http://dx.doi.org/10.1016/j.hpb.2017.04.010 HPB

ORIGINAL ARTICLE

A double blinded prospective randomized trial comparing the effect of anatomic versus non-anatomic resection on hepatocellular carcinoma recurrence

Xiaobin Feng[1,2,*], Yongjie Su[2,3,*], Shuguo Zheng[2], Feng Xia[2], Kuansheng Ma[2], Jun Yan[1,2], Xiaowu Li[2], Wei Tang[4], Shuguang Wang[2], Ping Bie[2] & Jiahong Dong[1,2]

[1]Hepato-pancreato-biliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, [2]Institute of hepatobiliary surgery, Southwest Hospital, Third Military Medical University, Chongqing, [3]Department of Hepatobiliary Surgery, Xiamen University Zhongshan Hospital, Xiamen, China, and [4]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Abstract

Background: The aim of this study was to determine the effect of anatomic resection (AR) versus non-anatomic resection (NAR) on recurrence rates in patients with hepatocellular carcinoma (HCC).

Methods: Eligible patients were randomized to AR or NAR from January 2006 to July 2007 at a single center. The primary outcome was the 2-year recurrence-free survival (RFS). Secondary outcomes were postoperative complications, time to first recurrence, 1-, 3-, and 5-year RFS, and overall survival (OS).

Results: Fifty-three (51%) and 52 (50%) patients underwent NAR and AR, respectively. A larger proportion of patients achieved margins ≥20 mm in the AR group (52% vs. 30%; P = 0.023). Complications (blood loss, transfusion requirement, and hospital stay) were similar between the two groups. Median follow-up was 33 (range, 2–77) months. Incidence of local recurrence at 2 years was 30% and 59% in the AR and NAR groups, respectively. Median time to first local recurrence in the AR group was significantly longer than in the NAR group (53 vs. 10 months, P = 0.010). There was no difference in overall RFS between the two groups (P = 0.290).

Discussion: AR decreased the 2-year local recurrence rate and increased the time to first local recurrence compared to NAR in patients with HCC.

Received 16 December 2016; accepted 9 April 2017

Correspondence

Jiahong Dong, Hepato-pancreato-biliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China. E-mail: dongjiahong@tsinghua.edu.cn

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths in China.[1] Although early diagnosis and treatment improve survival,[2] HCC is rarely cured and recurrence occurs in most patients despite optimal treatment.[3] Hepatectomy remains the best treatment option for patients with adequate liver function.[4–7]

Anatomic resection (AR) and non-anatomic resection (NAR) are the two most commonly used approaches in patients undergoing resection for HCC; however which option is superior remains controversial.[8,9] This is because the evidence supporting the use of AR in the prevention of HCC recurrence after surgery is limited to non-randomized studies.[10,11]

HCC circulating tumor cells have been detected in 81%–88% of patients at the time of surgery.[12,13] Early circulating tumor cells are thought to be spread by branches of the portal vein[12] and AR aims to resect the liver perfused by the supplying portal vein based on Couinaud's segments. Thus theoretically, AR should resect micrometastases (MMTs) within the anatomical segment and thus reduce the risk of recurrence.

Thus, it is reasonable to postulate that AR would be more beneficial than NAR for the clearance of MMTs and circulating tumor cells, thus decreasing the local recurrence (LR) caused by "nearby" MMTs, but not distant recurrence (DR).

*Feng and Su contribute equally to this work.

Please cite this article in press as: Feng X, et al., A double blinded prospective randomized trial comparing the effect of anatomic versus non-anatomic resection on hepatocellular carcinoma recurrence, HPB (2017), http://dx.doi.org/10.1016/j.hpb.2017.04.010

To test this hypothesis, a prospective randomized controlled trial enrolling HCC patients was performed to determine the effect of AR versus NAR on recurrence rates in patients with HCC.

Methods

Study design

Between January 2006 and July 2007, patients with localized HCC at the Institute of hepatobiliary surgery, Southwest Hospital, Third Military Medical University (Chongqing, China) were invited to participate in this study. HCC diagnosis was confirmed according to established guidelines.[10,11,14] The local institutional review board approved the protocol, and written informed consents were obtained from all patients before enrolment, in compliance with the 1975 Declaration of Helsinki (6th revision, 2008). This trial was registered at http://www.chictr.org (ChiCTR-TRC-0800-0073) and the CONSORT statement was followed.

Eligibility criteria were: (i) established HCC diagnosis; (ii) Child–Pugh class A and indocyanine green retention at 15 min (ICGR-15) less than 14%; (iii) no more than two tumors limited to one side of the liver; and (iv) aged 18–75 years. Exclusion criteria were: (i) moderate to severe portal hypertension diagnosed by preoperative enhanced CT scan and endoscopy; (ii) tumor invasion or thrombosis in major hepatic vessels; (iii) extrahepatic metastases; (iv) tumors located in the caudate lobe; (v) previous or concomitant malignancies; or (vi) cancer treatment within 6 weeks.

Randomization and blinding

Eligible patients were randomized to AR or NAR using computer-generated random numbers sealed in envelopes prepared by a biostatistician and kept by the staff at the clinical center. Patients were randomized in a 1:1 ratio, without blocks. The surgeon and the patients were blinded to this randomization protocol prior to the intraoperative evaluation. During follow-up, the outcome assessor was blinded to the randomization protocol until the end of the study. When the intraoperative evaluation showed that the patient was suitable for both AR and NAR, designated staff opened the next sealed envelope and the surgeon was informed of the patient's allocation.

Interventions

The same team of senior surgeons performed all AR and NAR in the present study. All these surgeons had an experience of at least 100 anatomic hepatectomies. All patients underwent open surgery. During parenchymal transaction, a Pringle maneuver including 15 min of ischemia followed by a 5-min reperfusion was performed in all patients.

AR, defined as the removal of the tumors and their related liver segments with a minimal extent of monosegmentectomy according to Couinaud's view, was performed.[15,16] No submonosegmentectomy was performed. When three or more segments were involved (but confined to one half of the liver, as per exclusion criteria), hemihepatectomy was favored. Intraoperative ultrasound guidance and methylene blue staining methods were routinely used.[17] NAR was defined as the surgical resection of detectable tumors with a histologically proven tumor-free margin, regardless of the segmental or lobar anatomy. A 2-cm margin was generally aimed at, when possible.

Follow-up, data collection and endpoints

Follow-up

After surgery, patients received anti-HBV therapy according to established guidelines.[11] Patients were screened using hepatic ultrasonography and α-fetoprotein (AFP) measurement every two months, dynamic computed tomography every four months, and chest radiography every six months. FDG-PET and hepatic angiography were scheduled as required. Elevated AFP levels systemically led to chest, abdomen, and bone imaging.

When tumor recurrence occurred, the patient was hospitalized and treated with repeated hepatic resection, radiofrequency ablation (RFA), ethanol injection, or transcatheter arterial chemoembolization (TACE).[10,11,14] Patients were followed up for at least five years (as of July 2012) or until death.

Endpoints

The primary outcome was 2-year LR incidence.

Secondary outcomes included operative outcomes (postoperative complications, treatment-related mortality, and hospital stay), time to first LR, 1-, 3-, and 5-year overall RFS, and overall survival (OS).

Tumor recurrence was defined as the appearance of new lesions with radiological features typical of HCC, diagnosed using at least two imaging modalities,[18,19] and reported by two independent radiologists blinded to group assignment. Recurrence was defined as local when it arose in the same hepatic section as the location of the initial primary tumor.[20,21] For patients with a single abnormal result for either AFP levels or imaging findings, 1–3 months of observation or fine needle biopsy was scheduled. Any recurrence during the first two years was defined as an early recurrence. Extrahepatic recurrence referred to any recurrence outside the liver. Overall recurrence rate was defined as the sum of local, distant, and extrahepatic recurrences. A postoperative complication was defined as a major adverse event after hepatectomy, excluding pain or transient febrile reaction to the operation. Treatment-related mortality was defined as any death within 90 days after hepatectomy.[22,23]

Statistical analysis

Based on previous studies,[20,24] a difference of 25% in LR rate was presumed to be significant. At least 98 eligible patients were needed to detect a 25% difference between groups in terms of 2-year LR incidence (30–55%) using a log rank test with a

Please cite this article in press as: Feng X, et al., A double blinded prospective randomized trial comparing the effect of anatomic versus non-anatomic resection on hepatocellular carcinoma recurrence, HPB (2017), http://dx.doi.org/10.1016/j.hpb.2017.04.010