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RESEARCH

Efficacy of radiotherapy combined with targeted therapy and immunotherapy for lymph node metastasis of liver cancer

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Abstract

Purpose To investigate the efficacy and safety of radiotherapy combined with targeted therapy and immunotherapy for liver cancer with lymph node metastasis (LNM).

Methods We analysed patients who received radiotherapy for liver cancer with LNM in our hospital from June 2020 to June 2023. 62 patients were enrolled in this study, who received radiotherapy with a median radiation dose of 60.0 Gy, combined with targeted therapy and/or immunotherapy. The objective response rate (ORR), overall survival (OS), progression free survival (PFS), and adverse events were observed to evaluate treatment efficacy and safety.

Results With a median follow-up of 18.5 months, the best ORR was 90.3%. The median OS was 26.0 months. The 1-year and 2-year OS rates were 78.93% and 57.37%, respectively. The median PFS was 17.0 months, and the 1-year and 2-year PFS rates were 59.06% and 49.22%, respectively. Multivariate analysis showed that alanine aminotransferase (HR = 2.34, 95% CI 1.07–5.11, $P = 0.033$), prothrombin time (HR = 4.51, 95% CI 1.76–11.57, $P = 0.002$), alpha fetal protein (HR = 2.94, 95% CI 1.34–6.45, $P = 0.007$), and the volume of LNM (HR = 3.05, 95% CI 1.25–7.46, $P = 0.014$) were independent predictors for OS, while non-regional LNM (HR = 3.19, 95% CI 1.24–8.16, $P = 0.016$) was an independent predictor for PFS. Toxicity was generally mild and moderate.

Conclusions Radiotherapy combined with targeted therapy and immunotherapy is an effective treatment option, and expected to become new treatment strategy for liver cancer with LNM.

Keywords Lymph node metastasis · Primary liver cancer · Radiotherapy · Targeted therapy · Immunotherapy

Abbreviations

LNM	Lymph node metastasis
LN	Lymph nodes
HCC	Hepatocellular carcinoma
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
PT	Prothrombin time
AFP	Alpha fetal protein
CA 19-9	Carbohydrate antigen 19-9
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
OAR	Organs at risk
BED	Biologically effective dose
ICI	Immune checkpoint inhibitor
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
LCR	Local control rate
CR	Complete remission
PR	Partial remission
SD	Stable disease

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AE Adverse events
TRAE Treatment-related adverse events

Introduction

Primary liver cancer is a high-incidence malignancy that poses a serious threat to human health (Bray et al. 2024). In China, liver cancer is particularly prevalent, with the number of cases constituting approximately half of the global incidence (National Health Commission of the People's Republic of China 2022). Due to its insidious onset, only about 20% of newly diagnosed liver cancer patients are eligible for radical treatment such as surgery or ablation. Over 80% of patients are diagnosed at an advanced stage, missing the opportunity for a cure. Lymph node metastasis (LNM) occur in approximately half of hepatocellular carcinoma (HCC) patients with extrahepatic metastases (Xia et al. 2014), and autopsy results reveal that the incidence of LNM in advanced liver cancer can be as high as 26%−37% (Uchino et al. 2011; Yang et al. 2019). Current treatment options for advanced liver cancer include systemic therapy, interventional therapy, and radiotherapy. Despite these options, the prognosis remains poor, with a one-year survival rate of less than 50% and a median survival time of only 3 months post-diagnosis. Thus, identifying new treatment approaches is crucial for improving outcomes in advanced liver cancer.

Systemic therapy for advanced liver cancer includes anti-angiogenic targeted therapy, immune checkpoint inhibitor (ICI), chemotherapy, traditional Chinese medicine. These treatments can achieve an objective response rate (ORR) of around 30% and extend median survival time to approximately 20 months. However, the efficacy of monotherapy with immunotherapy or targeted therapy is relatively low. Basic medical research suggests that immunotherapy and anti-angiogenic drugs can work synergistically to alter the tumor microenvironment from immunosuppressive to immune-enhancing. Consequently, the combination of anti-angiogenic targeted therapy and ICI has become a mainstream treatment for advanced liver cancer (Finn et al. 2020a, 2020b; Xu et al. 2019). With advancements in radiotherapy technology, its effectiveness in treating liver cancer has improved. Recently, radiotherapy has emerged as a significant treatment modality for advanced liver cancer (Robbins et al. 2019; Lazarev et al. 2018). Reports on the efficacy of radiotherapy for liver cancer with LNM indicate that it can alleviate symptoms such as pain, obstruction, compression, or bleeding, and control tumor progression, thus improving quality of life (Zhang et al. 2019; Matoba et al. 2020). Studies have shown that combining radiotherapy with targeted therapy or immunotherapy has a synergistic effect (Chiang et al. 2019), although there are relatively few studies on the combined use of radiotherapy, targeted therapy, and immunotherapy for advanced liver cancer.

This study aims to analyze the efficacy and safety of combining radiotherapy with targeted therapy and immunotherapy for advanced liver cancer with LNM, providing a clinical basis for this combined treatment approach.

Materials and methods

Patients

Patients with LNM of advanced liver cancer treated at our hospital from June 2020 to June 2023 were collected. Inclusion criteria: (1) Age ≥ 18 years old. (2) Primary liver cancer diagnosed clinically or pathologically according to the Primary Liver Cancer Diagnosis and Treatment Guidelines of China National Health Commission (National Health Commission of the People's Republic of China 2022). (3) LNM was pathologically proven or clinically detected by the following radiological findings: short axis diameter of contrast-enhanced lymph node ≥ 1 cm; or lymph node capsule invasion; or clustered lymph nodes fused with each other on MRI and/or CT. (4) Completed radiotherapy, targeted therapy and/or immunotherapy used concurrently or sequentially with an interval of no more than 3 months. Treatment plan was determined by senior physicians based on factors such as the status of intrahepatic tumors, LNM, baseline liver function, etc. Exclusion criteria: (1) History of previous radiotherapy at the same site. (2) Interventional or ablative treatments performed at the site of LNM. (3) Incomplete follow-up data. Initially, 79 patients with LNM of liver cancer were identified as potential candidates. Seventeen patients did not meet the inclusion or exclusion criteria, leaving 62 patients in the study.

All patients underwent comprehensive pre-treatment examinations. Within one week before treatment, patients should complete medical history collection, physical examination, performance status score, Child–Pugh score, laboratory tests. Imaging exams (including abdominal enhanced MRI, chest enhanced CT, whole-body bone SPECT, skull MRI, or PET-CT) should be conducted within one month before treatment to confirm the diagnosis of liver cancer with LNM.

Radiotherapy

All patients underwent enhanced CT simulation (Siemens, Germany) with a slice thickness of 5 mm. The gross tumor volume (GTV) was defined on enhanced CT as the visible LNM. The clinical target volume (CTV) was formed by expanding the GTV outward of 2–5 mm (National Health Commission of the People's Republic of China 2022; Yan

et al. 2024), and adjusted according to the position of surrounding organs at risk (OAR). Generally, irradiation of the lymphatic drainage area was not performed. The planning target volume (PTV) was expanded outward by 5–10 mm from the CTV. The prescribed radiation dose ranged from 52 to 66 Gy, delivered in 20–33 fractions, depending on OAR tolerance. At least 95% of the PTV received the prescribed dose, with dose uniformity of 95–110%. The OARs included liver, kidneys, stomach, small intestine, colon, rectum, bladder, esophagus, lungs, heart, spinal cord, etc. Dose constraints for OARs were refer to the Primary Liver Cancer Diagnosis and Treatment Guidelines of China (National Health Commission of the People's Republic of China 2022).

The radiotherapy plan was confirmed jointly by physicist and physician before implementation, which was carried out after verification. Intensity modulated radiotherapy as delivered using a linear accelerator (Elekta, Sweden), once daily, five times per week. Image-guided radiotherapy was performed at least once a week by a cone-beam computed tomography device (Elekta, Sweden), with treatment errors kept within 5 mm.

Drugs

Targeted therapy or immunotherapy were administered before and/or after radiotherapy up to 2 years or intolerable adverse events (AE) or disease progression. For those patients with disease progression, systemic therapy was adjusted according to oncologists' recommendations and patient preferences. Targeted therapies used included bevacizumab, lenvatinib, sorafenib, apatinib and regorafenib; ICIs included atezolizumab, pembrolizumab, camrelizumab, sintilimab, tislelizumab; which were used according to the drug instruction.

Follow up

Physical examination was performed weekly during radiotherapy and systemic therapy, with dynamic monitoring of symptoms, signs, and treatment-related adverse event (TRAE). Blood routine, liver and kidney function, and coagulation function were conducted weekly, tumor markers were checked every one or two weeks, and subsequently every 3 months. One month after radiotherapy, enhanced CT or MR scan was performed to evaluate the tumor response. Subsequently, efficacy and TRAE were assessed every 3 months. Overall survival (OS) was calculated from the first day of treatment to the date of the last follow-up or death. The last follow-up data of surviving patients, death data of deceased patients, or the last available data before loss to follow-up were considered as endpoint data.

Assessments

Treatment response of LNM was defined as the best tumor response observed during follow-up. Efficacy assessments followed the modified Response Evaluation Criteria in Solid Tumors version 1.1. Results were independently interpreted by two independent researchers, with disagreements resolved through discussion. Response evaluation was confirmed 4 weeks after the initial assessment. The ORR was defined as the proportion of patients achieving complete remission (CR) and partial remission (PR) among all enrolled patients after treatment. The local control rate (LCR) referred to the percentage of patients with CR, PR, and stable disease (SD) among all patients. Progression free survival (PFS) was defined as the time from the date of first treatment to the first evidence of definitive disease progression. OS was defined as the time from the date of first treatment to the last follow-up or death. Infield progression free survival (infield-PFS) referred to the time from the start of radiotherapy for LNM to the appearance of progressive disease or new lesions in the irradiated field, or death, with the first event being counted. TRAE were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Data cutoff date was March 31, 2024. Continuous variables were described using median and range, while categorical variables were described using frequencies (percentages) and analyzed using the χ^2 test. Survival curves were estimated using the Kaplan–Meier method and compared statistically using the log-rank test. Multivariate Cox proportional hazards analyses were performed to identify factors associated with OS and PFS. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 25.0 statistical analysis software.

Results

Patient characteristics

Baseline clinical characteristics of 62 patients were summarized in Table 1. The whole cohort included 57 (91.9%) males and 5 (8.1%) females, with a median age of 55 (range 29–79) years. One (1.6%) patient had a history of parasitic infection, 9 (14.5%) patients had a history of alcohol consumption, and 10 (17.7%) patients had a family history of tumors. The median GTV was 61.1 (range 3.6–474.7) cc. The median radiation dose was 60.0 (range 52.0–66.0) Gy, and the median biologically effective dose (BED) was 72.0 (range 62.4–79.2) Gy. All patients received radiotherapy,

Table 1 Clinical characteristics of patients with LNM in liver cancer

Characteristics	n (%)
Sex	
Male	57 (91.9%)
Female	5 (8.1%)
Age (years)	53.77 ± 10.46
HBsAg (IU/mL)	
Negative	3 (4.8%)
Positive	59 (95.2%)
HBV DNA (IU/mL)	
< 100	45 (72.6%)
≥ 100	17 (27.4%)
Cirrhosis	
Absent	18 (29.0%)
Present	44 (71.0%)
Ascites	
Absent	53 (85.5%)
Present	9 (14.5%)
Hepatic encephalopathy	
Absent	59 (95.2%)
Present	3 (4.8%)
Child–Pugh Score	
5	39 (62.9%)
6	13 (21.0%)
7	6 (9.7%)
8	4 (6.5%)
ALT (U/L)	
≤ 35	41 (66.1%)
> 35	21 (33.9%)
ALP(U/L)	
≤ 125	45 (72.6%)
> 125	17 (27.4%)
PT (s)	
≤ 14.5	52 (83.9%)
> 14.5	10 (16.1%)
AFP (ng/ml)	
≤ 400	44 (71.0%)
> 400	18 (29.0%)
CA19-9 (U/ml)	
≤ 35	51 (82.3%)
> 35	11 (17.7%)
GTV (cc)	
≤ 60	31 (50.0%)
> 60	31 (50.0%)
Number of LNM	
Single	12 (19.4%)
Multiple	50 (80.6%)
Location of LNM	
Regional	40 (64.5%)
Non regional	22 (35.5%)
TNM stage	
Any T, N1, M0	43 (69.4%)
Any T, any N, M1	19 (30.6%)
Pathologic type	
HCC	49 (79.1%)
Non HCC	13 (21.0%)
Systemic treatment	
Targeted therapy + Immunotherapy	50 (80.6%)
Targeted therapy	9 (14.5%)
Immunotherapy	1 (1.6%)
Absent	2 (3.2%)

LNM lymph node metastasis; *HBV* hepatitis B virus; *ALT* serum alanine aminotransferase level; *ALP* serum alkaline phosphatase level; *PT* prothrombin time; *AFP* alpha fetal protein; *CA 19–9* carbohydrate antigen 19–9; *GTV* gross tumor volum; *HCC* hepatocellular carcinoma

among which, 1.6% (1/62) received immunotherapy, 14.5% (9/62) received targeted therapy, and 80.6% (50/62) received a combination of targeted therapy and immunotherapy.

According to the NCCN Guidelines for Hepatobiliary Cancers (Benson et al. 2021), LNM of liver cancer were classified into regional and non-regional metastases. Regional LNM were defined as those originating from adjacent organs, including lymph nodes in the hepatic hilum, porta hepatis, and peritoneal cavity, while non-regional metastases originated from distant sites. In this study, 64.5% (40/62) of patients had regional LNM, while 35.5% (22/62) had non-regional LNM. We calculated the distribution of LNM in liver cancer (Fig. 1), and found that the most common site of LNM was the common hepatic artery lymph node (LN) (74.2%), followed by abdominal para-aortic LN (72.6%). Other sites of LNM were cardio-phrenic LN (25.8%), posterior pancreatic head LN (16.1%), hepatoduodenal ligament LN (14.5%), etc.

Tumor response and survival analyses

With a median follow-up time of 18.5 (range 10–45) months, CR, PR, and SD were achieved in 19 (30.6%), 37 (59.7%), and 4 (6.5%) patients, respectively. For the entire cohort, the ORR was 90.3% (56/62) and the LCR was 96.8% (60/62). Figure 2 showed a liver cancer patient with LNM near the abdominal aorta, achieving significant LNM shrinkage after radiotherapy combined with targeted therapy and immunotherapy.

The median OS was 26.0 (95% CI 10.7–41.3) months, and the median PFS was 17.0 (95% CI 4.4–29.6) months, while the median infield-PFS was not reached, as shown in Fig. 3. The 1-year, 2-year, and 3-year OS rates were 78.93%, 57.37%, and 49.12%, respectively. The 1-year, 2-year, and 3-year PFS rates were 59.06%, 49.22%, and 39.37%,

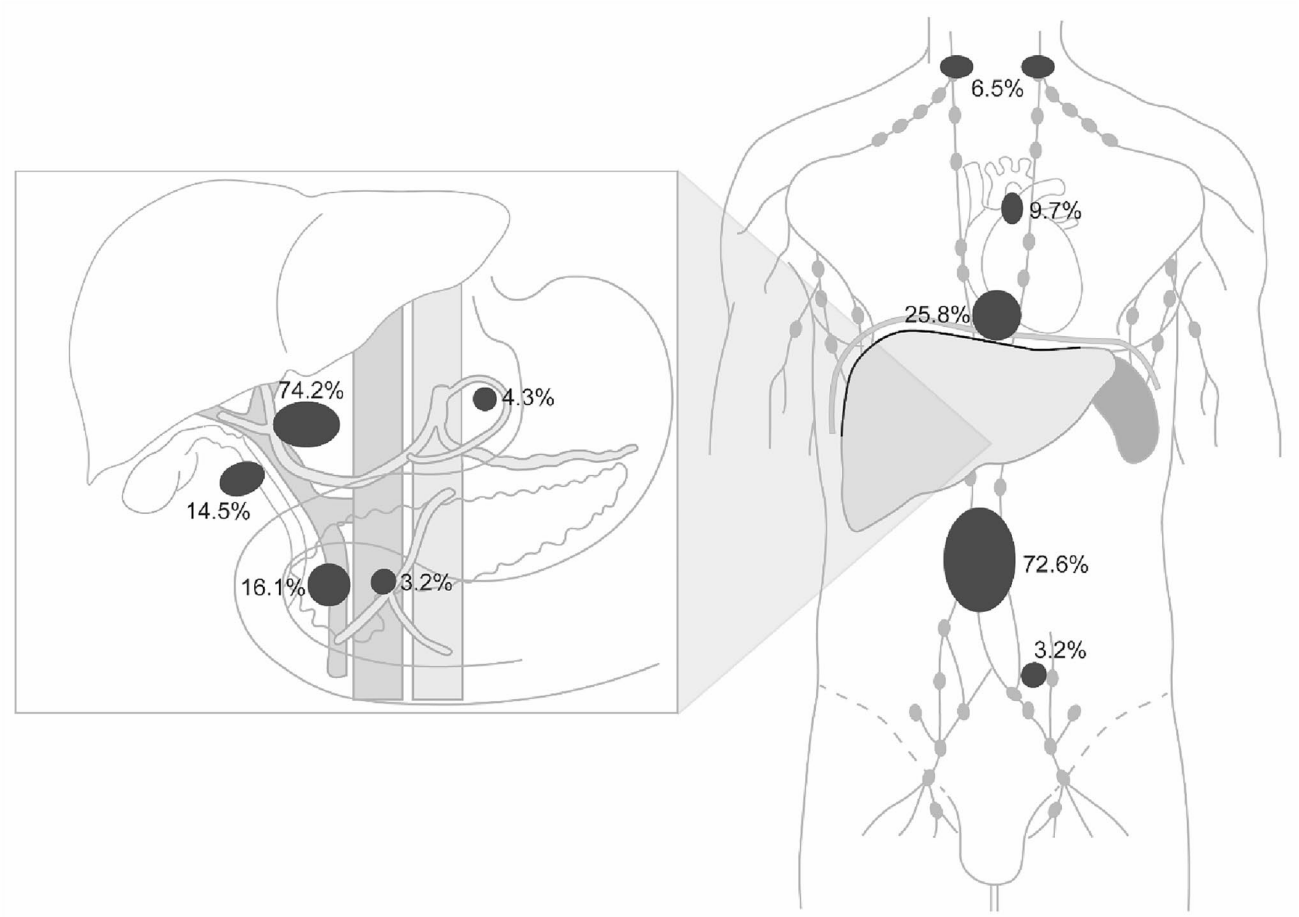

Fig. 1 Groups stratified based on the location of lymph node metastasis in liver cancer

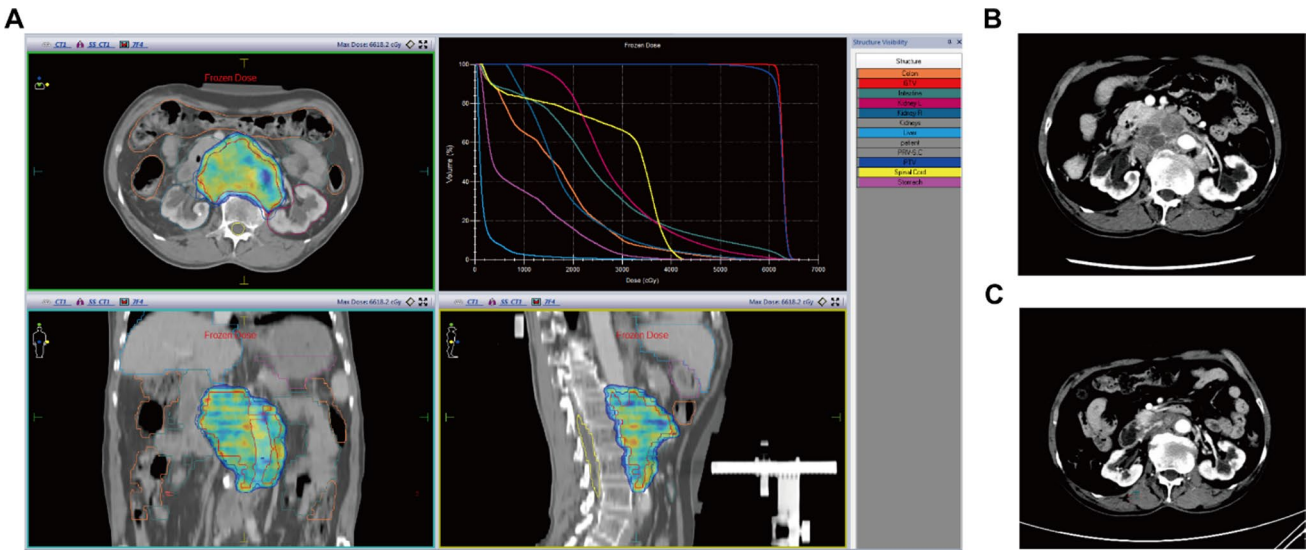

Fig. 2 CT scan (arterial phase) for a 53 years old man with right lobe hepatocellular carcinoma and paraaortic lymph node metastasis before and after radiotherapy. **A** intensity modulated radiotherapy plan and dose-volume histogram, **B** before radiotherapy, **C** one month after radiotherapy

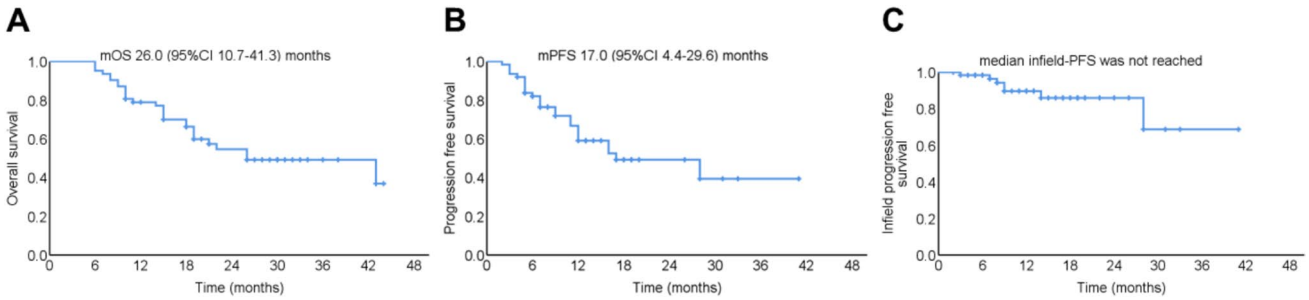

Fig. 3 Kaplan–Meier curves show **A** overall survival, **B** progression free survival, and **C** infield progression free survival for all patient cohort

respectively. The 1-year, 2-year, and 3-year infield-PFS were 89.65%, 85.92%, and 68.73%, respectively.

Prognostic factors of OS

Differences in survival data between subgroups were compared using the log-rank test. It was shown (Fig. 4 A-C) that the median OS significantly longer for patients with smaller GTV [median OS not reached vs. 15.0 (95% CI 10.9–19.1) months; $P=0.003$], single LNM [median OS not reached vs. 22.0 (95% CI 15.8–28.2) months; $P=0.031$], regional LNM [43.0 months, 95% CI not applicable vs. 18.0 (95% CI 9.0–27.0) months; $P=0.010$]. It was shown (Fig. 4D–H) that the median OS significantly longer for patients with low alpha fetal protein (AFP) level [median OS not reached vs. 18.0 (95% CI 12.0–24.0) months; $P=0.003$], normal alanine aminotransferase (ALT) level [43.0 months, 95% CI not applicable vs. 15.0 (95% CI 10.0–20.0) months; $P=0.012$], normal prothrombin time (PT) [43.0 (95% CI 10.8–75.2) months vs. 10.0 (95% CI 6.9–13.1) months; $P=0.001$], without hepatic encephalopathy [43.0 (95% CI 15.4–70.6) months vs. 9.0 (95% CI 4.2–13.8) months; $P<0.001$], and Child–Pugh A [43.0 (95% CI 15.8–70.2) months vs. 10.0 (95% CI 9.1–10.9) months; $P<0.001$].

Factors such as sex ($P=0.444$), age ($P=0.183$), HBV DNA copies ($P=0.088$), parasitic infection ($P=0.391$), drinking ($P=0.486$), smoking ($P=0.081$), family history of tumors ($P=0.314$), liver cirrhosis ($P=0.086$), ascites ($P=0.535$), tumor TNM stage ($P=0.718$), pathological type ($P=0.105$), histological grade ($P=0.918$), platelet count ($P=0.251$), aspartate aminotransferase (AST) ($P=0.577$), alkaline phosphatase (ALP) ($P=0.081$), albumin ($P=0.605$), total bilirubin ($P=0.605$), carcinoembryonic antigen ($P=0.739$), carbohydrate antigen 19–9 (CA 19–9) ($P=0.741$), and BED ($P=0.642$)did not show statistically significant differences in OS among subgroups.

For multivariate analysis, variables in univariate analysis with $P<0.05$ were enrolled in the Cox proportional hazards analyses ($\chi^2=45.76$, $P<0.001$). It was confirmed that GTV (HR = 4.22, 95% CI 1.61–11.06, $P=0.003$), ALT (HR = 3.42, 95% CI 1.47–7.97, $P=0.004$), PT (HR = 2.67, 95% CI 1.13–6.27, $P=0.025$), and Child–Pugh (HR = 5.28, 95% CI 1.59–17.53, $P=0.007$) were independent predictors for OS (Table 2).

Prognostic factors of PFS

It was shown (Fig. 5 A-C) that the median PFS significantly longer for patients with single LNM [median PFS not reached vs. 16.0 (95% CI 11.2–20.8) months; $P=0.015$], regional LNM [median PFS not reached vs. 7.0 (95% CI 4.6–9.4) months; $P<0.001$], without distant metastasis (M0) [28.0 months, 95% CI not applicable vs. 7.0 (95% CI 5.8–8.2) months; $P=0.002$], and normal CA 19–9 level [median PFS not reached vs. 12.0 (95% CI 4.6–19.4) months; $P=0.047$]. Patients achieving CR and PR have significantly longer median progression free survival (PFS) than those achieving SD and PD [28.0 (95% CI 9.0–47.0) months vs. 4.0 (95% CI 0–16.5) months; $P=0.049$] (Fig. 5 D).

There were no statistically significant differences in PFS among subgroups of GTV ($P=0.184$) and BED ($P=0.369$). No statistically significant were found between other clinical characteristics subgroups, such as sex, age, AFP, ALT, PT, hepatic encephalopathy, Child–Pugh score, and so on.

For multivariate analysis, variables in univariate analysis with $P<0.05$ were enrolled in the Cox proportional hazards analyses ($\chi^2=31.81$, $P<0.001$). It was found that non-regional LNM (HR = 3.54, 95% CI 1.32–9.49, $P=0.012$), M1 (HR = 2.75, 95% CI 1.07–7.02, $P=0.035$), and tumor response of SD and PD (HR = 3.60, 95% CI 1.11–11.73, $P=0.033$) were independent predictors for PFS (Table 2).

Toxicity

Toxicities commonly occurred but patients tolerated the treatment well. TRAE occurring during and after treatment were listed in Table 3, recorded according to the most severe TRAE. The main TRAE was hematologic toxicity, manifested as neutropenia, lymphocytopenia, thrombocytopenia,

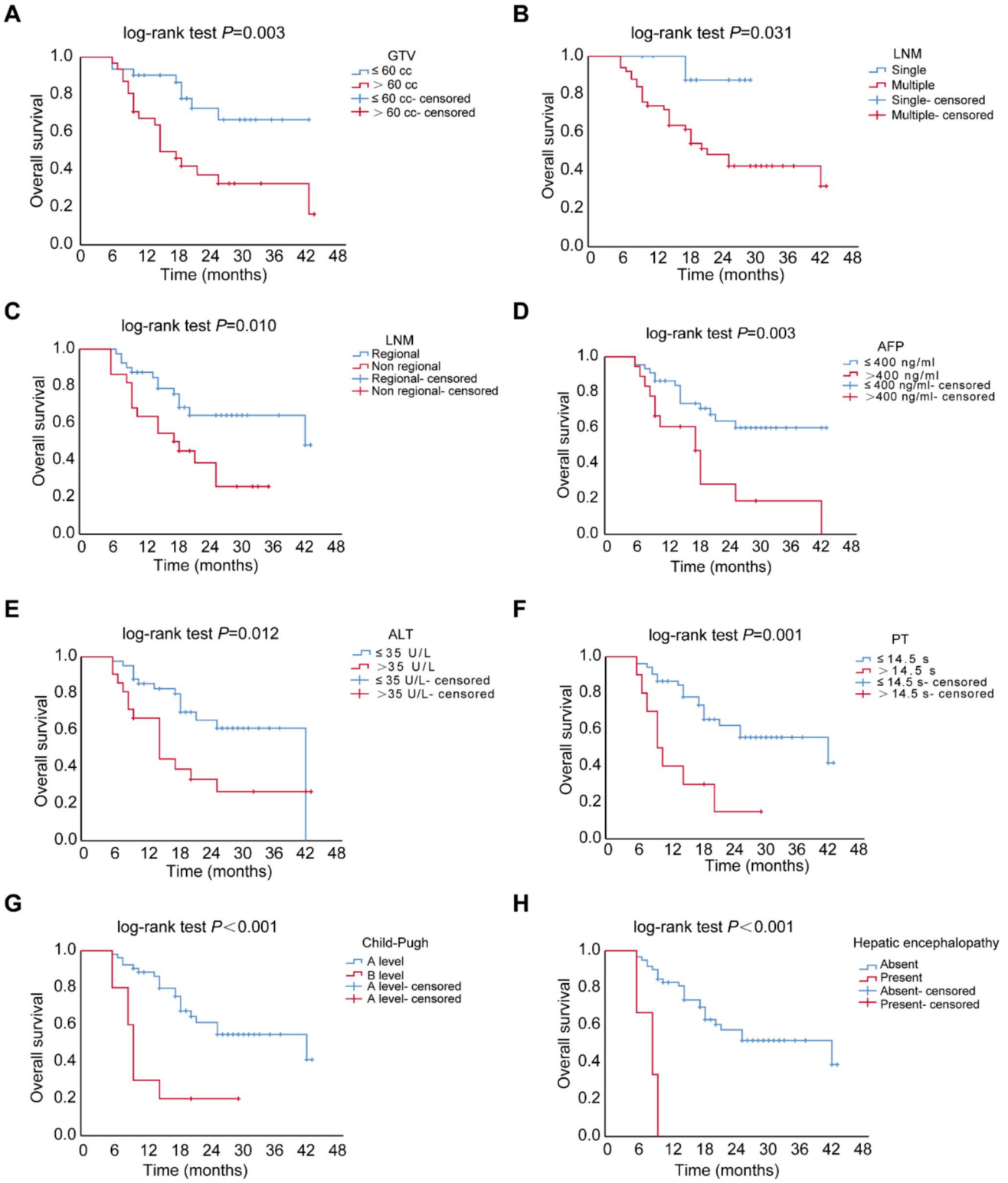

Fig.4 Subgroup analysis for overall survival of liver cancer with lymph node metastasis (LNM). **A** gross tumor volume (GTV), **B** Number of LNM, **C** Location of LNM, **D** alpha fetal protein (AFP), **E** alanine aminotransferase (ALT), **F** prothrombin time (PT), **G** Child–Pugh, **H** Hepatic encephalopathy

Table 2 Multivariate analysis of overall survival and progression free survival

	Overall survival			Progression free survival		
	HR	95% CI	*P*	HR	95% CI	*P*
ALT (U/L)			0.004			
≤35	1					
>35	3.42	1.47–7.97				
PT (s)			0.025			
≤14.5	1					
>14.5	2.67	1.13–6.27				
HE			0.576			
Absent	1					
Present	1.60	0.31–8.24				
Child–Pugh			0.007			
A	1					
B	5.28	1.59–17.53				
AFP (ng/ml)			0.108			
≤400	1					
>400	0.43	0.15–1.21				
GTV (cc)			0.003			
≤60	1					
>60	4.22	1.61–11.06				
Number of LNM			0.197			0.191
Single	1			1		
Multiple	3.97	0.49–32.30		4.12	0.49–34.34	
Location of LNM			0.502			0.012
Regional	1			1		
Non regional	1.33	0.58–3.06		3.54	1.32–9.49	
M stage						0.035
M0				1		
M1				2.75	1.07–7.02	
Tumor response						0.033
CR + PR				1		
SD + PD				3.60	1.11–11.73	
CA19-9 (U/ml)						0.525
≤35				1		
>35				1.37	0.52–3.62	

HR hazard ratio; *CI* confidence interval; *ALT* serum alanine aminotransferase level; *PT* prothrombin time; *HE* Hepatic encephalopathy; *AFP* alpha fetal protein; *GTV* gross tumor volum; *LNM* lymph node metastasis; *CR* complete remission; *PR* partial remission; *SD* stable disease; *PD* progression disease; *CA 19–9* carbohydrate antigen 19–9

and anemia. 34 (54.8%) patients experienced grade 3–4 neutropenia, most pronounced at 3 months after the end of radiotherapy; recovery was observed after granulocyte colony-stimulating factor therapy. 28 (45.2%) patients experienced grade 3–4 lymphocytopenia, most pronounced at the end of radiotherapy, with significant recovery observed 3 months after radiotherapy. 5 (8.1%) patients experienced grade 3–4 anemia, and 2 (3.2%) patients experienced grade 3 thrombocytopenia.

The second TRAE was hepatic impairment, with most patients experiencing grade 1–2 hepatic impairment, which recovered after hepatoprotective treatment. Among them, 5 (8.1%) patients exhibited grade 3 of gamma-glutamyl transferase increased, 3 (4.8%) patients exhibited grade 3–4 total bilirubin increased, 2 (3.2%) patients exhibited grade 3 ALP increased, 2 (3.2%) patients exhibited grade 3–4 AST increased, and one patient exhibited grade 3 ALT increased. At the end of radiotherapy, 4 (6.5%) patients had an increase in Child–Pugh score ≥ 2 point.

The third TRAE was radiation-induced gastrointestinal toxicities, including dyspepsia, dysphagia, nausea, vomiting, abdominal pain, diarrhea, abdominal distension,

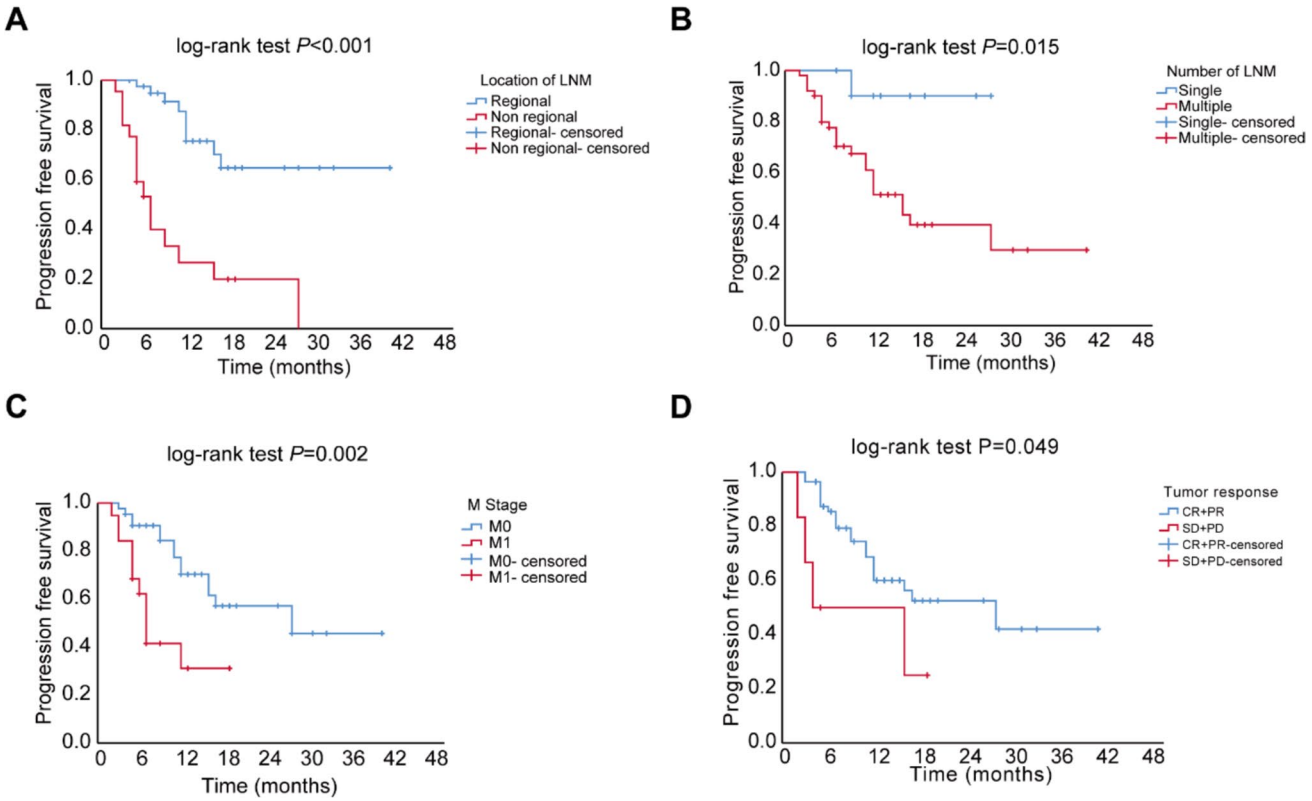

Fig. 5 Subgroup analysis for progression free survival of liver cancer with lymph node metastasis (LNM). **A** Location of LNM, **B** Number of LNM, and **C** M stage, **D** Tomor response

gastrointestinal ulcer, and gastrointestinal hemorrhage. Most gastrointestinal toxicities were mild to moderate, with one patient experienced grade 3 dyspepsia. The occurrence of rash, hematuria, proteinuria, hypertension, hyponatremia, thyroid-stimulating hormone increased, and lactate dehydrogenase increased were relatively mild. No treatment-related deaths were observed.

Patterns of failure

At the end point of data, tumor progression occurred in 26 (41.9%, 26/62) patients. The most common sites of progression were outside the irradiation field (84.6%, 22/26), including intrahepatic lesion progression (42.3%, 11/26), lymph node progression outfield of radiotherapy (38.5%, 10/26), lung metastasis (34.6%, 9/26), bone metastasis (15.4%, 4/26), peritoneal seeding metastasis (15.4%, 4/26), inferior vena cava tumor thrombus progression (3.8%, 1/26), adrenal metastasis (3.8%, 1/26), with no brain metastasis detected. 2 (7.7%, 2/26) patients showed progression of LNM within the irradiation field. 2 (7.7%, 2/26) patients had concurrent progression of LNM infield and outfield. Patients with performance status scores of 1–2 after progression underwent further anti-tumor treatment.

Among the 28 (45.2%, 28/62) deceased patients, the most common causes of death were progression of intrahepatic tumors or hepatic decompensation leading to liver failure in 16 (57.1%, 16/28) patients, gastrointestinal hemorrhage or other severe gastrointestinal adverse events in 4 (14.3%, 4/28) patients, lung metastasis in 3 (10.7%, 3/28) patients, peritoneal seeding metastasis in 2 (7.1%, 2/28) patients, severe infection in 2 (7.1%, 2/28) patients, and COVID-19 infection in one (3.6%, 1/28) patient.

Discussion

Liver cancer is a common malignant tumor with a high mortality rate, especially in patients with LNM, whose mortality rate is even higher. Some studies have shown that local resection of a single metastatic LN can improve survival rates and prognosis (Akasu et al. 2007). However, in most cases, surgical removal of metastatic LN is still technically challenging, especially for multiple metastatic LNs located retroperitoneally, which are difficult to completely resect (Yang et al. 2019). Non-surgical treatments include interventions, ablations, radiotherapy, and particle implantation. Although transcatheter arterial chemoembolization and

Table 3 Treatment-related adverse events

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	8 (12.9%)	10 (16.1%)	2 (3.2%)	0	0
Neutropenia	8 (12.9%)	14 (22.6%)	23 (37.1%)	11 (17.7%)	0
Lymphopenia	7 (11.3%)	15 (24.2%)	22 (35.5%)	6 (9.7%)	0
Thrombopenia	10 (16.1%)	7 (11.3%)	2 (3.2%)	0	0
Anemia	21 (33.9%)	6 (9.7%)	4 (6.5%)	1 (1.6%)	0
ALT increased	17 (27.4%)	4 (6.5%)	1 (1.6%)	0	0
AST increased	24 (38.7%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0
ALP increased	20 (32.3%)	2 (3.2%)	2 (3.2%)	0	0
GGT increased	20 (32.3%)	7 (11.3%)	5 (8.1%)	0	0
TBI increased	4 (6.5%)	4 (6.5%)	1 (1.6%)	2 (3.2%)	0
Hypoalbuminemia	13 (21.0%)	7 (11.3%)	0	0	0
Hyponatremia	4 (6.5%)	0	0	0	0
PT prolonged	7 (11.3%)	1 (1.6%)	1 (1.6%)	0	0
APTT prolonged	18 (29.0%)	0	0	0	0
Fatigue	23 (37.1%)	0	0	0	0
Rash maculo-papular	5 (8.1%)	0	0	0	0
Dysphagia	5 (8.1%)	1 (1.6%)	0	0	0
Dyspepsia	11 (17.7%)	1 (1.6%)	1 (1.6%)	0	0
Nausea	15 (24.2%)	6 (9.7%)	0	0	0
Vomiting	13 (21.0%)	7 (11.3%)	0	0	0
Abdominal distension	13 (21.0%)	5 (8.1%)	0	0	0
Abdominal pain	12 (19.4%)	5 (8.1%)	0	0	0
Diarrhea	2 (3.2%)	1 (1.6%)	0	0	0
Gastrointestinal ulcer	2 (3.2%)	6 (9.7%)	0	0	0
Gastrointestinal Hemorrhage	1 (1.6%)	2 (3.2%)	0	0	0
Ascites	5 (8.1%)	2 (3.2%)	1 (1.6%)	0	0
Hepatic encephalopathy	1 (1.6%)	0	0	0	0
Cough	4 (6.5%)	0	0	0	0

ALT serum alanine aminotransferase level; *AST* serum aspartate aminotransferase level; *ALP* serum alkaline phosphatase level; *GGT* serum γ-glutamyl transferase level; *TBI* serum total bilirubin level; *PT* prothrombin time; *APTT* Activated partial thromboplastin time

percutaneous ablation have been used to treat metastatic lymph nodes in specific abdominal areas, serious complications may occur, and their efficacy is uncertain (Yuan et al. 2019; Wu et al. 2015). Radiotherapy has unparalleled advantages (Palma et al. 2020; Harrow et al. 2022), due to its non-invasiveness and tolerability, with relatively low requirements on the function of important organs, particularly for metastatic LNs in difficult locations such as the abdominal cavity, retroperitoneum, or para-aortic regions where surgery or ablation is not feasible. There have been reports on the efficacy and safety of radiotherapy for liver cancer with LNM (Jo et al. 2022; Kim et al. 2022).

For advanced liver cancer, targeted therapy and immunotherapy were recommended as the standard systemic treatment for patients of HCC with extrahepatic metastases. Although single drug treatment has improved the survival time, the results are still not ideal (Kudo et al. 2018; Zhu et al. 2018; Qin et al. 2020). Radiotherapy, as an effective local treatment for LNM in liver cancer, may improve the survival rate of advanced liver cancer when combined with systemic treatment. Radiotherapy can activate systemic immune responses and synergize with immunotherapy (Lee and Seong 2021; Theelen et al. 2019). Previous studies have reported that combining radiotherapy with targeted therapy and/or immunotherapy is safe, which can reduce the risk of metastatic recurrence, and improve both local and systemic immunity (Pitroda et al. 2019). Chiang et al. (2019) evaluated radiotherapy combined with checkpoint Inhibition in unresectable liver cancer. The patients had ORR of 100%, with a median tumor shrinkage of 38.7% (30.5–84.4%), mPFS of 14.9 (8.6–19.0) months, 1-year LCR of 100%, and 1-year OS of 100%. Wada et al. (2018) reported that the PFS and OS of sorafenib combined with radiotherapy were 10.6 months and 31.2 months, respectively, which were significantly better than that of sorafenib alone. These studies demonstrated the efficacy and safety of

radiotherapy combined with targeted therapy or immunotherapy in advanced liver cancer. However, there were few clinical research reports on radiotherapy combined with targeted therapy and immunotherapy for advanced liver cancer.

Wang et al. (2023) reported the radiotherapy data of 148 HCC patients with abdominal LNM, including 92 (62.2%), 34 (23.0%), and 6 (4.1%) patients received radiotherapy alone, radiotherapy combined with targeted therapy, and radiotherapy combined with immunotherapy, while 16 (10.8%) patients received radiotherapy combined with targeted therapy and immunotherapy. With a median follow-up of 13.6 months, the ORR was 81.1%, median OS was 22.0 months, 1-year and 2-year OS were 65.0% and 49.7%, respectively. The 1-year and 2-year rates of freedom from local progression were 79.9% and 70.6%, respectively. Choi et al. (2024) reported a prospective phase II study that administered radiotherapy to 40 patients with 1 to 5 oligometastatic HCC. 16 (40.0%), 2 (5.0%), 18 (45.0%), and 1 (2.5%) patient received radiotherapy alone, radiotherapy combined with chemotherapy, radiotherapy combined with targeted therapy, and radiotherapy combined with immunotherapy, respectively. Only 3 (7.5%) patients received radiotherapy combined with targeted therapy and immunotherapy. With a median follow-up of 15.5 months, the median OS was not reached, 1-year and 2-year OS were 88.9% and 80%, respectively. The median PFS was 5.3 months, the 1-year and 2-year PFS were 21.2% and 0%, respectively. In our study, 80.6% of the patients received radiotherapy combined with targeted therapy and immunotherapy. the ORR was 90.3%, the median OS was 26 months, the 1-year, 2-year, and 3-year OS rates were 78.93%, 57.37%, and 49.12%, respectively. The median PFS was 17.0 months, the 1-year, 2-year, and 3-year PFS rates were 59.06%, 49.22%, and 39.37%, respectively. The survival data for liver cancer with LNM in this study has beneficial clinical outcomes, possibly due to the aggressive treatment strategy of using radiotherapy combined with targeted therapy and immunotherapy in overwhelming majority (80.6%) of the patients. This was different from the patients treated in the study by Wang et al. (2023) with (62.2%) and 34 (23.0%) patients received radiotherapy alone, and radiotherapy combined with targeted therapy, respectively. Additionally, 80.6% of the patients included in this study had multiple LNM, and 35.5% had distant LNM, indicating a more advanced tumor status in the patients. This was different from the patients included in the study by Choi et al. (2024), who had controlled primary lesions and only oligometastatic lesions. There were no significant differences in OS among the subgroups of treatment regimens, which may be related to the small proportion of other subgroups. Our results may influence the selection of treatment options for patients with advanced liver cancer. With the exclusion of contraindications, advanced liver cancer with lymph node metastasis could be treated with radiotherapy of metastatic lymph node, combined targeted therapy and immunotherapy.

The prognosis of HCC patients with LNM varies greatly, depending on baseline liver function, intrahepatic tumor status, presence of distant metastasis, and factors related to LNM. Baseline liver function (Lee et al. 2015; Wee et al. 2016), such as Child–Pugh score, the status of intrahepatic tumors and the presence of distant metastases, as well as LN related factors, such as the location and number of LNM (Kim et al. 2017), have been reported to be associated with OS. Wang et al. (2023) reported that BED was the only independent prognostic factor for local control. Uncontrolled intrahepatic tumors, tumor thrombus, LNM $\geq$ 4 cm, and grade 3–4 lymphocytopenia were identified as poor prognostic factors for OS. Some studies (Jo et al. 2022; Kim et al. 2022; Choi et al. 2024) reported that age, Child–Pugh score, AFP level, and the time from primary lesion control to oligo-metastasis were independent factors for PFS. In this study, we found that patients with large volume of LNM (GTV > 60 cc), multiple LNM, non-regional LNM, AFP elevated (> 400 ng/ml), ALT elevated (> 35 U/L), PT prolonged (> 14.5 s), hepatic encephalopathy present, and high Child–Pugh score suggested poor prognosis of OS. Multivariate analysis showed that GTV, AFP, ALT and PT were independent prognostic factors of OS. Additionally, patients with multiple LNM, non-regional LNM, distant metastases (M1) present, and CA 19–9 elevated (> 35 U/ml) indicated a poor prognosis for PFS. Multivariate analysis showed that non-regional LNM were independent prognostic factors for PFS. This was consistent with the results reported in previous studies (Kim et al. 2017). PFS does not have a significant impact on OS. We did not find a relationship between BED, lymph node response to radiotherapy and prognosis, possibly due to the radiotherapy dose of patients in this study was high enough, with a median BED 72.0 (range 62.4–79.2) Gy, which was significantly higher than previously reported. The ORR was as high as 90.3%, which could not reflect the difference between subgroups.

Previous studies (Choi et al. 2024; Lehrer et al. 2021) have reported that the toxicity associated with oligometastatic radiotherapy was mostly mild and well tolerated, with no significant difference in AEs between radiotherapy combined with systemic therapy and systemic therapy alone. Chen et al. (Chen et al. 2023) conducted a prospective study of radiotherapy combination with PD-1 inhibitors and reported a high toxicity rate of 56% for grade 2 toxicity and 12% for grade 3 toxicity. Li et al. (2024) reported that radiotherapy combined with tirellizumab showed varying degrees of TRAEs in all 20 enrolled HCC patients. The most common TRAEs was lymphopenia (90.0%), thrombopenia (70.0%) and leukopenia (65.0%). Grade 3 TRAEs occurred in 8 (40%) patients. The most common grade 3 TRAEs were lymphopenia (15.0%) and neutropenia (15.0%). Wang

et al. (2023) reported that acute toxicity of radiotherapy for abdominal LNM in liver cancer is relatively mild. 3 (2.0%) and 3 (2.0%) patients had grade 3 leukopenia and hyperbilirubinemia, 6 (4.1%), 5 (3.4%), and 46 (31.1%) patients with grades 3–4 thrombocytopenia, transaminase and lymphopenia, respectively. A total of 11 (7.5%) patients had grades 1–2 gastroduodenal ulcer, only one patient had grade 3 ulcer. In addition, 4 patients had grade 1–2 gastrointestinal hemorrhage. In this study, the most common TRAEs were acute hematological toxicity, with 34 (54.8%), 28 (45.2%), and 5 (8.1%) patients experiencing grade 3–4 neutropenia, lymphocytopenia and anemia, respectively. 2 (3.2%) patients presenting grade 3 thrombocytopenia. The second was liver damage, with grade 3–4 liver damage less than 10%. Gastrointestinal and other toxicities were mild. There were no treatment-related deaths. These differences in reported AEs are due to the different treatment regiments for patients with different tumor status and different liver and bone marrow function status. Overall, we believe that the AEs of radiotherapy combined with targeted therapy and immunotherapy in liver cancer with LNM patients are acceptable.

The most common sites of progression were outside the irradiation field (84.6%, 22/26), and the most common causes of death were progression of intrahepatic tumors or hepatic decompensation leading to liver failure in 16 (57.1%, 16/28) patients. It is recommended to closely monitor liver function during treatment, to maintain good liver function, and preferably irradiate the entire tumor area if the patient tolerate well.

This study had some limitations. First, it was a retrospective analysis conducted at a single institution, making selection bias unavoidable. Second, the treatment history of enrolled patients was varied, and the choice of treatment regimens largely depended on the patients' economic status, which could potentially impact the prognosis of advanced liver cancer. Third, the small sample size may limit the generalizability of findings. Therefore, further multicenter prospective clinical studies with larger sample sizes are likely required to better identify the subpopulations of liver cancer who would benefit the most from combination of radiotherapy with targeted therapy and immunotherapy.

Conclusion

Combining radiotherapy with targeted therapy and immunotherapy is a promising treatment approach for advanced liver cancer with LNM. This regimen improves treatment response, progression-free survival, and overall survival, with manageable toxicity. Further prospective studies are warranted to validate these findings and refine treatment strategies for advanced liver cancer.

Author contributions H. Y. project administration, writing—original draft; J. X. data collection; Z. L. data analysis; N. L. data validation; X. G. follow up patients; M. W. investigation; D. W. formal analysis; N. L. resources, supervision; J. D. writing—review & editing; X. X. final approval of the version to be published. All authors participated in data interpretation, drafting, and finalizing the report. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, Approval No. II2024-040–01.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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