A comparison of portal vein embolization with PHEMA [poly(2-hydroxyethyl methacrylate)] and a histoacryl/lipiodol mixture in patients scheduled for extended right hepatectomy

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Short title: Portal vein embolization with PHEMA

Summary

Aim: To determine whether PHEMA [poly(2-hydroxyethyl methacrylate)] is suitable for portal vein embolization in patients scheduled to right hepatectomy and whether it is as effective as the currently used agent (a histoacryl/lipiodol mixture).

Material and methods: Two groups of nine patients each scheduled for extended right hepatectomy for primary or secondary hepatic tumor, had right portal vein embolization in an effort to induce future liver remnant (FLR) hypertrophy. One group had embolization with PHEMA, the other one with the histoacryl/lipiodol mixture. In all patients, embolization was performed using the right retrograde transhepatic access.

Results: Embolization was technically successful in all the 18 patients, with no complication related to the embolization agent. Eight patients of either group developed FLR hypertrophy allowing extended right hepatectomy. Likewise, one patient in each group had recanalization of a portal vein branch. Histology showed that both embolization agents reach the periphery of portal vein branches, with PHEMA penetrating somewhat deeper into the periphery.

Conclusion: Poly(2-hydroxyethyl methacrylate) has been shown to be an agent suitable for embolization in the portal venous system comparable with existing embolization agent (histoacryl/lipiodol mixture).

Key words:

Extended right hepatectomy - portal vein embolization - embolization-induced left liver lobe hypertrophy

Introduction

Occasionally, extended right hepatectomy is the only therapeutic option for the treatment of hepatic malignancies. Its use is limited by the size of the future liver remnant (FLR) needed to maintain liver function at the necessary level. While there has been ongoing lively debate regarding the extent of resection, most authors accept that FLR volumes below 20–25% of total liver volume (TLV) in patients with intact liver, and FLR volumes below 30–40% in patients with chronic liver disease or those after extensive chemotherapy are unable to maintain the liver function needed for homeostasis (Abdalla 2001, Azoulay 2000, Zorzi 2007). The current strategy used to increase the percentage of FLR is portal vein embolization in the region to be resected; however, the procedure has been shown to induce hypertrophy of the non-embolized hepatic segment. The first paper reporting induction of FLR hypertrophy following ligation of a portal vein branch dates back to 1920 (Rous 1920). The first to use this technique in clinical practice was Kinoshita (Kinoshita 1986) embolizing portal vein branches in a liver segment to be resected thus inducing FLR hypertrophy. The technique has been accepted since, with a variety of embolization agents (van Lienden 2013, Denys 2012); however, there is no evidence that the outcomes with a particular agent would be clearly superior to those of other ones. Our study was designed to test embolization with PHEMA, an agent used in other branches of medicine (and indications), and to compare the outcome with that of a mixture of lipiodol (Lipiodol Ultra-fluide, Guerbet, France) and histoacryl a (n-butyl cyanoacrylate) (Histoacryl, B. Braun Medical, Germany) currently used for embolization in the Czech Republic.

A brief history of use of PHEMA in medicine:
Large mesh size hydrogels derived from 2-hydroxyethyl methacrylate (HEMA) were developed in the early 1960s. Thanks to their properties (optical, biocompatibility, and availability), they were used to manufacture hydrogel soft contact lenses. The agent was approved by the US Food and Drug Administration (FDA) for this purpose in 1972 and also launched on the international market by Bausch&Lomb (Efron 2010, Horák 1992).

At present, HEMA-based hydrogels are used to produce contact lenses, intraocular lenses, implants for soft tissue reconstruction, dressings and bandages for rapid healing of common wounds as well as deep trophic defects and burns, plates for cell cultures and subsequent transplantation (keratinocytes), and carriers for tissue engineering (porous gels). There have been literature reports of their applications as blood detoxicators,, artificial corneas, vitreous replacement, breast implants, hemodialysis membranes, swellable implants for the treatment of post-traumatic male incontinence, and so on (Inst. M.Ch. 2003, Brynda 1985).

PHEMA was used with success for renal tumor embolization as early as the 1990s. The result of a joint project of IKEM with the Institute of Macromolecular Chemistry of the Academy of Sciences of the Czech Republic was an agent based on PHEMA dissolved in 70% ethanol and mixable with a non-ionic contrast agent up to a 1 : 1 ratio allowing monitoring of the course of embolization by fluoroscopy. PHEMA dissolved in alcohol and mixed with a

contrast was applied (using 4–5F catheters) as a viscous liquid to shrink, upon contact with an aqueous medium (that is, also with blood), forming an indissolvable polymer (Figure 1).

As PHEMA is biologically inert and stable, the effect of embolization can be expected to be a permanent one. The clinical aim of the project is to evaluate the use of PHEMA as an embolization agent for occlusion of the portal venous system in patients scheduled for liver resection with predicted too small FLR. Demonstration of the utility of PHEMA for the above procedure would allow us expand our options in the pre-operative prepping of patients with liver malignancies.

Material and methods

Patients were divided into two groups, one with embolization using the traditional technique (histoacryl/lipiodol mixture), and the other one with PHEMA. Embolization was performed using PHEMA solutions (at a concentration of 10.95 mass% and kinematic viscosity of 82×10^{-6} m^2s^{-1}) in 70% ethanol supplied by GEL-MED International, Prague, Czech Republic (Group 1: 9 patients). As a rule, PHEMA was mixed at a 1:1 ratio with a conventional iodinated contrast agent (Optiray 350, Hennef, Germany). Group 2 was also made up of 9 patients receiving embolization with a histoacryl/lipiodol mixture at ratios of 8:1 to 10:1 (Table 1). All patients enrolled into the study were indicated for extended right hepatectomy and right portal vein embolization. The decision to indicate the patients for embolization was made during an interdisciplinary consultation when planning liver resection. The decision about the embolization agent to be used was not made by regularrandomization. When Principal Investigator was present in bcath lab, PHEMA was used, otherwise histoacryl/lipiodol was employed, but the groups of patients did not differ in their main characteristics (Table 1)The embolization was performed using ipsilateral lobe puncture via retrograde catheterization and was finished after the right side of the portal venous system was completely filled with the embolization agent (followed by fluoroscopy). Based on the portal venous system anatomy, the physician performing the catheterization decided whether or not to embolize the fourth hepatic segment.

Embolization technique:

Both materials were injected by 4-5 F catheters under fluoroscopic control (histoacryl/lipiodol mixture has higher density and therefore it is better “visible”). The filling of portal vein branches was followed by fluoroscopy and the injection was interrupted when the filling was complete to avoid reflux to the nontarget branches. PHEME compared to histioacryl/lipiodol does not stick to the vessel wall or catheter and the injection could be easily repeated.

Amount of embolizing material used:

PHEMA average 27 (15-40) ml + the same amount of Optiray 350l

Histioacryl/lipiodol mixture 1:10 – 1:15 average 9.5 (8-13) ml

In most cases, the embolization tract was occluded with surgical gelatin (Geli Putty, Gelita Medical GmbH, Eberbach, Germany), less often using metal coils (William Cook Europe, Bjaeverskov, Denmark). After embolization, patients experiencing post-procedural pain received analgesics and/or other sedatives as needed.

Total liver volume (TLV) was calculated using CT volumetry with standard Volume software (Siemens, Erlangen, Germany) from 8-mm cross sections. In patients with definable liver tumor (i.e., non-functioning parenchyma), its volume was determined using the same volumetric program with the tumor volume subsequently subtracted from TLV.

As s rule, FLR volume was calculated using CT volumetry both prior to and after an average 8–10 weeks post-embolization, both in absolute numbers (ml) and as percentage: FLR% = 100 × FLR / TLV (Table 1). Based on the volume parameters, some patients were subsequently scheduled for right liver lobe resection.

Histomorphological evaluation of the resected liver tissue was performed in 6 patients after embolization with a histoacryl/lipiodol mixture and in 7 patients after PHEMA embolization**.** addition to tumors assessment each liver resected tissue was histologically assessed in at least At least 4 representative samples of non-neoplastic liver parenchyma were obtained from each resection specimen and the tissue was routinely processed by the standard paraffin technique after 4% paraformaldehyde fixation. The sections (4 μm) were stained with hematoxylin and eosin (HE), Sirius red, orcein, Schmorl´s method, periodic acid-Schiff (PAS) reaction after diastase digestion, and Prussian blue.
Proliferative activity of hepatocytes was detected immunohistochemically with a primary mouse monoclonal antibody raised against the Ki-67 antigen (clone MIB-1, DAKO, Glostrup, Denmark). Additionally, TUNEL (Terminal deoxynucleotidyl transferase-mediated dUTP-biotin Nick End Labeling; Roche Diagnostics GmbH, Mannheim, Germany) assay was performed to detect apoptosis in paraffin-embedded sections. Quantitative assessment of proliferative activity and apoptosis was performed using an Olympus BX41 light microscope in at least 4500 (Ki-67) and 1500 (TUNEL) hepatocytes in randomly selected high-power fields (400×). Positive hepatocytes were defined as those with dark brown stained nuclei and the results were expressed as a proliferation and apoptotic index, e.g. a ratio (expressed as a percentage) of Ki-67 and TUNEL-positive hepatocytes to the total number of hepatocytes, respectively.

Results

Embolization was performed with angiographically documented right portal venous system occlusion in all cases (Figures 2 and 3). There were no procedure-related complications except for one case of bleeding managed conservatively. The outcome of embolization in terms of change of FLR volume calculated for both groups is shown in Table 1. No patient developed post-hepatectomy liver failure due to insufficient function of the remnant liver parenchyma. Three patients in the histoacryl/lipiodol group and two in the PHEMA group did

not eventually had hepatectomy, one for insufficient FLR hypertrophy in each group, and the remaining ones for tumor generalization.

Histology

Histology and immunohistochemistry. The histoacryl/lipidiol mixture occluded braches of portal veins 1608 ±1279 μm (range 230–3960 μm) in diameter and induced a marked foreign body giant-cell granulomatous reaction. PHEMA occluded peripheral smaller-caliber portal vein branches 90 ±74 μm (range 10–290 μm) in diameter. The giant-cell granulomatous reaction to PHEMA was minimal compared to the histoacryl/lipidiol mixture and it was expressed only focally (Figure 4).

Centrilobular sinusoidal dilation and congestion with atrophy of hepatocytes in zone 3 of the liver lobule was detected in both groups of patients (Figure 5). Furthermore, centrilobularly accentuated mixed micro- and macrovesicular steatosis involving 10% and 50% of hepatocytes in two patients in histoacryl/lipiodol group, and 10%, 10% and 20% of hepatocytes in three patients after PHEMA embolization was found. Confluent necrosis of liver parenchyma was not observed in any of the patients.

Hepatocyte proliferative activity of the liver parenchyma embolized with either the histoacryl/lipidiol mixture or PHEMA was low, with a proliferation index of 0.59% and 0.52%, respectively. In the control non-embolized parenchyma, the index of proliferative activity was 1.17%.

By contrast, the embolized liver parenchyma displayed a higher apoptotic index compared to the non-embolized tissue, being 5.78% in the histoacryl/lipidiol mixture group, 8.83% in PHEMA group, and 1.75% in the control non-embolized group. In agreement with an earlier report (18), centrilobular accumulation of apoptotic hepatocytes after portal vein embolization was discernible in both groups of patients (not shown).

Discussion

Surgical removal of liver tumors, either primary or secondary, often remains the only therapeutic option giving patients some hope for long-term survival. For a long time, one of the limiting factors was the FLR volume. At the same time, it is a well-known fact that the risk of liver failure after resection as well as total post-procedural morbidity correlate with the liver parenchymal volume left after surgical resection (Ribero d 2007, Vauthey 2000). The only clinical available technique for increasing the liver parenchymal volume to be left after resection (i.e., FLR) is occlusion of the portal venous system in the area to be resected. The idea of portal vein embolization was developed in Japan in the late 1980s based on two publications. The first report documented observation of lobar atrophy of the liver due to cholangiocarcinoma invading the portal vein (Takayasu 1986). The other report described lobar atrophy of the liver following portal vein branches embolization in an effort to limit intraportal spread of hepatocellular carcinoma (Kinoshita 1986). At the same time, the authors documented an increase in the volume of the liver segments with patent portal veins over time.

The technique of portal vein embolization gained widespread acceptance, first in Japan, followed by Europe (deBaere 1993) and North America (Abdalla 2002). Essentially, the

procedure involves occlusion of the portal vein branches in the liver segments to be resected thus completely rerouting blood flow through the portal vein to FLR branches (Denys2000). The actual mechanism of liver regeneration following portal vein embolization is a complex process not fully understood yet. Histologically, portal vein embolization induces atrophy of the embolized liver segment as the outcome of simultaneous hepatocyte apoptosis and atrophy. Non-embolized liver segments show intensive mitotic activity as early as days after portal vein embolization and, at the same time, hepatocyte hypertrophy reflected in an increase in FLR volume within weaks post-embolization (Harada 1997, Fujii 2000, Komori 2006).

The relevant literature contains a number of papers reporting the use of various types of embolization agents or combinations thereof (surgical gelatin, metal coils, Amplatz occluder, ethanol, cyanoacrylate mixed with lipiodol, thrombin). None of the above modalities has been shown to be superior to the other therapeutic options. While a combination of cyanoacrylate with lipiodol seems to induce the greatest FLR hypertrophy, the outcomes have never been statistically significant (Van Lienden 2013, deBaere 1993, Abulkhir 2008,Bent 2009, Guiu 2013). In our study, the alcohol-based PHEMA solution was chosen assuming it would reach the portal venous system distally, similar to the cyanoacrylate/lipiodol mixture (as confirmed by histology – PHEMA penetrated even deeper in the portal vein branches than the cyanoacrylate/lipiodol mixture (Fig. 4)) and enhanced by the action of alcohol on the endothelium. The agent did indeed meet our expectations as we were able to occlude properly the portal venous system with the occlusion, if performed appropriately in terms of its technical aspect, being permanent in all but one case resulting in FLR hypertrophy exceeding the original TLV value by more than 5%. To confirm that deeper penetration of the agent means as well bigger FLR hypertrophy would require much bigger study. There were no complications related to the type of technique of embolization agent application; only in two cases was partial recanalization of the portal venous system documented, most likely due to incomplete embolization (in fact, of one portal vein branch in one PHEMA group patient and two portal vein branches in the histoacryl/lipiodol mixture group; he was a male patient (patient JP♂**)** not developing left lobe hypertrophy at all, Table 1). The rate of FLR is consistent with literary data although, needless to say, the outcomes are affected by the technique of FLR calculation or different indication criteria for embolization. No significant clinical or histological differences between the two embolization materials were documented.

It can be thus reasonably concluded that PHEMA dissolved in alcohol is a suitable agent for portal venous system embolization in patients scheduled for extended hepatectomy, and is likely to be suitable also for other types of embolization. Large clinical studies are obviously warranted to support this claim.

Acknowledgments:

Approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer University Hospital on 18 December 2009

The study was supported by project NT 11273-4/2010 awarded by the Internal Grant Agency and project 13-00939S of the Grant Agency of the Czech Republic.

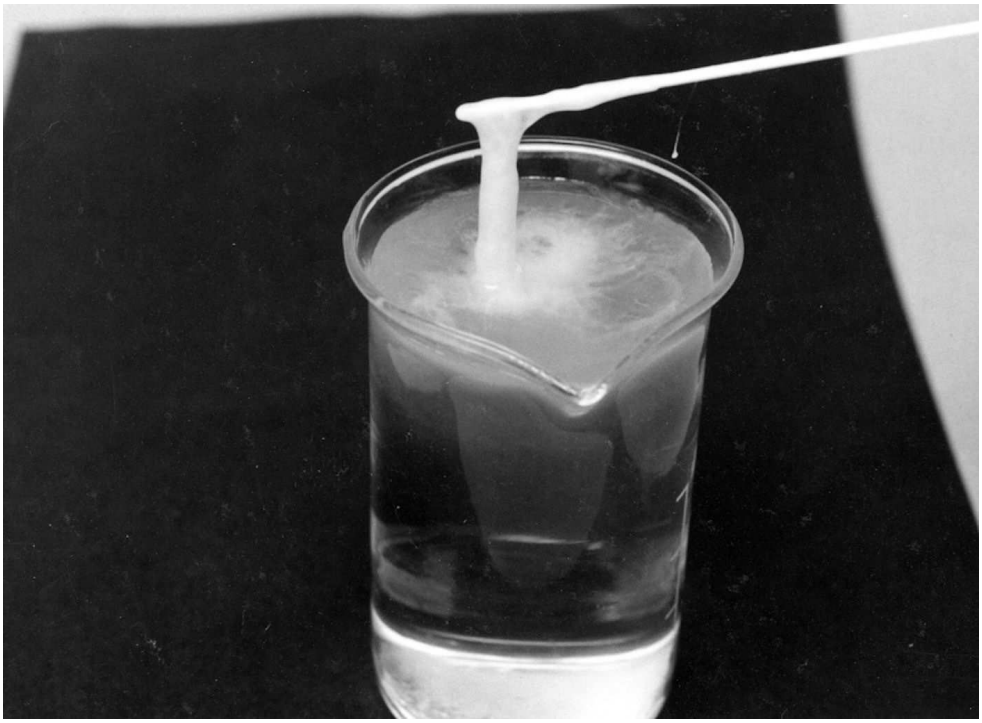

Figure 1: Precipitation of PHEMA injected to water

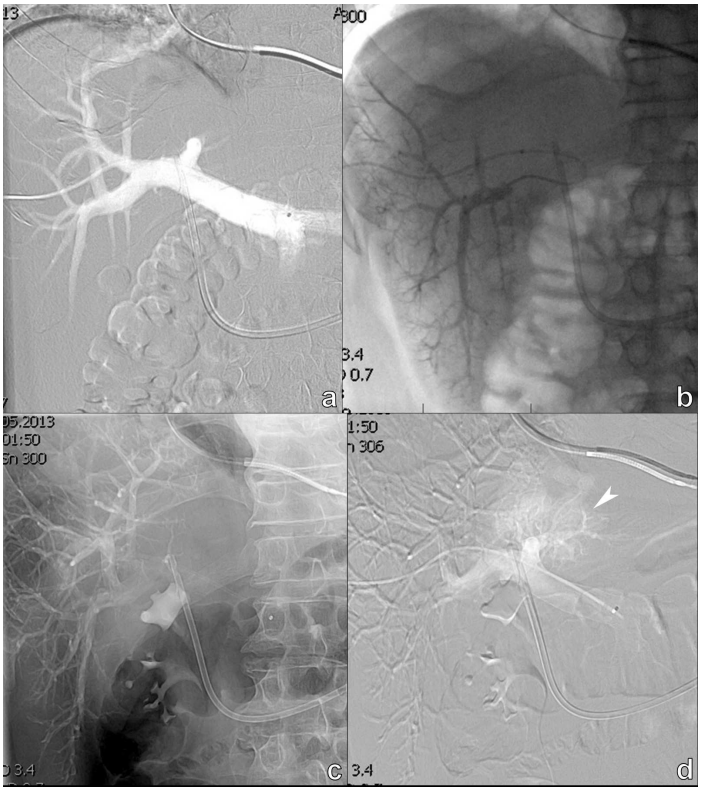

Figure 2: Portal vein angiogram, catheter inserted percutaneously from the right side (a). Injection of contrast-labelled PHEMA into the portal vein (b). PHEMA fills the right-side portal venous system (c). Control angiogram documents occlusion of the right-side portal venous system, with only portal vein branches for the left lobe filling ◄ (d).

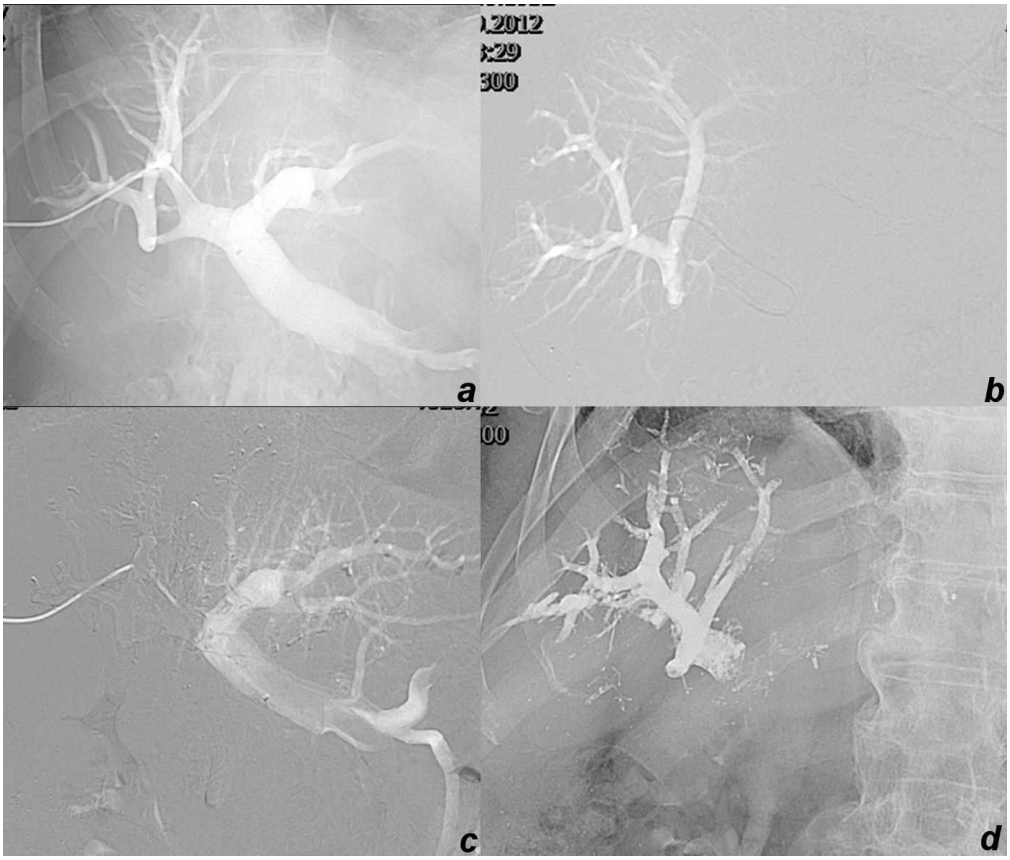

Figure 3: Portal vein angiogram, catheter inserted percutaneously from the right side (a). Contrast injected into a retrograde accessed right portal vein (b). Control angiogram documents occlusion of the right-side portal venous system with the histoacryl/lipiodol mixture, with only portal vein branches for the left lobe filling (c). The histoacryl/lipiodol mixture fills the right-side portal venous system (d).

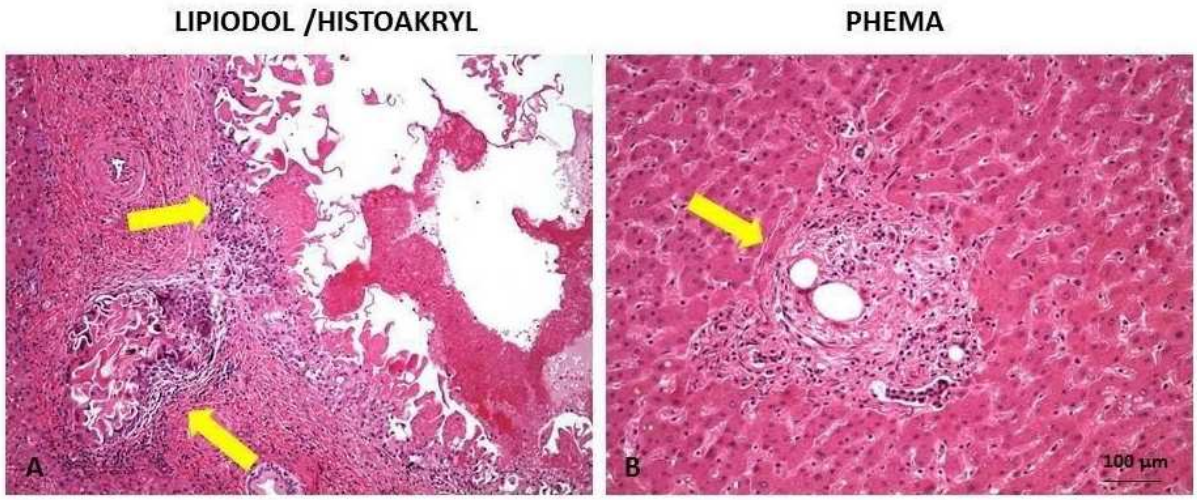

Figure 4: Detail of a portal vein branch with embolized agent. The histoacryl/lipiodol mixture (A) occludes, compared with PHEMA (B), larger-caliber portal vein branches (arrows); a granulomatous foreign-body type reaction is evident around the embolized agent; however, the reaction is minimal after PHEMA embolization. HE, original magnification x100.

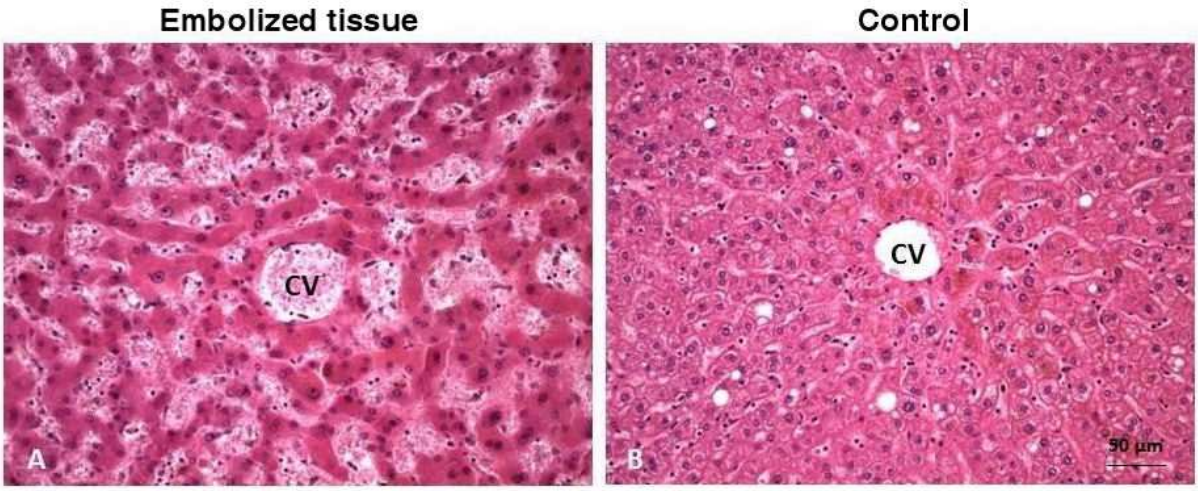

Figure 5: Histomorphological changes in the liver parenchyma post-embolization. Sinusoidal dilatation and congestion in the centrilobular zone with mild atrophy of hepatocytes in the embolized tissue (A), compared to the non-embolized control (B). CV – central vein. HE, original magnification ×200.

Table 1: Group of patients characteristics: KT III – Klatskin tumor III, mCRC – colorectal carcinoma metastasis, HCC – hepatocellular carcinoma, m – metastasis, CA – carcinoma, FLR hypertrophy – Change of FLR after embolization in percents or ml.

Histoacryl / Lipiodol	Age / years		Weeks post-E	TLV (ml)	FLR (ml)	FLR (%)	FLR post-E (ml)	FLR post- E (%)	hypertrophy of FLR (%)	Reason for not performing resection
SV♂	53	KTIII	16	1406	286	20,3%	457	32,5%	59,8%	
MV♀	68	MCRCa	4	1016	232	22,8%	250	24,6%	7,8%	
ZF♂	60	MCRCa	20	1224	150	12,3%	236	19,3%	57,3%	Insufficient FLR volume
LS♀	62	HCC	10	1776	309	17,4%	446	25,1%	44,3%	
AL♀	64	KTIII	7	1145	300	26,2%	566	49,4%	88,7%	
HV♀	73	KTIII	9	2131	621	29,1%	795	37,3%	28,0%	
PS♂	70	KTIII	9	1897	307	16,2%	300	15,8%	-2,3%	Tumor generalization
JP♂	61	MCRCa	6	1308	426	32,6%	670	51,2%	57,3%	Tumor generalization
SK♂	66	KTIII	5	2276	563	24,7%	616	27,1%	9,4%	
mean	64		10	1575	355	22,4%	482	31,4%	38,9%	
SD	6		5	430	145	6,1%	185	11,8%	28,4%	
PHEMA										
JH♂	68	KTIII	6	1142	305	26,7%	348	30,5%	14,1%	
AK♀	60	KTIII	10	1304	300	23,0%	360	27,6%	20,0%	
JM♂	54	MCRCa	7	1630	320	19,6%	410	25,2%	28,1%	
DC♀	65	HCC	3	1855	490	26,4%	570	30,7%	16,3%	
MP♂	45	KTIII	5	1485	386	26,0%	492	33,1%	27,5%	
ZS♀	65	KTIII	20	1248	176	14,1%	343	27,5%	94,9%	
JN♂	67	KTIII	8	1529	214	14,0%	423	27,7%	97,7%	Tumor generalization
VH♂	54	MCRCa	10	1909	355	18,6%	395	20,7%	11,3%	Insufficient FLR volume
JM♂	71	KTIII	6	1361	320	23,5%	410	30,1%	28,1%	
mean	61		8	1496	318	21,3%	417	28,1%	37,6%	
SD	8		5	250	86	4,7%	69	3,4%	31,9%	

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