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The role of definitive local treatment in metastatic hepatocellular carcinoma patients

A SEER-based study

Mingxue Su, MD[a], Yuanyuan Zhao, MD[b,c], Jianjun Liu, MD[d,*]

Abstract

In the present study, we aimed to investigate the survival benefit from definitive local treatment (LT) for hepatocellular carcinoma patients with distant metastasis (mHCC).

We retrospectively analyzed mHCC patients from Surveillance, Epidemiology, and End Results (SEER) Database. The patients' clinical and pathological characteristics were analyzed. Overall survival (OS) was calculated by Kaplan-Meier method. Independent risk factors associated with disease special mortality (DSM) were identified by multivariable regression analysis.

A total of 7187 mHCC patients from SEER database were identified. A total of 258 (3.6%) patients had received surgery treatment (ST), 64 (0.9%) patients underwent radiotherapy (RT), and 6865 (95.5%) patients were identified to no surgery or radiation therapy group (NSR). Compared with the patients in NSR group, patients who received ST (hazard ratio [HR]: 0.26, 95% confidence interval [CI] 0.22–0.31, $P < .001$) and RT (HR: 0.51, 95% CI 0.38–0.67, $P < .001$) had decreased DSM. Patients with age >50 years, female, and T3 or higher stage were associated with increased DSM.

The present study demonstrated the survival benefit of definitive LT in mHCC patients. However, a large randomized clinical trial to validate the role of LT in mHCC is necessary in the future.

Abbreviations: DSM = disease special mortality, LT = local treatment, mHCC = hepatocellular carcinoma patients with distant metastasis, NSR = no surgery or radiation therapy group, OS = Overall survival, RT = radiotherapy, SEER = Surveillance, Epidemiology, and End Results, ST = surgery treatment.

Keywords: local treatment, metastatic hepatocellular carcinoma, SEER, survival

1. Introduction

Hepatocelullar carcinoma (HCC) is the third leading cause of cancer deaths worldwide. Owing to the high prevalence of chronic hepatitis C and non-alcoholic fatty liver disease, the incidence of HCC has increased rapidly worldwide in the past decade. In 2016, it is estimated that >39,230 new HCC patients will be diagnosed.[1,2] In addition, the HCC is an aggressive cancer with poor survival, especially in the HCC patients with distant metastasis (mHCC) the median survival of most mHCC patients is <6 months.

As the multi-kinase inhibitor, sorafenib, has become the standard treatment for mHCC patients, the survival of mHCC has been prolonged. However, the survival of HCC is still unsatisfied. Compared with traditional chemotherapy, the median overall survival (OS) of the HCC patients treated with sorafenib was only prolonged for another 2.8 months.[3,4] In addition, the drug sensitivities of HCC treated with sorafenib were widely varied; only 30% of HCC patient can obtain survival benefits from sorafenib.[5] Therefore, developing useful and efficient treatments for general-population patients were needed.

According to the theory of "seed and soil," before tumor cells metastasis, the clustering of metastatic site marrow–derived cells arrived earlier. These cells are stimulated by endocrine factors which are released from the primary tumor, and can make the local microenvironment of the target metastasis organ more receptive to tumor cell colonization.[6,7] Thereby, the treatments of removal for the primary tumor are developing for malignancies with distant metastasis. In fact, the survival benefit of local

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MS and YZ participated equally in this study.

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[a] *Department of Infectious Diseases and Liver Diseases, The First Affiliated Hospital of University of Science and Technology of China, Anhui Provincial Hospital, Hefei,* [b] *Department of Breast Surgery, Key Laboratory of Breast Cancer in Shanghai, Collaborative Innovation Center of Cancer Medicine, Fudan University Shanghai Cancer Center,* [c] *Department of Oncology, Shanghai Medical College, Fudan University, Shanghai,* [d] *Department of Head-Neck and Breast Surgery, The First Affiliated Hospital of University of Science and Technology of China, Anhui Provincial Cancer Hospital, Hefei, China.*

[*] *Correspondence: Jianjun Liu, Department of Head - Neck and Breast Surgery, Department of Oncology Surgery, Anhui Provincial Cancer Hospital, The First Affiliated Hospital of University of Science and Technology of China, No. 107, West 2nd Ring Road, Hefei 230000, China (e-mail: drjianjunliu@163.com).*

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Table 1

Characteristics of patients from SEER database.

	NSR group		Local treatment			
			RT group		ST group	
	No.	%.	No.	%.	N.	%.
Age, y (mean ± SD)	62.4 ± 13.5		60.1 ± 13.0		42.3 ± 26.7	
Sex						
Male	5300	77.2	49	76.6	176	68.2
Female	1565	22.8	15	23.4	82	31.8
Race						
API	1056	15.4	5	7.8	61	23.6
AI	86	1.3	1	1.6	6	2.3
African-American	1040	15.1	8	12.5	26	10.1
White	4659	67.9	50	78.1	164	63.6
Unknown	24	0.3	0	0	1	0.4
Marital status						
Yes*	4830	70.4	55	85.9	136	52.7
No	1717	25.0	9	14.1	112	43.4
Unknown	318	4.6	0	0	10	3.9
Insurance status						
Yes	4677	68.1	56	87.5	174	67.4
No	427	6.2	2	3.1	6	2.3
Unknown	1761	25.7	6	9.4	78	30.2
Year of diagnosis						
2004–2006	1761	25.7	6	9.4	78	30.2
2007–2009	2102	30.6	14	21.9	79	30.6
2010–2013	3002	43.7	44	68.7	101	39.1
Pathological type						
Hepatocellular carcinoma	5509	80.2	58	90.6	143	55.4
Cholangiocarcinoma	258	3.8	2	3.1	18	7.0
Hepatocellular carcinoma and cholangiocarcinoma	81	1.2	1	1.6	5	2.0
Others	1017	14.8	3	4.7	92	35.6
AJCC T stage						
T2 or less	2020	29.4	42	65.6	84	32.6
T3 or more	713	10.4	15	23.4	76	29.5
Unknown	241	35.2	7	11.0	98	37.9
AJCC N stage						
N0	3438	50.1	40	62.5	125	48.4
N1	1413	20.6	15	23.4	32	12.4
Unknown	2014	29.3	9	14.1	101	39.1

AI = American Indian/Alaska Native, AJCC = American Joint Committee on Cancer, API = Asian or Pacific Islander.
* Including divorced, separated and widowed.

treatment (LT) has been confirmed in prostate cancer, kidney cancer, colon cancer, breast cancer, and ovarian cancer.[8–12] However, the survival benefit of LT in mHCC patients had not been carefully evaluated. In the present study, based on a large multipopulation database, we identified the survival benefit of LT for mHCC.

2. Methods

2.1. Surveillance, Epidemiology, and End Results database

Patients were identified from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database was derived from a large population-based collaboration program, which was

Table 2

Multivariate analysis of the patients with metastatic hepatocellular cancer at diagnosed.

	Multivariate analysis		
	HR	95% CI	*P*
Age at diagnosis, y (≤50 vs >50)	1.144	1.051–1.246	.002
Sex (female vs male)	1.076	1.003–1.155	.041
AJCC T stage			
T3-T4 versus T1-T2	1.129	1.065–1.198	<.001
Type of treatment			<.001
NSR	Ref		
Radiotherapy	0.455	0.336–0.617	
Surgery treatment	0.333	0.275–0.403	

AJCC = American Joint Committee on Cancer, CI = confidence interval, HR = hazard ratio, NSR = no surgery or radiation therapy.

Table 3

The survival of mHCC patients based on the risk group (months).

	LT		NSR		LT		NSR	
	mOS	95% CI	mOS	95% CI	mDSS	95% CI	mDSS	95% CI
Lower-risk group	45.2	33.3–57.1	8.7	6.9–10.4	48.8	36.4–61.2	11.5	9.2–13.8
Middle-risk group	24.7	17.4–32.0	5.1	4.5–5.6	26.3	18.5–34.1	6.2	5.4–7.0
Higher-risk group	12.1	8.7–15.5	4.0	3.7–4.4	12.8	9.2–16.5	4.9	4.4–5.4

CI = confidence interval, LT = local treatment, mDSS = median disease special survival, mHCC = hepatocellular carcinoma patients with distant metastasis, mOS = median overal survival, NSR = no surgery or radiation therapy.

surveyed by the National Cancer Institute. There are 18 population-based cancer registries participating in this program, and the data are updated annually. More than 28% American population's cancer incidence and survival data were collected in this database.[13]

2.2. Patients

HCC patients with distant metastasis (CS mets at dx code: 10–60) between January 1998 and December 2013 were selected in the present study. The inclusion criteria were as follows: patients diagnosed with distant metastasis were included, either confirmed by radiographic or pathological examination; patients without any other malignancies The mHCC patients were grouped by the treatments they had received. Patients who underwent surgery (surgery site codes: 10–70) or radiotherapy (RT) (radiation-specific codes: 2–4) were assigned to surgery treatment (ST) group or RT group respectively, and the remaining patients who had no surgery or RT were selected into no surgery or radiation therapy group (NSR) group. In the LT group, patients were excluded if they had received external beam RT.

2.3. Statistical analysis

The data of patients' clinicpathological characteristics such as age at diagnosis, sex, race, tumor site, size, marital status, surgery, histology, grade, the status of positive lymph node were collected. The pathological characteristics, such as T stage, lymph nodal, stage and tumor stage were restaged according to the 7th edition AJCC staging system.[14] The endpoint OS was defined as the time from surgery to any reason of death or the last follow-up. And the disease special survival (DSS) was defined as the time from surgery to cancer-related death or the last follow-up.

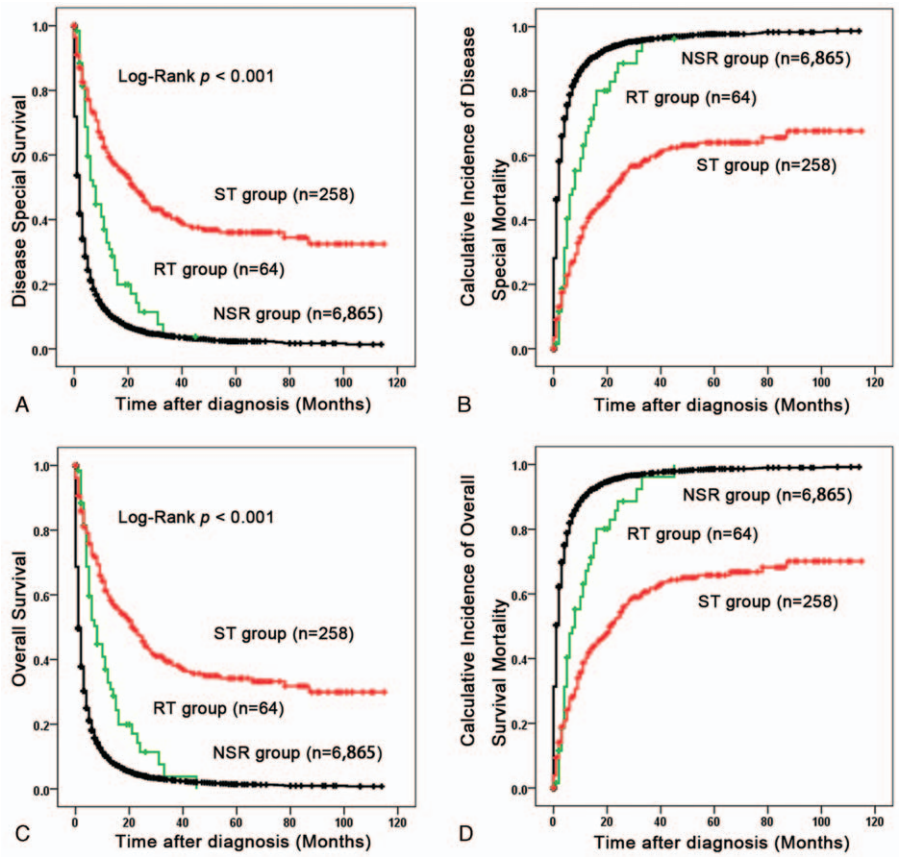

Figure 1. Disease special survival (A) and cumulative incidence. Disease special mortlity (B) for hepatocellular carcinoma patients with distant metastasis (mHCC) based on the treatment they received. Disease special survival (C) and cumulative incidence overall mortlity (D) for mHCC based on the treatment they received. NSR = no surgery or radiation therapy, RT = radiotherapy, ST = surgery treatment.

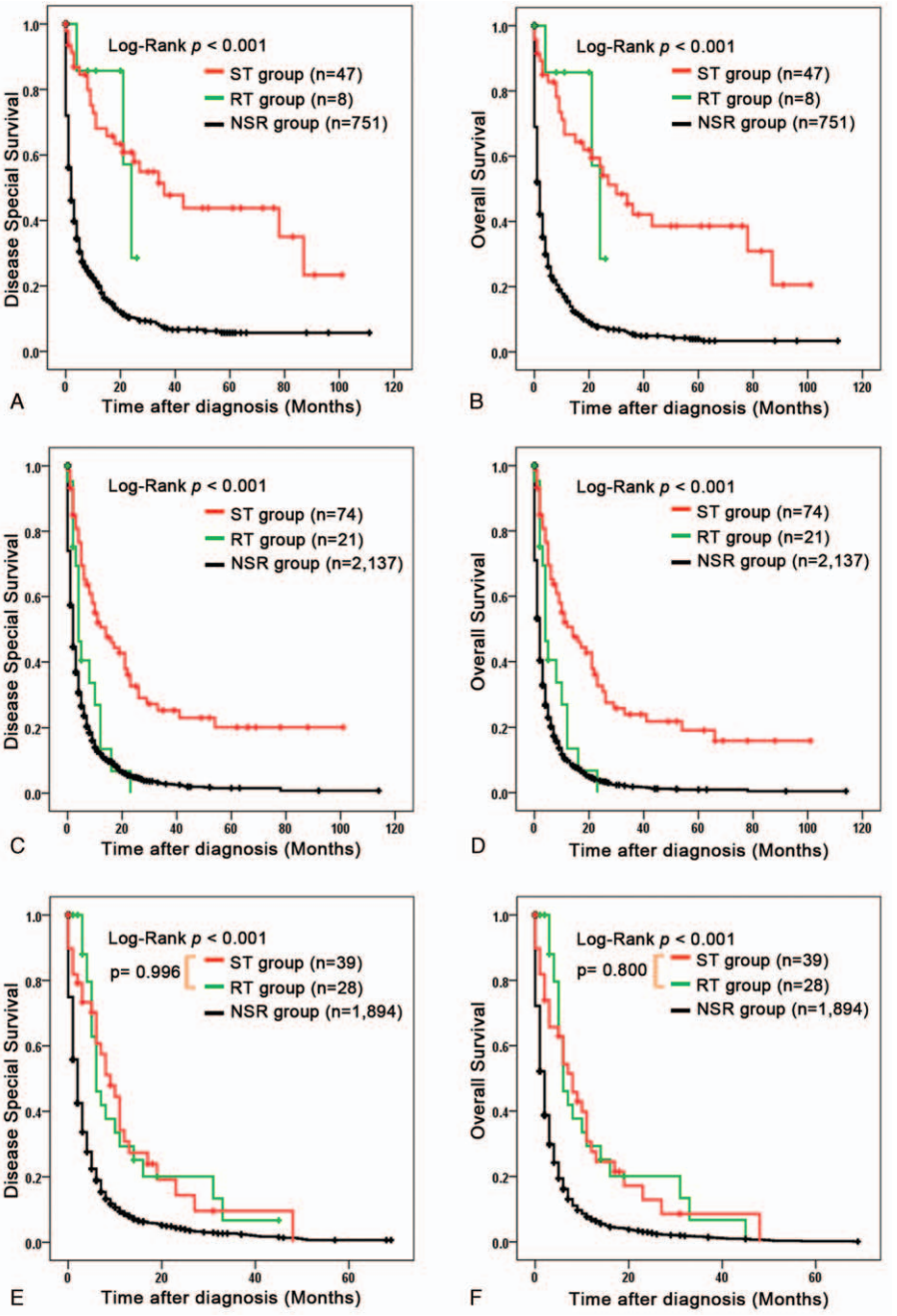

Figure 2. The disease special survival of hepatocellular carcinoma patients with distant metastasis (mHCC) patients with lower risk (A), middle risk (C), and higher risk (E). The overal survival of mHCC patients with lower risk (B), middle risk (D), and higher risk (F). NSR = no surgery or radiation therapy, RT = radiotherapy, ST = surgery treatment.

OS or DSS estimation and survival curves were performed by the Kaplan-Meier method and validated by the log-rank test. Independent risk factors associated with disease special mortality (DSM) were identified by the Cox regression analysis. Owing to the intrinsic limitation of retrospect study, a potential selection bias may exist. Therefore, a propensity score-matched analysis was also planned. Propensity score analysis was performed using the all the independent prognostic factors from the results of the Cox regression analysis at the 0.02 level of significance.

All analyses were performed by the software statistical package for social sciences (SPSS) version 20.0 (SPSS Inc, Chicago, IL) and the R software version 3.13 (http://www.r-project.org/). All the statistical tests were 2-sided. *P* value <.05 was considered to be statistically significant.

3. Result

3.1. Patients

Between 1998 and 2010, a total of 7187 mHCC from SEER database were identified. Of these, the mean age at diagnosis was 61.7 years. A total of 1662 (23.1%) female patients and 5525

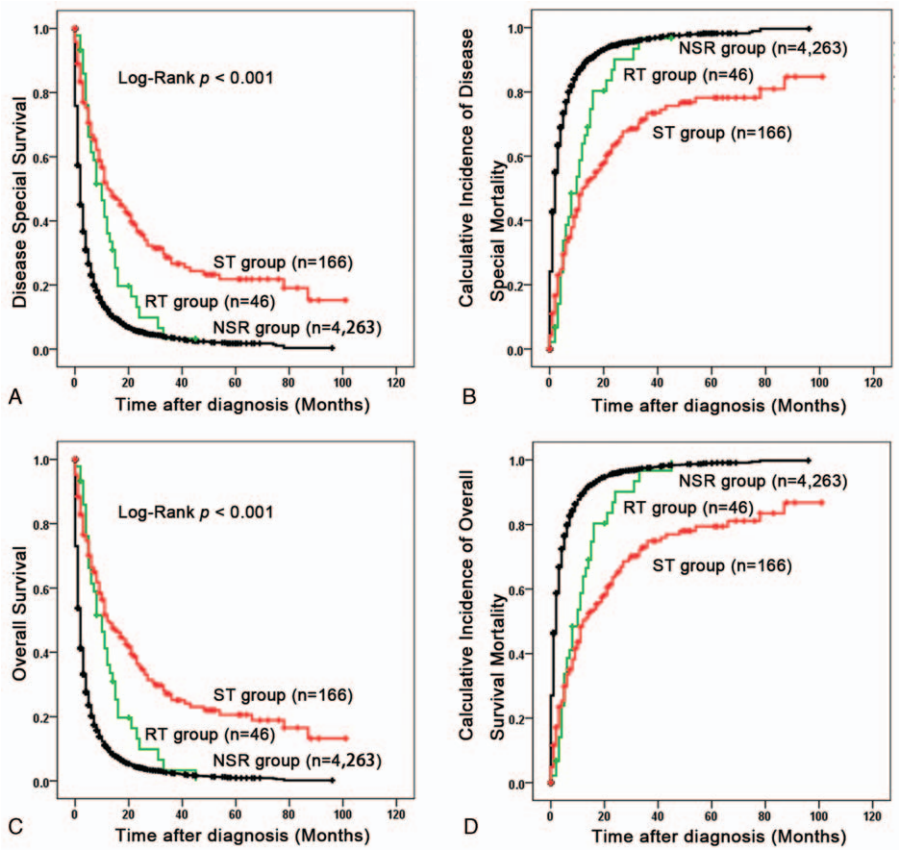

Figure 3. Disease special survival (A) and cumulative incidence. Disease special mortlity (B) for hepatocellular carcinoma patients with distant metastasis (mHCC) who diagnosed by pathological confirmation based on the treatment they received. Disease special survival (C) and cumulative incidence overall mortlity (D) for mHCC diagnosed by pathological confirmation based on the treatment they received. NSR = no surgery or radiation therapy, RT = radiotherapy, ST = surgery treatment.

(76.9%) male patients were there in the primary cohort. The major race of those patients was white (67.8%), and 1122 (15.6%) patients were from Asian or Pacific Islander. There were 6626 (92.2%) patients who died before this analysis. Overall, 258 (3.6%) patients had received ST and 64 (0.9%) patients had received RT. The remaining 6865 (95.5%) patients who had not received any LT were assigned to NSR group. The clinical–pathological characteristics were listed in Table 1.

3.2. Factors associated with increased DSM

As shown in the Table 2, patients with age >50 years, female, and T3 stage or higher were associated with increased DSM. According to the multivariable regression analysis, we proposed a risk model: lower risk group, <1 risk factor; middle risk group, 2 risk factors; higher risk group, 3 risk factors. Although patients with increased risk factor were associated with worse survival, the survival of LT group was still better than that of NSR group (Table 3).

3.3. Overall effect of LT

As shown in the Figure 1, the ST group had significantly better OS than that of NSR ($P < .001$) and RT group ($P < .001$). In addition, the DSS and OS in NSR group were also worse than that of RT group ($P < .001$, $P < .001$, respectively). The 1-year DSM in ST, RT, and NSR were 60.7%, 32.9%, and 11.7%, respectively. Additionally, patients who received ST (hazard ratio [HR]: 0.26, 95% confidence interval [CI] 0.22–0.31, $P < .001$) and RT (HR: 0.51, 95% CI 0.38–0.67, $P < .001$) have decreased DSM, compared with the patients in NSR group.

To determine whether RT and ST have the same survival benefit in the HCC patients with distant organ metastasis, we performed a subset analysis based on the risk model. As shown in the Figure 2, Compared with RT, patients with lower risk or middle risk may have better survival in ST group. However, in the high-risk group, the DSS and OS benefit in ST group and RT group were similar ($P = .99$; $P = .80$; respectively).

3.4. Subanalysis of LT

To account of mHCC patients who might exactly benefit from definitely LT, we made a subgroup analysis. To avoid selected bias, only HCC or (and) cholangiocarcinoma HCC patients diagnosed by pathological confirmation were included. As shown in the Figure 3, after a median follow-up of 4.7 months, the 1-year DSM was still higher in ST group (51.5%) and RT (31.3%) group than that of NSR group (11.9%). Furthermore, compared with NSR group, the patients who underwent ST or RT were still independently associated with decreased DSM (HR: 0.33, 95% CI 0.27–0.40, $P < .001$; HR: 0.50, 95% CI 0.37–0.68, $P < .001$; respectively).

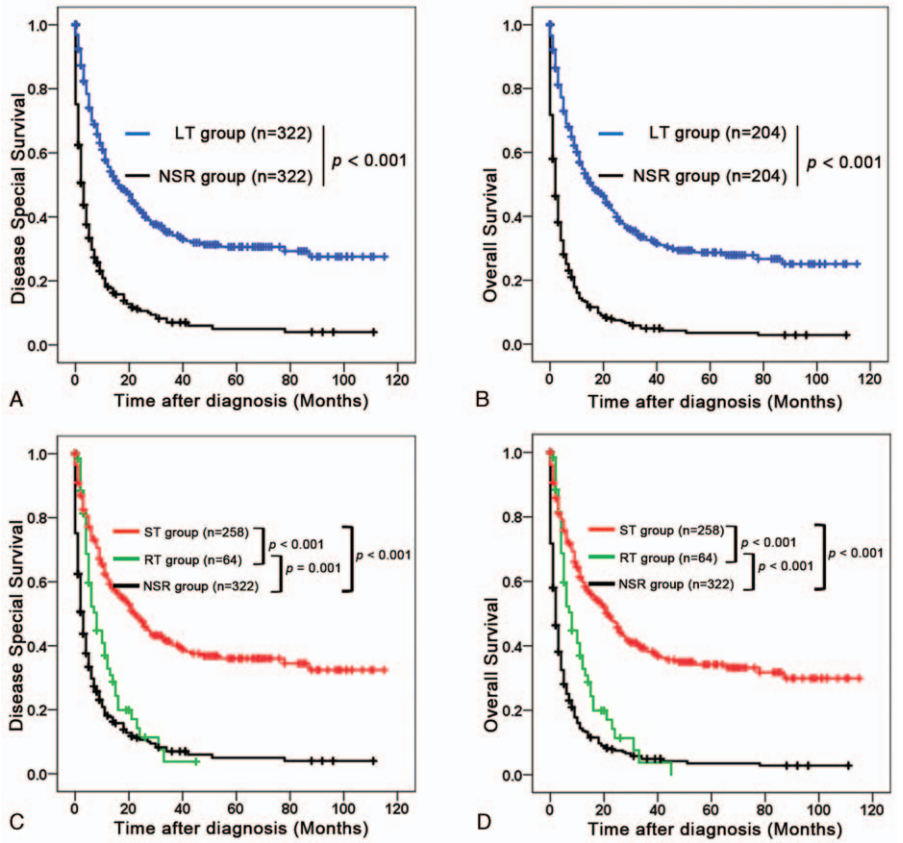

Figure 4. Disease special survival (A and C) for matched hepatocellular carcinoma patients with distant metastasis (mHCC) patients based on the treatment they received. Overall survival (B, and D) for matched mHCC patients based on the treatment they received. NSR = no surgery or radiation therapy, RT = radiotherapy, ST = surgery treatment.

3.5. Propensity score matching analysis

Based on the results of multivariable analysis, a propensity score matching analysis was performed. Quartiles of the propensity score were estimated by the age at diagnosis, sex, and T stage. The aged at diagnosis was used as continuous variable. The LT group and NSR group were matched by 1:1. A total of 644 patients were included in the subanalysis. The matched patients' clinical characteristics are listed in supplement Table 1, http://links.lww.com/MD/C157. As shown in the Figure 4, after matching, the LT patients had significantly better survival than that of NSR patients (all $P \leq .001$).

4. Discussion

Unlike other high-incidence cancer, the effective treatment for HCC patients with distant organ metastasis was still scarce. In the present large multipopulation-based study, we identified the survival benefit from definitively LT for mHCC patients. We also demonstrated that the patient's age at diagnosis, sex type, and T stage were associated with patient's survival. Moreover, ST and RT have the similar survival benefit in patients with 3 risk factors, whereas, in patients with $\leq$2 risk factors, the ST has a better survival benefit than RT.

Primary tumor resection is the only potential curable therapy for early-stage HCC, whereas the 5-year OS rate is >60%. However, >80% patients have multicenter tumor or are diagnosed at advanced stage, who are unable to undergo radical resection.[15,16] Given the multikinase inhibitor sorafenib had proven to provide survival benefit for HCC, it has become the standard therapy for HCC with distant organ metastasis after 2008. However, the drug resistance of Sorafenib in HCC was widely varied; >57% patients were tumor-progressive after being treated with Sorafenib.[3] Therefore, an alternative treatment regimen is required. Indeed, the proportion of HCC patients from SEER database receiving palliative surgery had not decreased significantly in recent years (data not shown).

As the theory of tumor burden-decreasing treatment had been identified with survival benefit in several malignancies, the roles of LT such as palliative surgery or RT in advance malignancies were widely discussed.[8–12] In 2014, a retrospective study demonstrated the survival benefit of LT for M1 stage prostate cancer. The researchers retrospectively analyzed 8185 prostate cancer patients from SEER database. Compared with non-LT group, the authors demonstrated the definitive LT, radical surgery, and RT were more effective for prostate cancer patients with distant metastasis (HR: 0.37, $P < .001$; HR: 0.57, $P < .001$, respectively).[8] In fact, the LT, such as surgery and RT, for HCC with distant organ metastasis was still scarcely discussed.

The LT like tumor radiofrequency ablation (RAF) and cryoablation had demonstrated higher rates of local control and lower morbidity in early HCC patients with small tumor, well-differentiated grade, and less satellite lesions.[17–20] In a 10-year retrospective study, Shiina et al[21] demonstrated RAF could be locally curative for early HCC patients. In addition, a recent randomized control trail demonstrated that, compared with RAF, the cryoablation also had a similar survival benefit, but

lower local tumor progression.[22] However, there were few prospective data estimating the survival benefit of LT in mHCC. Given that the survival benefit of HCC patients may be different because of the various patients' tumor characteristics, the local tumor ablation for mHCC is still unclear. In this study, we first demonstrate the potential survival benefit of primary tumor in mHCC based on the SEER database. Furthermore, we identified the risk factors associated with increased DSM in HCC patients with distant metastasis, which included age at diagnosis, sex type, and T stage. Our study identified the effectiveness of definite LT in a large multipopulation dataset. Compared with NSR group, the patients' 1-year DSM decreased nearly 40% in LT group. Moreover, we also identified that ST had a better survival benefit than RT in patients with <2 risk factors. It should be useful for providing better treatment allocation in mHCC patients.

There are still some limitations which should be acknowledged. First, there may be a selection bias in the present study, as the patients with incomplete information were excluded in present study. Second, only the information that SEER database had provided had been carefully analyzed, whereas the other individual information such as patients' performance status, patients tumor location, and liver function, which may affect clinical decision-making, was ignored. Furthermore, the local therapy type in metastatic cancer was affected by primary tumor characteristic, such as olligometastases, oligo-recrrence, and sync-oligometastases.[23–25] However, the above information was not provided in the present dataset. Lastly, owing to the inefficient information of site-specific EBRT code, it was impossible to examine the survival effects of EBRT in primary tumor.

In summary, based on a multi-institution and multipopulation database, we first demonstrated the survival benefit of definitive LT in HCC patients with distant metastasis. The mHCC patients' age, sex type, and tumor T stage affect the survival benefit from LT, and those factors should been taken into account before the clinical-decision made. However, our results should be validated by a large randomized clinical trial in future.

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