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Proton Beam Therapy versus Radiofrequency Ablation for Patients with Treatment-Naïve Single Hepatocellular Carcinoma: A Propensity Score Analysis

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Keywords
Liver cancer · Survival analysis · Proton beam radiotherapy · Percutaneous radiofrequency ablation · Propensity score matching

Abstract
Introduction: Proton beam therapy (PBT) is known to be an effective locoregional treatment for hepatocellular carcinoma (HCC). However, few comparative studies in treatment-naïve cases have been reported. The aim of this study was to compare the survival outcomes of PBT with those of radiofrequency ablation (RFA) in patients with treatment-naïve solitary HCC. ***Methods:*** Ninety-five consecutive patients with treatment-naïve HCC, a single nodule measuring ≤5 cm in diameter, and a Child-Pugh score of ≤8 who were treated with PBT at the University of Tsukuba Hospital between 2001 and 2013 were enrolled in the study. In addition, 836 patients with treatment-naïve HCC treated by RFA at the University of Tokyo Hospital during the same period were analyzed as controls. Recurrence-free survival (RFS) and overall survival (OS) were compared in 83 patient pairs after propensity score matching. ***Results:*** The 1-year, 3-year, and 5-year RFS rates were 86.6%, 49.5%, and 35.5%, respectively, in the PBT group and 59.5%, 34.0%, and 20.9% in the RFA group ($p = 0.058$); the respective OS rates were 97.6%, 77.8%, and 57.1% in the PBT group and 95.1%, 81.7%, and 67.7% in the RFA group ($p = 0.16$). Regarding adverse effects, no grade 3 or higher adverse events were noted in the PBT; however, two grade 3 adverse events occurred within 30 days of RFA in the RFA group: one hemoperitoneum and one hemothorax. ***Discussion:*** After propensity score matching, PBT showed no significant difference in RFS and OS compared to RFA. PBT can be an alternative for patients with solitary treatment-naïve HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth and ninth most common cancer in men and women, respectively, and is the second leading cause of death from cancer worldwide [1, 2]. The guidelines published by the Japan Society of Hepatology, European Association for the Study of the Liver, and American Association for the Study of Liver Diseases recommend surgical resection as the first-line treatment for solitary HCC [3–5]. However, because of comorbid chronic liver disease, only 20% are candidates for surgery [6]. Several non-surgical locoregional curative treatments are available for localized HCC, including radiofrequency ablation (RFA) and radiotherapy.

RFA has become the standard treatment for patients with tumors measuring ≤3 cm that are not suitable for surgery [3–5] and has been found to have the best outcomes in patients with small solitary tumors measuring <2 cm in diameter [7, 8]. At high-volume centers, the indications for RFA are generally extended to include tumors measuring up to 5 cm [9–11]. However, RFA has several limitations, including reduced effectiveness due to heat loss if the tumor is large or close to large blood vessels [12] and risk of intrahepatic bile duct injury if the tumor is adjacent to Glisson's capsule [12, 13].

Proton beam therapy (PBT) for HCC was first developed and reported in Japan in the 2000s [14, 15]. PBT has distinctive physical properties that lead to dosimetric advantages that differ from those of conventional radiotherapy [16, 17]. These properties are advantageous in terms of maximizing liver preservation, considering that liver tissue is more prone to radiation damage [18]. Physicians referred patients who refused surgery or were difficult to treat with other treatment for PBT. Previous studies have shown that PBT enables safe and excellent local control of HCC with low risk in large blood vessels or bile duct injury [19–23].

Because it is less invasive than surgery and has excellent local control rates, PBT is considered a potential treatment option alongside RFA. Nevertheless, PBT has been used in only a limited number of centers, and most reports on PBT focus on a single-arm without comparison with other treatments. Kim et al. recently reported a randomized controlled trial comparing PBT and RFA for recurrent or residual HCC [24]. Since the study enrolled patients with previous treatment history for HCC, the primary endpoint was 2-year local progression-free survival. Therefore, for patients with treatment-naïve HCC, it is still unknown whether overall survival (OS) after PBT is comparable with that after RFA.

Propensity score matching (PSM) is often used in retrospective studies when comparing data to reduce the risk of patient selection bias. Several research groups have compared the survival outcomes of RFA with those of stereotactic body radiation therapy in patients with HCC [25–29]. However, no studies have compared PBT and RFA for treatment-naïve HCC with PSM. Therefore, in this study, we investigated the efficacy of PBT and RFA in patients with a single, early-stage HCC by comparing their long-term prognosis after PSM, which controls for confounding factors.

Materials and Methods

Study Population

Consecutive patients with treatment-naïve HCC who underwent PBT at the University of Tsukuba Hospital from January 2001 to December 2013 or RFA at the University of Tokyo Hospital during the same period were enrolled in the study. Patients with a single lesion were included, considering the potential comparability issues with multiple lesions. The other inclusion criteria were as follows: lesion ≤5 cm in diameter, absence of extrahepatic metastasis or vascular invasion, Child-Pugh class ≤ B8, total bilirubin ≤3.0 mg/dL, and Eastern Cooperative Oncology Group performance status of 0–1. We included patients who underwent transarterial chemoembolization (TACE) after RFA or PBT for the same target lesions within 3 months because small tumors are often treated with RFA alone, while larger tumors are commonly treated with RFA + TACE based on the clinical practice guidelines [5]. Patients who were treated with palliative intent because of other active malignancy were excluded. HCC was diagnosed using dynamic computed tomography (CT) or magnetic resonance imaging; enhancement in the arterial phase with washout in the late phase was considered a definite sign of HCC [5].

PBT Procedure

Proton beams of 155–250 MeV were generated using a synchrotron accelerator and delivered using a rotating gantry. All dose distributions were calculated using the pencil-beam algorithm. The clinical target volume was defined as the area surrounding the gross tumor volume plus 3–5 mm in all directions. The clinical target volume margins were adjusted in cases with proximity to vessels or intestinal tracts. The irradiation protocol was decided based on the tumor location to maintain the safety of the porta hepatis and intestinal tract. Thus, the dosages were as follows: 66 Gy (relative biological effectiveness [RBE]) in 10 fractions for tumors located in peripheral lesions, 72.6 Gy (RBE) in 22 fractions for those adjacent to the porta hepatis, and 74 Gy (RBE) in 37 fractions for those close to the intestinal tract [21]. The total irradiation dose was 72.6 (range, 66–74) Gy (RBE): 66 Gy (RBE) in 10 fractions (n = 43), 70 Gy (RBE) in 35 fractions (n = 8), 72.6 Gy (RBE) in 22 fractions (n = 37), and 74 Gy (RBE) in 37 fractions (n = 7). The normal tissue dose constraints were applied, namely, a maximum exposure limit of 50 Gy (RBE) for the spinal cord, stomach, and duodenum and 60 Gy (RBE) for the colon. The dose to the skin was adjusted to be as narrow as possible so that it was not covered by the 95% isodose line.

Table 1. Characteristics of patients in the PBT and RFA groups before and after PSM

	All patients			After PSM		
	PBT (*n* = 95)	RFA (*n* = 836)	*p* value	PBT (*n* = 83)	RFA (*n* = 83)	*p* value
Mean age, years (SD)	70.0 (11.0)	69.3 (9.1)	0.532	70.3 (10.7)	70.9 (9.3)	0.670
Sex, *n* (%)						
Male	69 (73)	507 (61)	0.03	59 (71)	61 (74)	0.850
Female	26 (27)	329 (39)		24 (29)	22 (26)	
Etiology, *n* (%)						
HBV	16 (17)	110 (13)	0.403	15 (18)	14 (17)	1.00
HCV	56 (59)	612 (73)	0.005	52 (63)	46 (55)	0.391
Child-Pugh class, *n* (%)						
A	79 (83)	691 (83)	0.993	69 (83)	72 (87)	0.663
B	16 (17)	146 (17)		14 (17)	11 (13)	
Median platelet count [IQR], 1.00/μL	12.2 [8.6, 15.1]	11.4 [8.2, 15.2]	0.318	12.1 [8.3, 14.9]	13.2 [9.5, 18.3]	0.017
Mean albumin (SD), g/dL	3.7 (0.5)	3.7 (0.50)	0.598	3.7 (0.6)	3.8 (0.5)	0.304
Mean total bilirubin level (SD), mg/dL	0.8 (0.4)	0.8 (0.5)	0.086	0.8 (0.4)	0.8 (0.4)	0.903
Median AST [IQR], U/L	45.0 [28.5, 62.0]	50.0 [35.0, 69.0]	0.067	48.0 [31.5, 62.0]	42.0 [29.0, 62.0]	0.271
Median ALT [IQR], U/L	37.0 [23.5, 61.0]	43.0 [27.0, 67.0]	0.141	42.0 [24.0, 67.5]	36.0 [20.5, 55.5]	0.088
Mean PT (SD), *n* (%)	85.1 (15.7)	84.6 (13.8)	0.740	85.2 (15.7)	86.7 (12.9)	0.518
Mean ALBI score (SD)	−2.45 (0.49)	−2.40 (0.43)	0.278	−2.45 (0.50)	−2.51 (0.41)	0.366
Median FIB-4 index [IQR]	4.38 [2.61, 6.68]	4.83 [2.98, 7.56]	0.161	4.47 [2.88, 7.21]	3.76 [2.40, 6.66]	0.335
Median AFP [IQR], ng/mL	11.0 [5.0, 113.5]	14.0 [5.8, 51.8]	0.957	9.0 [5.0, 33.5]	16.0 [5.0, 48.4]	0.941
Median DCP [IQR], ng/mL	37.0 [20.0, 138.5]	21.0 [15.0, 44.0]	<0.001	30.0 [19.0, 69.3]	33.5 [19.0, 127.5]	0.328
Median diameter [IQR], mm	30.0 [21.0, 40.0]	22.0 [17.0, 28.0]	<0.001	28.0 [19.5, 34.0]	27.0 [20.0, 36.0]	0.365
≤20 mm, *n* (%)	24 (25.3)	347 (41.5)		24 (28.9)	23 (27.7)	
>20 mm, ≤30 mm, *n* (%)	31 (32.6)	330 (39.5)		31 (37.3)	27 (32.5)	
>30 mm, *n* (%)	40 (42.1)	159 (19.0)		28 (33.7)	33 (39.8)	
Sequential treatment from transarterial therapy, *n* (%)	14 (15)	217 (26)	0.023	14 (17)	14 (17)	1.000

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; DCP, des-gamma-carboxy prothrombin; IQR, interquartile range; PBT, proton beam therapy; PSM, propensity score matching; PT, prothrombin time; RFA, radiofrequency ablation; SD, standard deviation.

RFA Procedure

RFA was performed on an inpatient basis, and the details of the procedure have been described elsewhere [30]. In brief, RFA was performed using a 17-G internally cooled electrode system (Cool-Tip RF Ablation System, Medtronic Japan Co., Tokyo, Japan; VIVA RF Electrode, StarMed Co., Goyang, Korea) with a 2- or 3-cm exposed tip, which was inserted under real-time ultrasound guidance. For large tumors, the electrode was repeatedly inserted into different sites so that the entire tumor could be covered by the presumed necrotic volume. CT with a section thickness of 5 mm was performed 1–3 days after RFA to evaluate its effectiveness. Complete ablation was defined as hypoattenuation of the entire tumor with an adequate surrounding margin. The procedure was repeated until complete ablation was obtained.

Follow-Up

After completion of treatment, patients in both groups underwent abdominal CT or magnetic resonance imaging and laboratory tests, including measurement of serum tumor markers, namely, alfa-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), every 2–4 months. The evaluation of recurrence was confirmed by radiologists at both centers. Tumor recurrence was diagnosed using the same criteria as applied to the initial diagnosis of HCC. The recurrence patterns were categorized as follows: local tumor progression with recurrence inside or adjacent to the treatment site, intrahepatic recurrence apart from the treatment site, and extrahepatic metastasis [31]. Regardless of the type, the first recurrence was treated as an event. Adverse events were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 [32]. We also examined changes in liver function before and 6 months after treatment using albumin-bilirubin (ALBI) score in both groups [33].

Information on initial treatment for HCC and patient survival status was collected. Cause of death was defined according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer devised by the Liver Cancer Study Group of Japan [34]. The observation period for recurrence of HCC and patient survival was censored on December 31, 2020.

Statistical Analysis

PSM was applied to reduce the potential confounding effects of treatment and selection bias. The covariates included in the propensity score model are shown in Table 1. Multiple imputations for missing covariates were performed based on the multivariate

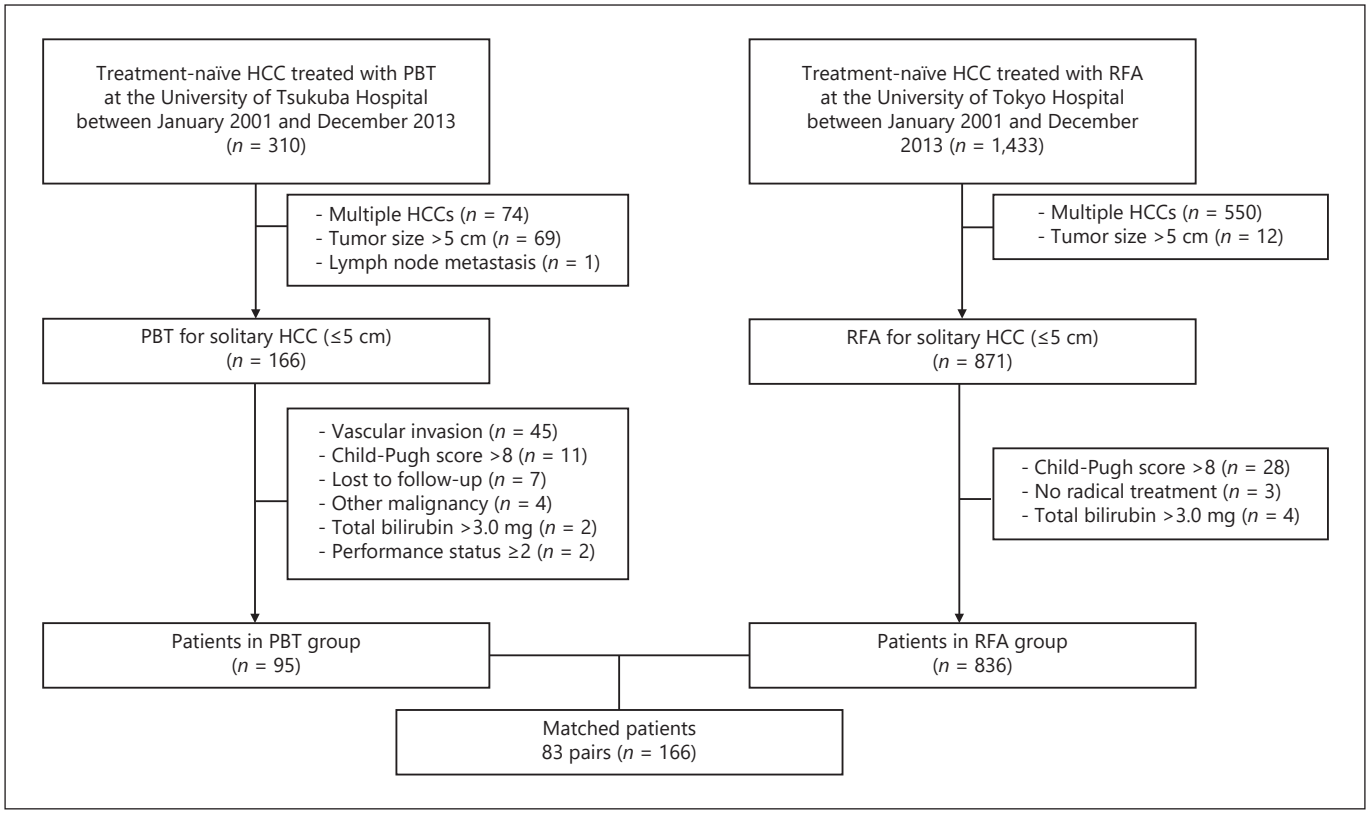


Fig. 1. Flow diagram showing the patient selection procedure. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; PBT, proton beam therapy.

imputation by chained equations method. The propensity score was then estimated based on LASSO logistic regression, and finally, the score was averaged for each patient [35]. After estimating the propensity score, the patients in each treatment group were matched 1:1 using nearest neighbor matching without replacement from a low to high propensity score with a caliper distance set at 0.25 standard deviations of the logit of the propensity score. Cases that did not match were discarded. We evaluated whether there was sufficient overlap between the two groups and confirmed their comparability with regard to the propensity score distribution.

Recurrence-free survival (RFS) and OS were calculated from the date of treatment as the criteria in the RFA group and the date of initiation of PBT in the PBT group to the date of recurrence, death, or last follow-up. The RFS and OS rates were estimated by the Kaplan-Meier method, and inferences on the hazard ratios (PBT/RFA) were conducted with the Cox proportional hazard model with robust inference [36]. A sensitivity analysis was also performed, excluding patients who underwent TACE before PBT or RFA. Competing risk analysis was used to analyze the difference in each competing event such as local tumor progression, recurrence excluding local tumor progression, and death. The cumulative incidence curve was estimated using the Fine and Gray regression model for competing risks [37]. Subgroup analyses for RFS and OS with the covariates were conducted using the Cox proportional hazard model for the matched sample. All statistical analyses were performed using R version 4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria). A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

The study included 95 patients who underwent PBT and 836 who underwent RFA (shown in Fig. 1). Besides the three follow-up losses in Figure 1, 1 patient in the PBT group was excluded from the analysis of recurrence due to the lack of recurrence data but was included in the OS analysis because survival information was available at follow-up. The baseline characteristics of all patients (n = 931) are presented in Table 1. The median follow-up duration was 64.5 (range, 1–223) months in the PBT group and 80.6 (range, 1–236) months in the RFA group. Patients in the PBT group were more likely to be male, less likely to have hepatitis C infection, and more likely to have higher DCP levels and a larger tumor. More patients in the RFA group

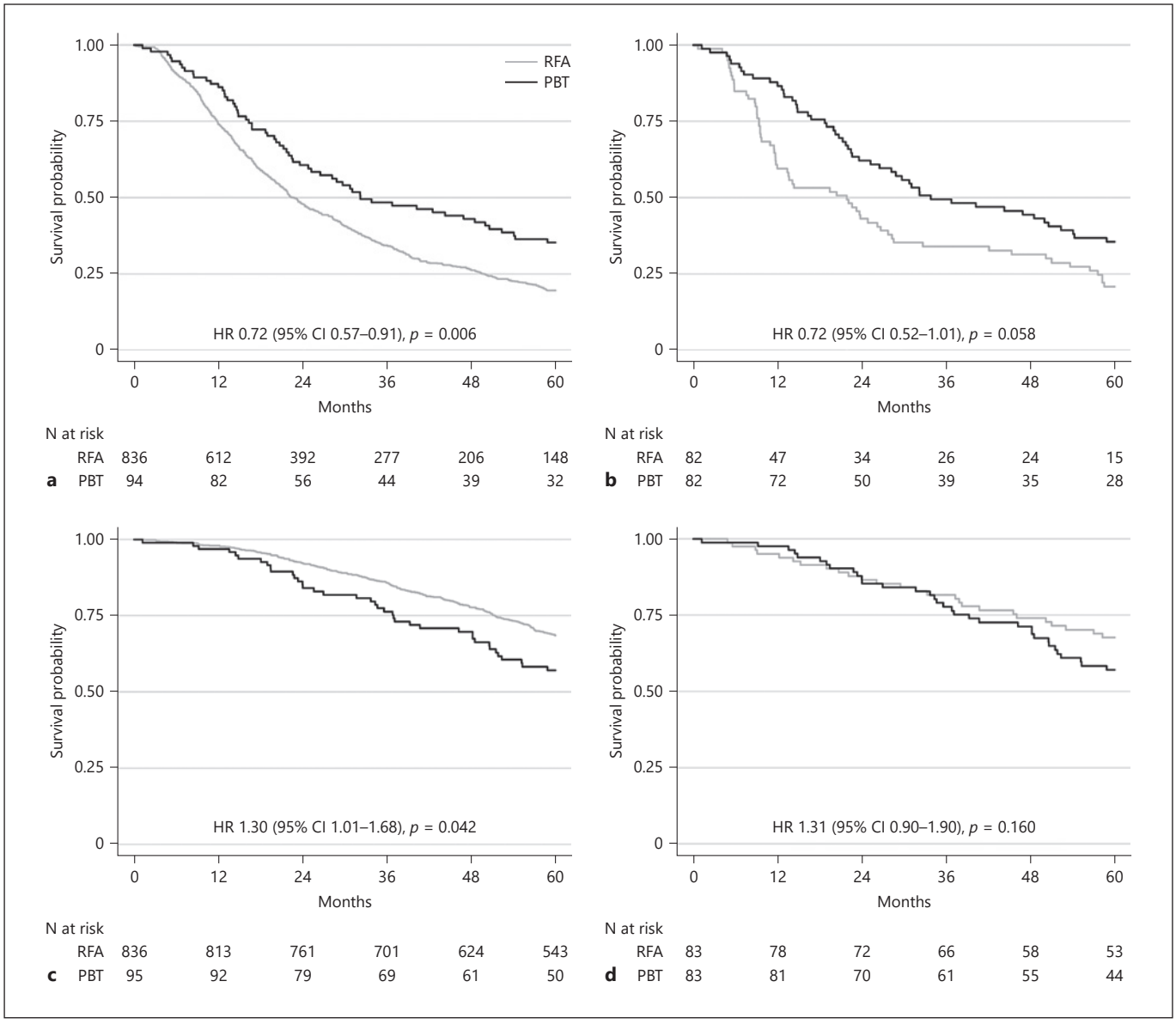
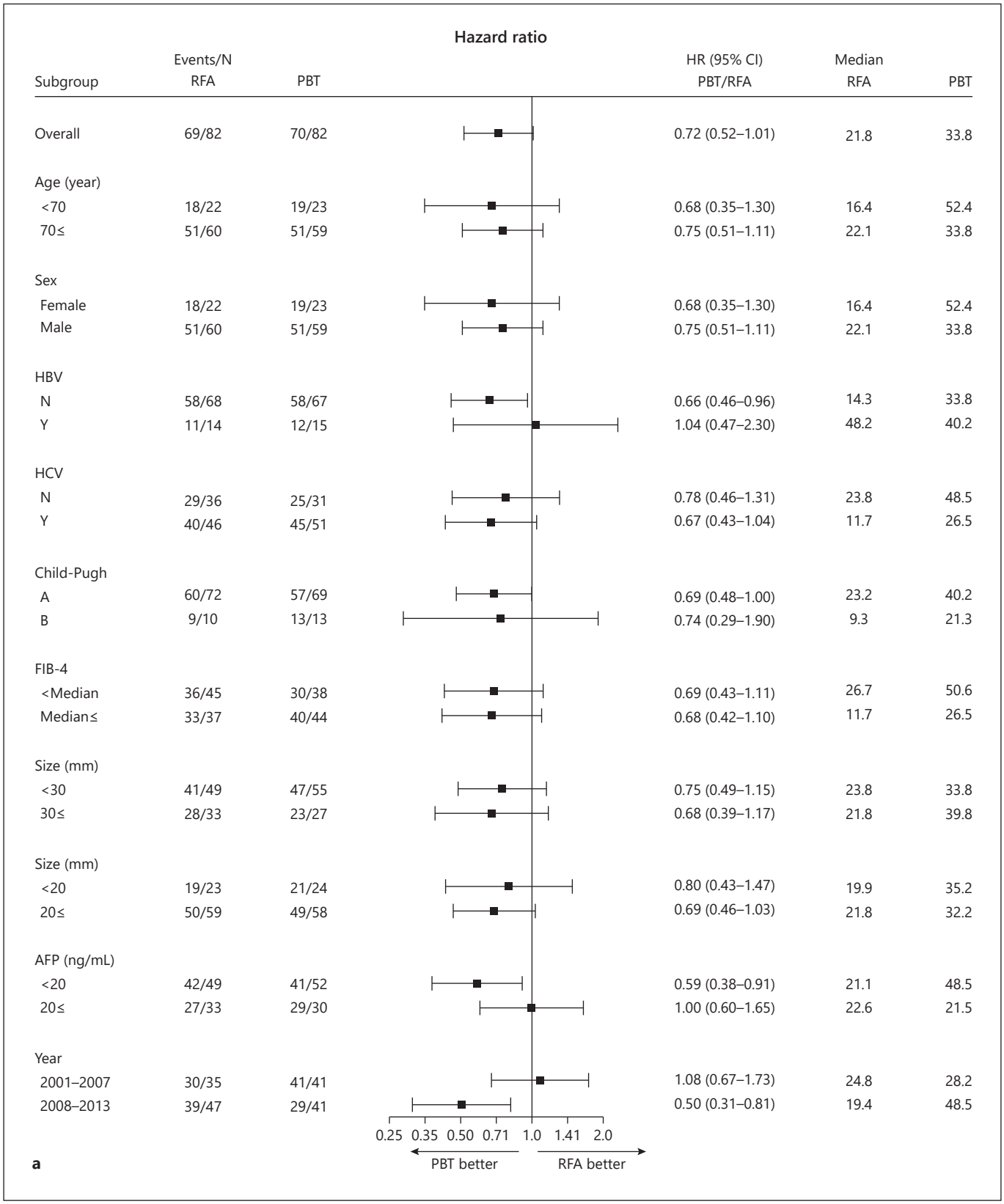


Fig. 2. Survival rates. **a** Recurrence-free survival rates for all tumors. **b** Recurrence-free survival rates for tumors selected for PSM. **c** OS rates for all tumors. **d** OS rates for tumors selected for PSM. CI, confidence interval; HR, hazard ratio; PBT, proton beam therapy; RFA, radiofrequency ablation.

received combined transarterial treatment. PSM achieved an adequate balance for all covariates between the PBT and RFA groups.

Recurrence and Survival

Figure 2 shows the RFS and OS data for all tumors and for tumors selected for PSM. In the matched cohort, recurrence of HCC was observed in 53 patients who were initially treated with PBT and in 60 of those who were initially treated with RFA. Median RFS was 33.8 months in the PBT group and 21.8 months in the RFA group. The 3- and 5-year RFS rates were 49.5% and 35.5%, respectively, in the PBT group and 34.0% and 20.9% in the RFA group. There was no significant difference in RFS between PBT and RFA (hazard ratio 0.72, 95% confidence interval [CI] 0.52–1.01, $p = 0.058$). In the matched cohort, there were 58 deaths in the PBT group and 51 deaths in the RFA group. The causes of death were cancer progression in 32



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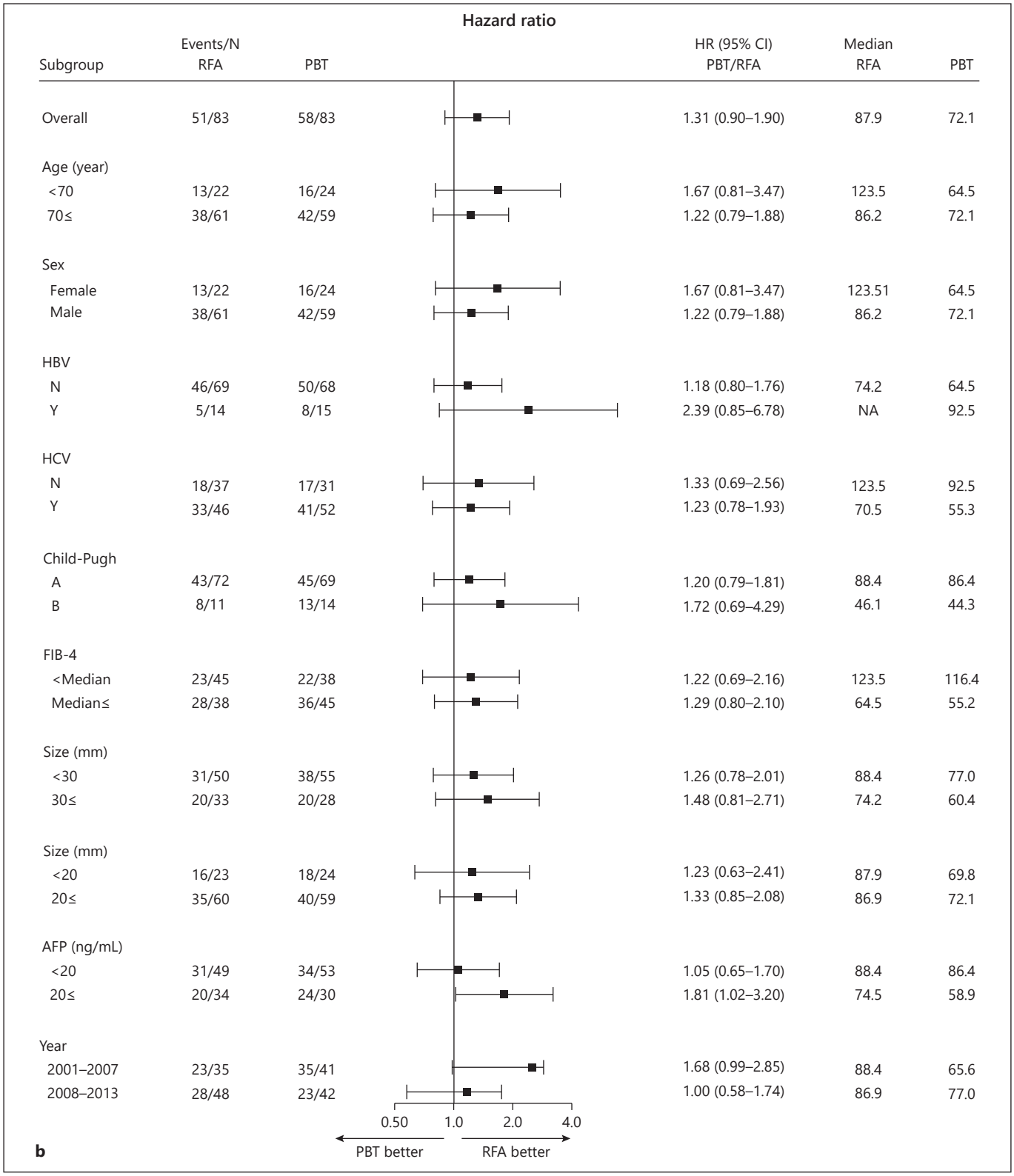

Fig. 3. Forest plot analysis of recurrence-free and OS rates after matching. **a** Recurrence-free survival rates. **b** OS rates. PBT, proton beam therapy; RFA, radiofrequency ablation; AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus.

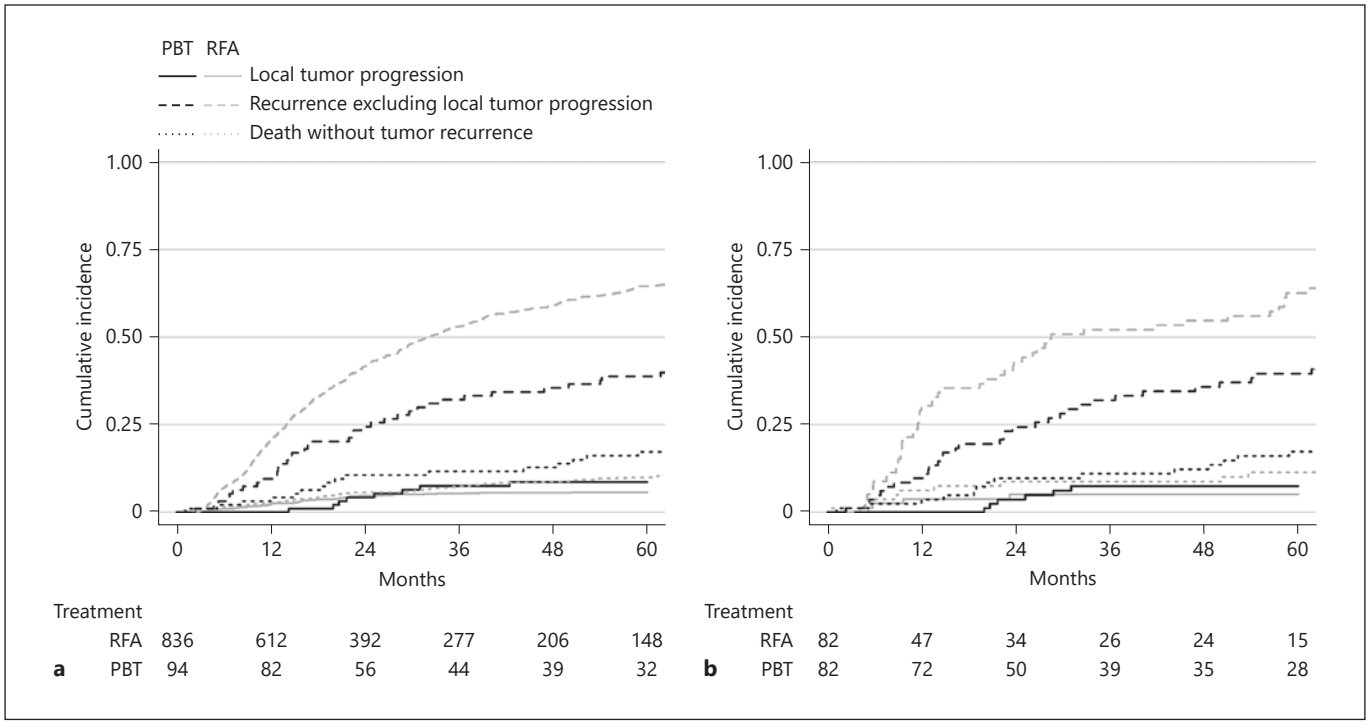

Fig. 4. Cumulative probabilities of death and recurrence before (**a**) and after (**b**) matching. Local tumor progression for PBT (straight black line) and RFA (straight gray line). Recurrence excluding local tumor progression for PBT (dashed black line) and RFA (dashed gray line). Death without tumor recurrence for PBT (dotted black line) and RFA (dotted gray line). PBT, proton beam therapy; RFA, radiofrequency ablation; HR, hazard ratio.

patients in the PBT group and 26 in the RFA group; liver failure in 6 and 9, respectively; a cause unrelated to the liver in 17 and 13; and unspecified in 3 and 3. For matched patients, the 3- and 5-year OS rates were 77.8% and 57.1%, respectively, in the PBT group and 81.7% and 67.7% in the RFA group; median OS was 72.1 months and 87.9 months, respectively. There was no significant difference in OS between PBT and RFA (hazard ratio 1.31, 95% CI: 0.90–1.90, $p = 0.160$). A sensitivity analysis excluding patients who underwent TACE before PBT or RFA showed similar results (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528537). The effects of PBT and RFA on median OS and RFS were also consistent across subgroups according to baseline characteristics, with no significant differences according to tumor size or liver function (Fig. 3). For Child-Pugh A, the median OS were 86.4 and 88.4 months in the PBT and RFA groups, respectively, with a hazard ratio of 1.20 (95% CI: 0.79–1.81), and for Child-Pugh B, the median OS were 44.3 and 46.1 months, respectively, with a hazard ratio of 1.72 (95% CI: 0.69–4.29). No significant difference was noted between RFA and PBT in either group.

According to the competing risk analysis results, at both 3 and 5 years, the cumulative probability of local tumor progression was 7% in the PBT group and 5% in the RFA group ($p = 0.29$). The respective 3- and 5-year cumulative probability rates of recurrence excluding local tumor progression were 32% and 40% in the PBT group and 52% and 63% in the RFA group, respectively ($p = 0.016$). The cumulative probability of death without tumor recurrence was 11% at 3 years and 17% at 5 years in the PBT group and 9% and 11%, respectively, in the RFA group ($p = 0.27$) (Fig. 4).

The initial recurrences comprised local tumor progression, intrahepatic recurrence, and extrahepatic recurrence in 8, 43, and 4 patients in the PBT group and 4, 56, and 0 patients in the RFA group, respectively (Fig. 5). A total of 39 of the 49 patients (80%) initially treated with PBT who developed intrahepatic recurrence were treated with RFA ($n = 15$), TACE ($n = 14$), or PBT ($n = 10$). In the PBT group, 25 patients received curative treatment (RFA or PBT), and 24 patients were given non-curative ones. The rational for non-curative treatment selection were as follows: patient or tumor

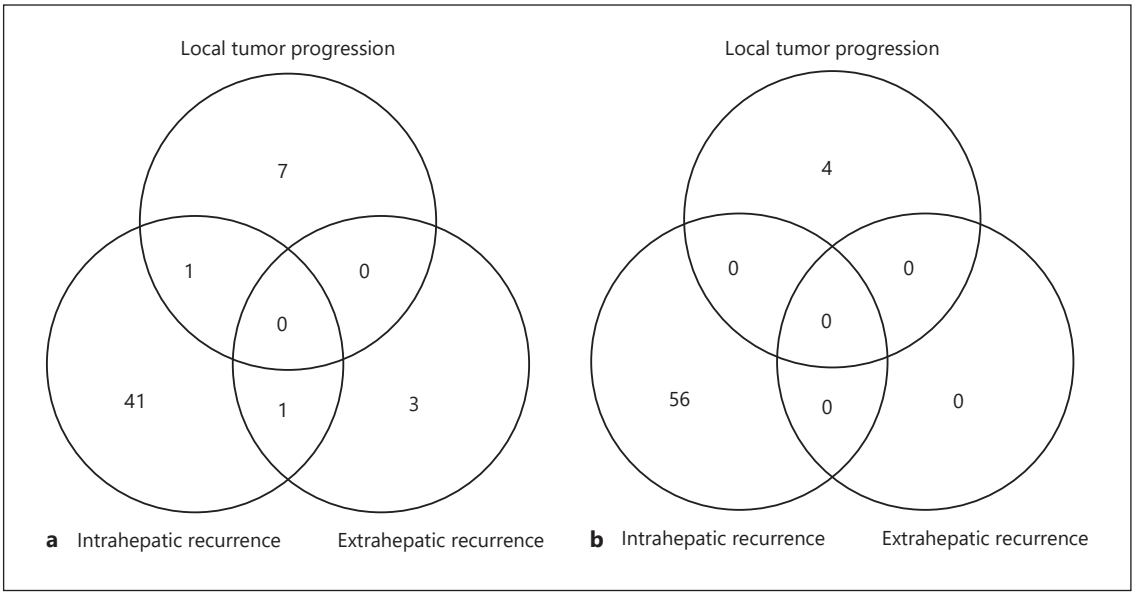

Fig. 5. Venn diagram for initial recurrence site. **a** PBT. **b** RFA. PBT, proton beam therapy; RFA, radiofrequency ablation.

factors other than liver function in 9 cases (patient age, tumor location, etc.), physician's choice with ≤3 nodules in 7, multiple recurrences with ≥4 nodules in 4, economic reason in 1, and unknown details in 3. Although 58 of the 60 patients (97%) initially treated with RFA who developed intrahepatic recurrence were treated with RFA (n = 56), TACE (n = 1), or systemic therapy (n = 1). The proportion of patients who received any treatment or any curative treatment (RFA or PBT) was higher in the RFA group ($p < 0.01$, respectively, Fisher's exact probability test).

Adverse Events

All patients in the PBT group completed the scheduled treatment without serious toxicity. There were no severe complications or any grade 3 or higher adverse events, except for hematologic abnormalities. Grade 1–2 dermatitis occurred as an acute toxicity in all patients, and grade 1 rib fracture occurred as a late toxicity in 3 patients. In the RFA group, two grade 3 adverse events occurred within 30 days of RFA: hemoperitoneum in 1 and hemothorax in 1. Neoplastic seeding occurred in one case as a delayed grade 3 adverse event. The mean (±SD) ALBI scores before and 6 months after treatment were −2.46 ± 0.41 and −2.80 ± 0.57 in the PBT group, −2.51 ± 0.41 and −2.39 ± 0.53 in the RFA group, respectively.

Conclusion

This study is the first to compare RFS and OS for patients with treatment-naïve solitary HCC treated with PBT versus RFA. PSM showed a trend indicating the superiority of PBT for RFS and RFA for OS, but there was no statistically significant difference between PBT and RFA for either RFS or OS.

In clinical practice, most HCC treated by RFA in Japan is less than 2 cm in size [38]. In patients with HCC measuring 2 cm or greater, the incidence of local tumor progression was relatively higher [39]. In general, HCC larger than 2.5 cm often requires multiple overlapping ablations, and it is technically difficult to obtain adequate three-dimensional ablative margins. In contrast, PBT can achieve stable radiation margins for HCC larger than 10 cm [40]. In this study, the median tumor size in the RFA group after PSM was 2.7 cm, which was larger than the general indication for RFA and considered to have an impact on RFS. The higher RFS in PBT may suggest its higher ability in local tumor control over RFA. However, there was no significant difference in local tumor progression rates between the two groups in the competing risk analysis (Fig. 4). On the other hand, tumor recurrence other than local tumor progression was fewer in the PBT group. Since PBT can treat with wider margin without being affected by the

cooling effect, it is possible that it could have prevented recurrence from satellite nodules near the target lesion. We also could not exclude the possibility that treatment evaluation and subsequent surveillance for recurrence may not be technically comparable between the two treatment modalities. While tumors shrink gradually after PBT and some treated HCCs show persistent enhancement at 6 or 12 months, the treatment effect was immediately evaluable after RFA; the difference in sensitivity to detect recurrence after treatment may result in lead-time bias [41, 42].

Since recurrence is quite frequent in the treatment of HCC, the treatment for recurrent tumors also affects the OS as well as the initial treatment. Whereas 93% of the RFA group underwent curative treatments, only 51% of the PBT group underwent RFA or PBT upon intrahepatic recurrence. The difference in the treatment modality may explain the inconsistency between RFS and OS. Deterioration of liver function after treatment might narrow the treatment choice at recurrence. However, the change in liver function assessed using the ALBI score showed that the PBT did not decrease liver function compared with the RFA. In fact, among 24 patients with non-curatively treated recurrence in the PBT group, the primary reasons were not related to poor liver function, except for 3 with unknown reasons. Therefore, there might be differences in treatment availability for recurrence across facilities even after PSM. Regarding secondary treatment for local tumor progression after PBT, although repeated PBT was reported to be well tolerated and safe, PBT was limited due to cumulative radiation dose and cost [43]. Meanwhile, RFA does not have a limitation for secondary treatment. Furthermore, death unrelated to liver disease was more common in the PBT group, indicating the presence of other comorbidities. Therefore, performance status or comorbidity assessment affects the selection of treatments. Unfortunately, due to deficiencies in some patients, the performance status analysis was not implemented in this study.

In terms of toxicity, even though the liver is radiosensitive, the dosimetric advantage of PBT by allowing significant dose reduction for non-targeted liver parenchyma may have limited the effects on liver function. For toxicity other than liver function, in the PBT group, there were no grade 3 or higher acute and late adverse events, and the adverse effects of skin and soft tissue were manageable. Although there were no Grade 3 or higher late adverse events from PBT, fibrosis due to irradiation may increase the risk of cholangitis and liver abscess in secondary treatment such as RFA and TACE at recurrence. Due to the above reasons, the low invasiveness and good local controllability of PBT suggest that it may be more advantageous, especially in elderly patients with HCC larger than 3 cm.

The PSM analysis is used to improve comparability and is one of the notable points of this research. Several studies have used PSM for comparing stereotactic body radiation therapy and RFA. These reports either did not report on long-term survival or included only some of the confounding prognostic factors [25–29]. The PSM analysis in our present study included 16 factors (Table 1); not only did we use tumor size and tumor markers and summarize liver function scoring, but each of the factors potentially related to synthetic capacity and fibrosis was also adjusted for [44, 45]. For these reasons, potential factors or comorbidity status may affect the discrepancy between OS and RFS, which was not adjusted by propensity scores. Although PSM cannot completely exclude the influence of factors not used, unlike randomization, since no randomized controlled trial for treatment-naïve HCC is conducted, this study is unique and meaningful because it is the only available evidence for newly diagnosed HCC comparing PBT and RFA.

This study had several limitations. First, although we considered as many factors as possible, this study employs a retrospective design; certain hidden factors, such as medical comorbidities and socioeconomic status, might have affected the outcome. Second, both groups were from single institutions. The University of Tsukuba Hospital and the University of Tokyo Hospital are the largest centers in Japan performing PBT and RFA, respectively, so the generalizability of the results may differ from that in multicenter studies. Third, the number of matched cases was not substantial enough to detect a clinically meaningful difference in the OS. Therefore, further prospective multicenter studies with greater numbers of cases are required to confirm our findings.

In conclusion, PBT showed no significant difference in RFS and OS compared to RFA after PSM. PBT can be an alternative to RFA for treatment-naïve solitary HCC.

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Statement of Ethics

The study was approved by the institutional review boards of University of Tsukuba Hospital (Number H29-26) and University of Tokyo (Number 12080) and was performed in accordance with the Declaration of Helsinki and the ethical guidelines for epidemiologic research developed by the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare. In view of the retrospective study design, and with the insitutional review boards' approval, we obtained patient consent via the opt-out method using the hospital's website. This study is registered with the UMIN Clinical Trials Registry (UMIN 000034661).

Conflict of Interest Statement

Ryosuke Tateishi has received lecture fees from STARmed Co., Ltd., Medtronic plc, Merk Sharp & Dohme, Chugai Pharmaceutical Co., Ltd., Bristol-Meyers Squibb, Giliad Sciences, AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Eisai Co., Ltd., and Bayer Co., Ltd. Hayato Nakagawa has received lecture fees from Bristol-Meyers Squibb, Giliad Sciences, AbbVie GK, Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd. Yoshinari Asaoka has received consultation fees from Eisai Co., Ltd. Shuichiro Shiina has received lecture fees from Starmed Co., Ltd., Medtronic plc, Japan Lifeline Co., Ltd., Canon Medical Co., Ltd., Shionogi Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Giliad Sciences, AbbVie GK, Eisai Co., Ltd., and Bayer Co., Ltd. Kazuhiko Koike has received lecture fees from Eisai, Bayer, MSD, Abbvie, Gilead, and Otsuka Pharmaceutical Co., Ltd.

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Author Contributions

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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