Tumor size drives the prognosis after hepatic resection of solitary hepatocellular carcinoma without vascular invasion

Tumor Size Drives the Prognosis After Hepatic Resection of Solitary Hepatocellular Carcinoma Without Vascular Invasion

Hiroji Shinkawa, Shogo Tanaka, Shigekazu Takemura, Takuma Ishihara, Kouji Yamamoto, Shoji Kubo

Citation	Journal of Gastrointestinal Surgery. 24(5); 1040-1048
Published	2019-06-13
Type	Journal Article
Textversion	Author
Relation	This is a post-peer-review, pre-copyedit version of an article published in Journal of Gastrointestinal Surgery. The final authenticated version is available online at: https://doi.org/10.1007/s11605-019-04273-2.
DOI	10.1007/s11605-019-04273-2

Shinkawa, H., Tanaka, S., Takemura, S. et al. Tumor Size Drives the Prognosis After Hepatic Resection of Solitary Hepatocellular Carcinoma Without Vascular Invasion. *Journal of Gastrointestinal Surgery.* 24, 1040–1048 (2020). Doi:10.1007/s11605-019-04273-2

Original Report

Tumor size drives the prognosis after hepatic resection of solitary hepatocellular carcinoma without vascular invasion

Running head: single HCC without VI

Hiroji Shinkawa,MD, PhD[1], Shogo Tanaka, MD, PhD[1], Shigekazu Takemura, MD, PhD[1], Takuma Ishihara, MSc[2], Kouji Yamamoto, PhD[3], and Shoji Kubo, MD, PhD[1]

[1]Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

[2]Division of Data Management, Gifu University Hospital Innovative and Clinical Research Promotion Center, 1-1 Yanagido, Gifu City 501-1194, Japan

[3]Department of Medical Statistics, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

Corresponding author: Hiroji Shinkawa, MD

Department of Hepato-Biliary-Pancreatic Surgery,

Osaka City University Graduate School of Medicine,

1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

Tel: +81-6-6645-3841

Fax: +81-6-6646-6057

E-mail: m1297198@msic.med.osaka-cu.ac.jp

Conflicts of Interest: The authors declare no conflicts of interest in association with the

present study.

Financial support: This work was supported by the Health, Labour and Welfare Policy Research Grants from the Ministry of Health, Labour, and Welfare of Japan (Policy Research for Hepatitis Measures [H30-Kansei-Shitei-003]).

Authorship: All authors participated equally in the study as per the guidelines of the International Committee of Medical Journal Editors and have provided final approval for its publication.

Abstract

Purpose: We assessed the association of tumor size with patient survival following diagnosis of solitary hepatocellular carcinoma without vascular invasion.

Methods: The overall population comprised 638 patients who initially underwent hepatic resection with curative intent for a solitary hepatocellular carcinoma without macroscopic vascular invasion (487 had no microscopic vascular invasion). We set 5 cm as the tumor cutoff size for a solitary tumor based on the Milan criteria, and we used a multivariate Cox proportional hazards model and propensity score matching to evaluate the impact of tumor size on survival.

Results: Tumor size was significantly associated with a proportional increase in cancer-specific survival in the overall population (P = 0.001) and the subgroup with no microscopic vascular invasion (**P =** 0.029); however, multivariate analysis revealed no significant risk associated with recurrence-free survival (P = 0.055 and 0.59, respectively). After propensity score matching, the cancer-specific survival of patients with tumors >5 cm was significantly worse than for those with tumors ≤5 cm in the overall population (P = 0.0077); the corresponding 2-year cumulative recurrence rates were **4**5.8% and 23.5%, respectively (P = 0.0027). Finally, the proportions of extrahepatic to total recurrences were 8% for those with tumors ≤5 cm and 29.1% for those with tumors >5 cm in the unmatched overall population (P < 0.001).

Conclusion: Tumor size was associated with recurrence within 2 years of surgery and with poor cancer-specific survival in patients with solitary hepatocellular carcinoma, even in the absence of microscopic vascular invasion.

Key words: hepatocellular carcinoma, tumor size, extrahepatic recurrence, prognosis

Introduction

Hepatic resection is commonly used to cure hepatocellular carcinoma (HCC). As surgical techniques have improved, the indications for surgery have expanded to include multiple HCCs and advanced HCCs with macroscopic vascular invasion.[1, 2] However, due to the high recurrence rate, long-term survival remains poor after surgery.[3-5]

Several tumor-related factors are known to affect survival outcomes after hepatic resection, including their size, differentiation, vascular invasion, and multiplicity.[4, 6] The American Joint Committee on Cancer/International Union Against Cancer staging system stratifies patients with HCC according to the tumor-node-metastasis classification.[7] In this, tumor size, vascular invasion, and multiplicity are used to determine the T (tumor) classification. In the latest edition, HCCs ≤2 cm are considered "early HCC" and are classified as T1a tumors and solitary HCCs >2 cm without vascular invasion are classified as T1b regardless of the maximum tumor size.[7, 8] This classification was based on a report showing that tumor size had no effect on long-term survival in patients with a single tumor without vascular invasion.[4] For the same reason, the Barcelona Clinic Liver Cancer staging system,[9] widely accepted in clinical practice for the treatment of HCC, does not include tumor size as an indication for surgery for solitary tumors without vascular invasion. By contrast, the Milan criteria[10] for liver transplantation in patients with HCC uses a tumor size of 5 cm to indicate risk in patients with a single tumor without macroscopic vascular invasion. Transplant patients with tumors exceeding this size are considered at an increased risk of recurrence and to have a poor prognosis.[10] Recently, several studies have demonstrated that large solitary tumors were associated with a poor prognosis after hepatic resection, even in patients without vascular invasion.[11, 12] Thus, there remains some controversy as to whether increased tumor size is associated with a poor survival after hepatic resection for a solitary HCC without vascular invasion.

Various liver-related factors are also known to affect the survival outcomes of patients with HCC, including background liver function and chronic hepatitis. Indeed, Kluger et al. demonstrated that the condition of the underlying liver rather than the tumor size was the more significant prognostic factor.[13] Patients negative for hepatitis B surface antigen and hepatitis C antibody, so-called “non-B non-C” HCC, have also been shown to have larger tumors and better outcomes than patients with HCC positive for either the hepatitis B or the hepatitis C viruses.[14] Therefore, assessing the impact of tumor size on prognosis requires adjustment for confounding background variables, including liver-related factors.

In this study, we aimed to examine the influence of increased tumor size on recurrence and survival in patients with solitary tumors without vascular invasion.

Patients and Methods

Study design and participants

This was a retrospective study of patients who initially underwent hepatic resection with curative intent for HCC at Osaka City University Hospital between July 1990 and December 2016. The study was conducted in accordance with the guidelines of our institutional ethics committee and the Declaration of Helsinki.

We included patients with pathologically solitary tumors and no macroscopic vascular invasion as the whole patient population, but also identified a subgroup of patients without microscopic vascular invasion. We examined the influence of increased tumor size on recurrence and survival by propensity score matching (PSM) and a Cox proportional hazards modeling with restricted cubic splines.

Follow-up

Curative hepatic resection was defined as the histological absence of tumor cells along the parenchymal transection line. Every 3 months, we measured HCC-specific tumor marker

levels and performed ultrasonography or dynamic computed tomography. Recurrence was defined as the appearance of a new tumor lesion with the radiologic features of HCC and/or tumor marker elevation. When recurrence was detected, the patient received further treatment by hepatic resection, radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization, or other modalities, as indicated. For long-term survival after surgery, we measured the cancer-specific survival (CSS) to focus on the factors associated with HCC.

Histology

Histological tumor classification and grading of background liver damage were evaluated according to the system of the Liver Cancer Study Group of Japan.[15] The grade (severity of active hepatitis) and stage (degree of hepatic fibrosis) of non-cancerous hepatic tissue were determined based on the histologic activity index.[16,17] The terminology for hepatic anatomy was according to The Brisbane 2000 Terminology of Liver Anatomy and Resections.[18]

Statistical analysis

All analyses were performed using the R software program (version 3.4.3, www.r-project.org). P values of <0.05 were considered to indicate statistical significance. Categorical and continuous variables were compared using chi-square and Mann–Whitney U tests, respectively. Fisher's exact test was used to assess differences in the recurrence rate.

A multivariate Cox proportional hazards model was developed to detect the association between baseline tumor size and recurrence-free survival (RFS) or CSS, with adjustments made for age (≤65 or >65 years), gender, surgical period (1990–1999 or 2000–2016), Child–Pugh grade (A or B/C), alanine aminotransferase (≤30 or >30 IU/l), α-fetoprotein (≤20 or >20 ng/ml), tumor differentiation (poor or well/moderate), grading score (0–2 or 3–4), liver cirrhosis, major hepatectomy (≥2 sections), microscopic vascular

invasion (in those without macrovascular invasion), and presence of viral hepatitis (hepatitis B surface antigen-positive and/or anti-hepatitis C virus antibody-positive). The baseline tumor size was modeled with restricted cubic splines to allow for nonlinear associations. A nonlinear relationship between tumor size and RFS or CSS was confirmed by testing the coefficient for nonlinear terms in the Cox model using the F-test.

We conducted PSM to adjust for potential confounders between patients with tumors ≤5 cm and those with tumors >5 cm in whole population. The tumor size cutoff of 5 cm was set based on the Milan criteria for a solitary tumor.[10] Propensity scores were generated using a binary logistic regression model for the following background characteristics: age, gender, surgical period, Child–Pugh grade, alanine aminotransferase, α-fetoprotein, tumor differentiation, grading score, liver cirrhosis, major hepatectomy, microscopic vascular invasion, and viral hepatitis[19]. One-to-one PSM was performed using a caliper of 0.25 standard deviations of the logit of the propensity score.

The cumulative RFS rates and CSS rates were evaluated in the PSM cohorts using the Kaplan–Meier method. To evaluate the relationship between early recurrence and tumor size, we compared the cumulative recurrence rate within 2 years after surgery between the groups with tumors ≤5 cm and >5 cm, given 2 years after surgery as the inflection point.[20] In the whole population after PSM, the overall hazard function for recurrence was evaluated to depict the chronological change in recurrence rates after surgery. The differences between the curves were evaluated by log-rank tests.

Results

Patient characteristics

In total, 1031 patients initially underwent hepatic resection with curative intent for HCC and we enrolled the 638 patients with a pathologically solitary tumor without

macroscopic vascular invasion as the whole patient population (Table 1). Of these, 487 were included in the subgroup of patients without microscopic vascular invasion.

Postoperative recurrence rates

Postoperative recurrence occurred in 381 patients (59.7%), of whom 42 (11.0%) had extrahepatic recurrence. Of the remaining 339 patients with intrahepatic recurrence, HCC recurrences after two postoperative years were observed in 163 patients (54.3%) in the group with tumors measuring ≤5 cm and in 10 patients (25.6%) with tumors measuring >5 cm (P = 0.001). In the subgroup without microscopic vascular invasion, 291 patients (59.8%) had postoperative recurrence and 24 of these (8.2%) had extrahepatic recurrence.

Relationship between tumor size and survival

A multivariate Cox proportional hazard model revealed that tumor size was not significantly associated with the proportional increase in RFS risk (P = 0.055), but it did show a significant increase in the CSS risk for the whole patient population (P = 0.001) (Fig. 1A and B). Comparable results were seen in the subgroup without microscopic vascular invasion (P = 0.59 and 0.029, respectively) (Fig. 2A and B). The nonlinear relationship between tumor size and RFS or CSS was not statistically significant in either the whole population (P = 0.84 and 0.92, respectively) or the subgroup without microscopic vascular invasion (P = 0.91 and 0.54, respectively).

Survival outcomes in the whole population

In the whole population, 93 patients (14.6%) had HCCs measuring >5 cm. Figure 3 shows the Kaplan–Meier survival curves for the RFS and CSS between the ≤5 cm and >5 cm groups in the unmatched cohort. The 5-year RFS rates after surgery in the ≤5 cm and >5 cm groups were 36% and 34%, respectively (P = 0.31; Fig. 3A); the corresponding 5-year CSS rates after surgery were 82% and 74%, respectively (P = 0.0026; Fig. 3B).

The PSM cohort comprised 166 patients, grouped into 83 with tumors measuring

≤5 cm and 83 with tumors measuring >5 cm. The background characteristics between the groups are shown for the unmatched and PSM cohorts in Table 2. In the unmatched cohort, the proportions of patients with Child–Pugh grade B or C and with viral hepatitis were lower in the >5 cm group than in the ≤5 cm group. After PSM, background patient characteristics were balanced between the two groups.

Figure 4 shows the Kaplan–Meier survival curves for the RFS and CSS between the ≤5 cm and >5 cm groups after PSM. The 5-year RFS rates after surgery in the ≤5 cm and >5 cm groups were 41% and 37%, respectively (P = 0.43; Fig. 4A); the corresponding 5-year CSS rates were 85% and 78%, respectively (P = 0.0077; Fig. 4B).

Cumulative recurrence rate within two years of surgery and annual hazard of recurrence

To evaluate the relationship between early recurrence and tumor size, we evaluated the cumulative incidence of recurrence within two years of surgery in the PSM cohort. The two-year cumulative recurrence rates in the ≤5 cm and >5 cm groups were 23.5% and 45.8%, respectively (P = 0.0027; Fig. 5A).

The hazard rates of postoperative recurrence in the whole population subject to PSM (Fig. 5B) peaked at two years for both the ≤5 cm group (0.19/year) and the >5 cm group (0.23/years), and gradually decreased until five to six years postoperatively. However, the hazard rates increased again to reach a second peak at around seven years for both the ≤5 cm group (0.099/year) and the >5 cm group (0.11/year).

Extrahepatic HCC recurrence

The rates of extrahepatic recurrence in the whole population were similar in the ≤5 cm group (326/545; 59.8%) and >5 cm group (55/93; 59.1%) (P = 0.91). However, the proportion of patients with extrahepatic recurrence among all patients experiencing recurrence was significantly lower in the ≤5 cm group (26/326; 8%) than in the >5 cm group (16/55; 29.1%) (P < 0.001). Table 3 shows the number of extrahepatic recurrences by site and tumor size.

Intrahepatic HCC recurrence and treatment

We evaluated the relationship between the number of recurrent intrahepatic tumors and the treatments administered in the whole population. Multiple intrahepatic recurrence was observed in 109 of 300 patients with intrahepatic recurrence (36.3%) in the ≤5 cm group and in 19 of 39 patients with intrahepatic recurrence (48.7%) in the >5 cm group (P = 0.16). Respectively, one, two, and three or more recurrences occurred in 191 (63.7%), 31 (10.3%), and 78 (26.0%) patients in the ≤5 cm group and in 20 (51.3%), 7 (17.9%), and 12 (30.8%) patients in the >5 cm group.

Of the 300 patients with intrahepatic recurrence in the ≤5 cm group, 158 (52.7%) received treatment with curative intent, including 72 who underwent repeat hepatectomy and 86 who underwent local ablation therapy. Of the 39 patients with intrahepatic recurrence in the >5 cm group, 15 (38.5%) received treatment with curative intent, including nine who underwent repeat hepatectomy and six who underwent local ablation therapy.

Discussion

The current study revealed that tumor size was significantly associated with a proportional increase in CSS risk in both the whole population and the subgroup without microscopic vascular invasion. However, no significant risk for RFS was observed in either group in the multivariate Cox proportional hazards analysis. To explain this discrepancy, we evaluated the cumulative recurrence rate within two postoperative years and the survival outcome after surgery between groups with tumors measuring ≤5 cm and >5 cm. Then, to clarify the true oncological impact of tumor size on recurrence and survival, we conducted PSM analysis by adjusting for potential confounders (including tumor-related or liver-related risk factors) between these groups. After PSM, the CSS of the >5 cm group was significantly worse than that of the ≤5 cm group in both the whole population and the subgroup without

microscopic vascular invasion. Although the RFS did not differ significantly between the ≤5 cm and >5 cm groups, the cumulative recurrence rate within 2 years of surgery was significantly higher in the latter. Furthermore, the proportion of extrahepatic recurrence was approximately 4-fold higher in the >5 cm group compared with the ≤5 cm group in the unmatched cohort. The proportion of multiple intrahepatic recurrences in the >5 cm group tended to be approximately 1.4-fold higher than that in the ≤5 cm group. These results indicate that tumor size might be associated with increased risk of recurrence and death within 2 years of surgery, even in the absence of vascular invasion.

Vascular invasion is known to be a major risk factor for recurrence and overall death after hepatic resection for HCC,[21] and tumor size has been reported to be associated with increased rates of both microscopic and macroscopic invasion.[6] In previous reports, however, it was concluded that tumor size did not affect the prognosis of patients with solitary HCCs in the absence of vascular invasion.[4, 5, 22, 23] Shindoh et al. demonstrated the favorable overall survival of patients with early HCC (≤2 cm) but showed no size-proportional increase in the overall survival risk.[7, 8] In the current study, we confirmed that there was a proportional prognostic impact of tumor size on the CSS in both the whole population and in the subgroup of patients without microscopic vascular invasion.

The discrepancy between our results and those of previous studies may have resulted from our inclusion of patients with pathologically diagnosed solitary HCCs without vascular invasion, allowing for assessment of the true prognostic risk associated with tumor size. Another reason might be that we controlled for the confounding effects of liver-related factors. Lim et al. demonstrated that patients with large HCCs were more likely to have favorable liver functions and non-B non-C hepatitis statuses.[5] Following on from this, Utsunomiya et al. showed that patients with non-B non-C-HCC had better RFS and overall survival rates than those with HCC and hepatitis B or C virus positivity.[14] In our study, the

proportions of patients with Child–Pugh grades B or C and with viral hepatitis before PSM in were lower the >5 cm group than in the ≤5 cm group. Thus, controlling for the confounding effects of liver-related factors might also have affected the results.

Tumor size was not significantly associated with an increased RFS risk in our multivariate Cox proportional hazard model. Survival analysis using PSM revealed that there was no significant difference in RFS between the ≤5 cm and >5 cm groups, though a significantly increased risk of death was confirmed in the >5 cm group. To explain this discrepancy, we focused on the timing of recurrence. Early recurrence within 2 years after surgery has been considered a factor associated with poor prognosis.[20, 24] When we compared the cumulative recurrence rate within 2 years of surgery in the PSM group, we found that recurrence was significantly higher in the >5 cm group than in the ≤5 cm group. Furthermore, the chronological changes in the annual hazard of recurrence indicated that the hazard rates were bimodal for both the ≤5 cm and >5 cm groups, and that the difference between groups was widest in the PSM cohort at two years postoperatively.

Early recurrence within 2 years is considered to arise from residual micrometastasis.[20, 25] It is also thought that extrahepatic recurrence results from hematogenous spread from the original tumor, and that multiple intrahepatic recurrences are also likely to include metastases from the original tumor. In this study, although the postoperative recurrence rates were similar in both size groups, the proportion of extrahepatic recurrence was approximately 4-fold higher in the >5 cm group of the unmatched cohort. The proportion of multiple recurrences to total intrahepatic recurrences also tended to be higher in the >5 cm group than in the ≤5 cm group. These results indicated that patients in the >5 cm group might be at increased risk for residual micrometastasis from the original tumor despite there being no evidence of vascular invasion.

Survival among patients with extrahepatic recurrence of HCC is typically very poor,[26]

whereas that of patients with intrahepatic recurrence tends to be amenable to curative treatment, including hepatic resection and local ablation. However, the survival outcomes of patients with recurrence of multiple HCCs is typically poorer than in those with a solitary HCC because the former is usually more aggressive, which limits treatment options.[27] In this study, treatment with curative intent was more frequently adopted in the ≤5 cm group (52.7%) than in the >5 cm group (38.5%). Thus, the higher rates of extrahepatic and multiple intrahepatic recurrences are possible reasons for the unfavorable overall survival rates of patients with tumors measuring >5 cm.

Another plausible reason for the discrepancy in results is the influence of multicentric recurrence. This can be defined as the presence of a newly developed HCC in the remnant liver that is typically detected as a solitary nodule in the late period after surgery (e.g., >2 years).[25] Patients with multicentric recurrence can receive treatment with curative intent and have relatively high survival rates.[27] In this study, because of the long study period of 26 years, the effects of multicentric recurrence could have accumulated during follow-up. Indeed, intrahepatic recurrences were observed after 2 years in 163 patients (54.3%) in the ≤5 cm group and in only 10 patients (25.6%) in the >5 cm group. Therefore, this accumulation of multicentric recurrence might obscure the true difference in RFS rates between these groups.

The present study had some limitations. First, the retrospective study design may have resulted in bias because patient enrollment was not controlled. Second, the study period was approximately 26 years and there will have been many technological and practice advances over that period. However, we minimized this confounding effect by dividing the data by era (e.g., 1990–1999 and 2000–2016).

In conclusion, tumor size was associated with an increased risk of recurrence within 2 years of surgery and with poor CSS rates after hepatic resection among patients with a solitary HCC, even when there was no vascular invasion. Higher rates of extrahepatic and

multiple intrahepatic recurrences could account for the unfavorable CSS rates among patients with tumors >5 cm and no vascular invasion, and hematogenous metastasis from the original tumor may explain the association of tumor size with poor CSS risk. Further prospective study should seek to resolve these issues.

Acknowledgments

This work was supported by the Health, Labour and Welfare Policy Research Grants from the Ministry of Health, Labour, and Welfare of Japan (Policy Research for Hepatitis Measures [H30-Kansei-Shitei-003]).

REFERENCES

1. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, Kudo M, Ku Y, Sakamoto M, Nakashima O, Kaneko S, Kokudo N. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65(5): 938-943.
2. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 2008;134(7): 1908-1916.
3. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232(1): 10-24.
4. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, Curley SA, Ellis LM, Regimbeau JM, Rashid A, Cleary KR, Nagorney DM. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20: 1527-1536.
5. Lim C, Mise Y, Sakamoto Y, Yamamoto S, Shindoh J, Ishizawa T, Aoki T, Hasegawa K Sugawara Y, Makuuchi M, Kokudo N. Above 5 cm, size does not matter anymore in patients with hepatocellular carcinoma. World J Surg 2014;38(11): 2910-2918.
6. Tsai TJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, Hsia CY, Wu CW. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. Surgery 2000;127(6): 603-608.
7. Chun YS, Pawlik TM, Vauthey JN. 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. Ann Surg Oncol 2018;25(4): 845-847.
8. Shindoh J, Andreou A, Aloia TA, Zimmitti G, Lauwers GY, Laurent A, Nagorney DM,

Belghiti J, Cherqui D, Poon RT, Kokudo N, Vauthey JN. Microvascular invasion does not predict long-term survival in hepatocellular carcinoma up to 2 cm: reappraisal of the staging system for solitary tumors. Ann Surg Oncol 2013;20(4): 1223-1229.

9. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Hemibach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68(2): 723-750.
10. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11): 693-699.
11. Huang WJ, Jeng YM, Lai HS, Sheu FY, Lai PL, Yuan RH. Tumor size is a major determinant of prognosis of resected stage I hepatocellular carcinoma. Langenbecks Arch Surg 2015;400(6): 725-734.
12. Hwang S, Lee YJ, Kim KH, Ahn CS, Moon DB, Ha TY, Song GW, Jung DH, Lee SG. The Impact of Tumor Size on Long-Term Survival Outcomes After Resection of Solitary Hepatocellular Carcinoma: Single-Institution Experience with 2558 Patients. J Gastrointest Surg 2015;19(7): 1281-1290.
13. Kluger MD, Salceda JA, Laurent A, Tayar C, Duvoux C, Decaens T, Luciani A, Van Nhieu JT, Azoulay D, Cherqui D. Liver resection for hepatocellular carcinoma in 313 Western patients: tumor biology and underlying liver rather than tumor size drive prognosis. J Hepatol 2015;62(5): 1131-1140.
14. Utsunomiya T, Shimada M, Kudo M, Ichida T, Matsui O, Izumi N, Matsuyama Y, Sakamoto M, Nakashima O, Ku Y, Takayama T, Kokudo N; Liver Cancer Study Group of Japan. A comparison of the surgical outcomes among patients with

HBV-positive, HCV-positive, and non-B non-C hepatocellular carcinoma: a nationwide study of 11,950 patients. Ann Surg 2015;261(3): 513-520.

15. Kudo M, Kitano M, Sakurai T, Nishida N. General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Nationwide Follow-Up Survey and Clinical Practice Guidelines: The Outstanding Achievements of the Liver Cancer Study Group of Japan. Dig Dis 2015;33(6): 765-770.
16. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19(6): 1513-1520.
17. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, Wollman J. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1(5): 431-435.
18. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg 2013;257(3): 377-382.
19. Leyrat C, Caille A, Donner A, Giraudeau B. Propensity score methods for estimating relative risks in cluster randomized trials with low-incidence binary outcomes and selection bias. Stat Med 2014;33(20): 3556-3575.
20. Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, Giulini SM. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. Ann Surg 2006;243(2): 229-235.
21. Di Sandro S, Sposito C, Lauterio A, Najjar M, Droz Dit Busset M, Buscemi V, Flores Reyes M, De Carlis R, Mazzaferro V, De Carlis L. Proposal of Prognostic Survival Models before and after Liver Resection for Hepatocellular Carcinoma in Potentially Transplantable Patients. J Am Coll Surg 2018;226:1147-1159.
22. Thng Y, Tan JK, Shridhar IG, Chang SK, Madhavan K, Kow AW. Outcomes of

resection of giant hepatocellular carcinoma in a tertiary institution: does size matter? HPB (Oxford) 2015;17(11): 988-993.

23. Zhang H, Yuan SX, Dai SY, Zhang JM, Huang X, Lu CD, Lu JH, Wu FQ, Lau WY, Wu MC, Yang T, Shen F. Tumor size does not independently affect long-term survival after curative resection of solitary hepatocellular carcinoma without macroscopic vascular invasion. World J Surg 2014;38(4): 947-957.
24. Ueno M, Uchiyama K, Ozawa S, Hayami S, Shigekawa Y, Tani M, Yamaue H. Adjuvant chemolipiodolization reduces early recurrence derived from intrahepatic metastasis of hepatocellular carcinoma after hepatectomy. Ann Surg Oncol 2011;18(13): 3624-3631.
25. Sasaki K, Shindoh J, Margonis GA, Nishioka Y, Andreatos N, Sekine A, Hashimoto M, Pawlik TM. Effect of Background Liver Cirrhosis on Outcomes of Hepatectomy for Hepatocellular Carcinoma. JAMA Surg 2017;152(3): e165059.
26. Taketomi A, Toshima T, Kitagawa D, Motomura T, Takeishi K, Mano Y, Kayashima H, Sugimachi K, Aishima S, Yamashita Y, Ikegami T, Gion T, Uchiyama H, Soejima Y, Madeda T, Shirabe K, Maehara Y. Predictors of extrahepatic recurrence after curative hepatectomy for hepatocellular carcinoma. Ann Surg Oncol 2010;17(10): 2740-2746.
27. Takeishi K, Maeda T, Tsujita E, Yamashita Y, Harada N, Itoh S, Harimoto N, Ikegami T, Yoshizumi T, Shirabe K, Maehara Y. Predictors of intrahepatic multiple recurrences after curative hepatectomy for hepatocellular carcinoma. Anticancer Res 2012;35(5): 3061-3066.

Table 1. Clinicopathological characteristics of all included patients

Variable	Patients (n = 638)
Males, n(%)	490 (76.8)
Age, years [a]	67(60–72)
Period of surgery, n(%)	
1990–1999	193(30.3)
2000–2016	445(69.7)
Child–Pugh Grade	
A/B/C	569/68/1
Alanine aminotransferase (IU/l) [a]	41(25–68.8)
α-fetoprotein > 20 ng/ml, n(%)	253(39.7)
Tumor size	
<2 cm, n(%)	146(22.9)
2-5 cm, n(%)	399(62.5)
>5 cm, n(%)	93(14.6)
Diff. degree[#]	
well or moderate, n(%)	494(77.4)
poor, n(%)	144(22.6)
Microscopic vascular invasion, n(%)	151(23.7)
Grading score*	
0–2, n(%)	582(91.2)
3–4, n(%)	56(8.8)
Liver cirrhosis, n(%)	232(36.4)
Major hepatectomy (≥2 sections), n(%)	81(12.7)
Viral hepatitis, n(%)	494(77.4)

[#] degree of tumor differentiation, *severity of active hepatitis based on the histologic activity index score, [a] median and interquartile range

Table 2. Clinicopathological characteristics by tumor size and propensity score matching

Variables	unmatched cohort			propensity score-matched cohort		
	≤5 cm (n = 545)	>5 cm (n = 93)	P	≤5 cm (n = 83)	>5 cm (n = 83)	P
Sex (male)	412 (75.6)	78 (83.9)	0.081	75(90.4)	69(83.1)	0.17
Age >65 years	298 (54.7)	55 (59.1)	0.42	45(54.2)	47(56.6)	0.76
Period						
1990–1999	169(31.0)	24(25.8)	0.31	22(26.5)	22(26.5)	>0.99
2000–2016	376(69.0)	69(74.2)		61(73.5)	61(73.5)	
Child–Pugh Grade						
A	480(88.1)	89(95.7)	0.029	79(95.2)	80(96.4)	0.70
B or C	65(11.9)	4(4.3)		4(4.8)	3(3.6)	
ALT > 30 (IU/l)	366(67.2)	60(26.7)	0.62	55(66.3)	53(63.9)	0.75
AFP >20 (ng/ml)	216(39.6)	37(39.8)	0.98	26(31.3)	28(33.7)	0.74
Diff. degree[#]						
well or moderate	419(76.9)	75(80.6)	0.42	70(84.3)	68(81.9)	0.68
poor	126(23.1)	18(19.4)		13(15.7)	15(18.1)	

micro VI	125(22.9)	26(28.0)	0.36	18(21.7)	20(24.1)	0.71
Grading score*						
0–2	498(91.4)	84(90.3)	0.74	77(92.8)	76(91.6)	0.77
3–4	47(8.6)	9(9.7)		6(7.2)	7(8.4)	
Liver cirrhosis	205(37.6)	27(29.0)	0.11	29(34.9)	25(30.1)	0.51
Major hepatectomy	40(7.3)	41(44.1)	<0.001	32(38.6)	31(37.3)	0.87
Viral hepatitis	446(81.8)	48(51.6)	<0.001	49(59.0)	48(57.8)	0.88

Data are presented as n(%). Abbreviations: ALT, alanine aminotransferase; AFP, α-fetoprotein; micro VI, microscopic vascular invasion. # degree of tumor differentiation, *severity of active hepatitis based on the histologic activity index score.

Table 3. The sites of extrahepatic recurrence by tumor size in the whole population

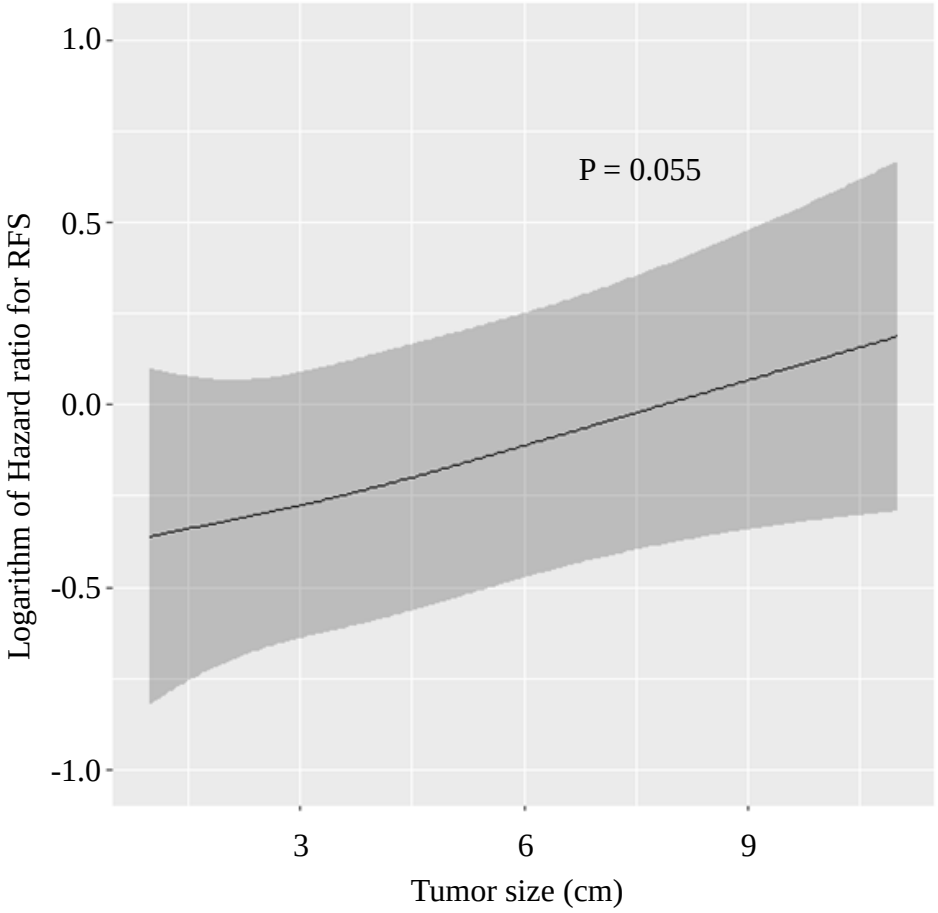
Extrahepatic recurrence site	Tumor size	
	≤5 cm	>5 cm
Bone	8	7
Lung	8	6
Lymph node	5	1
Peritoneum	3	2
Adrenal gland	2	1
Brain	0	2
Total	26	16

In the size >5 cm group, bone and lung recurrence overlapped in one patient, and brain and lung recurrence overlapped in two patients.

Figure Legends

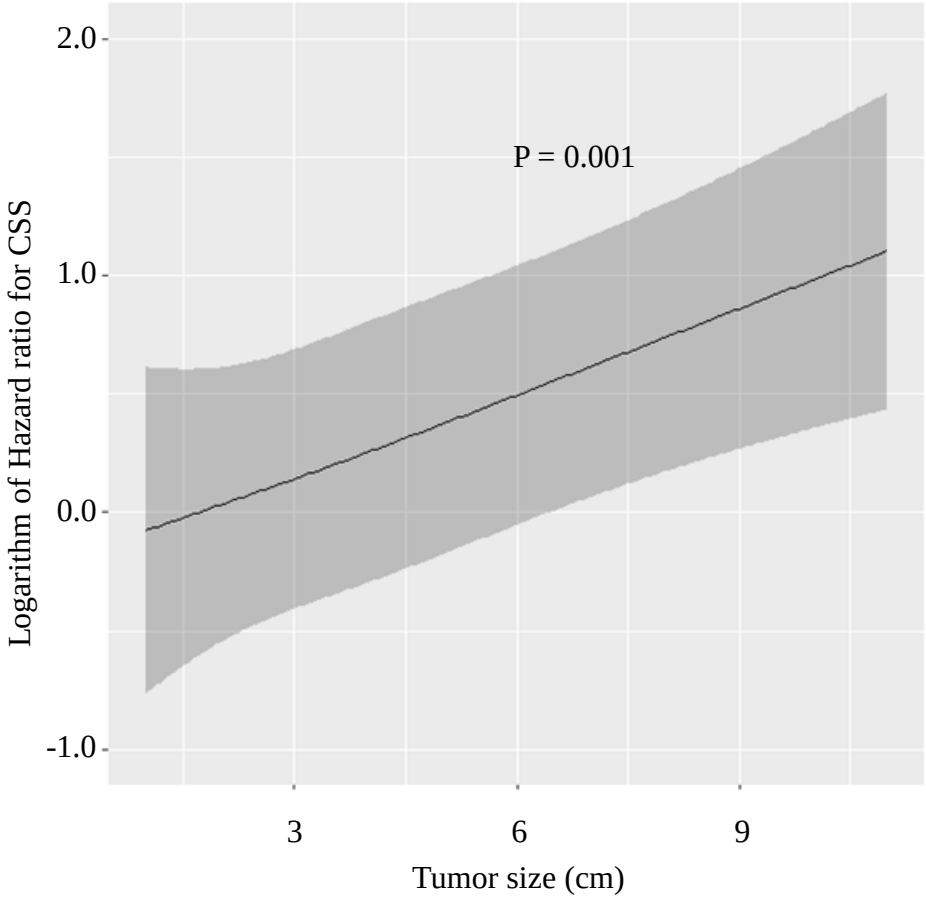
Figure 1. The Cox proportional hazard ratios for patients with no macroscopic vascular invasion. (A) For the recurrence-free survival, the hazard ratio for a change in tumor size from 2.0 to 5.0 cm was 1.16 (95% confidence interval, 0.93–1.45). (B) For the cancer-specific survival, the hazard ratio for a change from 2.0 to 5.0 cm was 1.41 (95% confidence interval, 1.01–1.97).

Fig.1A



Tumor size (cm)	Hazard ratio	95% confidence interval
2.0	reference	
5.0	1.16	0.93-1.45

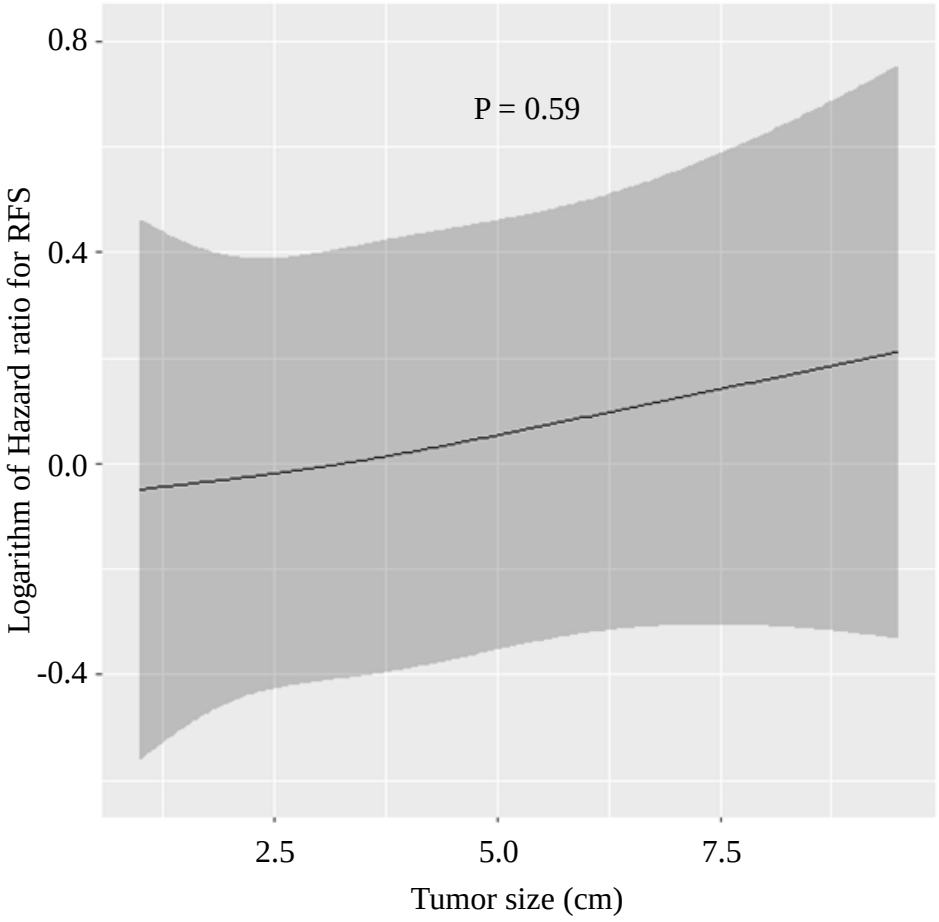
Fig.1B



Tumor size (cm)	Hazard ratio	95% confidence interval
2.0	reference	
5.0	1.41	1.01-1.97

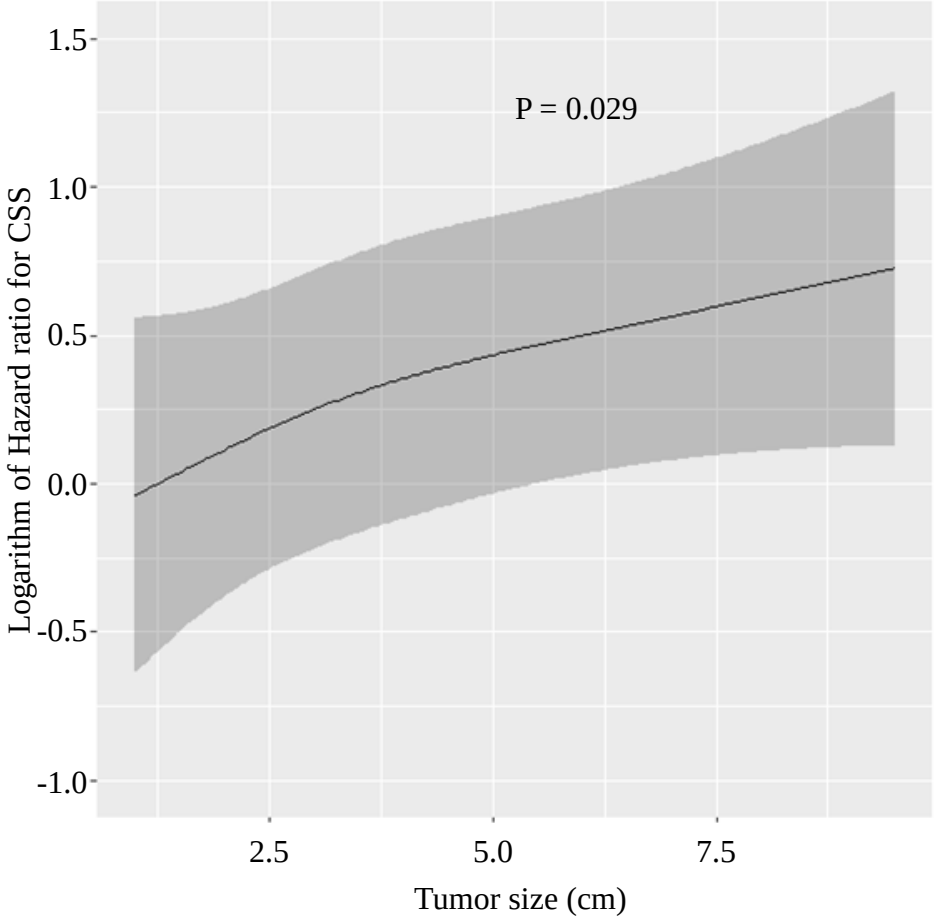
Figure 2. The Cox proportional hazard ratios for patients with no microscopic vascular invasion. (A) For the recurrence-free survival, the hazard ratio for a change in tumor size from 2.0 to 5.0 cm was 1.09 (95% confidence interval, 0.85–1.39). (B) For the cancer-specific survival, the hazard ratio for a change from 2.0 to 5.0 cm was 1.38 (95% confidence interval, 1.04–1.82).

Fig.2A



Tumor size (cm)	Hazard ratio	95% confidence interval
2.0	reference	
5.0	1.09	0.85-1.39

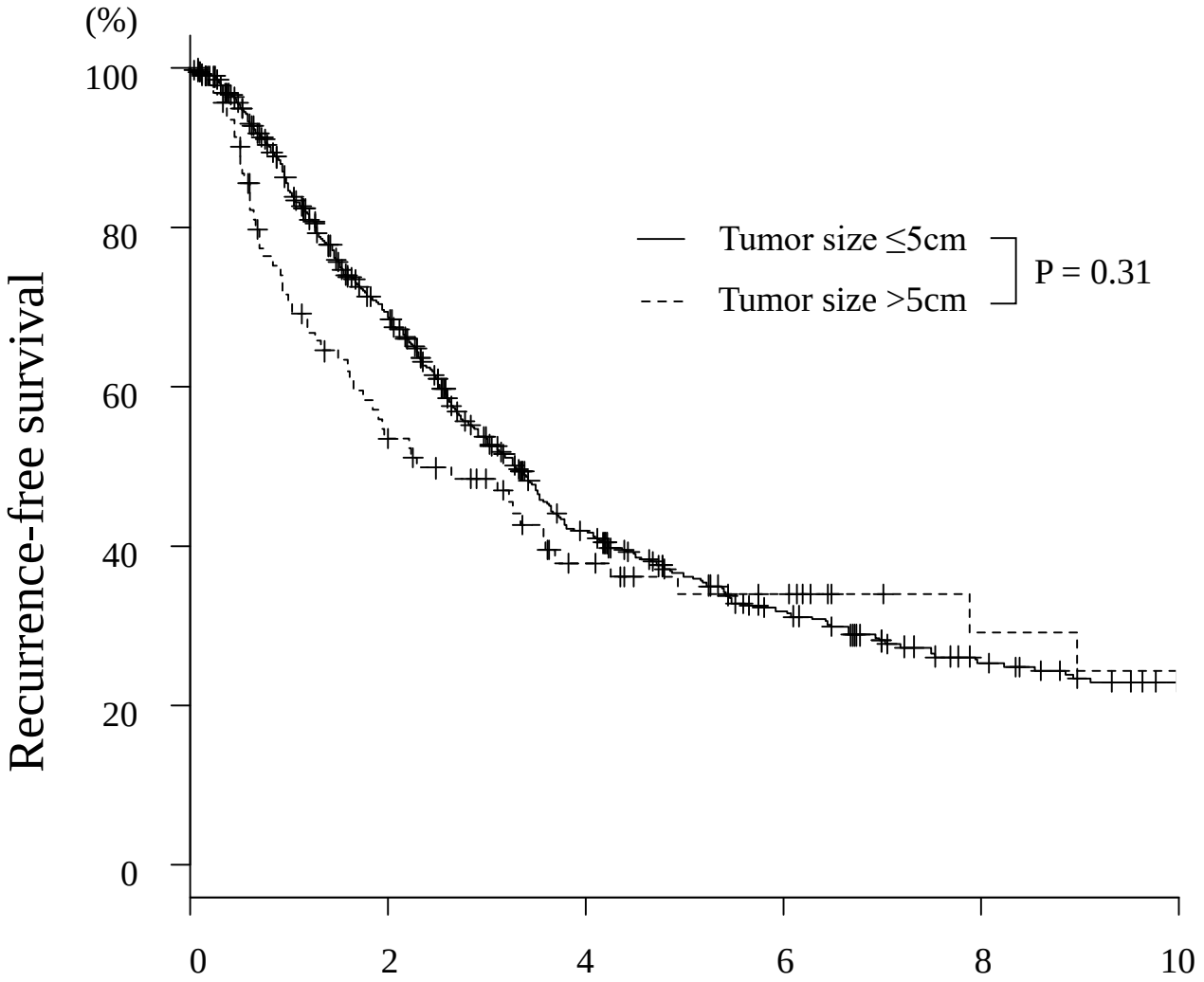
Fig.2B



Tumor size (cm)	Hazard ratio	95% confidence interval
2.0	reference	
5.0	1.38	1.04-1.82

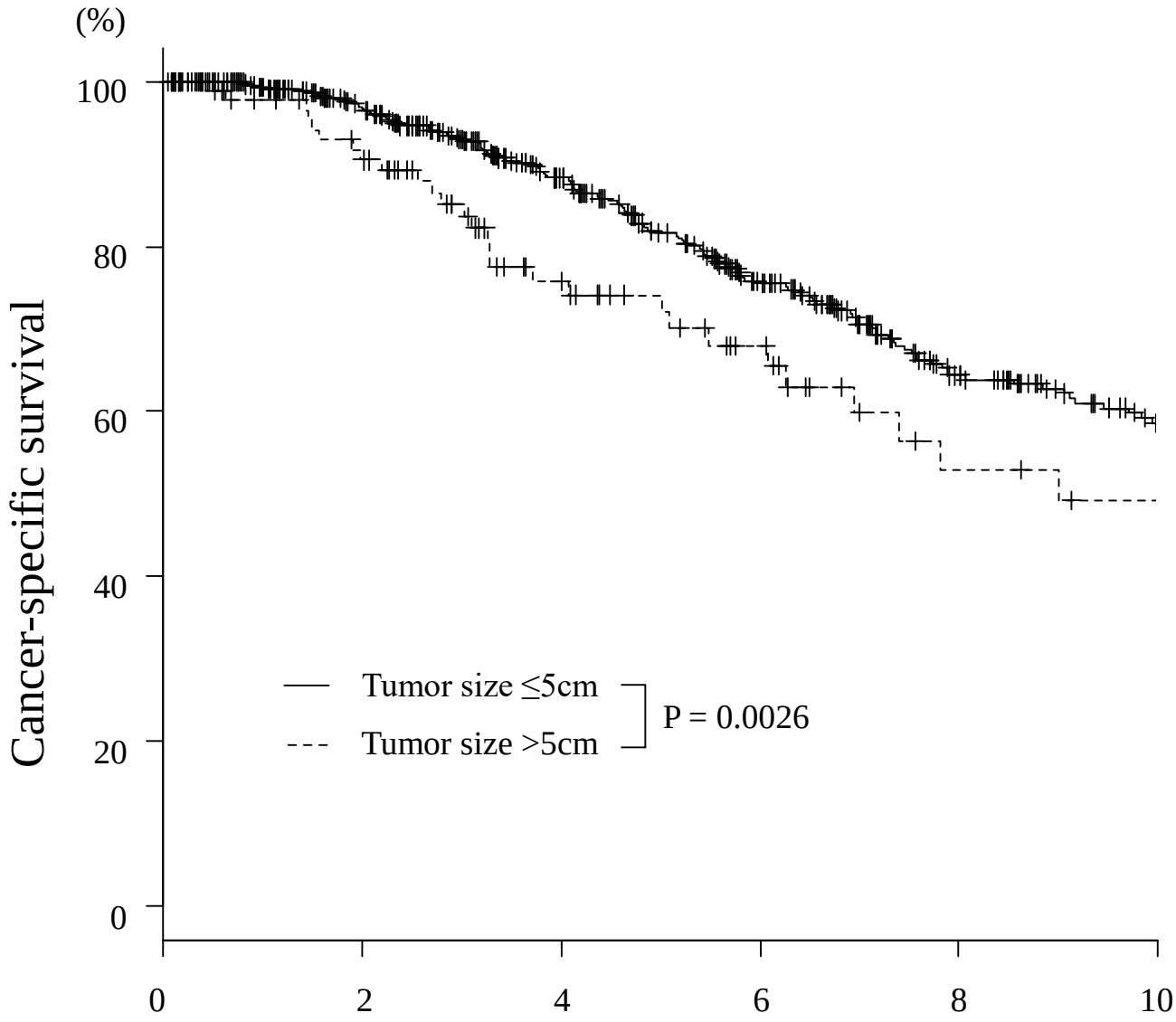
Figure 3. Kaplan–Meier survival curves for the unmatched cohort in the whole population. (A) Recurrence-free survival in patients with tumors ≤5 cm (n = 545) and >5 cm (n = 93). (B) Cancer-specific survival in patients with tumors ≤5 cm (n = 545) and >5 cm (n = 93).

Fig.3A



Number at risk						
Tumor size ≤5cm	545	314	155	96	59	43
Tumor size >5cm	93	44	22	14	6	5

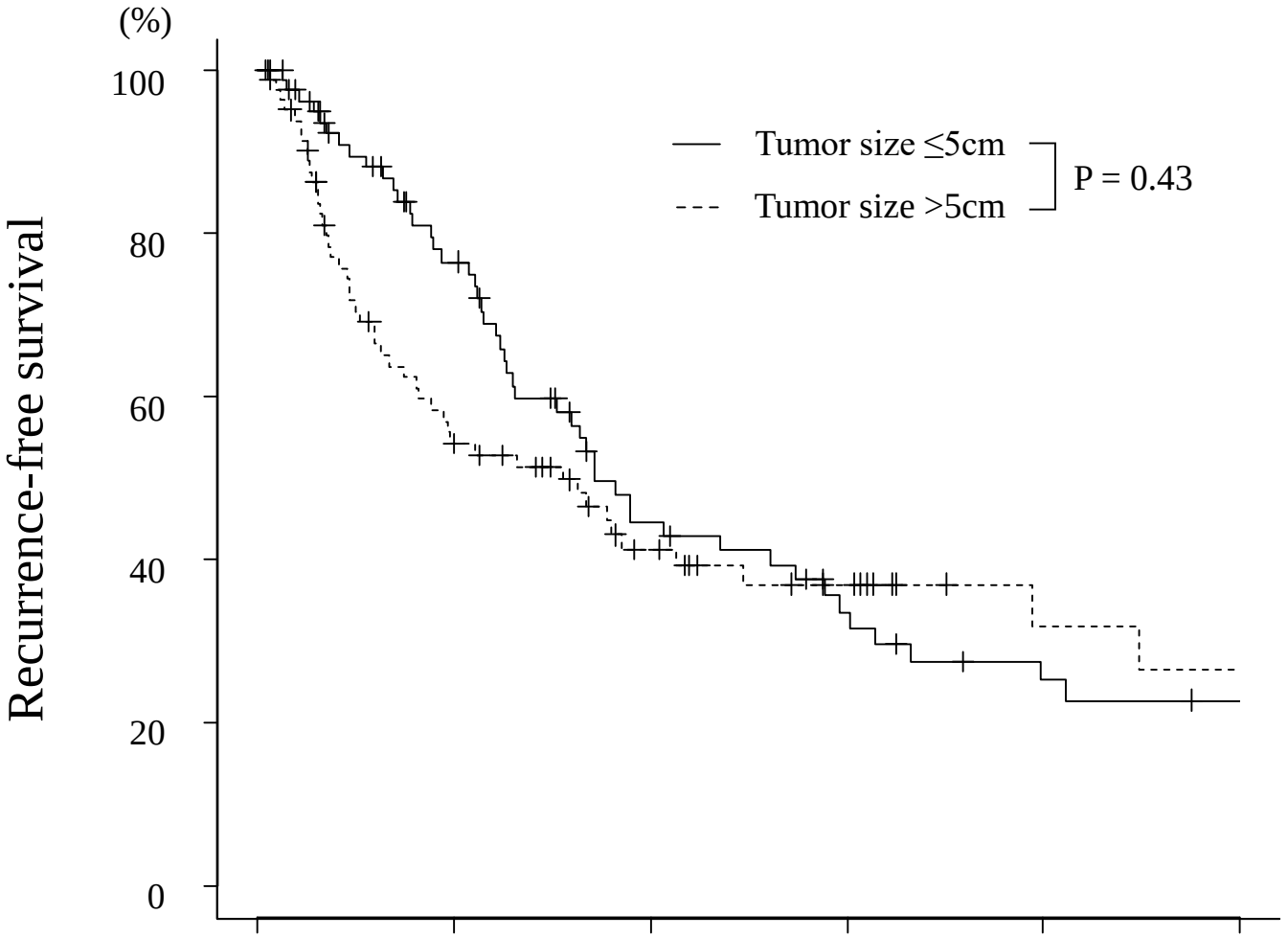
Fig.3B



Number at risk						
Tumor size ≤5cm	545	438	322	221	132	92
Tumor size >5cm	93	74	44	29	15	12

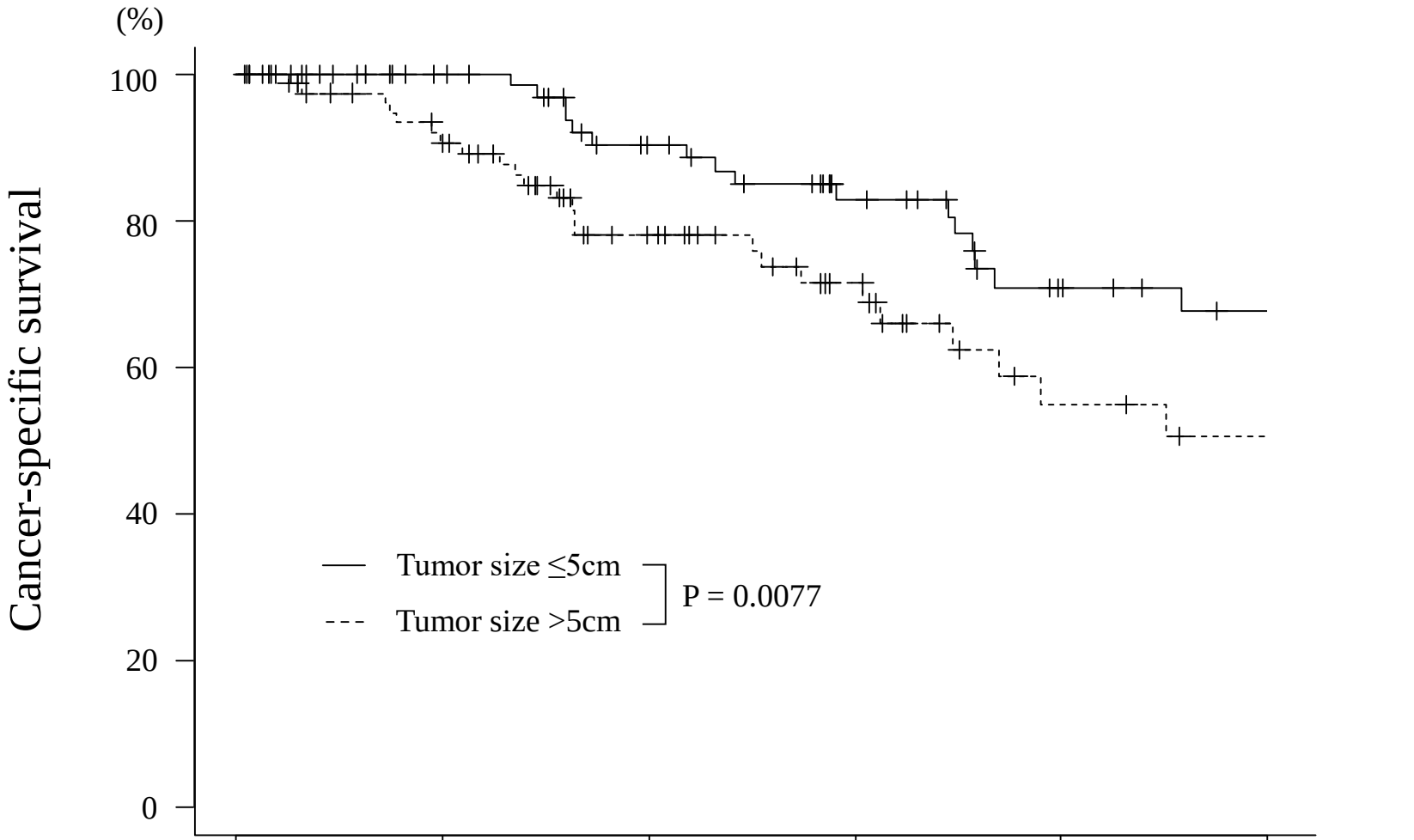
Figure 4. Kaplan–Meier survival curves for the propensity score-matched cohort in the whole population. (A) Recurrence-free survival in patients with tumors ≤5 cm (n = 83) and >5 cm (n = 83). (B) Overall survival in patients with tumors ≤5 cm (n = 83) and >5 cm (n = 83).

Fig.4A



Number at risk						
Tumor size ≤5cm	83	52	26	17	10	8
Tumor size >5cm	83	40	22	14	6	5

Fig.4B



Number at risk						
Tumor size ≤5cm	83	67	52	39	26	21
Tumor size >5cm	83	66	42	28	14	11

Figure 5. Cumulative recurrence within 2 years of surgery and annual hazard of recurrence. (A) Cumulative recurrence rate within 2 years of surgery in patients with tumors ≤5 cm (n = 83) and >5 cm (n = 83) in the propensity score-matched cohort of the whole population. (B) The annual hazard of recurrence.

Fig.5A

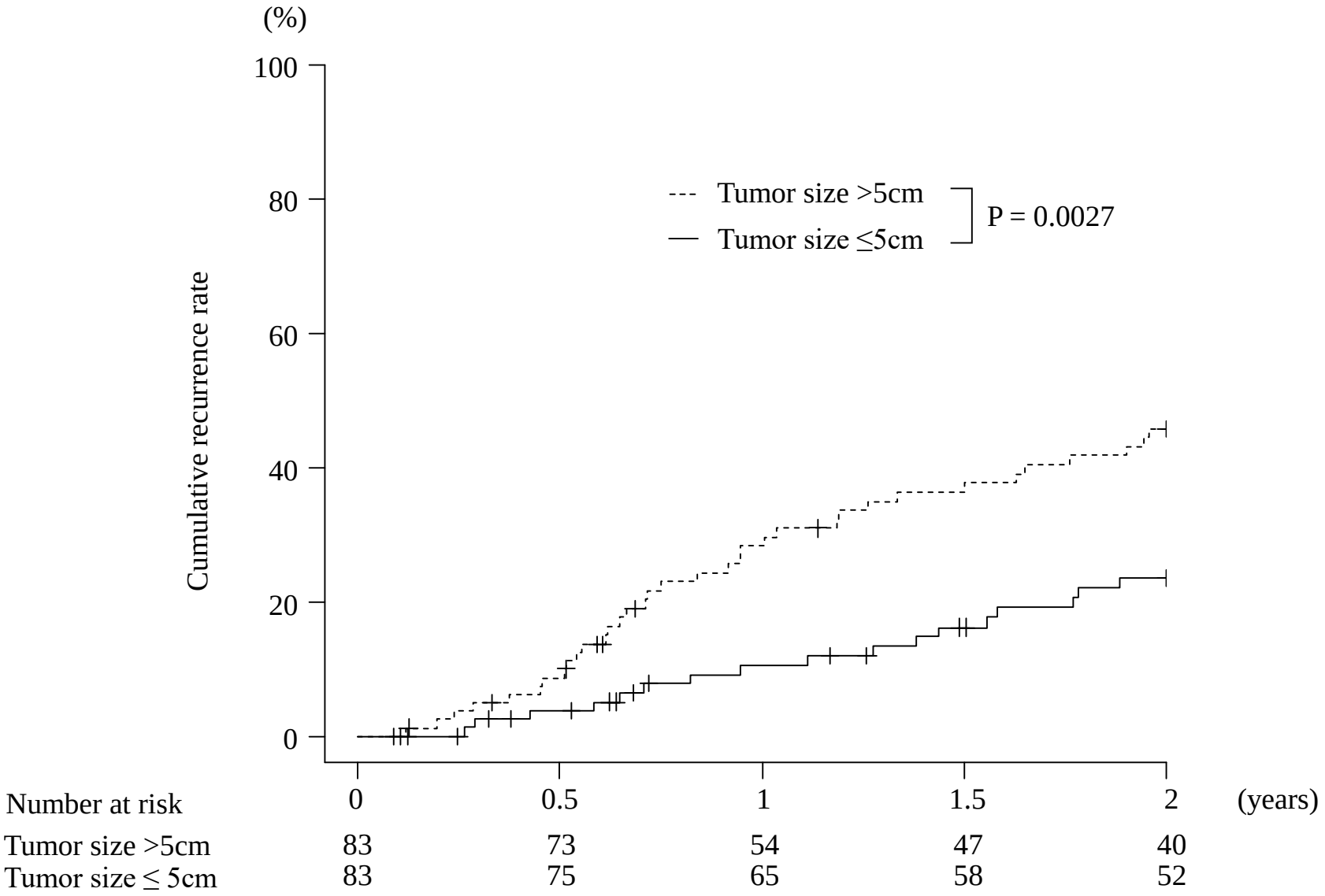
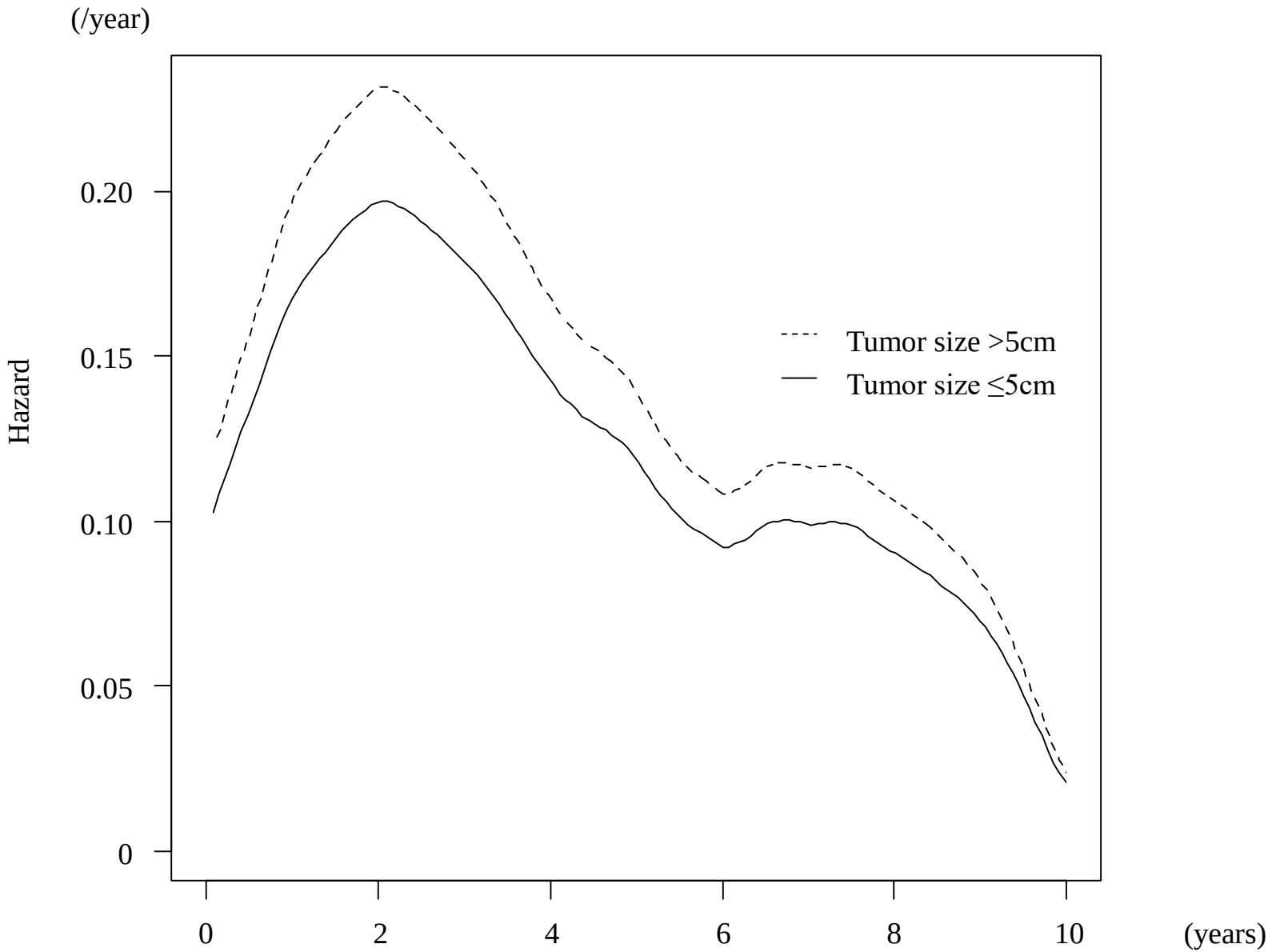

(%)
100
80
60
40
20
0
Cumulative recurrence rate
--- Tumor size >5cm
— Tumor size ≤5cm
P = 0.0027
0
0.5
1
1.5
2
(years)
Number at risk
Tumor size >5cm 83 73 54 47 40
Tumor size ≤ 5cm 83 75 65 58 52

Fig.5B


(/year)
Hazard
0.20
0.15
0.10
0.05
0
Tumor size >5cm
Tumor size ≤5cm
0
2
4
6
8
10
(years)