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Original Research Article

Postoperative radiotherapy following null-margin hepatectomy in patients with hepatocellular carcinoma adhering to the major vessels: A propensity score-matched survival analysis cohort study

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ABSTRACT

Background & Aims: This study aims to analyze the prognosis of null-margin (≤1.0 mm) hepatectomy (NH) in patients with hepatocellular carcinoma (HCC) adhering to the major vessels and explore the value of postoperative radiotherapy (RT) in these patients.
Methods: HCC patients who underwent null-margin or wide-margin (≥1.0 cm) hepatectomy (WH) by our team from January 2008 to March 2016 were recruited and analyzed retrospectively. The patients were divided into the NH, NH + RT, and WH groups. Propensity score matching (PSM) was performed to balance baseline characteristics.
Results: A total of 357 patients were recruited. Of these, 84, 49, and 224 patients were given NH alone, NH plus RT, and WH, respectively. After PSM, the 5-year overall survival (OS) and disease-free survival (DFS) rates of the NH group were significantly worse than those of the WH group (51.5 % vs. 71.4 %, $P = 0.003$; 32.2 % vs. 50.9 %, $P = 0.005$). The OS and DFS rates of the NH + RT group were significantly higher than those of the NH group (75.6 % vs. 56.1 %, $P = 0.012$; 46.6 % vs. 30.2 %, $P = 0.015$) and similar to those of the WH group (75.6 % vs. 75.1 %, $P = 0.354$; 46.6 % vs. 56.6 %, $P = 0.717$). In addition, patients in the NH + RT group experienced significantly lower early ($P = 0.023$) and intrahepatic ($P = 0.015$) recurrences than those in the NH group.
Conclusions: Patients with HCC adhering to the major vessels who underwent NH alone had a poorer prognosis, and the addition of RT to NH provide a significant survival benefit for these patients, which may yield outcomes comparable to the efficacy of WH.

1. Introduction

Hepatocellular carcinoma (HCC) adhering to the major vessels is a complex centrally located HCC, which is almost impossible to undergo radical resection in the past. The development of preoperative assessment including the Indocyanine Green clearance test and three-dimensional image reconstruction systems, as well as surgical techniques, makes it possible for surgeons to perform resection in patients with complex centrally located HCC [1]. In recent years, surgeons in our team have performed hepatectomy for patients with the tumor adhering to the major vessels [2,3]. Considering that the majority of HCC patients were accompanied by viral hepatitis and liver cirrhosis, preservation of

Abbreviations: NH, null-margin hepatectomy; HCC, hepatocellular carcinoma; RT, radiotherapy; WH, wide-margin hepatectomy; PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; SDRVO, selective and dynamic region-specific vascular occlusion; IMRT, intensity-modulated radiotherapy; PORT, postoperative radiotherapy; CTV), clinical target volume; PTV, planning target volume; MVI, microvascular invasion; SBRT, stereotactic body radiotherapy.

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enough functional liver parenchyma is critical. Therefore, surgeons explored using a selective and dynamic region-specific vascular occlusion (SDRVO) technique to carefully peel the tumor away from the vascular surface, so as to preserve the main intrahepatic vessels and the maximum possible volume of remnant liver [2,4–7]. While the resection margin of these patients' hepatectomy was usually ≤ 1.0 mm, which is defined as null-margin hepatectomy (NH), leading to higher tumor recurrence and worse survival [8–15]. Therefore, the development of effective perioperative therapeutic strategies is urgently required for improvement in the survival of patients with NH.

Our previous prospective phase II study has revealed the efficacy and safety of postoperative intensity-modulated radiotherapy (IMRT) in HCC patients with a surgical margin of < 1.0 cm [16]. Recently, based on data from the phase II study, we conducted a propensity score matched study [17] to compare the prognosis in patients with or without postoperative radiotherapy (PORT) who received hepatectomy with a surgical margin of < 1.0 cm. It showed that the survival rates were significantly higher in patients who underwent PORT than those of patients who did not. Of which, there were 53.8 % of patients received NH due to the tumors adhering to the major vessels. In our previous study [17], narrow margin was defined as a surgical margin < 1.0 cm; wide margin was defined as a surgical margin ≥ 1.0 cm and null margin was defined as a surgical margin ≤ 1.0 mm. In this study, we will further analyze the prognosis of patients who received null-margin resection and explore the effects of PORT following NH in these patients. Furthermore, patients who underwent wide-margin hepatectomy (WH) were also included to compare outcomes with the patients who received NH with or without PORT. For making the results more convincing, we used propensity score matching (PSM) to reduce the differences of clinicopathological characteristics for the groups.

2. Patients and Methods

2.1. Patients

A retrospective analysis of consecutive patients who underwent NH or WH for HCC between January 2008 to March 2016 was performed. The inclusion criteria in this study were as follows: (1) age ≥ 18 years; (2) histopathological proved HCC received hepatectomy; (3) Eastern Cooperative Oncology Group Performance Status ≤ 1; (4) without any lymph node or distant metastasis; (5) Child-Pugh class A or B; (6) no dysfunction of major organs; (7) macroscopically complete removal of tumor; the exclusion criteria were (1) prior second tumor; (2) combining severe diseases, such as acute myocardial infarction, arrhythmias, infection; (3) receiving other types of neoadjuvant and adjuvant treatments except for PORT; (4) follow-up time or survival time < 6 months. A total of 357 patients treated by our team were recruited in this study. Among them, 133 had undergone NH because of tumors adhering to the major vascular structures. These patients were divided into two groups: patients who did not receive PORT (NH group, n = 84), and patients who underwent PORT (NH + RT group, n = 49). The remaining 224 patients presenting with tumors distant from the major vessels and receiving WH were classified as the WH group. Of which, the data of the NH + RT group were extracted from the prospectively held database [16]. This study was approved by the Independent Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences. All patients provided written informed consent in accordance with the Declaration of Helsinki.

2.2. Surgery

The extent of HCC resection was based on the tumor size, degree of hepatic cirrhosis and relation of the tumor to the major vascular structures. For hepatectomy with a surgical margin of ≥ 1.0 cm confirmed by postoperative pathology, it was considered as resection with a safe surgical margin. We defined the pathological margin ≥ 1.0 cm as WH. In cases where the tumor adhered to the major vessels, for complete tumor removal and preservation of remnant liver function, the only option was to carefully peel tumor from the vascular surface with a Cavitron Ultrasonic Surgical Aspirator. Thus, the resection margin was usually ≤ 1.0 mm. We defined the tumor exposed on the cut surface or the pathological margin ≤ 1.0 mm as NH [17], and NH was considered as a special type of R1 resection [2]. All operations were completed by the same surgical team in an attempt to standardize operative quality and safety.

2.3. Radiotherapy

All patients in the NH + RT group underwent postoperative IMRT. Treatment planning and delivery have been described previously [16]. In brief, the clinical target volume (CTV) was defined as the tumor bed plus a 1.0-cm margin and 1.5-cm margin in regions where the tumor adhered to major vascular structures. The planning target volume (PTV) included a 0.5-cm margin in the anterior–posterior and left–right directions and a 1.0-cm margin in the cranial–caudal direction around the CTV. The dose prescription of IMRT was for PTV. The prescription dose to 95 % of the PTV was planned at 60 Gy in 30 fractions over 6 weeks, but the final prescription dose was determined according to dose constraints of organs at risk. And the dose constraints for the organs at risk were shown in our previous prospective phase II study [16].

2.4. Follow-up and definitions

All postoperative patients were followed at 3-monthly intervals for the first 2 years, every 6 months during the next 3 years, and annually thereafter. The follow-up program was according with the previous study [17]. Recurrence was defined as an intrahepatic or extrahepatic new lesion on imaging. In addition, intrahepatic recurrence was categorized as marginal (a single lesion located less than 2 cm from the resection plane), nodular (a single lesion located more than 2 cm from the resection plane) and diffuse (more than one nodule scattered throughout the remaining liver) [17]. Early and late recurrences were defined as recurrence within or after 2 years after the initial liver resection, according to previous studies [18–20]. After the detection of a recurrence, further treatment such as repeat hepatectomy, local ablation, arterial chemoembolization, or other therapeutic modalities including molecular targeted therapy would be undertaken by the Multidisciplinary Liver Cancer Team in our institute. Overall survival (OS) was defined as the time interval between the date of surgical resection and the date of death or last follow-up. Disease-free survival (DFS) was defined as the time interval between the date of surgical resection and the date of disease relapse or death or last follow-up.

2.5. Statistical analysis

The chi-square test was used for the categorical variable. Survival rates were evaluated by the Kaplan-Meier method, and differences between groups in survival curves were analyzed by the log-rank test. A probability value < 0.05 was considered to be significant. PSM was performed to overcome confounding and selection biases among patients between the three groups using the following matching variables: the number of primary tumors, tumor size, T (tumor) stage, histological grade, liver capsule invasion, the type of surgery, microvascular invasion (MVI), and presence of microsatellite. Patients in the NH group were matched in a 1:2 ration with those in the WH group. And patients in the NH + RT group were matched in a 1:1 ration with those in the NH group and 1:2 ration with those in the WH group, respectively. We used a nearest-neighbor matching algorithm to balance baseline covariates without reducing the matched sample size. Statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Table 1
Demographic and clinicopathologic features of patients before and after PSM.

Variable	Before PSM				After PSM							
	NH (n = 84)	NH + RT (n = 49)	WH (n = 224)	*P*-value	NH (n = 84)	WH (n = 168)	*P*-value	NH + RT (n = 49)	NH (n = 49)	*P*-value	NH + RT (n = 49)	WH (n = 98)	*P*-value
Age (years)				0.347			1.000			0.258			0.428
Median (range)	57 (27–75)	52 (33–80)	56 (24–79)		57 (27–75)	56 (27–79)		52 (33–80)	57 (31–75)		52 (33–80)	54.5 (24–76)	
≤60	56(66.7)	38(77.6)	151 (67.4)		56(66.7)	112 (66.7)		38(77.6)	33(67.3)		38(77.6)	70(71.4)	
>60	28(33.3)	11(22.4)	73(32.6)		28(33.3)	56(33.3)		11(22.4)	16(32.7)		11(22.4)	28(28.6)	
Gender				0.680			0.180			0.790			0.744
Male	67(79.8)	41(83.7)	188 (83.9)		67(79.8)	145 (86.3)		41(83.7)	40(81.6)		41(83.7)	84(85.7)	
Female	17 (20.2)	8(16.3)	36(16.1)		17(20.2)	23(13.7)		8(16.3)	9(18.4)		8(16.3)	14(14.3)	
Chronic hepatitis				0.903			1.000			1.000			0.865
HBV+/HCV+	74(88.1)	42(85.7)	197 (87.9)		74(88.1)	148 (88.1)		42(85.7)	42(85.7)		42(85.7)	85(86.7)	
No. of primary tumors				0.007			0.473			0.475			0.370
1	68(81.0)	49 (100.0)	189 (84.4)		68(81.0)	142 (84.5)		49 (100.0)	47(95.9)		49 (100.0)	94(96.4)	
≥2	16(19.0)	0(0.0)	35(15.6)		16(19.0)	26(15.5)		0(0.0)	2(4.1)		0(0.0)	4(4.1)	
Tumor size (cm)				0.034			0.222			0.402			0.439
≤5	51(60.7)	33(67.3)	169 (75.4)		51(60.7)	115 (68.5)		33(67.3)	29(59.2)		33(67.3)	72(73.5)	
>5	33(39.3)	16(32.7)	55(24.6)		33(39.3)	53(31.5)		16(32.7)	20(40.8)		16(32.7)	26(26.5)	
AFP (ng/mL)				0.763			0.616			0.806			0.591
≤400	63(75.0)	38(77.6)	163 (72.8)		63(75.0)	121 (72.0)		38(77.6)	39(79.6)		38(77.6)	72(73.5)	
>400	21(25.0)	11(22.4)	61(27.2)		21(25.0)	47(28.0)		11(22.4)	10(20.4)		11(22.4)	26(26.5)	
Child-Pugh class (score)				0.761			0.616			0.315			0.478
A (5–6)	83(98.8)	49 (100.0)	222 (99.1)		83(98.8)	167 (99.4)		49 (100.0)	48(98.0)		49 (100.0)	97(99.0)	
B (7)	1(1.2)	0(0.0)	2(0.9)		1(1.2)	1(0.6)		0(0.0)	1(2.0)		0(0.0)	1(1.0)	
BCLC stage				0.009			0.624			0.328			0.121
0	10(11.9)	5(10.2)	39(17.4)		10(11.9)	23(13.7)		5(10.2)	7(14.3)		5(10.2)	18(18.4)	
A	61(72.6)	43(87.8)	160 (71.4)		61(72.6)	126 (75.0)		43(87.8)	40(81.6)		43(87.8)	76(77.6)	
B	13(15.5)	0(0)	25(11.2)		13(15.5)	19(11.3)		0(0)	2(4.1)		0(0)	4(4.1)	
C	0(0)	1(2.0)	0(0)		0(0)	0(0)		1(2.0)	0(0)		1(2.0)	0(0)	
CNLC stage				0.011			0.320			0.317			0.284
Ia	41(48.8)	33(67.3)	144 (64.3)		41(48.8)	99(58.9)		33(67.3)	29(59.2)		33(67.3)	72(73.5)	
Ib	31(36.9)	15(30.6)	55(24.6)		31(36.9)	50(29.8)		15(30.6)	18(36.7)		15(30.6)	22(22.4)	
IIa	8(9.5)	0(0)	13(5.8)		8(9.5)	9(5.4)		0(0)	0(0)		0(0)	1(1.0)	
IIb	4(4.8)	0(0)	12(5.4)		4(4.8)	10(6.0)		0(0)	2(4.1)		0(0)	3(3.1)	
IIIa	0(0)	1(2.0)	0(0)		0(0)	0(0)		1(2.0)	0(0)		1(2.0)	0(0)	
Vascular adhesion				0.948						0.802			
HV	36(42.9)	20(40.8)						20(40.8)	20(40.8)				
PV	24(28.6)	15(30.6)						15(30.6)	13(26.5)				
IVC	7(8.3)	5(10.2)						5(10.2)	3(6.1)				
HV + PV	10(11.9)	4(8.2)						4(8.2)	8(16.3)				
HV + IVC	3(3.6)	3(6.1)						3(6.1)	2(4.1)				
PV + IVC	1(1.2)	0(0)						0(0)	0(0)				
HV + PV + IVC	3(3.6)	2(4.1)						2(4.1)	3(6.1)				
T Stage (AJCC, 7th ed.)				0.764			0.613			0.159			0.828
T1	58(69.0)	31(63.3)	155 (69.2)		58(69.0)	113 (67.3)		31(63.3)	38(77.6)		31(63.3)	67(68.4)	
T2	16(19.0)	11(22.4)	48(21.4)		16(19.0)	36(21.4)		11(22.4)	6(12.2)		11(22.4)	20(20.4)	
T3	6(7.1)	6(12.2)	16(7.1)		6(7.1)	15(8.9)		6(12.2)	2(4.1)		6(12.2)	8(8.2)	
T4	4(4.8)	1(2.0)	5(2.2)		4(4.8)	4(2.4)		1(2.0)	3(6.1)		1(2.0)	3(3.1)	
Histological grading (WHO)				0.115			0.525			0.270			0.527
Well	8(9.5)	6(12.2)	26(11.6)		8(9.5)	21(12.5)		6(12.2)	7(14.3)		6(12.2)	13(13.3)	
Moderate	53(63.1)	38(77.6)	135 (60.3)		53(63.1)	98(58.3)		38(77.6)	32(65.3)		38(77.6)	70(71.4)	
Poor	22(26.2)	3(6.1)	56(25.0)		22(26.2)	42(25.0)		3(6.1)	9(18.4)		3(6.1)	13(13.3)	
Unclear	1(1.2)	2(4.1)	7(3.1)		1(1.2)	7(4.2)		2(4.1)	1(2.0)		2(4.1)	2(2.0)	
Resection type				0.748			0.826			0.835			0.571
Anatomical resection	28(33.3)	19(38.8)	74(33.2)		28(33.3)	58(34.7)		19(38.8)	18(36.7)		19(38.8)	33(34.0)	

(*continued on next page*)

Table 1 (*continued*)

Variable	Before PSM				After PSM								
	NH (n = 84)	NH + RT (n = 49)	WH (n = 224)	*P*-value	NH (n = 84)	WH (n = 168)	*P*-value	NH + RT (n = 49)	NH (n = 49)	*P*-value	NH + RT (n = 49)	WH (n = 98)	*P*-value
Non-anatomical resection	56(66.7)	30(61.2)	149 (66.8)		56(66.7)	109 (65.3)		30(61.2)	31(63.3)		30(61.2)	64(66.0)	
Presence of microsatellite	4(4.8)	2(4.1)	9(4.0)	0.958	4(4.8)	8(4.8)	1.000	2(4.1)	2(4.1)	1.000	2(4.1)	2(2.0)	0.858
Microvascular invasion	13(15.5)	9(18.4)	36(16.1)	0.903	13(15.5)	29(17.3)	0.720	9(18.4)	8(16.3)	0.790	9(18.4)	20(20.4)	0.769
Major vascular invasion	0(0.0)	1(2.0)	0(0.0)	0.043	0(0.0)	0(0.0)	1.000	1(2.0)	0(0.0)	1.000	1(2.0)	0(0.0)	0.333
Liver capsule invasion	49(58.3)	21(42.9)	132 (58.9)	0.113	49(58.3)	108 (64.3)	0.358	21(42.9)	26(53.1)	0.312	21(42.9)	49(50.0)	0.414

HBV, Hepatitis B virus; HCV, Hepatitis C virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer Staging; AJCC, American Joint Committee on cancer; WHO, World Health Organization; PSM, propensity score matching; RT, radiotherapy; NH, null-margin hepatectomy alone; NH + RT, null-margin hepatectomy plus postoperative RT; WH, wide-margin hepatectomy; IVC, inferior vena cava; PV, portal vein; HV, hepatic vein.

3. Results

3.1. Patients, Tumors, and treatment characteristics

In total, 357 patients were eligible for the analysis. 49 patients underwent NH plus PORT, 84 patients underwent NH alone, and 224 patients underwent WH. The clinicopathologic characteristics of these groups are summarized in Table 1. Compared with the NH + RT group, there was a higher proportion of patients with poorly differentiated tumors (6.1 % vs. 26.2 %, $P = 0.030$; 6.1 % vs. 25.0 %, $P = 0.034$), more cases had ≥ 2 primary tumors (0.0 % vs. 19.0 %, $P = 0.001$; 0.0 % vs. 15.6 %, $P = 0.003$) and more cases presented with liver capsule invasion (42.9 % vs. 58.3 %, $P = 0.085$; 42.9 % vs. 58.9 %, $P = 0.040$) in the NH and WH groups. Compared with the NH group, fewer patients had tumors size > 5 cm in the WH group (39.3 % vs. 24.6 %, $P = 0.011$). After PSM, we created 3 new-matched cohorts of the NH group (n = 84) vs. the WH group (n = 168); the NH + RT group (n = 49) vs. the NH group (n = 49); the NH + RT group (n = 49) vs. the WH group (n = 98). After adjusting for propensity scores, the patient and tumor characteristics were well-balanced between the matched groups (Table 1).

The median postoperative IMRT dose was 60 Gy (range, 50–60 Gy). Among the 49 patients who underwent PORT, 93.9 % achieved postoperative IMRT with a total dose of more than 55 Gy.

3.2. Survival rates

The median follow-up duration was 47 months (6–140 months) among all 357 patients. Before PSM, the 5-year OS rates of the NH, NH + RT, and WH groups were 51.5 %, 75.6 % and 73.8 %, respectively. The 5-year DFS rates of the NH, NH + RT, and WH groups were 32.2 %, 46.6 % and 50.3 %, respectively. Patients in the NH group had significantly lower OS and DFS rates than in the NH + RT ($P = 0.003$, Fig. 1**A**; $P = 0.014$, Fig. 1**B**) and WH ($P = 0.001$, Fig. 1**A**; $P = 0.003$, Fig. 1**B**) groups. While patients in the NH + RT and WH groups showed similar OS ($P = 0.435$, Fig. 1**A**) and DFS ($P = 0.773$, Fig. 1**B**).

After PSM, 84 patients from the NH group were matched to 168 patients from the WH group. The 5-year OS and DFS rates were still significantly lower in the NH group than those in the WH group (51.5 % vs. 71.4 %, $P = 0.003$, Fig. 1**C**; 32.2 % vs. 50.9 %, $P = 0.005$, Fig. 1**D**).

After PSM, 49 patients of the NH + RT group were matched to 49 patients of the NH group, and 98 patients of the WH group, respectively. In the matched cohort of the NH + RT and NH groups, the 5-year OS and DFS rates were still significantly different (75.6 % vs. 56.1 %, $P = 0.012$, Fig. 1**E**; 46.6 % vs. 30.2 %, $P = 0.015$, Fig. 1**F**). In addition, in the matched cohort of the NH + RT and WH groups, the 5-year OS and DFS rates were still no significant difference (75.6 % vs. 75.1 %, $P = 0.354$, Fig. 1**G**; 46.6 % vs. 56.6 %, $P = 0.717$, Fig. 1**H**).

3.3. Patterns of recurrence

Treatment failure was documented in 184 (51.5 %) of the 357 patients. 133 (37.3 %) patients showed disease recurrence within 2 years of the initial resection, while 57 (16.0 %) patients showed disease recurrence after 2 years. The incidence and patterns of recurrence between groups before and after PSM are presented in Table 2.

Before PSM, patients receiving NH alone showed a significantly higher incidence of early recurrence than those who received NH plus PORT, or WH ($P = 0.016$). There appeared no significant difference in intrahepatic recurrence between the three groups ($P = 0.193$, Fig. 2**A**). Regarding marginal recurrence, 9.5 % of patients in the NH group, 2.8 % of patients in the WH group, and no patient in the NH + RT group developed marginal recurrence ($P = 0.007$). Patients in the NH group experienced significantly higher extrahepatic recurrences than the other two groups ($P = 0.014$, Fig. 2**B**).

In the matched cohort of the NH + RT and NH groups, patients in the NH + RT group showed a significantly lower rate of early recurrence (28.6 % vs 51.0 %, $P = 0.023$) and intrahepatic recurrence ($P = 0.015$, Fig. 2**C**). Whereas there was no significant difference in extrahepatic recurrence rates between the matched groups ($P = 0.324$, Fig. 2**D**). Regarding the patterns of intrahepatic recurrence, patients who had undergone PORT showed significantly lower rates of diffuse ($P = 0.049$) and marginal ($P = 0.005$) recurrence than those who did not.

In the matched cohort of the NH + RT and WH groups, there was no significant difference in early (28.6 % vs 33.7 %, $P = 0.615$), intrahepatic ($P = 0.928$, Fig. 2**E**), and extrahepatic ($P = 0.941$, Fig. 2**F**) recurrence. Regarding the patterns of intrahepatic recurrence, there was also no significant difference in marginal ($P = 0.211$) and diffuse ($P = 0.183$) recurrence between the matched groups.

In total, 127 patients who developed recurrence received salvage treatments, including transcatheter arterial chemoembolization, surgery, radiofrequency ablation, radiotherapy, or systemic therapy. Additionally, 40 patients received supportive care owing to their poor performance status. The types of treatments received by the remaining patients are unknown.

3.4. Toxicity

IMRT was well tolerated without classical or non-classical radiation-induced liver disease, with a low rate of grade-3 toxicities. Only 5 (10.2 %) patients developed grade-3 acute toxicities, including leukopenia (8.2 %), thrombocytopenia (2.0 %), and increased alanine aminotransferase (2.0 %) levels. All patients who experienced grade-3 toxicities recovered after symptomatic treatment without interruption of radiotherapy. Only three patients experienced grade-2 gastritis or duodenitis. Moreover, there were no grade-4 or −5 radiation-related toxicities.

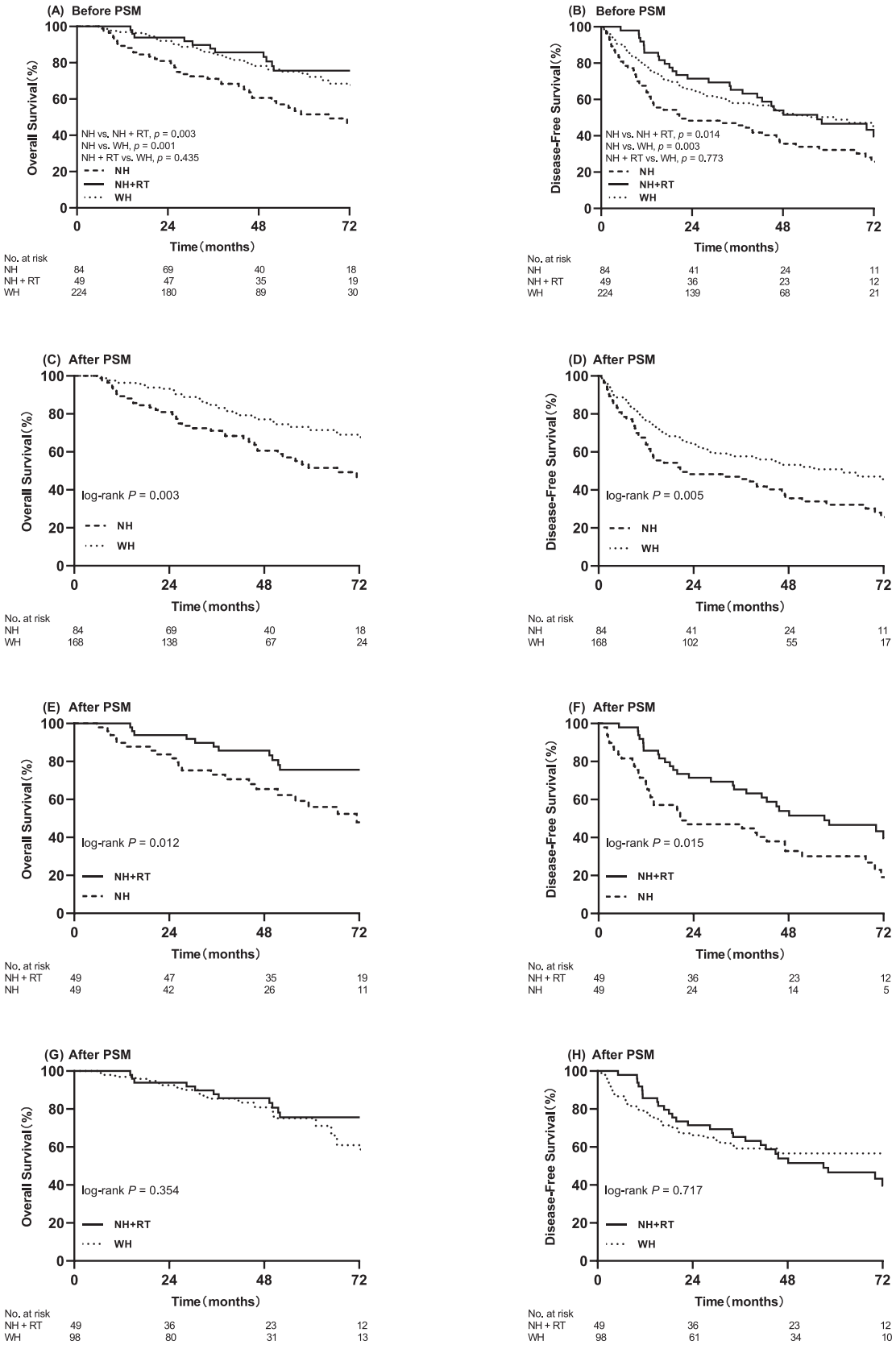

Fig. 1. Overall survival and disease-free survival between groups before and after PSM. PSM, propensity score matching; NH, null-margin hepatectomy alone; NH + RT, null-margin hepatectomy plus postoperative radiotherapy; WH, wide-margin hepatectomy.

Table 2
Incidence and pattern of HCC recurrence before and after PSM.

Pattern of recurrence	Before PSM			After PSM		
	NH (n = 84)	NH + RT (n = 49)	WH (n = 224)	NH + RT (n = 49)	NH (n = 49)	WH (n = 98)
Total recurrence	56 (66.7)	27 (55.1)	101 (46.3)	27 (55.1)	34 (69.4)	38 (39.2)
Early or late recurrence						
ER(<2 years)	42 (50.0)	14 (28.6)	77 (34.4)	14 (28.6)	25 (51.0)	32 (33.7)
LR(≥2 years)	14 (16.6)	13 (26.5)	30 (13.4)	13 (26.5)	9 (18.4)	6(6.1)
Intrahepatic recurrence	44 (52.4)	23 (46.9)	92 (42.2)	23 (46.9)	31 (63.3)	36 (37.1)
Marginal	8(9.5)	0(0)	6(2.8)	0(0)	7 (15.2)	3(3.1)
Diffuse	20 (23.8)	5 (10.2)	41 (18.3)	5 (10.2)	12 (24.5)	18 (18.4))
Nodular	12 (14.3)	18 (36.7)	39 (17.4)	18 (36.7)	10 (20.4)	13 (13.3)
Unclear	4(4.8)	0(0)	6(2.7)	0(0)	2(4.1)	2(2.0)
Extrahepatic recurrence	20 (23.8)	7 (14.3)	22 (10.3)	7 (14.3)	9 (18.4)	11 (11.5)

HCC, hepatocellular carcinoma; ER, early recurrence; LR, late recurrence; PSM, propensity score matching; RT, radiotherapy; NH, null-margin hepatectomy alone; NH + RT, null-margin hepatectomy plus postoperative RT; WH, wide-margin hepatectomy.

4. Discussion

In this retrospective research, we analyzed the prognosis of NH in patients with HCC adhering to the major vessels and validated the value of adjuvant RT after NH in these patients.

In clinical practice, more than 60 % of patients with centrally located HCC had tumors adherent to major vessels [2]. Surgeons in our team had performed NH for these patients using an SDRVO technique since May 2006 and indicated that the operation was safe [2]. NH was considered as a special type of R1 resection by surgeons [2] and associated with a risk of tumor recurrence and a poor prognosis [8–15]. Similarly, Nara et al. reported that 165 patients with HCC who underwent marginal (≤1.0 mm) resection compared with 374 patients who underwent non-marginal (>1.0 mm) resection, the marginal resection group showed a worse recurrence-free survival than the non-marginal group ($P = 0.003$) [18]. Aoki et al. also reported that a negative but 0-mm surgical margin was associated with poorer overall and recurrence-free survival than a wider (>0 mm) margin in the non-anatomical resection group [10]. In our study, the result showed that the 5-year OS (51.5 %) and DFS (32.2 %) rates for patients who underwent NH alone were significantly worse than those for patients who received NH plus PORT or WH. And after PSM, the baseline characteristics were well balanced, the survival rates for patients who underwent NH alone were still significantly worse.

However, the current guidelines do not expressly recommend standard perioperative treatment protocols for centrally located HCC. With the development of RT techniques, IMRT has been clinically performed as neoadjuvant or adjuvant therapy in the management of HCC. In the last decade, several retrospective and prospective studies have demonstrated its efficacy in improving prognosis, especially among patients with centrally located HCC, narrow margin, MVI, and portal vein tumor thrombus [16,17,21–29]. A recent systematic review showed that PORT decreased the risk of recurrence and conferred an oncological benefit for patients with high-risk recurrent HCC after hepatectomy but without increasing severe radiation-related adverse events [30]. As for the study on PORT following NH, Shi et al.[23] conducted a study in HCC patients with MVI-positive who received marginal resection (<1.0 mm). Patients were assigned into the postoperative stereotactic body radiotherapy (SBRT) and surgery alone groups, with 38 patients for each group, respectively. The total dose of SBRT was 35 Gy (biological effective dose = 59.5 Gy). The overall incidence of radiotherapy-related toxicities was 31.6 % (12/38), and no grade-3 or above toxicities developed. In the SBRT and surgery alone groups, the 5-year DFS rates were 56.1 % versus 26.3 % ($P = 0.005$) and 5-year OS rates were 75 % versus 53.7 % ($P = 0.053$), respectively. It showed that SBRT on the resection margin provides a safe and effective therapeutic modality of adjuvant setting in HCC with marginal resection. In our study, postoperative IMRT was performed by means of a conventional fractionated scheme and the median prescription dose was 60 Gy. To ensure the target volume completely covers the regions at risk, CTV was defined as the tumor bed with a 1.5-cm margin in regions where the tumor adhered to the major vessels. These patients had no marginal recurrence and did not develop radiation-induced liver disease. It indicated that the prescription and target volume of our study are appropriate. Furthermore, in our study, both before and after PSM, patients receiving NH plus PORT showed more favorable OS and DFS compared with those receiving NH alone, comparable to the efficacy of WH. Based on previous trial and our data, we believe that both conventional RT and SBRT schemes are safe and effective for patients who received NH.

As for how PORT improved survival, due to NH being considered a special type of R1 resection, occult microscopic HCC cells may be left behind at the surgical margin and in the remaining liver tissue around initial HCC after NH [31–34]. There is a higher tendency to marginal recurrence and intrahepatic spread after NH alone, which may affect survival. In our study, between the matched groups of patients undergoing PORT or NH alone, it showed that patients undergoing PORT did not develop marginal recurrence and PORT reduced the probability of early and intrahepatic recurrences. We speculate that the addition of PORT to NH may control occult microscopic HCC cells at the resection margin and in the remnant liver tissue around initial HCC after NH, which could prevent the spread of the residual tumor and lower the likelihood of recurrence, thus improving survival in the patients who received NH. In addition to the well-matched baseline due to the application of PSM, it was the first time that the survival and recurrence patterns between NH plus PORT and WH were contrasted, and no significant difference was revealed.

Some limitations are present in this study. First, this is a single-center study with a small number of patients who underwent PORT following NH. Second, NH for complex centrally located HCC is a technically demanding procedure, which limits the generalizability of the approach. In addition, selection bias was possible despite the use of PSM due to the nonrandomized, retrospective study design.

5. Conclusion

In conclusion, the present study revealed that patients with HCC adhering to the major vessels who underwent null-margin resection alone had a poor prognosis, and PORT has a significant survival benefit for these patients. Moreover, PORT combined with null-margin resection may be equally effective as wide-margin resection.

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Author contributions

Concept and design: WW, YL. Acquisition, analysis, or interpretation of data: WW, LL. Drafting of the manuscript: LL, BC, XZ. Statistical analysis: LL, BC, XZ. Obtained funding: WW. Administrative, technical,

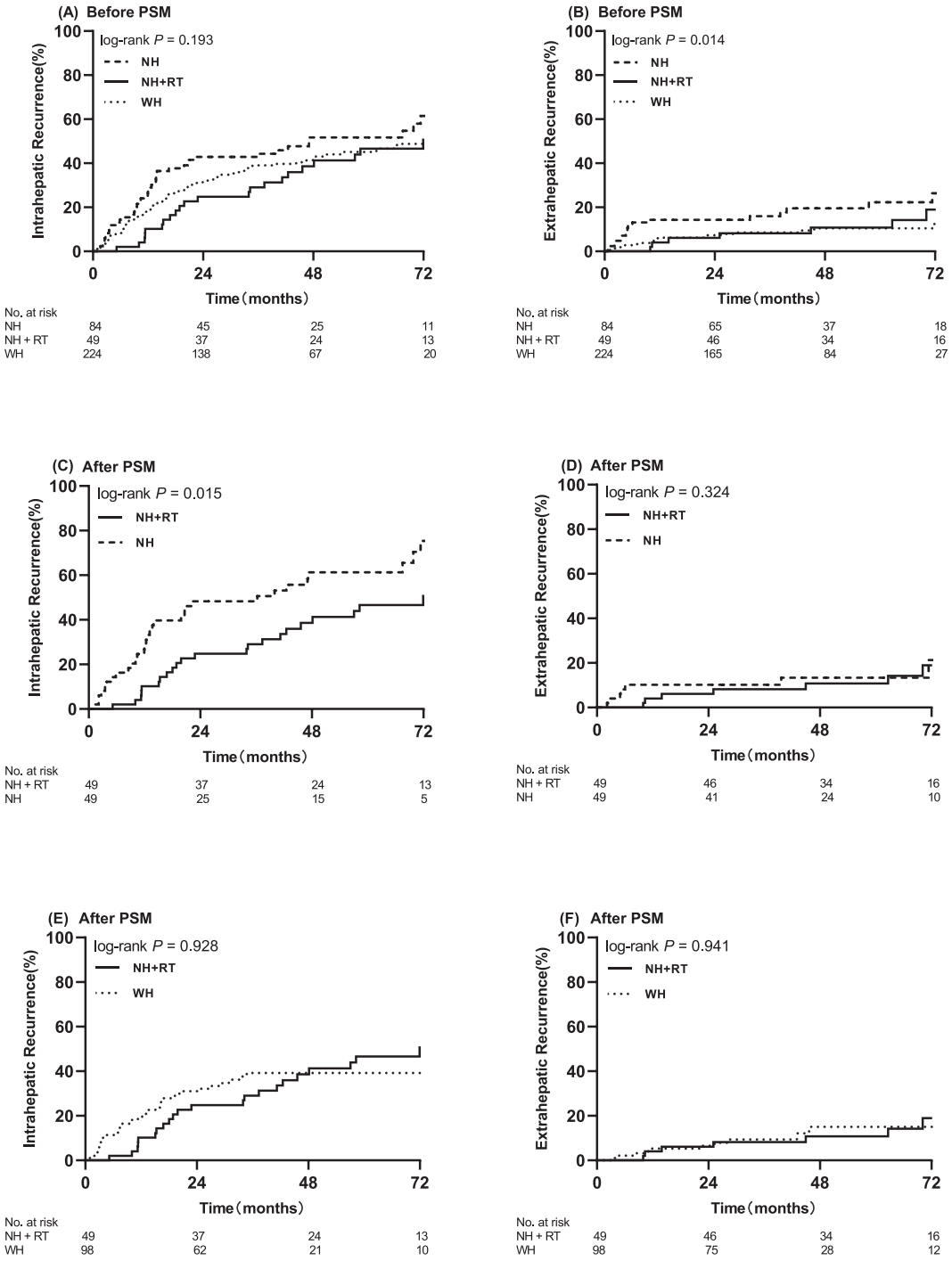

Fig. 2. Cumulative incidence of intrahepatic recurrence, and extrahepatic recurrence between groups before and after PSM. PSM, propensity score matching; NH, null-margin hepatectomy alone; NH + RT, null-margin hepatectomy plus postoperative radiotherapy; WH, wide-margin hepatectomy.

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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.

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