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SYSTEMATIC REVIEW

Surgical resection for large hepatocellular carcinoma and those beyond BCLC: systematic review with proposed management algorithm

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Abstract

Background Hepatocellular carcinoma (HCC) accounts for the sixth most common cancer and ranks third in mortality worldwide with inhomogeneity in terms of resection for advanced-stage disease.

Methods A systematic review of published literature using the PubMed, Medline, and Google Scholar databases from 1995 to 2020 was conducted to identify studies that reported outcomes of resection for solitary HCC > 10 cm, BCLC B/C, and multinodular HCC. Our aim was to assess overall survival for resection, identify poor prognostic factors, and to compare it to trans-arterial chemotherapy (TACE) where data was available.

Results Eighty-nine articles were included after a complete database search in the systematic review as per our predefined criteria. Analysis revealed a 5-year overall survival of 33.5% for resection of HCC > 10 cm, 41.7% for BCLC B, 23.3% for BCLC C, and 36.6% for multinodular HCC. Peri-operative mortality ranged from 0 to 6.9%. Studies comparing resection versus TACE for BCLC B/C had a survival of 40% versus 17%, respectively.

Conclusion Our systematic review justifies hepatic resection wherever feasible for hepatocellular carcinomas > 10 cm, BCLC B, BCLC C, and multinodular tumors. In addition, we identified and proposed an algorithm with five poor prognostic criteria in this group of patients who may benefit from adjuvant TACE.

Keywords Hepatocellular carcinoma · Barcelona clinic liver cancer B/C · Resection · Survival · Systematic review

Introduction

Hepatocellular carcinoma (HCC) accounts for the sixth most common cancer and ranks third in mortality worldwide as per GLOBOCAN 2020 with 906,000 new cases and 830,000 deaths annually [1]. From the inception of BCLC (Barcelona Clinic Liver Cancer) classification in 1999, the criteria for surgical resection have been very limited [2]. Extended Toronto criteria expanded the limit of curative resection with liver transplant for HCC; however, these criteria still do not include BCLC stage C and poorly differentiated tumors [3]. The recommended management of BCLC stage B HCC is transarterial chemoembolization (TACE) and of BCLC C with macrovascular invasion is sorafenib [2]. However, the results of these palliative treatments for BCLC B and C translate in a 5-year survival of about 20% for BCLC B and 6% for BCLC C [4]. Globally, there is inhomogeneity in terms of resection for HCC with vascular invasion. The Japanese, Chinese, and Hongkong guidelines are more liberal and allow resection in the presence of vascular invasion [5–7], whereas the AASLD (American Association for the Study of Liver Diseases) and EASL-EORTC (European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer) guidelines which follow the BCLC recommendations are stricter and allow resection for 2–3 nodules within 3 cm or single nodule of any size without vascular invasion [8, 9].

Systematic reviews and current literature do not support BCLC recommendations and reveal that surgical resection

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although not recommended can achieve a median 5-year OS of 35–42% for BCLC B and 20% for BCLC C [10–13]. We conducted a systematic review to assess outcomes of patients with large HCC (> 10 cm) and BCLC intermediate and advanced stage with an aim to possibly imply a change in treatment algorithm to include surgical resection as a first-line treatment option wherever feasible to improve long-term outcome.

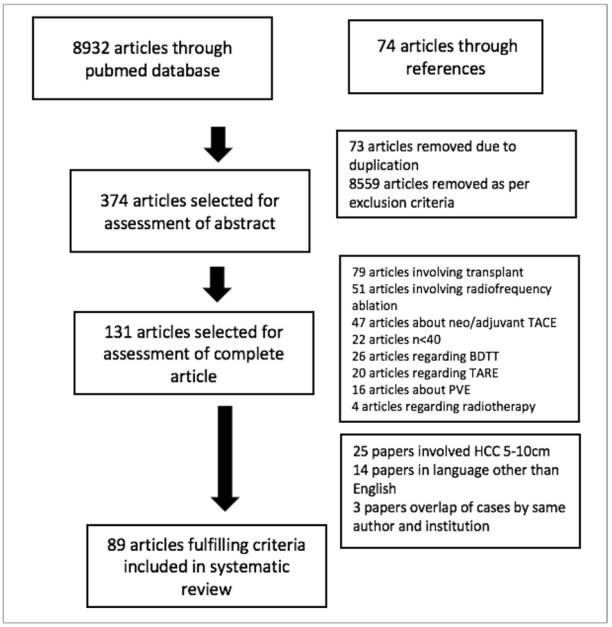

Fig. 1 CONSORT diagram. TACE, transarterial chemoembolization; BDTT, bile duct tumor thrombi; TARE, transarterial radioembolization; PVE, portal vein embolization

Materials and methods

A thorough literature search from Pubmed database (http://pubmed.ncbi.nlm.nih.gov), Medline, and Google Scholar from 1995 to 2020 with the MeSH terms "hepatocellular carcinoma"[All Fields] AND "resect"[All Fields] OR "resectability"[All Fields] OR "resectable"[All Fields] AND "mortality"[All Fields] OR "survival"[All Fields] was conducted. All the articles were retrieved and rechecked by the first two authors independently as per PRISMA guidelines [14]. The PICO format of the study design is shown in Figs.1 and 2.

Inclusion criteria:

1. Patients with HCC who underwent surgical resection for tumors > 10 cm (1995 to 2020)
2. Tumors with BCLC B/C (1999–2020)
3. Advanced tumors with portal vein thrombus
4. Resection versus TACE done for advanced tumors.

Exclusion criteria:

1. Any other histology apart from HCC.
2. Number of patients < 40.
3. Articles without survival data.
4. Overlapping literature was excluded to include the largest cohort.
5. For multinodular tumors, metachronous tumors were excluded.
6. Cohort studies without subgroup survival data for tumors > 10 cm or BCLC B/C or advanced tumors including portal vein thrombus.
7. Neoadjuvant or adjuvant radiotherapy was excluded as it is not standard of care.
8. Articles focusing on radiofrequency ablation, transarterial radioembolization (TARE), or transplantation were

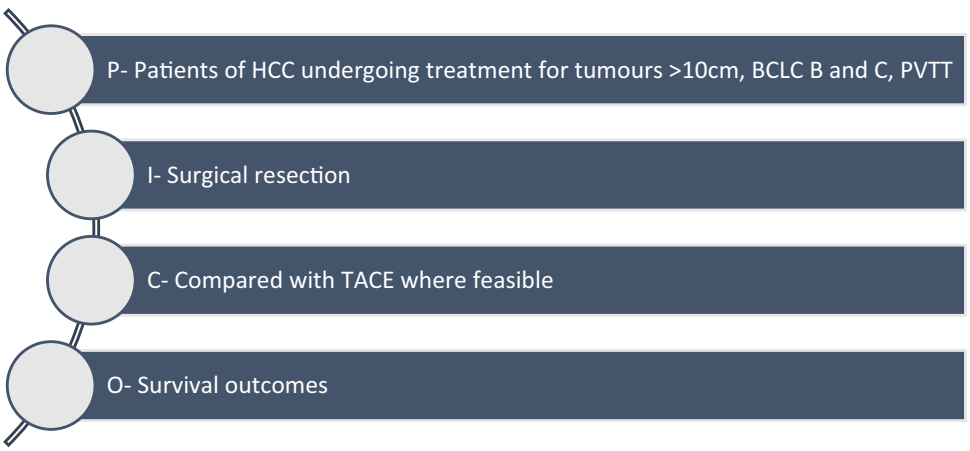

Fig. 2 PICO format of study design

excluded as well as those focusing on preoperative or adjuvant TACE.
9. Articles in language other than English.
10. Solitary large tumors between 5 and 10 cm owing to their inherent good biology.

Data extraction and analysis

We used the MeSH terms in the Pubmed, Medline, and Google Scholar databases as follows ("hepatocellular carcinoma") AND (resection) AND (survival OR outcome). The articles extracted were first assessed by the titles of the manuscripts to exclude the ones not relevant to the systematic review. Following this, the abstracts were reviewed to sort the articles for full-text evaluation. The number of patients, presence of microvascular, macrovascular invasion, cirrhosis, tumor size, BCLC stage, multinodularity, mortality, and prognostic factors were assessed where available.

Statistical analysis

The data was recorded using Statistical Product and Service Solutions (SPSS), IBM Corp, for Windows version 24.0 (SPSS Inc.). The Synthesis Without Metanalysis (SWiM) guidelines were followed, and study results were reported using the checklist provided in Appendix 1 [15]. The studies were analyzed to include prognostic factors of tumor size, BCLC staging, multiple tumors, microvascular invasion, macrovascular invasion, and specific factors mentioned as per each study. Factors influencing overall survival (OS) were compiled as well as 1, 3, and 5-year OS and DFS where described. The values were described as the median in each specific group. Hazard ratios were compared for BCLC B/C patients who underwent resection or TACE in a forest plot.

Results

We identified 8932 articles through database search and 74 articles through references of retrieved manuscripts. A complete assessment of the full text of 131 articles led to inclusion of 89 articles in the systematic review as per predefined criteria (CONSORT diagram—Fig. 1). Articles excluded were 79 articles involving liver transplantation, 51 articles involving radiofrequency ablation (RFA), 47 articles regarding neoadjuvant or adjuvant TACE, 22 articles with sample size less than 40, 26 articles regarding bile duct tumor thrombi, 20 articles regarding transarterial radioembolization (TARE), 16 articles regarding portal vein embolization (PVE), and 4 articles regarding radiotherapy.

These articles were identified as large HCC (> 10 cm) grouped in Tables 1, 2, and 3, BCLC B/C grouped in Table 4, TACE versus resection grouped in Table 5, and multinodular HCC grouped in Table 6.

Twenty studies of large HCC, 5 studies comparing with TACE, and 12 studies comparing < 10 cm tumors with > 10 cm tumors which included a total of 4026 patients. Among intermediate and advanced HCC, 28 studies with a total of 2050 patients with BCLC B and 4434 patients with BCLC C were analyzed. There were 14 papers of multinodular HCC with 4091 patients, whereas resection versus TACE included 5915 patients who underwent resection compared with 7690 patients of TACE as identified in 27 studies.

BCLC B patients were divided as large HCC > 10 cm, multinodular, and BCLC B/C.

Large HCC (> 10 cm)

There are no definite criteria for large HCC; however, the management of HCC > 10 cm is challenging. We identified 20 studies of resection in large HCC as shown in Table 1. Five studies that compared resection versus TACE have been described in Table 5. A comparison of survival outcomes between > 10 and < 10 cm tumors was available in 12 studies as shown in Table 3. A total of 4026 patients with a median age of 52 (range 39–63.9) and median tumor size of 12.3 cm (range 12–14.7 cm) were analyzed. The other variables assessed were cirrhosis which ranged from 5 to 86.3%, microvascular invasion 29–87.5%, macrovascular invasion 10–55.8%, and perioperative mortality 0.78–6.9%. Survival analysis revealed a 5-year overall survival (OS) range from 16.7 to 60% with a mean of 33.5%. Vascular invasion was an independent prognostic factor for OS in 14 studies. Other prognostic factors (Table 2) included intraoperative blood loss > 2000 ml, cirrhosis, AFP > 200 U/mL, hepatitis C, child status B, multiple tumors, capsular invasion, and microscopic resection margin positive (R1). On comparing tumors > 10 to < 10 cm, morbidity and mortality were similar, but overall survival was significantly better in 8 studies for tumors < 10 cm, whereas it was not statistically significant in 3 studies. For tumors > 10 cm, the 5-year OS ranged from 16.7 to 60%, whereas it was 39 to 71.3% for tumors < 10 cm. For solitary tumors > 5 cm, resection is still considered as the first-line treatment option as per EASL-EORTC guidelines due to the inherent good prognosis of these tumors, and there is some ambiguity to include them in BCLC A or B; hence, we have not included studies with solitary tumors between 5 and 10 cm [8].

Multinodular HCC

There were 4091 patients with multinodular HCC in 14 papers. Peri-operative mortality was between 0 and 3.7% with > 90% patients of child A status. One-year DFS and 5-year DFS ranged from 79.1 to 45.7% and 4 to 34.5%,

Table 1 Studies with outcomes of resection of huge HCC (> 10 cm)

Sr. no	Author	Origin and study period	Age	*n*	Median size cm	Cirrhosis (%)	MiVI (%)	MaVI (%)	Peri-op mortality (%)	Recurrence (%)	Median OS (months)	5 year-OS (%)	Factors influencing OS
1	Lee et al. (1998) [16]	Taiwan (1991–1996)	55.4	40	14.3	NA	87.5	NA	2	NA	NA	34	Venous invasion, multiple tumors
2	Poon et al. (2002) [17]	Hongkong (1991–2000)	50.9	120	NA	26.7	69.2	16.7	5	78	MaVI neg 38 MaVI pos/ multiple 10.5	27.5	AST > 50U/L,MaVI, multiple tumors
3	Zhou et al. (2003) [18]	Shanghai (1964–1999)	47	621	13	81.6	NA	20.5	4.5	NA	NA	MVI- 29.4 MVI + 16.9	Capsule inv, sat nod, MaVI
4	Yeh et al. (2003) [19]	Taiwan (1982–2001)	47.8	211	NA	29.9	NA	55.8	4.3	65.3	MaVI- 56 MaVI + 18.4	16.7	Blood loss, rupture, sat, capsule, MaVI
5	Liau et al. (2005) [20]	New York (1985–2002)	62	82	14.7	10	29	NA	2	61	32	33	Vascular inv, blood loss > 2 L
6	Pawlik et al. (2005) [21]	Multicenter (1981–2000)	55	300	NA	26	53	16.3	5	NA	Overall 20.3 MaVI- 24 MaVI + 9.1	26.9	AFP level, vascular invasion, tumor number, presence of severe fibrosis
7	Chen et al. (2006) [22]	Wuhan (1972–2002)	39	634	NA	86.3	NA	21.9	2.2	NA	NA	18.2	Capsule infiltration, Sat nod, MaVi, Blood loss
8	Pandey et al. (2007) [23]	Singapore (1995–2006)	55	166	13	48.2	61.4	NA	3	NA	20	28.6	Vascular inv, sat nod, cirrhosis
9	S G Lee et al. (2007) [24]	Korea (1997–2003)	47	100	13.3	NA	47	22	2	76	NA	31	MaVI
10	Young et al. (2007) [25]	UK (1994–2006)	53	42	14	5	64	31	7	57	NA	45	None significant
11	Choi et al. (2009) [26]	Korea (1996–2006)	50.8	50	NA	26	68	10	NA	58	NA	40.2	Multinodular
12	Yamashita et al. (2011) [27]	Japan (1995–2007)	60	53	13.2	NA	45	NA	2	60.3	NA	35	T4, vascular invasion
13	Shrager et al. (2012) [28]	New York (1992–2010)	57.7	130	14.2	39.8	38.9	52.4	6.9	76.2	MaVI/sat neg 40.3 Overall—17	MaVI/Sat neg 37.2 18.8	Gross vascular invasion/Satnod
14	Ariizumi et al. (2012) [29]	Japan (1990–2008)	NA	177	13	20	NA	40	NA	37.8	NA	42	Solitary without MaVI 5-year OS 79
15	Zhang et al. (2013) [30]	China (2002–2010)	NA	81	NA	NA	NA	NA	NA	58	NA	60	T size no significance in absence of MaVI
16	Yang et al. (2014) [31]	China (2006–2012)	45	258	13.2	66.1	47.7	NA	0.78	NA	NA	33	Vascular invasion, UICC stage, nodular

Table 1 (continued)

Sr. no	Author	Origin and study period	Age	*n*	Median size cm	Cirrhosis (%)	MiVI (%)	MaVI (%)	Peri-op mortality (%)	Recurrence (%)	Median OS (months)	5 year-OS (%)	Factors influencing OS
17	Hwang et al. (2015) [32]	Korea (2000–2012)	47.8	471	13.6	NA	56.3	10.4	1.7	76	NA	35	AFP > 100, PET uptake, MiVI, sat nod
18	Zhu et al. (2015) [33]	China (2007–2011)	46.8	244	12	27	NA	43	3.7	39.8	29.4	30.3	MaVI, multinod
19	Wakayama et al. (2016) [34]	Japan (1990–2013)	63.9	53	12.4	NA	NA	NA	NA	79.2	NA	42.9	age, hepatitis C, multiple, T > 10 cm, micro portal vascular invasion
20	Fang et al. (2019) [35]	China (2007–2017)	NA	84	NA	85.7	29.7	NA	NA	NA	NA	41.1	f/h/o HCC < CTP B, T > 10 cm, vascular invasion, R1

Table 2 Prognostic factors for large HCC

Significant prognostic factors affecting survival of large HCC
1. Vascular invasion (micro and macro)
2. Multiple nodules, satellite nodules
3. Capsular invasion
4. Blood loss > 2000 ml
5. UICC stage
6. AFP > 100 ng/mL
7. CTP B
8. Age, family h/o HCC, hepatitis C
9. Microscopic resection margin positive (R1)
10. FDG hypermetabolic tumor

respectively, whereas 1-year and 5-year OS ranged from 95.8 to 71% and 11 to 59.3%, respectively, with a mean 5-year OS of 36.6%. Factors affecting OS included symptomatic disease, HBsAg +, T > 5 cm, > 3 nodules, microvascular invasion, higher AFP, lower albumin (≤ 3.5 mg/dl), tumor rupture, and R1 resection status.

BCLC B and C

We identified 28 studies evaluating outcomes of resection for intermediate and advanced HCC (Table 4). Studies comparing resection versus TACE were included in Table 5. A total of 2050 patients with BCLC B and 4434 patients with BCLC C were analyzed. Survival of BCLC B patients undergoing resection was favorable with 1-year DFS of 52% (range 7.5–85%) and 5-year DFS of 22% (range 7.8–28.6%). Overall survival for BCLC B revealed a 1-year OS of 82.7% (range 64.4–100) and 5-year OS of 41.7% (range 0–78.8%). BCLC C patients had a 1-year DFS of 32% (7.5–77) and 5-year DFS range of 0–28.6% with a 1-year OS of 58.5% (34.4–86.5) and 5-year OS of 23.3% (0–57.6). Factors influencing DFS or OS included tumor size, number and grade, macrovascular and microvascular invasion, absence of capsule, higher AFP (> 30 to > 2000 ng/mL), lower albumin < 4 g/dl, hepatitis B, cirrhosis—CTP B, tumor thrombus in hepatic veins or IVC, and extra hepatic spread. Prognostic factors that portended a worse outcome in patients with portal vein tumor thromboses were hepatic vein thrombus and more proximal tumor thrombi in the portal vein.

Resection versus TACE

Literature comparing resection with TACE included 5915 patients who underwent resection compared with 7690 patients of TACE as identified in 27 studies (Table 5). All of these studies except one suggested resection improved survival significantly compared to TACE. Periprocedural mortality was comparable between the two groups. More

Table 3 Studies comparing resectable HCC with tumor size < 10 to > 10 cm

Sr. no	Author	> 10 cm					< 10 cm				
		n	Morbidity (%)	Mortality (%)	MaVI (%)	5-year OS (%)	*n*	Morbidity (%)	Mortality (%)	MaVI (%)	5-year OS (%)
1	Lee et al. [16]	40	27.5	2	NA	34	245	28.2	2.9	NA	48.8 ($p < 0.05$)
2	Poon et al. [17]	120	35	5	16.7	27.5	368	36.4	4.6	3.5	51.6 ($p < 0.05$)
3	Zhou et al. [18]	621	NA	4.5	20.5	26.2	2039	NA	2.3	9	54.3 ($p < 0.05$)
4	Yeh et al. [19]	211	16.1	4.3	55.8	16.7	985	21.6	5.5	32.9	39.5 ($p < 0.05$)
5	Liau et al. [20]	82	50	2	NA	33	111	48	6	NA	39 ($p = 0.56$)
6	Young et al. [25]	42	NA	NA	31	45	85	NA	NA	30	57 (NS)
7	Choi et al. [26]	50	NA	NA	10	40.2	447	NA	NA	7.8	65.9 ($p < 0.05$)
8	Yamashita et al. [27]	53	24.5	3.8	NA	35	412	22.3	2.4	NA	54 ($p < 0.05$)
9	Zhang et al. [30]	81	NA	NA	0	60	528	NA	NA	0	71.3
10	Yang et al. [31]	258	10.9	0.78	NA	33	293 (5-10 cm)	9.1	0.68	NA	39 (NS)
11	Zhu et al. [33]	244	28.3	3.7	43	30.3	495	15.6	2.2	7	51.9 ($p < 0.05$)
12	Wakayama et al. [34]	53	NA	NA	NA	42.9	521	NA	NA	NA	71.3 ($p < 0.05$)

MaVI macroscopic vascular invasion, *OS* overall survival, *NS* not significant

patients of CTP B were included in the TACE-only group. Recurrence rate after surgical resection ranged from 58 to 92%. The 5-year survival for resection and TACE were 40 (range 18–63%) and 17 (range 0–45.1%), respectively.

Discussion

The criteria for surgical resection have been limited in BCLC classification due to the poor long-term survival outcomes [2, 8, 9]. However, it is considered for BCLC B and C by an increasing number of hepatobiliary surgeons. This is due to improved survival outcome as compared to adherence to BCLC recommendations [10–15]. AASLD guidelines and EASL-EORTC recommend TACE for BCLC B and sorafenib for BCLC C stage HCC [8, 9] which needs change and resection should be recommended as a treatment option wherever feasible. Our systematic review has shown results compatible with previously published literature with a 5-year OS of 33.5% for resection of HCC > 10 cm, 41.7% for BCLC B, 23.3% for BCLC C, 36.6% for multinodular HCC, and 40% for resection as compared to 17% for TACE.

Transplant befitting HCC follow a stringent criterion and by and large do not include a major proportion of HCC patients. Apart from this, there is a critical shortage of livers for transplant, and BCLC C patients are ineligible for the same [106, 107]. Once we circumvent these issues, the transplant waiting list time forms a critical rate-limiting step that leads to progression and increases dropout rates significantly by each passing month [108, 109]. Liver donor liver transplant has evolved as a feasible option to increase the donor pool especially in Asia with comparable survival even for larger tumors [110, 111]. However, LDLT poses significant morbidity and risks to the donor but still does not bridge the gap between supply and demand. The recent literature on liver grafts from extended donors (steatosis > 40%, age > 65 years, and cold ischemia time > 14 h) has the possibility to increase the donor pool without affecting survival or recurrence outcomes [112]. However, we will need to have more literature on this before it is accepted as standard practice.

Large HCC have a management dilemma owing to the large size of the tumor where even TACE or sorafenib are not likely to have any significant benefit. It has been seen that larger tumors have higher chances of poor differentiation and vascular invasion [35]. Tumor size alone however is not a determinant of survival when compared to tumors < 10 cm [25, 31, 35]. Major vascular invasion is a robust prognostic indicator with as much as a 50% increase in mortality risk [21]. Serum AFP level and tumor size correlate with survival only in the absence of major vascular invasion [21]. In the presence of major vascular invasion, these factors lose prognostic importance. In huge HCC, solitary tumors

Table 4 Surgical resection for BCLC B/C HCC

Sr. no	Author	Origin and study period	BCLC B/C (n)	Cirrhosis (%)	MaVI (%)	Morbidity/ Mortality (%)		DFS (%) 1/3/5 year			OS (%) 1/3/5 year			Factors affecting DFS/OS
1	Torzilli et al. (2008) [36]	Italy (2001–2006)	B 24 C 28	83.3 71.4	NA	29.2 39.3	0 3.6	85 77	44 17		85 80	67 74	-	Tumor size, tumor grade
2	Chang et al. (2012) [37]	Taiwan (1991–2006)	B 318 C 160	31.4 39.7	0 100	-	2.7	-	-	28.6 21.7	81.2 57.6	59.4 33.8	46.5 29.1	Alb < 4, ICG > 10%, Creat > 1.2, higher grade, MaVI
3	Yang T et al. (2012) [38]	China (2001–2007)	C 511	76.7	30.5	31.3	2.3	48.2	30.3	24	69.9	41.2	30.5	MaVI, extrahepatic spread, biliary invasion
4	J Wang et al. (2012) [39]	Taiwan (2003–2008)	C 68	-	32.4	-	-	-	-	-	-	-	-	Median OS 33.4 months HBV, AFP > 200, MaVI,
5	Roayaie et al. (2013) [40]	New York (1992–2010)	C 165	-	100	-	3–6	40	-	18	-	-	14	AFP > 30 ng/ml, T > 7 cm, tumor in hepatic veins/ IVC
5	Zhang et al. (> 10 cm tumors) (2014)[41]	China (2004–2010)	B 23 C 51	73.4	NA	29	-	7.5 -	0 -		76.2 44.9	9.5 0	0 0	HBsAg, cirrhosis, and radical resection
6	Renner et al. (2015) [42]	Germany (1997–2011)	B 46 C 14	100 100	0 42.9	43.5 64.3	13 21.4	-	-	-	-	-	-	Median OS BCLC B 3.03 years, BCLC C 0.73 year Multiple, MaVI > MiVI
7	Xin Wang et al. (2016) [43]	China (2001–2012)	B 78	93.6	NA	-	-	62.5	-	16.6	85.9	-	29.8	T > 5 cm, T number ≥ 4
8	Wada et al. (2016) [44]	Japan (1991–2013)	B 85	50.6	NA	NA	NA	55.5	26.5	17.4	85.5	76	63.4	Tumor size and tumor number
9	Liu et al. (2016) [45]	China (2005–2013)	B 204 C 54	72	C-100	15.9	-	-	-	-	-	-	36.9 28.9	AFP, T > 5 cm, microvascular portal vein invasion, macrovascular invasion, multiple tumor nodules
9	Furukawa et al. (2017) [46]	Japan (2013–2014)	B 13 C 40	NA	NA	18.3	1.5	NA	NA	NA	100 86.5	78.8 63.3	78.8 57.6	Vascular inv, postop comp
10	Bhandare et al. (2017) [47]	India (2010–2015)	B 63 C 11	43	NA	18.7 5.5	8	NA	56.6 32.7	NA	NA	62.7 37.5	NA	Lymphovascular emboli

Table 4 (continued)

Sr. no	Author	Origin and study period	BCLC B/C (n)	Cirrhosis (%)	MaVI (%)	Morbidity/ Mortality (%)		DFS (%) 1/3/5 year			OS (%) 1/3/5 year			Factors affecting DFS/OS
11	Matsuma et al. (2018) [48]	Japan (2000–2014)	B 65	53	NA	NA	NA	70.5	28	22.1	95.2	67.6	44.8	MiVI, cirrhosis
12	Li et al. (2018) [49]	China (2001–2014)	B 613 C 169	57.4	12.6	34	0.7	NA	NA	NA	92 65.1	62 20.1	32 10.6	MaVI
13	Wang et al. (2019) (BCLC B) [50]	China (2009–2010)	MVI + 84 MVI- 239	52.4 54	NA	NA	NA	26.5 47.5	12.2 34.2	7.8 25.2	67.8 82.1	38.8 64.4	24 49.5	Low alb, MVI, > 2 nodules, no capsule, high CA 19.9, HbsAg +, Larger tumor diameter
14	Di Sandro et al. (2019) [51]	Italy (2003–2016)	B 131	NA	NA	12	2.7	59	38	34	77	51	44	CTP B, MELD score, R1, T > 5 cm, > 2 nodules
15	Tsilimigras et al. (2020) [52]	Multicenter (2005–2017)	B 129 C 25	38.3	NA	50	NA	56.9	27.1	22.2	64.4	62.4	51.6	AFP > 400 ng/mL, R1 for OS
Outcomes of studies with Macroscopic portal vein tumor thrombus (BCLC C)														
16	Ohkubo et al. (2000) [53]	Japan (1985–1997)	47	36	NA	-	-	31.2	17.9	-	53.9	33.2	23.9	T > 10 cm and intrahepatic mets
17	Wu et al. [54]	Taiwan (1990–1998)	112	72	NA	-	2.6	-	-	21	-	-	26.4- 28.5	-
18	Pawlik et al. (2005) [55]	Multicenter (1984–1999)	102	56	NA	-	5.9	-	-	-	45	17	10	Moderate to severe fibrosis and high nuclear grade
19	Zhou et al. (2006) [56]	China (1980–2002)	381	-	-	-	-	-	-	-	47	16	12	< 2 years- PV infusion chemo, AFP > 20, R1 > 2 years ALT > 80
20	Inoue et al. (2009) [57]	Japan (1995–2006)	49	-	NA	-	0	38- 34	34- 22	23- 18	65- 58	46–41	41- 39	-
21	Ban et al. (2009) [58]	Japan (1992–2008)	45	-	NA	23–21	0	30.4	21.2	0	69.6	37.4	22.4	AFP > 2000, intrahepatic mets, serosal invasion
22	Shi et al. (2010) [59]	China (2001–2003)	406	78.8	NA	32.8	0.2	13.3	4.7	-	34.4	13	-	Type III and IV PVTT, AFP > 20, T > 5 cm
23	Tao Zhang et al. (2014) [60]	China (2005–2009)	178	62.9	NA	30.3	1.1	30.5	8.4	-	50	11.4	-	Major vascular invasion, cirrhosis

Table 4 (continued)

Sr. no	Author	Origin and study period	BCLC B/C (n)	Cirrhosis (%)	MaVI (%)	Morbidity/ Mortality (%)		DFS (%) 1/3/5 year			OS (%) 1/3/5 year			Factors affecting DFS/OS
24	Xiao et al. (2014) [61]	China (2001–2008)	66	83.8	NA	-	-	28.6–15.8	10.7–5.3	10.7–5.3	53.6- 39.5	25- 15.8	25- 5.3	AFP > 400, T > 9.1 cm, MaVI, tumor rupture, number of tumors
25	Pesi et al. (2015) [62]	Italy multicenter (1987–2009)	62	90.3	NA	14.5	4.8	31.7	20.8	15.6	53.3	30.1	20	Hepatic vein thrombus worse than portal vein thrombus
26	Kojima et al. (2015) [63]	Japan (2001–2010)	52	-	NA	19.2	-	-	-	-	73.1	40.4	19.2	Adjuvant hepatic arterial infusion chemotherapy improved survival
27	Chen et al. (2019) [64]	China (2003–2012)	1590	48–60	NA	29.8- 31.4	-	-	12.5	-	-	16.6	-	T > 5 cm, satellite nodules, absence of capsule, cirrhosis, Bil > 17.1 μmol/l, AFP > 400, PVTT type III, early recurrence < 1 year
28	Yang et al. (2020) [65]	China (2014–2016)	48	72.9	NA	-	-	64.4	27.6	-	57.6	54.6	-	Bile duct tumor thrombi

Table 5 Outcomes of resection versus TACE in intermediate and advanced HCC

Author	Origin and study period	Resection						TACE/LRT							
		n	Solitary tumor (%)	Mortality (%)	MaVI (%)	Recurrence (%)	5-year OS (%)	*n*	Solitary tumor (%)	Mortality (%)	Complete/Overall response (%)	MaVI (%)		5-year OS (%)	
For tumors > 10 cm															
1. Mok et al. (> 10 cm) (2003) [66]	Taiwan (1990–2001)	56	56.6	1.7	23.2	71.7	24.5	75	66.7	9.3	6.7/26.7%	40		8.2 ($p < 0.05$)	
2. Yamashita et al. (> 10 cm) (2011) [27]	Japan (1995–2007)	53	NA	3.8	NA	60.3	35	12	NA	NA	NA	NA		0 ($p < 0.05$)	
3. Min et al. (> 10 cm) (2014) [67]	Korea (2000–2009)	84	72.6	2.4	29.8	-	39.8	267	39.3	0.4	-	51.3		9.7 ($p < 0.05$)	
4. Chan et al. (> 10 cm) (2015) [68]	Taiwan (2005–2010)	104	72.1	-	44.3	-	51.6	88	37.5	-	-	55.7		6 ($p < 0.05$)	
5. Bogdanovic et al. (> 10 cm) (2021) [69]	Serbia (2001–2018)	68	94.1	5.9	NA	NA	31	35	68.6	5.7	NA	NA		7 ($p < 0.05$)	
BCLC B/C															
		n	Mortality (%)	CTP A/B	MaVI (%)	1 OS	3 OS	5 OS	n	Mortality (%)	CTP A/B	MaVI (%)	1 OS	3 OS	5 OS
6. Lin et al. (BCLC B) (2010) [70]	Taiwan (2001–2007	93	5.4	100/0	NA	83	62	49	73	3.8	100/0	NA	39	5	2 ($p < 0.05$)
7. Hsu et al. (BCLC B/C) (2012) [71]	Taiwan (2002–2010)	268	2.7	93/7	NA	81	63	43	455	8.2	79/21	NA	68	30	15 ($p < 0.05$)

Table 5 (continued)

Author	Origin and study period	Resection						TACE/LRT							
		n	Solitary tumor (%)	Mortality (%)	MaVI (%)	Recurrence (%)	5-year OS (%)	*n*	Solitary tumor (%)	Mortality (%)	Complete/ Overall response (%)	MaVI (%)		5-year OS (%)	
8. Zhong et al. (BCLC B) (2013) [72]	China (2000–2007)	257	3.1	-	-	84	59	37	135	5.7	-	-	69	29	14 ($p<0.05$)
9. Jianyong et al. (BCLC B) (2014) [73]	China (2002–2008)	433	1.6	75/25	-	84.1	71.1	61.2	490	1	78/22	-	85.2	62.2	45.1 ($p<0.05$)
10. J Zhong et al. (BCLC B/C) (2014) [74]	China (2000–2007)	908	1.9	-	27	88	62	39	351	1.7	-	24	81	33	16 ($p<0.05$)
11. Liu et al. (BCLC B/C) (2014) [75]	Taiwan (2002–2013)	PS0 232 PS > 0 119	-	94/6 83/17	18 26	88	74	-	PS0 308 PS > 0 250	-	89/10/1 (C) 66/28/6 (C)	23.1 40	74	49	($p<0.05$)
12. Yin et al. (BCLC B/C) (2014) (RCT) [76]	China (2008–2010)	88	-	98/2	-	76.1	51.5		85	-	87/13	-	51.8	18.1	($p<0.05$)
13. Yuan et al. (BCLC C) (2015) [77]	China (2005–2013)	339	1.5	86/14	NA	58	26	18	105	1.9	87/13	NA	49	14	12 ($p<0.05$)

Table 5 (continued)

Author	Origin and study period	Resection						TACE/LRT							
		n	Solitary tumor (%)	Mortality (%)	MaVI (%)	Recurrence (%)	5-year OS (%)	*n*	Solitary tumor (%)	Mortality (%)	Complete/Overall response (%)	MaVI (%)		5-year OS (%)	
14. Liu et al. (BCLC C) (2015) [78]	Taiwan (2002–2013)	264	-	90/10	35	86	75	57	389	-	74/26	46	73	49	36 ($p < 0.05$)
15. Ciria et al. (BCLC B) (2015) [79]	Spain (2007–2012)	36	0	89/11	NA	83.3	52.8	44.4	44	2.3	66/34	NA	68.2	47.7	38.6 (NS)
16. Kim et al. (BCLC B) (2016) [80]	Korea (2005–2009)	52	-	98.1/1.9	NA	92	65	51.8	225	-	83.1/16.9	NA	78.2	39.2	27.9 ($p < 0.05$)
17. Lee et al. (BCLC C) (2016) [81]	Korea (2000–2011)	40	-	87.5/12.5	-	64.7	49.9	-	80	-	72.5/27.5	-	46.2	7.7	($p < 0.05$)
18. Zhao et al. (BCLC B) (2016) [82]	China (2003–2008)	274	-	-	-	70	46	37	169	-	-	-	38	15	12 ($p < 0.05$)
19. Zheng et al. (BCLC C) (2016) [83]	China (2000–2008)	96	1	78/22	100	86.5	60.4	33.3	134	0	75/25	100	77.6	47.8	20.9 ($p < 0.05$)
20. H Kim et al. (BCLC B) (2017) [84]	Korea (Multicenter, 2003–2005, 2008–2010)	83	-	95/5	-	90	75	63	597	-	75.4/24.6	-	79	35	22 ($p < 0.05$)

Table 5 (continued)

Author	Origin and study period	Resection						TACE/LRT							
		n	Solitary tumor (%)	Mortality (%)	MaVI (%)	Recurrence (%)	5-year OS (%)	*n*	Solitary tumor (%)	Mortality (%)	Complete/ Overall response (%)	MaVI (%)		5-year OS (%)	
21. Tada et al. (BCLC B) (2017) [85]	Japan (Multicenter, 2000–2015)	170	-	100/0	-	-	63.4	53.1	319	-	100/0	-	-	53	34.1 ($p < 0.05$)
22. Guo et al. (BCLC B/C) (2018) [86]	China (2008–2013)	B 239 C 67	-	93.3/6.7 92.5/7.5	C 77.6	Median OS C 42 m	B 45 m	B 357 C 131	-	88/12 81.7/18.3	C 84	Median OS B 36 m C 24.5 m ($p < 0.05$)			
23. Chen et al. (BCLC B) (2018) [87]	Markov model (31 studies)	701	-	92/8	-	88.1	44.2	31.8	1034	-	97/4	-	77	29.1	18.6 ($p < 0.05$)
24. Wei Zhang et al. (BCLC B/C) (2018) [88]	China (2008–2014)	276	0.2	-	21	65.9	45.7	43.8	136	0	-	31.2	29.5	13.6	7.3 ($p < 0.05$)
25. Jian Yang et al. (BCLC B) (2018) [89]	China (2008–2015)	102	3.9	92/8	-	80	47.1	26.2	261	1.9	85/15	-	64.8	24.7	8.4 ($p < 0.05$)
26. Chong Zhong et al. (BCLC B/C) (2018) [90]	China (2005–2013)	280	1	-	-	63.7	31.9	25.3	899	0.2	-	-	47.9	16.9	10.3 ($p < 0.05$)

Table 5 (continued)

Author	Origin and study period	Resection						TACE/LRT						
		n	Solitary tumor (%)	Mortality (%)	MaVI (%)	Recurrence (%)	5-year OS (%)	*n*	Solitary tumor (%)	Mortality (%)	Complete/Overall response (%)	MaVI (%)	5-year OS (%)	
27. Yuanqi Wang et al. (BCLC C) (2020) [91]	China (Multicenter, 2010–2017)	133	0	92.5/7.5	100	60.78	43.51	-	186	0	83.3/16.7	100	34.07	11.86	($p < 0.05$)

without major vascular invasion have a moderate prognosis and should be considered for upfront resection if feasible with an estimated 5-year OS of 33.5%.

In our analysis, BCLC B and C staged patients had a median 5-year OS of 41.7% and 23.3%, respectively. This is consistent with other systematic reviews [10–15] and supports our conviction of resection first approach for these patients. Portal vein thrombus is a poor prognostic factor with more proximal thrombus leading to worse outcome [53, 59, 61]; however, this has not been corroborated in all studies [62]. This points out that the location of portal vein thrombus may not be prognostic, but the presence of hepatic vein thrombus is universally a predictor of poor outcome [62]. Chen et al. identified a 3-year survival milestone which is achieved by one in nine patients of portal vein tumor thrombus [64].

Intermediate and advanced BCLC stages have a significant survival benefit of resection over TACE (Fig. 3). All but one of the 27 studies included suggested that TACE as a treatment modality led to worse survival outcomes compared to resection (Table 5). Wang et al. compared the hepatic resection group with the TACE group (resectable TACE group—patients who could be candidates for resection), and their results still favored hepatic resection in terms of statistically significant better survival [91]. Surgical resection improves survival as compared to TACE in multinodular HCC as well. [96–98, 104]. Fukami et al. analyzed the nationwide registry of Japan and compared 1944 patients of surgical resection to 1302 patients of TACE [104]. Survival analysis favored resection over TACE with a 5-year OS of 59.3% versus 42.1%, respectively [104].

Finally, we acknowledge the limitations to our analysis due to the heterogeneity and retrospective nature of the published literature without controls. In the absence of any level I evidence, the consistent observation in the published literature does suggest resection as a definite option till further evidence is generated.

Proposed algorithm

We would like to propose resection for patients with > 10 cm solitary tumors, BCLC B, BCLC C, and multinodular tumors when feasible and adjuvant TACE in the presence of risk factors as stated below.

Preoperative TACE targets the tumor directly, whereas adjuvant TACE is possibly directed at the micrometastases in the liver through the proximal hepatic artery. This is the reason why preoperative TACE has not shown a survival benefit whereas adjuvant TACE has improved survival as evident in a growing body of literature [113–116]. Microvascular invasion-positive patients have the greatest benefit in OS and DFS with adjuvant TACE [116]. This occurs most

Table 6 Studies assessing outcomes of multinodular HCC

Sr. no	Author	Origin and study period	*n*	CTP A/B (%)	MaVI (%)	Mortality (%)	DFS 1/3/5 year (%)			OS 1/3/5 year (%)			Factors influencing OS
1	Ikai et al. (1998) [92]	Japan (1985–1995)	150	-		-	-	-	-	-	-	14	Vascular invasion
2	Hanazaki et al. (2002) [93]	Japan (1983–1998)	65	83.1/16.9	-	-	48.4	20.3	13.5	85.3	40.8	29.5	HBsAg +
3	Ng et al. (2005) [94]	Multicenter (1982–2001)	380	95/5	-	2.7	54	38	26	74	50	39	Symptomatic disease, cirrhosis, multinodular tumor, microvascular tumor invasion, R1
4	Wang et al. (2007) [95]	Taiwan (1990–2006)	112	-	-	2.7	45.7	29.2	18.4	86.1	55.5	29.9	AFP level > 400 ng/mL, total tumor size > 5 cm, largest tumor size > 5 cm, total tumor number > 3, microvascular invasion, and multiple-site resection
5	Ho et al. (2009) [96]	Taiwan (1981–2000)	294	94.6/5.4	8.2	-	60.5	32.3	24.8	77.4	51.9	36.6	Serum albumin, AFP level, AST level, ALP level, tumor size, portal vein thrombosis, and treatment methods
6	Ruzzenente et al. (2009) [97]	Italy (1991–2007)	136	-	-	-	-	-	22	-	-	47	AFP > 100, number > 3, size > 5 cm, treatment method
7	Huang et al. (> 15 cm, 2012) [98]	China (1998–2008)	116	-	100	3.4	48	16	4	71	23	11	Resection criteria, tumor differentiation, cirrhosis
8	Zhao et al. (2012) [99]	China (2004–2008)	162	100/0	-	2.47	56	40	31	86	51	35	Age > 40 years, AFP > 20 lg/L, GGT > 64 U/L, microvascular invasion, and tumor exceeding the UCSF criteria
9	Nojiri et al. (2014) [100]	Japan (1992–2011)	107	98.1/1.9	-	-	-	43.8	30.5	-	62	38.1	Four or more tumors, tumors 5 cm or larger, vein invasion, intrahepatic metastases, AFP (≥ 400 ng/ml), and a lower preoperative serum albumin level (≤ 3.5 mg/dl)
10	Goh et al. (2014) [101]	Singapore (2000–2011)	110	90.9/9.1	4.5	1.8	57	-	19	82	-	44	Child–Pugh status, number of nodules > 3 margin positivity, tumor rupture, and microvascular invasion

Table 6 (continued)

Sr. no	Author	Origin and study period	*n*	CTP A/B (%)	MaVI (%)	Mortality (%)	DFS (%)	DFS 1/3/5 year	OS (%)	OS 1/3/5 year	Factors influencing OS
11	Wang et al. (2019) [102]	Multicenter (2003–2015)	263	90.9/9.1	-	1.5	57.1	35.8 26.6	81.5	52.4 39.1	AFP level > 400 µg/L, sum of tumor size of the two nodules > 8 cm, tumor size ratio of large/small nodule > 1.5, distance between the two nodules ≤ 3 cm, unilateral hemiliver in distribution of the two nodules, microvascular invasion, and blood transfusion
12	Peng et al. (2019) [103]	China (2015–2018)	Lap 35 Open 80	94.3/5.8 93.8/6.2	-	0	71.9 79.1	51.4 - 46.2	95.8 92.8	77 - 77.1	Lap similar oncological outcomes
13	Fukami et al. (2019) [104]	Japanese nationwide (2000–2007)	1944	-	13	-	-	- 34.5	-	- 59.3	Age, serum albumin, serum AFP, macrovascular invasion, tumor size, and TACE
14	Tsilimigras et al. (2019) [105]	Multicenter (2000–2017)	164	-	-	3.7	-	- 24.7	-	- 52.8	Overall tumor burden

likely due to the fact that HCC with poor prognostic features is known to lead to short-interval intrahepatic recurrence. TACE allows to target these lesions early and improve DFS and OS. Important prognostic factors which have a detrimental effect on survival and should be chosen to decide on adjuvant TACE include (1) T > 10 cm, (2) AFP > 400 ng/mL, (3) microvascular or capsule invasion, (4) macrovascular invasion (not involving main portal vein), and (5) multiple/ satellite nodules. It is an unanswered query of how many cycles of adjuvant TACE should be given as literature supports both single and multiple cycles without any comparison between them [114]. We propose that post resection of intermediate and advanced HCC in the presence of any of the above factors, the patient should receive at least 1 cycle of adjuvant TACE starting within 1 month post-surgery to a maximum of four cycles if feasible (Fig. 4).

Conclusion

Our systematic review justifies hepatic resection wherever feasible for hepatocellular carcinomas > 10 cm, BCLC B, BCLC C, and multinodular tumors followed by assessment of risk factors for planning adjuvant TACE especially in absence of any adjuvant systemic therapy till date. A growing body of evidence especially from the east strongly supports surgery as an option in order to improve survival in absence of any level I evidence.

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Authors' contributions • Study conception and design—Mahesh Goel, S. K. Mathur, Shraddha Patkar.
• Acquisition of data—Saneya Pandrowala and Shraddha Patkar.
• Analysis and interpretation of data—Saneya Pandrowala, Shraddha Patkar, Mahesh Goel, S. K. Mathur.
• Drafting of manuscript—Saneya Pandrowala, Shraddha Patkar, Mahesh Goel, Darius Mirza, S. K. Mathur.
• Critical revision of manuscript— Saneya Pandrowala, Shraddha Patkar, Mahesh Goel, Darius Mirza, S. K. Mathur.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare no competing interests.

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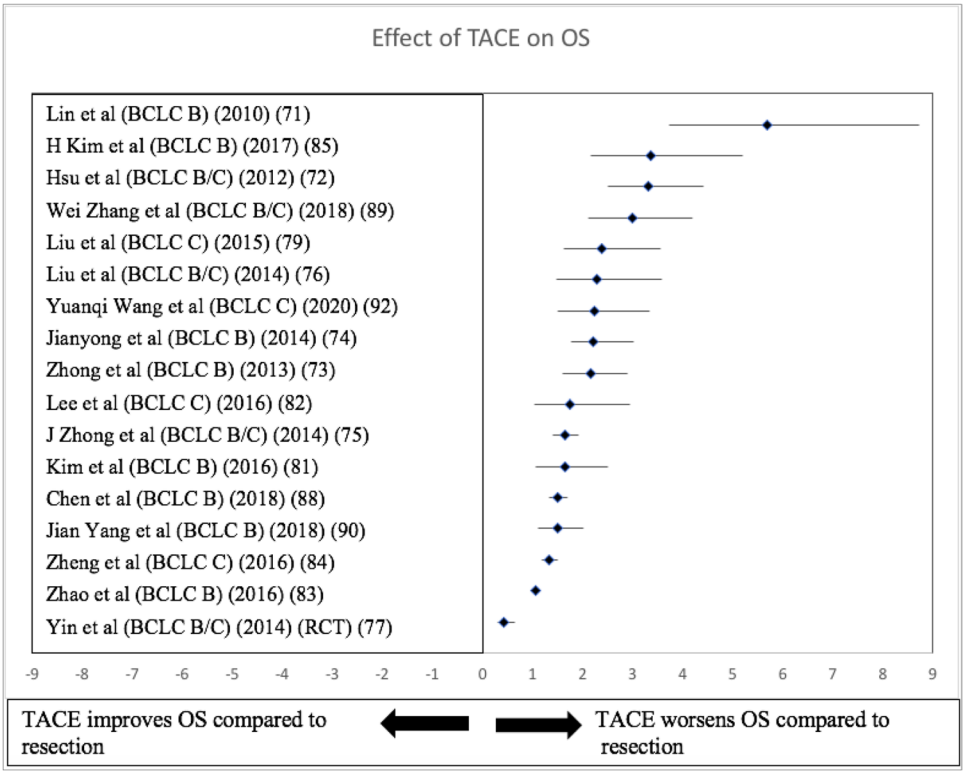

Fig. 3 Forrest plot for effect of TACE as treatment method versus resection on overall survival

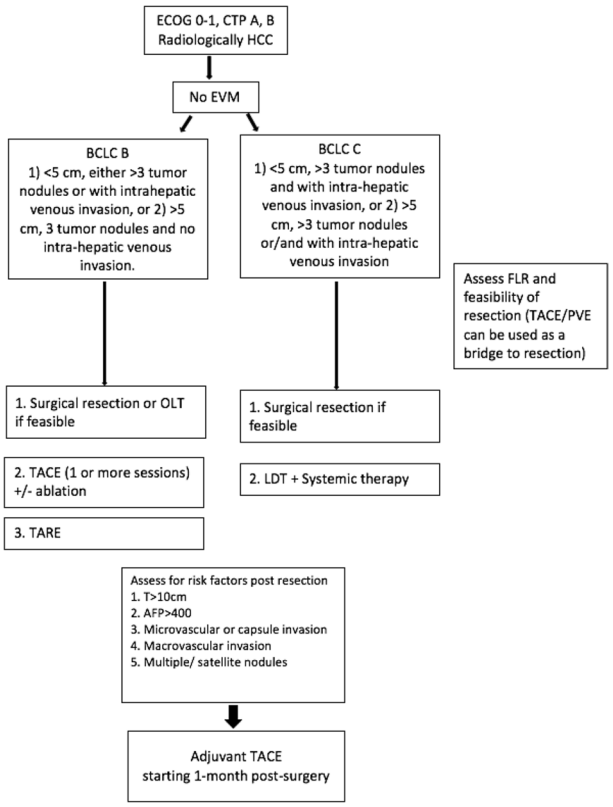

Fig. 4 Proposed management algorithm for intermediate and advanced BCLC

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