# Prognostic Impact of Lymph Nodes Metastases in Hepatocellular Carcinoma

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***Abstract: Purpose:*** Explore the clinicopathological characteristics of HCC patients and evaluate the impactof LN metastasis on survival. ***Material and Methods:*** Clinical data of 261 HCC patients treated at Clinical Oncology Department, Tanta University were retrieved from the collected database. Patients with LNsmetastases were compared with those without LNsmetastases. ***Results:*** Patients without LNs metastases had a significantly better Child-Pugh score ($p$=0.004), smaller size of intra-hepatic focal lesion and better tumor morphology ($p$=0.003). The most frequent extra-hepatic metastases sites were LNs (44.4%) and bone (43.3%). The most common metastatic LNs were the para-aortic (25.7%), porta-hepatis (21.8%). Patients received active treatment to control intra-hepatic disease had significantly higher median survival than patients underwent only supportive and palliative measures ($p$<0.001). The cumulative survival rates at 1- and 2-years after initial diagnosis of HCC were 28.7% and 5.3%, respectively. Five risk factors (performance status, size of primary intra-hepatic tumor, ascites, Child-Pugh score and L.Nsmetastases) were associated with significant effect on overall survival in univariate analysis ($p$<0.001, =0.001, <0.001, <0.001 and <0.001, respectively). On multivariate analysis, performance status, ascites and LN metastases were independent risk factor of overall survival ($p$<0.001, =0.022 and =0.013 respectively). ***Conclusion:*** Lymph nodemetastasis was the commonest site of extra-hepatic metastases of primary HCC and presented with a multifocal, large tumor size (≥ 5 cm) with poor Child-Pugh score and was one of the independent risk factors affecting overall survival. Effectivetreatment for intra-hepatic lesions would benefit HCC patients with extra-hepatic metastases.

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**Key words:** Hepatocellular carcinoma, lymph nodesmetastases, prognostic factors.

## 1. Introduction

Hepatocellular carcinoma (HCC) is the commonest primary liver tumor and the third leading cause of cancer-related death [1, 2].

HCC is an aggressive tumor known for its tendency to directly invade the portal and hepatic veins, with most extra-hepatic HCC occurs in patients with an advanced intra-hepatic tumor stage. A measurable number of patients develop extra-hepatic distant metastases, most commonly to the lungs, abdominal lymph nodes, bones, adrenal glands, and diaphragmatic surface. So, it is critical to detect extra-hepatic sites of metastasis before any therapeutic intervention to avoid unnecessary maneuvers as well as to evaluate for recurrence [3, 4].

According to the TNM staging system, the presence of extra-hepatic spread from HCC is categorized as advanced cancer. Greater than 70% of patients presenting with advanced HCC may not benefit from surgery and may instead be more suitable for locoregional therapies [5, 6].

Lymph node metastasis was rarely reported in early cases of HCC underwent surgical resection (1.2-7.5%) [7-10] while detected in 27-42% in autopsy studies of advanced cases [11, 12]. The most common spread is regional, particularly in peri-hepatic, peri-pancreatic, and retroperitoneal locations, but distant lymph nodes metastases may also be seen. No consensus has yet been reached on the treatment strategy for LNs metastases from HCC [9, 13, 14].

The seventh edition (2010) of American Joint Committee on Cancer (AJCC) Cancer Staging Manual has classified N1 diseases into stage IVa because the survival of N1 disease is associated with a dismal prognosis comparable with that of M1 disease [15]. The prognosis of patients with extra-hepatic metastases is generally very poor (5-year overall survival rate of 12% and median survival following diagnosis ranging from 6 to 20 months) [16].

We aimed to explore the clinicopathological characteristics of HCC patients and evaluate the impact of LNs metastases on survival.

## 2. Material and Methods

Throughout the period between January 2011 and December 2014, 261 available patients diagnosed with HCC were treated at Clinical Oncology Department, Tanta University. Their clinical data were retrieved from the collected database. The following variables were included in the analyses: age, gender, performance status according to the Eastern Cooperative Oncology Group (ECOG), duration of complaint, date of diagnosis, hepatitis-C antibody, albumin level, bilirubin level, serum alpha-fetoprotein (AFP) level, Child–Pugh score, intra-hepatic tumor

status, extra-hepatic spread, pathological data, lines of treatment and survival status.

The diagnosis of HCC was made when two different imaging examinations revealed typical hyper-vascular radiological features of hepatic focal lesion (arterial hyper-enhancement and washes out at venous phase) on top of cirrhosis with or without an elevated serum alpha-fetoprotein level or when there was a histopathological diagnosis either from primary or metastatic lesions.

The staging of tumors were assessed by contrast-enhanced computed tomography (CT) scans, magnetic resonance imaging (MRI), ultrasounds, chest X-rays, bone scintigraphy and metastatic lesion biopsy, which is performed if the diagnosis of HCC metastases was critical for the decision of treatment or other malignancies needed to be ruled out.

**Statistical Analysis**

The overall survival was defined as the time interval from the date of diagnosis of HCC to the date of death from any cause or to the last visit before the date of censor of this study on June 30, 2015. The survival rate and the median survival time were estimated by the Kaplan-Meier survival analysis. Factors related to survival were analyzed with the Cox proportional hazards regression model. Difference in survival between the groups was assessed by the log-rank test. All the statistical analysis was performed with Statistical Package for the Social Science V.21.0 for Windows (SPSS Inc., Chicago, IL, USA), and a *p*-values <0.05 was considered to be statistically significant.

## 3. Results

Of 261 available patients diagnosed to have HCC during the study period, there were 218 (83.5%) male and 43 (16.5%) female patients with a ratio 5: 1. The median age was 59 years (range 30–85 years). The hepatic reserve was calculated using the Child–Turcotte–Pugh (CTP) score [17]. Evaluation of the primary tumor stage was done according to the Cancer of the Liver Italian Program Score (CLIP score) [18], that incorporates measures of tumor size, vascular invasion, Alpha-fetoprotein (AFP) level, and hepatic function as measured by Child–Pugh score. A comparison of the clinico-pathological data between patients with or without lymph nodes metastases revealed that the group of patients without lymph nodes metastases had a significantly better Child-Pugh score ($p$=0.004), a significantly smaller size of intra-hepatic focal lesion and better tumor morphology ($p$=0.003). Table 1 summarizes the clinical data of all patients.

**Sites of Extra-hepatic Metastases**

A reported 197 (75.5%) patients were found to have extra-hepatic metastases including LNs &distant metastases. Pathological confirmation of non metastatic HCC was performed in 31 out of 64 patients (48.4%), and extra-hepatic metastatic disease were biopsy proved in 19 out of 197 patients (10.6%) and other sites were detected through radiological studies. The sites of metastases are summarized in Table 2 & 3. The most frequent sites were lymph nodes in 116 (44.4%) patients, bone in 113 (43.3%) patients and lung in 42 (16.1%) patients.

The 116 patients with lymph nodes metastases involved 219 metastatic lymph node regions. The most common metastatic lymph nodes were the para-aortic in 67 (25.7%) patients, followed by the porta-hepatis in 57 (21.8%) patients.

The enlarged nodes were 2–3.5 cm in diameter with arterial phase enhancement and interval size increase was seen on repeated investigations.Histopathological confirmation of malignancy within the LNs was performed in 11 patients.

**Treatment**

Active treatment to control intra-hepatic disease was carried out including liver resection (n=6), radio-frequency (RF) ablation (n=16), trans-arterial chemo-embolization (TACE) (n=20) and combined TACE & RF (n=7). Chemotherapy was given for 30 patients in a trial to control the disease with the most common chemotherapeutic agents used was Capecitabin (Xeloda) that was given for 2-5 cycles. Other patients received supportive and palliative treatment.

Patients with directed treatment to intra-hepatic lesion (surgery, TACE, RF or combined TACE/RF) had median survival of 10, 12, 14& 13 months respectively, while patients underwent only supportive and palliative measures had median survival of 8 months. The prognosis of HCC patients with active intra-hepatic lesions associated with extra-hepatic metastases treated with palliative measures and received supportive treatment was significantly poor ($p$<0.001).

**Prognosis of HCC patients with extra-hepatic metastases**

The risk factors affecting overall survival for all the patients were analyzed using previously reported clinical variables. Table 4 shows the results of the univariate and multivariate analyses. Six risk factors (performance status, size of primary intra-hepatic tumor, ascites, Child-Pugh score, portal vein thrombosis and lymph nodes metastases) were associated with significant effect on overall survival in univariate analysis ($p$<0.001, =0.001, <0.001, <0.001, =0.048 and <0.001, respectively). On multivariate analysis, performance status, ascites and lymph nodes metastases were independent risk factor of overall survival ($p$<0.001, =0.017 and =0.008 respectively).

The cumulative overall survival rates for the whole group at 1- and 2-years after initial diagnosis of HCC were 28.7% and 5.3%, respectively (Figure 1). Figures 2 & 3 showed the overall survival according to performance status ($p$<0.001) and ascites ($p$=0.017). With median survival time 9 (range 1-48) months, the median survival time for patients with or without lymphatic metastases were 8 (range 1-24) months and 10.5 (range 1-48) months, respectively, ($p$=0.008, Figure 4).

**Table (1): Characteristics of 261 patients with HCC according to LN status**

| Characters | LNs metastases 116 (44.4%) | No LNs metastases 145 (55.6%) | *p*-value | Whole patients 261 (100%) |
|---|---|---|---|---|
| **Age:** Median 59 years, range 30-85 years | | | | |
| <60 | 63 (47.7) | 69 (52.3) | 0.280 | 132 (50.6) |
| ≥60 | 53 (41.1) | 76 (58.9) | | 129 (49.4) |
| **Sex** | | | | |
| Male | 96 (44) | 122 (56) | 0.765 | 218 (83.5) |
| Female | 20 (46.5) | 23 (53.5) | | 43 (16.5) |
| **HCV** | | | | |
| Yes | 95 (43.4) | 124 (56.6) | 0.493 | 219 (83.9) |
| No | 4 (66.7) | 2 (33.3) | | 6 (2.3) |
| Unknown | 17 (47.2) | 19 (52.8) | | 36 (13.8) |
| **Performance Status** | | | | |
| 0-1 | 45 (42.9) | 60 (57.1) | 0.672 | 105 (40.2) |
| >1 | 71 (45.5) | 85 (54.5) | | 156 (59.8) |
| **Primary tumor location** | | | | |
| Right lobe | 44 (40) | 66 (60) | 0.158 | 110 (42.1) |
| Left lobe | 21 (58.3) | 15 (41.7) | | 36 (13.8) |
| Both lobes | 51 (44.3) | 64 (55.7) | | 115 (44.1) |
| **Number of primary tumor** | | | | |
| Solitary | 49 (44.5) | 61 (55.5) | 0.978 | 110 (42.1) |
| Multiple | 67 (44.4) | 84 (55.6) | | 151 (57.9) |
| **Size of focal lesion(s)** | | | | |
| <5 cm | 23 (30.3) | 53 (69.7) | **0.003** | 76 (29.1) |
| ≥5 cm | 93 (50.3) | 92 (49.7) | | 185 (70.9) |
| **Ascites** | | | | |
| No | 73 (42.4) | 99 (57.6) | 0.523 | 172 (65.9) |
| Mild | 25 (45.5) | 30 (54.5) | | 55 (21.1) |
| Moderate/severe | 18 (52.9) | 16 (47.1) | | 34 (13.0) |
| **Bilirubin mg/dL:** Median 1.0 (range 0.6-3.6) | | | | |
| **Albumin g/dL:** Median 3.1 (range 2.1-4.4) | | | | |
| **Child-Pugh Score** | | | | |
| A | 52 (36.4) | 91 (63.6) | **0.004** | 143 (54.8) |
| B & C | 64 (54.2) | 54 (45.8) | | 118 (45.2) |
| **Tumor morphology** | | | | |
| Single nodule & ≤50% area | 49 (44.5) | 61 (55.5) | **0.003** | 110 (42.1) |
| Multiple nodules & ≤50% area | 40 (36.0) | 71 (64.0) | | 111 (42.5) |
| Massive or >50% area | 27 (67.5) | 13 (32.5) | | 40 (15.3) |
| **Alpha-Fetoprotein** | | | | |
| <400 | 43 (39.8) | 65 (60.2) | 0.206 | 108 (41.4) |
| ≥400 | 73 (47.7) | 80 (52.3) | | 153 (58.6) |
| **Portal vein thrombosis** | | | | |
| No | 90 (44.6) | 112 (55.4) | 0.947 | 202 (77.4) |
| Yes | 26 (44.1) | 33 (55.9) | | 59 (22.6) |
| **Cancer of the Liver Italian Program (CLIP) Score** | | | | |
| <4 | 101 (44.3) | 127 (55.7) | 0.901 | 228 (87.4) |
| ≥4 | 15 (45.5) | 18 (54.5) | | 33 (12.6) |

**Table (2): Sites of LNs metastases**

| Characters | LNs metastases 116/261 (44.4%) |
|---|---|
| **Lymph nodes metastases** | |
| Solitary site | 63 (24.1) |
| Multiple sites | 53 (20.3) |
| **Sites of Lymph nodes metastases** | |
| **Regional LNs** | |
| Para-aortic | 67 (25.7) |
| Porta-hepatis | 57 (21.8) |
| Celiac | 36 (13.8) |
| Peripancreatic | 15 (5.7) |
| Aortocaval&Retrocaval | 10 (3.8) |
| **Distant LNs** | |
| Mediastinal | 19 (7.3) |
| Supraclavicular | 10 (3.8) |
| Cervical | 2 (0.8) |
| Hilar | 2 (0.8) |
| Iliac | 1 (0.4) |

**Table (3): Sites of extra-hepatic metastases**

| Characters | LN metastasis 116 (44.4%) | No LN metastasis 145 (55.6%) | *p*-value | Whole patients 261 (100%) |
|---|---|---|---|---|
| **Distant extra-hepatic metastasis** | | | | |
| Yes | 63 (43.8) | 81 (56.3) | 0.802 | 144 (55.2) |
| No | 53 (45.3) | 64 (54.7) | | 117 (44.8) |
| **Sites of Metastases** | | | | |
| Bone | 43 (38.1) | 70 (61.9) | 0.069 | 113 (43.3) |
| Lung | 29 (69.0) | 13 (31.0) | **<0.001** | 42 (16.1) |
| Adrenal | 7 (63.6) | 4 (36.4) | 0.191 | 11 (4.2) |
| Skin | 3 (100) | 0 (0) | 0.051 | 3 (1.1) |
| Brain | 0 (0) | 3 (100) | 0.119 | 3 (1.1) |
| **Number of Metastatic organs** | | | | |
| Single organ | 45 (38.5) | 72 (61.5) | | 117 (44.8) |
| Multiple organs | 18 (66.7) | 9 (33.3) | **0.028** | 27 (10.4) |
| No | 53 (45.3) | 64 (54.7) | | 117 (44.8) |

**Table (4): Univariate and multivariate analysis of prognostic factors predicting survival for HCC patients**

| Variable | Odd Ratio | 95% CI | *p*-value |
|---|---|---|---|
| **Univariate analysis** | | | |
| Sex (M vs. F) | 1.058 | 0.756-1.483 | 0.741 |
| Smoking (yes vs. no) | 0.984 | 0.759-1.274 | 0.900 |
| Age (≤60 vs. > 60 years) | 1.082 | 0.840-1.396 | 0.541 |
| **Performance status (0-1 vs. >1)** | **2.733** | **2.088-3.579** | **<0.001** |
| Number of primary tumor (solitary vs. multiple) | 1.117 | 0.865-1.444 | 0.395 |
| **Size of primary tumor (<5 cm vs. ≥5 cm)** | **1.655** | **1.240-2.209** | **0.001** |
| **Ascites (No vs. yes)** | **1.982** | **1.518-2.587** | **<0.001** |
| Serum albumin (≤3.5 vs. >3.5 g/dL) | 0.811 | 0.564-1.166 | 0.258 |
| Total bilirubin (<2 vs. ≥2 mg/dL) | 1.117 | 0.865-1.444 | 0.395 |
| AFP (≤400 vs. >400 ng/mL) | 1.236 | 0.956-1.597 | 0.106 |
| **Child-Pugh score (A vs. B & C)** | **1.805** | **1.384-2.354** | **<0.001** |
| **Portal vein thrombosis (yes vs. no)** | **1.349** | **1.003-1.813** | **0.048** |
| CLIP score (<4 vs. ≥4) | 1.401 | 0.936-2.096 | 0.101 |
| **Lymph node metastasis (yes vs. no)** | **0.575** | **0.438-0.756** | **<0.001** |
| Distant metastases (yes vs. no) | 0.870 | 0.673-1.124 | 0.287 |
| **Multivariate analysis** | | | |
| Performance status (0-1 vs. >1) | 2.356 | 1.741-3.189 | <0.001 |
| Ascites (no vs. yes) | 1.664 | 1.094-2.530 | 0.017 |
| Lymph node metastasis (yes vs. no) | 0.672 | 0.500-0.902 | 0.008 |

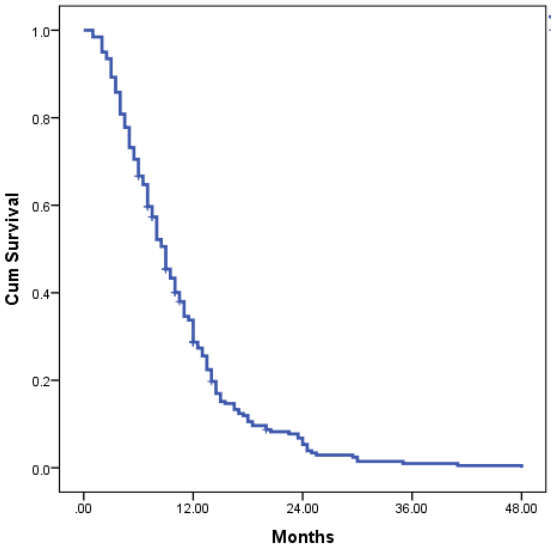


Fig (1): Overall survival for the whole group

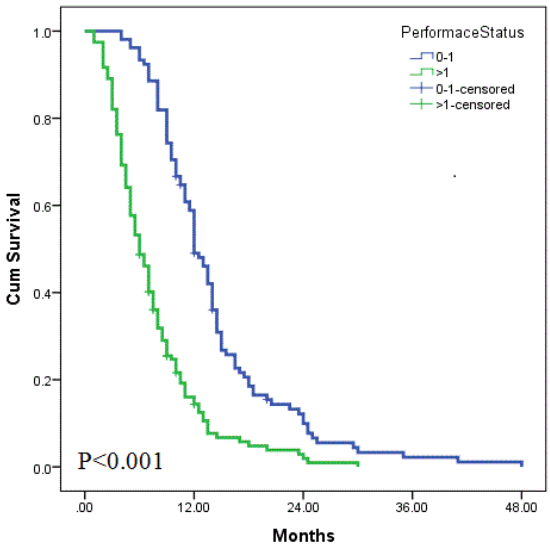


Fig (2): Overall survival according to performance status

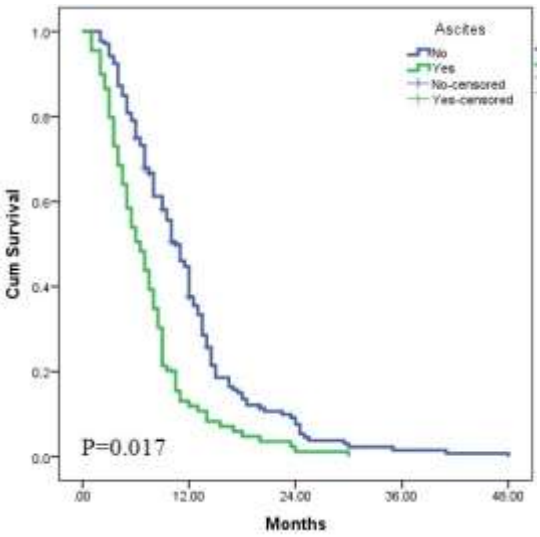


Fig (3): Overall survival according to presence of ascites.

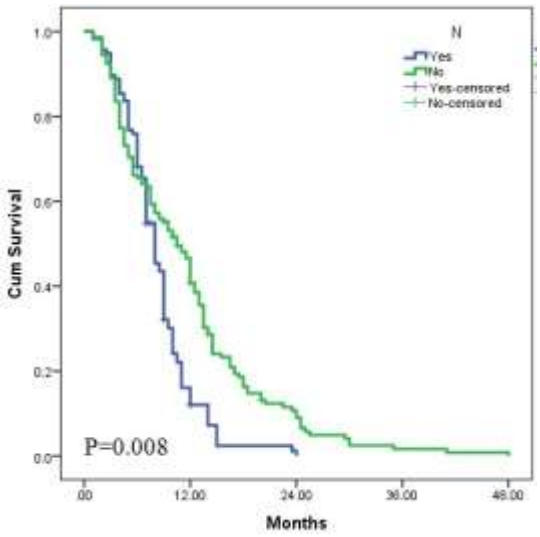


Fig (4): Overall survival according to lymph nodes metastases.

## 4. Discussion

HCC is one of the most aggressive neoplasm with extra-hepatic metastases are common at the time of initial diagnosis [19, 20]. In the present study, the most frequent extra-hepatic metastatic sites were lymph nodes, bone and lung. Survival analysis showed lymph nodes metastases to be one of the risk factor affecting overall survival indicating that HCC patients with lymph nodes metastases had poor prognosis.

Lymphatic spread of HCC wascommon.Regional lymphadenopathy included porta-hepatic, peri-pancreatic, gastroduodenal, portocaval,aortocaval, and para-aortic nodal groups [21]. Tri-phasic CT scanning can be helpful in differentiating malignant from benign lymphadenopathy when arterial phase enhancement of the lymph nodes is seen or there is interval size increase on repeated investigations. The size of the malignant lymph nodes was not a reliable criterion of malignancy, as reported by Dodd *et al.*[22]. Therefore, arterial phase enhancement, interval size increase, or proof of malignant cells within lymph nodes at biopsy should be the only criterion used to document malignant lymph node involvement.

Previous reports have showed that lung, abdominal lymph nodes, and bone were the most common sites of extra-hepatic metastases of HCC [4, 23, 24]. Sun *et al.*indicated that the incidence of loco-regional lymph nodes metastases was 5.1% (49/968) in a study which evaluated the value of routine lymphadenectomy in resectable HCC [9]. According to

the study performed by the Liver Cancer Study Group of Japan, 417 of 1374 patients had lymph nodes metastases (30.3%) in autopsy series [25]. These reported series were based on conventional workup using CT, MRI, chest X-ray and bone scintigraphy, or by histopathological examination of surgically resected specimens or by autopsy.

Recently published report compared PET/CT with conventional medical imaging in the detection of extra-hepatic metastases of HCC concluded that 18F-FDG PET/CT has a higher sensitivity to detect metastases as some lymph nodes metastases were negative on conventional imaging but were positive on 18F-FDG PET/CT. However, carefully selected non-diabetic patients with normal range glucose should be chosen with this imaging modality [26].

The most frequent nodal metastases were para-aortic lymph nodes. On survival analyses, HCC patients with lymph nodes metastases had a significantly worse overall survival than patients without lymph nodes metastases and correlated significantly with multifocal, large tumor size (≥5 cm) with poor Child-Pugh score. This result agrees with the results of other studies that HCC with lymph nodes metastases shortened the overall survival of the patients [7, 10, 27].

Patients who received directed treatment to the intra-hepatic lesion had significant better survival than patients who received just palliative or supportive treatment ($p$<0.001). The majority of HCC patients with extra-hepatic metastases do not die of metastatic dissemination but rather die of hepatic failure due to progression of intra-hepatic HCC. Therefore, treatment of intra-hepatic HCC is almost always required to improve survival when hepatic function and extent of disease permit [4, 23, 26].

A newer molecular targeting agent, Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Basel, Switzerland), has been recently shown to prolong survival in patients with advanced HCC. However, a survival benefit was not demonstrated in the sub-group analysis of patients with extra-hepatic metastases [28].

There are some limitations in the present study. Firstly, it is a single institutional study with the population size is relatively small. A multicenter study is needed to include more patients into such a type of study. Secondly, not all extra-hepatic metastases especially LNs had histopathologic confirmation, although the diagnosis was based on clinical characteristics and imaging studies. Our future perspective is to conduct a prospective study in a multi-institutional setting focusing on histopathologic confirmation of metastases, selective intra-hepatic interference and use of newer targeted therapy.

In conclusion, our present study indicated that lymph nodes metastases were the most frequent site of extra-hepatic metastases of primary HCC. HCC with LNs metastases tends to be with a multifocal, larger tumor size (≥ 5 cm) with poor Child-Pugh score. Lymph nodemetastasis wasone of the main prognostic factors significantly affecting overall survival in HCC patients. Effective treatment for intra-hepatic lesions would benefit selected patients with extra-hepatic metastases.

**5. Conflict of Interest:** None

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