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Radiotherapy efficacy and prognostic factors in hepatocellular carcinoma patients with cardiophrenic angle or superior diaphragmatic lymph nodes metastasis

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Abstract

Aim: To investigate radiotherapy efficacy and prognostic factors in patients with hepatocellular carcinoma (HCC) with cardiophrenic angle or superior diaphragmatic lymph node metastasis (LNM).

Methods: We retrospectively analyzed 72 patients with HCC presenting with cardiophrenic angle or superior diaphragmatic LNM at Zhongshan Hospital of Fudan University from 2010 to 2023. Response rates, survival rates, local control rates, prognostic risk factors, and side effects of external beam radiation therapy (EBRT) were compared between patients with EBRT (EBRT group) and those without EBRT (non-EBRT group).

Results: The overall response rates in the EBRT group and the non-EBRT group were 68.8% (22/32) and 7.5% (3/40), while median survival was 16.1 (95%CI: 8.09-24.12) and 5.9 months (95%CI: 3.05-7.76) respectively (HR = 2.87, $P < 0.001$). The survival was significantly prolonged with a daily dose > 4 Gy ($P = 0.014$). EBRT ($P < 0.001$) was identified as a factor correlated with the local control rate. Multivariate analysis revealed that tumor thrombosis, multiple intrahepatic tumors, a maximal intrahepatic tumor diameter ≥ 5 cm, abdominal LNM, and lack

of EBRT were poor prognostic factors. Gastrointestinal (GI) bleeding in patients with bioequivalent dose 10 (BED10) ≤ 70 and > 70 were 0% (0/22) and 30.0% (3/10), respectively (P = 0.024).

Conclusion: EBRT was a safe and effective treatment for HCC patients with cardiophrenic angle or superior diaphragmatic LNM and might prolong overall survival. Dose > 4 Gy per day and BED10 ≤ 70 would be recommended for LNM. Patients with tumor thrombosis, multiple intrahepatic tumors, a maximal intrahepatic tumor diameter ≥ 5 cm, abdominal LNM, and lack of EBRT had a poor prognosis.

Keywords: Cardiophrenic angle, superior diaphragmatic, lymph node, hepatocellular carcinoma, radiation therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common neoplasms, encompassing 75%-85% of primary liver cancers[1]. The incidence of patients with HCC with lymph node metastasis (LNM) is low[2], but when present, it signifies a dismal prognosis. Our previous study indicated that the median survival of HCC patients with abdominal LNM in the external beam radiation therapy (EBRT) group and the non-EBRT group was 9.4 and 3.3 months, respectively[3]. Consequently, radiotherapy has shown potential in extending the overall survival (OS) of HCC patients with abdominal LNM. However, occurrences of cardiophrenic angle or superior diaphragmatic LNM in HCC patients are rare, with other tumor types rarely manifesting in these locations[4-6].

The cardiophrenic angle or superior diaphragmatic lymph nodes (LNs) are located behind the xiphoid process, positioned between the diaphragm and the heart. The lymph of pericardium, the anterior thoracic and abdominal walls, the pleura, and the diaphragm flow into cardiophrenic angle or superior diaphragmatic LNs in patients with ovarian cancer[7]. The lymphatic drainage tube spread on the liver capsule, rather than in the liver. The primary tumor always invades the capsule when LNM from HCC occurs under the liver capsule. Past research has categorized the cardiophrenic angle LNs into anterior, middle, and posterior groups[8,9]. However, there remains a notable absence of published studies about the effects of radiotherapy and recommendation of radiation dose on cardiophrenic angle or superior diaphragmatic LNM.

The objective of this study was to collect information on patients with HCC with images depicting cardiophrenic angle or superior diaphragmatic LNM and to evaluate characteristics at diagnosis and survival outcomes.

METHODS

Patient eligibility

We retrospectively studied 72 patients with HCC treated at Zhongshan Hospital of Fudan University from January 2010 to September 2023. Among these individuals, a diagnosis of cardiophrenic angle or superior diaphragmatic LNM was established based on pathological or clinical characteristics. These 72 patients represented 2.5% of the total HCC patient population within our Radiation Oncology department. Patients were divided into an EBRT group and a non-EBRT group, with 32 and 40 patients, respectively.

The inclusion criteria for the target population included: (1) Clinical diagnosis of cardiophrenic angle or superior diaphragmatic LNM; (2) Pathological or clinical diagnosis of HCC; (3) Child-Pugh classification A or B; (4) Karnofsky (KPS) scores ≥ 80. The clinical baseline data for the patients are detailed in Table 1. Six patterns of HCC-associated LNM before [Figure 1] and after [Figure 2] radiotherapy were summarized as follows:

Table 1. Clinical baseline data of patients with HCC in two groups at the time of diagnosis of cardiophrenic angle or superior diaphragmatic LN metastasis

Characteristics	EBRT group (*n* = 32)	Non-EBRT group (*n* = 40)	*P*
Age (years)			0.420
< 60 years old	23 (71.9%)	32 (80.0%)	
≥ 60 years old	9 (28.1%)	8 (20.0%)	
Sex, *n* (%)			0.796
Male	29 (90.6%)	38 (95.0%)	
Female	3 (9.4%)	2 (5.0%)	
HBsAg, *n* (%)			0.970
Positive	27 (84.4%)	35 (87.5%)	
Negative	5 (15.6%)	5 (12.5%)	
Child-Pugh classification, *n* (%)			0.720
A	29 (90.6%)	34 (85.0%)	
B	3 (9.4%)	6 (15.0%)	
Tumor thrombosis			0.204
Positive	12 (37.5%)	21 (52.5%)	
Negative	20 (62.5%)	19 (47.5%)	
Extrahepatic metastasis			0.234
Positive	10 (31.3%)	18(45.0%)	
Negative	22 (68.7%)	22 (55.0%)	
Intrahepatic lesions, *n* (%)			0.009
None	7 (21.9%)	3 (7.5%)	
Solitary	14 (43.8%)	9 (22.5%)	
Multiple nodules (≥ 2)	11 (34.4%)	28 (70.0%)	
Intrahepatic tumor size (cm), *n* (%)			0.000
≤ 5	21 (65.6%)	7 (17.5%)	
5 ~ 10	7 (21.9%)	19 (47.5%)	
≥ 10	4 (12.5%)	14 (35.0%)	
Site of LN, *n* (%)			
Abdominal LN			0.287
Yes	16 (50.0%)	25 (62.5%)	
No	16 (50.0%)	15 (37.5%)	
Thoracic LN			0.273
Yes	4 (12.5%)	9 (22.5%)	
No	28 (87.5%)	31 (77.5%)	
LN number			0.227
Solitary	14 (43.8%)	12 (30.0%)	
Multiple (≥ 2)	18 (56.3%)	28 (70.0%)	
Intrahepatic tumor resection			0.092
Yes	20 (62.5%)	17 (42.5%)	
No	12 (37.5%)	23 (57.5%)	
TACE			1.000
Yes	28 (87.5%)	36 (90.0%)	
No	4 (12.5%)	4 (10.0%)	
Radiofrequency ablation			0.073
Yes	7 (21.9%)	2 (5.0%)	
No	25 (78.1%)	38 (95.0%)	
Targeted drugs (Sorafenib or Lenvatinib)			0.403
Yes	10 (31.3%)	9 (22.5%)	

No	22 (68.8%)	31 (77.5%)	
Immune therapy (Carrilizumab 200mg D1, q3W)			0.159
Yes	7 (21.9%)	3 (7.5%)	
No	25 (78.1%)	37 (92.5%)	
Chemotherapy			0.323
Yes	0 (0.0%)	3 (7.5%)	
No	32 (100.0%)	37 (92.5%)	
AFP status (μg/L), *n* (%)			0.751
< 400	18 (56.3%)	21 (52.5%)	
≥ 400	14 (43.8%)	19 (47.5%)	

AFP: Alpha-fetoprotein; HbsAg: hepatitis B surface antigen; LN: lymph node; TACE: transcatheter arterial chemoembolization; HCC: hepatocellular carcinoma; EBRT: external beam radiation therapy.

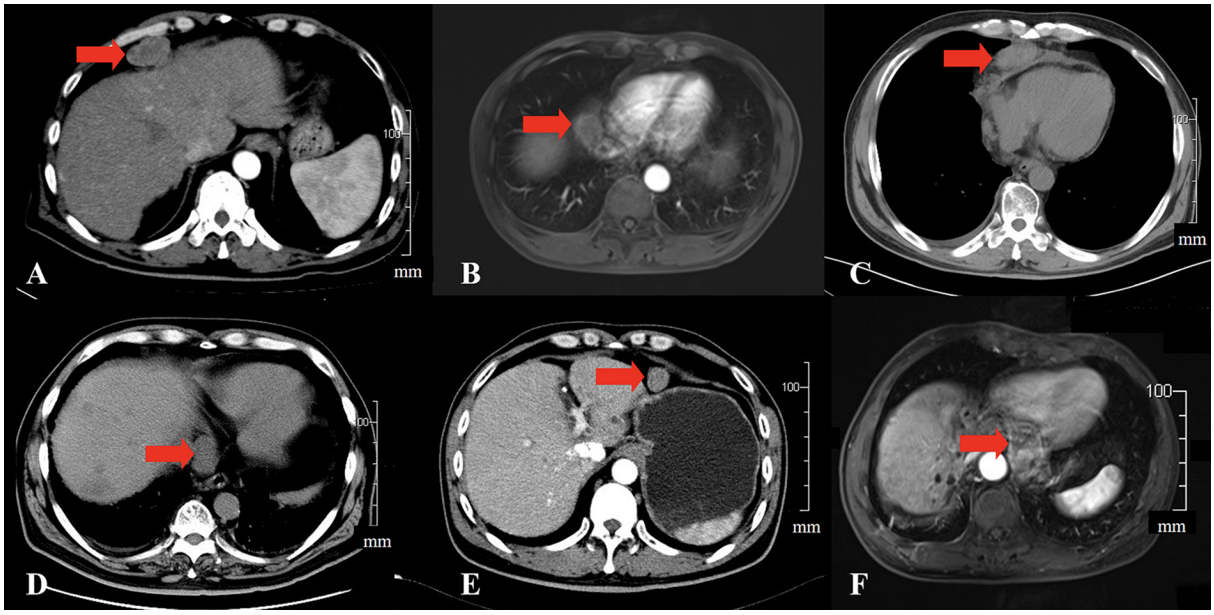

Figure 1. Different types of cardiophrenic angle or superior diaphragmatic LNs before radiotherapy. (A) Right superior diaphragmatic LN; (B) Right middle cardiophrenic angle LN; (C) Right pericardium cardiophrenic angle LN; (D) Right posterior cardiophrenic angle LN; (E) Left anterior cardiophrenic angle LN; (F) Left posterior cardiophrenic angle LN. LN: Lymph node.

(1) Right superior diaphragmatic LN: LN located on the right side above the diaphragm.

(2) Right middle cardiophrenic angle LN: LN situated at the angle between the heart and liver.

(3) Right pericardium cardiophrenic angle LN: LN adjacent to the right side of the pericardium.

(4) Right posterior cardiophrenic angle LN: LN located at the posterior section of the cardiophrenic angle on the right side.

(5) Left anterior cardiophrenic angle LN: LN located at the anterior section of the cardiophrenic angle on the left side.

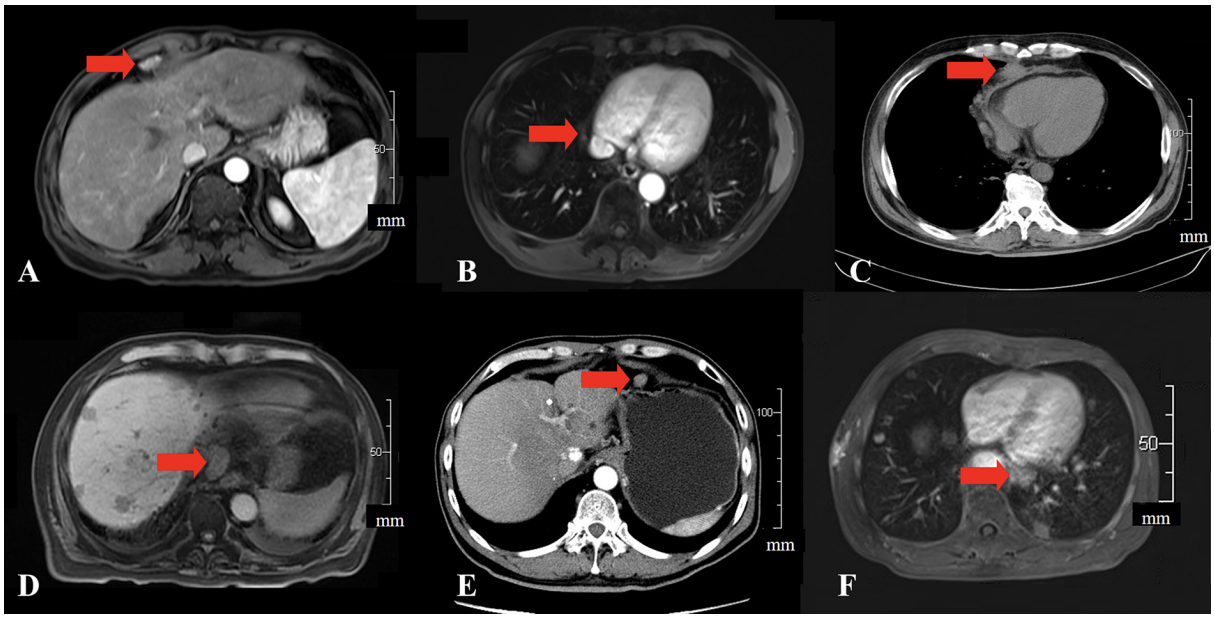

Figure 2. Different types of cardiophrenic angle or superior diaphragmatic LNs after radiotherapy. (A) Right superior diaphragmatic LN; (B) Right middle cardiophrenic angle LN; (C) Right pericardium cardiophrenic angle LN; (D) Right posterior cardiophrenic angle LN; (E) Left anterior cardiophrenic angle LN; (F) Left posterior cardiophrenic angle LN. LN: Lymph node.

(6) Left posterior cardiophrenic angle LN: LN located at the posterior section of the cardiophrenic angle on the left side.

Anterior LNs were divided into left and right based on the apex of the heart. Posterior LNs were classified as left and right based on the left edge of the aorta.

Extrahepatic metastasis: excluding cardiophrenic angle or superior diaphragmatic LNs metastasis.

Diagnostic criteria

The diagnostic criteria for intrahepatic tumors were: (1) Pathological diagnosis; (2) Clinical diagnosis: alpha-fetoprotein (AFP) levels ≥ 400 μg/L with one positive imaging result or AFP levels < 400 μg/L with two positive imaging results[10,11].

The clinical diagnostic criteria for cardiophrenic angle or superior diaphragmatic LNM were as follows:

(1) Evidence of liver capsule invasion by intrahepatic tumors in HCC patients. In cases where patients underwent surgery for intrahepatic tumors and exhibited cardiophrenic angle or superior diaphragmatic LN enlargement post-surgery, a review of preoperative imaging and surgical records was conducted to determine the presence of tumor invasion into the capsule.

(2) Images revealed cardiophrenic angle or superior diaphragmatic LN enlargement, and the short diameter in the maximum cross section was ≥ 1 cm.

(3) Dynamic follow-up of imaging materials for at least two periods revealing a progressive increase in LN size.

Treatment procedure

All participants in the study signed the informed consent form before undergoing therapy. Approval for this study was granted by the institutional review board of the Ethics Committee of Zhongshan Hospital, Fudan University. Among the 72 patients, 32 patients received radiotherapy targeting the cardiophrenic angle or superior diaphragmatic LN (EBRT group). The remaining 40 patients did not undergo such radiotherapy (non-EBRT group). The patient characteristics are shown in Table 1.

The treatment plan comprised contrast-enhanced 4-dimensional computed tomography (CT); abdominal compression was performed to reduce respiratory liver motion[12,13]. Each patient was in the supine position. The delineation of volumes included: Gross tumor volume (GTV): enlarged LN and intrahepatic tumor; Internal target volume (ITV): the total GTVs of inhalation and exhalation; Clinical target volume (CTV): 3-5 mm external expansion of ITV of LNM without the surrounding lymph drainage area; Planning target volume (PTV): 3-5 mm external expansion of CTV. 95% of PTVs received the prescribed dose.

Efficacy and toxicity evaluation

The pretreatment evaluation included history collection, physical examination, routine blood tests, liver and kidney function, AFP, chest CT, abdominal enhanced CT, and/or enhanced magnetic resonance imaging (MRI). Toxicity was assessed using Radiation Therapy Oncology Group (RTOG) criteria[14]. All patients were monitored for acute toxicity each week during radiotherapy and within three months following the treatment. These evaluations comprised hematologic examinations and enhanced CT or MRI scans. Late toxicity was assessed from three months to one year post-radiotherapy, with reexaminations occurring every three months during this period. The LN response rates were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 guidelines[15,16]. Two radiation therapists compared radiography results before and after radiotherapy.

Complete remission (CR) of cardiophrenic angle or superior diaphragmatic LN was defined as the complete disappearance of metastatic evidence on the imaging examination. A partial response (PR) was defined as a reduction of ≥ 30% in the short diameter of the LNs compared to their diameter before treatment. Progressive disease (PD) was defined as an increase of ≥ 20% in the long or short diameters of the LNs compared to the optimal treatment response. Stable disease (SD) was defined as the LN response between PR and PD[16]. Local control rate was calculated as the number of patients with CR, PR, and SD divided by the total number of patients alive at the last imaging evaluation. Overall response rate was calculated as the number of patients with CR and PR divided by the total number of evaluable cases after LNM was diagnosed. AFP after radiotherapy referred to AFP levels measured within three months after the end of radiotherapy. An AFP decrease was defined as a change from a positive to negative value (≤ 20 μg/mL) or a decrease of ≥ 10%. An AFP increase referred to a value increase of ≥ 10%. A stable AFP level referred to an AFP value that fluctuated between an AFP decrease and an AFP increase. AFP levels consistently below 20 μg/mL were not considered increasing or decreasing. AFP was recorded before radiotherapy and within three months after radiotherapy in the EBRT group.

Statistical Analysis

SPSS 27.0 software (SPSS, Chicago, IL, USA) was used for all statistical analyses. Chi-square tests or Fisher's tests were employed to compare patients' characteristics, LN remission rates, and local control rates between the two groups. The Kaplan-Meier method and Cox regression models were utilized for the survival analysis and local control. For the multivariate analysis, backward stepwise regression (likelihood ratio) was applied. Factors with univariate P values < 0.01 were selected as input, and $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

The median time from the diagnosis of HCC to the appearance of cardiophrenic angle or superior diaphragmatic LNM in 72 patients was 12.2 months (from 0 to 154.3 months). All patients with cardiophrenic angle or superior diaphragmatic LNM had liver capsule invasion.

Patient characteristics

Diagnosis of intrahepatic tumors and cardiophrenic angle or superior diaphragmatic LNM were as follows:

(1) Diagnosis of intrahepatic tumors: Among the 72 patients, 41 were diagnosed based on pathology and 31 were diagnosed based on clinical findings. Of the 31 clinically diagnosed patients, 25 were diagnosed based on AFP levels ≥ 400 μg/L with one positive imaging result, and 6 were diagnosed based on AFP levels < 400 μg/L with two positive imaging results.

(2) Diagnosis of cardiophrenic angle or superior diaphragmatic LNM: One patient was diagnosed pathologically and 71 patients were diagnosed clinically, according to the criteria for cardiophrenic angle or superior diaphragmatic LNM mentioned above.

The median dose to the PTV in the EBRT group was 53.7 Gy (range, 42-68 Gy), administered at 1.84-8 Gy per day, 5 days per week. Ten (31.3%) patients received simultaneous radiotherapy for intrahepatic tumor and cardiophrenic angle or superior diaphragmatic LNs. Twelve (37.5%) patients received simultaneous radiotherapy for intrahepatic tumor and cardiophrenic angle or superior diaphragmatic LN and abdominal LN. Four (12.5%) patients received radiotherapy concurrently for both cardiophrenic angle or superior diaphragmatic and abdominal LNs. One (3.1%) patient received radiotherapy for both the cardiophrenic angle or superior diaphragmatic and mediastinal LNs. Five (15.6%) patients received radiotherapy for cardiophrenic angle or superior diaphragmatic LNs radiotherapy following intrahepatic tumor resection. Fifteen patients received conventional fraction EBRT and 17 patients received non-conventional fraction EBRT. The bioequivalent dose (BED10) in the EBRT group ranged from 50.4 to 96.0 Gy, with a median dose of 64.8 Gy.

Response of LNMs and intrahepatic tumors

The overall response rates of cardiophrenic angle or superior diaphragmatic LNMs in the EBRT and non-EBRT groups were 68.8% (22/32) and 7.5% (3/40), respectively ($P < 0.001$). Response of cardiophrenic angle or superior diaphragmatic LNMs in the EBRT group was as follows: 11 patients (34.4%) achieved CR, 11 patients (34.4%) had PR, 4 patients (12.5%) had SD, 1 patient (3.1%) experienced PD, and 5 patients (15.6%) did not have an imaging review after radiotherapy in the EBRT group.

Response of cardiophrenic angle or superior diaphragmatic LNMs in the non-EBRT group was as follows: 0 patients (0) achieved CR, 3 patients (7.5%) had PR, 13 patients (32.5%) had SD, 9 patients (22.5%) experienced PD, and 15 patients (37.5%) did not have an imaging review after diagnosis of LNM.

Response of intrahepatic tumors in EBRT group: (1) Three months after radiotherapy: 2 patients (6.3%) achieved CR, 2 patient (6.3%) had PR, 11 patients (34.4%) had SD, 5 patients (15.6%) experienced PD, 1 patient (3.1%) died, and 11 patients (34.4%) did not undergo an imaging review; (2) Six months after radiotherapy: 4 patients (12.5%) achieved CR, 2 patient (6.3%) had PR, 6 patients (18.8%) had SD, 8 patients (25.0%) experienced PD, 5 patient (15.6%) died, and 7 patients (21.9%) did not undergo an imaging review.

Survival analysis

Three patients in the EBRT group (32 patients) and one patient in the non-EBRT group (40 patients) were alive as of September 1st, 2023. The median follow-up time was 24.5 months (range: 3.5-158.3 months) since HCC was diagnosed in 72 patients. Median survival times in the EBRT group and non-EBRT group were 16.1 months (95%CI: 8.09-24.12) and 5.9 months (95%CI: 3.05-7.76), respectively, since LNM was diagnosed ($P < 0.001$, HR = 2.87) [Figure 3A]. The 1- and 2-year survival rates of the EBRT and non-EBRT groups were 65.6% and 22.5%, 36.1% and 5.6%, respectively. Median survival times of the EBRT and non-EBRT groups since the detection of LNs were 21.9 months (95%CI: 17.38-27.03) and 9.0 months (95%CI: 5.40-11.60), respectively, with a statistically significant difference ($P = 0.003$, HR = 2.08) [Figure 3B].

Median survival times in the type B LN group and the type non-B LN group were significantly different (9.2 months *vs.* 13.8 months, $P = 0.034$) [Figure 3C]. Median survival times in the type B LN group and the type C LN group were significantly different (9.2 months *vs.* 23.0 months, $P = 0.021$) [Figure 3D]. The OS was significantly prolonged with daily dose > 4 Gy ($P = 0.014$) or > 5 Gy ($P = 0.021$) [Figure 4].

Local control

The 0.5-, 1-, and 2-year local control rates of the EBRT and non-EBRT groups were 100% and 100%, 92.9% and 45.2%, 69.6% and 45.2%, respectively. The local control rates of the EBRT group and the non-EBRT group were statistically different ($P < 0.001$) [Figure 5]. The local control rates of the type B LN group and the type non-B LN group were statistically different ($P = 0.017$) [Figure 6A]. The local control rates between the type B LN group and the type C LN group were statistically different ($P = 0.041$) [Figure 6B].

Prognostic factors

The multivariate analysis suggested that tumor thrombosis, multiple intrahepatic tumors, a maximal intrahepatic tumor diameter ≥ 5 cm, abdominal LNM, and lack of EBRT were poor prognostic factors [Table 2]. Prognosis was independent of age, sex, hepatitis B surface antigen (HBsAg) status, liver function, extrahepatic metastasis, thoracic LNs, LN number, and systemic treatments received.

AFP

At the time of cardiophrenic angle or superior diaphragmatic LNM diagnosis, the number of patients with APF positive results (AFP ≥ 20 μg/L) in the EBRT group and non-EBRT group were 16 (50.0%) *vs.* 26 (65.0%), respectively. Four (12.5%) patients in the EBRT group had an AFP increase after radiotherapy, whereas 14 (35.0%) patients in the non-EBRT group had an AFP increase after the LNM diagnosis ($P = 0.028$). Eight (25.0%) patients in the EBRT group had an AFP decrease after radiotherapy, while 6 (15.0%) patients in the non-EBRT group had an AFP decrease after the diagnosis of cardiophrenic angle or superior diaphragmatic LNM ($P = 0.287$).

Side effects

Side effects experienced by patients in the EBRT group included gastrointestinal (GI) reactions, liver toxicity, and bone marrow suppression. The number of patients with grade 1, 2, and 3 GI reactions were 9 (28.1%), 3 (9.4%), and 4 (12.5%), respectively. The number of patients with grade 1 and 3 liver toxicity was 5 (15.6%) and 1 (3.1%), respectively. The number of patients with grade 1 and 2 bone marrow suppression was 6 (18.8%) and 7 (21.9%), respectively [Table 3].

When the BED10 dividing values were 60, 80 and 90, there was no statistical significance in GI reactions, liver toxicity and bone marrow suppression ($P > 0.05$). GI bleeding in patients with BED10 ≤ 70 and > 70 was 0% (0/22) and 30.0% (3/10), respectively ($P = 0.024$).

Table 2. Univariate and multivariate analyses (*n* = 72), related to survival in all patients

Independent variable	Patients (*n* = 72)	Kaplan-Meier survival				Univariate analysis		Multivariate analysis	
		1 year (%)	2 year (%)	Median (mo)	*P*	HR, 95%CI	*P*	HR, 95%CI	*P*
Age (years)					0.536				
< 60 years old	55	39.9%	16.0%	8.5		1			
≥ 60 years old	17	47.1%	29.4%	9.1		0.84 (0.48-1.47)	0.538		
Sex, *n* (%)					0.914				
Male	67	43.2%	19.3%	9.1		1			
Female	5	20.0%	20.0%	6.1		0.95 (0.35-2.63)	0.914		
HBsAg, *n* (%)					0.592				
Positive	62	41.9%	17.5%	8.9		1			
Negative	10	40.0%	30.0%	8.6		0.83 (0.41-1.67)	0.595		
Child-Pugh classification, *n* (%)					0.621				
A	63	39.6%	19.0%	8.6		1			
B	9	55.6%	22.2%	15.4		1.20 (0.59-2.44)	0.623		
Tumor thrombosis					0.000				
Positive	33	21.2%	6.1%	5.3		1		1	
Negative	39	59.0%	31.0%	14.8		0.38 (0.23-0.63)	0.000	0.48 (0.28-0.81)	0.007
Extrahepatic metastasis					0.048				
Positive	28	28.6%	8.3%	6.9		1			
Negative	44	49.9%	26.1%	11.8		0.61 (0.37-1.00)	0.052		
Intrahepatic lesions, *n* (%)					0.000				
None or solitary	33	57.4%	41.5%	21.6		1		1	
Multiple nodules (≥ 2)	39	28.2%	0.0%	7.0		4.08 (2.19-7.60)	0.000	2.68 (1.39-5.16)	0.003
Maximal diameter of intrahepatic tumors (cm), *n* (%)					0.000				
< 5	28	78.6%	37.4%	21.5		1		1	
≥ 5	44	18.2%	7.8%	6.5		3.08 (1.82-5.20)	0.000	2.18 (1.19-3.98)	0.011
Site of LN, *n* (%)									
Abdominal LN					0.008				
Yes	41	29.3%	10.6%	7.0		1		1	
No	31	58.1%	30.8%	16.0		0.52 (0.32-0.85)	0.009	0.48 (0.29-0.79)	0.004
Thoracic LN					0.308				
Yes	13	46.2%	20.5%	7.5		1			
No	59	40.6%	19.4%	8.9		0.72 (0.38-1.36)	0.312		
LN number					0.012				
Solitary	26	57.7%	30.8%	17.9		1			
Multiple (≥ 2)	46	32.6%	12.7%	7.1		1.89 (1.14-3.14)	0.014		
Radiotherapy					0.000				
Yes	32	65.6%	36.1%	16.1		1		1	
No	40	22.5%	5.6%	5.9		2.87 (1.72-4.77)	0.000	2.06 (1.15-3.66)	0.015

System treatment					0.009		
Yes	19	57.9%	38.6%	14.8		1	
No	53	35.8%	13.2%	7.1		2.15 (1.20-3.88)	0.010
AFP status (μg/L), *n* (%)					0.015		
< 400	39	53.8%	25.6%	15.3		1	
≥ 400	33	26.9%	11.8%	7.0		1.83 (1.12-3.00)	0.017

RR: Relative ratio; HbsAg: hepatitis B surface antigen; LN: lymph node; AFP: alpha-fetoprotein.

Table 3. Side effects of the EBRT group

Side effects	Patients (*n* = 32)	RTOG classification			
		1	2	3	4
Gastrointestinal reactions	32				
Anorexia		9 (28.1%)	2 (6.3%)	0 (0.0%)	0 (0.0%)
Nausea/Vomit		0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)
Abdominal distension		2 (6.3%)	1 (3.1%)	0 (0.0%)	0 (0.0%)
Gastrointestinal ulcer		0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)
Gastrointestinal bleeding		0 (0.0%)	0 (0.0%)	3 (9.4%)	0 (0.0%)
Liver toxicity	32				
Elevated total bilirubin		1 (3.1%)	0 (0.0%)	0 (0.0%)	1(3.1%)
ALT		3 (9.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AST		3 (9.4%)	0 (0.0%)	1 (3.1%)	0 (0.0%)
ALP		3 (9.4%)	0 (0.0%)	1 (3.1%)	0 (0.0%)
Bone marrow suppression	32				
HB		2 (6.3%)	2 (6.3%)	0 (0.0%)	0 (0.0%)
WBC		6 (18.8%)	3 (9.4%)	0 (0.0%)	0 (0.0%)
PLT		4 (13.3%)	2 (6.3%)	0 (0.0%)	0 (0.0%)

ALT: Alanine transaminase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; HB: hemoglobin; PLT: platelets; WBC: white blood cell; RTOG: radiation therapy oncology group.

Causes of death

There were 29 deaths in the EBRT group and 39 deaths in the non-EBRT group by the end of the follow-up period. The differences in causes of death between the two groups were not statistically significant ($P > 0.05$) [Table 4]. No patient died of cardiophrenic angle or superior diaphragmatic LNM.

DISCUSSION

The liver capsule was invaded by the primary tumor before cardiophrenic angle or superior diaphragmatic LNM was clinically diagnosed in the 72 patients in our study. This characteristic helped us distinguish intrahepatic lesions growing toward the surface of the liver from LNM below the liver capsule. Cardiophrenic angle or superior diaphragmatic LNM is rarely seen in patients with HCC. Therefore, clinical data-based reports on the diagnosis and treatment of cardiophrenic angle or superior diaphragmatic LNM from HCC are limited. EBRT is an effective treatment for patients with HCC with abdominal LNM[17]. However, it is unclear whether radiotherapy has a survival benefit for patients with cardiophrenic angle or superior diaphragmatic LNM.

There are no critical organs around the cardiophrenic angle or superior diaphragmatic LNs, so LN involvement in this area is not fatal. This study found that the OS of patients in the EBRT group was longer

Table 4. Causes of death

Cause	EBRT group (*n* = 29)	Non-EBRT group (*n* = 39)	*P*
Uncontrolled intrahepatic tumor	21 (72.4%)	35 (89.7%)	0.064
Abdominal LNM	1 (3.4%)	1 (2.6%)	1.000
Extrahepatic metastasis	5 (17.2%)	1 (2.6%)	0.093
Non-tumor-related	2 (6.9%)	0 (0.0%)	0.178
Unknown	0 (0.0%)	2 (5.1%)	0.504

EBRT: External beam radiation therapy; LNM: lymph node metastasis.

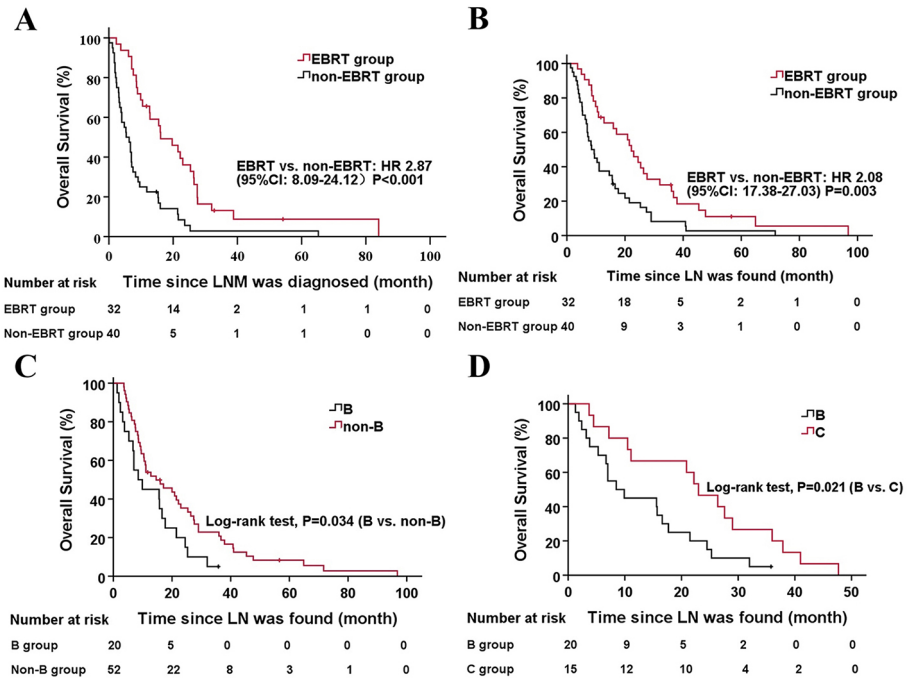

Figure 3. Overall survival. Comparison of overall survival between the EBRT group and the non-EBRT group. (A) Time since LNM was diagnosed (month); (B) Time since LN was found (month); (C) Type B *vs.* type non-B; (D) Type B *vs.* type C. Type B: Right middle cardiophrenic angle LN; Type non-B: right superior diaphragmatic LN, right pericardium cardiophrenic angle LN, right posterior cardiophrenic angle LN, left anterior cardiophrenic angle LN, and left posterior cardiophrenic angle LN; Type C: right pericardium cardiophrenic angle LN; LN: lymph node; LNM: lymph node metastasis; EBRT: external beam radiation therapy.

than that in the non-EBRT group. However, it was difficult to determine whether the survival benefit from radiotherapy was due to its effects on the intrahepatic lesions or on the LNM. In general, EBRT was beneficial, and LNs should be included in the radiation field as much as possible when EBRT is performed on intrahepatic lesions. The difference between the two groups in terms of cause of death was not significant. However, the incidence of uncontrolled intrahepatic tumors was higher in the non-EBRT group. The results of one study suggested that poor control of intrahepatic lesions led to a poor prognosis and that EBRT could improve tumor control rate and reduce mortality[18]. Once portal vein tumor thrombosis (PVTT) is present in patients with liver cancer, the disease progresses rapidly, leading to intrahepatic and extrahepatic metastasis, portal hypertension, jaundice, and ascites in a short period of time. The median survival time is only 2.7 months[19,20].

There was no consensus regarding radiotherapy for cardiophrenic angle or superior diaphragmatic LNM. However, many studies have demonstrated the benefits of radiotherapy for abdominal LNM from HCC[21].

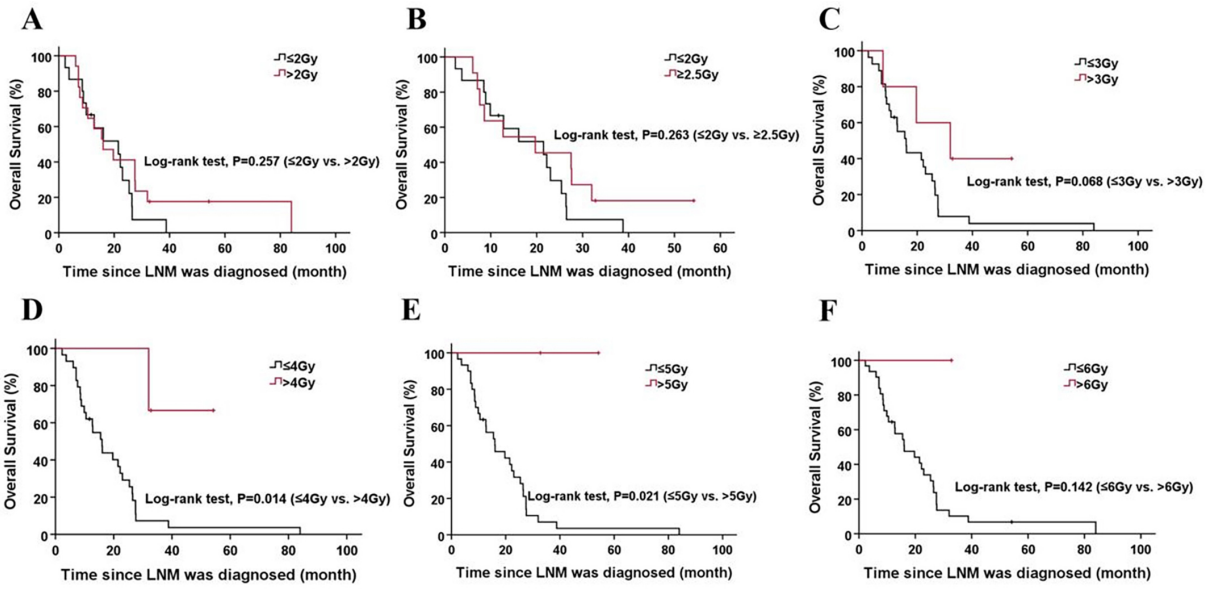

Figure 4. Overall survival outcomes for different fractionated doses in the EBRT group. (A) ≤ 2 Gy *vs.* > 2 Gy; (B) ≤ 2 Gy *vs.* ≥ 2.5 Gy; (C) ≤ 3 Gy *vs.* > 3 Gy; (D) ≤ 4 Gy *vs.* > 4 Gy; (E) ≤ 5 Gy *vs.* > 5 Gy; (D) ≤ 6 Gy *vs.* > 6 Gy. EBRT: External beam radiation therapy; LNM: lymph node metastasis.

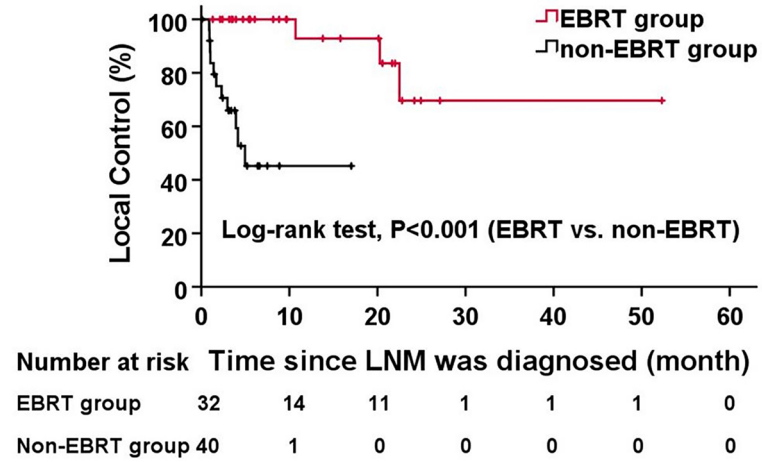

Figure 5. Local control. Comparison of local control between the EBRT group and the non-EBRT group. EBRT: External beam radiation therapy; LNM: lymph node metastasis.

Radiotherapy for LNM provides excellent local control and minimal toxicity when the radiation dose is ≤ 54 Gy[3]. It is reported that image-guided intensity-modulated radiation therapy (RT) is more effective in HCC patients with abdominal LNM, resulting in better short-term survival and local control[12]. Median survival in the EBRT group was 16.1 months since LNM was diagnosed and 21.9 months since LN was found. Thanks to the use of hypofractionated radiotherapy (HFRT) and the fact that cardiophrenic angle or superior diaphragmatic LNM is rarely fatal, median survival in our study was longer than that in previous reports[3]. External irradiation can relieve symptoms caused by tumors and may prolong survival[2]. The poor OS and local control of type B LN may be related to the lymph node's location at the junction of lymphatic drainage.

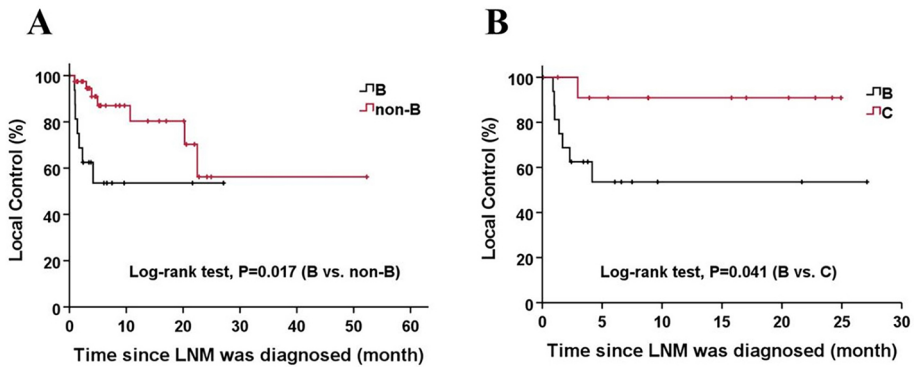

Figure 6. Local control. (A) Type B *vs.* type non-B; (B) Type B *vs.* type C.

Kim found that Child-Pugh classification, intrahepatic tumor status, presence of distant metastases, number and location of metastatic LNs, AFP serum levels, and the LN response to RT were significant prognostic factors for OS ($P < 0.05$)[22]. Therefore, patients with HCC with cardiophrenic angle or superior diaphragmatic LNM may benefit from radiotherapy. Both intrahepatic tumors and cardiophrenic angle or superior diaphragmatic LNM could be included in the target area.

A retrospective cohort study found an improvement in survival benefit from radiotherapy applied to treat an intrahepatic primary tumor or abdominal LNM[17,23,24]. Although this study did not reveal a direct relationship between the cardiophrenic angle or superior diaphragmatic LNM radiotherapy and the survival benefit, we still observed prolonged median survival. Further studies are expected to be performed with more patients.

Many studies have found that AFP is a prognostic factor for HCC[25-27]. This study found differences in AFP increases between the two groups. The proportion of patients with an AFP increase in the EBRT group was lower than in the non-EBRT group. These results indicate that radiotherapy had palliative effects.

Previous studies have revealed that the dose of radiotherapy for LNM from HCC ranges from 30 to 60 Gy (with fractionated dose of 1.8-9 Gy), which provides good local control for LNs[23,28]. When LN control reached CR or PR in our study, the median total radiation dose was 53.7 Gy (range, 45-62.5 Gy), with fractionated dose of 1.84-8 Gy and BED10 values of 58.5-96 Gy. Meanwhile, when LNs were controlled for at least 1 year, the median total radiation dose was 52 Gy (range, 45-60 Gy), with fractionated dose of 2 to 8 Gy and BED10 values of 58.5-96 Gy. This radiotherapy dose is also effective in LN control. HFRT is used for small HCC, recurrent HCC, and portal vein tumor thrombus (PVTT). Tsurugai *et al.* retrospectively extracted patients who were beyond the indication for stereotactic body radiation therapy (SBRT) due to exceeding GI constraints and treated them with HFRT at a prescribed dose of 42 Gy in 14 fractions, along with prophylactic proton pump inhibitors (PPIs) for 6 months[29]. It was found that HFRT could achieve good local control in patients with HCC adjacent to the GI tract, with a low incidence of GI toxicity. Among 66 patients, two developed grade 2 GI bleeding and one developed grade 3 GI bleeding. Image-guided techniques have made HFRT more accurate, reducing the frequency of radiotherapy and improving survival rates.

The GI tract is closely situated near the abdominal LNs. In our study, three patients experiencing GI bleeding did not take targeted drugs during radiotherapy, while two patients had a history of GI bleeding before radiotherapy. It was suggested that continuous treatment with PPIs for at least 6 months reduced

toxicity. Sucralfate and propranolol have shown efficacy in preventing GI bleeding[29]. According to Timmerman, the dose constraint of the GI tract varied depending on the fractionated dose[30].

In our center, patients undergoing radiotherapy were advised to use PPIs, mucosal protectants, and probiotics as prophylactic measures. Antiemetics were effective in managing nausea and vomiting. Enteral nutrition could be used if dysphagia occurred. Abdominal distension could be relieved by reducing the intake of gas-producing foods. Probiotics, with or without montmorillonite powder or loperamide hydrochloride capsules, were used in cases of diarrhea. Fasting, acid suppression, blood transfusion, and nutritional support were implemented for GI ulcer and bleeding. Abnormal liver function could be managed with hepatoprotective, anti-jaundice, and antioxidant drugs. Soft food was recommended during radiotherapy. Recombinant human granulocyte-colony stimulating factor was administered for leucopenia, and recombinant human interleukin-11 was utilized for treating thrombocytopenia.

There were several limitations in our study. Firstly, as a retrospective study, there were missing data points. Secondly, consensus was lacking on diagnostic criteria for cardiophrenic angle or superior diaphragmatic LNM. Thirdly, the sample size was small, and prospective data were unavailable. Lastly, it was difficult to distinguish whether the observed survival benefit was associated with intrahepatic tumor radiotherapy.

In conclusion, EBRT was a safe and effective treatment for HCC patients with cardiophrenic angle or superior diaphragmatic LNM and might prolong OS. Dose > 4 Gy per day and BED10 ≤ 70 would be recommended for LNM. Patients with tumor thrombosis, multiple intrahepatic tumors, a maximal intrahepatic tumor diameter ≥ 5 cm, abdominal LNM, and lack of EBRT had a poor prognosis.

DECLARATIONS

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Authors' contributions

Methodology, writing - original draft, investigation: Ye T
Supervision, conceptualization, methodology, writing - review and editing: Zeng Z
Writing - review and editing: Sun J
Resources, methodology: Du S, Chen Y
Methodology: Wu Z, Zhang X, Zhao Q, Wu Q, Zhang B
Resources: Yang P, Zhang J
Resources, data curation: Hu Y

Availability of data and materials

The data supporting the findings of our study are available from the corresponding author upon reasonable request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethics approval and consent to participate

We confirm that all methods were carried out in accordance with relevant guidelines and regulations. This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (2011-235).

Consent for publication

All patients signed informed consent forms before recruitment.

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