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CASE REPORT

Rare Gingival Metastasis Occurring After Conversion Therapy Followed by Resection of Initially Unresectable Hepatocellular Carcinoma: A Case Report

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Abstract: Gingival metastases from hepatocellular carcinoma (HCC) are exceedingly rare and highly prone to be misdiagnosed without biopsy. Here, we report an initially unresectable HCC patient who received effective conversion therapy but discovered gingival metastasis within one-month post-hepatectomy. A 53-year-old male with a huge liver tumor diagnosed as unresectable HCC received conversion therapy of hepatic arterial infusion chemotherapy (HAIC) combined with lenvatinib and tislelizumab. During the conversion therapy, he experienced sore gingiva which was regarded as a side effect of lenvatinib. Considering the significant shrinkage of tumor after 10-month treatment, salvage resection was conducted with negative margin and no postoperative complications. Gingival oligometastases were identified and resected half month after surgery. Throughout the 1-year follow-up period, the patient remained alive; however, there was a recurrence of the gingival metastasis at the same site six months postoperatively. Hence, clinicians should regard gingival swelling and pain not merely as potential adverse events of conversion therapy but also as potential indicators of gingival metastasis.

Keywords: hepatocellular carcinoma, conversion therapy, gingival metastasis, adverse event, immune checkpoint inhibitors, anti-angiogenic drugs, case report

Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 80% of liver cancers, ranking the sixth most common cancer and the third leading cause of cancer-related death.[1] In recent years, significant progress has been made in non-surgical treatments for HCC, especially in systemic therapy. The combination of anti-angiogenic drugs with immune checkpoint inhibitors (ICIs) achieved an objective response rate (ORR) of about 30% with an improved median survival time as long as 20 months and converted partial initially unresectable HCC into resectable HCC.[2–6] Additionally, local therapies, including transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), when combined with systemic therapy, could achieve a promising efficacy and an improved conversion rate of 20–50% in patients with initially unresectable HCC.[7–11]

Most studies reported the promising prospect of conversion therapy followed by sequential surgery but rarely paid attention to its limitations, such as optimal timing for surgery or tumor progression and metastasis during the treatment period. Postoperative recurrence and distant metastasis remained the main factors leading to poor prognosis of HCC patients receiving conversion therapy. The common extrahepatic metastatic sites of HCC include lung, lymph nodes,

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brain, adrenal gland, and bone.[12] Gingival metastasis, a rare kind of HCC metastasis, is challenging for timely detection and indicate a poor prognostic outcome.[13]

Here, we report an initially unresectable HCC patient who received effective conversion therapy but discovered gingival metastasis within one-month post-hepatectomy. The mechanism of gingival metastasis and lessons from this case have been discussed.

Case Presentation

In July 2022, a 53-year-old male patient complained upper abdominal bloating and pain for approximately one month. He had a history of chronic hepatitis B virus infection for over a decade and received entecavir as an antiviral treatment. After admission, laboratory tests revealed that the level of protein induced by vitamin K absence or antagonist-II (PIVKA-II) was elevated to 8864.02 mAu/mL, while serum alpha-fetoprotein (AFP) remained within the normal range at 1.93 ng/mL. The other laboratory tests are shown in Table 1. Magnetic resonance imaging (MRI) of the abdomen revealed a tumorous lesion in the left lobe of the liver, measuring 14.2*9.8 cm, with characteristic radiological features of HCC (a mass with long T1 and long T2 signals in the left lobe of the liver, hyperintensity on diffusion-weighted imaging (DWI), clear boundaries, and early enhancement during the arterial phase and washout in the portal vein phase), along with satellite lesion formation (Figure 1). The left branch of the portal vein, the left hepatic vein, and the middle hepatic vein were indistinct. The patient had no ascites or hepatic encephalopathy. The Child-Pugh score was 5 (class A). Referring to the EASL guidelines, based on the liver function, performance status, and imaging findings, the patient was diagnosed as HCC at BCLC stage A.[14]

Given the tumor's large size and insufficient residual liver volume to preserve normal liver function after hepatectomy, the multidisciplinary team (MDT) opted for a triple-therapy conversion approach, comprising HAIC (FOLFOX) combined with lenvatinib (8 mg orally once daily) and tislelizumab (200 mg via intravenous injection every 3 weeks). After 10 months of comprehensive treatment, an MRI examination was performed, which showed a significant shrinkage in tumor size, from 14.2*9.8 cm to 8.4*6.4 cm, and the left branch of the portal vein and the middle hepatic vein became visible (Figure 2). The laboratory test results are detailed in Table 1: the copy level of hepatitis B virus DNA was <10 IU/mL, and the PIVKA-II level decreased to normal, as shown in Figure 3. The adverse events related to the conversion therapy were elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and sore gingiva. These symptoms could be alleviated by

Table 1 Comparison of Laboratory Test Results Before and After Treatment in Patients

Laboratory Examination	Before	After
WBC	4.96*10^9/L	4.95*10^9/L
Hb	128g/L	141g/L
PLT	121*10^9/L	135*10^9/L
TBil	19.1 μmol/L	19.3 μmol/L
ALB	39.9 g/L	33.9 g/L
ALT	39 U/L	411 U/L
AST	47 U/L	546 U/L
GGT	177 U/L	80 U/L
AKP	133 U/L	85 U/L
LDH	192 U/L	757 U/L
PT	13.2 s	12.7 s
APTT	32.6 s	34 s
AFP	1.93 ng/mL	1.25 ng/mL
PIVKA-II	8864.02 mAu/mL	36.56 mAu/mL

Abbreviations: WBC, white blood cell; Hb, hemoglobin; PLT, platelet; TBil, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyl-transferase; AKP, alkaline phosphatase; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; AFP, alpha-fetoprotein; PIVKA-II, Protein Induced by Vitamin K Absence or Antagonist II.

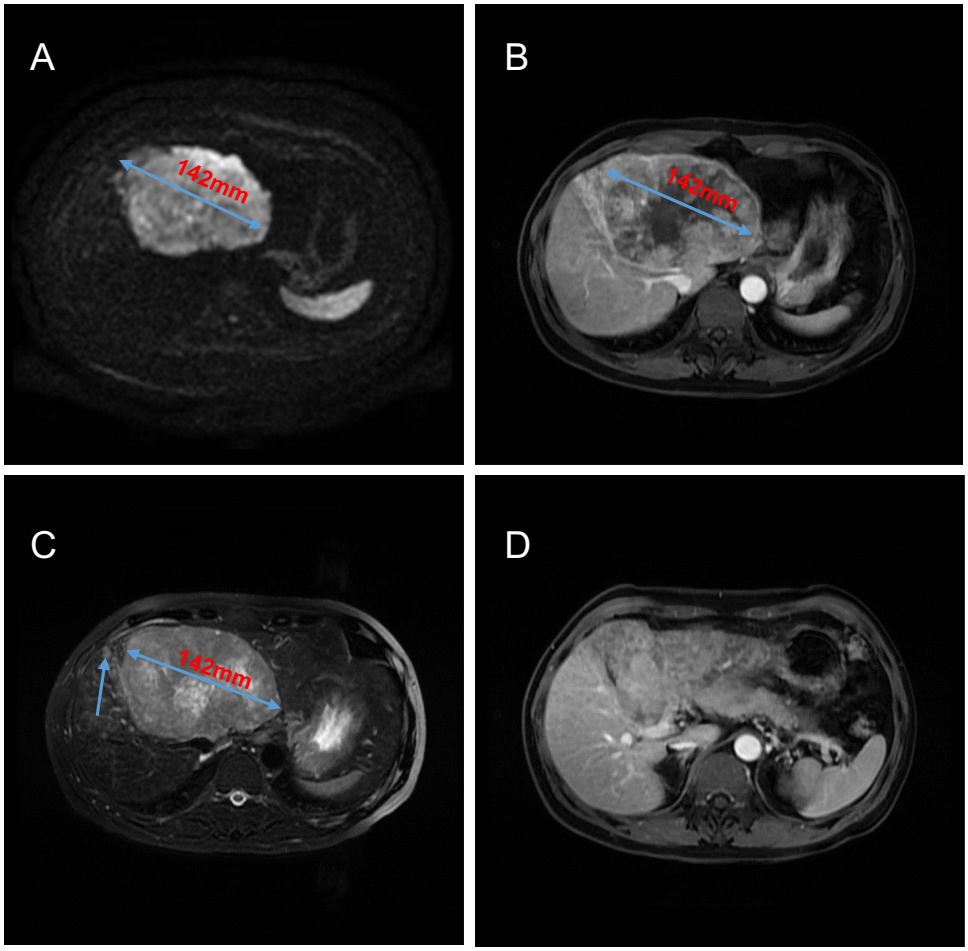

Figure 1 Patient's MRI Images on 202-07-19. (**A**) MRI-DWI, (**B**) MRI-T1, the maximum diameter of the tumor measures 142mm, (**C**) MRI-PVP, the arrow indicate the formation of satellite foci. (**D**) MRI-T2.

symptomatic treatment. Based on the tumor size at this time, it was calculated that the remaining liver volume after surgery could maintain adequate liver function. After an MDT discussion, it was unanimously agreed that the patient's condition was suitable for surgical resection. According to the guidelines for the use of tyrosine kinase inhibitors (TKIs) and ICIs, lenvatinib was discontinued for 2 weeks, and tislelizumab was discontinued for 4 weeks.[15] On May 20, 2023, the patient underwent hepatectomy. The surgical procedure was uneventful, lasting 3 hours with an estimated blood loss of about 150 mL. The first hepatic portal was clamped three times, for 15 minutes, 16 minutes, and 10 minutes, respectively. The patient recovered well with no severe complications and discharged 5 days after surgery. The postoperative pathological examinations revealed that the majority of the tumor was necrotic, with only small foci of residual tumor (Figure 4). The surgical margin was negative without microvascular invasion.

On June 3, 2023, the patient presented to the stomatology outpatient department at our hospital with a chief complaint of swelling in the right posterior dental region and palpated a mass in the right mandibular molar area. Upon examination, a soft, pale red mass measuring approximately 1 cm in diameter was observed on the buccal aspect of the gingiva between the first and second molars of the lower right jaw (teeth 46 and 47). The initial diagnosis was a gingival tumor. After obtaining the patient's informed consent, the mass was excised during an outpatient procedure on the same day. The postoperative pathological examination revealed the presence of ulceration, necrosis, and clusters of atypical cells. Immunohistochemical results confirmed the diagnosis of metastatic hepatocellular carcinoma (Figure 5). Subsequently, a PET-CT scan was performed, which showed no evidence of metastatic disease in other organs.

Following the excision of the gingival mass, the patient underwent a course of oral radiation therapy and continued receiving lenvatinib and tislelizumab as postoperative adjuvant treatment. Gingival metastasis recurred at the same site

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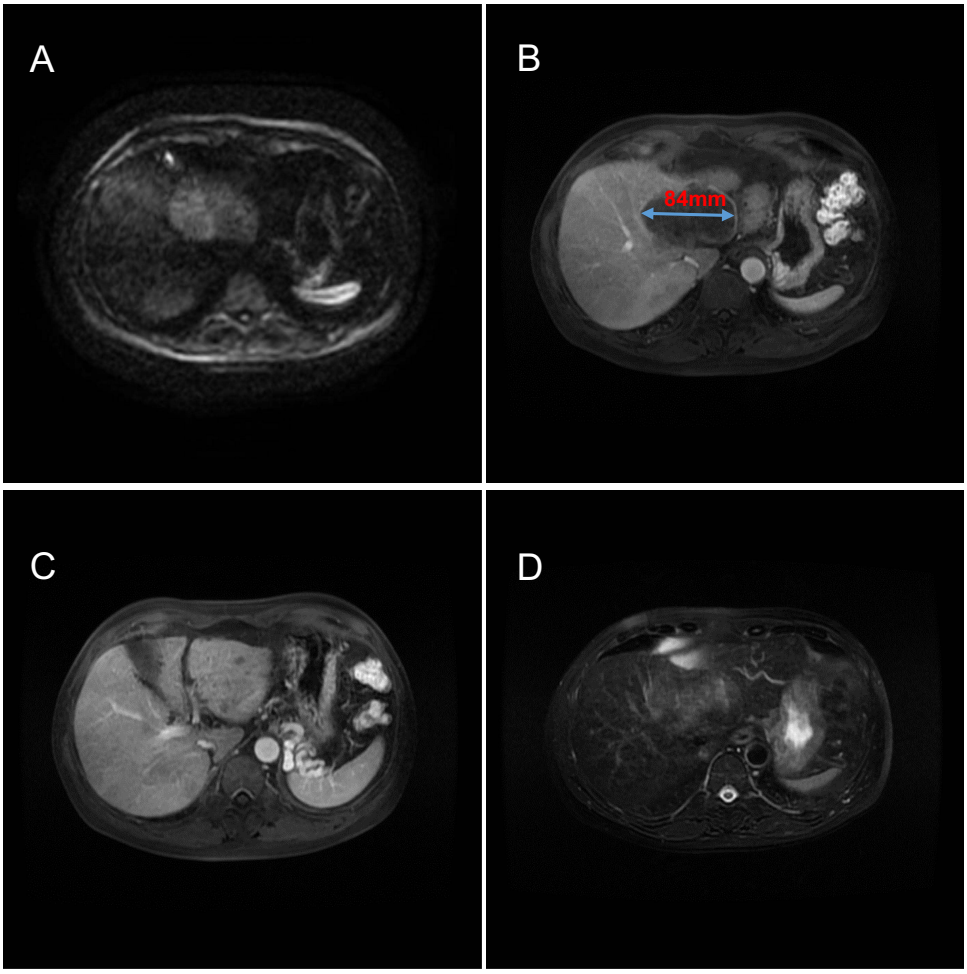

Figure 2 Patient's MRI Images on 2023-05-09, (**A**) MRI-DWI. (**B**) MRI-T1, the blue arrow indicates the maximum diameter of the tumor is 84 mm. (**C**) MRI-PVP. (**D**) MRI-T2.

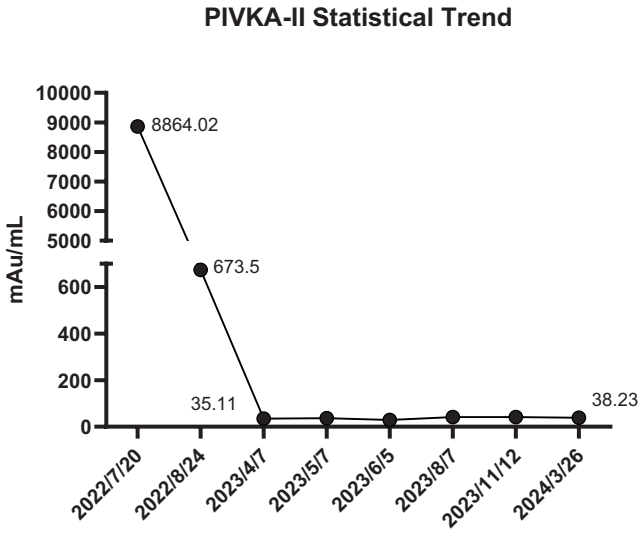

Figure 3 Trend of PIVKA-II from July 2022 to March 2024.

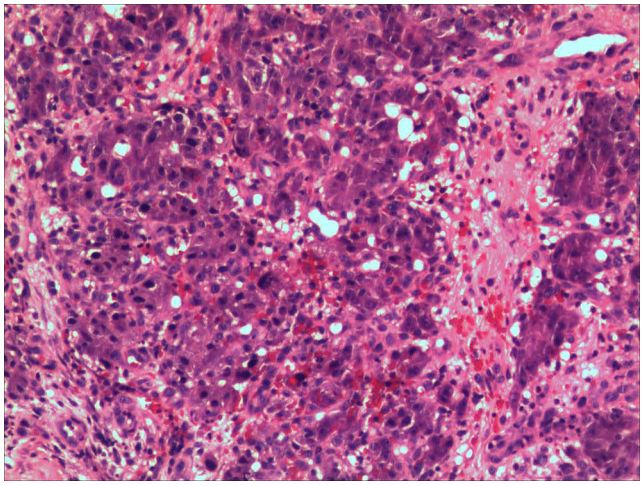

Figure 4 Histopathological findings of hepatocellular carcinoma.

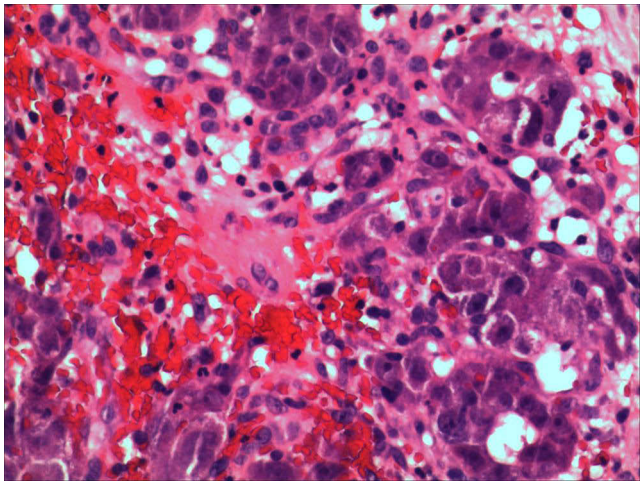

Figure 5 Histopathological findings of gingival metastasis.

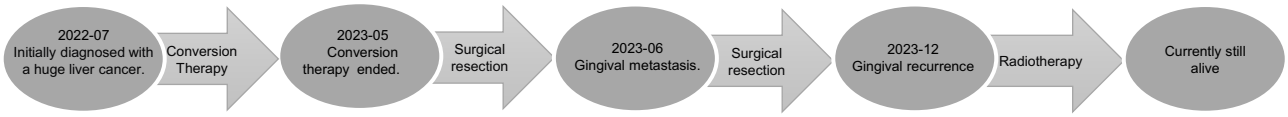

Figure 6 The treatment timeline.

six months after surgery. The patient received oral radiotherapy again. Currently, the patient remains alive. Meanwhile, no recurrence in the liver or metastasis to other organs has been observed. The treatment timeline is illustrated in Figure 6.

Discussion

The treatment landscape for HCC has undergone a significant shift in recent years. The successive advent of TKIs such as lenvatinib, donafenib, and ICIs such as pembrolizumab and tislelizumab, has brought about a remarkable improvement in the prognosis of advanced HCC patients. Notably, some patients have achieved tumor shrinkage and downstaging, enabling them to

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meet the criteria for surgical resection. Consequently, the concept of conversion therapy for HCC has emerged as a hot topic in liver cancer research. For instance, Zhu XD et al reported a conversion rate of 23.8% among patients with unresectable HCC treated with TKIs plus PD-1 inhibitors, accompanied by a remarkable 2-year survival rate of 95.8% in the conversion resection cohort.[16] The conversion rates were higher when received TKIs plus PD-1 inhibitors combined with loco-regional treatment.[17,18] A multi-center prospective study showed that TACE combined with lenvatinib plus camrelizumab as conversion therapy was promising active for HCC while the ORR was 76.4% and the conversion rate was 54.5%.[18] Another significant progresses in the treatment of HCC were HAIC based on the FOLFOX regimen (oxaliplatin + folinate calcium + 5-fluorouracil).[19] Several studies have demonstrated the roles of HAIC plus TKIs and ICIs in conversion therapy, with the ORR of 56.3%~94.4% and the conversion rates of 31.3%~66.7%.[20–22]

The case we presented was an initially unresectable HCC with a huge size. According to the previous study, HAIC presented better potential than TACE to control local tumors for huge HCC and thus may be the preferred conversion therapy.[23,24] Consequently, the patient received a triple therapy of HAIC plus lenvatinib and tislelizumab and the tumor responded well, which was evaluated as major partial response, proving the rationality and effectiveness of this treatment protocol. The potential synergistic anti-tumor mechanisms of the triple therapy might be explained as follows. Chemotherapy could modulate the tumor microenvironment and enhance the immune response by upregulating the expression of HLA1 on tumor cells and inducing immunogenic cell death in tumor cells to release antigen and stimulate the secretion of cytokines that promote the maturation of dendritic cells.[25–27] Additionally, anti-angiogenic drugs can promote the effective infiltration of effector immune cells into the tumor microenvironment by tumor vasculature normalization.[28]

As for the safety of this triple therapy, the common adverse events were manageable, including abnormal liver function, hypoalbuminemia, decreased neutrophil counts, anemia, hypertension, diarrhea, fatigue, decreased appetite, hypothyroidism, and so on.[29] In the case, we presented, the side effects were limited to elevated ALT, AST of which the incidences were approximately 20%. It could be ameliorated by hepatoprotective agents. Another symptoms that emerged during the conversion period were sore gingiva, which we initially attributed to a side effect to lenvatinib: stomatitis. This assumption was based on a study reporting an incidence rate of stomatitis about 15%.[2] The symptom was alleviated with anti-inflammatory medications, which further reinforced our misinterpretation. At last, half month after surgery, the patient discovered a mass in the oral cavity, which was confirmed to be a metastatic HCC. This case imparts a profound lesson for us.

The sore gingiva that occurred during this conversion treatment were not an adverse event of the conversion therapy but rather a manifestation of gingival metastasis. During the conversion treatment, highly invasive tumor cells might be screened out and colonized in a rare metastatic site: the gingival. The possible pathophysiological mechanisms for metastatic spread to the gingiva in liver cancer remain to be elucidated. Hematogenous spread occurs through the invasion of branches of the hepatic artery or portal vein. This process is followed by systemic circulation, which allows the metastatic cells to reach the blood vessels supplying the gingiva after passing through the pulmonary circulation. This pathway is considered the most likely mechanism for oral metastasis.[30,31] Considering that over 50% of HCC patients with gingival metastasis also presented cirrhosis, a hypothesis has been proposed that hemodynamic changes following esophageal varices may be one of the potential pathways for oral metastasis, especially in HCC patients with decompensated cirrhosis.[32] Additionally, the rich capillary networks associated with chronic inflammations and the presence of some inflammatory molecules may facilitate the progression of metastatic cells. Therefore, poor oral hygiene habits, such as smoking and drinking, may play a role in the pathogenesis of HCC gingival metastasis.[33] Furthermore, there was a hypothesis known as "concomitant tumor resistance", which suggested that the primary tumor could exert an inhibitory effect on metastatic lesions and the metastatic lesions would acceleratedly grow once the primary tumor was removed.[34] It further explains why no oral metastatic lesions were detected before surgery, while the metastatic lesions grew rapidly within half a month after surgery.

The most common site of distant metastasis for HCC is the lungs, and oral gingival metastasis is rare with only a few case reports available. Previous studies have demonstrated that the occurrence of gingival metastasis is associated with an extremely poor prognosis, resulting in a median survival period of just a few months.[35] This case is different from previous reports because of oligometastatic gingival metastasis during conversion therapy. In contrast, our patient survived for over one year and a half following the conversion surgery. This outcome may be attributed to the successful conversion surgery that reduced the tumor burden and resulted in only oral oligometastases.

Therefore, this case provided with some insights: On the one hand, following the administration of targeted therapy, clinicians should regard gingival swelling and pain not merely as potential adverse events but also as potential indicators of gingival metastasis. On the other hand, prior to surgical resection after successful conversion therapy, a detailed systemic examination, included a PET-CT scan, should be conducted routinely to detect any metastatic lesions in rare sites of body.

Conclusion

Sore gingiva may not only be an adverse effect of targeted therapy but may also be a sign of gingival metastasis, which needs to be taken with more caution.

Ethics Approval and Consent to Participate

Approval for the publication of the case details was granted by the Ethics Committee of Tongji Hospital affiliated with Huazhong University of Science and Technology. Written informed consent was obtained from the patient included in this study.

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Author Contributions

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

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Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Bray F, Laversanne M, Sung H. et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. *J Clin Oncol*. 2020;38(26):2960–2970. doi:10.1200/JCO.20.00808
3. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
4. Xu J, Shen J, Gu S, et al. Camrelizumab in Combination with Apatinib in Patients with Advanced Hepatocellular Carcinoma (RESCUE): a Nonrandomized, Open-label, Phase II Trial. *Clin Cancer Res*. 2021;27(4):1003–1011. doi:10.1158/1078-0432.Ccr-20-2571
5. Yau T, Kang YK, Kim TY, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: the CheckMate 040 Randomized Clinical Trial. *JAMA Oncol*. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564
6. Zhou H, Song T. Conversion therapy and maintenance therapy for primary hepatocellular carcinoma. *Biosci Trends*. 2021;15(3):155–160. doi:10.5582/bst.2021.01091
7. Llovet J, Finn RS, Ren Z, et al. LBA3 Transarterial chemoembolization (TACE) with or without lenvatinib (len) + pembrolizumab (pembro) for intermediate-stage hepatocellular carcinoma (HCC): Phase III LEAP-012 study. *Ann Oncol*. 2024;35:S1229. doi:10.1016/j.annonc.2024.08.2277
8. Kudo M, Lencioni R, Erinjeri JP, et al. 950P Outcomes by baseline tumour burden in EMERALD-1: a Phase III, randomised, placebo (PBO)-controlled study of durvalumab (D) ± bevacizumab (B) with transarterial chemoembolisation (TACE) in participants (pts) with embolisation-eligible unresectable hepatocellular carcinoma (uHCC). *Ann Oncol*. 2024;35:S658–S659. doi:10.1016/j.annonc.2024.08.1010
9. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. *J Clin Oncol*. 2024;42(3_suppl):LBA432–LBA432. doi:10.1200/JCO.2024.42.3_suppl.LBA432

10. Jin ZC, Chen JJ, Zhu XL, et al. Immune checkpoint inhibitors and anti-vascular endothelial growth factor antibody/tyrosine kinase inhibitors with or without transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (CHANCE2201): a target trial emulation study. *EClinicalMedicine*. 2024;72:102622. doi:10.1016/j.eclinm.2024.102622
11. Palmieri LJ, Dermine S, Coriat R. Potential Areas of Interest in a Trial of Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin for Hepatocellular Carcinoma. *JAMA Oncol*. 2019;5(12):1805–1806. doi:10.1001/jamaoncol.2019.4052
12. Wu W, He X, Andayani D, et al. Pattern of distant extrahepatic metastases in primary liver cancer: a SEER based study. *J Cancer*. 2017;8(12):2312–2318. doi:10.7150/jca.19056
13. Xue LJ, Mao XB, Geng J, Chen YN, Wang Q, Chu XY. Rare Gingival Metastasis by Hepatocellular Carcinoma. *Case Rep Med*. 2017;2017:3192649. doi:10.1155/2017/3192649
14. Galle PR, Forner A, Llovet JM, et al. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
15. Sun HC, Zhou J, Wang Z, et al. Chinese expert consensus on conversion therapy for hepatocellular carcinoma (2021 edition). *Hepatobiliary Surg Nutr*. 2022;11(2):227–252. doi:10.21037/hbsn-21-328
16. Zhu XD, Huang C, Shen YH, et al. Hepatectomy After Conversion Therapy Using Tyrosine Kinase Inhibitors Plus Anti-PD-1 Antibody Therapy for Patients with Unresectable Hepatocellular Carcinoma. *Ann Surg Oncol*. 2023;30(5):2782–2790. doi:10.1245/s10434-022-12530-z
17. Xin Y, Zhang X, Liu N, et al. Efficacy and safety of lenvatinib plus PD-1 inhibitor with or without transarterial chemoembolization in unresectable hepatocellular carcinoma. *Hepatol Int*. 2023;17(3):753–764. doi:10.1007/s12072-023-10502-3
18. Wu XK, Yang LF, Chen YF, et al. Transcatheter arterial chemoembolisation combined with lenvatinib plus camrelizumab as conversion therapy for unresectable hepatocellular carcinoma: a single-arm, multicentre, prospective study. *EClinicalMedicine*. 2023;67:102367. doi:10.1016/j.eclinm.2023.102367
19. Lyu N, Wang X, Li JB, et al. Arterial Chemotherapy of Oxaliplatin Plus Fluorouracil Versus Sorafenib in Advanced Hepatocellular Carcinoma: a Biomolecular Exploratory, Randomized, Phase III Trial (FOHAIC-1). *J Clin Oncol*. 2022;40(5):468–480. doi:10.1200/jco.21.01963
20. Liu D, Mu H, Liu C, et al. Hepatic artery infusion chemotherapy (HAIC) combined with sintilimab and bevacizumab biosimilar (IBI305) for initial unresectable hepatocellular carcinoma (HCC): a prospective, single-arm phase II trial. *J Clin Oncol*. 2022;40(16_suppl):4073. doi:10.1200/JCO.2022.40.16_suppl.4073
21. Dong W, Zhang S, Huo Z, et al. Lenvatinib in combination with PD-1 inhibitor and hepatic arterial infusion chemotherapy (HAIC) for patients with potentially resectable hepatocellular carcinoma: a retrospective analysis. *J Clin Oncol*. 2023;41(16_suppl):e16160–e16160. doi:10.1200/JCO.2023.41.16_suppl.e16160
22. Tan K, He X, Zhang H, et al. Efficacy and safety of tislelizumab combined with lenvatinib and FOLFOX4-HAIC in conversion therapy of middle-advanced stage hepatocellular carcinoma (HCC): a real-world retrospective study. *J Clin Oncol*. 2023;41(16_suppl):e16137–e16137. doi:10.1200/JCO.2023.41.16_suppl.e16137
23. Li QJ, He MK, Chen HW, et al. Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin Versus Transarterial Chemoembolization for Large Hepatocellular Carcinoma: a Randomized Phase III Trial. *J Clin Oncol*. 2022;40(2):150–160. doi:10.1200/jco.21.00608
24. Deng M, Cai H, He B, Guan R, Lee C, Guo R. Hepatic arterial infusion chemotherapy versus transarterial chemoembolization, potential conversion therapies for single huge hepatocellular carcinoma: a retrospective comparison study. *Int J Surg*. 2023;109(11):3303–3311. doi:10.1097/js9.0000000000000654
25. Lesterhuis WJ, Punt CJ, Hato SV, et al. Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice. *J Clin Invest*. 2011;121(8):3100–3108. doi:10.1172/jci43656
26. Mathew M, Enzler T, Shu CA, Rizvi NA. Combining chemotherapy with PD-1 blockade in NSCLC. *Pharmacol Ther*. 2018;186:130–137. doi:10.1016/j.pharmthera.2018.01.003
27. Khan KA, Kerbel RS. Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. *Nat Rev Clin Oncol*. 2018;15(5):310–324. doi:10.1038/nrclinonc.2018.9
28. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol*. 2018;15(5):325–340. doi:10.1038/nrclinonc.2018.29
29. Zhang TQ, Geng ZJ, Zuo MX, et al. Camrelizumab (a PD-1 inhibitor) plus apatinib (an VEGFR-2 inhibitor) and hepatic artery infusion chemotherapy for hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (TRIPLET): a phase II study. *Signal Transduct Target Ther*. 2023;8(1):413. doi:10.1038/s41392-023-01663-6
30. Fujihara H, Chikazu D, Saijo H, et al. Metastasis of hepatocellular carcinoma into the mandible with radiographic findings mimicking a radicular cyst: a case report. *J Endod*. 2010;36(9):1593–1596. doi:10.1016/j.joen.2010.05.009
31. Hou Y, Deng W, Deng G, Hu L, Liu C, Xu L. Gingival metastasis from primary hepatocellular carcinoma: a case report and literature review of 30 cases. *BMC Cancer*. 2019;19(1):925. doi:10.1186/s12885-019-6020-7
32. Allon I, Pessing A, Kaplan I, Allon DM, Hirshberg A. Metastatic tumors to the gingiva and the presence of teeth as a contributing factor: a literature analysis. *J Periodontol*. 2014;85(1):132–139. doi:10.1902/jop.2013.130118
33. Hirshberg A, Leibovich P, Buchner A. Metastases to the oral mucosa: analysis of 157 cases. *J Oral Pathol Med*. 1993;22(9):385–390. doi:10.1111/j.1600-0714.1993.tb00128.x
34. Chiarella P, Bruzzo J, Meiss RP, Ruggiero RA. Concomitant tumor resistance. *Cancer Lett*. 2012;324(2):133–141. doi:10.1016/j.canlet.2012.05.021
35. Lopes AM, Freitas F, Vilares M, Caramês J. Metastasis of malignant tumors to the oral cavity: systematic review of case reports and case series. *J Stomatol Oral Maxillofac Surg*. 2023;124(1s):101330. doi:10.1016/j.jormas.2022.11.006