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Case Report

A Case of Conversion Hepatectomy for Hepatocellular Carcinoma with Vascular Invasion after Atezolizumab-bevacizumab Treatment

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Summary

We report a hepatocellular carcinoma (HCC) case with vascular invasion successfully treated by conversion hepatectomy after treatment by atezolizumab-bevacizumab. A 74-year-old male patient was diagnosed with HCC and referred to our hospital. The tumor at the anterior section was 12.3 cm in diameter. It had invaded a portal vein branch of subsection 5 (S5) and peripheral branches of the middle hepatic vein. Serum alpha-fetoprotein (AFP) level was extremely high at 177408.3 ng/ml. The patient first received atezolizumab-bevacizumab treatment. After three cycles of atezolizumab-bevacizumab therapy, the tumor had decreased in size, the invasion into a portal and hepatic vein disappeared, the tumor enhancement completely vanished in the CT scan, and the tumor markers became within normal range. We decided to perform a conversion hepatectomy. The tumor was removed entirely by S5 partial resection, and pathological analyses showed a complete response to atezolizumab-bevacizumab treatment. There was no perioperative complication. The patient has survived for nine months without recurrence so far. Atezolizumab combined with bevacizumab might be an effective and appropriate option for the multidisciplinary treatment aiming for curative surgical resection.

Key Words: Hepatocellular carcinoma, Immune checkpoinat inhibitor, Conversion surgery

Introduction

Currently, there are numerous local hepatocellular carcinoma (HCC) treatments. Surgical resection has been the most radical local treatment. Advancements in surgical techniques and perioperative management have increased its safety, making it an even more crucial local treatment. With these advancements, surgical resection has been applied even for the advanced stage HCC, such as tumors having a vascular inva-

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sion[1,2]. However, the result was unsatisfactory, especially for the tumor with advanced vascular invasion, large tumor size, and multi-nodules[3,4]. American and European treatment guidelines do not recommend surgical treatment for the tumor with vascular invasion or multi-nodules[5,6].

Recently, dramatic advancements have been achieved in chemotherapy for HCC. Within these new chemotherapies, immune checkpoint inhibitors (ICIs) have achieved promising outcomes. IMbrave150 trial showed that atezolizumab, an antibody against programmed death-ligand 1 (PD-L1), combined with bevacizumab, an antibody against vascular endothelial growth factor (VEGF), resulted in better overall and progression-free survival than sorafenib in patients with unresectable HCC[7]. In addition, this combination therapy showed a high complete response (CR) rate of 10.2% in modified Response Evaluation Criteria in Solid Tumors (mRECIST). It suggests that this chemotherapy might help achieve conversion surgery for unresectable HCC. However, the efficacy and safety of this multidisciplinary treatment remain unclear, with limited literature.

Here we show a case of HCC with the portal and hepatic vein invasion successfully resected following combined therapy using atezolizumab and bevacizumab.

Case Presentation

A 74-year-old man was referred to our hospital due to his liver tumor without any symptoms.

Multidetector computed tomography (MDCT) revealed a liver tumor with 12.3 cm in maximum diameter in the anterior section (Fig. 1). The tumor showed substantial contrast enhancement in the arterial phase, and the enhancement was rapidly washed out at the delayed phase, suggesting HCC. The tumor involved a portal vein branch of S5 and peripheral branches of the middle hepatic vein.

Table 1 shows the result of his laboratory examinations. Alpha-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP) levels were highly upregulated to 177408.3 ng/mL and 15 mAU/mL, respectively. The patient was negative for hepatitis B surface antigen, the hepatitis B core antibody, and the signal of HBV-DNA. The hepatitis C virus antibody was neither detected. Based on CT and laboratory findings, we clinically diagnosed him with HCC involving branches of the hepatic vein and portal vein. We also found his ascending colon cancer of type 2 tumor. The colonoscopy and CT scan findings indicated its stage as cStage I (T2N0M0).

Due to his damaged liver with 22.4% of indocyanine green (ICG) R15, vascular involvement of the tumor, and highly elevated tumor marker level, we did not consider surgical resection. As the colon cancer was diagnosed at its early stage, we focused on treating HCC. In addition, a recent phase II trial showed the effectiveness of the combination therapy with atezolizumab, FOLFOXILI (FOLinic acid + Fluorouracil + Oxaliplatin + IRInotecan), and bevacizumab in metastatic colorectal cancer[8]. Because of these reasons, we treated him with combination chemotherapy using atezolizumab and bevacizumab, according to IMbrave 150 trial[7]. Atezolizumab (120 mg) and bevacizumab (15 mg/kg of body weight) were administered every three weeks. After three treatment cycles, the AFP level significantly decreased to 18.1 ng/ml (Table 1). The tumor size was reduced considerably from 12.3 to 5.6 cm. The contrast enhancement of the tumor completely disappeared (Fig. 2). The tumor response was a partial response (PR) according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)[9], and a complete response (CR) according to the modified RECIST (mRECIST)[10]. He did not experience any adverse events during his chemotherapy. We also did a urinary surveillance and found no proteinuria throughout the chemotherapy. The ascending colon cancer did not show tumor growth during this chemotherapy, confirmed by colonoscopy and CT scan. According to these findings, we decided to perform a conversion hepatectomy for his tumor. Although his laboratory examinations after chemotherapy showed slightly worse ICG R15 with 27.8%, we thought he could tolerate partial hepatectomy.

After 35 days intervals from his last treatment with bevacizumab, which was after 79 days from initiation of the chemotherapy, we performed the partial liver resection of S5. We also conducted a right hemicolectomy for his ascending colon cancer. The total operation time was 477 min, and the estimated blood loss was 530 ml. We achieved macroscopic curative resection for the liver tumor (Fig. 3A). He was discharged

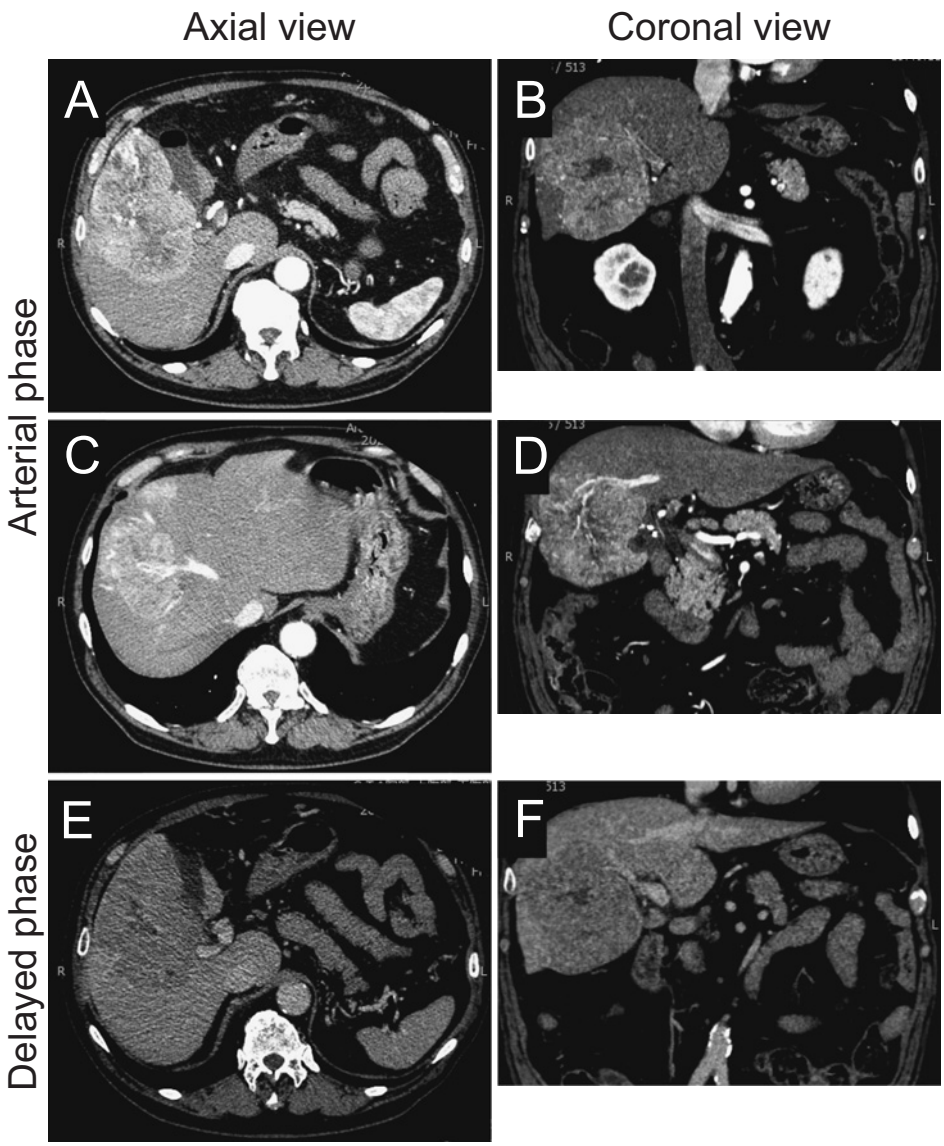

Figure 1

The multidetector computed tomography findings at the diagnosis. The tumor with 12.3 cm in diameter, located in the anterior section, with enhancement in the arterial phase and washed out in the delayed phase. **A**, **B:** The arterial phase in axial view **(A)** and coronal view **(B)**. The tumor invaded branches of subsection 5 of the portal vein. **C**, **D:** The arterial phase in axial view **(C)** and coronal view **(D)**. The tumor invaded peripheral branches of the middle hepatic vein. **E**, **F:** The enhanced media was washed out from the tumor at the delayed phase axial view **(E)** and coronal view **(F)**.

13 days after the operation with no postoperative complications. Histological findings showed coagulative necrosis infiltrating inflammatory cell clusters in the tumor area. There were no viable HCC cells (Fig. 3B and C). His non-tumor liver tissue showed cirrhotic changes with moderate fibrosis. The patient has been recurrence-free as of 9 months postoperatively.

Discussion

Surgical resection is the critical therapeutic modality for better survival outcomes in treating HCC. In contrast to American and European guidelines, Japanese clinical practice guidelines for HCC do not exclude surgical resection, even for tumors with large tumor sizes, macroscopic vascular invasion, and multimodule[11]. In the 19th follow-up survey of liver cancer in Japan, which was conducted by the Liver Cancer Study Group of Japan, the surgical resection showed the best 5-year survival rate of 56.8% over other treatment modalities, including the local ablation therapy (47.0%) and

Table 1 The laboratory date of the patient

	At the diagnosis	Before surgery
Hematological analysis		
WBC (/μL)	6200	5500
Hb (g/dL)	15.1	14.4
Platelet count (×E4/μL)	37.8	21.3
Coagulation test		
PT% (%)	98.6	115.5
APTT (second)		23.8
Blood chemistry		
TP (g/dl)	7.9	7.9
Alb (g/dl)	3.85	4.16
T-Bil (mg/dl)	1.27	1.99
AST (U/L)	51	24
ALT (U/L)	56	16
ALP (U/L)	123	60
LDH (U/L)	238	170
GGT (U/L)	178	30
BUN (mg/dl)	23	14
Cr (mg/dl)	0.80	0.66
Na (mEq/L)	136	139
K (mEq/L)	4.3	3.9
Cl (mEq/L)	100	103
C-Reactive protein (mg/dl)	6.17	< 0.06
Hepatitis viral markers		
HBsAg	Negative	Negative
HBcAb	Negative	
HBV-DNA (logIU/mL)	< 0.005	
HCVAb	Negative	Negative
Liver function test		
ALBI score	-2.39	-2.47
Modified ALBI grade		
ICG 15R (%)	22.4	27.8
Tumor markers		
AFP (ng/dl)	177408.3	20.8
DCP (mAU/ml)	—	15

WBC: white blood cell count, Hb: hemoglobin, PT: prothrombin time, APTT: activated partial thromboplastin time, TP: total protein, T-Bil total bilirubin, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, AIP: alkaline phosphatase, GGT: γ-glutamyl transferase, BUN: blood urea nitrogen, Cr: creatinine, T-Cho: total cholesterol, TG: triglyceride, HBsAg: hepatitis B surface antigen, HBs-AD: anti-hepatitis B surface antibody, HBc-Ab: anti-hepatitis B core antibody, HCV-AD: hepatitis C virus antibody, ALBI: albumin-bilirubin, AFP: alpha-fetoprotein, DCP: des-gamma-carboxy-prothrombin

the transcatheter arterial embolization (TAE) (24.8%). However, survival rates for patients with advanced vascular invasion are unsatisfactory. The 5-year survival rates of resected patients with VP2 (involvement to the 2nd branch of the portal vein) and VP3/4 (invading into the 1st branch/main trunk of the portal vein) were 29.2% and 25.0%, respectively[12]. These data suggest that the multidisciplinary treatment combining surgical resection and other therapy, such as chemotherapy, may improve the survival outcome of patients

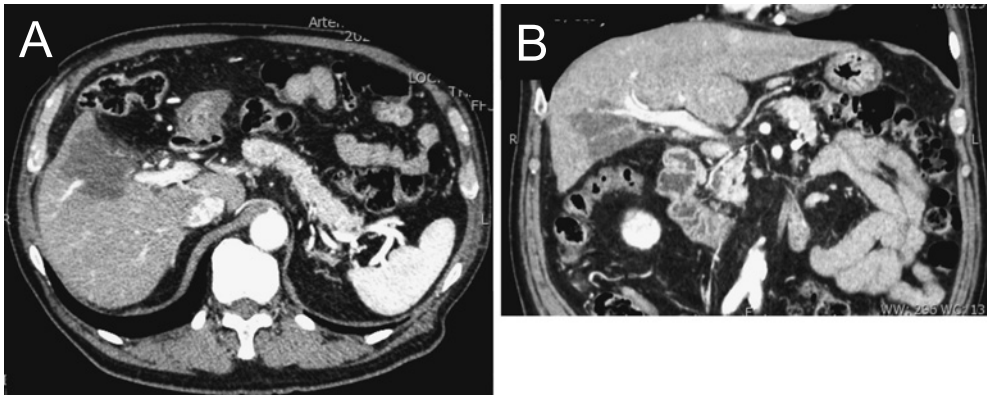

Figure 2

The multidetector computed tomography findings after atezolizumab-bevacizumab treatment. Atezolizumab-bevacizumab treatment resulted in a decrease in tumor size and an absence of tumor enhancement. Arterial phase, **A** transverse plane, **B** coronal plane. The tumor size was 5.6 cm, and the internal contrast effect diminished in the tumor. The tumor response was assessed as a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), and as a complete response (CR) according to the modified RECIST (mRECIST).

with advanced HCC.

With these backgrounds, the usefulness of conversion surgery, in which the unresectable tumor is resected following downstaging chemotherapy or TAE treatment, has been reported[13]. In our case, we did not think the surgical treatment was the best treatment modality for this patient as the tumor was large (more than 10 cm) and involved in major vasculature (portal vein and hepatic vein branches). In addition, the liver function was moderately damaged. We thought the surgical resection for curative intent would result in severe peri- and postoperative complications and treated patients with chemotherapy for later conversion surgery.

The chemotherapy of HCC has changed dramatically in this decade. Sorafenib has been used as a first-line chemotherapy for HCC since the SHARP trial showed its efficacy[14]. However, the response rate of sorafenib was limited. REFLECT trial showed that lenvatinib was non-inferior to sorafenib in overall survival with a high response rate[15]. In this trial, the tumor complete/partial response rate of lenvatinib was 2%/38% in modified RECIST, significantly higher than that of sorafenib[15]. With this advancement of chemotherapy, many case reports of conversion surgery for HCC that were initially unresectable have been published, especially since the efficacy of lenvatinib was reported[16-18]. The high response rate of lenvatinib may be responsible for the increasing number of reports.

As described in the introduction, atezolizumab combined with bevacizumab showed an extremely high complete response rate of 10.2% in the IMbrave150 trial[7]. In response to this result, we found few reports regarding the conversion surgery following this combination treatment, and the efficacy and safety were not apparent yet. To the best of our knowledge, 6 cases have been reported in the literature[19-24] (Table 2). Many of these cases have a relatively large tumor diameter (more than 5 cm) and have at least one of the following factors: vascular invasion, intrahepatic metastasis, or extrahepatic metastasis. In all 7 cases including our case, tumor response by atezolizumab and bevacizumab combination therapy was PR or CR according to mRECIST, and the tumor marker level was dramatically decreased. As a result, R0 resection was achieved in all cases. It is also worth noting that pathological CR (pCR) was observed in 4 cases within 6 cases describing pathological findings. These results confirm the efficacy of atezolizumab combined with bevacizumab. On the other hand, there was a wide range of treatment cycles between cases, and it is hard to determine the appropriate timing for the surgical resection. Due to the small number of reports, a standard protocol has not been established.

Conclusion

The atezolizumab combined with bevacizumab might be an effective and appropriate option for the

Figure 3

Macroscopic and microscopic findings of the resected tumor. **A:** Macroscopic findings. The tumor was successfully resected with enough surgical margin. **B**, **C:** Microscopic findings. **B:** Low-power field view of primary hepatocellular carcinoma (×100). **C:** High-power field view of **B** (×400). Histological findings showed coagulative necrosis with ghost cells and infiltration of inflammatory cells. No viable tumor cell was found in the tumor.

Table 2 Reported cases of hepatocellular carcinoma conversion surgery following atezolizumab + bevacizumab therapy

	Author	Ref.	Year	tumor size (mm)	Vascular invasion	Multiple or Single tumor	Extra-hepatic metastasis	Preoperative therapy	RE-CIST1.1	mRE-CIST	AFP (ng/ml)	DCP (mUA/ml)	R	pCR	Overall survival after initiation of chemotherapy (months)
1	Wang	19	2021	155	Yes	Multiple	No	TACE → AB × 15 cycles	NS	NS	NS	NS	0	NS	30 alive
2	Yano	20	2021	72	Yes	Single	Right adrenal grand	AB × 4 cycles → LEN (1 month)	SD	PR	41.2 → WNL	13716 → WNL	0	No	9.5 alive
3	Hoshino	21	2022	150	Yes	Single	Right adrenal grand	AB × 9 cycles	PR	CR	759 → 2.2	5681 → 20	0	Yes	11 alive
4	Hidaka	22	2022	NS	Yes	Single	No	TACE → AB × 2 cycles	SD	PR	3.2 → 6.4	20 → 24	0	No	7 alive
5	Fukunaga	23	2023	168	NS	Single	Lung	AB × 7 cycles	PR	CR	NS	43124 → WNL	0	Yes	19 alive
6	Miyata	24	2023	56.6	NS	Multiple	Peritoneum	AB ×15 cycles	SD	NS	8.9 → 3.7	2163 → 20	0	Yes	27 alive
7	our case		2023	123	Yes	Single	No	AB × 3 cycles	PR	CR	177408.3 → 20.8	NE	0	Yes	12 alive

NS: not stated, TACE: Transarterial chemoembolization, AB: Atezolizumab + Bevacizmab, LEN: Lenvatinib, CR: complete remission, PR: partial remission, SD: stable disease, WNL: within normal limit, NE: Not estimated

multidisciplinary treatment aiming for curative surgical resection. A prospective or large cohort study will reveal and confirm the efficacy and safety of this treatment.

References

1) Kokudo T, Hasegawa K, Matsuyama Y, et al.: Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: A Japanese nationwide survey. Hepatology **66**: 510-517, 2017. doi: 10.1002/hep.29225
2) Kokudo T, Hasegawa K, Matsuyama Y, et al.: Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol **65**: 938-943, 2016. doi: 10.1016/j.jhep.2016.05.044
3) Hirokawa F, Hayashi M, Miyamoto Y, et al.: Predictors of poor prognosis by recurrence patterns after curative hepatectomy for hepatocellular carcinoma in Child-Pugh classification A. Hepato-gastroenterology **62**: 164-168, 2015.
4) Yeh CN, Chen MF, Lee WC, et al.: Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. J Surg Oncol **81**: 195-202, 2002. doi: 10.1002/jso.10178
5) Bruix J, Sherman M, American Association for the Study of Liver D: Management of hepatocellular carcinoma: an update. Hepatology **53**: 1020-1022, 2011. doi: 10.1002/hep.24199
6) European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L: EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol **69**: 182-236, 2018. doi: 10.1016/j.jhep.2018.03.019
7) Finn RS, Qin S, Ikeda M, et al.: Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. The New England journal of medicine **382**: 1894-1905, 2020. doi: 10.1056/NEJMoa1915745
8) Antoniotti C, Rossini D, Pietrantonio F, et al.: Upfront FOLFOXIRI plus bevacizumab with or without atezolizumab in the treatment of patients with metastatic colorectal cancer (AtezoTRIBE): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol **23**: 876-887, 2022. doi: 10.1016/S1470-2045(22)00274-1
9) Schwartz LH, Litiere S, de Vries E, et al.: RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer **62**: 132-137, 2016. doi: 10.1016/j.ejca.2016.03.081
10) Schwartz LH, Seymour L, Litiere S, et al.: RECIST 1.1 - Standardisation and disease-specific adaptations: Perspectives from the RECIST Working Group. Eur J Cancer **62**: 138-145, 2016. doi: 10.1016/j.ejca.2016.03.082
11) Kokudo N, Takemura N, Hasegawa K, et al.: Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res **49**: 1109-1113, 2019. doi: 10.1111/hepr.13411
12) Kudo M, Izumi N, Ichida T, et al.: Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res **46**: 372-390, 2016. doi: 10.1111/hepr.12697
13) Arita J, Ichida A, Nagata R, et al.: Conversion surgery after preoperative therapy for advanced hepatocellular carcinoma in the era of molecular targeted therapy and immune checkpoint inhibitors. J Hepatobiliary Pancreat Sci **29**: 732-740, 2022. doi: 10.1002/jhbp.1135
14) Llovet JM, Ricci S, Mazzaferro V, et al.: Sorafenib in advanced hepatocellular carcinoma. The New England journal of medicine **359**: 378-390, 2008. doi: 10.1056/NEJMoa0708857
15) Kudo M, Finn RS, Qin S, et al.: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet **391**: 1163-1173, 2018. doi: 10.1016/s0140-6736(18)30207-1
16) Sato N, Beppu T, Kinoshita K, et al.: Conversion Hepatectomy for Huge Hepatocellular Carcinoma With Arterioportal Shunt After Chemoembolization and Lenvatinib Therapy. Anticancer Res **39**: 5695-5701, 2019. doi: 10.21873/anticanres.13768
17) Ohya Y, Hayashida S, Tsuji A, et al.: Conversion hepatectomy for advanced hepatocellular carcinoma after right portal vein transection and lenvatinib therapy. Surg Case Rep **6**: 318, 2020. doi: 10.1186/s40792-020-01078-3
18) Yokoo H, Takahashi H, Hagiwara M, et al.: Successful hepatic resection for recurrent hepatocellular carcinoma after lenvatinib treatment: A case report. World J Hepatol **12**: 1349-1357, 2020. doi: 10.4254/wjh.v12.i12.1349
19) Wang Y, Lu LC, Guan Y, et al.: Atezolizumab plus bevacizumab combination enables an unresectable hepatocellular carcinoma resectable and links immune exclusion and tumor dedifferentiation to acquired resistance. Exp Hematol Oncol **10**: 45, 2021. doi: 10.1186/s40164-021-00237-y
20) Yano S, Kawaoka T, Johira Y, et al.: Advanced

hepatocellular carcinoma with response to lenvatinib after atezolizumab plus bevacizumab. Medicine (Baltimore) **100**: e27576, 2021. doi: 10.1097/MD.0000000000027576

21) Hoshino T, Naganuma A, Furusawa A, et al.: A case of conversion hepatectomy for huge hepatocellular carcinoma with adrenal metastasis and vascular invasion after atezolizumab-bevacizumab treatment. Clin J Gastroenterol **15**: 776-783, 2022. doi: 10.1007/s12328-022-01644-2

22) Hidaka Y, Tomita M, Desaki R, et al.: Conversion surgery for hepatocellular carcinoma with portal vein tumor thrombus after successful atezolizumab plus bevacizumab therapy: a case report. World J Surg Oncol **20**: 228, 2022. doi: 10.1186/s12957-022-02691-2

23) Fukunaga A, Takata K, Itoh S, et al.: Complete tumor necrosis confirmed by conversion hepatectomy after atezolizumab-bevacizumab treatment for advanced-stage hepatocellular carcinoma with lung metastasis. Clin J Gastroenterol **16**: 224-228, 2023. doi: 10.1007/s12328-022-01744-z

24) Miyata T, Sugi K, Horino T, et al.: Conversion Surgery After Atezolizumab Plus Bevacizumab for Primary and Peritoneal Metastasis After Hepatocellular Carcinoma Rupture. Anticancer Res **43**: 943-947, 2023. doi: 10.21873/anticanres.16239