Review

Methods to Increase Future Liver Remnant Volume in Patients with Primarily Unresectable Colorectal Liver Metastases: Current State and Future Perspectives

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Abstract. *Radical liver resection of colorectal liver metastases (CLMs) is the only potentially curative treatment. But primary resectability of CLMs ranges from 15% to 20%. Insufficient future liver remnant volume (FLRV) is the main cause of primary unresectability of CLMs. Currently, there are several methods that can optimize FLRV and permit radical resection of CLMs. The basic methods include two-stage liver resection, portal vein embolization (PVE) and portal vein ligation. These methods have very low morbidity and mortality rate. Their disadvantage is the relatively long interval for increase of FLRV, with danger of tumour growth, and also the significant number of patients in whom optimal FLRV increase does not occur. For this reason, two other methods were developed - associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) and PVE with application of hematopoietic stem cells (HSCs). The advantage of ALPPS is the very rapid increase of FLRV, but the method is burdened by higher morbidity and mortality. PVE with HSC application is not associated with complications, it has a faster increase of FLRV compared to PVE and two-staged liver resection, but the role of autologous HSCs in carcinogenesis is not yet clear. All the methods offer secondary resectability for patients with primarily inoperable CLMs, with long-term survival comparable to primary CLM resections. The optimal choice of specific method must be made on a strictly individual basis for the given patient, and depends on the decision of the multidisciplinary team.*

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Colorectal carcinoma is one of the most common oncological diseases with increasing incidence in developed countries. Liver metastases from colorectal cancer (CLMs) develop in more than 80% of patients with colorectal carcinoma. The only potentially curative treatment in the context of a multimodal treatment procedure is radical liver resection. Unfortunately, in spite of all the advances in diagnostics and treatment, CLMs can be dealt with by radical surgery only in approximately one quarter of all patients.

One of the main reasons for unresectability of CLMs is insufficient future liver remnant volume (FLRV), where there is a danger of liver failure in the postoperative phase. Post-hepatectomic liver failure is characterized by insufficient liver function with development of cholestasis, coagulopathy, portal hypertension and ascites. In general, at least 20% remaining healthy liver tissue is required after liver resection. In patients with primary impairment of the liver by steatosis, cholestasis or cirrhosis, or in patients who have already undergone oncological treatment, preservation of at least 40% of FLRV is required. For these patients, it is also important not to rely only on determination of FLRV, but also to perform a functional liver examination, in particular, before a large liver resection (greater than three liver segments).

There are currently many methods that can increase insufficient FRLV before resection of CLMs. These are two-stage liver resection, portal vein embolization (PVE), portal vein ligation (PVL) and subsequent liver resection, PVE with combination of transarterial chemotherapy, associating liver partition and PVL for staged hepatectomy (ALPPS), and PVE with application of hematopoietic stem cells (HSCs) with subsequent liver resection. All of these procedures are a part of multimodal therapy with the aim of increasing the secondary resectability of CLMs and are discussed below.

Two-stage liver resection. This method is indicated for patients with bilobular CLMs, where in the first stage, clearance of CLMs is performed in the less affected liver lobe (most often on the left). In the second stage (usually after 8 weeks), following the necessary regeneration of the liver parenchyma, a hepatectomy is performed on the side of the CLMs (1, 2). Clavien *et al*. modified this method when they performed a metastasectomy of CLMs in the right lobe with concurrent ligation of the right portal vein with the aim of accelerating the growth of the left lobe of the liver (3). Based on a similar principle Adam *et al*. proposed clearance of CLMs from the left lobe with the application of absolute alcohol to the right portal vein with its ligation, which led to a further acceleration of the increase of FLRV (4). Some authors proposed the performance of a gentler method; radiofrequency or microwave ablation instead of resection of CLMs in the first period in the context of clearance of the subsequently unembolized liver lobe (5), but the long-term results of this procedure were worse (6). The mortality rate for two-stage resection is low (1-2%) and fully comparable with single-stage liver resections (7). The disadvantage of this method is the relatively long interval required for optimal increase of the FLRV after it is cleared of CLMs. From this aspect, there is a danger of further growth, not only of liver metastases but also of extrahepatic ones. Another problem is the formation of relatively strong adhesions after the first operation, which complicates the final hepatectomy. However, the long-term oncological results of this method are very good, and 5-year overall survival is around 50%.

PVE and PVL. The first PVE in clinical practice was performed by Makuuchi *et al*. (8) in 1984 before extended liver resection for hilar cholangiocarcinoma, with the aim of increasing the insufficient FLRV. This is a method increasing FLRV by 8-27% (9) in 72-80% of patients in an interval of 4-8 weeks. This is a safe method, where the long-term results are comparable to the results of primary liver resection. In a meta-analysis performed by Abulkhir *et al*., in 1,088 patients, the mortality rate was zero and morbidity rate was 2.2% (10). In a group of 358 patients with PVE, Shindoh *et al*. had 3.2% complications, 0% mortality rate after PVE (11). The same group compared the long-term results of 123 patients with primary resection of CLMs with 87 patients with PVE where it was possible to perform secondary liver resection (12). The 90-day morbidity and mortality rates in patients following primary and secondary liver resection were similar (22.0 and 4.1% *vs*. 31 and 7%). Patients with primarily insufficient FLRV who underwent an extended right hepatectomy after PVE had significantly better median overall survival compared with those who did not undergo an operation (50.2 *vs*. 24.7 months, $p<0.002$).

Liver hypertrophy may be slower in older patients and diabetics, in patients with biliary obstruction, malnutrition, infection, or damage to liver tissue by external noxious substance. The principle of FLRV increase are haemodynamic changes – increasing arterial flow in the unembolized lobe (so-called hepatic arterial buffer response). There is also an increase in portal venous flow in the unembolized lobe. This results in an increase in FLRV and atrophy of the embolized liver lobe. Along with the haemodynamic changes, there is up-regulation of various interleukins and growth factors, which further stimulates the increase of FLRV. Other factors supporting liver regeneration include nitric oxide, prostaglandin E_2, heat-shock protein 70, plasminogen activator inhibitors, haemeoxygenase-1,insulin, and oestrogen. However, there is not only an increase in FLRV, but also an improvement in liver functions after the performed hepatectomy in comparison with patients where a hepatectomy was performed without previous PVE (13). Embolization of segment 4 is important in preparation for extended right hepatectomy where the tumour reaches this segment. However, Huang *et al*. also described greater hypertrophy of FLRV in patients with PVE of the right liver lobe and fourth liver segment compared to patients where only PVE of the right liver lobe was performed ($p<0.0095$) (14).

There are many studies dealing with the efficacy of PVE compared with PVL (15, 16). These are methods which do not differ in terms of results. However, a transhepatic, less-invasive approach without the need for laparotomy or laparoscopy with formation of adhesions in the operating field after the liver resection constitutes a reason for PVE. PVL has a certain advantage in patients with bilobar CLMs, where in the first phase we perform removal of the CLMs of the contralateral (subsequently unembolized) liver lobe and at the same time PVL. In the second phase after increase in FLRV, hepatectomy of the liver lobe is carried out (17).

The relatively long interval of liver hypertrophy after PVE or PVL may be the cause of an increase in the volume of CLMs or growth of extrahepatic metastases, which in the case of approximately 20% of patients is the reason why curative liver resection cannot be performed. Both PVE and PVL can, by the same aforementioned mechanisms which stimulate the growth of liver tissue, cause an increase in the volume and number of CLMs. These are small CLMs which cannot be detected by radiodiagnostic methods before PVE and PVL. Pamecha *et al*. demonstrated significant growth activity in histological samples of CLMs after PVE compared with a control group of patients with CLMs where PVE was not performed (18). In a group of 42 patients with total of 432 CLMs with PVE of the right lobe, Pommier *et al*. showed significant growth in the volume of CLMs in 69% of cases on the side of the PVE ($p<0.0001$) and in 66% in the unembolized lobe ($p<0.0001$) (19). Before PVE, all patients underwent induction chemotherapy with oxaliplatin- or irinotecan-based regime complemented in 64% of patients with targeted therapy of bevacizumab or cetuximab. One

significant factor for the growth of CLMs was the slow response to induction chemotherapy evaluated according to the RECIST criteria. For primarily unresectable CLMs present only in the embolized lobe, in a group of 28 patients with PVE Hoekstra *et al*. discovered the occurrence of new CLMs in the unembolized lobe after the increase of sufficient FLRV in 25% of patients (20). Spelt *et al*. observed the effect of pre-procedural chemotherapy before PVE in a set of 34 patients with CLMs, of whom 24 had bilobary metastases (21). For some patients, oxaliplatin-based chemotherapy was used, and irinotecan-based chemotherapy was used for the others. The median number of chemotherapy cycles was seven. Half of the patients received targeted therapy using bevacizumab, cetuximab, panitumumab and erlotinib. PVE was performed 16 days after chemotherapy. Segments 5-8 were embolized in all patients. In the case of patients with bilobar CLMs, there were no differences between the growth of CLMs in the embolized and unembolized liver lobe. In 26 (76.5%) patients, a subsequent right-side or extended right-side hepatectomy was performed. In five of the patients, CLMs in the left lobe were removed by metastasectomy. In the embolized lobe, after PVE there was progress of CLMs according to RECIST criteria in only three cases and in the unembolized lobe also in three ($p<0.677$) cases. Simoneu *et al*. conducted a similar study with use of pre-procedural chemotherapy on a group of 109 patients, where the interval between chemotherapy and PVE was 4 weeks, and did not discover significant differences in the efficacy of the method in comparison with patients where only PVE was used (22). The study of Fischer *et al*. showed the positive effect on the long-term survival of patients if the patients (N=64) were treated with chemotherapy immediately after PVE before the actual liver resection (23).

There are still many questions that need to be answered concerning the optimal timing of pre-procedural chemotherapy. However, it would appear that this procedure will be an important factor for increasing the resectability of CLMs in patients with PVE under the assumption that the interval between both procedures is not longer than 14 days.

The question of influence of chemotherapy on liver regeneration following PVE remains unanswered. Some studies have shown a connection between prolonged chemotherapy and insufficient regeneration of the liver parenchyma (24-26). But other studies have not proven the impact of chemotherapy on liver regeneration (27, 28). However, prolonged chemotherapy (more than six cycles) also increases the percentage of postoperative complications proportionately to the number of cycles administered (29, 30).

Another problem still discussed is the disappearance of CLMs in an unembolized liver lobe after chemotherapy. This never actually involves the true disappearance of CLMs, but a so-called 'radiodiagnostic' rather than histopathological disappearance of CLMs. There are so-called 'sleeper' cancer cells with potential for further growth in the weeks or months after liver resection of the lobe on the PVE side. In a set of 29 patients where CLMs 'disappeared' in an unembolized lobe on the basis of examination using contrast-enhanced multi-detector computed tomography (MDCT) or magnetic resonance imaging (MRI) with liver-specific contrast, Sturesson *et al*. did not demonstrate a significant effect of proving disappearing CLMs using contrast-enhanced intraoperative ultrasound (CE-IOUS) and emphasized the localisation of these loci before the actual oncological treatment with subsequent PVE (31). In contrast to this, Arita *et al*. emphasized the significance of intraoperative CE-IOUS in the localisation of disappeared CLMs in a set of 32 patients, where he compared the sensitivity of contrast-enhanced MDCT with intraoperative CE-IOUS ($p<0.04$) (32). In the case of these patients we should proceed strictly individually. For those in whom the preoperative examination the loci are precisely localized, or where loci of sleeper CLMs are found during the operation using CE-IOUS, their resection is indicated (33). In other cases, it is necessary to monitor patients at short postoperative intervals (3 months) using CEUS, and in unclear cases then to use contrast-enhanced MDCT or MRI (34).

The main problem of PVE, and PVL, is the time needed for increase of sufficient FLRV, which is associated with the danger of progression of CLMs in the liver parenchyma. For this reason, a search is underway for other, newer methods, such as associating liver partition with PVL for staged hepatectomy (ALPPS), or PVE with application of autologous HSCs, in order to reduce the interval necessary for hypertrophy of FLRV.

ALPPS. This method represented a great historical breakthrough in liver surgery of patients with primary or secondary tumours of the liver where FLRV is insufficient. In 2007, Lang *et al*. became the first to use this method on a patient with Klatskin tumour (35). The method utilizes a two-stage procedure with maximum reduction of the time interval between both procedures, which is fundamental for reducing the growth of the tumour in the liver and its extrahepatic spread. The first procedure is ligation of the right portal vein and portal branches to segments 4A and 4B on the side of the CLMs, whilst leaving the supply of the liver by arterial blood, and the *in situ* dissection of the liver parenchyma between the lateral and medial sectors of the left hemi-liver. Cholangiography of the cystic duct for detection of biliary leak is performed as routine. The second procedure is the ligature and severing transection of the right artery, and bile duct and hepatic vein and removal of the right liver tissue lobe with the CLMs on the right side of the falciform ligament. In 2013, Gauzolino *et al*. described three modifications of conventional ALPPS: left ALPPS, the rescue (after failure of

PVE), and right ALPPS with technical modification (36). The method is characterized by two important aspects, namely the rapid increase in FLRV and the functional auxiliary role of arterial blood of the supplied liver lobe on the side of the CLMs (37). Optimum increase in FLRV occurs on average within 7 days after the first procedure (38, 39). Recent studies describe an increase in FLRV by 40-80% in an interval of 6-9 days after the first phase of the procedure, or a 22% daily increase of FLRV compared to approximately 3% increase after PVE (40, 41). The indication criteria for this method are the same as for the other methods, and Truant *et al*. also recommend that the FLRV to body weight ratio be greater than 0.5 (42). ALPPS is also used as a rescue procedure where PVE or PVL do not lead to the necessary increase of FLRV (43, 44). The advantage of this method is complete portal devascularisation of segment 4 with prevention of formation of collaterals between this segment and the right lobe of the liver, which can be a cause of PVE, or PVL failure if the vascularized segment 4 is left. At the same time, there is a redistribution of hepatotropic factors of portal blood to segments 2 and 3, and a significant stimulation of their increase (45, 46).

The role of neoadjuvant chemotherapy complemented by biological treatment in ALPPS is not wholly clear. In a meta-analysis of 160 patients after ALPPS, Hasselgren *et al*. found 71 patients with CLMs, in 78.6% of whom neoadjuvant chemotherapy had been performed, most often with combination of folinic acid, fluorouracil and oxaliplatin (FOLFOX) or fluorouracil, folinic acid and irinotecan (FOLFIRI) regime complemented by cetuximab or bevacizumab, with a median of eight application cycles, but without more detailed specification of its significance for direct and long-term results of ALPPS (47). In a set of 25 patients in whom ALPPS had been performed, Schnitzbauer *et al*. found no negative impact of neoadjuvant chemotherapy on liver hypertrophy (48). By way of contrast, in a group of 19 patients with CLMs where ALPPS had been performed, Kremer *et al*. described a significantly negative impact of chemotherapy on the regeneration of FLRV (49). But it remains a fact that in view of the short interval for FLRV increase, ALPPS allows earlier adjuvant chemotherapy in comparison with other methods.

A persistent problem of this method is the still higher morbidity and mortality compared with other procedures indicated for the increase of FLRV. Morbidity is given in the range of 16-64% and mortality in the range of 12-23%, where the main cause of morbidity is sepsis and bilious leakage, and for mortality it is hepatic insufficiency. The aforementioned meta-analysis of Schnitzbauer *et al*. gives 211 complications of various degrees according to the Clavien-Dindo grading system for 115 patients, with mortality of 9.6%. Two-thirds of deaths after the second phase of the procedure were deaths from liver failure, where patients over the age of 60 years constitute an at-risk group. If there are signs of liver failure after the first phase of the procedure (score >10 of Model of End stage Liver Disease), Oldhafer *et al*. recommend that the second phase of the procedure be deferred in spite of sufficient increase of FLRV (50). A multicentre analysis of nine hepatobiliary centres on a group of 62 patients defined the main causes of morbidity and mortality of patients who had undergone ALPPS (51). These included obesity, incidence of bilious leak, ascites after the first phase of procedure and infected or bilious peritoneal fluid after stage two.

In view of the fact that ALPPS is a relatively new method, the long-term oncological results are as yet unknown. This is a very promising method from the aspect of stimulation of FLRV increase in primarily inoperable patients with CLMs, but one where it is necessary to carefully select the patients in order to reduce perioperative morbidity and mortality.

PVE with application of HSCs. This is another method which, using autologous stem cells, attempts to increase the regenerative capacity of the liver parenchyma and reduce the interval necessary for the increase of FLRV after PVE. HSCs 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 some 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 localized in the area of the canals of Hering, oval cells that are able to differentiate into mature hepatocytes and bile duct cells. Nevertheless, their regenerative capacity is not substantial, and only 0.15% of all new hepatocytes are developed at the time of liver regeneration (52, 53). The liver regenerative ability fails in some liver diseases and during injury to the liver parenchyma by previous chemotherapy.

Bone marrow or blood are a potential source of HSCs that can support liver regeneration. Damage to the liver results in the mobilisation of HSCs, which may occur *via* blood flow to the liver. Their transdifferentiation into hepatocytes is a rare event (54). 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 hepatic progenitor cells in liver regeneration. 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 HSCs (55).

A combination of PVE with HSC application is safe for patients, without any immediate side-effects. In comparison with the PVE method, this method has better results in terms

of the time required for increase of FLRV, which is reduced to 2-3 weeks (56-58). There are two possible techniques for collecting HSCs. The first technique utilizes stimulation of HSCs using granulopoiesis growth factor applied subcutaneously for 4 days, with monitoring of HSCs in peripheral blood. Then large-scale leukapheresis is performed, with the gained product being rich in HSCs, which is subsequently administered *via* the ileocolic vein into the ramus of the portal vein on the side of the liver lobe without CLMs. On the day before leukapheresis, PVE is performed *via* the transparietal route. The second technique then uses bone marrow from the *crista iliaca* posterior superior in the operating theatre. The bone marrow aspirate is then centrifuged, the HSCs are separated, and the gained product is applied *via* the same route to the branch of the portal vein on the side of the FLRV as stated above. The growth of the contralateral liver lobe is monitored using CT volumetry of the liver.

In the context of the combination of PVE and application of HSCs, there remains the problem of the possible danger of proliferation of undetectable micrometastases, not only in the liver but in the body associated with both methods, which stimulates proliferation and growth. Tumorous tissue contains a great amount of stimulants (growth factors, matrix metalloproteinases, and cytokines) that can lead to the migration of HSCs into tumorous tissue, which can then stimulate the growth and spread of the tumour. The mechanism of actual interaction of stem cells with tumour cells is not yet precisely known. There is probably stimulation of neoangiogenesis in combination with immunosuppressive effect and inhibition of apoptosis. The growth of the tumour may also be supported by regenerative mechanisms of the actual liver tissue after PVE (see above). The possibility of differentiation of autologous stem cells into a tumour cell in the CLM environment remains an unresolved problem.

PVE with application of autologous HSCs is a highly promising method primarily from two aspects. This is a method without direct complications and a method which significantly reduces the interval necessary for the increase of FLRV. In view of the fact that, like ALPPS, this is a new method, long-term oncological results are not yet available. However, in view of the certain danger of proliferation of CLMs or extrahepatic metastases, further research is necessary, focusing on the mechanisms of tumour proliferation in connection with this method.

Conclusion

For the further development of methods leading to an increase in FLRV in patients where insufficient FLRV causes the unresectability of CLMs, several factors are fundamental. The first is the safety of the procedure for the patient, *i.e.* minimisation of morbidity and mortality associated with the given procedure. Another important factor is be the rapid increase in FLRV within several days or a maximum of one month in order to prevent the progress of the existing CLMs or appearance of new liver or extrahepatic metastases. In connection with a possible stimulation of tumour cell growth when the aforementioned methods are used, further research into the causes leading to the progress of a tumour in the intermediate period between the used method and subsequent liver resection will be necessary. Another unresolved question remains the use and, primarily, the optimal timing of chemotherapy and target therapy in the context of these methods from the aspect not only of possible influence on increasing the FLRV, but also the long-term oncological results. In the indications of the aforementioned methods, there must be an individualized approach based on the evaluation of the multidisciplinary team as to which is the method of choice for a patient with CLMs and insufficient FLRV.

References

1 Jaeck D and Pessaux P: Bilobar colorectal liver metastases: treatment options. Surg Oncol Clin N Am *17*: 553-568, 2008.

2 Narita M, Oussoultzoglou E, Jaeck D, Fuchschuber P, Rosso E, Pessaux P, Marzano E and Bachellier P: Two-stage hepatectomy for multiple bilobar colorectal liver metastases. Br J Surg *98*: 1463-1475, 2011.

3 Clavien PA, Petrowsky H, DeOliveira ML and Graf R: Strategies for safer liver surgery and partial liver transplantation. N Engl J Med *12*: 1545-1559, 2007.

4 Adam R, Miller R, Pitombo M, Wicherts DA, de Haas RJ, Bitsakou G and Aloia T: Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am *16*: 525-536, 2007.

5 Elias D, Santoro R, Ouellet JF, Osmak L, de Baere T and Roche A: Simultaneous percutaneous right portal vein embolization and left liver tumor radiofrequency ablation prior to a major right hepatic resection for bilateral colorectal metastases. Hepatogastroenterology *51*: 1788-1791, 2004.

6 Abdalla EK: Portal vein embolization (prior to major hepatectomy) effects on regeneration, resectability and outcome. J Surg Oncol *102*: 960-967, 2010.

7 Yang C, Rahbari NN, Mees ST, Schaab F, Koch M, Weitz J and Reissfelder C: Staged resection of bilobar colorectal liver metastases: surgical strategies. Langenbecks Arch Surg *400*: 633-640, 2015.

8 Makuuchi M, Takayasu K and Takuma T: Preoperative transcatheter embolization of the portal venous branch for patients receiving extended lobectomy due to the bile duct carcinoma. J Jpn Surg Assoc *45*: 1558-1564, 1984.

9 Asencio JM, Sabrido JLG and Olmedilla L: How to expand the safe limits in hepatic resections? J Hepatobiliary Pancreat Sci *21*: 399-404, 2014.

10 Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N and Long RJ: Preoperative portal vein embolization for major liver resection. A meta-analysis. Ann Surg *247*: 49-57, 2008.

11 Shindoh J, Tzeng CW, Aloia TA, Curley SA, Huang SY, Mahvash A, Gupta S, Wallace MJ and Vauthey JN: Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. J Gastrointest Surg *18*: 45-51,2014.

12 Shindoh J, Tzeng CW, Aloia TA, Curley SA, Zimmitti G, Wei SH, Huang SY, Gupta S, Wallace MJ and Vauthey JN: Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. Br J Surg *100*: 1777-1783, 2013.

13 Meier RP, Toso C, Terraz S, Breguet R, Berney T andres A, Jannot AS, Rubbia-Brandt L, Morel P and Majno PE: Improved liver function after portal vein embolization and an elective right hepatectomy. HPB *17*: 1009-1018, 2015.

14 Huang SY, Aloia TA, Shindoh J, Ensor J, Shaw CM, Loyer EM, Vauthey JN and Wallace MJ: Efficacy and safety of portal vein embolization for two-stage hepatectomy in patients with colorectal liver metastasis. J Vasc Interv Radiol *25*: 608-617, 2014.

15 Yokoyama Y, Nagino M and Nimura Y: Mechanisms of hepatic regeneration following portal vein embolization and partial hepatectomy: a review. World J Surg *31*: 367-374, 2007.

16 Van Gulik TM, van den Esschert JW, de Graaf W, van Linden KP, Busch ORC, Heger M, van Delden OM, Lameris JD and Gouma DJ: Controversies in the use of portal vein embolization. Dig Surg *25*: 436-444, 2008.

17 Pandanaboyana S, Bell R, Hidalgo E, Toogood G, Prasad KR, Bartlett A and Lodge JP: A systematic review and meta-analysis of portal vein ligation *versus* portal vein embolization for elective liver resection. Surgery *157*: 690-698, 2015.

18 Pamecha V, Levene A, Grillo F, Woodward N, Dhillon A and Davidson BR: Effect of portal vein embolisation on the growth rate of colorectal liver metastases. Br J Cancer *24*: 617-622, 2009.

19 Pommier R, Ronot M, Cauchy F, Gaujoux S, Fuks D, Faivre S, Belghiti J and Vulgrain V: Colorectal liver metastases growth in the embolized and non-embolized liver after portal vein embolization: Influence of initial response to induction chemotherapy. Ann Surg Oncol *21*: 3077-3083, 2014.

20 Hoekstra LT, van Lienden KP, Doets A, Busch OR, Gouma DJ and van Gulik TM: Tumor progression after preoperative portal vein embolization. Ann Surg *256*: 812-817, 2012.

21 Spelt L, Sparrelid E, Isaksson B andersson RG and Sturesson C:Tumour growth after portal vein embolization with pre-procedural chemotherapy for colorectal liver metastases. HPB (Oxford) *17*: 529-535, 2015.

22 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*: 461-468, 2012.

23 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*: 1103-1108, 2013.

24 De Graaf W, van Lienden KP, van den Esschert JW, Bennink RJ and van Gulik TM: Increase in future remnant liver function after preoperative portal vein embolization. Br J Surg *98*: 825-834, 2011.

25 Sturesson C, Nilsson J, Eriksson S, Spelt L and Andersson R: Limiting factors for liver regeneration after a major hepatic resection for colorectal cancer metastases. HPB 15: 646-652, 2013.

26 Takeda D1, Nitta H, Takahara T, Hasegawa Y, Itou N and Wakabayashi G: Effect of preoperative chemotherapy on postoperative liver regeneration following hepatic resection as estimated by liver volume. World J Surg Oncol *13*: 65-72, 2013.

27 Sturesson C, Keussen I and Tranberg KG: Prolonged chemotherapy impairs liver regeneration after portal vein occlusion - an audit of 26 patients. Eur J Surg Oncol *36*: 358-364, 2010.

28 Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM and Vauthey JN: Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg *94*: 1386-1394, 2007.

29 Covey AM, Brown KT, Jarnagin WR, Brody LA, Schwartz L, Tuorto S, Sofocleous CT, D'Angelica M, Getrajdman GI, DeMatteo R, Kemeny NE and Fong Y: Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg *247*: 451-455, 2008.

30 Tanaka K1, Kumamoto T, Matsuyama R, Takeda K, Nagano Y and Endo I: Influence of chemotherapy on liver regeneration induced by portal vein embolization or first hepatectomy of a staged procedure for colorectal liver metastases. J Gastrointest Surg *14*: 359-368, 2010.

31 Sturesson C, Nilsson J, Lindell G andersson RG and Keussen I. Disappearing liver metastases from colorectal cancer: impact of modern imaging modalities. HPB (Oxford) *17*: 983-987, 2015.

32 Arita J, Ono Y, Takahashi M, Inoue Y, Takahashi Y and Saiura A: Usefulness of contrast-enhanced intraoperative ultrasound in identifying disappearing liver metastases from colorectal carcinoma after chemotherapy. Ann Surg Oncol *2(Suppl 3)*: S390-397, 2014.

33 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*: 91-103, 2013.

34 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 *21*: 47-54, 2013.

35 Lang SA, Loss M and Schlitt HJ: "*in situ* split" (ISS) liver resection: new aspects of technique and indication. Zentralbl Chir *139*: 212-219, 2014.

36 Gauzolino R, Castagnet M, Blanleuil ML and Richer JP: The ALPPS technique for bilateral colorectal metastases: three "variations on a theme". Updates Surg *65*: 141-148, 2013.

37 Zhang GQ, Zhang ZW, Lau WY and Chen XP: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a new strategy to increase resectability in liver surgery. Int J Surg *12*: 437-441, 2014.

38 Ratti F, Schadde E, Masetti M, Massani M, Zanello M, Serenari M, Cipriani F, Bonariol L, Bassi N, Aldrighetti L and Jovine E: Strategies to increase the resectability of patients with colorectal liver metastases: A Multi-center Case-Match Analysis of ALPPS and conventional two-stage hepatectomy. Ann Surg Oncol *22*: 1933-1942, 2015.

39 Oldhafer KJ, Donati M, Jenner RM, Stang A and Stavrou GA: ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. World J Surg *38*: 1504-1509, 2014.

40 Li J, Girotti P, Königsrainer I, Ladurner R, Königsrainer A and Nadalin S: ALPPS in right trisectionectomy: A safe procedure to avoid postoperative liver failure? J Gastrointest Surg *17*: 956-961,2013.
41 Nadalin S, Capobianco I, Li J, Girotti P, Königsrainer I and Königsrainer A: Indications and limits for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Lessons learned from 15 cases at a single centre. Z Gastroenterol *52*: 35-42, 2014.
42 Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O and Pruvot FR: Remnant liver volume to body weight ratio > or =0.5%: A new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg *204*: 22-33, 2007.
43 Worni M, Shah KN and Clary BM: Colorectal cancer with potentially resectable hepatic metastases: optimizing treatment. Curr Oncol Rep *16*: 407-419, 2014.
44 Knoefel WT, Gabor I, Rehders A, Alexander A, Krausch M, Schulte am Esch J, Fürst G and Topp SA: *In situ* liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. Br J Surg *100*: 388-394, 2013.
45 de Santibañes E, Alvarez FA and Ardiles V: How to avoid postoperative liver failure: a novel method. World J Surg *36*: 125-128, 2012.
46 Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, Gupta S, Wallance MJ and Aloia TA: Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg *217*: 126-133, 2013.
47 Hasselgren K, Sandström P and Björnsson B: Role of associating liver partition and portal vein ligation for staged hepatectomy in colorectal liver metastases: a review. World J Gastroenterol *21*: 4491-4498, 2015.
48 Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Hörbelt R, Kroemer A, Loss M, Rümmele P, Scherer MN, Padberg W, Königsrainer A, Lang H, Obed A and Schlitt HJ: Right portal vein ligation combined with *in situ* splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg *255*: 405-414, 2012.
49 Kremer M, Manzini G, Hristov B, Polychronidis G, Mokry T, Sommer CM, Mehrabi A, Weitz J, Büchler MW and Schemmer P: Impact of neoadjuvant chemotherapy on hypertrophy of the future liver remnant after associating liver partition and portal vein ligation for staged hepatectomy. J Am Coll Surg 221: 717-728, 2015.
50 Oldhafer KJ, Stavrou GA and van Gulik TM; core group: ALPPS–Where do we stand, where do we go?: Eight recommendations from the First International Expert Meeting. Ann Surg *263*: 839-841, 2016.
51 Truant S, Scatton O, Dokmak S, Regimbeau JM, Lucidi V, Laurent A, Gauzolino R, Castro Benitez C, Pequignot A, Donckier V, Lim C, Blanleuil ML, Brustia R, Le Treut YP, Soubrane O, Azoulay D, Farges O, Adam R and Pruvot FR; e-HPBchir Study Group from the Association de Chirurgie Hépato-Biliaire et de Transplantation (ACHBT): Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): impact of the inter-stages course on morbi-mortality and implications for management. Eur J Surg Oncol *41*: 674-682, 2015.
52 Rehman K, Iqbal MJ, Zahra N and Akash MS: Liver stem cells: from preface to advancements. Curr Stem Cell Res Ther *9*: 10-21, 2014.
53 Papp V, Rokusz A, Dezso K, Bugyik E, Szabo V, Pavai Z: Expansion of hepatic stem cell compartment boosts liver regeneration. Stem Cells Dev *23*: 56-65, 2014.
54 Tögel F and Westenfelder C: Adult bone marrow-derived stem cells for organ regeneration and repair. Dev Dynamics *236*: 3321-3331, 2007.
55 Franchi E, Canepa MC, Peloso A, Barbieri L, Briani L and Panyor G: Two-stage hepatectomy after autologous CD133$^+$ stem cells administration: a case report. World J Surg Oncol *11*: 192, 2013.
56 Treska V, Liska V, Fichtl J, Lysak D, Mirka H, Bruha J, Duras P, Treskova I, Nahlik J, Simanek V and Topolcan O: Portal vein embolisation with application of haematopoietic stem cells in patients with primarily or non-resectable colorectal liver metastases. Anticancer Res *34*: 7279-7285, 2014.
57 am Esch JS II, Knoefel WT, Klein M, Ghodsizad A, Fuerst G, Poll LW and Piechaczek C: Portal application of autologous CD133$^+$ bone marrow cells to the liver: A novel concept to support hepatic regeneration. Stem Cells *23*: 463-470, 2005.
58 Canepa MC, Quaretti P, Perotti C, Vercelli A, Rademacher J and Peloso A: Autologous CD133$^+$ cells augment the effect of portal embolization. Minerva Chir *68*: 163-168, 2013.
59 Williamson JM, Thairu N, Katsoulas N, Stamp G, Ahmad R and du Potet E: Impact of portal vein embolization on expression of cancer stem cell markers in regenerated liver and colorectal liver metastases. Scand J Gastroenterol *45*: 1472-1479, 2010.
60 Pachos KA and Bird NC: Liver regeneration and its impact on post-hepatectomy metastatic tumor recurrence. Anticancer Res *30*: 2161-2170, 2010.

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