

## Is there new hope for patients with marginally resectable liver malignancies?

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### Abstract

Advances in surgical technique and better perioperative management have significantly improved patient outcomes after liver surgery. Even major hepatectomy can be performed safely with low morbidity and mortality. Post-resection liver failure is among the most feared complications after extended hepatectomy. In order to increase the future liver remnant (FLR) and to expand the pool of candidates for surgical resection, Schnitzbauer *et al* recently presented a new 2-stage surgical approach which combines right portal vein ligation (rPVL) with *in situ* splitting (ISS) of the liver parenchyma. In comparison to other current strategies, such as interventional portal vein embolization, hypertrophy of the FLR was more pronounced (median volume increase = 74%; range: 21%-192%) and more rapid (after a median of 9 d; range: 5-28 d) after rPVL and ISS. In this commentary, we discuss the technical aspects and clinical impact of rPVL combined with ISS. Based on the reported data, this new 2-stage therapeutic approach represents a promising new strategy for patients with locally advanced liver disease, previously regarded as marginally resectable or even unresectable, potentially enabling curative resection. However, morbidity is significant and mortality not negligible.

### INVITED COMMENTARY ON HOT TOPICS

Schnitzbauer *et al*<sup>[1]</sup> report a new 2-step technique for induction of short-term liver parenchymal hypertrophy in oncological patients, requiring extended right hepatectomy with limited functional reserve.

Complete tumor resection remains the only curative treatment option for patients with primary hepatic malignancies or liver metastases from other primary cancers. Recent advances in surgical technique and better perioperative care have substantially improved outcomes after liver resection. Even major hepatectomy can be performed safely with acceptable morbidity and mortality. Therefore, aggressive surgical approaches have become the treatment of choice for advanced primary and selected secondary hepatic malignancies. Postoperative liver failure is among the most feared complications after extended hepatectomy with small and/or altered parenchyma remnants. Depending on the preoperative liver function, a future liver remnant (FLR) of 25%-40% is considered sufficient to avoid post-resection liver fail-

ure, associated with high postoperative morbidity and mortality<sup>[2,3]</sup>. In patients in whom the FLR is expected to be marginal or insufficient, several techniques have been introduced to induce hypertrophy of the remaining liver tissue, including interventional embolization of the portal venous system (PVE) and surgical portal vein ligation (PVL)<sup>[4]</sup>. The rationale behind the occlusion of the PVE is an ipsilateral hepatic atrophy with compensatory contralateral parenchymal hypertrophy<sup>[5]</sup>. An increase of the FLR of more than 40% within 8 wk after PVE and PVL has been reported<sup>[6-8]</sup>. Both techniques are widely used and several studies have demonstrated that both PVE and PVL are safe and effective procedures to prevent posthepatectomy liver insufficiency<sup>[8-12]</sup>. In cases of advanced hepatic tumors affecting both liver lobes, portal vein occlusion can be combined with a 2-stage hepatectomy in which one liver lobe is cleared of tumors by surgical resection (and/or locally ablative techniques). After a waiting period of approximately 8 wk, which allows adequate parenchyma hypertrophy of the FLR, (extended) hepatectomy is performed to complete tumor resection<sup>[13-16]</sup>.

In line with this approach, Schnitzbauer *et al.*<sup>[11]</sup> recently presented a 2-step technique for induction of short-term liver parenchymal hypertrophy. In this retrospective analysis, 25 patients were included who preoperatively appeared to be marginally resectable but had a tumor-free left lateral lobe (liver segments II and III)<sup>[11]</sup>. Primary hepatic tumors included hepatocellular carcinoma ( $n = 3$ ), intra- and extrahepatic cholangiocellular carcinoma ( $n = 4$ ), malignant epithelioid hemangioendothelioma ( $n = 1$ ) and gallbladder cancer ( $n = 1$ )<sup>[11]</sup>. Sixteen patients were operated on for liver metastasis from colorectal ( $n = 14$ ), ovarian ( $n = 1$ ) and gastric cancer ( $n = 1$ )<sup>[11]</sup>. Technically, an explorative laparotomy was performed with right PVL (rPVL) and *in situ* splitting (ISS) by total or near total liver parenchyma dissection along the right side of the falciforme ligament<sup>[11]</sup>. The right extended lobe was then covered in a plastic bag to prevent adhesions and the abdomen was closed<sup>[11]</sup>. After a median interval of 9 d (range: 5-28 d), CT volumetry was performed to estimate parenchymal hypertrophy, which was followed by relaparotomy with extended hepatectomy<sup>[11]</sup>. The heterogeneous group of patients included in this study (different tumor entities ( $n = 8$ ), use ( $n = 12$ ) *vs* non-use ( $n = 13$ ) of preoperative chemotherapy) clearly shows that rPVL with ISS is technically feasible<sup>[11]</sup>.

In comparison to previously reported techniques of portal vein occlusion that aim at increasing the FLR, the authors demonstrated an impressive median volume increase of the left lateral lobe of 74% (range: 21%-192%) after a median waiting period of only 9 d (range: 5-28 d). Obviously, the more pronounced and more rapid hypertrophic effect of this new approach must be attributed to the ISS procedure in which the portal division into right and left is complete. However, the exact mechanism that is responsible for the additional hypertrophic effect is unclear. A potential explanation is that total splitting of the

hepatic parenchyma prevents the formation of arterio-portal and porto-portal collaterals between the left lateral and the right extended liver lobe<sup>[17]</sup>. These neocollaterals have previously been accused of hindering an adequate hypertrophic reaction of the non-occluded liver lobe<sup>[18,19]</sup>.

Besides induction of an optimal regenerative liver response, complete dissection of the liver parenchyma with consecutive devascularisation of segment IV prevents direct tumor progression into the tumor-free left lateral lobe. Likewise, intrahepatic tumor seeding along vascular structures into the non-occluded liver segments is not possible. Complete occlusion of portal branches to segment IV which prevents vascular collateralization from the non-occluded to the occluded liver lobes can also be accomplished by complete radiological embolization of the PVE<sup>[12,20,21]</sup>. However, embolization of the portal branches to segment IV bears a substantial risk of injuring the left portal vein and backflow of embolization material into the left PVE may result in inadvertent embolization and thrombosis of the portal vessels of the FLR. On the other hand, the use of PVL in this approach comes along with a patent portal system distal to the site of ligation which may result in portal refilling *via* arterio-portal collaterals within the occluded liver segments. Whether the combination of ISS with PVE, which allows occlusion of the whole PVE, would further increase hypertrophy of the FLR remains unclear.

Another advantage of the new approach is the faster parenchymal hypertrophy of the FLR compared to PVE or PVL, resulting in a short time interval between the first surgical procedure and extended hepatectomy. Completion surgery was performed after only 9 d compared to 14 d to 8 wk after either PVE or PVL. Thus, relevant tumor progression is prevented in this short time interval.

Besides the marked and rapid induction of liver parenchyma hypertrophy, this approach allows a reliable evaluation of resectability. During explorative laparotomy, the extent of intra- and extrahepatic disease can be assessed and intraoperative ultrasound can especially be used to re-evaluation preoperative imaging findings. In this study, all patients were resectable at the time of completion surgery. Contrasting results were recently published by Abulkhir *et al.*<sup>[6]</sup> who assessed the results of PVE and its impact on major liver resection in a meta-analysis. In their analysis, only 930 of 1088 patients (85%) underwent the planned laparotomy<sup>[6]</sup>. In 158 patients, hepatectomy was not possible mostly because of tumor progression and inadequate hypertrophy of the FLR<sup>[6]</sup>. Besides the designated hypertrophic effect of PVE, persistence of the embolized liver segments in the case of unresectability may be associated with adverse effects<sup>[22]</sup>. Kokudo *et al.*<sup>[23]</sup> previously demonstrated that PVE increases the growth of colorectal metastases in the embolized liver lobe compared to metastases in patients without PVE. This observation is most probably explained by the increased arterial blood flow in the occluded liver lobe in combination with the release of growth factors and up-regulation of proangiogenic factors and stress response

genes<sup>[23]</sup>. The question of whether these effects may result in advanced tumor progression if hepatectomy cannot be performed has yet to be answered<sup>[24]</sup>. On the other hand, persistent embolized liver segments may develop ascending infections with troublesome abscesses because the affected bile ducts are incompletely drained. Whether manipulation of liver parenchyma (harboring cancerous lesions) during rPVL and ISS may result in tumor spread into the tumor-free left lateral lobe remains unclear.

In summary, Schnitzbauer *et al*<sup>[1]</sup> demonstrated that rPVL in combination with ISS is technically feasible and induces rapid growth of the FLR. Although the exact mechanism of such an enhanced liver regeneration process has yet to be elucidated, this new therapeutic strategy yields hope for patients with locally advanced liver disease, previously regarded as palliative, and may increase the number of curative resections. Further studies are needed to support the impressive data published by Schnitzbauer *et al*<sup>[1]</sup> and to evaluate long-term outcomes after this procedure.

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