

Interferon-alpha 2b: An Effective Treatment for Hepatic Epithelioid Hemangioendothelioma

Xiaolei Liu

China-Japan Friendship Hospital

Zhiying Yang (✉ yangzhy@aliyun.com)

China-Japan Friendship Hospital

Research Article

Keywords: liver, epithelioid hemangioendothelioma, interferon

Posted Date: June 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-531395/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Hepatic epithelioid hemangioendothelioma (HEH) is a rare tumor and no standard treatment has been established. This study was aimed to prospectively investigate the effect of interferon-alpha 2b (IFN-a 2b) for HEH patients.

Methods: Since March 2014, a total of 62 pathologically diagnosed HEH patients were followed up regularly. IFN-a 2b was suggested to HEH patients with progressed disease. Safety was assessed each month and tumor assessment scan was performed every 3 months. The primary end point was objective response rate (ORR) and disease control rate (DCR).

Results: A total of 42 HEH patients were finally included in this study. Median patient age was 35.5 years (range 18-65 years old). No severe (grade ≥ 3) adverse event (AE) of IFN-a 2b was reported in the whole group. The most common treatment-related AEs were fever (50.0%) and fatigue (21.4%). Two patients had grade 2 level hypothyroidism and 1 patient had grade 2 level of leukopenia and thrombocytopenia. Partial response and complete response were achieved in 20 (47.6%) and 2 (4.8%) patients, respectively, and the ORR was 52.4%. Stable disease was observed in 12 (28.6%) patients and the DCR was 81.0%. Progressive disease was observed in 8 (19.0%) patients. The 1, 3 and 5-year progression free rate were 81.0%, 69.2% and 62.3%, respectively. Only 1 patient died due to the progression of disease during the study. The 1, 3 and 5-year overall survival rate were 100%, 97.2% and 97.2%, respectively.

Conclusion: IFN-a 2b is a safe and effective treatment for HEH patients.

Background

Epithelioid hemangioendothelioma (EH) was initially described in 1982 by Weiss and Enzinger^[1] and it can involve both soft tissues and visceral organs, including liver, lung, spleen and heart. Hepatic epithelioid hemangioendothelioma (HEH) is an extremely rare tumor (estimated incidence of less than one in 1,000,000 worldwide) with a clinical course intermediate between benign hemangioma and angiosarcoma^[2]. Surgical resection, liver transplantation, chemotherapy, and immunotherapy have all been implemented in HEH patients. However, due to the scarcity of the disease and difficulty of patients' inclusion, prospective clinical trial is very hard to conduct. Liver transplantation has been reported to achieve a satisfying long-term survival for HEH patients^[3-7]. But the shortage of organ donation limits the accessibility of liver transplantation for most HEH patients, unless they are in critical condition. Clinical researches regarding to surgical resection, anti-angiogenesis drugs, chemotherapy or transarterial embolization (TAE) have been reported with indeterminate results^[8-11]. At present, no standard treatment has been established for HEH patients yet.

interferon-alpha 2b (IFN-a 2b) as an immunotherapy has been used for the treatment of hematological malignancies^[12]. IFN-a therapy for EH has also been proposed for tumor reduction and metastasis prevention^[9, 13, 14]. Since 2014, our team has been investigating HEH patients and a total of 62 are under

regular follow-up now. According to our previous experience, IFN-a 2b showed effective responses in some HEH patients, but the result needs prospective verification in a larger group of patients. This study was aimed to prospectively investigate the effect of IFN-a 2b in the treatment of HEH patients, which may provide valid evidence for future clinical practice.

Patients And Methods

Since March 2014, a total of 62 pathologically diagnosed HEH patients have been investigated and followed up regularly. As no standard treatment has been established for HEH, IFN-a 2b was suggested to HEH patients who have progressed disease or reoccurrence after previous treatment. The inclusion criteria comprised the following: histologically confirmed HEH; tumor progression or reoccurrence; at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors Committee (RECIST) criteria ^[15]; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.

Patients received IFN-a 2b 300 million units by subcutaneous injection once every other day. Tolerability and safety were assessed each month by interviewing and monitoring the blood cell counts, liver, thyroid and renal function until month 6 and then every 3 months. Tumor assessment scan including computed tomography (CT) and magnetic resonance imaging (MRI) was performed every 3 months and treatment decisions were based on RECIST. Treatment was continued until disease progression, development of unacceptable toxicity or termination of patients' decision. For HEH patients with extrahepatic metastases, the assessment was based on the intrahepatic lesions. The primary end point was objective response rate (ORR) and disease control rate (DCR). The secondary end points included 1, 3 and 5-year progression free rate and survival rate. Safety assessments consisted of the monitoring and recording of adverse event (AE) according to Common Terminology Criteria for Adverse Events version 4.03, laboratory evaluations and vital signs.

The study protocol was approved by the ethics committee of China-Japan Friendship Hospital, and the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Statistical Analysis

Progression free survival and overall survival were estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patients

Overall, a total of 62 HEH patients were regularly followed up in our clinic and 42 HEH patients with progressed disease or reoccurrence were finally included in this study. Median patient age was 36 years

(range 18–65 years old) and patients' gender was almost equally distributed (male 52.4% and female 47.6%). Tumor progression was observed in 25 patients during observation with no treatment and in 6 patients after the treatment of chemotherapy or TAE. Reoccurrence was detected in 11 patients after curatively intended surgery or radiofrequency ablation (RF). The median time between diagnosis and treatment of IFN-a 2b was 9 months (range 2–57 months).

At baseline, all 42 patients had ECOG PS 0 with no severe liver injury. Mild abdominal pain occurred in 9 patients, but no other symptom was recorded. Extrahepatic metastases were detected in 23 patients and 50% patients had lung metastases (Table 1).

Table 1
Baseline demographic and clinical characteristics of patients receiving IFN-a 2b (N = 42)

Characteristics	No. (%)
Age, years	
Median	36
Range	18–65
Gender	
Male	22 (52.4)
Female	20 (47.6)
Symptoms	
Abdominal pain	9 (21.4%)
None	33 (78.6%)
Number of Intrahepatic Lesions	
Multiple	40 (95.2)
Solitary	2 (4.8)
Involved disease sites	
Lung	21 (50.0)
Bone	2 (4.8)
Spleen	1 (2.4)
Abdomen	1 (2.4)
None	19 (45.2)
Inclusion reasons	
Progression with no treatment	25 (59.5)
Reoccurrence after surgery or RF	11 (26.2)
Failure of previous treatment	6 (14.3)
ECOG PS	
0	42 (100)
1	0 (0)

IFN-a 2b, interferon-alpha 2b; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase;

Characteristics	No. (%)
Serum Liver Function	
Range of ALT (Median), U/L	16–79 (24)
Range of AST (Median), U/L	8–83 (25)
Range of ALP (Median), U/L	25–226 (93)
Range of GGT (Median), U/L	7-177 (41)
Range of TB (Median), $\mu\text{mol/L}$	9.4–44.8 (12.7)
IFN-a 2b, interferon-alpha 2b; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase;	

Safety

No severe (grade ≥ 3) AE of IFN-a 2b was reported in the whole group. The most common treatment-related AEs were fever (50.0%) and fatigue (21.4%). Mostly, fever only occurred in the first several shots and disappeared one month later. Lasting fever was not recorded. The other AEs included leukopenia, thrombocytopenia, alopecia, rash, decreased appetite, anemia and hypothyroidism (Table 2). Two patients had grade 2 level hypothyroidism and 1 patient had grade 2 level of leukopenia and thrombocytopenia. Thirteen patients (31.0%) had no treatment-related AE. Treatment related AEs which led to the interruption of IFN-a 2b occurred in no patient.

Table 2
Treatment-related adverse events with IFN-a 2b

Adverse Events	No. (%)		
	Any Grade	Grade 1	Grade 2
Fever	21 (50.0)	21 (50)	0
Fatigue	9 (21.4)	9 (21.4)	0
Leukopenia	2 (4.8)	1 (2.4)	1 (2.4)
Thrombopenia	2 (4.8)	1 (2.4)	1 (2.4)
Rash	2 (4.8)	2 (4.8)	0
Alopecia	2 (4.8)	2 (4.8)	0
Hypothyroidism	2 (4.8)	0	2 (4.8)
Decreased appetite	1 (2.4)	1 (2.4)	0
Anemia	1 (2.4)	1 (2.4)	0
None	13 (31.0)	/	/
IFN-a 2b, interferon-alpha 2b;			

Efficacy

The median follow-up time since the beginning of IFN-a 2b was 33 months (range 3–76 months). The median duration of IFN-a 2b treatment was 19 months (range 3–48 months). In the 42 patients, partial response (PR) and complete response (CR) were achieved in 20 (47.6%) and 2 (4.8%) patients, respectively, and ORR was 52.4%. Stable disease (SD) was observed in 12 (28.6%) patients and DCR was 81.0%. Progressive disease (PD) was observed in 8 (19.0%) patients (Fig. 1).

For the 34 patients with disease control, treatment of IFN-a 2b has been terminated in 21 patients (PR 14, CR 2 and SD 5), and all of the termination was conducted according to patients' decision except for the 2 patients with CR. Treatment of IFN-a 2b is still continued in 13 patients (PR 6, SD 7). For the 8 patients with PD, targeted therapy was used in 4 patients, while the others chose to observe.

PD was detected in 4 of the 21 patients who stopped the treatment IFN-a 2b, and the time was 10, 12, 12 and 36 months after the termination of IFN-a 2b, respectively. The 1, 3 and 5-year progression free rate were 81.0%, 69.2% and 62.3%, respectively. Only 1 patient died due to the progression of disease during the study. The 1, 3 and 5-year survival rate were 100%, 97.2% and 97.2%, respectively (Fig. 2). The detailed information and radiological changes of the whole group were provided in Supplemental File 1 and 2.

Discussion

HEH is an extremely rare hepatic tumor with varying biological behavior. Currently, there is no effective indicator to predict the malignancy. For most HEH patients, the tumor progresses slowly with no severe clinical symptoms. Due to the rarity of the disease, HEH patients were commonly misdiagnosed as metastatic carcinoma. Although several studies have reported the radiological characteristics of HEH [16–19], confirmed diagnosis still rely on the pathological examination.

No standard treatment has been established for HEH patients yet. Liver transplantation was reported to be an effective treatment with acceptable long-term outcomes [4, 7, 20, 21]. However, the scarcity of organ donation limits the accessibility of liver transplantation for HEH patients. Surgical resection was another treatment option, but the long-term results were not well [22–24]. Moreover, curative surgery is implausible for most HEH patients because of the multicentricity of the tumor. Studies regarding to chemotherapy, targeted therapy or immunotherapy have been reported, but the results were undetermined [10, 25–32]. Thalidomide as anti-angiogenic therapy has also been reported to control tumor progression, but tumor response has seldom been achieved [8, 33–36].

IFN- α 2b as an immunotherapy has been used for the treatment of hematological malignancies [12]. IFN- α therapy for EH has also been proposed for tumor reduction and metastasis prevention [9, 13, 14]. Kayler et al reported that IFN- α was used for treatment of metastatic HEH after liver transplantation [37]. IFN- α has also been reported to have antiproliferative activity through cancer cell growth inhibition, activation of immune cells, inhibition of vascularization, and induction of cytokines [12, 38].

Since 2014, a total of 42 HEH patients with progressed disease have received the treatment of IFN- α 2b. In this study, PR and CR were observed in 22 patients with an ORR of 52.4%. SD was observed in 12 patients and the DCR was 81.0%. Based on our knowledge, this is the most effective medicine ever reported for HEH patients. Moreover, comparing to previous studies of liver transplantation which reported the 5-year survival rate of 70–83% [4, 7], the HEH patients in this study achieved a 5-year survival rate of 97.2%. Although the median follow-up time was only 33 months in this study, the tendency of better long-term survival could be speculated. Moreover, the safety of long-term treatment with IFN- α 2b was fully verified. The median duration of IFN- α 2b was 19 months and no severe (grade \geq 3) AE was recorded. Considering the risk of hypothyroidism, serum level of thyroxin should be monitored regularly. The anti-tumor mechanism of IFN- α 2b is not fully investigated or understood, but the encouraging result of this study will provide evidence-based treatment suggestion for HEH patients. Since EH also happens in other organs such as lung and bone, further clinical study could be designed to verify the effect of IFN- α 2b for other EH patients. However, due to the scarcity of EH, inclusion of patients would be a hard long-period work.

There are two major limitations about this study. First, the disease is so rare that the group of HEH patients live across the whole country. For some patients who are very far from our center, they prefer to perform regular blood tests and radiological examination in local medical institution, and send us the images and results, which could lead to the potential inaccuracy of radiological comparison. Second, the

IFN-a 2b that the HEH patients used were not from the same pharmaceutical company. They purchased the IFN-a 2b which local medical institution could provide and the dosage was the same. Although there are the limitations we mentioned above, the results of this study still provide valuable clinical evidence for the treatment of HEH.

Conclusion

IFN-a 2b is a safe and effective treatment for HEH patients. Because of the extreme scarcity of the disease, randomized clinical trial would be unrealistic. Although this was a single-arm study, the results still provided valuable clinical evidence for the treatment of HEH patients. The encouraging result of IFN-a 2b makes it a promising option for other EH patients and further clinical trial is needed.

Abbreviations

EH

Epithelioid hemangioendothelioma; HEH:Hepatic epithelioid hemangioendothelioma; TAE:Transarterial embolization; IFN-a 2b:Interferon-alpha 2b; RECIST:Response Evaluation Criteria in Solid Tumors Committee; ECOG PS:Eastern Cooperative Oncology Group performance status; CT:Computed tomography; MRI:Magnetic resonance imaging; ORR:Objective response rate; DCR:Disease control rate; AE:Adverse event; RF:Radiofrequency ablation; PR:Partial response; CR:Complete response; SD:Stable disease; PD:Progressive disease

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of China-Japan Friendship Hospital, and the study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Consent for publication

Not applicable.

Availability of data and materials

All the patients' detailed clinical information and imaging were included in the supplementary files.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' Contribution

Both XL and ZY contributed to the design and implementation of the study. XL was in charge of patients' follow-up and data collection. The manuscript was originally written by XL and corrected by ZY.

Acknowledgements

The authors want to thank all of the patients and their families for assisting in the implementation of this study.

References

1. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer*. 1982;50(5):970–81.
2. Sardaro A, Bardoscia L, Petruzzelli MF, Portaluri M. Epithelioid hemangioendothelioma: an overview and update on a rare vascular tumor. *Oncol Rev*. 2014;8(2):259.
3. Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, et al. Hepatic epithelioid hemangioendothelioma and adult liver transplantation: proposal for a prognostic score based on the analysis of the ELTR-ELITA registry. *Transplantation*. 2017;101(3):555–64.
4. Rodriguez JA, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: the UNOS experience from 1987 to 2005. *J Gastrointest Surg*. 2008;12(1):110–6.
5. Nudo CG, Yoshida EM, Bain VG, Marleau D, Wong P, Marotta PJ, et al. Liver transplantation for hepatic epithelioid hemangioendothelioma: the Canadian multicentre experience. *Can J Gastroenterol*. 2008;22(10):821–4.
6. Nathan H, Pawlik TM. Limitations of claims and registry data in surgical oncology research. *Ann Surg Oncol*. 2008;15(2):415–23.
7. Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, et al. The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma: report of the European liver transplant registry. *Ann Surg*. 2007;246(6):949–57.
8. Mascarenhas RCV, Sanghvi AN, Friedlander L, Geyer SJ, Beasley HS, Van Thiel DH. Thalidomide inhibits the growth and progression of hepatic epithelioid hemangioendothelioma. *Oncology*. 2004;67(5–6):471–5.
9. Galvao FHF, Bakonyi-Neto A, Machado MAC, Farias AQ, Mello ES, Diz ME, et al. Interferon alpha-2B and liver resection to treat multifocal hepatic epithelioid hemangioendothelioma: a relevant approach to avoid liver transplantation. *Transplant Proc*. 2005; 37(10): 4354–4358.
10. Idilman R, Dokmeci A, Beyler AR, Bastemir M, Ormeci N, Aras N, et al. Successful medical treatment of an epithelioid hemangioendothelioma of liver. *Oncology*. 1997;54(2):171–5.

11. St Peter SD, Moss AA, Huettl EA, Leslie KO, Mulligan DC. Chemoembolization followed by orthotopic liver transplant for epithelioid hemangioendothelioma. *Clin Transplant*. 2003;17(6):549–53.
12. Zhang L, Tai YT, Ho MZG, Qiu L, Anderson KC. Interferon-alpha-based immunotherapies in the treatment of B cell-derived hematologic neoplasms in today's treat-to-target era. *Exp Hematol Oncol*. 2017;6:20.
13. Calabrò L, Di Giacomo AM, Altomonte M, Fonsatti E, Mazzei MA, Volterrani L, et al. Primary hepatic epithelioid hemangioendothelioma progressively responsive to interferon-alpha: is there room for novel anti-angiogenetic treatments? *J Exp Clin Cancer Res*. 2007;26(1):145–50.
14. Radzikowska E, Szczepulska-Wójcik E, Chabowski M, Oniszh K, Langfort R, Roszkowski K. Pulmonary epithelioid haemangioendothelioma – interferon 2-alpha treatment – case report. *Pneumonol Alergol Pol*. 2008;76(4):281–5.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92:205–16.
16. Amin S, Chung H, Jha R. Hepatic epithelioid hemangioendothelioma: MR imaging findings. *Abdom Imaging*. 2011;36(4):407–14.
17. Azzam RI, Alshak NS, Pham HP. AIRP best cases in radiologic-pathologic correlation: hepatic epithelioid hemangioendothelioma. *Radiographics*. 2012;32(3):789–94.
18. Chen Y, Yu RS, Qiu LL, Jiang DY, Tan YB, Fu YB. Contrast-enhanced multiple phase imaging features in hepatic epithelioid hemangioendothelioma. *World J Gastroenterol*. 2011;17(30):3544–53.
19. Lin J, Ji Y. CT and MRI diagnosis of hepatic epithelioid hemangioendothelioma. *Hepatobiliary Pancreat Dis Int*. 2010;9(2):154–8.
20. Agrawal N, Parajuli S, Zhao P, Satoskar R, Laurin J, Azumi N, et al. Liver transplantation in the management of hepatic epithelioid hemangioendothelioma: a single-center experience and review of the literature. *Transplant Proc*. 2011; 43(7): 2647–2650.
21. Fang C, Zhang W, Zheng S. Liver transplantation for hepatic epithelioid hemangioendothelioma: a case report and literature review. *Int J Clin Exp Med*. 2017;10(6):9693–6.
22. Jung DH, Hwang S, Hong SM, Kim KH, Lee YJ, Ahn CS, et al. Clinicopathological Features and Prognosis of Hepatic Epithelioid Hemangioendothelioma After Liver Resection and Transplantation. *Ann Transplant*. 2016;21:784–90.
23. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery*. 1991;110(4):726–34.
24. Lerut JP, Orlando G, Sempoux C, Ciccarelli O, Van Beers BE, Danse E, et al. Hepatic haemangioendothelioma in adults: excellent outcome following liver transplantation. *Transpl Int*. 2004;17(4):202–7.
25. Grotz TE, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? *HPB (Oxford)*. 2010; 12(8): 546–553.

26. Soape MP, Verma R, Payne JD, Wachtel M, Hardwicke F, Cobos E. Treatment of Hepatic Epithelioid Hemangioendothelioma: Finding Uses for Thalidomide in a New Era of Medicine. *Case Rep Gastrointest Med.* 2015; 2015: 326795.
27. Chevreau C, Le Cesne A, Ray-Coquard I, Italiano A, Cioffi A, Isambert N, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). *Cancer.* 2013;119(14):2639–44.
28. Kobayashi N, Shimamura T, Tokuhisa M, Goto A, Ichikawa Y. Sorafenib Monotherapy in a Patient with Unresectable Hepatic Epithelioid Hemangioendothelioma. *Case Rep Oncol.* 2016;9(1):134–7.
29. Sangro B, Iñarrairaegui M, Fernández-Ros N. Malignant epithelioid hemangioendothelioma of the liver successfully treated with Sorafenib. *Rare Tumors.* 2012;4(2):e34.
30. Pinet C, Magnan A, Garbe L, Payan MJ, Vervloet D. Aggressive form of pleural epithelioid haemangioendothelioma: complete response after chemotherapy. *Eur Respir J.* 1999;14(1):237.
31. Woo JH, Kim TJ, Lee KS, Kim TS, Kim BT. Epithelioid hemangioendothelioma in the thorax: clinicopathologic, CT, PET, and prognostic features. *Medicine.* 2016;95(30):e4348.
32. Agulnik M, Yarber JL, Okuno SH, von Mehren M, Jovanovic BD, Brockstein BE, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. *Ann Oncol.* 2013;24(1):257–63.
33. Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. *Clin Ther.* 2003;25(2):342–95.
34. Kassam A, Mandel K. Metastatic hepatic epithelioid hemangioendothelioma in a teenage girl. *J Pediatr Hematol Oncol.* 2008;30(7):550–2.
35. Raphael C, Hudson E, Williams L, Lester JF, Savage PM. Successful treatment of metastatic hepatic epithelioid hemangioendothelioma with thalidomide: a case report. *J Med Case Rep.* 2010;4:413.
36. Salech F, Valderrama S, Nervi B, Rodriguez JC, Oksenberg D, Koch A, et al. Thalidomide for the treatment of metastatic hepatic epithelioid hemangioendothelioma: a case report with a long term follow-up. *Ann Hepatol.* 2011;10(1):99–102.
37. Kayler LK, Merion RM, Arenas JD, Magee JC, Campbell DA, Rudich SM, et al. Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. *Transplantation.* 2002;74(1):128–30.
38. Asmana NR. Human interferon alpha-2b: a therapeutic protein for cancer treatment. *Scientifica (Cairo).* 2014; 2014: 970315.

Figures

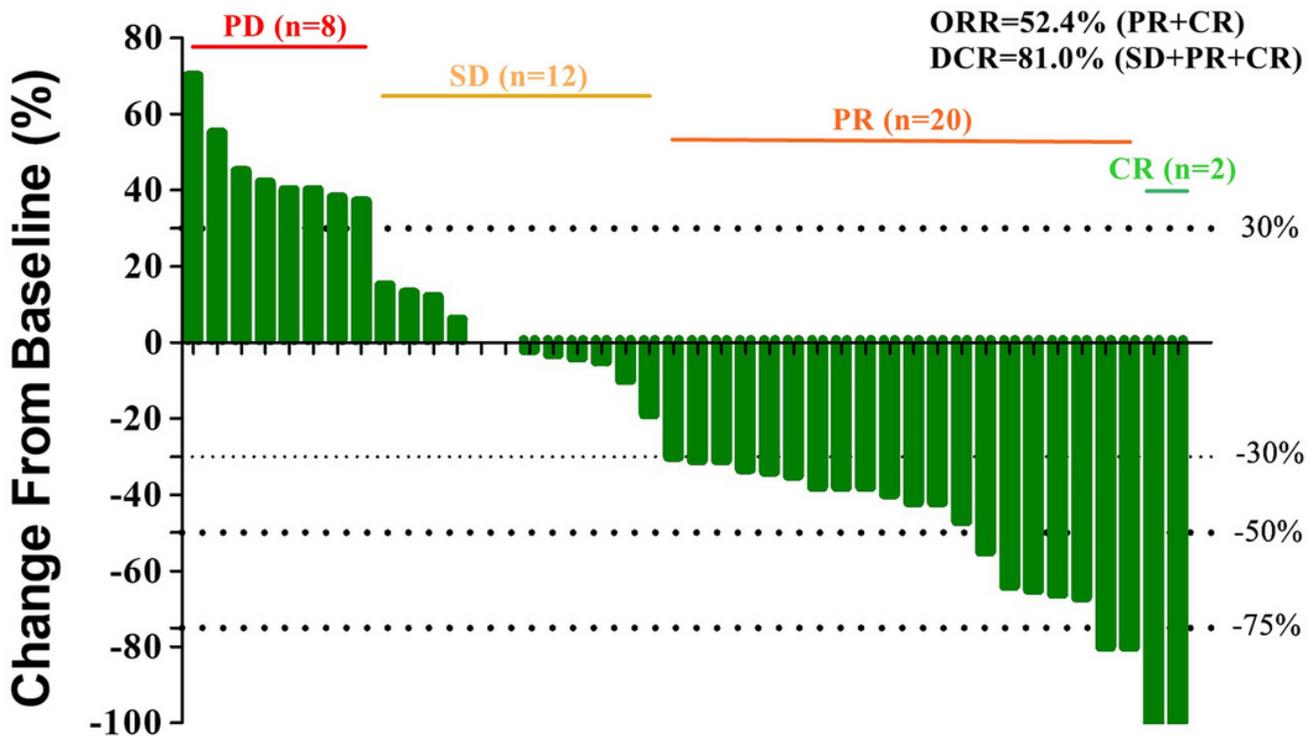


Figure 1

Percentage change from baseline in sums of diameters of target lesions by RECIST. CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

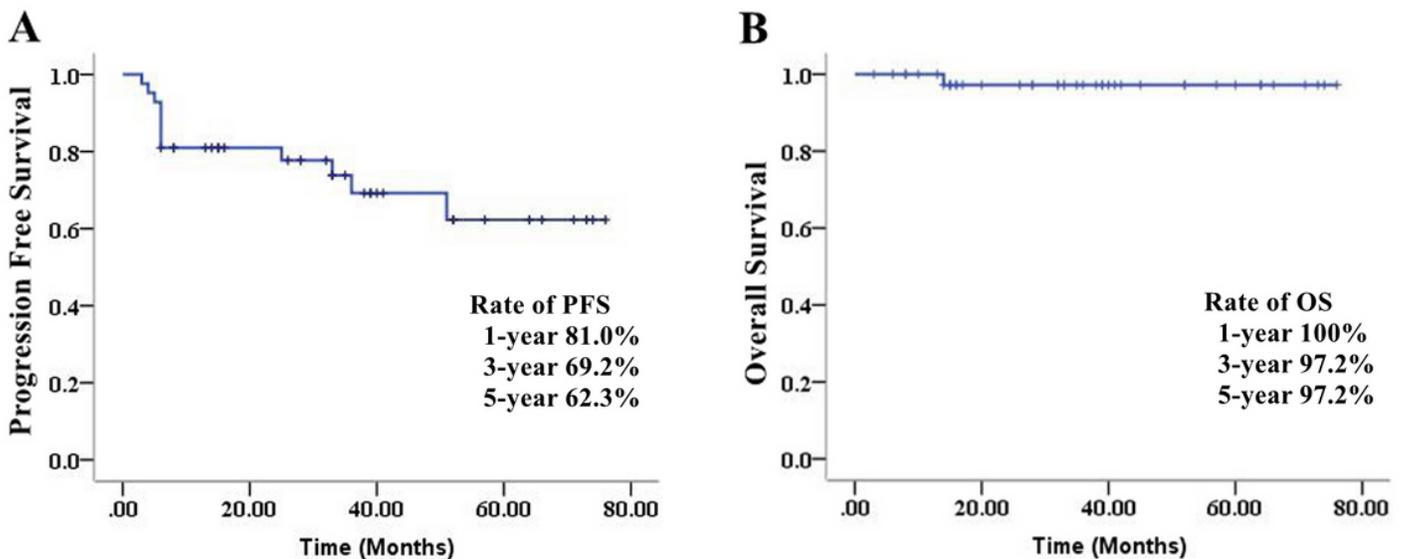


Figure 2

Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalFile1.xlsx](#)
- [SupplementalFile2.pdf](#)