Unresectable hilar cholangiocarcinoma treated with chemoradiotherapy: a 9-year survival case

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Abstract

Patients with advanced unresectable hilar cholangiocarcinoma have poor prognosis, and the survival is usually short. Herein, we report a 9-year survival case of unresectable hilar cholangiocarcinoma treated with chemoradiotherapy. A 64-year-old male patient presented with hilar cholangiocarcinoma. The tumor was located in the right hepatic duct, and it extended from the bifurcation of the anterior and posterior branches to the periphery. In the left side, the tumor extended from the umbilical portion to B2 and B3. However, there was no distant metastasis. The patient was then diagnosed with locally advanced, unresectable hilar cholangiocarcinoma and was treated with chemoradiotherapy. He received a total dose of 60 Gy in 30 daily fractions via intensity-modulated radiation therapy. In addition, he received gemcitabine chemotherapy for 5 years. There has been neither re-elevation of carbohydrate antigen 19-9 levels nor tumor relapse for 5 years during chemotherapy. Therefore, gemcitabine treatment was discontinued. However, the patient experienced tumor relapse 3 years after the last chemotherapy. Hence, chemotherapy with gemcitabine and cisplatin was initiated. At present, 1 year has passed after treatment for recurrence, and the patient has survived for 9 years since the initial treatment. Herein, we report a rare case of long-term survival with chemoradiotherapy in locally advanced unresectable hilar cholangiocarcinoma.

Keywords Hilar cholangiocarcinoma · Chemoradiotherapy · Long-term survival

Introduction

Hilar cholangiocarcinoma, also known as Klatskin tumors, accounts for 60–70% of all cholangiocarcinoma cases, and major surgical challenges are faced when managing this type of tumor as it is commonly located adjacent to the pivotal structures. However, in world-famous, high-volume centers, the 5-year survival rate of patients after surgery is 30–40%. Hence, the long-term outcomes of surgery for hilar cholangiocarcinoma have not reached satisfactory levels [1–5].

By contrast, the unresectability rates remain high at 24–66%, and it can be attributed to the tumor involving the bilateral second-order biliary radicals, main or bilateral portal vein or hepatic artery invasion, presence of hepatic lobar atrophy with contralateral second-order biliary radical or major vascular involvement, and distant metastases [4, 6, 7].

In terms of palliative therapies for unresectable hilar cholangiocarcinoma, chemoradiotherapy can achieve satisfactory local tumor control, and it may have survival benefits. Herein, we report a case of long-term survival with chemoradiotherapy in unresectable hilar cholangiocarcinoma.

Case report

A 64-year-old man was referred to our hospital due to elevated carbohydrate antigen 19-9 (CA19-9) levels and asymptomatic dilation of the intrahepatic bile duct. Mild liver dysfunction was detected during a laboratory examination. However, jaundice was not observed (total bilirubin [T-Bil] level, 0.6 mg/dL; alkaline phosphatase [ALP] level, 620 U/L; gamma-guanosine triphosphate [γ -GTP] level, 569 U/L; aspartate aminotransferase [AST] level, 36 U/L; and alanine aminotransferase [ALT] level, 112 U/L). The patient's CA 19-9 level was elevated at 97 U/mol.

Contrast-enhanced computed tomography (CT) revealed a lesion in the hilum of the biliary tract and dilation of the

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bilateral intrahepatic bile. The tumor was located in the right hepatic duct, and it extended from the bifurcation of the anterior and posterior branch to the periphery (Fig. 1a). In the left side, the tumor extended from the umbilical portion to B2 and B3 (Fig. 1b). However, there was no distant metastasis. The patient was diagnosed with Bismuth type IV hilar cholangiocarcinoma (T4N0M0 cStage IIIB). Moreover, we believe that it was difficult to secure a surgical margin due to bilateral extension to the periphery biliary tract, even when we performed right or left trisectomy. Therefore, this patient with locally advanced, unresectable hilar cholangiocarcinoma was treated with chemoradiotherapy. Since this treatment is not standard in Japan, an informed consent was obtained from the patient. Combination chemotherapy, such as cisplatin plus gemcitabine, was not standard at that time. In 2010, Valle et al. reported that cisplatin plus gemcitabine was associated with a significant survival advantage compared with gemcitabine alone [8]. Thus, we selected gemcitabine alone, which was a standard treatment regimen for unresectable hilar cholangiocarcinoma in 2008. He

then received at gemcitabine chemotherapy a standard dose (gemcitabine 1000 mg/m² on days 1, 8, and 15 in a 28-day cycle) and intensity-modulated radiation therapy (IMRT). Intracavitary radiation therapy was not used due to the range of progression. After 6 months, the CA19-9 level of the patient normalized (Fig. 2). Then, the chemotherapy dose was gradually decreased, and gemcitabine chemotherapy was continued for 5 years. The patient did not experience re-elevation of CA19-9 levels. Five years after the initial treatment, contrast-enhanced CT scan revealed that the size of the tumor decreased (Fig. 3). Therefore, chemotherapy with gemcitabine was discontinued.

Three years after the last chemotherapy, he complained of whitish stool and presented with significantly elevated CA19-9 levels. Based on the contrast-enhanced CT scan findings, tumor recurrence was suspected (Fig. 4). The tumor was located in the hilar area, and it invaded the liver parenchyma. Endoscopic retrograde cholangiography revealed stenosis of the hilar area and distal bile duct (Fig. 5). The length of the stenosis was 3 cm. Endoscopic biopsy of the stenosis revealed

Fig. 1 Computed tomography scan during the initial treatment. **a** The slightly enhanced tumor was located in the right hepatic duct, and it extended from the bifurcation of the anterior and posterior branch to the periphery. **b** The tumor extended from the umbilical portion to B2 and B3. The arrow represents the tumor

Fig. 2 Changes in CA19-9 levels. The CA19-9 level decreased after chemoradiotherapy and re-elevated during tumor relapse. After chemotherapy, it decreased and was controlled for more than 9 years

Fig. 3 The computed tomography scan image taken 5 years after the initial treatment showed that the size of the tumor decreased

Fig. 4 Computed tomography scan showing tumor relapse. The low-density tumor was found at the hilum of the liver. The arrows represent the low-density tumor

well-differentiated tubular adenocarcinoma (Fig. 6). Therefore, the patient was diagnosed with recurrence of hilar cholangiocarcinoma. However, there was no distant metastasis. A plastic stent was placed for the management of obstructive jaundice. After the jaundice improved, chemotherapy with gemcitabine and cisplatin chemotherapy (gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 on days 1 and 8 in a 21-day cycle) was started. Then, 8 years and 7 months after his initial treatment, the

Fig. 5 Endoscopic retrograde cholangiography revealed stenosis of the hilar area and distal bile duct. The arrow represents the stenosis area

Fig. 6 Hematoxylin and eosin staining indicates the well-differentiated tubular adenocarcinoma ($\times 200$ magnification)

regimen was changed to biweekly chemotherapy with gemcitabine and cisplatin. At present, he survived for 9 years since the initial treatment.

Discussion

Patients with unresectable hilar cholangiocarcinoma have poor prognosis. Based on a previous study, the median survival time (MST) of patients with this tumor who received the best supportive care was 5.9 months [9]. Chemotherapy is the most common treatment that can prolong survival (generally extended to 6–12 months) in patients with unresectable hilar cholangiocarcinoma. In another study, the MST of patients with unresectable hilar cholangiocarcinoma treated with gemcitabine and S-1 chemotherapy was 11 months [10]. Chemoradiotherapy for unresectable hilar cholangiocarcinoma remains a clinical challenge as its use has not been widely accepted. Few studies conducted in different countries worldwide have reported about the use of chemoradiotherapy for hilar cholangiocarcinoma. In 2017, Engineer et al. reported the outcomes of chemoradiotherapy for unresectable hilar cholangiocarcinoma. Their study showed that the MST of a patient who received chemoradiotherapy (gemcitabine + IMRT at 57 Gy) was 16 months [11]. Moreover, there were some case reports of long-term survival with radiotherapy alone in unresectable hilar cholangiocarcinoma treated. Chan et al. reported an individual with inoperable hilar cholangiocarcinoma who was treated with external radiation and intraluminal brachytherapy and survived for more than 6 years [12]. Meanwhile, Becker et al. revealed that a patient with unresectable hilar cholangiocarcinoma who was treated with chemotherapy and stereotactic radiotherapy survived for 4.6 years [13]. Then, Kaido et al. presented a patient with unresectable hilar cholangiocarcinoma who was completely treated with external radiation therapy and survived for more than 4 years [14]. Compared with patients who received non-surgical treatment, our patient survived for more than 9 years with chemoradiotherapy, and this case is quite rare. Moreover, the patient initially received gemcitabine chemotherapy and then gemcitabine and cisplatin chemotherapy during recurrence, which are standard treatment regimens for unresectable hilar cholangiocarcinoma. By contrast, the efficacy of radiotherapy alone is limited in terms of locoregional treatment, and the combination of chemotherapy and radiotherapy may be another treatment option for controlling cancer cells at the locoregional area and latent cells in distant organs.

Ruys et al. conducted a study including 217 patients with suspected hilar cholangiocarcinoma, including 160 with unresectable tumors [15]. Results showed that the median survival of patients with locally advanced disease (16 months) was better than that of patients with hepatic and extrahepatic metastases (5 and 3 months, $p < 0.001$). Moreover, liver metastasis (hazard ratio 2.26; 95% confidence interval [CI] 1.35–3.79, $p < 0.01$) and extrahepatic

metastasis (hazard ratio: 2.45; 95% CI 1.39–4.33, $p < 0.01$) were considered as independent poor prognostic factors in patients with unresectable tumors. The cause of unresectability in our case was not liver metastasis and extrahepatic metastasis but locally advanced disease, and it might lead to long-term survival. Mansour et al. suggested that chemoradiotherapy is also recommended for patients with locally advanced, unresectable hilar cholangiocarcinoma [16]. Moreover, in this case, the locally advanced tumor was not vertically extending with direct invasion to the liver parenchyma and vascular invasion, but horizontally extending. This tumor factor might attribute to good response to chemoradiotherapy. Furthermore, in the study of Ruys et al., most patients with unresectable indolent, slow-growing tumors had long-term survival, and these patients had a relatively good survival when adequate biliary drainage was maintained to prevent death from unresolved cholangitis. In our case, the size of the tumor was gradually increasing, and cholangitis was well treated with drainage and antibiotics. This management might lead to long-term survival.

Gaspersz et al. assessed the survival of patients ($n = 572$) with unresectable hilar cholangiocarcinoma [17]. They showed that the risk of survival in patients with unresectable perihilar cholangiocarcinoma increases over time, and poor prognostic factors become less relevant if patients have survived for 2 years. These results indicated that patients with unresectable hilar cholangiocarcinoma who have good response to any treatment have long survival expectancy. In our case, the size of the tumor decreased, and the CA19-9 level decreased after chemoradiotherapy. The patient survived for more than 9 years, and this might be attributed to his good response to treatment. Therefore, long-term follow-up is recommended for well-managed patients with chemoradiotherapy.

Conclusion

Curative resection is the most effective treatment for hilar cholangiocarcinoma. However, some patients develop locally advanced, unresectable hilar cholangiocarcinoma. Herein, we present a case of long-term survival with chemoradiotherapy in unresectable hilar cholangiocarcinoma. Thus, chemoradiotherapy might be another treatment option for patients with horizontally extending locally advanced tumors, such as a Bismuth type IV unresectable hilar cholangiocarcinoma.

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