Journal of Hepatocellular Carcinoma

Dovepress
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ORIGINAL RESEARCH

Effectiveness and Safety of Systemic Therapy and Stereotactic Body Radiotherapy in Oligoprogressive and Oligometastatic Hepatocellular Carcinoma

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Video abstract

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Purpose: This study explored the efficacy and safety of combining systemic therapy with stereotactic body radiotherapy (SBRT) for oligoprogressive (OP) and oligometastatic (OM) hepatocellular carcinoma (HCC).

Patients and Methods: From January 2017 to June 2023, 37 HCC patients (28 OP, 9 OM) receiving systemic therapy and SBRT were identified. OP is defined as up to 5 progressive lesions with others stable after systemic therapy and OM as newly identified metastatic disease with up to 5 metastatic lesions. SBRT was delivered in fractions of 5 Gy or more to all lesions. Clinical outcomes and toxicity were evaluated.

Results: The median follow-up was 32.8 months. The objective response rates (ORRs) were 47.2%, 44.4%, and 55.5% for overall, OP, and OM cohorts. SBRT treated 48 OP and 17 OM lesions, achieving an ORR of 64.7%. For overall, OP, and OM cohorts, the 2-year local failure rates were 3.0%, 4.0%, and 0%, with median progression-free survival (PFS) of 11.2, 11.2, and 10.2 months, and median overall survival (OS) of 34.9 months, 32.6 months, and not reached (NR), respectively. In the OP cohort, 12 patients switched to next-line systemic therapy (OP-N) and 16 remained on current therapy (OP-C). Median PFS and OS were 11.6 months and NR for OP-N versus 16.5 months and 32.6 months for OP-C (P=0.89 and 0.47). Grade 3 acute and late treatment-related adverse events occurred in 40.5% and 5.4% of patients.

Conclusion: Systemic therapy combined with SBRT was effective and safe for OP and OM HCC. SBRT may delay next-line systemic therapy by blocking OP.

Plain Language Summary:

- Combining systemic therapy with stereotactic body radiotherapy (SBRT) represents a promising treatment strategy for oligoprogressive (OP) and oligometastatic (OM) hepatocellular carcinoma.
- This study demonstrates that SBRT combined with systemic therapy may offer favorable short-term response and long-term outcomes while maintaining a good safety profile.
- OP patients who continue their current systemic therapy while receiving SBRT may block OP status and achieve outcomes comparable to those who switch therapies, highlighting the potential of this approach to delay treatment changes and improve outcomes.

Keywords: oligoprogressive, oligometastatic, hepatocellular carcinoma, stereotactic body radiotherapy, efficacy, safety

Received: 27 January 2025
Accepted: 22 May 2025
Published: 31 May 2025

Introduction

Globally, primary liver cancer is the sixth most common malignant tumor and the third cause of tumor-related deaths, with China reporting the highest incidence and mortality rates.[1,2] Hepatocellular carcinoma (HCC) represents 80% of liver cancers, and more than half of patients have advanced stage at initial diagnosis.[3,4] Oligometastatic disease (OMD) has been proposed as an intermediate state between localized and systemically metastasized disease. The 2020 European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) consensus broadly classifies OMD into oligoprogressive (OP) and oligometastatic (OM), typically defined as having five or fewer metastatic lesions.[5–7] With advancements in systemic therapy and imaging techniques for advanced HCC, the proportion of OP and OM cases has risen. Numerous studies have demonstrated that local therapies, including surgery, ablation, and radiotherapy, can enhance the prognosis for patients with various OP and OM tumors.[8–10] OM often benefits from locoregional therapy such as stopping the metastatic process and eliminating disease sources. While OP disease often shows dissociated responses after systemic therapy, applying local treatments to progressive lesions may help block this process.[11–13]

Stereotactic body radiotherapy (SBRT) is a precise local treatment that minimizes damage to normal tissues while delivering ablative doses of radiation, in contrast to conventional external beam radiotherapy.[14,15] Meta-analyses have highlighted the increasing use of SBRT for HCC, reporting 3-year local control rates of 84%–91%.[16,17] Additionally, SBRT combined with immunotherapy offers synergistic benefits, enhancing treatment effectiveness.[18] Integrating SBRT with systemic therapy is expected to improve survival in various tumors with OMD. Representatively, the SABR-COMET series of studies showed that systemic therapy of OM tumors combined with SBRT improved overall survival (OS).[19–21] In addition, the CURB study showed that adding SBRT to treatment for OP non-small cell lung cancer improved progression-free survival (PFS), although the benefit for breast cancer patients remains unclear.[22] However, data on the combination of systemic therapy and SBRT for OP and OM HCC are still lacking.[23]

The aim of this study was to evaluate the efficacy and safety of systemic therapy combined with SBRT for OP and OM HCC. A subgroup analysis was conducted to compare the efficacy of SBRT with maintaining the current systemic therapy versus SBRT with switching systemic therapy following oligoprogression.

Patients and Methods

Study Design and Study Population

This study was a single-center, retrospective, observational study. We screened advanced HCC patients receiving systemic therapy and eligible for SBRT at Peking University Cancer Hospital (Beijing, China), then identified OP and OM HCC patients as the study population (Figure S1). The inclusion criteria were as follows: 1) age ≥18 years; 2) histologically or clinically confirmed HCC; 3) patient with extrahepatic metastatic disease; 4) OP, defined as up to 5 progressive lesions where the remainder of lesions remained stable after systemic therapy; 5) OM, defined as newly identified metastatic disease with up to 5 metastatic lesions; 6) potential for all sites of OP and OM to be safely treated with SBRT. The exclusion criteria were as follows: 1) receiving SBRT without systemic therapy; 2) with second primary tumor; 3) incomplete follow-up data. Additionally, patients previously treated with any form of radiotherapy could be included, but re-irradiating the same tumor lesion was excluded. This study was approved by the institutional review board of the Peking University Cancer Hospital and Institute (2024YJZ22). Written informed consent was obtained from all patients.

Treatment

The optimal treatment modality was discussed and determined by our institutional multidisciplinary team.[24,25] Details dose and fraction schedules of SBRT and prescriptions of systemic therapy were shown in Tables S1 and S2.

SBRT was delivered as multiple fractions of greater than or equal to 5 Gy per fraction. According to the proximity of the organs at risk and the target volume, the prescription dose was adjusted accordingly.[26] The delineation of the target

volume was guided by the International Commission on Radiation Units and Measurements reports (ICRU) 50, 62, and 83. The planning goals were to deliver the prescribed dose to at least 95% of the planning target volume (PTV). Volumetric modulated arc therapy (VMAT) planning with 6-MV X-rays was performed. Treatment was delivered using the Varian Edge linear accelerator (Varian, Palo Alto, CA, USA). Cone-beam computed tomography (CBCT) scan was used to verify the target position.

Both targeted therapy and immunotherapy were included in systemic therapy. Targeted therapy included small molecule tyrosine kinase inhibitors (TKIs) and an anti-vascular endothelial growth factor (VEGF) antibody, while immunotherapy comprised anti-programmed cell death protein-1 (PD-1) antibodies and an anti-programmed cell death protein ligand-1 (PD-L1) antibody.

Follow-Up and Outcomes

Patients were evaluated 1 month after SBRT, every 3 months for the first 2 years, every 6 months for the following 3 years and annually thereafter. Follow-up included symptoms, clinical examination, complete blood count, biochemical examinations and imaging.

Clinical outcomes included tumor response, survival rates, and treatment-related adverse events (TRAEs). Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST),[27] while TRAEs were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Specifically, in the assessment of irradiated lesions and local progression in cases of bone metastatic lesions, the MD Anderson response criteria were employed as an additional evaluative measure, owing to the limitations of mRECIST.[28] Objective response rate (ORR) was defined as the proportion of patients with complete or partial responses (CR or PR) as the best overall response. Disease control rate (DCR) was defined as proportion of patients with CR, PR or stable disease (SD). Local failure was defined as tumor progress within the PTV. PFS was defined as the interval from the initiation of SBRT to the first radiographic progression or death. OS was defined as the interval from the initiation of SBRT to death from any cause. Early and late TRAEs were defined as those occurring within 90 days and beyond 90 days after SBRT, respectively.

Statistical Analysis

Continuous variables were described using median and ranges or interquartile range (IQR), and categorical variables were described using frequency and percentages. Between different groups, we used Fisher's exact test to compare categorical variables, and used the Mann–Whitney *U*-test (nonnormally distributed data) or Student's *t* test (normally distributed data) to compare continuous variables.

The ORR, DCR, and corresponding 95% confidence interval (CI) were estimated using the Clopper–Pearson method. We used waterfall plot to describe the best percentage change from baseline in the sum of the largest diameters of target lesions. The cumulative incidence of local failure was calculated using a competing risk model considering death as a competing event. PFS and OS were evaluated by Kaplan–Meier (K-M) method and log–rank test. Univariate and multivariate Cox proportional hazards regression models were used to determine prognostic factors associated with PFS. The selection of variables for the Cox proportional hazards model was guided by their clinical importance, not just their statistical significance in univariate analysis.

All statistical analyses were performed using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). A 2-tailed P value of <0.05 was considered statistically significant. The following R packages were used: "survival", "survminer", "tidycmprsk", "ggsurvfit", and "ggplot2".

Results

Baseline Characteristics and Treatment Profile

The baseline characteristics of 37 patients (28 OP, 9 OM) are summarized in Table 1. About 94.6% were male, with a median age of 60.0 years (range: 43–79). The most common HCC etiology was HBV infection (75.7%). Most patients had Child-Pugh class A (94.6%). The median sum of the largest diameters of lesions was 4.6 cm (range: 1.0–18.0), and that of OP/OM lesions

was 2.8 cm (range: 1.0–18.0). In the OP cohort, solitary OP lesion was common (64.3%), whereas 55.6% of OM patients had multiple metastases. All patients had a history of or current extrahepatic metastases, with the most frequent OP/OM sites being the lungs (30.8%) and bones (23.1%). Regarding current systemic therapies, 71.4% of OP patients received ≥2 lines, while the OM cohort predominantly underwent first-line treatment (66.7%). The most common systemic regimen was ICI+TKI (54.1%; OP: 53.6%, OM: 55.6%). The stratification of systemic therapies by treatment sequence – including first-line and subsequent-

Table 1 Baseline Characteristics

	Overall (N=37)	OP Cohort (N=28)	OM Cohort (N=9)
Median age [Min, Max], years	60.0 [43.0, 79.0]	60.5 [43.0, 79.0]	56.0 [48.0, 65.0]
Sex, n (%)			
Male	35 (94.6)	26 (92.9)	9 (100)
Female	2 (5.4)	2 (7.1)	0 (0)
ECOG, n (%)			
0	21 (56.8)	15 (53.6)	6 (66.7)
1	16 (43.2)	13 (46.4)	3 (33.3)
Etiology, n (%)			
HBV	28 (75.7)	21 (75.0)	7 (77.8)
HCV	3 (8.1)	2 (7.1)	1 (11.1)
Alcoholic	2 (5.4)	2 (7.1)	0 (0)
Others	4 (10.8)	3 (10.7)	1 (11.1)
Child-Pugh class, n (%)			
A	35 (94.6)	26 (92.9)	9 (100)
B	2 (5.4)	2 (7.1)	0 (0)
AFP, n (%)			
<400 ng/mL	19 (51.4)	12 (42.9)	7 (77.8)
≥400 ng/mL	18 (48.6)	16 (57.1)	2 (22.2)
Macrovascular invasion, n (%)			
No	24 (64.9)	19 (67.9)	5 (55.6)
Yes	13 (35.1)	9 (32.1)	4 (44.4)
Median sum of largest diameters of lesions [min, max], cm	4.60 [1.00, 18.0]	4.45 [1.00, 16.1]	4.60 [1.20, 18.0]
Median sum of largest diameters of OP/OM lesions [min, max], cm	2.80 [1.00, 18.0]	1.90 [1.00, 16.1]	4.60 [1.20, 18.0]
Number of lesions (per patient), n (%)			
1	8 (21.6)	5 (17.9)	3 (33.3)
2–5	24 (64.9)	18 (64.3)	6 (66.7)
>5	5 (13.5)	5 (17.9)	0 (0)
Number of OP/OM lesions (per patient), n (%)			
1	22 (59.5)	18 (64.3)	4 (44.4)
2–5	15 (40.5)	10 (35.7)	5 (55.6)
Location of OP/OM lesions (per lesion), n (%)			
Lungs	20 (30.8)	20 (41.7)	0 (0)
Bones	15 (23.1)	15 (31.3)	0 (0)
Liver	13 (20.0)	4 (8.3)	9 (52.9)
Lymph nodes	6 (9.2)	4 (8.3)	2 (11.8)
Tumor thrombosis	2 (3.1)	0 (0)	2 (11.8)
Adrenal glands	2 (3.1)	1 (2.1)	1 (5.9)
Brain	1 (1.5)	1 (2.1)	0 (0)
Other soft tissues	6 (9.2)	3 (6.3)	3 (17.6)
Current lines of systemic treatment, n (%)			
1	14 (37.8)	8 (28.6)	6 (66.7)
≥2	23 (62.2)	20 (71.4)	3 (33.3)

(*Continued*)

Table 1 (Continued).

	Overall (N=37)	OP Cohort (N=28)	OM Cohort (N=9)
Current systemic treatment, n (%)			
ICI+TKI	20 (54.1)	15 (53.6)	5 (55.6)
TKI	14 (37.8)	11 (39.3)	3 (33.3)
ICI	2 (5.4)	1 (3.6)	1 (11.1)
ICI+VEGF	1 (2.7)	1 (3.6)	0 (0)
Prior local treatment, n (%)			
No	5 (13.5)	3 (10.7)	2 (22.2)
Intra-arterial therapy	21 (56.8)	14 (50.0)	7 (77.8)
Resection	18 (48.6)	12 (42.9)	6 (66.7)
Radiotherapy	16 (43.2)	14 (50.0)	2 (22.2)
RFA	10 (27.0)	8 (28.6)	2 (22.2)
Liver transplantation	3 (8.1)	3 (10.7)	0 (0)

Abbreviations: OP, oligoprogressive; OM, oligometastatic; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; VEGF, vascular endothelial growth factor; RFA, radiofrequency ablation.

line regimens – is comprehensively detailed in Table S3. About 86.5% of patients received prior local treatments, with intra-arterial therapy being the most common (56.8%), followed by resection (48.6%) and radiotherapy (43.2%).

Response, Long-Term Outcomes and Failure Pattern

The median follow-up for all patients was 32.8 months (95% CI: 22.6–46.7), with 32.8 months (95% CI: 21.7–NA) for the OP cohort and 44.0 months (95% CI: 16.4–NA) for the OM cohort.

Best overall response is displayed in Table 2. One patient in the OP cohort died of an accident, and whose efficacy was recorded as not available (NA). In the overall, OP, and OM cohorts, ORRs were 47.2%, 44.4%, and 55.5%; DCRs were 75.0%, 74.1%, and 77.8%, respectively. Overall, 65 lesions (48 in the OP cohort and 17 in the OM cohort) were irradiated. Irradiated lesions achieved CR in 11 patients, with an ORR of 64.7% and a DCR of 100%. Best percentage change from baseline in the sum of the largest diameters of target lesions are shown in Figure 1A and B. We further investigated clinical and dosimetric factors associated with best response in irradiated lesions. Compared with the non-responders (NOR) group, objective responders (OR) exhibited a significantly longer time to best response (median:

Table 2 Tumor Response

	Overall Response			Response of Irradiated Lesions
	Overall[†]	OP Cohort[†]	OM Cohort	Overall[§]
Best response				
CR, n (%)	5 (13.9)	2 (7.4)	3 (33.3)	11 (32.4)
PR, n (%)	12 (33.3)	10 (37.0)	2 (22.2)	11 (32.4)
SD, n (%)	10 (27.8)	8 (29.6)	2 (22.2)	12 (35.3)
PD, n (%)	9 (25.0)	7 (25.9)	2 (22.2)	0 (0)
ORR, % (95% CI)	47.2 (30.4–64.5)	44.4 (25.5–64.7)	55.5 (21.2–86.3)	64.7 (46.5–80.3)
DCR, % (95% CI)	75.0 (57.8–87.9)	74.1 (53.7–88.9)	77.8 (40.0–97.2)	100 (89.7–100)

Notes: [†]One case of accidental death recorded as not available. [§]Three cases recorded as not available (One case of accidental death; two cases of new extrahepatic lesions).

Abbreviations: OP, oligoprogressive; OM, oligometastatic; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

5.8 vs 3.9 months, P=0.018), while no significant differences were observed in the number of OP/OM lesions, sum of the largest diameters of OP/OM lesions, or biological effective dose (BED) (Table S4).

The 2-year cumulative incidence of local failure was 3.0% in the overall cohort, 4.0% in the OP cohort and 0% in the OM cohort (Figure 2A and B). Median PFS was 11.2 months (95% CI: 9.3–21.5), and median OS was 34.9 months (95% CI: 18.6-NA) in the overall cohort (Figure 2C and E). For OP and OM cohorts, the median PFS was 11.2 (95% CI: 9.3–22.2) months and 10.2 (95% CI: 4.4-NA) months (Figure 2D); the median OS was 32.6 (95% CI: 16.6-NA) months and not reached (NR) (95% CI: 17.5-NA) months (Figure 2F), respectively.

At the end of follow-up, 70.3% (26/37) patients experienced treatment failure. The first failure patterns were progression in untreated, pre-existing lesions (7/37) and the development of new lesions (21/37).

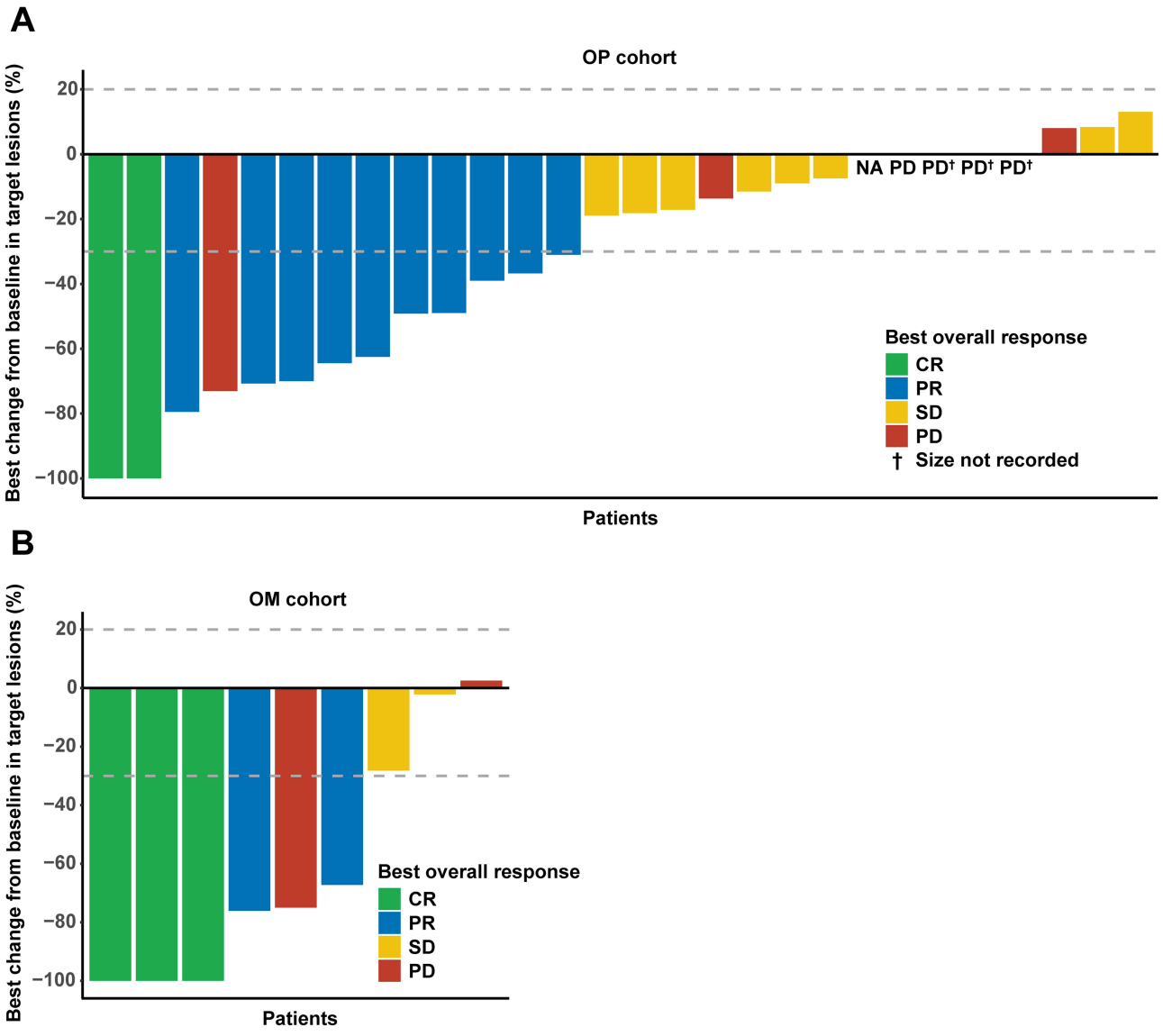

Figure 1 Waterfall plot of the best response in OP cohort (**A**) and OM cohort (**B**).
Note: †Size not recorded.
Abbreviations: OP, oligoprogressive; OM, oligometastatic; NA, not available (due to accidental death); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

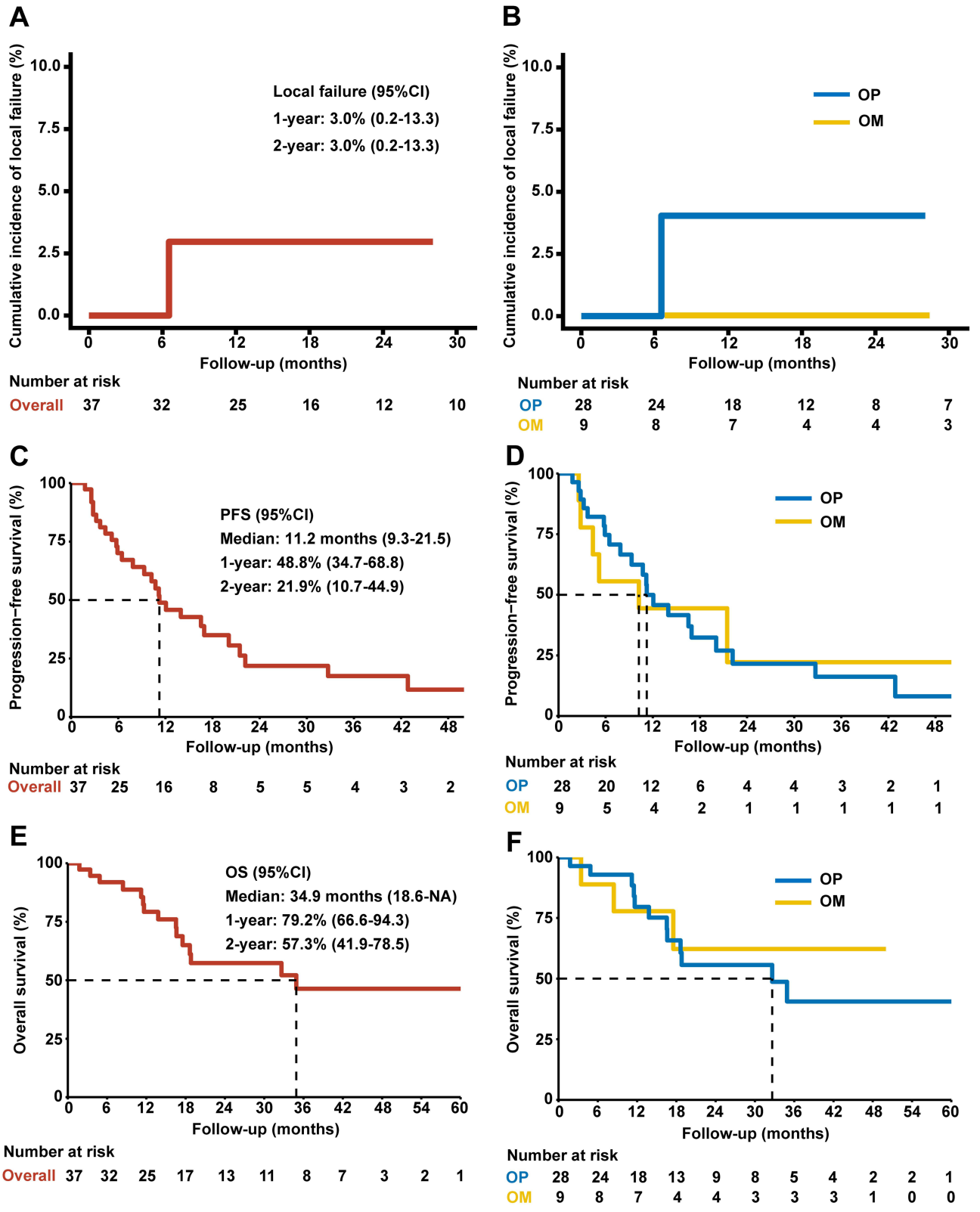

Figure 2 Cumulative local failure rates of overall (**A**), OP and OM cohorts (**B**); PFS of overall (**C**), OP and OM cohorts (**D**); OS of overall (**E**), OP and OM cohorts (**F**).
Abbreviations: OP, oligoprogressive; OM, oligometastatic; PFS, progression-free survival; OS, overall survival.

https://doi.org/10.2147/JHC.S519770

Prognostic Factors and Subgroup Analysis for PFS

Both univariate (HR=0.369, 95% CI: 0.148–0.917, P=0.032) and multivariate Cox regression analyses (HR=0.330, 95% CI: 0.112–0.980, P=0.047) demonstrated that OR of irradiated lesions served as an independent protective factor for PFS (Table S5).

For first-line and subsequent-line subgroup (Figure S2A), the median PFS was 10.2 (95% CI: 5.77 - NA) and 11.2 (95% CI: 9.30–32.7) months (P=0.71), respectively. For solitary and multi-site OP/OM lesions subgroup (Figure S2B), the median PFS was 16.5 (95% CI: 10.23–32.7) and 11.2 (95% CI: 4.37 - NA) months (P=0.45), respectively. The sum of the largest diameters of OP/OM lesions was stratified using a median cut-off of >2.8 cm. For the sum of the largest diameters of OP/OM lesions subgroup (Figure S2C), the median PFS was 10.7 (95% CI: 5.77 - NA) for lesions >2.8 cm vs 16.9 (95% CI: 7.87 - NA) months for lesions ≤2.8 cm (P=0.5), respectively.

Subgroup Analysis for OP Cohort

Twelve patients in the OP cohort switched to next-line therapy (OP-N), while 16 (57.1%) continued current systemic therapy (OP-C). Baseline characteristics were similar (Table S6), except all OP-N patients had ≥2 current systemic therapy lines (vs 50% in OP-C), and 83.3% of OP-N patients received targeted therapy plus ICI (vs 37.5% in OP-C).

In the OP-N and OP-C groups, the ORR was 41.7% and 46.7%; the DCR was 66.7% and 80%, respectively. Best percentage change from baseline in the sum of the largest diameters of target lesions are shown in Figure 3A and B. For survival, the median PFS was 11.6 and 16.5 months (HR=1.06, 95% CI: 0.45–2.51, P=0.89) (Figure 3C); median OS was NR and 32.6 months (HR=0.66, 95% CI: 0.21–2.08, P=0.47), respectively (Figure 3D).

Safety

Early and late TRAEs of any grade were observed in 97.3% (36/37) and 54.1% (20/37) of patients, respectively (Table 3). Grade 3 early TRAEs occurred in 40.5% (15/37) of patients, with lymphopenia (29.7%, 11/37) being most common. Grade 3 late TRAEs occurred in 5.4% (2/37) of patients, including lymphopenia (2.7%, 1/37) and anemia (2.7%, 1/37). No grade 4–5 AEs were observed. All patients completed the planned SBRT treatment. TRAEs led to discontinuation of part or whole systemic therapy in 6 (16.2%) patients.

To further investigate whether SBRT may increase TRAEs, we analyzed AE profiles in the OP cohort before and after SBRT (Table S7). Following SBRT treatment, the incidence of grade 1–2 AEs increased from 57.1% (16/28) to 96.4% (27/28). Grade 3 AEs showed an increase from 3.6% (1/28) to 35.7% (10/28), with the most notable grade 3 AE being lymphopenia (25%, 7/28) that was potentially SBRT-related. Notably, all new-onset toxicities resolved following appropriate clinical management.

Discussion

To the best of our knowledge, this is the first study investigating the combination of systemic therapy and SBRT for HCC patients with OP/OM. SBRT demonstrated favorable local control rates for irradiated OP/OM lesions, with a 2-year local failure rate of 3.0%. In the context of systemic therapy, the combination of SBRT achieved promising overall response rates and long-term survival outcomes, along with moderate toxicities. In the OP group, comparable outcomes were observed between the OP-N and OP-C subgroups, suggesting that SBRT may block OP status and potentially delay the need for treatment changes.

Targeted therapy and immunotherapy are the first-line recommendations for advanced HCC, such as Atezolizumab plus Bevacizumab or Camrelizumab plus Apatinib.[29,30] Several previous studies have shown a median PFS of 2.1–7.3 months and a median OS of 10.7–22.1 months for first-line therapy (Table S8). However, the efficacy of second- and post-line therapy was significantly reduced, with a median PFS of 2.6–5.2 months and a median OS of 8.5–14.6 months (Table S9). Patients with extrahepatic metastases are generally associated with poor outcomes, emphasizing the need for combined modality treatments. In recent years, the integration of local therapies into systemic treatment regimens has emerged as a promising approach to improve outcomes in advanced HCC.[31–35] Among patients with metastatic disease, oligometastatic disease represents a distinct subgroup, lying between widespread metastases and localized disease. Given the limited options for local ablative therapies in metastatic disease, SBRT stands out as a precise, non-invasive approach. Our study evaluated SBRT

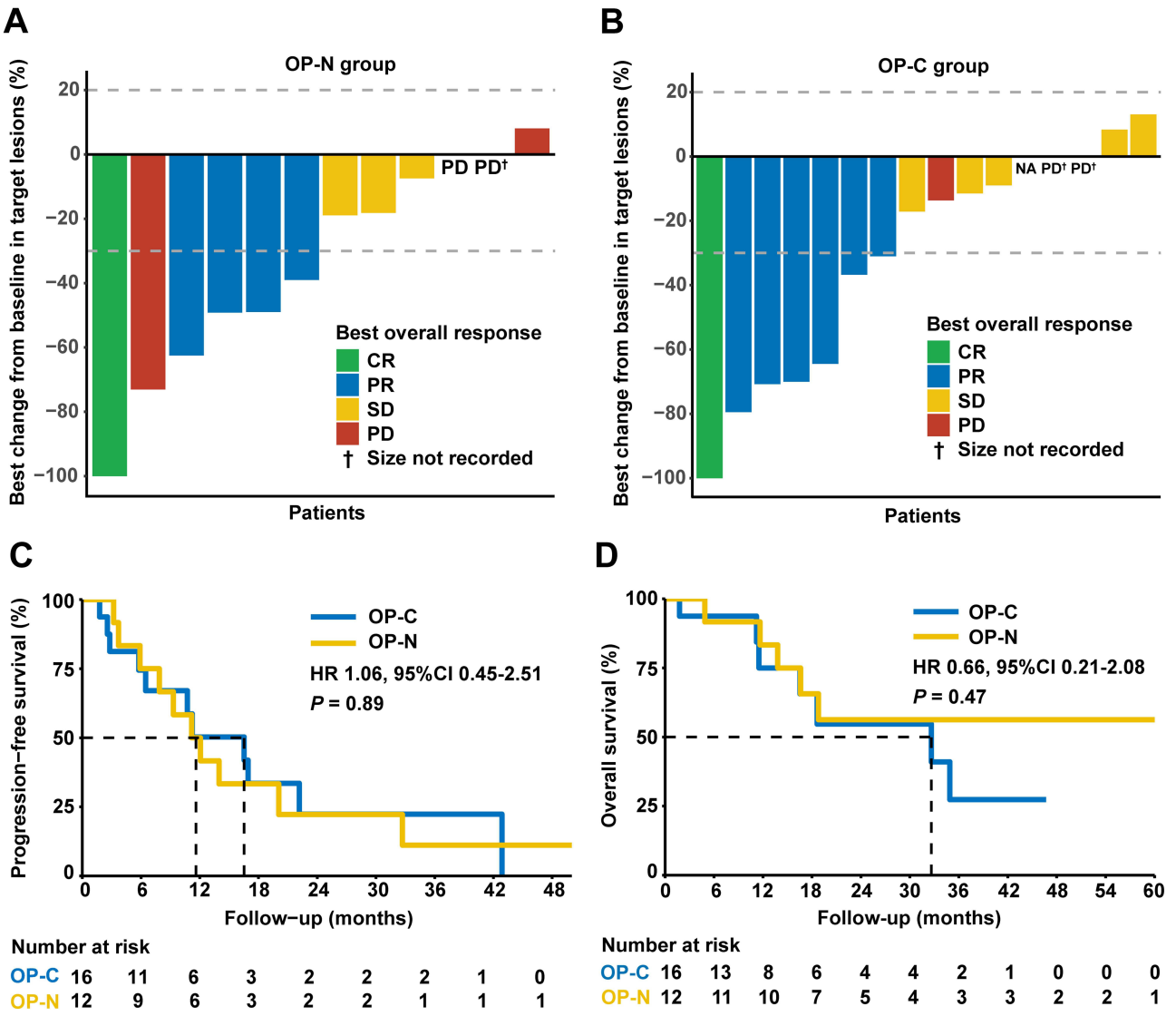

Figure 3 Waterfall plot of the best response in OP-N group (**A**) and OP-C group (**B**); PFS of OP-N and OP-C groups (**C**); OS of OP-N and OP-C groups (**D**).
Note: †Size not recorded.
Abbreviations: OP-N, oligoprogression with radiotherapy and next line systemic therapy; OP-C, oligoprogression with radiotherapy and current systemic therapy; NA, not available (due to accidental death); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; HR, hazard ratio.

combined with systemic therapy in patients with OP and OM HCC. Notably, all patients had extrahepatic metastases, and 62.2% had received two or more lines of systemic therapy. Despite advanced disease and heavy pretreatment, the combination of SBRT and systemic therapy demonstrated encouraging outcomes with a median PFS of 11.2 months and OS of 34.9 months, accompanied by manageable toxicity profiles. These findings highlight the feasibility of integrating ablative radiotherapy in this cohort. However, it should be noted that the observed clinical benefits might be partially attributed to the inherent biological characteristics of OP and OM HCC, as this subgroup may represent tumors with less aggressive behavior and intrinsically favorable prognosis. This potential selection bias underscores the need for further prospective studies to clarify whether the survival improvements are truly attributable to the therapeutic combination of SBRT and systemic therapy.

Systemic therapy combined with SBRT for OMD has become a major area of research in recent years. SBRT for OMD can halt the metastatic process and eradicate sources of disease.[36,37] In HCC, the Phase II study by Choi et al reported a median PFS of 5.3 months and a 2-year OS of 80% for OM patients, though 40% did not receive systemic therapy.[38] Compared to the study by Choi et al, which included patients with controlled primary tumors, all patients in

https://doi.org/10.2147/JHC.S519770

Table 3 Early and Late Treatment-Related Adverse Events

	Any Grade	Grade 1–2	Grade 3
Early TRAEs (within 3 months), n (%)			
Fatigue	10 (27.0)	10 (27.0)	0 (0)
Nausea	14 (37.8)	14 (37.8)	0 (0)
Proteinuria	8 (21.6)	8 (21.6)	0 (0)
Hand-foot syndrome	4 (10.8)	2 (5.4)	2 (5.4)
Hypothyroidism	1 (2.7)	1 (2.7)	0 (0)
Hematologic toxicity			
Leukopenia	16 (43.2)	16 (43.2)	0 (0)
Neutropenia	4 (10.8)	3 (8.1)	1 (2.7)
Lymphopenia	29 (78.4)	18 (48.6)	11 (29.7)
Anemia	8 (21.6)	8 (21.6)	0 (0)
Thrombocytopenia	15 (40.5)	15 (40.5)	0 (0)
Hepatobiliary toxicity			
Alanine aminotransferase increased	7 (18.9)	7 (18.9)	0 (0)
Aspartate aminotransferase increased	13 (35.1)	12 (32.4)	1 (2.7)
Blood bilirubin increased	17 (45.9)	17 (45.9)	0 (0)
Gastrointestinal toxicity			
Esophagitis	1 (2.7)	1 (2.7)	0 (0)
Abdominal pain	1 (2.7)	1 (2.7)	0 (0)
Diarrhea	3 (8.1)	2 (5.4)	1 (2.7)
Late TRAEs (after 3 months), n (%)			
Pneumonitis	6 (16.2)	6 (16.2)	0 (0)
Colitis	1 (2.7)	1 (2.7)	0 (0)
Lymphopenia	15 (40.5)	14 (37.8)	1 (2.7)
Anemia	5 (13.5)	4 (10.8)	1 (2.7)
Blood bilirubin increased	7 (18.9)	7 (18.9)	0 (0)

Abbreviation: TRAEs, treatment-related adverse events.

our study received systemic therapy and 59.5% (22/37) of patients in our study had intrahepatic lesions with a history of or current distant metastases. Despite these differences, the PFS in our OM cohort reached 10.2 months, suggesting SBRT combined with systemic therapy may improve outcomes in OM HCC. These results further support SBRT as an effective treatment option for this population.

With the increasing efficacy of systemic therapies, the incidence of OP HCC has risen. OP occurs when some lesions develop resistance, while others remain sensitive, creating an opportunity for local treatments such as SBRT. Given the low response rates of later-line systemic treatments, the addition of local therapies may improve patient outcomes. In our study, SBRT demonstrated an ORR of 44.4%, a median PFS of 11.2 months, and an OS of 32.6 months in OP cohort. Analysis of the waterfall plot revealed that, after SBRT, a significant proportion (75.7%, 28/37) of evaluable lesions in unirradiated sites continued to shrink, supporting the hypothesis that only a subset of lesions develop resistance, while others remain sensitive to ongoing systemic therapy. Through precise targeting of resistant lesions, SBRT may not only delay systemic disease progression but also prolong the period of sensitivity to systemic therapies, potentially leading to improved clinical outcomes. While SBRT for OP in other cancers have shown mixed results (CURB study),[22] our findings suggest that SBRT is an effective strategy for HCC patients with OP.

Subgroup analysis revealed that performing SBRT without changing systemic therapy achieved comparable PFS and OS to switching therapies. In the OP-C group, the ORR was 46.7%, with one patient achieving CR. This underscores the heterogeneity of OP HCC, where SBRT targets resistant lesions, while systemic therapy remains effective for sensitive ones. Similarly, studies have demonstrated that SBRT may delay the need for systemic therapy changes and potentially

improve outcomes in other tumors.[39,40] By blocking OP status, SBRT could prolong the use of current systemic therapy, reduce toxicity from frequent regimen changes and preserve future treatment options.

In this study, multivariate analysis revealed that patients achieving OR in irradiated lesions experienced significantly longer PFS, indicating that effective local tumor response may contribute to long-term survival benefits in OP and OM HCC patients. Possible reasons include that SBRT may enhance the efficacy of systemic therapies through immunomodulatory effects. Radiation therapy has been shown to release tumor antigens, activate immune cells, and convert "cold tumors" into "hot tumors", potentially improving the response to immunotherapy or targeted therapy.[18,41,42] In our study, the overall ORR following SBRT was numerically higher than historical data from systemic therapy alone, and the results suggest that effective local tumor control, particularly in achieving OR, may synergize with systemic therapy to improve overall outcomes in OP and OM HCC patients.

This study has some limitations. First, as a retrospective study, we excluded patients with incomplete medical records, which led to potential selection bias. Second, prognostic data specific to OP/OM HCC remain insufficient, and historical outcomes from advanced HCC treated with systemic therapy may not reflect their actual clinical course. Future studies should include head-to-head comparisons to clarify the additive benefits of SBRT. Third, as a single-center study with a relatively limited sample size, this investigation permitted only exploratory subgroup analyses in the OP cohort. Comparative efficacy evaluation between individual therapeutic agents was precluded by the study design. These findings require validation in larger studies. Finally, future research could explore potential biomarkers, such as lymphocyte subsets, to better identify target populations and elucidate the mechanisms underlying the synergy between SBRT and systemic therapy. Currently, our Phase 2 trial (NCT05917431) using SBRT combined with Tislelizumab and Regorafenib for advanced HCC is underway to validate these results.

Conclusion

The combination of SBRT and systemic therapy is a safe and effective option for HCC patients with OP or OM disease, demonstrating high local control rates, favorable PFS and OS, along with manageable toxicities. In OP HCC cases, maintaining current systemic therapy while incorporating SBRT may help slow disease progression, with outcomes appearing comparable to those achieved by switching systemic regimens. This strategy could potentially preserve subsequent treatment options. These findings highlight the emerging potential of SBRT as a valuable therapeutic strategy in the multidisciplinary management of advanced HCC, though larger prospective studies are needed to better characterize its clinical benefits and optimal integration within treatment algorithms.

Abbreviations

BED, biological effective dose; CBCT, cone-beam computed tomography; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; EORTC, European Organisation for Research and Treatment of Cancer; ESTRO, European Society for Radiotherapy and Oncology; HCC, hepatocellular carcinoma; ICRU, International Commission on Radiation Units and Measurements reports; K-M, Kaplan-Meier; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NA, not available; NOR, non-responders; NR, not reached; OMD, oligometastatic disease; OM, oligometastatic; OP, oligoprogressive; OP-C, oligoprogressive cohort continued current systemic therapy; OP-N, oligoprogressive cohort switched to next-line therapy; ORR, objective response rate; OR, objective responders; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival; PR, partial response; PTV, planning target volume; SBRT, stereotactic body radiotherapy; SD, stable disease; TKIs, small molecule tyrosine kinase inhibitors; TRAEs, treatment-related adverse events; VEGF, vascular endothelial growth factor; VMAT, volumetric modulated arc therapy.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Ethics Approval Statement and Informed Consent

This study was approved by the institutional review board of the Peking University Cancer Hospital and Institute (2024YJZ22), and the protocol conforms to the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Acknowledgments

The authors are grateful to all patients and their families. The figures in the video abstract were drawn by Figdraw (https://www.figdraw.com/).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Beijing Hospitals Authority Clinical Medicine Development of special funding support (ZLRK202327), Capital's Funds for Health Improvement and Research (No. 2024-2-2156), Beijing Hospitals Authority's Ascent Plan (DFL20220902), National Natural Science Foundation of China (82073333), and Beijing Municipal Administration of Hospitals Incubating Program (PX2023039). The funding source had no role in the study design, data curation, or the analysis and interpretation of data.

Disclosure

The authors report no conflicts of interest in this work.

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