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 impact of lymph node (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 LNs metastases were compared with those without LNs metastases. ***Results:*** Patients without LNs metastases had a significantly better Child-Pugh score (p=0.004), smaller size of intra-hepatic focal lesion (p=0.003), and better tumor morphology (p=0.003). The most frequent extra-hepatic metastases sites were LNs (44.4%) and bone (43.3%). The commonest LN sites 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 1- and 2-year overall survival (OS) rates were 28.7% and 5.3% respectively. Six factors (performance status, size of primary intra-hepatic tumor, ascites, Child-Pugh score, portal vein thrombosis, and LNs metastases) significantly affect the OS rate 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 LN metastases were independent risk factor of OS (p<0.001, =0.017, and =0.008 respectively). ***Conclusion:*** Lymph node metastasis was the commonest site of extra-hepatic spread of 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 OS. Selected patients with extra-hepatic spread may gain benefit from treatment of intra-hepatic lesions.
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Key words: Hepatocellular carcinoma, lymph nodes metastases, prognostic factors.

1. Introduction

Hepatocellular carcinoma (HCC) is the commonest primary hepatic tumor and the 3rd leading cause of cancer-related mortality [1, 2].

HCC tend to invade the hepatic and portal veins directly, with most extra-hepatic spread occurs in patients with an advanced intra-hepatic tumor stage. A measurable number of patients develop extra-hepatic distant spread, commonly to the abdominal lymph nodes (LN), bones, lungs, adrenal glands, and diaphragmatic surface. So, it is critical to detect extra-hepatic sites of metastasis before any therapeutic interference avoiding unnecessary maneuvers with evaluation of recurrence [3, 4].

Extra-hepatic spread from HCC is defined as advanced stage according to the TNM staging system. More than 70% of cases with advanced stage may gain benefit from locoregional therapy instead of surgical interference [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 LNs metastases may also be seen. There is disagreement on the treatment plan for LNs metastases from HCC [9, 13, 14].

The seventh edition (2010) of American Joint Committee on Cancer (AJCC) staging categorized N1 diseases as stage IVa because of their dismal prognosis comparable with that of M1 disease [15]. Generally, the prognosis of patients with extra-hepatic spread is poor (median survival ranging 6-20 months with 12% 5-year overall survival (OS) rate) [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 hypervascular 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

Throughout the study period, 261 patients with HCC were available (Table 1). Male were 218 (83.5%) with male to female ratio 5: 1. The median age was 59 (range 30–85) years. The hepatic reserve was calculated using the Child–Turcotte–Pugh (CTP) score [17]. Staging of the primary tumor 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. Comparing the clinico-pathological data between patients +/- LNs metastases revealed that patients without LNs metastases had a better Child-Pugh score (p=0.004), smaller size of intra-hepatic focal lesion (p=0.003), and better tumor morphology.

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. Lymph nodes were the most frequent sites (116 patients; 44.4%), followed by bone (43.3%) and lung (16.1%).

The 116 patients with LNs metastases involved 219 metastatic LN regions. The commonest sites 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 trans-arterial chemo-embolization (TACE) (n=20), radio-frequency (RF) ablation (n=16), combined TACE & RF (n=7), and liver resection (n=6). 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 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 patients with extra-hepatic metastases

Factors affecting the OS for all included patients were evaluated using the previously reported clinical variables (Table 4). Six factors (performance status, size of primary intra-hepatic tumor, ascites, Child-Pugh score, portal vein thrombosis, and LNs metastases) significantly affect the OS rate 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 OS rates for the whole group at 1- and 2-years were 28.7% and 5.3%, respectively (Figure 1). Figures 2 & 3 showed the OS according to performance status (p<0.001) and ascites (p=0.017). Median survival time was 9 months for all patients. The median survival time for patients with lymphatic metastases was 8 months versus 10.5 months for patients without lymphatic metastases (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 ≥60	63 (47.7) 53 (41.1)	69 (52.3) 76 (58.9)	0.280	132 (50.6) 129 (49.4)
Sex				
Male Female	96 (44) 20 (46.5)	122 (56) 23 (53.5)	0.765	218 (83.5) 43 (16.5)
HCV				
Yes No Unknown	95 (43.4) 4 (66.7) 17 (47.2)	124 (56.6) 2 (33.3) 19 (52.8)	0.493	219 (83.9) 6 (2.3) 36 (13.8)
Performance Status				
0-1 >1	45 (42.9) 71 (45.5)	60 (57.1) 85 (54.5)	0.672	105 (40.2) 156 (59.8)
Primary tumor location				
Right lobe Left lobe Both lobes	44 (40) 21 (58.3) 51 (44.3)	66 (60) 15 (41.7) 64 (55.7)	0.158	110 (42.1) 36 (13.8) 115 (44.1)
Number of primary tumor				
Solitary Multiple	49 (44.5) 67 (44.4)	61 (55.5) 84 (55.6)	0.978	110 (42.1) 151 (57.9)
Size of focal lesion(s)				
<5 cm ≥5 cm	23 (30.3) 93 (50.3)	53 (69.7) 92 (49.7)	**0.003**	76 (29.1) 185 (70.9)
Ascites				
No Mild Moderate/severe	73 (42.4) 25 (45.5) 18 (52.9)	99 (57.6) 30 (54.5) 16 (47.1)	0.523	172 (65.9) 55 (21.1) 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 B & C	52 (36.4) 64 (54.2)	91 (63.6) 54 (45.8)	**0.004**	143 (54.8) 118 (45.2)
Tumor morphology				
Single nodule & ≤50% area Multiple nodules & ≤50% area Massive or >50% area	49 (44.5) 40 (36.0) 27 (67.5)	61 (55.5) 71 (64.0) 13 (32.5)	**0.003**	110 (42.1) 111 (42.5) 40 (15.3)
Alpha-Fetoprotein				
<400 ≥400	43 (39.8) 73 (47.7)	65 (60.2) 80 (52.3)	0.206	108 (41.4) 153 (58.6)
Portal vein thrombosis				
No Yes	90 (44.6) 26 (44.1)	112 (55.4) 33 (55.9)	0.947	202 (77.4) 59 (22.6)
Cancer of the Liver Italian Program (CLIP) Score				
<4 ≥4	101 (44.3) 15 (45.5)	127 (55.7) 18 (54.5)	0.901	228 (87.4) 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	HR	95% CI	*p*
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

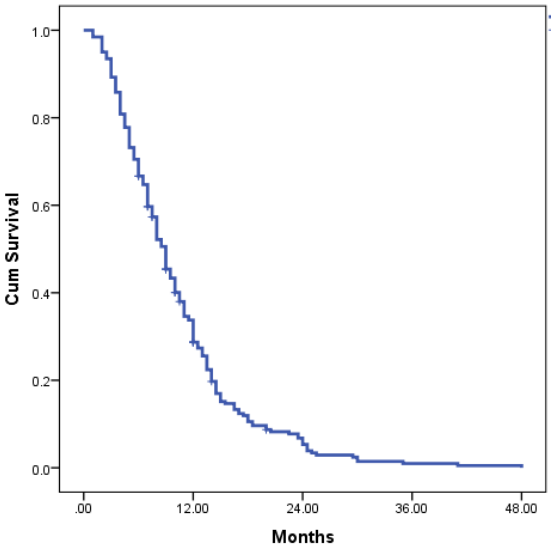

Fig (1): Overall survival for the whole group

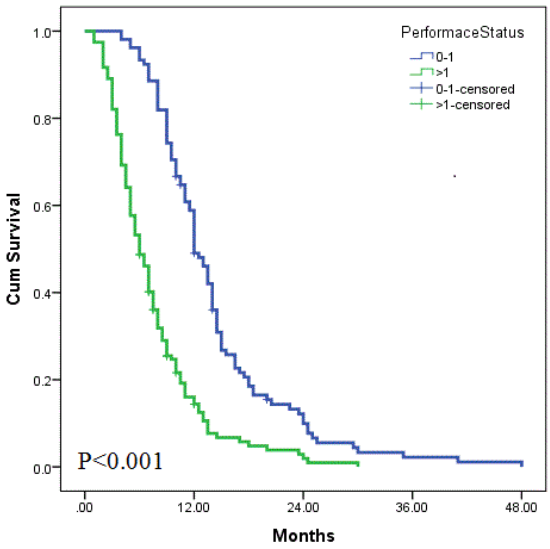

Fig (2): Overall survival according to performance status

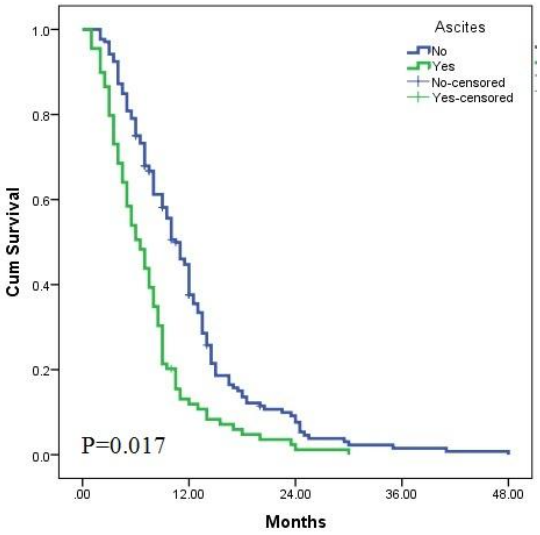

Fig (3): Overall survival according to presence of ascites.

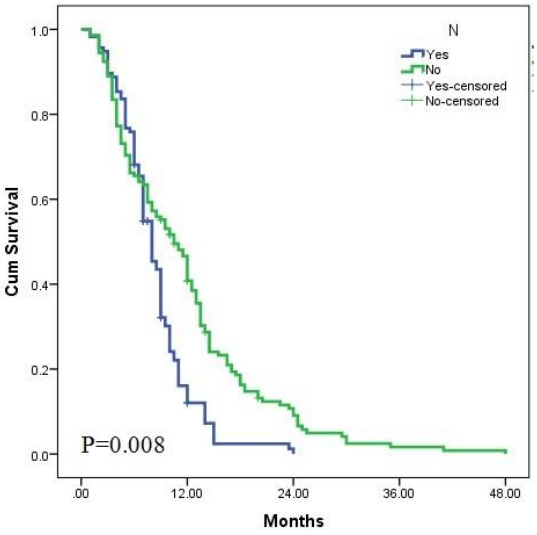

Fig (4): Overall survival according to lymph nodes metastases.

4. Discussion

HCC is considered among the aggressive tumors with extra-hepatic spread commonly seen at the time of initial diagnosis [19, 20]. In the current study, LNs, bone and lung were the most frequent extra-hepatic metastatic sites. Lymph node metastasis is one of the risk factors affecting OS indicating that HCC patients with LNs metastases had poor prognosis.

Lymphatic spread of HCC was common. Regional lymphadenopathy included porta-hepatic, peri-pancreatic, gastroduodenal, portocaval, aortocaval, and para-aortic nodal groups [21]. Tri-phasic CT scan can help in the differentiation between benign and malignant LNs when arterial phase enhancement of the LNs is seen or if there is interval size increase on repeated investigations. The size of the malignant LNs was not relied upon to define malignancy, as Dodd *et al.*[22] reported. So, proof of malignant cells within LNs at biopsy, arterial phase enhancement, or interval size increase should be the conclusive criterion used to document malignant LN involvement.

Previous studies showed that lung, bone, and abdominal LNs were the commonest sites of extra-hepatic spread of HCC [4, 23, 24]. Sun *et al.* [9] reported that the incidence of loco-regional LN spread was 5.1% among 968 patients on evaluating the value of routine lymphadenectomy in resectable HCC. According to a study performed by the Liver Cancer Study Group of Japan, 30.3% of cases had LN metastases in autopsy series [25]. These reported series

were based on pathological examination of surgically resected specimens, conventional radiological studies (CT, MRI, CXR, and bone scintigraphy), or by autopsy.

A report comparing conventional imaging versus PET/CT in the recognition of extra-hepatic metastases of HCC concluded that PET/CT has a higher sensitivity to detect metastases as some LN spread were negative on conventional imaging but were positive on 18F-FDG PET/CT. However, carefully selected patients with normal glucose range should be chosen with this imaging modality [26].

The most frequent nodal metastases were para-aortic LNs. On survival analyses, patients with LNs metastases had a significantly worse OS 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 major cause of death in patients with extra-hepatic metastases is from hepatic failure due to progression of intra-hepatic HCC rather than metastatic dissemination. Therefore, treatment of intra-hepatic lesion is essential to improve survival when hepatic function and extent of disease permit [4, 23, 26].

A molecular targeting agent, Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Switzerland), was reported to prolong survival in patients with advanced HCC. However, this benefit was not proven in the sub-group analysis of patients with extra-hepatic spread [28].

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

Conclusion: Lymph node metastasis was the commonest site of extra-hepatic spread of 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 OS. Selected patients with extra-hepatic spread may gain benefit from treatment of intra-hepatic lesions.

5. Conflict of Interest: None

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