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Spot Scanning Proton Beam Therapy for Surgery-inaccessible Hepatocellular Carcinoma: Preliminary Results

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Abstract

Background/Aim: Spot scanning proton beam therapy (SS-PBT) was employed for the treatment of surgery-inaccessible hepatocellular carcinoma, primarily influenced by respiratory movement.

Patients and Methods: Between October 2022 and December 2023, 12 patients were enrolled in this study to evaluate the efficacy of SS-PBT. The median follow-up time was 13.1 months.

Results: The one-year survival, progression-free survival, and local control rates were 79.5%, 57.1%, and 100%, respectively, without grade 2 or higher PBT-related toxicities. The clinical outcomes of these 12 patients appear comparable to data from prospective studies conducted at proton centers across Japan.

Conclusion: SS-PBT shows promise as a treatment option for surgery-inaccessible hepatocellular carcinoma.

Keywords: Spot scanning, proton beam therapy, hepatocellular carcinoma, liver cancer, radiotherapy.

Introduction

In 2020, 910,000 individuals worldwide were diagnosed with primary liver cancer, making it the sixth most commonly diagnosed cancer (1). Hepatocellular carcinoma (HCC) constitutes approximately 80% of primary liver cancers (2). Among the curative treatment options for HCC, surgical resection, radiofrequency ablation therapy, and liver transplantation are well-established approaches (3). Proton beam therapy (PBT) has also proved effective in

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treating HCC by delivering a highly localized and precise radiation dose, offering the potential for complete tumor eradication (4, 5). To elucidate the clinical efficacy of PBT for HCC, Mizumoto *et al.* conducted a multi-institutional prospective registry study involving patients with HCC treated at Japanese PBT institutions (6). The study systematically evaluated the efficacy of PBT, analyzing data from patients treated using standardized protocols between May 2016 and June 2018. The findings demonstrated that PBT was effective in a broad range of HCC cases, with the majority of treatments employing passive scattered proton beam therapy (PS-PBT).

At Shonan Kamakura General Hospital, spot scanning proton beam therapy (SS-PBT) was initiated in January 2022. The treatment of HCC began in October 2022, following the implementation of advanced motion control systems such as a real-time tumor tracking system and a respiratory gating system. In alignment with Japanese protocols, we treated patients with HCC deemed inoperable or challenging to treat surgically to assess the efficacy of SS-PBT for tumors affected by movement. This study presents preliminary clinical findings on SS-PBT for HCC, highlighting its potential to enhance outcomes for patients with HCC.

Patients and Methods

Ethical considerations. All patients provided written informed consent prior to the initiation of PBT. The study protocol received approval from the ethics committee at Shonan-Kamakura General Hospital (approval number 2564).

Study design. This study enrolled patients who met the following criteria: 1) HCC confirmed either through histology or characteristic imaging findings on four-phase multidetector-row computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI), specifically hypervascularity in the arterial phase with washout in the portal venous or delayed phase; 2) no lymph node involvement or distant metastasis; 3) no evidence of direct infiltration into the alimentary tract; 4) no more than three tumors within the liver; and 5) a performance status (PS) of 2 or lower based on the Eastern Cooperative Oncology Group classification. Eligibility for PBT was reviewed and approved by a multidisciplinary committee comprising professionals from various medical specialties.

Following the completion of PBT, patients were monitored every three months. Routine follow-ups included blood cell counts, serum chemistries, and measurements of alpha -fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II). Patients also underwent abdominal diagnostic imaging, such as contrast-enhanced CT or MRI. Treatment-related toxicities were assessed using the Common Terminology Criteria for Adverse Events, version 5.0. Local recurrence was defined as tumor enlargement within the irradiated field on contrast-enhanced CT or MRI following PBT.

Radiotherapy planning and treatment delivery. A SS-PBT system was installed at Shonan Kamakura General Hospital, with treatments commencing in January 2022. This equipment (PROBEAT M1, Hitachi Co. Ltd., Tokyo, Japan) utilizes a spot scanning system capable of storing proton beams for up to 8 s within the synchrotron (7). The proton beams are released in response to respiratory signals from either a real-time tumor tracking system or a respiratory gating system.

In the tumor tracking system, a fiducial marker, previously inserted near the tumor, guides beam delivery. When the fiducial marker enters a predefined 3-mm region, the synchrotron releases the stored proton beams to target the tumor. If the tracking system fails to detect the marker, for example, due to obstruction by bone structures or radiopaque substances such as fatty tissue, the respiratory gating system serves as a backup. During this process, a four-dimensional computed tomography (4D CT) scan identifies the optimal phase for irradiation. Patients without decreased renal function or a history of allergy to contrast agents underwent contrast-enhanced CT imaging, which was merged to precisely delineate the

Table I. *Dose constraints.*

	66 Gy/10 fractions	72.6Gy/22 fractions
Organ	Dose constraint	
Liver-GTV	$V_{30\ Gy}$<30% $V_{5\ Gy}$<50% $V_{2\ Gy}$>700 cc	
Alimentary tract	D_{max}<42 Gy	D_{max}<55 Gy
Kidney	D_{mean}<15 Gy $V_{12\ Gy}$<55% $V_{20\ Gy}$<30% $V_{28\ Gy}$<20%	
Spinal cord (canal)	D_{max}<31 Gy	D_{max}<40 Gy
Skin	D_{max}<50 Gy	D_{max}<66 Gy
Chest wall	$V_{49\ Gy}$<5 cc $V_{43\ Gy}$<13 cc $V_{40\ Gy}$<15 cc	$V_{65\ Gy}$<5 cc $V_{56\ Gy}$<13 cc $V_{53\ Gy}$<15 cc

D_x: X dose of the target volume; GTV, Gross tumor volume; V_{XGy}: the target volume irradiated with X Gy.

Table II. *Patients' characteristics.*

Age	Range (median)	61-89 (77.5)
Sex	Men/Women	8/4
Past hepatitis history	Presence (HCV/autoimmune)/Absence	4(3/1)/8
UICC Clinical stage	I/II/III/IV	4/5/3/0
Child-Pugh classification	A/B/C	12/0/0
Maximal tumor size (cm)	Range (Median)	1.1-13.2 (4.4)
Given dose/Fraction	66 Gy in 10fr/72.6 Gy in 22fr	3/9
Respiratory gaiting	Real-time tumor tracking/respiratory-gaiting	8/4

Fr: Fractions; HCV: hepatitis C virus; UICC: Union for International Cancer Control.

gross tumor volume (GTV). The exhalation phase, along with phases within a 3-mm range of the exhalation phase, was selected for treatment. The clinical target volume (CTV) was defined as the GTV plus 5 mm in all directions, modified to include microscopic disease progression and exclude the gastrointestinal tract. In cases with vascular invasion, a 10 mm margin was added in the directions of the portal vein and the inferior vena cava.

A planned target volume (PTV) was created by adding a 3 mm margin to the CTV to account for respiratory movement. In treatment planning, robust optimization planning was performed, incorporating a lateral margin of 5 mm and a beam margin of 3.5% uncertainty to address setup errors and respiratory movement (8). This approach ensured that multiple scenarios were generated to provide adequate coverage (9).

However, actual measurements to validate the setup were not conducted, and specific details regarding the robustness plan remained unavailable.

For general cases, a total dose of 66 Gy in 10 fractions was delivered to the PTV, ensuring that 95% of the PTV received at least 95% of the prescribed dose. For tumors involving the liver portal area and close to the alimentary tract, a dose of 72.6 Gy in 22 fractions was administered. For tumors near the alimentary tract, dose limits were set to 50 Gy for the duodenum and 55 Gy for the colon to minimize toxicities. Dose constraints are summarized in Table I. Doses are described as relative biological effectiveness (RBE)-weighted doses according to the International Commission on Radiation Units and Measurements (ICRU) report 93.

Proton beams were delivered starting from the distal position, with two to four scans on the same plane, depending on the monitor unit value, performed to ensure uniform coverage. The beam energy was then adjusted to irradiate subsequent distal planes, determined based on beam size (10). Irradiation concluded once the entire volume was treated. The beam delivery program assumed that the tumor remained stationary, activating the proton beam only when the tumor was within the predefined range. Consequently, treatment duration varied based on tumor volume and the stability of the patient's respiration.

In this system, two types of interplay control systems were utilized. The first is the real-time image-gated particle therapy system (7), which measures the tumor position in real-time. The second is the respiratory gating system (11), which accounts for the relationship between respiratory movement and fiducial marker movement. The tumor-tracking system was the primary method, while the respiratory gating system was employed only when the tumor-tracking system was unavailable. We

initiated proton beam therapy for HCC after the installation and validation of the above systems.

Statistical analyses. Kaplan-Meier methods were used to estimate overall survival (OS), progression-free survival (PFS), and local control (LC) rates. OS was calculated from the date of PBT initiation to the date of death or the most recent follow-up. LC was defined as the absence of local progression. PFS was measured from the beginning of PBT to the date of local progression, disease progression outside the primary site, or death from any cause. All statistical analyses were performed using SPSS software version 29 (SPSS Inc., Chicago, IL, USA).

Results

Between October 2022 and January 2024, a total of 12 patients with HCC were enrolled. Patient characteristics are shown in Table II. These patients were categorized as surgery-inaccessible cases, including large HCC with interstitial pneumonia and large HCC with intensive invasion of the inferior vena cava (12). Of the 12 patients, nine had tumors adjacent to the alimentary tract, and one had tumors with vascular invasion. All patients were treated under a respiratory control system: eight were treated using the real-time tumor tracking system, while the other four were treated using the respiratory gating system.

The median follow-up time was 13.1 months (range=2.7-22.3). The one-year OS, PFS, and LC rates were 79.5%, 57.1%, and 100%, respectively (Figure 1). No patients developed Grade 2 or higher PBT-related toxicity. Three patients died due to cardiac failure, multiple liver tumors, and probable late treatment-related toxicity from combined immune therapy. The remaining nine patients were alive at the time of analysis.

Discussion

The current study demonstrated that PBT produced favorable clinical outcomes in patients with HCC. In this study, the one-year estimated OS, LC, and PFS rates were

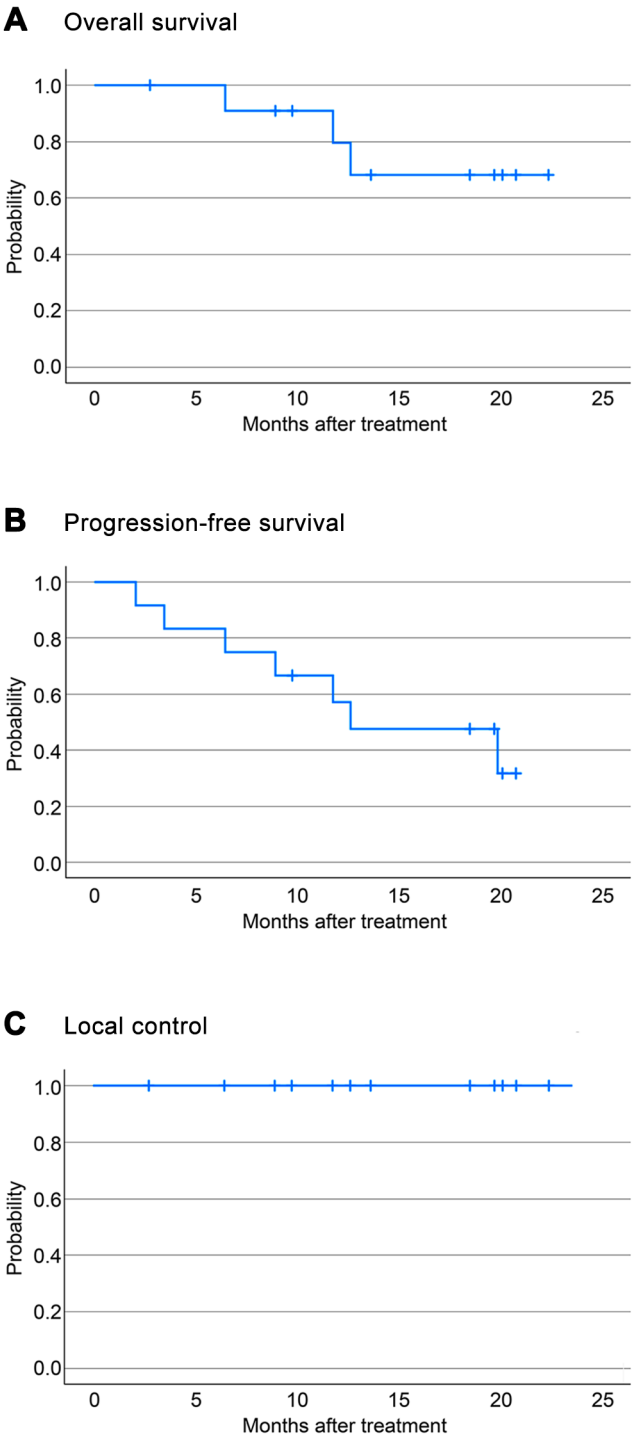

Figure 1. *Clinical results for 12 patients with 16 lesions are presented. With a median follow-up time of 13.1 months, A) the one-year overall survival rate was 79.5%, B) the one-year progression-free survival rate was 57.1%, and C) the one-year local control rate was 100%.*

79.5%, 100%, and 57.1%, respectively, with minimal toxicities.

In radiation therapy, controlling tumor motion caused primarily by respiration is essential (13). This is particularly important in PBT, as it is highly sensitive to motion. Treating moving targets requires careful planning to ensure accuracy and efficacy (14). The PS-PBT method irradiates the entire tumor throughout the treatment period as long as the tumor remains within the determined range, making it suitable for moving targets (15). In contrast, SS-PBT dynamically scans pencil beams across the tumor. This raises questions about whether a moving scanning beam can adequately cover a moving target. Therefore, PS-PBT remains a reliable option for moving targets in facilities offering both systems. However, a rapid transition is underway in most PBT facilities from PS-PBT to SS-PBT due to changes in machine supply.

For moving targets, such as liver cancer influenced by respiratory movement, tumor tracking (15) or respiratory gaiting systems (16) are utilized. These systems are effective in reducing positioning errors caused by respiratory uncertainties. Despite their effectiveness, uncertainties related to positioning and respiratory movement remain challenging. To mitigate the impact of uncertainties, robustness planning incorporating worst-case scenarios is utilized (14). A 3 mm margin is set to account for respiration and positioning uncertainties during robustness planning. In real-time tracking systems, proton beams are delivered when the fiducial marker enters a predefined 3-mm rectangular zone. For respiratory gating, proton beams are released during the expiratory phase and within 3 mm of the reconstructed phase.

Twelve patients with HCC were treated using SS-PBT equipped with real-time tumor tracking or respiratory gating systems. These patients were successfully treated, and tumor control was achieved. The adoption of SS-PBT is increasing due to its mechanical efficiency and the elimination of the need for large boluses, which are essential in PS-PBT. SS-PBT is well-suited for static and irregularly shaped tumors due to its precise targeting capabilities and ability to deliver intensity-modulated proton beam therapy.

Despite the growing popularity of SS-PBT, direct comparisons between PS-PBT and SS-PBT for moving targets, in terms of dose distribution, uncertainty, and outcomes, remain limited. Tumor motion due to respiration is highly complex. However, dose distributions calculated using actual beam delivery data from machine logs and positioning information closely matched the planned dose distributions (17). According to the data, the actual dose distributions were nearly equivalent to the planned dose distributions when more than five fractions were used. In this study, 10 or 22 fractions were utilized, and the actual dose distributions were expected to closely correspond to the planned dose distributions. Additionally, a prior study at our facility using auto-activation positron emission tomography (PET), which detects annihilation gamma rays generated after PBT, confirmed no excessive dose to the alimentary tract during liver cancer treatment. The results indicated that the actual dose distributions matched the planned dose distributions (18). However, in that study, most positron emitters were metabolized by the liver and subsequently washed out, leading to insufficient data during PET/CT imaging. To overcome this limitation, an online PET approach may provide a solution by capturing annihilation of gamma rays beam by beam, offering a more accurate depiction of proton beam movement and dose delivery (19).

A nationwide study in Japan on PBT for HCC demonstrated significant benefits, leading to government insurance coverage for this treatment (6). The study showcased promising results, particularly for tumors larger than 4 cm, with excellent outcomes regardless of tumor size, vascular invasion, or other factors. Our data, based on 12 surgery-inaccessible patients followed for a median of 13.1 months, aligns closely with the national study results. Despite the limited number of patients and follow-up time, our outcomes suggest SS-PBT is effective for HCC, even in challenging cases, with no treatment-related toxicities. SS-PBT performed well even for large tumors when combined with a real-time tracking or respiratory gating system.

Limitations of this study include the small number of patients and the short follow-up period as well as lack of communication about targeted therapy (20). Additionally,

robustness planning was not evaluated through actual treatment.

Conclusion

This preliminary study evaluated the effectiveness of SS-PBT for HCC. Although based on a small cohort, our findings align with larger studies, reinforcing the potential of SS-PBT as a valuable treatment option for HCC.

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This study received no external funding.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: Sachika Shiraishi, Koichi Tokuuye; Data curation: Yutaka Fujimoto, Sachika Shiraishi; Formal analysis: Sachika Shiraishi, Masahiro Yamanaka, Akihiro Yamano, Kazuki Matsumoto, Koichi Tokuuye; Investigation: Yutaka Fujimoto, Sachika Shiraishi; Project administration: Sachika Shiraishi; Resources: Yutaka Fujimoto, Sachika Shiraishi, Shintaro Shiba, Toshitaka Tsukiyama, Masahiro Kobayashi, Koichi Tokuuye; Supervision: Koichi Tokuuye; Visualization: Sachika Shiraishi; Writing – original draft: Yutaka Fujimoto, Sachika Shiraishi, Koichi Tokuuye; Writing – review & editing: all Authors.

References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3): 209-249, 2021. DOI: 10.3322/caac.21660

2 Rumgay H, Ferlay J, de Martel C, Georges D, Ibrahim AS, Zheng R, Wei W, Lemmens VEPP, Soerjomataram I: Global, regional and national burden of primary liver cancer by subtype. Eur J Cancer 161: 108-118, 2022. DOI: 10.1016/j.ejca.2021.11.023

3 Ng KKC, Chok KSH, Chan ACY, Cheung TT, Wong TCL, Fung JYY, Yuen J, Poon RTP, Fan ST, Lo CM: Randomized clinical trial of hepatic resection *versus* radiofrequency ablation for early-stage hepatocellular carcinoma. Br J Surg 104(13): 1775-1784, 2017. DOI: 10.1002/bjs.10677

4 Chiba T, Tokuuye K, Matsuzaki Y, Sugahara S, Chuganji Y, Kagei K, Shoda J, Hata M, Abei M, Igaki H: Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. Clin Cancer Res 11(10): 3799-3805, 2005. DOI: 10.1158/1078-0432.CCR-04-1350

5 Seo SH, Yu JI, Park HC, Yoo GS, Choi MS, Rhim H, Lee MW, Han S, Park B, Shim JS: Proton beam radiotherapy as a curative alternative to radiofrequency ablation for newly diagnosed hepatocellular carcinoma. Anticancer Res 44(5): 2219-2230, 2024. DOI: 10.21873/anticanres.17029

6 Mizumoto M, Ogino H, Okumura T, Terashima K, Murakami M, Ogino T, Tamamura H, Akimoto T, Waki T, Katoh N, Araya M, Onoe T, Takagi M, Iwata H, Numajiri H, Okimoto T, Uchinami Y, Maruo K, Shibuya K, Sakurai H: Proton beam therapy for hepatocellular carcinoma: multicenter prospective registry study in Japan. Int J Radiat Oncol Biol Phys 118(3): 725-733, 2024. DOI: 10.1016/j.ijrobp.2023.09.047

7 Chen H, Gogineni E, Cao Y, Wong J, Deville C, Li H: Real-time gated proton therapy: commissioning and clinical workflow for the Hitachi System. Int J Part Ther 11: 100001, 2024. DOI: 10.1016/j.ijpt.2024.01.001

8 Paganetti H: Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol 57(11): R99-117, 2012. DOI: 10.1088/0031-9155/57/11/R99

9 Inoue T, Widder J, van Dijk LV, Takegawa H, Koizumi M, Takashina M, Usui K, Kurokawa C, Sugimoto S, Saito AI, Sasai K, Van't Veld AA, Langendijk JA, Korevaar EW: Limited impact of setup and range uncertainties, breathing motion, and interplay effects in robustly optimized intensity modulated proton therapy for stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 96(3): 661-669, 2016. DOI: 10.1016/j.ijrobp.2016.06.2454

10 Fattori G, Zhang Y, Meer D, Weber DC, Lomax AJ, Safai S: The potential of Gantry beamline large momentum acceptance for real time tumour tracking in pencil beam scanning proton therapy. Sci Rep 10(1): 15325, 2020. DOI: 10.1038/s41598-020-71821-1

11 Jönsson M, Ceberg S, Nordström F, Thornberg C, Bäck SÅ: Technical evaluation of a laser-based optical surface scanning system for prospective and retrospective breathing adapted computed tomography. Acta Oncol 54(2): 261-265, 2015. DOI: 10.3109/0284186X.2014.948059

12 Shiba S, Shiraishi S, Tokuuye K, Shirata R, Omura M: Proton-beam Therapy for locally advanced hepatocellular carcinoma with inferior vena cava tumor thrombus: case report. In Vivo 38(4): 2080-2084, 2024. DOI: 10.21873/invivo.13667

13 Pflugfelder D, Wilkens JJ, Oelfke U: Worst case optimization: a method to account for uncertainties in the optimization of intensity modulated proton therapy. Phys Med Biol 53(6): 1689-1700, 2008. DOI: 10.1088/0031-9155/53/6/013
14 Sterpin E, Widesott L, Poels K, Hoogeman M, Korevaar EW, Lowe M, Molinelli S, Fracchiolla F: Robustness evaluation of pencil beam scanning proton therapy treatment planning: A systematic review. Radiother Oncol 197: 110365, 2024. DOI: 10.1016/j.radonc.2024.110365
15 Shimizu S, Miyamoto N, Matsuura T, Fujii Y, Umezawa M, Umegaki K, Hiramoto K, Shirato H: A proton beam therapy system dedicated to spot-scanning increases accuracy with moving tumors by real-time imaging and gating and reduces equipment size. PLoS One 9(4): e94971, 2014. DOI: 10.1371/journal.pone.0094971
16 Heinz C, Reiner M, Belka C, Walter F, Söhn M: Technical evaluation of different respiratory monitoring systems used for 4D CT acquisition under free breathing. J Appl Clin Med Phys 16(2): 4917, 2015. DOI: 10.1120/jacmp.v16i2.4917
17 Nankali S, Worm ES, Thomsen JB, Stick LB, Bertholet J, Høyer M, Weber B, Mortensen HR, Poulsen PR: Intrafraction tumor motion monitoring and dose reconstruction for liver pencil beam scanning proton therapy. Front Oncol 13: 1112481, 2023. DOI: 10.3389/fonc.2023.1112481
18 Shiraishi S, Yamanaka M, Shiba S, Tokuuye K: Assessing alimentary tract radiation in liver cancer treatment with proton beam therapy: a PET/CT imaging study. Jpn J Clin Oncol 54(11): 1180-1184, 2024. DOI: 10.1093/jjco/hyae085
19 Nishio T, Miyatake A, Ogino T, Nakagawa K, Saijo N, Esumi H: The development and clinical use of a beam ON-LINE PET system mounted on a rotating gantry port in proton therapy. Int J Radiat Oncol Biol Phys 76(1): 277-286, 2010. DOI: 10.1016/j.ijrobp.2009.05.065
20 Cheng JY, Huang BS, Chen YY, Wang CC, Chen YH: Combination of lenvatinib and proton beam therapy in the management of patients with advanced hepatocellular carcinoma. Anticancer Res 43(3): 1361-1371, 2023. DOI: 10.21873/anticanres.16284