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Safety and Efficacy of Multiple Sirt Treatments with Resin Microspheres® Y-90, Combined with Surgery as Bridge/Downstage to Hepatic Transplant: A Case Report and Literature Review

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Abstract

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and constitutes a major global health problem. Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) represents about 10% of total HCC, and it is by definition a highly heterogeneous tumor, which confers a negative impact on tumor prognosis compared to HCC. Selective Internal Radiation Therapy (SIRT) using yttrium-90 microspheres shows a good safety profile and local tumor control, and it is now considered among the therapeutic options for liver cancer downstaging before liver transplant (LT). We present the case of a young man with a diagnosis of hepatitis B cirrhosis and subsequent finding of advanced primary neoplasm with particularly aggressive histology of cHCC-CCA. The patient underwent two SIRT treatments in 6 months. The first SIRT treatment provided an adequate downstaging to surgery, then a successful SIRT retreatment after surgery, in a bridging purpose, allowed for liver transplantation, with complete necrosis at explant. We demonstrated the feasibility and safety of multi treatment approaches, with two successive SIRT treatments and surgery. We outline the efficacy of an aggressive downstaging strategy allowing a potentially curative therapy as liver transplant.

Keywords: Radioembolization; Y-90 microspheres; hepatocellular carcinoma; personalized dosimetry.

Introduction

HCC is a major global health problem, with 854,000 new cases and 810,000 deaths per year, one of the most frequent causes of cancer-related death globally [1, 2]. HBV infection remains the leading aetiology worldwide, along with alcohol and HCV, with increasing incidence metabolic risk factor [3]. HCC represents approximately 90% of primary liver cancers, approximately 10% of HCC have some histological features in common with cholangiocarcinoma (iCCA) [4]. Combined cHCC-CCA is a heterogeneous primary liver cancer that shows many phenotypes with features of both hepatocytic and cholangiocytic differentiation [5]. These neoplasms clinically and radiologically mimic HCC or iCCa. cHCC-CCA are very rare tumors comprising 1-5% of primary liver cancer, moreover, cHCC-CCA occurs in both cirrhotic and non cirrhotic liver [6]. The latest edition of WHO classification of 2019 defines them as a primary liver carcinoma with unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor [7]. In a recently published consensus paper, it was outlined the importance of mentioning that stem/progenitor cells are present. [8]. The substantial statement of the 2018 consensus was that primary liver cancer represents a spectrum of entities ranging from two extremes HCC and iCCA and includes cHCC-CCA [9]. Accordingly, their accurate diagnosis is of clinical importance as respective prognostic and therapeutic issues of HCC and iCCA are highly different. The histological diagnosis is often accidental, after a liver transplant or hepatic resection. The prognostic implications are, however, serious, as the risk of oncological recurrence in the case of major lesions (i.e. >3 cm) are significantly higher in the case of cHCC/iCCA than HCC [10].

Only 10% of patients will meet the criteria of potentially curative therapy with surgery or transplant at diagnosis. On the other hand, as the demand for organs surpasses supply, a patient can stay a long time in the waiting list. SIRT has recently entered the 2022 BCLC treatment recommendation update in

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the A stage, in patients not suitable for surgery, ablation or transplant with the aim of bringing more patients to curative therapy as hepatic transplant [11]. SIRT is a well-recognized therapy, it has been used for several years in the treatment of unresectable primary and secondary liver tumors in the BCLC B or C and has demonstrated a good control of the tumor in all the stage of BCLC in particular in intermediate stage [12]. IT is a highly selective locoregional treatment method capable of delivering a higher dose to the tumor than external radiation therapy, while minimizing systemic and normal hepatic parenchyma effects. Based on the intra-arterial delivery of Y90, a pure Beta radiation emitter, loaded onto microsphere of resine in our case (Sirtex Medical Europe Gmbh).

Case presentation

A 28-year-old patient, non cirrhotic inactive carrier for hepatitis B, with positive HBsAg and negative HBV DNA, presented for a routine follow-up in June 2019. The previous ultrasound in January 2019 was negative for liver lesions and did not show signs of liver cirrhosis. The patient had good performance status and normal liver function. As part of surveillance for HCC, alpha-feto protein (AFP) was determined and found to be high with 330 IU/ml. Ultrasound detected a large liver lesion and a subsequent computer tomography (CT) scan showed a multifocal HCC in segments V, VI, II (**Figure 1**) without significantly increased arterial enhancement (LI-RADS 3). The two lesions in segments V and VI had a diameter of 3.9 cm and 3.8 cm, respectively. Based on the size of the lesions and the location a vascular invasion was suspected. AFP increased to 1000 UI/ml within the following weeks. The patient was deemed eligible for SIRT in July 2019. The lesions in segments V and VI in the right lobe were treated with an activity of 1.5 GBq. At follow-up in October 2019 the nodules appeared to be reduced in size from 3.9 to 2.2 cm and 3.8 to 1.3 cm, respectively. With this successful downstaging, the patient met the criteria for resectability and underwent resection of the second segment soon after. Histologic evaluation shows features of cHCC-CCA. In December 2019 CT and magnetic resonance imaging (MRI) demonstrated signs of disease recurrence in the right lobe (**Figure 2**). It was decided to take the patient into consideration for a liver transplant and to perform a second SIRT end of February 2020 as a bridge to liver transplant. Dose calculation was performed with MIM SurePlan Liver 90Y voxel-based dosimetry software. The SPECT/ CT acquisitions of the work-up were used to determine the required activity of 1.88 GBq. With the software, it was possible to segment morphological images and through fusion and co-registration of these with nuclear-medical functional imaging, the target tissue could be defined. Radiation doses could be calculated and estimated with voxel dosimetry in the pre-treatment planning (**Figures 3** & **4**).

The deposition of the microspheres, in the second treatment, was optimal in the targeted liver segments V and VI as shown in the good match of the 99mTc-MAA SPECT/CT images and the posttreatment 90Y-bremsstrahlung SPECT/CT images (**Figures 5** and **6 A&B)**. Histology of the later surgically removed liver showed tumor necrosis, inflammatory cells at the edges of the necrotic areas, as well as microspheres (**Figure 7 A&B**). Liver transplant was performed in April 2020, but the post-transplant course was complicated by an episode of RAI 4/9 acute rejection (Banff scale), which required the use of high-dose steroids, and subsequent normalization of the transaminases. In the following twenty months the liver function was well under control, with no further alterations.

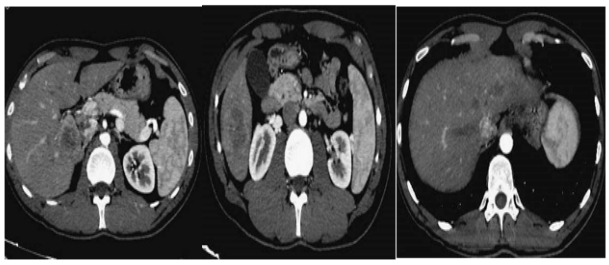

Figure 1: *Neoplastic lesions in segments five, six and II before the first treatment with SIR-Spheres Y-90 resin microspheres.*

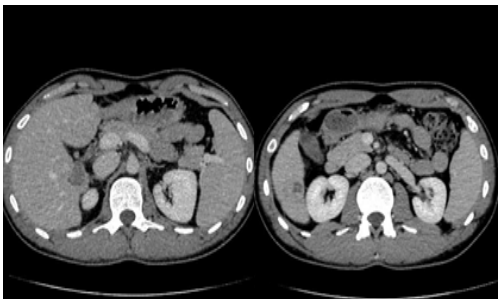

Figure 2: *Neoplastic lesions in segments five and six before second treatment with SIR-Spheres Y-90 resin microspheres.*

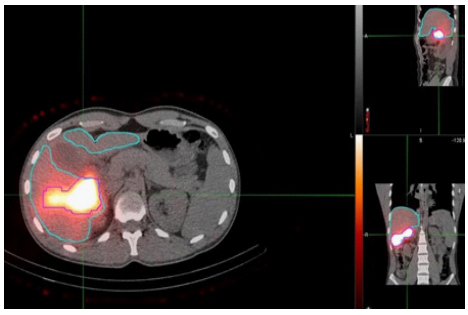

Figure 3: *Predicted doses based on MAA distribution by software simulation in the first treatment.*

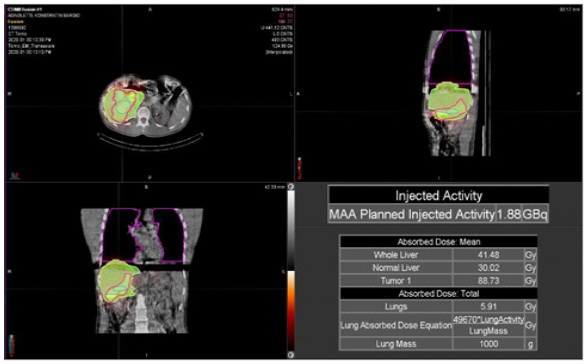

Figure 4: *Scaled injected activity and predicted doses based on MAA distribution by software simulation. Please note: Dose to tumor 1 was 88.73 Gy and represents the mean dose to the target area.*

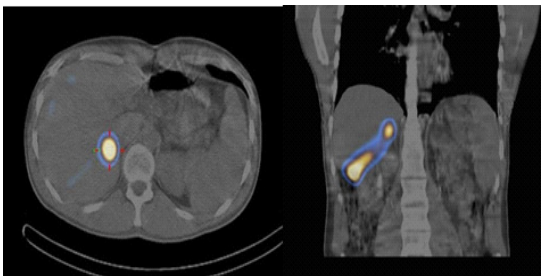

Figure 5: *SPECT/CT after selective injection of 99mTc-MAA in axial (A), and coronal (B) plane demonstrates good targeting of the tumor, no extrahepatic uptake.*

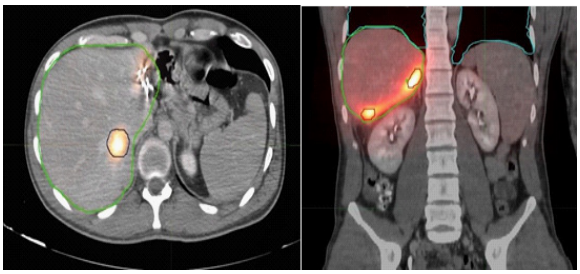

Figure 6: *SPECT/CT using the Bremsstrahlung 90Y emission after selective injection of resin microspheres in axial (A) and coronal (B) plane demonstrate good targeting of the lesion, no extrahepatic uptake.*

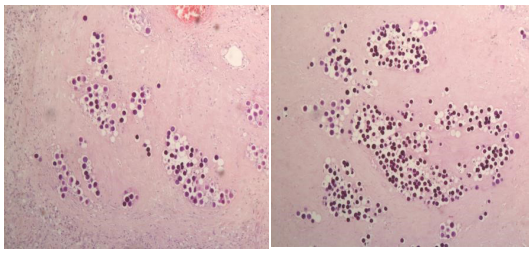

Figure 7: *Tissue samples of the explanted liver showing normal tissue and the tumor with necrosis and 90Y resin microspheres (A). At the edges of the necrotic areas, no viable tumor cells are present as well (B).*

Discussion

This case report illustrates how SIRT can be successfully used in the treatment of a patient initially deemed unsuitable for potentially curative therapy as resection or LT, and how an aggressive and multimodality approach is an important tool in the downstaging strategy. The epicrisis of the clinical case exposed demonstrates a very important concept when applied to this particular variant of HCC, recognized to be more aggressive and with limited access to LT. In the case of the treated patient, the use of an aggressive downstaging treatment schedule reduced the risk of oncological recurrence after transplant, making it comparable to that of HCC within the Milan criteria. The treatment with SIRT has now been included among the curative treatments of both hepatocarcinoma and cholangiocarcinoma; in our case, it has been demonstrated how this effectiveness has allowed not only the inclusion in the transplant list, but to significantly reduce posttransplant tumor recurrence. The oncological aggressiveness of the mixed variant of HCC is also caused by an often late diagnosis. As in the case of our patient, cHCC/CCa most often occurs in non-cirrhotic liver, therefore in patients not under active ultrasound or radiological surveillance. This makes even less feasible the initial transplant consideration and increases the importance of assessing the potential biological response of the neoplasm to locoregional treatments. Mazzafero demostrated in 2020 in the XXL trial that after effective and sustained downstaging of eligible hepatocellular carcinomas beyond the Milan criteria, LT improved tumor-free survival and overall survival compared with non-transplant therapies [13]. The previous guidelines 2018 suggest bridging to LT within the Milan criteria as a neoadjuvant therapy with the aim to limit the drop-out and the recurrences post LT, with low evidence, and with a strong grade of recommendation, particularly if the waiting time on the list is expected to be at least 6 months [2,14]. Progression after endovascular therapies seems to revest a prognostic role, and the treatment response a surrogate biomarker [15]. For the downstaging purpose, Ettorre et al demonstrated good results with SIRT [16]. A world review of 178 patients treated with SIRT mostly in a downstaging strategy shows promising results and a recent work of Salem group reports their experience of 207 transplants after SIRT in bridging and downstaging, with survival similar to non-oncologic transplant [17, 18]. Furthermore, after hepatic surgery, SIRT has proven to be a safe procedure, even after major hepatectomy [19, 20]. Hepatic function evaluation and accurate calculation of the liver absorbed dose with multi-compartimental analysis are mandatory [21]. In our case, we even performed safely the second SIRT at 6-month distance of the first one in the same territory without complications, with a dose to the normal liver of 30 Gy (Figure 2). In this case, we had a good targeting of the lesions demonstrated by a perfect match between pre-therapy 99mTc-MAA SPECT/CT and post-therapy SPECT/TC, with tumor absorbed mean dose of 88, 78 Gy, either predictive factors of good result [22]. We obtained a complete pathologic response at the histologic examination of the explanted liver. This data is important as we know that necrosis at explant is an independent factor of survival after transplant. It utterly confirms that the ablative propriety of SIRT fits the criteria of best treatment modality for bridging [23].

Conclusions

In this particular case of a young patient with extended disease (cholangio hepatocarcinoma) at presentation, we demonstrated the feasibility and safety of multi treatment approach, with two successive successful SIRT treatments, in this case, a first downstaging to surgery, and a successive neoadjuvant therapy as bridging to a successful transplant. We also outline the efficacy of an aggressive downstaging strategy bringing this patient to a potentially curative therapy as liver transplant.

References

1. Akinyemiju T, Abera S, Ahmed M, Alam N et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol. 2017; 3:1683-1691.

2. European Association for the Study of the Liver EASL. Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatic. 2018; 69:182-236.

3. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol. 2020; 72:250-261.

4. Gentile D, Donadon M, Lleo A, Aghemo A, Roncalli M et al. Surgical Treatment of Hepatocholangiocarcinoma: A Systematic Review. Liver Cancer. 2020; 9:15-27.

5. Komuta M, Yen MM. A review on the update of combined Hepatocellular Cholangiocarcinoma. Semin Liver Dis. 2020;

40:124-130.

6. Chu KJ, Lu CD, Dong H, Fu XH, Zhang HW et al. Hepatitis B virus related Combined epatocellularcholangiocarcinoma: clinicopathological and prognostic analysis of 390 cases. Eur J Gastroenterol Hepatol. 2014; 26:192-199.

7. Sempoux C, Kakar S, Kondo F, Schirmacher P. Combined Hepatocellular-Cholangiocarcinoma and Undifferentiated Primary Liver Carcinoma. 5th ed. France: Lyon IARC. 2019 .

8. Brunt E, Aishima S, Clavien PA, Fowler K, Goodman Z et al. cHCC-CCA: Consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentiation. Hepatology. 2018; 68:113-126.

9. Sciarra A, Young NP, Sempoux C. Updates in the diagnosis of combined HepatocellularCholangiocarcinoma. Hum Pathol. 2020; 96:48-55.

10. Gigante E, Ronot M, Bertin C, Ciolina M, Bouattour M et al. Combining imaging and tumour biopsy improves the diagnosis of combined hepatocellular-cholangiocarcinoma. Liver Int. 2019; 39:2386-2396.

11. Reig M, Forner A, Rimola J, Ferrer Fàbrega J, Burrel M et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022; 76:681-693.

12. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011; 54:868-878.

13. Mazzaferro V, Citterio D, Bhoori S, Bongini M, Miceli R et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. Lancet Oncol. 2020; 21:947-956.

14. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018; 67:358-380.

15. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation. 2020; 104:1136-1142.

16. Ettorre GM, Sandri GBL, Laurenzi A, Colasanti M, Meniconi RL et al. Yttrium-90 Radioembolization for Hepatocellular Carcinoma Prior to Liver Transplantation. World J Surg. 2017; 41:241-249.

17. Levi Sandri GB, Ettorre GM, Giannelli V, Colasanti M, Sciuto R et al. Trans-arterial radioembolization: a new chance for patients with hepatocellular cancer to access liver transplantation, a world review. Transl Gastroenterol Hepatol. 2017; 2:98.

18. Gabr A, Kulik L, Mouli S, Riaz A, Ali R et al. Liver Transplantation Following Yttrium-90 Radioembolization: 15-Year Experience in 207-Patient Cohort. Hepatology. 2021; 73:998-1010.

19. Zimmermann M, Schulze-Hagen M, Liebl M, Pedersoli F, Goerg F et al. Safety and Efficacy of Y-90 Radioembolization After Prior Major Hepatic Resection. Cardiovasc Intervent Radiol. 2017; 40:12061212.

20. Kessler J, Lewis A, Gagandeep S, Ituarte PHG, Park JJ. Radioembolization following Liver Resection: Safety and Dosing Considerations. J Vasc Interv Radiol. 2016; 27:46-51.

21. Antkowiak M, Gabr A, Das A, Ali R, Kulik L et al. Prognostic Role of Albumin, Bilirubin, and ALBI Scores: Analysis of 1000 Patients with Hepatocellular Carcinoma Undergoing Radioembolization. Cancers. 2019; 11:879.

22. Hermann AL, Dieudonné A, Ronot M, Sanchez M, Pereira H et al. Relationship of Tumor Radiationabsorbed Dose to Survival and Response in Hepatocellular Carcinoma Treated with Transarterial Radioembolization with 90 Y in the SARAH Study. Radiology. 2020; 296:673-684.

23. Vouche M, Habib A, Ward TJ, Kim E, Kulik L et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: Multicenter radiology-pathology correlation and survival of radiation segmentectomy: VOUCHE ET AL. Hepatology. 2014; 60:192-201.