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Editorial

Gallbladder neck cancer and perihilar cholangiocarcinoma - *siblings, cousins or look alikes*?

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The gallbladder neck cancer and perihilar cholangiocarcinoma present as painless progressive surgical obstructive jaundice. Sometimes it becomes difficult to differentiate between them even on cross-sectional imaging studies including computed tomography and magnetic resonance imaging. Staging laparoscopy and positron emission tomography may be useful in detecting metastases in gallbladder neck cancer, but are not recommended in perihilar cholangiocarcinoma. Most patients with gallbladder neck cancer and perihilar cholangiocarcinoma require preoperative biliary drainage. The differentiation is, however, important because their behavior and prognosis are totally different. Gallbladder neck cancer is biologically aggressive, thus long-term surviver are rare even after major resection. On the other hand, perihilar cholangiocarcinoma is often less aggressive and major proceduresresections are justified. Gallbladder neck cancer and perihilar cholangiocarcinoma, though not siblings, they tend to look alike sometimes. **(Korean J Hepatobiliary Pancreat Surg 2015;19:86-88)**

Key Words: Gallbladder neck cancer; Perihilar cholangiocarcinoma

A middle-aged or elderly patient presents with painless progressive jaundice of short duration - this is associated with dark urine, clay-colored stool, and pruritus; high-grade fever with chills. In some cases, a patient may also present rigors (cholangitis). These are the features of malignant surgical obstructive jaundice. Differential diagnosis includes pancreatic and periampullary cancer, gallbladder cancer, and cholangiocarcinoma. Ultrasonography easily differentiates between pancreatic and periampullary cancer on one hand vs. gall bladder cancer and perihilar cholangiocarcinoma on the other.

Malignant obstructive jaundice with high block is caused by perihilar cholangiocarcinoma or gallbladder neck cancer. Differentiation between these two is often difficult and becomes a diagnostic dilemma, especially in ethnic populations in whom and geographical areas where gallbladder cancer is common.[1] Pain (dull and diffuse of liver infiltration or biliary colic due to associated gall stones) indicates gallbladder neck cancer, while perihilar cholangiocarcinoma is usually painless. It must, however, be noted that perihilar cholangiocarcinoma associated with gallstones may have pain and a small gallbladder neck cancer with no infiltration of the liver may be painless. Features of gastric outlet obstruction suggest gallbladder neck cancer rather than perihilar cholangiocarcinoma. A mass on imaging suggests the presence of gallbladder neck cancer rather than perihilar cholangiocarcinoma. While, it should be noted that an obvious mass may not necessarily be seen in a small gallbladder neck cancer, mass-forming cholangiocarcinoma is also an uncommon variant. The pattern of biliary ductal involvement is essential, for instance, the primary biliary ductal confluence as well as the proximal common hepatic duct can be involved in both gallbladder neck cancer and perihilar cholangiocarcinoma. Furthemore, the involvement of the left hepatic duct or segment IV duct indicates the presence of perihilar cholangiocarcinoma. The isolated involvement of the right anterior sectoral duct that lies in the gallbladder bed suggests the presence of gallbladder neck cancer. However, the involvement of the long segment of bile ducts is more

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in favor of perihilar cholangiocarcinoma than gallbladder neck cancer. Essentially, multiple sites of involvement can be seen in papillary variants of both gallbladder neck cancer and perihilar cholangiocarcinoma. Major hilar vascular involvement (hepatic artery and portal vein) can be present in both gallbladder neck cancer and perihilar cholangiocarcinoma, but involvement of the left hepatic artery and/or left portal vein almost always suggests perihilar cholangiocarcinoma. To stage the disease and assess resectability of patients with gallbladder neck cancer or perihilar cholangiocarcinoma, cross-sectional imaging studies are required. These techniques are preferably combined with angiography to evaluate the vessels (hepatic artery and portal vein) while cholangiography is used to evaluate the extent of involvement of the bile ducts. For this reason, magnetic resonance imaging with angiography and cholangiography is preferred over computed tomography.

By and large, the involvement of the proper hepatic artery and the main portal vein, indicates the unresectability in both gallbladder neck cancer and perihilar cholangiocarcinoma. In perihilar cholangiocarcinoma, surgeons can be more aggressive and still perform vascular resection and reconstruction; but in gallbladder neck cancer, prognosis and outcome are rather poor; hence vascular resection is not recommended.[2]

Obtaining tissue diagnosis is difficult, especially if a mass is not seen on imaging. It can be obtained by endoscopic ultrasound-guided fine needle aspiration cytology but is not mandatory if the clinical and imaging findings are suggestive of malignant surgical obstructive jaundice. In the past, some Japanese surgeons used to perform multiple percutaneous transhepatic cholangioscopy to obtain tissue diagnosis in bid to assess the extent of the intrahepatic bile duct involvement in perihilar cholangiocarcinoma, however the magnetic resonance cholangiography is prefered because it provides the same information in a non-invasive manner. If the suspicion of gallbladder neck cancer is high, positron emission tomography scan may be considered to detect abdominal or extra-abdominal distant metastases. Also, staging laparoscopy must be strongly considered[3] as the yield in terms of detection of small surface deposits on the peritoneum, omentum or liver is high.[4] The low yield of positron emission tomography and staging laparoscopy in perihilar cholangiocarcinoma does not warrant their routine use.

Tumor markers such as CEA and CA19-9 are not effective to differentiate between gallbladder neck cancer and perihilar cholangiocarcinoma, but helpful in differentiating between the benign and malignant surgical obstructive jaundice. Benign differential diagnoses of high block include Mirizzi's syndrome, xanthogranulomatous cholecystitis, primary sclerosing cholangitis and others.

Nearly all patients with malignant surgical obstructive jaundice with high block need preoperative biliary drainage because a major liver resection will be required. This can be achieved endoscopically if the primary confluence is patent or may need percutaneous transhepatic intervention if the confluence is blocked. The target serum bilirubin level to be achieved is <3 mg/dl.

Computed tomographic volumetry of the liver is important to calculate the future liver remnant. The future liver remnant (left hemiliver or right hemiliver) is usually adequate in perihilar cholangiocarcinoma because only hemi-hepatectomy (right more often than left) is required. However, extended right hepatectomy will be required in gallbladder neck cancer and future liver remnant is often inadequate.

This necessitates portal vein embolization to induce atrophy-hypertrophy to achieve adequate future liver remnant. Staging laparoscopy can be performed before portal vein embolization to exclude distant metastases. Hepatic atrophy-hypertrophy takes about 4-8 weeks to occur, which, necessitates another staging laparoscopy just before laparotomy for possible resection.

Resection for gallbladder neck cancer differs from that for perihilar cholangiocarcinoma. The vast majority of patients with gallbladder neck cancer have infiltration of the liver. Gallbladder neck cancer involves the removal of segment IV either whole (i.e. extended right hepatectomy) or in part (segment IVb or 2-3 cm wedge of segment IV) besides the right liver (segments V-VIII). In perihilar cholangiocarcinoma, not only the hemiliver (right more often than left) but the caudate lobe also has to be removed because bile ducts of the caudate lobe drain into the hilum.

Hepatopancreatoduodenoctomy may be performed for not only long-segment cholangiocarcinoma involving the hilum as well as the intrapancreatic bile duct, but also for gallbladder neck cancer infiltrating liver as well as duodenum/pancreas. Although technically feasible, hep-

atopancreatoduodenoctomy is controversially associated with high mortality and poor outcome in terms of long-term survival.[5] A fortuitous situation is gallbladder neck cancer with infiltration of the common bile duct alone and no infiltration of liver − this can be treated with extended cholecystectomy with common bile duct resection.

The standard lymph node dissection for the gallbladder neck cancer and perihilar cholangiocarcinoma includes not only the removal of the nodes in the hepatoduodenal ligament, behind the duodenum, and the head of the pancreas but also along the common hepatic artery to the right of the celiac axis. Extended lymphadenectomy including para-aortic lymph nodes does not improve survival and is not recommended.[6]

Total hepatectomy and liver transplantation may be considered for perihilar cholangiocarcinoma with extensive bilateral ductal involvement in the absence of lymph nodal involvement, however it may not be an option for unresectable gallbladder neck cancer.

Adjuvant therapy is recommended after R2/R1 resection but is also advised after R0 resection in case of advanced (T2+ or node-positive) disease or in the presence of poor histological markers such as poor differentiation, perineural invasion and lymphovascular invasion.

While several centers have reported many long-term survivors after resection for perihilar cholangiocarcinoma,[7] very few centers have reported similar results of resection in gallbladder neck cancer. In one of the largest experiences of resection in gallbladder cancer with surgical obstructive jaundice, the Nagoya University group reported only 12 actual 5-year survivors.[8]

Gallbladder neck cancer and perihilar cholangiocarcinoma, though pathological *cousins*, are biologically different in behavior with gallbladder neck cancer being more aggressive than perihilar cholangiocarcinoma and having much poorer outcome with lower survival rates even after R0 resection. Therefore, it is important to differentiate between these two, however, this differentiation is difficult most of the times and may be even impossible at times.

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