Management of Recurrent Hepatocellular Carcinoma (HCC) after Curative Treatment
Securement of enough safe surgical margin is the only benefit of the surgical resection in the treatment of hepatocellular carcinoma.
• In a survey of autopsy cases of liver cirrhosis with small HCC, smaller HCC nodules were found in other liver slices in 50% of cases, and it is estimated that approximately 50% of HCC is already multicentric in the early stage.
Recurrence of HCC

- After liver transplantation, the 5-year recurrence rate is estimated at between 5% and 15% in the literature.
- Recurrence within Milan criteria after primary resection of HCC ranges between 60% to 80%.
- Recurrence is confined to the liver in 80% to 95% of cases.
- In 15% of cases, extra hepatic recurrence is associated.
- In about 50% of cases, recurrence is multifocal.
- Two types of recurrences may be distinguished: early recurrence and late recurrence.
- The literature is unclear regarding cut-off time with some authors considering cut-off at 12 mo and others 2 years. Usually, early recurrence is considered to occur up to 2 years after primary HCC and late recurrence more than 2 years after primary resection.
- Early recurrence is considered as metastatic occurrence and late recurrence as multicentric occurrence of HCC.
- Microvascular invasion, satellite nodule, poor differentiation, nonanatomic resection are risk factors for early recurrence.
- Late recurrence shares the same risk factors as primary HCC.
Patterns of Intrahepatic HCC Recurrence

• Local intrahepatic metastasis
  ; recurrence around the tumor through the portal blood flow or venous drainage

• Systemic intrahepatic metastasis
  ; recurrence caused by circulating tumor cells

• Multicentric intrahepatic recurrence
  ; caused by de novo development of HCC
Recurrent HCC after Curative Treatment

- Usually small in size than that of the initial treatment
- Apt to biologically favorable (selected)
- Reluctant to surgery
- Role of minimally invasive surgery
Major studies of outcomes of repeat hepatectomy for recurrent HCC

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Type of Study</th>
<th>Patients (n)</th>
<th>5 YSR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al (2012)</td>
<td>Retrospective study</td>
<td>82</td>
<td>22.4</td>
</tr>
<tr>
<td>Chan et al (2013)</td>
<td>Systematic review</td>
<td>1125</td>
<td>52 (22-83)</td>
</tr>
<tr>
<td>Yamashita et al (2013)</td>
<td>Retrospective study</td>
<td>163</td>
<td>60</td>
</tr>
<tr>
<td>Mise et al (2014)</td>
<td>Retrospective study</td>
<td>289</td>
<td>60.5</td>
</tr>
<tr>
<td>Sun et al (2017)</td>
<td>Retrospective study</td>
<td>43</td>
<td>56.4</td>
</tr>
</tbody>
</table>
Radiofrequency ablation versus surgical resection for intrahepatic hepatocellular carcinoma recurrence: a meta-analysis.

Chen X, Chen Y, Li Q, Ma D, Shen B, Peng C.

Abstract

BACKGROUND:
To compare the clinical efficacy and safety of radiofrequency ablation (RFA) versus surgical resection (SR) for intrahepatic hepatocellular carcinoma (HCC) recurrence by meta-analytical techniques.

METHODS:
Literature documenting a comparison of RFA and SR for intrahepatic HCC recurrence was identified by searching PubMed, Embase, Cochrane Library, and Web of Science databases, for those from inception to July 2014 with no limits. The heterogeneity was tested by the Cochrane Q statistic; the pooled estimates were measured using either fixed or random effect model. Furthermore, subgroup and sensitivity analyses were conducted to explore heterogeneity between studies and to assess the efficacy of different studies.

RESULTS:
Seven studies were included with a total of 718 patients (359 treated with RFA and 359 treated with SR). Our meta-analysis showed that the 1-, 3-, and 5-y overall survival rate and procedure-related mortality rate were similar in patients treated with RFA or SR. Meanwhile, SR was associated with significantly higher 1-, 3-, and 5-y re-recurrence-free survival rate and procedure-related morbidity rate compared with RFA. In the subgroup analysis of patients in China, the results concerning overall and re-recurrence-free survival were similar to the outcomes of the meta-analysis without regional restriction. In the subgroup analysis of intrahepatic recurrent HCC ≤3 cm, the 1-, 3-, and 5-y overall survival rate did not differ significantly in the comparison of RFA and SR.

CONCLUSIONS:
Although RFA was associated with lower re-recurrence-free survival, it seems to be as effective as SR for the treatment of intrahepatic HCC recurrence owing to comparable overall survival benefits. The advantages of being less invasive, highly target-selective, and repeatable may render RFA a preferred treatment option for selected patients.
Is radiofrequency ablation equal to surgical re-resection for recurrent hepatocellular carcinoma meeting the Milan criteria? A meta-analysis.
Zhang CS, Zhang JL, Li XH, Li L, Li X, Zhou XY.

Abstract

PURPOSE:
To evaluate the clinical efficacy and safety of radiofrequency ablation (RFA) with surgical re-resection (SRR) in patients with postoperative recurrent hepatocellular carcinoma (RHCC) meeting the Milan criteria.

METHODS:
A literature search was performed to identify comparative studies addressing outcomes of both RFA and SRR for RHCC meeting the Milan criteria. Pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using either the fixed effects model or the random effects model.

RESULTS:
Five nonrandomized controlled trials were included in the analysis. These studies included a total of 543 patients: 243 treated with RFA and 300 treated with SRR. The SRR group had a better 3-year recurrence-free survival rate compared with RFA group (OR 0.44, 95%CI 0.25-0.77, p=0.004). However, there were no obvious differences between RFA and SRR group in overall survival (OS) rates, re-recurrence rate and OS rates with tumors ≤ 3cm. What's more, the RFA group had a safety advantage with less complications of Clavien classification grade II or higher compared with SRR group (OR 0.21, 95%CI 0.05-0.94, p=0.04).

CONCLUSIONS:
RFA seemed to be superior to SRR in the treatment of patients with RHCC meeting the Milan criteria on account of clinical safety. However, these findings have to be carefully interpreted due to the lower level of evidence.
Male/63, HCC, HBV related

Postop. 30 month

Rt. hepatectomy

Laparoscopic partial hepatectomy
M/72, HCC, HBV and alcohol

Postop. 146 month

Intraoperative RFA
Limitation of Surgical Resection for the Recurrent HCC after Curative Treatment

• Negative attitude for the surgery (both doctor and patient)
• Small liver remnant (poor surgical margin)
• Tumor location being adjacent to major vascular or biliary structure
• Poor liver function reserve
• Technical difficulty
• Adhesion due to previous surgery
Intraplatelet 5-HT monitored during early follow-up, after liver resection may represent a useful marker of early HCC recurrence.

Urotensin II and the associated urotensin II receptor (UTR) are important in the carcinogenesis of hepatocellular carcinoma (HCC).

High NLR was an independent unfavorable prognostic factor.

High E3 ubiquitin ligase Parkin in patients with adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma.

Downregulation of GPR155 may serve as a prognosticator that also predicts initial recurrence sites independent of hepatitis virus infection.

High levels of serum 14-3-3 β were associated with metastasis and poor prognosis in HCC.

Pre-S deletions at the time of resection could predict tumor recurrence in HCC patients after curative resection.

Postsurgical quantity of small triploid CTCs (≥5 cells/6 ml blood), multiploid (≥pentasomy 8) CTSCs or CTM (either one ≥ 1) significantly correlated to HCC patients' poor prognosis, indicating that detection of those specific subtypes of CTCs and CTSCs in post-operative patients help predict neoplasm recurrence.

The ratio of miR-125b-5p expression in cancerous versus non-cancerous tissue (miR-125b ratio), but not miR-148a-3p, was significantly lower in the early recurrence group.

High autophagy related P62 expression activates the NRF2 pathway, promotes tumor recurrence.

MAP17, a small non-glycosylated membrane protein, was a novel diagnostic and prognostic biomarker for HCC patients and promoted HCC cell proliferation, invasion and migration via the Akt/mTOR pathway.

The overexpression of Filamin-A (FLNA), a cytoskeleton protein with scaffolding properties, predicts recurrence of HCC after hepatectomy.

Elevated serum IgG4:IgG ratio is associated with poor clinical outcomes in HCC patients.
The decision to perform a repeat hepatic resection must currently be based on the same guidelines as used in selecting a patient for an initial hepatic resection: a limited number of metastases, the technical ability to resect all gross disease, satisfactory general medical condition of the patient, and adequate functional hepatic reserve.