

Experiences in Hepatic Surgery and Transplantation after Radioembolization

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Abstract

Yttrium-90 microspheres radioembolization has shown to be an effective modality of treatment in patients with primary or metastatic liver tumours [1-4]. It is usually offered to patients with advanced liver cancers. However, surgical experience after radioembolization is very limited to anecdotal cases mainly related to hepatocellular carcinoma. We have treated patients with hepatocellular carcinoma or liver metastasis mainly from colon, breast, melanoma and neuroendocrine tumours. In our experience after such treatment we were able to downstage the tumour to surgery only in the case of hepatocellular carcinoma. Five patients had liver transplantation and 1 had right hepatic resection after Yttrium-90 microspheres radioembolization.

Of note 2 patients had neoplastic infiltration of a portal vein branch which resolved after treatment with Yttrium-90 microspheres radioembolization. The extra-hepatic spread was ruled out and later they were both transplanted.

Here we report our initial single center experience with Yttrium-90 microspheres radioembolization as down-staging and bridging method for hepatocellular carcinoma prior liver surgery, resection or liver transplantation.

Keywords: Hepatocellular carcinoma; Surgical perspective; Downstaging procedure; Liver transplantation; Yttrium-90 microspheres radioembolization

Abbreviations: HCC: Hepatocellular Carcinoma; MELD: Model for End Stage Liver Disease; RE: Radioembolization; Y90-RE: Yttrium-90 microspheres Radioembolization; LT: Liver transplantation; TACE: trans arterial chemoembolization; TNM: Unos tumor-node-metastases; BCLC: Barcelona Clinic Liver Cancer classifications; ECOG: Eastern Cooperative Oncology Group; INR: International Normalized Ratio; MRI: Magnetic Resonance Imaging; ALT: Alanine Transaminase; HCV: Hepatitis C Virus; AFP: Alpha Feto Protein; MBq: Mega Becquerel; CT: Computed Tomography; PET: Positron Emission Tomography; GIST: Gastro Intestinal Stromal Tumour

Introduction

Yttrium-90 microspheres radioembolization (Y90-RE) has shown to be an effective modality of treatment in patients with primary or metastatic liver tumours [1-4]. It is usually offered to patients with advanced liver cancers who are not otherwise candidates for local ablation, surgical resection, liver transplantation (LT) or have failed other previous treatment as TACE or chemotherapy. For such reasons, surgical experience after RE is very limited to anecdotal cases or small series [5-9].

With regard to hepatocellular carcinoma (HCC) there are few reports about LT [5-9]. Recently it has been reported a case of liver metastases who underwent hepatic resection after downstaging with RE [10].

In the last five years we have treated many patients with HCC or liver metastasis mainly from colon, breast, melanoma and neuroendocrine tumours. In our experience after such treatment we were able to downstage the tumour to surgery only in the case of HCC.

Here we report our initial single center experience with Y90-RE as down-staging method for HCC prior liver surgery, resection or LT.

Materials and Methods

Since April 2007, 129 patients with unresectable and untransplantable HCC were treated with Y90-RE at San Camillo Hospital in Rome in cooperation with the Interventional Radiology and Nuclear Medicine unit of National Cancer Institute "Regina Elena" of Rome.

Prior RE, the indication to treatment was discussed by a multidisciplinary panel of liver and transplant surgeons, anesthesiologists, interventional radiologists and hepatologists. Pre-LT assessment consisted of demographics, risk factors, comorbidities, diagnostic imaging by MRI and CT, determination of the level of underlying liver disease according to Child-Pugh, Model for End Stage Liver Disease (MELD), Unos tumor-node-metastases (TNM), Barcelona Clinic Liver Cancer (BCLC) classifications. The Eastern Cooperative Oncology Group (ECOG) classification was calculated for each patient. At our center the baseline characteristics of patients suitable for RE are the following: preserved liver function with normal bilirubin, INR <1.2 and absence of ascites and with ECOG performance status 0 or 1. In our experience the RE with Y90 is well tolerated in these patients.

RE was performed using Y90 resin microspheres (SIR-Spheres,

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Sirtex Medical, Sydney, Australia), all patients had pretreatment mesenteric angiography and ^{99}Tc -macroaggregated albumin scanning for nontarget embolization. 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 scans were done every 3-month intervals. Imaging reads were done by three radiologists, all imaging were reviewed from the last CT scan prior Y90 treatment. From the study population, 15 patients with advanced HCC were down-staged after RE, 14 patients were considered for LT and 1 for hepatic resection. The patients were selected for LT on the basis of the following criteria: age less than 65 years, absence of extra-hepatic spread, absence of gross vascular invasion, down-staging within Milan criteria for number and size of nodules [11,12].

Results

Fourteen (11%) patients with HCC at intermediate-advanced stage (BCLC B and C) met the above criteria after Y90-RE for LT. Twelve patients were treated with the intention of downsizing the tumor within the criteria and 2 were treated as bridge in order to pursue LT. Eight patients were treated before listing and 6 were treated while on the waiting list because of tumor progression.

In the group of those treated before listing, 6 (75%) patients were down-staged within the criteria (2 transplanted and 4 waiting for LT), 2 (25%) had disease control but later died of progressive liver failure on active waiting list.

In the group of those treated on the waiting list, 2 (33%) patients were transplanted, 3 (50%) died of liver failure on the active waiting list and 1 (16.7%) who was not down-staged within the criteria and is alive with stable disease 14 months after Y90-RE.

Of note in both groups there were 2 patients who had neoplastic infiltration of a portal vein branch. After treatment with Y90-RE in both patients disappearance of the thrombus was noted. The extra-hepatic spread was ruled out and later they were transplanted. Now they are both alive at 16 and 9 months after LT without signs of HCC recurrence. Furthermore 1 patient with an HCC 6 cm in diameter of the right lobe involving the inferior vena cava underwent a right hepatectomy 6 months after RE.

Side effects after RE were poor (fatigue, ALT increase, worsening of hepatic function) with only 1 case of hepatic decompensation and development of ascites.

In synthesis four patients had cadaveric donor liver transplantation after Y90-RE for HCC at intermediate-advanced stage (BCLC B and C). Here we report briefly our four transplanted cases.

Case Reports

Case 1

A 62-year-old male with HCV related cirrhosis with a MELD score of 10 was diagnosed with an unresectable advanced HCC in the right lobe (7.5 cm diameter) and an elevated alpha-fetoprotein (AFP) level >70,000 ng/mL. Macrovascular invasion of the right branch of the portal vein was confirmed by spiral computed tomography (CT) imaging.

The clinical case was discussed by a multidisciplinary panel and it was concluded that the patient was unsuitable for LT due to the size of the tumour and vascular invasion.

The patient received whole-liver treatment with an intra-arterial

infusion of ^{90}Y resin microspheres (SIR-Spheres; Sirtex Medical Ltd, Sydney, Australia). The radioembolization activity administered was 1702 MBq. The treatment was well tolerated. Follow-up 1 month later revealed a positive tumour response. AFP level 2 months after treatment was 15 ng/mL. CT imaging at 3 months post-radioembolisation documented a complete radiological response with total regression of the primary lesion and portal thrombus.

The patient was then regularly seen in the outpatient clinic for 22 months following treatment, during which time no other lesions developed in the liver. The patient was re-assessed and considered to be a suitable candidate for LT. Transplant assessment performed by positron emission tomography (PET), CT and bone scans did not reveal new HCC lesions within and outside the liver. In March 2009, the patient was placed on the transplant waiting list. While waiting for transplantation, a CT scan showed a suspected hypervascularized lesion at the site of the previous treated lesion, measuring <1 cm. A second segmental-liver treatment with ^{90}Y resin microspheres was performed (1665 MBq). The patient developed liver dysfunction (ascites and cholestasis with bilirubin which peaked at 7 mg/dl) which resolved after 2 months of conservative treatment. Later the patient was successfully transplanted by the piggy-back technique without venovenous bypass. Transplant surgery was unexpectedly more difficult than normal due to the presence of fibrous tissue between the inferior vena cava and the caudate lobe where the HCC was located probably due to the RE and resulting oedema. The post-operative course was uneventful and the patient was discharged on day 14 on tacrolimus (Prograf; Astellas Pharma) and prednisone. Pathological examination of the explanted liver showed two 5 mm HCC nodules surrounded by fibrous tissue (Figure 1). The lymph nodes were negative and no portal vein thrombus was found.

Case 2

A 56 year-old man with HCV and alcoholic related cirrhosis presented with 4 nodules of HCC at CT scan (48, 16, 18 and 12 mm in diameter) and a MELD score of 11. Alpha-fetoprotein was 6 ng/ml. At this time he was considered out of Milan criteria for size and number of nodules and then was referred for Y90-RE treatment. The patient received whole-liver treatment with an intra-arterial infusion of ^{90}Y resin microspheres. The radioembolization activity administered was 1650 MBq. A CT scan at 1 and 3 months after treatment showed a downstaging of the bigger lesion from 48 mm to 17 mm. RE was well tolerated with mild worsening of hepatic function characterized by an increment of total Bilirubin up to 3 mg/ml without clinical decompensation.

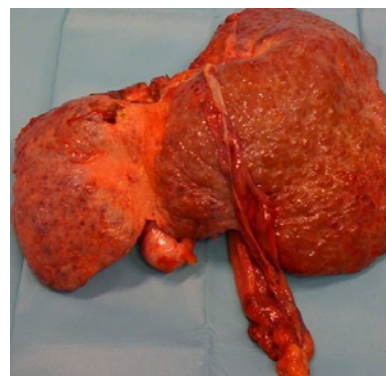


Figure 1: The explanted whole liver showed a fibrotic area in the right liver with a compensatory left liver hypertrophy.

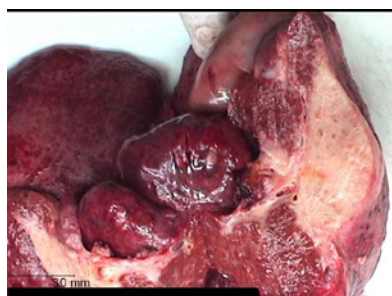


Figure 2: The explanted liver showed on the cutting surface a fibrotic area without macroscopic findings of HCC.

| Class 1: Potentially resectable or transplantable | Class 2: Difficult to resect or to transplant | Class 3: Certainly not resectable or transplantable |
|---|---|---|
| Child A | Child A to C | Child C |
| Out of Milan Criteria | Out of Milan Criteria | Multifocal disease |
| No extra-hepatic disease | No extra-hepatic disease | Extra-hepatic disease |

Table 1: Classification of the HCC patients candidate to Y90-RE.

He was then followed-up for HCC progression and 10 months after the RE the patient started the workup for transplantation and he entered the list with 3 nodules within Milan criteria. The patient was transplanted, the post-operative course was uneventful and was discharged on day 21 on tacrolimus (Prograf; Astellas Pharma) and prednisone. In the explanted liver 4 nodules of HCC were found, the bigger with a complete necrosis and fibrosis measured 17 mm and the other 3 nodules measured less than 1 cm. Two years after LT the patient was found with a solid palpable mass measuring 20 cm in diameter located in the pelvis. He had removal of the mass with associated small bowel resection. Histology revealed a GIST of the ileum. The follow-up is now of 30 months from LT without any recurrence of HCC.

Case 3

A 46 year-old man with HCV-related cirrhosis and severe portal hypertension with a MELD score of 14 was referred to us for LT. He was then assessed and listed. Due to his permanence on the waiting list after 7 months he developed a small nodule of HCC of segment VI of 15 mm in diameter. First it was decided not to treat the nodule due to its small size. After 5 months, while on the waiting list, the nodule became bigger reaching 3 cm in diameter. He underwent Y90-RE which was well tolerated. CT scan at 1 month showed a decrement in size to 17 mm in diameter. Two months later the patient was transplanted with a MELD score of 17. Pathological examination showed complete necrosis of HCC nodule. He is now 8 months after LT in good conditions without HCC recurrence.

Case 4

A 40 yrs old man with HCV and alcohol related cirrhosis was evaluated for liver transplantation after a first episode of variceal bleeding and because of repeated hospital admissions for hepatic encephalopathy. He had a Meld score of 14. During his permanence on the waiting list and due to his relatively good hepatic function an antiviral treatment was started reaching a virological response at the 6th month (genotype 3a). Two months later the patient developed a 22 mm HCC on the right lobe with radiological signs of segment VI portal vein branch macro-vascular invasion. He was then removed from the list and was referred for Y90-RE that determined a complete necrosis of

the nodule with a size reduction and patency of segment VI portal vein branch. RE treatment was well tolerated. CT scan at 1-3 and 9 months and a PET scan showed stable disease without progression within and outside the liver. Furthermore the CT scan showed atrophy of the right liver and a compensatory hypertrophy of the left liver. We decided to put the patient again on the waiting list and he was later transplanted 13 months from RE. At this time MELD score was 17. Pathological examination showed an area of extensive fibrosis, HCC was not found (Figure 2) and neither neoplastic portal vein thrombi. The follow-up is now 9 months without tumour recurrence.

Discussion

RE using intra-arterial ⁹⁰Y-labelled microspheres has proved to be one of the most effective locoregional techniques for treating advanced liver tumours. It is offered to patients with advanced liver cancers who are not otherwise candidates for local ablation, surgical resection, liver transplantation (LT) or have failed other previous treatment as TACE [1,2]. Good indications for RE are primary hepatic tumors as HCC and liver metastases from breast and neuroendocrine tumors. It can be utilized even in patients with other type of liver metastases such as those from melanoma and gastrointestinal tumours when firstline chemotherapy has failed.

For such reasons, hepatic resection after RE is very limited to anecdotal cases [5-9]. Recently it has been reported a case of liver metastases who underwent hepatic resection after downstaging with RE [10].

With regard to hepatocellular carcinoma (HCC) there are few reports about LT after RE and downsizing within acceptable criteria [13]. Hepatic surgery for HCC after RE is so far a rare event and this can be explained by the following reasons: a) HCC worldwide occurs on liver cirrhosis, b) patients undergoing RE have advanced HCC and when a positive response is obtained patients are considered for LT which is the curative and best surgical treatment of cirrhosis and associated HCC [14]. In the case of liver metastases these are considered for RE when they are unresectable and when a previous chemotherapy as failed.

In our experience we have observed that the surgeons play an important role in the selection and management of the patients with liver tumours that are potential candidates for Y90-RE. The indication to treatment with RE is confirmed by a multidisciplinary panel where the figure of surgeon is of paramount importance in designing the treatment strategy of patients with liver tumours [15]. The surgeon attending the multidisciplinary panel should be an expert of both liver surgery and liver transplantation and furthermore of target liver therapies. The surgeon should be consulted first in order to determine if the patients is a potential candidate to radical treatments such as liver resection or liver transplantation or should be considered for other treatments.

We have classified HCC patients undergoing RE in three classes as showed in Table 1: 1) Potentially resectable or transplantable, 2) Difficult to resect or to transplant, 3) Certainly not resectable or transplantable.

From our point of view the field of HCC after RE is much more attractive. As shown by our experience a certain proportion of patients initially excluded from the transplant are downstaged and may undergo LT. Our experience with LT after Y90-RE is limited to four cases but it shows that RE can be utilized in the liver transplant setting as a bridge to transplant controlling tumour progression for those on the waiting

list or for the downstaging of tumours and/or resolution of vascular invasion enabling access to the organ waiting list for those outside the conventional criteria.

We want to make some clarifications on some technical problems encountered during the transplant surgery after RE. The RE induces a significant atrophy of the liver targeted area with compensatory hypertrophy of the liver untreated, this phenomenon was called, led by some experts in the field of RE, surgery targeted radiotherapy. Transplant surgery may results unexpectedly more difficult than normal due to the presence of fibrous tissue between the liver and diaphragm, or between the liver and inferior vena cava probably due to the RE and resulting oedema. In addition, the RE procedure requires occlusion with coils of the gastroduodenal artery which is generally used to make the arterial anastomosis of the transplant. We advice that the gastroduodenal artery is occluded distally so as not to impede the packaging of the anastomosis.

In conclusion, the Y90-RE is an important evolution of downstaging and bridging techniques and currently play an integral role in the management of patients with HCC before transplantation. This also represented an evolution for selection of transplant candidates and political allocation of livers.

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