Editorial

Better staging for tailored treatment of perihilar cholangiocarcinoma

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Cholangiocarcinomas, malignant tumors arising from the ductal epithelium of the biliary tree, are classified as either intrahepatic cholangiocarcinoma (ICC) or extrahepatic cholangiocarcinoma (ECC) according to its anatomical location. Alternatively, they can be divided into mass-forming, periductal-infiltrating, and intraductal-growing tumor depending on macroscopic appearance. The vast majority of ICCs are mass-forming and mass-forming-periductal-infiltrating mixed tumors, whereas ECCs are presented as periductal-infiltrating or intraductal-growing tumors. The hepatic hilum, the junction of the right and left hepatic ducts, is a common site of tumor development. Stringently speaking, a tumor whose location is limited to the hepatic ducts and their confluence is named hilar cholangiocarcinoma, which is a subtype of ECC. This narrow definition of hilar cholangiocarcinoma is not feasible for cancer classification because hilar cholangiocarcinoma defined by the above criteria is the early feature of more advanced disease with extension to the liver and the distal bile duct. Perihilar cholangiocarcinomas, which include ECCs developing in the hepatic hilum and ICCs extending to the hepatic hilum, can be defined as cholangiocarcinomas occurring above the cystic duct up to the secondary branches of the right and left hepatic ducts. The majority of perihilar cholangiocarcinomas are identified as an ECC, but the ICC presenting as a perihilar cholangiocarcinomas is not rare. Macroscopically, the majority of perihilar cholangiocarcinomas are periductal-infiltrating cancers. The aim of constructing cancer staging systems is to accurately predict patient survival after resection of the tumor, and to standardize treatments in accordance with tumor stage. Previous staging systems for cholangiocarcinomas were suboptimal to predict patient survival because unlike from patients with more common cancers, it was difficult to gather data sufficient to provide robust evidence from those with a rare malignant tumor of cholangiocarcinoma. In TNM classification of ICC, until the latest revision, the disease has been staged by the system for malignant liver tumors according to the prognostic data for hepatocellular carcinoma. In 2010, the 7th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) has for the first time proposed a novel staging specific to ICC. The current AJCC/UICC staging manual is based on the analysis of the data extracted from the Surveillance, Epidemiology and End Results (SEER) program on 598 patients who underwent cancer-directed surgery for ICC (1). Although the AJCC 7th edition of TNM staging for ICC has been shown to more accurately discriminate the ICCs in terms of patient survival in a Western population than the previous AJCC editions and the Japanese classifications (2), there are some concerns remained. In the use of the SEER data, only half of the patients had undergone lymph node dissection and surgical margin was unknown (1). Since lymph node metastasis and positive surgical margin are both strong independent predictors for recurrence of ICC (3), the power of the current AJCC staging system to predict operative outcomes appears still suboptimal.

As mentioned previously, the majority of perihilar cholangiocarcinoma are ECCs when conventional classification is applied. In the AJCC 6th edition of TNM staging manual published in 2002, perihilar cholangiocarcinoma was not separated from distal bile duct cancer and staged within the category of ECC. The AJCC 6th edition did not predict survival of 42 patients who underwent resection of perihilar cholangiocarcinoma (4), whereas it provided better prediction of survival in patients with perihilar cholangiocarcinoma compared to the 5th edition in a report from Nagoya University Graduate School of Medicine (NUGSM) in Japan. This report

concluded that regional lymph node metastasis should be more weighed for better staging (5). In a more recent study from the NUGSM, survival curve of 250 patients who had undergone resectional surgery for perihilar cholangiocarcinomas (167 EHCs and 83 IHCs) between 1979 and 2004 was analyzed according to the 6th edition of the AJCC classification (6). In results, survival was marginally better for patients with EHCs than for those with IHCs, but survival rates were similar for each tumor stage, supporting that the concept of perihilar cholangiocarcinoma separating from the category of EHC is feasible for cancer staging and classification. In the 7th edition of AJCC manual, perihlar and distal bile duct tumors are separately staged. In the 6th edition, involved nodes were consolidated as the N1 group for hilar cholangiocarcinoma. In the 7th edition they were categorized as N1 and N2 as in the 5th edition, while for ICC and distal bile duct cancer, the presence (N1) or absence (N0) of lymph node metastasis is used for tumor staging. Lymph node metastasis is likely more common and lymph node dissection is likely more aggressive in distal bile duct cancer than in perihilar cholangiocarcinoma (7,8). It appears strange that the current AJCC manual classifies lymph node metastasis based on location for perihilar cholangiocarcinoma but not for distal bile duct cancer. In the N category for perihilar cholangiocarcinoma, N1 is defined as regional lymph node metastasis including nodes along the cystic duct, common bile duct, hepatic artery and portal vein, and N2 is defined as metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes. Regardless of T status, a tumor with N2 or distant metastasis (M1) is classified as Stage IVB. This staging system, however, does not necessarily mean that N2 and distant metastasis are weighed equally as a predictor for worse survival. It should be noted that the current AJCC staging system for perihilar cholangiocarcinoma is based on pathologic criteria and may be not so useful for determining respectability or predicting outcome (9).

In the recent issue of *Annals of Surgery*, the NUGSM group (10) determined the number of lymph node counts needed for adequate staging of perihilar cholangiocarcinoma and demonstrated that lymph node metastasis was the most important predictor for poor prognosis in patients who underwent tumor resection with curative intent. In addition, the NUGSM group suggested that distant lymph node metastasis (N2) is not contraindication to tumor resection as the primary treatment, and the number of involved nodes is more important than node location in predicting patient survival after surgery. These findings were derived from the analysis of 320 patients and 4,090 lymph nodes retrieved with a relatively high rate (45.6%) of lymph node metastasis. The adequate number of lymph nodes for tumor staging determined by the NUGSM group is 5 or more, which is in vicinity of 7 recommended by the Memorial Sloan-Kettering Cancer Center (7). The adequacy of these numbers will be validated in a large population and translated into the future cancer staging system.

Preoperative management and surgical procedures for perihilar cholangiocarcinoma are more complex than those for ICC and distal bile duct cancer. Preoperatively, biliary drainage for cholangitis or progressive jaundice is common and approximately half of the patients receive portal vein embolization for prevention from liver failure after extended hepatectomy (11). At surgery, hepatectomy including resection of the caudate lobe is performed for most patients, concurrent resection and reconstruction of portal vein is required in about one third of patients, and hepatic artery resection and reconstruction or additional pancreatoduodenectomy may be mandatory to achieve microscopically free surgical margin (R0 resection) in approximately 10% of patients (11). Consequently, R0 resection of advanced perihilar cholangiocarcinoma is associated with high operative morbidity and mortality. Even in high-volume centers such as NUGSM and Memorial Sloan-Kettering Cancer Center, postoperative complications occur in more than half of the patients (11,12). Among complications after surgery, liver failure, cholangitis and intra-abdominal abscess can be lethal. Although the recent operative mortality in high-volume centers ranges from 1.4% to 6.2%, the mortality rate in 1990s reported from such centers was 9-10% (11,12). Despite considerable risks associated with surgical resection of perihilar cholangiocarcinoma, it is the only way to achieve long-term survival or cure the disease. The survival rate of pM0, R0 and pN0 patients is improving presumably because of continuing reduction in operative mortality. In 243 patients with pM0, R0 and pN0 treated at the NUGSM, the 5-year survival rate arrived at 67.1%, while the 5-year survival rate of pM0, R0 and pN1 patients is still around 20% (11). These findings suggest the need for adjuvant or neoadjuvant chemotherapy in patients with node-positive hilar cholangiocarcinoma. In a retrospective comparison of 67 patients who received surgery alone and 48 patients who received surgery followed by adjuvant chemotherapy, chemotherapy improved median survival time from 36 to 41 months, although the impact of chemotherapy on survival was less than that of nodal status (13). In Japan,

a randomized controlled trial (UMIN000000820) was conducted to evaluate the efficacy of gemcitanine after resection of cholangiocarcinima and its registration was completed on December 2010. The early experience with liver transplantation for perihilar cholangiocarcinoma was disappointing owing to a high tumor recurrence rate (53-84%) (14). The recent success of neoadjuvant chemotherapy combined with external and internal radiotherapy followed by liver transplantation for 287 patients with end-stage liver disease and early-stage perihilar cholangiocarcinoma with a 65% rate of recurrence-free survival after 5 years (14) suggests the possibility of neoadjuvant chemotherapy also for those awaiting resection of perihilar cholangiocarcinoma. Since it was difficult for preoperative imaging to accurately assess lymph node status in patients with perihilar cholangiocarcinoma, routine excisional biopsy of hilar lymph nodes has been carried out as staging surgery before liver transplantation for perihilar cholangiocarcinoma (14). In a recent report evaluating the diagnostic accuracy of positron emission and computed tomography (PET-CT) for 123 suspected cholangiocarcinomas including 87 ECCs or perihilar cholangiocarcinomas, the accuracy of PET-CT in the diagnosis of regional lymph node metastases was 75.9% (15). Depending on the lymph node status, which will be more accurately assessed preoperatively with advancement in diagnostic imaging, individual treatment of patients with perihilar cholangiocarcinoma would be promising.

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