International Journal of Surgery Case Reports 125 (2024) 110591

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

Conversion hepatectomy after chemotherapy including nivolumab for multiple liver metastases of hepatoid adenocarcinoma of the stomach: A case report and literature review

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ARTICLE INFO

Keywords:
Hepatoid adenocarcinoma of the stomach
Conversion surgery
Hepatectomy
Liver metastasis
Nivolumab

ABSTRACT

Introduction: Currently, there is no evidence of the effectiveness of surgical intervention for Stage IV gastric cancer (GC); however, there are scattered reports of hepatectomy for liver metastasis of GC after chemotherapy including nivolumab.

Presentation of case: We report a case of a 79-year-old man with a history of laparoscopic distal gastrectomy with D2 lymph node dissection for GC, pathologically diagnosed as hepatoid adenocarcinoma of the stomach (HAS), with a combined positive score (CPS) for programmed death (PD)-ligand 1 was >5. Six months after gastrectomy, magnetic resonance imaging (MRI) showed multiple masses in both lobes of the liver, and the patient was treated with a regimen consisting of nivolumab and capecitabine with oxaliplatin (CapeOX). After 11 courses of nivolumab and CapeOX therapy, MRI revealed reduced tumor sizes in both lobes of the liver. The patient underwent left lateral sectionectomy and partial resection of the liver. No new recurrences were observed, and the patient has survived for 15 months after hepatectomy.

Discussion: The recent emergence of PD-1 inhibitors has improved the prognosis of unresectable advanced or recurrent GC. Hepatectomy for liver metastasis of GC can be effective if the conditions are met. In this case, both the resected gastric tumor and metastasis in the left lateral hepatic segment had a CPS > 5, suggesting that nivolumab with CapeOX therapy could control the disease status from unresectable to resectable liver metastasis.

Conclusion: Using multidisciplinary treatment, R0 surgery was successfully performed in a patient with multiple unresectable liver metastases of HAS.

1. Introduction

The incidence and mortality rates of gastric cancer (GC) ranking fourth among all causes of death due to malignant diseases worldwide, are steadily declining [1]. The standard treatment for Stage IV GC is chemotherapy, and there is currently no high-quality evidence regarding the effectiveness of surgical intervention. A recent retrospective global cohort study (CONVO-GC-1) reported that the median survival time (MST) of patients with StageIV GC who underwent conversion surgery was 36.7 months and that most conversion surgeries were performed in patients who responded to first-line chemotherapy [2]. On the other hand, the CheckMate 649 trial confirmed that nivolumab, a programmed death (PD)-1 inhibitor, in combination with an anticancer agent prolonged overall survival (OS) and progression-free survival (PFS) compared to an anticancer agent alone in previously untreated curatively unresectable advanced or recurrent GC [3]. There are scattered reports on the efficacy of hepatectomy for liver metastasis after chemotherapy with nivolumab [4–6]. However, there has been no reports of anti-cancer drugs with nivolumab for the hepatoid adenocarcinoma of the stomach (HAS), which is a special type of GC. HAS is a tumor consisting of large eosinophilic cells with trabeculae separated by sinusoidal vascular channels observed on hematoxylin and eosin staining. HAS presents with high levels of alpha-fetoprotein (AFP), which occur in liver metastasis cases. It has an average survival period of 10–18 months, with 5-year survival rates ranging from 8.3 to 9 % [7]. There has is no specific treatment guideline for HAS.

Herein, we report a case of HAS with multiple liver metastasis treated with nivolmab and capecitabine with oxaliplatin (CapeOX) followed by conversion hepatectomy. This case has been reported in line

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https://doi.org/10.1016/j.ijscr.2024.110591
Received 20 September 2024; Received in revised form 2 November 2024; Accepted 8 November 2024
Available online 15 November 2024

Abbreviations

GC	gastric cancer
HAS	hepatoid adenocarcinoma of the stomach
MRI	magnetic resonance imaging
CT	computed tomography
CapeOX	capecitabine with oxaliplatin
PD	programmed death
CPS	combined positiive score
MST	median survival time
OS	overall survival
PFS	progression free survival
AFP	alpha-feto-protein
CEA	carcinoembryonic antigen
PET-CT	positron emission tomography computed tomography
HER2	human epidermal growth factor receptor 2
MSI	microsatellite instability
PD-L1	programmed death-ligand 1
DFS	disease-free survival

hepatocellular phase (Fig. 1) and positron emission tomography computed tomography (PET-CT) showed multiple masses over 10 in both lobes of the liver with fluorodeoxyglucose accumulation, too. Four monthes after gastrectomy, blood tests revealed elevated serum AFP (reference range: 0.89–8.78 ng/mL) (Fig. 2). Therefore, we diagnosed as multiple recurrent liver metastasis and there was no evidence of further metastatic lesions in other organs. Immunohistochemical analysis of the resected GC showed no reactivity for human epidermal growth factor receptor 2 (HER2), microsatellite instability (MSI) and the combined positive score (CPS) for PD-ligand 1 (PD-L1) was >5. Considering that S-1 had no therapeutic effect, the patient was treated with a regimen consisting of nivolumab (360 mg/day on day 1) and CapeOX (oxaliplatin 130 mg/m^2 on day 1, and capecitabine 2000 mg/m^2 on days 1–14, with a rest period on days 15–21). After 11 courses of nivolumab and CapeOX therapy (oxaliplatin was completed in 6 courses), MRI showed reduced tumor sizes in both lobes of the liver. In the hepatocellular phase, a total of five sites of defect were observed in two right lobes and two lateral areas (Fig. 3). The total length diameter of the two liver metastases reduced from 66 to 16 mm, with a reduction rate of 76 % -this was considered partial response according to RECIST 1.1. As there were no obvious metastasis to other organs in the images and hepatic function was preserved (Child-Pugh A and indocyanine green retention test at 15

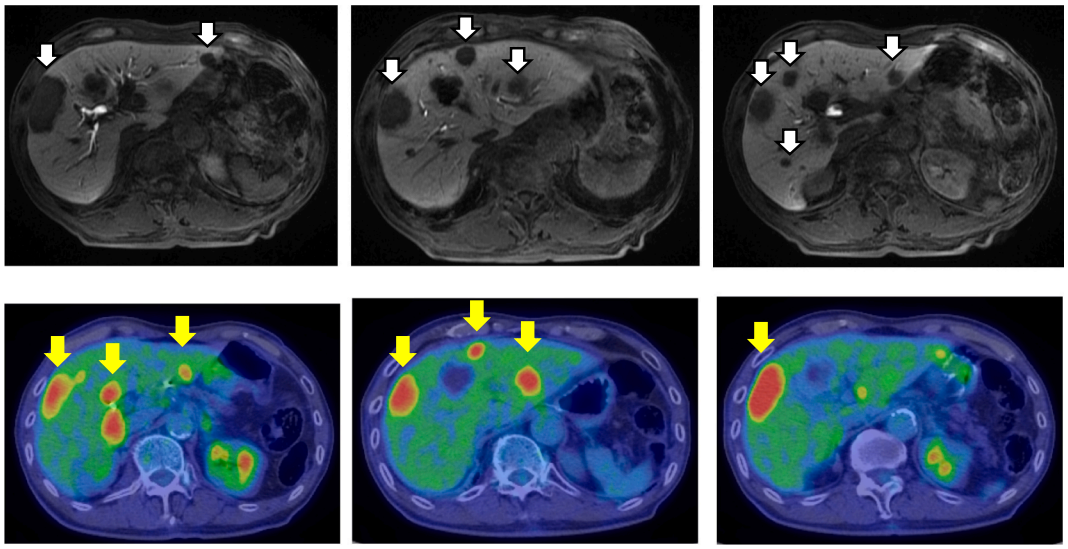

Fig. 1. MRI and PET-CT findings. MRI showing multiple masses in both lobes of the liver in the hepatocellular phase (white arrow). PET-CT showing multiple (over 10) masses in both lobes of the liver with fluorodeoxyglucose accumulation (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with the SCARE checklist criteria [8].

2. Presentation of case

We report a 79-year-old man who underwent laparoscopic distal gastrectomy with D2 lymph node dissection 2 weeks later after diagnosis of GC without distant metastasis in our hospital. The final diagnosis was T3N0M0 stage IIA according to the 8th International Union Against Cancer Tumor-Node-Metastasis classification [9]. Immunostaining was positive for alpha-feto-protein (AFP), and pathologically diagnosed as HAS. No lymphovenous invasion was observed. However, a tumor thrombus was found in a dilated vein within the subserosal layer. Since there was a high possibility of liver metastasis recurrence, we administered adjuvant S-1 chemotherapy (80 mg/m2/day on days 1–28, with a rest period on days 29–42) 4 weeks after gastrectomy. After 3 courses of S-1 therapy (six months after gastrectomy), magnetic resonance imaging (MRI) showed multiple masses over 10 in both lobes of the liver in the min: 7.0 %), the patient underwent left lateral sectionectomy and partial resection (segment 4,5 and 8) of the liver. Pathological findings revealed viable tumor cells in the resected specimens of left lateral segment and segment 4, no viable tumor cells in resected specimens of segment 5 and 8. In the resected tumor of left lateral hepatic segment, CPS for PD-L1 was >5. The patient was discharged 16 days after surgery without postoperative complications. There have been no new recurrences in PET-CT and MRI (Fig. 4), and the patient has continued the nivolumab regimen in an outpatient clinic and survived for 15 months after hepatectomy.

3. Discussion

Recent years, the emergence of PD-1 inhibitors has contributed to improve the prognosis of patients with unresectable, advanced, or recurrent GC. The CheckMate649 trial demonstrated the additive effects of nivolumab, which is a widely used as a therapeutic agent [3].

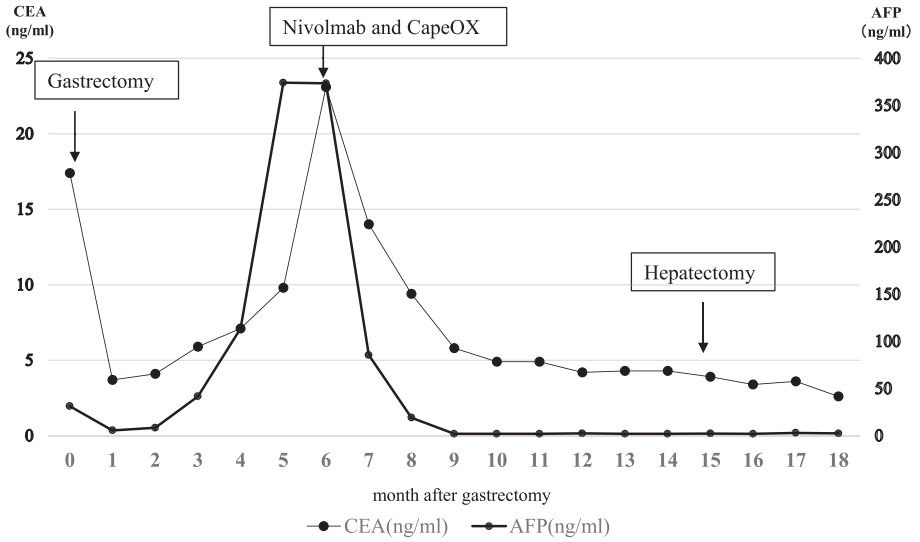

Fig. 2. This graph shows the evolution of tumor markers after gastrectomy. Serum AFP and carcinoembryonic antigen (CEA) were elevated on blood tests 4 months postoperatively.

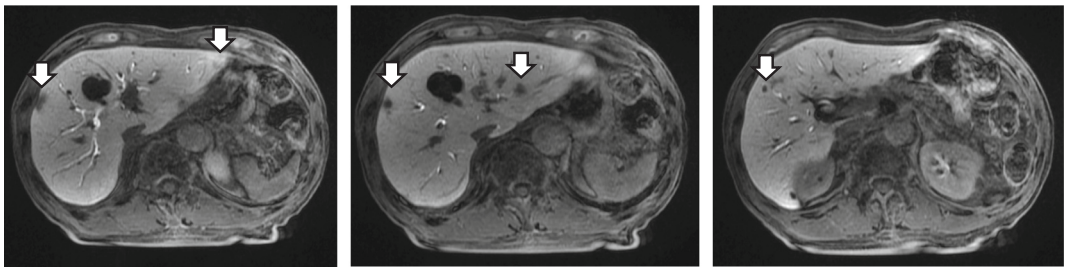

Fig. 3. MRI findings. MRI after chemotherapy showing prominent reduction of multiple masses in both lobes of the liver in the hepatocellular phase (white arrow).

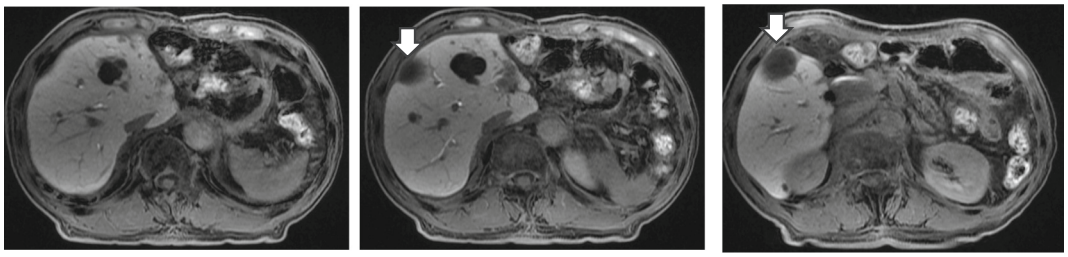

Fig. 4. MRI findings. MRI after hepatectomy showing no recurrence and fluid collection on the dissected surface of the liver in the hepatocellular phase (white arrow).

Even if R0 resection can be achieved, the usefulness of hepatectomy for liver metastasis remains controversial [10]. Monroy et al. reported a meta-analysis using random-effects models to assess overall survival (OS) and disease-free survival (DFS) at 1, 3, and 5 years postoperatively. The OS rates in 1, 3, and 5 years after surgery were 69.79 %, 34.79 %, and 24.68 %, whereas DFS was 41.39 %, 23.23 %, and 20.18 %, respectively [11]. They reported that well-to-moderate differentiation, small hepatic tumoral size, early nodal stage, R0 resection, unilobar compromisation, and solitary lesions were associated with higher OS, and MST after hepatectomy for liver metastasis of GC was 24.5 months. This report suggests that hepatectomy for liver metastasis of GC may be effective if these conditions are met. The present case fulfilled following conditions: small hepatic tumoral size (after chemotherapy), early nodal stage, R0 resection, suggesting that hepatectomy may improve the prognosis. Recently, there have been some reports of improved prognosis with hepatectomy for liver metastasis in ordinary GC after chemotherapy with nivolumab [4–6].

HAS is a rare subtype of GC and accounts for <1 % of all GCs. According to previous reports, HAS has worse prognosis than ordinary GC and a higher rate of liver metastasis than peritoneal dissemination recurrence [12]. Various drugs, such as platinum, antimetabolites, molecular targeted agents, have been introduced for chemotherapy [12], but no standard treatment for HAS, including chemotherapy, has been established. Currently, HAS is treated as an ordinary GC, and hepatectomy for liver metastasis resulted in a favorable outcome [13]. On the other hand, Yang et al. reported that approximately 40 % of HAS cases had a CPS $\geq$ 1, but the percentage of CPS for PD-L1 > 5 was unknown [14]. We could not find any reports of relationship between CPS for PD-L1 and HAS as far as we searched.

In this case, we introduced a regimen of nivolumab and CapeOX,

Table 1
Summary of recent case reports of hepatectomy for liver metastasis of GC after nivolumab administration.

Case	Source (refs.) year	Age Gender	CPS for PD-L1 (gastric tumor)	HER2	MSI	Doses of nivolumab	Combination anticancer agent	Surgery for liver metastasis	Postoperative chemotherapy	Outcome (period after hepatectomy)
1	Cen et al. [4] 2023	69 Female	>5	Negative	Negative	18	None	Partial hepatectomy of segment 4 and 8	None	Alive (25 months)
2	Kawai et al. [5] 2024	68 Male	>5	Negative	Negative	16	SOX	Partial hepatectomy on the surface scarred lesion	DS	Alive (unknown)
3	Kawai et al. [5] 2024	71 Male	Negative	Negative	–	8	None	Partial hepatectomy of segment 7 and scarred lesion	None	Alive (7 months)
4	Kawai et al. [5] 2024	51 Female	>5	Negative	–	15	SOX	Partial hepatectomy of segment 7	DS	Alive (6 months)
5	Katsumata [6] 2024	54 Male	>5	Negative	–	4	SOX	Partial hepatectomy	S1	Alive (18 months)
6	Present case	79 Male	>5	Negative	Negative	11	CapeOX	Left lateral segmentectomy and partial hepatectomy of segment 4,5,8	Nivolumab	Alive (15 months)

SOX: S1 with oxaliplatin, CapeOX: capecitabine with oxaliplatin, DS: S1 with docetaxel.
HER2: human epidermal growth factor receptor 2, MSI: maicrosatellite instability.

because the patient had a recurrence of liver metastasis while receiving S-1 as adjuvant chemotherapy, according to the Japanese guideline for GC treatment [15]. Hepatectomy was suggested after the liver metastasis were judged to be resectable according to Japanese guideline for liver cancer treatment [16]. As liver function was preserved and MRI at the end of 8th and 11th courses of chemotherapy showed no change in the size of the liver metastases, we performed hepatectomy for live metastasis. In recent reports, hepatectomy after nivolumab was effective for liver metastasis of GC usually for CPS $>$ 5. (Table.1) Both the resected gastric tumor and metastasis in the left lateral hepatic segment had a CPS $>$ 5, suggesting that nivolumab with CapeOX therapy could help convert the disease status from unresectable to resectable liver metastasis. Since we used unestablished treatment for this rare disease, standardizing this treatment may have some limitations.

For liver metastasis of GC, biopsy of the liver metastasis and CPS may be indicators for the choice of chemotherapy including nivolumab.

4. Conclusion

R0 surgery was successfully performed in a patient with multiple unresectable liver metastasis of HAS using multidisciplinary treatment. This multimodal treatment including nivolumab therapy may be a treatement potion for HAS with liver metastasis.

Informed consent

Informed consent was obtained from the patient for presentation of the details of this case, along with the images for the purposes of publication. No personal identification information has been displayed in the images.

Ethical approval

This study protocol was reviewed and the need for approval was waived by the Institutional Review Board of the Onomichi General Hospital Ethics Review Committee.

Funding

The authors have received no financial support for the research, authorship, or publication of this manuscript.

Author contribution

Shohei Shiozaki: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Conceptualization, Writing – Original Draft, Writing-Review & Editing, Visualization.

Senichiro Yanagawa: Conceptualization, Methodology, Validation, Data Curation, Writing-Review & Editing, Supervision, Project administration.

Yuji Yamamoto: Validation, Writing- Review & Editing.

Daisuke Takei: Validation, Writing – Review & Editing.

Akihiko Oshita: Validation, Writing – Review & Editing.

Toshio Noriyuki: Validation, Writing – Review & Editing, Project administration.

Guarantor

Senichiro Yanagawa.

Research registration number

N/A.

Conflict of interest statement

None.

Acknowledgements

The authors thank the patient for providing consent to publish the clinical information and data in this report.

We would like to thank Editage (www.editage.com) for English language editing.

Data availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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