

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 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 LN metastases were compared with those without L. Nsmetastases. **Results:** Patients without L.Ns 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 (24.1%), portahepatis (23.4%). 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, as cites, 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 L.N metastases were independent risk factor of overall survival ($p<0.001$, $=0.022$ and $=0.013$ respectively). **Conclusion:** Lymph nodesmetastases 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 nodes regions. The most common metastatic lymph nodes were the para-aortic in 67 (25.7%) patients, followed by the portahepatis 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 Capecitabine (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 node 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	LN's metastases 116 (44.4%)	No LN's metastases 145 (55.6%)	<i>p</i> -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 Metastasis				
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)	0.028	117 (44.8)
Multiple organs	18 (66.7)	9 (33.3)		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

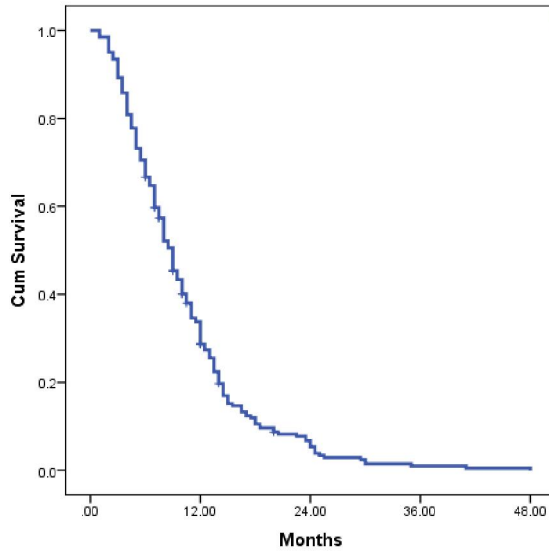


Fig (1): Overall survival for the whole group

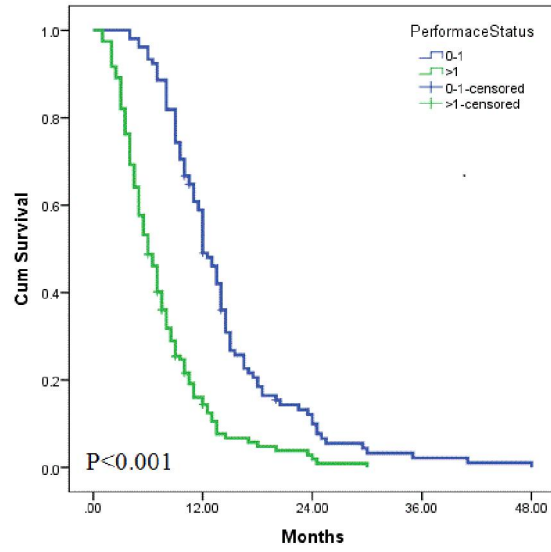


Fig (2): Overall survival according to performance status

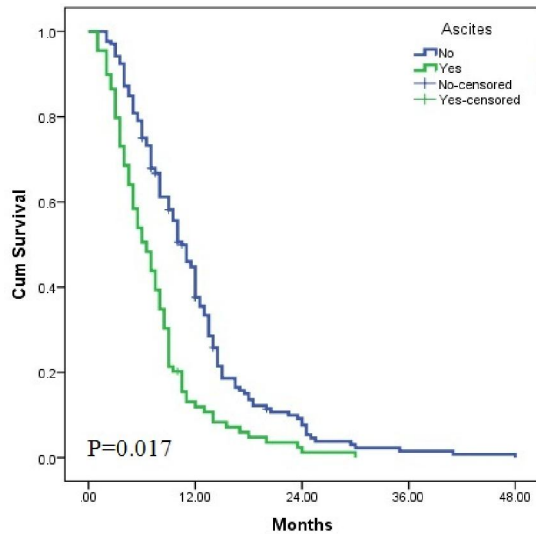


Fig (3): Overall survival according to presence of ascites.

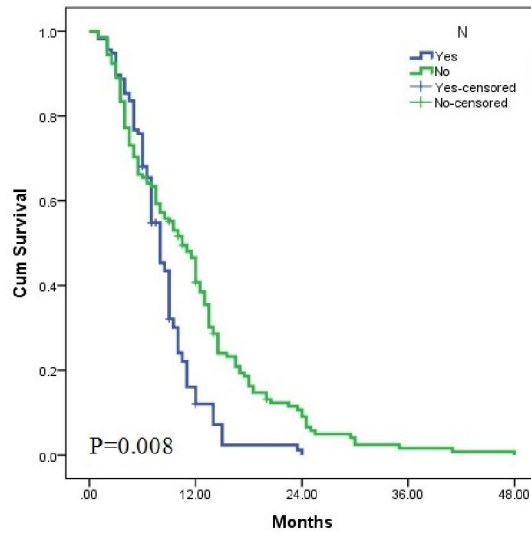


Fig (4): Overall survival according to lymph nodes metastases.

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 was common. Regional lymphadenopathy included porta-hepatic, peri-pancreatic, gastroduodenal, portocaval, aorticaval, 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 was 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 subgroup 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 node metastasis was one 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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References

1. Jemal A.; Bray F.; Center MM.; Ferlay J.; Ward E. & Forman D.: Global cancer statistics. *CA Cancer J Clin*, 2011; 61(2): 69–90.
2. Omata M.; Lesmana LA.; Tateishi R.; Chen PJ.; Lin SM.; Yoshida H.; *et al.*: Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int*, 2010; 4(2): 439–74.
3. Sneag DB.; Krajewski K.; Giardino A.; O'Regan KN.; Shinagare AB.; Jagannathan JP.; *et al.*: Extrahepatic Spread of Hepatocellular Carcinoma: Spectrum of Imaging Findings. *AJR*, 2011; 197(4): W658–W664.
4. Natsuzaka M.; Omura T.; Akaike T.; Kuwata Y.; Yamazaki K.; Sato T.; *et al.*: Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol*, 2005; 20(11): 1781–7.
5. Thomas MB.; Jaffe D.; Choti MM.; Belghiti J.; Curley S.; Fong Y.; *et al.*: Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. *J Clin Oncol*, 2010; 28(25): 3994–4005.
6. Ishii H.; Furuse J.; Kinoshita T.; Konishi M.; Nakagohri T.; Takahashi S.; *et al.*: Extrahepatic spread from hepatocellular carcinoma: who are candidates for aggressive anti-cancer treatment? *Jpn J Clin Oncol*, 2004; 34(12): 733–9.
7. Lee CW.; Chan KM.; Lee CF.; Yu MC.; Lee WC.; Wu TJ.; *et al.*: Hepatic resection for hepatocellular carcinoma with lymph node metastasis: clinicopathological analysis and survival outcome. *Asian J Surg*, 2011; 34(2): 53–62.
8. Changchien CS.; Chen CL.; Yen YH.; Wang JH.; Hu TH.; Lee CM.; *et al.*: Analysis of 6381

- hepatocellular carcinoma patients in southern Taiwan: prognostic features, treatment outcome, and survival. *J Gastroenterol*, 2008;43(2):159–70.
9. Sun HC.; Zhuang PY.; Qin LX.; Ye QH.; Wang L.; Ren N.; *et al.*: Incidence and prognostic values of lymph node metastasis in operable hepatocellular carcinoma and evaluation of routine complete lymphadenectomy. *J Surg Oncol*, 2007; 96(1): 37–45.
 10. Xiaohong S.; Huikai L.; Feng W.; Ti Z.; Yunlong C. & Qiang L.: Clinical significance of lymph node metastasis in patients undergoing partial hepatectomy for hepatocellular carcinoma. *World J Surg*, 2010; 34(5): 1028–33.
 11. Kaczynski J.; Hansson G. & Wallerstedt S.: Metastases in cases with hepatocellular carcinoma in relation to clinicopathologic features of the tumour: an autopsy study from a low endemic area. *Acta Oncol*, 1995; 34: 43–8
 12. Nakashima T.; Okuda K.; Kojiro M.; Jimi A.; Yamaguchi R.; Sakamoto K.; *et al.*: Pathology of hepatocellular carcinoma in Japan. 232 Consecutive cases autopsied in ten years. *Cancer*, 1983; 51: 863–77.
 13. Park YJ.; Lim DH.; Paik SW.; Koh KC.; Lee JH.; Choi MS.; *et al.*: Radiation therapy for abdominal lymph node metastasis from hepatocellular carcinoma. *J Gastroenterol*, 2006; 41: 1099–106.
 14. Schwartz JD. & Beutler AS.: Therapy for unresectable hepatocellular carcinoma: review of the randomized clinical trials-II: systemic and local non-embolization-based therapies in unresectable and advanced hepatocellular carcinoma. *Anticancer Drugs*, 2004; 15(5): 439–52.
 15. Edge SB.; Byrd DR.; Compton CC.; Fritz AG.; Greene FL. & Trotti A.: *AJCC Cancer Staging Manual*, 7th edition. Springer, New York. 2010.
 16. El-Serag HB.: Hepatocellular carcinoma. *N Engl J Med*, 2011; 365(12): 1118–27.
 17. Pugh RN.; Murray-Lyon IM.; Dawson JL.; Pietroni MC. & Williams R.: Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*, 1973; 60(8): 646–9.
 18. The Cancer of the Liver Italian Program (CLIP) investigation: Prospective validation of the CLIP score: A new prognostic system for patients with cirrhosis and Hepatocellular carcinoma. *Hepatology*, 2000; 31: 840-5.
 19. Chan KM.; Yu MC.; Wu TJ.; Lee CF.; Chen TC.; Lee WC.; *et al.*: Efficacy of surgical resection in management of isolated extrahepatic metastases of hepatocellular carcinoma. *World J Gastroenterol*, 2009; 15(43): 5481–8.
 20. Taketomi A.; Toshima T.; Kitagawa D.; Motomura T.; Takeishi K.; Mano Y.; *et al.*: Predictors of extrahepatic recurrence after curative hepatectomy for hepatocellular carcinoma. *Ann Surg Oncol*, 2010; 17: 2740–6.
 21. Moron FE. & Szklaruk J.: Learning the nodal stations in the abdomen. *The British Journal of Radiology*, 2007; 80: 841–8.
 22. Dodd GD.; Baron RL.; Oliver JH.; Federle MP. & Baumgartel PB: Enlarged abdominal lymph nodes in end-stage cirrhosis: CT-histopathologic correlation in 507 patients. *Radiology*, 1997; 203(1): 127–130.
 23. Ochiai T.; Ikoma H.; Okamoto K.; Kokuba Y.; Sonoyama T. & Otsuji E.: Clinicopathologic features and risk factors for extrahepatic recurrences of hepatocellular carcinoma after curative resection. *World J Surg*, 2012; 36(1): 136–43.
 24. Tanaka K.; Shimada H.; Matsuo K.; Takeda K.; Nagano Y.; Togo S.; *et al.*: Clinical features of hepatocellular carcinoma developing extrahepatic recurrences after curative resection. *World J Surg*, 2008; 32(8): 1738–47.
 25. Liver Cancer Study Group of Japan: Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg*, 1990; 211(3): 277–87.
 26. Xia F.; Wu L.; Lau W.; Li G.; Huan H.; Qian C.; *et al.*: Positive Lymph Node Metastasis Has a Marked Impact on the Long-Term Survival of Patients with Hepatocellular Carcinoma with Extrahepatic Metastasis. *PLoS ONE*, 2014; 9(4): e95889
 27. Uka K.; Aikata H.; Takaki S.; Shirakawa H.; Jeong SC.; Yamashina K.; *et al.*: Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. *World J Gastroenterol*, 2007; 13(3): 414–420.
 28. Cheng AL.; Kang YK.; Chen Z.; Tsao CJ.; Qin S.; Kim JS.; *et al.*: Efficacy and safety of Sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo-controlled trial. *Lancet Oncol*, 2009; 10(1): 25–34.