



## Original Research

# Effect of the normal liver mean dose on intrahepatic recurrence in patients with hepatocellular carcinoma after receiving liver stereotactic body radiation therapy

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## ABSTRACT

**Background and purpose:** This study aims to evaluate whether dosimetric parameters affect the intrahepatic out-field recurrence or distant metastasis-free survival following the stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma (HCC).

**Materials and methods:** A total of 76 patients with HCC who were treated with SBRT from January 2015 to May 2020 were included in this retrospective study. The main clinical endpoints considered were intrahepatic out-field free survival (OutFFS) and distant metastasis-free survival (DMFS). The target parameters and the liver were documented including tumor diameters, gross tumor volume (GTV), Liver minus GTV volume (LGV), and Liver minus GTV mean dose (LGD). Multivariable Cox regression with forward stepwise selection was performed to identify independent risk factors for OutFFS and DMFS. Maximally selected rank statistics were used to determine the most informative cut-off value for age and LGD.

**Results:** The median follow-up was 28.2 months (range, 7.7–74.5 months). LGD higher than 12.54 Gy [HR, 0.861 (0.747–0.993);  $p = 0.040$ ] and age greater than 67-year-old [HR, 0.966(0.937–0.997);  $p = 0.030$ ] are two independent predictors of OutFFS, previous TACE treatment [HR, 0.117(0.015–0.891);  $p = 0.038$ ] was an independent predictor of DMFS.

**Conclusions:** The results of this study suggested that the higher the dose received by the normal liver (greater than 12.54 Gy) the better the intrahepatic out-field recurrence-free survival (RFS) rate. Further study is warranted to confirm and to better understand this phenomenon.

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most frequent cause of cancer-related mortality worldwide [1]. Despite good local control for patients with HCC receiving stereotactic body radiation therapy (SBRT), some still developed metastatic diseases thus, resulting in a poor prognosis [2]. Cancer recurrence, including intrahepatic recurrence and distant metastasis, may be due to microscopic disease extensions (MDEs) of the primary liver tumor [3]. For HCC, little research has been done to verify the existence of MDEs and the possible effect of the “incidental dose” on the MDEs; the mean normal liver dosage is usually evaluated for its effect on the

radiation-induced liver disease (RILD) [4], however, its relationship to the HCC post-radiation progression was rarely studied.

SBRT is a radiation therapy technique focus on ablative doses of radiation precisely on the visible tumor with an emphasis on high conformality and steep dose fall off, the nature of this technique allows the maximum dose to target HCC while minimizing the dose to avoid the normal tissue thus minimizing the risk of complications. SBRT is typically delivered in 3–5 fractions, with a relatively low risk of radiation-induced liver disease (RILD). However, studies have shown that a lower radiation dose outside of the planning target volume (PTV) increases the risk of distant metastasis in the early-stage lung cancer treated with SBRT, possibly because of the microscopic diseases around

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the tumor that have not been eradicated [5,6]. For prostate radiotherapy, high incidental doses outside the tumor have shown a significant effect on reducing the treatment failure [7]. Similar studies have demonstrated the relationship between regional control and incidental dose in draining the lymphatics [8,9]. According to the clinical guideline, SBRT is now widely applied as treatment in patients with HCC that are not suitable for surgery, TACE, or other loco-regional treatment [10, 11]. The treatment failure pattern is mainly caused by intra-hepatic recurrence [12]. Theoretically, prophylactic normal liver irradiation could affect the risk of recurrence by eliminating the micro-metastasis.

The present investigation originated from a previous study that correlated the remnant liver parameters in a large cohort of patients that underwent hepatectomy. The study found that severe ischemia was strongly correlated with early distant metastasis [13]. Similarly, our study aims to determine if there is a correlation between the dosimetric parameters of normal liver and cancer recurrence in patients with HCC receiving SBRT.

## Materials and methods

### Patients

We enrolled a total of 76 patients with HCC that were treated with SBRT from January 2015 to May 2020, informed written consent was obtained and this study was approved by the institutional review board of the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2021-513). SBRT was considered a primary treatment for patients with HCC that are not suitable for surgery because it was technically or medically inoperable or because of patients' refusal; tumors not suitable for transcatheter arterial chemoembolization (TACE) or radiofrequency ablation (RFA) because of tumor hypovascularity or its location in the liver dome or near the major vessels; and the recurrent lesions after multiple treatments including TACE and RFA. The inclusion criteria were as follows: (1) HCC based on biopsy-proven HCC or clinical guideline defined HCC [11,14,15], (2) HCC treated with SBRT, (3) patients with at least one clinical and radiographic follow-up data, (4) patients with complete treatment plan data, (5) ECOG score: 0–2, (6) age  $\geq$  18 years, (7) normal liver volume:  $>700\text{cm}^2$ , and (8) Child-Pugh class

A or B. Patients that were excluded are: (1) those who received other locoregional treatments after radiotherapy before disease progression happens and (2) those with lymph node metastasis, distant metastasis, or double primary malignancies. Of 122 patients, 76 (62.3%) were assessed for response and are eligible for final analysis. Seven patients were not considered because they had a pathology confirmation of cholangiocellular carcinoma. Six patients were excluded because they received other locoregional treatments before disease progression. 33 patients were excluded because of incomplete follow-up or treatment plan data (Fig. 1).

### Stereotactic body radiation therapy procedure

All patients received Helical Tomotherapy (Hi-ART System, Accuray). The respiratory liver motion was reduced using an abdominal compression technique [16,17], and the patient underwent a 4D-CT scan with a slice thickness of 3 mm (Siemens Somatom Sensation; Siemens Healthineers Corporation). The gross tumor volume (GTV) included all tumors detected via dynamic CT scan and MRI; an internal target volume (ITV) was generated after including the extension of GTV on the 4D-CT scanning. The planning target volume (PTV) was created as ITV plus a radial margin of 3 mm. Treatment planning was performed on the Monte Carlo algorithm (Monaco®). Patients were treated with a radiation dose of 48–60 Gy in 6–10 fractions, patients underwent on-board megavoltage CT daily for image guidance. The variance in dosage was because of the tumor location near the intestine.

### Data collection and outcome measurements

Treatment plan data for each patient including GTV volume, LGV, and LGD were recorded. The outcome of interest were OutFFS and DMFS. All time-to-event outcomes were calculated from the beginning of the treatment with censoring of the date of the patient's last clinical follow-up. Local failure was defined as an infield recurrence of disease within the PTV. Demographic data (sex, hepatitis B infection,  $\alpha$ -feto-protein (AFP) level  $> 400$  ng/ml,  $> 200$  ng/ml,  $> 15$  ng/ml, and previous treatments) were summarized with counts and percentages. Patient age and tumor size (cm) before the treatment were summarized with median and interquartile ranges.

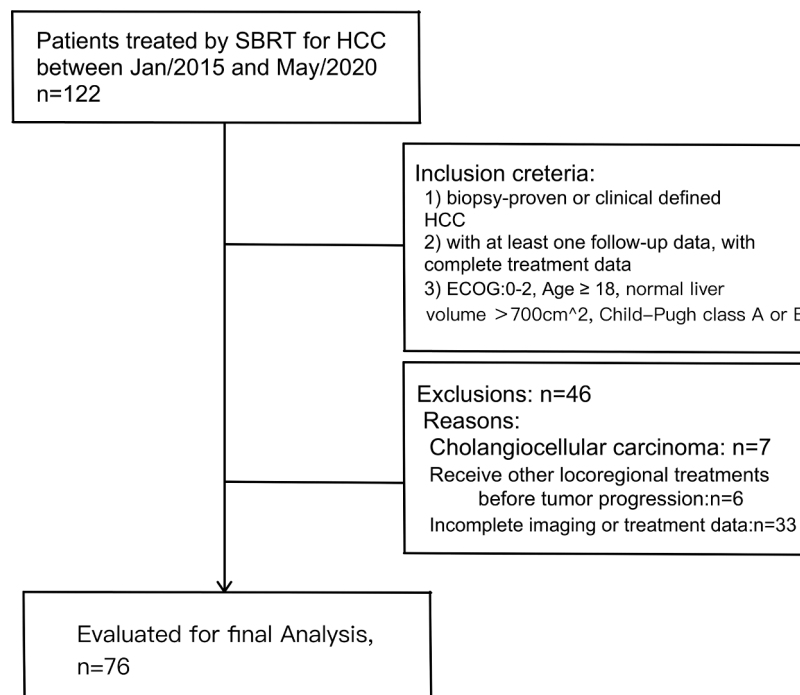


Fig. 1. Flow diagram for the patient selection process.

## Statistical analysis

Median (interquartile range [IQR]) was reported for continuously coded variables. Frequency and proportion were reported for categorical variables. Multicollinearity existed between the normal liver volume and normal liver mean dose (i.e., the larger the normal liver was, the lesser the mean dose necessary for the normal liver). Accordingly, we used the Cox regression model with forwarding selection, which could discard highly related variables to calculate hazard ratios (HRs). To quantify the prognostic effect of age and LGD on OutFFS, a multivariable Cox regression model with penalized spline (P-spline) was used [18]. P-spline provides a flexible model for examining the relationship between age, LGD, and the natural logarithm of HRs without prior knowledge of the type of relationship while adjusting for the effects of covariates. Given the variability in the prescription, planning and tumor characteristics and the true dose threshold (if one exists) for the mean normal liver dosage or patients age are unknown, a method was employed in identifying an optimal cut-point that significantly corresponds most to the outcome of interest using the maximally selected rank statistics [19]. This allows for exploratory identification of the cut-point along with a continuous variable that provides the greatest separation of treatment outcomes between two groups. Survival rate estimates were compared across strata using the log-rank test. All statistical data mentioned above were analyzed using R version 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria; [www.r-project.org](http://www.r-project.org)) with the R package “smoothHR” and “survminer”. All tests were 2-sided, and  $p < 0.05$  was considered statistically significant.

## Results

### Baseline patient characteristics

The clinical features of 76 patients are summarized in Table 1. The median age of the patients was 62.5 [IQR 52–70.5]. Most patients have their AFP levels greater than 400 ng/ml (82.9%) and had RFA as their previous treatments (75%). The median tumor size was 2.7 cm [IQR 1.5–3.3]. As shown in Table 2, the median biologically effective dose (BED) was 86.4 Gy [IQR 86.4–102.6]. The median LGV was 1181.77 cc [IQR 965.3–1334.1], and the median LGD was 9.12 Gy [IQR 7.55–12.70]. The median follow-up was 28.2 months (range, 7.7–74.5 months). Intrahepatic Out field recurrence was the main cause of failure which accounts for 31.6%, distant metastasis was the secondary cause of failure (22.4%).

### The effect of age on outffs

As shown in Table 3, the effect of age was statistically significant in

**Table 1**  
Patient and treatment characteristics.

Patient and treatment characteristics		n(%)
		Median(IQR)
Total		76
Sex	Male	58(76.3)
	Female	18(23.7)
Age		62.5(52–70.5)
Hepatitis B infection	Yes	71(93.4)
	No	5(6.6)
AFP level	>400 ng/ml	63(82.9)
	>200 ng/ml	58(76.3)
	>15 ng/ml	33(43.4)
Previous Treatments	Surgery	43(56.6)
	RFA	57(75)
	TACE	26(34.2)
Tumor Size(cm)		2.7(1.5–3.3)

IQR, interquartile range; n, number.

**Table 2**  
Treatment details and outcomes.

Treatment details and outcomes		n(%)
		Median(IQR)
Total		76
Dose(Gy)(range)		60(48–60)
BED10(range)		86.4(86.4–102.6)
GTV Volume(cc)		12.3(5.9–23.8)
Liver-GTV volume(cc)		1181.77(965.3–1334.1)
Liver-GTV mean dose(Gy)		9.12(7.55–12.70)
Failure Pattern	Local	4(5.3)
	Out-field	24(31.6)
	Distant	17(22.4)

Gy, Gray; fx, fraction.

the univariable ( $p = 0.023$ ) and multivariable analyses ( $p = 0.030$ ) Fig. 2. A shows a nonlinear relationship between decreased age and risk (lnHR) of Intrahepatic Out Field Free Survival (OutFFS). Maximally selected rank statistics demonstrated that the most informative cut-off value of age for OutFFS was 67-year-old (Fig. 3), and patients whose age was greater than 67-year-old have better OutFFS.

### Effects of the normal liver dosage on outffs

As shown in Table 3, the effect of the LGD was statistically significant in the univariable ( $p = 0.025$ ) and multivariable analyses ( $p = 0.040$ ). Fig. 2B shows a nonlinear relationship between decreased normal liver dose and risk (lnHR) of Intrahepatic Out Field Free Survival (OutFFS). Maximally selected rank statistics showed that the most informative cut-off number of remnant liver dosage for OutFFS was 12.54 Gy (Fig. 4A). Fig. 4B shows that radiation dosage equal or greater than 12.54 Gy had better out-field progression-free survival [HR, 0.861(0.747–0.993); ( $p = 0.040$ )].

### Effects of the dosimetric parameters or clinical factors on DMFS

No statistically significant correlations were found between any dosimetric parameters with DMFS, previous TACE treatment was the only clinical factor that is directly related to the DMFS ( $p = 0.038$ ).

## Discussion

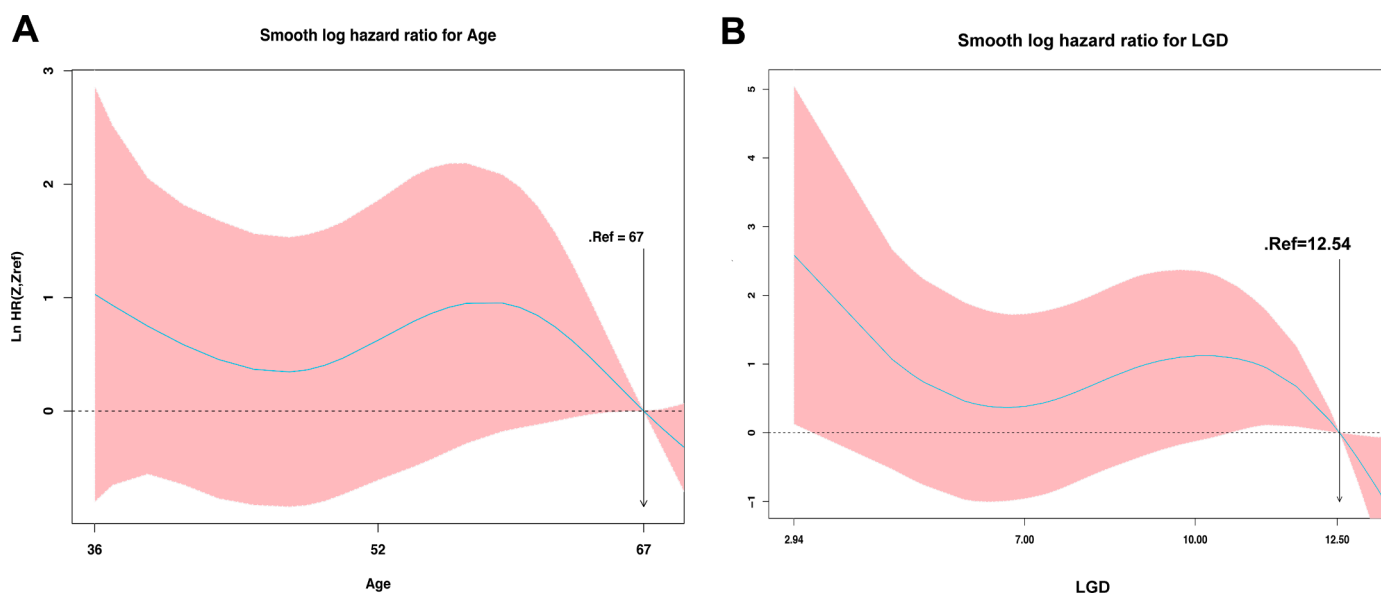
Our study retrospectively analyzed the dosimetric parameters and clinical data of 76 patients with HCC who underwent SBRT, and first demonstrated higher normal liver mean dosage was associated with lower intra-hepatic outfield recurrence for SBRT patients.

However, despite excellent local control rates after receiving SBRT, tumor recurrence remains the major problem. Most patients suffer from treatment failures in the liver outside the PTV (outfield failure) [12, 2–22]. Few studies summarized the OutFFS and DMFS in SBRT-treated patients. Kim et al. [20] have reported 1- and 2- year OutFFS and DMFS were 80.9%, 62.5%, and 62.3%, 42.7%. The 1- and 2 - year OutFFS in Que’s study [21] were 52.5% and 49.5%, whereas in our study, the 1- and 2- year OutFFS and DMFS were 77.5%, 89.5%, and 70.6%, 77.6%, respectively. The OutFFS rate in our research is quite the same as that of Kim’s, however, the DMFS was higher. Several factors that include study design, sample size, and treatment planning system/algorithm could explain the difference in metastasis-related survival rates. We studied if the dosimetric factors were related to the DMFS, Local control rates, Overall Survival and Progression Free Survival. however, no significant correlations were found between any factors with DMFS, Local control rates, Overall Survival and Progression Free Survival.

In our study, age and LGD were considered independent predictors for OutFFS, LGD is usually used during the evaluation of the liver

**Table 3**  
Multivariable Cox regression analyses for Intrahepatic Out Field Free Survival and Distant Metastasis Free Survival.

	Intrahepatic Out Field Free Survival				Distant Metastasis Free Survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value
<b>Age</b>	0.964(0.934–0.995)	<b>0.023</b>	0.968(0.939–0.998)	<b>0.039</b>	0.986(0.950–1.024)	0.475	1.030(0.976–1.087)	0.283
<b>BED</b>	1.009(0.965–1.055)	0.694	1.016(0.971–1.065)	0.488	1.014(0.960–1.070)	0.618	1.025(0.967–1.087)	0.407
<b>Hepatitis B infection</b>	0.384(0.115–1.268)	0.121	4.570(0.899–23.220)	0.067	1.252(0.165–9.510)	0.828	13.015(0.754–224.789)	0.078
<b>Diameter</b>	1.039(0.768–1.405)	0.804	1.332(0.909–1.953)	0.142	1.185(0.811–1.732)	0.381	1.470(0.962–2.247)	0.075
<b>AFP level</b>	1.000(0.999–1.000)	0.805	1.000(0.999–1.000)	0.789	1.000(0.999–1.001)	0.74	1.000(0.999–1.000)	0.576
<b>Previous treatments</b>								
TACE	0.642(0.268–1.539)	0.32	0.822(0.263–2.565)	0.736	0.120(0.016–0.911)	<b>0.04</b>	0.117(0.015–0.891)	<b>0.038</b>
RFA	1.123(0.448–2.813)	0.805	1.329(0.469–3.768)	0.593	1.438(0.409–5.053)	0.571	2.530(0.549–11.666)	0.234
Surgery	0.429(0.193–0.953)	<b>0.038</b>	0.677(0.228–2.010)	0.482	0.527(0.196–1.418)	0.205	0.814(0.205–3.235)	0.77
<b>GTV volume</b>	0.993(0.972–1.015)	0.54	1.007(0.997–1.042)	0.666	0.986(0.955–1.018)	0.379	0.965(0.928–1.003)	0.073
<b>Liver minus GTV mean dose</b>	0.853(0.743–0.980)	<b>0.025</b>	0.861(0.747–0.993)	<b>0.040</b>	0.968(0.833–1.123)	0.666	1.050(0.866–1.274)	0.62
<b>Liver minus GTV volume</b>	1.000(0.999–1.001)	0.987	0.999(0.997–1.001)	0.181	1.001(0.999–1.002)	0.402	1.001(0.999–1.003)	0.559



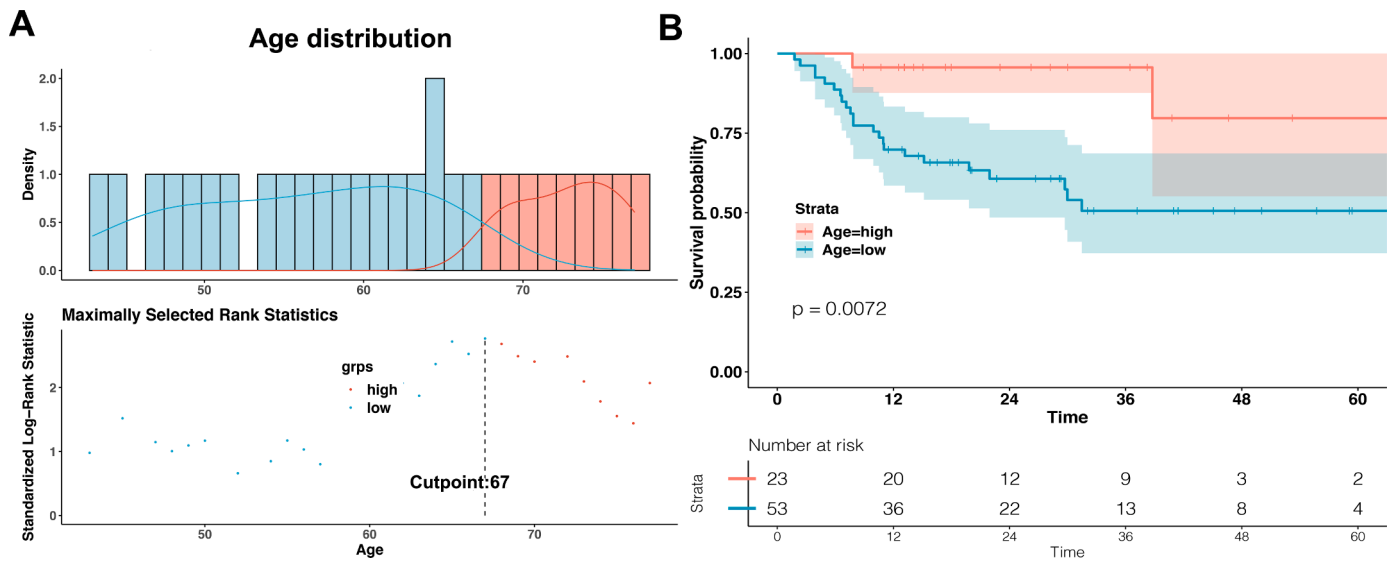
**Fig. 2.** Non-linear dependent effect of (A) Age and (B) LGD on Intrahepatic Out Field Free Survival (OutFFS). The estimated logarithm HR (blue line) with 95% CI (pink) for the association of the Age and LGD with OutFFS. SmoothHR—the optimal extended Cox-type additive hazard regression adjusted for covariates. Age, LGD were used as continuous variables, and the effect of them on the risk of mortality was modeled using a penalized spline (P-spline) expansion. Age=67 and LGD = 12.54 was used as the reference value for calculating the HR. Ln HR > 0 represents a higher cancer specific mortality risk. HR hazard ratio, CI confidence interval, LGD, Liver minus GTV mean dose.

toxicity, and we discovered that it could also affect the intra-hepatic recurrence outcome. There was a lack of clarity on the methodological assessment of the LGD cut-off. In this study, the maximally selected ranked statistics were used, because it has also been used in several studies in selecting the most informative cut-off value for the consecutive variance of data [23–25].

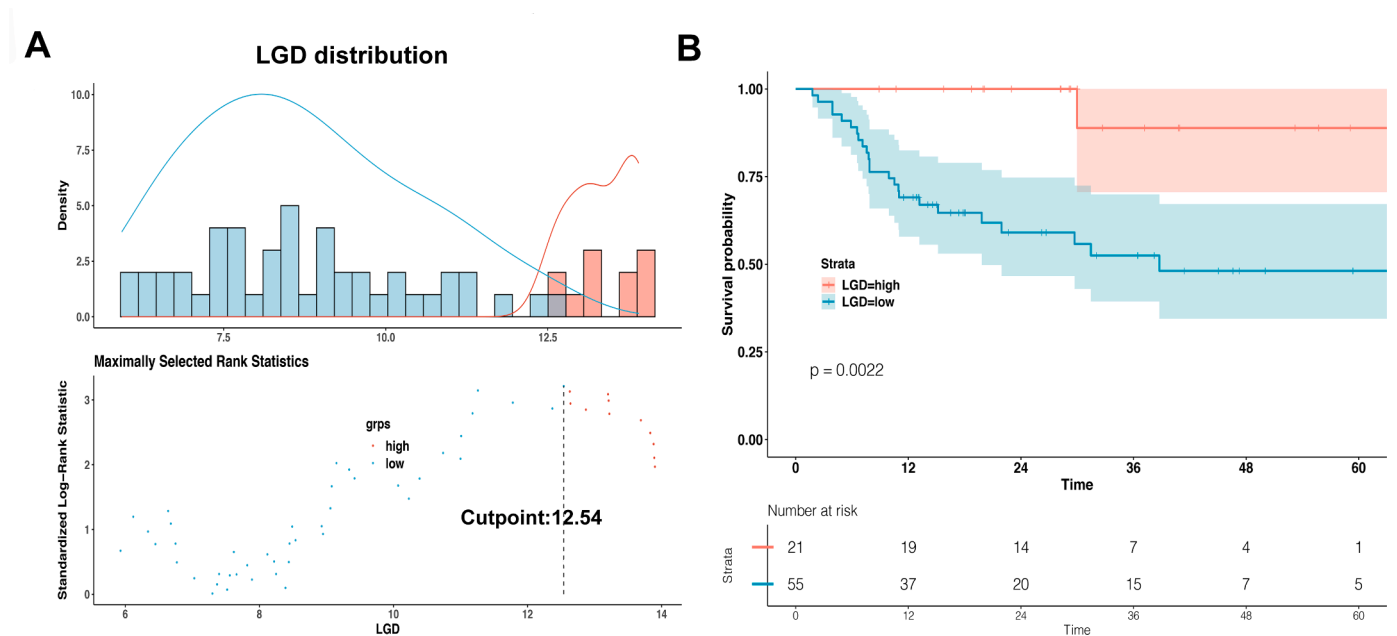
Current treatment planning goals focus on highly conformal radiation dose distribution with steep dose fall-off to protect the surrounding normal liver parenchyma from unnecessary radiation dose, however, the surgical alternatives to SBRT include hepatic lobectomy which requires large portions of the adjacent normal liver to be resected. Considering the evidence indicating inferior DFS outcomes of minor hepatectomy compared to major hepatectomy [26,27], clinicopathological studies of HCC have observed microscopic satellite lesions 5–10 mm from the gross tumor [28], and several studies [29–31] have also reported that narrow-margin (< 1 cm) resection is an independent risk factor for poorer DFS, while giving radiation dose to the narrow-margin resected liver could significantly improve the DFS and OS [32]. It seems that prophylactic treatment (whether it is surgical removal or radiation) all favors a better DFS possibly because of the eradication of MDEs, which could explain our results: Patients who have higher normal liver dosage

might have higher “incidental dosage” located around the tumor, which might eradicate the MDEs.

Given the results in our study, for patients with HCC maybe we should not set strict dosage restrictions on the remnant liver. Previous studies demonstrated a well correlated normal liver functional mapping by using sulfur colloid (SC), single-photon emission computed tomography (SPECT), computed tomography (CT) [33], or deformable image registration (DIR) [34] methods, more treatment-related details in patients with higher normal liver dosage need to be studied using these techniques. In the era of immunotherapy and the abscopal effect, more attentions are necessary to radiation-induced immune response, such as the non-target effect caused by low dose ionizing radiation, which includes damage or response in the nearby or distant tissues [35], our study might be useful for the future studies in determining whether the dosage is immune-stimulative or immune-suppressive, thus might guide the combination of immunotherapy or other chemotherapy usage given that several clinical trials have already proved some patients with HCC can benefit from the immune checkpoint inhibitors(ICIs) and system therapy [36–38]. In the previous study, a mean hepatic tolerable physical radiation dose of 21 and 6 Gy for the whole liver was appropriate to prevent RILD in patients with Child-Pugh classes A and B, respectively



**Fig. 3.** The scatter plot of maximally selected rank statistic (A) shows the cutoff value of Age distribution. The Kaplan-Meier curves of Out-Field Progression Free Survival (B) shows that the Age  $\geq 67$  (red line) has higher OFPFS rates than Age  $< 67$  (blue line).



**Fig. 4.** The scatter plot of maximally selected rank statistic (A) shows the cutoff value of two Liver minus GTV dosages. The Kaplan-Meier curves of Out-Field Progression Free Survival (B) shows that the Liver minus GTV mean dose  $\geq 12.54$  (red line) has higher OFPFS rates than Liver minus GTV dose  $< 12.54$  (blue line). (LGD, Liver minus GTV mean Dose).

[39]. However, in our study, none of the patients experienced symptomatic RILD, therefore, it is safe to render more “incidental doses” to the remnant liver to get a better recurrence survival outcome.

Our study has several limitations. First, it is limited by the relatively small sample size, the threshold of 12.54 Gy needs to be proved by multiple-center randomized control trials, given that it is a retrospective study, some of the patients’ clinical data or dosimetric data were missing, which might interfere with the final results, there is a sex bias in our study, most of our study population are males over 75%, which certainly cannot represent the normal group of patients with HCC. Second, although it has been verified that HCC is a radiation-sensitive tumor [40], the dosage distribution of the normal liver instead of the mentioned out-of-the-field mean dosage is more persuasive in revealing the possible effect of MDEs elimination. Further experiments and future

validation is warranted between the remnant liver dosage distribution and MDEs elimination.

**CRedit authorship contribution statement**

**Qi-Qiao Wu:** Conceptualization, Writing – original draft. **Yi-Xing Chen:** Conceptualization, Writing – original draft. **Shi-Suo Du:** Methodology. **Yong Hu:** Methodology. **Ping Yang:** Writing – review & editing. **Jing Sun:** Writing – review & editing. **Xin-Yue Wang:** Writing – review & editing. **Wei-Xun Wu:** Writing – review & editing. **Shu-Min Zhang:** Writing – review & editing. **Zhao-Chong Zeng:** Writing – review & editing.



## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.tranon.2022.101492](https://doi.org/10.1016/j.tranon.2022.101492).

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