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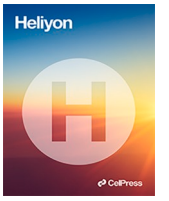

Portal vein embolization with N-butyl-cyanoacrylate improves liver hypertrophy compared to microparticles – A Swedish multicenter cohort study

Dennis Björk [a], Martin Delle [b], Fredrik Holmquist [c], Kristina Hasselgren [a], Per Sandström [a], Gert Lindell [d], Ernesto Sparrelid [e,1], Bergthor Björnsson [a,*]

[a] *Department of Surgery, Linköping University Hospital and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden*
[b] *Department of Radiology, Karolinska Universitetssjukhuset, Huddinge and CLINTEC (Department of Clinical Science, Intervention and Technology), Karolinska University, Sweden*
[c] *Department of Medical Imaging and Physiology, Skåne University Hospital Comprehensive Cancer Center, Clinical Sciences Lund, Faculty of Medicine, Lund University, Lund, Sweden*
[d] *Department of Surgery, Skåne University Hospital Comprehensive Cancer Center, Lund University, Lund, Sweden*
[e] *Division of Surgery, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*

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ABSTRACT

Background: An adequate future liver remnant (FLR) is fundamental for major liver resections. To achieve sufficient FLR, portal vein embolization (PVE) may be used. The most effective material for PVE has yet to be determined. The aim of this study was to investigate the differences in FLR growth between n-butyl-cyanoacrylate glue (NBCA) and microparticles.
Material/methodsa: retrospective study was performed at three Swedish hepatobiliary centers and included patients who underwent PVE 2013–2021. Electronic medical records were reviewed, and procedure-related data were collected. Data were analyzed with respect to embolizing material.
Results: A total of 265 patients were included: 160 in the NBCA group and 105 in the microparticle group. The NBCA group had a higher degree of hypertrophy (12.1 vs. 9.4 % points, $p = 0.003$) and a higher resection rate (68 vs. 59 %, $p = 0.01$) than the microparticle group. Procedure-related data all indicated the superiority of NBCA. No difference in inducing hypertrophy was observed when comparing patients who received chemotherapy before PVE with those who received chemotherapy before and after PVE within the NBCA group.
Discussion/conclusion: This retrospective multicenter study supports the superiority of NBCA compared to microparticles in the setting of PVE. Chemotherapy after PVE does not seem to negatively affect hypertrophy.

* Corresponding author. Department of Surgery, Linköping University Hospital, S-581 85, Linköping, Sweden.
E-mail address: bergthor.bjornsson@liu.se (B. Björnsson).
[1] Shared senior authorship.

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1. Introduction

Portal vein embolization (PVE) is a well-established method for inducing liver hypertrophy in the future liver remnant (FLR) for patients undergoing liver resection. In a normal healthy liver, 80 % can be resected without liver failure. If the patient has received preoperative chemotherapy, 70 % can be resected, and if the patient is suffering from chronic liver disease, such as cirrhosis, 60 % can be safely resected [1,2]. PVE is used to avoid postoperative liver failure after major liver resection. The method of inducing liver hypertrophy by selectively blocking portal vein blood flow has been known since the 1920s [3], when the first animal models were developed. In the 1980s and 1990s, the first human clinical implementations were described [4,5]. PVE momentarily blocks portal blood flow to the embolized side and directs the total portal blood flow to the nonembolized side of the liver [6]. Portal vein blood flow has hepatotrophic properties [7], including hormonal factors, such as insulin and hepatic growth factor [7,8]. PVE rapidly induces hepatocyte proliferation on the nonembolized side [9]. After the initial proliferation of hepatocytes, the proliferation of various hepatic cells follows, such as Kupffer cells, endothelial cells and bile duct cells [10]. After this initial step of replication, the hepatocytes increase in size, which leads to liver hypertrophy. Many molecular pathways have been proposed, but the mechanism of hypertrophy after PVE is not fully understood.

A wide variety of materials have been used for PVE, either as single therapy or in various combinations [11]. The ideal embolic agent should be easy to administer, produce reliable occlusion, induce sufficient FLR hypertrophy, be well tolerated and be cost effective. Permanent embolic agents seem to have the best effect, and the most commonly used agents are n-butyl-cyanoacrylate (NBCA) glue and microparticles/coils [12]. Two previous smaller retrospective studies have shown the superiority of NBCA compared with microparticles [13,14], but larger reviews have failed to replicate these results [15]. The only available randomized controlled trial in this field, the BestFLR Trial by Luz et al. [16], including 60 patients with malignant tumors, showed superiority for NBCA over microparticles in the setting of PVE before major hepatic surgery. Data suggest that NBCA produces a higher FLR hypertrophy, is more time efficient, exposes patients to less radiation and is less expensive than other embolic agents [12,14,16,17].

PVE has been proven to be a safe procedure with low rates of morbidity and mortality [18,19], with most series reporting a procedure-related mortality rate of 0 %.

The aim of this study was to compare the use of NBCA and microparticles with respect to FLR growth after the PVE procedure in a large cohort.

2. Materials and methods

2.1. Patients

This retrospective study was performed at three of the six Swedish hepatobiliary centers: Linköping University Hospital, Karolinska Comprehensive Cancer Center and Skåne University Hospital Comprehensive Cancer Center Lund. These centers have a total catchment area of approximately 5.5 million people. All consecutive patients undergoing PVE from January 2013 to December 2021 were identified and included in the study. All patients included in the study were discussed at a multidisciplinary tumor board prior to treatment.

Electronic medical records were reviewed for clinical data, including age, sex, weight, height, preoperative laboratory data and chemotherapy. Overall liver function was evaluated using blood samples, including albumin, bilirubin and international normalized ratio (INR). To assess the physical health of each patient, the American Society of Anesthesiologists (ASA) score [20], Eastern Cooperative Oncology Group (ECOG) score [21] and body mass index (BMI) were recorded.

The decision to perform PVE was based on measurement of sFLR, patient medical history and previous treatment. For healthy patients, PVE was performed if the sFRL fell below 20 %. If the patients had chemotherapy, the cutoff value for sFLR was set to 30 %, and if the patients had preexisting liver disease, such as cirrhosis, the cutoff was set to 40 %.

A sample size calculation was performed before the study was initiated. In total, a minimum of 196 patients were required to find a difference of five percent with a statistical significance of $p < 0.05$ and a power of 0.8.

2.2. PVE procedure

The PVE procedures were performed in angiographic suites by experienced interventional radiologists. In general, the PVE procedure was carried out under general anesthesia with ultrasound-guided puncture of intrahepatic portal branches. For the study period, Linköping University Hospital and Skåne University Hospital Comprehensive Cancer Centre Lund mainly used NBCA for PVE. At Karolinska Comprehensive Cancer Centre, a majority of the patients underwent PVE with microparticles. Patients undergoing right-sided PVE with NBCA combined with PVE of liver segment 4 with coils, particles or plugs were considered to be in the NBCA group.

NBCA was administered in an iodized oil (Lipiodol) solution with a concentration of NBCA:lipiodol varying from 1:2 to 1:10.

In relation to the PVE procedure, data were collected for fluoroscopy time, radiation dose, dose-area product (DAP) and contrast used during the procedure. DAP is a measurement of radiation exposure where the absorbed dose is multiplied by the area irradiated.

2.3. Evaluation of FLR

Digital radiological imaging was processed for measurement of the FLR before and after PVE. Computed tomography (CT) or magnetic resonance imaging (MRI) was used. Radiological measurements were performed at each center according to local routine and

extracted from digital medical records. The standardized FLR (sFLR) percentage was calculated using radiological measurement of the FLR divided by estimated total liver volume (eTLV) according to Vauthey [22]: $eTLV = -794.41 + 1267.28 \times$ body surface area (BSA). Body surface area was calculated according to Mosteller [23]:

$$BSA = \sqrt{(\text{height [cm] x weight [kg]}/3600)}.$$

Relative growth of the FLR was defined as the percentage increase in the FLR volume after the PVE procedure.

The degree of hypertrophy (DH) was calculated as the percentage point difference between the sFLR before and after PVE. The kinetic growth rate (KGR) was calculated according to Shindoh et al. [24], DH divided by time elapsed between the PVE procedure and evaluating post-PVE CT expressed in weeks.

In the study, an FLR >30 % was set as the cutoff point for a sufficient FLR after PVE since many of the patients had previous chemotherapy, but cirrhosis was rare [1,2]. The decision to perform liver resection was based on local multidisciplinary tumor boards. Overall liver function was evaluated using blood samples.

2.4. Complications after PVE

Complications attributable to the PVE procedure were classified according to the Clavien–Dindo classification [25]. All complications were recorded, stating the highest-ranking complication. Grade 3a and higher complications were considered severe complications.

2.5. Statistical analysis

Continuous variables are reported as the mean values and standard deviation. Categorical variables are reported with numbers and proportions. Continuous variables were analyzed using t tests, and categorical variables were analyzed using chi-square tests. Multivariable analysis was performed with linear regression with the stepwise method and a cutoff point of 0.2. A p value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS Statistics version 28.0.1.0 (142), IBM Inc., Armonk, New York, USA.

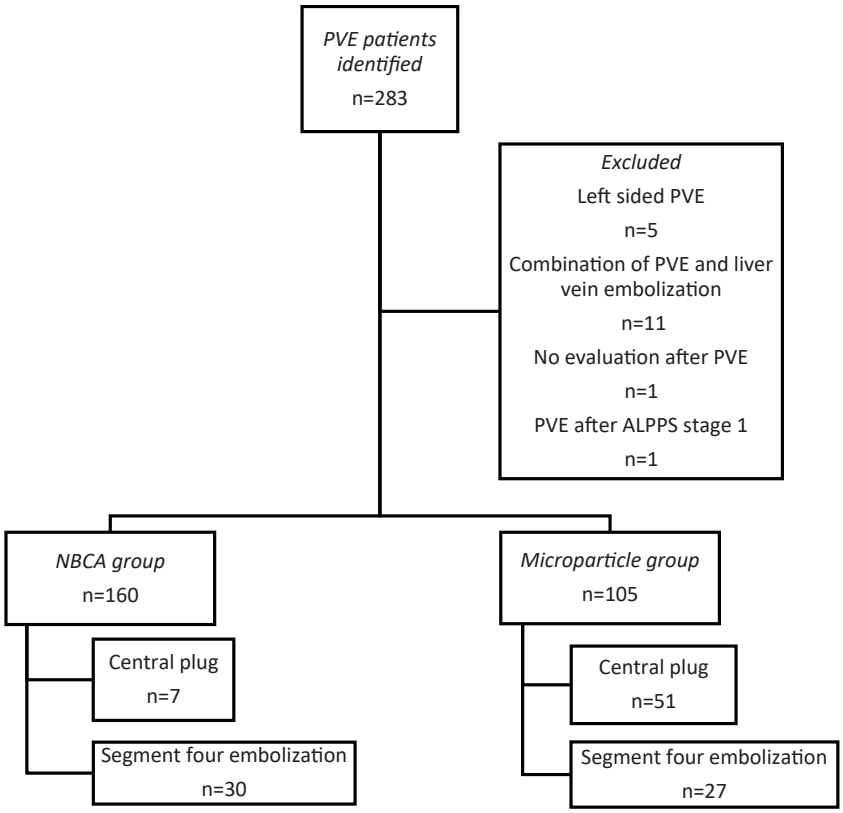

Fig. 1. Patient selection.

3. Results

3.1. Patients

A total of 283 patients were identified. Eighteen patients were excluded due to left-sided PVE, PVE after the first stage of the ALPPS (Associated Liver Partition and Portal Vein Ligation for Staged hepatectomy) procedure with insufficient growth of the FLR or combined PVE and liver vein embolization, resulting in 265 patients eligible for inclusion (see Fig. 1). During the study period, a total of 3486 liver resections were performed at the three abovementioned hepatobiliary centers included in the study. This results in a PVE rate of 7.6 % before liver resection.

Of the 265 patients, 160 patients (60 %) underwent the PVE procedure with NBCA, and 105 patients (40 %) underwent the procedure with microparticles. In the microparticle group, 54 patients underwent the PVE procedure with microparticles and coils. The remaining 51 patients were embolized with microparticles, coils and plugs. Baseline characteristics were similar between the NBCA group and the microparticle group (Table 1), except for diagnosis and chemotherapy. A chi-square test showed a significant difference between the two groups ($p = 0.045$), where colorectal liver metastases were more common in the NBCA group and perihilar cholangiocarcinoma was more common in the microparticle group. The overall dominant diagnosis was colorectal liver metastasis (47 %), followed by perihilar cholangiocarcinoma (31 %). No difference was observed between the groups regarding the number of liver lesions or largest lesion diameter. Chemotherapy was provided to 45 % of the patients before PVE, and the vast majority (97 %) of those patients had colorectal liver metastasis. A significant difference was observed between the NBCA group and the microparticle group, with chemotherapy being more common in the NBCA group (50 % vs. 35 %, $p = 0.02$).

The number of patients not reaching resection after PVE was 31 in the microparticle group and 47 in the NBCA group. In the microparticle group, 16 patients had intraoperative tumor progression not detected on preoperative radiology: two patients had gallbladder cancer, ten patients had perihilar cholangiocarcinoma, of which one patient received chemotherapy before, but not after, PVE, two patients had intrahepatic cholangiocarcinoma and two patients had colorectal liver metastases, in which both patients received chemotherapy before PVE, but not after. Furthermore, nine patients had insufficient growth of the FLR: two patients with perihilar cholangiocarcinoma, two patients with gallbladder cancer, one patient with intrahepatic cholangiocarcinoma, one with hepatocellular carcinoma and three patients with colorectal liver metastases, of which two patients received chemotherapy before, but not after, PVE. Four patients had tumor progression on preoperative radiology: one patient with perihilar cholangiocarcinoma, one with intrahepatic cholangiocarcinoma and two patients with colorectal liver metastases, of which both had chemotherapy before, but not after, PVE. One patient with gallbladder cancer, without chemotherapy before PVE, had reduced physical status and was not fit for surgery. One patient diagnosed with perihilar cholangiocarcinoma who did not receive chemotherapy had tumor regression on preoperative radiology and did not proceed to resection.

In the NBCA group, 18 patients had intraoperative tumor progression: three patients with gallbladder cancer, eight with perihilar

Table 1
Demographics, diagnosis and chemotherapy.

	NBCA n = 160 (60.4 %)	Microparticles n = 105 (39.6 %)	p value
Sex			0.427
Male, n (%)	99 (62)	70 (67)	
Female, n (%)	61 (38)	35 (33)	
Diabetes, n (%)	27 (17)	11 (11)	0.146
Cirrhosis, n (%)	4 (2.5)	4 (3.8)	0.542
Age, years mean (std deviation)	65.1 (11.2)	65.1 (11.0)	0.974
BMI, kg/m^2 mean (std deviation)	25.3 (3.7)	25.9 (4.5)	0.257
Bilirubin, mean (std deviation)	22.1 (55.7)	27.8 (44.3)	0.371
ECOG			0.554
ECOG 0, n (%)	57 (35.6)	35 (33.3)	
ECOG 1, n (%)	89 (55.6)	64 (61.0)	
ECOG 2, n (%)	14 (8.8)	6 (5.7)	
ASA			0.205
ASA 1, n (%)	26 (16.3)	21 (20.0)	
ASA 2, n (%)	78 (48.8)	58 (55.2)	
ASA 3, n (%)	56 (35.0)	26 (25.8)	
Diagnosis			0.045
Colorectal liver metastasis, n (%)	85 (53.1)	40 (38.1)	
Perihilar cholangiocarcinoma, n (%)	42 (26.2)	40 (38.1)	
Gallbladder cancer, n (%)	12 (7.5)	9 (8.6)	
Hepatocellular carcinoma, n (%)	11 (6.9)	6 (5.7)	
Intrahepatic cholangiocarcinoma, n (%)	7 (4.4)	9 (8.6)	
Other[a], n (%)	3 (1.9)	1 (1)	
Number of liver lesions, mean (std deviation)	4 (4.8)	4 (5.1)	0.768
Largest lesion size, mm mean (std deviation)	49 (34)	44 (31)	0.244
Chemotherapy before PVE, n (%)	80 (50)	35 (33)	0.02
Chemotherapy before and after PVE, n (%)	26 (16)	1 (1)	<0.01

[a] Gastrointestinal stroma cell tumor, anal cancer metastasis, neuroendocrine tumor, malignant melanoma metastasis.

cholangiocarcinoma, two patients with intrahepatic cholangiocarcinoma of which one received chemotherapy before and after PVE, one patient with hepatocellular carcinoma and four patients with colorectal liver metastases of which three received chemotherapy before, but not after, PVE. Twenty-three patients in the NBCA group had tumor progression on preoperative radiology: four patients with perihilar cholangiocarcinoma, two with hepatocellular carcinoma, one patient with liver metastases from anal cancer, four with gallbladder cancer, one with intrahepatic cholangiocarcinoma and 11 patients with colorectal liver metastases, of which seven received chemotherapy before PVE and three received chemotherapy both before and after PVE. Six patients had reduced physical status and did not proceed to resection after PVE: one patient had colorectal liver metastases and received chemotherapy before and after PVE, one patient had intrahepatic cholangiocarcinoma, three patients had perihilar cholangiocarcinoma and one patient had intrahepatic cholangiocarcinoma.

3.2. PVE-related data

There was no significant difference in eTLV between the two groups (1615 vs. 1673 ml, $p = 0.097$). The patients in the NBCA group had significantly larger FLR (408 vs. 352 ml, $p = 0.01$) and sFLR (25.6 vs. 21.3 %, $p < 0.01$) prior to PVE (Table 2), and the sFLR after PVE was significantly higher in the NBCA group (37.5 vs. 30.7 %, $p < 0.001$). There was a difference in the DH in favor of NBCA (12.1 vs. 9.4 % points, $p = 0.003$), while no significant difference was seen in relative FLR growth. The percentage of patients reaching an FLR $\geq$30 % (74 vs. 45 %, $p < 0.001$) and resection rate after PVE (68 vs. 59 %, $p = 0.01$) were both higher in the NBCA group. The reasons for not proceeding to resection, in addition to insufficient FLR growth, also included radiological tumor progress, intraoperatively detected tumor progress and reduced physical status.

Thirty patients (19 %) in the NBCA group and 27 patients (26 %) in the microparticle group had right-sided PVE combined with simultaneous embolization of portal branches to liver segment four. When analyzing these patients, there were no significant differences seen between the NBCA and the microparticle groups regarding FLR growth, DH or KGR (data not shown in table). When excluding patients with liver segment four embolizations from the overall analysis, there were differences between the NBCA group and the microparticle group regarding absolute FLR growth (194 vs. 152 ml, $p = 0.013$), DH (12.1 vs. 9.0 % points, $p = 0.004$) and KGR (4.1 vs. 3.9 %/w, $p = 0.048$). No difference was observed regarding the relative growth of FLR (51.7 vs. 45.5 %, $p = 0.227$).

When comparing the NBCA group without a central plug with the microparticle group without a central plug, there was a statistically significant difference regarding absolute growth (195 vs. 152 ml, $p = 0.018$) and DH (12.3 vs. 8.9 % points, $p = 0.003$) in favor of the NBCA group, suggesting a benefit with a central plug when performing PVE with microparticles. However, a subgroup analysis of the microparticle group comparing central plugs in the right portal vein branch with no central plugs did not show statistical significance between the two groups regarding absolute or relative growth, DH or KGR. A multivariable analysis with relative FLR growth as the dependent factor did not reveal statistically significant effects of any of the included variables: PVE material, age, sex, BMI, ECOG score, ASA score, diabetes, cirrhosis, diagnosis, chemotherapy, bilirubin level, PVE method, segment 4 embolization, lesion size, lesion number and central vascular plug.

Fluoroscopy time, radiation dose, DAP and contrast use were all significantly lower in the NBCA group (Table 3). The use of NBCA resulted in lowering the exposure time to two-thirds of that in the microparticle group. The radiation dose was reduced by 38 %, and DAP was reduced by 36 %. The differences remained after excluding patients with simultaneous embolization of liver segment 4.

All PVE procedures were performed using the transhepatic approach. The ipsilateral approach was used in 96 % of the procedures. The technical success rate for the PVE procedures was 100 %.

3.3. Complications

Overall, the most common complications related to the PVE procedure were pain and the need for antibiotic treatment. In the NBCA group, 32 patients (19 %) had some type of complication related to the PVE procedure. Of these 32 patients, one had a complication classified as severe: bile leakage requiring drainage. In the microparticle group, 24 patients (23 %) had some type of complication. Of these 24 patients, one patient had complications classified as severe: pleural effusion requiring drainage. No patient had a complication

Table 2
Outcome of PVE with NBCA or microparticles.

	NBCA (n = 160)	Microparticles (n = 105)	p value
eTLV, ml mean (std deviation)	1615 (272)	1673 (283)	0.097
FLR before PVE, ml mean (std deviation)	408 (146)	352 (123)	0.01
sFLR before PVE, % mean (std deviation)	25.6 (9.2)	21.3 (7.4)	<0.01
FLR after PVE, ml mean (std deviation)	596 (176)	509 (177)	<0.001
sFLR after PVE, % mean (std deviation)	37.5 (11.7)	30.7 (10.5)	<0.001
FLR growth, ml mean (std deviation)	192 (115)	157 (112)	0.014
FLR growth, % mean (std deviation)	53.6 (35.0)	47.6 (36.7)	0.182
Time between PVE and CT, weeks mean (std deviation)	4.2 (3.6)	3.6 (1.8)	0.074
Degree of hypertrophy, % points mean (std deviation)	12.1 (7.4)	9.4 (6.6)	0.003
KGR, %/w mean (std deviation)	4.0 (4.3)	3.1 (2.6)	0.057
FLR $\geq$30 % after PVE, n (%)	118 (74)	47 (45)	<0.001
Resection after PVE, n (%)	109 (68)	62 (59)	0.01

Table 3
PVE procedure data.

	NBCA	Particles	p value
Fluoroscopy, minutes mean (std deviation) [*n*]	42 (24) [*n = 132*]	62 (33) [*n = 69*]	<0.01
Radiation dose, mGy mean (std deviation) [*n*]	537 (472) [*n = 132*]	866 (618) [*n = 67*]	<0.01
Dose-area product, $Gycm^2$ mean (std deviation) [*n*]	53.3 (42.3) [*n = 132*]	83.2 (85.1) [*n = 69*]	0.007
Contrast volume, ml mean (std deviation) [*n*]	103 (53) [*n = 91*]	180 (73) [*n = 78*]	<0.01

grade higher than 3a, and no postinterventional mortality was recorded.

3.4. Subgroups

When analyzing the CRLM patients separately, only sFRL before PVE (24.5 vs. 21.1 %, p = 0.037) and after PVE (35.7 vs. 30.9 %, p = 0.025) showed significant differences between the NBCA and microparticle groups. No difference was observed regarding the growth of FLR, DH or KGR.

When the PHCC patients were analyzed as a subgroup, the DH was significantly higher in the NBCA group (12.3 vs. 8.6 % points, p = 0.017) (Table 4).

In the NBCA group, we compared patients who underwent chemotherapy before PVE with those who underwent chemotherapy before and after PVE since the microparticle group had only one patient who received chemotherapy after PVE. The comparison was limited to colorectal liver metastasis, since only 1 % of the patients in the NBCA group receiving chemotherapy had other diagnoses. There was no significant difference between the groups with respect to FLR growth, DH or KGR (Table 4). When comparing patients with no chemotherapy with the group of patients who received chemotherapy before and after PVE, significant differences were found (data not shown).

3.5. Main findings

NBCA led to a significantly greater absolute FLR growth and a higher DH. There was a significant difference in favor of NBCA in patients reaching resection after PVE. The use of chemotherapy after PVE does not negatively affect FLR growth. The complication rates were low in both groups, with only one patient in each group reporting a severe complication. Procedure-related data all

Table 4
Subgroup analysis of outcomes after PVE.

Colorectal liver metastasis	NBCA (n = 85)	Particles (n = 40)	p value
FLR before PVE, ml mean (std deviation)	390 (133)	344 (105)	0.056
sFLR before PVE, % mean (std deviation)	24.5 (8.8)	21.1 (8.0)	0.037
FLR after PVE, ml mean (std deviation)	572 (168)	510 (185)	0.064
sFLR, after PVE, % mean (std deviation)	35.7 (10.5)	30.9 (12.1)	0.025
FLR growth, ml mean (std deviation)	181 (99)	166 (133)	0.505
FLR growth, % mean (std deviation)	51.8 (30.0)	49.1 (41.6)	0.716
Time between PVE and CT, weeks mean (std deviation)	4.4 (4.0)	3.5 (1.6)	0.066
Degree of hypertrophy, % points mean (std deviation)	11.2 (5.8)	9.9 (7.9)	0.339
KGR, %/w mean (std deviation)	3.6 (2.9)	3.3 (2.9)	0.580
Perihilar cholangiocarcinoma	**NBCA (n = 42)**	**Particles (n = 40)**	**p value**
FLR before PVE, ml mean (std deviation)	431 (157)	332 (122)	0.002
sFLR before PVE, % mean (std deviation)	27.8 (10.4)	19.8 (5.8)	<0.001
FLR after PVE, ml mean (std deviation)	618 (195)	475 (149)	<0.001
sFLR, after PVE, % mean (std deviation)	40.1 (13.3)	28.4 (7.3)	<0.001
FLR growth, ml mean (std deviation)	187 (120)	143 (83)	0.061
FLR growth, % mean (std deviation)	50.0 (35.9)	48.5 (36.9)	0.855
Time between PVE and CT, weeks mean (std deviation)	3.8 (2.5)	3.8 (1.9)	0.935
Degree of hypertrophy, % points mean (std deviation)	12.3 (8.4)	8.6 (4.9)	0.017
KGR, %/w mean (std deviation)	4.4 (6.1)	2.5 (1.3)	0.051
Colorectal liver metastasis in the NBCA group	**Chemotherapy before PVE (n = 55)**	**Chemotherapy before and after PVE (n = 24)**	**p value**
FLR before PVE, ml mean (std deviation)	378 (131)	423 (129)	0.157
sFLR before PVE, % mean (std deviation)	23.5 (7.4)	27.3 (10.8)	0.071
FLR after PVE, ml mean (std deviation)	552 (161)	618 (179)	0.110
sFLR, after PVE, % mean (std deviation)	34.2 (8.2)	39.5 (13.7)	0.088
FLR growth, ml mean (std deviation)	174 (92)	195 (111)	0.399
FLR growth, % mean (std deviation)	51.7 (29.2)	48.9 (26.3)	0.688
Time between PVE and CT, weeks mean (std deviation)	3.9 (2.2)	5.8 (6.5)	0.051
Degree of hypertrophy, % points mean (std deviation)	10.7 (5.1)	12.2 (6.6)	0.282
KGR, %/w mean (std deviation)	3.5 (2.5)	3.7 (3.8)	0.737

indicated the superiority of NBCA.

4. Discussion

To the best of our knowledge, this is the largest comparison between NBCA and microparticles in the setting of PVE. In this study, we found a higher DH and higher resection rate in the NBCA group. The use of chemotherapy after PVE did not seem to affect the outcome of the PVE procedure. All procedure-related data indicated the superiority of NBCA. We did not observe a significant difference in the relative FLR growth between NBCA and microparticles.

Our aim was to investigate whether there was a difference between NBCA and microparticles in the setting of PVE regarding growth of the FLR. Absolute growth was higher in the NBCA group, but no difference regarding relative FLR growth was found in this study. In that respect, our findings differ from earlier small studies by Jaberi et al. [13] and Guiu et al. [14], the randomized controlled trial BestFLR Trial by Luz et al. [16] and a systematic review by Ali et al. [17]. de Baere et al. showed a negative correlation between FLR volume before PVE and hypertrophy after PVE [26], meaning that a larger FLR before PVE results in a smaller FLR hypertrophy after PVE. This was confirmed in a recent systematic review by Soykan et al. [27] and may explain the lack of significance between NBCA and microparticles in the relative growth of the FLR, as both the FLR and sFLR were significantly larger in the NBCA group before the PVE procedure. The larger FLR and sFLR in the NBCA group before the PVE procedure may in part be an explanation for the higher percentage of patients in the NBCA group reaching FLR $\geq$30 %.

NBCA had a higher DH than microparticles. Low DH has previously been shown by Ribero et al. [28] and Narula et al. [29] to be a negative predictor for postoperative liver failure. Although postoperative outcomes are not within the scope of this article, DH might serve as an indicator in favor of NBCA.

No negative effects on FLR growth were observed in patients receiving chemotherapy before versus before and after PVE in patients with colorectal liver metastases having PVE with NBCA. This is consistent with the previous findings by Covey et al. [30] and Nafidi et al. [31], indicating that chemotherapy can be administered after PVE without the risk of insufficient FLR growth.

We found significant differences regarding the PVE procedure, where fluoroscopy time, radiation, DAP and contrast volume used all showed results in favor of NBCA. This is consistent with previous findings by Ali et al. [17] and Jaberi et al. [13]. These advantages combined with a lower total cost for NBCA, as presented by Ali et al. in a Swedish context [17], suggest that NBCA should be the preferred method for PVE. In a majority of the patients in this study, the ipsilateral approach was used. This approach has the advantages of not risking injury to the FLR and allowing for easy access to segment four portal branches [11]. This study showed an overall high success rate of 100 % in both groups. Adverse events were rare, and only one severe complication was identified in each group, in line with other reports [17,32].

Additional embolization with a central vascular plug has been demonstrated to produce an increase in the growth of the FLR compared with NBCA alone as well as having the benefit of reducing the risk of nontarget embolization of the FLR [33], thereby adding to the benefits of NBCA. Our data suggest a possible benefit with a central vascular plug in the setting of PVE with microparticles, where results are comparable with NBCA alone.

This study has some limitations that must be recognized. It is a retrospective analysis of patients from three of the six Swedish hepatobiliary centers and thus does not cover all Swedish patients during the study period. The results may be affected by local treatment traditions and interventional techniques. Selection of patients for the PVE procedure may also be affected by the multicenter design, where one center favored microparticles and the two others favored NBCA. Interventional procedures were performed during a time span of nine years, and no consideration was given to technical advances during this period. No functional measurements of the FLR were performed, and only overall liver function was tested using blood samples. Economic arguments in favor of NBCA are limited to a Swedish setting, which may limit the generalizability of the results presented.

Despite these shortcomings, our results provide evidence supporting the ongoing shift toward NBCA over microparticles in portal vein embolization. NBCA produces sufficient FLR growth and higher DH and resection rates. NBCA is less time-consuming and lowers radiation exposure for patients. The PVE procedure with NBCA is safe and has a high success rate.

Ethics declaration

This study was approved for multicenter research by the Swedish Ethical Review Authority (Dnr: 2019-01297).

Informed consent was not required for this study by the decision of the Swedish Ethical Review Authority due to the retrospective study design.

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Data availability statement

The study data have not been deposited into a publicly available repository but will be available on request.

CRediT authorship contribution statement

Dennis Björk: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Martin Delle:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Fredrik Holmquist:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Kristina Hasselgren:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Per Sandström:** Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Gert Lindell:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Ernesto Sparrelid:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Bergthor Björnsson:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Dennis Björk: No interest to declare. Martin Delle: No interest to declare. Fredrik Holmquist: No interest to declare. Kristina Hasselgren: No interest to declare. Per Sandström: No interest to declare. Gert Lindell: No interest to declare. Ernesto Sparrelid: No interest to declare. Bergthor Björnsson: No interest to declare.

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