ORIGINAL ARTICLE

Sequential transarterial chemoembolization and portal vein embolization before resection is a valid oncological strategy for unilobar hepatocellular carcinoma regardless of the tumor burden

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Abstract

Objective: To investigate the long-term oncological outcome of patients with resectable hepatocellular carcinoma (HCC) undergoing sequential transarterial chemoembolization (TACE) and portal vein embolization (PVE).

Methods: Analysis of all Child A HCC patients who underwent TACE-PVE before major liver resection from 2006 to 2012 was performed according to whether or not they underwent surgical resection as planned.

Results: 54 patients (50 men, 93% median 69-years (range 44–87)) were included. Thirty-nine (72%) patients underwent resection, including 19/25, 16/23, and 4/6 of patients with BCLC A, B, and C ($p = 0.839$). Twenty-two (56%) had tumor recurrence (median delay 10 months) including 9/19, 11/16, and 2/4 of the patients with BCLC A, B, and C ($p = 0.430$). Survival was significantly better in resected patients as compared to those who were not resected (median overall survival (OS): 44 vs. 18 months; $p < 0.001$). Recurrence was associated with a poorer prognosis as compared to patients without recurrence (median OS 43 months vs. not reached; $p < 0.001$). BCLC stage did not influence survival ($p = 0.13$).

Conclusion: In patients with large unilobar HCC, TACE-PVE leads to resection in most patients, with a good oncological outcome regardless of the tumor burden. When this strategy fails, patients can be managed with TACE despite prior PVE.

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Introduction

Despite advances in the management of patients with HCC, large HCCs (i.e. >10 cm) still represent a therapeutic challenge. According to current Western guidelines based on the Barcelona-Clinic Liver Cancer (BCLC) staging system, most of these patients are not considered to be resectable and are candidates for locoregional treatments.[1] At the same time, surgery is still the only curative treatment, but is associated with high risk of postoperative liver failure (PLF) and poor clinical outcome because most HCC develop on chronic liver disease.

Preoperative portal vein embolization (PVE) before liver resection has been proposed to induce compensatory contralateral hypertrophy of the future liver remnant (FLR), and prevent PLF, especially for major liver resections, which require the removal of a large quantity of functional liver.[2–5] It has

been shown that preoperative sequential selective transarterial chemoembolization (TACE) and PVE before resection increased the rate of FLR hypertrophy and resulted in a high rate of complete tumor necrosis associated with longer recurrence-free survival.[6–9]

However, not all patients undergo liver resection mainly because of insufficient liver hypertrophy, and/or tumor progression. There are very little data on the oncological outcome and management of this subgroup of patients. Therefore, a realistic picture of the outcome of patients undergoing sequential TACE-PVE on an intention-to-treat basis is lacking. Thus the purpose of this study was to investigate the long-term oncological outcome of patients with HCC who underwent sequential TACE-PVE on an intention to treat basis.

Patients and methods

Patient's selection

This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local Ethics Committee. Between March 2006 and December 2012 all patients with HCC who underwent sequential TACE-PVE were studied. Baseline patient (demographic data, underlying liver disease and function) and tumor (size, location, number of lesions, vascular invasion, BCLC stage) characteristics were obtained from the prospective institutional database.

These included surgical data, operative results, tumoral and non-tumoral pathological data, details on additional treatments following recurrence or non-resection and long-term outcome.

Inclusion criteria were 1/HCC diagnosed according to EASL-EORTC recommendations,[1] 2/no extrahepatic disease based on chest/abdominal-pelvic CT performed within 6 weeks before TACE, 3/indication for sequential TACE-PVE. The decision to treat patients with sequential TACE-PVE to increase the rate of FLR hypertrophy and obtain a higher rate of complete tumor necrosis was made by an institutional multidisciplinary tumor board including hepatologists, oncologists, pathologists, hepatic surgeons, and interventional radiologists. This approach was used in all patients with resectable unilobar HCC and underlying liver disease (i.e. cirrhosis, fibrosis, steatohepatitis or steatosis), who were deemed to require major (>3 Couinaud segments) right-sided or left-sided hepatectomy regardless the volume of future liver remnant (FLR). This approach was indicated in Child A patients with preserved liver function, absence of clinically obvious portal hypertension defined by the presence of esophageal varices (≥grade 2) or ascites or the association of low platelet count (<100.000/mm^3) and splenomegaly (largest diameter in transversal plane on CT > 12 cm),[10] and with good performance status (ECOG 0–2). Eventually, the decision to operate was not based on the initial volumetry but rather on the regenerative capacity of the liver as assessed by the degree of hypertrophy. In this setting, PVE acted as a stress test of the non-tumoral liver. A degree of hypertrophy of <5% suggested poor regenerative ability, and thus patients who did not reach this cutoff value were not offered resection.[11]

Imaging work up

All patients underwent a baseline CT examination before the sequential procedure, an intermediate CT between TACE and PVE, and a follow-up CT 4–6 weeks after PVE. All contrast-enhanced multiphased CT of the chest and abdomen were performed on a 64-section multidetector CT scanner (LightSpeed VCT; GE HealthCare, Milwaukee, WI, USA). Following unenhanced abdominal CT, arterial, portal and delayed venous phase acquisitions were obtained 35, 80, and 180 s, respectively following the initiation of contrast injection. All CT examinations were retrospectively reviewed in consensus by two experienced abdominal radiologists (MR and BG).

Transarterial chemoembolization

TACE procedures were performed before PVE. The procedure was performed under local anesthesia as selectively as possible depending on tumor distribution reserve. A conventional approach (cTACE), or drug-eluting beads (DEB-TACE) were used, with the latter in more recent patients. TACE procedures were performed by a team of experienced interventional radiologists.

cTACE included an intraarterial injection of a mixture of chemotherapy (150 mg of doxorubicin; Adriamycin; Pharmacia Upjohn, Kalamazoo, MI, USA), emulsified in iodized oil (Lipiodol, Gerbet, Aulnay-sous-Bois, France). Embolization was achieved by injection of gelatin sponge (Gelitaspon, Gelita Medical B.V., Amsterdam, Netherlands) or polyvinyl alcohol particles (Bead Block, Biocompatibles, Farnham, UK).

The drug-eluting beads procedure included 100–300 μm and/or 300–500 μm sized particles (Biocompatibles, Farnham, UK), as described in the guidelines.[12] Bead loading was performed with an intended dose of 150 mg/patient. In the absence of adverse effects or complications, patients were discharged 24–48 h after the procedure.

Portal vein embolization

Procedures were performed under general anesthesia, as previously reported.[13] PVE was performed without embolization of the portal branches supplying segment 4 with a mixture of N-butyl-2-cyanoacrylate and iodized oil (Lipiodol, Guerbet, Aulnay-sous-Bois, France). Embolization was completed with 0.035-inch coils (Tornado 0.035, Cook, Limerick, Ireland), and polyvinyl alcohol particles (Beadblock, Biocompatibles, Farnham, UK), when necessary. In the absence of adverse effects or complications, patients were discharged 24–48 h after the procedure.

Patient follow-up and management

Resected patients

Resected liver specimens were retrospectively reviewed by a liver pathologist blinded to imaging data. The amount of residual tumor