Review Article

Trans-arterial radio-embolization: a new chance for patients with hepatocellular cancer to access liver transplantation, a world review

Giovanni Battista Levi Sandri[1], Giuseppe Maria Ettorre[1], Valerio Giannelli[2], Marco Colasanti[1], Rosa Sciuto[3], Giuseppe Pizzi[4], Roberto Cianni[5], Gianpiero D'Offizi[6], Mario Antonini[7], Giovanni Vennarecci[1], Pierleone Lucatelli[8]

[1]Division of General Surgery and Liver Transplantation, [2]Division of Hepatology, S. Camillo Hospital, Rome, Italy; [3]Division of Nuclear Medicine, [4]Division of Interventional Radiology, IFO Regina Elena National Cancer Institute, Rome, Italy; [5]Division of Interventional Radiology, S. Camillo Hospital, Rome, Italy; [6]Division of Hepatology and Infectious Disease, [7]Anesthesiology and Intensive Care Unit, National Institute for Infectious Disease "L. Spallanzani", Rome, Italy; [8]Vascular and Interventional Radiology Unit, Department of Radiological, Oncological and Anatomo-pathological Sciences, Sapienza University of Rome, Rome, Italy

Contributions: (I) Conception and design: GB Levi Sandri, P Lucatelli; (II) Administrative support: GM Ettorre, G D'Offizi, M Colasanti, M Antonini, G Vennarecci; (III) Provision of study materials or patients: R Sciuto, G Pizzi, R Cianni, V Giannelli; (IV) Collection and assembly of data: GB Levi Sandri, P Lucatelli; (V) Data analysis and interpretation: GB Levi Sandri, P Lucatelli; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Giovanni Battista Levi Sandri. Division of General Surgery and Liver Transplantation, San Camillo Hospital Rome, circ.ne Gianicolense 87, Rome 00151, Italy. Email: gblevisandri@gmail.com.

Abstract: Liver transplantation (LT) for hepatocellular carcinoma (HCC) within the Milan criteria (MC) is nowadays a curative procedure. Yttrium-90 microspheres radioembolization (Y90-RE) has shown to be an effective and safe treatment of primary liver tumors. The aim of this work is to offer a view on the publications which report on the use of Y90-RE as bridge or downstaging prior to LT. Twenty articles have been considered for this world review. About 178 LT in patients were treated with Y90-RE prior to LT. Most of patients had a downstaging strategy. In all series alpha-fetoproteins decreased between Y90-RE and LT. Therefore, Y90-RE may have an important role in the bridge and downstaging treatments.

Keywords: Yttrium; hepatocellular carcinoma (HCC); liver transplantation (LT); radioembolization; bridging; downstaging

Received: 26 October 2017; Accepted: 22 November 2017; Published: 27 November 2017.
doi: 10.21037/tgh.2017.11.11
View this article at: http://dx.doi.org/10.21037/tgh.2017.11.11

Introduction

Hepatocellular carcinoma (HCC) is the first liver cancer, representing the 3° cause of cancer-related mortality (1,2). Liver function and tumor stage influence the strategy. The Barcelona Clinic Liver Cancer (BCLC) proposed to classify HCC stage in order to prognosticate the outcome of patients (3) BLCC-0/A reflect patients which may be treated with a curative intent. However, both intermediate and advanced stages (BCLC B–C) include a wide range of HCC patients which are not candidates for a curative surgery. Some stage B or C BCLC patients may amenable of curative treatments (4,5). Locoregional treatment (in example transarterial chemoembolization, radiofrequency ablation) to decrease HCC progression and in cases of patients out of Milan criteria (MC) to downstage the disease. Yttrium-90 microspheres radioembolization (Y90-RE) is the latest novelty treatment for patients with un-resectable liver malignancies (6,7). Liver transplantation

(LT) for HCC within the MC is a well-established procedure (8) whereas in cases of extended criteria its application (i.e., UCSF, up-to-seven criteria) (9,10) need future investigations. Patients transplanted within MC after a downstaging therapy seem to achieve similar outcomes as those who meet the criteria since the diagnosis (11).

The aim of this work is to offer a view on the publications which report on the use of Y90-RE as bridge or downstaging prior to LT.

Methods

An electronic search was performed to identify all studies dealing with radioembolization and transplantation. The PubMed/MEDLINE database on December 2015 was searched. The search strategy was ("radioembolization" AND "HCC") AND ("Liver Transplantation" OR "downstaging" OR "bridge"). The references of the identified articles were also reviewed for additional eligible studies. Totally, we found less than 80 papers and all study typologies, including case reports and small series, were considered for the study. We summarized all reported cases of LT after Y90-RE in *Table 1*.

Discussion

According with the literature, the worldwide reported experience is now about 178 LT in patients treated with Y90-RE. In patients with advanced BCLC stage, Y90-RE treatment has superior results compared with trans-arterial chemo embolization (TACE) (32). Y90-RE was first of all described as an alternative option for non-resectable liver tumors (7,21,33-35). Accordingly in selected patients, Y90-RE is considered an effective tool for the downstaging strategy (36,37).

A difference up to 30% at the pathological specimen examination was described compared between the radiological evaluation of Y90-RE efficiency (38,39). In our previous study we report a rate of 78.9% of downstaging within the MC, rate which is comparable to the results described with locoregional treatments (i.e., TACE, RFA, PEI) in others studies (40-42), and with Y90-RE by Kulik and colleagues (43). In order to confirm the survival benefit with Y90-RE for patients with initial tumor out of MC, the follow up need to be longer in future studies. Looking at the literature, most of patients were out of MC at Y90-RE procedure (*Table 1*).

Y90-RE action is generally related to the radiation effect released on the tumor with a minor contribution from micro-embolization (21,33), while TACE is based on chemotherapy effect associated to the ischemic effect. In case of HCC with macro-vascular invasion, causing an endothelial vascular injury, Y90-RE due to the high dose of radiations delivered on the hyper-perfused tumor allow to treat those patients (36).

Due to the important heterogeneity of patients in BCLC-B recent studies are proposing to identify a subgroup of patients who could have a major benefit from Y90-RE instead of TACE (5). Besides, Y90-RE begins to be an alternative of conventional treatment for some authors even as a treatment in patients classified as advanced BCLC-B or early BCLC-C (33). Furthermore, in LT setting for BCLC-B/C patients, Y90-RE is now frequently used as bridge or downstaging strategy to prevent tumor progression and the potential drop-out from the LT waiting list.

The safeness of the Y90-RE procedure for HCC even with cirrhosis has been described first by the ENRY study and our data confirm in the results in the transplantation setting (32). The potential effect of the procedure on the patient MELD score was not observed in our experience. We do not observe statistically significant difference of MELD at 3 and 6 months from the procedure. In four patients had a MELD increased was observed but not Y90-RE related according to the radiation-induced liver disease definition (30).

In all reported experiences, a decrease value of alpha-fetoprotein has been described between Y90-RE and LT (*Table 1*).

In conclusion, LT in patients after Y90-RE treatment is growing worldwide. Radioembolization is gaining a major role at the expense of the traditional treatment in case of intermediate or advanced HCC. Many centers are using Y90 prior to LT and more data are now available to the scientific community. More prospective studies are needed but it is a promising beginning.

Table 1 World reported series of liver transplantation after Y90-RE

Author (reference)	Cases (n)	Male/ female	Age (years)	Etiology	Milan criteria	SIRT-LT	Alpha-fetoprotein Y90 (UI)	Alpha-fetoprotein LT (UI)	Survival (months)	Free survival (months)
Kulik 2005 (12)	1	1/0	44	HCV	Out	42 days	–	–	4	–
Kulik 2006 (13)	8	–	–	–	8-out	–	–	–	–	–
Kim 2006 (14)	1	1/0	50	HCV	Out	3 months	1,272	123	15	15
Sotiropoulos 2008 (15)	1	1/0	55	HBV	Out	15 days	–	–	14	14
Heckman 2008 (16)	16	–	–	–	2-out; 14-in	–	10 [3–1,567]	–	–	–
Nalesnik 2009 (17)	13	10/3	59	5-HCV; 3-alcohol; 3-cryptogenetic; 1-NASH; 1-autoimmune	6-out; 7-in	4.3 months	–	–	–	–
Luna 2009 (18)	1	1/0	58	NASH	Out	12 months	5	5	42	42
Lewandowski 2009 (19)	9	–	–	–	–	–	–	–	17	–
Khalaf 2010 (20)	1	1/0	54	HBV	Out	2 months	217	-	12	12
Ettorre 2010 (21)	1	1/0	62	HCV	Out	12 months	70,000	15	8	8
Iñarrairaegui 2012 (22)	2	–	59.5	–	2-out	22.5 months	9	-	50.5	50.5
Tohme 2013 (23)	20	16/4	60	8-HCV; 3-HBV; 4-alcohol; 5-other	6-out; 14-in		17 [6–508]		75	67
Vouche 2013 (24)	8	5/3	59	5-HCV; 1-alcohol; 1-NASH; 1-cryptogenetic	–	–	13 [1.5–484.6]	–	–	–
Yu 2014 (25)	3	2/1	56	–	Out	7 [3–10] months	4,380 [17.9-10,195]	508 [4.6-1,069]	24 [22-26]	24 [22–26]
Kulik 2014 (26)	17	–	–	14-HCV; 6-other	–	7.8 months	–	–	–	–
Vouche 2014 (27)	33	–	–	–	–	6.3 months	–	–	53.4	–
Mohamed 2015 (28)	9	–	–	–	2-out; 7-in	9 months	–	–	41	41

Table 1 *(continued)*

Table 1 *(continued)*

Author (reference)	Cases (n)	Male/ female	Age (years)	Etiology	Milan criteria	SIRT-LT	Alpha-fetoprotein Y90 (UI)	Alpha-fetoprotein LT (UI)	Survival (months)	Free survival (months)
Abdelfattah 2015 (29)	9	4/5	53.8	5-HCV; 2-cryptogenetic; 1-HBV; 1-Wilson's disease	4-out; 5-in	13 months	124 [5–499]	–	26 [13-70]	26
Ettorre 2017 (30)	22	22/0	55	17-HCV; 2-HBV; 2-alcohol; 1-NASH	19 out; 3 in	13 months	10,7	7	30.2	29.6
Radunz 2017 (31)	40	32/8	59	12-alcohol; 8-HBV; 9-HCV; 6-NASH; 2-cryptogenetic; 3-other	25-out; 15-in	4.3 months	22.5 [1–13,926]	24.4 [3.1–6,373]	46	13 [4–56]

Y90-RE, yttrium-90 microspheres radioembolization; LT, liver transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. El-Serag HB. Hepatocellular Carcinoma. N Engl J Med 2011;365:1118-27.
2. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
3. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
4. Raoul JL, Sangro B, Forner A, et al. Evolving strategies for the management of intermediate stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212-20.
5. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular carcinoma: proposal for a subclassification to faclitate treatment decisions. Semin Liver Dis 2012;32:348-59.
6. Nicolay NH, Berry DP, Sharma RA. Liver metastases from colorectal cancer: radioembolization with systemic therapy. Nat Rev Clin Oncol 2009; 6:687-97.
7. Rayar M, Sulpice L, Edeline J, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. Ann Surg Oncol 2015;22:3102-8.
8. Mazzaferro V, Regalia E, Doci R, et al. Liver trasnplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
9. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-403.
10. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with

hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
11. Lei J, Wang W, Yan L. Downstaging Advanced Hepatocellular Carcinoma to the Milan Criteria May Provide a Comparable Outcome to Conventional Milan Criteria. J Gastrointest Surg 2013;17:1440-6.
12. Kulik LM, Mulcahy MF, Hunter RD, et al. Use of yttrium-90 microspheres (TheraSphere) in a patient with unresectable hepatocellular carcinoma leading to liver transplantation: a case report. Liver Transpl 2005;11:1127-31.
13. Kulik LM, Atassi B, Van Holsbeeck L, et al. Yttrium-90 Microspheres Treatment of Unresectable Hepatocellular Carcinoma: Downstaging to Resection, RFA and Bridge to Transplantation. J Surg Oncol 2006;94:572-86.
14. Kim DY, Kwon DS, Salem R, et al. Successful embolization of hepatocelluar carcinoma with yttrium-90 glass microspheres prior to liver transplantation. J Gastrointest Surg 2006;10:413-6.
15. Sotiropoulos GC, Hilgard P, Antoch G, et al. Liver transplantation for hepatocellular carcinoma after yttrium therapy: a case report. Transplant Proc 2008;40:3804-5.
16. Heckman JT, Devera MB, Marsh JW, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. Ann Surg Oncol 2008;15:3169-77.
17. Nalesnik MA, Federle M, Buck D, et al. Hepatobiliary effects of 90yttrium microsphere therapy for unresectable hepatocellular carcinoma. Hum Pathol 2009;40:125-34.
18. Luna LE, Kwo PY, Roberts LR, et al. Liver transplantation after radioembolization in a patient with unresectable HCC. Nat Rev Gastroenterol Hepatol 2009;6:679-83.
19. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9:1920-8.
20. Khalaf H, Alsuhaibani H, Al-Sugair A, et al. Use of yttrium-90 microsphere radioembolization of hepatocellular carcinoma as downstaging and bridge before liver transplantation: a case report. Transplant Proc 2010;42:994-8.
21. Ettorre GM, Santoro R, Puoti C, et al. Short-term follow-up of radioembolization with yttrium-90 microspheres before liver transplantation: new perspectives in advanced hepatocellular carcinoma. Transplantation 2010;90:930-1.
22. Iñarrairaegui M, Pardo F, Bilbao JI, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol 2012;38:594-601.
23. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. J Vasc Interv Radiol 2013;24:1632-8.
24. Vouche M, Kulik L, Atassi R, et al. Radiological-pathological analysis of WHO, RECIST, EASL, mRECIST and DWI: Imaging analysis from a prospective randomized trial of Y90 ± sorafenib. Hepatology 2013;58:1655-66.
25. Yu YD, Kim DS, Jung SW, et al. Usefulness of radioembolization in identifying patients with favorable tumor biology before living donor liver transplantation. Transplantation 2014;98:e47-50.
26. Kulik L, Vouche M, Koppe S, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. J Hepatol 2014;61:309-17.
27. Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology 2014;60:192-201.
28. Mohamed M, Katz AW, Tejani MA, et al. Comparison of outcomes between SBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. Adv Radiat Oncol 2015;1:35-42.
29. Abdelfattah MR, Al-Sebayel M, Broering D, et al. Radioembolization using yttrium-90 microspheres as bridging and downstaging treatment for unresectable hepatocellular carcinoma before liver transplantation: initial single-center experience. Transplant Proc 2015;47:408-11.
30. Ettorre GM, Levi Sandri GB, Laurenzi A, et al. Yttrium-90 Radioembolization for Hepatocellular Carcinoma Prior to Liver Transplantation. World J Surg 2017;41:241-9.
31. Radunz S, Treckmann J, Baba HA, et al. Long-Term Outcome After Liver Transplantation for Hepatocellular Carcinoma Following Yttrium-90 Radioembolization Bridging Treatment. Ann Transplant 2017;22:215-21.
32. Sangro B, Carpanese L, Cianni L, et al. Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation. Hepatology 2011;54:868-78.

33. Iñarrairaegui M, Thurston KG, Bilbao JI, et al. Radioembolization with use of yttrium-90 resinmicrospheres in patients with hepatocellular carcinoma and portal vein thrombosis. J Vasc Interv Radiol 2010;21:1205-12
34. Sulpice L, Rayar M, Boucher E, et al. Treatment of recurrent intrahepatic cholangiocarcinoma. Br J Surg 2012;99:1711-7.
35. Sato K, Lewandowski RJ, Bui JT, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres: assessment of hepatic arterial embolization. Cardiovasc Intervent Radiol 2006;29:522-9.
36. Yao FY, Hirose R, La Berge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl 2005;11:1505-14.
37. Ettorre GM, Levi Sandri GB, Santoro R, et al. Bridging and downstaging to transplantation in hepatocellular carcinoma. Future Oncol 2014;10:61-3.
38. Riaz A, Kulik R, Lewandowski RJ, et al. Radiologic-Pathologic Correlation of Hepatocellular Carcinoma treated with Internal Radiation Using Yttrium-90 Microspheres. Hepatology 2009;49:1185-93.
39. Burrel M, Llovet JM, Ayuso C, et al.: MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: An explant correlation. Hepatology 2003;38:1034-42.
40. Yao FY, Kerlan RK Jr, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008;48:819-27.
41. Ravaioli M, Grazi GL, Piscaglia F, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 2008;8:2547-57
42. De Luna W, Sze DY, Ahmed A, et al. Transarterial chemoinfusion for hepatocellular carcinomas downstaging therapy and a bridge toward liver transplantation. Am J Transplant 2009;9:1158-68.
43. Barakat O, Wood RP, Ozaki CF, et al. Morphological features of advanced hepatocellular carcinoma as a predictor of downstaging and liver transplantation: an intention-to-treatanalysis. Liver Transpl 2010;16:289-99.

doi: 10.21037/tgh.2017.11.11
Cite this article as: Levi Sandri GB, Ettorre GM, Giannelli V, Colasanti M, Sciuto R, Pizzi G, Cianni R, D'Offizi G, Antonini M, Vennarecci G, Lucatelli P. Trans-arterial radio-embolization: a new chance for patients with hepatocellular cancer to access liver transplantation, a world review. Transl Gastroenterol Hepatol 2017;2:98.

