

## ORIGINAL ARTICLE

# Multimodal treatment of unresectable hepatocellular carcinoma to achieve complete response results in improved survival

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## Abstract

**Introduction:** With technological advances, questions arise regarding how to best fit newer treatment modalities, such as transarterial therapies, into the treatment algorithm for patients with hepatocellular carcinoma (HCC).

**Methods:** Between 2005 and 2011, 128 patients initially treated with transarterial radioembolization or chemoembolization using drug-eluting beads were identified. The response was graded retrospectively. Toxicity was measured 1, 3, and 6 months after the first and last treatments.

**Results:** Sixty-five patients (53%) were advanced stage. Twenty patients (16%) had an initial complete response, but with additional treatments, this was increased to 46 (36%). Patients with a complete response as their best response to treatment had a median survival [95% confidence interval (CI)] of 5.77 (2.58, upper limit not yet reached) years, significantly longer than those whose best response was a partial response, 1.22 (0.84, 2.06) years and those with stable disease as their best response, 0.34 (0.29, 0.67) years. Repeated treatments did not increase toxicity.

**Discussion:** This retrospective review of patients treated for intermediate and advanced stage HCC revealed a significant survival advantage in patients who achieved a complete response. These data support use of a multi-modality approach to intermediate and advanced stage HCC, combining liver-directed treatments as necessary to achieve a complete response.

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## Introduction

Hepatocellular cancer (HCC) is the most common primary cancer of the liver, and develops almost exclusively in the setting of chronic liver damage. The most common causes are chronic infection with hepatitis B and cirrhosis secondary to hepatitis C or alcohol consumption. Based on 2011 Surveillance Epidemiology and End Results (SEER) data, the incidence of HCC tripled from

1975 to 2005, and although survival has improved slightly in the last decade, only 26% of patients with disease confined to the primary tumour site survive for 5 years.<sup>1</sup> In patients diagnosed after the disease has spread to the regional lymph nodes, 5-year survival is 9% and decreases to 2.6% in patients with metastatic disease.

The Barcelona Clinic Liver Cancer (BCLC) staging system stratifies these patients into five stages and is frequently used to determine prognosis and guide treatment.<sup>2</sup> The majority of patients present with multifocal disease, large tumours, extrahepatic disease or comorbidities such as liver failure which make them poor candidates for surgical intervention (BCLC stage B, C, or D). A 2010 meta-analysis looking at the natural history of HCC

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patients who receive only palliative treatment or placebo included in randomized trials determined that 1-year survival for BCLC stage B patients was 49.6%, compared with 25% for BCLC stage C patients and 11% for BCLC stage D patients.<sup>3</sup>

For BCLC stage B patients, multiple transarterial treatments have been developed in an attempt to extend survival and provide palliation. The various transarterial therapies are difficult to compare because of the lack of standardized treatment protocols, although recent meta-analyses have shown them to be superior to no treatment or systemic chemotherapy.<sup>4-6</sup>

More recently, embolic particles that slowly elute chemotherapeutic agents (transarterial chemotherapy with drug-eluting beads, termed here TACE/DEB), were introduced in an effort to increase the time that the tumour is exposed to the chemotherapy. For the treatment of HCC these beads are generally impregnated with doxorubicin.<sup>7</sup> PRECISION V, a randomized phase II trial of conventional TACE with versus TACE/DEB, including intrahepatic doxorubicin in both treatment arms, showed improved safety in the TACE/DEB arm and an improved response in patients with advanced disease at 6 months.<sup>8</sup>

Investigators also began to use radioactive beads for transarterial treatment of the tumour with localized radiation therapy. Yttrium-90-impregnated beads (Y-90) are most commonly used for radioembolization, and results have been encouraging, showing efficacy in a range of tumours affecting the liver including HCC.<sup>9</sup> Based on the promising results, many centres have extended the use of Y-90 to a subset of BCLC stage B and C patients with diffusely infiltrative tumours, portal vein invasion and even limited extrahepatic disease. Salem *et al.* performed a comparative analysis of 463 patients treated with TACE or radioembolization which showed no significant difference in the median 5-year survival. They concluded that a randomized trial of more than 1000 patients would be required to confirm statistical equivalence between the treatment modalities.<sup>10</sup>

Although multiple trials have shown the different treatment modalities to be effective, because of the similarities in efficacy, the variability in treatment protocols and the continuous changes in technology it will be challenging to prove superiority of either modality. The following manuscript demonstrates that a significant number of patients who were ultimately treated with both Y-90 and TACE/DEB survived longer than predicted. Tumour and patient-specific variables that determine whether patients benefit more from one therapy over the other were sought, with the notion that the choice and order of therapies may affect outcomes. To investigate this further, a retrospective review of all of the patients treated for locally aggressive HCC was performed to determine factors that correlate with response and survival.

## Patients and methods

Between 2005 and 2011, all patients with HCC who were treated at Providence Portland and Providence St. Vincent Medical Centers were identified. Patients were included if their first treatment for

HCC was either TACE/DEB or Y-90. In an attempt to provide an unbiased comparison, patients who were treated with other forms of transarterial chemoembolization, bland embolization or liver transplantation were excluded. Patients who were initially treated with TACE/DEB or Y-90 and had a response allowing an attempt at curative treatment with radiofrequency ablation or liver resection were included. Data were collected on patient demographics, tumour characteristics, procedural data and outcomes. Imaging was reviewed retrospectively by a board certified interventional radiologist and the treatment response was graded according to the European Association for the Study of the Liver modified Response Evaluation Criteria in Solid Tumors (RECIST), commonly referred to as the modified RECIST.<sup>11</sup> Responses were graded as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), each time a cross-sectional contrast imaging study was performed during follow-up. The best response was defined for each patient as the single best response achieved at any point during follow-up. This study protocol was approved by the Institutional Review Board, and informed consent was obtained from all patients for participation in the database.

HCC patients are reviewed at a multidisciplinary hepatobiliary conference attended by surgeons, interventional radiologists, hepatologists, medical oncologists and radiation oncologists. While the group's recommendations for treatment were based on consensus guidelines,<sup>12</sup> the type of liver-directed therapy was not dictated by an algorithm at the time these patients were enrolled and treated. The choice of either TACE/DEB or Y-90 was made by the treating interventional radiologist based on operator preference, previous local and systemic treatments, tumour characteristics, and anatomical factors such as potential for vascular shunting. In general, a total bilirubin cut-off of 2 mg/dl was used for both modalities, and radioembolization was preferred but not mandatory in patients with large or infiltrative tumours, and those with portal vein tumour thrombosis (PVTT).

Y-90 radioembolization was performed using Theraspheres (MDS Nordion, Kanata, ON, Canada). Pre-treatment visceral arteriography was performed to evaluate the vasculature, perform coil embolization of any normal or aberrant visceral vessels to prevent non-target embolization and determine the liver-to-lung shunt ratio. This was performed with injection of Technetium 99-m microaggregated albumin into the right or left hepatic arteries. Patients with shunts greater than 15% or a calculated Y-90 dose greater than 30 Gray to the lung were excluded from treatment with Y-90. Y-90 dose calculation was based on the body surface area method as described previously.<sup>13</sup> Calculated tissue doses ranged from 80 to 120 Gray. Therapeutic Y-90 embolization to the hepatic lobe harbouring the dominant tumour volume was performed 2 weeks after mapping arteriography. Radioembolization was sometimes repeated in patients with bilobar disease, who had the non-dominant lobe treated 4 weeks after the first treatment, and rarely to retreat disease within the same lobe.

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