Hepatectomy combined with diaphragmatic resection for hepatocellular carcinoma with diaphragmatic involvement: A propensity score-matched analysis.

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Synopsis: Hepatectomy combined with diaphragmatic resection is an acceptable treatment for hepatocellular carcinoma with diaphragmatic involvement.

ABSTRACT

Purpose: We evaluated the short- and long-term surgical outcomes of hepatectomy combined with diaphragmatic resection for hepatocellular carcinoma (HCC) with diaphragmatic involvement.

Methods: We retrospectively reviewed the surgical outcomes of HCC patients with diaphragmatic resection (DR group) and HCC patients without diaphragmatic resection (non-DR group). We applied 1:1 propensity score matching (PSM) to these subjects.

Results: The study included 46 patients in DR group and 828 patients in non-DR group. The DR group cases were pathologically more advanced, and both overall and relapse-free survival among the patients in this group with pathological diaphragmatic invasion were similar to cases with pathological diaphragmatic fibrous adhesion. There were 40 patients from each group subjected to PSM. In these matched cohorts, there was no statistically significant difference between the two groups regarding perioperative outcomes, overall survival, and relapse-free survival. Multivariate analyses of our matched HCC patients revealed that alpha-fetoprotein expression and tumor size were independent prognostic factors for overall survival and poor differentiation for relapse-free survival, whereas neither diaphragmatic invasion nor diaphragmatic resection were prognostic indicators. The most frequent site of recurrence in non-DR group was the liver, whereas the most frequent site of recurrence in DR group was the lung before and after PSM.

Conclusions: The short- and long-term surgical outcomes of DR HCC cases are equivalent to their non-DR counterparts under a matched clinicopathological background. Hepatectomy combined with DR is an acceptable treatment for HCC with either diaphragmatic fibrous adhesion or diaphragmatic invasion.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequently occurring primary liver cancer and is ranked as the sixth most common neoplasm and the third leading cause of cancer death worldwide [1]. Several factors are known to affect the prognosis of HCC, including alpha-fetoprotein (AFP), portal vein invasion, and tumor size [1-3]. On the other hand, the impact of diaphragmatic invasion on the prognosis in HCC is still unclear due to its rarity. Hepatic resection is the established treatment of choice for HCC, but the efficacy of a hepatectomy combined with diaphragmatic resection for treating HCC with diaphragmatic involvement is also still unclear.

A peripherally located large HCC arising from the liver is clinically prone to involvement of the diaphragm, particularly if the large tumor is located in segment VII or VIII [4]. However, it is difficult during an operation to discriminate between the histological invasion of the diaphragm and a strictly fibrous adhesion only [5]. In addition, HCCs with gross diaphragmatic involvement tend to have abundant blood flow from the surrounding mesenteries and diaphragm [6]. Hence, a forcible dissecting approach to the diaphragm typically triggers bleeding from the surface of the tumor, which is still being supplied abundantly from the diaphragm and peripheral mesenteries [6]. Thus, when a HCC tumor is suspected to have infiltrated the diaphragm, a hepatectomy combined with an en bloc resection of the diaphragm is thought to be important to avoid such intraoperative bleeding risk or tumor rupture. Several reports have justified this type of surgery [4-7]. However, although infiltration of the diaphragm of HCC is common in advanced cases, such as those harboring very large tumors, there has been no prior study that has matched the clincopathological background of these patients and this has caused a selection bias.

In our present study, we reviewed a cohort of HCC patients who underwent a hepatectomy with or without a diaphragmatic resection. We analyzed the clinicopathological features of these cases and the impact of a diaphragmatic resection on their surgical outcomes. We also assessed the short- and long-term outcomes of hepatectomy combined with diaphragmatic resection for HCC with diaphragmatic involvement in patients that had undergone propensity score matching (PSM).

PATIENTS AND METHODS

Between 1999 and 2018, 874 HCC patients underwent liver resection at the Department of Gastroenterological Surgery I, Hokkaido University Hospital. These cases could be divided into 46 HCC patients with diaphragmatic resection (DR group) and 828 HCC patients without diaphragmatic resection (non-DR group). In the DR group, postoperative pathological examination confirmed that 25 patients had diaphragmatic fibrous adhesion and 21 patients had diaphragmatic invasion. Among 21 patients who had pathological diaphragmatic invasion, nine cases showed pathological tumor invasion to the diaphragm muscle layer. In our present analysis, we defined diaphragmatic invasion as HCC with pathological diaphragmatic invasion, diaphragmatic fibrous adhesion as a HCC with diaphragmatic fibrous adhesion confirmed by pathology, and diaphragmatic involvement as HCC with either diaphragmatic fibrous adhesion without pathological invasion or pathological diaphragmatic invasion.

This study was approved by the institutional review board of Hokkaido University Hospital (approval number: 019-0340). All analyses in this study were performed in accordance with the ethical guidelines of Hokkaido University Hospital.

Preoperative management

Preoperative management was performed as described in our previous report [8]. Briefly, we evaluated all patients by abdominal and chest computed tomography (CT) prior to surgery. The volumes of the liver parenchyma and tumors were measured using a three-dimensional workstation, and the effective resection ratio (%) was calculated. The indocyanine green retention rate at 15 minutes (ICGR15) was measured to evaluate the functional liver reserve. We then used our algorithm which incorporates the ICGR15 and remnant liver volume to determine the optimal operative procedure, as previously described [8].

Surgical methods

The surgical methods used for liver resection have been previously described [8]. Briefly, transection of the liver parenchyma was performed using the hook spatula of an ultrasonic harmonic scalpel (Ethicon EndoSurgery, San Angelo, TX) and either a DS3.0 Dissecting Sealer (Medtronic, Minneapolis, MN) or bipolar cautery with a saline irrigation system. When the HCC lesion was found to be grossly adherent to the diaphragm, en bloc resection of the diaphragm was performed without an attempt to dissect the tumor away from the diaphragm. Prior to 2012, we used an electrocautery device for en bloc resection with part of the diaphragm, whereas we have applied a LigaSure Impact™ vessel sealing device (Covidien, Dublin, Ireland) to cut off the blood flow from the subphrenic artery since 2012, as previously described [6]. After liver resection, a thoracic drain was placed in the chest cavity and the diaphragm was closed by running sutures with non-absorbable monofilament thread. We defined anatomical resection in our current study as the anatomically complete removal of the lesion based on Couinaud’s classification (segmentectomy, sectionectomy, hemihepatectomy, and trisectionectomy).

Statistical analysis

Categorical variables were compared using the Fisher exact test between the groups. Continuous variables were expressed as medians with ranges, and compared using the Mann-

Whitney U test between the groups. The overall survival rates and relapse-free survival rates were calculated using the Kaplan–Meier method and compared between the groups using the log-rank test. Potential prognostic factors were identified by univariate analysis using the log-rank test. Independent prognostic factors were evaluated using a Cox proportional-hazards regression model. Differences in the clinicopathological backgrounds between the DR and non-DR cases were propensity score matched (PSM) at a 1:1 ratio. Nine variables (age, HCV antibody, Child-Pugh classification, AFP, tumor node metastasis (TNM) stage, tumor size, differentiation, portal vein invasion, and hepatic vein invasion) were entered into the propensity score, and the caliper was set to 0.20. In this study, $p < 0.05$ was considered significant. All statistical analyses were performed using JMP version 14 for Windows (SAS Institute, Cary, NC).

RESULTS

Differences in the clinicopathological features and perioperative surgical outcomes of HCC patients according to the presence or absence of diaphragm resection before and after propensity score matching

The clinicopathological features of the HCC patients with and without diaphragmatic resection are presented in Table 1. Sex, proportion of hepatitis B surface antigen, ICGR15, proportion of liver cirrhosis, tumor number, hepatic artery invasion status, and bile duct invasion status were similar between the DR and non-DR groups. On the other hand, significant differences were found between the groups in age, proportion of hepatitis C virus antibody, Child-Pugh classification, AFP expression, TNM stage, tumor size, histological differentiation, portal vein invasion status, and hepatic vein invasion status. We applied PSM to the patient backgrounds because of these clinicopathological differences between the groups. Forty patients each in the DR group and non-DR group were matched in this way, with no significant differences found in the clinicopathological features between the two PSM groups (Table 1). In our present study, portal and hepatic vein invasion refer to both macroscopic and microscopic vascular invasion. There were 20 macroscopic portal vein tumor thrombus (PVTT) (defined as PVTT involving the first or the second branches or main trunk of the portal vein) cases among DR group and 79 macroscopic PVTT cases among non-DR group in this study before PSM ($p<0.0001$). After PSM, three were also no significant difference between the DR and non-DR groups in terms of macroscopic PVTT ($p=1.0000$). The perioperative outcomes of the HCC patients with and without diaphragmatic resection are provided in Table 2. Prior to PSM, the DR patients showed a tendency for a longer operation time, more blood loss, and more extensive anatomical resection. Prior to PSM, postoperative complications in accordance with the Clavien-Dindo classification [9] were similar between the two study groups, whereas the postoperative hospital stay was longer in the DR group. However, these perioperative outcomes showed very similar distributions between the two groups after PSM (Table 2).

Surgical outcomes according to the presence or absence of diaphragm resection before and after propensity score matching

Before PSM, the overall 5-year survival rates in the DR and non-DR groups were 45.6% and 64.3%, respectively (p=0.0002; Fig. 1a), and the 5-year relapse-free survival rates were 15.3% and 33.9%, respectively (p=0.0002; Fig. 1b). We next examined the impact on prognosis of the presence or absence of pathological diaphragmatic invasion in the DR group. There was no significant differences between the HCC patients with diaphragmatic fibrous adhesion and those with diaphragmatic invasion in terms of overall survival (p = 0.5509) or relapse-free survival (p=0.0988; Fig. 1c, d). After PSM, the overall 5-year survival rates in the DR and non-DR groups were 48.5% and 32.3%, respectively (p=0.3919; Fig. 1e), and the 5-year relapse-free survival rates were 18.2% and 9.4%, respectively (p=0.8562; Fig. 1f).

Risk factors for survival in the HCC patients with and without diaphragm resection in the propensity score-matched cohort

In the DR and non-DR groups after PSM, univariate analysis revealed that the Child-Pugh classification, AFP expression, tumor size, differentiation, and portal vein invasion were significant prognostic factors for overall survival (Table 3). Multivariate analysis of these propensity score-matched HCC patients revealed AFP expression and tumor size as independent prognostic indicators of overall survival (Table 3). Univariate and multivariate analysis also revealed poor differentiation as an independent prognostic factor of relapse-free survival (Table 3). Notably however, neither diaphragmatic invasion nor diaphragmatic resection was found to be prognostic factors for both overall survival and relapse-free survival in the HCC subjects after PSM.

Recurrence sites in HCC patients with and without diaphragmatic resection

The sites of HCC recurrence in our current study subjects are listed in Table 4. Prior to PSM, more patients in the DR group experienced extra-hepatic recurrences at sites such as the lung, lymph node, brain, and peritoneum, whereas more cases in the non-DR group experienced intrahepatic recurrence. The most frequent sites of recurrence were the liver in the non-DR group (444 of 828 patients; 53.6%), and the lung in the DR group (23 of 46patients; 50.0%). After PSM however, more patients in non-DR group experienced intrahepatic recurrence, but there was no significant difference between the DR and non-DR groups in terms of extra-hepatic recurrence. The most frequent site of recurrence in non-DR group was the liver, whereas the most frequent site of recurrence in DR group was the lung after PSM. There was 1 case of a local recurrence at the diaphragm in the DR group. This patient had undergone a right anterior sectionectomy combined with diaphragmatic resection for a ruptured HCC, which was treated preoperatively using transcatheter arterial chemoembolization (TACE). We next examined the sites of HCC recurrence among patients with diaphragmatic fibrous adhesion and diaphragmatic invasion. There were no significant difference between patients with diaphragmatic fibrous adhesion and those with diaphragmatic invasion in terms of the liver, lung, bone, lymph node, brain, and adrenal gland, whereas more patients with diaphragmatic invasion experienced peritoneum recurrence (Table 5).

DISCUSSION

Diaphragmatic invasion by a HCC is not uncommon and does not exclude the possibility of a curative surgery. There are however few published data that indicate whether the increased risks involved in diaphragmatic resection are worth taking, other than a few studies [4, 5, 7, 10]. Yuki et al. have reported a direct diaphragmatic involvement in 10%–13% of HCC patients according to autopsy results [11]. In our current analyses of 874 HCC patients, 46 cases (5.2%) underwent a hepatectomy combined with diaphragmatic resection, among which 25 patients (2.8%) had diaphragmatic fibrous adhesion and 21 patients (2.4%) had diaphragmatic invasion. Our current results also indicate that diaphragmatic invasion by HCC is not uncommon, and that a hepatectomy combined with diaphragmatic resection for HCC with diaphragmatic involvement can be justified.

HCC with diaphragmatic involvement includes both cases of diaphragmatic fibrous adhesion without pathological invasion and pathological diaphragmatic invasion [7]. However, it is difficult to distinguish a histological diaphragmatic invasion from a fibrous adhesion, even based on macroscopic findings from the resected specimen [5]. Ultrasonography, CT, and hepatic angiography modalities are also not useful for making a preoperative diagnosis of pathological diaphragmatic invasion in a HCC patient and whilst chest radiography and magnetic resonance imaging may help to evaluate diaphragmatic involvement, they cannot identify invasion of the diaphragm by the tumor. Thus, a postoperative pathological diagnosis is the only method available to confirm pathological diaphragmatic invasion [7]. Among HCC patients with diaphragmatic involvement, the reported percentage of cases with pathological diaphragmatic invasion has been low. Liu et al. reported histological evidence of diaphragmatic invasion in 21.2% of patients that underwent an en bloc diaphragmatic resection [7]. Our current study identified pathological diaphragmatic invasion in 45.6% (21/46) of the DR group cases. On the other hand, Lau et al. described no differences in the clinical outcomes of patients with or without pathological diaphragmatic invasion [10]. Liu et al. also reported no difference in survival and recurrence rates between HCC patients with diaphragmatic invasion and those with a fibrous adhesion [7]. Our present results are consistent with the findings of these past reports. In other words, the surgical outcomes of a combined resection of the diaphragm in a HCC patient are comparable between cases of a diaphragmatic invasion and those with a fibrous adhesion. Hence, it would likely be better to perform en bloc diaphragmatic resection when HCC patients present with gross diaphragmatic involvement.

The prognostic impact of a diaphragmatic invasion by a HCC is controversial. According to the American Joint Commission on Cancer (AJCC) 8th edition staging system for HCC, cases with diaphragmatic invasion are classified as advanced stage (T4 and Stage III B), and are associated with a poor prognosis [12]. Serosal invasion including invasion to adjacent organs has been reported to correlate with a poor prognosis in HCC patients [13-15]. On the other hand, from the viewpoint of a hepatectomy plus diaphragmatic resection for HCC, there have been some reports that diaphragmatic invasion is not associated with a poor prognosis [4, 5, 7]. Our present analyses showed that the overall 5-year survival rate in the DR group was poorer than that of the non-DR group in the whole cohort prior to PSM (Fig. 1a). However, in our whole cohort before PSM, the DR group cases were pathologically more advanced than the non-DR group patients, as indicated by higher AFP expression, a larger tumor size, poorer histological differentiation, and a higher portal vein and hepatic vein invasion status (Table 1). Several factors are already known to be associated with a poor prognosis in HCC. Higher serum AFP levels correlate with a poor prognosis in HCC patients [16, 17]. Tumor size and poorer histological differentiation were also reported to be correlated with the prognosis in HCC [3, 18-21]. Vascular invasion, including portal and hepatic vein invasion, is also correlated with a poorer prognosis in HCC patients [22-26]. We performed PSM on the basis that matching evaluations are needed when there are background differences in the degree of pathological progression. Significantly, our DR group exhibited similar long-term surgical outcomes to the non-DR group HCC cases after PSM. Furthermore, multivariate analyses of our matched HCC patients revealed that AFP expression and tumor size were independent prognostic factors for overall survival and poor differentiation for relapse-free survival, whereas diaphragmatic invasion and diaphragmatic resection were not. Our present study is the first to analyze the diaphragmatic resection of HCC after PSM. Our data indicate a lower malignant potential of diaphragmatic involvement of HCC and that diaphragmatic involvement alone does not affect the prognosis and is not a contraindication for a hepatectomy.

There have been some reports regarding the operative risk of hepatectomy combined with diaphragmatic resection for HCC [4-7]. Liu et al. reported that en bloc resection of the diaphragm was associated with acceptable morbidity and mortality [7]. In our current whole cohort before PSM, the DR group tended to need a longer operation time, have higher blood loss, and have greater anatomical resection requirements, as indicated in Table 2. However, the DR group HCCs were pathologically more advanced, such as a larger tumor size as mentioned above. Poon et al. reported previously that HCC lesions above 10 cm in diameter required a larger hepatectomy and had more intraoperative blood loss, but that the affected patients had similar morbidity and mortality outcomes [27]. In our current propensity score-matched cohort, both the DR and non-DR groups exhibited similar short-time surgical outcomes. Because HCC with diaphragmatic involvement is frequently accompanied by other prognostic factors such as a larger tumor size or vascular invasion, the required degree of surgical invasiveness is generally found to be higher in these cases. However, the presence or absence of diaphragmatic resection does not affect the short-term prognosis under the same conditions. Taken together, we conclude from the evidence to date and our current findings that a hepatectomy combined with an en bloc resection of the diaphragm should be considered for patients with HCC presenting with gross diaphragmatic involvement in order to avoid intraoperative bleeding risk or tumor rupture.

The DR group of patients in our present study tended to have a higher rate of extra-hepatic recurrence in the whole cohort. The explanations for this finding include the larger tumors than the non-DR group in the first instance. Wakayama et al. have reported that a very large HCC is a prognostic indicator for an extra-hepatic recurrence [3]. Second, venous and lymphatic drainage from the diaphragm may lead to tumors cell entering the circulation if the diaphragm is involved with the HCC [4]. In our current study, half of the patients in DR group experienced lung recurrence. Our results may be caused by this mechanism. In addition, diaphragmatic invasion or rupture of the HCC has been associated with peritoneal seeding of tumor cells [28]. In our present study series also, we experienced a local recurrence at the diaphragm in a ruptured HCC case. Furthermore, more patients with diaphragmatic invasion experienced peritoneum recurrence than those with diaphragmatic fibrous adhesion in our study. These findings suggest collectively that a forcible dissecting approach to the diaphragm might cause extrusion of the tumor cells into the systemic circulation or possibly tumor rupture, resulting in dissemination of the HCC cells. Our observations and other prior findings have shown that a thoracotomy can be performed safely in liver surgery [29]. Hence, it is necessary to resect the diaphragm with an appropriate margin for HCC cases with diaphragmatic involvement.

In our study, HCCs of the DR group were pathologically more advanced. The patients of the DR group tended to have a higher rate of extra-hepatic recurrence, and most patients who underwent diaphragm resection suffered recurrence within 2 years of resection. Hence, it is important to develop a treatment strategy for preventing extra-hepatic recurrence after hepatectomy combined with diaphragmatic resection for HCC with diaphragmatic involvement. At present, the most common treatment for HCC with distant metastases is systemic chemotherapy. No adjuvant regimen has been established for HCC after surgical resection [30]. However, since the adjuvant therapy for advanced HCC is unknown, adjuvant therapy including molecularly targeted therapy such as multi-kinase inhibitor or immunotherapy such as an anti-PD-L1 antibody has the potential to reduce the risk of relapse of HCC with diaphragmatic involvement.

This study had several limitations of note, including its retrospective nature and use of single-center experiences. Major limitation of this study was the small number of patients after PSM. Since the number of cases in DR group was small, the number of cases after PSM was also small in both DR and non-DR group. In addition, in our current analysis, the difference in both overall and relapse-free survival between diaphragmatic invasion and diaphragmatic fibrous adhesion was not statistically significant. This result may also be affected by the small number of cases, and with larger numbers of patients, HCC with diaphragmatic invasion may have a worse prognosis than HCC with diaphragmatic fibrous adhesion. Therefore, a multicenter study including more cases of HCC patients with diaphragmatic resection is required for more accurate evaluation. However, this is still the first report on hepatectomy combined with resection of the diaphragm for HCC patients analyzed using the PSM methodology, which may have yielded more accurate analysis of surgical outcomes. Our current results thus provide some important insights into the surgical approach for patients with a HCC presenting with gross diaphragmatic involvement.

In conclusion, the short- and long-term surgical outcomes of DR and non-DR HCC patients are similar under a matched clinicopathological background. A hepatectomy combined with diaphragmatic resection is therefore an acceptable treatment for HCC with diaphragmatic fibrous adhesion or diaphragmatic invasion.

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Figure Legend

Figure 1. (a) Overall survival rates in the DR group were poorer than those of the non-DR group prior to propensity score matching (PSM) analysis (p = 0.0002). (b) The relapse-free survival rates in the DR group were also poorer than the non-DR group before propensity score matching analysis (p = 0.0002). (c, d) Prior to PSM analysis, there were no significant differences between the HCC patients with pathological diaphragmatic fibrous adhesion and those with pathological diaphragmatic invasion in terms of (c) survival (p = 0.5509) and (d) relapse-free survival (p = 0.0988). (e) The overall survival rates in the DR and non-DR groups were similar after PSM analysis (p = 0.3919). (f) The relapse-free survival rates in the DR and non-DR groups were similar after PSM analysis (p = 0.8562).

Table 1 Correlations between clinicopathological features with and without diaphragmatic resection before and after propensity score matching (PSM) method

Variable		Before PSM DR group (n = 46)	Before PSM non-DR group (n = 828)	Before PSM p value	After PSM DR group (n = 40)	After PSM non-DR group (n = 40)	After PSM p value
Age†				0.0189			0.9578
		62 (33-86)	65 (33-92)		62 (33-80)	61 (33-77)	
Gender				1.0000			1.0000
	Female	7	141		6	5	
	Male	39	687		34	35	
HBs antigen				0.1572			1.0000
	Negative	24	526		22	22	
	Positive	22	302		18	18	
HCV antibody				0.0302			1.0000
	Negative	39	574		33	33	
	Positive	7	254		7	7	
Child-Pugh Classification				0.0020			0.7370
	A	40	807		34	36	
	B	6	21		6	4	
ICG R15 †				0.6860			0.1820
		13.9 (1.8-34.6)	13.6 (2.5-94.4)		14.0 (1.8-34.6)	12.0 (4.7-29.7)	
Liver cirrhosis				0.2940			0.7695
	Absence	38	616		32	34	
	Presence	8	212		8	6	
AFP (ng/ml)†				<0.0001			0.4052
		1922.9 (2.0-5986980)	14.0 (0-1488000)		1922.9 (2.0-1816620)	91 (0-624717)	
TNM Stage				<0.0001			1.000
	I or II	2	433		2	1	
	III or IV	44	395		38	39	
Tumor number				0.1455			0.3675
	Single	26	561		25	20	
	Multiple	20	267		15	20	
Tumor size (cm)†				<0.0001			0.9885
		13.0 (4.0-20.5)	4.2 (0.3-23.0)		13.0 (4.0-20.5)	12.0 (3.0-23.0)	
Differentiation				0.0007			0.3348
	Well	0	126		0	0	
	Moderate	27	511		25	30	
	Poor	19	180		15	10	
	unknown	0	11		0	0	
Portal vein invasion				<0.0001			1.0000
	Absence	16	625		14	13	
	Presence	30	203		26	27	
Hepatic vein invasion				<0.0001			1.0000
	Absence	21	742		21	22	
	Presence	25	86		19	18	
Hepatic artery invasion				1.0000			0.4937
	Absence	46	824		40	38	
	Presence	0	4		0	2	
Bile duct invasion				0.2962			0.7370
	Absence	42	786		36	34	
	Presence	4	42		4	6	

Abbreviations: PSM, propensity score matching; DR, diaphragmatic resection; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; TNM, tumor node metastasis

† Expressed as median (range)

Table 2 Perioperative outcomes of HCC with and without diaphragmatic resection before and after PSM method

		Before PSM			After PSM		
Variable		DR group (n = 46)	non-DR group (n = 828)	p value	DR group (n = 40)	non-DR group (n = 40)	p value
Operation time (min)†				<0.0001			0.1688
		368 (248-838)	314 (78-1019)		377.5 (248-838)	350 (99-612)	
Blood loss (ml)†				<0.0001			0.5036
		620 (70-6230)	370 (0-35820)		595 (70-6230)	772.5 (20-20190)	
Anatomical resection				<0.0001			1.0000
	no	1	214		1	1	
	yes	45	614		39	39	
Postoperative complication‡				0.9704			1.0000
	III	4	60		2	2	
	IV	0	1		0	0	
	V	0	1		0	0	
Postoperative hospital stay (days)†				0.0091			0.7322
		19 (8-114)	15 (3-380)		19 (8-114)	17 (7-42)	

Abbreviations: HCC, hepatocellular carcinoma; PSM, propensity score matching; DR, diaphragmatic resection

† Expressed as median (range)

‡ Clavien-Dindo grading

Table 3 Univariate and multivariate analyses of prognostic factors for HCC with and without diaphragm resection in a propensity score-matched cohort

		Univariate analysis			
		Overall survival		Relapse-free survival	
Variable	**n**	**5-years (%)**	***P* value**	**5-years (%)**	***P* value**
Age			0.3453		0.5974
<65	51	43.0±8.1		14.1±6.2	
≥65	29	34.2±10.8		0.0±0.0	
Gender			0.6162		0.5656
Female	11	29.2±16.7		20.4±16.4	
Male	69	41.2±7.1		14.2±6.4	
HBs antigen			0.7197		0.1507
Negative	44	42.2±9.1		10.0±7.9	
Positive	36	37.3±9.3		18.5±9.8	
HCV antibody			0.5243		0.9220
Negative	66	41.0±7.2		11.8±6.7	
Positive	14	34.1±15.3		19.0±11.8	
Child-Pugh Classification			0.0370		0.0521
A	70	41.9±7.2		17.4±6.9	
B	10	22.2±13.8		0.0±0.0	
ICG R15 (%)			0.4105		0.1309
<10	23	35.5±11.7		15.8±8.3	
≥10	57	41.7±7.8		16.2±7.3	
Liver cirrhosis			0.9574		0.4306
Absence	66	42.4±7.4		14.4±7.3	
Presence	14	27.8±13.6		15.0±12.5	
AFP(ng/ml)			0.0123		0.6950
<100	21	70.9±11.3		5.7±5.2	
≥100	59	27.4±7.4		29.3±8.4	
TNM Stage			0.8919		0.9637
I or II	3	50.0±35.3		33.3±27.2	
III or IV	77	39.7±6.6		13.4±6.0	
Tumor number			0.7925		0.4542
Single	45	44.6±8.8		17.6±8.8	
Multiple	35	33.6±9.8		9.4±7.9	
Tumor size (cm)			0.0013		0.0834
<10	22	69.1±11.6		27.2±11.3	
≥10	58	28.1±7.3		0.0±0.0	
Differentiation			0.0454		0.0215
Well or Moderate	55	50.2±7.8		22.4±8.6	
Poor	25	22.8±9.5		0.0±0.0	
Portal vein invasion			0.0302		0.8001
Absence	27	51.7±14.7		0.0±0.0	
Presence	53	31.9±7.2		16.3±7.3	
Hepatic vein invasion			0.5114		0.1330
Absence	43	46.8±9.1		20.6±9.2	
Presence	37	33.6±9.1		0.0±0.0	
Hepatic artery invasion			0.4940		0.3682
Absence	78	41.1±6.7		14.2±6.3	
Presence	2	0.0±0.0		0.0±0.0	
Bile duct invasion			0.5217		0.6465
Absence	70	40.9±7.2		14.9±6.6	
Presence	10	27.4±16.2		0.0±0.0	
Pathological diaphragmatic invasion			0.6100		0.3290
no	62	36.1±7.2		18.0±7.3	
yes	18	55.4±12.7		0.0±0.0	
Diaphragmatic resection			0.3919		0.8562
no	40	32.3±8.5		18.2±7.9	
yes	40	48.5±9.6		9.4±8.2	

Multivariate analysis			
Overall survival			
	HR	**95% CI**	***P* value**
AFP > 100ng/ml	2.027	1.018-4.155	0.0476
Tumor size ≥ 10cm	2.662	1.142-6.947	0.0308
Relapse-free survival			
	HR	**95% CI**	***P* value**
Differentiation	1.903	1.074-3.308	0.0240

Abbreviations: HCC, hepatocellular carcinoma; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICG R15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; TNM, tumor node metastasis; HR, hazard ratio; CI, confidence interval

Table 4 Recurrence sites of HCC with and without diaphragmatic resection before and after PSM method

	Before PSM			After PSM		
Recurrence site	DR group (n = 46)	non-DR group (n = 828)	p value	DR group (n = 40)	non-DR group (n = 40)	p value
Liver	17 (36.9%)	444 (53.6%)	0.0332	16 (40.0%)	26 (65.0%)	0.0432
Lung	23 (50.0%)	116 (14.0%)	<0.0001	21 (52.5%)	15 (37.5%)	0.2611
Bone	6 (13.0%)	57 (6.8%)	0.1347	4 (10.0%)	6 (15.0%)	0.7370
Lymph node	8 (17.3%)	51 (6.1%)	0.0091	8 (20.0%)	5 (12.5%)	0.5458
Brain	5 (10.8%)	19 (2.2%)	0.0065	5 (12.5%)	3 (7.5%)	0.7119
Adrenal gland	1 (2.1%)	21 (2.5%)	1.0000	1 (2.5%)	1 (2.5%)	1.0000
Peritoneum	5 (10.8%)	11 (1.3%)	0.0009	4 (10.0%)	0 (0.0%)	0.1156

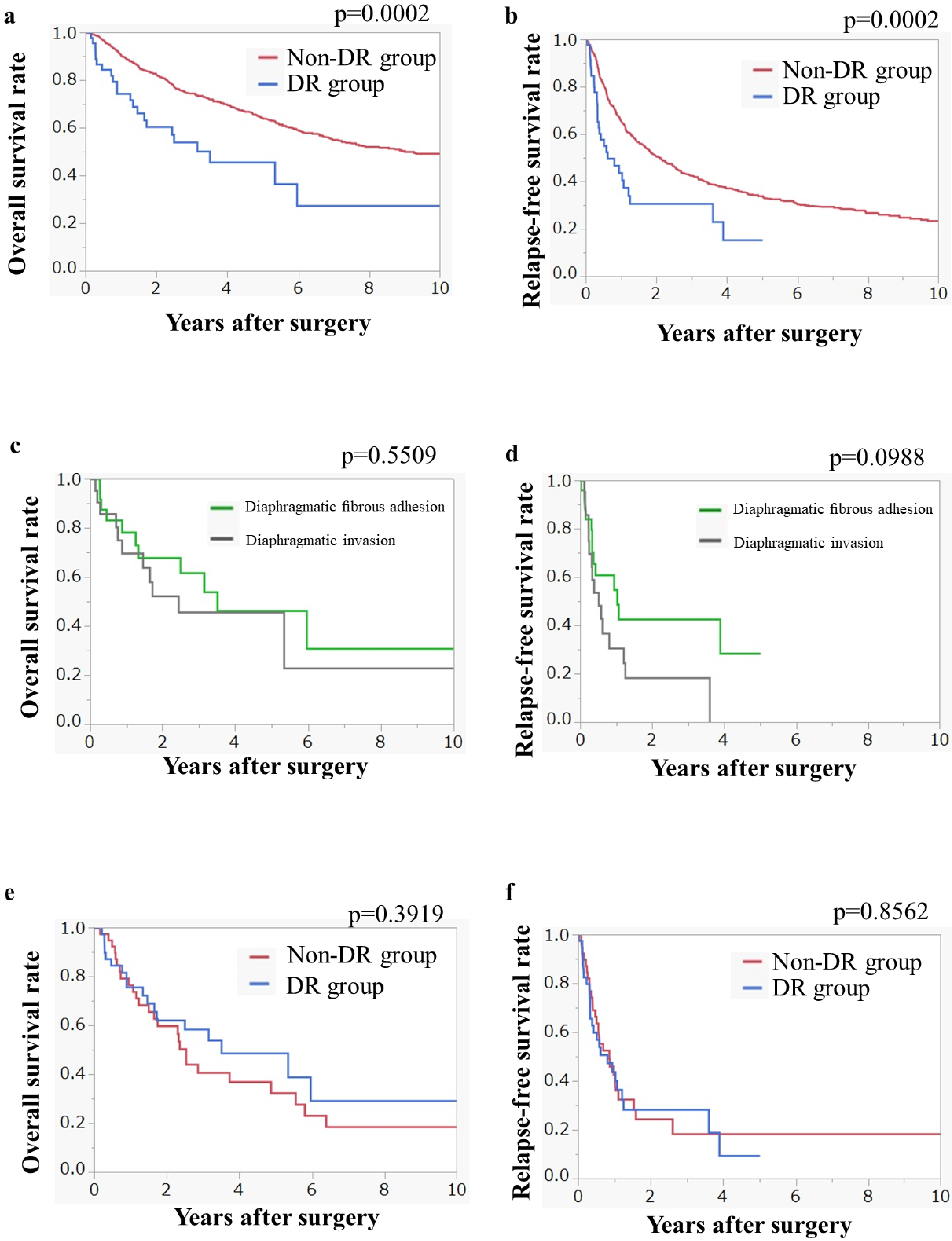
Abbreviations: HCC, hepatocellular carcinoma; PSM, propensity score matching; DR, diaphragmatic resection

Table 5 Recurrence sites of HCC with respect to the presence or absence of pathological diaphragmatic invasion amomg DR group

Recurrence site	diaphragmatic fibrous adhesion (n = 25)	diaphragmatic invasion (n = 21)	p value
Liver	9 (36.0%)	8 (38.1%)	1.0000
Lung	13 (52.0%)	10 (47.6%)	1.0000
Bone	2 (8.0%)	4 (19.0%)	0.3898
Lymph node	5 (20.0%)	3 (14.2%)	0.7098
Brain	3 (12.0%)	2 (9.5%)	1.0000
Adrenal gland	0 (0.0%)	1 (4.7%)	0.4565
Peritoneum	0 (0.0%)	5 (23.8%)	0.0148

Abbreviations: HCC, hepatocellular carcinoma; DR, diaphragmatic resection

Figure. 1


a
p=0.0002
Overall survival rate
Years after surgery
Non-DR group
DR group
b
p=0.0002
Relapse-free survival rate
Years after surgery
Non-DR group
DR group
c
p=0.5509
Overall survival rate
Years after surgery
Diaphragmatic fibrous adhesion
Diaphragmatic invasion
d
p=0.0988
Relapse-free survival rate
Years after surgery
Diaphragmatic fibrous adhesion
Diaphragmatic invasion
e
p=0.3919
Overall survival rate
Years after surgery
Non-DR group
DR group
f
p=0.8562
Relapse-free survival rate
Years after surgery
Non-DR group
DR group