EJMI

DOI: 10.14744/ejmi.2025.80526
EJMI 2025;9(1):29–35

Research Article

Evaluation of Pancreatic Atrophy in Patients with Hepatocellular Carcinoma Receiving Sorafenib Treatment

Ali Kaan Güren,[1] Gülçin Zengin,[2] Nargiz Majidova,[3] Nadiye Sever,[1] Rabia Ergelen,[2] Osman Köstek,[1] İbrahim Vedat Bayoğlu,[1] Murat Sarı[1]

[1]Division of Medical Oncology, Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Türkiye
[2]Department of Radiology, Marmara University Faculty of Medicine, Istanbul, Türkiye
[3]Department of Medical Oncology, VM Medical Park Maltepe Hospital, Istanbul, Türkiye

Abstract

Objectives: Sorafenib is frequently utilized both as first-line treatment where immunotherapies are inaccessible and as subsequent treatment in cases of progression with immunotherapy-based therapies in unresectable/metastatic HCC patients. We aim to reveal the relationship between sorafenib treatment and pancreatic atrophy.

Methods: The study was designed as a retrospective, single-center study. Patients with HCC who had a CT scan within 1 month before and 6 months after treatment were included in the study. Patients receiving 6 months of sorafenib were included in the sorafenib group, while patients receiving other treatments were included in the control group. Delta (Δ) value was found by subtracting the baseline pancreatic volume from the 6th month pancreatic volume. Baseline, 6-month and delta pancreatic volumes were compared between the two groups.

Results: 22 patients were included in the sorafenib group and 22 patients in the control group. Delta pancreas volume was 12.69±12.96 cm^3 in the sorafenib group and 1.10±2.83 cm^3 in the control group and this difference was statistically significant ($p<0.001$).

Conclusion: In our study, the incidence of pancreatic atrophy increased in sorafenib group compared to control group. Particularly in patients receiving sorafenib with prolonged survival, attention should be maintained in terms of pancreatic atrophy.

Keywords: Sorafenib, pancreatic atrophy, hepatocellular carcinoma

Cite This Article: *Güren AK, Zengin G, Majidova N, Sever N, Ergelen R, Köstek O. Evaluation of Pancreatic Atrophy in Patients with Hepatocellular Carcinoma Receiving Sorafenib Treatment. EJMI 2025;9(1):29–35.*

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver. It usually arises from a background of chronic liver disease and has an poor prognosis.[1] In the treatment of early stage disease, local ablative therapies (radiofrequency ablation (RFA), microwave ablation (MWA), transarterial chemoembolization (TACE) and bland embolization, transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT)) are successfully applied in addition to surgery.[2] In advanced disease (unresectable or metastatic), systemic therapies (tyrosine kinase inhibitors (TKI), immune checkpoint inhibitors, conventional chemotherapy) are used.[3,4]

Sorafenib is a multikinase inhibitor. It acts by inhibiting Raf-1 and B-Raf serine-threonine kinases and receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, 3 and platelet-derived growth factor re-

Address for correspondence: Ali Kaan Güren, MD. Division of Medical Oncology, Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Türkiye
Phone: +90 530 725 00 18 **E-mail:** alikaanguren@gmail.com

Submitted Date: February 10, 2025 **Revision Date:** March 05, 2025 **Accepted Date:** March 07, 2025 **Available Online Date:** April 11, 2025

ceptor β (PDGFR-β).[5,6] Sorafenib has been successfully used in the treatment of HCC for a long time in the treatment of HCC following the results of SHARP, Asia-Pacific and GIDEON studies.[7-9] However, it causes many side effects including diarrhea, fatigue, nausea and vomiting, rash, hand-foot skin reaction, stomatitis and hypertension[7-8]

Pancreatic atrophy is characterized by a reduction in pancreatic volume and may occur in various conditions such as aging, malnutrition, chronic pancreatitis, and diabetes. It can lead to a range of exocrine and endocrine insufficiency symptoms, including steatorrhea, weight loss, malabsorption, vitamin deficiencies, and diabetes.[10,11] Tyrosine kinase inhibitors (TKIs) are thought to contribute to pancreatic atrophy by inducing hypoxia through their anti-angiogenic effects and by suppressing cellular proliferation.[12,13]

Despite many new treatments for HCC, survival is still not as expected. In countries with limited availability of other therapies, sorafenib is still used as first-line treatment. In addition, sorafenib is used as an important alternative in second-line treatment after progression in patients in whom immunotherapies are used in the first-line setting. In this respect, the side effects of sorafenib should be clearly defined. The data in the literature regarding whether sorafenib induces pancreatic atrophy are limited. Based on this, we aim to investigate the potential association between sorafenib treatment and pancreatic atrophy.

Methods

Study Population and Data Collection

The study was designed as a retrospective, single-center study. Patients who received treatment for HCC at the Medical Oncology Clinic of Marmara University Pendik Training and Research Hospital between 01.01.2016 and 31.12.2024 were included in the study. Data of the patients were analyzed using patient files and hospital electronic information system. Sorafenib treatment was started at 800mg/day peroral. According to side effects, dose titration was performed as 600mg and 400mg, respectively.

Child-Pugh score, total bilirubin (1 point: <2 mg/dL, 2 points: 2-3 mg/dL, 3 points: >3 mg/dL), albumin (1 point: >3.5 g/dL, 2 points: 2.8-3.5 g/dL, 3 points: <2.8 g/dL), International Normalized Ratio (INR) (1 point: <1. 7, 2 points: 1.7-2.3, 3 points: >2.3), ascites (1 point: none, 2 points: mild, 3 points: moderate-severe) and hepatic encephalopathy (1 point: none, 2 points: grade 1-2, 3 points: grade 3-4). According to the Child-Pugh classification, a total score of 5–6 points corresponds to class A, 7–9 points to class B, and 10–15 points to class C. Performance scores were calculated using the Eastern Cooperative Oncology Group Performance Score (ECOG PS).

Pancreatic volume measurements were performed using a semi-automated software (Philips IntelliSpace Portal, Version 5.0, Philips Healthcare, A msterdam, Netherlands) from images with a slice thickness of 5 mm obtained in the portal venous phase with a 256- and 128-slice CT scanner.

Study Design

Patients with HCC who had a CT scan within 1 month before and 6 months after treatment were included in the study. Patients who had received sorafenib for at least 6 months were included in the sorafenib group. A control group was randomly assigned to patients who had never received sorafenib and received chemotherapy or immunotherapy and/or bevacizumab. Delta (Δ) value was found by subtracting the baseline pancreatic volume from the 6th month pancreatic volume. Baseline, 6-month and Delta pancreatic volumes were compared between the two groups.

Statistical Analysis

SPSS version 22.0 (IBM corp.) was analyzed for all statistics. While evaluating the study data, the conformity of the parameters to normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro Wilks tests. In the analysis of continuous variables between two groups, Independent Samples t-test was used if the data were normally distributed and Mann-Whitney U Test was used if the data were not normally distributed. Significance was evaluated at $p<0.05$ level.

Results

A total of 190 HCC patients were screened. There were 32 patients who received sorafenib for 6 months or longer. Of these, 22 patients had CT scans taken before and 6 months after treatment. The sorafenib group included 22 patients and the control group included 22 patients. The median age was 64 years in the sorafenib group and 63 years in the control group. There were 12 males in the sorafenib group and 13 males in the control group.

Hepatitis B virus (HBV) was diagnosed in 63.6% (n=14) in the sorafenib group and 59.1% (n=13) in the control group. Hepatitis C virus (HCV) was diagnosed in 9.1% (n=2) in the sorafenib group and 13.6% (n=3) in the control group. HBV and Hepatitis D virus (HDV) together were diagnosed in 4.5% (n=1) in both groups. The number of cases with unknown cause was 22.7% (n=5) in the sorafenib group and 18.1% (n=4) in the control group. There was no statistically significant difference between the two groups for all these variables. In the sorafenib arm, 12 patients had 1 dose reduction (600mg) and 4 patients had 2 dose reductions (400mg). Baseline characteristics of the patients are displayed in Table 1. In the control group, 18 patients received atezolizumab plus bevacizumab, 3 patients received

Table 1. Baseline Characteristics

	Sorafenib Group (n=22)	Control Group (n=22)	P
Age (min-max)	64 (43-85)	63 (51-78)	0.274*
Gender (%)			
Male	12 (54.5)	13 (59)	0.764**
Female	10 (45.5)	9 (41)	
Etiology (%)			
HBV	14 (63.6)	13 (59.1)	0.719**
HCV	2 (9.1)	3 (13.6)	
HBV and HDV	1 (4.5)	1 (4.5)	
Alcohol	0 (0)	1 (4.5)	
Unknown	5 (22.7)	4 (18.1)	
Child-Turcotte-Pugh Score (%)			
5	16 (72.7)	17 (77.2)	0.871**
6	4 (18.1)	4 (18.1)	
7	2 (9.1)	1 (4.5)	
ECOG PS (%)			
0-1	19 (86.3)	20 (90.1)	0.962**
2	3 (13.6)	2 (9.1)	
Sorafenib Treatment Line (%)			-
First Line	8 (36.3)	-	
Second Line	14 (63.6)	-	
Sorafenib Dose Reduction (%)			-
800mg	6 (27.2)	-	
600mg	12 (54.5)	-	
400mg	4 (18.1)	-	

*Independent Samples Test; ** Mann-Whitney U Test; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HDV: Hepatitis D Virus; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

tremelimumab plus durvalumab and 1 patients received chemotherapy.

Fatigue (45.4%), diarrhea (31.8%), nausea and vomiting (22.7%), rash (18.1%), thyroiditis (13.6%), hand-foot syndrome (9.1%), hoarseness (4.5%), stomatitis (4.5%) and proteinuria (4.5%) were observed in patients receiving sorafenib. These findings are shown in Table 2.

Baseline and 6-month pancreatic volume measurements and volume changes of the patients according to the groups are displayed in Figure 1. The baseline pancreas volume was 82.92±14.89 cm^3 in the sorafenib group and 83.29±13.58 cm^3 in the control group. The 6th month pancreas volume was 70.23±15.83 cm^3 in the sorafenib group and 82.18±13.83 cm^3 in the control group. There was no statistically significant difference between the two groups for these two variables (p=0.559, p=227; p>0.05, respectively). Delta pancreas volume was 12.69±12.96 cm^3 in the sorafenib group and 1.10±2.83 in the control group and this difference was statistically significant (p<0.001). The changes in pancreatic volume in an sample patient are displayed in Figure 2. These findings are displayed in Table 3.

Table 2. Sorafenib-related adverse events

	n=22, (%)
Fatigue	10 (45.4)
Diarrhea	7 (31.8)
Nausea and vomiting	5 (22.7)
Rash	4 (18.1)
Thyroiditis	3 (13.6)
Hand-foot syndrome	2 (9.1)
Hoarseness	1 (4.5)
Stomatitis	1 (4.5)
Proteinuria	1 (4.5)

Discussion

Sorafenib has been utilized frequently as a systemic multikinase inhibitor in patients with advanced HCC and various side effects have been observed with its long-term use. In our study, sorafenib treatment was associated with the development of pancreatic atrophy after 6 months in patients with advanced HCC. The majority of clinical symptoms observed in HCC patients are due to the primary liver disease

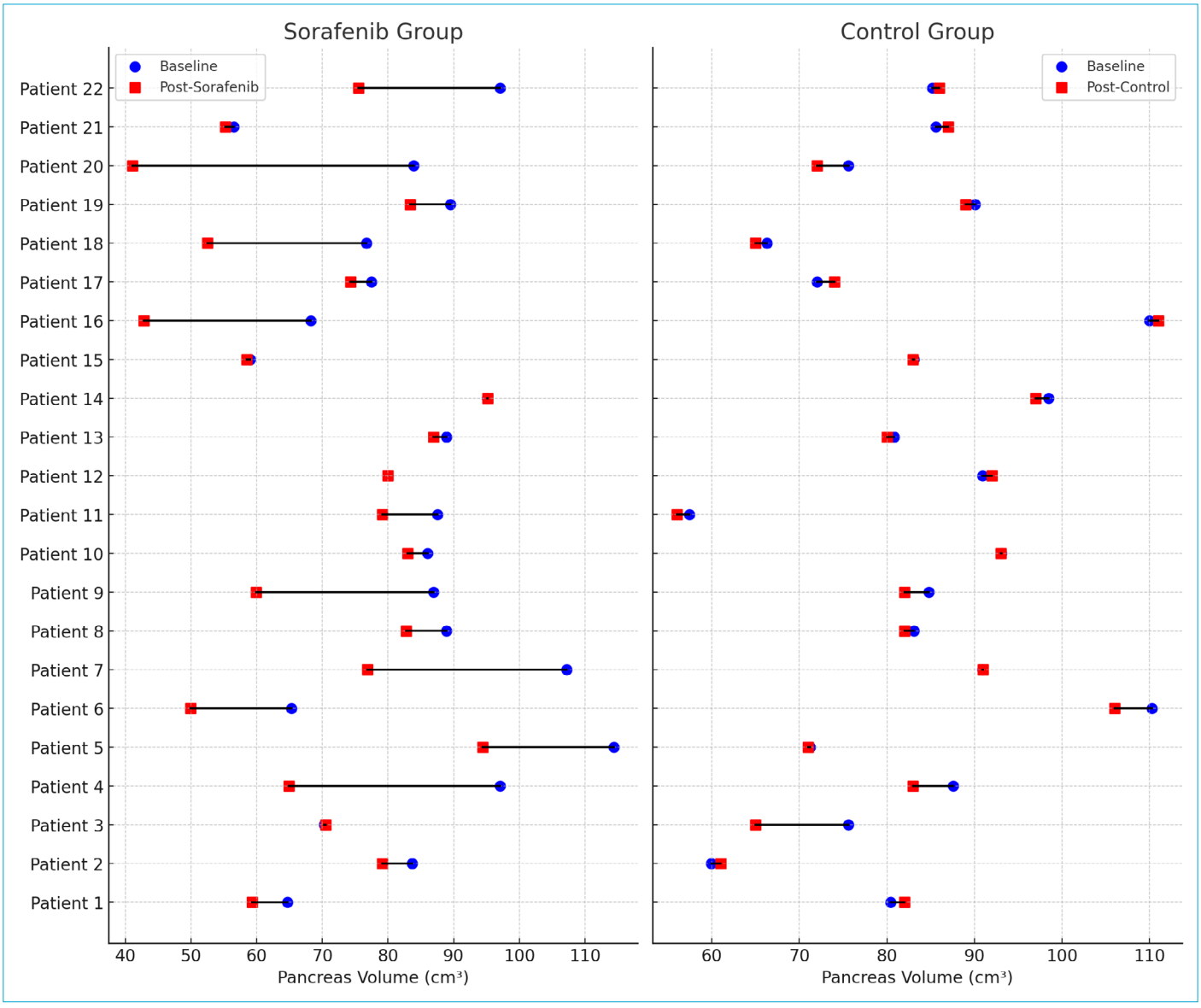

Figure 1. Alterations in pancreatic volumes in sorafenib and control groups.

itself or tumor progression, and the potential adverse effects of sorafenib may be masked by this condition. Therefore, it is important to consider changes in pancreatic morphology in the routine evaluation of patients on sorafenib, especially for early recognition of possible treatment-related complications.

Previous studies have demonstrated the development of pancreatic atrophy in patients receiving sorafenib.[14–16] In one such study compared pancreatic volume changes across three groups: sorafenib, bevacizumab plus chemotherapy, and chemotherapy alone. Significant pancreatic

Table 3. Pancreas Volume Measurement Results

	Sorafenib Group (n=22) Mean±SD	Control Group (n=22) Mean±SD	p
Baseline Pancreas Volume (cm³)	82.92±14.89	83.29±13.58	0.559*
Post Sorefenib Pancreas Volume (cm³)	70.23±15.83	82.18±13.83	0.227*
Delta (Δ) Pancreas Volume (cm³)	12.69±12.96	1.10±2.83	<0.001**

*Independent Samples Test; ** Mann-Whitney U Test.

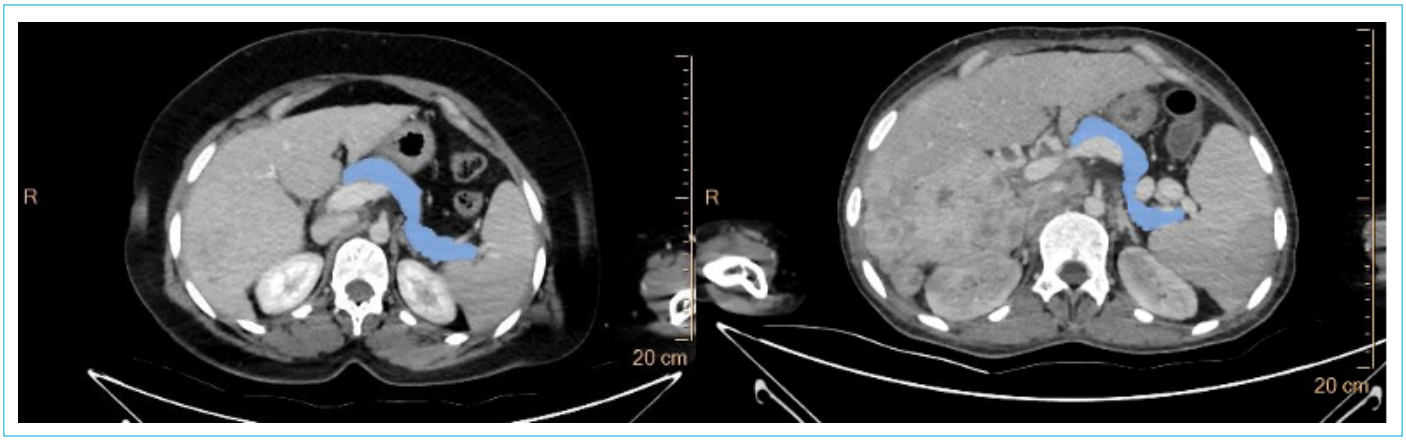

Figure 2. Alteration in pancreatic volume in patient.

volume reduction was observed in patients treated with sorafenib or bevacizumab-containing regimens, whereas this change was not statistically significant in those receiving chemotherapy alone.[17] A separate investigation focused on the occurrence of malabsorption in HCC patients under sorafenib, its possible link to pancreatic insufficiency, and the therapeutic role of pancreatic enzyme supplementation. The study found that approximately 10% of patients experienced malabsorption associated with pancreatic insufficiency, and enzyme supplementation led to complete symptom resolution and stabilization of pancreatic volume.[18] Another study, overall survival was found to be longer in hepatocellular carcinoma (HCC) patients who developed pancreatic atrophy after more than two years of sorafenib treatment, compared to those who did not.[16] In our study, we also observed a significant reduction in pancreatic volume among patients treated with sorafenib compared to other treatment groups. Pancreatic atrophy and insufficiency should be considered, particularly in patients presenting with gastrointestinal symptoms.

Sorafenib causes numerous adverse events including hand-foot syndrome, diarrhea, loss of appetite, nausea, vomiting, hypertension, thrombocytopenia, leukopenia, hepatotoxicity, hypothyroidism, fatigue and proteinuria.[7,8,19] Although various adverse events are manageable, 11.4% of 149 patients treated with sorafenib in the Asia-Pacific study required dose reduction due to hand-foot skin reaction and 7.4% due to diarrhea.[8] In the SHARP study, treatment was discontinued in 38% patients due to adverse events, while dose reduction was performed in 26% patients.[7] In our study, dose reduction was performed in 72% patients. Sorafenib is a difficult treatment to tolerate and management of adverse events is very crucial. In this respect, adverse events should be defined.

In the IMBRAVE-150 study evaluating the efficacy of atezolumab plus bevacizumab combination in patients with advanced HCC who had not received systemic treatment before, progression free survival (PFS) was 6.8 months and overall survival (OS) was 19.2 months in the atezolumab plus bevacizumab arm, while PFS was 4.3 months and OS 13.4 months in the sorafenib arm.[20] In the HIMALAYA study conducted in advanced HCC patients who had not received systemic therapy before, PFS was 3.78 months and OS 16.4 months with tremelimumab + durvalumab, while PFS was 4.07 months and OS 13.8 months with sorafenib.[21] In the CheckMate 459 study, there was no difference in OS between nivolumab and sorafenib in patients with advanced HCC who did not receive systemic therapy (16.4 months vs 14.7 months).[22] Although the successful results of the IMBRAVE-150 study put the combination of atezolumab plus bevacizumab ahead of sorafenib, no significant difference was found between the survival differences in other studies. Therefore, sorafenib continues to be used as first-line treatment in low-income countries due to medication costs. For these considerations, we believe that sorafenib is still a treatment that should not be disregarded.

In the DECISION study, the efficacy of sorafenib in Radioactive Iodine-Resistant Differentiated Thyroid Cancer (DTC) was investigated and PFS was found to be 10.8 months versus 5.8 months.[23] In other studies, sorafenib was found superior to chemotherapy in patients with DTC.[24] In a study investigating the efficacy of sorafenib in desmoid tumors, 2-year PFS was found to be 81%.[25] In patients with longer expected survival, more attention should be paid to sorafenib side effects, especially pancreatic atrophy.

The limitations of our study were the limited number of patients and the inability to calculate the cumulative doses

of all patients. Especially because of the limited number of patients, the characteristics of patients with pancreatic atrophy and the factors that may affect atrophy could not be analyzed in detail. In addition, the long-term effects of atrophy could not be demonstrated because only HCC patients were included in our study and because of the expected survival in HCC patients.

In conclusion, since HCC is a disease with a highly aggressive course, numerous adverse events that may develop may be masked by the clinic of the primary disease. Especially in patients receiving sorafenib who are in favorable condition and have a longer survival expectancy, attention should be paid in terms of pancreatic atrophy.

Disclosures

Ethics Committee Approval: Approved by the Marmara University Faculty of Medicine Ethics Committee on 09 February 2024 with protocol number 02.2024.174.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.K.G.; Design – A.K.G., G.Z.; Supervision –O.K.; Materials – N.M., N.S.; Data collection & processing – G.Z., R.E.; Analysis and/or interpretation – A.K.G.; Literature search –A.K.G.; Writing – A.K.G.; Critical review – O.K., İ.V.B., M.S.

References

1. Nagaraju GP, Dariya B, Kasa P, Peela S, El-Rayes BF. Epigenetics in hepatocellular carcinoma. Semin Cancer Biol 2022;86(3):622–32.
2. Brown ZJ, Tsilimigras DI, Ruff SM, Mohseni A, Kamel IR, Cloyd JM, et al. Management of hepatocellular carcinoma: a review. JAMA Surg 2023;158(4):410–20.
3. Alawyia B, Constantinou C. Hepatocellular carcinoma: A narrative review on current knowledge and future prospects. Curr Treat Options Oncol 2023;24(7):711–24.
4. Wen N, Cai Y, Li F, Ye H, Tang W, Song P, et al. The clinical management of hepatocellular carcinoma worldwide: A concise review and comparison of current guidelines: 2022 update. Biosci Trends 2022;16(1):20–30.
5. Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006;66(24):11851–8.
6. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. 43-9006 Exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64(19):7099–109.
7. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378–90.
8. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10(1):25–34.
9. Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, et al. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with sorafeNib): Second interim analysis. Int J Clin Pract 2014;68(5):609–17.
10. Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: A review. JAMA 2019;322(24):2422–34.
11. Löhr JM, Panic N, Vujasinovic M, Verbeke CS. The ageing pancreas: A systematic review of the evidence and analysis of the consequences. J Intern Med 2018;283(5):446–60.
12. Takahashi H, Nasu K, Minami M, Kojima T, Nishiyama H, Ishiguro T, et al. Organ atrophy induced by sorafenib and sunitinib - quantitative computed tomography (CT) evaluation of the pancreas, thyroid gland and spleen. Pol J Radiol 2016;81:557–65.
13. Shinagare AB, Steele E, Braschi-Amirfarzan M, Tirumani SH, Ramaiya NH. Sunitinib-associated pancreatic atrophy in patients with gastrointestinal stromal tumor: A toxicity with prognostic implications detected at imaging. Radiology 2016;281(1):140–9.
14. Ganten MK, Schuessler M, Bruckner T, Ganten TM, Koschny R. Pancreatic atrophy in hepatocellular carcinoma patients receiving long-term treatment with sorafenib. Oncology 2015;89(2):88–94.
15. Hescot S, Vignaux O, Goldwasser F. Pancreatic atrophy—a new late toxic effect of sorafenib. N Engl J Med 2013;369(15):1475–6.
16. Xu L, Zhou DS, Zhao J, Spolverato G, Zhang YJ, Li SP, et al. Long-term therapy with sorafenib is associated with pancreatic atrophy. J Surg Res 2015;199(2):314–21.
17. Phillip V, Zahel T, Bärtl K, Rasch S, Ebert O, Schmid RM, et al. Influence of sorafenib and bevacizumab on pancreatic volume—a monocentric CT based analysis. Pancreatology 2016;16(4):621–4.
18. Díaz-González Á, Belmonte E, Sapena V, Sanduzzi-Zamparelli M, Darnell A, Díaz A, et al. Pancreatic insufficiency in patients under sorafenib treatment for hepatocellular carcinoma. J Clin Gastroenterol 2021;55(3):263–70.
19. Abdel-Rahman O, Lamarca A. Development of sorafenib-related side effects in patients diagnosed with advanced hepatocellular carcinoma treated with sorafenib: A systematic-review and meta-analysis of the impact on survival. Expert Rev Gastroenterol Hepatol 2017;11(1):75–83.
20. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382(20):1894–905.

21. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Ann Oncol 2024;35(5):448–57.
22. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): A randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23(1):77–90.
23. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 3 trial. Lancet 2014;384(9940):319–28.
24. Majidova N, Aghamaliyeva S, Guliyev M, Dinc G, Akyıldız A, Ozcan E, et al. Sorafenib vs chemotherapy in the treatment of locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer: Real-world data from Turkey. J Chemother 2024;[Epub ahead of print]:1–6.
25. Gounder MM, Mahoney MR, Van Tine BA, Ravi V, Attia S, Deshpande HA, et al. Sorafenib for advanced and refractory desmoid tumors. N Engl J Med 2018;379(25):2417–28.