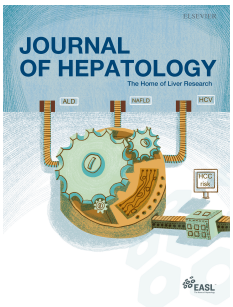

Efficacy of Stereotactic Ablative Radiotherapy in Patients with Oligometastatic Hepatocellular Carcinoma: A Phase II Study

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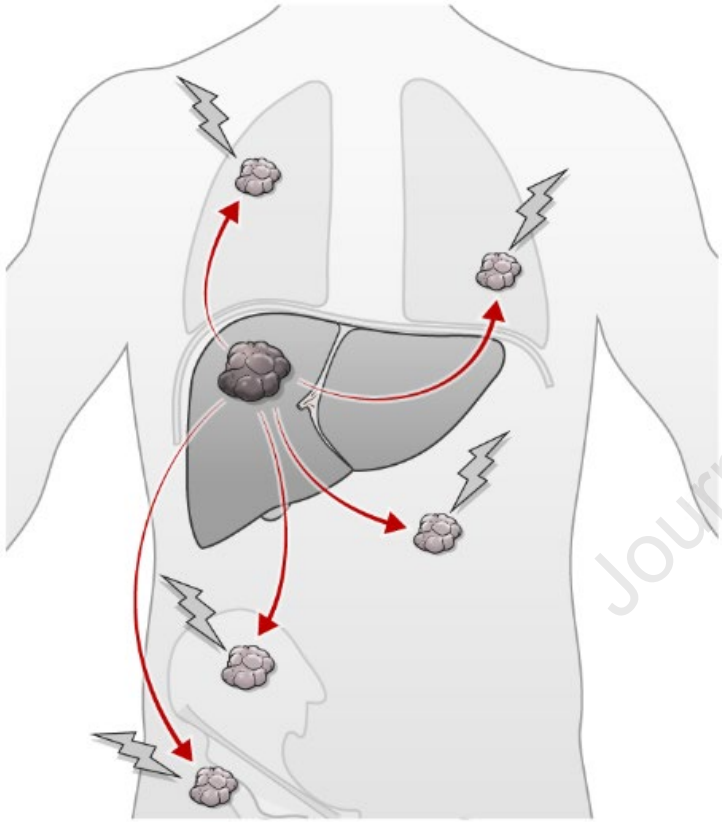
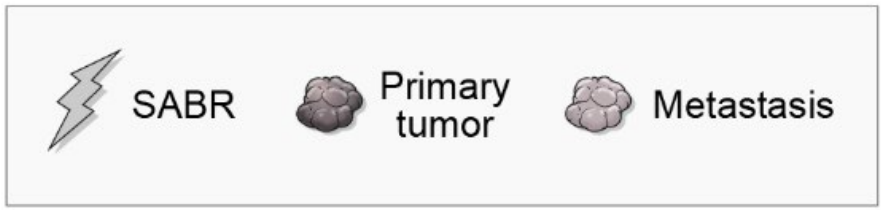
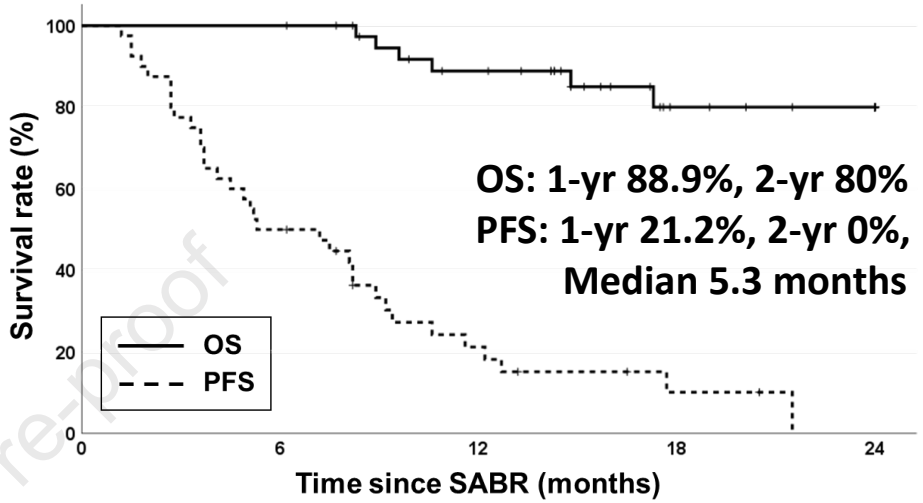
SABR
to oligometastatic HCC

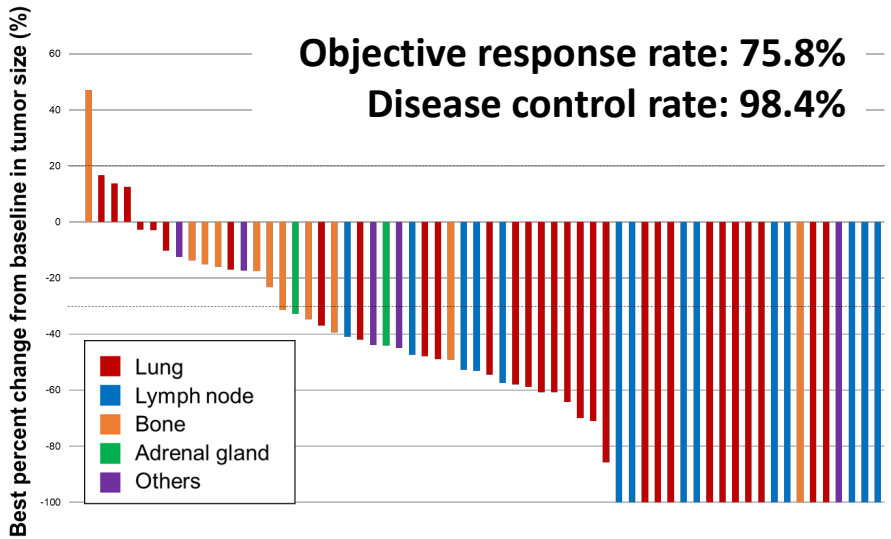




Overall survival & Progression free survival



The best response(%) in tumor size from baseline by site (n = 62 lesions)



Research Article

Efficacy of Stereotactic Ablative Radiotherapy in Patients with Oligometastatic Hepatocellular Carcinoma: A Phase II Study

Short running title: SABR in oligometastatic HCC

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Survival; Toxicity; Quality of life

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Authors' contributions: Study concept and design: J.S.; Acquisition of data: S.H.C., B.M.L., J.K., D.Y.K.; Analysis and interpretation of data: S.H.C., J.S.; Drafting of the manuscript: S.H.C., J.S.; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: S.H.C., J.S.; Funding acquirement: S.H.C., J.S.; Administrative, technical, or material support: S.H.C., B.M.L., J.K., J.S.; Study supervision: J.S.

Clinical Trial Number: NCT05173610

Abstract

Background & Aims: Stereotactic ablative radiotherapy (SABR) has demonstrated curative potential with survival benefits in patients with oligometastatic disease (OMD). However, limited evidence exists regarding its use in oligometastatic hepatocellular carcinoma (HCC). We aimed to prospectively investigate the efficacy and safety of SABR in patients with oligometastatic HCC.

Methods: We enrolled patients with controlled primary HCC and one to five metastatic lesions amenable to SABR. The primary endpoint was treatment efficacy defined as overall survival (OS) and progression-free survival (PFS). The secondary endpoints included time to local progression, objective response rate, disease control rate, toxicities, and quality of life (QOL), assessed using the EORTC QLQ-C30 before, and 0, 1, and 3 months after SABR.

Results: Overall, 40 consecutive patients received SABR on 62 lesions between 2021 and 2022. The most common locations for OMD were the lungs (48.4%), lymph nodes (22.6%), and bone (17.7%). After a median follow-up of 15.5 months, the 2-year OS was 80%. Median PFS was 5.3 months, with 1- and 2-year rates of 21.2% and 0%, respectively. A shorter time to OMD from the controlled primary independently correlated with PFS (p=0.039, hazard ratio 2.127) alongside age, Child–Pugh class, and α-fetoprotein (p=0.002, 0.004, 0.019). The 2-year time to local progression, objective response rate, and disease control rate were 91.1%, 75.8%, and 98.4%, respectively. Overall, 10% of the patients experienced acute toxicity, and 7.5% experienced late toxicity, with no grade 3+ toxicity. All QOL scores remained stable, whereas the patients without systemic treatments had improved insomnia and social functioning scores.

Conclusions: SABR is an effective and feasible option for oligometastatic HCC, excellently controls local tumors, and improves survival without adversely affecting QOL.

Electronic word count: 275

Impact and implications

SABR is a non-invasive treatment approach capable of efficiently ablating the target lesion; however, the OMD concept or SABR benefits have not been well-defined in HCC. According to this study, SABR is an effective and safe treatment option for oligometastatic HCC, yielding excellent local tumor control and survival improvement without worsening patients' QOL, regardless of tumor sites. We also demonstrated that patients with late OMD presentation after the controlled primary and lower AFP levels benefit from SABR, potentially improving PFS and potentially leading to a longer OS. This is the first prospective study of SABR in oligometastatic HCC, providing insights to develop novel strategies to improve oncologic outcomes.

Highlights

- SABR is a safe and effective treatment option for oligometastatic HCC.
- AFP levels, Child–Pugh class, and timing of OMD presentation impact outcomes in SABR.
- Patients with late OMD presentation after the controlled primary benefit from SABR.

Introduction

HCC is one of the most common solid malignancies worldwide. A significant proportion of patients with HCC are diagnosed at advanced stages and are amenable to systemic therapies. Recent therapeutic advances have dramatically changed the systemic treatment landscape for advanced HCC, substantially improving patient survival.[1-4] Furthermore, recent advances in imaging techniques and cancer-specific follow-up strategies enable the early detection of metastatic cancers, suggesting a paradigm shift for metastatic cancer management.

The concept of oligometastasis, first proposed in 1995,[5] represents a pivotal phase between localized disease and widespread metastasis. Evidence shows that local ablative therapies (LAT) (including radiotherapy [RT], surgery, or thermal ablation) for metastases can extend survival and may offer a potential cure in some cases.[6-9] The oncological benefits of LAT for oligometastatic diseases (OMD) include halting the metastatic process, eradicating disease sources, and alleviating symptoms.[10,11] Several randomized trials have recently highlighted the advantages of local treatments,[12-19] primarily for oligometastatic lung, colorectal, and prostate cancers, inducing a growing clinical adoption of these strategies in OMD.

Stereotactic ablative RT (SABR) is a modern technique that delivers a high radiation dose in three to five fractions with exceptional precision to a single tumor site. SABR is a non-invasive treatment modality capable of effectively ablating the target lesion in an outpatient setting. Additionally, SABR can activate the systemic immune response and synergize with immunotherapy.[20] A growing body of research and the findings from the SABR-COMET trial[17-19] suggest that SABR is an effective LAT for OMD across various cancer types.[14-16,21]

However, the OMD concept or SABR benefits have not been well-defined in HCC. As the benefits of SABR might differ across different tumor types or subtypes of oligometastasis,

well-designed cancer-specific trials are essential. Therefore, we aimed to conduct the first prospective trial to assess the clinical efficacy of SABR in patients with one to five oligometastasis from HCC.

Patients and methods

Study design and participants

This prospective study was a single-arm, open-label, single-center, phase II trial registered with ClinicalTrials.gov (NCT05173610). Patients were eligible if they had previously untreated oligometastatic HCC with the primary tumor definitively treated at least 3 months before enrollment, and imaging revealed no progression at that site. All metastatic lesions were amenable to SABR, with a maximum of three metastases allowed in one organ and no more than five overall. Patients were aged ≥19 years, with a good performance status (Eastern Cooperative Oncology Group score 0–1) and a life expectancy of at least 3 months, as determined by the enrolling physician. Systemic treatment was permitted for all patients, either concurrently or sequentially, with SABR at the discretion of the hepatologist. In case systemic treatment was stopped within a few weeks either because of poor tolerance due to toxicity or because of patients' refusal, those patients were still included but considered not to have received systemic treatment. Patients were ineligible if they had serious medical complications preventing RT, RT history at the potential SABR site, malignant pleural effusion, or brain metastasis requiring surgery. Patients with tumors within 3 mm from the spinal cord were excluded. The Institutional Review Board of the Severance Hospital, Korea, approved this study (4-2021-1101), which was conducted following ethical guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Procedures

Patients received SABR to all radiologically identifiable (1–5) metastatic sites to achieve disease control while minimizing potential toxicities. **Table S1** presents the details of dose and

fractionation schemes depending on the target location. Subsequently, 48–60 Gy in four fractions was applied to the peripheral lung tumor, and 24 Gy in three fractions was primarily applied to the spine SABR. Furthermore, 48–64 Gy in eight fractions was applied to the central lung tumor, lymph node, and adrenal gland close to critical organs. Dose constraints for organs-at-risk were determined following the protocol of Timmerman et al.[22] However, lower doses or higher fractionations than specified in the protocol were permitted in some cases to ensure organs-at-risk dose limits were not exceeded. The gross tumor volume encompassed all visible tumors based on radiologic information. The clinical target volume was established by adding a margin for microscopic disease spread to the gross tumor volume, as determined by the clinical physician's judgment. The clinical target volume was expanded by 2–5 mm to the planning target volume to account for organ motion and setup error, depending on the irradiated site. Intensity-modulated RT using volumetric modulated arc therapy (Elekta VMAT; Elekta, Stockholm, Sweden) and three-dimensional conformal RT were allowed for treatment. At each fraction, patients underwent a cone beam computed tomography scan for setup and target verification before treatment. Standard dosimetric radiation quality assurance was performed on all cases and approved by the principal investigator. Each SABR fraction was delivered at least 18 h apart, treating no more than two sites daily.

Outcome measures

The primary endpoint was treatment efficacy, defined as overall survival (OS) and progression-free survival (PFS). OS referred to the time from the start date of SABR to the date of death or last follow-up. PFS was calculated from the start date of SABR to the date of disease progression, death, or last follow-up. The secondary endpoint included time to local progression (TTLP, the time from the beginning of SABR to the date of disease progression

within the SABR field or immediately adjacent area, even when systemic progression occurred earlier), objective response rate (the proportion of patients who achieved complete or partial response as their best overall response), disease control rate (the proportion of patients who achieved complete response, partial response, or stable disease as their best overall response), and adverse events. All outcomes were assessed based on the Response Evaluation Criteria in Solid Tumors version 1.1.[23] The progression events were classified into infield (local progression), outfield (intrahepatic), and outfield (distant) failures based on their relationship with the SABR field. Treatment-related adverse events were defined as physician-assessed, radiation-related toxicities, graded based on the Common Terminology Criteria for Adverse Events version 5.0. Acute toxicity refers to events that occurred during SABR or within 3 months after its completion. Late toxicity occurred after 3 months of treatment. Follow-up after SABR was scheduled weekly during the treatment, 1 month after treatment, 3-month intervals for the subsequent year, and 6-month intervals for the subsequent year. Blood tests, including complete blood count, liver function test, tumor marker (α-fetoprotein [AFP]), and imaging studies, were performed at every follow-up visit; further tests were conducted at the clinician's discretion.

Quality of life (QOL) assessment

The patient QOL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).[24] This instrument assesses global health status, five functions, and nine symptom domains. All the scores were linearly transformed into a numerical scale ranging from 0–100 following the EORTC QLQ-C30 scoring manual. A higher score indicated better functioning for function-related scales and more severe symptoms for symptoms-related items. The assessment was performed before

(V0), at the end (0 month after) (V1), 1 month after (V2), and 3 months after (V3) SABR. We conducted separate analyses for patients receiving systemic treatments during the questionnaire assessment period ("systemic treatment group," n = 18) and those not receiving systemic treatments ("non-systemic treatment group," n = 22) to assess SABR effect on QOL while minimizing the influence of concomitant systemic agents.

Statistical analysis

Study's sample size was determined based on data from two retrospective studies: One reporting a median OS of 8.1 months in patients who received SABR for HCC and bone metastases[25] and another reporting 30 months in patients who received local therapy for HCC and lung oligometastasis.[26] A sample size of 35 patients was required to achieve an 80% power with a one-sided 0.2 alpha level, assuming a 10% drop rate, to detect a 3-month improvement in median survival.[27] Additionally, we aimed to register 40 patients considering the potential reclassification of cases initially diagnosed as OMD at study enrollment but later confirmed as poly-metastases during short-term follow-up imaging studies.

OS, PFS, and TTLP were calculated using the Kaplan–Meier method, and the differences were compared using the stratified log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to derive effect sizes and determine independent associations of prognostic factors with survival rates (OS and PFS). The means of continuous variables between the two groups were compared using the Student's t-test, and differences in the proportions of categorical variables were assessed using the chi-squared test. Significant changes in the EORTC QLQ-C30 scores were determined by non-parametric Friedman repeated measure analysis.[28] All statistical tests with a p value of 0.05 or lower were considered significant. Statistical analyses were conducted using IBM SPSS software version

27.0 (IBM Corp., Armonk, NY, USA) and R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Graphical representations were also performed on GraphPad Prism software version 10.0 (GraphPad Software, Inc., San Diego, CA, USA).

Results

Patient characteristics

The study included 40 patients with 62 oligometastatic lesions who received SABR between October 2021 and October 2022. **Table 1** presents the patient and treatment characteristics at the time of SABR. OMD occurred at a median of 32.1 months (range, 8.3–273.2) after the initial HCC diagnosis and at a median of 9.8 months (range, 0–89.2) after controlling the primary tumor. SABR was conducted at a median of 1.4 months (range, 0.3–7.1) after OMD diagnosis. Among the patients, 35 had *de novo,* and five experienced recurrent OMD, developing new lesions after initial OMD control through resection or systemic treatment. All patients had one (67.5%) or more (32.5%) OMD lesions, with the most frequent sites being the lungs (48.4%). Most patients (n = 36) received SABR for lesions in a single organ, while four received SABR for multiple organs simultaneously. The patients had previously received a median of three (range, 1–14) treatments before SABR, with one or more transarterial chemoembolization (or transarterial radioembolization) being the most commonly performed (65%), followed by liver resection (55%) and systemic treatment (37.5%). Overall, 24 patients (60%) received systemic treatment concurrently or sequentially (six before SABR and eight after SABR) with SABR.

Clinical outcome and survival

The median follow-up duration was 15.5 months (interquartile range [IQR]: 11.3–23.4), during which 62 lesions in 40 patients were assessed for treatment response. Six patients (15%) experienced the primary outcome event—death from any cause (three died of disease and three from other causes). Median OS was not reached during the study period, with 1-year and 2-

year rates of 88.9% and 80%, respectively. Median PFS was 5.3 months (95% CI: 1.7–8.9), and the 1-year and 2-year rates were 21.2% and 0%, respectively. Among the patients, 33 (82.5%) patients experienced disease progression events: one infield, eight outfield (intrahepatic), 22 outfield (distant), and two outfield (both intrahepatic and distant). One patient (2.5%) exhibited infield failure at 5.3 months after SABR. Ten patients (25%) experienced intrahepatic failures at a median of 3.6 months (IQR: 2.4–5.7). Overall, 24 patients (60%) exhibited distant failures at a median of 6.2 months (IQR: 3.4–9.1). Median TTLP was not reached over the study period, with 1- and 2-year rates at 91.1%. **Fig. 1** illustrates Kaplan–Meier survival curves.

The objective response rate per lesion was 75.8%, with 21 achieving complete response and 26 achieving partial response after SABR. Additionally, 14 lesions showed stable disease, resulting in a 98.4% disease control rate per lesion [**Table S2**]. An 84-year-old patient who underwent SABR for a single OMD in the C6 spine experienced progressive disease (PD). Radiologic progression and worsening pain at 5.3 months after SABR necessitated retreatment, and the patient died from aspiration pneumonia at 8.9 months. **Fig. 2** illustrates a waterfall plot showing the best response in the target lesion after SABR. **Fig. 3** shows a swimmer plot summarizing the treatment course and outcomes for each patient.

Age (<61 years), Child–Pugh class, AFP level (<200 vs. ≥200 ng/mL), and time to OMD from the controlled primary (<10 vs. ≥10 months) were identified as independently significant prognostic factors in univariate and multivariate analyses for PFS ($p = 0.002$, hazard ratio [HR] 3.316; $p = 0.004$, HR 0.150; $p = 0.019$, HR 0.266; and $p = 0.039$, HR 2.127, respectively) [**Table 2**]. No factor showed significance in the univariate analysis for OS [**Table S3**]. There was no significant difference in outcomes of the systemic treatment and SABR combination **[Table S4].**

Survival analysis was stratified by AFP level and time to OMD from the controlled primary [**Fig. S1**]. Patients with AFP <200 ng/mL had median and 1-year PFS rates of 7.5 months (95% CI, 4.1–10.9) and 24.4%, respectively, and patients with AFP ≥200 ng/mL had median and 1-year PFS rates of 3.6 months (95% CI, 0–8.1) and 0%, respectively ($p = 0.045$). Similarly, patients with time to OMD ≥10 months had median and 1-year PFS rates of 8.9 months (95% CI, 7.9–9.9) and 26.3%, respectively, and patients with time to OMD <10 months had median and 1-year PFS rates of 3.7 months (95% CI, 1.7–5.7) and 15%, respectively ($p = 0.025$).

The effect of SABR on QOL

Table 3 presents the mean and standard deviation of the QOL scores at these specific time points. No significant differences in baseline QOL scores were observed between systemic and non-systemic treatment groups. Within the systemic treatment group, no significant longitudinal changes were observed in the mean scores for all QOL scores. In the non-systemic treatment group, significant improvements were observed in the mean insomnia scores in the symptom domain and social functioning in the functional domain before and after SABR ($p = 0.008$ and 0.041, respectively). **Fig. 4** illustrates the improvement in insomnia and social functioning scores after SABR. The QLQ-C30 questionnaire did not report any detrimental effect on QOL.

Treatment-related toxicities

All patients completed their planned treatment courses without interruption. Five patients (12.5%) experienced SABR-related adverse events. Four (10%) reported acute toxicity, and

three (7.5%) reported late toxicity. Among the patients who reported acute toxicity, one patient (2.5%) exhibited grade 1 toxicity, and three (7.5%) exhibited grade 2 toxicity, with no occurrences of grade 3–5 toxicities. The most common events were dyspepsia and dysphagia, followed by nausea, bone pain, and diarrhea. Grade 1 and 2 toxicities resolved spontaneously over time without leaving any chronic sequelae. Among patients with late toxicity, one patient (2.5%) exhibited grade 1 toxicity, and two (5.0%) exhibited grade 2 toxicity, with no instances of grade 3 to 5 toxicities. The most common event was dyspepsia, followed by diarrhea and cough. No clinically significant radiation pneumonitis events were observed in patients who received lung SABR. **Table 4** presents the details of adverse events.

Discussion

The first-line treatment for metastatic HCC is systemic treatment, and combination strategies involving local therapies have not been thoroughly explored. In this prospective study, we evaluated the efficacy and safety of SABR in oligometastatic HCC. With a median follow-up duration of 15.5 months, 85% of the patients were alive at the last follow-up, demonstrating a 2-year OS rate of 80%. Disease progression primarily occurred as outfield distant failures or intrahepatic failures, with one event of infield failure resulting in an excellent local tumor control rate. The time to OMD from the controlled primary, age, Child–Pugh class, and AFP level were significant prognostic factors for PFS, although not for OS. Treatment-related toxicities were mostly mild and well-tolerated, indicating that SABR is an effective and safe LAT that ensures patients' QOL in oligometastatic HCC.

Surgery had traditionally been the primary method for ablating metastases in patients with oligometastasis; however, contemporary options, such as RT, offer effective and less invasive alternatives.[14-19,21] In a propensity-matching study by Kim et al. involving patients with HCC and lung oligometastasis,[26] the group receiving combined local therapy and systemic treatment exhibited significantly higher survival rates than the group treated with systemic treatment alone. The pooled survival results in a recent meta-analysis[29] on local treatment for oligometastatic HCC favored the application of local treatment. However, the included studies primarily evaluated local therapies other than RT, and all were retrospective in nature.

Since 2020, Asian investigators have intensively investigated the role of SABR in oligometastatic HCC.[25,30-32] These studies were retrospective and exhibited heterogeneity in the inclusion criteria (especially OMD location); however, 1-year PFS ranged from 22% to 47%, 2-year OS from 29% to 67%, 2-year local control rate from 90% to 91%, and grade 2+ acute toxicity from 20% to 26%. Chen et al. conducted a prospective study involving a

combination of SABR with a PD-1 inhibitor.[33] In contrast to ours, this study included oligometastatic cases and patients with recurrent HCC, with a majority receiving SABR for intrahepatic recurrences. Reported survival rates (2-year OS: 83% and PFS: 45%) were similar to others; however, the toxicity rates were high at 56% for grade 2 and 12% for grade 3. This difference stemmed from varying patient indications and combination with the PD-1 inhibitor. Our study demonstrated similar PFS and local control rates, but the OS and toxicity rates were superior to previous studies. Our favorable toxicity profile aligns with a recent meta-analysis suggesting that the rates of acute or late grade 3+ toxicities after SABR are 1–2%.[34]

SABR-COMET trial[17,19] showed that the SABR group had significantly higher OS and PFS than the control group. Approximately 20% of SABR arms achieved survival beyond 5 years without disease progression, indicating the potential curative nature of SABR in selected patients. PFS was lower than expected in the SABR-COMET trial, and a meta-analysis[34] indicated that approximately half of the patients with oligometastasis experience progression at 1 year, even with RT. Our study reported a 1-year PFS of 21.2% with an 83.5% disease progression rate but a longer OS despite the inclusion of cancer types generally associated with a better prognosis than that of oligometastatic HCC in the SABR-COMET trial. Additionally, in our study, a series of salvage therapies proved effective, with only three patients dying of the disease. Twenty-three patients underwent multiple SABR sessions at new metastatic sites upon disease progression. Our findings suggest that early and proactive consideration of systemic treatments or salvage SABRs would benefit patients who received SABR for OMD. We believe that despite being a single-arm trial, our study holds significance as a prospective trial that can pave the way for future research.

The combination of immunotherapy and RT is studied as a promising treatment for several solid cancers because of the observed synergistic effect. Emerging evidence indicates

that these effects are evident, particularly when RT is administered at high biologically effective doses (≥100 Gy) in a few fractions (≤10). Ablative RT can transform tumors into an *in situ* cancer-specific vaccine by boosting the release of tumor-associated antigens, increasing PD-L1 expression, better activating tumor-directed T lymphocytes to augment local tumor ablation, and better eliminating occult micrometastatic disease.[35-37] Kim et al. demonstrated that RT induced PD-L1 expression in tumor cells, indicating the potential antitumor effect of anti-PD-L1 agents for HCC.[38] Another study measured initial soluble PD-L1 (sPD-L1) levels before and after RT.[39] A high initial sPD-L1 level was significantly associated with tumor aggressiveness and poorer OS. The change in sPD-L1 pattern varied with the RT dose scheme: the level increased immediately after RT but decreased at 1 month after conventional RT; however, it increased continuously after SABR. Hence, although future clinical studies are needed, combining immune checkpoint inhibitors with RT holds promise as a treatment for HCC, with potentially enhanced efficacy using SABR.

Some studies report no or even contrary effects[40,41]; however, a substantial body of literature consistently shows a positive correlation between late metastatic presentation and improved patient outcomes.[32,42-45] Similarly, patients with a longer time to OMD from the controlled primary in our study exhibited superior oncologic outcomes. The patient who demonstrated target lesion PD after SABR and experienced a dismal prognosis was an early OMD presentation case with a time interval of 4.3 months. Patients with early-presenting OMD, owing to their higher risk of systemic progression, may benefit from the early initiation of systemic therapy with SABR. Similar to previous research on HCC,[25,31,32] we identified baseline AFP levels and Child–Pugh class as significant factors influencing PFS. However, concerning OS, none of the prognostic factors, including the time interval, showed significance. These results can be explained by the relatively short follow-up duration and the fact that only six patients died, whereas a substantial number of patients are still undergoing follow-up. Long-

term follow-up data would be important to determine the major prognostic factors for OS. Despite these challenges, metastatic presentation timing and other factors may serve as useful indicators of the underlying tumor biology and contribute to patient selection for SABR. Future prospective trials may provide further guidance on SABR timing and patient selection.

In this study, we evaluated SABR effect on QOL using the EORTC QLQ-C30 questionnaire, a useful tool for evaluating patient-reported outcomes and its effects on physical and emotional well-being and overall QOL.[24,46,47] Similar to the findings in the SABR-COMET trial,[19] overall QOL scores remained stable after SABR. This pattern was consistent with patients with oligometastatic prostate cancer in the SABR[21] and STOMP trials[15]. Additionally, in our study, patients not receiving systemic treatment significantly improved insomnia and social functioning scores. This suggests a positive effect of SABR on QOL, whereas the lack of QOL improvement in the systemic treatment group may be attributable to mild discomfort from the treatments. Most importantly, our results indicate that SABR did not worsen patients' QOL. Future patient-reported outcome research focusing on patient stratification based on disease courses with extended follow-up may provide more detailed insights.

This study had some limitations. First, there was no parallel control group, and the study included a small, selected patient cohort with a limited follow-up duration. Second, the diverse therapy history among the enrolled patients could have affected HCC prognosis. Third, this study only included *de novo* and recurrent OMD patients without oligoprogressive patients. Since oligoprogression may be regarded as a separate clinical entity from *de novo* OMD or oligorecurrence, subsequent studies with all these aspects would be necessary. Fourth, heterogeneity in the use of systemic therapy limited the relevant analyses. The limited use of the current standard of care, atezolizumab-bevacizumab combination treatment, because of the constraints from national health reimbursement policies influenced the study. In this study, only

three patients received this combination, and one received an immune checkpoint inhibitor. Therefore, immunotherapy's effect on the potential benefits of SABR could not be sufficiently explored. A further study involving a larger patient cohort should be conducted to provide more clarity on this issue.

In conclusion, SABR is a safe and feasible treatment option for oligometastatic HCC, yielding excellent local tumor control and survival improvement regardless of tumor sites. Patients demonstrating late OMD presentation after the controlled primary and lower AFP levels benefit from SABR, manifesting potential improvements in PFS, potentially leading to extended OS. To the best of our knowledge, this is the first prospective study of SABR in oligometastatic HCC, providing insights to develop novel strategies to improve patient survival and QOL. A phase 3 randomized trial is required to conclusively prove the survival benefits of SABR in patients with oligometastatic HCC, compared to those of standard systemic therapy.

Abbreviations

AFP, α-fetoprotein; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR, Hazard ratio; IQR, Interquartile range; LAT, Local ablative therapy; OMD, Oligometastatic disease; OS, Overall survival; PFS, Progression-free survival; PD, Progressive disease; QOL, Quality of life; RT, Radiotherapy; sPD-L1, Soluble PD-L1; SABR, Stereotactic ablative radiotherapy; TTLP, Time to local progression

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

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Tables

Table 1. Patient characteristics

Variables		No.	(%)
Age (median, years)		61 (25–85)	
Sex	Male	33	(82.5)
	Female	7	(17.5)
ECOG performance status	0	16	(40.0)
	1	24	(60.0)
Etiology	HBV	25	(62.5)
	Non-B, Non-C	9	(22.5)
	HCV	4	(10.0)
	Alcoholic	2	(5.0)
Liver cirrhosis	Yes	22	(55.0)
	No	18	(45.0)
Child–Pugh class	A	36	(90.0)
	B	4	(10.0)
AFP (median, ng/mL)		4.7 (1.3–4763.5)	
Time to OMD from the first Dx of HCC (median, months)		32.1 (8.3–273.2)	
Time to OMD from the controlled primary (median, months)		9.8 (0.0–89.2)	
Location of metastases (per lesion)	Lung	30	(48.4)
	Lymph node	14	(22.6)
	Bone	11	(17.7)
	Adrenal gland	2	(3.2)
	Others	5	(8.1)
Number of metastases (per patient)	1	27	(67.5)
	2	5	(12.5)
	3	7	(17.5)
	4	1	(2.5)
Systemic treatment	TKI	18	(45.0)
	ICI + VEGF inhibitor	3	(7.5)
	Cytotoxic chemotherapy	2	(5.0)
	ICI	1	(2.5)
	None	16	(40.0)
Timing of systemic treatment	Concurrent	10	(41.7)
	Sequential	14	(58.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B virus; HCV, Hepatitis C virus; AFP, α-fetoprotein; Dx, Diagnosis; OMD, Oligometastatic disease; SABR,

Stereotactic ablative radiotherapy; TKI, Tyrosine kinase inhibitor; ICI, Immune checkpoint inhibitor; VEGF, Vascular endothelial growth factor

Table 2. Results of univariate and multivariate analyses of factors associated with progression-free survival

Variables	Univariate			Multivariate		
	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**
Age (<61 vs. ≥61 years)*	0.040	2.134	1.036–4.399	0.002	3.316	1.540–7.143
Sex	0.894	0.937	0.360–2.439			
ECOG performance status	0.766	0.899	0.445–1.816			
Etiology	0.741	0.955	0.729–1.252			
Liver cirrhosis	0.900	1.138	0.153–8.470			
Child–Pugh class (A vs. B)	0.004	0.182	0.056–0.589	0.004	0.150	0.042–0.538
AFP (<200 vs. ≥200 ng/mL)	0.045	0.365	0.137–0.977	0.019	0.266	0.088–0.806
Time to OMD from the controlled primary (<10 vs. ≥10 months)*	0.025	2.215	1.103–4.448	0.039	2.127	1.037–4.362
Location of metastases (single organ vs. multiple organs)	0.175	0.478	0.164–1.390			
Number of metastases (1 vs. >1)	0.886	1.056	0.502–2.220			
Combination of systemic treatment with SABR	0.803	0.915	0.453–1.848			
CR of target lesion	0.078	2.025	0.925–4.435			

*Median value was used as the cutoff.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; OMD, Oligometastatic disease; SABR, Stereotactic ablative radiotherapy; CR, Complete response; HR, Hazard ratio

Table 3. Change in EORTC QLQ-C30 scale scores over time after stereotactic ablative radiotherapy

Scales in mean (±SD)	Follow-up after SABR				
	Baseline (V0)	**0 month (V1)**	**1 month (V2)**	**3 months (V3)**	***p* value**
Systemic treatment group (n = 18)*					
Symptom scales					
Dyspnea	13.0 (20.3)	13.0 (20.3)	11.1 (16.2)	18.5 (26.1)	0.896
Pain	12.0 (14.9)	22.2 (30.3)	15.7 (17.6)	22.2 (24.9)	0.087
Fatigue	22.2 (20.2)	27.2 (26.5)	25.3 (14.2)	31.5 (21.6)	0.354
Insomnia	22.2 (22.9)	29.6 (30.0)	20.4 (25.9)	33.3 (28.0)	0.215
Appetite loss	11.1 (19.8)	20.4 (25.9)	20.4 (23.3)	24.1 (31.9)	0.765
Nausea and vomiting	6.5 (13.0)	9.3 (14.3)	7.4 (13.1)	13.0 (16.7)	0.256
Constipation	13.0 (23.3)	14.8 (28.5)	7.4 (14.3)	18.5 (23.5)	0.973
Diarrhea	11.1 (16.2)	13.0 (20.3)	25.9 (21.6)	27.8 (26.2)	0.624
Financial difficulties	9.3 (15.4)	14.8 (26.1)	3.7 (10.8)	16.7 (28.6)	0.310
Functioning scales					
Physical functioning	86.7 (19.5)	88.2 (20.4)	92.0 (11.6)	83.0 (23.7)	0.967
Role functioning	88.0 (22.7)	77.8 (30.3)	93.5 (13.0)	86.1 (25.7)	0.254
Cognitive functioning	91.7 (10.3)	89.8 (14.2)	96.3 (9.1)	87.0 (21.8)	0.186
Emotional functioning	79.6 (23.6)	76.9 (23.0)	82.9 (14.4)	79.2 (25.9)	0.822
Social functioning	87.0 (16.7)	14.8 (26.1)	94.4 (12.8)	84.3 (25.9)	0.551
Global health status	72.2 (16.9)	65.3 (23.3)	66.7 (23.6)	56.5 (23.0)	0.213
Non-systemic treatment group (n = 22)					
Symptom scales					
Dyspnea	9.1 (18.4)	7.6 (14.3)	15.2 (24.6)	15.2 (24.6)	0.392
Pain	14.4 (20.8)	16.7 (24.1)	12.1 (16.4)	10.6 (15.0)	0.596
Fatigue	18.7 (17.9)	18.7 (16.6)	18.2 (12.6)	15.2 (13.5)	0.910
Insomnia	16.7 (17.1)	18.2 (19.9)	19.7 (24.5)	3.0 (9.8)	0.008

Appetite loss	15.2 (26.7)	19.7 (28.5)	9.1 (21.0)	12.1 (19.4)	0.528
Nausea and vomiting	2.3 (10.7)	6.1 (13.2)	4.6 (10.5)	6.1 (12.1)	0.266
Constipation	6.1 (13.2)	7.6 (14.3)	7.6 (14.3)	12.1 (24.2)	0.634
Diarrhea	6.1 (22.2)	10.6 (23.9)	13.6 (24.5)	12.1 (16.4)	0.072
Financial difficulties	13.6 (19.7)	15.2 (22.4)	9.1 (15.2)	10.6 (23.9)	0.123
Functioning scales					
Physical functioning	87.6 (17.3)	84.9 (21.3)	86.1 (20.0)	91.2 (15.0)	0.783
Role functioning	89.4 (18.9)	86.4 (26.6)	89.4 (15.0)	95.5 (11.7)	0.392
Cognitive functioning	93.9 (9.7)	92.4 (11.2)	92.4 (11.2)	94.7 (9.5)	0.696
Emotional functioning	89.4 (16.7)	85.6 (18.4)	89.8 (14.3)	93.9 (10.0)	0.343
Social functioning	86.4 (18.3)	86.4 (21.6)	93.2 (13.3)	93.9 (12.1)	0.041
Global health status	64.4 (19.6)	68.2 (20.5)	73.9 (15.5)	69.3 (15.3)	0.184

*Patients who received systemic treatments during the EORTC QLQ-C30 assessment period.

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SD, Standard deviation; SABR, Stereotactic ablative radiotherapy

Table 4. Summary of adverse events

Adverse event	No. of patients (%)	
	Acute	Late
Any grade	4 (10.0)	3 (7.5)
Grade ≥2	3 (7.5)	2 (5.0)
Dyspepsia		
Grade 1	1 (2.5)	1 (2.5)
Grade 2	1 (2.5)	1 (2.5)
Dysphagia		
Grade 1	0	0
Grade 2	2 (5.0)	0
Nausea		
Grade 1	0	0
Grade 2	1 (2.5)	0
Bone pain		
Grade 1	0	0
Grade 2	1 (2.5)	0
Diarrhea		
Grade 1	1 (2.5)	1 (2.5)
Grade 2	0	0
Cough		
Grade 1	0	0
Grade 2	0	1 (2.5)

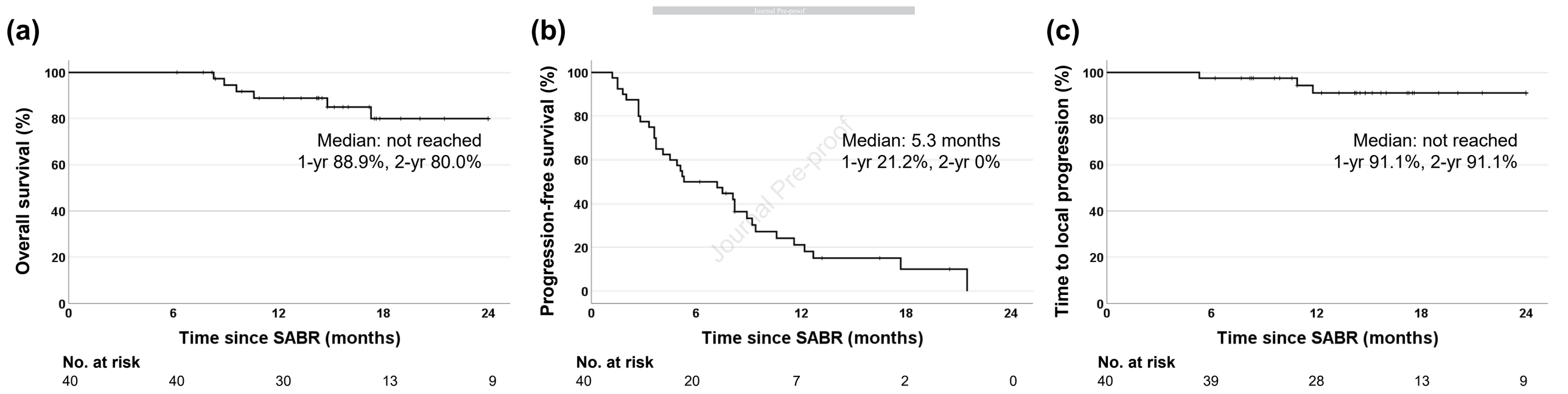
Figure legends

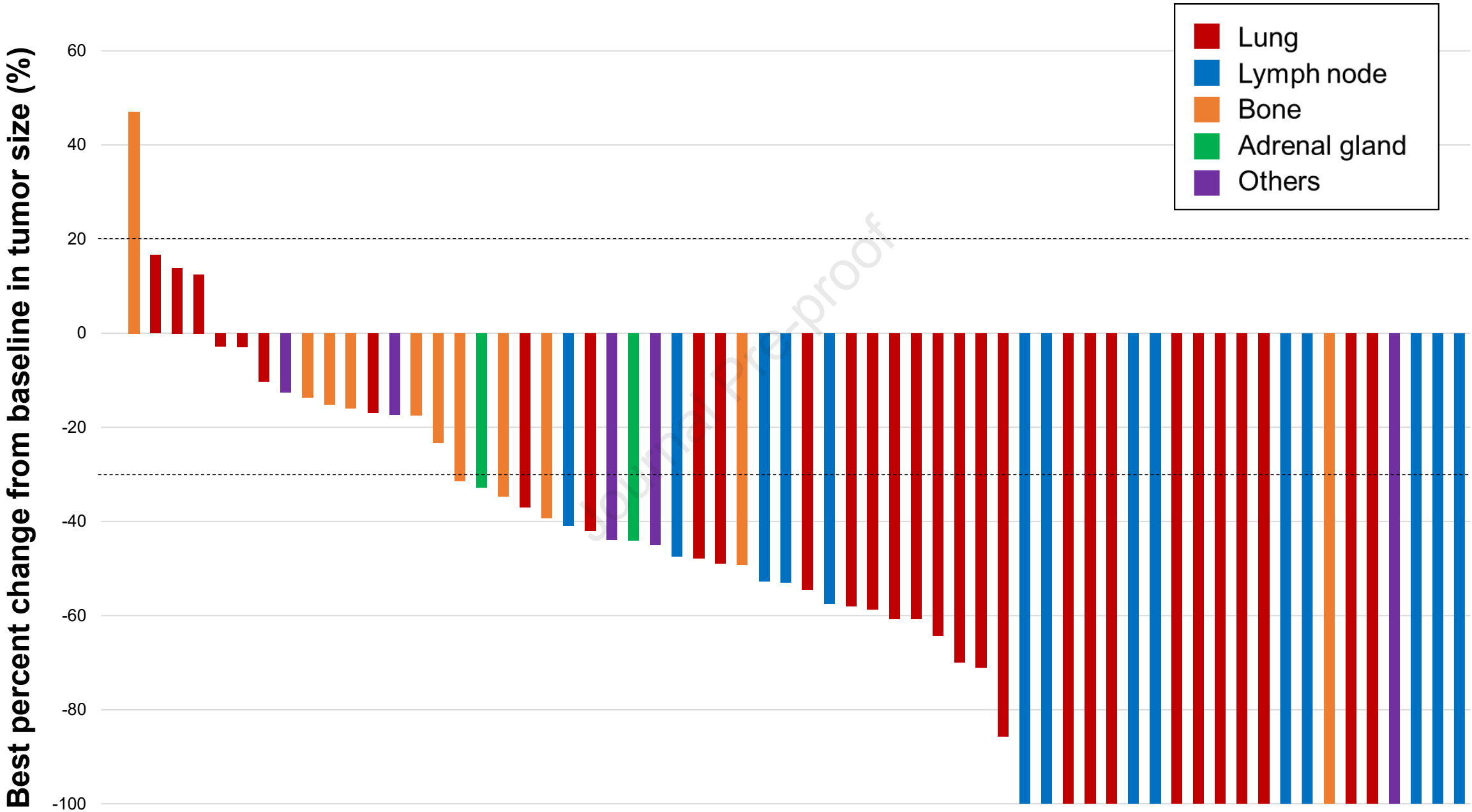
Fig. 1. Kaplan–Meier curves of (A) overall survival, (B) progression-free survival, and (C) time to local progression

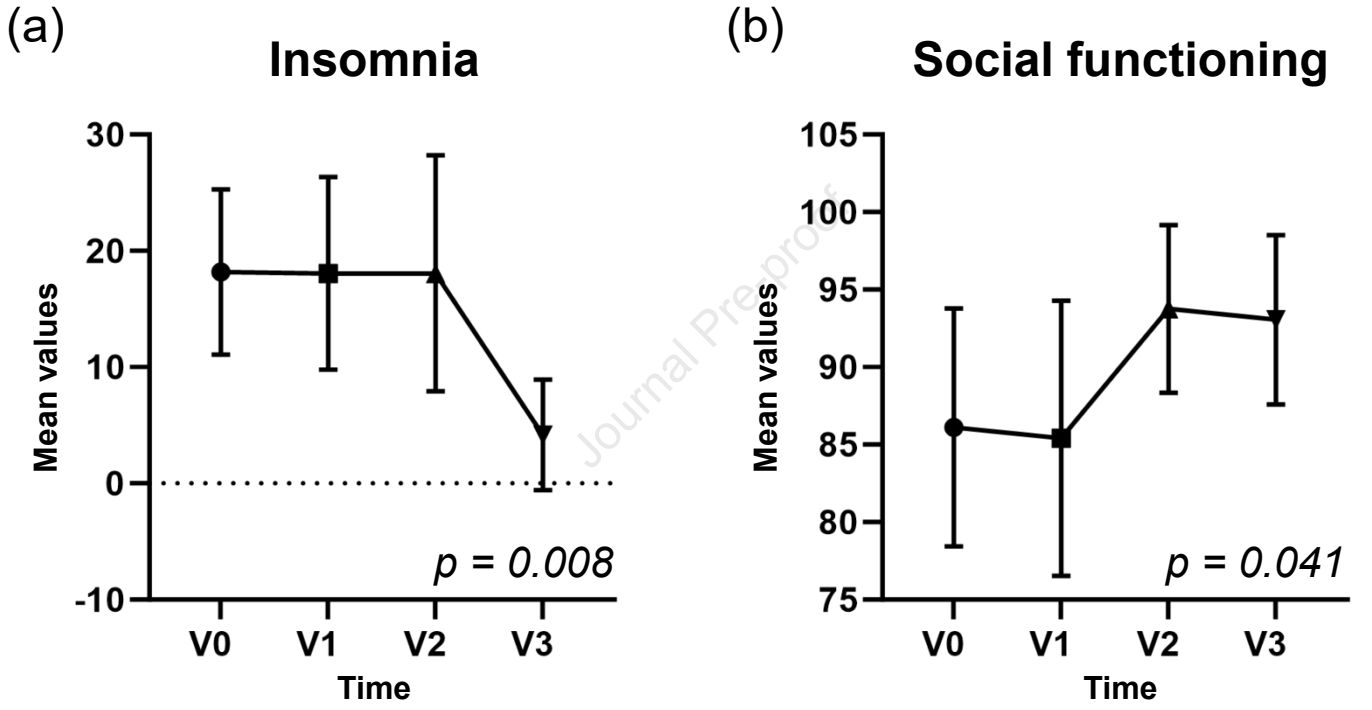
Fig. 2. Waterfall plot of the best response (%) in tumor size from baseline characterized by lesion site (n = 62, per lesion)

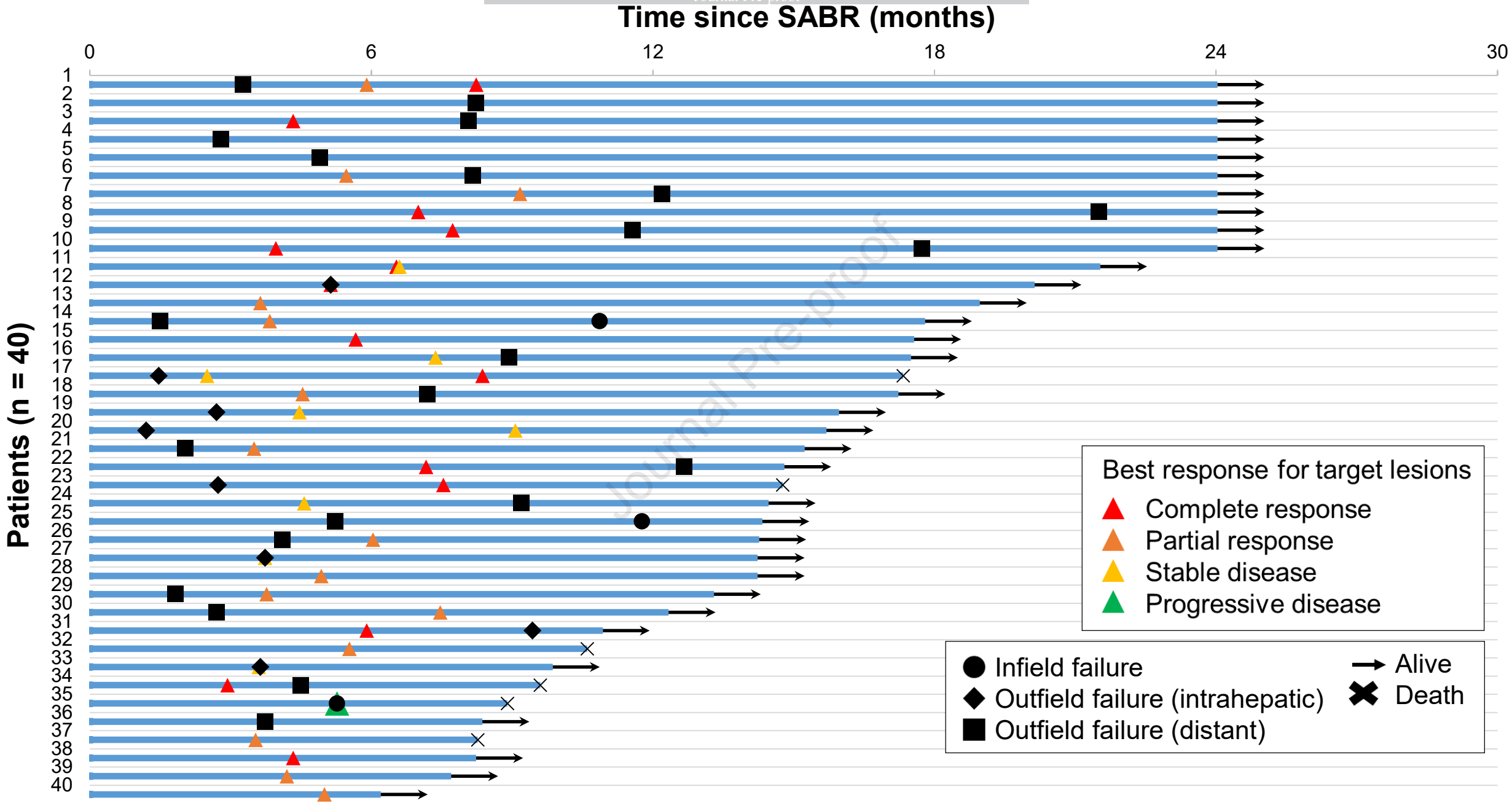
Fig. 3. Swimmer plot showing the treatment course and outcomes (n = 40, per patient)

Fig. 4. Change in insomnia and social functioning subscales of the EORTC QLQ-C30 overtime in the non-systemic treatment group (Mean scores with 95% confidence intervals, V0: before SABR [baseline], V1: 0 month after SABR, V2: 1 month after SABR, V3: 3 months after SABR)









Highlights

- SABR is a safe and effective treatment option for oligometastatic HCC.
- AFP levels, Child–Pugh class, and timing of OMD presentation impact outcomes in SABR.
- Patients with late OMD presentation after the controlled primary benefit from SABR.