REVIEW ARTICLE

A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90

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Abstract

Background: Curative liver resection is the treatment of choice for both primary and secondary liver malignancies. However, an inadequate future liver remnant (FLR) frequently precludes successful surgery. Portal vein embolization is the gold-standard modality for inducing hypertrophy of the FLR. In recent times, unilobar Yttrium-90 selective internal radiation therapy (SIRT) has been reported to induce hypertrophy of the contralateral, untreated liver lobe. The aim of this study is to review the current literature reporting on contralateral liver hypertrophy induced by unilobar SIRT.

Methods: A systematic review of the English-language literature between 2000 and 2014 was performed using the search terms "Yttrium 90" OR "selective internal radiation therapy" OR "radioembolization" AND "hypertrophy".

Results: Seven studies, reporting on 312 patients, were included. Two hundred and eighty four patients (91.0%) received treatment to the right lobe. Two hundred and fifteen patients had hepatocellular carcinoma (HCC), 12 had intrahepatic cholangiocarcinoma, and 85 had liver metastases from mixed primaries. Y90 SIRT resulted in contralateral liver hypertrophy which ranged from 26 to 47% at 44 days–9 months. All studies were retrospective in nature, and heterogeneous, with substantial variations relative to pathology treated, underlying liver disease, dosage and delivery of Y90, number of treatment sessions and time to measurement of hypertrophy.

Conclusion: Unilobar Y90 SIRT results in significant hypertrophy of the contralateral liver lobe. The rate of hypertrophy seems to be slower than that achieved by other methods.

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Introduction

Liver resection (LR) with negative margins is the only potentially curative treatment in the majority of patients with both primary and secondary malignant disease.[1] However, an adequate future liver remnant (FLR) is imperative to avoid postoperative liver failure. In patients with a preserved liver function, a FLR of at least 25–30% is deemed sufficient by most clinicians to prevent liver failure.[2] However, in patients with impaired liver function (e.g. cirrhosis), a FLR of up to 40% should be preserved.[3,4] Inadequate FLR is one of the most common reasons for precluding otherwise suitable patients from potentially curative LR.

At present, the two techniques most commonly used to induce FLR hypertrophy in patients with inadequate FLR are portal vein embolization (PVE) and portal vein ligation (PVL). In head-to-head comparisons, the two techniques have been shown provide equivalent degrees of hypertrophy,[5,6] estimated to be between 10 and 46% at 2–8 weeks.[7] PVE is thus

preferentially utilised as it is minimally invasive in nature and avoids a laparotomy.

Presently, selective internal radiation therapy (SIRT) with Yttrium-90 (also known as radioembolization) has become an increasingly utilized treatment modality for locally advanced liver tumours, with radiological tumour response rates of between 42 and 70% reported.[8–10] In addition to documented efficacy for local tumour control, recent reports have described that the delivery of unilobar SIRT may result in a significant hypertrophy of the contralateral liver lobe.[11–19] This finding is relatively recent and has the potential of increasing resectability rates as it allows both tumour down-staging and induces FLR hypertrophy.

To date, there have been multiple reports—largely heterogeneous case series—describing this phenomenon. The aim of this study was to perform a systematic review of the English language literature to summarize the current evidence on liver hypertrophy following unilobar SIRT.

Methods

Systematic literature search

A systematic literature search was performed from the PubMed and Scopus databases from January 1 2000 to August 20 2014. SIRT with Y90 is a relatively new technology, and searches extending earlier than this would not yield additional results. The search terms "Yttrium 90" OR "selective internal radiation therapy" OR "radioembolization" AND "hypertrophy" were used. From the titles identified, all abstracts were screened by two authors (Teo JY and Goh BKP) to identify studies reporting on the degree of liver hypertrophy after Y90 SIRT. Subsequently, full-text articles of potentially eligible articles were screened. All references of the included studies were screened for potential relevant studies not identified by the initial literature search. The final decision on eligibility was reached by consensus between the two screening authors. There were no cases of disagreement and hence no requirement for adjudication by an independent third reviewer. When more than one study was published from the same centre, and the cohorts were overlapping, only the most recent study was included in the analysis.

Inclusion and exclusion criteria

Inclusion criteria were (i) case series reporting on $\geq$ 2 patients; (ii) undergoing unilobar SIRT with Y90 microspheres; (iii) and reporting on hypertrophy of the contralateral lobe at any time point. When volume changes at more than one independent time point were reported, the maximal volume increase was extracted and analysed.

Exclusion criteria were (i) case reports; (ii) studies which did not report volumetric changes; (iii) review articles which did not present unique data. (iv) Articles not published in English.

Data extraction

From the included studies, the following data were extracted: number of patients, pathology of disease being treated, modality and site of Y90 delivery, number of treatment sessions, method of volumetric measurement, time to determination of liver hypertrophy and degree of hypertrophy achieved.

Results

Fig. 1 shows the PRISMA flow chart for the study.[20] Nine studies, published between 2008 and 2014 were identified.[11–19] Three studies[11,12,15] were reported from the same centre with overlapping patient cohorts. Two studies[11,12] were excluded; and only the most recent (and largest) report[15] was included. Finally, 7 studies reporting on a total of 312 patients were included in the final analysis. Table 1 shows a summary of the data variables collected. All identified studies were retrospective in nature. As there was clearly a great degree of clinical heterogeneity among studies—most notably in terms of time to volumetric measurement—a meta-analysis was not performed as any result obtained would be of questionable value and difficult to interpret.

The published series were heterogeneous in terms of pathology treated, dosage and delivery of Y90, and time to measurement of hypertrophy. However, it was clear that unilobar Y90 SIRT resulted in significant hypertrophy of the contralateral lobe—the reported average hypertrophy achieved ranged from 26 to 47% over time periods of 44 days to 9 months. Of the 312 patients 284 (91.0%) received SIRT to the right lobe. In terms of underlying pathology, 215 (68.9%) patients were treated for hepatocellular carcinoma (HCC), 12 (3.8%) for intrahepatic cholangiocarcinoma and 85 (27.2%) for liver metastases from various primaries.

Comparison between SIRT and PVE

Only one study[18] attempted a direct head-to-head comparison between SIRT and PVE. Garlipp *et al.* performed a matched-pair analysis of patients with secondary liver malignancy confined to the right hemiliver. Patients were well matched for (i) baseline FLR; (ii) history of platinum-based chemotherapy; (iii) platelet count and (iv) extent of embolization. Although subject to the usual biases inherent in such a study, PVE was reported to result in significantly greater hypertrophy (PVE: 61.5%; SIRT: 29.0%) within a shorter median time frame (PVE: 33 days (range 24–56 days); SIRT: 46 days (range 27–79 days). In this study, tumour growth in both arms was not reported.

Rate of hypertrophy with SIRT

Two studies attempted to describe the time-dependant changes in liver volume.[15,17] The studies by both Vouche *et al.*[15] and Fernandez-Ros *et al.*[17] suggested that the kinetics of post-Y90 hypertrophy are slow, with gradual increases in volume, and no demonstrated plateau. However, due to differences in patient

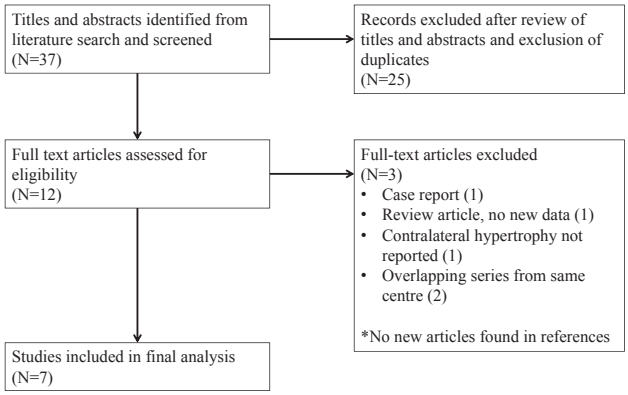

Figure 1 Flow diagram of study identification and selection

populations and treatment specifics, the Vouche *et al.*[15] study reported 45% hypertrophy at 9 months, whereas the Fernandez-Ros *et al.*[17] study reported 45% hypertrophy in 26 weeks, thus clearly demonstrating the importance of underlying patient and disease characteristics in influencing the eventual degree of growth achieved. Importantly, in the study by Vouche *et al.*,[15] which reported in detail the percentage hypertrophy at various time points, FLR growth above baseline was only 7% at 1 month and 24% at 3 months.

Other findings

The study by Teo *et al.*[16] was the first to report that HCC patients with hepatitis B experience a significantly greater degree of hypertrophy after SIRT (44.5%) compared to those with hepatitis C or alcoholic cirrhosis (7.7%). Although acknowledging the limitation of their small sample size, the authors postulated that the difference in hypertrophy was due to differences in underlying pathogenesis, with cirrhosis being a more important factor in patients with hepatitis C or alcoholic liver disease.

All identified studies reported predominantly on the phenomenon of post-SIRT hypertrophy as the primary outcome, and therefore outcomes on the treated tumours were not explicitly reported. However, a consistent finding was that hypertrophy of the untreated lobe is accompanied by a corresponding decrease in size of the tumour-bearing hemiliver, resulting in no net change in liver volume. This suggested that Y90 radioembolization resulted in good local tumour control which is consistent with previous studies reporting on oncological outcomes of Y90 radioembolization.[8,9]

Discussion

An adequate FLR is essential for a safe and successful major hepatectomy. The safety and efficacy of PVE for reliably producing significant hypertrophy in the FLR prior to the planned LR has been well-established.[7] This method should be regarded as the "gold standard" against which novel techniques are judged. However, a major drawback of PVE 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 animal models[21,22] and humans.[23]

Given 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.[24] 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.[25,26] 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 usually reported with PVE in the literature.[7]

The current systematic review demonstrated that unilobar Y90 SIRT resulted in significant hypertrophy of the contralateral liver lobe. However, all studies to date have been retrospective and observational in nature. The true degree and kinetics of hypertrophy, as well as the impact on these by tumour type, underlying liver disease, previous hepatotoxic chemotherapy, dose and delivery of radiation and other factors are as yet relatively unstudied and unknown.

PVE has been reported to give rise to FLR hypertrophy of 10–46% after 2–8 weeks.[5] The current systematic review showed hypertrophy of 26–47% at time intervals of from 44 days to 9 months after unilobar SIRT with Y90. Thus while the degree of growth achieved is comparable to that achieved with PVE alone, and superior to that achieved after PVE + TACE, the kinetics of hypertrophy after SIRT are likely to be different from PVE. This is further borne out in the study by Vouche *et al.*,[15] which showed only limited hypertrophy in the early post-treatment period.

The recent development of another novel technique for inducing liver hypertrophy, i.e. associating liver partition with portal vein ligation for staged hepatectomy (ALPPS), should also be mentioned. This technique allows for extremely rapid hypertrophy of the FLR, but at the risk of increased morbidity and a significant mortality rate. Two recent review papers[27,28] concluded that mean FLR hypertrophy in excess of 80% at 7–10 days was achievable, but at the risk of a 35–44% rate of significant morbidity, a 30-day mortality rate of 6% and 90-day mortality of 11%. In view of the significant morbidity and mortality, ALPPS is therefore at present best considered to be an experimental technique. It should only be used in highly selected patients in a clinical trial setting.[29]

The technique of Y90 SIRT is relatively safe and, in contrast to PVE, has the theoretical benefit of providing concomitant tumour control, with tumour response ranging from 42 to

Table 1 Summary of studies reporting on post-SIRT hypertrophy after unilobar SIRT

Paper	Number of patients	Age	Pathology treated	SIRT modality	Site of Y90 delivery	Number of treatment sessions	Method of volume measurement	Time to measurement	Percentage hypertrophy (mean/median (range))
Ahmadzadehfar *et al.* 2013 Germany[13]	24	Median 53 (range 44–78)	Metastatic disease (mixed) 17 – bi-lobar	Resin microspheres	Right lobe	Single	FDG PET/CT	Mean 44 days, median 36 days	Mean 47%, median 34% Only right lobe disease – mean 57%, median 70%
Edeline *et al.* 2013 France[14]	34	Not stated	Primary – HCC	30 Glass, 4 resin microspheres	23 right, 11 left	Single	CT	3 months Not stated	Mean 29% Mean 42% (maximal)
Vouche *et al.* 2013 USA[15]	83	Median 68 (range 36–89)	67 HCC, 8 IHC, 8 CRC mets	Glass microspheres	Right lobe	Single	MRI/CT	1- >9 months	Median overall 26% (–14–86) Median 45% at 9 months (5–186)
Theysohn *et al.* 2013 Germany[16]	45	Mean 71.9	HCC	Glass microspheres	Right lobe	Single	CT	6 Months	Mean 30.8%
Fernandez-Ros *et al.* 2013 Spain[17]	83	Median 66	52 HCC, 4 IHC, 13 CRC mets, 14 others	Resin microspheres	66 right, 17 left	Single	CT/MRI	26 weeks	Mean 45%
Garlipp *et al.* 2013 Germany, France[18]	26	Mean 59.2	Metastatic disease (mixed)	Resin microspheres	Right lobe	Single	MRI	Median 46 days (27–79 days)	Mean 29%, median 25.3%
Teo *et al.* 2014 Singapore[19]	17	Median 72 (range 42–78)	HCC	Resin microspheres	Right lobe	Single	CT	Median 5 months	Mean 34.2%

HCC, hepatocellular carcinoma; IHC, intrahepatic cholangiocarcinoma; CRC mets, colorectal cancer metastases; FDG PET, fluorodeoxyglucose positron-emission-tomography; CT, computed tomography; MRI, magnetic resonance imaging.

70%,[8,9] by the RECIST criteria. In situations where a large, bulky tumour abuts major vascular and/or biliary structures that must be saved, or when the ability to achieve adequate oncological margins are a concern, then Y90 SIRT is theoretically advantageous in providing both tumour control/downsizing while increasing the FLR.[29] Unfortunately, in the only study to date which has attempted a direct head-to-head comparison between these modalitiees,[18] tumour growth in both arms was not reported.

In addressing the mechanism of hypertrophy, several[11,17,19] studies have described changes consistent with portal hypertension following Y90 SIRT. These include increases in portal vein and spleen diameter with corresponding decreases in platelet count. Whether these changes reflect the underlying mechanism of hypertrophy, or if they are an indirect consequence of radiation-induced atrophy of the treated lobe, is unknown.

This review has several limitations. Most importantly, the studies identified are all retrospective in nature and are likely to be subject to selection and reporting bias. The patient cohorts are also vastly heterogeneous, with great variations in pathology treated, underlying liver disease, dosage and delivery of Y90, number of treatment sessions and time to measurement of hypertrophy—many of which may well influence the magnitude of treatment effect. Lastly, owing to study heterogeneity, a meta-analysis was not attempted as it would be difficult to interpret the data in any meaningful way.

Conclusion

Administration of unilobar SIRT results in significant hypertrophy of the contralateral liver lobe. The rate of hypertrophy seems to be slower than that achieved by other methods. Nevertheless, as SIRT is most often utilised in a palliative setting, on patients with presumably inferior functional reserve and liver function, the published literature may well underestimate the true potential of this modality. In conclusion, the phenomenon of post-Y90 hypertrophy provides a novel and exciting option in the multidisciplinary management of patients with liver tumours. Prospective studies are required to determine the kinetics of hypertrophy, as well as pre-procedural factors predictive of hypertrophy. In addition, the functional

capacity of the hypertrophied liver is yet to be ascertained, and the oncological outcomes of patients undergoing LR after Y90 SIRT must be established.

Conflicts of interest

Brian Goh has received travel grants from Sirtex Medical.
David Ng has received travel grants from Sirtex Medical.
Pierce Chow has received travel and research grants from Sirtex Medical.

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