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Case: Authentic multimodal therapy and liver resection for an initially unresectable intrahepatic cholangiocarcinoma

Koichiro Sakata[a,*], Daiki Kijima[b], Taizo Yamaguchi[c], Takashi Furuhashi[a], Toshihiko Abe[a], Haruki Iwamoto[c], Katsuhiko Morita[b]

[a] Japan Seafares Relief Association, Ekisaikai Moji Hospital, 1-3-1 Kiyotaki, Mojiku, Kitakyushu, Fukuoka, 801-8550, Japan
[b] JCHO Shimonoseki Medical Center, 3-21-25 kamishinchi-machi, Shimonoseki, Yamaguchi, 750-0061, Japan
[c] Iwamoto Clinic, 1-2-8 Shimoishida, Kokuraminamiku, Kitakyushu, Fukuoka, 802-0832, Japan

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ABSTRACT

INTRODUCTION: Although curative resection is an outstanding prognostic factor of intrahepatic cholangiocarcinoma (ICC), certain segments remain unresectable. The standard therapy for initially unresectable ICC is uncertain. In this case report, we reported the feasibility of multimodal chemotherapy and curative resection.

CASE: A 59-year-old Asian woman with back pain was referred to the hospital by her family physician regarding liver mass visible on ultrasonography. At admission, the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were high, and images showed characteristic signs of ICC with intrahepatic metastases and invasions to on the right Glisson's sheath. Multimodal therapy was applied to the ICC, which could not be resected at first. The therapy comprised hepatic arterial chemoembolization with drug-eluting beads (DEB-TACE), angiographic subsegmentectomy (AS), and systemic chemotherapy. Downstaging of the ICC, which results in curative resection, was planned due to non-normalization of the tumor markers, and pathological analysis revealed complete remission. At 34 months after the surgery, the patient was alive without relapse.

DISCUSSION: Recently, chemotherapy and/or an interventional approach were reported to be feasible, although unresectable advanced ICC has a poor prognosis. Some studies have reported that multimodal chemotherapy and R0 resection of initially unresectable ICC can prolong survival time. However, some reports have shown high morbidity and mortality associated with initially unresectable ICC treated with multimodal chemotherapy and R0 resection. Our study resulted in complete remission without complications.

CONCLUSION: Multimodal chemotherapy and hepatic curative resection on locally advanced ICC are feasible treatment approaches for initially unresectable ICC.

1. Introduction

Curative resection is an important prognostic factor in intrahepatic cholangiocarcinoma (ICC); however, certain segments remain unresectable. Recently, the efficacy of combined therapy with systemic chemotherapy, interventional therapy, and hepatic curative resection for very advanced inoperable ICCs have been reported [1–4]. This paper reports the feasibility of multimodal chemotherapy including hepatic arterial chemoembolization with drug-eluting beads (DEB-TACE), angiographic subsegmentectomy (AS), systemic chemotherapy following radical surgery. This case report was in accordance with the SCARE criteria [5].

2. Case report

Here, we reported ICC in a 59-year-old Japanese woman with back pain, who had been referred to our hospital by her family physician. There were no special notes in her past medical, drug, and family history, or in her relevant physical examination and other significant clinical findings including no alcoholic habits. At admission, the CEA and CA19-9 levels were 910.5 ng/mL and 1965.3 U/mL, respectively. There were no evidences of hepatitis infection. (Table 1). Computed tomography (CT) findings revealed the presence of two low-density masses 68 mm in diameter in hepatic segments 2 and 3 and 72 mm in diameter in segment 8, with early enhancement of the peripheral area as the main loci. Magnetic resonance cholangiopancreatography revealed dilation of the distal intrahepatic bile duct from the tumors. Radiological findings as irregular masses of relatively low atten-

* Corresponding author.
E-mail address: k.sakata@kousei-h.jp (K. Sakata).

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Table 1
Laboratory test results.

WBC	9300	$10^4/\mu l$	PT(%)	96.1	%
RBC	415	$10^4/\mu l$	PT(INR)	1.02	
Hb	12.2	g/dl	APTT	29.8	sec
Ht	37.3	%			
Plt	27.3	$10^4/\mu l$	ICGR15	6.8	%
CRP	0.77	mg/dl			
Alb	4.3	g/dl	CEA	910.5	ng/ml
T-bil	0.71	mg/dl	CA19-9	1965.3	U/ml
ALT	25	IU/l	AFP	5	ng/ml
AST	31	IU/l	PIVKAII	13	mAU/ml
ALP	206	IU/l			
γ-GTP	101	IU/l			
BUN	10.7	mg/dl	HCV Ab	(-)	
Cre	0.67	mg/dl	HBV Ab	(-)	
Na	141	mEq/l	HBV Ag	(-)	
K	4.2	mEq/l			
Cl	103	mEq/l			

uation in the early phase that demonstrate minimal contrast enhancement at the periphery with focal intrahepatic bile duct dilatation showed peripheral cholangiocarcinoma. These tumors were clinically diagnosed as ICC and were suspected to invade the right Glisson's sheath with multiple intrahepatic metastases classed as stage IVA according to the TMN classification, and were deemed initially unresectable (Figs. 1 and 2). After hepatic arterial chemoembolization therapy with drug-eluting beads (DEB-TACE), angiographic-subsegmentectomy (AS) and systemic chemotherapy with Gemcitabine and S1 were performed, tumor shrinkage was confirmed, and the tumor markers decreased to just above the normal range (Fig. 3). Thus, the patient was referred to our hospital for surgery. CT revealed that the tumor did not invade the right Glisson's sheath and the intrahepatic metastases disappeared (Fig. 4). After the simulation of hepatic resection, left lateral segmentectomy and 8th subsegmentectomy were performed (Fig. 5). Blood loss was 600 mL, and the operative time was 470 min. Pathological examination after R0 resection revealed that no viable neoplastic cells remained in the specimen (Fig. 6). The patient was discharged on day 29 after surgery without complications, and no chemotherapy was administered. Two years and 10 months after the surgery, the patient is alive without relapse (Fig. 7).

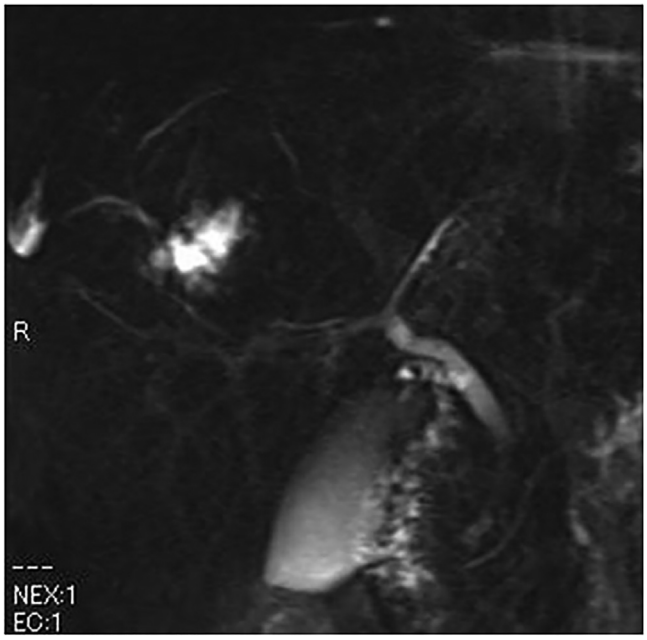

Fig. 2. MRI images at admission.
Peripheral dilation of the intrahepatic bile duct of the 8th branch can be seen, suggesting bile duct invasion.

3. Discussion

Curative R0 resection resulted in improved survival and has been reported to be an extremely important prognostic variable of ICC [6,7]. However, a portion of the ICC that had been diagnosed as unresectable at admission remained. In ICC, larger tumor size, multifocal disease, lymph node metastasis, and vascular invasion

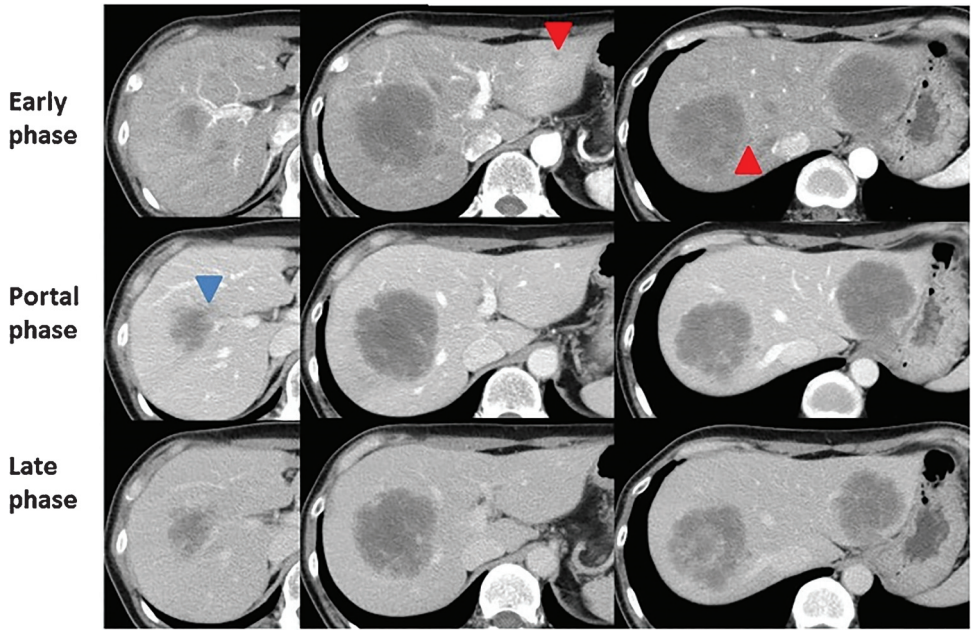

Fig. 1. CT images at admission.
Computed tomography (CT) showed two low-density masses of 68 mm in diameter in hepatic segments 2 and 3 and 72 mm in diameter in segment 8 as the main loci. These tumors were diagnosed as intrahepatic cholangiocarcinoma and were suspected to invade the right Glisson's sheath (blue triangle) with multiple intrahepatic metastases (red triangles).

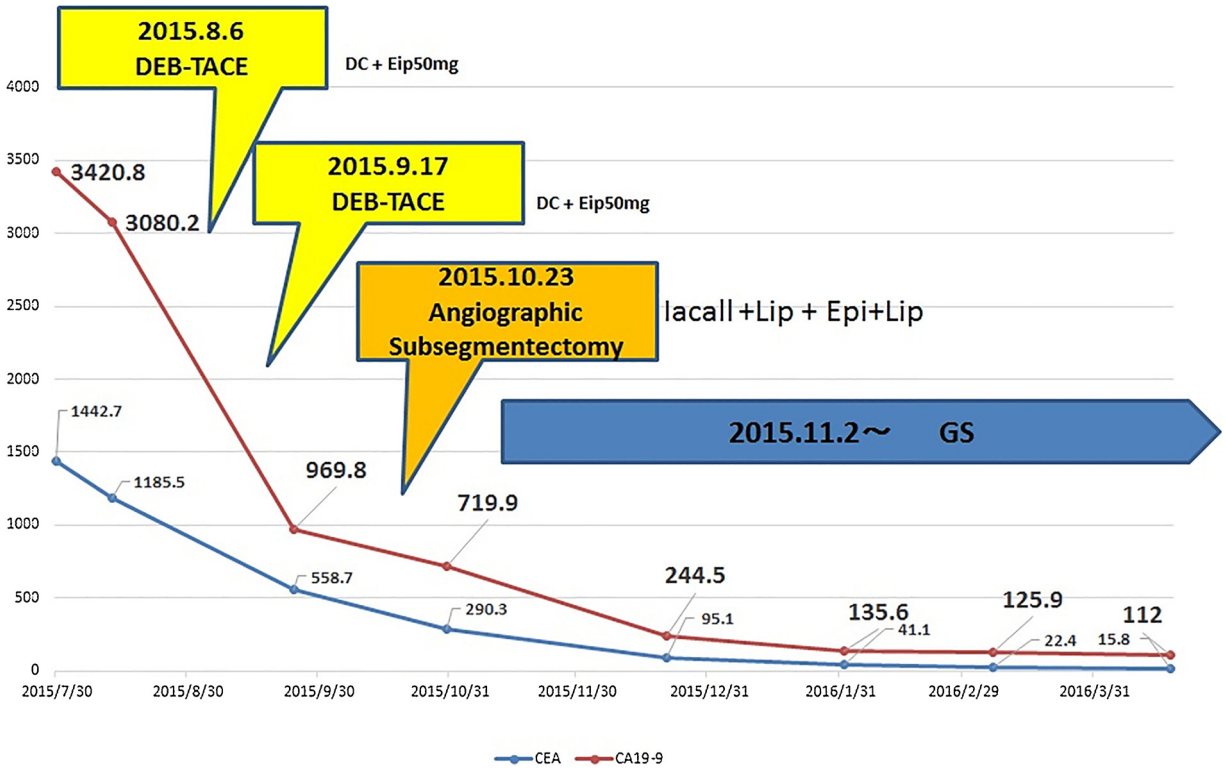

Fig. 3. Changes in tumor markers following multimodal therapy.
After two rounds of DEB-TACE with epirubicin and AS, tumor markers decreased to 20% of the initial level. After the systemic chemotherapy with gemcitabine and S1, the tumor markers decreased to just above the normal range.

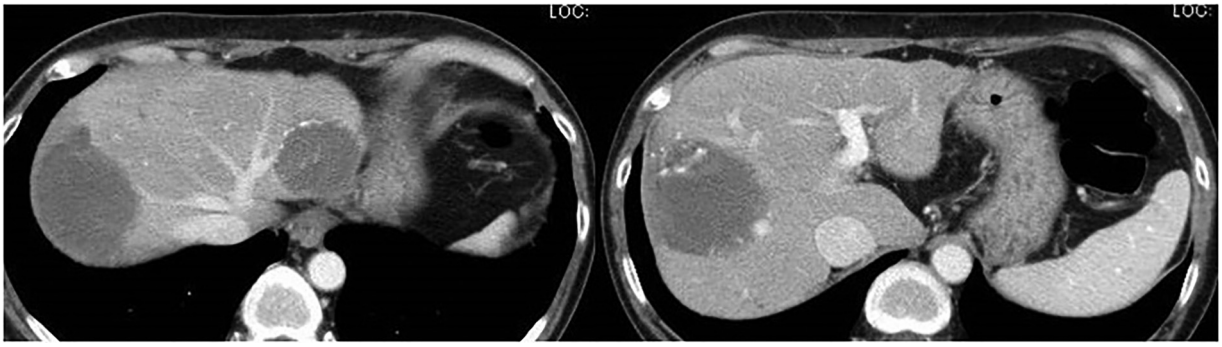

Fig. 4. CT images after multimodal therapy.
CT images revealed tumor shrinkage and disappearance of the invasion to the right Glisson's sheath and of the intrahepatic metastases.

were considered as poor prognostic factors for survival [8]. In this case, MRI scans at admission revealed intrahepatic multifocal disease and vascular invasion. Thus, the surgical approach was not indicated.

Recently, chemotherapy and/or interventional approach, i.e., hepatic angiographic infusion of anticancer agents, transarterial chemoembolization (TACE), and transarterial radioembolization, revealed prolongation of survival [1–5]. According to the reported clinical outcomes of doxorubicin treatment for unresectable ICC, the ratio of partial response and stable disease was 15% and 80%, respectively. Furthermore, the availability of DEB-TACE has been mentioned in particular [9]. In this case report, DEB-TACE was introduced two times with epirubicin and AS. AS was associated with a high disease-free survival rate for hepatocellular carcinoma as hepatectomy [10]. In the present case, tumor size was reduced and tumor markers were decreased to 20% of the levels at admission.

The overall survival in the combined therapy of hepatic arterial infusion and systemic chemotherapy was longer than that in patients who received systemic chemotherapy alone [11]. Thus, systemic chemotherapy with gemcitabine and S1 was introduced. However, tumor markers did not decrease to within the normal range. Consequently, it was assumed that viable tumor cells remained. The patient was referred to our hospital for surgical indication of hepatectomy to reevaluate the possibility of R0 resection.

Table 2 shows the successful radical resection of the initially unresectable ICC [1,11–19]. In previous reports (Table 2), several effective anticancer agents for ICC were administered: mitomycin C, epirubicin; gemcitabine; cisplatin; 5-furuolouracil, capecitabine, and S1. Epirubicin, gemcitabine, and S1 were selected for the present case. The successful downstaging and R0 resection rate increased from 7.7% to 36.4% using anticancer drugs, and the rate elevated from 17.7% up to 73.3% with radiation. In some reports,

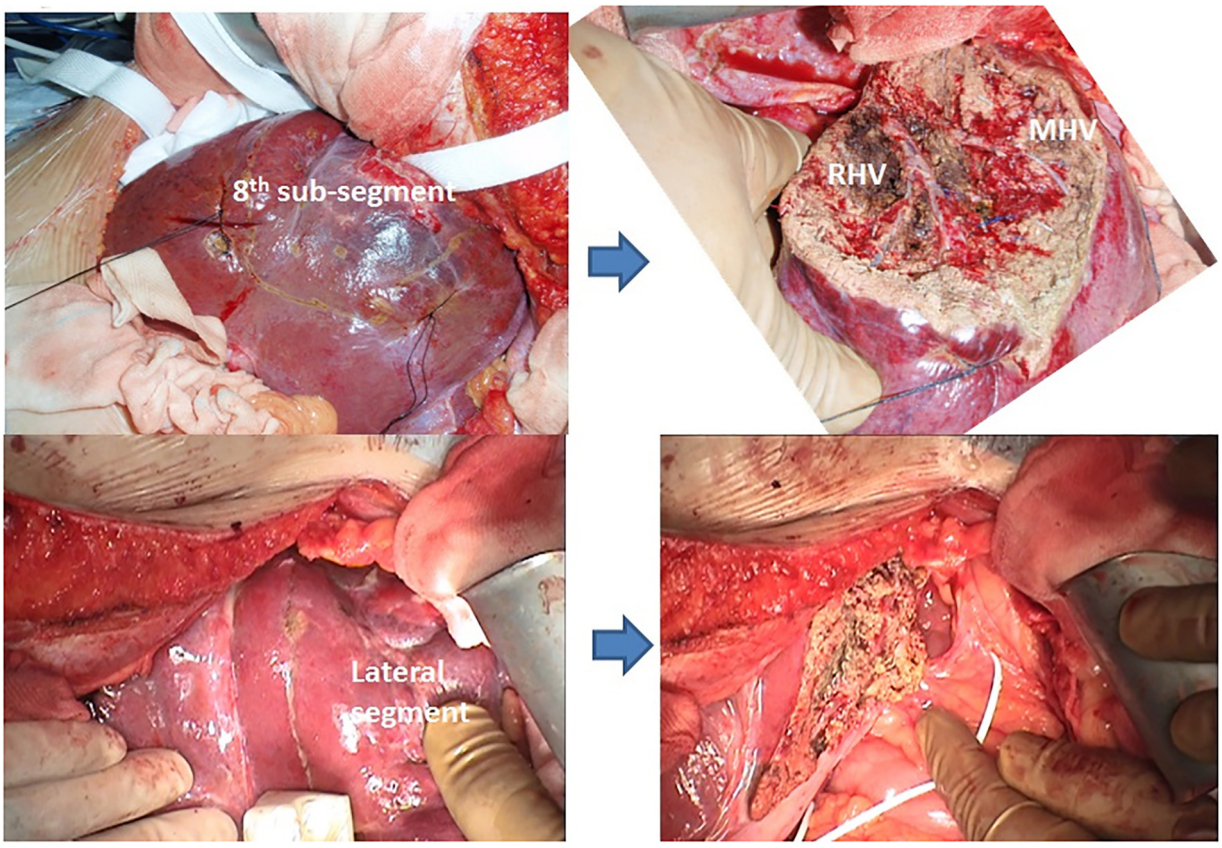

Fig. 5. Operation images. The image illustrates a left lateral segmentectomy and 8th subsegmentectomy.

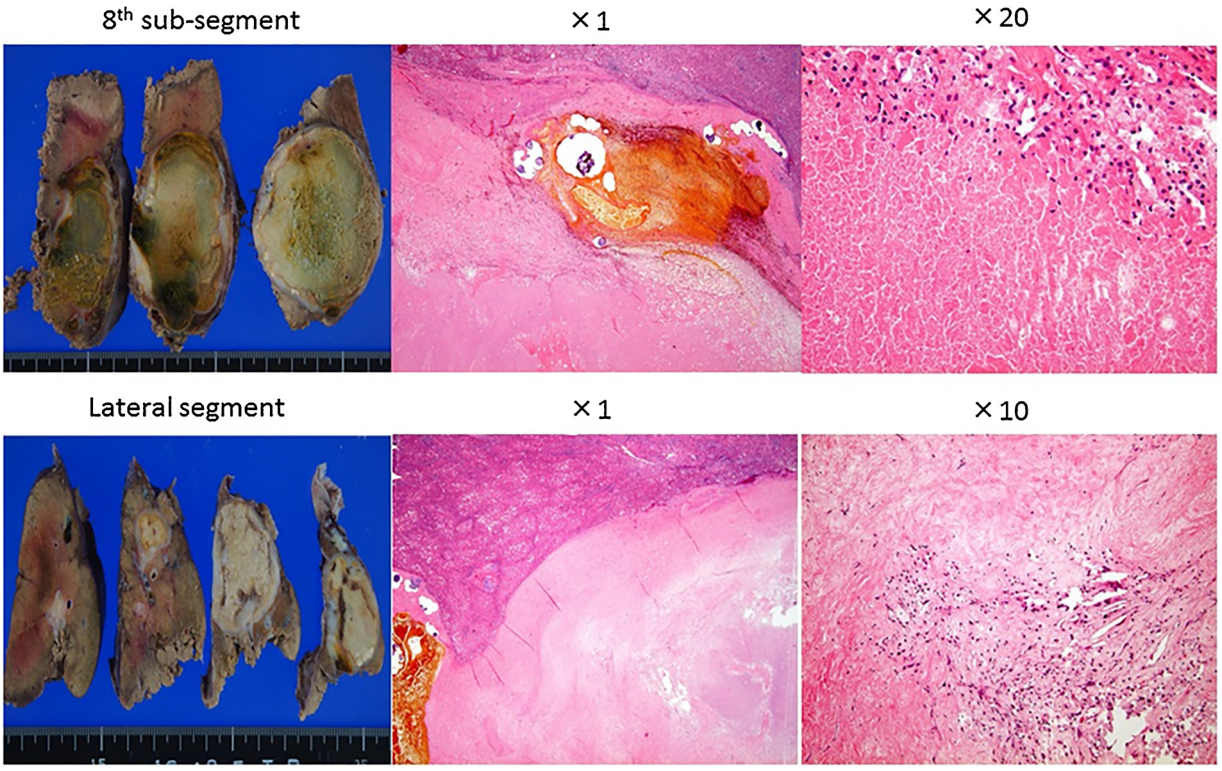

Fig. 6. Pathological examination. No viable neoplastic cells were present in the specimen.

Table 2
Results of neoadjuvant therapy following radical surgery for initially unresectable ICC.

author	year	Number(*)		age median(min-max)	chemotherapy	Route	radiation	radiation dose (method)	Procedure	Operated number	resection rate (%)	R number	number	MST(M)	Rec	Comments
Wu	2007	1	ICC	75	MMC + Epirubicin	TACE	(−)		Hepatectomy	1	(−)	R0	R0:1	42	0	
Kato A	2012	7	ICC	67 (57–84)	GEM	i.v.	(−)		Hepatectomy	4	36.4	R0	R0:4	28.5	0	
Aoki Y	2014	1	ICC	83	GEM + CDDP	i.v.	(−)		Hepatectomy	1	(−)	R0	R0:1	8	0	
Rayar M	2015	45	ICC	68 (39–79)	GEM, 5-FU, OXP, CDDP	TAR	(+)	(yttrium-90)	Hepatectomy	8	17.8	R0	R0:8	17.8	2	morbidity 25%
Marchan EM	2015	10	CCA	58.3 (38–71)	XEL or 5-FU	p.o. or i.v.	(+)	59 Gy (Ir brachytherapy HDR/external boost)	Transplantation	8	80	R0	R0:8		0	pCR 38%
Konstantinidis IT	2016	104	ICC	62 (30–88)	FUDR, MMC, GEM	HAI and/or SYS	(−)		Hepatectomy	8	7.7	R0	R0:2	36.9	6	morbidity 25% (2:perooperative death)
Takayamagi R	2017	1	ICC	23	GEM + CDDP	i.v.	(−)		Hepatectomy	1	(−)	R0	R0:1	31	1	CR
Sumiyoshi T	2018	7(15)	ICC	70 (60–78)	S1 or CDDP + CPT11	p.o. or i.v.	(+)	50Gy	Hepatectomy	5	71.4	R0	R0:4	18	3	PR(4), SD(1)
Sugiyama K	2018	1	ICC	63	5-FU + CDDP	TAC	(+)	40Gy	Hepatectomy	1	(−)	R1	R1:1	17	0	

Number(*): Entered as ICC or CCA, ICC: Intrahepatic cholangiocarcinoma, CCA: Cholangiocellar carcinoma, MMC: Mitomycin C, GEM: Gemcitabine, CDDP: Cisplatin, OXP: Oxaliplatin, XEL: Capecitabine, 5-FU: 5-Furuolouracil, FUDR: Doxifluridine, S1: Tegafur/Gimeracil/Oteracil, CPT-11: Irinotecan, Ir: Iridium192, HDR: high dose rate, TACE: Transcatheter Arterial Chemo-Embolization, i.v.: Intravenous, TAR: Transarterial radiation, p.o.: per os, HAI: Hepatic arterial infusion, SYS: Systemic chemotherapy, TAC: Transarterial chemotherapy, R0: cor-responds to complete disease remission, R1: clinical complete disease remission, but with unexpected identification of a tumor, MST: Median survival time, Rec: Recurrence, CR: Complete remission, PR: Partial response, SD: Staple disease.

Fig. 7. Postsurgical changes in the levels of tumor markers.
Tumor marker levels decreased to within the normal range after surgery.

the morbidity rate was reported to be 25%. Although transplants had a higher R0 resection rate of 80% and a higher overall survival rate of 75%, the mortality rate was 12.5% (1/8 patients). Pathological examination revealed no residual malignant cells after multimodal therapy in our case. To our knowledge, a pathological complete remission rate of 38% is the highest level in the chemoradiation series. Neoadjuvant therapy for initially unresectable ICC aims to reduce tumor size and to prolong survival, and to get chances of conversion for surgical resection. Conversion rate was reported up to 12.5% in the series of DEB-TACE [20]. Our strategy for unresectable ICC was intrahepatic arterial chemo-embolization with DEB-TACE initially. This combination therapy with interventional approach and systemic chemotherapy followed by radical surgical resection has potential as an effective approach for initially unresectable and locally advanced ICC.

Conflict of interest statement

None.

Funding sources

None.

Ethical approval

This case study report was approved in the ethical committee at Ekisaikai Moji Hospital (Reference number 52).

Consent

Authors obtained written and signed consent to publish a case report from the patient.

Author contribution

Koichiro Sakata: study concept or design.
Daiki Kijima, Taizou Yamaguchi: data collection, data analysis or interpretation.
Koichiro Sakata, Takashi Furuhashi, Toshihiko Abe, Haruki Iwamoto, Katsuhiko Morita: writing the paper.

Registration of research studies

We have nothing to declare. This is a case report.

Guarantor

Koichiro Sakata.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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We have nothing to declare.

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