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**Systematic review of the outcomes of surgical resection for intermediate and advanced Barcelona Clinic Liver Cancer stage hepatocellular carcinoma: A critical appraisal of the evidence**

Koh YX *et al*. Resection for BCLC Stage B/C HCC

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**Abstract**

***AIM***

To perform a systematic review to determine the survival outcomes after curative resection of intermediate and advanced hepatocellular carcinomas (HCC).

***METHODS***

A systematic review of the published literature was performed using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC. The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child’s A or B status). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary versus multifocal HCC.

***RESULTS***

We identified 74 articles which met the inclusion criteria and were analyzed in this systematic review. Analysis of the resection outcomes of the included studies were grouped according to (1) BCLC stage B or C HCC, (2) Size of HCC and (3) multifocal tumors. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0). In examining the morbidity and mortality following liver resection in large HCC, the pooled RR for morbidity [RR (95%CI) = 1.00 (0.76-1.31)] and mortality [RR (95%CI) = 1.15 (0.73-1.80)] were not significant. Within the spectrum of BCLC B and C lesions, tumors greater than 10 cm were reported to have median 5-year OS of 33.0% and multifocal lesions 54.0%.

***CONCLUSION***

Indication for surgical resection should be extended to BCLC stage B lesions in selected patients. Further studies are needed to stratify stage C lesions for resection.

**Key words:** Barcelona Clinic Liver Cancer; Hepatocellular carcinoma; Hepatectomy; Milan criteria

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**Core tip:** This is a systematic review of the current literature reporting the surgical outcomes of liver resection for Barcelona Clinic Liver Cancer (BCLC) Stage B and C hepatocellular carcinomas (HCC). Based on this review, there is robust evidence that indications for primary surgical resection of HCC should be extended to include BCLC stage B lesions in selected patients. There is a need for further studies that stratify BCLC stage C lesions and potentially extend surgical indications for resectable lesions.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) remains a significant disease burden worldwide today[1]. Appropriate treatment for HCC is complex because radical oncological clearance and preservation of adequate liver function need to be carefully balanced. Several staging systems have been developed to guide management of HCC[2-7].

Surgical resection for HCC within the “Milan Criteria” or Barcelona Clinic Liver Cancer (BCLC) stage A is the widely accepted standard of care[8]. However, surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial[4-7]. Presently, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend surgical resection for these patients[4,7,9].

However, despite the recommendations from these two large reputable organizations, many international high-volume tertiary centers, especially centers in Asia, still routinely perform surgical resection for large solitary lesions, multifocal lesions and lesions with macrovascular invasion[10-16]. Critical appraisal of both Western and Asian literature is needed to resolve the controversies.

The aim of this study was to perform a systematic review and summarize the current literature to determine the long-term survival outcomes after curative resection of intermediate and advanced HCCs.

**MATERIALS AND METHODS**

A systematic review of the published literature was performed using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for BCLC stage B or C HCC.

The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child’s A or B status) and in good general status (PS 0-2). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary versus multifocal HCC.

The Medical Subject Heading (MeSH) major topic was “hepatocellular carcinoma”. The keywords used were “liver tumor”, “hepatoma”, “liver neoplasm”, “liver cancer”, “Barcelona Clinic Liver Cancer”, “multifocal” and “vascular invasion”. The keywords used for surgical resection were “hepatectomy”, “liver resection”, “liver surgery”, “partial hepatectomy”, “hemi-hepatectomy”, “sectionectomy”, “segmentectomy”, “non-anatomical resection”, “anatomical resection”, “curative surgery” and “surgical procedures”. The keywords used for liver reserve were “Child A/B”, “Child Pugh A/B”, “early liver disease” and “early liver cirrhosis”. Key references of the short-listed studies were also searched manually.

Two authors conducted the search independently, with the search results obtained by both authors discussed with the senior author Goh BK. The final list of studies to be short-listed was decided by consensus between all three authors. This study was conducted in accordance to the PRISMA guidelines[17].

***Data extraction***

All short-listed studies were assessed independently according to a modified Newcastle-Ottawa scale. The three main factors assessed were: (1) selection of the patients; (2) comparability of the study groups; and (3) outcome assessment. The scoring scale ranged from 0-9 and studies of score 6 or greater were considered high quality and included in this study. The following data was extracted from the included studies: first author, year of data collection, year of publication, country of origin, characteristics of study population, number of patients, clinico-pathological characteristics, OS and DFS.

***Inclusion criteria***

The inclusion criteria were: (1) studies reporting surgical resection of lesions fulfilling the criteria of BCLC stage B (intermediate) or BCLC stage C (advanced) HCC, studies reporting surgical resection for large HCC, multifocal HCC and HCC with vascular invasion; (2) evaluation of at least one of the clinico-pathological or survival characteristics mentioned in the “parameters and outcomes of interest” section below; and (3) for studies reported by the same institution (and/or) authors with overlapping cohorts, only the study with the larger sample size or the one with higher quality was included. Major resection was defined as resection of 3 segments or more whereas minor resection involved 2 segments or less[18].

Studies which described adjunctive treatments such as radiofrequency ablation (RFA), selective internal radiation therapy (SIRT), trans- arterial chemoembolization (TACE) and infusional chemotherapy were also included.

***Exclusion criteria***

All studies that did not meet the inclusion criteria were excluded. In addition, the following exclusion criteria were used: (1) studies that did not report the survival outcomes of surgically resected HCC; (2) studies that focused on transplant, RFA, TACE and SIRT; (3) studies that focused on DNA, biochemical and proteomic analysis of HCC; (4) studies that focused on radiological imaging techniques; (5) studies reporting patients with Child-Pugh grade C or unknown status; (6) studies reporting tumor rupture, extra-hepatic metastases and/or lymph node metastases; (7) studies which included palliative (R2) resections; and (8) studies written in languages other than English.

***Definitions, parameters and outcomes of interest***

The most updated BCLC staging criteria was used as the reference staging system [4,7,9]. Adequate liver function was defined as Child-Pugh grade A or B. The main outcomes of interest were the OS and DFS. Clinico-pathological characteristics including age, gender, Child-Pugh status, hepatitis status, tumor size, number of nodules, extent of macrovascular invasion, extent of liver resection, post-operative morbidity, mortality and recurrent disease were recorded.

***Statistical methods***

If the data on the OS or DFS was not provided explicitly in a study, the information was derived from the survival graphs if present, or calculated from the primary data using a measurement method as described by Lim *et al*[8]. The 1, 3 and 5 year OS and DFS were summarized graphically using bubble plots, with the sample size of each cohort relative to the size of the bubble.

The inverse variance (IV) method was used to pool the RR across studies. A fixed 0.5 zero-cell correction was used when the number of events for one of the groups was zero. Pairwise comparisons of subtypes were done. If there were no events in an outcome of interest for both groups that were compared, the study was excluded from the meta-analysis for the specific outcome.

Heterogeneity between the studies was evaluated using the chi-squared test of heterogeneity. A random effects model was used. Sensitivity analyses were performed by excluding each study individually from the pool of studies combined for each outcome. Pooled results from these subgroups were computed and compared with the pooled results from the set of studies without these exclusion criteria. All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, United States) and Review Manager 5 (Nordic Cochrane, Copenhagen, Denmark).

**RESULTS**

The systematic review identified 1908 articles, from which 130 articles were selected for full text review. 74 articles met the inclusion criteria and were analyzed in this systematic review[10-14,19-87]. 56 articles were excluded for the following reasons[88-143]: Three because they were not published in the English language[88-90], 11 because other treatment modalities were used as primary treatment[91-101], 19 because of overlapping cohorts[102-120], nine due to incomplete data[121-129], two due to inclusion of palliative liver resection[130-131], and 12 because the study populations included patients with other types of hepatic malignancies[132-143] (supplementary Figure 1). Analysis of the resection outcomes of the included studies were grouped according to (1) BCLC stage B or C HCC; (2) Size of HCC; and (3) multifocal tumors.

***BCLC Stage B or C HCC***

Studies which classified HCC according to BCLC Staging System[4-7] utilized the following common definitions: Stage B – single tumor more than 5 cm in diameter; 2 to 3 tumors of which at least one is more than 3 cm in diameter; or more than 3 tumors of any diameter; Stage C – any tumor with radiologically evident and histologically proven macrovascular invasion, N1 disease or M1 disease.

The baseline characteristics of the patients are presented in Table 1. There are 6103 BCLC stage B cases in 19 studies and 3449 BCLC stage C cases in 32 studies. The clinical outcomes are summarized in Table 2. The study recruitment periods extended from 1982 to 2011. Figure 1a-c are bubble plots showing OS and DFS, with bubble size indicating relative sample size. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0 – 42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0).

***Size of HCC***

HCC analyzed according to size criterion were categorized as: Large HCC – greater than or equal to 10 cm in diameter; and Small HCC – less than 10 cm in diameter.

The baseline characteristics are presented in Table 3. There are 2437 cases of large HCC in 21 studies and 5436 cases of small HCC in 14 studies. The clinical outcomes are summarized in Table 4. The study recruitment periods extended from 1964 to 2011. supplementary Figure 2A and b are forest plots showing the morbidity and mortality respectively of the included studies. The pooled RR for morbidity [RR (95%CI) = 1.00 (0.76-1.31)] and mortality [RR (95%CI) = 1.15 (0.73-1.80)] were not significant. The median 5-year OS of large HCC was 33.0 % (range: 16.7-79.0) and the median 5-year OS of small HCC was 52.3% (range 21.0-89.2).

***Multifocal HCC***

The baseline characteristics are presented in supplementary Table 1. There are 1095 cases in 9 studies. The clinical outcomes are summarized in supplementary Table 2. The study recruitment periods extended from 1992 to 2011. supplementary Figure 3 displays the bubble plot showing overall and disease free survival rate of the included studies, with bubble size indicating relative sample size. The median 5-year OS was 54.0% (29.9-75.5). supplementary Figure 4 was plotted to show 5 year OS for those studies with sample size greater or equal to 100 against the midpoint of recruitment period. The trend line was fitted using weighted least squares regression with sample size as weight. An uptrend with weighted slope 0.38 was seen in the plot.

**DISCUSSION**

***BCLC Stage B or C HCC***

Presently, a major controversy in the management of HCC is the role of surgical resection for intermediate (BCLC stage B) and advanced (BCLC stage C) stage HCC. According to EASL and the AASLD guidelines, surgical resection is not offered for BCLC stages B and C HCC because of the poor 5-year overall survival rates[7,9].

However, the results of this systematic review demonstrate that the median 5 year OS after surgical resection for BCLC B is 38.9% (range: 10.0%-57.0%). These outcomes are clearly not attainable by other modalities such as TACE which only confers a 40% two year survival and median survival of 20 months for similar lesions[144].

This systematic review demonstrates that for BCLC C lesions, surgical resection results in uniformly poor results with a median 5-year OS of 20% (range: 0%-42.0%). However, proponents of resection argue that the tumor thrombus has the potential to cause portal vein obstruction, intractable ascites, esophageal variceal bleeding and liver failure[66-68]. This frequently leads to an even more rapid demise of these patients.

In general, the prognosis for tumor thrombus located within the main trunk has been reported to be poorer as compared to more distal lesions[58,62,68]. Some authors have advocated for portal vein resection for 1st order portal vein tumor thrombus with minimal bifurcation involvement, citing results of 5-year OS over 20% which was superior to thrombectomy alone[53,75]. However, statistical analysis could not be performed due lack of stratification based on the extent of PV invasion, heterogeneous surgical procedures and different extents of hepatic vein and inferior vena cava involvement.

***Size of HCC***

The median 5 year OS in these large lesions was 33% (range: 16.7%-79.0%). The 10 cm arbitrary cut-off used by many studies represents the more advanced cases in the spectrum of BCLC B HCC[32-43]. In addition, BCLC C lesions that were > 10 cm, usually with worse prognosis, were not excluded from the analysis in these studies, confounding the results. Despite this, the relatively favorable survival still indicates that surgical resection is beneficial for selected lesions within the combined spectrum of large HCCs[32-43].

***Multifocal HCC***

The EASL guidelines do not recommend surgical resection as first line therapy for all multifocal lesions[4,7,9]. On the other end of the spectrum, the APASL guidelines support resection of all lesions regardless of multifocality[2]. The APASL guidelines are supported by the fact that that over 65% OS has been reported after surgical resection for multifocal HCC within the “Milan criteria”[8]. In addition, studies from large specialized liver centers have showed favorable 5-year OS of over 50% after surgical resection for multifocal HCC[13,77,82]. This was further improved to between 55%-75% 5-year OS when performed in combination with RFA for bilobar lesions[76,78,80]. In this review, the median 5-year OS for all surgically resected multifocal HCC analyzed in this systematic review is 54.0% (range: 29.9%-75.5%), supporting surgical resection as the primary management of multifocal HCC.

It is important to highlight that surgical series of the aforementioned groups represent the entire spectrum of tumors beyond the “Milan criteria”, and the wide range of survival reported for these lesions can be attributed to the heterogeneity of tumors encompassing large solitary and multifocal lesions of various sizes. Differentiation of the outcomes of purely single or multifocal HCC within this heterogeneous selection and is often not pursued in many studies and making interpretation of the data difficult.

Based on this review, it is evident that arbitrary classifications by the current guidelines do not adequately measure the extent of tumor burden, or prognosticate the continuum of outcomes after resection in the wide spectrum of tumors beyond the “Milan criteria”. The “up-to-seven” criteria described by Mazzaferro *et al*[145]which is a better surrogate measure of tumor burden, could be useful for selection of patients with appropriately sized large solitary HCC or multifocal HCC with an acceptable number of lesions to undergo surgery[145,146].

As evidenced by the results of this systematic review, long-term survival results after surgical resection are acceptable and represent the best possible therapeutic option for selected BCLC stage B HCC. This review showed that resection beyond criteria advised by the AASLD and EASL guidelines, has achieved survival exceeding that accorded by non-curative methods such as TACE and sorafenib which typically confers a median OS between 8-12 mo[147-152].

There are several limitations of this systematic review. Firstly, the studies in this review comprise a group of highly selected patients who underwent surgical resection. They do not represent the entire spectrum of patients with BCLC stage B or C HCC and will be biased towards patients who are more suitable surgical candidates. Secondly, there exists a myriad of neo-adjuvant and adjuvant treatment protocols included in these studies. However, the evidence does not show definitive benefit in terms of survival and thus the effect is not likely to be significant[153-155].

In conclusion, the results of the current systematic review provides evidence that indications for surgical resection of HCC should be extended to include selected BCLC stage B lesions and further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

**Article Highlights**

***Research background***

Hepatocellular carcinoma (HCC) remains a significant disease burden worldwide today. Appropriate treatment for HCC is complex because radical oncological clearance and preservation of adequate liver function need to be carefully balanced. Several staging systems have been developed to guide management of HCC.

***Research motivation***

Surgical resection for HCC within the “Milan Criteria” or Barcelona Clinic Liver Cancer (BCLC) stage A is the widely accepted standard of care. However, surgical treatment for BCLC stage B (intermediate) or C (advanced) lesions remains controversial. Presently, the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines do not recommend surgical resection for these patients. However, despite the recommendations from these two large reputable organizations, many international high-volume tertiary centers, especially centers in Asia, still routinely perform surgical resection for large solitary lesions, multifocal lesions and lesions with macrovascular invasion. Critical appraisal of both Western and Asian literature is needed to resolve the controversies.

***Research objectives***

The aim of this study was to perform a systematic review and summarize the current literature to determine the long-term survival outcomes after curative resection of intermediate and advanced HCCs.

***Research methods***

We conducted a systematic review of the published literature using the PubMed database from 1st January 1999 to 31st Dec 2014 to identify studies that reported outcomes of liver resection as the primary curative treatment for BCLC stage B or C HCC. The primary end point was to determine the overall survival (OS) and disease free survival (DFS) of liver resection of HCC in BCLC stage B or C in patients with adequate liver reserve (*i.e.*, Child’s A or B status) and in good general status (PS 0-2). The secondary end points were to assess the morbidity and mortality of liver resection in large HCC (defined as lesions larger than 10 cm in diameter) and to compare the OS and DFS after surgical resection of solitary versus multifocal HCC.

***Research results***

We included a total of 74 articles in this systematic review. Analysis of the resection outcomes of the included studies were grouped according to (1) BCLC stage B or C HCC, (2) Size of HCC and (3) multifocal tumors. The median 5-year OS of BCLC stage B was 38.7% (range 10.0-57.0); while the median 5-year OS of BCLC stage C was 20.0% (range 0.0-42.0). The collective median 5-year OS of both stages was 27.9% (0.0-57.0). In examining the morbidity and mortality following liver resection in large HCC, the pooled RR for morbidity [RR (95%CI) = 1.00 (0.76-1.31)] and mortality [RR (95%CI) = 1.15 (0.73-1.80)] were not significant. Within the spectrum of BCLC B and C lesions, tumors greater than 10 cm were reported to have median 5-year OS of 33.0% and multifocal lesions 54.0%.

***Research conclusions***

In conclusion, the results of the current systematic review provides evidence that indications for surgical resection of HCC should be extended to include selected BCLC stage B lesions and further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

***Research perspectives***

As evidenced by the results of this systematic review, long-term survival results after surgical resection are acceptable and represent the best possible therapeutic option for selected BCLC stage B HCC. This review showed that resection beyond criteria advised by the AASLD and EASL guidelines, has achieved survival exceeding that accorded by non-curative methods such as TACE and sorafenib which typically confers a median OS between 8-12 months. Further studies should seek to identify the optimal criteria for the consideration of the criteria for liver resection.

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**Table 1 Characteristics of patients classified as BCLC stage B or C hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | ***n*** | **Male (%)** | **Cirrhosis (%)** | **HBV (%)** | **HCV (%)** | | **Median tumor diameter (cm)** |
| **BCLC Stage B** |  |  |  |  |  |  | |  |
| Régimbeau *et al*[25] | 1999 | 94 | 75 (79.8) | 37 (39.4) | 35 (37.2) | 10 (10.6) | 12.0 | |
| Hanazaki *et al*[19] | 2001 | 133 | 105 (78.9) | NS | NS | NS | 8.6 | |
| Ng *et al*[10] | 2005 | 380 | 278 (73.2) | 380 (100.0) | 281 (73.9) | 20 (5.3) | NS | |
| Chen *et al*[26] (TP1) | 2006 | 959 | 816 (85.1) | 717 (74.8) | 776 (80.9) | NS | 14·9 | |
| Chen *et al*[26] (TP2) | 2006 | 1143 | 968 (84.7) | 897 (78.5) | 940 (82.2) | NS | 11·1 | |
| Cho *et al*[26] | 2007 | 230 | 46 (20.0) | 35 (15.2) | 40 (17.4) | 5 (2.2) | 7.1 | |
| Vitale *et al*[31] | 2009 | 124 | NS | NS | NS | NS | NS | |
| Yang *et al*[11] | 2009 | 260 | 228 (87.7) | 198 (76.2) | 239 (91.9) | NS | 9.6 | |
| Zhou *et al*[29] (SX) | 2009 | 56 | 49 (87.5) | 50 (89.3) | 55 (98.2) | 0 (0.0) | 9.5 | |
| Zhou *et al*[29] (TCSX) | 2009 | 52 | 48 (92.3) | 49 (94.2) | 51 (98.1) | 0 (0.0) | 9.0 | |
| Delis *et al*[27] | 2010 | 66 | 45 (68.2) | NS | 36 (54.5) | 15 (22.7) | 8.4 | |
| Lin *et al*[30] | 2010 | 93 | 75 (80.6) | NS | 60 (64.5) | 22 (23.7) | 8.0 | |
| Ramacciato *et al*[28] | 2010 | 51 | 37 (72.5) | 44 (86.3) | NS | NS | 8.2 | |
| Xu *et al*[21] | 2010 | 165 | NS | NS | NS | NS | NS | |
| Wei *et al*[22] | 2011 | 51 | NS | NS | NS | NS | NS | |
| Zhou *et al*[20] | 2011 | 85 | 74 (87.1) | 65 (76.5) | 68 (80.0) | 6 (7.1) | NS | |
| Chang *et al*[32] | 2012 | 318 | 263 (82.7) | 97 (30.5) | 201 (63.2) | 57 (17.9) | 7.4 | |
| Hsu *et al*[34] | 2012 | 268 | 213 (79.5) | NS | 176 (65.7) | 48 (17.9) | NS | |
| Ma *et al*[23] | 2012 | 178 | 158 (88.8) | 79 (44.4) | 140 (78.7) | 41 (23.0) | NS | |
| Torzilli *et al*[12] | 2013 | 737 | 586 (79.5) | 360 (48.8) | 158 (21.4) | 208 (28.2) | 6.0 | |
| Zhong *et al*[120] | 2013 | 660 | NS | NS | NS | NS | NS | |
| **BCLC Stage C** |  |  |  |  |  |  | |  |
| Ohkubo *et al*[79] | 2000 | 47 | 41 (87.2) | NS | 20 (42.6) | 11 (23.4) | | NS |
| Wu *et al*[57] (SX 1st bifurcation) | 2000 | 15 | 13 (86.7) | NS | 14 (93.3) | 2 (13.3) | | 10.8 |
| Wu *et al*[57] (SX 1st) | 2000 | 97 | 83 (85.6) | NS | 67 (69.1) | 25 (25.8) | | 8.8 |
| Minagawa *et al*[58] | 2001 | 18 | NS | NS | NS | NS | | 5.3 |
| Poon *et al*[59] | 2003 | 20 | 18 (90.0) | NS | 17 (85.0) | NS | | 8.6 |
| Fan *et al*[60] (SX, CHT) | 2005 | 84 | 76 (90.5) | NS | NS | NS | | 10.5 |
| Fan *et al*[60] (SX) | 2005 | 24 | 20 (83.3) | NS | NS | NS | | NS |
| Pawlik *et al*[10] | 2005 | 102 | 87 (85.3) | NS | NS | NS | | 10 |
| Chen *et al*[62] (SX 1st) | 2006 | 286 | 248 (86.7) | NS | 172 (60.1) | NS | | 7.7 |
| Chen *et al*[62] (SX Main) | 2006 | 152 | 135 (88.8) | NS | 95 (62.5) | NS | | 8.1 |
| Ikai *et al*[64] | 2006 | 78 | 57 (73.1) | NS | 24 (30.8) | 36 (46.2) | | NS |
| Le Treut *et al*[63] | 2006 | 26 | 22 (84.6) | NS | NS | NS | | 9 |
| Kamiyama *et al*[66] (RTSX) | 2007 | 15 | 13 (86.7) | NS | NS | NS | | 6.47 |
| Kamiyama *et al*[66] (SX) | 2007 | 28 | 25 (89.3) | NS | NS | NS | | 11 |
| Takizawa *et al*[65] | 2007 | 12 | 8 (66.7) | NS | NS | NS | | 8.24 |
| Ban *et al*[69] | 2009 | 45 | NS | NS | NS | NS | | NS |
| Inoue *et al*[70] (TB) | 2009 | 20 | 19 (95.0) | NS | 6 (30.0) | 12 (60.0) | | NS |
| Inoue *et al*[70] (EN) | 2009 | 29 | 26 (89.7) | NS | 10 (34.5) | 15 (51.7) | | NS |
| Kondo *et al*[68] (SX, Main) | 2009 | 5 | NS | NS | NS | NS | | NS |
| Kondo *et al*[68] (SX, 1st-3rd) | 2009 | 43 | NS | NS | NS | NS | | NS |
| Peng *et al*[67] (TC) | 2009 | 51 | 46 (90.2) | NS | 31 (60.8) | 5 (9.8) | | 9.04 |
| Peng *et al*[67] (SX) | 2009 | 53 | 50 (94.3) | NS | 40 (75.5) | 3 (5.7) | | 8.39 |
| Vitale *et al*[31] | 2009 | 48 | NS | NS | NS | NS | | NS |
| Shi *et al*[71] | 2010 | 406 | 361 (88.9) | NS | 354 (87.2) | 3 (0.7) | | NS |
| Xu *et al*[21] | 2010 | 95 | NS | NS | NS | NS | | NS |
| Lin *et al*[72] (TP1) | 2011 | 21 | NS | NS | NS | NS | | NS |
| Lin *et al*[72] (TP2) | 2011 | 47 | NS | NS | NS | NS | | NS |
| Peng *et al*[14] | 2011 | 201 | 187 (93.0) | NS | 172 (85.6) | 4 (2.0) | | NS |
| Wei *et al*[22] | 2011 | 17 | NS | NS | NS | NS | | NS |
| Chang *et al*[32] | 2012 | 160 | 140 (87.5) | 60 (37.5) | 112 (70.0) | 20 (12.5) | | 7.5 |
| Huang *et al*[56] (SX) | 2012 | 54 | 40 (74.1) | NS | 41 (75.9) | 2 (3.7) | | 21.4 |
| Huang *et al*[56] (SXTC) | 2012 | 62 | 42 (67.7) | NS | 50 (80.6) | 0 (0.0) | | 20.5 |
| Liu *et al*[74] | 2012 | 65 | 54 (83.1) | NS | NS | NS | | NS |
| Ma *et al*[23] | 2012 | 46 | 41 (89.1) | 25 (54.3) | 41 (89.1) | 0 (0.0) | | NS |
| Li *et al*[75] | 2013 | 13 | 11 (84.6) | NS | NS | NS | | 10.2 |
| Nitta *et al*[77] | 2013 | 35 | 28 (80.0) | NS | 7 (20.0) | 21 (60.0) | | 7 |
| Roayaie *et al*[78] | 2013 | 164 | 132 (80.5) | NS | 61 (37.2) | 70 (42.7) | | 90 |
| Tang *et al*[76] | 2013 | 186 | 166 (89.2) | NS | 159 (85.5) | 23 (12.4) | | 9.53 |
| Torzilli *et al*[12] | 2013 | 297 | 228 (76.8) | 169 (56.9) | 61 (20.5) | 100 (33.7) | | 6.0 |
| Zhong *et al*[120] | 2013 | 248 | NS | NS | NS | NS | | NS |

TP: Time period; SX: Surgery; TC: TACE; CHT: Chemotherapy; TB: Thrombectomy; EN: Enbloc, RT: Radiotherapy.

**Table 2 Clinical outcomes of liver resection in BCLC stage B or C hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Recruitment period** | ***n*** | **Overall survival (%)** | | | **Median OS (mo)** | **Disease free survival (%)** | | | **Median DFS (mo)** |
| **1-yr** | **3-yr** | **5-yr** | **1-yr** | **3-yr** | **5-yr** |
| **BCLC stage B** |  |  |  |  |  |  |  |  |  |  |
| Régimbeau *et al*[25] | 1984-1996 | 94 | 69.0 | 45.0 | 31.0 | NS | 51.0 | 35.0 | 21.0 | NS |
| Hanazaki *et al*[19] | 1983-1997 | 133 | 70.0 | 38.0 | 28.0 | NS | 65.0 | 26.0 | 20.0 | NS |
| Ng *et al*[10] | 1982-2001 | 380 | 74.0 | 50.0 | 39.0 | 36.9 | 54.0 | 38.0 | 26.0 | 15.6 |
| Chen *et al*[26] (TP1) | 1990-2003 | 959 | 67.8 | 50.7 | 27.9 | 16 | 56.5 | 34.7 | 18.9 | 10.0 |
| Chen *et al*[26] (TP2) | 1990-2003 | 1143 | 71.2 | 58.8 | 38.7 | 19 | 61.5 | 38.6 | 23.8 | 17.0 |
| Cho *et al*[26] | 1998-2001 | 230 | 85.0 | 59.3 | 52.9 | NS | 58.3 | 40.0 | 31.7 | NS |
| Vitale *et al*[31] | 2000-2007 | 124 | 85.0 | 56.0 | NS | NS | NS | NS | NS | NS |
| Yang *et al*[11] | 1992-2002 | 260 | 87.0 | 55.5 | 38.2 | 45.5 | 82.4 | 51.0 | 35.0 | 36.7 |
| Zhou *et al*[29] (SX) | 2001-2003 | 56 | 69.6 | 32.1 | 21.1 | NS | 39.2 | 21.4 | 8.9 | NS |
| Zhou *et al*[29] (TCSX) | 2001-2003 | 52 | 73.1 | 40.4 | 30.7 | NS | 48.9 | 25.5 | 12.8 | NS |
| Delis *et al*[27] | 2002-2008 | 66 | 69.0 | 37.0 | 32.0 | 36.0 | 60.0 | 33.0 | 29.0 | 29.0 |
| Lin *et al*[30] | 2001-2007 | 93 | 83.0 | 49.0 | 30.0 | 27.6 | NS | NS | NS | NS |
| Ramacciato *et al*[28] | 2000-2006 | 51 | NS | NS | 56.1 | 68.0 | NS | NS | 41.3 | NS |
| Xu *et al*[21] | 1991-2004 | 165 | 75.6 | 57.4 | 40.2 | NS | NS | NS | NS | NS |
| Wei *et al*[22] | 2003-2007 | 51 | 84.3 | 54.9 | NS | NS | 70.2 | 45.4 | NS | NS |
| Zhou *et al*[20] | 1995-2002 | 85 | 93.8 | 56.2 | 47.0 | 56.0 | 74.3 | 34.4 | 14.8 | 36.0 |
| Chang *et al*[32] | 1991-2006 | 318 | 81.2 | 59.4 | 46.5 | NS | 55.8 | 39.4 | 31.9 | 6.0 |
| Hsu *et al*[34] | 2002-2010 | 268 | 82.0 | 68.0 | 46.0 | NS | NS | NS | NS | NS |
| Ma *et al*[23] | 1998-2011 | 178 | 77.0 | 26.0 | 10.0 | 27.9 | 49.0 | 18.0 | NS | 16.8 |
| Torzilli *et al*[12] | 1990-2009 | 737 | 88.0 | 71.0 | 57.0 | NS | 63.0 | 38.0 | 27.0 | NS |
| Zhong *et al*[120] | 2000-2007 | 660 | 91.0 | 67.0 | 44.0 | NS | NS | NS | NS | NS |
| **BCLC stage C** |  |  |  |  |  |  |  |  |  |  |
| Ohkubo *et al*[79] | 1985-1997 | 47 | 53.9 | 33.2 | 23.9 | NS | 31.2 | 17.9 | NS | NS |
| Wu *et al*[57] (SX 1st bifurcation) | 1990-1998 | 15 | 80.0 | 44.0 | 26.4 | NS | 67.0 | 32.0 | 21.1 | NS |
| Wu *et al*[57] (SX 1st) | 1990-1998 | 97 | 68.0 | 34.0 | 28.5 | NS | 51.0 | 22.0 | 20.4 | NS |
| Minagawa *et al*[58] | 1989-1998 | 18 | 82.0 | 42.0 | 42.0 | 40.8 | NS | NS | NS | 7.8 |
| Poon *et al*[59] | 1989-2000 | 20 | 30.0 | 13.3 | 13.3 | 6.0 | 15.0 | 5.0 | 5.0 | 2.9 |
| Fan *et al*[60] (SX, CHT) | 1997-2002 | 84 | 29.3 | 15.6 | NS | 15.1 | NS | NS | NS | NS |
| Fan *et al*[60] (SX) | 1997-2002 | 24 | 22.7 | 0.0 | NS | 10.1 | NS | NS | NS | NS |
| Pawlik *et al*[10] | 1984-1999 | 102 | 45.0 | 17.0 | 10.0 | 11.0 | NS | NS | NS | NS |
| Chen *et al*[62] (SX 1st) | 1990-2003 | 286 | 58.7 | 22.7 | 18.1 | 18.8 | NS | NS | NS | NS |
| Chen *et al*[62] (SX Main) | 1990-2003 | 152 | 39.5 | 5.7 | 0.0 | 10.1 | NS | NS | NS | NS |
| Ikai *et al*[64] | 1990-2002 | 78 | 45.7 | 21.7 | 10.9 | 8.9 | NS | NS | NS | NS |
| Le Treut *et al*[63] | 1988-2004 | 26 | 38.5 | 20.0 | 13.0 | 9.0 | NS | NS | NS | NS |
| Kamiyama *et al*[66] (RTSX) | 1990-2006 | 15 | 86.2 | 43.5 | 34.8 | 19.6 | NS | NS | NS | NS |
| Kamiyama *et al*[66] (SX) | 1990-2006 | 28 | 39.0 | 13.1 | 13.1 | 9.1 | NS | NS | NS | NS |
| Takizawa *et al*[65] | 1992-2003 | 12 | 63.6 | 53.0 | 26.0 | 26.0 | NS | NS | NS | NS |
| Ban *et al*[69] | 1992-2008 | 45 | 69.6 | 37.4 | 22.4 | 20.0 | 30.4 | 21.2 | 0.0 | NS |
| Inoue *et al*[70] (TB) | 1995-2006 | 20 | 58.0 | 46.0 | 39.0 | NS | 34.0 | 34.0 | 23.0 | NS |
| Inoue *et al*[70] (EN) | 1995-2006 | 29 | 65.0 | 41.0 | 41.0 | NS | 38.0 | 22.0 | 18.0 | NS |
| Kondo *et al*[68] (SX, Main) | 1996-2004 | 5 | 20.0 | NS | NS | NS | NS | NS | NS | NS |
| Kondo *et al*[68] (SX, 1st-3rd) | 1996-2004 | 43 | 54.0 | 33.0 | 27.0 | NS | NS | NS | NS | NS |
| Peng *et al*[67] (TC) | 1996-2004 | 51 | 50.9 | 33.8 | 21.6 | 13.0 | NS | NS | NS | NS |
| Peng *et al*[67] (SX) | 1996-2004 | 53 | 33.3 | 17.0 | 8.5 | 9.0 | NS | NS | NS | NS |
| Vitale *et al*[31] | 2000-2007 | 48 | 55.0 | 44.0 | 0.0 | NS | NS | NS | NS | NS |
| Shi *et al*[71] | 2001-2003 | 406 | 34.4 | 13.0 | NS | NS | 13.3 | 4.7 | NS | NS |
| Xu *et al*[21] | 1991-2004 | 95 | 37.5 | 18.2 | 14.2 | NS | NS | NS | NS | NS |
| Lin *et al*[72] (TP1) | 1996-2006 | 21 | 77.0 | 19.0 | 5.0 | 21.0 | NS | NS | NS | NS |
| Lin *et al*[72] (TP2) | 1996-2006 | 47 | 76.0 | 51.0 | 36.0 | 36.0 | NS | NS | NS | NS |
| Peng *et al*[14] | 2002-2007 | 201 | 42.0 | 14.1 | 11.1 | 20.0 | NS | NS | NS | NS |
| Wei *et al*[22] | 2003-2007 | 17 | 52.9 | 29.4 | NS | NS | 35.2 | 17.6 | NS | NS |
| Chang *et al*[32] | 1990-2009 | 34 | 45.0 | 20.0 | 20.0 | NS | NS | NS | NS | NS |
| Huang *et al*[56] (SX) | 1991-2006 | 160 | 57.6 | 33.8 | 29.1 | NS | 35.3 | 27.2 | 25.0 | NS |
| Huang *et al*[56] (SXTC) | 1998-2008 | 54 | 71.0 | 35.0 | 11.0 | NS | NS | NS | NS | NS |
| Liu *et al*[74] | 1998-2008 | 62 | 71.0 | 24.0 | 6.0 | NS | NS | NS | NS | NS |
| Ma *et al*[23] | 2000-2009 | 65 | 84.0 | NS | NS | 17.0 | 79.0 | NS | NS | 14.0 |
| Li *et al*[75] | 1998-2011 | 46 | 37.0 | 16.0 | NS | 16.9 | 16.0 | NS | NS | 7.7 |
| Nitta *et al*[77] | 1997-2009 | 13 | 53.8 | 15.4 | NS | NS | NS | NS | NS | NS |
| Roayaie *et al*[78] | 2006-2008 | 35 | 78.0 | 37.4 | 32.7 | NS | 45.0 | 11.8 | 11.8 | NS |
| Tang *et al*[76] | 1992-2010 | 164 | 50.0 | 23.0 | 14.0 | 13.1 | 40.0 | 20.0 | 18.0 | 8.1 |
| Torzilli *et al*[12] | 2006-2008 | 186 | 40.1 | 13.6 | NS | 10.0 | NS | NS | NS | NS |
| Zhong *et al*[120] | 1990-2009 | 297 | 76.0 | 49.0 | 38.0 | NS | 46.0 | 28.0 | 18.0 | NS |
| Ohkubo *et al*[79] | 2000-2007 | 248 | 81.0 | 46.0 | 20.0 | NS | NS | NS | NS | NS |

TP: Time period; SX: Surgery; TC: TACE; CHT: Chemotherapy; TB: Thrombectomy; EN: Enbloc, RT: Radiotherapy.

**Table 3 Characteristics of patients classified as large or small hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | ***n*** | **Male (%)** | **Cirrhosis (%)** | **HBV (%)** | **HCV (%)** | **Median tumor diameter (cm)** |
| **Large HCC** |  |  |  |  |  |  |  |
| Poon *et al*[36] | 2002 | 120 | 99 (82.5) | 32 (26.7) | 103 (85.8) | NS | 13.8 |
| Yeh *et al*[38] | 2003 | 211 | 164 (77.7) | 63 (29.9) | 163 (77.3) | 16 (7.6) | 13.9 |
| Zhou *et al*[37] | 2003 | 621 | NS | NS | NS | NS | NS |
| Liau *et al*[41] | 2005 | 82 | 48 (58.5) | 8 (9.8) | NS | NS | 14.7 |
| Nagano *et al*[40] | 2005 | 26 | 19 (73.1) | 5 (19.2) | 14 (53.8) | 3 (11.5) | 14.8 |
| Pawlik *et al*[10] | 2005 | 300 | 222 (74.0) | NS | 188 (62.7) | NS | NS |
| Lee *et al*[43] | 2007 | 100 | 77 (77.0) | NS | NS | NS | 12·5 |
| Pandey *et al*[44] | 2007 | 166 | 143 (86.1) | 80 (48.2) | 130 (78.3) | 2 (1.2) | 13.0 |
| Shah *et al*[42] | 2007 | 24 | NS | NS | 9 (37.5) | 1 (4.2) | 13.1 |
| Young *et al*[45] | 2007 | 42 | 29 (69.0) | 2 (4.8) | NS | NS | 14.0 |
| Shimada *et al*[46] | 2008 | 85 | 72 (84.7) | NS | 27 (31.8) | 19 (22.4) | 12.0 |
| Taniai *et al*[47] | 2008 | 29 | 26 (89.7) | 12 (41.4) | 6 (20.7) | 17 (58.6) | 13.5 |
| Choi *et al*[50] | 2009 | 50 | 34 (68.0) | 13 (26.0) | 33 (66.0) | 1 (2.0) | NS |
| Miyoshi *et al*[49] | 2009 | 22 | 19 (86.4) | 5 (22.7) | NS | NS | 12 |
| Ng *et al*[48] | 2009 | 44 | 33 (75.0) | NS | 15 (34.1) | 3 (6.8) | 12.4 |
| Yamashita *et al*[51] | 2011 | 53 | 48 (90.6) | NS | 18 (34.0) | 22 (41.5) | 13.2 |
| Truant *et al*[35] | 2012 | 52 | 38 (73.1) | 23 (44.2) | 6 (11.5) | NS | 14.0 |
| Allemann *et al*[55] | 2013 | 22 | NS | 9 (40.9) | 4 (18.2) | 2 (9.1) | 13.5 |
| Ariizumi *et al*[54] | 2013 | 107 | NS | NS | NS | NS | NS |
| Shrager *et al*[52] | 2013 | 130 | 98 (75.4) | NS | 56 (43.1) | 23 (17.7) | 14.2 |
| Yang *et al*[53] | 2013 | 258 | 212 (82.2) | 171 (66.3) | 195 (75.6) | NS | 13.2 |
| **Small HCC** |  |  |  |  |  |  |  |
| Miyoshi *et al*[49] | 2009 | 230 | 160 (69.6) | 114 (49.6) | NS | NS | 3.4 |
| Allemann *et al*[55] | 2013 | 79 | NS | 61 (77.2) | 10 (12.7) | 13 (16.5) | 4.9 |
| Poon *et al*[36] | 2002 | 368 | 295 (80.2) | 203 (55.2) | 311 (84.5) | NS | 5.4 |
| Yeh *et al*[38] | 2003 | 778 | 776 (99.7) | 591 (76.0) | 616 (79.2) | 305 (39.2) | 4.5 |
| Zhou *et al*[37] | 2003 | 2039 | NS | NS | NS | NS | NS |
| Liau *et al*[41] | 2005 | 111 | 80 (72.1) | 40 (36.0) | NS | NS | 6.1 |
| Nagano *et al*[40] | 2005 | 143 | 112 (78.3) | 81 (56.6) | 17 (11.9) | 87 (60.8) | 3.3 |
| Shah *et al*[42] | 2007 | 165 | NS | NS | 73 (44.2) | 36 (21.8) | 4.7 |
| Young *et al*[45] | 2007 | 43 | 30 (69.8) | 10 (23.3) | NS | NS | 5.0 |
| Taniai *et al*[47] | 2008 | 291 | 225 (77.3) | 156 (53.6) | 135 (46.4) | 78 (26.8) | 3.7 |
| Choi *et al*[50] | 2009 | 447 | 344 (77.0) | 244 (54.6) | 331 (74.0) | 26 (5.8) | NS |
| Yamashita *et al*[51] | 2011 | 412 | 328 (79.6) | NS | 60 (14.6) | 311 (75.5) | 3.8 |
| Truant *et al*[35] | 2012 | 37 | 28 (75.7) | 26 (70.3) | 1 (2.7) | NS | 4.7 |
| Yang *et al*[53] | 2013 | 293 | 236 (80.5) | 201 (68.6) | 216 (73.7) | NS | 6.7 |

HCC: hepatocellular carcinoma.

**Table 4 Clinical outcomes of liver resection in large or small hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Recruitment period** | | **n** | **Overall survival (%)** | | | **Median OS (mo)** | **Disease free survival (%)** | | | **Median DFS (mo)** |
| **1-yr** | **3-yr** | **5-yr** | **1-yr** | **3-yr** | **5-yr** |
| **Large HCC** | |  |  |  |  |  |  |  |  |  |  |
| Poon *et al*[36] | | 1991-2000 | 120 | 60.6 | 37.8 | 27.5 | 18.8 | 32.0 | 14.1 | 9.5 | 5.5 |
| Yeh *et al*[38] | | 1982-2001 | 211 | 48.1 | 24.0 | 16.7 | NS | 32.9 | 18.8 | 12.7 | NS |
| Zhou *et al*[37] | | 1964-1999 | 621 | 68.0 | 37.3 | 26.2 | NS | NS | NS | NS | NS |
| Liau *et al*[41] | | 1985-2002 | 82 | 73.0 | 49.0 | 33.0 | 32.0 | 80.0 | 44.0 | 24.0 | 22.0 |
| Nagano *et al*[40] | | 1985-2001 | 26 | 41.0 | 29.3 | 29.3 | 10.1 | 65.4 | 49.0 | NS | 29.0 |
| Pawlik *et al*[10] | | 1981-2000 | 300 | 64.9 | 36.7 | 26.9 | 20.3 | NS | NS | NS | NS |
| Lee *et al*[43] | | 1997-2003 | 100 | 66.0 | 44.0 | 31.0 | NS | 43.0 | 26.0 | 20.0 | NS |
| Pandey *et al*[44] | | 1995-2006 | 166 | 65.0 | 35.0 | 28.6 | 20.0 | NS | NS | NS | NS |
| Shah *et al*[42] | | 1993-2004 | 24 | 69.0 | 63.0 | 54.0 | NS | 41.0 | 23.0 | NS | 8.4 |
| Young *et al*[45] | | 1994-2006 | 42 | 70.0 | 45.0 | 45.0 | NS | 62.0 | 49.0 | 43.0 | NS |
| Shimada *et al*[46] | | 1988-2004 | 85 | NS | NS | 31.5 | NS | NS | NS | NS | NS |
| Taniai *et al*[47] | | 1987-2006 | 29 | 51.9 | 33.6 | 33.6 | NS | 48.4 | 21.5 | 21.5 | NS |
| Choi *et al*[50] | | 1996-2006 | 50 | 70.0 | 50.2 | 40.2 | NS | 49.0 | 38.6 | 38.6 | 9.0 |
| Miyoshi *et al*[49] | | 1987-2004 | 22 | 71.8 | 60.3 | 45.2 | 20.5 | 53.3 | 29.1 | 18.2 | 12.0 |
| Ng *et al*[48] | | 1990-2008 | 44 | 66.4 | 38.1 | 27.8 | 21.5 | 49.6 | 23.9 | 19.1 | 10.7 |
| Yamashita *et al*[51] | | 1995-2007 | 53 | 74.0 | 43.0 | 35.0 | NS | 50.0 | 40.0 | 24.0 | NS |
| Truant *et al*[35] | | 2000-2010 | 52 | NS | NS | 43.3 | NS | NS | NS | 39.3 | NS |
| Allemann *et al*[55] | | 1997-2009 | 22 | 84.0 | 72.0 | 45.0 | 27.0 | 64.0 | 28.0 | 27.0 | 10.0 |
| Ariizumi *et al*[54] (S) | | 1990-2008 | NS | 81.0 | 60.0 | 47.0 | 14.3 | 41.0 | 18.0 | 12.0 | NS |
| Ariizumi *et al*[54] (M) | | 1990-2008 | NS | 88.0 | 83.0 | 79.0 | 38.5 | 76.0 | 54.0 | 48.0 | NS |
| Shrager *et al*[52] | | 1992-2010 | 130 | 56.9 | 30.2 | 18.8 | 17.0 | 31.8 | 13.4 | 11.5 | 6.7 |
| Yang *et al*[53] | | 2002-2011 | 258 | 84.0 | 62.0 | 33.0 | NS | 61.0 | 24.0 | 6.0 | NS |
| **Small HCC** | |  |  |  |  |  |  |  |  |  |  |
| Miyoshi *et al*[49] | | 1987-2004 | 230 | 89.3 | 74.6 | 60.4 | 48.2 | 68.0 | 43.7 | 26.7 | 20.0 |
| Allemann *et al*[55] | | 1997-2009 | 79 | 75.0 | 42.0 | 21.0 | 24.0 | 50.0 | 18.0 | 14.0 | 15.0 |
| Poon *et al*[36] | | 1991-2000 | 368 | 83.3 | 64.2 | 51.6 | 62.8 | 64.6 | 41.8 | 28.2 | 25.4 |
| Yeh *et al*[38] | | 1982-2001 | 778 | 81.4 | 57.3 | 39.5 | NS | 61.2 | 40.7 | 32.1 | NS |
| Zhou *et al*[37] | | 1964-1999 | 2039 | 85.0 | 65.1 | 54.3 | NS | NS | NS | NS | NS |
| Liau *et al*[41] | | 1985-2002 | 111 | 80.0 | 58.0 | 39.0 | 40.0 | 70.0 | 49.0 | 31.0 | 28.0 |
| Nagano *et al*[40] | | 1985-2001 | 143 | 93.1 | 74.5 | 44.7 | 53.4 | 80.0 | 46.5 | 31.0 | 33.9 |
| Shah *et al*[42] | | 1993-2004 | 165 | 88.0 | 70.0 | 53.0 | NS | 76.0 | 53.0 | 43.0 | 38.0 |
| Young *et al*[45] | | 1994-2006 | 43 | 82.0 | 63.0 | 57.0 | NS | 71.0 | 54.0 | 48.0 | NS |
| Taniai *et al*[47] | | 1987-2006 | 291 | 81.0 | 61.4 | 45.0 | NS | 74.6 | 37.1 | 25.4 | NS |
| Choi *et al*[50] | | 1996-2006 | 447 | 91.3 | 77.2 | 65.9 | NS | 72.7 | 53.1 | 45.4 | 35.0 |
| Yamashita *et al*[51] | | 1995-2007 | 412 | 89.0 | 67.0 | 54.0 | NS | 72.0 | 45.0 | 37.0 | NS |
| Truant *et al*[35] | | 2000-2010 | 37 | NS | NS | 89.2 | NS | NS | NS | 60.7 | NS |
| Yang *et al*[53] | | 2002-2011 | 293 | 83.0 | 66.0 | 39.0 | NS | 56.0 | 26.0 | 9.0 | NS |

HCC: hepatocellular carcinoma; M: Multi nodules; S: Single nodule.



**Figure 1 Bubble plot of overall survival and disease-free survival of BCLC B, C and large tumors.**