

Real-world Efficacy of CyberKnife Combined with Systemic Therapy for Primary Liver Cancer: Early Dynamic Changes in Alpha-Fetoprotein as a Core Prognostic Factor

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Abstract

Background: CyberKnife combined with systemic therapy has been increasingly administered to patients with liver cancer, yet its survival benefits in the real world remain unclear. Moreover, the prognostic value of early dynamic changes in alpha-fetoprotein (AFP) following CyberKnife treatment requires further validation.

Methods: This retrospective study included 175 patients with liver cancer who received their first CyberKnife treatment between January 2018 and March 2025. Subjects were stratified into the CyberKnife monotherapy group (n=87) and the CyberKnife plus systemic therapy group (n=88) based on treatment modalities. The study compared overall survival, progression-free survival, and objective response rates between the two groups of patients, using multivariate Cox regression to adjust for baseline confounders and identify independent prognostic factors.

Results: The median follow-up was 23.6 months. Kaplan-Meier analysis showed that the median overall survival (OS) in the CyberKnife monotherapy group was significantly longer than that in the combination therapy group (57.5 vs. 19.8 months, $p=0.005$). The median progression-free survival (PFS) was 35.1 vs. 11.3 months ($p=0.003$). However, after adjustment for baseline confounders via multivariate Cox regression, combination therapy showed no independent association with OS (95% CI: 0.63–2.32, $P=0.564$) or PFS (95% CI: 0.64–2.46, $P=0.518$). Post-treatment AFP elevation (versus AFP decline) was an independent adverse prognostic factor for OS (95% CI: 1.23–5.19, $P=0.012$) and PFS (95% CI: 1.32–5.50, $P=0.006$). In addition, we conducted several sensitivity analyses, and the results were consistent with the main analysis: there was no significant difference in survival rates between the two groups, and elevated AFP levels remained a significant factor for poor prognosis.

Conclusions: Among patients with liver cancer treated with CyberKnife, changes in AFP levels 2–3 months after treatment are a stronger independent prognostic factor than the treatment modality itself; combination with systemic therapy did not provide additional survival benefits.

Background

Primary liver cancer (PLC) is a common malignant tumor worldwide, and both its incidence and mortality rates have been on the rise in recent years [1, 2]. Global cancer statistics for 2024 indicate that liver cancer ranks sixth in incidence and third in mortality among all cancers [3]. Surgical resection, liver transplantation or local ablation can achieve curative outcomes for patients with early-stage disease. Nevertheless, the majority of patients are diagnosed at intermediate or advanced stages in real-world clinical practice and are often ineligible for radical surgery [4, 5]. Stereotactic body radiotherapy (SBRT), particularly the CyberKnife system, has become an important local treatment option for unresectable or oligometastatic PLC due to its high precision, low fractionation, and high dose, with local control rates reaching 70%–90% [6, 8]. In recent years, to improve overall survival (OS) in patients with PLC, there has been a growing clinical trend toward combining local therapy with systemic therapy (including targeted therapy, immunotherapy, or chemotherapy) [9, 10]. Multiple studies have demonstrated that the

combination of systemic therapy on the basis of transarterial chemoembolization (TACE) or ablation can prolong survival in some patients [11, 13]. However, evidence regarding the efficacy of CyberKnife combined with systemic therapy—particularly whether it provides a survival benefit in real-world settings—remains limited [14]. On the one hand, CyberKnife itself has a high local control rate, and there is debate over whether combining it with systemic therapy can further reduce distant metastasis or improve OS [15]; on the other hand, there is significant selection bias in clinical practice—patients with better liver function and lower tumor burden typically receive CyberKnife therapy alone, while those with more severe disease and poorer liver function are more likely to require combination therapy with systemic treatment [16, 17]. This selection bias makes it difficult for survival outcomes from univariate comparisons to directly reflect the treatment effect itself; therefore, rigorous statistical methods are needed to control for confounding factors [18, 19].

Alpha-fetoprotein (AFP) is the most commonly used serum marker for PLC [20]. Tumor burden and treatment response are closely correlated with AFP levels [21][22]. Previous studies have demonstrated that dynamic post-treatment AFP alterations, particularly early AFP decline, carry predictive value for long-term patient survival [23, 24]. Both the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) list AFP as an important indicator for monitoring treatment efficacy [25, 26]. However, there are currently very few reports on whether the pattern of AFP changes 2–3 months after CyberKnife treatment can predict prognosis, or whether combination therapy with systemic treatment might interfere with these changes [27]. Based on real-world retrospective data, this study focuses on two key questions: whether the combination of CyberKnife and systemic therapy provides a survival benefit for patients with liver cancer; and whether early post-treatment changes in AFP levels have independent prognostic significance. Given the high loss-to-follow-up rate in the cohort, we will also conduct sensitivity analyses to assess the reliability of our main conclusions [19, 28].

Methods

Study design and patient population

This retrospective study collected clinical data of patients with PLC who received CyberKnife stereotactic body radiotherapy at the Second Affiliated Hospital of Guangxi University of Chinese Medicine between January 2018 and March 2025. Inclusion criteria: (1) All cases were diagnosed with PLC based on imaging or histological findings; (2) Clinical data were complete; for patients who underwent multiple CyberKnife treatments, only data from the first treatment were included; (3) Karnofsky Performance Status (KPS) score of ≥ 60 , expected survival of at least 3 months, no other concurrent cancers, and no significant functional impairment of vital organs such as the heart, lungs, or kidneys; (4) For patients with prior liver-directed therapy, an interval of at least 3 months was required between the last previous treatment and CyberKnife intervention, and comprehensive baseline imaging assessments were completed prior to treatment initiation. This study has been approved by the hospital's ethics committee

(Approval No.: KY2025-145). Written informed consent was obtained from all enrolled patients, and the study protocol complied with the normative requirements for retrospective clinical research.

Treatments

Systemic therapeutic regimens

The observation window was defined as the 3-month period before and after a patient's first CyberKnife treatment. Patients who received any systemic anticancer therapy (including targeted therapy, immunotherapy, or a combination of targeted and immunotherapy or chemotherapy) during this window were classified into the systemic therapy combination group [29], while those who did not receive such therapy were classified into the CyberKnife monotherapy group. All treatment regimens were administered in accordance with standard clinical practice or drug labeling instructions, with drug combinations and treatment cycles determined by the attending physician. As this study is a single-center, long-term, real-world retrospective analysis covering a broad time span and characterized by rapidly evolving clinical protocols, specific drugs and combination regimens were not further subdivided. Patients were classified solely based on their initial treatment modality during the observation window, and changes in subsequent treatment lines were not counted.

CyberKnife treatment protocol

All patients received CyberKnife treatment manufactured by Accuray. Within one week prior to treatment, three to four gold fiducial markers with a diameter of 0.8 mm were implanted into the tumor under ultrasound or computed tomography (CT) guidance to serve as tracking markers. Target volume delineation included the gross tumor volume (GTV), clinical target volume (CTV, extending 3-5 mm beyond the GTV), and planned target volume (PTV, extending 3-5 mm beyond the CTV). Adjacent organs at risk (OARs), including normal liver, stomach, duodenum, spinal cord and kidneys, were contoured simultaneously. Positioning was corrected in real time using gold marker tracking technology. Prescribed doses were individualized: 40–60 Gy in 3–5 fractions for peripheral tumors, and 35–50 Gy in 5–8 fractions for central or gastrointestinal-adjacent tumors. Planning requirements: The PTV must cover at least 95% of the prescribed isodose line; V15 for normal liver <30%; maximum point dose for the spinal cord <25 Gy; and maximum point dose for the stomach/duodenum <30 Gy. All plans are evaluated using dose-volume histograms.

Response assessment and follow-up

Patients underwent imaging follow-up every 3 months during the first year after CyberKnife treatment, and subsequently every 6 months until disease progression, death, or the end of follow-up (June 30, 2025). Contrast-enhanced CT or magnetic resonance imaging (MRI) was performed at each follow-up visit, and treatment response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [30,31]. The objective response rate (ORR) includes complete response (CR) and partial response (PR), while the disease control rate (DCR) is calculated by adding disease stabilization (SD) to the ORR. OS was calculated from the start of CyberKnife treatment until all-cause death or the last

follow-up visit. PFS was similarly calculated from the start of treatment until the first radiographic progression or all-cause death; patients who had not experienced an event at the time of the last follow-up were treated as lost to follow-up. Evaluation of baseline AFP changes: AFP levels before CyberKnife treatment and 2–3 months post-treatment were compared. Patients were classified into three groups based on the percentage change relative to baseline: decreased (post-treatment AFP < 20 µg/L, or a decrease of ≥10% from baseline), stable (change of <10%), and increased (an increase of ≥10% from baseline) [32].

Statistical analyses

Data analysis for this study was performed using SPSS 27.0 (IBM, Armonk, New York). For categorical variables, we used frequencies (percentages) for description, and differences between groups were compared using the χ^2 test or Fisher's exact test. For survival analysis, survival rates were estimated using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. Cox proportional hazards regression models were applied to identify prognostic factors: univariate analyses were performed first, and variables with $P < 0.20$ in univariate analyses together with treatment grouping were subsequently incorporated into the multivariate model. The proportional hazards assumption was verified globally via Schoenfeld residual testing ($P > 0.05$). All statistical graphs and figures were generated with GraphPad Prism 11.0 software.

Results

(1) Patient characteristics and baseline comparisons

This study initially enrolled 315 patients with liver cancer who received their first treatment with CyberKnife. Of these, 140 (44.4%) were lost to follow-up, and ultimately 175 (55.6%) were included in the analysis. Baseline comparisons between patients lost to follow-up and those retained for analysis revealed no statistically significant differences in age, sex, BCLC stage, ALBI grade, Child-Pugh score, tumor size, AFP concentration, portal vein tumor thrombus and prior anti-tumor treatments (all $p > 0.05$; Table 1), indicating that loss to follow-up was likely completely at random. Of the 175 patients with complete follow-up records, 87 (49.7%) received CyberKnife therapy alone, and 88 (50.3%) received CyberKnife combined with systemic therapy. Baseline intergroup comparisons demonstrated that the CyberKnife monotherapy group presented more favorable pathological subtypes, earlier BCLC stages, superior liver function (reflected by ALBI grade and AST concentration), lower pre-treatment AFP levels, smaller tumor diameters, and a lower proportion of patients with prior treatment history (all $p < 0.05$; Table 2). These differences indicate significant baseline imbalances between the two groups; therefore, subsequent analyses were adjusted using multivariate Cox regression.

2 Survival analysis

The median follow-up duration was 23.6 months (IQR: 19.0–28.1). Kaplan–Meier survival analysis revealed that the median OS was 57.5 months (95% CI: 31.9–83.1) in the CyberKnife monotherapy group

versus 19.8 months (95% CI: 9.2–30.5) in the combination therapy group. The 1-year and 2-year OS rates of 83.8% vs. 66.7% and 65.5% vs. 45.7%, respectively. The median PFS was not reached for the monotherapy group, while it was 11.3 months (95% CI: 5.6–17.0) for patients receiving combined treatment. However, this survival difference was primarily due to imbalances in baseline characteristics between the two groups (Figure 1). After adjustment for multiple factors using Cox regression, combination therapy showed no independent association with OS (HR = 1.21, 95% CI: 0.63–2.32, $p = 0.564$) or PFS (HR = 1.25, 95% CI: 0.64–2.46, $p = 0.518$). Post-treatment elevated AFP (versus decreased AFP) was identified as an independent adverse prognostic factor for both OS (HR = 2.52, 95% CI: 1.23–5.19, $p = 0.012$) and PFS (HR = 2.70, 95% CI: 1.32–5.50, $p = 0.006$) (Figure 2). Tumor size, ALBI grade, BCLC stage and pathological subtype were also independent prognostic factors for OS (all $p < 0.05$) (Table 3).

3 Short-term tumor response

Tumor responses assessed according to mRECIST criteria are shown in Table 4. The ORR was 32.2% in the CyberKnife monotherapy group versus 19.3% in the combination therapy group ($p = 0.052$). The DCR reached 93.1% and 84.1% for the two groups, respectively ($p = 0.061$). After adjusting for baseline confounders via multivariate logistic regression, combination therapy exhibited no independent association with ORR (adjusted OR = 0.48, 95% CI: 0.20–1.17, $p = 0.108$) or DCR (adjusted OR = 2.35, 95% CI: 0.67–8.26, $p = 0.182$).

(4) Sensitivity analyses

To evaluate the influence of high loss-to-follow-up rates on the primary findings, extreme case scenario analyses were performed in the full cohort ($N = 315$). Even under the best-case scenario (assuming all lost-to-follow-up patients remained alive), combination therapy failed to demonstrate an independent survival benefit (HR=1.13, 95% CI: 0.61–2.11, $P=0.691$), while elevated AFP remained a significant predictor of poor prognosis (HR = 3.00, 95% CI: 1.46–6.19, $p = 0.003$). Under the worst-case scenario (assuming all lost-to-follow-up patients died), the difference for combination therapy was still non-significant (HR=1.18, 95% CI: 0.84–1.67, $P=0.335$), and elevated AFP retained significant prognostic value (HR=1.73, 95% CI: 1.15–2.61, $P=0.008$) (Table 5). Cox regression after propensity score stratification by tertiles also revealed no independent association between combination therapy and OS (HR=1.07, 95% CI: 0.52–2.22, $P=0.854$), whereas elevated AFP remained significantly associated with poorer survival (HR = 2.45, 95% CI: 1.08–5.53, $p = 0.032$) (Table 6). When the analysis was repeated within the overlap region of the propensity scores (0.20–0.90), the results were consistent with those of the main analysis. E-value analysis demonstrated that the point-estimate E-value for the association between elevated AFP and OS was 4.48, indicating strong robustness of this association against unmeasured confounding. However, the E-value corresponding to the lower limit of the confidence interval is 1.76, suggesting that even weak to moderate unmeasured confounding could potentially nullify this statistical significance. The global P-value for the proportional hazards assumption test was 0.471, indicating that the Cox model meets the necessary assumptions.

5 Exploratory subgroup analysis by systemic therapy subtype

In the exploratory subgroup analysis, due to the limited sample sizes in the immunotherapy monotherapy group (n=11) and the chemotherapy-containing regimen group (n=12), only descriptive Kaplan-Meier analyses were performed (Figure S1). Unadjusted univariate comparisons revealed significant between-subgroup differences in OS distributions (log-rank $p = 0.003$). The median OS was longest in the CyberKnife monotherapy group (57.5 months), followed by the targeted therapy monotherapy group (35.2 months), while the targeted therapy plus immunotherapy group, the immunotherapy monotherapy group, and the chemotherapy-containing regimen group had medians of 19.8, 12.3, and 11.7 months, respectively. Given the insufficient sample sizes of the two aforementioned subgroups, only the targeted monotherapy group (n = 28) and targeted plus immunotherapy group (n = 32) were incorporated into multivariate Cox regression models. After adjusting for baseline confounders, neither the targeted monotherapy group (OS: HR = 0.92, 95% CI: 0.39–2.14, $p = 0.844$; PFS: HR = 0.90, 95% CI: 0.39–2.11, $p = 0.812$) nor the targeted plus immunotherapy group (OS: HR = 1.29, 95% CI: 0.54–3.06, $p = 0.566$; PFS: HR = 1.42, 95% CI: 0.61–3.31, $p = 0.418$) demonstrated independent survival benefits (Table S1).

Discussion

Based on single-center real-world retrospective data, this study systematically explored the prognostic value of CyberKnife combined with systemic therapy and early dynamic AFP changes post-treatment for overall survival in patients with liver cancer. The principal findings are summarized as follows: (1) There were no significant differences in baseline characteristics between the non-follow-up group and the follow-up group; sensitivity analyses under extreme scenarios confirmed that the high non-follow-up rate did not lead to bias in the conclusions; (2) After multivariate adjustment, CyberKnife combined with systemic therapy showed no independent survival benefit either in the overall cohort or stratified by systemic therapy subtype, and this negative finding remained consistent across multiple sensitivity analyses; (3) Dynamic AFP alterations measured 2–3 months after treatment, particularly elevated AFP levels, served as a powerful independent adverse prognostic factor with superior predictive performance compared with treatment modality. The E-value analysis suggests that this association is reasonably robust to unmeasured confounders; (4) Tumor size, ALBI score, BCLC stage, and histological type are also independent prognostic factors, which is consistent with the findings of previous studies.

In the diagnosis and treatment of liver cancer, AFP is the most widely used serum biomarker, and its dynamic changes often reflect tumor burden and treatment efficacy [21,22]. The results of this study show that patients whose AFP levels increased by $\geq 10\%$ from baseline within 2–3 months after CyberKnife treatment had poorer outcomes in terms of both OS (HR = 2.52, 95% CI: 1.23–5.19, $p = 0.012$) and PFS (HR = 2.10, $p = 0.024$), suggesting that an early elevation in AFP has independent prognostic significance. The 2–3 month time window post-CyberKnife treatment was selected because tumor necrosis induced by CyberKnife often causes transient AFP elevation, which may lead to misjudgment if assessed too early. By 2–3 months after treatment, such interference largely resolves; meanwhile, this time point is sufficiently early to timely identify patients with ineffective treatment response. Previous

studies have mainly focused on dynamic AFP changes following TACE or systemic therapy, while dedicated investigations regarding the pattern of AFP dynamics after SBRT remain scarce [27]. Campani et al. reported in the AtezoBev trial that patients with a $\geq 20\%$ AFP reduction at 3 weeks post-treatment achieved more favorable prognosis [23]. Another study by Chang et al. demonstrated that a $\geq 25\%$ decline in AFP at 4 weeks after anlotinib administration was correlated with improved disease control rate [24]. This study attempted to apply the aforementioned concept to CyberKnife treatment scenarios, and the results indicate that early changes in AFP levels can indeed serve as a real-time indicator for monitoring treatment efficacy. Mechanistically, elevated AFP levels often indicate the presence of residual viable tumor cells in the body, or the occurrence of microvascular invasion or even early distant metastasis [33]. For such patients, the prognosis remains poor even when combined with systemic therapy [34], necessitating timely adjustments to the treatment regimen and more aggressive interventions. For patients with elevated AFP levels following CyberKnife treatment, it is clinically recommended to perform a follow-up contrast-enhanced MRI or CT scan as soon as possible, while also convening a multidisciplinary discussion to consider whether a change in treatment strategy is necessary [26]. However, it should also be noted that AFP-negative HCC accounts for 20%–40% of cases, and AFP alone is insufficient for monitoring these patients [20]. Future research may incorporate novel biomarkers such as AFP-L3 and PIVKA-II to improve the sensitivity of early disease identification [35].

In recent years, the combination of local and systemic therapy has gradually become one of the primary treatment strategies for mid- to late-stage PLC. The EMERALD-1 trial was the first to demonstrate, in patients with unresectable HCC, that TACE combined with durvalumab and bevacizumab significantly prolongs PFS; this also represents the first positive Phase III evidence supporting the combination of TACE and systemic therapy [9]. Subsequently, trials such as LEAP-012 further explored the efficacy of TACE in combination with lenvatinib and pembrolizumab, and similarly demonstrated a trend toward survival benefit [36]. However, the evidence mentioned above primarily focuses on TACE or ablation in combination with systemic therapy; data on the efficacy of SBRT (particularly CyberKnife) in combination with systemic therapy remain very limited [14]. In this study, patients receiving combination therapy exhibited substantially worse baseline prognostic profiles than those treated with CyberKnife monotherapy, including poorer liver function, heavier tumor burden and more advanced BCLC stage. The inferior survival observed in the combination group on univariate analysis became non-significant after adjustment via multivariate Cox regression (HR for combination therapy versus OS = 1.211, $P = 0.564$). Such negative findings are consistent with the conclusions of several prior observational studies [17,37].

Furthermore, CyberKnife monotherapy achieves a high local control rate of 70%–90% [6,8]. Even when combined with systemic therapy, no independent survival benefit was observed in the real-world setting. We speculate several potential explanations for this negative finding. First, high-precision high-dose irradiation delivered by CyberKnife enables effective control of local lesions and reduces the risk of distant metastasis, so the added value of systemic therapy is naturally limited. Second, patients receiving combined treatment often have poorer hepatic functional reserve, which may prevent them from tolerating standard-dose systemic therapy, leading to suboptimal drug exposure and restricted therapeutic efficacy [38]. Third, the synergistic effect between the radiotherapy-induced abscopal effect

and immunotherapy may require longer follow-up duration to manifest [39]. Notably, the patients enrolled in this study spanned a long time period (2018–2025). Participants recruited in the earlier phase might not have access to contemporary immunotherapy combination regimens (e.g., targeted therapy plus immunotherapy). Such differences across treatment eras may partially confound the evaluation of efficacy for combined treatment. The loss-to-follow-up rate in the present study reached 44.4%, which is not uncommon in real-world retrospective studies. To verify the robustness of our findings, we conducted multiple sensitivity analyses, including best- and worst-case scenario assumptions (all lost-to-follow-up patients assumed alive or deceased), propensity score stratification, restriction to the overlapping propensity score range, and E-value analysis [19,28,40]. All sensitivity analyses yielded consistent results with the main analysis: combination therapy failed to confer an independent survival benefit, whereas elevated AFP remained a significant predictor of increased mortality risk. The point estimate E-value for elevated AFP (HR = 2.52) was 4.48, indicating that a confounding factor with an association of equal strength to the change in AFP—and capable of simultaneously influencing both treatment assignment and prognosis—would be required to fully explain the observed association; such a scenario is highly unlikely in clinical practice. Furthermore, the p-value for the global proportional hazards hypothesis test was 0.47, further supporting the applicability of the Cox model [41]. Although these analyses strengthen the credibility of the conclusions, the risk of residual bias resulting from the high dropout rate cannot be ignored; prospective studies are still needed to validate these findings and optimize follow-up strategies.

This study has the following limitations. First, inherent selection bias and confounding variables originating from the single-center retrospective design cannot be completely eliminated. Although multivariate regression and propensity score-based adjustments were applied, unmeasured confounding may still persist. Second, substantial heterogeneity existed across systemic therapeutic regimens, including various targeted agents, immunotherapies, chemotherapies and their combinations. Several subgroups had limited sample sizes, precluding reliable stratified analyses stratified by specific drug regimens. Third, there may be variability in the timing and methods of AFP testing, although we standardized the evaluation window to 2–3 months. Fourth, the loss-to-follow-up rate was relatively high (44.4%). Despite validation via multiple sensitivity analyses, residual bias may remain and impair the generalizability of our findings. Fifth, patient-reported outcome measures including quality of life, dynamic changes in liver function, and subsequent lines of therapy were not incorporated into the present analysis. All these factors may exert potential impacts on overall survival. Further multicenter prospective studies are required to validate our conclusions and investigate whether dynamic AFP changes can be reliably applied to guide individualized therapeutic decision-making.

Conclusions

The present study revealed that the addition of systemic therapy to CyberKnife failed to deliver incremental survival benefits. In contrast, early post-treatment dynamic trends of AFP served as an independent prognostic predictor and could be used for therapeutic response monitoring. Therefore, clinical decisions should comprehensively consider liver function, tumor burden, and AFP response to avoid the indiscriminate use of systemic therapy in combination with CyberKnife.

Abbreviations

PLC
Primary liver cancer
AFP
Alpha-fetoprotein
OS
Overall survival
PFS
Progression-free survival
SBRT
Stereotactic body radiotherapy
CR
Complete response
PR
Partial response
SD
Stable Disease
ORR
Objective response rate
DCR
Disease control rate
AST
Aspartate aminotransferase
ALT
Alanine aminotransferase
KPS
Karnofsky Performance Status
BCLC
Barcelona Clinic Liver Cancer stage
ALBI
Albumin-Bilirubin grade
PLT
Platelet count
PVT
Portal vein tumor thrombus.

Declarations

Data Sharing Statement

The data presented in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study is a retrospective study. No patient biological samples were collected, and no personally identifiable information was involved. Following review by the Ethics Committee, the requirement for informed consent was waived. All data were anonymized and used solely for the purposes of this study. The study protocol was approved in writing by the Ethics Committee of the Second Affiliated Hospital of Guangxi University of Chinese Medicine (Approval No.: KY2025-145), and the study was conducted in strict accordance with the relevant provisions of the Declaration of Helsinki.

Consent for Publication

The author hereby declares that this manuscript complies with the publication guidelines for the protection of patient privacy in medical journals and does not contain any personally identifiable information; all clinical data have been anonymized, and the author assumes full responsibility for the manuscript's compliance with privacy regulations.

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Author Contributions

All authors made substantial contributions to this study. The study design was developed by Fasheng WU, Xinlan Lin, and Weishan He; data collection was conducted by Yajing Lin, Juzheng Shi, and Xiuping Liang; and data analysis was performed by Jingzhou Sheng, Ye Chen, and Yongqi Li; Peipei Yuan and Huiyi Liu were responsible for creating the figures; the first draft of the manuscript was written by Xinlan Lin and Jia Hu; and Guihua Yue, Fasheng Wu, and Weishan He reviewed and revised the manuscript. All authors participated in academic discussions, manuscript revisions, and approval of the final version, agreed on the target journal for submission, and jointly assume joint responsibility for the entire content of this study.

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Disclosure

The authors report no conflicts of interest in this work.

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Tables

Table 1 Baseline characteristics: comparison between patients lost to follow-up and retained patients

Variable	Lost-to-Follow-Up Group n=140	Follow-Up Group n=175	p
Gender,n%			
Male	126(90)	146(82.9)	0.091
Female	14(10)	29(16.6)	
Age, years,n%			
<60years	84(60)	100(57.1)	0.609
≥60years	56(40)	75(42.9)	
Pathological Type, n%			
HCC	130(92.9)	160(91.4)	0.641
Other	10(7.1)	15(8.6)	
KPS,n%			
<80	11(7.9)	18(10.3)	0.459
≥80	129(92.1)	157(89.7)	
BCLC,n%			
A	44(31.4)	48(27.4)	0.110
B	44(31.4)	75(42.9)	
C	52(37.1)	52(29.7)	
ALBI grade,n%			
1	33(23.6)	41(23.4)	0.456
2	90(64.3)	120(68.6)	
3	17(12.1)	14(8)	
ALT,n%			
<40 U/L	99(70.7)	128(73.1)	0.633
≥40 U/L	41(29.3)	47(26.9)	
AST,n%			
<40 U/L	89(63.6)	111(63.4)	0.979
≥40 U/L	51(36.4)	64(36.6)	

PLT,n(%)			
<100×10 ⁹ /L	28(20)	30(17.1)	0.516
≥100×10 ⁹ /L	112(80)	145(82.9)	
Child-Pugh classification,n(%)			
A	102(72.9)	138(78.9)	0.214
B	38(27.1)	37(21.1)	
Etiology,n(%)			
HBV	111(79.3)	128(73.1)	0.205
Other	29(20.7)	47(26.9)	
Accompanied by PVT,n(%)			
No	100(71.4)	139(79.4)	0.099

Table 1 Baseline characteristics: comparison between patients lost to follow-up and retained patients

Variable	Lost-to-Follow-Up Group n=140	Follow-Up Group n=175	p
Yes	40 (28.6%)	36 (20.6%)	
Previous treatment, n (%)			
Yes	37 (26.4%)	56 (32%)	0.281
No	103 (73.6%)	119 (68%)	
Treatment group, n (%)			
Combined group	62 (44.3%)	88 (50.3%)	0.289
CyberKnife group	78 (55.7%)	87 (49.7%)	
AFP, ng/ml, n (%)			
<20	55 (39.3%)	82 (46.9%)	0.376
20-400	36 (25.7%)	42 (24%)	
>400	49 (35%)	51 (29.1%)	
Number Of Tumors, n (%)			
<2	43 (30.7%)	65 (37.1%)	0.232
≥2	97 (69.3%)	110 (62.9%)	
Tumor size, cm, n (%)			
<3 cm	53 (37.9%)	50 (28.6%)	0.075
3-5 cm	37 (26.4%)	66 (27.7%)	
≥5 cm	50 (35.7%)	59 (33.7%)	

^b KPS, Karnofsky Performance Status score; BCLC, Barcelona Clinic Liver Cancer stage; ALBI, Albumin-Bilirubin grade; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; PLT, Platelet count; Portal vein tumor thrombus; AFP, Alpha-fetoprotein.

Table 2 Baseline comparison of 175 patients in the follow-up cohort: CyberKnife monotherapy group versus combination therapy group

Variable	CyberKnife group (n=87)	Combined group (n=88)	p ^a
Gender, n (%)			
Male	71 (81.6)	75 (85.2)	0.520
Female	16 (18.4)	13 (14.8)	
Age, years, n (%)			
<60 years	47 (54)	52 (59.1)	0.499
≥60 years	40 (46)	36 (40.9)	
Pathological Type, n (%)			
HCC	84 (96.6)	76 (86.4)	0.016
Other	3 (3.4)	12 (13.6)	
KPS, n (%)			
≥80	10 (11.5)	9 (10.2)	0.788

Table 2 Baseline comparison of 175 patients in the follow-up cohort: CyberKnife monotherapy group versus combination therapy group

Variable	CyberKnife group n=87	Combined group n=88	p ^a
≥80	77(88.5)	79(89.8)	
BCLC,n(%)			
A	33(37.9)	15(17)	0.001
B	40(46)	35(39.8)	
C	14(16.1)	38(43.2)	
ALBI grade,n(%)			
1	23(26.4)	18(20.5)	0.033
2	53(60.9)	67(76.1)	
3	11(12.6)	3(3.4)	
AST,n(%)			
<40 U/L	66(75.9)	62(70.5)	0.420
≥40 U/L	21(24.1)	26(29.5)	
AST,n(%)			
<40 U/L	64(73.6)	47(53.4)	0.006
≥40 U/L	23(26.4)	41(45.6)	
PLT,n(%)			
<100×10 ⁹ /L	17(19.5)	12(13.6)	0.294
≥100×10 ⁹ /L	70(80.5)	76(86.4)	
Child-Pugh classification,n(%)			
A	66(75.9)	72(81.8)	0.335
B	21(24.1)	16(18.2)	
Etiology,n(%)			
HBV	64(73.6)	64(72.7)	0.901
Other	23(26.4)	24(27.3)	
Accompanied by PVTT,n(%)			
No	73(83.9)	66(75)	0.145

Yes	14 16.1	22 25	
Previous treatment,n %			
No	67 77	52 59.1	0.011
Yes	20 23	36 40.9	
AFP,ng/m,n %			
≤20	45 51.7	37 42	0.019
20-400	25 28.7	17 19.3	
≥400	17 19.5	34 38.6	
Number Of Tumors,n %			
≤2	34 39.1	31 35.2	0.598
≥2	53 60.9	57 64.8	
Tumor size,cm,n %			

Table 2 Baseline comparison of 175 patients in the follow-up cohort: CyberKnife monotherapy group versus combination therapy group

Variable	CyberKnife group n=87	Combined group n=88	p ^a
≤3 cm	35 40.2	15 17	0.001
3-5 cm	33 37.9	33 37.5	
≥5 cm	19 21.8	40 45.5	
Combination Therapy Type, n (%)			
Targeted Therapy	-	28 31.8	
Immunotherapy	-	11 12.5	
Chemotherapy ^b	-	12 13.6	
Targeted Immunotherapy	-	37 42.0	

KPS,Karnofsky Performance Status score;BCLC,Barcelona Clinic Liver Cancer stage;ALBI,Albumin-Bilirubin grade;ALT,Alanine aminotransferase;AST,Aspartate aminotransferase;PLT,Platelet count;Portal vein tumor thrombus;AFP,Alpha-fetoprotein.

^a Bold values indicate statistical significance ^b Chemotherapy regimens included chemotherapy alone (6 cases), chemotherapy plus immunotherapy (4 cases), chemotherapy plus targeted therapy (1 case), and chemotherapy plus immunotherapy plus targeted therapy (1 case).

Table 3 Univariate and multivariate Cox regression analyses for OS and PFS among 175 patients

Variable	OS (N=175, events=75)				PFS (N=175, events=174)			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	HR [95%CI]	p	HR [95%CI]	p	HR [95%CI]	p	HR [95%CI]	p
Group (refer to CyberKnife)	1.996 [1.217-3.275]	0.006	1.211 [0.632-2.318]	0.564	2.099 [1.276-3.452]	0.004	1.250 [0.636-2.457]	0.518
Gender (refer to Male)	0.839 [0.428-1.645]	0.610			0.810 [0.413-1.588]	0.539		
Age (refer to <60)	1.015 [0.627-1.643]	0.951			1.008 [0.623-1.632]	0.913		
Etiology (refer to HCC)	1.899 [0.817-4.416]	0.126	2.960 [1.067-8.208]	0.037	1.571 [0.674-3.664]	0.296		
KPS (refer to <80)	0.718 [0.354-1.456]	0.358			0.795 [0.393-1.610]	0.524		
BCLC (refer to A)		0.001		0.008		0.001		0.004

Table 3 Univariate and multivariate Cox regression analyses for OS and PFS among 175 patients

Variable	OS N=175 events=75				PFS N=175 events=174			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	HR 95%CI	p	HR 95%CI	p	HR 95%CI	p	HR 95%CI	p
B	3.437 1.594-7.410	0.002	2.039 0.813-5.115	0.129	3.516 1.641-7.534	0.001	2.877(1.183-6.999)	0.020
C	8.835 4.067-19.195	0.001	6.153 1.920-19.715	0.002	8.338 3.924-17.714	0.001	6.867(2.188-21.550)	0.001
ALBI grade(refer to 1)		0.003		0.008		0.004		0.008
2	1.586 0.837-3.007	0.157	1.234 0.608-2.503	0.561	1.436 0.757-2.722	0.268	0.786(0.384-1.608)	0.509
3	4.010 1.760-9.136	0.001	4.737 1.568-14.308	0.006	3.726 1.636-8.490	0.002	3.032(1.059-8.680)	0.039
ALT(refer to <40)	1.479 0.882-2.480	0.138			1.367 0.815-2.293	0.237		
AST(refer to <40)	2.455 1.502-4.012	0.001			2.374 1.446-3.898	0.001		
PLT(refer to 100)	0.904 0.493-1.660	0.745			0.932 0.508-1.709	0.802		
CP refer to A	2.306 1.374-3.872	0.002			2.393 1.425-4.018	0.001		
Etiology (refer to HBV)	1.345 0.797-2.270	0.268			1.215 0.719-2.052	0.466		
Accompanied by PVTT, (refer to No)	3.714 2.188-6.302	0.001			3.587 2.129-6.044	0.001		
Previous treatment (refer to No)	1.396 0.849-2.295	0.189			1.469 0.894-2.415	0.129		
AFP (refer to <20)		0.015				0.005		

20-400	0.792 [0.410- 1.531]	0.489			0.877 [0.454- 1.694]	0.696		
>400	1.901 [1.111- 3.253]	0.019			2.189 [1.278- 3.747]	0.004		
Number Of Tumors (refer to<2)	0.979 [0.600- 1.596]	0.931			1.084 [0.664- 1.768]	0.747		
Tumor size,cm,(refer to<3)		0.001		0.003		0.001		
3-5	3.249 [1.563- 6.752]	0.002	2.521 [1.081- 5.880]	0.032	3.099 [1.490- 6.443]	0.002		
≥5	5.660 [2.734- 11.718]	0.001	4.886 [1.943- 12.286]	0.001	4.695 [2.260- 9.750]	0.001		
Changes in AFP Levels(refer to decrease)		0.003		0.035		0.001		0.024
Stable	1.565 [0.877- 2.793]	0.130	1.299 [0.611- 2.765]	0.497	1.394 [0.782- 2.486]	0.260	1.459 [0.695- 3.060]	0.318
Increase	2.941 [1.580- 5.472]	0.001	2.524 [1.227- 5.191]	0.012	3.273 [1.755- 6.103]	0.001	2.696 [1.321- 5.503]	0.006

KPS,Karnofsky Performance Status score;BCLC,Barcelona Clinic Liver Cancer stage;ALBI,Albumin-Bilirubin grade;ALT,Alanine aminotransferase;AST,Aspartate aminotransferase;PLT,Platelet count;Portal vein tumor thrombus;AFP,Alpha-fetoprotein;Stereotactic PFS,progression-free survival;OS,overall survival

^a Bold values indicate statistical significance

Table4:Best tumor response evaluated by mRECIST

mRECIST	CyberKnife group n=87	Combined group n=88	Unadjusted p-value*	Adjusted OR(95%) [†]	Adjusted p-value
Response n(%)			0.066		
CR	1(1.1)	0(0)			
PR	27(31.0)	17(19.3)			
SD	53(60.9)	57(64.8)			
PD	6(6.9)	14(15.9)			
ORR(CR+PR)	28(32.2)	17(19.3)	0.052	0.483 (0.1999-1.173)	0.108
DCR(CR+PR+SD)	81(93.1)	74(84.1)	0.061	2.353(0.671-8.259)	0.182

* χ^2 test; [†] Multivariate logistic regression adjusted for baseline variables such as CP score, ALBI classification, tumor size, BCLC stage, age, and sex.

Table 5: Sensitivity Analysis of Extreme Scenarios (N=315):

Variable	Best-case scenario (all lost to follow-up are alive)	Worst-case scenario (all lost to follow-up are dead)
CyberKnife group vs Combined group	HR=1.134(95%CI 0.610-2.108) P=0.691	HR=1.184(95%CI 0.840-1.668) P=0.335
Changes in AFP after CyberKnife (decrease)	P=0.012	P=0.028
Stable	HR=1.658(95%CI 0.831-3.309) P=0.151	HR=1.169(95%CI 0.811-1.685) P=0.402
Increase	HR=3.004(95%CI 1.459-6.186) P=0.003	HR=1.733(95%CI 1.152-2.608) P=0.008
Other significant variables (p < 0.05)	Medical history, tumor size	Pathological type, BCLC stage, CP score, pre-treatment AFP, tumor size

*Repeated Multivariate Cox Regression After Extreme-Case Assumptions

Table 6: Summary of Sensitivity Analysis (PS Stratification and Restricted Overlap Areas)

Analytical Methods	Combined Treatment HR95%CI	p	Elevated AFP HR 95%CI	p
Multivariate Cox analysis	1.2110.632-2.318	0.564	2.5241.227-5.191	0.012
Cox stratification by PS (tertiles)	1.0710.517-2.220	0.854	2.4451.081-5.531	0.032
Restriction to the PS overlap region (0.20–0.90)	0.9600.462-1.997	0.914	2.2461.028-4.906	0.042

* All baseline variables were adjusted for PS stratification and restricted overlap areas.

a Global test of the proportional hazards assumption ($p = 0.471$); no significant violation was found.

Figures

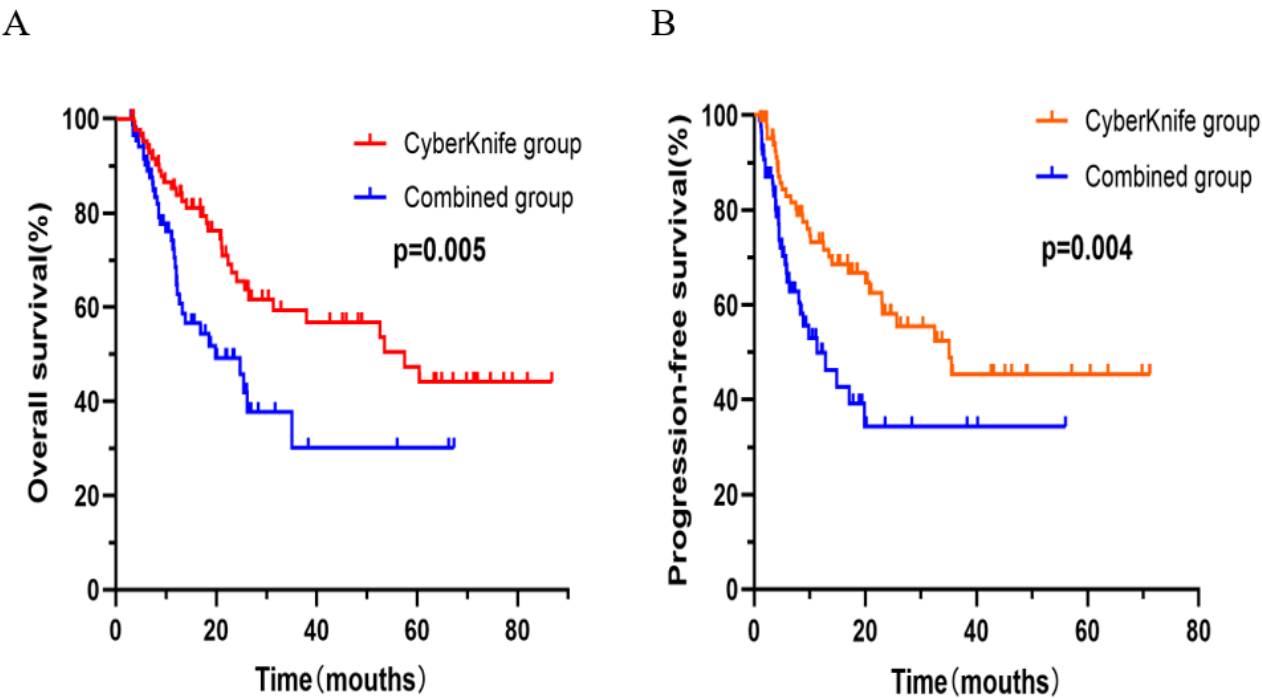


Figure 1

Kaplan-Meier curves for (A) overall survival and (B) progression-free survival, stratified by treatment method. The unadjusted analysis showed that the survival in the CyberKnife monotherapy group was significantly better than that in the combination therapy group (log-rank $p < 0.05$); however, this difference was primarily attributable to imbalances in baseline characteristics between the two groups (see Table

2). After adjustment using multivariate Cox regression, combination therapy was not independently associated with OS or PFS.

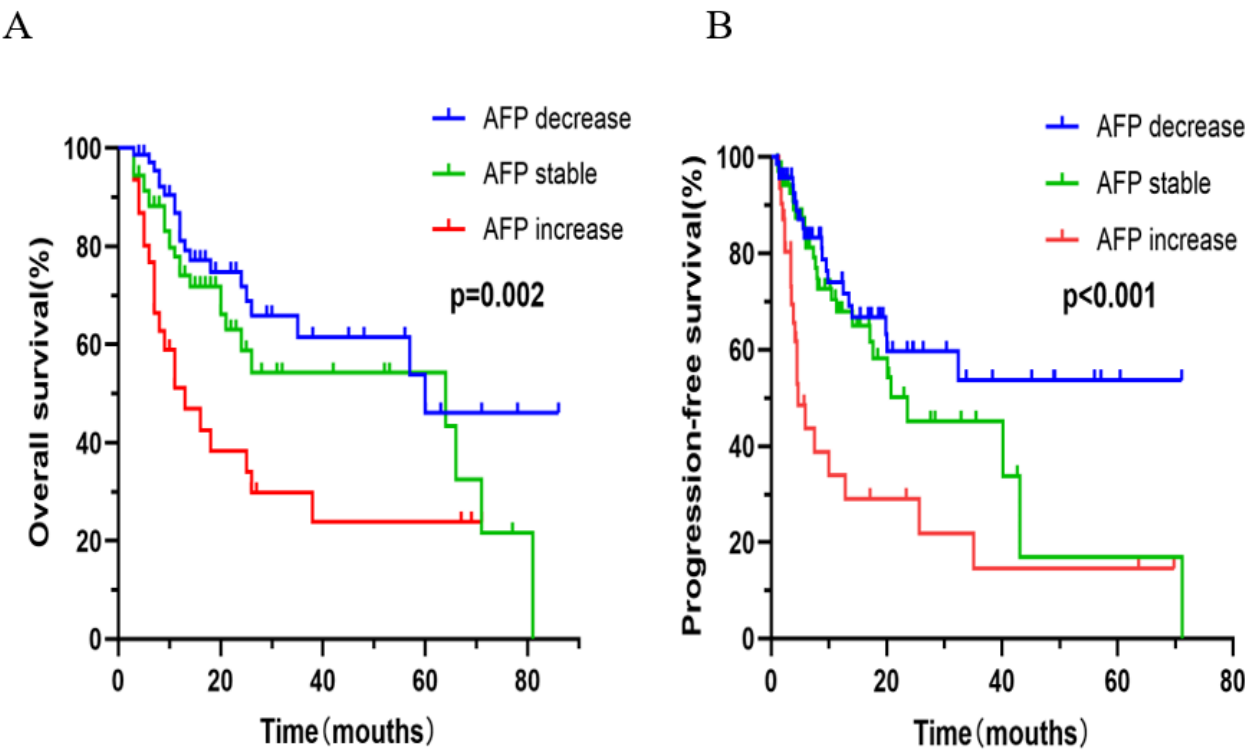


Figure 2

Kaplan-Meier curves for (A) overall survival and (B) progression-free survival, grouped by changes in AFP levels 2–3 months after treatment.

Supplementary Files

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