Hepatic Resection as a Safe and Effective Treatment for Hepatocellular Carcinoma Involving a Single Large Tumor, Multiple Tumors, or Macrovascular Invasion

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Abstract: This systematic review examined whether the available evidence justifies using hepatic resection (HR) during later stages of hepatocellular carcinoma (HCC), which contravenes treatment guidelines but is current practice at many medical centers. Official guidelines and retrospective studies recommend different roles for HR for patients with large/multinodular HCC or with HCC involving macrovascular invasion (MVI).

Several databases were systematically searched for studies examining the safety and efficacy of HR for treating HCC involving a single large tumor (>5 cm) or multiple tumors, or for treating HCC involving MVI.

We identified 50 studies involving 14,808 patients that investigated the use of HR to treat large/multinodular HCC, and 24 studies with 4389 patients that investigated HR to treat HCC with MVI. Median inhospital mortality for patients with either type of HCC was significantly lower in Asian studies (2.7%) than in non-Asian studies (7.3%, \( P < 0.001 \)). Median overall survival (OS) was significantly higher for all Asian patients with large/multinodular HCC than for all non-Asian patients at both 1 year (81% vs 65%, \( P < 0.001 \)) and 5 years (42% vs 32%, \( P < 0.001 \)). Similar results were obtained for median disease-free survival at 1 year (61% vs 50%, \( P < 0.001 \)) and 5 years (26% vs 24%, \( P < 0.001 \)). However, median OS was similar for Asian and non-Asian patients with HCC involving MVI at 1 year (50% vs 52%, \( P = 0.45 \)) and 5 years (18% vs 14%, \( P = 0.94 \)). There was an upward trend in 5-year OS in patients with either type of HCC.

HR is reasonably safe and effective at treating large/multinodular HCC and HCC with MVI. The available evidence argues for expanding the indications for HR in official treatment guidelines.

(International Committee of Medical Journal Editors guidelines were followed for performing this review and reporting the results.)

(B)Hepatocellular carcinoma (HCC) is the third cause of cancer-related deaths, and its prevalence is expected to increase in coming decades.1 HCC staging significantly affects treatment decisions and patient prognosis. Of the several staging systems proposed, the Barcelona Clinic Liver Cancer (BCLC) system2 is the only one recommended by the American Association for the Study of Liver Diseases (AASLD)3 and the European Association for the Study of the Liver (EASL).4 Most major HCC staging systems recommend hepatic resection (HR) only for patients with early-stage HCC (BCLC stage A). To be eligible for such treatment, patients usually need to fit the restrictive Milan criteria: HCC involving either a single tumor <5 cm or up to 3 nodules <3 cm, preserved or minimally compromised liver function (Child–Pugh A or B), and no vascular invasion.5,6 Associations like the AASLD and EASL do not recommend HR for patients in later stages of HCC (BCLC stage B or C), whose disease often involves multiple tumors, macrovascular invasion (MVI), or portal hypertension.

Many medical centers also routinely categorize patients with single large tumors (>5 cm) as stage B, although some experts recommend classifying them as stage A. C.7 HR is contraindicated for stage B and C patients because of the substantial risk that remnant liver function will be insufficient or that the cancer will recur after surgery. Instead, the BCLC system recommends only palliative treatments, in particular transarterial chemoembolization for stage B patients and sorafenib or other drugs for stage C.3,4

Despite official recommendations, many clinicians do not restrict HR to early-stage HCC. In fact, studies in various countries have reported it to be an effective treatment option.
| Study | Country | Total Patients | Single Tumor, n (%) | Tumor Size (cm) | Child–Pugh A | Cirrhosis | HBV | HCV | Notes |
|-------|---------|----------------|-------------------|----------------|-------------|-----------|-----|-----|-------|
| Abdel-Wahab et al15 | Egypt | 20 | – | 6.9 ± 1.5 | 14 (70) | 18 (90) | 3 (15) | 14 (70) | Tumor size 5–10 cm |
| Alleman et al16 | Switzerland | 22 | – | 15.2 ± 3.8 | 15 (72) | 15 (83) | 3 (17) | 13 (72) | Tumor size ≥ 10 cm |
| Ariizumi et al17 | Japan | 177 | 63 (36) | 13 (10–24) | 143 (81) | 35 (20) | 60 (34) | 117 (66) | Tumor size ≥ 10 cm |
| Chen et al18 | China (central) | 525 | 392 (75) | 7.4 (IQR, 5.7–10.4) | 311 (98) | 97 (31) | 79 (47) | 159 (31) | Tumor size ≥ 10 cm |
| Chang et al19 | Taiwan | 41 | – | 8.0 (IQR, 5.5–10.3) | 37 (93) | 15 (37) | 27 (68) | 48 (12) | Central hepatectomy |
| Cheng et al20 | Taiwan | 41 | – | 6.5 (IQR, 5.5–8.5) | 56 (89) | 30 (48) | 43 (68) | 15 (25) | |
| Chirica et al21 | France | 20 | – | 10 cm | 20 (100) | 12 (60) | 6 (30) | 6 (30) | Stage IV (TNM); 7 patients (35%) showed macrovascular invasion |
| Cho et al22 | South Korea | 61 | 61 (100) | 7.1 ± 1.1 | 56 (92) | 35 (58) | 40 (67) | 5 (8) | Tumor size > 5 cm and < 10 cm |
| Choi et al23 | South Korea | 50 | 29 (58) | ≥ 10 | 48 (96) | 13 (26) | 33 (66) | 1 (2) | Tumor size ≥ 10 cm |
| Delis et al24 | Greece | 66 | 51 (77) | 8.7 (5.2–11.2) | 66 (100) | 59 (89) | 36 (55) | 15 (23) | Tumor size ≥ 5 cm |
| Gahn et al25 | Serbia | 32 | 30 (94) | 10.25 (mean) | 22 (69) | 32 (100) | 13 (41) | 4 (13) | BCLC-B |
| Hanazaki et al26 | Japan | 133 | 104 (78) | 8.6 ± 3.8 | 93 (70) | 69 (52) | – | – | Tumor size > 5 cm |
| Ho et al27 | Taiwan | 294 | 0 (0) | 50 ± 3.5 | 229/242 (95) | 188 (64) | 200/281 (71) | 82/54 (32) | Tumor number ≥ 2 |
| Hsu et al28 | Taiwan | 268 | 160 (60) | ≥ 7: 146 | 248 (93) | – | 176 (66) | 48 (18) | Beyond Milan criteria; 179 (67%) had macrovascular invasion |
| Huang et al29 | Taiwan | 139 | – | ≥ 10: 104 | – | 80/139 (58) | 68/96 (71) | 10/96 (11) | Tumor size ≥ 10 cm, tumor rupture and/or involvement of adjacent organs |
| Ikai et al30 | Japan | 4972 | – | 5–10 | – | – | – | – | Tumor size 5–10 cm |
| Ishizawa et al31 | Japan | 126 | 0 (0) | > 10 | 105 (83) | 103 (82) | 12 (10) | 93 (74) | Tumor number ≥ 2 |
| Lee et al32 | South Korea | 100 | 80 (80) | 13.3 ± 3.0 | 88 (88) | – | 83 (83) | – | Tumor size > 10 cm; 22 (22%) had macrovascular invasion |
| Liu et al33 | USA | 82 | 71 (87) | 14.7 ± 4.1 | 73/78 (94) | 88/10 (10) | 4 (5) | – | Tumor size ≥ 10 cm |
| Lin et al34 | Taiwan | 93 | 49 (53) | 8.0 ± 3.3 | 93 (100) | – | 60 (65) | 22 (24) | BCLC-B |
| Liu et al35 | Hong Kong | 54 | – | 10.3 (5–25) | – | 15 (28) | 46 (85) | – | Tumor size ≥ 5 cm; treated using anterior resection approach; 30 (56%) showed “venous infiltration” by tumor |
| Liu et al36 | Hong Kong | 60 | 41 (68) | 10.5 (8–13) | – | 19 (32) | 55 (92) | 2 (3) | Tumor size ≥ 5 cm; treated using anterior resection approach; 64 patients (61%) showed “venous infiltration” by tumor |
| Liu et al37 | Hong Kong | 60 | 41 (68) | 10.7 (12–15) | – | 19 (32) | 51 (85) | 1 (2) | Tumor size ≥ 5 cm; treated using conventional resection approach; 39 patients (65%) showed “lymphovascular permeation” by the tumor |

Notes: Child–Pugh classification, Cirrhosis, HBV, HCV.
| Study                  | Country/Region                          | Tumor Number | Tumor Size | Number | Follow-up | Surgery/Therapy                                                                 |
|-----------------------|-----------------------------------------|--------------|------------|--------|-----------|--------------------------------------------------------------------------------|
| Luo et al (2015)      | China (southern)                        | 0 (0)        | 8.7 ± 3.5  | 60 (71) | 64 (75)   | Tumor number ≥2                                                                |
| Mok et al (2015)      | Taiwan                                  | 31 (55)      | >10        | –      | 28 (50)   | Tumor size > 10 cm; 16 (29)                                                   |
| Nagano et al (2015)   | Japan                                   | 15 (58)      | >10        | 22 (85) | 5 (19)    | Tumor size > 10 cm; 3 (12)                                                    |
| Ng et al (2015)       | Hong Kong, USA, France, Japan            | –            | –          | 361 (95)| 101 (27)  | Single nodule >5 cm or multiple nodules                                         |
| Ng et al (2015)       | Australia                               | 23 (52)      | 12.4 (10–20)| 35 (80) | 15 (34)   | Tumor size ≥10 cm; 3 (7)                                                      |
| Pandey et al (2015)   | Singapore                               | 95 (57)      | 13 (10–24) | 166 (100)| 80 (48)   | Tumor number ≥2                                                                |
| Poon et al (2015)     | Hong Kong                               | 79 (66)      | 13.8 ± 3.0 | –      | 32 (27)   | Tumor size > 10 cm; 103 (86)                                                  |
| Ramacciato et al (2015)| Italy                                  | 31 (100)     | 8.2 ± 2.3  | 16 (52) | 25 (81)   | Tumor size > 10 cm; 7 (23)                                                   |
| Ruzzenente et al (2015)| Italy                                 | 0 (0)        | 3.3 ± 1.4  | 5 (25)  | 19 (95)   | Tumor size > 10 cm; 15 (75)                                                   |
| Schiffman et al (2015)| USA                                     | 61 (78)      | ≥5         | 12 (15) | 32 (41)   | Tumor number ≥3; 2–3 nodules                                                  |
| Shah et al (2015)     | Canada                                  | –            | 13.1 ± 2.9 | 24 (100)| –         | Tumor size ≥5 cm; 18 patients (23%) had macrovascular or microvascular invasion |
| Shimada et al (2015)  | Japan                                   | 37 (44)      | 12 (10–26) | –      | 9 (11)    | Tumor size > 10 cm; 19 (25)                                                   |
| Shragar et al (2015)  | USA                                     | 95 (74)      | 14.2 ± 3.84| 116 (65)| –         | Tumor size > 10 cm; 116 patients (89%) underwent resection; 66 patients (52%) had macrovascular invasion; 23 (18%) were treated with both resection and tumor thrombectomy |
| Taniai et al (2015)   | Japan                                   | 13 (45)      | 13.5 ± 2.8 | 23 (79) | 12 (41)   | Tumor size > 10 cm; 17 (59)                                                   |
| Totorzilli et al (2015)| France, Italy, Japan, Argentina, USA     | 6 (1–25)     | –          | 360/659 (55)| 158/566 (28)| Tumor size > 10 cm; 208/566 (37)                                              |
| Truant et al (2015)   | France                                  | 43 (83)      | 14 (8–22.9)| –      | 0 (0)     | BCLC-B                                                                           |
| Wakabayashi et al (2015)| Japan                                | –            | 6.7 ± 4.1  | 21 (75) | –         | Tumor size ≥5 cm; 27 patients (52%) had microvascular and/or macrovascular invasion |
| Wang et al (2015)     | Taiwan                                  | 0 (0)        | 5–10       | 34 (71)| –         | Multiple intrahepatic lesions                                                 |
| Study                  | Country                  | Total Patients | Single Tumor, n (%) | Tumor Size (cm) | Liver Function, n (%) | Comorbidities, n (%) | Notes                                                                 |
|-----------------------|--------------------------|----------------|---------------------|----------------|-----------------------|----------------------|----------------------------------------------------------------------|
| > 10: 24              | –                        | 62 (55)        | 69 (62)             | 35/99 (35)     | Tumor number ≥2; 18 patients (39%) had macrovascular invasion |                      |

| Wang et al54          | Taiwan                   | 243            | –                   | –              | –                     | –                    | BCLC-B with multiple or single large (>5 cm) tumors                    |
| Wang et al53          | China (southern)         | 189            | –                   | 5–10: 189      | –                     | –                    | Tumor size 5–10 cm                                                    |
| Yamashita et al55     | Japan                    | 53             | –                   | >10: 8.35      | –                     | –                    | Tumor size >10 cm                                                     |
| Yamashita et al55     | Japan                    | 53             | –                   | 13.2 ± 0.4     | –                     | 18 (34)              | 22 (42)                                                              |
| Yang et al56          | China (eastern)          | 86             | –                   | ≥5             | 217 (83)              | 63 (73)              | Tumor size 10 cm                                                      |
| Yang et al57          | China (central)          | 260            | 260 (100)           | 9.63 ± 4.07    | 198 (76)              | 2.39 (92)            | Tumor size 15 cm                                                      |
|                       |                          | 86             | 0 (0)               | 6.98 ± 3.67    | 60 (70)               | 71 (83)              | 80 (93)                                                             |
|                       |                          |                |                     |                |                       |                      | Tumor number ≥2; 61 patients (71%) had ‘vein invasion’               |
|                       |                          |                |                     |                |                       |                      | Beyond Milan criteria                                                 |
| Yin et al58           | China (eastern)          | 88             | 0 (0)               | 9.5 ± 3.0      | 87 (99)               | 69 (78)              | 81 (92)                                                             |
| Young et al59         | UK                       | 42             | 24 (57)             | 14 (10–37)     | –                     | 2 (5)                | 7 (17)                                                              |
|                       |                          |                |                     |                |                       |                      | Tumor size >10 cm; 13 patients (33%) had macrovascular invasion       |
|                       |                          |                |                     |                |                       |                      | BCLC-B                                                              |
| Zhong et al57         | China (southern)         | 660            | 515 (78)            | 8.3 (5–20)     | 660 (100)             | 514 (78)             | 614 (93)                                                             |
|                       | China (northern)         | 85             | 85 (100)            | >5             | 80 (94)               | 65 (76)              | 68 (80)                                                             |

BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, HCV = hepatitis C virus, IQR = interquartile range.

Reported as mean ± SD, median (range), or median (IQR), unless indicated otherwise.

Number of patients with tumor(s) of the indicated size or size range.

HBV or HCV infection.

This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the BCLC-B subgroup were obtained from the authors.
for patients in later stages of disease, leading to calls to expand the indications for HR. For example, patients with ≥4 nodules in Japan are routinely treated by HR when they show Child–Pugh A or B liver function and no vascular invasion. Consensus-based HCC treatment guidelines of the Japan Society of Hepatology advocate considering HR for a broader range of HCC patients, including those with Child–Pugh B liver function, multiple tumors (regardless of size), or minimal portal invasion.

We are unaware of studies assessing the strength of evidence for or against HR as a treatment for large/multinodular HCC or for HCC with MVI. Here we systematically review the literature on treating such patients with HR, and we find strong evidence that it is a safe and effective therapy for selected patients. Our results suggest that official guidelines should expand the indications for HR to provide more than just palliative options to many currently considered to have unresectable cancer.

METHODS

Database Searching

The following databases were searched for original research articles by the end of March 2014: PubMed, the Cochrane Database of Systematic Reviews, the Directory of Open-Access Journals (www.doaj.org), and the Web of Knowledge. The following search string was used: “hepatoma” or “liver cancer” or “liver neoplasm” or “liver tumor” or “hepatocellular carcinoma” AND “resection” or “hepatectomy” or “surgery” AND “intermediate” or “advanced” or “huge” or “large” or “multinodular” or “vascular invasion”.

FIGURE 1. Flowchart of study selection. HCC = hepatocellular carcinoma.

Study Inclusion Criteria

Studies were included in our review if they evaluated the efficacy of HR to treat adults with primary HCC involving a single large tumor (>5 cm) or multiple tumors of any size, or to treat adults with HCC involving MVI; reported data on at least one of the outcomes of in-hospital mortality, median survival, overall survival (OS) and disease-free survival (DFS); and were published in English on or after January 1, 2000. In the case of multiple studies based on the same population, we selected the study with the largest number of participants.

Studies were excluded if they evaluated HR specifically as a treatment for recurrent HCC or HCC with microvascular invasion. Although difficult to detect before surgery, microvascular invasion can be diagnosed by postoperative histopathology, but this is not routine clinical practice and so was not performed in many of the studies we found in the literature.

Definitions

HCC in the included studies was diagnosed based on pathology. Large HCC was diagnosed by preoperative imaging and then confirmed histologically as a single tumor >5 cm in diameter with no evidence of additional tumors. MVI was defined as tumor invasion of 1 or more of the following: segmental branches, right/left and main portal vein, hepatic vein, superior mesenteric vein, and inferior vena cava.

OS was measured from when HR was performed until death or the end of follow-up. DFS was measured from when HR was performed until a diagnosis of recurrence. Postoperative complications were those reported to occur within 30 days of surgery.
| Study          | Country          | Total Patients | Single Tumor, n (%) | Tumor Size, cm | Liver Function, n (%) | Comorbidities, n (%) | Characteristics of Vascular Invasion |
|---------------|------------------|----------------|---------------------|----------------|------------------------|-----------------------|-------------------------------------|
| Ban et al62   | Japan            | 45             | –                   | ≥7.0 ± 2.41    | 38 (84)                | –                     | Including the main portal vein      |
| chang et al86 | Taiwan           | 165            | 36 (23)             | 7.5 (5.0–11.0) | 156 (98)               | 60 (40)               | BCLC-B                             |
| Chen et al66  | China (central)  | 438            | 362 (83)            | 7.7 and 8.11   | –                      | –                     | PVTT                               |
| Chen et al65  | China (southern)| 88             | 45 (51)             | ≥10.1 ± 3.5    | 74 (84)                | 73 (83)               | PVTT                               |
| Fan et al63   | China (eastern)  | 84             | 58 (69)             | ≥10: 391       | 66 (79)                | –                     | PVTT                               |
| Huang et al64 | China (western)  | 116            | –                   | 20.7 ± 4.8     | 116 (100)              | 41 (35)               | Involving the main branches of the PV or HV; 62 patients (53%) treated with both resection and adjunction chemotherapy                                    |
| Ikai et al50  | Japan            | 976            | –                   | –              | –                      | –                     | Involving the first-order branches or main trunk of PV |
| Inoue et al57 | Japan            | 49             | –                   | –              | 42 (86)                | –                     | PVTT                               |
| Le Trew et al66 | France         | 26             | –                   | 9 (3–24)      | 26 (100)               | 17 (65)               | Involving the major PV              |
| Liang et al58 | Japan           | 53             | 33 (62)             | ≥10: 271       | 37 (70)                | 41 (77)               | PVTT                               |
| Ohkubo et al57 | Japan           | 47             | 19 (40)             | ≥10: 15.1      | 43 (91)                | 17 (36)               | PVTT                               |
| Pawlik et al31 | USA, France,   | 102            | 43 (42)             | 10 (2–22)     | 92 (90)                | –                     | Involving the major PV or HV         |
| Peng et al72  | China (southern)| 63             | –                   | 9.0 ± 3.0      | 58 (92)                | 49 (78)               | PVTT                               |
| Peng et al73  | China (southern)| 201            | 95 (47)             | >5: 1257       | 197 (98)               | 176 (88)              | PVTT                               |
| Poon et al74  | Hong Kong       | 20             | –                   | 8.6 ± 3.6      | 11 (55)                | 17 (85)               | PVTT                               |
| Roxyaie et al35 | USA            | 165            | –                   | 9.0 ± 5.6      | 165 (100)              | 112 (68)              | Involving the major PV or HV; 2 patients (10%) received postoperative chemotheraphy |
| Ruzzenente et al44 | Italy         | 73             | –                   | –              | 73 (100)               | –                     | Macrovascular invasion               |
| Shi et al70   | China (eastern) | 406            | –                   | ≥5: 3761       | 397 (98)               | 320 (79)              | Macrovascular invasion               |
| Tang et al71  | China (eastern) | 186            | 101 (54)            | ≥5: 3.4        | 171 (92)               | 149 (80)              | PVTT                               |
| Torzilli et al, 2013 | France, Italy, | 297            | 6 (1–30)            | –              | 169/265 (64)           | 70/244 (29)           | Involving the major portal or HV     |
| Wang et al70  | Taiwan          | 68             | –                   | –              | 68 (100)               | –                     | BCLC-C                             |
| Wu et al70    | Taiwan          | 97             | –                   | 8.8 ± 5.1      | 84 (87)                | 70 (72)               | BCLC-C                             |
| Zhong et al70 | China* (southern)| 248           | 159 (64)            | 8.7 (1–20)     | 248 (100)              | 198 (80)              | PVTT                               |
| Zhou et al68  | China (eastern) | 381            | 250 (66)            | ≥5: 3347       | 340 (89)               | 343 (90)              | PVTT                               |

BCLC = Barcelona Clinic liver cancer stage, HV = hepatic vein, PV = portal vein, PVTT = portal vein tumor thrombus.
+ Total no. of patients recruited into the study; the total n for clinical assessments (Child–Pugh A, cirrhosis, HBV, HCV), if different, is indicated in the corresponding data fields.
1 Reported as mean ± SD or as median (minimum to maximum), unless indicated otherwise.
2 Number of patients with the indicated size or size range.
3 Reported separately for 2 subgroups with PVTT, which were combined for the purposes of our review.
§ Reported separately for 2 subgroups with PVTT, which were combined for the purposes of our review.
* This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the BCLC-C subgroup were obtained from the authors.

### Data Extraction and Analysis

Four authors (J.-H.Z., Y.K., L.W., Y.Y.W.) extracted data from included studies using a predefined template, and a sixth author (A.C.R.) checked the extracted data against the original articles. Data were extracted on demographic and clinicopathological characteristics of patients, in-hospital mortality, postoperative complications, and both OS and DFS at 1, 3, and 5 years after HR. Survival data were taken directly from tables or the text whenever possible; if such data were presented only in graphs, they were extracted by manual interpolation. Study-level data were analyzed using simple descriptive statistics (mean, median, range) after aggregating studies based on type of HCC (large/multinodular vs MVI) or patient ethnicity (Asian vs non-Asian). Differences between continuous data were analyzed using the sample size-weighted Mann–Whitney U test. Differences between categorical data were analyzed using the chi-squared test. For the included studies, 1-, 3- and 5-year OS and DFS were summarized graphically using bubble plots, in which relative sample size was proportional to bubble size. Changes in 5-year OS over time were analyzed using least-squares weighted regression according to sample.
size as implemented in Microsoft Excel 2013 for personal computer.

**RESULTS**

Our systematic review identified 50 studies involving 14,808 participants investigating the efficacy and/or safety of HR to treat multinodular HCC, defined as involving multiple tumors regardless of size, or to treat large HCC, defined as involving a single tumor >5 cm (Table 1, Figure 1). Whereas most studies of large HCC used the cut-off of 5 cm, some focused specifically on so-called “huge” or “giant” HCC involving tumors ≥10 cm. Most studies on large/multinodular HCC examined patients who had been treated only with HR, whereas some studies included patients who had been treated with a combination of HR and adjunct therapy. Some of the included studies contained a substantial proportion of patients with MVI, but their outcomes data were usually aggregated with those of patients without such invasion.

We also identified 24 studies with 4389 participants investigating the efficacy and/or safety of HR to treat HCC involving MVI (Table 2). In these studies, all patients had MVI.

Heterogeneity of patient clinicopathology and treatment across the included studies precluded pooling the data and performing meta-analyses. Instead, study-level data were analyzed using simple descriptive statistics after aggregating studies based on type of HCC (large/multinodular vs MVI) or patient ethnicity (Asian vs non-Asian). Three studies were dismissed based on type of HCC (large/multinodular vs MVI) or patient ethnicity (Asian vs non-Asian). Studies were excluded from ethnic subgroup analysis because the cohorts included patients from Asian and non-Asian countries, and data for each ethnic group were not reported separately.

In both sets of studies for large/multinodular HCC and for HCC with MVI, most patients were from Asia, and the midpoints of the enrollment periods fell between 1990 and 2005 (Tables 3 and 4). Most patients had preserved liver function (Child–Pugh A). The median rate of cirrhosis was 57% (range, 11%–91%) in Asian studies, lower than the 81% (range, 0%–100%) in non-Asian studies ($P = 0.21$). Cirrhosis was significantly more frequent among Asian patients with HCC with MVI (median, 78%; range, 35–89%) than among Asian patients with large/multinodular HCC (median, 50%; range, 11%–91%; $P = 0.025$). Otherwise, we did not observe significant differences in cirrhosis frequency between the 2 ethnic groups or HCC types.

The median rate of hepatitis B virus (HBV) infection was 75% (range, 10%–93%) in Asian patients with either type of HCC, significantly higher than the 32% (range, 10%–55%) in non-Asian patients ($P < 0.001$). Conversely to the trend with HBV infection, the median rate of hepatitis C virus (HCV) infection in Asian patients was 16% (range, 1%–74%), significantly lower than the 25% (range, 4%–75%) in non-Asian patients ($P < 0.001$).

**Postoperative Complications**

The postoperative complications observed most frequently in our cohorts were bleeding, sepsis, intraabdominal abscesses, liver insufficiency, ascites, cardiac and pulmonary complications, and biliary leakage. When patients of Asian and non-Asian ethnicity were aggregated, the complication rate was found to be only slightly higher in those with HCC involving MVI (median, 30.2%; range, 4.0%–42.0%) than in those with large/multinodular HCC (median, 27.0%; range, 1.6%–72%; $P = 0.176$). When patients with either type of HCC were aggregated, the complication rate was significantly lower for Asian patients (median, 26.8%; range, 1.6%–40.3%) than for non-Asian ones (median, 32.3%; range, 21.5%–72.0%; $P < 0.001$).

**In-Hospital Mortality**

When patients of Asian and non-Asian ethnicity were aggregated, in-hospital mortality was found to be similar for patients with large/multinodular HCC (median, 2.7%; range, 0%–18%) and for those with HCC involving MVI (median, 2.7%; range, 0%–24%; $P = 0.73$). When patients with either type of HCC were aggregated, in-hospital mortality was found to be significantly lower for Asian patients (median, 2.7%; range, 0%–24%) than for non-Asian ones (median, 7.3%; range, 0%–18%; $P < 0.001$). This difference was due almost entirely to the mortality difference between Asian and non-Asian patients with large/multinodular HCC, as only 2 studies of non-Asian HCC patients with MVI were included in our review.

**Overall and Disease-Free Survival Across All Studies**

Median OS across all studies investigating large/multinodular HCC decreased from approximately 81% at 1 year to 42% at 5 years (Figure 2). Median OS across all studies investigating HCC with MVI decreased from approximately 50% at 1 year to 18% at 5 years.

Median DFS across all studies investigating HCC with large/multinodular HCC fell from 61% at 1 year to 26% at 5 years (Figure 3). The corresponding DFS rates for HCC with MVI were 32% and 18%.

**Overall Survival by Patient Ethnicity and Type of HCC**

Given the notable differences between Western and Asian attitudes toward using HR for later-stage HCC, we compared survival outcomes separately in Asian and non-Asian cohorts.

OS at 1 year after surgery to treat large/multinodular HCC was significantly higher among Asian patients (median, 81%; range, 41%–94%) than among non-Asian patients (median, 65%; range, 50%–73%; $P < 0.001$). The same trend was observed at 5 years after surgery: OS for Asian patients (median, 42%; range, 17%–66%) was significantly higher than for non-Asian patients (median, 32%; range, 0%–56%; $P < 0.001$).

In contrast, 1-year OS after surgery to treat HCC with MVI was similar for Asian patients (median, 50%; range, 18%–81%) and non-Asian patients (median, 52%; range, 38%–52%; $P = 0.45$). The same trend was observed at 5 years after surgery: OS for Asian patients (median, 18%; range, 2%–40%) was similar to that for non-Asian patients (median, 14%; range, 13%–20%; $P = 0.94$).

**Disease-Free Survival by Patient Ethnicity and Type of HCC**

Among patients with large/multinodular HCC, median 1-year DFS was 61% (range, 28%–82%) for Asian patients, compared with 50% (range, 32%–62%) for non-Asian patients ($P < 0.001$). The same trend was observed for 5-year DFS, although these rates were substantially lower than at 1 year: median survival was 26% (range, 10%–39%) for Asian patients, compared with 24% (range, 0%–43%) for non-Asian patients ($P < 0.001$).

How median DFS compares between Asian and non-Asian patients with HCC and MVI is unclear, as only 1 non-Asian
### TABLE 3. Postoperative Complications, In-Hospital Mortality and Survival of Patients With Hepatocellular Carcinoma Involving Large and/or Multiple Tumors After Hepatic Resection

| Study                          | Enrolment period | Total Patients | Postoperative Complications, % | In-Hospital Mortality, % | Median Survival, mo | OS, % | DFS, % |
|--------------------------------|------------------|----------------|-------------------------------|-------------------------|---------------------|-------|--------|
|                                |                  |                |                               |                         |                     |       |        |
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study on this type of HCC was included in the subgroup analysis. Among Asian patients, 1-year median DFS was 32% (range, 8%–55%), whereas 5-year median DFS was 18% (range, 0–22%).

Survival Over Time

Given striking advances in HCC diagnosis, treatment and management in recent decades, we wanted to know whether the efficacy of HR in our cohorts has changed over the 4 decades spanned by the included studies. OS at 5 years showed an upward trend for patients with either type of HCC (Figure 4). A similar upward trend was observed in DFS at 5 years for patients with large/multinodular HCC, whereas DFS did not change appreciably for patients with MVI (data not shown).

**TABLE 4.** Postoperative Complications, In-Hospital Mortality and Survival of Patients With Hepatocellular Carcinoma Involving Macrovascular Invasion Treated by Hepatic Resection

| Study           | Enrollment period | Total Patients | Postoperative Complications, % | In-hospital Mortality, % | Median Survival, mo | OS, % 1 y 3 y 5 y | DFS, % 1 y 3 y 5 y |
|-----------------|-------------------|----------------|--------------------------------|-------------------------|---------------------|------------------|------------------|
| Ban et al⁶²      | 1992–2008         | 45             | 22.2                           | 0                       | 20                  | 70               | 37               | 22               | 30               | 21               | 0               |
| Chang et al⁸⁸    | 1991–2006         | 160            | –                              | 2.7³                    | ca. 22               | 58               | 34               | 29               | ca. 32           | ca. 24           | 22              |
| Chen et al⁹⁴     | 1990–2003         | 438            | 17.4                           | 0.2³                    | 19/10               | 52               | 16               | 12               | –                | –                | –               |
| Chen et al⁹⁵     | 2006–2008         | 88             | 19.3                           | 4.5                     | 9                   | 31               | 15               | –                | –                | –                | –               |
| Fan et al⁹⁵      | 1997–2002         | 84             | –                              | 15                      | –                   | 39               | 16               | –                | –                | –                | –               |
| Huang et al⁹⁶    | 1998–2008         | 116            | 30.2                           | 3.4                     | ca. 21              | 71               | 23               | 11               | 48               | 16               | 4               |
| Ikai et al⁹⁸     | 1992–2003         | 976            | –                              | ca. 12                  | –                   | 50               | 26               | 18               | –                | –                | –               |
| Inoue et al⁹⁷    | 1995–2006         | 49             | –                              | ca. 34                  | –                   | 60               | 45               | 40               | 35               | 30               | 20              |
| Le Treut et al⁹⁸ | 1998–2004         | 26             | 38.5                           | 11.5                    | 9                   | 38               | 20               | 13               | –                | –                | –               |
| Liang et al⁹⁹    | 2001–2005         | 53             | –                              | 1.9                     | 6                   | 23               | 6                | –                | 8                | 4                | –               |
| Ohkubo et al⁹⁰   | 1985–1997         | 47             | –                              | 2.1                     | –                   | 54               | 33               | 24               | –                | –                | –               |
| Pawlik et al⁹¹   | 1984–1999         | 102            | 5.9                            | 11                      | –                   | 45               | 17               | 10               | –                | –                | –               |
| Peng et al⁹²     | 1997–2001         | 63             | –                              | 1.9                     | 7.8                 | 18               | 15               | 2                | –                | –                | –               |
| Peng et al⁹³     | 2002–2007         | 201            | 4.0                            | 0.5                     | 20                  | 42               | 14               | 11               | 23               | 9                | 3               |
| Poon et al⁹⁴     | 1989–2000         | 20             | –                              | 5.0                     | 6                   | 30               | 13               | 13               | 15               | 5                | 5               |
| Rozyte et al⁹⁵   | 1992–2010         | 165            | –                              | 7.3                     | 13                  | ca. 52           | ca. 22           | 14               | ca. 40           | ca. 20           | 18              |
| Ruozzente et al⁹⁶ | 1994–2007        | 17             | –                              | 10                      | –                   | –                | –                | 20               | –                | –                | –               |
| Shi et al⁹⁷      | 2003–2006         | 406            | 32.8                           | 0.2                     | –                   | 34               | 13               | 13               | 15               | 5                | 5               |
| Tang et al⁹⁷     | 2006–2008         | 186            | 36.0                           | 23.7                    | 10                  | 40               | 14               | 14               | 32               | 6                | –               |
| Torzilli et al⁹⁸ | 1990–2009         | 297            | ca. 42.0                       | 3                      | ca. 36              | 76               | 49               | 38               | 46               | 28               | 18              |
| Wang et al⁹⁹     | 2003–2008         | 68             | –                              | 0                       | 33                  | 55               | –                | –                | –                | –                | –               |
| Wu et al⁹⁰       | 1990–1998         | 15             | 40.0                           | 0                       | ca. 24              | ca. 81           | ca. 45           | 26               | ca. 54           | ca. 32           | 21              |
| Zhong et al⁹ⁱ    | 2000–2007         | 248            | ca. 27.0                       | 4.4                     | –                   | 81               | 46               | 20               | 55               | 29               | 20              |
| Zhou et al⁹²     | 1980–2002         | 381            | –                              | ca. 9                   | 47                  | 16               | 12               | –                | –                | –                | –               |

ca. = approximately (for data estimated from published graphs), DFS = disease-free survival, OS = overall survival.

³ Including intermediate and advanced stage hepatocellular carcinoma (BCLC stages not reported).

⁴ The first value refers to 286 patients in whom portal vein tumor thrombosis occurred within the resected area or within 1 cm from the resection edge and extended into the first branch of the main portal vein. The second value refers to 152 patients in whom portal vein tumor thrombus extended into the main portal vein.

⁵ This reference presented aggregate data for BCLC-B and -C patients in the study cohort; data specific to the subgroup of patients with BCLC-C HCC were obtained from the authors.

**FIGURE 2.** Overall survival of patients with large/multinodular HCC or HCC with macrovascular invasion at 1, 3, and 5 years after surgery. HCC = hepatocellular carcinoma.

**FIGURE 3.** Disease-free survival of patients with large/multinodular HCC or HCC with macrovascular invasion at 1, 3, and 5 years after surgery. HCC = hepatocellular carcinoma.

**DISCUSSION**

Official HCC staging systems and clinical practice guidelines, such as those adopted by the AASLD and EASL, recommend HR only for early-stage HCC, even though medical centers around the world also use the procedure to treat patients...
with later stages of disease. Here we systematically examine the evidence for using HR to treat some types of classically “unresectable” HCC, and we find that the procedure can be safe and effective. These results argue for expanding the indications for HR.

Most treatment guidelines do not recommend HR for HCC involving multiple tumors because such patients are considered to be at high risk of intrahepatic and extrahepatic spread. Our results show that HR can be safe and effective in such patients. We also found HR to be safe and effective for patients with a single large tumor (>5 cm). AASLD and EASL guidelines neither unambiguously exclude nor recommend HR for patients with a single large tumor, and surgeons around the world routinely classify them as BCLC stage B and, therefore, unresectable.6,7 Regardless of whether these patients should be categorized as stage A or B, our findings suggest that they can be treated effectively with HR. Our results are consistent with those of a systematic review,81 examining the prognosis of patients with single or multinodular large HCC; in that study, large HCC was defined more restrictively as at least 1 tumor >10 cm, rather than >5 cm in our review, and those authors considered studies published since 1992, whereas we excluded anything published before 2000.

Thus, our findings are consistent with the suggestion that HR can be effective independently of tumor size, number, and MVI.84 In fact, the median in-hospital mortality in our studies, which ranged from 2.7% to 7.3% depending on the ethnicity or type of HCC, is comparable to the 4.0% reported in a meta-analysis of 69 studies in which Asian and non-Asian patients with HCC in various stages were treated using resection.83 The median rate of postoperative complications in our studies, which ranged from 26.8% to 32.3% depending on the ethnicity or type of HCC, is also comparable to the 28.1% reported in that study.83 Among all patients with large/multinodular HCC in our review, 5-year OS was 42% and 5-year DFS was 26%. These figures are certainly lower than the corresponding 5-year OS of 67% and DFS of 37% for patients with early-stage HCC,14 but they are not even 2-fold lower, suggesting that HR can be considered not only a reasonable but also an effective approach in carefully selected patients with advanced HCC.

HCC spreads primarily by invading the portal vein, resulting initially in intrahepatic metastases and later in extrahepatic ones.86 Vascular invasion, whether macro or micro, predicts HCC recurrence.4 We found that HR can be safe and effective for patients with MVI, in contrast to the officially recommended alternatives, such as ablative therapies, transplantation, and systemic chemotherapy, which show no survival benefit in many patients.85 Thus, HR may be the most promising option for patients with vascular invasion.

This systematic review provides the most updated and comprehensive examination of the use of HR to treat large/multinodular HCC and HCC involving MVI. Its strength lies in the large numbers and ethnic diversity of patients involved, but its weakness lies in the diversity of disease profiles and treatment approaches, which prevented us from pooling and meta-analyzing the data. Therefore, we limited our analysis to simple descriptive statistics to compare groups of Asian and non-Asian patients and subgroups of patients with either type of HCC. In addition, we focused only on overall outcomes of in-hospital mortality, postoperative complications, OS, and DFS. Although this approach limits the clinical detail of our review, it still provides a valuable overview of research findings that can inform clinical practice.

The preponderance of Asian cohorts in our included studies likely reflects the fact that HCC is more prevalent in Asian countries and so presents a greater health burden. The Asian cohorts in our review showed higher rates of HBV infection than the non-Asian cohorts, but lower rates of HCV infection. The higher rate of HBV infection is consistent with the fact that the vast majority of Chinese patients with HCC are HBV positive, and Chinese from the mainland, Hong Kong, and Taiwan accounted for more than 60% of all patients in our cohorts. The lower rate of HCV infection contrasts with the high proportion of HCC patients in Japan who are HCV positive85 and probably reflects the fact that less than one-third of the patients in our cohorts were from that country.

Non-Asian patients in our included studies showed not only a higher rate of HCV infection than Asian patients but also a higher rate of cirrhosis. This is consistent with previous studies showing that most patients (Asian or non-Asian) with both HCV infection and HCC also have advanced fibrosis or cirrhosis.86,87 These comorbidities may help explain why in-hospital mortality was significantly higher for non-Asian patients than for Asian ones in our review. Consistent with this idea, median OS and DFS were significantly lower for non-Asian patients with large/multinodular HCC than for Asian patients. That liver comorbidities can significantly determine outcomes after HR is supported by a meta-analysis of more than 35,000 resections.83 This substantial difference in clinical profile between Asian and non-Asian HCC patients in our review may help explain why guidelines from liver associations in the United States and Europe do not recommend HR to treat later stages of HCC, whereas Asian liver centers are less restrictive about using HR.88–91 At the same time, the difference in prognoses for Asian and non-Asian patients may also reflect differences in numerous other risk factors, including level of α-fetoprotein, stage of tumor differentiation, surgical method, and need for blood transfusion.41,81

Portal hypertension is a contraindication for HR according to most treatment guidelines,3 because it significantly affects prognosis of HCC patients after resection.92,93 Nevertheless, several studies in our systematic review included substantial proportions of HCC patients with portal hypertension. Our findings suggest that even such patients can be treated safely and effectively by resection. In fact, data from 2 medical centers suggest that it can be a good therapeutic option, giving 5-year OS of 41%94 and 56%,10 which compare well with the
corresponding rates of 42% for patients in our cohort with large/multinodular HCC and 18% for patients with MVI. Analysis of 5-year OS as a function of enrollment period showed a slight upward trend for patients with both types of HCC. These slight increases reflect the stunning drop in perioperative and postoperative mortality associated with HR over the last 20 years. This drop is probably due to improved surgical techniques, more sensitive diagnosis of HCC during the asymptomatic phases, and more accurate liver function assessment, allowing physicians to exclude patients at high risk of liver decompensation or death following HR. An increase in OS over time was also reported in a systematic review examining HR to treat early-stage HCC, in a study comparing patients with single or multinodular large HCC treated by HR before or after December 1996, and in a study of patients treated between 1981 and 2008 by hepatectomy of ≥4 lobes. Contrary to this trend, we did not observe any clear change in 5-year DFS in our cohort of patients with MVI. This is consistent with the notion that such HCC is a terminal condition with extremely poor prognosis, which is unlikely to change despite improvements in surgical technique or perioperative care.

Recurrence is a major challenge to treat patients with HCC; it occurs in approximately 70% of patients by 5 years after HR, and it is the most frequent cause of death among HCC patients after HR. Recurrence can be indirectly assessed by comparing OS and DFS. In our cohorts, median OS at 1 year was 16 to 23 percentage points higher than the corresponding median DFS, depending on whether we compared Asians with non-Asians, or one type of HCC against the other. The corresponding difference between median OS and DFS at 1 year in a systematic review of HR to treat patients with early-stage HCC was on the low end of this range (14 percentage points). By 5 years, the difference between median OS and DFS in our cohorts had fallen to 9 to 12 percentage points, whereas the corresponding difference among patients with early-stage HCC had increased to 30 percentage points. This comparative analysis suggests that using HR in patients with large/multinodular HCC or with HCC involving MVI is not associated with a significant increase in recurrence.

Future studies will need to address a question that our review could not: how much does recurrence contribute to the mortality of patients like ours who show higher prevalence of comorbidities and mortality risk factors than those with early-stage HCC? The generally poorer prognosis for our patients helps explain why median 5-year OS in our cohort, which ranged from 14% to 42% depending on HCC type and patient ethnicity, was lower than the median of 67% (range, 27%–81%) in a systematic review of early-stage HCC treated by HR.

Future research should also focus on refining HR to improve outcomes, reduce recurrence, and increase the range of patients to which it can be applied. These refinements may include 2-stage HR surgical techniques to prevent large tumor rupture during excision and the combination of HR with percutaneous isolated hepatic perfusion or transarterial embolization. The greatest priority may well be reducing the unacceptably high recurrence rate after HR. Although transplantation is usually considered the most effective option for dealing with postresection recurrence, donors are often scarce and as many as 20% of HCC patients on transplant waiting lists must drop out because their cancer progresses beyond transplantation criteria.

While our results indicate that HR can be safe and effective in patients in later stages of HCC, we still recommend that the therapy be considered for each patient on a case-by-case basis.

A key parameter to take into account is preoperative liver function: most patients in our cohort had Child–Pugh A function, leaving open the question of whether HR is appropriate for patients with Child–Pugh B or C function. Another consideration is the skill and experience of the surgeon, which can significantly affect the success of HR in complicated HCC. We note that Zhang et al and Torzilli et al have developed and validated detailed criteria for deciding whether HR is appropriate for patients in later stages of HCC.

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