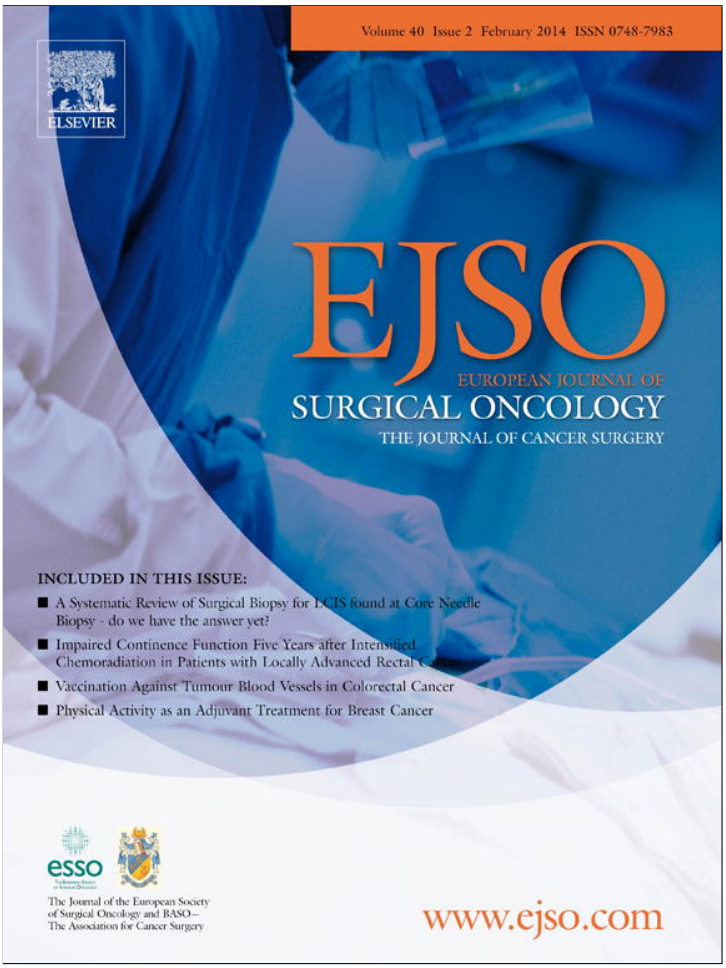

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How I do it

Outflow modulation to target liver regeneration: Something old, something new☆

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Abstract

Background: Stimulation of hepatic hypertrophy is a useful aid to accomplish hepatic resections when the future liver remnant (FLR) is small. Although inflow occlusion, especially through portal flow, has been extensively studied, the role of outflow modulation has not yet been described.
Methods: Description of outflow modulation to tailor hypertrophy of future liver remnant in the context of bilobar metastatic disease. A patient with small FLR (segments I and IV) was managed with a two-stage procedure. The first stage consisted of a right hepatectomy and modulation of the left hepatic vein outflow through reduction of its diameter, with macroscopic congestion of segments II–III. The second stage consisted of a left lateral sectionectomy six weeks later. Postoperative courses were uneventful without any sign of liver failure.
Results: Following the first stage procedure computed tomography revealed distinct hypertrophy rates between sections. The non-congested area had an increase of 156% in the volume of segment IV (from 137 to 351 cm^3) and 100% in the volume of segment I (from 20 to 40 cm^3). The congested area, segments II–III, increased only 24% (from 205 to 253 cm^3).
Conclusion: Modulation of liver outflow allows maintenance of function in the segments to be resected while avoiding their hypertrophy. This process prevents liver failure and optimizes regeneration of hepatic territories to be preserved.

Keywords: Outflow modulation; Liver hypertrophy; Hepatectomy

Introduction

Stimulation of hepatic regeneration has been used to allow liver resection in patients with a small liver remnant.[1–3] Through a selective portal vein occlusion, surgical or percutaneous, it is possible to induce compensatory hypertrophy of the future liver remnant (FLR) segments. Such an approach has enabled extensive liver resections in patients with multiple metastasis and safer resections in patients with underlying liver disease.[2,4]

It is well known that the ability of the liver to regenerate can be compromised by hepatic dysfunction. Lately, hepatic congestion due to outflow impairment has been shown to limit hepatic regeneration.[5]

Although blood flow modulation through the portal vein has been widely used (such as in portal vein embolization, portal vein ligation, associating liver partition and portal vein ligation for staged hepatectomy [ALPPS]), the modulation of hepatic outflow to target liver regeneration has not yet been reported.

Technical aspects of outflow modulation

A case study of the use of outflow modulation was undertaken with a 52-year-old female with colorectal cancer and synchronous bilateral liver metastasis. The patient initially underwent a resection of the primary adenocarcinoma (pT3N1M1 – stage IV, liver disease only).

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After eight courses of oxaliplatin-based chemotherapy, the disease was stable and limited to the liver. A computed tomography (CT) scan identified one lesion on the left lobe and six lesions on the right liver (one of them located within the boundaries of segments VIII and IV).

The initial surgical plan was to perform a right hepatectomy and a wedge resection of the left lesion. However, the intraoperative ultrasonography (IOUS) revealed three additional tumors deep in the left lobe (none of them greater than 5 mm), making the lobe unsuitable for preservation. The FLR would consist solely of segments I and IV (estimated volume of 157 cc – Fig. 1(a)). The remnant liver volume to body weight ratio was 0.3 and thus well below the critical cutoff to accomplish a safe resection. Due to this discovery, the initial plan had to be changed.

The usual option for this case would be a staged procedure, with a left sectionectomy combined with right portal vein embolization, followed by a right hepatectomy. This approach was considered too risky due to two major concerns: i) potential postoperative liver failure due to a very small functioning liver remnant, and ii) the possible progression of the lesion between segments VIII and IV. To overcome these potential problems, an unusual staged procedure would be needed: first, a right hepatectomy, followed by a left sectionectomy after hypertrophy of the remnant liver.

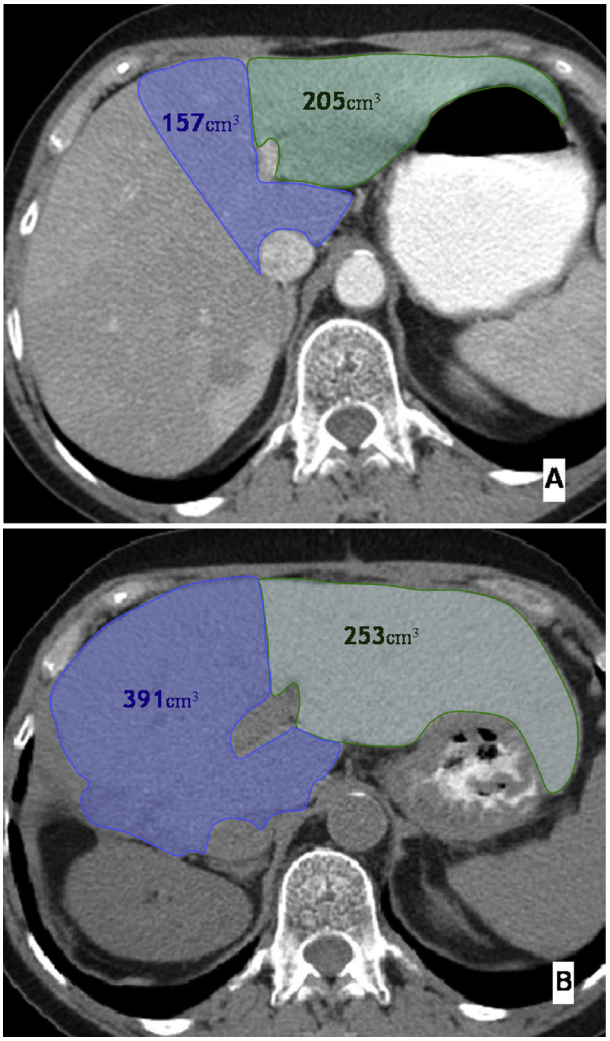

Figure 1. Computed tomography based volumetry before the first (a) and second (b) stages of liver resection. Modulated congestion of bisegment II/III associated to right hepatectomy led to significant hypertrophy rate of segments IV/I (156% – from 157 to 391 cm^3) and only modest hypertrophy rate of segments II/III (24% – from 205 to 253 cm^3).

As there was a need to optimize hypertrophy of segments I and IV, the initial surgery consisted of a right hepatectomy and induction of congestion of the left lobe. First, a right hepatectomy was carried out. Next, to induce the desired segmental congestion, a silicone tube was wrapped around the left hepatic vein outside the liver. The diameter of the silicone loop around the vein was progressively diminished. When macroscopic signs of congestion in segments II and III became evident, a Doppler study was performed in order to ensure that hepatopetal flow was still present inside these segments. This was achieved when the diameter of the vessel was reduced by half. Finally, a tie on the silicone tube was performed to maintain the diameter of the vessel according to the size of the loop. By the end of the procedure, this restrictive silicone loop was left *in situ*. The patient was discharged home on the fifth postoperative day. Her recovery was uneventful with no signs of hepatic dysfunction.

Another course of systemic chemotherapy was done before reassessment, within four weeks after the first liver surgery. A new CT scan revealed an increase of 156% in the volume of segment IV (from 137 to 351 cm^3), 100% in the volume of segment I (from 20 to 40 cm^3), and only 24% in the volume of segments II–III (from 205 to 253 cm^3) Fig. 1(a) and (b).

The second stage of the procedure was performed six weeks after the first (Fig. 2). As the IOUS did not show any additional lesions in segments I and IV, a left sectionectomy was carried out. The final remnant liver after the staged procedure consisted of segments I and IV. The recovery of the patient was free of complications. Only minor alterations of function tests were observed and the patient was discharged on the second postoperative day.

Discussion

In the absence of underlying liver dysfunction, a remnant liver volume of 20–30% of the total preoperative non-tumoral volume, or a remnant liver volume to body weight ratio of more than 0.6, is usually required. To allow resection in patients with insufficient remnants, portal vein occlusion to induce hypertrophy of the FLR is frequently used. A hypertrophy rate of up to 38% after portal occlusion, and up to 80% following liver resection, can be expected after approximately one month.[4,6,7]

The conventional approach for patients with bilobar disease is clearance of the left liver/lobe followed by right

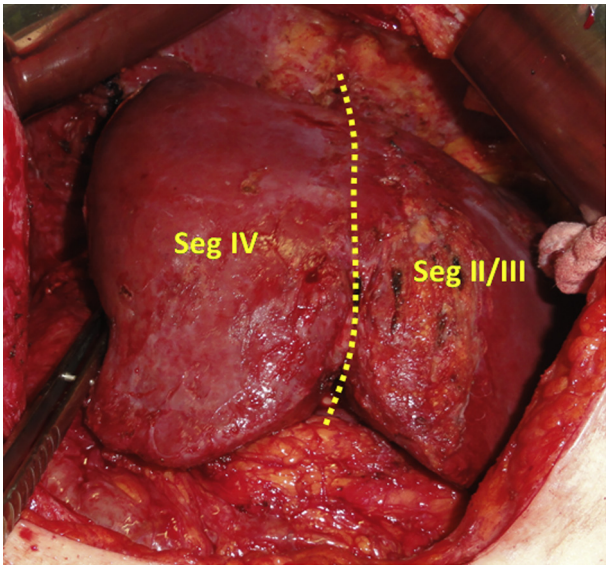

Figure 2. Surgical findings before the second stage hepatectomy – six weeks after right hepatectomy and partial obstruction of the left hepatic vein. No macroscopic congestion is observed on segments II/III. Hypertrophy of segment IV is obviously greater.

portal vein (+- segment IV branches) embolization. Unfortunately, in this case, clearance of the left liver would have demanded a left lateral sectionectomy. In the best possible scenario, through such an approach – expecting a hypertrophy rate of 38% –, the remnant liver (segments I and IV) would not be sufficient to perform a safe second resection (217 cc for an adult weighing 55 kg). As the expected hypertrophy rate following liver resection is much greater, we chose to carry out the right hepatectomy during the first procedure.

In order to favor the hypertrophy of segments I and IV over segments II and III, a modulation of the outflow through the left hepatic vein was performed. A series of papers have shown the effects of congestion on hypertrophy of the liver. Indeed, the causal relationship between congestion and liver regeneration has been consistently reported after living donor transplantation.[8,9] Patients submitted to right liver resection with middle hepatic vein harvesting have a smaller regeneration rate of segments I and IV, compensated by an increased regeneration rate of segments II and III.[10] Similarly, right grafts without middle hepatic vein reconstruction have an impaired regeneration of the anterior sector due to segmental congestion.[11] Interestingly, this difference in rates of hypertrophy between sectors has no influence on global volume after regeneration of the liver.[10,11] Bearing this in mind, we sought to induce a greater proportional hypertrophy of segments I and IV through induction of congestion in segments II and III. In this case we observed a much greater increase in the volume of segment IV (156%) and segment I (100%) than in segments II–III (24%).

The mechanism of liver regeneration after partial liver resection or portal occlusion is not fully understood. Probably, hypertrophy of the hepatic parenchyma occurs due to an increased carriage of hepatotrophic factors by the portal vein. Thus, the proportional increase in portal flow observed after partial hepatic resection or portal vein occlusion induces hypertrophy of the remaining parenchyma. Despite playing a major role in hepatic perfusion, the portal blood flow is regulated not only by the inflow, but also by the outflow. It is known that severe reduction of the outflow induces portal flow inversion in the compromised territory. Consequently, severe liver congestion can diminish the hypertrophy rate or even induce segmental atrophy.[12]

Sequential portal vein embolization (PVE) and ipsilateral hepatic vein occlusion increase FLR by inducing more severe liver damage than PVE alone, probably due to backflow interruption.[13] This might also explain the hypertrophy rates seen in ALPPS, since hepatic veins tributaries are sectioned during hepatotomy. However, these strategies are different from outflow modulation, whose main goal is the re-distribution of the portal flow while keeping the function of the segments to be resected.

The reduction of outflow avoids the expected increase of portal inflow in the congested area, and hence its hypertrophy. At the same time, the redirection of the portal flow should increase the perfusion of the area where hypertrophy is needed (Fig. 3).

On the other hand, the maintenance of liver function in the congested area might be desired to avoid early postoperative liver failure. Since segments I and IV would not be sufficient to avoid liver failure in this patient, maintenance of the left lateral section basal function was clearly obtained despite the outflow modulation. As long as the congestion does not induce inversion of the portal flow, the parenchymal function seems to be preserved. In other words, blood flow to the congested area should be low enough to preclude hypertrophy but high enough to maintain hepatocellular function.

Rationale to modulate outflow are the temporal aspects related to hypertrophy and hepatic congestion. Most of

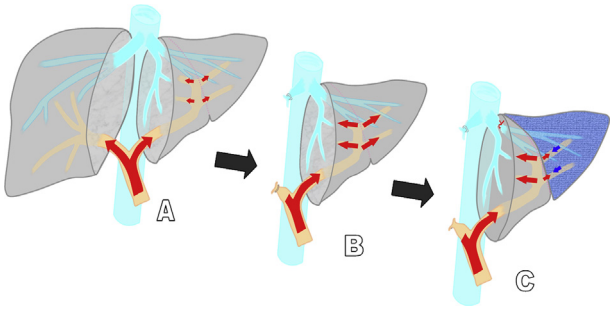

Figure 3. Schematic outflow modulation to optimize hypertrophy of segment IV and avoid hypertrophy of segments II/III after right hepatectomy. (a) Normal portal flow; (b) Usual increase in the portal flow to the left liver after right hepatectomy; (c) Redistribution of portal flow – increased inflow to segment IV after territorial congestion of segments II/III. Red arrows represent portal inflow and blue arrows represent venous resistance to portal inflow secondary to congestion.

the regeneration occurs during the first week. This is the same amount of time required to start the opening of collaterals that will allow proper drainage of the congested area.[6,12,14,15] Thus, the resolution of congestion after this period will allow only a modest hypertrophy of congested area. This combination offers the perfect scenario for the induction of hepatic hypertrophy in the target segments.

Despite the small volume of the non-congested remnant liver (segments IV and I) there was a slight alteration (not reported) of liver function tests after the first procedure (right hepatectomy and induced congestion of the left lobe). This led to the logical conclusion that, under moderate congestion, the hepatic parenchyma was able to maintain a reasonable functional capacity during the critical period (first week after hepatectomy), while inhibiting regeneration in the congested area.

The combination of multiple bilobar and profound liver tumors observed in this case study is not unusual. In such patients, even with a combination of wedge resections and/or local ablation, complete clearance of the liver can be difficult to accomplish. To our understanding, this is a population in which outflow modulation might be useful no matter the means of access (open surgery, laparoscopy, or interventional radiology). The development of interventional radiology methods for outflow modulation might overcome the barriers imposed by eventual anatomical variations of segment IV drainage, avoiding undesirable congestion of the future liver remnant.

Future research should focus on determination of the ideal degree of congestion, the impact of underlying liver disease on regeneration, and its association with portal vein embolization.

Although seen as deleterious, hepatic congestion can be a valuable tool in hepatic surgery when used to favor the hypertrophy of the remnant liver. To the best of our knowledge, this is the first paper to report outflow modulation to target segmental liver regeneration.

Conflict of interest statement

No conflicts of interest.

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