REVIEW

Strategy for improving the prognosis of patients with intrahepatic cholangiocarcinoma by surgical treatment: Considerations based on experience and a literature review

Seiki Tashiro, PhD; Tatsuya Taeji, PhD; Hidenori Miyake, PhD; Hitomi Kamo, MD; Yuko Sumise, MD; Shigebaru Takai, PhD; and Kazuo Yoshioka, PhD

1Taoka Hospital, Tokushima, Japan, 2The University of Tokushima (Professor Emeritus), Tokushima, Japan, 3Hasuda Clinic, Kumamoto, Japan,
4Tokushima Municipal Hospital, Tokushima, Japan

Abstract: The prognosis of patients with intrahepatic cholangiocarcinoma (ICC) is still poor, and the 5-year survival rate in patients undergoing radical surgery (R0) is less than one-third. Since the prognosis depends mainly on tumor factors, so early diagnosis is necessary. To extend the survival time of these patients with a poor prognosis, cases of long-term survival were examined based on the results of our experiences and the literature. It was found that the hepatitis virus was highly involved in the carcinogenesis of ICC, and patients who were infected with hepatitis virus had rather good survival. J. Med. Invest. 68 : 15-21, February, 2021

Keywords: intrahepatic cholangiocarcinoma (ICC), hepatocellular carcinoma (HCC), hepatitis virus, nibolumab, lenvatinib

INTRODUCTION

The prognosis of patients with intrahepatic cholangiocarcinoma (ICC) is less than one-third of patients undergoing curative resection (R0) surviving for more than 5 years. The prognosis depends on a high recurrence rate. So it is important to find more effective adjuvant therapy to prevent this recurrence. The aim of this review article is to develop a strategy to prolong the survival of these difficult groups of ICC patients.

THE HEPATITIS VIRUS IN ICC; ROLE OF THE HEPATITIS VIRUS

In the primary liver cancers, ICC developing from the bile duct epithelium was relatively rare, accounting for only 21 (7.2%) of the 292 cases of liver cancers in the 18 years (1980-98) at Kumamoto University Hospital (1). It was said that ICC and hepatitis virus were not related, but according to Shen et al. (2), 198 of 429 cases (46.4%) were positive for HBsAg, and the number of cases has been increasing in recent reports. Epidemiological studies in Japan and Asia have shown that chronic hepatitis, such as hepatitis B and hepatitis C, and progression to liver cirrhosis are also important factors in the development of ICC, and the reasons for this were shown by the RIKEN team. These studies were performed by a joint research group (including 37 other collaborators) with Hidetoshi Nakagawa as the leader and Akihiro Fujimoto as the vice leader of the Genome Research Team of the RIKEN Center for Biomedical Sciences (3, 4). To summarize these results, the collaborative research group used a next-generation sequencer and a supercomputer to decipher and identify all genomic mutations occurring in ICC. Next, they compared the genome mutations of 60 hepatocellular carcinoma (HCC) identified by the same genome-wide sequence analysis and found an average of 4,300 mutations per tumor on the whole genome of ICC. The base substitution pattern of these mutations was similar to that of HCC. They also discovered that the genome sequence of hepatitis B virus has been inserted into the genomes of multiple ICCs, indicating a strong involvement in cancer. Furthermore, it was also found that several mutated genes in ICC were consistent with genes that mutated frequently in HCC. On the other hand, mutations in genes specifically found in cholangiocarcinoma outside the liver (extrahepatic cholangiocarcinoma) were also found in ICC. These cases have proven to have a very poor prognosis.

SURGICAL PROCEDURE FOR R0 RESECTION

First and second authors' experiences from 1980 to 1998 at Kumamoto University Hospital.

In the beginning, full resection was the only means to cure ICC, and we applied the concepts, technologies of vascular surgery, and hepatic transplant surgery, so worked on how to perform surgery aimed at R0 resection. In three cases, we performed surgery aiming at R0 applying these techniques for advanced ICC patients. The three cases that underwent these operations are presented below.

Case 1: A 51-year-old woman

The patient was admitted to our clinic on May 24, 1990, with jaundice as the chief complaint. Computed tomography (CT) showed a low-density mass (6 cm in diameter) with an irregular shape in segments IV and V and two small, low-density masses in segments VI and VIII.

Superior mesenteric arteriography showed encasement of the right hepatic artery, which branched off the superior mesenteric artery of approximately 5 cm in length. The left hepatic artery branched off from the left gastric artery, and the medial branch of the left hepatic artery was connected with the right anterior branch, making collateral vessels due to stenosis of the right anterior hepatic artery. On transarterial portal vein imaging, smooth encasement was shown approximately 2 cm in length on the trunk of the portal vein. On the basis of these imaging studies, ICC with lymph node involvement in the hepatoduodenal...
ligament was diagnosed. Therefore, liver resection of the right 3 segments with hepatoduodenal ligamentectomy (combined en bloc resection of the extrahepatic bile duct, the hepatic artery, the portal vein, and lymph node dissection in the hepatoduodenal ligament) and lymph node dissection around the abdominal aorta were carried out. The histological summary according to the Japanese Classification of Primary Liver Cancer was as follows: mass forming type + periductal type, moderately differentiated tubular adenocarcinoma, Mt (4)-A(2), 5.6 cm × 3.9 cm × 3 cm, P (1) 3 × 3 cm², L (1) 1 × 1 cm², Hg, Fc (-), S1, N2, Vp0, Vv0, B1(RHD), PV2 (by metastatic lymph node), A2 (by metastatic lymph node), IM3, P0, Z0, EV(0), NL : n3 (No 3 1 / 6, 12p 1 / 1, 13a 1 / 5, 14 1 / 1, 16 (para-aortic lymph node) 4 / 11), pv2, a1, T4, N1, M1, stage IVB, Hr 3 (PAML) + Hr0 (L), + D2++α (para-aortic lymph node dissection), SM (-), and Curability B (with no cancer at the surgical margin).

She survived 5 years and 10 months after surgery, but died on April 1, 1996. The cause of death was multiple metastases to the liver and lumbar and pelvic bones. It was thought that this patient should have been given adequate postoperative chemotherapy.

Fortunately, in this case, the right hepatic artery branched from the superior mesenteric artery, and the left hepatic artery branched from the left gastric artery; therefore, the circulation of the remaining liver in the left lateral segment was maintained, and there was thus no need to remove or reconstruct the left hepatic artery. It could be resected en bloc, including the bilia
tary tract, the portal vein, right hepatic artery, and lymph nodes in the hepatoduodenal ligament, and each vessel could be easily rebuilt. Thus, surgery could be performed without cancer at the stump. However, this patient experienced recurrence and died 5 years and 10 months after the surgery, suggesting the need for postoperative adjuvant chemotherapy. The regimen and the administration period, etc., require further study.

Case 2: A 54-year-old man

The patient had experienced dull abdominal pain in the epigastrum since May 1992. A large tumor in the liver was seen on ultrasonography (US) ordered by his primary care doctor. The patient was referred and admitted to our clinic on July 3, 1992. US showed a large, low-echoic mass (10 × 8 cm) in segments I and IV and obstruction of the middle hepatic vein. In addition, two small low-echoic masses (2.1 cm and 1.2 cm in diameter) were observed in segments V and VIII. Dynamic CT demonstrated a large mass in segments I ~ IV, and the inferior vena cava (IVC) was not detected in the hepatic portion. The tumor was 9 cm in diameter and had low intensity on T1-weighted imaging with a stricture at the origin of the right hepatic vein, and high intensity on T2-weighted imaging of magnetic resonance imaging (MRI). Arteriography of the common hepatic artery showed a large tumor with light staining in segment IV, with a few small light tumor stains surrounding the main tumor. The IVC was occluded on IVC venography, and the IVC blood flow was flowing into the intrahepatic vein with collateral veins through the right inferior hepatic vein, and it was drained from the right hepatic vein to the suprahepatic IVC. Based on the preoperative imaging diagnosis, an infiltrative obstruction in the hepatic portion of the IVC due to a large ICC from SI to SV was diagnosed, but there were no clear extrahepatic lymph node metastases. Venography of the IVC showed obstruction of the hepatic IVC and many collateral veins in the liver through the right inferior hepatic vein. It is impossible to perform removal of liver cancer invading the IVC without total hepatic vein exclusion (THVE) (5-7). Although THVE is a simple exclusion, it has an acceptable range of only 40 to 60 minutes. Therefore, it was decided to perform liver resection and IVC resection and reconstruction under hepatic cooling reperfusion. Left and caudal lobectomy with resection of the IVC by in situ hypothermic-perfused liver surgery was carried out. First, in situ hypothermic-perfused liver surgery was started using the veno-venous bypass technique under total hepatic vascular exclusion. After IVC resection, an approximately 10-cm defect of the IVC was reconstructed with a 20-mm expanded EPTFE graft (ringed Gore-Tex) (5). Veno-venous time and total hepatic exclusion time were 187 and 181 minutes, respectively. Bypass flow was 1.3 - 2.1 L/min. Next, the two daughter tumors in segment V were extirpated.

The macroscopic findings were as follows: T4, N0, M0, Stage IV, Curability 3, P3, Vv3. In the cut face of the resected specimen, the IVC was surrounded and compressed by the S IV and S I tumors, and it was closed. The histology of the tumor was moderately differentiated adenocarcinoma. The patient had a good quality of life postoperatively. After postoperative adjuvant therapy with 5-fluorouracil (5-Fu) 250 mg/day + cis-diamine dichloroplatinum (CDDP) 125 mg for 2 weeks, he was discharged 7 weeks after surgery. However, he died of lung and liver metastases 10 months after surgery.

Hepatic resection under liver cooling reperfusion was performed in 3 cases including this case, and the postoperative course was good in all cases. THVE with a hepatic temperature of 23 - 25°C for 3 hours was temporary and transient to avoid postoperative liver injury, since it has been found that THVE under cooling reperfusion is possible for 3 hours.

Case 3: A 59-year-old man

The patient was admitted to our clinic with general fatigue and epigastric pain as chief complaints. He had no jaundice, anemia, or swollen superficial lymph nodes. The liver was palpable 10 cm below the xiphoid process, with an elastic hard consistency, rounded edge, and uneven surface. The spleen was not palpable, and ascites and edema were absent. Blood chemistry showed slightly elevated transaminase levels, and there were no abnormal coagulation findings. The indocyanine green (ICG) test was within normal limits. Hepatic US showed a large mass without a halo in segments II, III, IV, V, and VI of the liver. This mass clearly compressed the right hepatic vein and IVC. CT also demonstrated a large mass in segments I ~ IV, and the inferior vena cava (IVC) was not detected in the hepatic portion. The tumor was 9 cm in diameter and had low intensity on T1-weighted imaging with a stricture at the origin of the right hepatic vein, and high intensity on T2-weighted imaging of magnetic resonance imaging (MRI). Arteriography of the common hepatic artery showed a large tumor with light staining in segment IV, with a few small light tumor stains surrounding the main tumor. The IVC was occluded on IVC venography, and the IVC blood flow was flowing into the intrahepatic vein with collateral veins through the right inferior hepatic vein, and it was drained from the right hepatic vein to the suprahepatic IVC. Based on the preoperative imaging diagnosis, an infiltrative obstruction in the hepatic portion of the IVC due to a large ICC from SI to SV was diagnosed, but there were no clear extrahepatic lymph node metastases. Venography of the IVC showed obstruction of the hepatic IVC and many collateral veins in the liver through the right inferior hepatic vein. It is impossible to perform removal of liver cancer invading the IVC without total hepatic vein exclusion (THVE) (5-7). Although THVE is a simple exclusion, it has an acceptable range of only 40 to 60 minutes. Therefore, it was decided to perform liver resection and IVC resection and reconstruction under hepatic cooling reperfusion. Left and caudal lobectomy with resection of the IVC by in situ hypothermic-perfused liver surgery was carried out. First, in situ hypothermic-perfused liver surgery was started using the veno-venous bypass technique under total hepatic vascular exclusion. After IVC resection, an approximately 10-cm defect of the IVC was reconstructed with a 20-mm expanded EPTFE graft (ringed Gore-Tex) (5). Veno-venous time and total hepatic exclusion time were 187 and 181 minutes, respectively. Bypass flow was 1.3 - 2.1 L/min. Next, the two daughter tumors in segment V were extirpated.

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and ALT was 480 U/l on the 2nd day, and they then gradually decreased. On the 9th day, AST and ALT were 46 U/l and 64 U/l, respectively, and they then continued in double digits. How-

decreased. On the 9th day, AST and ALT were 46 U/l and 64 U/l on the 2nd day, and they then gradually decreased to 8.7 mg/dl on the third day, but it then increased for ever, total bilirubin increased to 13.0 mg/dl on the next day and were considered as the causes of liver failure: (1) hepatic resec-
tion function further deteriorated. Renal failure also developed, and were well imaged without any obstruction. Bleeding from gastric ulcers occurred from the 78th day after the operation, and liver function further deteriorated. Renal failure also developed, and he died of liver failure 3.5 months after surgery. Three factors were considered as the causes of liver failure: (1) hepatic resec-
tion was too large, with 75% massive resection of the liver (re-
sidu al liver; 25%); (2) damage to the peripheral small bile duct epithelium due to prolonged low temperature; and (3) since there was an intraperitoneal infection due to bile leakage from the cut surface of the liver, postoperative liver regeneration was delayed. It was thought that, due to the overlying of these causes, recovery of sufficient liver function could not be achieved.

In their first paper on extracorporeal hepatectomy, Pichlmayr et al. (8) stated that “postoperative cholestasis could have sign-
ificant hazard in the postoperative course after an ex situ procedure.” At autopsy, the weight of the remaining liver was 1,180 g, which was twice as large as that at the time of surgery, and it was a jaundiced liver. However, dilatation of the intra-
hepatic bile duct was not observed. There was no intrahepatic metastatic lesion or recurrence. The anastomoses of the portal vein, hepatic artery, and inferior vena cava were also opened. Pichlmayr et al. (8) performed the world’s first extracorporeal liver resection on the ex situ perfused liver for malignant tumors in the liver on February 1988, and 10 cases were performed by March 1990. The first 10 cases were performed by Pichlmayr et al., and four (45%) of them developed liver failure; one died at 44 days, and three cases died of liver failure even after liver retransplantation. These four patients underwent a greater than 65% massive hepatectomy. The eleventh case succeeded in resec-
tion of S IV and S VIII for metastatic liver cancer by Sugimachi et al. on March 22, 1990 (9). The twelfth case was our case and was performed on June 22, 1990 (10). In our case, 75% massive hepatectomy was performed, and only 25% remained. Therefore, it was thought that the surgical indication for extracorporeal liver resection should be stricter than for conventional liver re-
section. Currently, adjuvant therapy such as anti-PD-1 antibody and lenvatinib should be performed before and/or after surgery (details described below). Also recently, as adjuvant therapy, LIU Xiaoliang et al. (11) performed programmed cell death protein1 (PD-1) blockade therapy and/or radiotherapy for three patients with high tumor mutation burden (TMB), high microsatellite instability (MSI-H), deficient mismatch repair (dMMR), and/or positive programmed cell death ligand 1 (PD-L1) expression. They provided the first report on the therapeutic responses of ICC patients treated with combined PD-1 blockade with stereo-
tactic body radiotherapy (SBRT) (cyberknife) in the background of low TMB, MSS, pMMR, and negative PD-L1 expression. One stage 4A ICC patient and two postsurgical recurrent ICC patients were involved in this study, and the responses to the combined therapy of both locally irradiated tumor(s) and the abscopal tumors or metastases were assessed by magnetic res-
onance imaging (MRI) and positron emission tomography-com-
puted tomography (PET-CT). The stage IVA ICC patient (patient A) had a TMB of 1.2 muts/Mb with MSS, pMMR, and PD-L1 expression < 1%. Both the intrahepatic lesion and the lymph node metastases were well controlled for 7 months, and partial response (PR) was achieved, with the sum of lesion diameters decreased by 40.9%. Postsurgical recurrent ICC patients (Patient B) had a TMB of 3.8 muts/Mb with MSS, pMMR, and PD-L1 expression < 1%. Both the recurrent intrahepatic lesion and the lymph node metastases were well controlled by the combined therapy, and the sum of lesion diameter decreased by 86.3% (PR). The other postsurgical recurrent patient (Patient C) had a TMB of 0.98 muts/Mb with MSS, pMMR, and PD-L1 expression < 1%, and achieved complete response (CR) that was maintained for 11 months. Abscopal effects were observed in all three patients. This study provided the first evidence for the effectiveness of combined SBRT and PD-1 blockade therapy in late-stage or re-
current ICC patients with low TMB, MSS, pMMR, and negative PD-L1 expression, and potentially expanded the indications for the combined therapy to such patients who were previously not suitable for immunotherapy. Furthermore, PD-1 blockade with stereotactic body radiotherapy (SBRT) seems to be appropriate for cases where surgery is not possible due to reduced immunity. The progress of another case of anti-PD inhibitor treatment (12) that achieved a good response will be detailed later. In addition, drugs such as geranylgeranylacetone (13) (a non-toxic HSP70 inducer) to prevent postoperative liver failure are necessary, and it may be important to consider once again whether R0 surgery is possible with massive hepatectomy under low-temperature in situ perfusion of the liver in the body.

Liver resection and results of ICC patients at The University of Tokushima Hospital

ICC surgeries (14 males and 9 females) were performed over the 9 years from April 1994 to July 2002 at The University of Tokushima Hospital, where the first author went after Kumamoto University Hospital. The patients’ average age was 65 years. In 11 cases of peripheral type and 12 cases of portal hilar type, the operation methods were: right, 3-segment resection, 4 cases; left 3-segment resection, 1 case; extended right hepatic lobectomy, 1 case; extended left hepatic lobectomy, 7 cases; right hepatic lobectomy, 1 case; right anterior segmentectomy, 1 case; right posterior segmentectomy, 2 cases; and partial liver resection, 3 cases. In total, major hepatic resection was performed for 20 cases (87%), and resection of the extrapleural bile duct was also carried out in 14 (60.1%) of these 23 cases, 8 (39.8%) were infect-
ed with the hepatitis C virus (HCV). The cumulative survival rates of the HCV-associated ICCs are shown in Figure 1. Survival curves of patients who were HCV-positive were significantly better (p = 0.0049) than of those who were HCV-negative, but the reason is not clear. However, an article (14) later revealed the reasons. Recently, lymph node metastasis was found to be significantly lower in hepatitis B virus (HBV)-associated ICC

Figure 1. Survival curves of patients who were HCV-positive were significantly better (p = 0.0049) than of those who were HCV-negative.
patients than in those without HBV infection. Seogsong et al. (14) found that HBV infection in cancer-associated lymphangiogenesis/HBV infection could be involved in the suppression of cancer-associated fibroblasts adopting lymphatic endothelial morphology and function (mucenhyal-to-lymphatic endothelial transition), which resulted in the low extent of cancer-associated lymphangiogenesis and led to a relatively low incidence (14). They also showed decreased lymph node metastases in HBV-associated ICC. They did not discuss HCV infection, but all of our cases were HCV-infected, so that they had an improved survival rate compared with non HCV-infected cases. It was suggested that a similar mechanism might work to improve survival after resection of HCV-positive ICC. The case of a patient who survived for a long time after resection is presented. The patient was a 67-year-old woman who had undergone subtotal gastrectomy with lymph node dissection 14 years earlier. After a periodic follow-up visit, ALP and GPT were increased, and US and CT showed dilatation of the left intrahepatic bile duct and atrophy of the left lateral hepatic segment. She was referred to our department. After careful examination, she was diagnosed as having a small (2.5 cm in diameter), HCV-positive ICC with invasion to the hilar bile duct, and extended left lobectomy combined with resection of the caudate lobe and the extrahepatic bile duct, and lymphadenectomy and hepaticojejunostomy with the Roux-en-Y method for ICC, were performed. Lymph nodes along the lesser curvature of the stomach, left gastric artery, and the common hepatic artery had already been dissected in the operation for gastric cancer, so only the lymph nodes in the hepatoduodenal ligament with the extrahepatic bile duct were dissected in this procedure. She died of other disease at 8.5 years, and there was no recurrence at that time. Factors that contributed to long-term survival were: diagnosis of small tumors by periodic examination after gastric cancer surgery; hepatitis C virus infection; no lymph node metastases; easy flow of lymph in the ICC of the left lobe; and lymph nodes were dissected during gastric cancer surgery. Thus, it was thought that this patient survived for a long time without recurrence because of the overlapping of these four conditions.

Recent experience with combined HCC and ICC in Taoka Hospital

An 88-year-old man with left back pain visited the orthopedic department on March, 2019. CT showed an abnormality in the left intrahepatic bile duct and atrophy of the left lateral hepatic segment. He was referred to our department. After careful examination, he was diagnosed as having a small (2.5 cm in diameter), HCV-positive ICC with invasion to the hilar bile duct, and extended left lobectomy combined with resection of the caudate lobe and the extrahepatic bile duct, and lymphadenectomy and hepaticojejunostomy with the Roux-en-Y method for ICC, were performed. Lymph nodes along the lesser curvature of the stomach, left gastric artery, and the common hepatic artery had already been dissected in the operation for gastric cancer, so only the lymph nodes in the hepatoduodenal ligament with the extrahepatic bile duct were dissected in this procedure. He died of other disease at 8.5 years, and there was no recurrence at that time. Factors that contributed to long-term survival were: diagnosis of small tumors by periodic examination after gastric cancer surgery; hepatitis C virus infection; no lymph node metastases; easy flow of lymph in the ICC of the left lobe; and lymph nodes were dissected during gastric cancer surgery. Thus, it was thought that this patient survived for a long time without recurrence because of the overlapping of these four conditions.

LYMPH NODE METASTASES AND THE SIGNIFICANCE OF LYMPH NODES DISSECTION

There have been very few reports of the pattern of lymphatic spread of ICC. This pattern was elucidated to help define the extent of radical lymph node dissection. Thirty-nine consecutive patients who underwent hepatectomy with radical lymph node dissection were reviewed retrospectively (1). Lymph node metastases were detected in 24 (62%) of the 39 patients. The metastatic nodes were found in the hepatoduodenal ligament, along the common hepatic artery, around the abdominal aorta, on the posterior surface of the head of the pancreas, along the left gastric artery, along the superior mesenteric artery, around the celiac artery, along the lesser curvature of the stomach, and around the cardia only in the left peripheral and hilar types of cholangiocarcinoma, whereas all other sites included both the left or right peripheral type and the hilar type cholangiocarcinoma. ICCs, irrespective of their intrahepatic location, spread mainly to the nodes in the hepatoduodenal ligament, and then to the para-aortic nodes, retropancreatic nodes, or common hepatic artery nodes. In addition to these routes of spread, the left peripheral type or hilar type of cholangiocarcinoma tends to spread along the left gastric nodes through the lesser curvature. From our clinicopathological findings and the anatomical features, the efferent lymphatic flow from the liver is complicated and extensive (1).

A recent meta-analysis of 13 studies, including 1,337 patients from 2000 to 2018 by Zhao et al. (17) showed that there were no significant differences in overall survival, disease-free survival, or recurrence between a lymph node dissection group and a non-lymphnode dissection group. They also found that postoperative morbidity was significantly higher in the lymph node dissection group. Therefore, they concluded that routine or prophylactic lymph node dissection could not be recommended because of the uncertain survival benefit. Furthermore, many multivariable analyses showed that the significant independent predictor of poor prognosis is not the omission of lymph node dissection, but the pathological lymph node metastasis itself. However, it is not clear whether there is metastasis without dissection. If there are cancer cells in the sentinel lymph node (18-21), the lymph nodes in the area of the tumor are dissected. If there are no cancer cells in the sentinel node, lymph node dissection is not performed. Thus, it is more reasonable to search for the sentinel lymph node at the location of the tumor. Therefore, in the near future, we plan to inject indigo carmine into the liver tissue on the tumor side several times around the circumference during the operation to search for metastases to determine the need for dissection. If the sentinel nodes do not stain well, the lymph nodes of the hepatoduodenal ligament, which is the main flow of lymph from the liver, are dissected, and if frozen section examination is positive for cancer cells, radical dissection is performed, but if it is negative, radical dissection may not be considered.

ADJUVANT CHEMOTHERAPY FOR ICC

Despite R0 resection, the 5-year survival rate is low, at only 30%. Multifocal, node- or margin-positive disease is at a higher risk of recurrence after resection. A recent adjuvant therapy phase III trial from the Partenariat de Recherche en Oncologie Digestive-Actions Concertées dans les Cancers Colo-Rectaux
and selective inhibitory activity against receptor tyrosine kinases. At postoperative 4 years 11 months, the serum CA19-9 concentration increased again to 8,769 U/ml at postoperative 4 years because of a continuous increase in serum levels. Furthermore, they started the administration of a PD-1 inhibitor (nivolumab, 3 mg/m²) every 2 weeks. The patient underwent resection of liver segment VIII, dissection of regional lymph nodes, and resection of lesions on the diaphragm. The patient developed recurrent lesions in the 5th month after surgery, and the cholangiocarcinoma expanded to right thoracic vertebral Th7-8 in the 6th month. The patient received nivolumab plus lenvatinib, and the lesions in the liver decreased in size and disappeared after this treatment. Additionally, the metastases in the right thoracic vertebral pedicle were stable after 9 months of therapy. Although the details of the operation and postoperative course are not described for the second case, both cases are described as having shown a complete response in combination with chemotherapy. Recently, based on basic research on immunotherapy and molecular drug therapy, a small number of clinical trials has tried to determine whether it may also be effective for ICC. If this adjuvant therapy is used widely in patients with ICC, prognosis must be improved. This is a great pleasure for ICC patients with a poor prognosis and for the physicians who treat them.

PROPOSED STRATEGY OF SURGICAL TREATMENT FOR ICC PATIENTS

After summarizing the review of ICC, we developed a Proposed Strategy to improve the prognosis of ICC patients, as shown in Table 1. We decided to use the level because the tumor factors would be better expressed at the level than at the stage. Please see Table 1 for detail.

We expect that further investigations will prove the feasibility of our proposed strategy.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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Table 1. Proposed strategy for ICC patients

| Tumor progression | Preoperative diagnosis | Surgical treatment | Adjuvant therapy |
|-------------------|------------------------|-------------------|-----------------|
| Level 1           | Size: ≤3 cm Number: 1 lesion LNM-, Bl-, Vl-, Sl-, M- | R0 liver resection | Not applicable follow-up every 6 months for 5 years every 1 year thereafter |
| Level 2           | Size: >3 cm and ≤10 cm Number: <3 lesions LNM+, Bl+, Vl+, Sl+, M- | R0 liver resection Radical LN dissection (according to sentinel node navigation) Bile duct resection | No standard therapy Option (1) Anti PD-1 inhibitor (2) Lenvatinib |
| Level 3           | Size: >10 cm Number: ≥3 and <5 lesions LNM+, Bl+, Vl+, Sl+ or - M- | Extended liver resection Radical LN dissection (according to sentinel node navigation) Bile duct resection and/or Vascular resection | Neoadjuvant therapy (1) Anti PD-1 inhibitor (2) Lenvatinib (then when the tumor progression is reduced to Level 3 or less, surgery can be considered) |
| Level 4           | Size: >10 cm Number: ≥5 lesions LNM+, Bl+, Vl+, Sl+ M+ | (Inoperable) | |

LNM: lymph node metastasis; Bl: bile duct invasion; Vl: vascular invasion; Sl: serosal invasion; M: distant metastasis; +: positive; -: negative.

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