

Portal Vein Embolisation with Application of Haematopoietic Stem Cells in Patients with Primarily or Non-resectable Colorectal Liver Metastases

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Abstract. *Background:* Insufficient future liver remnant volume (FLRV) is the main cause of low resectability of liver metastases from colorectal cancer (CLMs). One option for enhancing FLVR growth is the use of portal vein embolisation (PVE) with the application of autologous haematopoietic stem cells (HSCs). *Patients and Methods:* PVE with the application of HSCs was used in 11 patients (group 1) with primarily non-resectable CLMs due to insufficient FLRV without signs of extrahepatic metastases. The control group (group 2) consisted of 14 patients in whom only PVE was performed. We evaluated the product quality, FLRV growth, CLM volume, median survival and progression-free survival (PFS). *Results:* Product quality was achieved in all collections. In all group-1 patients, sufficient FLRV growth occurred within three weeks. In the first and second weeks, FLRV increased optimally in most patients ($p < 0.006$). In 13 out of the 14 group-2 patients, optimum FLVR growth was observed within three weeks following PVE ($p < 0.002$). More rapid FLVR growth was observed in group 1 patients ($p < 0.01$). CLM volume was significantly increased in both the group-2 ($p < 0.0005$) and group-1 ($p < 0.008$) patients at the time of liver resection. There was no significant difference in the growth of the CLM volume between the groups ($p < 0.18$). The median survival was 7.3 and 6.8 months for group 1 and 2 patients, respectively, and the two-year PFS was 28% and 22% ($p < 0.18$), respectively. *Conclusion:* PVE with HSC application is a promising method for effectively stimulating FLRV growth in patients with primarily non-resectable CLMs.

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Tissue regeneration using stem cells has become a recent trend in medicine and is currently used as a therapy employed by a wide range of clinical specialties (1, 2). Stem cells acquired from the bone marrow or stimulated peripheral blood are considered an appropriate source of cells for regenerative medicine given their relatively easy availability in sufficient amounts (3).

Colorectal liver metastases (CLMs) are quite frequent in the setting of colon carcinoma. Approximately 25% of patients with colorectal carcinoma have synchronous CLMs at the time of diagnosis, and 60% exhibit metachronous CLMs. CLMs develop over varying periods after surgery for the primary tumor. Multimodal treatment procedures, the basis of which is the surgical resection of CLMs, offer a 5-year survival rate of between 25% and 74%. Nevertheless, only 15-20% of patients have primarily resectable CLMs. The remaining patients have no chance of successful radical resection for various reasons; insufficient future liver remnant volume (FLRV) plays a crucial role in this condition (4, 5).

One of the possibilities for increasing the FLRV volume is portal vein embolisation (PVE). Once the volume of the contralateral liver lobe increases, curative liver resection can be performed. Nevertheless, in some patients, the increase in FLRV is very low and only lasts for four to eight weeks; therefore, there is a risk of further progression of the malignancy in the liver parenchyma or associated lymph nodes. A specific possibility for increasing the regeneration rate of the liver parenchyma is the use of the regenerative and differentiation capacity of stem cells combined with PVE. The aim of our report is to present the first data on the use of PVE with the application of haematopoietic stem cells (HSCs) in patients with primarily non-resectable CLMs.

Patients and Methods

We used the PVE method with the application of HSCs for the first time in September 2010 after approval by the Ethics Committee of the University Hospital in Pilsen (No. 25/2010). By March 2014, we had

performed the procedure in 11 patients with primarily non-resectable CLMs (group 1). The patients included nine men and two women with an average age of 62.1 (range=51-75) years. The study included patients with primarily non-resectable CLMs due to insufficient FLRV and no evidence of extrahepatic spreading of the tumor based on ultrasonography (USG), computed tomography (CT), positron-emission CT (PET-CT), or magnetic resonance imaging (MRI).

We determined that an insufficient FLRV was a volume less than 30% of the total volume of the healthy hepatic tissue. For patients whose liver parenchyma was damaged by the primary disease (*e.g.* steatosis and cirrhosis), or who underwent chemotherapy/biological treatment, we considered an insufficient FLRV to be a volume less than 40% of the total liver volume. We performed liver volumetry at study entry for the determination of FLRV (Somatom Definition; Siemens, Munich, Germany). The average baseline FLRV was 30.5% (range=21.4-38.6%). We evaluated the function of the liver parenchyma according to clinical and laboratory parameters and using an indocyanine green retention test (Limon; Pulsion Medical Systems AG, Eschborn, Germany). All patients were thoroughly informed about the proposed treatment procedure with warnings about any potential risks (in particular, progression of the tumour) and provided their written informed consent. The indication for the operation was determined by a multi-disciplinary team.

Briefly, the procedure methodology was as follows. HSCs were obtained *via* the apheresis method from peripheral blood. We achieved the stimulation of the HSCs in the bone marrow and their release into the peripheral blood using granulocyte-colony stimulating factor (filgrastim; Neupogen, Amgen Europe B.V., Breda, the Netherlands) at a dosage of 10 µg/kg/day applied subcutaneously in one daily dose for four days. From day 4 after the application of filgrastim, the stem cells circulating in the peripheral blood were monitored [detected with flow cytometry as cluster of differentiation 34⁺ (CD34⁺) cells. On day 5 after the mobilisation, leukapheresis was performed using a dialysis catheter introduced into the femoral vein and connected to a Cobe Spectra continuous blood cell separator (Termo BCT, Lakewood, CO, USA) using a programme that was specific for mononuclear leukocytes (The MNC Programme, software version 6.1, Retain International, London, UK). Approximately two volumes of the patient's blood were processed, and an anti-coagulant solution based on citrate and citric acid (ACD-A; Baxter, Deerfield, IL, USA) was used at a ratio of 1:12-1:14 to whole blood. For the prevention of citrate toxicity, all patients underwent calcium supplementation to ensure that the calcium levels were within normal limits (in fractions for a total dose of 10-20 ml CaCl₂). The obtained product was analysed in the laboratory, and the basic quality parameters were specified: volume; concentration and absolute white blood cell count, CD34⁺ and CD 133⁺ cell counts; erythrocyte and thrombocyte counts; viability of CD34⁺ and CD 133⁺ cells; and sterility. The minimum requirement for the number of stem cells in the product was $\geq 1 \times 10^7$ CD34⁺ in the total volume of 200 ml of the product. Samples for the determination of all tests were taken within a closed system. Before the mobilisation, all patients were also examined to eliminate blood-borne diseases (*e.g.* Acquired Immune Deficiency Syndrome, hepatitis B and C, and syphilis). The product was not further handled, and it was stored until the next day at 2-8°C with continuous monitoring of the storage conditions. The following day, the product was transported from the laboratory to the operating room for use in the procedure.

The day before leukapheresis, we performed PVE transperitally using a mixture of Histoacryl (Braun, Melsungen AG, Germany) and Lipiodol (Cedex, Liege, France) at a 1:10 ratio. The day after

Table I. *Product quality parameters.*

Product parameter	Median (range)
Volume	116 (103-142) ml
WBC	300 (106-501) $\times 10^9/l$
PLT	1,907 (1,404-2,459) $\times 10^9/l$
CD34 ⁺	0.27% (0.08-0.61%)
CD34 ⁺	10.97 (2.96-23.30) $\times 10^7$ *
CD133 ⁺	0.19% (0.03-0.50%)
	5.83 (1.19-19.10) $\times 10^7$ *

WBC: White blood cells; PLT: platelets; CD: cluster of differentiation; *In total preparation.

the leukapheresis, under general anaesthesia, we created an incision in the right hypogastrium, introduced a catheter *via* the *vena ileocolica* into the contralateral branch of the portal vein and applied the obtained HSC product. We monitored growth in the contralateral liver lobe using CT liver volumetry at weekly intervals after the PVE HSC procedure.

The control group comprised 14 patients who underwent PVE only within the same time interval based on the same indication criteria, *i.e.* with primarily non-resectable CLMs (group 2). This group included 10 men and four women with an average age of 60.1 (range=46-74) years.

Statistical analysis was performed using SW SAS 9.4 software (SAS Institute Inc., Cary, USA). The primary endpoint was the rate of FLRV growth, the secondary endpoint was the CLMs volume growth.

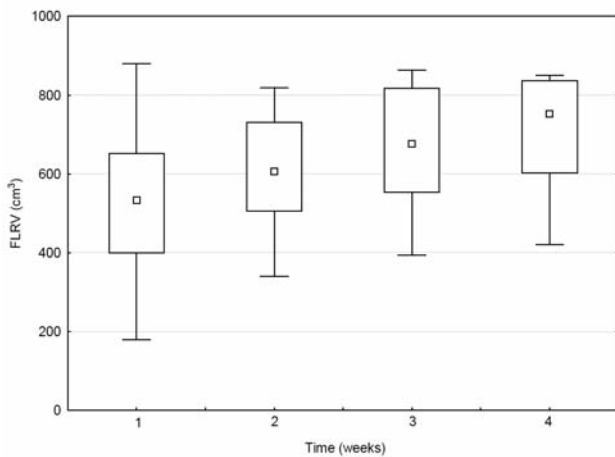
Results

The HSCs were extracted and applied without complications, as planned for all 11 patients. Following leukapheresis, mild citrate toxicity occurred in some patients; 10 lt of blood was processed (6-12 l) with an extraction duration of 138 min (129-154 min). The required HSC dose was achieved in 100 % of the collections. The product quality parameters are summarised in Table I.

PVE was performed in both groups of patients without complications. The average total volume of liver (TLV) and FLRV in group 1 before the procedure was 1698.8 \pm 381.0 and 533.3 \pm 186.1 cm³, respectively. The average volume of CLMs before the procedure was 86.6 \pm 128.6 cm³. The average TLV and FLRV in group 2 before the procedure was 1892.0 \pm 509.1 cm³ and 559.1 \pm 191.3 cm³, respectively. The average volume of CLMs before the procedure was 112.9 \pm 150 cm³.

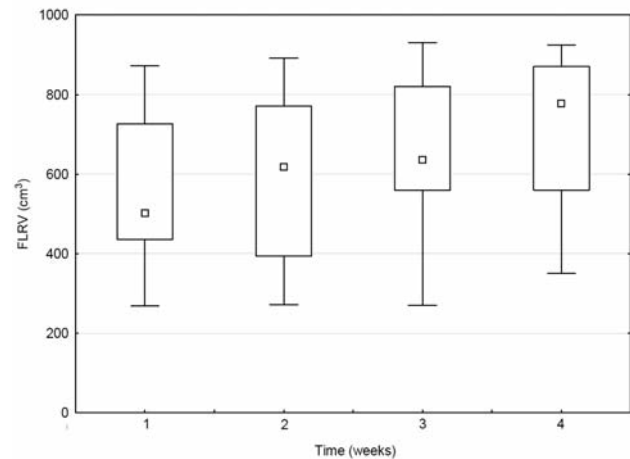
In all 11 (100%) patients of group 1, the required FLRV growth was achieved within three weeks after the procedure; however, the optimum FLRV growth was achieved in most patients by week 1 or 2 ($p < 0.006$) (Figure 1).

We were able to perform liver resection in 8 of the group-1 patients (four right hepatectomies and four extended right hepatectomies). The procedure could not be performed in



FLRV (time - week)	Average rank	Sum of ranks	Mean	SD
FLRV 0	1.3	15.0	533.3	186.1
FLRV 1	2.0	24.0	612.4	147.3
FLRV 2	3.0	36.0	673.8	150.7
FLRV 3	3.8	45.0	715.4	142.1

Figure 1. Future liver remnant volume (FLRV) growth after portal vein embolization with hematopoietic stem cells application.



FLRV (time - week)	Average rank	Sum of ranks	Mean	SD
FLRV 0	2.1	15.0	614.6	249.7
FLRV 1	2.0	14.0	613.0	242.8
FLRV 2	2.3	16.0	639.3	226.3
FLRV 3	3.6	25.0	702.9	232.5

Figure 2. Rate of future liver remnant volume (FLRV) growth after portal vein embolization.

three patients; in two patients, CLM progression occurred, and in one patient, despite a sufficient increase in FLRV, resection was not possible due to the presence of severe intra-abdominal adhesions following previous surgeries. In these patients, adjuvant oncological treatment was continued.

In 13 out of the group-2 patients, sufficient FLRV growth was achieved within three weeks after PVE ($p < 0.002$); none of the group-2 patients had optimum growth in the first two weeks after the procedure (Figure 2).

We performed liver resection in seven of the group-2 patients (two right hepatectomies, for extended right hepatectomies, and one right hepatectomy combined with radiofrequency ablation). The planned surgery was not performed in seven patients (50%). Six patients experienced dissemination of their underlying disease despite sufficient FLRV growth; in one patient, sufficient FLRV growth had not occurred even eight weeks after the procedure.

By comparing the two groups of patients, faster FLRV growth was observed in the group 1 patients ($p < 0.01$) (Figures 3).

The CLM volume in groups 1 and 2 had increased significantly at the time of the indication for hepatectomy compared with the baseline values ($p < 0.0005$ and $p < 0.008$, respectively). A comparison of both groups of patients revealed that there was no significant difference in the growth of the CLM volume ($p < 0.18$) (Figures 4, 5 and 6).

The median survival time was 7.3 and 6.8 months in group 1 and 2 patients, respectively. In addition, the two-year progression-free survival was 28% and 22%, respectively.

Discussion

The expected incidence of colorectal carcinoma in the USA was 42.5/100,000 inhabitants in 2013. In the same year, the expected occurrence of new cases of this disease was estimated to be 140,000. If we assume the occurrence of CLMs in more than 80% of patients with colorectal carcinoma, the total number of patients with CLMs is also highly significant. Unfortunately, despite diagnostic and treatment advancements, CLMs can be surgically resolved in only approximately one-fourth of all patients (6, 7).

One of the main causes of non-resectability of CLMs is a low FLRV. Generally, we recommend that at least 30% healthy tissues should be preserved after resection. In patients with primary liver disease or in patients after previous chemotherapy or a combination of chemotherapy with biological treatment, we require preservation of at least 40%. In these patients, it is preferable not to rely on the determination of the residual volume of the liver alone; functional examination of the liver should also be performed, particularly before a large liver resection (of more than three liver segments) (8).

Currently, there are a few ways to achieve FLRV growth, including the so-called stage procedures that use a range of techniques to achieve an increase in the healthy liver tissue volume on one hand and methods for reducing CLM volume on the other. The former methods include PVE with subsequent liver resection and repeated resections, often in

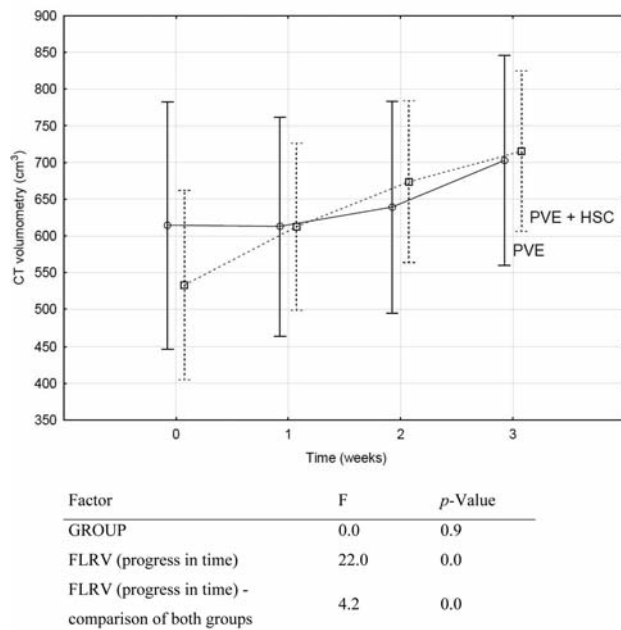


Figure 3. Rate of future remnant liver volume (FLRV) growth in both patient groups.

combination with thermoablation methods and recently developed ALLPS procedure (associating liver partition with portal vein ligation for staged hepatectomy). Chemo-biological oncological neoadjuvant therapy uses downsizing of the CLMs with the option for subsequent liver resection (9-13).

Our Department has been using the PVE method for long-term increases in FLRV. In total, we have resolved this issue in 52 patients and were able to perform a major (more than three liver segments) liver resection in 70% of the patients. PVE was first implemented by Makuuchi *et al.* in 1982 during the successful treatment of hilar cholangiocellular carcinoma (14). Since then, there have been several reports (15-18) addressing the efficacy of PVE in staging procedures for primarily non-resectable liver tumors. The principle of PVE is based on increasing the flow-rate of portal blood in a non-embolised liver lobe. The arterial liver blood flow is also increased as a compensatory mechanism, creating the so-called hepatic arterial buffer response. The complex process of atrophy-hypertrophy develops. PVE results in increased proliferation of hepatocytes in the contralateral lobe supported in particular by the entire range of cytokines (19), including growth factors, the production of which is increased with PVE.

The major problem with PVE is insufficient FLRV growth, which may occur in diabetics, as a consequence of the re-canalisation of the embolised branch of the vena portae and in the hepatic parenchyma damaged, *e.g.*, by

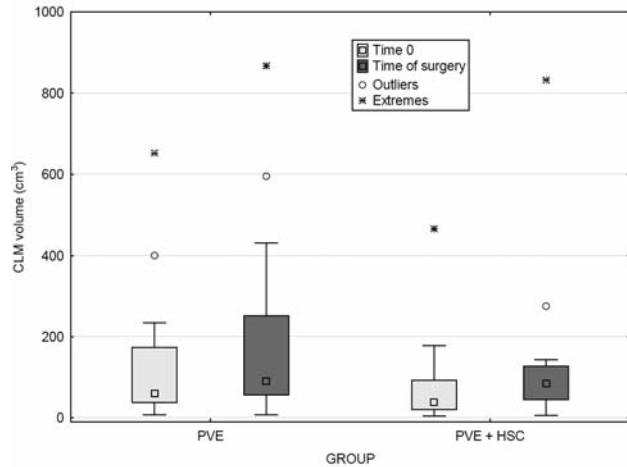


Figure 4. The final FLRV in both patient groups.

previous oncological treatment. In most cases, however, the cause is unknown (20, 21). FLRV regeneration following PVE occurs normally within an interval of four to eight weeks and is associated with an increased risk of growth of micrometastases in the liver. Kokudo *et al.* demonstrated an increased proliferative activity of CLMs based on an increase in the Ki-67 index in CLMs following PVE (22). A similar finding was described by Hayashi *et al.* (23) when measuring the growth in a primary liver tumor following PVE. They determined a significant growth in tumor volume after PVE compared with the condition before PVE (2.37 cm³/day compared with 0.59 cm³/day).

Given the somewhat casuistic information in previous publications (24-26), we decided to implement the method in clinical practice based on our very positive experience with the application of autologous stem cells in an experiment with piglets (27, 28). The reason for choosing to implement the method was extensive experience with the collection and use of autologous stem cells in the treatment of patients with lymphoproliferative disorders.

Stem cells have been identified in a variety of organs and play a critical role in tissue maintenance and repair. The hepatic parenchyma is able to ensure its own self-regeneration to an extent using its own hepatocytes. Adult hepatocytes exhibit a very low level of cell turnover; however, they possess the ability to proliferate in response to liver damage. However, as soon as this ability is insufficient, differentiation of the so-called hepatic progenitor cells is warranted; these cells are localised in the area of the canals of Hering – oval cells that are able to differentiate into mature hepatocytes and bile duct cells (29). Nevertheless, their regenerative capacity is not substantial, and only 0.15% of all new hepatocytes are developed at the time of liver regeneration (30-33). The ability for liver

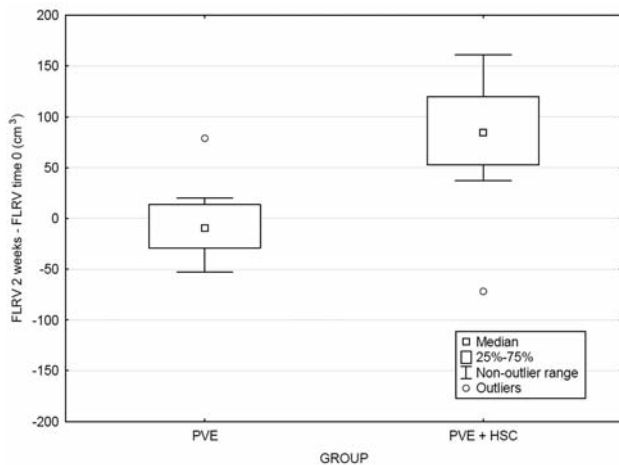


Figure 5. Growth of colorectal liver metastases (CLM) volume in the embolised liver lobe in both patient groups.

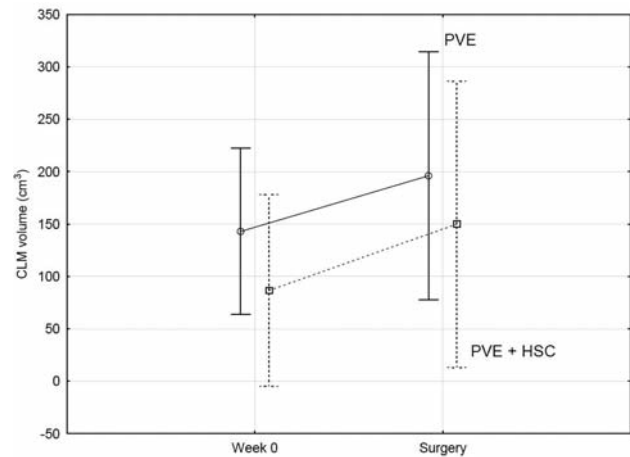


Figure 6. Colorectal liver metastases (CLM) volume in both patient groups at week 0 and at time of surgery.

regeneration fails in some liver diseases and during injury to the liver parenchyma by previous chemotherapy.

Bone marrow or blood-derived stem cells are a potential cell source that can support liver regeneration (34). The bone marrow contains two distinct stem cell populations: HSCs and mesenchymal (MSCs) cells. Both these types contribute to the regeneration of hepatic tissue. Damage to the liver results in the mobilisation of HSCs (or possibly also MSCs), which may occur *via* blood flow to the liver. Their transdifferentiation into hepatocytes is a rare event (35). Only very small numbers of transdifferentiated cells are detected in the injured liver. If the reparative process has already started in the liver, HSCs may provide support for endogenous stem cell-mediated repair of the liver. The secretion of various cytokines, suppression of the immune reaction, increase in angiogenesis, inhibition of apoptosis and enhancement of tissue proliferation are some of the mechanisms of regeneration stimulation mediated by bone marrow stem cells (36).

In our study, we verified that a combination of PVE with HSC application is safe for patients, without any immediate side-effects. In those patients, there was significantly faster FLRV growth compared to the group of patients treated with PVE only. Therefore, it was possible to perform radical liver resection sooner. This combined treatment most likely also had an effect on the CLM volume growth and occurrence of new CLMs in both the embolized and non-embolized parts of the liver parenchyma; the CLM volume growth was higher in patients following PVE, which required a longer time for optimum FLRV growth.

Within the scope of this study, the problem of an increase in the CLM volume in the embolized part of the liver parenchyma after both PVE and PVE with HSC application needs to be discussed. This issue is associated with the

unresolved problem of the possible risk of the proliferation of non-detectable micrometastases, not only in the liver but throughout the body, related to the method used for FLRV stimulation. As apparent in our population of patients, the stimulation of tumor growth occurred particularly in patients post-PVE. Therefore, some protective effect of HSCs against the development of metastases in the liver is hypothetically possible. Nevertheless, the progression of CLMs was also observed in the group of patients that underwent HSC application. The tumour tissue contains a large number of stimulating substances (*e.g.*, growth factors, matrix metalloproteinases, and cytokines), which may lead to the migration of HSCs to the tumour tissue, where they may subsequently stimulate the growth and spread of the tumour. The mechanism of the interaction of stem cells with tumour cells is not yet precisely known. There is most likely stimulation of neoangiogenesis with immunosuppression and apoptosis inhibition (37-39). A probable mechanism that supports the growth of metastases in the liver is the differentiation of mesenchymal cells in the tumour into the so-called carcinoma-associated fibroblast-like cells, which then support tumour growth. Tumour growth may also be supported by the regenerative mechanisms of the hepatic tissue post-PVE when the whole range of growth factors, matrix metalloproteinases and cytokines develops in the liver, which may stimulate and concurrently enable proliferation of the tumour tissue (40). Most likely, the arterial buffer response after PVE also plays an important role in tumour development. The possibility of the differentiation of autologous stem cells into tumour cells under the metastatic environment remains an unresolved issue. The mechanism of CLM progression is unclear, and obviously, evaluating a number of clinical and laboratory

parameters in a large number of patients will be necessary to determine the risk of tumor progression after the PVE alone and in combination with HSC application.

We are aware that our study has several fundamental limitations. Above all, it contains a low number of patients and a short duration of monitoring. Another limitation is that an optimum method for the detection of HSCs in the liver tissue parenchyma has not yet been developed. In addition, the above-mentioned possibility of the stimulation of carcinogenesis in the liver parenchyma in connection with this method remains an unresolved issue.

Nevertheless, despite the aforementioned limiting factors, we assume that the PVE method combined with HSC application has potential for patients with primarily non-resectable CLMs. The mobilisation, collection and subsequent application of HSCs are well tolerated and are not associated with major complications. To finally confirm the method as a treatment option, a larger population of patients will be needed, optimally in multicentre studies, as well as for longer monitoring durations.

Acknowledgements

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References

- Michalopoulos GK: Liver regeneration. *J Cell Physiol* 213: 286-300, 2007.
- Duncan AW, Dorrell and Grompe M: Stem cells and liver regeneration. *Gastroenterology* 137(2): 466-481, 2009.
- Esrefoglu M: Role of stem cells in repair of liver injury: Experimental and clinical benefit of transferred stem cells on liver failure. *World J Gastroenterol* 19(40): 6757-6773, 2013.
- Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Tabernero J, Van Cutsem E and Vauthey JN: The OncoSurgery Approach to Managing Liver Metastases from Colorectal Cancer. A Multidisciplinary International Consensus. *Oncologist* 17(10): 1225-1239, 2012.
- Adams RB, Aloia TA, Loyer E, Pawlik TM, Taouli B and Vauthey JN: Selection for hepatic resection of colorectal liver metastases: expert consensus statement. *HPB (Oxford)* 15(2): 91-103, 2013.
- Spolverato G, Ejaz A, Azad N and Pawlik TM: Surgery for colorectal liver metastases: The evolution of determining prognosis. *World J Gastrointest Oncol* 5(12): 207-221, 2013.
- Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, Alexander DD, Choti MA and Poston G: Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 4: 283-301, 2012.
- Treska V, Safranek J, Lysak D, Mirka H, Skalicky T, Slauf F and Hes O: A complex oncosurgical approach to increasing the resectability of colorectal cancer metastases – a case report. *Biomed Pap Med* 158(1): 154-157, 2014.
- Shindoh J, D Tzeng CW and Vauthey JN: Portal vein embolization for hepatocellular carcinoma. *Liver Cancer* 1(3-4): 159-167, 2012.
- Ribero D, Amisano M, Bertuzzo F, Langella S, Lo Tesoriere R, Ferrero A, Regge D and Capussotti L: Measured versus estimated total liver volume to preoperatively assess the adequacy of the future liver remnant: Which method should we use? *Ann Surg* 258(5): 801-806, 2013.
- Okabe H, Beppu T, Nakagawa S, Yoshida M, Hayashi H, Masuda T, Imai K, Mima K, Kuroki H, Nitta H, Hashimoto D, Chikamoto A, Ishiko T, Watanabe M, Yamashita Y and Baba H: Percentage of future liver remnant volume before portal vein embolization influences the degree of liver regeneration after hepatectomy. *J Gastrointest Surg* 17(8): 1447-1451, 2013.
- Ratti F, Cipriani F, Gagliano A, Catena M, Paganelli M and Aldighetti L: Defining indications to ALPPS procedure: technical aspects and open issues. *Updates Surg* 66(1): 41-49, 2014.
- Fiorentini G, Aliberti C, Mulazzani L, Coschiera P, Catalano V, Rossi D, Giordani P and Ricci S: Chemoembolization in colorectal liver metastases: The rebirth. *Anticancer Res* 34(2): 575-584, 2014.
- Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Guntér P, Yamazaki S, Hasegawa H and Ozaki H: Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 107(5): 521-527, 1990.
- Huang SY, Aloia TA, Shindoh J, Ensor J, Shaw CM and Loyer EM: Efficacy and safety of portal vein embolization for two-stage hepatectomy in patients with colorectal liver metastasis. *J Vasc Interv Radiol* 25(4): 608-617, 2014.
- Kasai Y, Hatano E, Iguchi K, Seo S, Taura K, Yasuchika K and Mori A: Prediction of the remnant liver hypertrophy ratio after preoperative portal vein embolization. *Eur Surg Res* 51(3-4): 129-137, 2013.
- Shindoh J, Tzeng CW, Aloia TA, Curley SA, Zimmitti G, Wei SH, Huang SY, Gupta S, Shibata T and Uemoto S: Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg* 100(13): 1777-1783, 2013.
- Fischer C, Melstrom LG, Arnaoutakis D, Jarnagin W, Brown K, D'Angelica M, Covey A, DeMatteo R, Allen P, Kingham TP, Tuorto S, Kemeny N and Fong Y: Chemotherapy after portal vein embolization to protect against tumor growth during liver hypertrophy before hepatectomy. *JAMA Surg* 148(12): 1103-1108, 2013.
- Liska V, Treska V, Mirka H, Kobr J, Sykora R, Skalicky T, Sutnar A, Bruha J, Fiala O, Vyxcital O, Chlumska A, Holubec L, Kormunda S, Trefil L, Racek J and Matejovic M: Tumour necrosis factor- α stimulates liver regeneration in porcine model of partial portal vein ligation. *Hepatogastroenterology* 59(114): 496-500, 2012.
- Mihara K, Sugiura T, Okamura Y, Kanemoto H, Mizuno T, Moriguchi M, Aramaki T and Uesaka K: A predictive factor of insufficient liver regeneration after preoperative portal vein embolization. *Eur Surg Res* 51(3-4): 118-128, 2013.
- Treska V, Skalicky T, Sutnar A, Vaclav L, Fichtl J, Kinkorova J, Vachtova M and Narsanska A: Prognostic importance of some clinical and therapeutic factors for the effect of portal vein embolization in patients with primarily inoperable colorectal liver metastases. *Arch Med Sci* 9(1): 47-54, 2013.

- 22 Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, Ohta K, Yamaguchi T, Matsubara T, Takanashi T, Nakajima T, Muto T, Ikari T, Yanagisawa A and Kato Y: Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolisation. *Hepatology* 34: 267-272, 2001.
- 23 Hayashi S, Baba Y and Ueno K: Acceleration of primary liver tumor growth rate in embolised hepatic lobe after portal vein embolisation. *Acta Radiol* 48: 721-727, 2007.
- 24 Esch JS II, Knoefel WT, Klein M, Ghodsizad A, Fuerst G, Poll LW, Piechaczek C, Burchardt ER, Feifel N, Stoldt V, Stockschrader M, Stoecklein N, Tustas RY, Eisenberger CF, Peiper M, Haussinger D and Hosch SB: Portal application of autologous CD133+ bone marrow cells to the liver: A novel concept to support hepatic regeneration. *Stem Cells* 23: 463-470, 2005.
- 25 Canepa MC, Quaretti P, Perotti C, Vercelli A, Rademacher J, Peloso A, Barbieri L, Franchi E, Briani L, Gaspari A, Brugnattelli S, Pedrazzoli P, Dionigi P and Maestri M: Autologous CD133+ cells augment the effect of portal embolization. *Minerva Chir* 68(2): 163-168, 2013.
- 26 Ghodsizad A, Fahy BN, Waclawczyk S, Liedtke S, Gonzalez Berjon JM, Barrios R, Mehrabi A, Karck M, Ruhparwar A and Kogler G: Portal application of human unrestricted somatic stem cells to support hepatic regeneration after portal embolization and tumor surgery. *ASAIO J* 58(3): 255-261, 2012.
- 27 Liska V, Slowik P, Eggenhofer E, Treska V, Renner P, Mirka H, Kober J, Sykora R, Schlitt HJ, Holubec L, Chlumska A, Skalicky T, Matejovic M and Dahlke MH: Intraportal injection of porcine multipotent mesenchymal stromal cells augments liver regeneration after portal vein embolization. *In Vivo* 23: 229-236, 2009.
- 28 Avritscher R, Abdelsalam ME, Javadi S, Ensor J, Wallace MJ, Alt E, Madoff DC and Vykoukal JV: Percutaneous intraportal application of adipose tissue-derived mesenchymal stem cells using a balloon occlusion catheter in a porcine model of liver fibrosis. *J Vasc Interv Radiol* 24(12): 1871-1878, 2013.
- 29 Best J, Dollé L, Manka P, Coombes J, van Grunsven LA and Syn WK: Role of liver progenitors in acute liver injury. *Front Physiol* 4: 258, 2013.
- 30 Rehman K, Iqbal MJ, Zahra N and Akash MS: Liver stem cells: from preface to advancements. *Curr Stem Cell Res Ther* 9(1): 10-21, 2014.
- 31 Papp V, Rókus A, Dezső K, Bugyik E, Szabó V, Pávai Z, Paku S and Nagy P: Expansion of hepatic stem cell compartment boosts liver regeneration. *Stem Cells Dev* 23(1): 56-65, 2014.
- 32 Chen L, Zhang W, Zhou QD, Yang HQ, Liang HF, Zhang BX, Long X and Chen XP: HSCs play a distinct role in different phases of oval cell-mediated liver regeneration. *Cell Biochem Funct* 30(7): 588-596, 2012.
- 33 Ogawa S and Miyagawa S: Potentials of regenerative medicine for liver disease. *Surg Today* 39: 1019-1025, 2009.
- 34 Tögel F and Westenfelder C: Adult bone marrow-derived stem cells for organ regeneration and repair. *Dev Dynamics* 236: 3321-3331, 2007.
- 35 Lin H, Otsu M and Nakauchi H: Stem cell therapy: an exercise in patience and prudence. *Phil Trans R Soc B* 368: 20110334, 2012.
- 36 Franchi E, Canepa MC, Peloso A, Barbieri L, Briani L, Panyor G, Dionigi P and Maestri M: Two-stage hepatectomy after autologous CD133+ stem cells administration: a case report. *World J Surg Oncol* 11(1): 192, 2013.
- 37 Williamson JM, Thairu N, Katsoulas N, Stamp G, Ahmad R, du Potet E, Levicar N, Gordon M, Stebbing J, Habib NA and Jiao LR: Impact of portal vein embolization on expression of cancer stem cell markers in regenerated liver and colorectal liver metastases. *Scand J Gastroenterol* 45(12): 1472-1479, 2010.
- 38 Ma S, Chan KW, Hu L, Lee TK, Wo JY and Ng IO: Identification and characterization of tumorigenic liver cancer stem/progenitor cells. *Gastroenterology* 132: 2542-2556, 2007.
- 39 Pachos KA and Bird NC: Liver regeneration and its impact on post-hepatectomy metastatic tumor recurrence. *Anticancer Research* 30: 2161-2170, 2010.
- 40 Simoneau E, Aljiffry M, Salman A, Abualhassan N, Cabrera T, Valenti D, El Baage A, Jamal M, Kavan P, Al-Abbad S, Chaudhury P, Hassanain M and Metrakos P: Portal vein embolization stimulates tumour growth in patients with colorectal cancer liver metastases. *HPB (Oxford)* 14(7): 461-468, 2012.

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