectively; $P = .008$), and higher 60-day mortality (22% [$n = 2$] vs 0%, respectively; $P = .03$) (Table 4, Table E2 [online], and Table E3 [online]).

Pathologic Results

Dilatation of the sinusoids, trabecular atrophy, and granulomas were commonly seen in the embolized liver, detected in 93% ($n = 43$), 80% ($n = 37$), and 98% ($n = 45$) of the 46 operated participants, whereas no cases of moderate or severe sinusoidal dilatation or trabecular atrophy or granulomas were seen in the FLR. When comparing the embolized liver in the NBCA plus iodized oil and PVA particles plus coils groups, there was no difference in the presence of trabecular atrophy (79% [19 of 24 participants] vs 82% [18 of 22 participants]; $P = .97$), sinusoidal dilatation (92% [22 of 24 participants] vs 95% [21 of 22 participants]; $P = .47$), centrolobular congestion (71% [17 of 24 participants] vs 86% [19 of 22 participants]; $P = .29$), and granuloma formation (96% [23 of 24 participants] vs 100% [22 of 22]; $P > .99$). Central necrosis was absent in both groups in the embolized liver (Fig 4; Table E4 [online]).

Discussion

In patients with liver cancer, portal vein embolization (PVE) is recommended to promote liver growth before major hepatectomies, but an optimal embolization strategy is not yet established. In the Best Future Liver Remnant, or BestFLR, trial, when performing PVE, liquid embolic *N*-butyl-cyanoacrylate (NBCA) plus iodized oil produced greater absolute liver hypertrophy at CT compared with polyvinyl alcohol (PVA) particles plus coils (46% vs 30% at 14 days [$P < .001$] and 57% vs 37% at 28 days [$P < .001$], respectively) before major hepatectomies. This superior hypertrophy of NBCA plus iodized oil was seen earlier and with fewer participants than the sample size calculation projected, and the trial was prematurely ended for benefit. Faster (at 14 days) and greater liver growth triggered by PVE with NBCA plus iodized oil was seen with traditional static volumetric assessments (changes in the liver volume and degree of hypertrophy) and with dynamic measurements such as kinetic growth rate. Another advantage of adopting NBCA plus iodized oil as the embolic material is needing only half of the amount of contrast material volume and performing PVE with less fluoroscopy and total procedure time. Those findings are probably related to the immutable necessity to inject several vials of PVA (ie, median of 12.6 vials per PVE) mixed with contrast material followed by the placement of several individual coils.

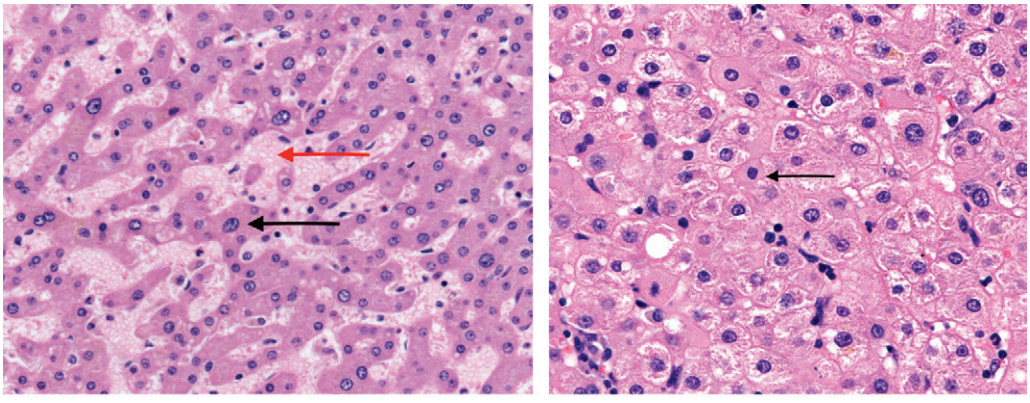
PVE with PVA particles plus coils is an established technique for liver hypertrophy before major hepatectomies (13,24–27), and indeed all participants but one in our trial

Table 4: Participant Outcomes

Parameter	PVA Particles Plus Coils Group (n = 30)	NBCA Plus Iodized Oil Group (n = 30)	All Participants (n = 60)	P Value
Surgery accomplishment (total)				.75
Yes	23 (77)	24 (80)	47 (78)	
No	7 (23)	6 (20)	13 (22)	
Types of hepatectomy*				.78
Right hepatectomy	10 (45)	11 (46)	21 (46)	
Right hepatectomy plus segment I	8 (36)	3 (12)	11 (24)	
Extended right hepatectomy	2 (9)	6 (25.0)	8 (17)	
Extended left hepatectomy	2 (9)	4 (17)	6 (13)	
Reason for not performing planned hepatectomy				.46
Cholangitis	2 (29)	0 (0)	2 (15)	
Disease progression	5 (71)	5 (83)	10 (77)	
Poor personal status	0 (0)	1 (17)	1 (8)	
Surgical complications (Clavien-Dindo grade ≥III)				.87
No	18 (78)	19 (79)	37 (79)	
Yes	5 (22)	5 (21)	10 (21)	
Clinically relevant PHLF				.27
No	16 (73)	21 (88)	37 (80)	
Yes	6 (27)	3 (13)	9 (20)	
60-day postoperative mortality				.49
No	22 (100)	22 (92)	44 (96)	
Yes	0 (0)	2 (8)	2 (4)	
Overall mortality				.67
No	27 (93)	26 (87)	53 (90)	
Yes	2 (7)	4 (13)	6 (10)	

Note.—Except where indicated, data are numbers of participants, with percentages in parentheses. NBCA = *N*-butyl-cyanoacrylate, PVA = polyvinyl alcohol, PVE = portal vein embolization, PHLF = posthepatectomy liver failure (International Study Group Liver Surgery classes B and C).

* One participant from the PVA particles plus coils group was submitted to liver transplant after a multidisciplinary tumor board discussion.



a. b.

Figure 4: Histologic evaluation after portal vein embolization (hematoxylin-eosin stain; original magnification, × 400. **(a)** Photomicrograph of liver parenchyma from embolized liver with *N*-butyl-cyanoacrylate (NBCA) plus iodized oil. Sinusoidal dilation (red arrow) and trabecular atrophy (black arrow) are shown. No necrosis is identified. **(b)** Photomicrograph of liver parenchyma from nonembolized liver from participant in NBCA plus iodized oil group. Liver parenchyma without sinusoidal dilation or trabecular atrophy, without major changes (arrow), is shown.

were ready for surgery in this embolic group 4 weeks after PVE. Most participants in the PVE with NBCA plus iodized oil group were ready for surgery within 2 weeks after PVE. Indeed, 87% of participants in the PVE with NBCA plus iodized oil group reached sufficient liver growth for the proposed hepatectomy 14 days after PVE, whereas only 53% reached this same goal in the PVE with PVA particles plus coils group (P = .008). A shorter time lapse for accomplishing the planned liver surgery after PVE (ie, 14 days) can help to avoid tumor progression, allowing for more patients to benefit from liver cancer surgery. Faster volume sufficiency after PVE was a paradigm shift in our own center. We now assess all patients at the 14th day after PVE with NBCA plus iodized oil and not

after 28 days as previously performed, thus allowing earlier surgical intervention.

Objective parameters of poorer outcomes after liver surgery (28), such as hospital and intensive care stay, Clavien-Dindo grade III and higher complications, 60-day mortality, and total death, were all more frequent in participants who developed PHLF, which is the principal cause of morbidity and mortality after major hepatectomies (29,30). Regardless of the difference in PHLF between groups, present in 13% (n = 3) and 27% (n = 6) of participants in the NBCA plus iodized oil and PVA particles plus coils groups, respectively, it did not reach statistical significance (P = .27). This was probably because of the small sample size, which, although true, is not a study weakness, as this trial was not intended to detect differences for this outcome.

Several authors have reported atrophy of hepatocytes and dilatation of sinusoids in the embolized lobe after PVE (31). Despite seeing superior liver hypertrophy results in the PVE with NBCA plus iodized oil group in our trial, there were no differences in the pathologic aspects between the groups. In both groups, sinusoidal dilation and trabecular atrophy were frequent and equally seen in the embolized liver, whereas this aspect was absent in the FLR parenchyma. Previous reports have associated the regenerative edge of this liquid embolic material with its strong inflammatory reaction, which results from its heat creation in the early exothermic polymerization phase and release of formaldehyde (32) leading to a release of regenerative mediators. Although scarcely reported, this inflammatory reaction has also been attributed to perioperative technical challenges (33). Although these latter data were not specifically surveyed in our trial, neither group had any major perioperative technical issues.

Our study had limitations. First, it is important to highlight that our study was conducted in a single center and our sample size was small. One possible bias was the possibility of not mastering one of the applied techniques (embolization with PVA particles plus coils or with NBCA plus iodized oil). However, this argument cannot stand on its own because PVA particles plus coils was the standard PVE technique of our department before the initiation of the trial and PVE with NBCA plus iodized oil, although less adopted, was also locally feasible. Second, liver function was not evaluated before and after PVE. Volume does not reflect liver parenchyma quality, and liver volumetric increase may not be paralleled and may even exceed liver function, as recently shown in surgical series (34). Still, for decades, liver CT volumetry has been the reference standard in preoperative assessment and decision making to determine patients suitable for major hepatectomies (35,36). All participants were rediscussed after PVE in a multidisciplinary meeting to establish the final surgical decision. Future studies aiming to compare liver regenerative strategies, (PVE, associating liver partition and portal vein ligation for staged hepatectomy, and liver venous deprivation [37]) should include volumetric and functional liver evaluation.

In conclusion, the Best Future Liver Remnant, or BestFLR, trial demonstrated that portal vein embolization with *N*-butyl-cyanoacrylate plus iodized oil promotes greater and faster liver growth as seen at CT, compared with standard polyvinyl alcohol particles plus coils, allowing for earlier surgical intervention for patients with primary and metastatic liver cancer.

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