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Efficacy of Local Treatment in Lymph Node Metastasis from Hepatocellular Carcinoma

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Keywords

Lymph node · Hepatocellular cancer · Incidence · Metastatic liver cancer · Propensity score

Abstract

Introduction: We aimed to investigate the significance of lymph node metastasis from hepatocellular carcinoma and the efficacy of local treatment. ***Methods:*** We included patients diagnosed hepatocellular carcinoma with lymph node metastasis. The pattern of lymph node metastasis was evaluated based on imaging examinations and stratified by three locations: regional (group A), beyond regional intra-abdomen (group B), and extra-abdomen (group C) lymph node metastasis. ***Results:*** Among 14,474 patients, 852 (5.8%) were identified as having lymph node metastasis. Regarding the location of presentation, group A showed the highest incidence, followed by groups B and C. The 1-year overall survival of patients was 31.7%. The survival significantly differed according to the location of lymph node metastasis. The 1-year overall survival rates were 39.8%, 25.5%, and 22.2% in groups A, B, and C, respectively. All patients underwent systemic treatment, with others receiving additional local treatment. Local treatment yielded superior overall survival compared with no local treatment. After propensity score matching, local treatment was associated with improved survival. Additionally, patients were stratified based on disease status at the time of diagnosis of lymph node metastasis: lymph node alone and combined extra-nodal metastasis. The survival benefits of local treatment were observed in both groups. ***Conclusions:*** Our findings demonstrated the clinical significance of lymph node metastasis from hepatocellular carcinoma, which was well discriminated according to location, favoring regional metastasis. In patients with hepatocellular carcinoma presenting lymph node metastasis, active application of local treatment for lymph node metastasis can improve oncologic outcomes.

Introduction

Lymph node (LN) metastasis is among the important patterns of progression and recurrence in various solid malignancies [1–3]. However, it has not been well studied

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Table 1. Patient characteristics

	N	%
Age (median, IQR)	58 (50–65)	
Sex		
Male	736	86.4
Female	116	13.6
Diagnosis		
B-viral	643	75.5
C-viral	51	6.0
NBNC	158	18.5
CPS		
A	510	59.9
B	319	37.4
C	23	2.7
PVTT		
Yes	543	63.7
No	309	36.3
Primary tumor status		
Controlled	170	20.0
Not controlled	682	80.0
Metastasis status		
LN alone	532	62.4
LN + extra-nodal metastasis	320	37.6
Lung	236	27.7
Bone	91	10.7
Peritoneum	61	7.2
Adrenal gland	21	2.4
Spleen	8	0.9
Tumor marker		
AFP (median, IQR)	110 (8–2,041)	
PIVKA-II (median, IQR)	469 (39–2,000)	

IQR, interquartile range; NBNC, non-B-viral non-C-viral; CPS, Child-Pugh score; PVTT, portal vein tumor thrombosis; LN, lymph node; AFP, alpha-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II.

in HCC. Specifically, the incidence, clinical features, and prognostic significance of LN metastasis in HCC remain unclear. Further, it is not uniformly described in the staging system. In the Barcelona Clinic Liver Cancer staging system, LN metastasis is included in the advanced stage together with other features, as extrahepatic spread [4]. The Modified Union for International Cancer Control staging system describes LN metastasis; however, LN metastasis is simply designated as N1 category [5]. Accordingly, accurate treatment for LN metastasis remains to be established.

There has been increasing attention on local treatment of advanced tumors since the SABR-COMET study [6], which demonstrated the importance of local treatment in metastatic disease. In malignancies, including lung and prostate cancer, there are confirmed effects of local treatment for metastatic disease [7, 8]. However, the efficacy of local treatment for LN metastasis in HCC remains unclear [9, 10]. Hence, local treatment for LN metastasis has been limited except for clinical cases requiring cytoreduction. We aimed to investigate the clinical characteristics and prognostic significance of LN metastasis in HCC, as well as the significance of local treatment for LN metastasis in HCC.

Materials and Methods

Patient Enrollment

There were 14,474 patients diagnosed with HCC in Severance hospital from 2001 to 2019. Among them, 13,622 patients lacked LN metastasis while 25 patients were not followed up in our institution. Consequently, we included 852 patients. HCC was diagnosed using imaging examinations and serum tumor markers based on the guidelines of the Korean Liver Cancer Study Group

Table 2. Comparison of patient characteristics depending on local treatment

	Before PSM					After PSM				
	local treatment (n = 265)		no local treatment (n = 587)			local treatment (n = 184)		no local treatment (n = 184)		
	N	%	N	%	p value	N	%	N	%	p value
Age (median, IQR)	58 (50–67)		58 (50–65)		0.145	58 (50–68)		60 (53–67)		0.711
Sex										
Male	228	86.0	508	86.5	0.843	155	84.2	153	83.2	0.778
Female	37	14.0	79	13.5		29	15.8	31	16.8	
Diagnosis										
B-viral	192	72.5	451	76.8	0.076	128	69.6	142	77.2	0.247
C-viral	23	8.7	28	4.8		16	8.7	11	6.0	
NBNC	50	18.9	108	18.4		40	21.7	31	16.8	
CPS										
A	192	72.5	318	54.2	<0.001	127	69.0	127	69.0	1.000
B	72	27.2	247	42.1		56	30.4	56	30.4	
C	1	0.4	22	3.7		1	0.5	1	0.5	
PVTT										
Yes	95	35.8	214	36.5	0.864	75	40.8	66	35.9	0.075
No	170	64.2	373	63.5		109	59.2	118	64.1	
Primary tumor status										
Controlled	119	44.9	51	8.7	<0.001	38	20.7	38	20.7	1.000
Not controlled	146	55.1	536	91.3		146	79.3	146	79.3	
Metastasis status										
LN alone	226	85.3	306	52.1	<0.001	145	78.8	145	78.8	1.000
LN + extra-nodal metastasis	39	14.7	281	47.9		39	21.2	39	21.2	
Tumor marker										
AFP (median, IQR)	42 (6–1,318)		158 (9–2,474)		0.048	88 (8–2,091)		99 (6–1,656)		0.892
PIVKA-II (median, IQR)	313 (27–2,000)		629 (47–2,000)		0.038	483 (34–2,000)		177 (34–2,000)		0.356

IQR, interquartile range; NBNC, non-B-viral non-C-viral; CPS, Child-Pugh score; PVTT, portal vein tumor thrombosis; LN, lymph node; AFP, alpha-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II.

[5]. This study was approved by the institutional review board of Severance Hospital (4-2021-1379). The need for informed consent was waived due to the retrospective study design.

Evaluation of LN Metastasis

LN metastasis was clinically diagnosed based on CT scan findings by expert radiologists according to the following criteria [11]: short-axis diameter of the LN >1 cm; contrast-enhanced LN observed in the arterial phases; and an increase in the size of the previously identified LN. Magnetic resonance imaging or positron emission tomography-computed tomography was performed if additional diagnostic procedures were required to confirm LN metastasis.

Treatment

The Barcelona Clinic Liver Cancer staging system recommended that LN-positive patients be treated using systemic therapy [4]. Local treatments for LN metastasis, including radiotherapy (RT) and lymphadenectomy, were chosen through multidisciplinary team discussion. Local treatments were administered if there were symptoms of LN metastasis requiring palliation and/or when LN was the solitary extrahepatic metastasis. Most patients underwent RT rather than surgery due to their medical condition or preference for nonsurgical options. Among 265 patients who received local treatment for LN metastasis, 241 patients (28.3%) underwent RT, while 24 patients (2.8%) performed lymphadenectomy. The local treatment group comprised patients who received both local and systemic treatments for LN metastasis, while no local treatment group comprised patients who only underwent systemic treatment. The most commonly used systemic chemotherapy regimen was sorafenib. Approximately 587 patients received systemic treatment with sorafenib (69.0%) followed by treatment with lenvatinib (n = 92, 10.8%). Regimens such as regorafenib and cisplatin-based combination chemotherapy, were administered in 4.46% (n = 38) and 10.45% (n = 89), respectively. For RT, all patients underwent CT simulation for RT planning. In order to reflect the movement of the LN during respiration, 4-dimensional CT was also taken. Among 241 patients, 80 patients received 3-dimensional conformal RT (33.20%), while 161 patients received intensity-modulated RT (66.80%). The most commonly used radiation dose was 45 Gy/25 fractions (n = 97, 40.3%), followed by 60 Gy/25 fractions (n = 80, 33.2%) and 75 Gy/25 fractions (n = 62, 25.7%). For patients receiving intensity-modulated RT, simultaneous-integrated boost was performed. Either 2.4 Gy

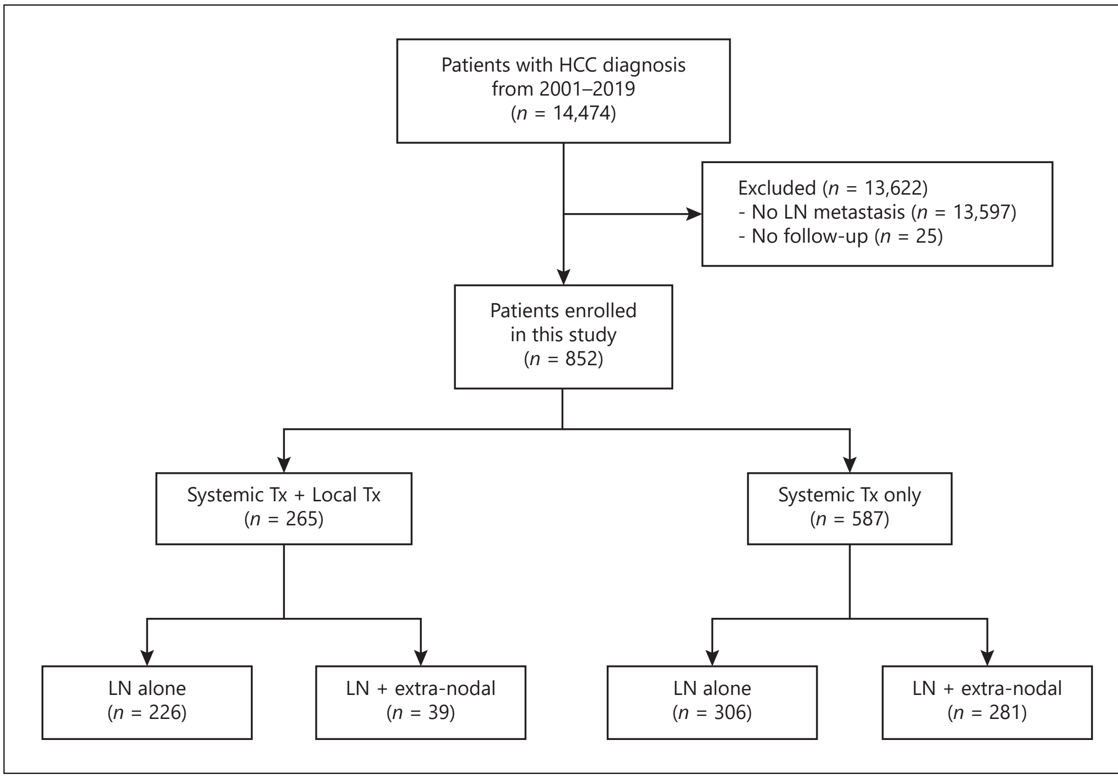

Fig. 1. Summary of the treatment scheme.

or 3 Gy fractional radiation dose was applied to gross tumor volume, while 1.8 Gy fractional radiation dose was applied to planning target volume during 25 fractions. The planning target volume was defined as 5-mm margin from gross tumor volume including the nodal area of involved LN.

Follow-Up

The treatment response was assessed based on CT scans performed at intervals of 2–3 months according to the response evaluation criteria in solid tumor criteria [12]. Complete LN disappearance on CT scans was defined as a complete response, while a size reduction >30% was defined as a partial response. Progressive disease was defined as a ≥20% increase in size and stable disease was defined as the response between partial response and progressive disease. Additionally, we identified serum tumor markers with imaging studies to confirm the response.

Statistics Analysis

The overall survival (OS) was defined as the time from diagnosis of LN metastasis to the date of death or the last follow-up. Survival analysis was performed using the Kaplan-Meier method. Groups were stratified into two groups based on local treatment. Between-group comparisons of baseline characteristics were performed using the χ^2 test and Fisher's exact test. Between-group propensity score matching (PSM) was performed using 1:1 nearest neighbor matching and a caliper width of 0.2 standard deviations. The R package "MatchIt" was used [13]. Matching variables were selected as the unbalanced variables between both groups. Statistical analyses were performed using the R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS software (version 25.0; IBM Inc., Armonk, NY, USA).

Results

Clinical Characteristics

Table 1 shows the patient characteristics. The median age of the patients was 58 years (interquartile range, 50–65 years). Among 852 patients, 736 (86.4%) patients were men and 510 (59.9%) had Child-Pugh score A. Local treatments, such as RT or surgery, were performed on 265 patients (31.1%), while 587 (68.9%) were administered systemic treatment. LN alone metastasis was defined as disease with only LN metastasis without any extra-nodal metastasis. Contrastingly, combined with extra-nodal metastasis status (LN + extra-nodal metastasis) was defined as disease with LN and extra-nodal metastases. There were 532 (62.4%) patients who showed LN alone metastasis at LN diagnosis (Fig. 1). The most commonly occurred extra-nodal metastasis was lung (n = 236, 27.7%) followed by bone (n = 91, 10.7%), peritoneum (n = 61, 7.2%), adrenal gland (n = 21, 2.4%), and spleen (n = 8, 0.9%).

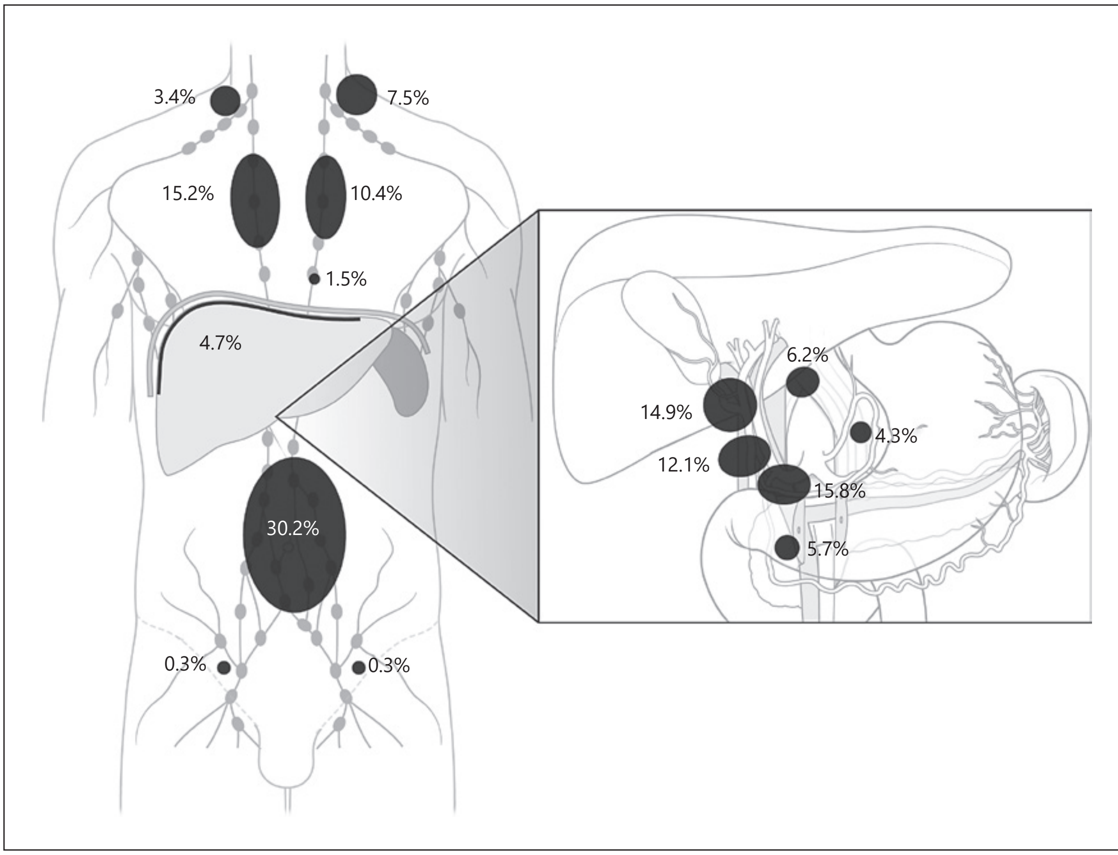

Fig. 2. Groups stratified based on the location of lymph node metastasis in HCC.

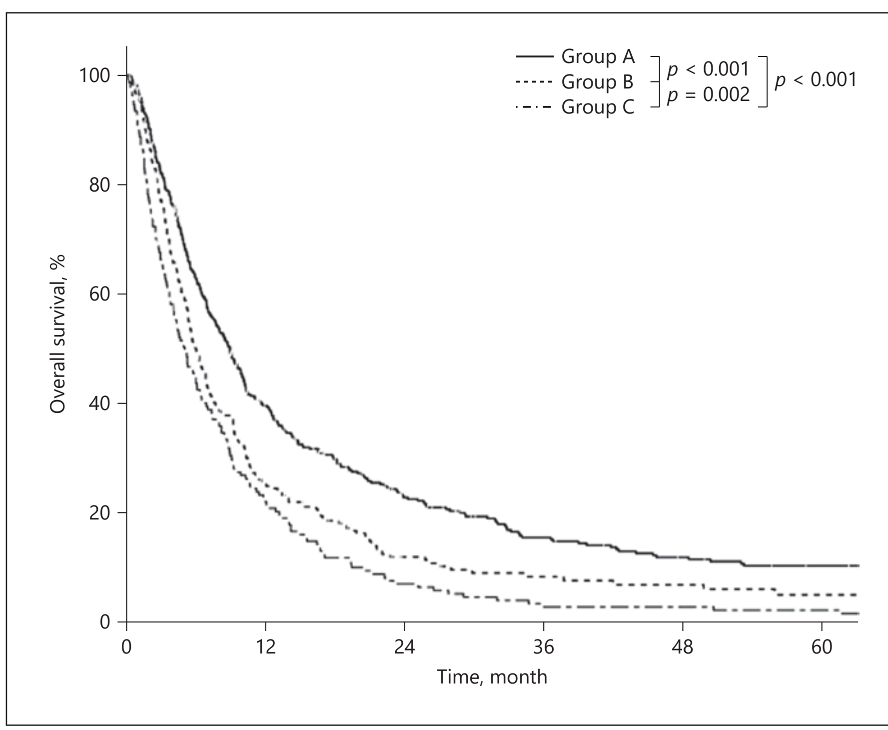

Fig. 3. Overall survival according to the location of the metastatic lymph node.

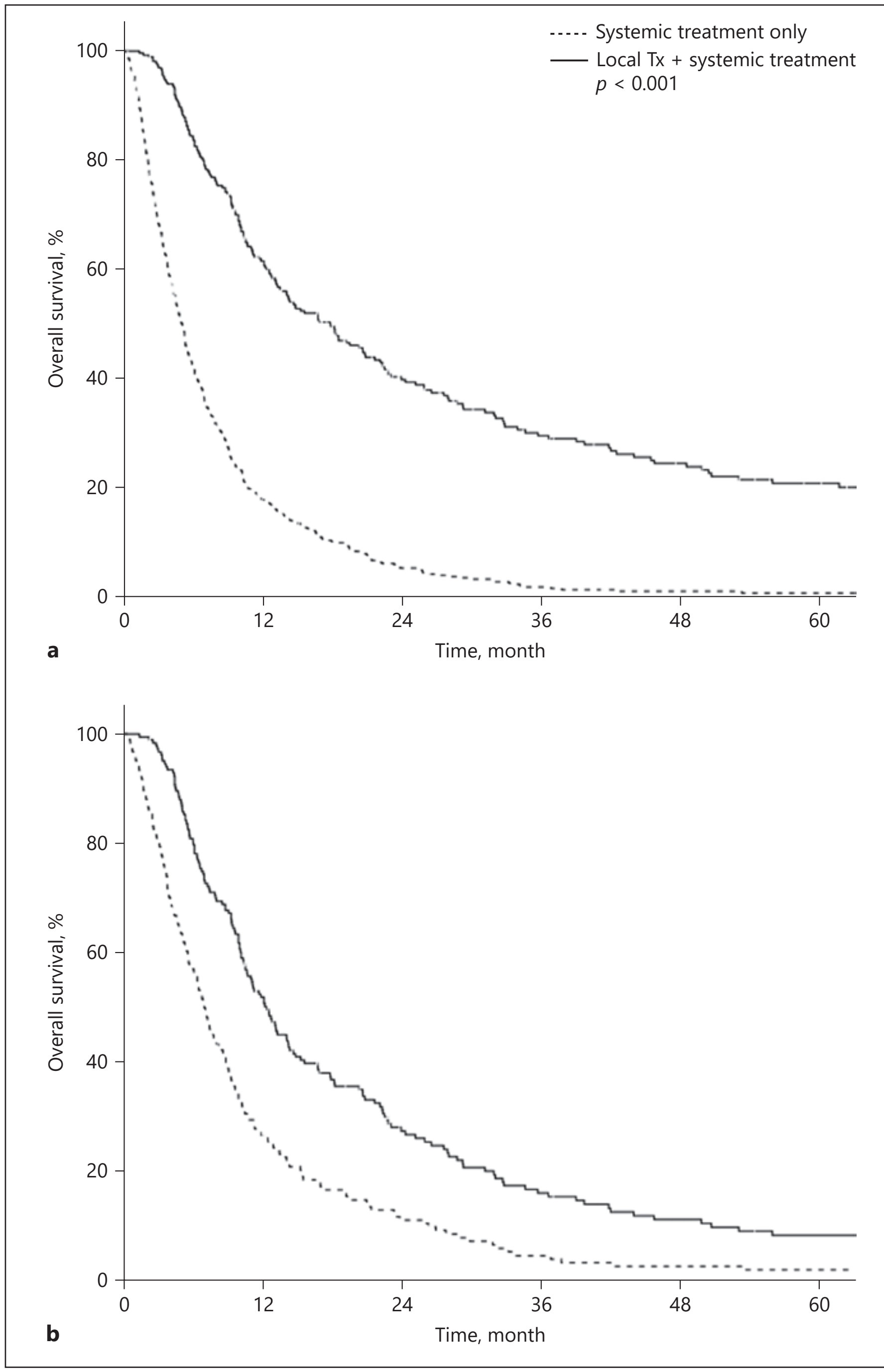

Fig. 4. Difference in overall survival between local treatment and non-local treatment before (**a**) and after (**b**) propensity score matching.

Table 2 presents the between-group comparisons of the patient characteristics. Compared with the no local treatment group, the local treatment group showed better liver function and better tumor control of the primary liver tumor (Child-Pugh A: 72.5% vs. 54.2%, $p < 0.001$; primary tumor control: 44.9% vs. 8.7%, $p < 0.001$). Additionally, LN + extra-nodal metastasis was less frequent in the local treatment group than in the no local treatment group (LN + extra-nodal metastasis: 14.7% vs. 47.9%, $p < 0.001$). Compared with the local treatment group, the no local treatment group showed significantly higher levels of the tumor marker, α-fetoprotein, and protein induced by vitamin K absence or antagonist-II.

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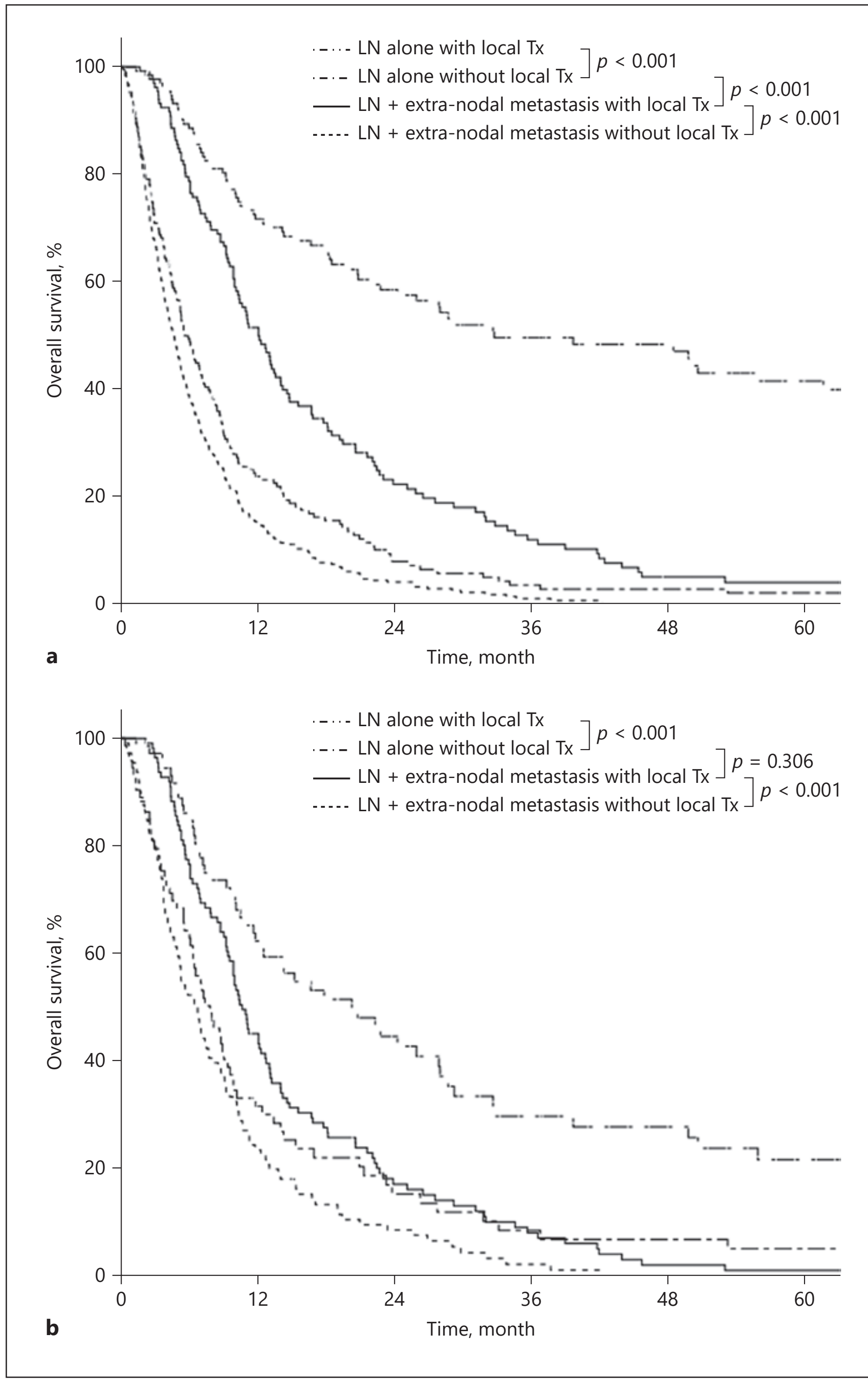

Fig. 5. Difference in overall survival according to local treatment and extra-nodal metastasis status before (**a**) and after (**b**) propensity score matching.

Patterns of LN Metastasis

In our study, the incidence of LN metastasis was approximately 5.8%. Based on the patterns of LN metastasis, the patients were divided into group A (regional LN metastasis, including hilar LN, hepatoduodenal LN, inferior phrenic LN, and caval LN), group B (beyond regional intra-abdominal LN metastasis), and group C (extra-abdomen LN metastasis). The groups were stratified based on the most distant LN. Group A showed the highest incidence of LN metastasis (n = 414, 48.6%), followed by group B (n = 267, 31.3%) (Fig. 2).

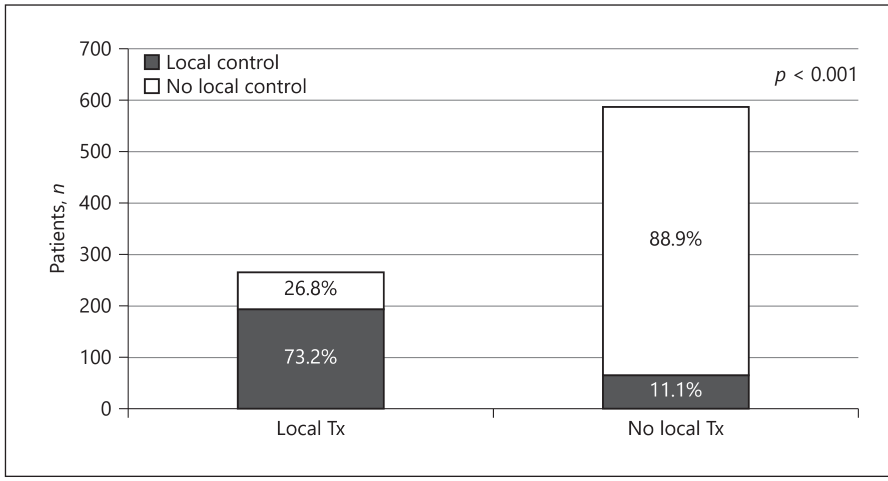

Fig. 6. Comparison of lymph node tumor control between the local treatment and no local treatment groups.

Toxicity

The most commonly occurred adverse events from RT were radiation-induced gastro-duodenal ulcer (n = 29, 12.0%) followed by anorexia (n = 28, 11.6%). The most of the radiation-induced gastro-duodenal ulcer showed grade 1 or 2, while 3 patients showed grade 3. In surgery group, 3 patients experienced biliary tract obstruction (12.5%), while 2 patients experienced delayed healing (8.4%) (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000529201).

Survival Outcomes

The 1-year OS rate of all patients with LN metastasis was 31.7%. There were no significant differences in the OS according to the location of LN metastasis. Groups A and C showed the best and worst OS, respectively. The 1-year OS rates were 39.8%, 25.5%, and 22.2% in groups A, B, and C, respectively ($p < 0.001$) (Fig. 3).

The local treatment group showed better OS than the no local treatment group. The 1-year OS rates were 61.6% and 17.9% in the local and no local treatment groups, respectively ($p < 0.001$) (Fig. 4a). Additionally, we performed subgroup analysis based on the presence of extra-nodal metastasis to determine the survival benefit of local treatment. The groups were further stratified as follows: LN metastasis alone with local treatment, LN metastasis alone without local treatment, LN + extra-nodal metastasis with local treatment, and LN + extra-nodal metastasis without local treatment. The 1-year OS rates in patients with LN alone metastasis were 71.8% and 23.9% in the local treatment and no local treatment groups, respectively ($p < 0.001$). The 1-year OS rates in patients with LN + extra-nodal metastasis in the local treatment and no local treatment groups were 51.5% and 15.2%, respectively ($p < 0.001$; Fig. 5a).

We performed PSM to compensate for the non-random assignments to each group based on the Child-Pugh score, primary tumor control, and extra-nodal metastasis status. Table 2 presents a comparison of the patient characteristics after PSM. After PSM, there were 184 matched pairs and both groups were well balanced (all $p > 0.05$). The observed OS benefits of local treatment remained after PSM. The 1-year OS rates were 51.8% and 26.6% in the local treatment and no local treatment groups, respectively ($p < 0.001$) (Fig. 4b). After PSM, the survival benefits of local treatment were demonstrated in both LN alone and LN + extra-nodal metastasis ($p < 0.001$). The 1-year OS rates in patients with LN alone metastasis in the local treatment and no local treatment groups were 62.3% and 31.6%, respectively ($p < 0.001$). Moreover, the survival benefits of local treatment were confirmed in patients with LN + extra-nodal metastasis (1-year OS: local treatment vs. no local treatment; 45.0% vs. 23.4%, $p < 0.001$) (Fig. 5b).

Comparison of Disease Progression

There was a significant difference in LN tumor control according to local treatment. Local treatment enhanced the LN tumor control rate (Fig. 6). A good response (complete or partial response) of metastatic LN was observed in 194 (73.2%) and 65 (11.1%) patients treated with and without local treatment, respectively, until the end of follow-up ($p < 0.001$). Local treatment prolonged the median time to progression (local treatment vs. no local treatment; 7.37 vs. 2.27 months, $p < 0.001$).

The disease progression pattern significantly differed according to the location of LN metastasis (online suppl. Fig. 1). More patients maintained LN alone metastasis status in group A, while more patients progressed to extra-nodal metastasis in group B ($p < 0.001$). Most patients in group C showed LN + extra-nodal metastasis status at diagnosis, and 120 (70.2%) patients maintained this status.

Conclusion

Our findings demonstrated the clinical characteristics and prognostic significance of LN metastasis in HCC. Local treatment of LN metastasis in HCC improved survival. Survival outcomes significantly differed depending on the location of the involved LN. Local treatment prolonged survival in both patients with LN alone metastasis and LN + extra-nodal metastasis.

The reported incidence of LN metastasis in HCC has varied across studies (1.6–5.9%) [14, 15]. The incidence increased in autopsy cases involving pathologic confirmation of LN metastasis [16, 17]. A large-scale study reported that the incidence of LN metastasis in patients who underwent routine lymphadenectomy was 5.1% [10]. In our study, the incidence of LN metastasis was 5.8%. Although LN metastasis was not pathologically confirmed, all metastatic nodes were confirmed through multidisciplinary team discussions. Further, the incidence rate of LN metastasis was consistent with previous findings [10, 14, 15]. In our study, the most common LN metastasis location was regional LN, followed by beyond regional, intra-abdominal, and extra-abdomen LN.

The survival rates significantly differed according to the extent of LN involvement. More patients maintained LN metastasis alone status in the regional LN metastasis group than in the regional or extra-abdominal LN. There are significant differences in clinical features and survival based on the extent of LN involvement in several malignancies. In non-small-cell lung cancer, the staging system differs according to the extent of LN involvement, with the survival rates of N1, N2, and N3 stages being 37%, 23%, and 9%, respectively. There was a significant difference in survival between the nodal categories [18]. Furthermore, the nodal category differs according to the involved LN location in breast cancer. Internal mammary LN or supraclavicular LN is considered as advanced stages of regional metastasis in breast cancer [19]. Patients who show involvement of the internal mammary LN have a poor prognosis [20].

In this study, several regimens were used for radiation dose fractionation. This heterogeneity mainly resulted from proximity of target volume to nearby radiosensitive organs such as stomach and duodenum. Recently, the hypofractionation RT is more preferred if safe distance could be reserved from radiosensitive organs.

The efficacy of local treatment has been reported for several malignancies [21–24]. Recently, the SABR-COMET study reported improved OS in patients who received RT for oligometastatic lesions [6]. However, the benefit of local treatment in metastatic HCC remains unclear [25, 26]. In our study, the local treatment group showed better OS than the no local treatment group. Consistent with our finding, local treatment for patients with oligometastasis in several malignancies enhanced survival [8, 22, 23, 27]. Moreover, we observed that local treatment had survival benefits for both patients with LN alone and those with LN + extra-nodal metastasis.

The mechanisms underlying the survival benefit of local treatment remain unclear; however, local treatment increased the progression time by delaying the disease spread or altering the systemic anticancer immune response. Consistent with our findings, local treatment prolonged the time to progression in non-small-cell lung cancer [27]. This prolonged progression time could have contributed to an enhanced survival. A recent study demonstrated that LN metastasis in HCC showed epithelial-mesenchymal transition high feature with fibrous tumor stroma and high immune cell infiltration compared with other HCC organ metastasis in early-stage HCC [28]. The epithelial-mesenchymal transition makers are key factors in tumor migration and invasion, which indicates that LN metastasis is a key factor in metastasis to other organs in HCC [29]. Local treatment allows LN tumor control and may eventually block the path to extranodal organ metastasis. The decreased incidence of extranodal organ metastasis, in turn, enhances survival. Patients with LN alone metastasis who underwent local treatment survived beyond 5 years. Local treatment disturbed the extra-nodal organ metastasis and eliminated the remaining tumor burden, which eventually allowed long-term survival in the LN alone metastasis group.

This study has some limitations resulting from its retrospective nature. First, there could have been selection bias in the use of local or systemic treatment based on the patient and tumor characteristics. However, local treatment showed survival benefits even after PSM. Second, the LN metastases were not pathologically identified. Nonetheless, this is the first study to analyze the patterns of LN metastasis in HCC and demonstrate that local treatment of LN metastasis improved oncologic outcomes using the largest reported cohort.

In conclusion, this study demonstrated the incidence of LN metastasis in HCC based on its location. The prognosis was well discriminated according to the location of LN metastasis, favoring regional LN metastasis. Local treatment improved the prognosis of LN metastasis in both LN alone and LN + extra-nodal metastases. Therefore, local treatment of LN metastasis in HCC should be considered more, and further studies are warranted to provide improved treatment options.

Statement of Ethics

This study protocol was reviewed and approved by institutional review board of Severance Hospital, approval number (4-2021-1379). The need for informed consent was waived by the institutional review board of Severance Hospital due to the retrospective study design.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization and supervision: Jinsil Seong; data curation and writing – original draft: Byung min Lee; formal analysis: Byung min Lee and Jinsil Seong; methodology: Jin-Young Choi and Jinsil Seong; writing – review and editing: Jin-Young Choi and Jinsil Seong.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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