# Hepatocellular carcinoma with right atrial tumor thrombus: a systematic review

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# Abstract

Background: Hepatocellular carcinoma with right atrial tumor thrombus is uncommon but with a dismal prognosis. Methods: By comprehensive retrieval of literature published between 2000 and 2019, 53 reports were obtained with 187 patients recruited into this study. The extracted data included patient characteristics, tumor characteristics, treatment, follow-up and outcomes. Statistical analyses applied were student t , Fisher exact and I 2 tests. Patients were devided into 6 groups according to treatment of choices: transarterial chemoembolization (TACE), surgery, radiotherapy, chemotherapy, interventional treatment and supportive care. Results: The overall survival rate of this cohort was 40.8%. The survival rate of patients receiving TACE was 33.3% and that of surgical patients was 41.9%. The survival time of patients with TACE was longer than surgical patients, but lack of a statistical significance. Patients had a follow-up of 15.7±16.6 (median 10) months. The patients receiving radiotherapy had the longest follow-up among all groups. Intra- and/or extrahepatic recurrence of hepatocellular carcinoma was the major mobidity. The mortality rates in a decremental sequence for patients receiving different treatments were supportive care >radiotherapy >surgery >TACE >interventional treatment. No difference was found in mortality between patients reported from case reports and those from non-case reports. Conclusions: Even though advanced hepatocellular carcinoma with right atrial thrombus is an aggressive malignancy, the the present study showed that patients' prognosis was improved and survival time elongated with active treatments such as TACE and surgery. The present systematic review reveals improved outcomes with active treatments against conservative treatments.


# Background

Hepatocellular carcinoma (HCC) is an aggressive malignancy with a potential to invade intrahepatic vasculature [1]. HCC with a tumor thrombus extending into the right atrium (RA) via the inferior vena cava (IVC) is rare, with a documented incidence of 1–4.8% in autopsy series [1, 2], but it is increasingly reported clinically with the development of medical imaging techniques [3]. The advanced HCC can be managed by non-surgical treatments, such as conservative treatment, transarterial chemoembolization (TACE) and radiotherapy [4]. Nevertheless, HCC patients with RA tumor thrombus often have a dismal prognosis and limited survival time, and respond poorly to standard treatments [4]. Moreover, RA tumor thrombi often lead to sudden death as a result of right heart failure, tricuspid orifice occlusion, or pulmonary embolism [4]. Therefore, aggressive surgical treatment of HCC with RA tumor thrombus have been attempted. However, there is no consensus on the therapeutic regimens of advanced HCC [3]. This article aims to give an overview of advanced HCC with RA tumor thrombus and to discuss the management and outcomes.

# Methods

The English language literature were carefully retrieved in the PubMed database for articles published 2000–2019. The keywords entered in this search to identify articles were "hepatocellular carcinoma", "liver tumor", "tumor thrombus" and "right atrium". The screening of the bibliographic references helped in

completing the literature retrieval. The inclusion criteria were clinical research, case series, or case report on HCC with RA thrombus with substantial patient information for statistical analysis. Seventy articles were found related to the topic and keywords in the literature search. The exclusion criteria were articles reporting: HCC with right ventricle metastasis (n=6), HCC with portal vein or IVC thrombus without RA extension (n=3), RA invasion by metastatic esophageal/pancreas/colon carcinoma (n=3), HCC with RA thrombus where patient information was scanty (n=2), fibrolamellar HCC with RA thrombus (n=1), liver transplantation in Budd-Chiari syndrome (n=1) and cardiac complications after liver transplantation (n=1). In total, 17 articles were excluded and 53 articles were included as materials of the present review.

The data independently extracted from each study were patient characteristics, tumor characteristics, treatment, follow-up and outcomes. Data extraction consisted of tabulating all the necessary information of each report. This process was repeated three times to avoid omissions and ensure the integrity and credibility from the data. Publication bias that might come from the case reports and case series might affect the cumulative evidence.

The quantitative data were expressed in mean±standard deviation and were compared by independent samples *t*-test. The categorical variables were compared by Fisher exact test with continuity correction. $p<0.05$ was considered statistically significant. The extent of heterogeneity was determined by an $I^2$ method, and a $p$ value of <0.1 was taken as a statistically significant level of heterogeneity.

# Results

*Patient Characteristics*

In total 53 articles were collected [1-53], including 5 (9.4%) retrospective studies [3, 11, 23, 50, 53], 4 (7.5%) case series [1, 21, 43, 49], and 44 (83.0%) case reports [2, 4–10, 12–20, 22, 24–42, 44–48, 51, 52], with 187 patients involved.

Patients were at the age of 58.7±12.4 (range, 23-84; median, 60) years (n=93). Gender was known for 105 patients: 88 (83.8%) were male and 17 (16.2%) were female ($\chi^2=96.0$, $p<0.001$). In total 166 (88.8%) patients had a medical history of liver disease (Table II).

Patients were devided into 6 groups according to treatment of choices: TACE, surgery, radiotherapy, chemotherapy, intervention and supportive care. Besides, some patients were not treated, while treatment was not described in others.

In 8 patients with recurrent HCC, previous treatment was hepatectomy in 2 (25%) patients [1, 30], TACE in 3 (37.5%) patients [1, 19], and TACE plus direct-acting antiviral therapy (sofosbuvir) [5], radiofrequency ablation plus doxorubicin and sorafenib chemotherapy [15], and TACE plus radiofrequency ablation plus sorafenib [40] in 1 (12.5%) patient each.

The clinical symptoms were described for 36 patients, with pedal edema being the most common (Table I). Blood test results on admission were shown in Table III.

The timing of diagnosis of RA thrombi was described for 53 patients: at HCC recurrence in 5 (9.4%) patients [1, 5, 13, 15, 30], at HCC progression in 13 (24.5%) patients [1, 17, 19, 34, 36–38, 40, 42, 48, 51], and at the first HCC diagnosis in 35 (66.0%) patients [2, 4, 6–10, 12, 14, 16, 18, 20–22, 24–29, 31–33, 35, 39, 41, 44–47, 49, 52].

The time interval between diagnoses of HCC and of RA tumor thrombus was 33.5±22.1 (range, 9–56; median, 35) months (n=4) for patients with recurrent HCC and 33.4±46.2 (range, 2–144; median, 12) months (n=9) for patients at HCC progression ($t$=0.002, $p$=0.998).

*Tumor Characteristics*

The size of liver tumor was described for 57 patients. The calculated tumor size was 8.4±4.1 (range, 1.3–21; median, 7.6) cm, with only 3 (5.3%) tumors of 3 patients <3 cm [1, 6, 51].

The location of liver tumors were described for 56 patients: 16 (28.6%) were located in the left lobe [2, 8, 12, 16–18, 21, 27, 31, 35, 46, 47, 52, 53], one of which extended to the right lobe at a later stage [17], while 35 (62.5%) tumors were located in the right lobe [1, 6, 7, 9, 10, 13, 14, 20–22, 24, 28, 29, 34, 39, 41, 42, 48, 49, 53], and 5 (8.9%) involved both lobes [25, 26, 32, 33, 53] ($\chi^2$=37.0, $p$<0.001). There was no significant difference in tumor size between tumors located in the left and in the right lobes (8.6±4.2 cm vs. 8.9±4.4 cm, $t$=-0.207, $p$=0.837).

The segmental locations of liver tumors were described for 31 patients, and a total of 68 segments were invaded with 1–4 invaded segments in each patient [2, 10, 13, 18, 21, 22, 25, 27–29, 34, 41, 42, 53]. Segments 7 and 8 were the most commonly invaded by liver tumors (Figure 1).

Apart from RA thrombus, tumor thrombus in the alternative vasculature developed in 106 (56.7%) patients, and IVC thrombus was the most common (Table IV). The maximal size of RA tumor thrombus was 4.6±2.3 (range, 2–15; median, 4.4) cm (n=42). RA tumor thrombus-induced tricuspid orifice occlusion of different degrees was noted in 3 patients [10, 15, 31].

Simultaneous lung metastasis was found in 6 patients [2, 8, 10, 17, 37, 47]. Diaphragm metastasis occurred in 1 patient [7].

*Treatment*

Liver tumor was resected while RA tumor thrombi was not resected but treated with subsequent chemotherapy with bevacizumab in 1 patient [48], and RA and IVC tumor thrombi were removed while liver tumor was not resected but treated by microwave ablation/TACE in 2 patients [26, 16]. Their survival time was 6, 6 and 7 months, respectively (median, 6 months).

The 30 patients with a one-stage operation for both HCC and RA thrombus survived 14.4±12.8 (range, 1.3–56; median, 11.2) months (n=25) [2–4, 12, 13, 18, 20, 21, 25, 28–30, 35, 42, 43, 45, 49–52]. One patient receiving a two-stage operation survived 6 months [38]. The surgical operation was performed under cardiopulmonary bypass (CPB) in 18 patients [2, 3, 18, 21, 28–30, 35, 38, 43, 45, 51, 52], under veno-venous bypass in 1 patient [25] and with total hepatic vascular exclusion (THVE) with no CPB in 15 patients [3, 4, 12, 13, 20, 42, 49, 50].

The operation time was 9.1±2.5 (range, 5.6–12.3; median 9.0) hours (n=12) [4, 7, 12, 25, 29–31, 35, 42, 45, 51, 52], the CPB time was 40.6±23.9 (range, 16–100; median, 38) min (n=9) [2, 7, 12, 29, 30, 45, 50, 51, 52], and the hepatic occlusion time was 29.4±26.3 (range, 10-87; median, 19) min (n=11) [4, 12, 13, 20, 25, 29–31, 42, 45, 52]. The total blood loss amount was 3.562,0±2,692.2 (range, 650-8,200; median, 2,692) mL (n=10) [7, 13, 25, 29–31, 35, 42, 51, 52].

TACE, solely or combined with chemotherapy/radiotherapy/surgery, was done 1–7 times per patient, and thalidomide 100 mg bid was the usual regimen. Complete/partial regression of liver and RA tumor, α-fetoprotein decrease and symptom-free were observed at 1–4 months [1]. Selective embolization with pirarubicin 30 mg, oxaliplatin 200 mg, hydroxycamptothecine 20 mg and iodized-oil was also reported obtaining similar effects to thalidomide [46].

Systemic chemotherapy with sorafenib were applied in 4 patients [9, 14, 27, 47].

Two patients received interventional treatment: mechanical thrombectomy of the right atrial mass with subcutaneous enoxaparin and oral sorafenib in one patient who did not respond to sorafenib and died [41], and percutaneous microwave ablation in another patient in whom intrahepatic tumor recurrence occurred 3 months later and patient was alive as the tumor was completely ablated by TACE and salvage microwave ablation [22].

Radiotherapy included external beam radiotherapy with 2500 cGy in 5 fractions in one patient, the RA mass was reduced at 1 month but died of multiple metastasis [15] and hypofractionated radiotherapy in 18 patients with 2 alive at a follow-up of 3–40 month [23]. The outcomes of each group were shown in Table V.

*Follow-up and Survival data*

Patients had a follow-up of 15.7±16.6 (range, 0.5–97; median 10) months (n=75). The patients receiving radiotherapy had the longest follow-up among all groups (Table VI). Intra- and/or extrahepatic recurrence of HCC was the major mobidity (Table VII).

The overall survival rate of this cohort was 40.8% (20/49). The survival rate of patients receiving TACE was 33.3% (4/12) and that of surgical patients was 41.9% (13/31) ($\chi^2$=0.3, $p$=0.735). The prognosis of the patients with different treatments was shown in Table V. The survival time of TACE patients was longer than that of surgical patients, but lack of a statistical significance (20.0±3.4 months vs. 13.3±12.1

months, $t$=-1.455, $p$=0.151). The mortality rates in a decremental sequence for patients receiving different treatments were supportive care > radiotherapy > surgery > TACE > interventional treatment (Table VI). No difference was found in mortality between patients reported from case reports and those from non-case reports (Table VIII).

The pathology of HCC was available for 18 patients: 10 (55.6%) were moderately differentiated [2, 11, 13, 25, 35, 42, 52], 3 (16.7%) were moderately to poorly differentiated [7, 18, 33], and 5 (27.8%) were poorly differentiated [4, 11, 12, 29, 30].

# Discussion

The etiology of HCC in the present study is similar to that reported by Wakayama et al. [50], with hepatitis B virus infection being the most common etiology, followed by hepatitis C virus infection. Advanced HCCs are agressive and refractory, often with multiple focuses, portal and hepatic vein invasions, and extra-hepatic metastases to the lungs, adrenal gland and mediastinal lymph node [50]. RA thrombus is an uncommon sequel of advanced HCCs, but prognosis is poor with limited treatment options [41]. The incidence of tumor thrombus may be higher in those patients with a serum α-fetoprotein level >1,000 μg/L and a tumor size >5 cm [10].

Lou et al. [23] applied hypofractionated radiotherapy as a salvage treatment for 1,897 patients with recurrent HCC, 104 patients (5.5%) were with IVC/RA tumor thrombus. The 1-, 2- and 3-year survival rates of patients with IVC/RA tumor thrombus were 22.2%, 11.1%, and 5.6%, respectively, with a mean survival time of 11.6±2.5 months [23].

TACE has become a acceptable and safe treatment for unresectable HCCs [54, 55], but extrahepatic collateral artery supply to the tumor thrombus may require sequential repeated TACE, and marked arteriovenous shunts associated with tumor thrombus may limit the therapeutic effect of TACE [56]. TACE with and without combined radiotherapy, and chemotherapy with thalidomide have been reported, but with no reliable evidences of benefits from these treatments [3]. The patients with IVC/RA tumor thrombus treated with TACE had a mean survival time of 4.2 (range, 1.5–76.7) months as reported by Chern et al. [55]. Wang et al. [3] reported the median survival time of such patients was 4.6 months. Duan et al. [11] retrospectively observed 11 cases of HCC with IVC/RA tumor thrombus treated with combined TACE and external beam radiation. They noted that all patients died of disease progression, and the median survival time was 21 months. The clinical effects of TACE in the treatment of HCC with IVC/RA tumor thrombus were heterogeneous and warrant further observations [3]. Nevertheless, TACE helps tumor thrombectomy by stablizing the tumor thrombi, reducing the size, easy removal and preventing fragmentation [42].

Liver resection with thrombectomy has been advocated for HCC patients with IVC/RA tumor thrombus, but its therapeutic effect remains debated. Patients may still show a poor prognosis even with surgical treatment [3]. The surgical indications of HCC patients for major hepatectomy are noncirrhotic or cirrhotic patients at Pugh-Child Class A with no portal hypertension and the indocyanine green clearance value is

≤12% at 15 minutes [57]. However, higher values of indocyanine green clearance are not an absolute surgical contraindication as for the possible clearance impairment by tumor-related vascular obstruction [57]. Pesi et al. [35] summarized that RA tumor thrombus removal could be performed in three ways: 1) with the use of THVE of the liver without CPB, which is indicated for tumor thrombi with an initial contiguity to the RA; 2) normothermic CPB with THVE; and 3) CPB with hypothermic circulatory arrest, but its use is limited due to potentially intraoperative bleeding, possible brain damage and postoperative liver dysfunction. Wang et al. [3] reported that they performed cavoatrial thrombectomy for HCC patients with RA thrombus by modifying procedures as minimally invasive as possible depending on the extension of the tumor thrombus. When the tumor thrombus just slightly entered the RA, median sternotomy or thoracotomy and CPB were not used, but THVE was used instead. As a result, a significant survival benefit of surgical treatment for HCC patients with IVC/RA tumor thrombus was obtained.

Based on Response Evaluation Criteria in Solid Tumor (RECIST), sorafenib showed a Despite a dismal response rate of 2%, but a remarkable improvement of overall survival [58]. A modified RECIST (mRECIST) was termed by modifying the target lesion from the whole lesion to only the contrast-enhanced hepatic lesion at the arterial phase of a dynamic imaging technique [59]. Edeline et al. [58] suggested, after retrospectively studied 53 patients with advanced HCC, that mRECIST should be used for the standard assessment of treatment efficacy due to its wider applicability to patients and the usefulness in guiding the continuation of sorafenib.

HCC with macrovascular invasion is an extensively debated topic. Guidelines often struggle to fit these cases in, leaving them in a "grey area". There is increasing evidence suggesting that alternative strategies to sorafenib might improve patients' survival advanced HCC with macrovascular invasion but lack of sufficient evidence [60]. A recent meta-analysis by Chen et al. [61] revealed that the overall survival is higher in hepatectomy than in TACE group, and that hepatectomy was superior over TACE in 1-year and 3-year, but not in 5-year.

Sorafenib is an effective and safe drug for improving the survival of patients with advanced HCC. Recently, regorafenib was reported to improve survival in a phase 3 clinical trial; however, it is unable to meet the critical needs of treatments of progressed patients or those intolerable to sorafenib [62]. The limited armamentarium with the systemic treatment of HCC prompts physicians to seek more effective treatments to extend patients survival.

The prognosis of patients with HCC and tumor thrombus is poor, and the survival time of untreated patients is limited to only 3 days–2 months, whereas liver resection with cavoatrial thrombectomy improves patients' survival to 5–56 months [35]. The present study revealed an enhanced survival rate and an elongated survival time of HCC patients receiving active treatments.

The main finding of this study was an improved survival rate of patients receiving TACE and of surgical patients. The survival time of patients with TACE was even longer than that of surgical patients, but lack of a statistical significance. Thus, active aggressive treatments are advised for advanced HCC patients.

That patient information from heterogeneous reports, based on some case series and a multitude of single case reports, might bring about possible publication biases at an outcome level, and constituted the major drawback of this study. Even though cohort studies, case-control studies and case series are considered to form a hierarchy of increasing risk of bias, these studies reflected closely a routine practice or the usual setting where the intervention would be implemented. The heterogeneity between the studies was not significant. Patients with smaller HCCs have been probably offered surgery while more extensive HCCs have undergone TACE (if not chemotherapy or best supportive care only). Limitations are expected and do not diminish the value of the work.

# Conclusions

Even though advanced HCC with RA thrombus is an aggressive malignancy, the the present study showed that patients' prognosis was improved and survival time elongated with the advances of active treatments such as TACE and surgical treatments. Authors are aware of a selection bias. Nevertheless, active treatments carry improved outcomes compared to non-active treatments. More patient information from retrospective studies on large patient populations are warranted for obtaining more precise results in future studies.

# Abbreviations

CPB: cardiopulmonary bypass;

HCC: hepatocellular carcinoma;

IVC: inferior vena cava

RA: right atrium;

TACE: transarterial chemoembolization;

THVE: total hepatic vascular exclusion.

# Declarations

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# Tables

Table I. Medical history of liver disease

| Liver disease | n (%) |
|---|---|
| Hepatitis B | 108 (57.8) |
| Hepatitis B infection [3, 20, 22, 26] | 58 (53.7) |
| Hepatitis B antigen positive [10, 13, 21, 23, 32–34, 46, 47, 50] | 33 (30.6) |
| Chronic hepatitis B [8, 11, 12, 15, 17, 25, 44] | 17 (15.7) |
| Hepatitis C | 17 (9.1) |
| Chronic hepatatis C [1, 18, 19, 29, 30, 38, 42, 45, 52] | 10 (58.8) |
| Hepatitis C virus antibody positive [5, 27, 31, 50] | 5 (29.4) |
| Hepatitis C virus RNA very high [24] | 1 (5.9) |
| Hepatitis C virus-related end-stage liver disease [1] | 1 (5.9) |
| Chronic hepatitis, unspecified [39] | 1 (0.5) |
| Hepatitis, autoimmune [40] | 1 (0.5) |
| Cirrhosis [1, 19, 34, 45, 51] | 7 (3.7) |
| Hepatocellular carcinoma [1, 5, 15, 19, 20, 23, 30, 34, 36–38, 40, 45, 48, 51] | 32 (17.1) |
| Human immunodeficiency virus infection [44] | 1 (0.5) |

Table II. 96 clinical symptoms in 36 patients

| Symptom | n (%) |
|---|---|
| Edema, lower extremity [5, 7–10, 14, 16, 34, 39, 42, 45, 46, 51] | 13 (13.5) |
| Ascites [1, 5, 8, 19, 21, 24, 34, 39, 42, 51] | 10 (10.4) |
| Abdominal distension/increase of abdominal volume [1, 16, 19, 24, 26, 32, 34, 45, 51] | 9 (9.4) |
| Abdominal pain [1, 8, 14, 21, 24, 32, 33, 38, 39] | 9 (9.4) |
| Dyspnea [1, 5, 16, 19, 28, 32, 39, 51] | 9 (9.4) |
| Shortness of breath [6, 8, 15, 24, 41, 44] | 6 (6.3) |
| Poor appetite [6, 9, 14, 19, 32] | 5 (5.2) |
| Weight loss [8, 12, 13, 32] | 4 (4.2) |
| Asymptomatic [2, 20, 22, 25] | 4 (4.2) |
| Altered mental status [6, 16] | 2 (2.1) |
| Asthenia/weakness [13, 19] | 2 (2.1) |
| Chest distress [19, 46] | 2 (2.1) |
| Chest pain [41, 44] | 2 (2.1) |
| Epigastralgia [6, 7] | 2 (2.1) |
| Others | 17 (17.7) |

Table III. Blood test results

| Parameter | Mean±SD | Range | Median | Normal/abnormal | n |
|---|---|---|---|---|---|
| Total bilirubin (mg/dL) [1–4, 8–10, 14, 15, 17–21, 25, 32, 33, 38, 45, 46, 51, 52] | 1.5±0.8 | 0.4-2.9 | 1.1 | 10/16 | 26 |
| Album (g/dL) [1–4, 7, 8, 18–21, 25, 30, 32, 35, 38, 44–46, 51, 52] | 3.5±0.7 | 1.9-5.1 | 3.6 | 10/16 | 26 |
| α-fetoprotein (μg/L) [1, 2, 4, 6–12, 14–17, 19–22, 24–27, 29–33, 35, 38–41, 46, 47, 51, 52] | 25,411.9±104988.5 | 2.01-687,460 | 585 | 18/34 | 51 |
| Alkaline phosphatase (U/L) [1, 6, 14, 17–19, 32, 33] | 219.6±170.9 | 40-491 | 141.5 | 3/5 | 8 |
| Aspartate aminotransferase (U/L) [1, 2, 6, 7, 10, 14, 15, 17–21, 25, 27, 32, 33, 35, 52] | 114.8±103.3 | 19-441 | 61 | 3/19 | 22 |
| Indocyanin green retention test at 15 min (%) [2, 4, 18, 35, 51, 52] | 23.3±16.4 | 8.7-61.4 | 20.7 | 1/7 | 8 |

Table IV. Tumor thrombus-invaded vasculatures

| Tumor thrombus-invaded vasculature | n (%) |
|---|---|
| Inferior vena cava [1, 2, 4, 5, 6, 8–11, 13–41, 44–52] | 80 (42.8) |
| Portal vein [6–8, 12, 17, 19, 26, 33–35, 37, 39, 40, 44] | 17 (9.1) |
| Left [33, 35] | 2 (11.8) |
| Main [6, 12] | 2 (11.8) |
| Unspecified | 13 (76.5) |
| Hepatic vein | 46 (25.6) |
| Left [2, 26, 50, 53] | 5 (10.9) |
| Left & middle [1, 18, 35, 45, 50] | 6 (13.0) |
| Middle [1, 25, 29, 50, 52, 53] | 10 (21.7) |
| Right [4, 10, 20, 28, 40, 49, 50, 53] | 21 (45.7) |
| Accessory [22] | 1 (2.2) |
| Unspecified [7, 9, 44] | 3 (6.5) |
| Renal vein | 2 (1.1) |
| Left [16] | 1 (50) |
| Right [48] | 1 (50) |
| Segmental/subsegmental pulmonary artery [17, 41] | 2 (1.1) |

Table V. Patients’ outcomes

| Treatment | Alive | Dead | Unknown |
|---|---|---|---|
| TACE (n=38) | 8 (21.1) | 9 (23.7) | 21 (55.3) |
| *Sole TACE (n=21)* | *1 (4.8)* | *2 (9.5)* | *18 (85.7)* |
| *TACE+chemotherapy (n=3)* | *2 (66.7)* | *1 (33.3)* | |
| *TACE+radiotherapy (n=11)* | *2 (18.2)* | *6 (54.5)* | *3 (27.3)* |
| *TACE+radiotherapy+surgery (n=1)* | *1 (100)* | | |
| *TACE+surgery (n=2)* | *2 (100)* | | |
| Surgery (n=27) | 9 (33.3) | 14 (51.9) | 4 (14.8) |
| *Sole surgery (n=21)* | *7 (33.3)* | *11 (52.4)* | *3 (14.3)* |
| *Surgery+TACE (n=3)* | | *3 (100)* | |
| *Surgery+chemotherapy (n=3)* | *2 (66.7)* | | *1 (33.3)* |
| Radiotherapy (n=19) | 2 (10.5) | 17 (89.5) | |
| Chemotherapy (n=4) | | | 4 (100) |
| Intervention (n=2) | 1 (50) | 1 (50) | |
| *Interventional+chemotherapy (n=1)* | | *1 (100)* | |
| *Interventional+ TACE (n=1)* | *1 (100)* | | |
| Supportive (n=7) | | 5 (71.4) | 2 (28.6) |
| Untreated (n=4) | | 1 (25) | 3 (75) |

TACE: transarterial chemoembolization.

Table VI. Morbidity, mortality and follow-up

| Treatment | Morbidity, n (%) | Mortality, n (%) | Follow-up, mean±SD (range; median) (month) |
|---|---|---|---|
| TACE (n=38) | 2 (5.3) | 9 (52.9, 9/17) | 13.2±13.3 (1.3–56; 6.5) |
| Surgery (n=27) | 14 (51.9) | 14 (60.9, 14/23) | 18.7±19.7 (0.5–97; 12) |
| Radiotherapy (n=19) | 1 (5.3) | 17 (89.5, 17/19) | 21.5±20.5 (7–36; 39.5) |
| Chemotherapy (n=4) | -- | -- | -- |
| Intervention (n=2) | 1 (50) | 1 (50, 1/2) | 9.0±9.9 (2–16; 9) |
| Supportive (n=7) | -- | 5 (100, 5/5) | 2.3±2.2 |
| Untreated | -- | -- | 3.2±2.6 (1.3–5; 3.2) |

TACE: transarterial chemoembolization.

Table VII. Morbidities

| Morbidity | Surgery (n=14) | TACE (n=2) | Radiotherapy (n=1) | Intervention (n=1) |
|---|---|---|---|---|
| Hepatic recurrence (n=15) | 12 (85.7) | 1 (50) | 1 (100) | 1 (100) |
| *Intrahepatic (n=3)* | *2 (16.7)* | | | *1 (100)* |
| *Extrahepatic (n=6)* | *5 (41.7)* | | *1 (100)* | |
| *Intra- & extrahepatic (n=3)* | *3 (25)* | | | |
| *Diffuse (n=1)* | | *1 (100)* | | |
| *Unspecified* | *2 (16.7)* | | | |
| Lung infection (n=1) | | 1 (50) | | |
| Organ failure/septic shock (n=2) | 2 (14.3) | | | |

TACE: transarterial chemoembolization.

Table VIII. A comparison of mortality between patients reported in case reports and those in non-case reports, n (%)

| Treatment | Case report | Non-case report | $\chi^2$ | p value |
|---|---|---|---|---|
| TACE | 2 (40, 2/5) | 8 (24.2, 8/33) | 0.0 | 0.833 |
| Surgery | 8 (50, 8/16) | 6 (66.7, 6/9) | 0.0 | 0.833 |
| Radiotherapy | 1 (100, 1/1) | 2 (0, 0/2) | 0.0 | 0.833 |
| Chemotherapy | ? (?/4) | | | |
| Intervention | 1 (50, 1/2) | | | |
| Supportive | 5 (71.4, 5/7) | | | |
| Untreated | 1 (33.3, 1/3) | ? (?/1) | | |

TACE: transarterial chemoembolization.

# Figures

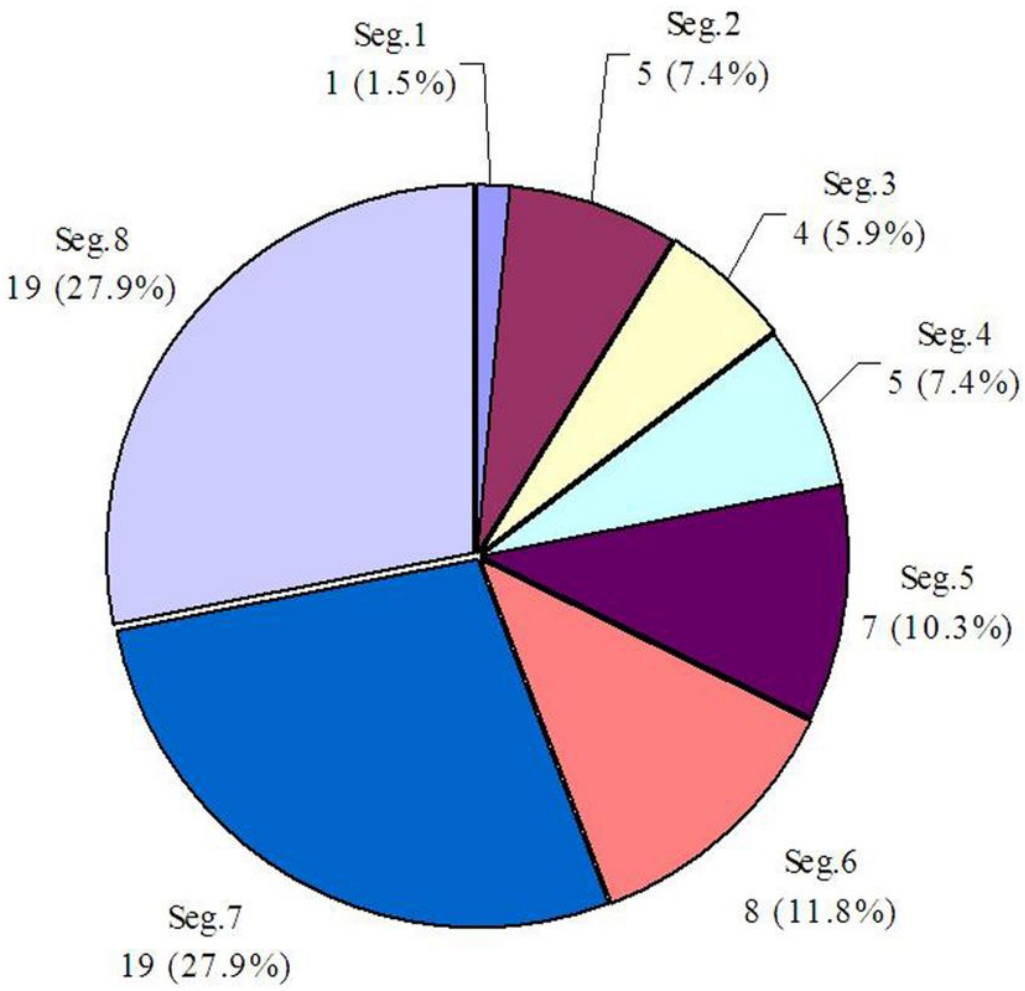


**Figure 1**

The distribution of segmental invasion of the liver by hepatocellular carcinoma. Seg.: segment.

# Supplementary Files

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