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STANDARDIZATION FOR SPECIMEN HANDLING AND PATHOLOGIC REPORT ON MARGIN FOR PANCREATICODUODENECTOMY

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Pancreatic cancer showed a very dismal prognosis with a 5-year survival rate of less than 5%. Most patients were already inoperable or unresectable status at the time of diagnosis. The only curable treatment option is a curative surgical resection with negative resection margins. The importance of R0 resection (grossly and microscopically negative margins) is more prominent in pancreatic cancer surgery than other gastrointestinal organ malignancy. In pancreatic cancer, the pathologic evaluation of retroperitoneal margin is more important for estimation of R0 resection than other anatomical margin, such as pancreatic neck margin. Reported positive rates for retroperitoneal margin of pancreatic head cancer range from 17% to 85% according to researchers. This wide range of positive margin rates is due to the lack of consensus about the definition of positive retroperitoneal margins for pancreatic head cancer. Some studies insisted that positive margin can be defined as the presence of tumor cells at less than one millimeter from resection margins not the presence of tumor cells at the margins and strict definition of R1 well discriminates the prognosis of patients with pancreatic head cancers. However, there is no pathologic standard gross protocol for evaluation of retroperitoneal margin of pancreatic ductal adenocarcinoma. We studied a standardized gross examination protocol for specimen handling of pancreaticoduodenectomy and investigated clinicopathologic parameters. Detailed clinicopathologic data were reviewed for cohort of 52 patients with a diagnosis of pancreatic ductal adenocarcinoma who underwent pancreaticoduodenectomy with curative intent at Samsung Medical Center, Seoul, Korea between July 2012 and April 2013. Exclusion criteria included macroscopic residual tumor (R2 resection), requiring the total pancreatectomy and ductal adenocrcinomas arising from intraductal papillary mucinous neoplasm. Finally, forty-five patients were analyzed in the present study. All patients underwent a standard lymphadenectomy including hepatoduodenal ligament and the right side of the celiac trunk. If the invasion of portomesenteric veins was suspected intraoperatively, en-bloc resection of portomesenteric vein with reconstruction was carried out. The surgeons indicated the SMA margins in the operative room by suturing the inferior and superior SMA margins respectively. And in cases of en-bloc portomesenteric vein resection, attached veins were indicated by same methods. All the specimens were delivered to the department of pathology and fixed overnight in formalin with retroperitoneal side up position, the retroperitoneal side margin were compartmented into SMA margin, portal groove margin, and pancreatic neck margin by three different colors. After color marking, the specimen was sliced obliquely to the axial plane of the specimen. Pathologist measured the distance from most front tumor cells to SMA, portal groove and pancreatic neck margin, respectively. In cases of portomesenteric vein resection, presence of venous invasion and venous margin status were reported and portal groove margin did not checked. Bile duct margin and both duodenal margins as well as above three margins were also evaluated. If any margins had the presence of tumor cells within 1 mm from margins, pathologist reported as 'revised R1'. Present series group consisted of 29 men (64.4%) and 16 women (35.6%) with median age of 63 years (Range, 44–88). Eleven patients (24.4%) of total 45 patients underwent en-bloc portomesenteric vein resection with reconstruction. All patients showed a pathologic T3 classification and thirty-four patients (75.6%) had a N1 status. Perineural invasion and lymphovascular invasion were identified in 97.8% and 77.8% of total tumors respectively. Eight patients (17.8%) had poorly differentiated tumors. In the present series, eight patients (17.8%) had the presence of tumor cells at any margins (classic R1) and twenty-six patients (57.8%) had the presence of tumor cells within 1 mm from any margins. Consequently, rate of revised R1 in the present series was 75.6%. Compared with classic R1 rate (5.3%) in the previous series group, there was a significant difference ($p < 0.001$). And classic R1 rate between two groups was significantly different (24.4% vs. 5.3%, $p < 0.001$). The involvement of pancreatic neck margin (safety margin $\leq$1 mm) was observed in 0 patients (0%). And the involvement of portal groove margins and SMA margins were observed in 20 patients (58.8%) and 22 patients (47.8%) respectively. Four patients (8.9%) of total 45 patients had the involvement of both margins. In the revised R1 group, half of patients had radiologic invasion of the portal vein and there was a no significant difference compared with revised R0 group. The 23.5% of revised R1 group underwent portomesenteric vein resection with reconstruction. In revised R1 groups, 5 patients (14.7%) were treated with preoperative chemo-concurrent radiotherapy. And presence of jaundice, histologic grade, bile duct invasion, duodenal invasion, and nodal metastasis had no significant differences between two groups. Only more than 2.5 cm of tumor size had marginal significance between two groups ($p = 0.053$). The present study revealed that rate of revised R1 with standardized protocol was 75.6% and this result is comparable to the rates of previous studies. However, the proportion of 2 or more involved margin in the present study is only 8.9% compared with two studies (32% and 45%, respectively). Poor tumor differentiation, large tumor size, and the tumor requiring the portomesenteric vein resection were associated with R1

resections. This present study failed to reveal the predictive factors of R1 resection. However, tumor size of more than 2.5 cm may be associated with R1 resection. Because of a relatively small number of cohorts, tumor differentiation and port mesenteric vein resection had not statistical significances. In conclusion, we report that most pancreatic head cancers have a narrow margin clearance of less than 1 mm with the standardized protocol. So, we suggest that a standardized gross examination protocol for pancreatic head cancer specimens should be necessary to generate the comparable data from different institutes.

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IG G4-RELATED SCLEROSING CHOLANGITIS

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Introduction: Immunoglobulin G4 related disease (IgG4-RD) is a newly recognized fibroinflammatory condition characterized by distinguishing clinical, pathologic and serologic features. IgG4-RD has been described in various organs: biliary tree, salivary glands, periorbital tissues, kidney, lung, lymph node, aorta, prostate, thyroid, and pericardium. IgG4-associated cholangitis (IAC) was introduced which refer to the biliary manifestation of IgG4-RD. Since various cholangiographic features of IAC are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma (CCC), it is often difficult to discriminate IAC from these progressive or malignant diseases on the basis of cholangiographic findings alone. Therefore, multidisciplinary approach is very important in order to avoid the misdiagnosis of PSC and malignant diseases.

Clinical features:

Demographics and clinical manifestation: The overall IAC epidemiology remains largely undefined yet. In the literature, men appear to be more commonly affected IAC same as PSC however, patient's age at clinical onset is around two decades older in IAC than in PSC, and no case of IAC have been reported in children contrary to PSC. Obstructive jaundice is the most common clinical presentation in IAC which is rarely observed at diagnosis in PSC. And also, other organ involvement can often be found in IAC, IAC is especially common associated with autoimmune pancreatitis (AIP).

Laboratory test: Level of alkaline phosphatase (ALP) and serum bilirubin level tend to be higher in patients with IAC in comparison with PSC. And also, a serum IgG4 increase is characteristic of IAC. However, it may not be diagnostic of the disease because some patients with IAC did not have increased levels of IgG4 at the time of diagnosis. And high level of the tumor marker CA 19-9 are common in patients with IAC therefore, CA19-9 levels do not seen to help to distinguish between IAC and CCC.

Cholangiography: Confluent stricture and prestenotic dilatation is a characteristic feature of IAC. These cholangiographic findings are different from PSC which shows band-like stricture, beaded appearance, pruned-tree appearance, and diverticulum-like out pouching. IAC associated with autoimmune pancreatitis (AIP) frequently shows a structure of the distal common bile duct. This stricture might be caused by both the thickening of the bile duct and the effect of inflammation and/or edema of the pancreas.

Histopathology: The histological appearances of IAC are basically similar to those observed in other IgG4-RD. The inflammation is typically transmural with a massive lymphoplasmacytoid infiltration, and is at times associated with moderate tissue eosinophilia. The cellular infiltrates are evenly distributed throughout the wall of the duct and peri ductal tissue. Obliterative phlebitis and perineural inflammatory extension are noted, especially the outer layer of the bile duct wall. The inflammatory process is intermingled with a unique storiform pattern of fibrosis as the inflammation progressed. However, the biliary lining epithelium is usually intact, despite the dense per luminal inflammation. This is contrast to PSC, which often involves luminal side and lining epithelium of bile ducts and produces erosion. And also, neutrophils are commonly seen rather than lymphocyte or plasma cell in PSC. On immunohistochemistry, IgG4 antibodies mark many plasma cells, and these cells are diffusely distributed in the inflamed area. A recently published consensus document proposed that >100 IgG4-positive plasma cells per high-power field (HPF) in surgical specimens and >10/HPF in biopsy samples are required for diagnosis of positive IgG4 immunohistochemistry.

Diagnosis: Many patients who have turned out to have IAC have only been diagnosed after a major surgical resection because it is difficult to diagnosis without careful consideration. If surgery is needed, it is required major surgery which has high morbidity and mortality because of anatomic localization. Therefore, accurate diagnosis is very important, for this reason, many studies proposed several diagnostic approaches. There have been published two diagnostic criteria. All of them include clinical feature, imaging, serology, histology, other organ involvement, and response to steroid therapy as important markers for IAC diagnosis.

Treatment: Corticosteroid is a treatment of choice for IAC. However, there are few data on what the duration of treatment of IAC should be. In the recent consensus, typical protocol is to treat with 40 mg/day of prednisone for 4 weeks and then, evaluate steroid response such as biliary stricture, biochemical abnormality, serum IgG4 level and CA 19-9. If there is good response for steroid, patients are followed by a 5-mg/week taper for a total of 11 weeks on treatment.[2] If there is suboptimal response, additional procedure like biliary stent insertion or surgical correction are considered. When the disease is recurred, it can be treated with immunomodulatory drug combination as well as steroid.[2,3,10] There is careful to comment prognosis of IAC because there have not been sufficient data about natural history and long term follow-up. However, there has been no one who develops cholangiocarcinoma or needs liver transplantation due to progressed liver cirrhosis in patients with adequate treatment. Among patients who are not undergone any treatment for IAC, someone needed liver transplantation because