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Review

Selective Internal Radiation Therapy (SIRT) as Conversion Therapy for Unresectable Primary Liver Malignancies

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Key Words
Cholangiocellular carcinoma · Hepatocellular carcinoma · Radioembolization · Surgery · Yttrium-90

Abstract
Background: Many patients with primary liver cancers are not candidates for surgery, and systemic therapies are seldom effective. Selective internal radiation therapy (SIRT) has been shown to obtain partial and even complete response in unresectable primary tumors. As a "side effect", SIRT can induce contra-lateral liver hypertrophy. Tumor response to SIRT can be sufficient to allow disengagement from normal vital structures whose involvement is the cause of the initial unresectability. The contra-lateral hypertrophy can thereby increase the future liver remnant (FLR) volume to over the safe threshold so that extended hepatectomy can be performed. ***Summary:*** A review of the available literature was performed to assess the tumor response and liver hypertrophy that can be expected after SIRT, in order to de-

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lineate whether SIRTcan play a role in conversion therapy for resectability of primary liver malignancies. ***Key Message:*** Available data suggest that SIRT in unresectable hepatocellular and cholangiocellular carcinomas can provide a considerable down-sizing of the tumors to possibly allow resection. Hypertrophy of the contra-lateral lobe represents a favorable collateral effect that can help in achieving safer subsequent major hepatectomy. In patients whose FLR volume represents the only surgical concern, portal vein embolization remains the treatment of choice.

Introduction

A liver resection with negative margins is the only potentially curative treatment in the majority of patients with primary malignant disease, either from hepatocellular carcinoma (HCC) or cholangiocellular carcinoma (CCC) [1, 2]. Even in cases of tumor recurrence, surgery can still provide acceptable safety and comparable long-term survival rates to those after their first hepatectomy [3–5]. When evaluating patients for resection, two main aspects have to be considered to disqualify them from surgery resulting from an unresectable tumor. The first is represented by the close proximity of the tumor to normal vital hepatic structures such as the portal venous bifurcation, the bile duct bifurcation and/or the hepatic veins, which can make any type of intervention impossible. In these clinical circumstances, Selective internal radiation therapy (SIRT) radio-embolization (RE) with Yttrium-90 (Y90)-labeled microspheres is currently adopted in a palliative setting for unresectable liver cancers [6, 7]. SIRT has been shown to obtain partial and even complete response in unresectable primary and secondary tumors, demonstrating a good safety profile and achieving a survival benefit [6–8]. The second aspect is represented by the presence of an inadequate future liver remnant (FLR), which is imperative to avoid post-hepatectomy liver failure and premature death [9]. In this regard, portal vein embolization (PVE) is commonly performed to induce contra-lateral hypertrophy, allowing for safe major hepatectomy [9]. As a favorable collateral effect, SIRT has also been shown to induce liver hypertrophy of the untreated segments [6–8]. The aim of the present review is to explore the possibility of considering SIRT as conversion therapy for unresectable HCC/CCC, taking primarily into account the tumor response rates and, secondly, the increase in FLR volume achievable with RE in comparison to what can be obtained with PVE.

Tumor Response after SIRT of Primary Liver Tumors

The tumor involvement of normal vital hepatic structures is a common cause of unresectability. The possibility of obtaining an objective tumor response through SIRT, by shrinking the tumor and disengaging it from such structures can increase the chance of performing a hepatic resection [10]. Table 1 shows a summary of the response rates for CCC [11–19] derived from the current literature; one additional study was retrieved and reported separately [20]. Data regarding HCC were also summarized with some overlap of studies [21–31]. Taking the collated results together, a wide range of partial response (PR) rates can be estimated for CCC, from between 4.7% to 82.3%, with most of the literature reporting a PR of around 25–35% (RECIST [Response Evaluation Criteria in Solid Tumors] criteria), but with very low chances of obtaining a complete response (CR) [11–19]. However, some studies have reported necrosis of target lesions that can be more than 50% in up to 75% of CCCs

Table 1. Summary of literature reporting response rates of HCC/CCC after SIRT

Author (year)	Patients n°	SIRT modality	Tumor response criteria	Tumor Response rate	Median OS (mo)
Cholangiocarcinoma					
Soydal (2015) [11]	16	Resin	RECIST	PR: 30%	9.8
Filippi (2015) [12]	18	Resin	RECIST	PR: 82.3%	14.8
Camacho (2014) [13]	21	Resin	RECIST mRECIST EASL	PR: 4.7% PR: 62% PR: 9.5%	16.3
Rafi (2013) [14]	19	Resin	RECIST	PR: 11%	11.5
Mouli (2013) [15]	46	Glass	WHO	PR: 25%	14.6 (solitary) 5.7 (multifocal)
Hoffmann (2012) [16]	33	Resin	RECIST	PR: 36%	22
Haug (2011) [17]	26	Resin	RECIST	PR: 22%	11.7
Saxena (2010) [18]	25	Resin	RECIST	PR: 26%	9.3
Ibrahim (2008) [19]	24	Glass	WHO	PR: 27%	14.9
HCC					
Mazzaferro (2013) [21]	52	Glass	EASL	CR: 9.6%; OR: 40.4%	15
Salem (2011) [22]	123	Glass	WHO/RECIST EASL	OR: 49% OR: 72%	20.5
Hilgard (2010) [22]	108	Glass	WHO/RECIST EASL	OR: 41% (CR 6%; PR 35%) OR: 40% (CR 3%; PR 37%)	16.4 10 (PVTT)
Salem (2010) [24]	291	Glass	EASL	OR: 57% (CR 23%; PR 34%)	17.2 (Child-Pugh A) 7.7 (Child-Pugh B)
Kooby (2010) [25]	27	Resin	WHO/RECIST	PR: 11%	6
Carr (2010) [26]	99	Glass	WHO/RECIST	OR: 41% (CR 3%; PR 38%)	11.5
Lewandowski (2009) [27]	43	Glass	WHO/RECIST EASL	PR: 61% (CR 0%) OR: 86% (CR 47%; PR 39%)	35.7
Kulik (2008) [28]	108	Glass	WHO/RECIST EASL	PR: 42% RR: 70%	NR
Sangro (2006) [29]	24	Resin	WHO/RECIST	DC: 100% RR: 23.8%	7
Salem (2005) [30]	43	Glass	WHO/RECIST EASL	PR: 47% PR: 79%	24 (Okuda I) 13 (Okuda II)
Carr (2004) [31]	65	Glass	WHO/RECIST	PR: 38.4%	21 (Okuda I) 10 (Okuda II)

OS=overall survival; OR (PR+CR)=objective response; DC=disease control; RR=reduction rate; WHO=World Health Organization; mRECIST=modified RECIST; EASL=European Association for the Study of the Liver; PVTT=portal vein tumor thrombosis.

thereby leading to the down-sizing of the tumor [15, 19]. For HCC, the CR rate is reported to be about 10% [21] with an objective response rate (RECIST) of about 40% [21–31]. It can be hypothesized, in the best clinical scenario, that a partial/objective response can be sufficient to induce the disengagement of the tumor from vital hepatic structures, which would

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otherwise represent the main surgical contraindication [20]. To the best of our knowledge, only one study from Rayar et al. [20] was specifically aimed at verifying the conversion rate from unresectability to resectability of CCC. In 37 patients with unresectable CCC, hepatectomy was finally performed in eight cases (21.6%), all with tumor-negative margins [20]. Other surgical experiences after RE have been reported in the setting of neoadjuvant therapy rather than conversion therapy. In the study by Mouli et al.[15], five out of 46 patients with CCC were subsequently resected (10.8%). Regarding HCC, still in the setting of neo-adjuvant therapy, in the 2010 study by Salem et al. [22], only two out of 291 patients with HCC were subsequently resected (1.6%) and 32 were transplanted (11.0%), respectively. Apart from down-staging possibilities allowing liver transplantation, the available literature suggests that RE can be followed by curative surgical treatment.

Volumetric Changes after SIRT

Along with studies demonstrating good tumor response rates after SIRT, several reports on volume changes in treated and untreated liver areas have been published in recent years. The most relevant aspect is that RE is able to induce contralateral hypertrophy. To date (as of November 2015), seven full articles and one abstract attempted to describe the time-dependent changes in liver volume [32–40]. A detailed list of collated studies is reported in Table 2. Taking available data together, even if obtained at different time-points after SIRT, it can be estimated that a maximum hypertrophy above 40% of the untreated segments can be expected. The optimal time to measurement of FLR is more complicated to ascertain. The studies by Fernandez-Ros et al. [35] and Vouche et al. [36] have suggested that the kinetics of post-Y90 hypertrophy are slow, with gradual increases in volume, and without a clear plateau. The latter study reported 45% hypertrophy at nine months, whereas the former study reported a similar figure at about six months, suggesting that other factors can influence the degree of growth that can be achieved. Of note, in the study by Vouche, of 83 patients deemed unresectable before SIRT , five subsequently underwent hepatic resection (6.0%). Considering all the available information, it can be summarized that the literature reports an increase in the FLR at three months after RE ranging between 21 to 32%; the longer the follow-up, the greater the amount of hypertrophy that can be obtained.

These studies reported on the phenomenon of post-SIRT hypertrophy as the primary outcome, but a consistent finding was that hypertrophy of the untreated lobe is accompanied by a corresponding decrease in size of the tumor-bearing hemi-liver, resulting in no net change in the liver volume. This suggests that SIRT results in both good local tumor control, consistent with previous studies reporting on oncological outcomes, and an increase of the FLR.

SIRT Versus PVE

Since its first description in 1986, PVE has been commonly adopted when faced with an inadequate FLR volume, with high technical and clinical success rates [41–43]. The morbidity is low but the local tumor progression after PVE can be a pending cause of unresectability, possibly due to the increased arterial supply to the tumor in the embolized hemiliver [43, 44]. In the absence of close proximity or tumor engagement of normal vital hepatic structures, and when the only surgical concern is represented by an inadequate FLR volume, upfront hemihepatectomy after PVE is considered as the treatment of choice. This approach

Table 2. Summary of literature reporting volumetric changes after SIRT

Author (year)	Patients n°	Tumor types	SIRT modality	Area of Y90 treatment	Hypertrophy of untreated liver
Bishay (Abstract; 2015) [32]	15	HCC: 33.3% CCC: 26.7% Other: 40%	Resin: 100%	Right lobe: 100%	Maximal increase of 30.7% at 6 months; 3 months: 29.1%.
Theysohn (2014) [33]	45	HCC: 100%	Glass: 100%	Right lobe: 100%	Maximal increase of 50.5% at 6 months; 3 months: 45.4%
Teo (2014) [34]	17	HCC: 100%	Resin: 100%	Right lobe: 100%	Mean FLR increase of 42.3% at a median of 5 months of follow-up
Fernández-Ros (2014) [35]	83	HCC: 62.7% CCC: 4.8% Other: 32.5%	Resin: 100%	Right hemi-liver: 72.3% Left hemi-liver: 16.9%	Maximal increase of 45.0% at 6.5 months; 3 months: 18.0%
Vouche (2013) [36]	83	HCC: 80.7% CCC: 9.6% Other: 9.7%	Glass: 100%	Right lobe: 100%	Maximal increase of 45% after 9 months from SIRT; 3 months: 24%
Ahmadzadehfar (2013) [37]	24	mCRC: 62.5% Other mets: 37.5%	Resin: 100%	Right lobe: 100% (7 pts subsequent left lobe)	Maximal increase of 47.0% observed after a median of 44 days from SIRT.
Edeline (2013) [38]	34	HCC: 100%	Glass: 88.2% Resin: 11.8%	Right hemi-liver: 67.6% Left hemi-liver: 32.4%	Maximal increase of 42% at a median of 6.5 from RE; 3 months: 29%
Garlipp (2013) [39]	26	mCRC: 46.2% Other mets: 53.8%	Resin: 100%	Right lobe: 100%	Observed increase at a median of 46 days: 29% (median)
Gaba (2009) [40]	20	HCC: 85% CCC: 15%	Glass: 100%	Right lobe: 100%	At a mean of 18 months follow-up the median increase was of 40%

mCRC=colorectal-cancer liver metastases; mets=metastases.

does not only have greater clinical evidence of effectiveness [43], it can be considered as the most cost effective, given the high costs of SIRT [45]. However, in the presence of involvement of non-expendable anatomical hepatic structures during surgery, it seems reasonable to proceed with SIRT knowing that contra-lateral hypertrophy can be obtained. In this regard, only one study [39] has to date, attempted a direct head-to-head comparison between SIRT and PVE in terms of liver hypertrophy. Garlipp et al. [39] performed a matched-pair analysis of patients with secondary liver malignancy confined to the right hemi-liver. Patients were well matched for baseline FLR, a history of platinum-based chemotherapy, platelet count, and 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% and SIRT: 29.0%) within a shorter median time frame (PVE: 33 days, range 24–56 days; SIRT: 46 days, range 27–79 days). Tumor growth rates in both arms were not reported in this study. Other factors known to interfere with the regenerative capacity of the liver, such as liver cirrhosis and portal hypertension, were excluded from the analysis, making the results more reliable. Of note, in the analysis of the initial 35 patients included in this study, 50% of subjects who had a baseline FLR ratio less than 25% showed an increase above 25% at follow-up, suggesting that volume hypertrophy induced by SIRT may be sufficient to achieve an adequate FLR volume in a con-

siderable proportion of patients. The authors suggested that RE with the aim of inducing hypertrophy may be preferable to PVE in patients whose lesions are at risk of becoming unresectable due to invasion of normal vital structures if tumor progression occurs. In patients who need only a maximum FLR volume increase, without immediate threatening of the potential plane of resection, PVE may remain the treatment of choice. At this point, the safety of the two procedures should be mentioned. Taking into consideration the largest SIRT experience published to date for primary tumors, a transient increase in bilirubin within the first month after RE has been observed in about half the cases, persisting at three months in only 5.8% of patients, but without irreversible liver failure directly ascribed to SIRT [8]. These figures are slightly higher than the all-causes major complication rates reported after PVE (2.5%) [43, 44].

Area for Future Surgical Development

As stated previously, patients receiving SIRT are not typically surgical candidates. As the final result of RE, the main benefit obtainable in patients with HCC/CCC, initially deemed unresectable, could be represented by the down-sizing of the tumor, disengagement of the tumor from normal vital hepatic structures, and allowing potential subsequent major hepatectomy. It should be noted that the response to SIRT can effectively cause the tumor to become detached from blood vessels, but that the fibrotic effect on the surrounding parenchyma can still represent a technical problem in disengaging the tumor from such structures. This aspect must be considered when evaluating resectability after RE. The simultaneous increase in the FLR volume should be considered as a favorable "side effect" of a treatment primarily designed to prevent tumor progression in the embolized lobe. All studies published to date, except one, have reported the number of patients successfully resected (or transplanted) after RE in the setting of a neo-adjuvant approach, which is an additional aspect to the effectiveness of SIRT. However, there is still a scarcity of literature from an intention-to-treat point of view aimed at verifying tumor conversion rates after SIRT. In this regard, unresectability must be clearly defined to delimit the field of SIRT as such a therapy. Unresectable cancers are those that cannot be removed due either to the number of metastatic foci, or because the tumor is in a surgical danger zone, with (or without) an insufficient FLR to avoid postoperative liver failure. The unresectability criteria used in the study by Garlipp et al. [39] can fulfil these semantic features: patients considered having unresectable local disease were candidates for extended hepatic resections with insufficient FLR and/or with close proximity of the tumor to normal vital structures (portal vein bifurcation/bile duct bifurcation/inferior vena cava or supra-hepatic veins) that can not be preserved or reconstructed during surgery. Such patients should be enrolled in a study of the effectiveness of SIRT as a conversion therapy. It must be emphasized that SIRT cannot replace PVE in patients whose FLV represents the only surgical concern considering the need to preserve a FLR of at least 30% in patients without chronic liver disease and of at least 40% in patients with chronic liver disease [9].

Conclusions

The available literature suggests that in a considerable proportion of patients with primary liver tumors, a good response can be expected after SIRT. Even if incomplete, a PR may also be sufficient to disengage the tumor from normal vital structures, allowing for sub-

sequent surgical resection. Multidisciplinary committees must include expert hepatobiliary surgeons, not only to judge the unresectability of tumors, but also to judge the possibility of performing hepatectomy once down-sizing of the tumor (as well as hypertrophy of the contra-lateral lobe) is achieved. Intention-to-treat studies in this regard are warranted.

Disclosure

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Conflict of Interest

None declared.

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