

# Iatrogenic Liver Regeneration

The new frontier of hepatic resection.

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**T**he introduction of innovative and more aggressive approaches to surgical hepatic resection has the potential to improve patients' long-term survival with less mortality and morbidity. The concept of future liver remnant (FLR) is an essential consideration when performing these procedures, reflecting an overall change in thinking toward what is left behind as opposed to how much of the liver is taken out. In brief, the FLR is measured as an absolute volume or relative index compared with total liver volume (TLV). FLR is considered to be sufficient if it is > 25% of TLV in the patients with normal liver function. Higher FLR of > 40% of TLV is deemed necessary for patients with impaired liver function.<sup>1</sup>

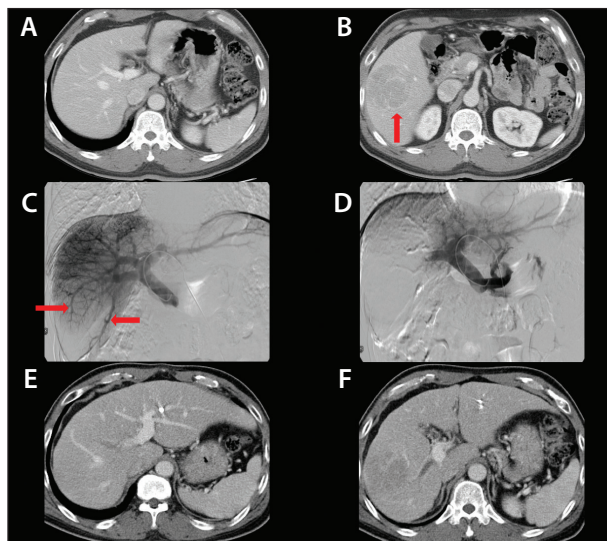
For patients with inadequate FLR, the FLR should be increased prior to major hepatic resection through accelerated liver hypertrophy. These techniques serve to facilitate hypertrophy of the FLR and also act as a crude biological test of the hepatic reserve of the liver. The most frequently used method to increase FLR is portal vein embolization (PVE); however, the associating liver partition and portal vein (PV) ligation for staged hepatectomy (ALPPS) technique can also be used. Other methods, such as transarterial radioembolization (TARE) and stem cell infusion through the portal venous system can be used independently or in combination. This article describes the various methods to increase FLR before major hepatectomy.

## PVE

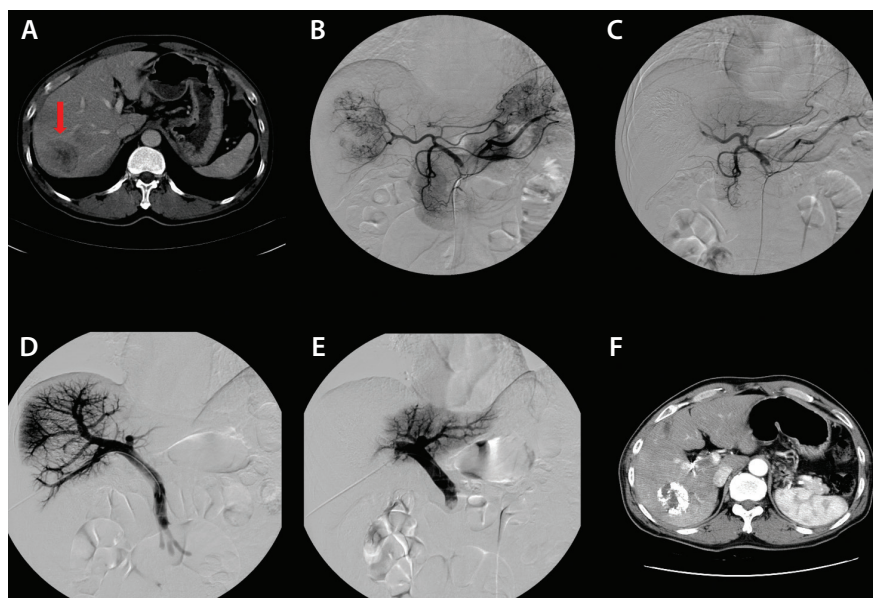
PVE has been shown to be safe and effective in inducing hypertrophy of the FLR since its first introduction by Hirohashi et al 25 years ago.<sup>2</sup> Percutaneous transhepatic puncture of the PV is the main point of access. For PV puncture, an ipsilateral or contralateral approach to the embolized portal venous segments, which approximate the Couinaud segmental anatomy, is decided by tumor location, size, operator preference,

and experience. Percutaneous transsplenic access has been used in salvage situations.<sup>3</sup>

PVE is associated with a low rate of major complications,<sup>4</sup> and a variety of embolic materials may be used alone or in combination. The exact mechanism of FLR hypertrophy is not yet known; however, mechanical factors associated with increased portal venous blood flow of unembolized segments after PVE is one mechanism.<sup>5</sup> Biochemical factors are also responsible for liver growth. Upregulation of hormonal factors (eg, hepatocyte growth factor, transforming growth factor alpha) after PVE contributes to hypertrophy of the FLR as well.<sup>6,7</sup>



**Figure 1.** CT scan showing a large hepatocellular carcinoma (HCC) (arrow) in segment 4 with a small left hepatic lobe volume (A, B). Right PVE via a contralateral approach was performed (C, D). Note that the PV branches (arrows) are draped around the tumor in the right hepatic lobe. A 3-week follow-up CT scan shows extensive hypertrophy of left hepatic lobe without significant growth of the right lobe HCC (E, F).



**Figure 2.** Combined TACE and PVE for HCC. There is a tumor in segment 8 (arrow) (A). TACE was performed with arterial devascularization of the tumor (B, C). After 1 week, right-sided PVE was performed via an ipsilateral approach (D, E). Two weeks after PVE, shrinkage of the lipiodol-laden mass with hypertrophy of left lateral segment FLR was seen (F).

The extent of FLR hypertrophy after PVE is generally 30% to 50% of the unembolized segment itself and 5% to 20% of the TLV (Figure 1).<sup>8</sup> Liver regeneration reaches its peak 2 to 3 weeks after PVE.<sup>9</sup> The degree of kinetic growth rates will vary by patient, and absence of a significant degree of hypertrophy may result in post-operative mortality and morbidity.<sup>10</sup> Sustained further hypertrophy of FLR has been observed up to 6 months after PVE in patients who could not undergo planned hepatic resection.<sup>11</sup> The drop-off rate of planned surgery after PVE may be as high as 20% due to disease progression or insufficient hypertrophy of the FLR.<sup>12</sup> For these patients, transcatheter arterial chemoembolization (TACE), TARE, ALPSS, or hepatic vein embolization

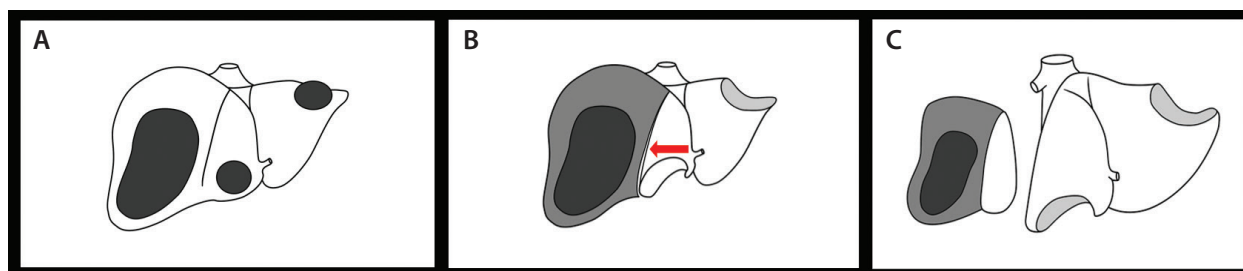
may be applied for further sustained growth.<sup>13</sup>

Despite the encouraging results seen with PVE, there is a concern for rapid progression of tumors within the 2- to 4-week waiting period after PVE.<sup>14</sup> Compensatory increase of hepatic arterial inflow after PVE may be responsible for the rapid growth of tumors in the treated area. Upregulated hormonal factors may potentially lead to upregulation of tumors in the nonembolized segments. In order to control tumor growth during the waiting period, systemic chemotherapy or TACE before or after PVE can be used as a combination method (Figure 2).<sup>15,16</sup> Cessation of blood flow in both the hepatic artery and PV appears to result in increased hyper-

trophy of the FLR as compared with the PVE-only method. Controversy remains as to whether chemotherapy before or after PVE plays a negative role in liver regeneration.<sup>17</sup>

### ALPPS

ALPPS may be used as a salvage procedure when PVE fails.<sup>18</sup> ALPPS is a novel technique that can be employed even for extensive hepatic tumors that were previously considered unresectable (Figure 3). This technique results in a vast increase in the volume of the FLR in a short period of time. However, this technique continues to provoke heated debate because of its high mortality and morbidity rates. The advantages

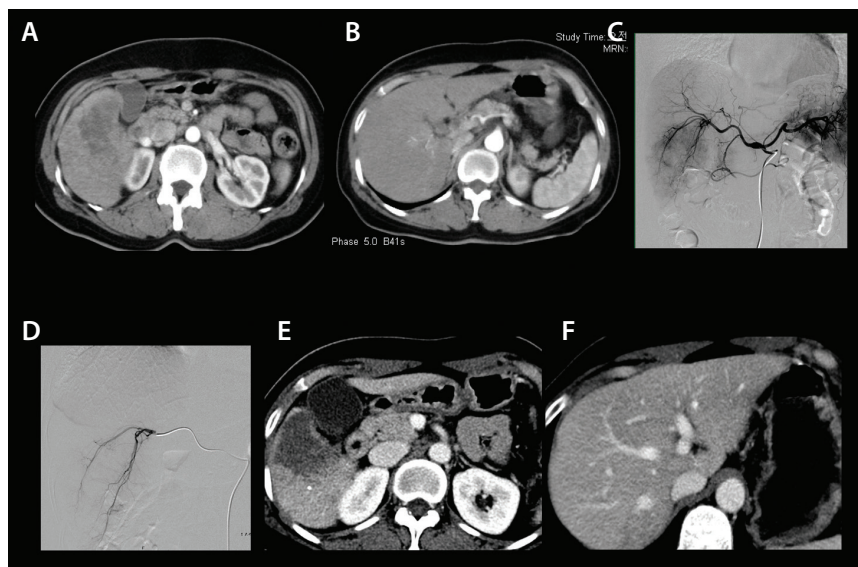


**Figure 3.** Schematic illustration of ALPPS for multiple bilobar tumors (A). In the first stage, right PV ligation and partition of both lobes (arrow) is performed with tumor resection in the left hepatic lobe (B). In the second stage, a right hepatic lobectomy can be done with good hypertrophy of the FLR (C).

of ALPPS are rapid hypertrophy of the FLR and a higher rate of complete resection compared to other techniques. Disadvantages of ALPPS include major complications, more deaths, and early tumor recurrence.<sup>19</sup> Some modified forms of ALPPS have reduced the morbidity and mortality of the procedure, but they cannot be widely recommended over the original procedure at this time.<sup>20</sup> More evidence regarding longer-term oncologic outcomes needs to be gathered to determine the safety and effectiveness of ALPPS for patients with a tumor involving the FLR. Further study could help to determine the ideal indications and patient selection for this novel procedure.

## TARE

In addition to PVE or ALPPS, TARE using yttrium-90 microspheres also leads to a volume increase of non-embolized liver parenchyma (Figure 4). A systematic review of TARE in 312 patients between 2000 and 2014 was performed and reported FLR hypertrophy ranging from 26% to 47% at 44 days through 9 months.<sup>21</sup> Garlipp et al compared the effectiveness of PVE versus TARE in inducing contralateral hepatic hypertrophy. Substantial FLR hypertrophy was seen in both groups, but PVE produced significantly more hypertrophy than TARE (61.5% vs 29%;  $P < .001$ ).<sup>22</sup> Despite less contralateral liver hypertrophy in the TARE group, TARE provides effective treatment of ipsilateral liver tumors along with induction of hypertrophy and may be beneficial compared to TARE given its reduced risk of tumor progression. TARE also has the advantage of being a one-step procedure as compared with combined TACE and PVE for tumor control. It should be noted that hypertrophy after TARE generally takes longer than with PVE<sup>22</sup>; however, the current body of scientific literature has examined the hypertrophic effects only as an ancillary observation of tumor-directed TARE. Intention-to-treat studies focusing on the facilitation of hypertrophy, potentially modulating (and perhaps increasing) the amount of radioactivity or its distribution, will be required to determine the optimal method of FLR hypertrophy using a TARE technique.



**Figure 4.** TARE for HCC. An infiltrative HCC in segment 6 with apparently small left lobe volume is seen on CT (A, B). TARE was selectively performed in segment 6 hepatic arteries with 0.57 GBq of yttrium-90 (C, D). Three months after TARE, a necrotized HCC mass with extensive hypertrophy of left hepatic lobe was seen (E, F).

## CONCLUSION

The interventional specialist plays a key role in the multidisciplinary team, ensuring that FLR volume is adequate and increasing the FLR volume when necessary. PVE, ALPPS, TARE, and other experimental treatments are used for this purpose. The greatest amount of FLR hypertrophy has been seen with ALPPS, followed by PVE, while the least amount has been seen with TARE. However, PVE is currently considered the procedure of choice. If PVE fails to achieve a sufficient FLR, additional methods may be utilized, including ALPPS, TARE, hepatic vein embolization, and stem cell infusion through the portal vein.<sup>23</sup>

If there is concern for rapid tumor growth before surgery, TACE and/or systemic chemotherapy can be combined with PVE to minimize this possibility. TARE may be applied instead of the TACE-PVE combination if a one-step procedure is desired. The longer time for hypertrophy after TARE may allow for the “test of time” approach to ensure that additional disease does not develop, and further study into the optimal method of TARE in this setting is warranted. ALPPS can be a viable alternative option to PVE, especially when tumor involvement is extensive, although further data collection on ALPPS is necessary to verify its safety and effectiveness. Continued technical improvements in PVE, ALPPS, and TARE, as well as the potential to combine these techniques, may allow for faster and greater hypertrophy of the FLR along with preservation of liver function and a low surgical resection drop-off rate. ■

Courtesy of Jong-Yun Won, MD, Severance Hospital, Yonsei University, Seoul, South Korea.

1. Hemming AW, Reed AJ, Howard RJ, et al. Preoperative portal vein embolization for extended hepatectomy. *Ann Surg*. 2003;237:686-693.
2. Hirohashi K, Kinoshita H, Iwasa, et al. Preoperative portal vein embolization for hepatocellular carcinoma. *Nihon Geka Gakkai Zasshi*. 1991;92:1316-1319.
3. Ko HK, Ko GY, Sung KB, et al. Portal vein embolization via percutaneous transsplenic access prior to major hepatectomy for patients with insufficient future liver remnant. *J Vasc Interv Radiol*. 2016;27:981-986.
4. Yeom YK, Shin JH. Complications of portal vein embolization: evaluation on cross-sectional imaging. *Korean J Radiol*. 2015;16:1079-1085.
5. Kawai M, Naruse K, Komatsu S, et al. Mechanical stress-dependent secretion of interleukin 6 by endothelial cells after portal vein embolization: clinical and experimental studies. *J Hepatol*. 2002;37:240-246.
6. Hayashi H, Beppu T, Sugita H, et al. Serum HGF and TGF- $\beta$ 1 levels after right portal vein embolization. *Hepatol Res*. 2010;40:311-317.
7. Kusaka K, Imamura H, Tomiya T, et al. Expression of transforming growth factor- $\alpha$  and - $\beta$  in hepatic lobes after hemihepatic portal vein embolization. *Dig Dis Sci*. 2006;51:1404-1412.
8. Aoki T, Kubota K. Preoperative portal vein embolization for hepatocellular carcinoma: consensus and controversy. *World J Hepatol*. 2016;8:439-445.
9. May BJ, Talenfeld AD, Madoff D. Update on portal vein embolization: evidence-based outcomes, controversies, and novel strategies. *J Vasc Interv Radiol*. 2013;24:241-254.
10. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. *J Am Coll Surg*. 2013;216:201-209.
11. Shin JH, Yoon HK, Kwon J, et al. Volumetric analysis of the liver after right portal vein embolization: mid-term follow-up based on embolization score. *Clin Radiol*. 2010;65:288-296.
12. Loffroy R, Favelier S, Chevallier O, et al. Preoperative portal vein embolization in liver cancer: indications, techniques and outcomes. *Quant Imaging Med Surg*. 2015;5:730-739.
13. Hwang S, Ha TY, Ko GY, et al. Preoperative sequential portal and hepatic vein embolization in patients with hepatobiliary malignancy. *World J Surg*. 2015;39:2990-2998.
14. Al-Sharif E, Simoneau E, Hassanain M. Portal vein embolization effect on colorectal cancer liver metastasis progression: lesions learned. *World J Clin Oncol*. 2015;6:142-146.
15. Ronot M, Cauchy F, Gregori B, et al. Sequential transarterial chemoembolization before resection is a valid oncological strategy for unilobar hepatocellular carcinoma regardless of tumor burden. *HPB (Oxford)*. 2016;18:684-690.
16. Kang BK, Kim JH, Kim KM, et al. Transcatheter arterial chemoembolization for hepatocellular carcinoma after attempted portal vein embolization in 25 patients. *Vasc Interv Radiol*. 2009;193:446-451.
17. Simoneau E, Alanazi R, Alshenaifi J, et al. Neoadjuvant chemotherapy does not impair liver regeneration following hepatectomy or portal vein embolization for colorectal cancer liver metastases. *J Surg Oncol*. 2016;113:449-455.
18. Cai YL, Song PP, Tang W, Cheng NS. An updated systematic review of the evolution of ALPPS and evaluation of its advantages and disadvantages in accordance with current evidence. *Medicine (Baltimore)*. 2016;95:e3941.
19. Oldhafer KJ, Donati M, Jenner RM, et al. ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. *World J Surg*. 2014;38:1504-1509.
20. de Santibanes E, Alvarez FA, Ardiles V, et al. Inverting the ALPPS paradigm by minimizing first stage impact: the mini-ALPPS technique. *Langenbecks Arch Surg*. 2016;401:557-563.
21. Teo JY, Allen JC Jr, Ng DC, et al. A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90. *HPB (Oxford)*. 2016;18:7-12.
22. Garlipp B, de Baere T, Damm R, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. *Hepatology*. 2014;29:1864-1873.
23. Treska V, Liska V, Fichtl J, et al. Portal vein embolisation with application of haematopoietic stent cells in patients with primarily or non-resectable colorectal liver metastases. *Anticancer Res*. 2014;34:7279-7285.

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*Disclosures: None.*