RESEARCH ARTICLE

Systematic Review of Single Large and/or Multinodular Hepatocellular Carcinoma: Surgical Resection Improves Survival

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Abstract

Background: The role of surgical resection for patients with single large (≥ 5cm) and/or multinodular (≥ 2) hepatocellular carcinoma (HCC) is still controversial. This systematic review was performed to evaluate the safety and efficacy of resection for patients with single large and/or multinodular HCC. Materials and Methods: Databases (the PubMed, Web of Science, Embase, and Cochrane databases) were systematically searched to identify relevant studies exploring the safety and efficacy of resection for single large and/or multinodular HCC, published between January 2000 and December 2014. Perioperative morbidity and mortality, overall survival, and disease-free survival of the resection group were calculated. In addition, these outcome variables were also calculated for the control group in the included studies. Results: One randomized controlled trial and 42 non-randomized studies involving 9,580 patients were eligible for analysis. Eight (1,594 patients) of the 43 studies also reported the outcomes of transarterial chemoembolization (TACE). Although 51.4% of patients featured cirrhosis, 90.7% of them demonstrated Child-Pugh A liver function in the resection group. The median rates of morbidity (24.5%) and mortality (2.5%) after resection were significantly higher than that of TACE (11.0%, *P*<0.001; 1.9%, *P*<0.001). However, patients who underwent resection had significantly higher median one-, three-, and five-year overall survival (76.1%, 51.7%, and 37.4%) than those who underwent TACE (68.3%, 31.5%, and 17.5%, all *P*<0.001). The median 1-, 3-, and 5-year DFS rates after resection were 58.3%, 34.6%, and 24.0%, respectively. Conclusions: Although tumor recurrence after resection for patients with single large and/or multinodular HCC continues to be a major problem, resection should be considered as a strategy to achieve long-term survival.

Keywords: Hepatocellular carcinoma - large - multinodular - surgical resection - overall survival

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer among malignant tumors and the third most common cause of cancer-related deaths (Siegel et al., 2014). Its incidence is increasing in many countries. Recent advances in diagnostic methods and the widespread application of screening programs in high-risk populations have facilitated the detection of early-stage HCC. However, a substantial proportion of patients still present with single large (≥ 5 cm) or multinodular tumors (≥ 2). Surgical resection is considered as the first-line treatment for early-stage HCC, with five-year overall survival (OS) up to 67% (Lim et al., 2012). The prognosis of patients with single large and/or multinodular HCC is generally poor. Instead of curative treatment strategies, locoregional therapies, particularly transarterial chemoembolization (TACE) have been used primarily in selected patients with single large and/or multinodular tumors (Bruix et al., 2014; EASL-EORTC. 2012).

According to these treatment guidelines (Bruix et al., 2014; EASL-EORTC. 2012), the role of resection is mainly fit for patients with early-stage HCC and those who have preserved liver function. The restrictive treatment criteria for resection may result in some candidates who are suitable for resection receiving TACE. Although TACE is suggested to be the first-line treatment for patients with single large and/or multinodular HCC, some retrospective studies with large sample size in different countries have already indicated that resection could offer low mortality and favorable survival benefits (Chen et al., 2006; Hsu et al., 2012; Torzilli et al., 2013; Zhong et al., 2014a). These results revealed that resection should be considered as an optional treatment for single large and/or multinodular HCC. Moreover, the only randomized controlled trial in this field also demonstrated that resection is superior to

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TACE for patients with HCC beyond Milan criteria (Yin et al., 2014), Therefore, the question of whether resection is acceptable and applicable for patients with single large and/or multinodular HCC remains controversial. Here we perform a systematic review for the evidence published from 2000 to 2014 on outcomes of resection in patients with single large and/or multinodular HCC and preserved liver function. In addition, in order to compare the efficacy of resection with the standard therapy of TACE for patients with single large and/or multinodular HCC, we also reviewed the efficacy of TACE among the included studies.

Materials and Methods

Search strategy

Literatures of the PubMed, Web of Science, Embase, and Cochrane databases were systematically searched using the following search terms to identify studies in December 2014: "hepatocellular carcinoma" or HCC or "liver cancer" or "liver neoplasm" or "liver tumor" or "primary liver carcinoma", single large or giant or huge or multinodular, "surgical resection" or "hepatic resection" or hepatectomy or "curative resection" or "liver resection" or surgery. The Cochrane systematic review methodology was used for this review.

Eligibility criteria

Original studies were included if they reported the outcomes of initial resection in patients with primary single large and/or multinodular HCC with preserved liver function. Only studies published in English between January 2000 and December 2014 may be eligible included. Patients who underwent explicit non-curative or palliative treatments were excluded. Namely, only patients with primary HCC after potential curative resection were included into analysis. For duplicated publications, only those with largest sample size or longer follow-up were included. For reducing the selective bias and measure bias, only studies with a sample size of more than 50 were included. The references of retrieved articles were manually searched to locate other potential relevant studies. The outcomes included perioperative mortality and morbidity, OS, or disease-free survival (DFS).

Data extraction

Two investigators (XDY and JHZ) independently and critically appraised the eligibility of relevant studies based on the inclusion criteria through scrutinizing the title and abstract of each record. Discrepancies were resolved by a third investigator (JC). Three authors (XDY, JHZ, JC) extracted the following data from included studies: patient demographics, disease characteristics, perioperative morbidity and mortality, OS, DFS, and tumor recurrence. Due to the clinical heterogeneity among different studies and the lack of control group, we did not perform meta-analysis.

Data analysis

Continuous variables were calculated using SPSS software (version 16.0, SPSS Inc., Chicago, IL) and expressed as median (range). All the analysis was carried out by Excel 2013.

Results

Study selection

There were 1040 and 40 articles identified from the literature of the databases and manual search of reference lists, respectively. After carefully read the full papers, 19 articles were excluded because of sample size less than 50, or without sufficient long-term outcome data. Finally, 43 articles, including one randomized controlled trial (Yin et al., 2014) and 42 retrospective case series (Hanazaki et al., 2001; Poon et al 2002; Yang et al., 2002; Mok et al., 2003; Yeh et al 2003; Zhou et al., 2003; Liau et al., 2005; Ng et al., 2005; Pawlik et al., 2005; Chen et al., 2006; Liu et al., 2006; Cho et al., 2007; Lee et al., 2007; Pandey et al., 2007; Ishizawa et al., 2008; Shimada et al., 2008; Wang et al., 2008; Choi et al., 2009; Ho et al., 2009; Yang et al., 2009; Delis et al., 2010; Lin et al., 2010; Luo et al., 2011; Yamashita et al., 2011; Zhou et al., 2011; Chang et al., 2012; Cheng et al., 2012; Hsu et al., 2012; Huang et al., 2012; Truant et al., 2012; Ai et al., 2013; Ariizumi et al., 2013; Shrager et al., 2013; Torzilli et al., 2013; Jin et al., 2014; Lei et al., 2014; Lim et al., 2014; Liu et al., 2014; Liu et al., 2014; Min et al., 2014; Nojiri et al., 2014; Zhong et al., 2014a) were included into analysis (Figure 1). The population recruitment periods extended from 1964 to 2014.

Patients' characteristics and disease characteristics

Characteristics of the included patients and details of the disease characteristics were shown in Table 1. Four studies (Wang et al., 2008; Ho et al., 2009; Nojiri et al., 2014; Yin et al., 2014) mainly described patients with multiple tumors. And the rest studies presented patients with single large with or without multinodular tumors. In total, 9580 patients from 43 different papers were reviewed. The sample size ranged from 50 to 1143. The majority were males from 59.0 to 93.0 (median 81.2) percent. The median rate of patients with hepatitis B virus infection and hepatitis C virus infection were 68.3% (range,10.0-93.0%) and 17.9% (range, 1.0-74.0%), respectively. The median rate of cirrhosis was

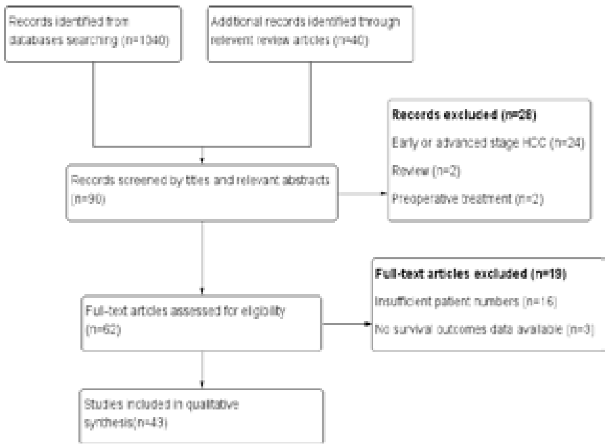

Figure 1. PRISMA Flow Diagram for Selection of Articles Included; HCC, Hepatocellular Carcinoma

Table 1. Patients Demographics and Tumor Characteristics

Study	No.	Age (Y)	Men (%)	CTPA (%)	HBV (%)	HCV (%)	Cirrhosis (%)	Tumor characteristics			Involvement (n, %)		
								Tumor size (cm)	Single (n, %)	Multiple(n,%)	Microvascular	Macrovascular	Rucurrence
Ai et al.2013	178	52.36 (9-82)	137 (77)	104 (58)	136 (76)	NS	143 (80)	7.64±2.36	NS	NS	0 (0)	0 (0)	35 (21)
Ariizumi et al.2013	54	67 (35-84)	47 (87)	50 (93)	13 (24)	40 (74)	2 (4)	13 (10-19)†	54 (100)	0 (0)	9 (17)	3 (6)	NS
	53	64 (34-79)	45 (85)	41 (77)	14 (26)	38 (72)	13 (25)	13 (10-24)	0 (0)	53 (100)	32 (60)	6 (11)	NS
Chang et al.2012	318	60.4±14.3	263 (83)	311 (98)	201 (64)	57 (19)	97 (31)	7.4 (5.7-10.4)	135 (43)	NS	238 (75)	0 (0)	173 (55)
Chen et al.2006	1143	50±11	968 (85)	1082 (95)	940 (82)	NS	897 (79)	11·1±3·2	928 (81)	215 (19)	464 (41)¶	NS	885 (77)
	959	49±9	816 (85)	877 (91)	776 (81)	NS	717 (75)	14·9±4·7	765 (80)	194 (20)	395 (41)	NS	840 (88)
Cheng et al.2012	63	58 (50-66)	50 (79)	56 (89)	43 (68)	15 (25)	30 (48)	7.23±2.34	NS	NS	18 (29)	12 (19)	39 (62)
Cho et al.2007	61	54.3±10.5	46 (75)	56 (92)	40 (67)	5 (8)	35 (58)	7.1±1.1	61 (100)	0 (0)	23 (38)	NS	NS
Choi et al.2009	50	50.8±12.5	34 (68)	48 (96)	33 (66)	1 (2)	13 (26)	≥10	22 (44)	12 (24)	34 (68)	5 (10)	29 (58)
Delis et al.2010	66	65 (59-76)	45 (68)	59 (89)	36 (55)	15 (23)	59 (89)	8.4 (5.2-11.2)	51 (77)	15 (23)	18 (27)	9 (14)	45 (69)
Hanazaki et al.2001	133	63±10	105 (79)	93 (70)	NS	NS	69 (52)	8.6±3.8	104 (78)	29 (22)	57 (43) ¶	NS	73 (69)
Ho et al.2009	294	57.0±11.8	240 (82)	229 (95)	200 (71)	82 (32)	188 (64)	5.0±3.5	0 (0)	294 (100)	NS	NS	NS
Hsu et al.2012	78	< 65 (60%)	62 (80)	73 (93)	51 (66)	14 (18)	NS	≥7 (54%)	47 (60)	NS	52 (67)¶	NS	NS
Huang et al.2012	139	51 (11-85)	110 (79)	NS	68 (70)	10 (101)	80 (58)	≥10	NS	NS	98 (71)¶	NS	99 (71)
Ishizawa et al.2008	126	65 (32-90)	97 (77)	105 (83)	12 (10)	93 (74)	103 (82)	3.5 (1.1-14)	0 (0)	51 (40)	34 (27)	NS	100 (79)
Jin et al.2014	62	58 (29-79)	48 (77)	51(82)	41 (66)	11 (18)	NS	8 (5.1-18)	62 (100)	0 (0)	NS	NS	NS
Lee et al.2007	100	47±12	77 (77)	88 (88)	83 (83)	NS	NS	13.3±3.0	80 (80)	20 (20)	47 (47)	22 (22)	74 (76)
Lei et al. 2014	433	53(44-63)	315(73)	328(76)	388(90)	8(2)	NS	7(6-8)	171(40)	262(61)	NS	NS	NS
Liau et al.2005	82	62±14	48 (59)	73 (94)	24 (32)**	NS	8 (10)	14.7±4.1	71 (87)	NS	22 (29) ¶	NS	50 (61)
Lim et al. 2014	172	67(22-85)	136(79)	147(85)	43(25)	87(51)	66(38)	6.5(5-10)	172(100)	0(0)	80(47)	10(6)	76(44)
Lin et al.2010	93	59±15.6	75 (81)	93 (100)	60 (65)	22 (24)	NS	8.0±3.3	49 (53)	44 (47)	NS	NS	NS
Liu et al.2006	60	52 (45-59)	52 (87)	NS	55 (92)	2 (3)	19 (32)	10.5 (8-13)	41 (68)	19 (32)	37 (62)¶	NS	33 (56)
Liu et al.2014	232	59±14	190 (82)	218 (94)	128 (55)	30 (13)	NS	>5	NS	93 (40)	NS	42 (18)	NS
Liu et al.2014	83	55±9	72 (87)	73 (88)	55 (66)	NS	39 (47)	7.9±2.7	60 (72)	23 (28)	34 (41)¶	NS	NS
	70	32±5	53 (76)	56 (80)	61 (87)	NS	32 (46)	7.3±2.1	49 (70)	21 (30)	33 (47)	NS	NS
Luo et al.2011	85	47.5±12.8	70 (82)	NS	70 (82)	2 (2)	64 (75)	8.7±3.5	0 (0)	85 (100)	50 (59)	NS	55 (66)
Min et al.2014	84	52.7±11.7	70 (83)	75 (89)	62 (74)	3 (4)	NS	≥10	61 (73)	23 (27)	25 (30)¶	NS	NS
Mok et al.2003	56	54.2±13.9	46 (82)	NS	43 (77)	16 (29)	28 (50)	>10	31 (55)	NS	34 (61)	13 (23)	37/53 (70)
Ng et al.2005	380	58.4±11.4	278 (73)	361 (95)	281 (74)	20 (5)	101 (26)	>5	308 (81)	72 (19)	200 (53)	31 (8)***	199 (52)‡
Nojiri et al.2014	107	64.5±8.9	85 (79)	105 (98)	27 (25)	55 (51)	55 (51)	6.2±5.4	0 (0)	107 (100)	54 (51)¶	NS	51 (64)
Pandey et al.2007	166	55 (12-83)	143 (82)	NS	130 (78)	2 (1)	80 (48)	13 (10-24)	NS	71 (43)	102 (61)¶	NS	NS
Pawlik et al.2005	300	55 (13-87)	222 (74)	241 (80)	188 (63)	NS	NS	≥10	190 (63)	110 (37)	159 (53)	49 (16)	NS
Poon et al.2002	120	50.9±12.8	99 (83)	NS	103 (86)	NS	32 (27)	13.8±3.0	NS	41 (34)	83 (69)	20 (17)	94 (78)
Shimada et al.2008	85	61 (19-85)	71 (84)	NS	27 (32)	19 (25)	9 (11)	13±3.1	37 (44)	48 (56)	NS	NS	NS
Shrager et al.2013	130	57.7±12.8	98 (75)	116 (95)	56 (43)	23 (18)	51 (40)	14.4±3.84	95 (74)	34 (26)	49 (39)	NS	97 (61)
Torzilli et al.2013	737	66 (9-93)	586 (80)	NS	158 (28)	208 (37)	360 (56)	6 (1-25)	456/666 (69)	210/666 (32)	NS	0	NS
Truant et al.2012	52	63 (21-85)	38 (73)	NS	6 (12)**	NS	0 (0)	14 (8-22.9)	43 (83)	9 (7)	27 (52)¶	NS	26 (50)
Wang et al.2008	112	59±13	98 (87)	NS	69 (62)	35 (35)	62 (55)	≥5	0 (0)	112 (100)	56 (50)	NS	93 (89)
Yamashita et al.2011	53	60±2	48 (91)	38 (72)	18 (34)	22 (42)	NS	13.2±0.4	NS	NS	24 (45)¶	NS	32 (62)
Yang et al.2002	86	46.1 (22-67)	77 (90)	NS	63 (73)	NS	66 (77)	≥15	NS	NS	74 (86)	NS	NS
Yang et al.2009	260	≥50 (40.4%)	228 (88)	217 (84)	239 (92)	NS	198 (76)	9.63±4.07	260 (100)	0 (0)	143 (55)¶	NS	NS
Yeh et al.2003	211	47.8±14.3	164 (78)	52/63 (83)	163/199 (82)	16/138 (12)	63 (30)	13.9±3.4	NS	NS	NS	116/208 (56)	130/199 (65)
Yin et al.2014	88	51.6±9.0	82 (93)	87 (99)	81 (92)	3 (3)	69 (78)	9.5±3.0	0 (0)	88 (100)	NS	NS	62 (71)
Zhong et al.2014	660	45 (17-79)	598 (91)	660 (100)	614 (93)	13 (2)	514 (78)	8.3 (5-20)	515 (78)	145 (22)	NS	0 (0)	NS
Zhou et al.2003	621	47 (9-82)	1061 (87)§	NS	821/1,087 (76)	NS	953/1168 (82)	13 (10-29)	379 (61)	242 (39)	NS	NS	NS
Zhou et al.2011	85	≥65 (31.8%)	74 (87)	80 (94)	68 (80)	6 (7)	65 (77)	9.63±4.07	85 (100)	NS	34 (40)	NS	NS

*, CTPB or CTPC; †, median (range); §, combined data of primary liver cancer≥10cm; **, HBV or HCV; CTP, Child–Pugh grade; HBV, hepatitis B virus serology positive; HCV, hepatitis C virus serology positive; NS, not stated; ¶, combined data of vascular invasion; ***, tumor invasion of adjacent organs; ‡, intrahepatic tumor recurrence

51.4% (range, 0-89.0%). However, most patients were with Child-Pugh A liver function (median, 90.7%; range, 58.0-100%).

Outcomes measures

The outcomes of the 43 studies are summarized in Table 2. The median perioperative morbidity was 24.5% (range, 5.4-60.6%). The median perioperative mortality was 2.5% (range, 0-9.6%). The median 1-, 3-, and 5-year OS after resection were 76.1% (range, 48.1-96.0%), 51.7% (range, 24.0-88.0%), and 37.4% (range, 16.7-79.0%), respectively. The median 1-, 3-, and 5-year DFS after resection were 58.3% (range, 32.0-92.0%), 34.6% (range, 14.1-67.0%), and 24.0% (9.5-48.0%), respectively.

Comparison of outcomes of SR with TACE

Eight (Lin et al., 2010; Luo et al., 2011; Hsu et al., 2012; Jin et al., 2014; Lei et al., 2014; Liu et al., 2014; Yin et al., 2014; Zhong et al., 2014a) of the 43 studies also reported the safety and efficacy of TACE for these patients as summarized in Table 3. The median perioperative morbidity and mortality after TACE were 11.0% (range, 7.2-28.6%) and 1.9% (range, 0-5.0%), respectively, which were significantly lower than that after resection (all $P<0.001$). Moreover, the median 1-, 3-, and 5-year OS after TACE were 68.3% (range, 39.0-84.1%), 31.5%

Table 2. Outcomes of Liver Resection in Patients with Single Large and/or Multinodular Hepatocellular Carcinoma

Study	Recruitment period	Country	No.	Perioperative morbidity (%)	Perioperative mortality (%)	Overall survial (%)			Disease-free survival(%)		
						1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Ai et al.2013	2007-2011	Southern China	178	53 (30.0)	0 (0)	95	88	NS	92	67	NS
Ariizumi et al.2013	1990-2008	Japan	54	NS	NS	NS	NS	79	NS	NS	48
			53	NS	NS	NS	NS	31	NS	NS	12
Chang et al.2012	1991-2006	Taiwan	318	NS	9 (2.7)	NS	NS	46.5	NS	NS	28.6
Chen et al.2006	1996-2003	Central China	1143	199 (17.4)	8 (0.7)	71.2	58.8	38.7	61.5	38.6	23.8
	1990-1996		959	281 (29.3)	35 (3.6)	67.8	50.7	27.9	56.5	34.7	18.9
Cheng et al.2012	1999-2005	Taiwan	63	8 (12.7)	5 (7.9)	87.5	NS	51.3	50	NS	15
Cho et al.2007	1998-2001	Korea	61	NS	1 (1.6)*	85	59.3	52.9	58.3	40	31.7
Choi et al.2009	1996-2006	Korea	50	12 (24.0)	0 (0)	70.2	50.2	40.2	49	38.6	38.6
Delis et al.2010	2002-2008	Greece	66	40 (60.6)	0 (0)	69	37	32	60	33	29
Hanazaki et al.2001	1983-1997	Japan	133	45 (33.8)	8 (6.0)	NS	38	28	NS	26	20
Ho et al.2009	1981-2000	Taiwan	294	NS	NS	77.4	51.9	36.6	60.5	32.3	24.8
Hsu et al.2012	2002-2010	Taiwan	78	16 (20.0)	1 (1.3)	81	63	43	NS	NS	NS
Huang et al.2012	2001-2005	Taiwan	139	13 (9.4)	6 (4.3)	61.9	39.4	28.9	40.5	22.7	18.5
Ishizawa et al.2008	1994-2004	Japan	126	19 (15.0)	NS	96	72	58	NS	NS	NS
Jin et al.2014	1998-2013	Korea	62	5 (8.0)	2 (3.2)	83.2	75.5	65	NS	NS	NS
Lee et al.2007	1997-2006	Korea	100	NS	2 (2.0)*	66	44	31	43	26	20
Lei et al. 2014	2002-2008	Southern China	433	114(26.3)	10(2.3)	85.2	71.7	61.2	NS	NS	NS
Liau et al.2005	1985-2002	America	82	41 (50.0)	2 (2.0)	NS	NS	33	NS	NS	28
Lim et al. 2014	1994-2010	Japan	172	NS	1(0.3)	NS	NS	58	NS	NS	26
Lin et al.2010	2001-2007	Taiwan	93	NS	5 (5.4)*	83	49	30	NS	NS	NS
Liu et al.2006	1999-2004	Southern China	60	20 (33.3)	1 (1.7)	NS	NS	NS	NS	NS	NS
Liu et al.2014	2002-2013	Taiwan	232	NS	NS	89	83	NS	NS	NS	NS
Liu et al.2014	2003-2012	Southern China	83	19 (22.9)	1 (1.2)	85	75	40	65	36	11
			70	16 (23.0)	0 (0)	93	79	47	87	28	17
Luo et al.2011	2004-2006	Southern China	85	25 (29.4)	2 (2.4)	70.6	35.3	23.9	NS	NS	NS
Min et al.2014	2000-2009	Korea	84	NS	2 (2.4)	73.8	54.8	39.8	NS	NS	NS
Mok et al.2003	1990-2001	Taiwan	56	3 (5.4)	1 (2.0)	60.7	24.5	24.5	NS	NS	NS
Ng et al.2005	1982-2001	Four countries†	380	104 (27.0)	9 (2.4)*	74	50	39	54	38	26
Nojiri et al.2014	1992-2011	Japan	107	NS	NS	NS	62	38.1	NS	43.8	30.5
Pandey et al.2007	1995-2006	Singapore	166	NS	5 (3.0)	NS	NS	28.6	NS	NS	NS
Pawlik et al.2005	1981-2000	Four countries†	300	NS	15 (5.0)	64.9	36.7	26.9	NS	NS	NS
Poon et al.2002	1991-2000	Southern China	120	42 (35.0)	4 (3.3)	60.6	37.8	28.5	32	14.1	9.5
Shimada et al.2008	1988-2004	Japan	85	NS	1 (1.2)	NS	NS	31.5	NS	NS	NS
Shrager et al.2013	1992-2010	America	130	28 (21.5)	9 (6.9)	56.9	30.3	18.8	NS	NS	NS
Torzilli et al.2013	1990-2009	Four countries§	737	310 (42.0)	23 (3.1)	88	71	57	63	38	27
Truant et al.2012	2000-2010	France	52	14 (26.9)	5 (9.6)	NS	NS	43.4	NS	NS	39.3
Wang et al.2008	1990-2006	Taiwan	112	NS	3 (2.7)	86.1	55.5	29.9	45.7	29.2	18.4
Yamashita et al.2011	1995-2007	Japan	53	13 (24.5)	2 (3.8)	74	43	35	NS	NS	24.0*
Yang et al.2002	1985-1996	Southern China	86	27 (31.5)	3 (3.5)	58.2	35.7	17.64	NS	NS	NS
Yang et al.2009	1992-2002	Central China	260	48 (18.5)	6 (2.3)	87	55.5	38.2	82.4	51	35
Yeh et al.2003	1982-2001	Taiwan	211	34 (16.1)	9 (4.3)	48.1	24	16.7	32.9	18.8	12.7
Yin et al.2014	2008-2010	Eastern China	88	9 (10.2)	1 (1.1)	76.1	51.5	NS	NS	NS	NS
Zhong et al.2014	2000-2010	Southern China	660	178 (27.0)	17 (2.6)	91	67	44	NS	NS	NS
Zhou et al.2003	1964-1999	Northern China	621	NS	28 (4.5)	68	37.3	26.2	NS	NS	NS
Zhou et al.2011	1995-2002	Southern China	85	NS	NS	93.8	56.2	47	74.3	34.4	14.8

*, Within same hospital stay; †, China, America, France, Japan; §, France, Italy, Japan, America; NS, not stated

Table 3. Comparison of OutcomesRegarding Single Large or Multinodular Hepatocellular Carcinoma Undergoing Surgical Resection or Transarterial Chemoembolization

	Perioperative morbidity (%)	Perioperative mortality (%)	Overall survival (%)			Disease-free survival (%)		
			1yr	3yr	5yr	1yr	3yr	5yr
SR (n=9580) *								
Median	24.5	2.5	76.1	51.7	37.4	58.3	34.6	24
Minimum	5.4	0	48.1	24	16.7	32	14.1	9.5
Maximum	60.6	9.6	96	88	79	92	67	48
TACE (n=1594) †								
Median	11	1.9	68.3	31.5	17.5	-	-	-
Minimum	7.2	0	39	2	15	-	-	-
Maximum	28.6	5	84.1	62.2	45.1	-	-	-

*, patients who undergoing SR included in our review; †, patients who undergoing TACE reported among eight included studies

(range, 2.0-62.2%), and 17.5% (range, 15.0-45.1%), respectively, which were also significantly lower than that after resection (all $P<0.001$).

Discussion

Most western hepatobiliary surgeons do not recommended resection for patients with single large and/or multinodular HCC, even if those with Child-Pugh A liver function. Instead, palliative treatment with TACE is recommended as the first-line therapy for these patients. High rate of hospital mortality and low rate of DFS are two main reasons which limited the extensive usage of resection.

With the improvement of perioperative care and surgical technique, zero hospital mortality rates can be achieved in some big liver centers (Imamura et al., 2003, Jarnagin et al., 2002). Our results demonstrated that the median hospital mortality after resection was 2.5% in patients with single large and/or multinodular HCC. The result of mortality was lower than that (4.0%) reported in a meta-analysis of 69 studies in which patients in various stages of HCC were treated with resection (Ramacciato et al., 2012). The second attention is the low rate of DFS after resection. In patients with early stage HCC, the five-year median DFS is 37% (Lim et al., 2012). However, the five-year median DFS (24.0%) in our study is comparable to that (range, 15.0-35.0%) reported in a systematic review of 22 studies in which patients with huge (> 10 cm) HCC were treated with resection (Tsoulfas et al., 2012). In our study, patients with single large and/or multinodular HCC who underwent resection have significantly higher five-year median OS than those who underwent TACE ($P<0.001$). Though TACE is considered as standard treatment modality for single large and/or multinodular HCC in western official guidelines, TACE-related mortality also should not be ignored, with a median rate of 2.4% reported by meta-analysis (Marelli et al., 2007). Moreover, the five-year OS is less than 17% in patients with huge (> 10 cm) HCC after TACE therapy (Poon et al., 2000; Huang et al., 2006).

Large-volume units with fully equipped and experienced in the management of complicated HCC demonstrated that tumor size does not influence patients' survival, although more complex surgical techniques are required for giant tumors (Young et al., 2007; Yang et al., 2009; Zhong et al., 2013; Zhang et al., 2014; Zhong et al., 2014b; Zhong et al., 2015). Resection of large HCC without macrovascular invasion has been achieved comparably favorable outcomes with small tumors, which could not be achieved through other palliative treatments (Yeh et al., 2003; Ariizumi et al., 2013). Eight of the included retrospective studies also revealed that resection provided superior outcomes than TACE in patients with single large and/or multinodular HCC (Lin et al., 2010; Luo et al., 2011; Hsu et al., 2012; Jin et al., 2014; Lei et al., 2014; Liu et al., 2014; Yin et al., 2014; Zhong et al., 2014a). Moreover, the recent randomized controlled trial which involving 173 patients with resectable multiple HCC beyong Milan criteria also revealed that resection was associated with significantly better OS than TACE ($P<0.001$) (Yin et al., 2014).Therefore, tumor size and tumor number should not be considered as contraindication to resection.

Although postoperative tumor recurrence remains high, our findings showed that resection is reasonable and associated with survival benefits. First, with the improvement of skillful surgical techniques and perioperative care, the rates of perioperative morbidity and mortality are acceptable. With regard to the tumor recurrence after resection, repeated resection or radiofrequency ablation may be available for some patients. In addition, postoperative effective adjuvant treatment options for reducing risk of recurrence also improve patients' survival (Zhong et al., 2012, Zhong et al., 2014c, Zuo et al., 2015). However, the durable long-term survival outcomes of a treatment strategy combining these modalities have not been fully assessed, and ongoing trials targeting the population to benefit from the multidisciplinary management are still awaited.

The majority of the published experiences concerning the resection treatment in patients with single large and/or multinodular HCC are reported by Asian countries, where a great number of patients are with chronic hepatitis B liver disease. However, in western countries, more patients are with hepatitis C virus infection and cirrhosis, which are more likely to develop tumor recurrence because of strong hepatic inflammatory activity and progressive liver disease (Fong ZV and Tanabe KK. 2014).This may help to explain why the Barcelona Clinic Liver Cancer classification system has been approved as guidance for HCC treatment algorithms by the European Association for the Study of Liver and the American Association for the Study of Liver Disease, but still be debated by the main

Asian associations for the study of liver diseases (Kudo et al., 2011). Therefore, external validation is keenly needed from different study groups.

There are some limitations in this review which must be considered. First, substantial clinical heterogeneity among the included patients owing to the regional differences may limit the ability of the results to be expanded and extrapolated. Second, the favorable results of resection might partly be due to a high selection of patients with a well preserved liver function and limited intrahepatic tumor spread. Thirdly, width recruitment periods of this study may also produce bias because of the surgical technique improvement in recent decade. Randomized trials with large sample size are therefore required to further examine the role of resection in these patients.

In conclusion, available studies showed that surgical resection provides long-term survival in patients with single large and/or multinodular HCC and preserved liver function. However, the strategy of resection should be carried out with caution in selective patients because of the unignored perioperative morbidity and mortality.

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