

Combined major liver resection and radiofrequency ablation for multifocal hepatocellular carcinoma

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- There is no conflict of interest
- No financial disclosure



Hepatocellular carcinoma (HCC)

- Liver transplantation
 - Offer best survival
 - May exceed liver transplant criteria
 - Milar criteria and UCSF criteria
 - Lack of liver graft

Mazzaferro V et al. N Engl J Med 1996
Yao FY et al. Hepatology 2001



- Liver resection
 - Gold standard
 - Depends on
 - Anatomical location
 - Major vessel involvement
 - Multifocality
 - Liver function
 - Presence of distant metastasis
- Low rate tumor resectability ~ 20% - 37%

Fong Y et al. Ann Surg 1999
Poon RT et al. Ann Surg 2002



- Radiofrequency ablation (RFA)
 - Most ideal for smaller size tumor
 - Best < 3cm
 - Safe and effective up to 8 cm in size
 - But higher recurrence rate

Poon RT et al. Arch of Surg. 2004



Multifocal and bilobar HCC

- Transarterial chemoembolisation (TACE)
 - Unresectable multifocal HCC
 - Palliative in nature

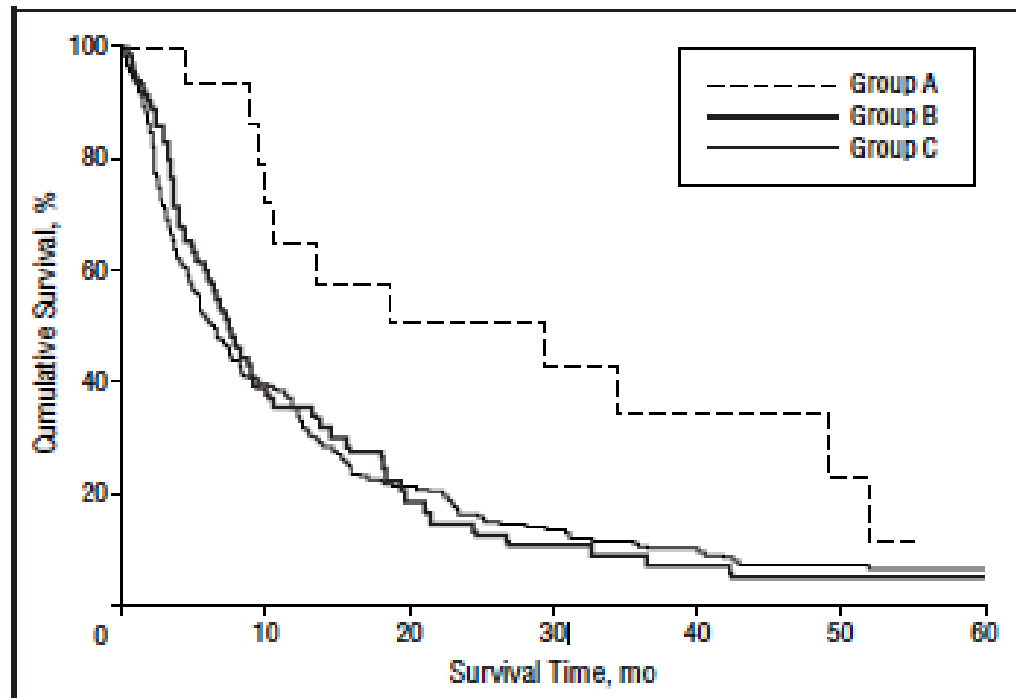
Lo CM et al. Hepatology 2002
Forner A et al. Semin Liver Dis 2010



Hepatic Resection for Bilobar Hepatocellular Carcinoma

Is It Justified?

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Conclusions: Hepatic resection for HCC in patients with stage IVa bilobar disease results in a better survival outcome than nonresectional therapies. It should be considered in selected patients with low operative risks and satisfactory liver function.

Arch Surg. 2003;138:100-104



Significance of Reduction Surgery in Multidisciplinary Treatment of Advanced Hepatocellular Carcinoma With Multiple Intrahepatic Lesions

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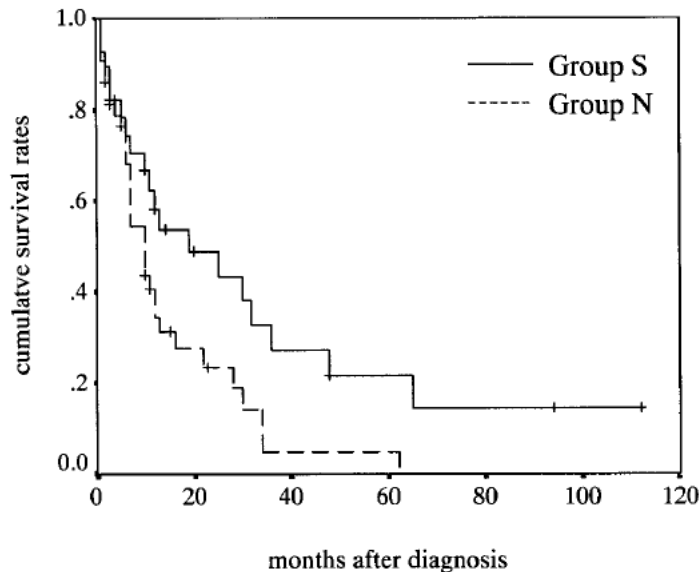


Fig. 1. Cumulative survival curves obtained by the Kaplan-Meier method for groups N and S.

Conclusions: When combined with intraoperative adjuvant therapy for remaining satellite tumors, reduction surgery provided survival benefit for patients with HCC with multiple intrahepatic lesions in those groups of patients selected by criteria determined in this study.

J. Surg. Oncol. 2003;82:98–103. © 2003 Wiley-Liss, Inc.



Hepatic and Pancreatic Tumors

Combined Hepatectomy and Radiofrequency Ablation for Multifocal Hepatocellular Carcinomas: Long-term Follow-up Results and Prognostic Factors

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Conclusions: Combined hepatectomy and RFA is an effective and safe treatment modality for multifocal HCCs. Resected tumor size was a significant prognostic predictor of long-term survival.



TABLE 1. The 3-year and 5-year overall survival results of combined radiofrequency ablation (RFA) and hepatectomy for multifocal hepatocellular carcinomas (HCCs). NS not significant, HBsAg hepatitis B surface antigen, HCVAb hepatitis C virus antibody, ICG-R15 indocyanine green dye retention rate 15 min after injection of a 0.5-mg/kg dose, AFP α -fetoprotein.

| Characteristics | No. of patients | 3-Year survival rate (%) | 5-Year survival rate (%) | Median survival (months) ^b | P value ^c |
|----------------------------------|-----------------|--------------------------|--------------------------|---------------------------------------|----------------------|
| Overall | 53 | 80 | 55 | 67 | |
| Age | | | | | |
| Younger (≤ 53 years) | 26 | 85 | 85 | NA | NS (0.193) |
| Older (> 53 years) | 27 | 74 | 37 | 58 | |
| Gender | | | | | |
| Male | 42 | 78 | 52 | 67 | NS (0.945) |
| Female | 11 | 81 | 81 | NA | |
| HbsAg | | | | | |
| Present | 42 | 82 | 66 | NA | NS (0.587) |
| Absent | 11 | 67 | 33 | 58 | |
| HCVAb | | | | | |
| Present | 6 | 100 | 50 | 58 | NS (0.192) |
| Absent | 47 | 77 | 62 | NA | |
| Child-Pugh class | | | | | |
| Class A | 47 | 79 | 63 | 67 | NS (0.956) |
| Class B | 6 | 83 | 42 | 58 | |
| ICG-R15 | | | | | |
| $< 10\%$ | 24 | 78 | 78 | NA | NS (0.830) |
| $\geq 10\%$ | 29 | 81 | 50 | 67 | |
| AFP | | | | | |
| $< 100 \mu\text{g/l}$ | 34 | 81 | 61 | 67 | NS (0.531) |
| $\geq 100 \mu\text{g/l}$ | 19 | 77 | 51 | NA | |
| Operation time | | | | | |
| < 4 h | 20 | 94 | 63 | NA | NS (0.141) |
| ≥ 4 h | 33 | 70 | 52 | 67 | |
| Estimated blood loss | | | | | |
| < 0.5 l | 25 | 87 | 44 | 44 | NS (0.638) |
| ≥ 0.5 l | 28 | 73 | 55 | 67 | |
| Extent of the resection | | | | | |
| $< \text{Bisegmentectomy}$ | 29 | 95 | 63 | NA | NS (0.463) |
| $\geq \text{Bisegmentectomy}$ | 24 | 65 | 43 | 58 | |
| Resected tumor size ^a | | | | | |
| ≤ 5 cm | 37 | 89 | 67 | NA | 0.004 |
| > 5 cm | 16 | 57 | 29 | 58 | |
| Resected tumor number | | | | | |
| Single | 40 | 84 | 63 | NA | NS (0.776) |
| 2-6 | 13 | 66 | 44 | 44 | |
| Edmonson-Steiner grade | | | | | |
| Grade I or II | 48 | 82 | 68 | 67 | NS (0.102) |
| Grade III or IV | 5 | 6 | 0 | 58 | |
| Tumor encapsulation | | | | | |
| Present | 42 | 89 | 59 | NA | NS (0.709) |
| Absent | 11 | 53 | 35 | 58 | |
| Microvascular invasion | | | | | |
| Present | 26 | 79 | 68 | 58 | NS (0.601) |
| Absent | 27 | 91 | 73 | 67 | |
| Cirrhosis of the liver | | | | | |
| Present | 28 | 84 | 56 | 67 | NS (0.676) |
| Absent | 25 | 71 | 71 | NA | |
| Ablated tumor size ^a | | | | | |
| ≤ 2 cm | 42 | 85 | 58 | 67 | NS (0.072) |
| > 2 cm and ≤ 4 cm | 11 | 61 | 61 | NA | |
| Ablated tumor number | | | | | |
| Single | 42 | 74 | 59 | 67 | NS (0.071) |
| 2-3 | 11 | 100 | 0 | 58 | |

^aWhen a patient had multiple HCCs, the largest tumor was selected

^bEstimation of median survival was limited to the largest survival time when it was censored (NA, not available)



Combined resection and radiofrequency ablation for multifocal hepatocellular carcinoma: Prognosis and outcomes

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Table 1 Reasons for adopting combination therapy *n* (%)

| | Combination group (<i>n</i> = 19) |
|---|---------------------------------------|
| Bilobar disease | 14 (73.6) |
| Proximity to major vessel or bile duct | 5 (26.3) |
| Dense adhesion | 3 (15.8) |
| Large resection required for small tumors | 5 (26.3) |
| ICG rate at 15 min > 14.4% | 5 (26.3) |
| Low platelet count (< 100 × 10 ⁹ /L) | 3 (15.8) |
| Severe cirrhosis | 9 (47.4) |

ICG: Indocyanine green.

Table 3 Types of resection performed according to Brisbane terminology (2005) of liver resection *n* (%)

| | Combination group (<i>n</i> = 19) | Resection group (<i>n</i> = 54) |
|----------------------------|---------------------------------------|-------------------------------------|
| Right hepatectomy | 1 (5.3) | 17 (31.5) |
| Extended right hepatectomy | 0 (0) | 6 (11.1) |
| Right trisectionectomy | 0 (0) | 2 (3.7) |
| Left hepatectomy | 3 (15.8) | 3 (5.6) |
| Extended left hepatectomy | 2 (10.5) | 4 (7.4) |
| Left trisectionectomy | 0 (0) | 3 (5.6) |
| Left lateral sectionectomy | 3 (15.8) | 1 (1.9) |
| Segmentectomy | 1 (5.3) | 11 (20.4) |
| Wedge resection of liver | 9 (47.4) | 7 (13) |

CONCLUSION: Safe and effective for selected patients with multifocal hepatocellular carcinoma, the combination of resection and intraoperative RFA widens the applicability of surgical intervention for the disease.



Multifocal and bilobar HCC

- Liver resection
 - Remove the largest tumor bulk
- RFA
 - Target lesions in the liver remnant
 - Achieve complete ablation



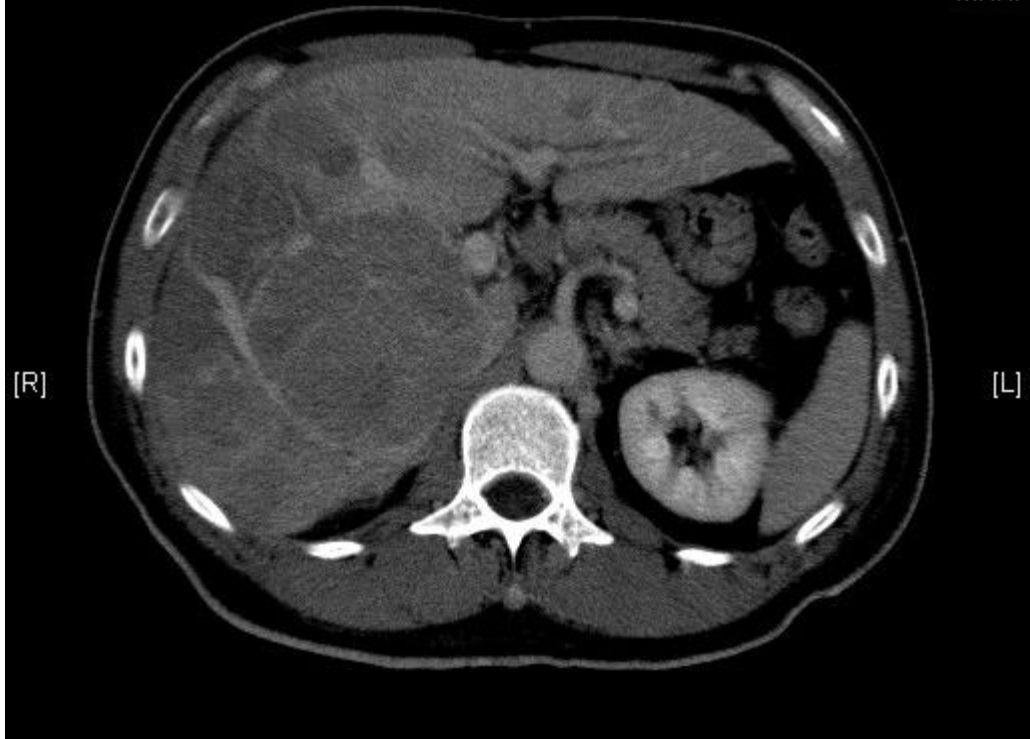
Aim

- Compare the result of combined major hepatectomy and RFA with major hepatectomy alone for bilobar multifocal HCC



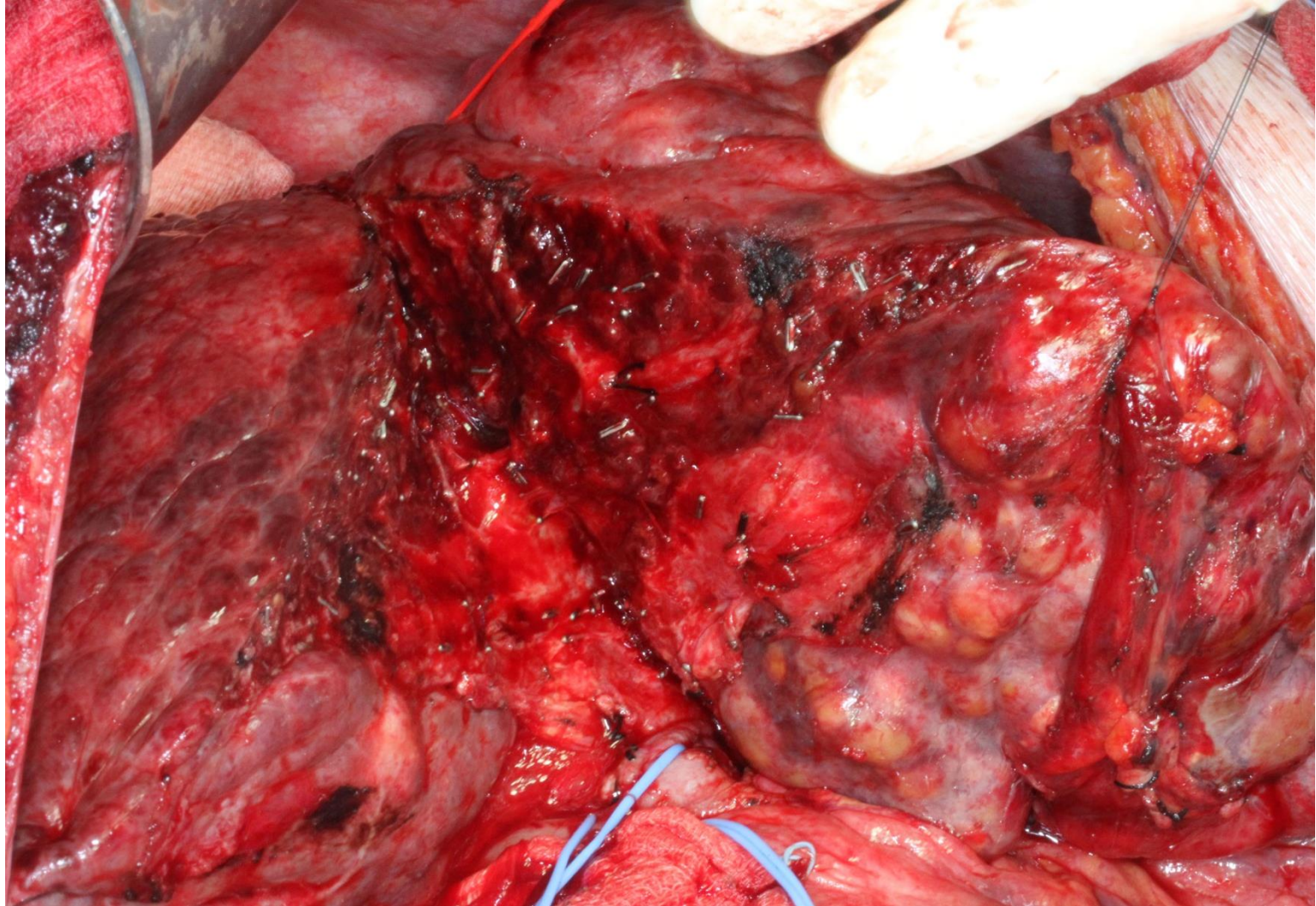
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Materials and methods

- Retrospective review from Jan 2001 to Dec 2013
 - Bilobar involvement
 - Multifocal diseases
 - Major liver resection + RFA vs major resection alone
- Patient selection
 - Baseline characteristics
 - Matched by propensity score matching in a ratio of 1:2
 - Number of tumor nodules
 - Bilobar disease
 - Size of the tumor
 - Microvascular invasion
 - Age
 - Sex
 - Child Pugh Grading
 - TMN 7th edition staging



Surgical technique

- Intraoperative ultrasound to confirm tumor location
- Anatomical resection for largest group of tumor with clear resection margin
- RFA for smaller lesions in the liver remnant aiming for complete tumor ablation



Follow up and monitoring

- 3 – monthly in the first year and quarterly thereafter if no recurrence
- CT or MRI 1 month after hepatectomy
- Every 3 – 4 months in the first year
- Every 6 months in subsequent years



Statistical analysis

- Continuous variables
 - Median (interquartile range)
 - Mann-whitney U-test
- Categorical variables
 - χ^2 test or Fisher's exact test
- In-hospital death
 - Death while patient was in hospital after hepatectomy
- Clavien –Dindo classifications
- Kaplan-Meier method
 - Overall survival and disease-free survival



Results

| P-value of comparing patients' characteristics of two groups | Matched - RFA & major resection group (n=16) vs. Major resection alone (n=32) |
|--|---|
| 1. Microvascular invasion | 0.527 |
| 2. Number of tumor nodules | 0.18 |
| 3. Size of the tumor (length) | 0.965 |
| 4. Bilobar involvement | 1 |
| 5. Age | 0.784 |
| 6. Sex | 1 |
| 7. TMN 7 th staging | 1 |
| 8. Child Pugh Grade | 1 |
| Comparable confounding factors | All 8 |



| Patients' characteristics | RFA & resection group (n=16) | Resection (n=32) | P-value |
|---------------------------------|------------------------------|------------------|---------|
| Age [Median (Range)] | 59 (34-76) | 58.5 (27-74) | 0.784 |
| Sex [Male: Female] | 13:3 | 25:7 | 1 |
| Hepatitis B (positive) | 15 (93.8%) | 29 (90.6%) | 1 |
| Comorbid disease [yes (%)] | 5 (31.3%) | 9 (28.1%) | 1 |
| Heart | 4 (25%) | 8 (25%) | 1 |
| Lung | - | - | - |
| Renal | - | - | - |
| DM | 4 (25%) | 4 (12.5%) | 0.494 |
| Gastrointestinal | 1 (6.3%) | 1 (3.1%) | 1 |
| Child Pugh Grade | | | 1 |
| A | 15 (93.8%) | 30 (93.8%) | |
| B | 1 (6.3%) | 2 (6.3%) | |
| Pre-op ICG % | 12.7 (3-34.9) | 11.45 (4.1-29.9) | 0.152 |
| Ascites | | | - |
| Absent | 16 (100%) | 32 (100%) | |
| MELD | 7.8 (6-18) | 7.5 (6-12) | 0.25 |
| No. of tumour nodules [Yes (%)] | | | 0.18 |
| 2 | 4 (25%) | 15 (46.9%) | |
| 3 | 4 (25%) | 5 (15.6%) | |
| 4 | 2 (12.5%) | 1 (3.1%) | |
| 5 | 1 (6.3%) | 0 (0%) | |
| 6 | 1 (6.3%) | 0 (0%) | |
| Multiple | 4 (25%) | 11 (34.4%) | |



Preoperative liver function

| Patients' characteristics | RFA & resection group (n=16) | Resection (n=32) | P-value |
|---------------------------|------------------------------|------------------|---------|
| Serum Bilirubin | 9 (5-57) | 15 (4-33) | 0.098 |
| Creatinine | 78.5 (61-120) | 81.5 (59-127) | 0.694 |
| INR | 1.1 (0.9-1.8) | 1 (0.9-1.3) | 0.04 |
| Albumin | 38.5 (27-43) | 40 (29-46) | 0.041 |
| Platelet count | 197 (49-615) | 187 (89-483) | 0.861 |
| AFP | 205 (3-738300) | 116.5 (2-530600) | 0.948 |
| AST | 61 (21-882) | 66.5 (24-768) | 0.71 |
| ALT | 49 (12-187) | 51.5 (12-275) | 0.956 |



Type of resection

| Patients 'characteristics | RFA & resection group (n=16) | Resection (n=32) | P-value |
|---|------------------------------|------------------|---------|
| Types of resection | | | 0.383 |
| Right Hepatectomy | 4 (25%) | 0 (0%) | |
| Right Extended Hepatectomy | 3 (18.8%) | 13 (40.6%) | |
| Left Hepatectomy | 4 (25%) | 0 (0%) | |
| Left Extended Hepatectomy | 2 (12.5%) | 6 (18.7%) | |
| Right Trisegmentectomy | 2 (12.5%) | 6 (18.8%) | |
| Left Extended Hepatectomy+Caudate lobectomy | 1 (6.3%) | 1 (3.1%) | |
| Right Trisegmentectomy+Caudate lobectomy | 0 (0%) | 2 (6.3%) | |
| Central Bisegmentectomy | 0 (0%) | 2 (6.3%) | |
| Left Trisegmentectomy+Caudate lobectomy | 0 (0%) | 2 (6.3%) | |



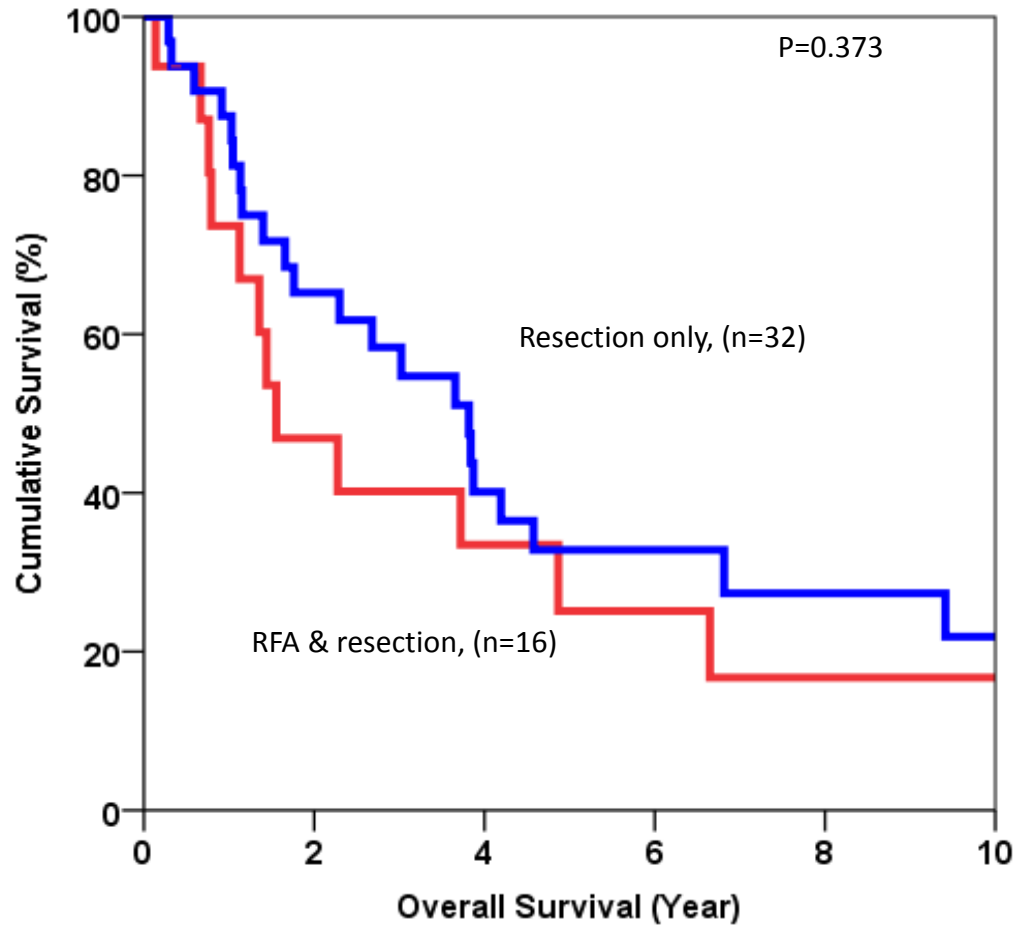
| Patients 'characteristics | RFA & resection group (n=16) | Resection (n=32) | P-value |
|-----------------------------|------------------------------|------------------|---------|
| Blood loss (L) | 0.87 (0.12-12.3) | 0.91 (0.2-3.75) | 0.954 |
| Blood replacement (L) | 0 (0-5.47) | 0 (0-1.92) | 0.59 |
| Blood transfusion (yes, %) | 4 (25%) | 6 (18.8%) | 0.9 |
| Hospital stay (days) | 10.5 (4-50) | 13 (4-69) | 0.259 |
| Hospital mortality (yes, %) | 1 (6.3%) | 0 (0%) | 0.721 |
| Total OT duration (mins) | 448.5 (254-775) | 455 (231-1015) | 0.991 |



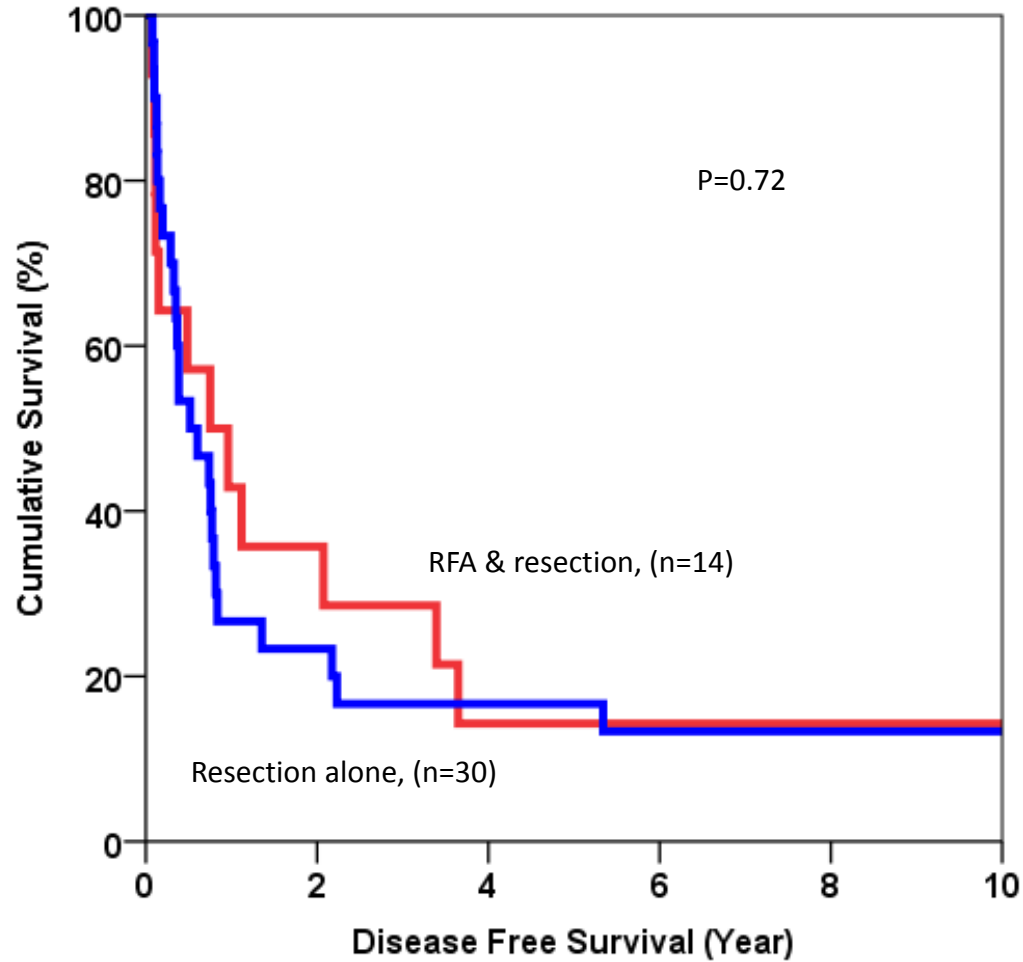
| Patients 'characteristics | RFA & resection group (n=16) | Resection (n=32) | P-value |
|----------------------------------|---------------------------------|---------------------|---------|
| Microvascular invasion [yes (%)] | 11 (68.8%) | 19 (59.4%) | 0.527 |
| Pattern of recurrence [No. (%)] | | | 0.511 |
| No recurrence | 4 (25%) | 3 (9.4%) | |
| Intrahepatic recurrence | 7 (43.8%) | 15 (46.9%) | |
| Extrahepatic recurrence | 1 (6.3%) | 2 (6.3%) | |
| Both recurrence | 4 (25%) | 12 (37.5%) | |
| Non tumourous liver | | | 0.198 |
| Non-cirrhotic | 3 (18.8%) | 4 (12.5%) | |
| Chronic Hepatitis | 2 (12.5%) | 12 (37.5%) | |
| Cirrhotic | 11 (68.8%) | 16 (50%) | |
| Differentiation [Yes (%)] | | | 0.653 |
| Well | 1 (6.3%) | 4 (12.5%) | |
| Moderate | 13 (81.3%) | 22 (68.8%) | |
| Poor | 1 (6.3%) | 5 (15.6%) | |
| NA | 1 (6.3%) | 1 (3.1%) | |
| Resection Margin [Yes (%)] | | | 1 |
| Not involved | 15 (93.8%) | 29 (90.6%) | |
| Involved | 1 (6.3%) | 3 (9.4%) | |
| UICC 7 staging | | | 1 |
| IIA | 4 (25%) | 7 (21.9%) | |
| IIIA | 12 (75%) | 25 (78.1%) | |
| Follow up duration (months) | 18.67 (4.53-146.7) | 34.47 (3.48-182.88) | 0.411 |
| Time to recurrence (months) | 7.4 (0.87-43.77) | 5.4 (0.93-165.83) | 0.871 |



Overall survival rate



Disease-free survival rate



Discussion

- Surgical resection
 - Location of the tumors
 - Liver function
 - Size of the liver remnant
- TACE
 - Multifocal disease which is inoperable



Radiofrequency ablation

- Preferred modality of local ablation for unresectable liver tumors

Poon RT et al. Ann Surg 2002

- As effective as hepatectomy for HCC < 5cm

Livraghi T et al. Radiology 2000

Poon RT et al. Arch Surg 2004

Chen MH et al. Radiology 2004



- Achieve a clear resection margin and complete ablation of tumor
- Safe and feasible
 - Similar blood loss, operative duration and post-operative complications and mortalities
- Similar overall and disease-free survival
- Increase the operability for those patients who used to be declined for surgery



Table 1

**American Joint Committee on Cancer (AJCC)
TNM Staging for Liver Tumors (7th ed., 2010)**

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- T1** Solitary tumor without vascular invasion
- T2** Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- T3a** Multiple tumors more than 5 cm
- T3b** Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein
- T4** Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** Regional lymph node metastasis

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis

Anatomic Stage/Prognostic Groups

| | | | |
|-------------------|-------|-------|----|
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage IIIA | T3a | N0 | M0 |
| IIIB | T3b | N0 | M0 |
| IIIC | T4 | N0 | M0 |
| Stage IVA | Any T | N1 | M0 |
| Stage IVB | Any T | Any N | M1 |

Histologic Grade (G)

- G1** Well differentiated
- G2** Moderately differentiated
- G3** Poorly differentiated
- G4** Undifferentiated

Fibrosis Score (F)

The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

- F0** Fibrosis score 0-4 (none to moderate fibrosis)
- F1** Fibrosis score 5-6 (severe fibrosis or cirrhosis)



- Feasibility of such aggressive management as long as adequate future liver remnant
 - Similar survival
- Small scale retrospective study on selected group of advanced HCC patients



Conclusion

- Safe and feasible in selected patients
- Similar survival with bilobar and multifocal HCC managed with major hepatectomy alone
- Increase the operability
- Implication of the staging



- Thank you

