Plenary Presentation

- Presentation Date: Saturday, April 25, 2015
- TIME: 10:50-11:50
- Chaired by: Dong Goo Kim, Woo-Jung Lee

P-01

Flat Type of Intraductal Papillary Mucinous Neoplasm of the Pancreas Differs from Papillary or Tubular Types in Terms of The Expression of Oncogenic Protein and Survival Outcome : A Proposal of a New Classification

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Background: Despite histologic overlaps, current criteria in distinction between intraductal papillary mucinous neoplasm (IPMN) and pancreatic intraepithelial neoplasia (PanIN) are mainly focused on the size of cyst, not on the histologic features. To describe clinicopathologic characteristics and to predict prognosis of IPMN more precisely, a new classification of IPMN needs to be investigated.

Methods: Ninety eight patients with surgical resection proven IPMN who had cyst ≥ 10mm were analyzed. Definitions of histologic classification were as follows; 1) papillary and mucinous (PM, long papilla and abundant mucin; classic IPMN), 2) tubular (T, dominant tubular pattern), and 3) flat (F, flat or micropapillary epithelium without long papilla or mucin pool; PanIN). The expressions of oncogenic protein were analyzed.

Results: Mean age was 64.5 years and 66.3% (n=65) were male. Gastric, intestinal, and pancreatobiliary subtype were found in 60.2% (n=59), 21.4% (n=21), and 18.4% (n=18), respectively. In noninvasive group (NI), gastric subtype was dominant in all PM (73.1%), T (75.0%), and F-IPMN (86.4%). Invasive IPMN consisted 46.9% (n=46) in all patients (PM 43.5%, T 17.4%, F 39.1%). Among invasive group (INV), intestinal (75.0%) in PM-INV, pancreatobiliary (50.0%) in T-INV, and gastric (72.2%) subtype in F-INV were dominant (p<0.001). Cystic portion of INV-IPMN showed higher MUC1 expression (PM 20.0%, T 62.5%, F 66.7%, p=0.009) and APC loss (35.0%, 50.0%, 88.9%, p=0.003) in F-INV. In invasive portion, MUC1 (26.3%, 87.5%, 88.9%, p<0.001), S100A4 (31.6%, 62.5%, 66.7%, p=0.011), and SMAD4 loss (5.3%, 37.5%, 77.8%, p<0.001) were highly expressed in F-INV. Disease-specific 5-year survival rate (5-YSR; 88.8%, 87.5%, 35.7%, p=0.002) and recurrence-free 5-YSR (68.4%, 72.9%, 28.6%, p=0.046) were lowest in F-INV.

Conclusions: Because of distinct morphological and immunohistological characteristics with poorer prognosis, F-IPMN should be classified into PanIN with large cyst separately which differs from classic IPMN, and such classification can provide clues to develop a more appropriate classification of PanIN and IPMN.

Keywords: Intraductal papillary mucinous neoplasm, Pancreatic intraepithelial neoplasia, Pancreatic neoplasm, Oncogenic protein

P-02

Impact of Braun Anastomosis on Reduction in Delayed Gastric Emptying Following Pancreaticoduodenectomy: Prospective Randomized Control Study

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Background: Delayed gastric emptying (DGE) is one of major morbidity after pylorus preserving pancreaticoduodenectomy (PPPD). The purpose of this study was to investigate incidence and severity of DGE between Braun anastomosis group and without Braun anastomosis group in PPPD.

Methods: From February 2013 to June 2014, 60 patients were recruited for this prospective randomized control trial(RCT). Incidence of DGE and its severity were analyzed according to Braun anastomosis in PPPD.

Results: PPPD without Braun anastomosis (PPPD-B) was done in 30 patients and 30 patients underwent Braun anastomosis following PPPD (PPPD+B). Comparative analysis between PPPD+B and PPPD-B group showed no differences in sex, age, diagnosis, operation time, hospital stays, and postoperative complications including pancreatic fistula (p>0.05). The DGE was developed in 14 patients (46.7%) in PPPD+B group and 19 patients (63.3%) in PPPD-B group with no statistically significant difference (p=0.15). However, Grade B and C DGE were significantly higher in PPPD-B group (36.7% vs. 33.3% in grade A, 10% vs. 23.3% in grade B, and 0 vs. 6.7% in grade C; p=0.047).

Starting time of sips of water was faster in PPPD+B group (0.97 ± 0.18 vs. 1.30 ± 0.7; p=0.017). The day of possible intake in half amount of food was also earlier in PPPD+B group (6.37 ± 3.37 vs. 10.47 ± 7.80; p=0.012).
Conclusion: Current RCT demonstrates that Braun anastomosis could reduce clinically relevant DGE in PPPD.
Keywords: Pancreaticoduodenectomy, Delayed gastric emptying, Braun anastomosis

P-03

Surgical Outcome of T2 Gallbladder Cancer Based on Location of Tumor and Surgical Treatments

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Background: The gallbladder has a unique anatomical relationship with liver, and the clinical significance of tumor location remains unclear. This study aimed to determine the prognostic impact of tumor location and suggest the optimal surgical stretagy iun T2 gallbladder cancer.
Methods: 131 patients with T2 gallbladder cancer underwent R0 resection from October 1994 to December 2014. Data regarding the clinicopathologic factors of these patients were collected. The location of tumor was categorized as “hepatic side” versus “peritoneal side” and “fundus” versus “body” versus “neck” through preoperative imaging study. Univariate and multivariate analysis of clinicopathologic factors were performed.
Results: Among the 131 patients with T2 gallbladder cancer, the most significant predicting factor for the survival and recurrence is the nodal status. The 5-year survival rate was 96.8% for the N0 patients and 79.4% for the N1 patients. Survival was no statistical difference according to tumor location (p=0.133; hepatic-side versus peritoneal-side, p=0.551; fundus versus body versus neck). With respect to surgical procedure, 5-year survival rate for patients with peritoneal-side cancer was no significant difference according to hepatic resection (p=0.607). However, the 5-year survival was 96.2% for hepatic-side patient with hepatic resection, and 60% for those without hepatic resection. Hepatic resection was important factor associated with overall survival in patients with hepatic-side cancer (p=0.021). 5-year survival rate was no statistical difference according to bile duct resection in the patients with fundus and body-located tumor (p=0.599). Although the difference was not statistically significant (p=0.374), survival of neck-located patients with bile duct resection was better than that of patients without bile duct resection. 5-year was 100% for patient with neck-located cancer with bile duct resection, and 79.5% for those without bile duct resection.
Conclusions: Considering the location of tumor, the optimal surgical procedure for each patients should be considered. In patients with hepatic-side cancer, hepatic resection is effective procedure for improving survival. Bile duct resection is considered to be additional procedure for improving survival in selected patient with neck-located cancer.
Keywords: Gallbladder cancer, Hepatic resection, Bile duct resection, Tumor location

P-04

Proposal of Modified TNM Staging System for Intrahepatic Cholangiocarcinoma Based Tumor Growth Type

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Background: Because noticeable changes were made to 7th AJCC TNM staging for intrahepatic cholangiocarcinoma (IHCC), we validated the prognostic impact of tumor staging after macroscopic curative resection of IHCC.
Methods: A cohort of 659 IHCC patients who underwent R0 (n=539) or R1 (n=120) resection were selected with exclusion of R2 resection (n=111). Study patients were followed up for ≥24 months or until death with no patient lost during survival analysis.
Results: Anatomical resection was performed in 599 (90.9%) and concurrent bile duct resection was conducted in 97 (14.7%). Median survival periods following R0, R1, and R2 resections were 28, 12, and 3 months, respectively (p=0.000). In the R0 resection group, the 1-, 3-, 5-, and 10-year tumor recurrence rates were 36.4%, 57.9%, 64.7%, and 65.0%, respectively; the 1-, 3-, 5-, and 10-year patient survival rates were 73.1%, 44.2%, 33.0%, and 23.1%, respectively. Independent risk factors for tumor recurrence and patient survival were tumor growth type, tumor size >5 cm, perineural invasion, and lymph node metastasis.

According to 7th AJCC staging system, the prognostic contrast was marginal in stage T2–4 tumors without lymph node metastasis (p >0.8). With our redefined staging system with tumor growth types and risk factors including tumor number and perineural/lymphovascular invasion, clear prognostic contrast was achieved among T1–3 stages (p=0.000) (Fig. 1).

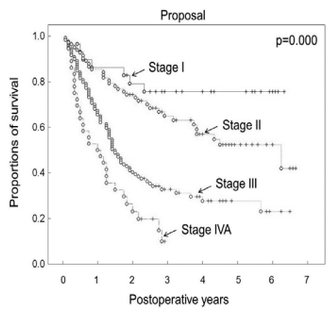
Conclusions: Growth type of IHCC seems to be essential for determining tumor stage. Although the stratification of 7th AJCC IHCC staging system seems reasonably established, refinements and further validation could improve prognostic predictability.

Proposed modification of the tumor staging system for intrahepatic cholangiocarcinoma

Tumor stage	
T1	Intraductal-growing tumor without any risk factor
T2	Mass-forming tumor without any risk factor
T3a	Tumor with any risk factor
T3b	Tumor with periductal invasion
T4	Locally advanced tumor not permitting macroscopic curative resection

Risk factors: multiple tumors, lymphovascular/perineurial invasion, and vascular/serosal invasion

TNM stage	
I	T1N0M0
II	T2N0M0
III	T3aN0M0, T3bN0M0
IVA	T4N0M0, any TN1M0
IVB	any T, any N, M1



Keywords: Intrahepatic cholangiocarcinoma; Resection; Recurrence; Lymphovascular invasion; Perineural invasion

P-05

Alterations of Hepatocellular Bile Salt Transporters and Effects of Immunosuppressants after Warm Ischemic Injury in Rats

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Warm ischemia (WI) and subsequent endogenous bile salt (BS) toxicity have been identified as important factors of intrahepatic bile duct strictures after liver transplantation. We aimed to identify the alterations of hepatocellular BS transporters and effects of immunosuppressants on it after WI in rats. We designed warm ischemic rat model mimicking donation after cardiac death throughout specific operation: ligation of hepatic artery, clamping of portal vein during 30 minutes, and catheterization of bile duct. Male Sprague-Dawley rats (250-310 g) were used. After designed operations, 30 rats were divided into three groups: WI only (n = 10), sirolimus (WI+S, n = 10), and tacrolimus (WI+T, n = 10). They were sacrificed for procurement of liver at 1 week and 3 weeks (on halves). As control, 6 rats underwent sham-operation. Using liver tissue, protein expression of hepatocellular BS uptake (NTCP, OATP1B3) and export (MRP2, MDR2) transporters were quantitatively measured by Western blot. At 1 week after WI, all 4 transporters were significantly increased (mean 767.6% in NTCP, 122.1% in OATP1B3, 530.5% in MRP2, and 282.7% in MDR2; all p = 0.007) compared to control (100.0%). At 3 weeks, all transporters were decreased again. However, NTCP was still significantly high (mean 174.0%; p = 0.005), and other transporters showed no significant differences compared to control (p = 0.095). In rats treated with sirolimus or tacrolimus, NTCP was significantly reduced at 1 week (p = 0.014 in WI+S vs. 0.027 in WI+T) and 3 weeks (p = 0.028 vs. 0.009), compared to WI only group [figure 1]. In OATP1B3, there was no significant effect of both immunosuppressants. In export transporters, MRP2 was significantly reduced at 1 week (both p = 0.014), and MDR2 was at 3 weeks (both p = 0.047) [figure 2, 3]. In conclusion, hepatocellular BS transporters are significantly increased after WI in rats. Sirolimus and tacrolimus have buffering effects on these WI induced alterations of BS transporters.

Keywords: Hepatic bile salt, Bile acid transporter, Transporter expression, Warm ischemic injury, Liver transplantation, Tacrolmus, Sirolimus, Rat, Animal study

P-06

Expanded Selection Criteria of Living Donor Liver Transplantation for Hepatocellular Carcinoma Using Total Tumor Size and 18F-FDG-PET/CT

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Rationale: Several expanded criteria based on morphological features, including tumor size and number, have been proposed to identify appropriate candidates for liver transplantation (LT) among patients with hepatocellular carcinoma (HCC). However, the definitions within these criteria are still complex, and the benefit of expanding the pool of eligible patients remains controversial.

Methods: From March 2005 to May 2013, patients with HCC who underwent living donor LT (LDLT) at the National Cancer Center, Korea (NCCK) were enrolled. Overall survival (OS) and disease-free survival (DFS) were investigated in patients classified according to the NCCK criteria using 18F-fluorodeoxyglucose positron-emission tomography/computed tomography and total tumor size

(cutoff 10 cm).
Results: Of a total of 280 patients, 164 (58.6%) were pathologically confirmed to have HCC that fulfilled the NCCK criteria, whereas 132 patients (47.1%) satisfied the Milan criteria. The five-year OS and DFS rates were significantly higher for patients who fulfilled the NCCK criteria (85.2% and 84.0%, respectively) than those for patients who did not fulfill the NCCK criteria (60.2% and 44.4%, respectively; $p < 0.001$). The NCCK criteria showed better correlation with preoperative imaging and explant pathological reports than the Milan criteria (Cohen's Kappa 0.850 vs. 0.583). The receiver operating characteristic curves for disease-free survival using the NCCK criteria at one, three, and five years showed similar area under the curve values compared with the Milan and University of California, San Francisco (UCSF) criteria (NCCK vs. Milan, $p = 0.484$; NCCK vs. UCSF, $p = 0.189$ at five-years).
Conclusions: The NCCK criteria incorporate both tumor biological and morphological characteristics, and represent simple and useful expanded criteria for identifying LDLT patients for HCC. Patient identification on the bases of this criteria showed an excellent agreement between preoperative imaging and pathological results and favorable survival outcomes.
Keywords: HCC, PET/CT