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Robotic Parenchyma-Sparing Repeat Hepatectomy After Durvalumab Plus Tremelimumab for Recurrent Hepatocellular Carcinoma Abutting the Left Glissonean Pedicle Following Prior Atezolizumab-Bevacizumab Failure: A Case Report

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Abstract

Immune checkpoint inhibitor (ICI)-based combination therapies have expanded the treatment options for hepatocellular carcinoma (HCC), and tumor shrinkage achieved with these regimens can make limited, parenchyma-sparing resection possible. We report the case of a 67-year-old man with multiple HCCs who had received atezolizumab plus bevacizumab without response and then underwent portal vein embolization followed by open right hepatectomy. Forty-eight months after hepatectomy, magnetic resonance imaging revealed new HCC lesions in segments 3 and 4 of the remnant left liver; the segment 4 lesion abutted the main left Glissonean pedicle, which had to be preserved. Durvalumab plus tremelimumab was administered for three courses and produced marked tumor shrinkage, separating the tumor from the pedicle. Robot-assisted partial resection of segments 3 and 4 was performed with indocyanine green fluorescence guidance, despite dense adhesions from the previous surgery. The patient was discharged without post-hepatectomy liver failure or complications. Pathology showed well-differentiated HCC without vascular invasion. The patient is alive without recurrence and without systemic therapy 69 months after the initial diagnosis. This case suggests that durvalumab plus tremelimumab can be effective even after atezolizumab-bevacizumab failure, that patient selection for first-line ICI combinations remains an important open question, and that robotic parenchyma-sparing hepatectomy is a reasonable surgical option after systemic therapy.

Categories: General Surgery, Oncology, Gastroenterology
Keywords: conversion surgery, durvalumab plus tremelimumab, hepatocellular carcinoma, parenchyma-sparing hepatectomy, robotic liver resection

Introduction

Systemic therapy for unresectable hepatocellular carcinoma (HCC) has changed substantially with the introduction of immune checkpoint inhibitor (ICI)-based combination regimens. Atezolizumab plus bevacizumab and durvalumab plus tremelimumab improved overall survival over sorafenib in the IMbrave150 and HIMALAYA trials, respectively, and both are now standard first-line options [1-3]. More recently, nivolumab plus ipilimumab has also shown an overall survival benefit in the first-line setting [4]. Clinicians can therefore choose among several ICI combinations with different mechanisms, but robust criteria for choosing between them are still lacking.

These regimens can produce tumor shrinkage substantial enough to allow curative-intent resection of initially unresectable or borderline resectable HCC, a strategy known as conversion surgery [5-7]. Our group has previously reported conversion to robotic liver resection after atezolizumab plus bevacizumab, including a case with a pathological complete response and a case of multiple HCCs adjacent to major vessels [8,9]. In contrast, reports of resection after durvalumab plus tremelimumab remain few, and responses to this regimen after failure of atezolizumab plus bevacizumab have varied [10,11].

When systemic therapy is used to shrink a tumor before surgery, the goal is often not only to make resection possible but also to make it smaller. Preserving liver parenchyma is especially important in patients who have already undergone major hepatectomy, because injury to the remnant Glissonean pedicle would have been fatal. Preserving parenchyma is also crucial in those likely to need further treatment for recurrence. Robotic liver resection offers magnified three-dimensional vision and articulated instruments that may help with precise dissection around major Glissonean pedicles, even in a reoperative field [12,13].

We report the case of a patient with recurrent HCC in the remnant left liver after right hepatectomy, whose tumor abutted the left Glissonean pedicle. The patient had previously not responded to atezolizumab plus bevacizumab, but durvalumab plus tremelimumab produced marked shrinkage that enabled robotic

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parenchyma-sparing resection, and the patient remains alive without recurrence or systemic therapy 64 months after the initial diagnosis.

Case Presentation

A 67-year-old man with non-viral metabolic dysfunction-associated steatotic liver disease was referred to our hospital for multiple HCCs in the right liver, including tumors in segments 7 and 5 (Figures *1A*, *1B*). To spare liver parenchyma, atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) was administered for four courses. However, the tumors did not shrink (Figures *1C*, *1D*), and the response was judged as progressive disease according to mRECIST (segment 7: 42 to 50 mm; segment 5: 32 to 39 mm, +20.3%). After portal vein embolization, curative-intent open right hepatectomy was successfully performed. No adjuvant therapy was given, and the patient remained recurrence-free on regular surveillance.

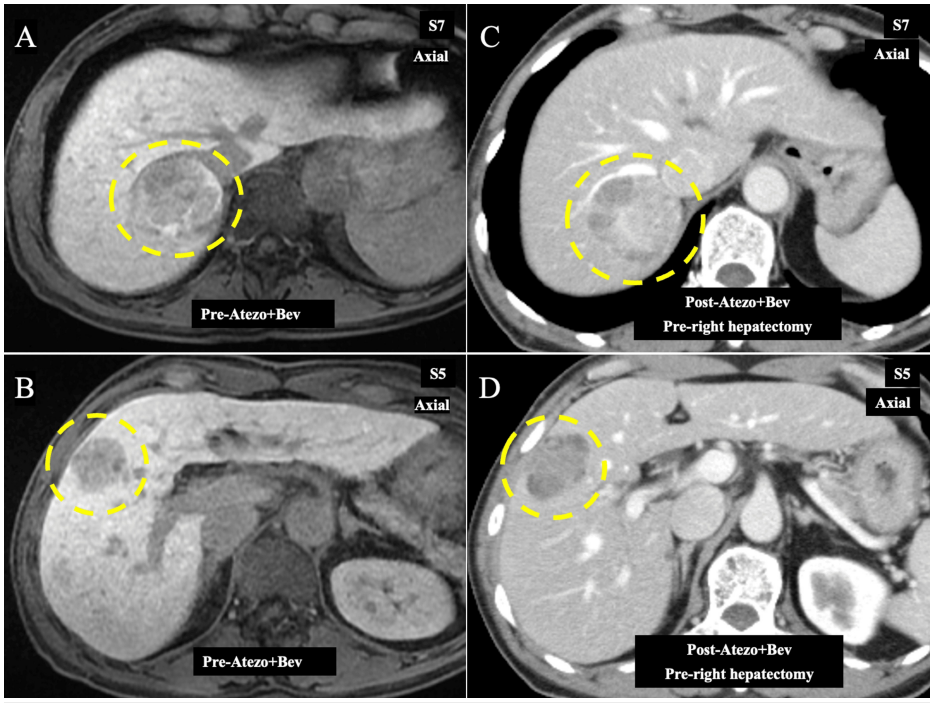


FIGURE 1: Imaging findings before and after atezolizumab plus bevacizumab for the initial hepatocellular carcinomas.

(A, B) Gadoxetic acid-enhanced MRI (hepatobiliary phase) before atezolizumab plus bevacizumab showed tumors in segment 7 (A) and segment 5 (B) (yellow dashed circles). (C, D) Contrast-enhanced CT after four courses of atezolizumab plus bevacizumab, before right hepatectomy, showed no meaningful shrinkage of the segment 7 (C) and segment 5 (D) tumors (yellow dashed circles).

Forty-eight months after right hepatectomy, follow-up enhanced CT scans and MRI showed new lesions in segment 4 (25 mm) and segment 3 (17 mm) of the remnant left liver, suggestive of HCC recurrence (Figures *2A*-*2C*). The segment 4 lesion was in direct contact with the main left Glissonean pedicle. Because the patient had a remnant left liver after right hepatectomy, preservation of this pedicle was essential, and immediate resection would have risked injury to the inflow of the entire remnant liver. We therefore planned systemic therapy first, followed by resection once the tumor had shrunk away from the pedicle.

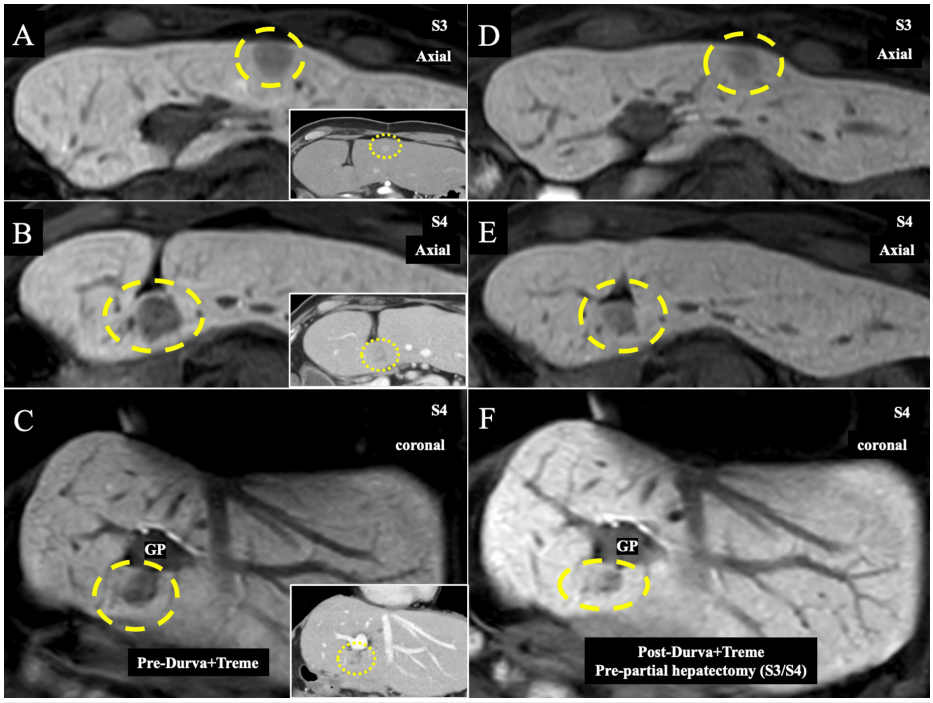


FIGURE 2: MRI and enhanced CT findings before and after durvalumab plus tremelimumab for recurrent hepatocellular carcinoma.

(A-C) Before treatment, MRI showed tumors in segment 3 (A, axial) and segment 4 (B, axial; C, coronal) of the remnant left liver; the segment 4 tumor abutted the main left Glissonean pedicle (yellow dashed circles). The findings of enhanced CT scans are also shown in the lower right insets of A-C, respectively. (D-F) After three courses of durvalumab-based therapy, before partial hepatectomy of segments 3 and 4, both tumors had markedly decreased in size, and the segment 4 tumor had receded from the left Glissonean pedicle (yellow dashed circles).

GP: left Glissonean pedicle

Durvalumab plus tremelimumab was started using the single tremelimumab regular interval durvalumab (STRIDE) regimen: tremelimumab 300 mg plus durvalumab 1,500 mg in the first course, followed by durvalumab 1,500 mg monotherapy every four weeks in the second and third courses. There were no clinically relevant immune-related adverse events during the whole course. After three courses, MRI showed marked shrinkage of both lesions (segment 4: 25 to 14 mm; segment 3: 17 to 13 mm, -35.7%), and the segment 4 lesion had receded from the left Glissonean pedicle (Figures *2D*-*2F*). The response was judged as a partial response according to mRECIST. Preoperative liver function was Child-Pugh class A (5 points) and liver damage grade A, with an indocyanine green retention rate at 15 minutes (ICG-R15) of 5.8% and an ICG plasma disappearance rate (K-ICG) of 0.291. Serum alpha-fetoprotein (AFP) was 2.0 ng/mL, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) was 19 mAU/mL. The detailed preoperative data are summarized in Table *1*.

Parameter	Result	Reference range
WBC	4.5 × 10^3/μL	3.3–8.6 × 10^3/μL
Hemoglobin	10.2 g/dL	13.7–16.8 g/dL
Platelet	22.0 × 10^4/μL	12.0–39.0 × 10^4/μL
BUN	14.3 mg/dL	8.0–20.0 mg/dL
Creatinine	0.83 mg/dL	0.65–1.0 mg/dL
AST	23 U/L	13–30 U/L
ALT	14 U/L	10–30 U/L
T-Bil	0.5 mg/dL	0.4–1.5 mg/dL
γ-GTP	25 IU/L	<50 IU/L
ALP	88 U/L	38–113 U/L
PT	99%	70–130 %
AFP	2.0 ng/mL	<10 ng/mL
PIVKA-II	19 mAU/mL	<40 mAU/mL
ICG-R15	5.8%	<10%
K-ICG	0.291	≥0.200

TABLE 1: Preoperative laboratory findings.

WBC: white blood cell count; BUN: blood urea nitrogen; AST: aspartate transaminase; ALT: alanine transaminase; T-Bil: total-bilirubin; γ-GTP: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; PT: prothrombin time activity; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; ICG-R15: indocyanine green retention rate at 15 minutes; K-ICG: ICG plasma disappearance rate

Surgery was planned four weeks after the last dose of durvalumab, and curative-intent robot-assisted partial resection of segments 4 and 3 was performed. Dense adhesions from the previous right hepatectomy were present around the hepatoduodenal ligament and were carefully divided. The round ligament was identified and dissected, and the segment 4 tumor was localized at its central side using ICG fluorescence imaging (Figures *3A*, *3B*). The segment 4 tumor was resected first. Liver parenchymal transection was performed with the saline-linked coagulation (SLiC) method, a previously reported novel technique for robotic hepatectomy [13]. The tumor abutted the main left Glissonean pedicle, which was carefully preserved while the tumor was dissected away from it. The segment 3 tumor, also identified by ICG fluorescence, was then resected in the same manner (Figures *3C*, *3D*). The operative time was 411 minutes, the console time was 323 minutes, and the estimated blood loss was 54 mL. There were no intraoperative complications.

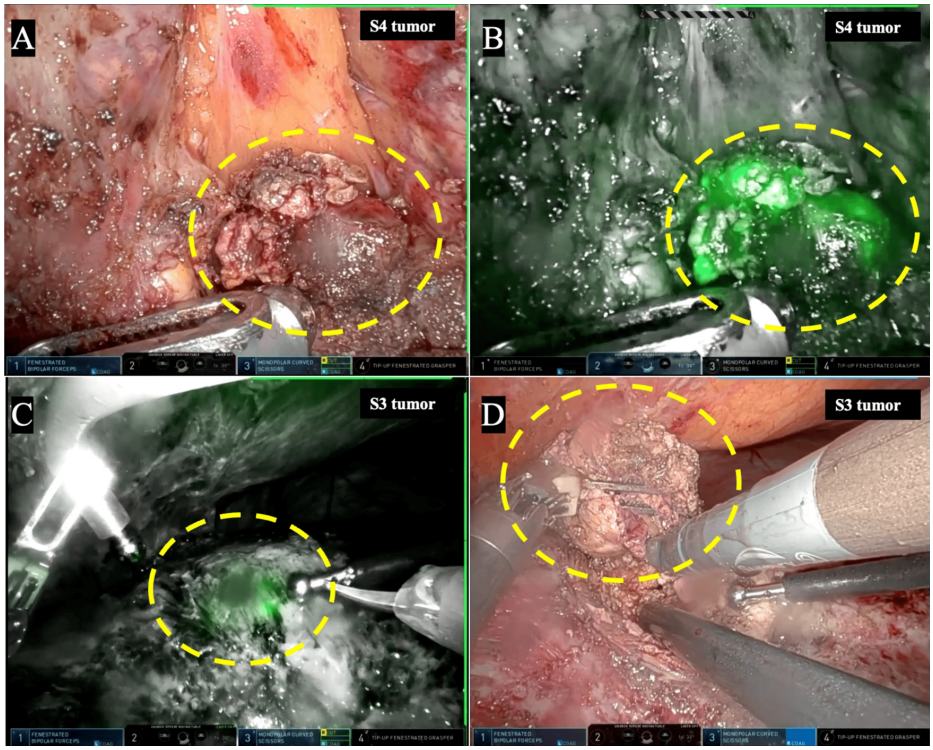


FIGURE 3: Intraoperative findings during robot-assisted partial hepatectomy of segments 3 and 4.

(A) The segment 4 tumor under white light (yellow dashed circle). (B) The same segment 4 tumor visualized by indocyanine green (ICG) fluorescence imaging under near-infrared light. (C) The segment 3 tumor visualized by ICG fluorescence imaging. (D) Resection of the segment 3 tumor under white light.

The postoperative course was uneventful, without post-hepatectomy liver failure or other complications, and the patient was discharged home on postoperative day 10. Histopathological examination showed well-differentiated HCC of the trabecular type, with some tumor cells containing fat. The background liver showed mild chronic inflammation in the portal tracts and mild steatosis without fibrosis. The surgical margin was considered negative. No adjuvant therapy was given. The patient has remained free of recurrence on follow-up imaging and tumor markers and is alive with a satisfactory performance status, without any anticancer drug therapy, 64 months after the initial diagnosis of HCC and 10 months after the second hepatectomy. Figure *4* summarizes the clinical course, including the progression of tumor markers, and Table *2* provides an overview of therapeutic interventions.

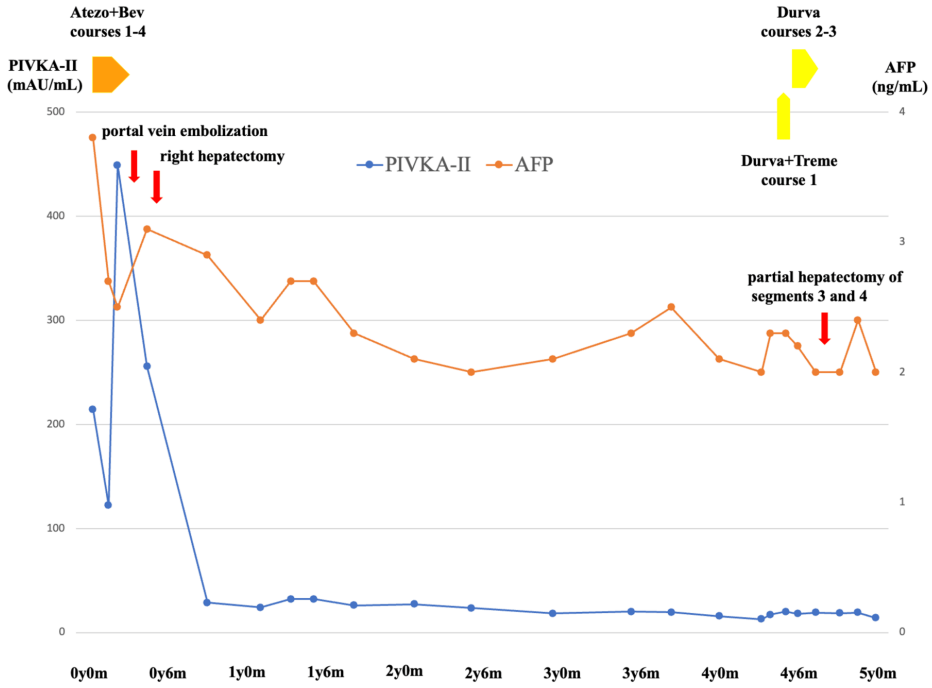


FIGURE 4: Clinical course and changes in serum AFP and PIVKA-II levels.

Timing of atezolizumab plus bevacizumab (courses 1-4), portal vein embolization, right hepatectomy, durvalumab plus tremelimumab (course 1), durvalumab monotherapy (courses 2-3), and partial hepatectomy of segments 3 and 4 is shown. The figure is the authors' own creation.

AFP: alpha-fetoprotein (ng/mL); PIVKA-II: protein induced by vitamin K absence or antagonist-II (mAU/mL)

Items	Location and size	Type of BT used	Diagnostic response	mRECIST status	Type of surgery performed	Surgical blood loss	LOS
Initial HCCs	S7 (42 mm), S5 (32 mm)	Atezo + Bev	+20.3%	PD	Open right hepatectomy	1,780 mL	18 days
Recurrent HCCs	S4 (25 mm), S3 (17 mm)	Durva + Treme	-35.7%	PR	Robotic S3, S4 partial hepatectomy	54 mL	10 days

TABLE 2: Summary of therapeutic interventions and comparison of the initial and recurrent lesions.

HCC: hepatocellular carcinoma; BT: biological therapy; PD: progressive disease; PR: partial response; LOS: length of postoperative stay

Discussion

This case has three clinically relevant features. First, durvalumab plus tremelimumab produced marked shrinkage of recurrent HCC in a patient whose earlier tumors had not responded to atezolizumab plus bevacizumab, enabling curative resection and long-term recurrence-free survival without ongoing drug therapy. Second, it raises the practical question of how to select among first-line ICI combinations. Third, it illustrates how robotic parenchyma-sparing hepatectomy can complete a strategy of systemic therapy followed by limited resection, even in a reoperative field.

Durvalumab plus tremelimumab combines programmed death-ligand 1 (PD-L1) blockade with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade. In the STRIDE regimen, a single priming dose of tremelimumab is thought to expand and diversify tumor-reactive T cells, after which durvalumab maintains the response [2,14]. In the HIMALAYA trial, this regimen improved overall survival compared with sorafenib, and the survival benefit was maintained at four years, with a plateau in the survival curve suggesting durable benefit in a subset of patients [2,3].

In our patient, the earlier tumors did not respond to atezolizumab plus bevacizumab, whereas the recurrent tumors responded well to durvalumab plus tremelimumab. Several explanations are possible. The recurrent tumors arose about four years later and may have differed biologically from the original tumors. In addition, the added CTLA-4 blockade may have overcome resistance to PD-L1 blockade alone, and the long ICI-free interval may have allowed immune function to recover. Small retrospective studies have reported disease control with durvalumab plus tremelimumab after atezolizumab plus bevacizumab, but responses have varied, and objective response rates in this setting appear lower than in the first-line setting [10,11]. Our case shows that a lack of response to one ICI combination does not necessarily predict a lack of response to another.

The absence of an anti-vascular endothelial growth factor (VEGF) agent in this regimen is also relevant to surgery. Bevacizumab is associated with impaired wound healing and bleeding, and an adequate washout period is usually needed before elective surgery. Durvalumab plus tremelimumab avoids this concern, which may make it easier to schedule resection once sufficient tumor shrinkage is achieved. On the other hand, it carries a higher risk of immune-related adverse events, particularly during the priming phase, which must be monitored and resolved before surgery [2,14].

Regarding selecting patients for first-line ICI combinations, with atezolizumab plus bevacizumab, durvalumab plus tremelimumab, and nivolumab plus ipilimumab all available, choosing the first-line regimen has become an important clinical question [1,2,4]. No head-to-head trial has compared these regimens, and no validated biomarker currently guides the choice. In practice, selection is based mainly on clinical factors. Atezolizumab plus bevacizumab may be avoided in patients with high-risk varices, bleeding tendency, significant proteinuria, or recent or planned surgery, whereas regimens containing CTLA-4 inhibitors may be less suitable for patients at high risk of immune-related adverse events.

Several biological factors have been proposed as possible predictors. Non-viral, particularly metabolic dysfunction-associated, HCC may respond less well to ICI therapy in some analyses [15]. Activating mutations in the Wnt/beta-catenin pathway have been associated with an immune-excluded tumor microenvironment and resistance to ICIs [16]. Translational analyses of atezolizumab plus bevacizumab have identified pre-existing immunity and VEGF-related gene signatures associated with response [17]. However, none of these factors has been validated for choosing between ICI combinations. In our patient, the background liver showed mild steatosis without fibrosis, and the tumor responded to a CTLA-4-containing regimen after an earlier anti-PD-L1/anti-VEGF regimen had failed. Accumulating such cases, together with tissue-based and circulating biomarker studies, will be needed to define which patients benefit most from each first-line ICI combination, both in palliative and conversion settings.

The broader role of ICI combinations before surgery is also being explored. In phase II trials of resectable HCC, perioperative nivolumab with or without ipilimumab and neoadjuvant cemiplimab were feasible and produced major pathological responses in some patients [18,19]. A recent expert consensus from Japan has also proposed oncological resectability criteria for HCC in the era of novel systemic therapies [5]. Our case suggests that ICI combinations may also be useful when the aim is to reduce the extent of resection, not only to convert unresectable disease to resectable disease.

Concerning robotic parenchyma-sparing hepatectomy after systemic therapy, when systemic therapy shrinks a tumor away from a major vessel or Glissonean pedicle, the surgical goal should be to remove the tumor while preserving as much functional liver as possible. In this patient, the remnant left liver was the only liver left after a right hepatectomy, and injury to the left Glissonean pedicle would have been fatal. Shrinkage of the tumor allowed limited resection of segments 3 and 4 with preservation of the pedicle, and the patient had no post-hepatectomy liver failure. Liver parenchyma preservation also keeps options open for future treatment if HCC recurs again, which is common in this disease.

Robotic surgery was particularly useful in this reoperative setting. Dense adhesions around the hepatoduodenal ligament after open right hepatectomy were divided under magnified three-dimensional vision, and ICG fluorescence imaging helped localize both tumors without wide mobilization [20]. Articulated instruments and the SLiC-Scissors method allowed precise parenchymal transection along the left Glissonean pedicle with minimal blood loss [13]. Our previous reports of robotic resection after atezolizumab plus bevacizumab showed similar advantages [8,9]. Taken together, these experiences suggest that robotic parenchyma-sparing hepatectomy is a reasonable choice for conversion surgery and limited resection after systemic therapy.

This report has limitations. It describes a single patient, and the follow-up after the second hepatectomy is still short. As viable HCC was present in the resected tumor, the long-term outcome cannot be attributed to systemic therapy alone. The relative contributions of durvalumab plus tremelimumab and surgery to recurrence-free survival cannot be separated.

Conclusions

Durvalumab plus tremelimumab produced marked shrinkage of recurrent HCC abutting the left Glissonean

pedicle after right hepatectomy, even though earlier tumors had not responded to atezolizumab plus bevacizumab. This enabled robotic parenchyma-sparing curative-intent resection without liver failure. ICI combinations are likely to play a growing role before surgery, but how to select patients for each first-line regimen remains an important question. When systemic therapy is followed by resection, minimally invasive, parenchyma-sparing approaches such as robotic liver resection should be considered.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Takahisa Fujikawa, Yusuke Uemoto, Keiji Nagata

Acquisition, analysis, or interpretation of data: Takahisa Fujikawa, Yusuke Uemoto, Keiji Nagata

Drafting of the manuscript: Takahisa Fujikawa

Critical review of the manuscript for important intellectual content: Takahisa Fujikawa, Yusuke Uemoto, Keiji Nagata

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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