의학석사 학위논문

유두상 점액성 종양의 고등급 이형성증과 침습적 악성종양군의 임상 병리학적 특징 비교

Clinicopathologic characteristics of intraductal papillary mucinous neoplasm of the pancreas with high grade dysplasia and an associated invasive carcinoma: a single center retrospective study

울 산 대 학 교 대 학 원

의 학 과

서 기 석

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이 논문을 의학석사 학위 논문으로 제출함

2022 년 8 월

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서기석의 의학석사 학위 논문을 인준함

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Abstract

Background Intraductal papillary mucinous neoplasm (IPMN) is a cystic precursor to pancreatic cancer and shows a variety of disease spectrum from low-grade dysplasia, high-grade dysplasia to invasive carcinoma. The purpose of this study is to clarify the difference of clinicopathologic entity between IPMN-HGD and IPMN-associated invasive carcinoma.

Methods Total 461 patients who had diagnosed as IPMN by pathologic reports after surgery from January 2006 to December 2018 were reviewed. Patients who diagnosed as low-grade dysplasia, intermediate-grade dysplasia, IPMN concomitant carcinoma were excluded. Final 280 patients were enrolled; IPMN-HGD was 171, inv-IPMN was 109.

Results In terms of clinicopathologic data**, t**he median diameter of main pancreatic duct was 7.5mm in IPMN-HGD and 9.4mm in inv-IPMN (95% CI, p=0.012). The number of patients whose CA19-9 level was above normal value was 15(8.8%) in IPMN-HGD, and 49(45.0%) in inv-IPMN group (95% CI, p<0.001). In terms of survival, the estimated overall 5-year survival was 90.1% in IPMN-HGD and 57.2% for patients in inv-IPMN group (p<0.001). The estimated 5-year recurrence-free survival was 84.0% in IPMN-HGD group, and 46.4% in inv-IPMN group (p<0.001). In univariate analysis and multivariate analysis, invasiveness was the most influential factor affecting overall survival, followed by elevated CA 19-9 level. (HR=4.123, HR=1.915, respectively, 95% CI, p=0.005). Furthermore, recurrence pattern was different between IPMN-HGD, inv-IPMN group. Total 52 patients recurred, 7 patients in IPMN-HGD and 45 patients in inv-IPMN group respectively. All 7 patients in IPMN-HGD group locally recurred at remnant pancreas, but only 5 patients (11%) of inv-IPMN group recurred locally and more than 70% of patients already had distant recurrence. Therefore, completion TP was done in 6 patients of IPMN-HGD group (72%), and among them, 5 patients was finally diagnosed as IPMN-HGD and survive long-term without death. However, only 3 patients (6%) of inv-IPMN group locally resected by completion TP and more than 90% patients was unresectable and had palliative chemotherapy, RFA, other else.

Conclusion Significant survival and recurrence difference were observed between IPMN-HGD and inv-IPMN group. Therefore, we need to pay attention to disease progression and early resection before invasive IPMN should also be considered.

Contents

List of tables and figures

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a cystic precursor to pancreatic cancer characterized by intraductal papillary proliferation of mucin-producing epithelial cells within the pancreatic duct[1]. IPMN demonstrate a wide spectrum of cellular atypia, ranging from low-grade dysplasia to invasive carcinoma[2-4]. In the Baltimore consensus, the definition of pancreatic cystic diseases was revised and terms including malignant or carcinoma-in-situ of IPMNs were abandoned[5, 6]; So, nowadays low-grade dysplasia, high-grade dysplasia, IPMN-associated invasive carcinoma are being used widely. Most IPMNs has low malignant potential, and superior survival rates and disease prognosis of low-grade dysplasia (including intermediate-grade dysplasia before revision) was well explored by many studies, and treatment of choice has been the active surveillance without early surgical resection[7].

However, IPMNs can progress to high-grade dysplasia (HGD) and invasive cancer and the precursor lesions with HGD are considered to have a significant potential for progression to invasive carcinoma and thus surgically resected.[8, 9] Although, IPMN-HGD and IPMN-associated invasive carcinoma are frequently included under the term "malignancy" so far, several papers presented that IPMN-HGD have much better survival compared to those with IPMN-associated invasive carcinoma.[2, 10] Since, its natural history following resection is not well known; we need to clarify the difference between these two disease entities to uncover the prognostic factors of survival difference[11]. Furthermore, the long-term survival outcomes of IPMN-HGD, IPMN-associated invasive carcinoma remain unclear so far and there is little evidence for the usefulness of serum biomarkers for them[12-15]. Therefore, in this study, we aimed to explore the long-term survival outcomes and the diagnostic and prognostic significance of host-derived biomarkers (CEA, CA 19-9) in comparison of IPMN-HGD and IPMN-associated invasive carcinoma

Methods

Terminology

IPMN is defined as a grossly visible, predominantly papillary or rarely flat, noninvasive mucin-producing epithelial neoplasm arising in the main pancreatic duct or branch ducts[16]. Pathologic definition and classification system that more accurately reflects was revised at 2015 international Baltimore consensus meeting; Nowadays, 2-tiered system (low-grade vs. high-grade) has been proposed for all precursor lesions and high-grade dysplasia is to be reserved for only the up[5]. In this study, we used the pathologic reports from 2006 to 2018 and the terms, both before and after the revision,were mixed together. It means that, without retrospective central review of slides, the definition of 'intermediate grade dysplasia' has been on disagreement between medical centers or operators. Therefore, this study used only obvious terms, high-grade dysplasia and associated invasive carcinomain pathologic reports after first operation. Also, IPMN associated with invasive carcinoma was specified at pathologic reports by different names. "Invasive carcinoma arising from IPMN", "IPMN associated invasive carcinoma", "Invasive carcinoma derived from IPMN". All of these were included as associated invasive carcinoma group[17].

Patients

Review of a retrospectively maintained database identified 461 patients who was pathologically diagnosed as intraductal papillary mucinous neoplasm (IPMN) from 2006 to 2018 after operation in the Asan Medical Center, Seoul, Korea. Patients who were finally diagnosed as low-grade dysplasia, intermediate-grade dysplasia, and IPMN concomitant carcinoma were excluded. Central review of pathologic slides could not be done yet in this study, pathologic diagnosis such as "PDAC with background IPMN", "Carcinoma with concomitant IPMN" was considered as concomitant cancer and excluded at last. Finally, a total of 280 patients with IPMN-HGD and IPMN-associated invasive

carcinoma (inv-IPMN) were enrolled in this study. Clinical information, including patients' age and gender, pre-operative clinical and laboratory data, including biomarkers and pathologic data, including tumor size (with the size of the non-invasive IPMN and invasive cancer clearly separated), lymph node metastasis, perineural and vascular invasion and resection margin status were obtained. Cutoff values of each variable were referred to previous studies and literatures of IPMNs; age 65 year old, CEA 5 ng/ml, CA19-9 37 u/ml. The primary endpoint of this study was 5-year overall survival, and the secondary endpoint of the study was 5-year recurrence-free survival and prognostic factors of survival and recurrence, such as the value of CEA, CA 19-9 and the size of main pancreatic duct. This study was approved by the Institutional Review Board of Asan Medical Center.

Statistical analysis

For the purpose of performing a comparative analysis, patients were stratified into 2 groups based on degree of dysplasia as follows: high-grade dysplasia, and IPMN-associated invasive carcinoma (inv-IPMN). The clinical and pathologic characteristics of these groups were compared using statistical methods as follows. Continuous variables were presented as median and interquartile range (IQR) and were compared using a Wilcoxon-Mann-Whitney test. To compare the categorical variables, a chi-squared test or a fisher-exact test were performed. Kaplan-Meier survival estimated and a log-rank test were used to estimate the survival in IPMNs with different grades of dysplasia and invasive carcinoma. To evaluate the independent factors associated with survival we used a cox-proportional hazard regression. Possible factors related to development of PDAC in patients underwent resection were evaluated using univariate and multivariate regression models. A backward step-wise elimination with a threshold of $p = 0.200$ was used to select the variables for the final multivariate model. P-value <0.05 was considered statistically significance[8].

Kinetics of CA 19-9 and assessment of recurrence, survival outcomes

CA 19-9 has not been checked routinely in clinical setting; In ASAN medical center, we checked tumor marker in 7 days and 1-month after pancreatectomy. In our study, we collected CA 19-9 data, if possible, at intervals of 7 days, 1-month, 4-month, 6-month, 1-year, 2-year, 3-year, 5-year. The difference of value between last post op data and preop data was calculated by the means of velocity (f=CA 19-9 (PODmax) - CA 19-9 (POD1month)/medial follow up period) to compare recur group and non-recur group in both IPMN-HGD and inv-IPMN. In recurrence group, PODmax was the date of recurrence, and in non-recur group, PODmax could be a last follow-up date or date of death. When recurrence occurred, mean CA19-9 value of recurred cases in recurrence group and mean CA19-9 value of non-recurred cases in recurrence group in specific time has also been separated and calculated to show the tendency of elevation of CA 19-9 at specific recurrence timing.

Recurrence was defined by recurred cystic lesion which was more than high-grade dysplasia after initial pancreatectomy and was confirmed by pathology (biopsy or re operation) or radiologic techniques (CT/MR/PET). The sites of recurrence were classified as the remnant pancreas and distant organs. Distant recurrence (Extra pancreatic-) was defined as appearance of tumors outside the pancreas, including the local area, lungs, liver, bone, and peritoneum[18]. Histological diagnosis such as percutaneous biopsy has not been done in medical center, and only cases which had completion pancreatectomy were confirmed pathologically. Under the assumption that initial operation was R0 resection, we excluded the probability of de-novo IPMNs regardless of time interval before recurrence[18].

Post-operative follow-up data were collected from information obtained during routine surveillance clinic visits. In general, patients were followed for recurrence or progression every 3-6 months if they have IPMN-associated invasive carcinoma and 6-12 months if they have IPMN-HGD with imaging studies that included at least one of the following: computed tomography (CT) scan, magnetic resonance imaging (MRI), or endoscopic ultrasonography (EUS)[8]. In patients with an initial resection of an

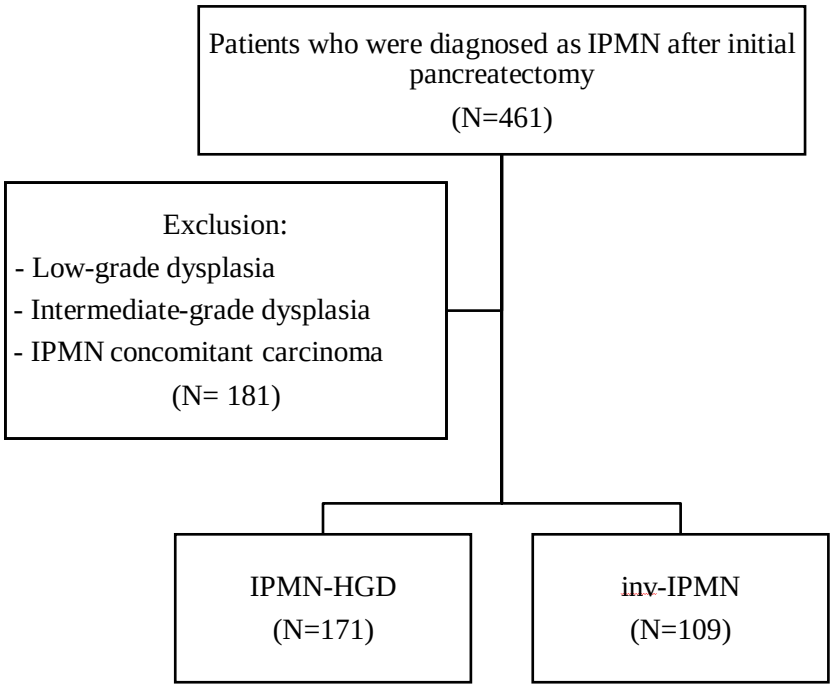
IPMN-associated invasive carcinoma, recurrence was determined by cross-sectional imaging and defined by the typical patterns of recurrence. That means local/regional recurrence was defined by the development of soft tissue in the tumor resection bed and systemic recurrence was determined by evidence of liver, lung, or peritoneal metastases. Survival time was calculated from the time of surgical resection to death and the survival analysis in the study could not be disease specific thus patients who died of causes other than pancreatic cancer was not censored along with those who were still alive at last follow-up[19].

Results

Patient characteristics

From 2006 to 2018, a total of 280 patients who met inclusion criteria underwent resection for an IPMN (**Figure 1)**. The clinical pathological characteristics of the patients with IPMN with high-grade dysplasia (IPMN-HGD) and IPMN-associated invasive carcinoma (inv-IPMN) were compared in **Table 1**. The median age was 63.5 years old for patients with IPMN-HGD and 64.8 years old in those found to have inv-IPMN. The number of patients whose age above 65 year was 84 (49.1%) in IPMN-HGD and 61 (56.0%) in inv-IPMN (p=0.264). Both IPMN-HGD and inv-IPMN was male-dominant, 2.36:1 for IPMN-HGD, 1.84:1 for inv-IPMN (95% CI, p=0.333). In respect of medical history, total 76 patients had hypertension on medication in IPMN-HGD (44.4%), and 51 patients in inv-IPMN (46.8%, 95% CI, 0.701). Total 63 patients had diabetes mellitus (DM) on oral medication (36.8%), 3 patients were using insulin for DM (1.8%) in IPMN-HGD and 39 patients on oral medication (35.8%), 7 was insulin-dependent (6.4%) in inv-IPMN (95% CI, p=0.121). Median body mass index (BMI) was 23.79 in IPMN-HGD and 22.57 in inv-IPMN (95% CI, p=0.002). 39 patients were current smoker when operation was go-on (22.8%) in IPMN-HGD, and 26 patients (23.9%) in inv-IPMN (95% CI, p=0.840).

Figure1. Inclusion and exclusion criteria of the study



Pre-operative radiologic, laboratory data was reviewed in **Table 1**. The median diameter of main pancreatic duct was 7.5mm in IPMN-HGD and 9.4mm in inv-IPMN (95% CI, p=0.012). The median value of maximum cyst size in pre-operative CT imaging was 35mm in IPMN HGD group, and 34.4mm in inv-IPMN (95% CI, p=0.768). The presence of mural nodule was checked by 3 imaging techniques; CT guided-, MR-guided and EUS-guided. CT-guided diagnosis of mural nodule was 96 cases in IPMN-HGD and 51 cases in inv-IPMN (p=0.146). MR guided diagnosis and EUS-guided diagnosis was 81 cases (50.6%) and 24 cases (41.0%) in IPMN-HGD, 41 cases (23.8%) and 14 cases (30.4%) in inv-IPMN (p=0.130, p=0.392 respectively). The median size of mural nodule was 6.9mm in IPMN-HGD, and 8.5mm in inv-IPMN (95% CI, p=0.094). Total number of patients who had pancreatitis when operation was going-on, was both 26 patients in IPMN-HGD (15.2%), and inv-IPMN (23.9%, 95% CI, p=0.070). The mean level of CEA was 3.06 in IPMN-HGD, and 4.33 in inv-IPMN. In particular, the number of patients whose CEA level was above normal value was 16 (9.4%) in IPMN HGD group and 17 (15.6%) in inv-IPMN (95% CI, p=0.114). The mean level of CA19-9 was 17.29 in IPMN-HGD group and 265 in inv-IPMN. In particular, the number of patients whose CA19-9 level was above normal

value was 15 (8.8%) in IPMN-HGD, and 49 (45.0%) in inv-IPMN group (95% CI, p<0.001). Location of IPMN was sub-divided into 3 groups and 101 patients was on pancreas head in IPMN-HGD (59.1%), and 64 patients in IPMN-associated PDAC (58.8%). 60 patients were on pancreas body/tail in IPMN HGD (35.1%), and 25 patients in inv-IPMN (22.9%). 10 patients were on whole pancreas (diffuse type) in IPMN-HGD (5.8%), and 20 patients in inv-IPMN (18.3%, 95% CI, p=0.002).

Post-operative clinicopathologic data was reviewed between two groups in **Table 2**. The median size of IPMN in pathologic report was 4.17cm in IPMN-HGD, and 4.47cm in inv-IPMN (95% CI, p=0.399). No lymph node metastasis was seen in IPMN-HGD but 27 patients have LN metastasis in final pathology in inv-IPMN (25%, 95% CI, p=0.280). In terms of pathologic duct type of IPMN, 16 patients were main duct type (9.3%), 41 patients were branch duct type (23.8%) and 115 patients was mixed type (66.9%) in IPMN-HGD. 20 patients were main duct type (19.4%), 26 patients were branch duct type (23.1%) and 62 patients was mixed type (57.5%) in inv-IPMN (95% CI, 0.047). Resection margin positive was seen in 30 patients in IPMN-HGD, and 23 patients in inv-IPMN. 26 patients (15.1%) were low-grade dysplasia, 4 patients (2.3%) were high-grade dysplasia and no patient showed cancer in IPMN-HGD. 6 patients (5.6%) were low-grade dysplasia, 5 patients (4.6%) were high-grade dysplasia, 12 patients (11.1%) were cancer in inv-IPMN. The median follow-up period was 61.7 month in overall survival; median 48.21 month follow-up period in IPMN-HGD group and median 48.06 month follow-up period in inv-IPMN group.

Table 1. Clinicopathological features of the patients, Pre-operative data

	IPMN-HGD (n=171)	inv-IPMN (n=109)	P-value
Age, n(%), mean ± SD Yr	63.52 ± 9.99	64.86 ± 9.60	0.264
Sex, M:F	2.36:1	1.84:1	0.333
HTN, n(%)	76(44.4%)	51(46.8%)	0.701
Diabetes mellitus, n(%)			0.121
OHA	63(36.8%)	39(35.8%)	
Insulin-using	3(1.8%)	7(6.4%)	
Current smoker, n(%)	39(22.8%)	26(23.9%)	0.840
MPD diameter, mean ± SD, mm	7.5 ± 5.62	9.4 ± 7.28	0.012
Presence of mural nodule, n(%)			
CT-guided	96(56.1%)	51(47.2%)	0.146
MR-guided	81(50.6%)	41(41.0%)	0.130
EUS-guided	24(23.8%)	14(30.4%)	0.392
Pancreatitis, n(%)	26(15.2%)	26(23.9%)	0.070
CEA, n(%)			
< 5 ng/mL	155(90.6%)	92(84.4%)	0.114
>5 ng/mL	16(9.4%)	17(15.6%)	
CA 19-9, n(%)			
< 37 u/ml	156(91.2%)	60(55.0%)	<0.001
> 37 u/ml	15(8.8%)	49(45.0%)	
Location, n(%)			
Head	101(59.1%)	64(58.8%)	0.002
Body-tail	60(35.1%)	25(22.9%)	
Whole-pancreas(diffuse)	10(5.8%)	20(18.3%)	

HTN;hypertension, OHA;oral hypoglycemic agent, MPD;main pancreatic duct, MR;magnetic resonance, EUS;endoscopic ultrasonographic, HGD;high grade dysplasia, IPMN;intraductal papillary mucinous neoplasm

Table 2. Clinicopathologic features of the patients, Post-operative data

	IPMN-HGD (n=171)	inv-IPMN (n=109)	P-value
IPMN size, mean ± SD, cm	4.17 ± 2.82	4.47 ± 2.84	0.399
LN metastasis, n(%)	0	27(25%)	0.280
Pathologic duct type, n(%)			
Main duct type	16(9.3%)	20(19.4%)	0.047
Branch duct type	41(23.8%)	26(23.1%)	
Mixed type	115(66.9%)	62(57.5%)	
Operation, n(%)			
PD/PPPD/SSPPD/L-PPPD/R-PD	100(58.1%)	59(54.6%)	0.230
LDPS/DPS/LDP/DP/R-DP	53(30.8%)	23(21.3%)	
TP	13(7.6%)	26(24.1%)	
CP/L-CP	5(2.9%)	0	
Uncinectomy	1(0.6%)	0	
Median-overall survival, mean ± SD, m	83.42 ± 30.57	36.31 ± 37.95	0.072
5-yea-overall-survival rates, mean ± SD, (%)	90.1 ± 2.3	57.2 ± 4.9	<0.001
5-year-recurrence-free-survival rates, mean ± SD, (%)	84.0 ± 2.4	46.4 ± 4.8	<0.001

HGD;high grade dysplasia, IPMN;intraductal papillary mucinous neoplasm, LN;lymph node, PD;pancreaticoduodenectomy, PPPD;pylorus-preserving pancreaticoduodenectomy, L-PPPD;laparoscopic pylorus-preserving pancreaticoduodenectomy, R-PD;robotic pancreaticoduodenectomy, LDPS;laparoscopic distal pancreatectomy and splenectomy, TP;total pancreatectomy, CP;central pancreatectomy,

Survival outcomes

During 5 years, 15 patients in IPMN-HGD and 46 patients in inv-IPMN group died and the estimated

overall 5-year survival was 90.1% for patients with an IPMN-HGD, 57.2% for patients with an inv-IPMN group ($p<0.001$). The median overall survival after resection for IPMN-HGD was 83.42 months, but patients with inv-IPMN had a poor survival compared to patients with IPMN-HGD (36.31 months, 95% CI, $p<0.001$). The estimated 5-year recurrence-free survival was 84.0% for patients with an IPMN-HGD group, and 46.4% for patients with an inv-IPMN group ($p<0.001$) (**Figure 2)**

In subgroup by IPMN duct type, 5 year OS was significantly different between IPMN-HGD and inv-IPMN in main duct types; 3 patient died in IPMN-HGD and 9 patient died in inv-IPMN (80.8% vs. 55.6% in 5-yr OS, $p<0.13$). In contrast, there was no statistical significance about 5-year RFS between IPMN-HGD and inv-IPMN in main duct type. In mixed duct type, both 5-year OS and 5-year RFS was significantly different. 10 patients died in IPMN-HGD and 23 patient died in inv-IPMN (89.7% vs. 63.0% in 5-yr OS, 83.6% vs. 48.7% in 5-yr RFS, $p<0.001$) (**Figure 3)**

Prognostic factor analysis

To identify the risk factors associated with overall survival rates in patients with IPMN, the univariable and multivariable regression analyses were performed. In the univariable regression model, patients' age, invasiveness of IPMN, CEA level, CA19-9 level, lymph node metastasis was associated with poor survival of IPMN. However, in multivariable logistic regression model after adjustment revealed that patients' age, invasiveness, CA19-9 level, lymph node metastasis were the risk factors related to poor survival, except CEA level. Invasiveness of IPMN was the most powerful factor about overall survival (HR=4.123, 2.419-7.027, 95% CI). The results were summarized in **Table 3**. Main pancreatic duct type didn't influence on poor survival rates, especially main duct type, mixed duct type in univariate analysis in terms of overall survival.

In univariable and multivariable analysis of prognostic factors in recurrence-free survival, age, invasives of IPMN, CEA level, CA19-9 level, lymph node metastasis was associated with poor

recurrence-free survival in univariable analysis. In the same way, age, invasiveness, CA 19-9 level, lymph node metastasis were the risk factors in multivariable analysis **Table 4**.

Kinetics of CA 19-9 and recurrence

Median recurrence date in total cases was 9.4months in the study. Recurrence started at POD 4month, median CA 19-9 at recurred point in recur group vs. median CA19-9 at no recurred point in recur group were compared (191.95u/mL vs. 37.358u/mL at 4 month). Peak CA 19-9 of recurred point in recur group was occurred at 2-year after operation; 3436.133 u/mL. In IPMN HGD, recurrence occurred at 1-year after operation and in inv-IPMN group, recurrence occurred at 4-month after operation; median recurrence period was 1.6 month vs. 9.8month. ΔCA 19-9 (PODmax – POD1month) was calculated in each group; 0.319 in recur group and -0.09 in non-recur group in IPMN-HGD vs. 176.75 in recur group and -0.719 in non-recur group in inv-IPMN. Red-line in graph was median recurrence date.

Recurrence patterns

Recurrence was defined by recurred cyst more than IPMN-HGD after 1-month from initial pancreatectomy either by pathologic confirms (biopsy or pathology) or radiologic confirms (CT/MR/PET). Recurred cases were collected and total 52 patients recurred after surgical intervention. In IPMN-HGD group, 7 patients recurred and in inv-IPMN group, 45 patients recurred, respectively. All 7 cases in IPMN-HGD group recurred at remnant pancreas; 3 patients recurred proximal to distal and 4 patients recurred distal to proximal. In inv-IPMN group, 5 cases (11%) recurred at remnant pancreas; 4 cases recurred at remnant distal pancreas and 1case recurred at remnant proximal pancreas. 11 cases (24%) at peritoneum as peritoneal seeding, and 6 cases (13%) at liver, 5 cases (11%) at lung, 18 cases (41%) at distant organs such as bone, IVC and so on. In terms of adjuvant treatment after recurrence in IPMN-HGD group, 1 patient could not get treatment due to sepsis (14%), and the other 5

patients had completion total pancreatectomy (completion TP); completion total pancreatectomy (completion TP) alone was 4 cases (72%) and completion total pancreatectomy plus adjuvant chemotherapy was 1 case (14%), respectively. In inv-IPMN group, 18 patients couldn't get any treatment (41%), and 3 patients had completion total pancreatectomy; completion total pancreatectomy alone was 2 cases (4%), and completion total pancreatectomy plus adjuvant chemotherapy was 1 case (2%). Other treatment such as liver RFA was done in 25 patients in inv-IPMN group (53%). About recurred lesion pathology after completion total pancreatectomy, 4 patients who had completion TP alone were diagnosed as IPMN-HGD and the other 1 patient who had completion TP and chemotherapy was diagnosed as invasive IPMN in IPMN-HGD group. In contrast, 2 patients were diagnosed as IPMN-HGD, and the other 2 patients was diagnosed as invasive IPMN in inv-IPMN group. Patient who got completion TP and chemotherapy in each group eventually died within 1 year of re-operation due to cancer progression. The results were summarized in **Table 5**.

Figure 2. Overall survival and recurrence-free survival in IPMN-HGD and inv-IPMN

(Figure 2-A; 5-Yr OS, and Figure 2-B; 5-Yr RFS in IPMN-HGD and inv-IPMN)

Outcome	Overall (n=280)	IPMN-HGD (n=171)	inv-IPMN (n=109)	P*
5-year OS	61 (76.7%)	15 (90.1%)	46 (57.2%)	.<001
5-year RFS	77 (67.9%)	20 (84.0%)	57 (46.4%)	.<001

*Log-rank test was used.

Figure 2-A

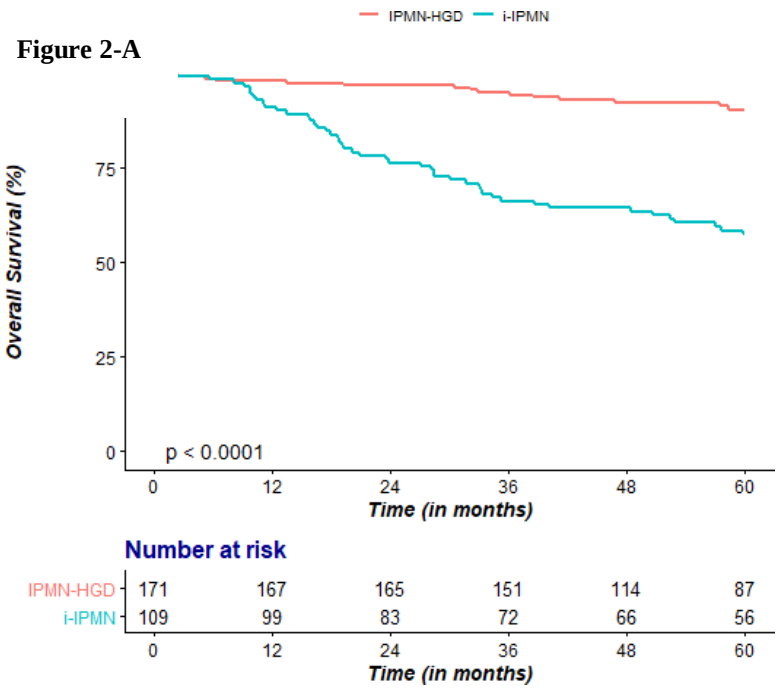


Figure 2-B

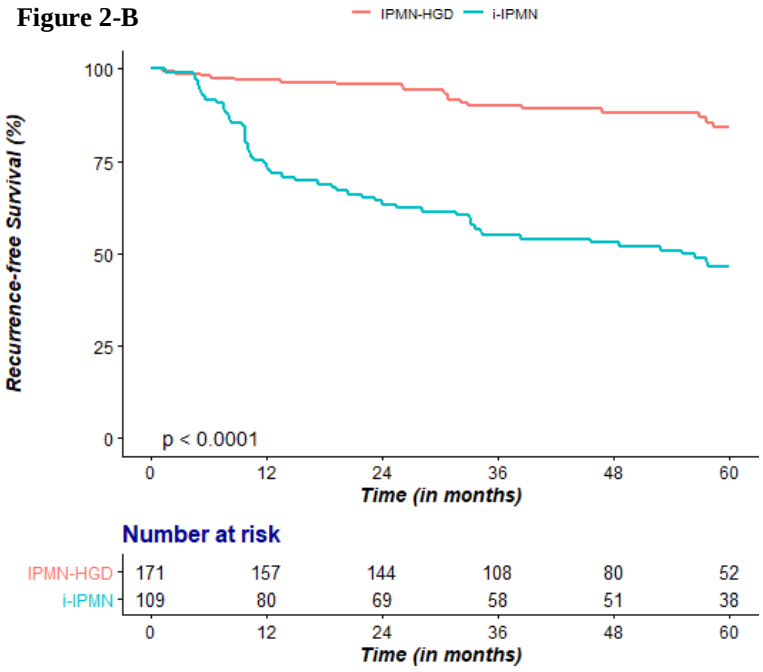
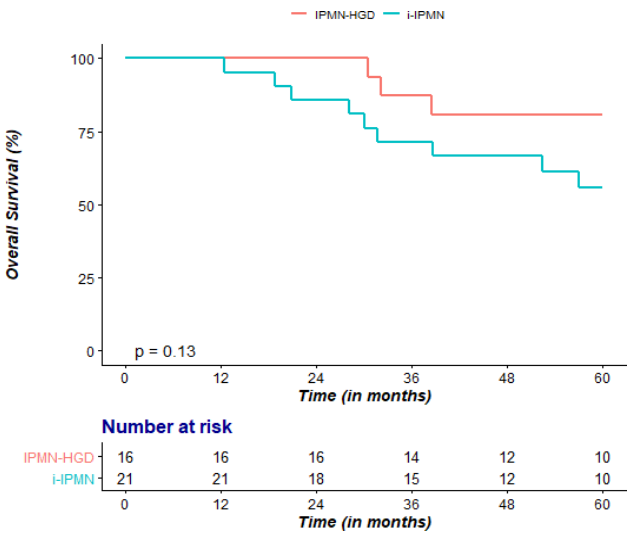


Figure3. Event frequencies and Kaplan Meier estimates of clinical outcomes, stratified by duct type.

(Figure 3-A;5-Yr OS in main duct type vs. mixed duct type, Figure 3-B; 5-Yr RFS in main duct type vs. mixed duct type)

Outcome	Main duct type				Mixed duct type			
	Overall (n=37)	IPMN-HGD (n=16)	inv-IPMN (n=21)	P*	Overall (n=177)	IPMN-HGD (n=114)	inv-IPMN (n=63)	P*
5-year OS	12 (66.2%)	3 (80.8%)	9 (55.6%)	0.13	33 (79.9%)	10 (89.7%)	23 (63.0%)	.<001
5-year RFS	16 (52.5%)	4 (67.3%)	12 (41.9%)	0.062	45 (69.6%)	14 (83.6%)	31 (48.7%)	.<001

* Log-rank test was used.



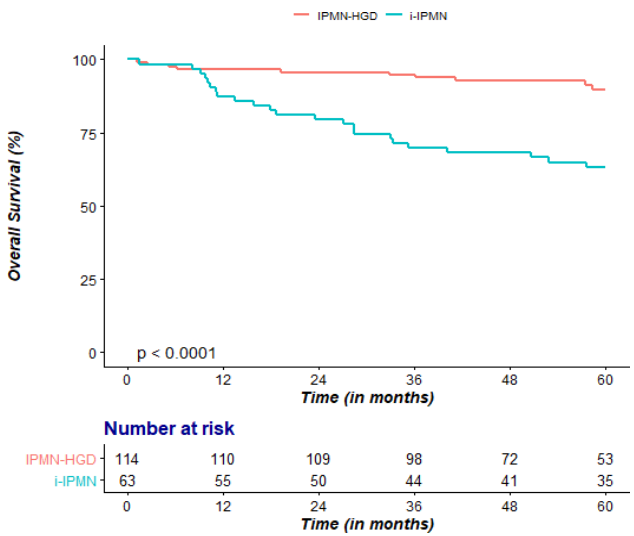
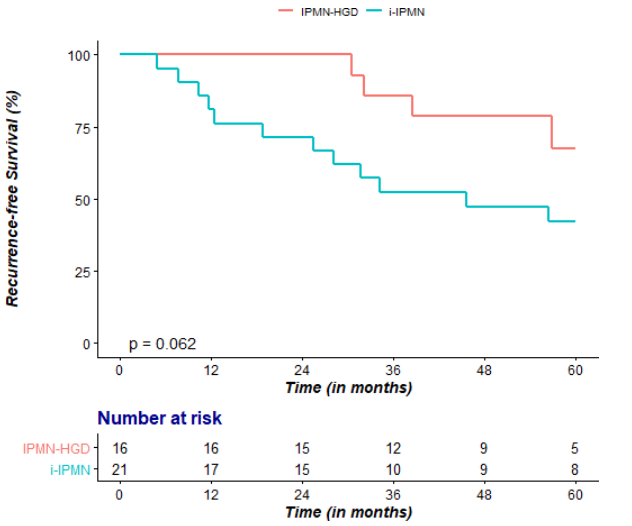


Figure 3-A



Main duct

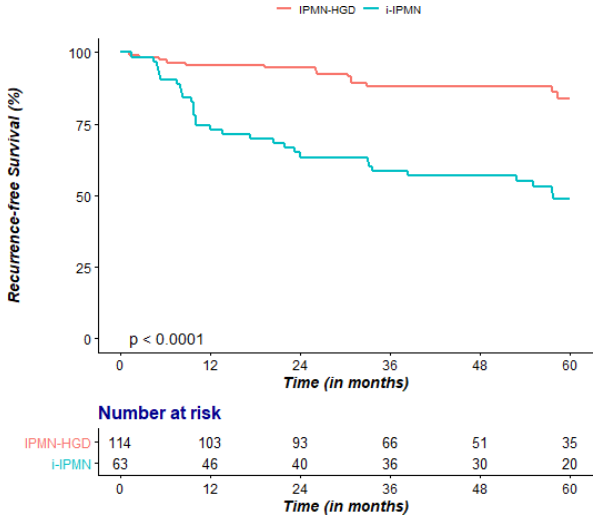


Figure 3-B

Mixed duct

Table 3. Univariate analysis and multivariate analysis of risk factors associated with Overall survival in IPMN HGD and inv-IPMN

Variables	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	p
Age, yr	1.036	0.002	1.038	0.004
Sex, M:F	0.631	0.035		
Invasiveness, n	5.838	<0.001	4.123	<0.001
CEA >5 ng/mL	1.827	0.040		
CA19-9, >37 u/ml	3.601	<0.001	1.915	0.005
IPMN size, cm	1.060	0.081		
MPD diameter, mm	1.042	0.003		
Lymph node metastasis, n	1.217	<0.001	1.128	0.013
Pathologic duct type (main D.type)	1.603	0.152		
Pathologic duct type (mixed D.type)	0.941	0.820		
Pathologic duct type (main or mixed D.type)	1.023	0.928		

HGD;high grade dysplasia, IPMN;intraductal papillary mucinous neoplasm, HR;hazard ratio, ,main D;main duct, mixed D;mixed duct, MPD;main pancreatic duct

Table 4. Univariable and multivariable Cox regression analyses of 5-year recurrence-free survival.

Variables		Univariable		Multivariable	
		HR (95% CI)	P	HR (95% CI)	P
Invasiveness	**No**	Ref		Ref	
	Yes	5.09 (3.06, 8.47)	<.001	3.02 (1.71, 5.33)	<.001
Age		1.03 (1.01, 1.06)	0.01	1.03 (1.00, 1.05)	0.044
Sex	**Male**	Ref		Ref	
	Female	0.58 (0.37, 0.91)	0.017	0.76 (0.48, 1.22)	0.264
CEA_preop, ng/mL	**≤5**	Ref		Ref	
	>5	1.85 (1.04, 3.31)	0.037	1.52 (0.84, 2.77)	0.167
CA19_9_preop, u/mL	**≤37**	Ref		Ref	
	>37	3.82 (2.44, 5.98)	<.001	1.84 (1.12, 3.00)	0.016
Size	**per 1cm increase**	1.04 (0.97, 1.12)	0.255		
Size, cm	**≤5**	Ref			
	>5	1.28 (0.78, 2.10)	0.328		
LN.metastasis	**No**	Ref		Ref	
	Yes	5.88 (3.56, 9.70)	<.001	2.55 (1.44, 4.51)	0.001
Pathologic_duct_type	**Main D.**	Ref			
	Branch D.	0.57 (0.28, 1.14)	0.11		
	Mixed D	0.62 (0.35, 1.09)	0.096		

*Multivariable analysis included risk factors with P<0.05 either in the univariable analysis of OS or the univariable analysis of RFS.

Figure 4. CA 19-9 change value in IPMN-HGD and inv-IPMN; comparison of recurrence group vs. non-recurrence group

(Figure 4-A; CA19-9 value difference between total recur group and non-recur group. Figure 4-B; value difference in IPMN-HGD, Figure 4-C; value difference in inv-IPMN)

Figure 4-A

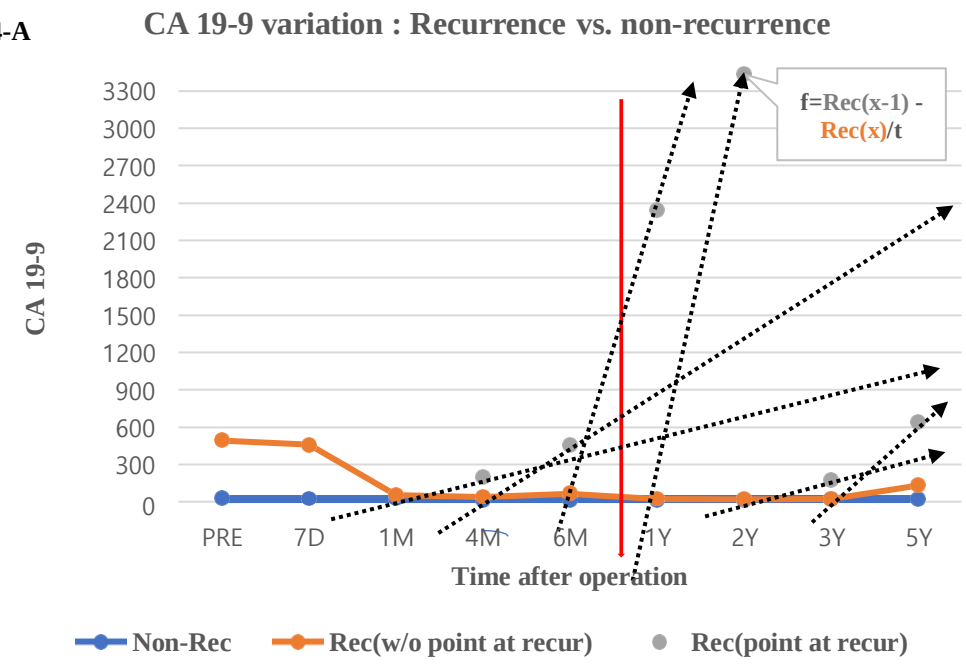


Figure 4-B

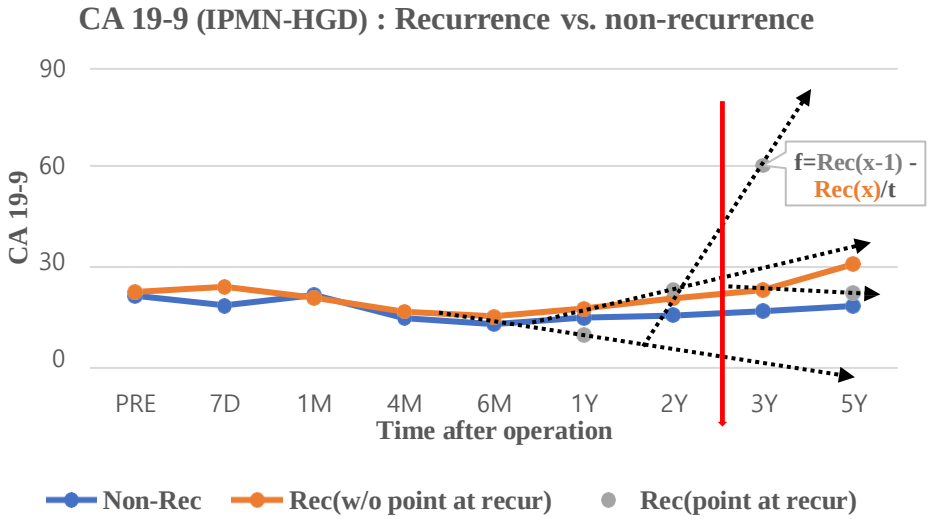


Figure 4-C

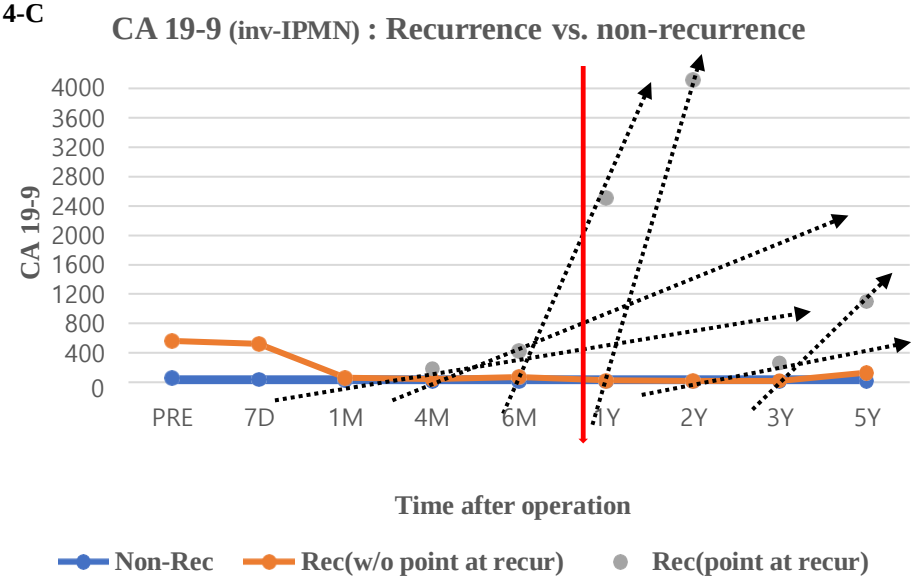


Table 5. Difference of recurrence patterns between IPMN-HGD and inv-IPMN

Variables	IPMN-HGD (n=7)	inv-IPMN (n=45)
	N(%)	N(%)
Recurrence site		
Remnant pancreas	7(100%)	5(11%)
Peritoneum		11(24%)
Liver		6(13%)
Lung		5(11%)
Others (Bone, IVC etc)		18(41%)
Treatment after recurrence		
No treatment	1(14%)	18(41%)
Completion TP	5(72%)	2(4%)
Completion TP + CTx	1(14%)	1(2%)
Others (RFA, RTx etc)	0	25(53%)

CA19-9 after recurrence, median ± SD, u/ml	30.7 ± 10.96	811.07 ± 47.24
Median overall recurrence, median ± SD, month	31 ±2.3	25.2 ± 9.7
ΔCA 19-9 (Recur-1-month post-op)	0.319	176.75
ΔCA 19-9 (POD_{max}-1-month post-op)	-0.09	-0.719

HGD;high grade dysplasia, IPMN;intraductal papillary mucinous neoplasm, TP;total pancreatectomy, CTx; chemotherapy, RTx; radiotherapy

Discussion

Considering the cystic nature and intraductal spread of IPMN, it is difficult to measure the tumor size and quantitate its invasiveness using the conventional TNM pathologic system[2, 14]. So maximum cyst size did not show a large trend as the invasiveness increased in this study. Del Chiaro, Marco compared clinicopathologic data of 796 IPMN patients into 3 groups; low-grade dysplasia, high-grade dysplasia, and IPMN-associated invasive carcinoma[20]. The proportion of patients older than 70 years increased in high-risk groups (IPMN-LGD 43.3% vs. IPMN-HGD 56.2% vs. inv-IPMN 53.3%, p=0.005)[20]. Likewise, in our study, IPMN-HGD group had a tendency to occur as early as 1.5 years of age than inv-IPMN group. Even though, there was no statistical significance of the mean age of two groups, it could back up the fact that the disease progression from adenoma to carcinoma has been considered to take about 3~6 years to develop[19].

Main pancreatic duct (MPD) dilatation could be the single best predictor of IPMN-HGD and invasiveness, in some papers. Beckman, Ross investigated that, compared with MPD dilatation below

5mm, the risk of IPMN-HGD and inv-IPMN was 7-fold higher (OR=6.57, 95% CI 3.94-10.98) and 15-fold higher (OR=15.6, 95% CI 8.21-27.65) for an MPD dilatation of 10mm or more, respectively[20, 21]. There was no strong evidence of linearity between MPD dilatation and the risk of both IPMN-HGD and inv-IPMN but predicted probabilities of invasiveness increased as MPD dilatation increased. In our study, MPD dilatation more than 7mm could be cutoff to identify the high risk of IPMN-HGD/inv-IPMN and the mean MPD dilatation of inv-IPMN group was 9.4mm, close to 10mm. However, the accurate cutoff-value of MPD diameter to predict invasiveness is unclear and radiologic, clinical data should be added up as a way of a nomogram[22]. The current studies show that an elevated CA 19-9 is associated with the presence of IPMN-associated invasive cancer and concomitant PDAC, but not independently to high-grade dysplasia; Using the 37 u/mL the specificity and sensitivity for CA 19-9 were 84.5% and 40.8% respectively. In our study, the proportion of elevated CA 19-9(>37 u/mL) was 8.8% in IPMN-HGD and 45% in inv-IPMN, and high CA19-9 value could be predictive measurement of invasiveness.

Diffuse type IPMN means mucinous cyst affecting the whole pancreas and diffuse main pancreatic duct involvement was associated with an increased percentage of high-grade dysplasia than focally involved main duct[23]. Therefore, as the current treatment guidelines state, surgical resection such as total pancreatectomy is needed due to a risk of local progression[24]. In our study, inv-IPMN group has much more diffuse-type IPMN cases than IPMN HGD; 18.3% vs. 5.8% and near 20% of inv-IPMN group needed initial total pancreatectomy. Diffuse IPMN does not mean directly invasive cancer and poor survival. However, in retrospective review in 2018, Poiraud discussed 93 patients who have done total pancreatectomy due to IPMN and 25 patients(27%) was IPMN-LGD, 14 patients(15%) was HGD and 54 patients(58%) was inv-IPMN group, and especially in inv-IPMN group of that study, 37 patients(75.9%) was high T stage(T3-T4), 32 patients(60.4%) was lymph node positive, 24 patients(44.4%) had perineural invasion[21, 25]. From this point of view, retrospectively thinking, more cases of diffuse-type IPMN could be found in inv-IPMN group, already in progress. In fact, 33.2% of diffuse type IPMN of inv-IPMN group recurred at distant organ or peritoneum during observation in

our study.

Focusing on IPMN-HGD, high-grade dysplasia had a better survival rate; overall survival or 5-year recurrence-free survival of IPMN HGD was 90.1%, 84.0%, respectively, which was superior to 57.2%, 46.4% of those from IPMN-associated invasive carcinoma, and statistical significance was achieved. Invasiveness was the most influential factor affecting overall survival, followed by elevated CA 19-9 level[26]. This correlation between elevated CA 19-9 and poor prognosis has been presented before. D. cipriani stated 5-year overall survival rate for patients with an elevated CA19-9 as 81% compared to 91%(p=0.006), and cox regression analysis confirmed the association between higher CA 19-9 levels and worse survival (HR 1.943, 1.196-3.156, 95% CI, P=0.007)[15]. Therefore, because the non-invasive IPMN has superior survival outcomes, early resection of IPMN before progression to invasive form can be important for better prognosis.

Main duct type IPMN had more probability of progression to invasive form than branch duct type IPMN but comparison between main duct type IPMN and mixed duct type IPMN has not been explored mainly[24]. In our study, 5 year overall survival of mixed duct type was better than main duct type. After matching of pathologic duct type, overall survival and recurrence-free survival was better in IPMN-HGD group than inv-IPMN group; only 5-yr RFS in main duct type between IPMN-HGD and inv-IPMN was not significantly different. Regarding that pathologic duct type could not influence on survival rate in univariable analysis, IPMN-HGD has quite superior survival rate regardless of duct type.

IPMN-associated invasive carcinoma followed the clinicopathologic characteristics and prognostic outcomes of PDAC in regards of recurrence patterns[18]. In our study, total 52 cases recurred and all 7 cases of IPMN-HGD locally recurred in remnant pancreas. In contrast, 40 patients(89%) of recurred inv-IPMN recurred in distant organs or peritoneum[27]. Possible explanations of distant metastasis could be various; one of the causes was false negative diagnosis of missing invasive component, another could be leakage of cystic fluid during operation but sure thing was that in 7 cases of recurrence in IPMN-HGD group, more than 70 percentage (5 patients) had completion total pancreatectomy and

among them, 4 patients finally diagnosed as pathological high-grade dysplasia, and had long term survival; no patients died[19]. However, in inv-IPMN groups, only 8% patients had completion total pancreatectomy, and nearly 90% patients were already unresectable and, with only palliative treatment, prognosis was poor. The mean value of CA 19-9 level at recurrence was different by 30.7 u/ml in IPMN-HGD group, and 811.07 u/ml in inv-IPMN group, but there was no statistical significance. In terms of resection margin in initial surgery, this study showed no correlation between positive pancreatic duct margin with HGD or inv-IPMN and recurrence of remnant pancreas.

Prediction of recurrence of IPMNs has always been an important task. In IPMN, prediction of malignancy and invasiveness has been done by nomogram; scoring system using variables such as age, sex, CEA, CA19-9, presence of mural nodule, MPD diameter[11] and in prostate cancer, PSA velocity, direction of PSAV acceleration has been studied for prediction of the progression and recurrence of prostate malignancy[28]. With same context we tried to calculate the CA 19-9 change value between IPMN-HGD and inv-IPMN and recur group and non-recur group. In IPMN-HGD group, recurrence occurred in late period (over 1-2 years) and CA 19-9 elevation obviously was shown after the median recurrence time; no significant different before and at median recurrence date. In IPMN HGD, checking serial CA 19-9 value and change value could not be useful to predict recurrence. In inv-IPMN group, recurrence occurred generally earlier than IPMN-HGD (before 1-year) and CA 19-9 value elevated before the median recurrence date. The slope of CA 19-9 change value got steeper as time pass and the closure it got to median recurrence date[29] CA19-9 elevation was an early and reliable sign for PDAC recurrence. Because inv-IPMN showed similar aggressive behavior with conventional PDAC, CA 19-9 change value could be an option for prediction of recurrence but more studies should be followed because in this study obvious elevation of CA19-9 before the recurrence could not be evaluated; positive predictive value and specificity, sensitivity could not be calculated.

One of the strength point of this study is that the number of IPMN cases was large enough considering the retrospective study. Over the 10 years, near 300 cases of IPMN could be collected and existing

variables could be clearly verified. Furthermore, all of the pathologic reports were reviewed by pathologists in single-medical center and more objectivity was guaranteed. In contrast, several limitations must be noted when discussing the findings of this study. Most of all, central pathologic review was not done. Many terms and definitions changed in 2015 Baltimore consensus and previous low-grade dysplasia, high-grade dysplasia and IPMN associated invasive carcinoma could be relocated to other group. Among them, intermediate-grade dysplasia must have been reviewed because some of those could be redefined to high-grade dysplasia in terms of revised classification of IPMN. The term "PDAC concomitant with IPMN" means that lesion occurs separated from the IPMN by an uninvolved segment of pancreatic duct[30]. In this study, we tried not to involve concomitant cases in invasive group but previous grouped concomitant cases could be regrouped to associated with invasive cancer group after the central review. So, following this study, we are trying to review the pathologic slides of IPMN by single-pathologist in single medical center, and aim to distinguish ambiguous concept clearly and ensure objectivity more. Second, the definition of recurrence could be quite difficult in IPMN. In high-grade dysplasia group, locally recurred cases were originated from recurred cyst in active surveillance. However, in invasive group, de-novo IPMN could not be excluded in actually, and distant recurrence was not pathologically diagnosed so classification to recurred group in some cases was only based on clinical decision.[18] Also, because this study was the retrospective study, conclusions should be applied with caution. Furthermore, the histologic type of IPMN was insufficient in this group such as tubular and colloid carcinoma. Generally, five-year survival rate of colloid carcinoma has been better than tubular carcinoma with/without lymph node metastasis[31]. After central pathologic review, we are trying to make subgroup by histologic subtype and explore the prognostic impact of histologic factors in further study. Our study couldn't consider the effect of adjuvant chemotherapy mainly and finally, there were follow-up loss of data and surgical outcomes could be underestimated. In fact, most cases were collected for more than 10 years but some cases were missed before 1 year of follow-up period. It is the cause of relative short median follow up period, 48~52month.

Conclusion

There was significant survival difference between IPMN-HGD and inv-IPMN group, therefore early detection and active surgical intervention should be regarded before the progression into invasive carcinoma[14]. These data also emphasized the difference of recurrence characteristics between HGD and inv-IPMN. HGD almost recur in remnant pancreas and second surgery for these high-risk lesions might improve survival, but IPMN-associated invasive carcinoma could largely recur in extra-pancreatic ways, and it significantly shortened the survival, meaning that we need to pay attention to this possibility in all IPMN cases[18]. Pathologic definition of malignant IPMN could not be recommended any more, yet clinical definition of malignancy in IPMN has been used frequently due to chance of progression and invasiveness[5, 6]. Regarding superior surgical outcomes and clinicopathologic prognosis, high-grade dysplasia could be re-classified and be divided clearly from an associated invasive carcinoma.

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국문요약

연구배경 : 유두상 점액성 종양은 췌장암의 낭성 전구체로서 저등급 이형성증부터 고등급 이형성증, 침습적 형태까지 다양한 스페트럼의 진행 과정을 가진다. 이 연구의 목적은 유두상 점액성 종양의 고등급 이형성증 군과 침습적 형태군의 임상병리학적 특징을 비교하고 제시하고자 하였다.

연구방법 : 2006 년 1 월부터 2018 년 12 월 사이, 서울아산병원에서 유두상 점액성 종양으로 수술 후 병리학적 진단받은 전체 461 명의 환자군을 조사하였다. 이중 최종 조직검사 결과 저등급 이형성증, 중간 이형성증, 유두상 점액성 종양/췌장암 동시 존재군 환자 181 명이 제외되었고, 최종적으로 280 명의 환자군이 연구에 참여하였다. 이중 고등급 이형성증은 171 명, 침습적 형태군은 109 명이었다.

연구결과 : 고등급 이형성군에서 수술 전 주췌관의 직경은 7.5mm, 침습적 형태군에서는 9.4mm 였다(95% CI, p=0.012). 고등급 이형성군에서 수술전 CA19-9 이 정상범위 이상인 환자의 비율이 15 명이었고(8.8%), 침습적 형태군에서는 49 명이었다(45%)(95% CI, p<0.001). 다음으로 고등급 이형성군에서 5 년 전체생존율은 90.1%였고, 침습적 형태군에서는 57.2%였다 (p<0.001). 그리고, 5 년 무재발 생존율은 고등급 이형성 군에서 84.0%였고, 침습적 형태군에서는 46.4%였다 (p<0.001). 생존율에 영향을 주는 요인에 대해 단변량, 다변량 조사를 시행한 결과, 낭종의 침습도가 높을수록 생존율이 저하되었고, 수술 전 CA19-9 값이 높을수록 예후가 좋지 않았다 (HR=4.123, HR=1.915, 2.419-7.027, 95% CI, p=0.005). 그 뿐만 아니라, 두 군은 재발 패턴 또한 상당한 차이가 있었다. 전체 52 명의 환자가 재발하였고, 그 중 고등급 이형성군에서 7 명, 침습적 형태군에서 45 명이 재발하였다. 고등급 이형성군에서 재발한 7 명은 모두 잔여 췌장에 국소 재발하였으나, 침습적 형태군에서는 전체 5 명의 환자만이(11%) 국소 재발하였고, 70%이상의 환자는 재발 당시 원격 재발을 동반하고 있었다. 따라서 완료 전췌장 절제술이 고등급 이형성증 군에서는 71%에 해당하는 6 명의 환자에서 시행된 대에 반해, 침습적 형태군에서는 6%에 해당하는 3 명의 환자에 불과했고, 90% 이상에서는 수술적 절제가 불가능해 고식적 항암치료, 방사선 치료 등의 치료를 시행하였고, 그에 따른 사망률은 높고 예후는 좋지 않았다.

연구결론 : 유두상 점액성 종양의 고등급 이형성군과 침습적 형태군 사이에는 생존율 및 재발 형태의 측면 등에서 상당한 차이를 보였다. 따라서, 고등급 이형성증을 침습적 암종과 별개의 질환으로 나누어 침습적 형태로의 진행 전에 조기 진단과 수술을 함으로써 보다 좋은 예후를 추구할 수 있을 것으로 사료된다.