Long-term survival of a patient with locally advanced hilar cholangiocarcinoma (Klatskin tumor): a case report and review on high level evidence

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SUMMARY

Cholangiocarcinoma, malignant tumor of epithelial cells of bile ducts has poor overall survival and prognosis. We report a case of non-resectable cholangiocarcinoma with a 57-month survival after incomplete R2 surgical margin resection of the tumor. A 52-year old man with generalized itching, jaundice, brownish urine, mild abdominal pain and weight loss of 8 kg in last two months presented. Imaging and surgical workups showed hilar cholangiocarcinoma (Klatskin tumor). Along with incomplete R2 margin resection we performed stent embedding and post-operative adjuvant chemotherapy. Based on current literature data there is no superiority of adjuvant chemotherapy after complete R0 resection compared to incomplete R2 resection. However, it seems that partial resection along with stent embedding and applied adjuvant chemotherapy in cases of locally advanced non-resectable cholangiocarcinoma may increase survival rate.

KEY WORDS: *Cholangiocarcinoma; Survival; Stents*

INTRODUCTION

Cholangiocarcinoma, malignant tumor of epithelial cells of bile ducts cover about 3% of all gastrointestinal tumors and 10-15% of all hepatobiliary tumors. The overall survival (OS) of this type of carcinoma is low and it has poor prognosis (1-5). Cholangiocarcinoma is the second prevalent hepatocellular carcinoma among the primary hepatic tumors (6, 7). The peak of incidence is at ages 50-70. The reason of its high mortality seems to lay in its clinical manifestations (jaundice and weight loss) and lack of an effective therapeutic modality. Patients with unresectable tumors usually die after 6-12 months due to cachexia, hepatic failure and bile duct infection (8, 9). Risk factors of this carcinoma include cases of chronic inflammation such as primary sclerosing cholangitis, inflammatory bowel disease, cirrhosis, hepatitis and smoking (10-14).

In the presented case patient had a 57-month survival in spite of incomplete R2 surgical resection of the tumor. We present this case and investigate the "why" and "therefore" of this long-term survival using a review on high level evidence literature.

CASE REPORT

A 52-year old man complaining of itching and jaundice referred to Iran University of Medical Sciences, Firoozgar hospital, Tehran, Iran (www.firoozgar.iums.ac.ir) in November 2013. The patient had generalized itching, jaundice, brownish urine, and mild abdominal pain. There was no similar familial history or patient's past surgical history. There was no positive medical history for allergies. Patient was not cigarette smoker or opium addict. The patient had 8 kg weight loss during recent 2 months. In his physical examination, the sclera was jaundice, the abdomen was soft without tenderness or rebound tenderness, and there were no other positive findings.

PARACLINICAL OBSERVATIONS

Results of the primary laboratory assays were as follows; WBC: 5.2 10^9/L, hemoglobin: 7.94 mmol/L, platelet: 178 10^9/L, INR: 1, AST: 53 U/L, ALT: 126 U/L, ALP: 968 U/L, total bilirubin: 0.31 mmol/L, direct bilirubin: 0.19 mmol/L, and CA19-9: 73 U/mL.

Ultrasonography reported a normal gallbladder with dilated biliary intrahepatic ducts. Endoscopic ultrasonography was performed that evidenced liver hilar stenosis and presence of 11×11 mm nodule in portal space. In computer tomography (CT) scan (Figure 1), dilated biliary ducts were evident. Patient became candidate for endoscopic retrograde cholangiopancreatography (ERCP) and received a stent that was embedded at the place of stenosis.

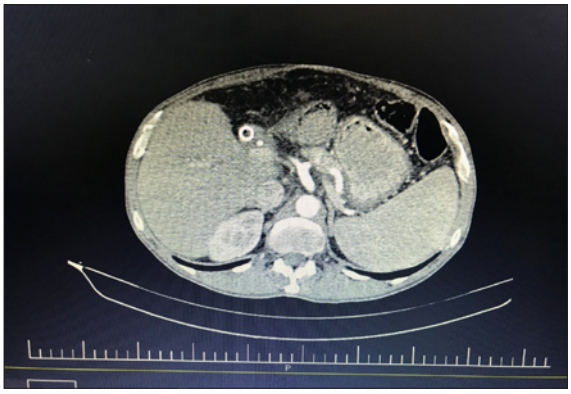

Figure 1. Residual Klatskin tumor with stent in billiary tract

WORKUPS AND FOLLOW UP

After one month the patent referred with similar complains. He had following lab results; ALP: 1170 U/L, total bilirubin: 0.11 mmol/L, and direct bilirubin: 0.07 mmol/L. Icterus existed and a level of CA19-9 tumor marker was high. Cholangiopancreatography was performed again and patient became candidate for surgery. During surgery gallbladder appeared a little dilated, had a mass and narrowing at common hepatic, right hepatic and left hepatic duct (bismuth IIIb) with a severe adhesion to hilar vessels. Therefore, complete R0 resection was not possible, and

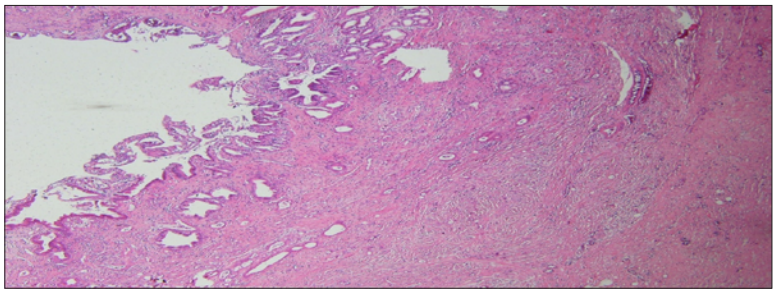

Figure 2. Common bile duct wall with thickening and dispersed invasive tumor glands in desmoplastic stroma (hematoxylin - eosin, magnification ×40)

R2 resection was performed as palliative surgery. Pathological report confirmed well-defined cholangiocarcinoma of common bile duct, with involvement of common, right and left hepatic ducts (Figs 2 and 3). The chemotherapy regimen was as follows; first course including 8-turn cycle with Kytril®, Fluorouracil (5FU) and granulocyte colony stimulating factor (G-CSF), and oral treatment with Capecitabine; second course (a year after) included Kytril® and Oxaliplatin. Eight months after the first course of chemotherapy, percutaneous transhepatic cholangiography (PTCD) was performed due to icterus. The patient failed to tolerate oral Capecitabine. Hence, this second course was done after another CT scan. At the time of reporting this case, the patient had referred to take his third course of chemotherapy. His 57-month survival prompted us to report this Klatskin tumor case.

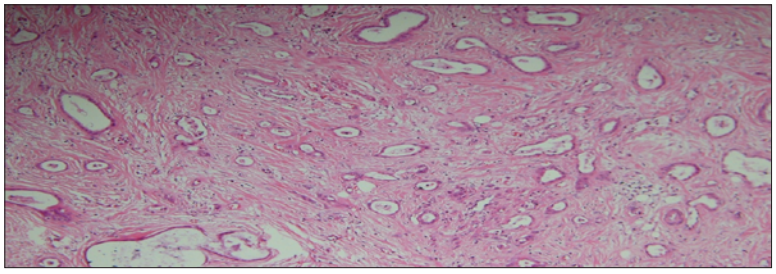

Figure 3. Tumor glands were well differentiated and with only mild atypia (hematoxylin - eosin, magnification ×40)

DISCUSSION

Cholangiocarcinoma of hilar and perihilar origin has poor prognosis and survival. DeOliveira et al. (2007) reported the 5-year survival of extrahepatic, intrahepatic and distal tumors of bile ducts in 10%, 40% and 23% cases and with median survival at 13, 28 and 18 months, respectively. These information were obtained from a 30-year experience of single medical institution (15). In study of Kahaleh et al. (2008), patients who were not able to undergo surgery were investigated. In this study only stents were embedded to inoperable patients and as a result mean of their survival was 8.5 months (16). However, the present case shows a 57-month survival in spite of perihilar position of the tumor. Mihalache et al. showed that stent embedding along with chemotherapy could increase survival rate (17).

Since 2016, several meta-analyses have reported survival rates of cholangiocarcinoma. In the first study dealing with distal cholangiocarcinoma Zhou et al. showed that median 5-year OS was 37% (range 13-50%) and 44% (range 27-63%) after R0 surgical resection. The risk factors of shorter OS were R1 surgical resection (relative risk 2.36, 95% CI 1.89-2.93), lymph node metastasis (relative risk 2.35, 95% CI 1.89-2.93), pancreatic invasion (relative risk 2.13, 95% CI 1.39-3.27), perineural invasion (relative risk 1.96, 95% CI 1.64-2.34), vascular invasion (relative risk 1.99, 95% CI 1.40-2.82), lymphatic invasion (relative risk 1.84, 95% CI 1.47-2.31) and tumor grade ≥T3 (relative risk 1.56, 95% CI 1.25-1.93) (18). Wellner et al. showed that post-operative adjuvant chemotherapy did not influence 5-year OS (19). In the study of Li et al. dealing with intrahepatic cholangiocarcinoma positive surgical margin resulted in inferior OS (hazard ratio 1.86, 95% CI 1.54-2.25) and progression free survival (hazard ratio 2.03, 95% CI 1.03-4.01) (20). Tang et al. showed that surgical margin less than 10 mm increased the hazard (hazard ratio 1.59, 95% CI 1.09-2.32) (21).

In their meta-analysis for hilar cholangiocarcinoma Bird et al. reviewed 24 papers with 4599 participants. The prognostic factors in this study were lymph node involvement (hazard ratio 1.78, 95% CI 1.65-1.93), resection margin status (hazard ratio 1.77, 95% CI 1.57-1.99), perineural invasion (hazard ratio 1.54, 95% CI 1.40-1.68), tumor differentiation (hazard ratio 1.54, 95% CI 1.38-1.72), portal vein resection (hazard ratio 1.54, 95% CI 1.15-1.70), microvascular invasion (hazard ratio 1.49, 95% CI 1.34-1.68), T category (hazard ratio 1.49, 95% CI 1.30-1.70) and age (hazard ratio 1.16, 95% CI 1.04-1.28) (22). Other studies have shown that adjuvant chemotherapy and radiotherapy can increase survival rate in the cases of non-resectable hilar cholangiocarcinoma (23-25).

According to the literature, R0 surgical resection is the most superior way to increase survival. Some studies supported the protective role of stent embedding. However, there was not enough evidence on protective role of adjuvant chemotherapy. Based on current high level evidence there is no superiority in administration of adjuvant chemotherapy in patients with R0 surgical resection. However, it seems that surgery with partial resection along with stent embedding and adjuvant chemotherapy in locally advanced cholangiocarcinoma patients with non-resectable tumor may increase survival rate. In our opinion this topic should be investigated further in future.

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Declaration of Interests

Authors declare no conflicts of interest

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