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

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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

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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) BCLC-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 tranarterial 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 alphafetoprotein 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>
<thead>
<tr>
<th>Author (reference)</th>
<th>Cases (n)</th>
<th>Male/ female</th>
<th>Age (years)</th>
<th>Etiology</th>
<th>Milan criteria</th>
<th>SIRT-LT</th>
<th>Alpha-fetoprotein Y90 (UI)</th>
<th>Alpha-fetoprotein LT (UI)</th>
<th>Survival (months)</th>
<th>Free survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulik 2005 (12)</td>
<td>1</td>
<td>1/0</td>
<td>44</td>
<td>HCV</td>
<td>Out</td>
<td>42 days</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Kulik 2006 (13)</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>8-out</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Kim 2006 (14)</td>
<td>1</td>
<td>1/0</td>
<td>50</td>
<td>HCV</td>
<td>Out</td>
<td>3 months</td>
<td>1,272</td>
<td>123</td>
<td>15</td>
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<tr>
<td>Sotiropoulos 2008 (15)</td>
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<td>1/0</td>
<td>55</td>
<td>HBV</td>
<td>Out</td>
<td>15 days</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>2-out; 14-in</td>
<td>–</td>
<td>10 [3–1,567]</td>
<td>–</td>
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<td>Nalesnik 2009 (17)</td>
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<td>10/3</td>
<td>59</td>
<td>5-HCV; 3-alcohol; 3-cryptogenic; 1-NASH; 1-autoimmune</td>
<td>6-out; 7-in</td>
<td>4.3 months</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Luna 2009 (18)</td>
<td>1</td>
<td>1/0</td>
<td>58</td>
<td>NASH</td>
<td>Out</td>
<td>12 months</td>
<td>5</td>
<td>5</td>
<td>42</td>
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<td>Lewandowski 2009 (19)</td>
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<td>1/0</td>
<td>54</td>
<td>HBV</td>
<td>Out</td>
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<td>2</td>
<td>–</td>
<td>59.5</td>
<td>–</td>
<td>2-out</td>
<td>22.5 months</td>
<td>9</td>
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<td>6-out; 14-in</td>
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<td>8</td>
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<td>59</td>
<td>5-HCV; 1-alcohol; 1-NASH; 1-cryptogenic</td>
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<td>–</td>
<td>13 [1.5–484.6]</td>
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<td>14-HCV; 6-other</td>
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<td>7.8 months</td>
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<td>33</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>6.3 months</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>53.4</td>
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<tr>
<td>Mohamed 2015 (28)</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2-out; 7-in</td>
<td>9 months</td>
<td>–</td>
<td>–</td>
<td>41</td>
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Table 1 (continued)
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Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.

References


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