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ScienceDirect

EJSO the Journal of Cancer Surgery

EJSO xx (2017) 1–7 www.ejso.com

Salvage hepatectomy for local recurrence of hepatocellular carcinomas offers survival comparable to that of matched patients who undergo primary hepatectomies

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Accepted 29 March 2017
Available online ■ ■ ■

Abstract

Background: The feasibility of salvage hepatectomy for locally recurrent hepatocellular carcinomas (HCCs) is unclear, especially for patients with viable parts of previously multinodular tumors.
Methods: We reviewed charts of patients who underwent initial hepatectomies between 2000 and 2014 to select those with local recurrences (LR) after non-surgical treatments. Their postoperative outcomes, including morbidity, recurrence-free survival (RFS), and overall survival (OS) were compared with matched patients who underwent initial hepatectomies for primary HCCs (PR). Their local recurrence patterns were divided into recurrent solitary tumors (Subgroup A); and recurrent parts of multinodular tumors (Subgroup B).
Results: Among 664 patients, hepatectomy for LR was performed in 62 patients. Matched 59 patients were selected as PR. Clinicopathologic profiles at initial surgery were comparable between the LR and PR groups. Incidence of major morbidity (LR vs. PR, 7% vs. 5%, $P = 1.00$), 5-year RFS (21% vs. 37%, $P = 0.28$), and 5-year OS (69% vs. 69%, $P = 0.62$) were comparable. In the LR group, Subgroup B showed worse 5-year RFS (A vs. B, 29% vs. 0%, $P < 0.01$) and 5-year-OS (80% vs. 53%, $P = 0.01$). Postoperative recurrence occurred in 46 patients, but local and extrahepatic recurrence was seen only in 2 patients and 2 patients, respectively.
Conclusion: Salvage hepatectomy for locally recurrent HCCs is feasible, and results in prognosis comparable with hepatectomy for primary HCCs. Although the risk of postoperative recurrence was high in Subgroup B, rare local recurrence suggests the usefulness of salvaging uncontrolled tumor by nonsurgical treatment.

Keywords: Hepatocellular carcinoma; Local recurrence; Salvage hepatectomy; Multinodular

Introduction

Intrahepatic recurrence of hepatocellular carcinoma (HCC) reportedly occurs in 60–70% of post-hepatectomy patients.[1,2] Repeated treatment with hepatectomy and other local treatment, including radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), or transarterial chemoembolization (TACE), contributes to patients' longer survival.[3,4] So far, outcomes of repeat hepatectomy[2,5–15] or salvage hepatectomy (SH) for local recurrence (LR) after percutaneous ablation therapy[16–20] have been reported.

Salvage hepatectomy is indicated for HCCs that were insufficiently treated, or for LR after loco-regional treatment. Outcomes of SH have been reported mainly for recurrent HCCs after RFA. However, patients who undergo multiple treatments (not limited to RFA) may suffer LRs, occasionally as part of multinodular HCCs, with other tumors well controlled by preceding treatments. Whether SH for such patients is feasible as for those with solitary HCCs is unclear.

In this study, we evaluated outcomes of SH in patients with insufficient tumor response or LR after non-surgical loco-regional treatment. In addition, we explored whether SH is indicated for patients with multiple initial HCC tumors that had been partially controlled with nonsurgical treatments.

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http://dx.doi.org/10.1016/j.ejso.2017.03.021

Please cite this article in press as: Kishi Y, et al., Salvage hepatectomy for local recurrence of hepatocellular carcinomas offers survival comparable to that of matched patients who undergo primary hepatectomies, Eur J Surg Oncol (2017), http://dx.doi.org/10.1016/j.ejso.2017.03.021

Patients and methods

Patients

This work has been approved by our institutional review board. We retrospectively reviewed records of patients who underwent hepatectomy for HCCs between 2000 and 2014 to select the patients who underwent first hepatectomy for the HCCs with insufficient treatment effect or local recurrence (group LR). Patients with combined or mixed hepatocellular and cholangiocellular carcinoma were excluded. The types of recurrent tumors at the time of hepatectomy in the LR group were classified as Subgroup A, who suffered recurrences of initially solitary tumors treated previously; and Subgroup B, whose previously treated HCC was multinodular. Representative computed tomography (CT) images of each type are shown in Fig. 1. For comparison, matched patients who underwent primary hepatectomy for HCC (the PR group) during the same period were selected using propensity scoring. Short- and long-term outcomes, including postoperative morbidity, recurrence-free survival (RFS) and overall survival (OS) from the time of hepatectomy, were compared between Groups LR and PR. Morbidity was defined according to Clavien–Dindo classification; events ≥ grade IIIa were defined as major morbidity.[21] In the LR group, treatment history before hepatectomy, pathological tumor stage (per the Liver Cancer Study Group of Japan staging system[22]), RFS, OS, and tumor recurrence patterns were compared between Subgroups A and B. In Subgroup B, numbers of unresected tumors at the time of SH for local recurrence were evaluated. Tumor pathological characteristics and postoperative outcomes were also compared among patients according to their most recent treatment that resulted in local recurrence: RFA, PEI, or TACE.

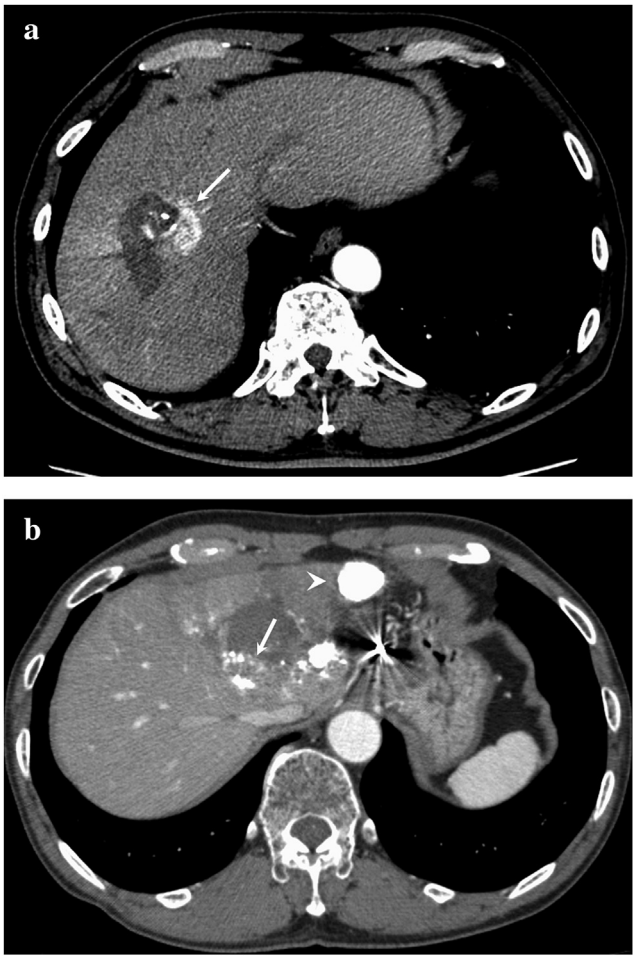

Figure 1. CT images of representative cases of (a) recurrent solitary liver tumors (Subgroup A) and (b) recurrent tumors from multinodal liver cancers (Subgroup B). Arrows: arterial enhancement lesion, indicating local recurrence. Arrowhead: accumulation of lipiodol without arterial enhancement, indicating complete necrosis following preceding TACE.

Definition of local recurrence or insufficient treatment

Diagnosis of tumor recurrence was made based on CT or magnetic resonance imaging. Local recurrence after RFA or PEI was defined as emergence of new lesions within or adjacent to the treated region; after TACE, local recurrence was defined as appearance of new lesions in the area of lipiodol accumulation. Insufficient treatment that was identified by first post-treatment CT through an arterial enhancement region within the treated area was also defined as local recurrence.

Strategy of hepatectomy for recurrent HCCs

Indication of hepatectomy for recurrent HCCs was decided using the same criteria as for primary HCCs, from the Japan Society of Hepatology guideline[23] and Makuuchi criteria.[24] The maximal extent of hepatectomy was decided based on the indocyanine green retention rate at 15 min (ICG-R15) in addition to tumor location and extent. Resection of ≥3 Couinaud's segments was considered a major hepatectomy.

Pathologic evaluation of resected specimens included tumor size, number, differentiation grade, macroscopic and microscopic vasculobiliary invasion, and resection margin. Resection margin was considered positive when cancer cells were exposed on the dissection surface; exposure of only the tumor capsule was considered negative.[25] Postoperatively, each patient was followed up every 3–6 months, with tumor markers (α-fetoprotein [AFP] and des-γ-carboxy prothrombin [DCP]) and CT. Diagnoses of tumor recurrences were based on CT findings. After tumor recurrence, further treatment was performed based on the same criteria as above.

Statistics

Continuous data were expressed as medians and ranges and compared by the Mann–Whitney *U* test. Categorical

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