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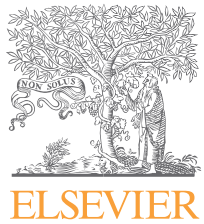

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Bridging and downstaging to transplantation in HCC

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1. Introduction

Selective internal radiation therapy (SIRT) with yttrium-90 microspheres is a promising treatment modality in patients with either primary or metastatic liver tumours. It is usually recommended for patients with advanced disease who are not candidates for local ablation, surgical resection, liver transplantation (LT) or for patients who have failed other treatments. [1]

2. Patient population

Since April 2007, 177 patients with unresectable and untransplantable HCC have been considered for SIRT at the General Surgery and Transplantation Center of the National Institute of Infectious Disease "L. Spallanzani". Treatment was conducted in cooperation with the Interventional Radiology and Nuclear Medicine Unit of the National Cancer Institute "Regina Elena". Eligibility for SIRT was reviewed by a multidisciplinary panel. Pre-LT screening included: a review of the patient's clinical history (age, risk factors, comorbidities), diagnostic imaging by MRI and CT, determination of the level of underlying liver disease according to Child–Pugh and Model for End Stage Liver Disease (MELD) and disease stage according to UNOS Tumor-Node-Metastases (TNM) and Barcelona Clinic Liver Cancer (BCLC) classifications. The Eastern Cooperative Oncology Group (ECOG) performance status was also assessed for each patient.

Patients were considered eligible for SIRT if they presented with: preserved liver function with normal bilirubin, INR < 1.2 and absence of ascites and with ECOG performance status '0' or '1'. SIRT is performed using

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Table 1 – Baseline patient characteristics and HCC features in 7 transplant recipients

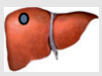
Pt no.	Age	HCC location	Vascular thrombosis	Milan criteria	Interval SIRT-LT (mo)
1	63		–	OUT	12
2	64		YES	OUT	30
3	40		YES	OUT	14
4	50		–	IN	2
5	59		–	IN	8
6	48		–	OUT	9
7	48		–	OUT	13

Table 2 – Radiological and pathological features before and after SIRT in 7 transplant recipients

Pt no.	Radiological Milan		Pathological Milan	Microvascular invasion
	Before Y-90	After Y-90		
1	5 nodules	IN	4 nodules (0.5, 0.7, 1.0, 1.7 cm)	NO
2	2 nodules (8 cm, 1 cm)	IN	2 nodules (0.5, 0.5 cm)	NO
3	1 nodule (3 cm)	IN	No HCC	NO
4	1 nodule (3 cm)	IN	1 nodule (1.7 cm)	NO
5	2 nodules	IN	5 nodules (1.0, 1.5, 2.0, 2.5, 3.5 cm)	NO
6	5 nodules	IN	5 nodules (0.5–1.2 cm)	NO
7	4 nodules	IN	3 nodules (0.5, 0.5, 1.8 cm)	NO

^{90}Y resin microspheres (SIR-Spheres, Sirtex Medical, Sydney, Australia). All patients had pretreatment mesenteric angiography and 99Tc-macroaggregated albumin scanning for the assessment of non-target distribution of the ^{90}Y microspheres and the embolisation of aberrant vessels. All patients were followed-up for toxicities and adverse events. During follow-up all patients were monitored by CT scans at 1 month and subsequently at 3-month intervals.

Overall 36 of 177 patients with intermediate–advanced stage (BCLC B and C), who received SIRT were considered possible candidates for LT. Patients were selected for LT based on: age <65 years, downstaging to within Milan criteria for number and size of nodules, and an absence of extra-hepatic spread or gross vascular invasion.[2] Among the 36 patients considered for LT after SIRT, 19 were excluded from the LT programme due to drug or alcohol abuse, HIV infection beyond the LT criteria or disease progression. Of the remaining 17 patients, SIRT had been used to downstage 13 patients and as a bridging treatment for LT in 4 patients. Ten patients were treated with SIRT before being put on the LT waiting list and 7 patients received SIRT while on the waiting list because of tumor progression.

3. Transplantation

Seven patients had a liver transplantation post-SIRT. Six patients had cadaveric donor liver transplantation and 1 patient received living donor liver transplantation. Analyses of the baseline characteristics of these patients prior to SIRT (Table 1) show that two patients had had neoplastic infiltration of a portal vein branch which disappeared after SIRT. Evaluation of the explanted livers found that one patient did not meet the Milan criteria (patient 5; Table 2). Side effects after SIRT included: fatigue, ALT increase and worsening of hepatic function, and one case of hepatic decompensation and the development of ascites. All patients were transplanted with the so-called “piggy back” technique without any complications to the vascular anastomosis. SIRT induced significant atrophy of the liver targeted area with compensatory hypertrophy of the untreated liver and appeared to increase the difficulty of the inferior vena

Table 3 – Treatment follow up of the 7 transplant recipients

Pt no.	Age	MELD	Follow up		Status
			LT	SIRT	
1	63	12	36	48	Alive
2	64	10	27	55	Alive
3	40	10	17	30	Alive
4	50	11	16	18	Alive
5	59	8	4	12	Alive
6	48	10	3	12	Alive
7	48	13	11	24	Alive

cava dissection during LT. All patients were alive at follow-up as shown in Table 3.

4. Conclusions

In summary, SIRT using intra-arterial ^{90}Y-labelled microspheres has proved to be one of the most effective locoregional techniques for treating advanced HCC at our centre. As outlined above, a certain proportion of patients initially excluded from the transplant list were downstaged following SIRT and became potential candidates for LT.

Our experience with LT after SIRT is limited to 7 cases, but shows that SIRT can be utilised in the liver transplant setting as a bridge to transplant, controlling tumour progression for those on the waiting list. Alternatively, SIRT can be used to downstage tumours and/or achieve resolution of vascular invasion, thereby enabling access to the organ waiting list for those outside the conventional criteria.

In conclusion, SIRT represents an important evolution of our downstaging and bridging techniques and currently plays an integral role in the management of our patients with HCC before transplantation.[3,4] This procedure may ultimately lead to an evolution in our selection of transplant candidates and the allocation of livers; although additional long-term follow-up data are needed.

Conflict of interest statement

The authors have no conflict of interests.

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