© Med Sci Monit, 2011; 17(3): RA76-83
PMID: 21358616

www.MedSciMonit.com
Review Article

Received: 2010.04.30
Accepted: 2010.09.23
Published: 2011.03.01

Safety and efficacy of partial hepatectomy for huge (≥10 cm) hepatocellular carcinoma: A systematic review

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Source of support: Important National Science & Technology Specific Projects (No-EHBH-RCT-2008-012)

Summary

Huge (≥10 cm) hepatocellular carcinoma (HCC) is not uncommon at clinical presentation, and the surgical outcomes of such tumors are poor. This systematic review aimed to assess the safety and efficacy of partial hepatectomy for huge HCC.

We performed a search on Medline and PubMed databases for all relevant studies published prior to December 2009. After exclusions, 21 studies remained for appraisal and data extraction.

All studies were classified as level-4 evidence. The median overall perioperative morbidity and mortality rates were 29.2% (range: 13.6–72%) and 3.5% (range: 0–18.2%), respectively. The overall median survival since the partial hepatectomy was 20.7 months (range: 10.1–32 months), with median 1-, 3- and 5-year survival of 60.7% (range: 41–72.2%), 34% (range: 0–60.3%) and 28.6% (range: 0–54%), respectively. The median disease-free survival since the partial hepatectomy was 11.3 months (range: 5.5–32months), with median 1-, 3- and 5-year disease-free survival rates of 48.7% (range: 32–65.4%), 27.5% (range: 14.1–49%) and 20.7% (range: 9.5–43%), respectively.

Partial hepatectomy can be performed safely and is associated with long-term survival in a subset of patients with huge HCC, but the evidence of benefit is currently weak.

key words: **hepatocellular carcinoma • partial hepatectomy • survival**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=881443
Word count: 2849
Tables: 4
Figures: –
References: 36

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Background

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with an estimated 500,000 deaths per year [1]. Advances in diagnostic imaging and widespread application of screening programs in high-risk populations have allowed detection of small HCC, but huge (≥10 cm) HCC is not uncommon at clinical presentation [2,3]. Milan criteria (a single tumor ≤5 cm, or no more than 3 tumors, all ≤3 cm) have widely been applied to select patients with HCC for transplantation. Patients with huge HCC are not candidates for transplantation [4]. Nonsurgical therapies such as transarterial chemoembolization (TACE), percutaneous ethanol injections (PEI), radiofrequency ablation (RFA) and microwave coagulation therapy (MCT) are generally considered as ineffective for huge HCC [5]. Partial hepatectomy is therefore the only treatment that is potentially curative for these patients, but its role remains controversial. Tumor size is a major determinant of outcome after hepatic resection for HCC [2]. Early studies have shown partial hepatectomy for huge HCC resulted in a high operative mortality and dismal long-term survival [6–9]. More recent studies, on the other hand, indicated partial hepatectomy to be safe and effective for huge HCC [10–13]. Currently, randomized clinical trials (RCTs) to compare partial hepatectomy with other therapies are considered to be unethical and not feasible because of poor patient compliance and the need for a large sample size. Hence, we performed this systematic review to assess the safety and efficacy of partial hepatectomy for huge HCC.

Literature Search Strategy

Electronic literature searches were performed of the Medline and PubMed databases, from the time of inception to December 2009. The keywords "huge hepatocellular carcinoma", "large hepatocellular carcinoma", "hepatectomy" and "hepatic resection" were searched as MeSH subject headings and text words. Reference lists of all retrieved articles were searched for additional studies. All relevant articles identified were selected with predetermined criteria.

Selection Criteria

All articles that reported on partial hepatectomy for huge HCC and that provided operative procedures, morbidity, mortality, survival, recurrence and disease-free survival data were retrieved. Studies were classified into 5 levels of evidence as set out by the Oxford Centre for Evidence-based Medicine Levels of Evidence [14]:
Level 1 systematic reviews of RCTs, individual RCTs with narrow confidence interval.
Level 2 systematic reviews of cohort studies, individual cohort study (including low-quality RCT).
Level 3 systematic reviews of case-control studies, individual case-control study.
Level 4 case series, poor-quality cohort and case-control studies.
Level 5 expert opinion.

As no randomized controlled trials were available, all relevant observational case series were considered for inclusion. Letters, reviews, abstracts, editorials, expert opinions, non-English language papers and animal studies were excluded. Studies that included other liver cancers were also excluded. In dual (or multiple) publications of a single cohort of patients, only the first published article was analyzed. However, if a more recent publication that incorporated the data of the first article into a larger cohort with a longer follow-up, we instead used the more recent publication.

Data Extraction and Critical Appraisal

Data extraction was performed independently by 2 authors (Y.M.Z. and B.L.) using predefined criteria. The 2 investigators independently reviewed all the retrieved articles that met the inclusion and exclusion criteria as stated under the section "Selection Criteria". Discrepancies between the 2 reviewers were resolved by discussion and consensus. Each included study was appraised for its level of evidence [14]. The 2 reviewers extracted data on the following categories: (1) number of patients undergoing partial hepatectomy for huge HCC; (2) patient characteristics; (3) operative procedures; (4) postoperative morbidity and mortality; (5) recurrence rate; (6) survival (median, 1-, 3-, 5- and 10-year overall survival), disease-free survival (median, 1-, 3-, 5- and 10-year survival); (7) prognostic factors. A meta-analysis was not possible because none of these studies were randomized trials. All relevant text, tables and figures were reviewed for data extraction. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all the included studies.

Quantity of Evidence

Literature search using the above-described search strategy identified 354 studies. After applying the predetermined selection criteria, 329 studies consisting of non-English articles (n=67), case reports (n=48), review (n=34), duplicate series (n=3), no long-term follow-up (n=51) and tumor size <10 cm (n=126) were excluded, leaving 25 for retrieval and full-text review [6–13,15–31]. Of the 25 studies, 4 more were excluded for the following reasons: 1 was without data on histopathologic types [16], 1 included patients with cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma [18], 1 was an earlier publication from a single center [20], and 1 evaluated volume reduction surgery [21]. Finally, 21 studies remained for data extraction [6–13,15,17,19,22–31].

Of these 21 studies, 1 is a multi-institutional study [11], and 1 is a bi-institutional study [23]. Six studies had more than 100 patients [10,11,13,17,24,25], 4 studies had from 50 to 100 patients [12,19,27,29], and the remaining 11 studies had fewer than 50 patients [6–9,15,22,23,26,28,30,31].

Quality of Evidence

Among the 21 studies, 11 retrospectively looked at huge HCC in comparison with smaller (<10 cm) HCC [8–10,12,17,22,23,26–30]. One study compared partial hepatectomy with multimodality nonsurgical therapy using hepatic arterial infusion, transcatheter arterial embolization, and percutaneous acetic acid injection for huge HCC [19]. The remaining 8 studies were case series with no control groups [6,7,11,13,15,24,25,31]. All these 21 studies were classified to be at level 4 evidence. There is no prior systematic review or meta-analysis published on this topic.

The clinicopathological characteristics of patients were clearly reported in the 21 studies (Table 1).

Table 1. Characteristics of the patients with huge hepatocellular carcinoma.

Author	Year	No. of patients	Male/ female	Mean age (years)	HBsAg Positive (%)	Anti-HCV Positive (%)	Mean ICG-R15 (%)	Liver cirrhosis (%)	Child-Pugh Class A (%)	Mean tumor size (cm)
Furuta et al. [6]	1992	21	19/2	57.8±13.7	7 (33.3)	—	—	7 (33.3)	—	13.4±2.7
Noguchi et al. [7]	1997	20	15/5	56.0±11.2	9 (45)	—	—	9 (45)	15 (85.0)	12.4±2.2
Lee et al. [8]	1998	40	35/5	55.4±15.5	27 (67.5)	0	8.7±5.6	9 (22.5)	—	14.3±3.8
Abdel-Wahab et al. [9]	2001	18	13/5	56.0±8.8	3 (16.8)	13 (72.2)	17±15	15 (83.4)	13 (72.2)	15.2 ±3.8
Poon et al. [10]	2002	120	99/21	50.9±12.8	103 (85.8)	—	11.8±5.9	32 (26.7)	—	13.8±3.0
Pawlik et al. [11]	2005	300	222/78	55 (13–87)*	188 (62.7)	—	—	—	241 (80.3)	—
Liau et al. [12]	2005	82	48/34	62.0±14.0	20 (24.4)	4 (4.8)	—	8 (10)	73 (94)	14.7±4.1
Chen et al. [13]	2006	634	563/71	39.0±9.5	469 (74.0)	—	—	547 (86.3)	559 (88.2)	14.1±2.6
Hanazaki et al. [15]	2002	33	27/6	60.0±10.0	—	—	—	13(39)	22 (66.6)	13.7±2.9
Yeh et al. [17]	2003	211	164/47	47.8±14.3	163 (81.9)	16 (11.6)	8.1±6.8	63 (29.9)	52 (82.5)	13.9±3.4
Mok et al. [19]	2003	56	46/10	54.2±13.9	43 (76.7)	16 (28.6)	—	28 (50)	—	—
Nagano et al. [22]	2005	26	19/7	56.2±12.2	14 (53.8)	3 (11.5)	11.8±6.7	5 (19.2)	22 (84.6)	14.8
Shah et al. [23]	2007	24	—	57±15	9 (38)	1 (4)	9.3±4.1	—	24 (100)	13.1±2.9
Pandey et al. [24]	2007	166	143/23	55 (12–83)*	130 (78.3)	2 (1.2)	—	80 (48.2)	166 (100)	13 (10–24)*
Lee et al. [25]	2007	100	77/23	47.0 ±1 2.0	83 (83)	—	8.9±5.6	—	88 (88.0)	13.3±3.0
Young et al. [26]	2007	42	29/13	53	—	—	—	2 (5)	—	14 (10–37)*
Shimada et al. [27]	2008	86	72/14	61 (19–85)*	27 (32)	19 (25)	10.8*	9 (11)	—	13.0 ±3.1
Taniai et al. [28]	2008	29	26/3	62.0±9.4	6 (20.6)	17(65.5)	17.4±14.6	1 2(41.3)	23 (79.3)	13.5±2.8
Choi et al. [29]	2009	50	34/16	50.8±12.5	33 (66.0)	1 (2.0)	7.46±4.86	13 (26)	48 (96)	—
Miyoshi et al. [30]	2009	22	19/3	58.5±15.6	—	—	12.7±8.3	5 (22.7)	19 (86.3)	12 (10–20)*
Ng et al. [31]	2009	44	33/11	62.4 (19–87)*	15 (34.0)	3 (6.8)	—	15 (34)	35 (83.3)	13.5±3.2

* median.

Nineteen studies reported on the operative procedures [6–13,15,17,19,22,23,25–30]. Sixteen studies reported on the morbidities [6–10,12,13,15,17,22,23,26,28–30]. All studies reported on the mortalities; in 1 study the mortality of the huge and the smaller HCC were not separately analyzed [26]; hence, its data could not be analyzed.

All studies reported on overall survivals. Thirteen studies reported on recurrence [6–10,12,15,19,23,25,28,29,31]. Eleven studies reported on disease-free survivals [8,10,12,17,19,22,23,25,26,28–31]. Thirteen studies reported on the duration of follow-up [9–12,17,19,23,25,27–31].

Characteristics of the Patients in the Study Population

There were 2124 patients in these 21 studies, and the median/mean ages were 56 years. Information on the sex was available in 20 studies (2100 patients), with 1703 males and 397 females, making a male: female ratio of 4.3:1. The median Hepatitis B antigen (HBsAg) and Anti-HCV positive rates were 58.2% (range: 16.8–85.8%) and 11.5% (range: 0–72.2%), respectively. The median mean indocyanine green retention rate at 15 min (ICG-R15) was 10.8% (range: 7.46–17.4%). The median proportion of patients with Child-Pugh class A was 85% (range: 66.6–100%). The median proportion of patients with cirrhosis was 31.6% (range: 5–86.3%). The median tumor size was 13.7cm (range: 12–15.2 cm) (Table 1).

In the 11 comparative studies of smaller HCC, huge HCC was found to be more commonly associated with: (1) young patients [8,17,22,26,28,30]; (2) a lower hepatitis C infection rate [8,12,17,22]; (3) a higher HBV infection rate [4,22]; (4) a higher preoperative serum alpha-fetoprotein (AFP) level [8,10,17,22,23,29]; (5) a lower level of ICG_{R15} [8,17,22,29,30]; (6) a higher preoperative serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level [11,14,28];

Table 2. Assessment of operative procedures, morbidity and mortality on hepatectomy for huge HCC.

Reference	Major resection (%)	Mean blood loss (mL)	Blood transfusion	Operative time (min)	Morbidity (%)	Perioperative mortality (%)
6	—	3927.0±3129.0	20 (95.2%)	257±104	9 (42.9)	3 (14.3)
7	18 (90)	—	—	—	5 (25)	3 (15)
8	37 (92.5)	3600.0±2300.0	2700.0 ±1 800.0 mL	438±114	11 (27.5)	1 (2)
9	—	—	1.88±1.41 unit	205±46	13 (72)	2 (11.1)
10	108 (90.0)	3200.0±3000.0	1200.0±1700.0 mL	—	42 (35.0)	4 (3.3)
11	178 (59.3)	—	—	—	—	15 (5.0)
12	70 (85)	1015.0	15 (18%)	234±76	41 (50)	2 (2)
13	323 (50.9)	480±350	440±250 mL	98±41	170 (26.8)	14 (2.2)
15	23 (69.6)	4404.0±5246.0	2417.0±2726.0 mL	—	13 (39)	5 (15)
17	173 (82.0)	2160.8±2180.3	1518.3±1976.1 mL	—	34 (16.1)	9 (4.3)
19	39/53 (73.6)	2100.0±1900.0	—	306±74	—	1 (1.7)
22	25 (96.2)	4354.1±4480.4	—	533.9±168.7	8 (30.8)	1 (3.8)
23	—	—	—	—	12 (50)	2 (8)
24	—	—	—	—	—	5 (3)
25	67 (67)	—	—	—	—	2 (2)
26	39 (93)	—	23 (55%)	240*	—	—
27	60 (61)	1387*	—	—	—	1 (1.2)
28	15 (51.7)	2693.0±1995.0	—	415±129	8 (27.6)	2 (6.9)
29	37 (74.0)	1390.0 ±1711.0	35 (70.0%)	284±80	12 (24.0)	0
30	16 (72.7)	1927±1655	7 (31.8%)	317±80	3 (13.6)	0
31	30 (68.1)	—	—	—	—	8 (18.2)

* median.

(7) a lower incidence of cirrhosis [8,10,12,17,22,26,28–30]; (8) a higher incidence of vascular invasion [8,10,17,22,23,28–30]; (9) a higher incidence of multiple tumors [8,10,22]; (10) a higher incidence of positive resection margin [10,23]; (11) a lower incidence of tumor capsule formation [9,17,22]; (12) a higher incidence of ruptured tumors [10,17]; (13) a higher incidence of satellite lesions [12,30]; and (14) a higher incidence of advanced pTNM stage [10,12,29].

Assessment of Operative Procedures, Morbidity and Mortality

Table 2 shows the operative procedures, morbidity and mortality of the studies. The median proportion of patients who underwent major resection was 73.6% (range: 50.9–96.2%) in the 17 studies providing these data. The median/mean blood loss varied from 480 to 4404 mL. Blood transfusion was required in 18–95.2% of patients. The median/mean operating time ranged from 98 to 533.9 min.

The median overall perioperative morbidity and mortality rates were 29.2% (range: 13.6–72%) and 3.5% (range: 0–18.2%), respectively. The rates of ascites, jaundice, pleural effusion, bile leakage, intra-abdominal bleeding, and wound infection ranged from 4.7% to 72% [6,9,13,23,29], 4.7% to 44.4% [6,9], 14.3% to 21.4% [6,13], 1.1% to 12.5% [9,13,23,29], 1.3% to 11.1% [6,9,13], and 1.6% to 16% [9,13,29], respectively. Among the 42 patients who had definitive known causes of perioperative death, 25 (59.5%) died from liver failure, 4 (9.5%) from hemorrhage, 5 from sepsis (11.9%), and 8 (19%) from other causes [6–9,12,13,19,24,25,27,31].

Compared with patients with smaller HCC, more major hepatectomy was carried out on patients with huge HCC [8,10,12,17,22,26,28–30]; as a consequence, there was more blood loss [8,10,12,17,22,28–30]. Five studies reported patients with huge HCC requiring more blood transfusions [8,10,17,26,29], while 3 studies showed there was no difference [9,12,30]. Five studies reported patients with huge HCC had a significantly longer operative time [8,9,26,28,30], but no difference was observed in the other 3 studies [12,22,29]. Only 2 [9,23] of 9 studies [8–10,12,17,22,23,28,29] reported morbidity being more common in patients with huge

Table 3. Assessment of survival on hepatectomy for huge HCC.

Reference	Median follw-up (mo)	Median OS (mo)	1y-OS (%)	3y-OS (%)	5y-OS (%)	10y-OS (%)
6	—	—	72.2	32.9	8.2	—
7	—	—	50	25	20	15
8	—	—	54	34	34	—
9	40±17*	—	50	0	0	—
10	56 (6–126)	18.8	60.6	37.8	27.5	—
11	32 (0.2–208)	—	64.9	36.7	26.9	17.8
12	33	32	—	—	33	—
13	—	—	—	35.1	18.2	3.5
15	—	—	—	32	27	—
17	16.4 (1.1–213.5)	—	48.1	24.0	16.7	13.1
19	14.5 (3–137)	17	60.7	24.5	24.5	—
22	—	10.1	41.0	29.3	29.3	—
23	34 (6–149)	—	—	—	54	—
24		20	—	—	28.6	25.9
25	31±27*	—	66	44	31	—
26	—	—	70	45	45	—
27	24 (2–213)	27.6	—	—	31.5	—
28	22.5 (2–125)	—	51.9	33.6	33.6	—
29	36 (2–128)	—	70.0	50.2	40.2	—
30	48.2 (12–192)	25.0	71.8	60.3	45.2	—
31	14.5 (0.03–169.9)	21.5	66.4	38.1	27.8	—

OS – overall survival; * mean; mo – month.

HCC. The mortality rate did not differ significantly between the 2 groups in the 10 studies providing this information [8–10,12,17,22,23,27–29].

Assessment of Overall Survival

Table 3 shows the results of overall survival after hepatectomy. The median follow-up for patients with huge HCC after hepatectomy was 32 months (range: 14.5–56months). The overall median survival since the partial hepatectomy was 20.7 months (range: 10.1–32 months), with median 1-, 3- and 5-year survival of 60.7% (range: 41–72.2%), 34% (range: 0–60.3%) and 28.6% (range: 0–54%), respectively. In 5 studies the 10-year survival rates were reported to be 3.5%–25.9%.

Assessment of Recurrence and Disease-Free Survival

Table 4 demonstrates the results of recurrence and disease-free survival after hepatectomy. Recurrence developed in 57.1% to 82.4% of patients after partial hepatectomy during the different follow-up periods as reported. The median rates of disease recurrence in the liver remnant and extrahepatically were 50% (range: 30.9–69.8%) and 23.8% (range: 16–43.3%), respectively.

The median disease-free survival since the partial hepatectomy was 11.3 months (range: 5.5–32months), with median 1-, 3- and 5-year disease-free survival rates of 48.7% (range: 32–65.4%), 27.5% (range: 14.1–49%) and 20.7% (range: 9.5–43%), respectively. A 10-year disease-free survival rate of 12.7% was reported in 1 study [17].

Comparison of Survival Outcome Between Patients with Huge and Smaller HCC

Compared with patients with smaller HCC, 8 studies reported patients with huge HCC had worse 5-year survival after hepatectomy [8,10,17,22,27–30], and 3 studies found no difference [12,23,26]. Although recurrences occurred mainly in the liver remnant, patients with huge HCC had a markedly increased extrahepatic recurrence (including concurrent extra- and intrahepatic recurrence) than patients with smaller HCC, as reported in 4 studies [10,22,28,29].

Table 4. Assessment of recurrence and disease-free survival on hepatectomy for huge HCC.

Reference	Recurrence (%)	Intrahepatic recurrence (%)	Extrahepatic recurrence (%)	Median DFS (mo)	1y -DFS (%)	3y-DFS (%)	5 y-DFS (%)
6	14/18 (77.7)	11/18 (61.1)	3/18 (16.6)	—	—	—	—
7	11/16 (68.7)	—	—	—	—	—	—
8	25/40 (62.5)	—	—	—	42	30	28
9	10/16 (62.5)	10/16 (62.5)	5/16 (31.3)	—	—	—	—
10	94 /114 (82.4)	51/114 (44.7)	43/114 (37.7)	5.5	32.0	14.1	9.5
12	50/80 (62.5)	—	—	32	—	—	28
15	18/25 (72)	14/25 (56)	4/25 (16)	—	—	—	—
17	—	—	—	—	32.9	18.8	12.7
19	38/53 (71)	37/53 (69.8)	23/53 (43.3)	—	—	—	—
22	—	—	19.2	29.0	65.4	49.0	—
23	17/24 (71)	12/24 (50)	5/24 (20.8)	8.4	—	—	—
25	74/98 (76)	49/98 (50)	25/98 (25.5)	—	43	26	20
26	—	—	—	—	62	49	43
28	15/26 (57.6)	9/26 (34.6)	6/26 (23.1)	—	48.4	21.5	21.5
29	29/50 (58)	16/50 (32)	13/50 (26)	—	49.0	38.6	38.6
30	—	8/22 (36.3)	—	12.0	53.3	29.1	18.2
31	24/42 (57.1)	13/42 (30.9)	10 (23.8)	10.7	49.6%	23.9	19.1

DFS – disease-free survival; mo – month.

Six studies reported that the 5-year disease-free survival rate of patients with huge HCC was markedly worse than that of patients with smaller HCC [8,10,17,28–30]. Three studies failed to detect this difference between the 2 groups of patients [12,22,26].

Mok et al. [19] reported the overall survival of patients with huge HCC who underwent partial hepatectomy (1-year 60.7%, 3-year 24.5%, 5-year 24.5%, median survival 17 months) was significantly better than the nonsurgical group (1-year 23.3%, 3-year 9.6%, 5-year 8.2%, median survival 7 months).

Predictors of Survival

In multivariate analysis, unfavorable predictors of survival in patients with huge HCC treated by partial hepatectomy were: cirrhosis [15,24,28,31], vascular invasion [10–13,22,24,25,27], multiple tumors [10,11,27], macroscopic residual tumor [10,27], high serum AFP level (>400 ng/mL or ⩾1000 ng/ mL) [11,17], excessive blood loss (>1000 mL, or >2000 mL, or 800 mL) [12,13,17], tumor rupture [17], satellite lesions [13,17,24], capsular infiltration [13], high-grade tumor differentiation [19,31], severe fibrosis (Ishak score) [11], advanced pTNM stage [28], gross type (nonsingle nodular) [29], ethnicity (Asians *vs.* non-Asians) [31], positive HBsAg, and the year of the hepatectomy (1988–1997) [27].

Discussion

Despite unfavorable clinicopathologic prognostic factors (e.g., high serum level of AFP, vascular invasion, multiple tumors, absence of tumor capsule formation, ruptured tumors and satellite lesions) common in huge HCC, tumor size alone failed to correlate with survival [11,12,23,26]. Tumor size *per se* should not be used as the sole criterion to exclude patients from partial hepatectomy who have an otherwise resectable tumor [11].

In the present systematic review, partial hepatectomy of huge HCC can be performed safely in most centers. The median overall perioperative morbidity and mortality rates were 29.2% (range: 13.6–72%) and 3.5% (range: 0–18.2%), respectively. Moreover, huge HCC has similar perioperative morbidity and mortality when compared with smaller tumors.

The overall median survival since the partial hepatectomy was 20.7 months (range: 10.1–32 months), with median 1-, 3- and 5-year survival of 60.7% (range: 41–72.2%), 34% (range: 0–60.3%) and 28.6% (range: 0–54%), respectively. The median disease-free survival since the partial hepatectomy was 11.3 months (range: 5.5–32months), with median 1-, 3- and 5-year disease-free survival rates of 48.7% (range: 32–65.4%), 27.5% (range: 14.1–49%) and 20.7% (range: 9.5–43%), respectively. A 10-year disease-free survival rate of 12.7% was reported in 1 study [17]. The survival outcome

of partial hepatectomy is considerably better than nonsurgical treatment [19]. Thus, hepatectomy is the best option in patients with huge HCC, and it provides acceptable long-term survival in a subset of patients.

As not all patients benefit from surgery, it is important to identify good candidates for liver resection. Several prognostic factors have been identified to have an impact on patients with huge HCC after resection. Vascular invasion, especially macroscopic invasion, seems to be the most important factor. Pawlik et al. [11] reported that patients with huge HCC with major vascular invasion had a median survival of only 9.1 months, compared with 24.0 months for patients without major vascular invasion. Ohkubo et al [32] showed tumor size ⩾10 cm was an independent prognostic factor of survival for patients with macroscopic portal vein invasion after partial hepatectomy, and the median survival of patients with tumor size <10 cm was 21 months, while that of patients with tumor size ⩾10 cm was only 6 months. Thus, patients with huge HCC associated with macroscopic vascular invasion are less favorable candidates for partial hepatectomy.

Liver failure after partial hepatectomy closely correlates to the volume and function of the remnant liver. Resection of huge HCC entails the removal of a large amount of liver parenchyma. In the present systematic review, 50.9%–96.2% of patients with huge HCC were treated by major hepatectomy. Therefore, an accurate evaluation of the liver functional reserve is crucial to avoid postoperative liver failure and mortality. The Child classification is insufficient to define the safe limit of the extent of partial hepatectomy. A study from Hong Kong identified an ICG-R15 of less than 14% as the safety limit for major hepatectomy [10]. Computed tomography (CT) volumetry is also helpful in determining whether the remnant liver volume is adequate [33]. A combination of CT volumetric measurements of the liver and the ICG-R15 can provide a better index for selection of patients for major hepatectomy than does use of ICG-R15 alone [34].

Resection of a huge HCC is technically challenging because of the difficulty in mobilization of the liver, especially if the tumor is located in the right hemiliver. The huge tumor can also pose difficulty in the control of the hepatic veins before or during liver transaction [10]. Thus, patients with huge HCC may have more blood loss, more blood transfusion requirement, and longer operative time, as reported in several studies [8,10,12,17,22,28–30]. The anterior approach (parenchymal transection without prior mobilization of the liver) provides a "no-touch" technique in resecting large tumors in the right hemiliver, reduces bleeding, decreases the chance of iatrogenic rupture of the tumors, and prolongs survival [35]. The liver hanging maneuver proposed by Belghiti et al makes the anterior approach technically easier and safer [36].

The analyses of pooled data are critically influenced by the nature of the constituent reports. In the present study, bias is likely to be introduced. Variations in the surgical techniques, tumor characteristics, perioperative management, adjuvant therapy, and treatment of recurrence make interpretation of the data even more difficult. In addition, the quality of all the studies included in this review is poor. Unfortunately, partial hepatectomy and nonsurgical treatment have not been compared by a randomized comparative trial. Furthermore, as patients with better conditions were selected for partial hepatectomy, while patients with more advanced disease or severe coexisting liver cirrhosis were selected for non-surgical treatment, this selection bias can account for a better prognosis after partial hepatectomy [19]. For these reasons, the results of this systematic review must be interpreted with caution.

Conclusions

In this systematic review, 21 observational studies were evaluated. The current literatures suggested that partial hepatectomy can be performed safely and is associated with long-term survival in a subset of patients with huge HCC. As no randomized controlled trial has addressed this question to date, the present study reports the best evidence on the subject.

Acknowledgements

The authors thank Professor W. Y. Joseph Law, from the Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, for his valuable help in revising the paper.

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