International Journal of Surgery 45 (2017) 35–41

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original Research

Adjuvant hepatic arterial infusion chemotherapy is beneficial for selective patients with Hepatocellular carcinoma undergoing surgical treatment

Jui-Hu Hsiao [a], Cheng-Chung Tsai [a], Tsung-Jung Liang [a], Chia-Ling Chiang [b], Huei-Lung Liang [b], I-Shu Chen [a], Yu-Chia Chen [a], Po-Ming Chang [a], Nan-Hua Chou [a], Being-Whey Wang [a, *]

[a] Division of Gastroenterologic Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, Taiwan
[b] Department of Radiology, Kaohsiung Veterans General Hospital, Taiwan

HIGHLIGHTS

- HAIC provided benefit for HCC patients with microvascular invasion and selective multiple tumor after surgery.
- HAIC is not suitable for every patients undergoing surgery.
- Solitary HCC patients should not receive adjuvant HAIC, especially in non-HBV patients.

ARTICLE INFO

Article history:
Received 10 March 2017
Received in revised form
7 July 2017
Accepted 15 July 2017
Available online 17 July 2017

Keywords:
Hepatocellular carcinoma
Hepatectomy
Hepatic arterial infusion chemotherapy
Multiple tumor
Survival

ABSTRACT

Background: Recurrence rate after curative surgical resection of Hepatocellular carcinoma (HCC) remains high. Postoperative hepatic arterial infusion chemotherapy (HAIC) has been suggested to improve survival. This study is to investigate the efficacy of HAIC in the patients with poor tumor factors such as vascular invasion or multiplicity.

Methods: From 2006 to 2014, 221 patients with HCC undergoing hepatectomy and pathologically staged as ≧ T2 (American Joint Committee on Cancer TNM staging system, 7th edition) were included. 61 patients received adjuvant HAIC with 5-fluorouracil, cisplatin, and epirubicin. 160 patients received surgery alone. The overall survival time (OST) and disease free survival time (DFST) were compared between the two groups.

Results: In all patients, the multivariate analysis of survival data showed that resection margin less than 10 mm was the independent poor prognostic factors. The median OST and DFST between the HAIC and surgery alone groups were 56.4 vs. 56.9 months ($p = 0.76$), and 50.6 vs. 54.5 months ($p = 0.905$), respectively. There was no significant difference. For patients with multiple tumors and concomitantly microvascular invasion, the OST was better in the HAIC group (69.7 vs. 54.6 months, $p < 0.05$).

Based on the image and operative finding, we classified multiple HCC's into two types. Type A: multiple small nodules were close to each other or a huge tumor with several satellite nodules. Type B: two or more tumors scattering in separate segments. Our study showed that type A group benefits from adjuvant HAIC much more than type B. (the median OST in type A versus type B were 85.06 vs. 41.53 months, $p = 0.0036$).

Conclusion: The surgical outcome for the patients with multiple HCC's and vascular invasion was poor. Our study showed adjuvant HAIC was beneficial in these patients and formed the basis for further randomized controlled trials.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, which may be related to infection with

* Corresponding author. Division of General Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, No. 386, Dazhong 1st Rd, Zuoying District, Kaohsiung 81362, Taiwan.
E-mail address: rehookimo@gmail.com (B.-W. Wang).

http://dx.doi.org/10.1016/j.ijsu.2017.07.071
1743-9191/

hepatitis B virus (HBV) and/or hepatitis C virus (HCV) [17,19]. It represents the second leading cause of cancer-related deaths worldwide [2]. The patient's prognosis is associated with cumulative tumor size, tumor location, cirrhosis, portal vein and/or microvascular tumor embolus and the histological grade of the primary tumor [9]. Barcelona-Clinic Liver Cancer, Okuda, Child-Pugh score, and the indocyanine green (ICG) clearance test were used to evaluate the respectability for operation [12,32]. Surgical resection is a curative treatment, but local recurrence rate remains high. The macroscopic tumor can be removed during liver resection, but microscopic tumor spreading might not be able to detect. Several treatments have been available in terms of local recurrence, such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE), transcatheter arterial chemoembolization (TACE), and hepatic arterial infusion chemotherapy (HAIC), liver transplantation, radioembolization, cryoablation, radiation therapy and stereotactic radiotherapy, and systemic chemotherapy [8,26,27].

Previous studies have reported the benefit on adjuvant HAIC in HCC patients undergoing liver resection [1,16,21,23]. We assumed that adjuvant HAIC would provide advantage for patients with microscopic tumor spreading after hepatic resection. Therefore, we conducted this study focusing on those patients with single HCC that had pathologically proved (micro or macro-) vascular invasion and those with multiple HCC's. The object is to see whether or not the adjuvant HAIC would improve the disease free and overall survival of HCC patients undergoing curative resection.

2. Material and method

2.1. Patients

From 2006 to 2014, there were a total of 597 HCC patients undergoing liver resection at our hospital. All specimens were examined by professional pathologist at our hospital. The conduction of adjuvant HAIC was according to the surgeons' preferential. Generally, those patients with pathologically diagnosed T1 lesion were considered not indicated for adjuvant HAIC and were excluded (American Joint Committee on Cancer TNM staging system, 7th edition). The patients with the following conditions were excluded from the present study: (1) 5 patients died within 3 months after surgery. (2 patients died of postoperative infection; 3 patients died of hepatic decompensation.), (2) 6 patients died of other cancer or other medical illness, (3) 10 patients with liver function impairment after surgery and did not recovered with thin 2 months, manifested by elevated AST (aspartate aminotransferase) and ALT (alanine aminotransferase) level > 100 IU/L. Among those with pathologically proved ≧ T2 tumors, 221 patients were enrolled in this retrospective cohort study in which 61 patients received adjuvant HAIC after surgery and 160 patients had operation only. All patients were regularly followed up at our hospital every 3 months.

2.2. Pre-operative evaluation and surgery

Before surgery, all patients received ultra-sonography, computed tomography (CT) or Magnetic resonance imaging (MRI) scans. Alpha fetoprotein, hepatitis B surface antigen (HBsAg), Antibody hepatitis B surface (Anti-HBs), anti-hepatitis C virus antibody, (anti-HCVAb), Serum aminotransferases: ALT and AST, and ICG test were checked.

Anatomical liver resection, multiple wedge resections, or en-bloc resection was performed according to tumor location and size. Intraoperative sonography was used to see peripheral blood vessels, tumor depth, and satellite nodules [29].

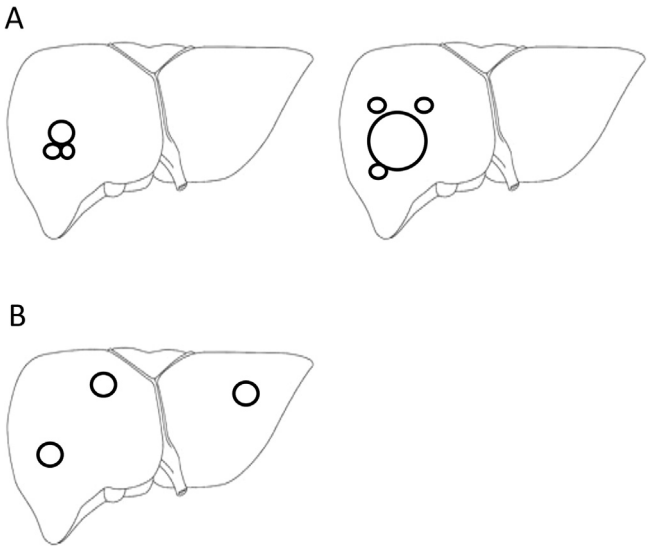

Fig. 1. Classification of Multiple HCC.
Type A: multiple small nodules that were close to each other or huge tumor (>=5 cm) with satellite nodules that involved three or more segments. Type B: three or more tumors that were scattered in separate segments.

2.3. Classification of multiple HCC's

Recent studies divided multifocal HCC into intrahepatic metastasis (IM) and multicentric origin type (MO) [6,9,28]. In the present study, we arbitrarily divided the patients into A and B type according to the gross growth pattern of the tumors [29]. Those with multiple small nodules that were close to each other or one huge tumor with satellite nodules were classified as type A; while those having two or more tumors scattering in separate segments were classified as type B. (Fig. 1). Type A tumors can be removed with lobectomy, segmentectomy or wedge resection in one block; Type B tumors can be removed with multiple wedge resections in different segments of liver or extended hepatectomy.

2.4. HAIC regimen

A temporary catheter was introduced by the radiologist through left subclavian artery and the tip of the catheter was placed in the proper hepatic artery. The patients received hepatic arterial infusion of chemotherapy via an intra-arterial pump within 3 months after surgery [10,22].

The regimen of HAIC consisted of infusion with chemotherapy for 5 days.: Cisplatin (10 mg/m^2, for 30 min) in 100 mL of 0.9% normal saline, was infused for 5 days; 5-FU (150 mg/m^2, for 24 h) in 250 mL of 0.9% normal saline with Leucovorin (15 mg/m^2, for 30 min) was infused for 5 days; Epirubicin (15 mg/m^2, for 30 min) in 100 mL of 0.9% normal saline was infused on Day1 and Day5.

This HAIC regimen has been used to treat those patients with huge unresectable HCC in our institute, and some patients had good response [15,24]. During the designated period in the present study, our tumor board agreed to perform adjuvant HAIC after curative resection of HCC for those with high risk factors such as microvascular invasion or later tumor stage.

2.5. Follow-up

All patients received CT or MRI scans within one month after surgery and were followed up every 3 months after the surgery. RFA or PEI was performed for those with no more than 3 recurrent