European Journal of Radiology 81 (2012) 2290–2297

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Selective and sequential transarterial chemoembolization: Survival in patients with hepatocellular carcinoma

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ARTICLE INFO

Article history:
Received 6 June 2011
Received in revised form 25 August 2011
Accepted 1 September 2011

Keywords:
Chemoembolization
TACE
Embolization
Hepatocellular carcinoma
HCC

ABSTRACT

Purpose: To assess the survival time of patients with HCC following transarterial chemoembolization performed in a highly selective and sequential way.
Patients and methods: 124 HCC patients (102 male, 22 female; mean age 63 ± 11 years) treated with selective and sequential chemoembolization at a single center were included. Selective chemoembolization was performed through a coaxially introduced microcatheter in a segmental or subsegmental hepatic artery. Treatment was stopped after complete stasis of the blood flow in the tumor-feeding vessel. The primary endpoint of the study was overall survival.
Results: The median overall survival of the entire patient population was 27.2 months (mo) (±8.9 mo, 95% CI 9.8 mo, 44.6 mo). When stratified according to liver function the median survival was 46.1 mo (±9.0 mo; 95% CI 28.5 mo, 63.7 mo) for Child-Pugh A and 11.1 mo (±4.3 mo; 95% CI 2.7 mo, 19.5 mo) for Child-Pugh B ($p < .001$). The median survival was 46.1 mo (±16.6 mo; 95% CI 13.5 mo, 78.7 mo) for BCLC stage A, 19.7 mo (±2.6 mo; 95% CI 14.6 mo, 24.8 mo) for BCLC stage B, and 14.4 mo (±5.0 mo; 95% CI 4.5 mo, 24.3 mo) for BCLC stage C ($p < .01$).
Conclusion: Selective and sequential chemoembolization offers long survival times in patients with HCC. Those patients with preserved liver function benefit more than patients with limited liver reserve.

1. Introduction

The incidence of hepatocellular carcinoma (HCC) is increasing worldwide with the number of hepatitis C infections emerging. Although patients with liver cirrhosis often undergo close surveillance with ultrasound and other imaging modalities, only 30% of the patients with newly diagnosed HCCs are eligible for a surgical treatment with a curative intention [1]. All other patients at advanced tumor stages require a palliative treatment approach.

Due to relatively slow progression with distant metastases generally occurring late, the basis of palliative HCC treatment is locoregional tumor destruction by percutaneous (e.g. radiofrequency ablation) or transarterial access. Among the transarterial methods chemoembolization is the most commonly used and can be regarded as the standard palliative treatment [2]. Until today several trials, both prospective and retrospective, have been published on transcatheter chemoembolization of HCC. The reported outcome of these trials differs substantially. While some authors detected a significant improvement of survival after chemoembolization of HCC compared to best supportive care [3–6], others report the opposite [7–9]. Some of these discrepancies must be attributed to differences in the study design and the patient population, others may relate to the way chemoembolization was performed.

The embolic agent is one factor that may affect the outcome following chemoembolization. Agents such as lipiodol, poly-vinyl alcohol (PVA), gelatine sponge particles, and microspheres have been proposed [10]. In addition, different chemotherapeutic agents are in use with chemoembolization. Another factor that may explain differences in patient survival is the position of the embolization catheter. Chemoembolization in its classical form has been performed in a lobar fashion via a macrocatheter placed in the right or left hepatic artery [11]. However, microcatheters, which have increasingly been used in interventional radiology since the 1990s, may be advanced in a coaxial fashion via the guiding catheter offering selective and supraselective catheterization of tumor-feeding vessels. Thereby high concentrations of both, the embolic and the chemotherapeutic agent, can be applied to the tumor while limiting the exposure of the normal liver parenchyma

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doi:10.1016/j.ejrad.2011.09.010

at the same time. In cases of more than one tumor-feeding vessel sequential chemoembolization can further reduce the exposure of the non-tumorous liver parenchyma. This selective and sequential way of chemoembolization bears three potential advantages over the lobar approach: a stronger tumoricidal effect, a decreased risk of liver-associated side effects, and the ability to access small tumor-feeders arising from non-hepatic vessels [10].

The aim of this study was to assess the overall survival of patients with HCC undergoing selective and sequential transarterial chemoembolization.

2. Patients

2.1. Study design

One hundred and twenty-four consecutive patients with HCC underwent selective and sequential chemoembolization in a university hospital setting. These were 102 men and 22 women with a mean age of 63 years (±11 years). Liver cirrhosis was present in 108 of the 124 patients. The primary tumor was verified in all patients either by biopsy and histopathology or according to EASL criteria [12]. Briefly, non-invasive diagnosis of HCC was verified if a nodule of more than 2 cm within an existing liver cirrhosis appeared arterially hypervascularized and with an enhanced venous 'wash-out' on one contrast-enhanced imaging modality, with the AFP level exceeding 400 ng/ml at the same time. In patients with AFP-levels below 400 ng/ml a tumor > 2 cm had to show the above-mentioned dynamics of the contrast agent in two different imaging modalities.

Data evaluation was performed retrospectively and data were reported according to the standards defined by the Society of Interventional Radiology [13]. The study was performed in accordance with guidelines of the local institutional review board. By assessment of the CT performed before the first chemoembolization, the tumor size, potential multifocality, potential vascular invasion, morphological signs of liver cirrhosis, and the presence of ascites were documented. From the patients' records the following information was retrieved: etiology of liver cirrhosis, potential encephalopathy, laboratory results including bilirubin, albumine, liver enzymes, prothrombin time (as Quick value or INR), thrombocytes, AFP, and Eastern Cooperative Oncology Group (ECOG) status. Based on these data all patients were rated according to Child-Pugh [14,15] in stages Child-Pugh A–C, according to Okuda [16] in stages Okuda 1–3, according to the Cancer of the Liver Italian Program (CLIP) [17] in stages 0–6, and according to the Barcelona Clinic Liver Cancer Group (BCLC) [18] in stages A–D. Survival data were based on the patients' records from our institution as well as records of their family physicians.

Table 1
Patient characteristics.

Demography	Age (years)	63 (±11 years)
	Male	102 (82%)
	Female	22 (18%)
Liver disease	Liver cirrhosis	108 (87%)
	No liver cirrhosis	16 (13%)
Cause of cirrhosis	Hepatitis B	23 (19%)
	Hepatitis C	33 (27%)
	Hepatitis B and C	7 (6%)
	Alcohol	13 (10%)
	Other	4 (3%)
	Unknown	28 (23%)
Liver function	Child-Pugh A	97 (78%)
	Child-Pugh B	27 (22%)
	Okuda 1	87 (70%)
	Okuda 2	37 (30%)
	CLIP 0	40 (32%)
	CLIP 1	43 (35%)
	CLIP 2	28 (23%)
	CLIP 3	12 (10%)
	CLIP 4	1 (1%)
	BCLC A	40 (32%)
	BCLC B	48 (39%)
	BCLC C	36 (29%)
Diagnosis of HCC	Histopathology	78 (63%)
	EASL	46 (37%)
Tumor extent	Unifocal	67 (54%)
	Multifocal	57 (46%)
	No portal vein thrombosis	97 (78%)
	Portal vein thrombosis	27 (22%)
	Segmental	19 (15%)
	Lobar	8 (7%)

Patient characteristics based on 124 patients included in the study.

2.2. Chemoembolization procedure

Transcatheter chemoembolization was performed with a femoral access via a 5 French (F) sheath. Either a 4F or 5F guiding catheter (Simmons, Cobra, Head Hunter, or Shepherd–Hook, Terumo Europe, Leuven, Belgium) was introduced into the celiac trunk. First the portal vein was visualized and its patency was documented through contrast injection into the splenic artery. Then arteriography was performed with intravascular contrast (Ultravist 300, Bayer-Schering Pharma, Berlin), with the catheter placed in the common or proper hepatic artery. In cases with anatomical variants the macrocatheter was positioned within the corresponding accessory or replaced vessel. Following the initial arteriography a microcatheter (Tracker or FASTracker, Boston Scientific, Cork, Ireland; Rebar, Micro Therapeutics, Irvine, USA; Renagade, Boston Scientific, Natick, USA) was advanced coaxially via the guiding catheter into the tumor-feeding vessel. If the tumor feeding vessel could not be catheterized selectively, the microcatheter was positioned as close to the tumor as possible in a segmental or subsegmental artery. If parts of the tumor were supplied from non-hepatic vessels, such as the inferior phrenic artery, the left gastric artery, the renal artery, or branches of the gastroduodenal artery, these non-hepatic tumor-feeders were selectively catheterized for chemoembolization. Lipiodol was used as the embolic substance in tumor feeders from the hepatic artery as well as in extrahepatic tumor feeders other than the inferior phrenic artery. Mitomycin C was applied as the chemotherapeutic agent. Lipiodol embolization was performed with a suspension generated from 7.5 ml of lipiodol (Guerbet, Sulzbach, Germany) mixed with 2.5 ml of a contrast agent (Ultravist 300, Bayer-Schering Pharma, Berlin) and 5 mg of Mitomycin C (medac, Hamburg, Germany). Chemoembolization was performed

Table 2
Patient survival.

	1-Year survival	2-Year survival	3-Year survival
All (n = 124)	79%	51%	42%
Child A (n = 97)	89%	62%	51%
Child B (n = 27)	26%	–	–
Okuda 1 (n = 87)	86%	60%	51%
Okuda 2 (n = 37)	52%	20%	6%
CLIP 0 (n = 40)	91%	73%	52%
CLIP 1 (n = 43)	88%	48%	26%
CLIP 2 (n = 28)	54%	4%	–
CLIP 3 (n = 12)	13%	–	–
CLIP 4 (n = 1)	–	–	–
BCLC A (n = 40)	90%	68%	55%
BCLC B (n = 48)	82%	36%	5%
BCLC C (n = 36)	46%	15%	–

One year, 2-year, and 3-year survival rates of patients undergoing selective and sequential chemoembolization.