

Contra-lateral liver lobe hypertrophy after unilobar Y90 radioembolization: An alternative to portal vein embolization?

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Abstract

Liver resection (LR) with negative margins confers survival advantage in many patients with hepatic

malignancies. However, an adequate future liver remnant (FLR) is imperative for safe LR. Presently, in patients with an inadequate FLR; the 2 most established clinical techniques performed to induce liver hypertrophy are portal vein embolization (PVE) and portal vein ligation. More recently, it has been observed that patients who undergo treatment *via* Y90 radioembolization experience hypertrophy of the contra-lateral untreated liver lobe. Based on these observations, several investigators have proposed the potential use of this modality as an alternative technique for increasing the FLR prior to liver resection. Y90 radioembolization induces hypertrophy at a slower rate than PVE but has the added advantage of concomitant local disease control and tumour down-staging.

Key words: Liver hypertrophy; Y90; Radioembolization; Portal vein embolization; Selective internal radiation therapy

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Core tip: Both portal vein embolization and Y90 radioembolization induce significant hypertrophy of the contralateral lobe. Y90 radioembolization induces hypertrophy at a slower rate than PVE but has the added advantage of concomitant local disease control and tumour down-staging.

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LIVER HYPERTROPHY

Liver resection (LR) with negative margins confers consistent survival advantage in patients with both primary (hepatocellular carcinoma/cholangiocarcinoma) or secondary malignant disease^[1]. In patients with well-preserved liver function, curative liver resection remains the standard of care. An adequate future liver remnant (FLR) is imperative for safe LR. Presently, in patients with a normal liver function, a FLR of at least 25% is deemed sufficient by most clinicians to avoid liver failure. However, in patients with an impaired liver function (*e.g.*, cirrhosis), a larger FLR of up to 40% should be preserved^[2-4]. An inadequate FLR is a major reason why otherwise suitable patients are precluded from potentially curative LR.

Presently, the 2 most well-established clinical techniques performed to induce liver hypertrophy in patients with an inadequate FLR are portal vein embolization (PVE) and portal vein ligation (PVL). In head-to-head comparisons, both these techniques have been shown to result in equivalent degrees of hypertrophy^[5,6], estimated to be between 10%-46% at 2 to 8 wk^[7]. PVE is preferentially utilised usually in view of its minimally invasive nature, and the avoidance of a laparotomy. However, a major drawback of both PVE and PVL is that tumour growth continues unabated while awaiting hypertrophy, which may eventually preclude resection especially in tumours which are in close proximity to major bilio-vascular structures. This is far from being a merely theoretical concern as increased tumour growth rates after PVE have been reported in both animal models^[8,9] and humans^[10].

Based on these concerns, a sequential approach combining transarterial chemoembolization (TACE) and PVE has been advocated, with proponents claiming both a significant rate of FLR hypertrophy as well as increased local tumour control. This approach was first shown to result in good FLR hypertrophy, with no increased risk of liver failure, as might be expected after occlusion of the liver's dual blood supply^[11]. These findings were replicated in subsequent larger studies, which also showed an improvement in both overall and disease-free survival in patients undergoing sequential treatment as opposed to PVE alone^[12,13]. However, in these studies, the mean increase in percentage of FLR achieved in the PVE + TACE arms was only 7.3%-22%, which was significantly less than that reported with PVE in the rest of the literature.

Y90 RADIOEMBOLIZATION

The first series to report the phenomenon of contralateral liver lobe hypertrophy after Y90 radioembolization was published in 2008^[14]. Subsequently, several groups have also published similar results from their retrospective experience^[15-22]. The main limitations of

these retrospective studies are that the patient cohorts were vastly heterogenous in terms of pathology treated, underlying liver disease, dosage and delivery of Y90, number of treatment sessions and time to measurement of hypertrophy. However, it was clear that unilobar Y90 radioembolization resulted in significant hypertrophy of the contralateral lobe - the reported average hypertrophy achieved ranged from 21%-47% at 44 d-9 mo. The degree of hypertrophy reported is thus comparable with that achieved with PVE/PVL, although the time to hypertrophy is clearly heterogenous, and precludes any meaningful direct comparison. To date, there have been no prospective trials directly comparing the efficacy of Y90 radioembolization to PVE/PVL in achieving liver hypertrophy.

Only one series^[21] has attempted a direct head-to-head comparison between these two modalities. In this study, a matched-pair analysis of patients with secondary liver malignancy confined to the right hemiliver was performed. Patients were well matched for: (1) baseline FLR; (2) history of platinum-based chemotherapy; (3) platelet count; and (4) extent of embolization. Although subject to the usual biases inherent in such a study, the authors demonstrated that PVE produced significantly more hypertrophy (61.5% vs 29.0%) within a shorter time frame (median 33 d vs 46 d). Another recent study^[18] attempted to study the relationship between the degree of hypertrophy with duration from treatment. In this study, median FLR growth progressed from 7% at one month to 45% at 9 mo post-radioembolization. Hence, based on current evidence it can be concluded that the kinetics of hypertrophy may differ between the two modalities, with post Y90 radioembolization causing a slower, more gradual increase in volume compared to PVE. Hence, the potential advantage of Y90 radioembolization in inducing liver hypertrophy would therefore lie in its ability to provide concomitant local tumour control and even down-staging. Tumour response to Y90 according to the RECIST criteria had been reported to range between 42%-70%^[23]. This decrease in tumour size, coupled with hypertrophy of the FLR holds great promise in potentially rendering previously unresectable disease curable.

It is worth mentioning here the recent development of another novel technique for inducing liver hypertrophy, *i.e.*, associating liver partition with portal vein ligation for staged hepatectomy (ALPPS). This technique allows for extremely rapid hypertrophy of the FLR, at the expense of increased morbidity and a significant mortality rate. A recent review of the literature^[24] concluded that a mean FLR hypertrophy of 80% at 7-10 d was achievable, but at the risk of a 35% significant morbidity rate and a 30-d mortality of 6%. In view of the significant morbidity and mortality, ALPPS is therefore best considered to be an experimental technique at present. It is to be used in highly selected patients in a clinical trial setting.

In light of current evidence, we therefore propose that instead of being an alternative to PVE, the technique of Y90 radioembolization is instead complementary. The former is best utilised in the setting where the tumour is technically resectable except for a concern over the adequacy of the FLR. PVE would then result in a greater degree of hypertrophy over a shorter time frame. However, in situations where a large, bulky tumour abuts major vascular and/or biliary structures which must be conserved or when the ability to achieve adequate oncological margins are a concern, then Y90 radioembolisation would provide the added advantage of both tumour control/downsizing while increasing the FLR.

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