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FULL PAPER

Prognostic stratification and nomogram for survival prediction in hepatocellular carcinoma patients treated with radiotherapy for lymph node metastasis

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Objective: To establish a prognostic model for overall survival prediction in patients with hepatocellular carcinoma (HCC) treated with external beam radiotherapy (RT) for lymph node (LN) metastasis.

Methods: 105 patients with HCC underwent RT for LN metastasis. The median age, biologically effective RT dose and follow-up period were 60 years, 59 Gy₁₀ and 5.7 months, respectively. 51 patients had symptoms related to LN metastasis.

Results: The median survival (MS) was 5.8 months for all patients. For patients with LN-related symptoms, MS was 3.8 months compared with 10.7 months for those without LN-related symptoms. On multivariate analysis of pre-RT factors, symptoms related to LN metastasis [hazard ratio (HR) 2.93], Child-Pugh Class B–C (HR 2.77), uncontrolled intrahepatic disease (HR 2.74) and non-nodal distant metastasis (HR 1.62) were significantly poor prognostic factors for survival (all $p < 0.05$). Prognostic grouping

into three groups by the number of risk factors also had a significant predictive value for survival, with patients having 0, 1, 2 and 3–4 risk factors demonstrating MS of 18.0, 11.7, 5.7 and 3.0 months, respectively ($p < 0.001$). A clinical nomogram based on the four prognostic factors was formulated and demonstrated good accuracy for predicting 6-month survival with a concordance index of 0.77.

Conclusion: In a heterogeneous group of patients with HCC treated with RT for LN metastasis, the presence of LN-related symptoms was highly associated with poor survival. The prognostic grouping and nomogram developed by the present study can be effectively used for the prediction of survival.

Advances in knowledge: Patients treated with RT for LN metastases harbour various clinical features. Prognostic model and nomogram can help in predicting survival in these patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common types of cancer in Asia owing to hepatitis B virus-associated chronic liver disease and is also increasing in incidence among Western countries.^{1,2} Lymph node (LN) metastasis from this disease is known as a poor prognostic indicator for survival while being uncommon according to surgical series.^{3–6} Meanwhile, the incidence ranges up to 25–42% in autopsy studies^{7,8} and along with the improvement of diagnostic imaging techniques and survival in patients with advanced HCC,^{9–11} the incidence is more likely to increase. LNs are also among the most frequent sites of extrahepatic spread.¹²

However, the optimal management for LN metastasis in HCC has not been established yet. Surgical

lymphadenectomy does not seem to improve survival^{3,5} and other local therapies such as transarterial chemo-embolization, radiofrequency ablation or percutaneous ethanol injection are not considered as an option in most cases. Furthermore, the only approved systemic agent with survival benefit in advanced HCC, sorafenib, also does not significantly improve survival in patients with extrahepatic foci such as the lung or LNs.^{9–11} Fortunately, during the past decade, external beam radiotherapy (RT) for LN metastasis of HCC demonstrated encouraging response and overall survival (OS) rates in several studies as well as a significant survival improvement in one study.^{13–21} Most of these studies focused on defining the prognostic factors in those patients. However, the reported prognostic factors for survival varied among studies and to date, there is no established prognostic model to explain the prognosis of

those patients. Moreover, some factors such as the presence of symptoms related to LN metastasis were neglected in most studies. In our previous report,¹⁹ the presence of LN-related symptoms was the most powerful indicator for poor survival along with poor liver function, while the number of investigated patients was relatively small.

Therefore, the present study was designed to validate the prognostic impact of LN-related symptoms in a larger cohort and to establish a risk stratification model as well as a clinical nomogram for predicting survival in patients with HCC treated with RT for LN metastasis.

METHODS AND MATERIALS

Ethical statement

This study was approved by the Institutional Review Board of our institution.

Patients and diagnosis

Between May 2004 and February 2015, a total of 105 patients were treated with external beam RT for LN metastasis of HCC and included in this study. Patients were initially diagnosed as having HCC using the guideline of the Korean Liver Cancer Study Group.¹ All LN metastases were diagnosed *via* histologic confirmation or at least one of the following imaging modalities: CT, MRI or fluorine-18 fludeoxyglucose-positron emission tomography. Histologic confirmation for the metastatic LN was carried out in only 10 (9.5%) patients. Patients with combined cholangiocarcinoma confirmed by biopsy of the intrahepatic lesion or with any history of other malignancies other than differentiated thyroid cancer within 5 years prior to RT were excluded. Patients who were planned to receive stereotactic ablative RT for metastatic LNs were also excluded.

The median age was 59 years (range, 30–81 years). Performance grade according to the Eastern Cooperative Oncology Group scale was 0–1 and 2–4 in 69 (65.7%) patients and 36 (34.3%) patients, respectively. Most of the patients had intact liver function with Child–Pugh Class A (71.4%); however, more than half of the patients (61.9%) had uncontrolled intrahepatic lesion at the time of RT. 41 (39.1%) patients had synchronous non-nodal distant metastasis and the most frequent sites were the lung, bone and adrenal gland.

Characteristics of metastatic lymph nodes

Most of the LN metastases were multiple in number of lesions and groups involved. 61 (58.1%) patients had synchronous multistation LN metastasis (e.g. para-aortic and perigastric LN metastasis, hepatoduodenal and mediastinal LN metastasis, supraclavicular and axillary LN metastasis etc.). There were about three times more intra-abdominal LN metastasis than extra-abdominal LNs and the most common site of involvement was the regional LN group composed of portocaval, hepatoduodenal and common hepatic LNs followed by the para-aortic group. Among extra-abdominal LNs, mediastinal and supraclavicular LNs were most commonly involved. In our study, the prognostic significance of the size of metastatic LNs was not analyzed since the number of involved lymphatic stations and locations of LN metastasis were expected to represent

the tumour burden and prognosis better according to past studies.^{16,17,19,21}

About half of the patients (48.6%) complained of symptoms caused by metastatic LNs and 13 of them had multiple symptoms. The most common symptom was pain which was present in 72.5% of patients who were symptomatic. Patients with non-painful palpable LN metastasis complaining of only bothering sensations were regarded as asymptomatic. The next most common symptoms were from the respiratory and gastrointestinal tracts. Among patients with respiratory symptoms, dyspnoea due to superior vena cava syndrome was also included, and

Table 1. Characteristics of metastatic lymph nodes (LNs)

Variables	Values
Number of metastatic LNs	
Single	31
Multiple	74
Involved LN groups	
Single station	44
Multistation	61
Symptoms related to LNs	
Absent	54
Present	51
Pain	37
Respiratory symptom	6
GI obstruction	6
Hoarseness	4
Oedema of extremity	4
Jaundice	2
Ptosis	1
Metastatic LN location	
Intra-abdominal	80
Portocaval, hepatoduodenal, common hepatic	51
Para-aortic, retrocaval, aortocaval	49
Peripancreatic	10
Perigastric	7
Others	2
Extra-abdominal	29
Mediastinal	21
Supraclavicular	13
Cervical	6
Pericardial	5
Axillary	3
Internal mammary	1

GI, gastrointestinal.

Table 2. Patient characteristics and univariate analysis

Variables	Number of patients (%)	MS (months)	<i>p</i> -value ^b
Age (years)			
<55	35 (33.0)	4.5	0.047
≥55	70 (67.0)	6.5	
Sex			
Male	91 (86.7)	5.5	0.164
Female	14 (13.3)	8.8	
HBV related			
Yes	79 (75.2)	6.0	0.595
No	26 (24.8)	5.3	
HCV related			
Yes	8 (7.6)	4.8	0.863
No	97 (92.4)	5.9	
LN-related symptom			
Absent	54 (51.4)	10.7	<0.001
Present	51 (48.6)	3.8	
ECOG performance status			
0–1	69 (65.7)	8.9	<0.001
2–4	26 (34.3)	3.9	
Child–Pugh Class			
A	75 (71.4)	8.9	<0.001
B–C	30 (28.6)	3.1	
Intrahepatic tumour			
Controlled	40 (38.1)	15.2	<0.001
Uncontrolled	65 (61.9)	4.2	
Treatment site			
Intra-abdominal LN only	29 (27.6)	6.5	0.865
Extra-abdominal LN ^a	76 (72.4)	5.5	
Non-nodal distant metastasis			
Absent	64 (60.9)	9.1	0.012
Present	41 (39.1)	4.0	
Involved LN groups			
Single station	44 (41.9)	10.5	0.001
Multistation	61 (58.1)	4.0	
BED			
≥60 Gy ₁₀	47 (44.8)	11.7	<0.001
<60 Gy ₁₀	58 (55.2)	3.9	
Response (RECIST)			
CR/PR	38 (36.2)	13.8	<0.001
SD/PD	52 (49.5)	4.0	
Unknown	15 (14.3)	2.3	

(Continued)

Table 2. (Continued)

Variables	Number of patients (%)	MS (months)	<i>p</i> -value ^{<i>b</i>}
Prior treatment			
TACE			
Yes	86 (81.9)	6.1	0.075
No	19 (18.1)	4.0	
Sorafenib			
Yes	24 (22.9)	5.8	0.951
No	81 (77.1)	5.7	

BED, biologically effective dose; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HBC, hepatitis C virus; LN, lymph node; MS, median survival; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumours; SD, stable disease; TACE, transarterial chemoembolization.

^aRadiotherapy to extra-abdominal LN with or without intra-abdominal LNs.

^bLog-rank test.

gastrointestinal symptoms were all obstructive symptoms such as dysphagia or dyspepsia due to mass effect of the metastatic LNs. Jaundice was present in only two patients. The details are shown in Table 1.

Treatment

Prior to RT, transarterial chemoembolization was performed in 86 (81.9%) patients for intrahepatic disease and 24 (22.9%) patients received systemic targeted therapy with sorafenib (Bayer HealthCare Pharmaceuticals, Leverkusen, Germany).

All patients underwent external beam RT with 6–15-MV X-rays. Except for three patients, all patients underwent either three-dimensional conformal RT (73.3%) or intensity-modulated RT (23.8%). The clinical target volume was defined with a 3–5-mm margin around the enlarged LN and the planning target volume was defined with a 5–15-mm margin around the clinical target volume considering the location of the LN. The median RT dose, fraction size and number of fractions were 45 Gy (range, 30–60 Gy), 2.5 Gy (range, 1.8–3.0 Gy) and 18 (range, 10–33), respectively. The median duration of treatment was 30 days (range, 11–54 days). Since the dose fractionation schemes were heterogeneous, the biologically effective dose (BED) with an α/β ratio of 10 (Gy₁₀) was calculated for each regimen. The median BED was 58.5 Gy₁₀ (range, 39–75 Gy₁₀) and 44.8% of the patients received a BED of 60 Gy₁₀ or higher.

Statistical analysis

In our previous report,¹⁹ OS was calculated from the day on which LN metastasis from HCC was diagnosed. However, because the intervals from diagnosis to RT initiation were so heterogeneous ranging up to almost 1.5 years (result not shown) in the present cohort, OS was measured from the day of RT initiation. Response rates were measured according to the revised response evaluation criteria in solid tumours v. 1.1.²²

The Statistical Package for Social Sciences v. 22.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for statistical testing. Since only pre-RT factors can be considered for deciding whether to treat the patient or not, and for explaining the expected survival to the patient before RT, RT-related factors

with significance ($p < 0.05$) on log-rank test were excluded from multivariate analysis. Based on the results of multivariate analysis, a risk stratification model regarding the number of adverse indicators of survival was developed and a clinical nomogram was

Table 3. Results of multivariate analysis of pre-radiotherapy factors

Variables	HR	(95% CI)	<i>p</i> -value ^a
Age (years)			
<55	1.341	(0.862–2.085)	0.193
≥55	1		
LN-related symptoms			
Absent	1	(1.778–4.815)	<0.001
Present	2.926		
ECOG performance status			
0–1	1	(0.996–2.565)	0.052
2–4	1.598		
Child–Pugh Class			
A	1	(1.603–4.801)	<0.001
B–C	2.774		
Intrahepatic tumour			
Controlled	1	(1.631–4.801)	<0.001
Uncontrolled	2.744		
Non-nodal distant metastasis			
Absent	1	(1.050–2.512)	0.029
Present	1.624		
Involved LN groups			
Single station	1	(0.910–2.387)	0.115
Multistation	1.474		

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LN, lymph node.

^aCox regression analysis.

formulated by using the rms package of R v. 3.2.3 (<http://www.r-project.org>). The predictive performance of the nomogram was measured by the concordance index (C-index).

RESULTS

Response and treatment toxicity

90 patients were available for radiological evaluation of the metastatic LNs after RT. Regarding maximal radiological response, the overall response rate was 56.7%. 13 patients had complete response, 38 patients had partial response, 28 patients had stable disease and 11 patients had progressive disease. Favourable factors for response were asymptomatic LNs (72.5 vs 38.5% for symptomatic LNs; $p = 0.001$) and BED of $\geq 60 \text{ Gy}_{10}$ (75.6 vs 40.0% for BED $< 60 \text{ Gy}_{10}$; $p = 0.001$).

No acute grade 3 or higher toxicity was observed according to the Radiation Therapy Oncology Group acute toxicity criteria. During post-RT follow-up, only three patients who received a BED of $\geq 60 \text{ Gy}_{10}$ experienced grade 3 RT-related gastrointestinal bleeding confirmed by oesophagogastroduodenoscopy post-RT at 4, 6 and 8 months, respectively. No other grade 3 or higher long-term toxicity, according to the Common Terminology Criteria for Adverse Events v. 3.0, was observed.

Prognostic factors and prognostic grouping model

The median follow-up for survivors was 5.7 months and the median survival (MS) was 5.8 months. On univariate analysis, age < 55 years ($p = 0.047$), the presence of LN-related symptoms ($p < 0.001$), poor performance status ($p < 0.001$), poor underlying liver function ($p < 0.001$), uncontrolled intrahepatic tumour ($p < 0.001$), the presence of non-nodal distant metastasis ($p < 0.012$), multistation LN involvement ($p = 0.001$), BED of $< 60 \text{ Gy}_{10}$ ($p < 0.001$) and the absence of radiological response (stable or progressive disease) to RT ($p < 0.001$) were significant indicators for inferior survival (Table 2). Among

these factors, excluding BED and response to RT as described previously, seven pre-RT factors were enrolled for multivariate analysis. On multivariate analysis, the presence of LN-related symptoms [hazard ratio (HR) 2.926; $p < 0.001$], poor underlying liver function (HR 2.774; $p < 0.001$), uncontrolled intrahepatic tumour (HR 2.774; $p < 0.001$) and the presence of non-nodal distant metastasis (HR 1.624; $p = 0.029$) maintained their significantly adverse impacts on survival (Table 3).

Given the results of the multivariate analysis, patients were stratified into 4 groups based on the number of poor prognostic factors as follows: Group 1, no risk factor; Group 2, 1 risk factor; Group 3, 2 risk factors; Group 4, 3–4 risk factors. There were 21 (20.0%) patients, 25 (23.8%) patients, 27 (25.7%) patients and 32 (30.5%) patients in Groups 1, 2, 3 and 4, respectively. The survival outcomes were significantly different between the 4 groups ($p < 0.001$, by log-rank test) with patients who have 0, 1, 2 and 3–4 factors demonstrating an MS of 18.0, 11.7, 5.7 and 3.0 months, respectively (Figure 1).

Nomogram formulation

A clinical nomogram was also developed using the four pre-RT factors associated with poor survival (Figure 2a). The model was internally validated using the bootstrap validation method and demonstrated good accuracy in estimating the actual 6-month OS rate with a bootstrap-corrected C-index of 0.77 (Figure 2b).

DISCUSSION

Clinically detected LN metastasis in HCC is relatively uncommon. However, higher incidences up to 42% are reported by autopsy studies^{7,8} and the incidence of LN metastasis in the clinical setting is expected to increase in the future owing to effective local treatment modalities as well as systemic agents.^{10,11,23,24} However, no definitive consensus on the treatment of LN metastasis has been reached yet, and the role of RT is still

Figure 1. Prognostic grouping based on the number of risk factors among the following: the presence of lymph node-related symptom, poor Child-Pugh score, uncontrolled intrahepatic tumour and the presence of non-nodal distant metastasis.

Figure 2. (a) Clinical nomogram for predicting median survival and 6-month overall survival (OS) rate. (b) Internal validation of the accuracy for 6-month OS prediction based on the bootstrap validation method demonstrating a concordance index of 0.77. DM, distant metastasis.

controversial. Therefore, it is very important to accurately predict the expected survival of the patient before delivering RT.

In our study, 48.6% of the patients had LN-related symptoms, 61.9% of patients had uncontrolled intrahepatic disease and 39.1%

of patients had non-nodal distant metastasis. The MS was 5.8 months which is somewhat poor compared with the 7–19-month MS observed in the past studies evaluating the role of RT for LN metastasis.^{13–21} However, the characteristics of patients were very heterogeneous among studies, making direct comparison

difficult. For example, in a group of patients with intra-abdominal LNs only, Park et al¹⁶ reported a similar poor MS of 7 months even in a group of patients where 73.3% of patients were asymptomatic, 82.2% of patients were Child–Pugh Class A, 75.6% of patients lacked distant metastasis and 77.8% of patients had the intrahepatic tumour controlled. Those factors were all proven to be significantly favourable regarding survival in the present study as well as in past reports. Therefore, establishing a prognostic grouping model or building a nomogram based on prognostic factors might be a more effective method to predict survival and determine the group of patients who would achieve long-term survival after RT.

The presence of LN-related symptoms, Child–Pugh Class B–C, uncontrolled intrahepatic disease and non-nodal distant metastasis were significant factors, indicating poor survival on multivariate analysis. Underlying liver function in HCC is the most widely known prognostic factor for survival not only in patients undergoing RT for LN metastasis,^{15,17,19–21} but for all patients with HCC at any stage of the disease.^{25–29} The status of the intrahepatic disease and the presence of distant metastasis were also confirmed to affect survival in the past studies.^{16,18,20,21} The most interesting finding is the great impact of LN-related symptoms on survival by nearly tripling the risk of death, exceeding the risks from poor hepatic function, uncontrolled intrahepatic disease and synchronous distant metastasis. There was an absolute difference of 7 months in MS between patients who were symptomatic and those who were asymptomatic. To date, our previous report was the only study emphasizing the impact of LN-related symptoms in patients undergoing RT.¹⁹ However, the number of studied patients was small. In the present study with the second largest number of patients to date,^{13–21} the impact of symptoms maintained its significance. Furthermore, no other study has even tried to evaluate the prognostic significance of symptoms.^{13–18,20,21} Although not confined to patients with LN metastasis undergoing RT, patients who were asymptomatic and patients with better quality of life measured by the European Organization for Research and Treatment of Cancer questionnaire were shown to achieve better survival outcomes in HCC.^{30,31} Therefore, given the significant impact on survival in our study, LN-related symptoms should always be taken into account in future studies.

Radiological response rate with RT was 56.7% and responders had more favourable survival on univariate analysis in concordance with other studies.^{13,20,21} Favourable factors for achieving radiological response were the absence of LN-related symptoms and RT dose >60 Gy₁₀. However, since the present study focused on predicting survival upon pre-RT factors, whether the LN responded to RT or not was not analyzed in the multivariate analysis.

For HCC, several prognostic groupings and nomograms have been made and used in various settings to predict OS or disease recurrence.^{19,27,28,32–38} However, in patients undergoing RT for LN metastasis, no prognostic grouping or nomogram has been suggested for use. In our study, a prognostic grouping by the number of risk factors was formulated based on the results of multivariate analysis. The prognostic grouping significantly distinguished the MS between the four groups ($p < 0.001$). Patients with few risk factors, especially those with no risk factors, were shown to achieve a long-term MS of 18 months after RT. In contrary, patients with three or more risk factors demonstrated a very poor MS of 3 months.

Although prognostic grouping models provide valuable information on prognosis, some limitations are obvious. For example, as found in our study, the risk of death is nearly doubled in patients with LN-related symptoms compared with those with non-nodal distant metastasis. However, despite this unequal impact of factors on survival, two different patients inhering only one risk factor, which is LN-related symptoms for one and distant metastasis for another, would be assigned to the same prognostic group. Therefore, calculation of individualized survival *via* a nomogram integrating different prognostic contributions of each factor would be more accurate, especially in a heterogeneous group of patients. A prognostic nomogram was established using the four pre-RT factors affecting survival from our study. To evaluate the predictive accuracy of a nomogram, the C-index is widely used. The bootstrap-corrected C-index for the nomogram formulated in the present study was 0.77, which is comparable or higher than those of past studies,^{33–38} suggesting the high accuracy of our nomogram for predicting 6-month survival rates. Therefore, in a heterogeneous group of patients with HCC who are referred for RT to LN metastasis, this nomogram can be used effectively to predict survival outcomes.

The retrospective nature might weaken the findings of our study. However, the large number of patients compared with the past reports,^{13–21} the inclusion of both intra-abdominal and extra-abdominal LN metastasis, the finding that LN-related symptoms are highly associated with survival and the accuracy of formulated prognostic models make this study worthwhile.

CONCLUSION

In patients with HCC treated with RT for LN metastasis, the presence of LN-related symptoms nearly tripled the risk of death. The prognostic grouping based on the number of risk factors and the clinical nomogram formulated in this study can be used effectively for survival prediction. Further studies defining the group of patients who would benefit from RT are required.

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