HBP SURGERY WEEK 2021
Grand Walker Hill Hotel, Seoul
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10:00-11:30 I Room B

Multifocal IPMN from the pathological perspective

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Disclosure of Conflict of Interest

"I, *Seung-Mo Hong* **Do Not** have a financial interest/arrangement or affiliation with one or more organization which could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation"

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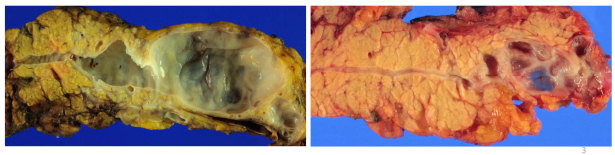
Intraductal papillary mucinous neoplasm (IPMN)

- Grossly visible (typically >5 mm) intraductal epithelial neoplasm of mucin producing cells arising in main pancreatic duct and/or its branches

WHO 2010: typically **>1 cm** in diameter



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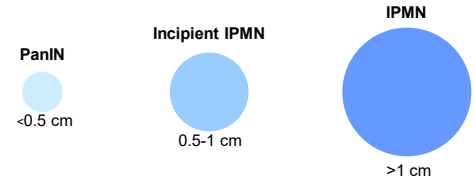
Incipient IPMN



- Lesions in 0.5 to 1 cm size with long finger-like papillae, intestinal-type mucin or *GNAS* mutations

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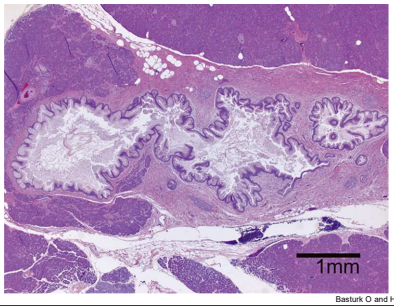
Basturk O and Hong SM et al. Am J Surg Pathol 2015

Incipient IPMN lined with intestinal-type papillae



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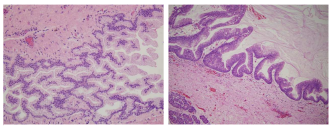
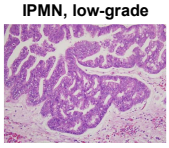
2019 WHO classification of IPMN



IPMN, low-grade



IPMN, high-grade

2010 (Previous)	2019 (Current)
IPMN, low-grade dysplasia	**IPMN, low-grade**
IPMN, intermediate-grade dysplasia	
IPMN, high-grade dysplasia	**IPMN, high-grade**
IPMN with an associated invasive carcinoma	

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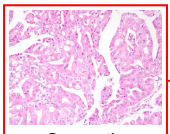
Histologic subtypes of IPMN in WHO 2019

Gastric Intestinal Pancreatobiliary



Oncocytic

→ New Entity in WHO 2019

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2019 WHO classification of IPMN

Grade		Histologic subtype		Localization	
2010 (Previous)	**2019 (Current)**	2010 (Previous)	**2019 (Current)**	2010 (Previous)	**2019 (Current)**
IPMN, low-grade dysplasia	**IPMN, low-grade**	Gastric	**Gastric**	Branch duct	Branch duct
IPMN, intermediate-grade dysplasia		Intestinal	**Intestinal**		
IPMN, high-grade dysplasia	**IPMN, high-grade**	Pancreatobiliary	**Pancreatobiliary**	Main duct	Main duct
		Oncocytic	**Separate entity**	Combined	Combined

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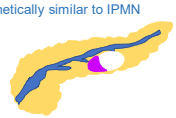
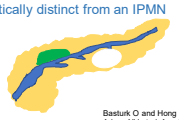
Concomitant Vs. Associated invasive carcinoma

- IPMN with associated invasive carcinoma : carcinoma arise in area of IPMN
- IPMN with concomitant invasive carcinoma : carcinoma is not continuous with IPMN
- Sampling of intervening tissue between IPMN and carcinoma to assess concomitant versus associated status

Associated invasive carcinoma
Genetically similar to IPMN



Concomitant invasive carcinoma
Genetically distinct from an IPMN



Basturk O and Hong SM et al. Am J Surg Pathol 2015
Adsay NV et al. Ann Surg 2016

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Multifocal IPMN

- A subset of IPMNs are multifocal
- Either **synchronously** or **metachronously** detected
- Reported prevalence: 20% (range, 0% ~ 83%)
- Different methodologies used for assessing multifocality
- Synchronous multifocal IPMNs: relying solely on imaging criteria

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Various prevalence of multifocal IPMN

Author Year Journal	Lesions	Period Treated	Criteria for Multifocality	Frequency, % (Multifocal/All Patients)
Cuillerier et al, 2000, Am J Gastroenterol	IPMN	1980–1996	Lesions separated by uninvolved pancreatic duct	2.2 (1/45)
Holme et al, 2001, HPB	IPMN	1994–1998	Multifocal intraductal changes	83.3 (5/6)
D'Angelica et al, 2004, Ann Surg	IPMN	1983–2000	Parenchymal margin without proliferative ducts	1.6 (1/63)
Salvia et al, 2004, Am Surg	MD-IPMN	1990–2002	Normal duct between lesions	0 (0/140)
Kawamoto et al, 2005, Radiographics	IPMN	2000	Lesions located in different parts of the pancreas	33.3 (12/36)
Pelaez-Luna et al, 2007, Am J Gastroenterol	BD-IPMN	1998–2005	> 1 BD-IPMN in distant anatomical areas of the pancreas	37.7 (57/147)*
Rodriguez et al, 2007, Gastroenterology	BD-IPMN	1990–2005	> 1 BD-IPMN not involving the main duct	25.5 (37/145)
Schmidt et al, 2007, Ann Surg	BD-IPMN MT IPMN	1991–2006	> 1 identifiable and distinct lesion	BD-IPMN: 40.8 (42/103) MT-IPMN: 65 (26/40)
Niedergethmann et al, 2008, World J Surg	IPMN	1996–2006	ND	2.1 (2/97)
Schnelldorfer et al, 2008, Arch Surg	IPMN	.	ND	IPMA: 5, IPMB: 11 IPMC; 13, IPMN invasive: 15
Waters et al, 2008, J Gastrointest Surg	IPMN	1991–2006	> 1 identifiable and distinct lesion	72.2 (13/18)
Nara et al, 2009, Pancreas	IPMN	1984–2006	ND	4.1 (5/123)
Salvia et al, 2009, Am J Surg	multifocal BD-IPMN	1990–2006	> 1 cystic lesions communicating with the main duct	ND
Woo et al, 2009, Br J Surg	BD-IPMN	1998–2005	> 1 identifiable and distinct lesion (macroscopic)	17.6 (15/85)

*Not all cases histopathologically confirmed.
BD-IPMN indicates branch-duct IPMN; MD-IPMN, main-duct IPMN; MT-IPMN, mixed-type IPMN; NA, not applicable; ND, not defined.

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Possible reasons of various prevalence of multifocal IPMNs

- Different techniques used in different studies
- Failure to histological documents multifocality
- Histopathologic examination of BD-IPMNs detected more multifocal IPMNs than reported preoperative radiologic examination (26% vs 15%)
- Grape-like localized BD-IPMN mimic multifocal IPMN
- Challenging distinction between large PanIN and small IPMN

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Hypothesis of multifocal IPMN

- **Clonally related neoplasms** arising from a single or few progenitor cells that exhibit **shared genetic alterations**
  - Haphazard intraductal growth of a single neoplasm could mimic true multifocality
- Familial setting: entire ductal epithelium having an **increased risk of developing a neoplasm**
  - Common germline inactivating mutation with a "second hit" on the remaining allele within each independent lesion
- **Entirely unrelated independent genetic events** in anatomically distinct areas of the pancreas.

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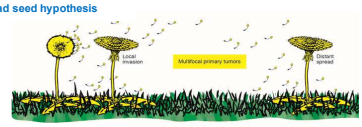
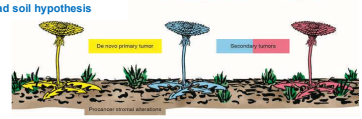
The seed and soil hypothesis in multifocal and recurrent tumors

Bad seed hypothesis



Bad soil hypothesis



Dotto PG. J Clin Inv 2014

Branch duct

Clonality assessment

- **Clonally related:** shared molecular alterations at all informative microsatellite loci and in *KRAS* gene
- **Clonally distinct:**
  - 2 cysts had completely discordant *KRAS* gene mutation or LOH patterns
  - The cysts shared some, but not all, molecular alterations (2 cysts harbored the same *KRAS* mutant clone, whereas only one of the two demonstrated a 2nd distinct pattern of LOH)
- **Clonally indeterminate**: either retention of heterozygosity or noninformative alleles at microsatellite loci, or harbored wild-type *KRAS* alleles

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Branch duct

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Parameter	Synchronous IPMN Group	Metachronous IPMN Group
Cases, all: N = 34	29 (85%)	5 (15%)
Age, median years (range)	68 (50–82)	64 (47–82)
Gender, male : female	11:18	2:3
Familial pancreatic cancer history	5 (17%)	1 (20%)
Degree of dysplasia	11 (38%)	1 (20%)
IPMN, low-grade dysplasia	12 (41%)	1 (20%)
IPMN, intermediate dysplasia	3 (10%)	3 (60%)
IPMN, high-grade dysplasia	3 (10%)	0 (0%)
IPMN with invasive carcinoma		
Duct location		
Main	0 (0%)	0 (0%)
Branch	25 (86%)	5 (100%)
Mixed	4 (14%)	0 (0%)
Predominant epithelial subtype		
Gastric-foveolar	23 (96%)	5 (100%)
Intestinal	0 (0%)	0 (0%)
Pancreatobiliary	1 (4%)	0 (0%)
Oncocytic	0 (0%)	0 (0%)
Not applied	5 (21%)	0 (0%)
Site of resected cyst		
Head	12 (41%)	5 (100%)
Uncinate	8 (27%)	0 (0%)
Neck	7 (23%)	1 (20%)
Body	14 (47%)	4 (80%)
Tail	15 (52%)	4 (80%)
Number of resected IPMNs, median (range)	2 (2–6)	2 (2–4)
Maximum cyst size, cm (range)	2 (0.5–6)	1.2 (0.4–5.5)

Median interval: 20 months

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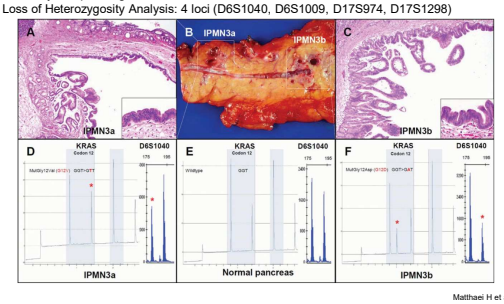
Branch duct

Multifocal IPMN

KRAS Pyrosequencing
Loss of Heterozygosity Analysis: 4 loci (D6S1040, D6S1009, D17S974, D17S1298)



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Branch duct

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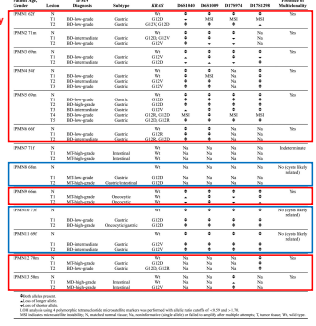
Clonal heterogeneity (69%)

Clonally related (23%)



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Branch duct

Multifocal IPMN

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- Low grade dysplasia
- Gastric subtype
- Clonal heterogeneity and distinct molecular alterations
- Independent lesions

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Targeted-NGS from 13 IPMN and PDAC patients who developed disease progression in remnant pancreas following resection of IPMN

Metachronous

Patient, Age, Gender	Family history	Operation	1st Lesion Diagnosis	1st Lesion Mutations	Neck Margin Diagnosis	Neck Margin Mutations	Months After 1st op.	2nd Lesion Diagnosis	2nd Lesion Mutations	Pattern of Progression
1) 76, m	no	Whipple	BD –IPMN HGD	*KRAS* p.G12D *GNAS* p.R201C	neg	/	46	PDAC G2	*KRAS* p.G12R	Likely independent
2) 64, m	no	Whipple	MD – IPMN HGD INV (Colloid)	*KRAS* p.G12D *GNAS* p.R201C *TP53* p.G245D *KRAS* p.G12D *GNAS* p.R201C *TP53* p.G245D	neg	/	68	PDAC G3	*KRAS* p.G12D *GNAS* p.R201C	Likely related
3) 74, m	no	Whipple	MIXED – IPMN HGD	*KRAS* p.G12D	neg	/	38	PDAC G2	*KRAS* p.G12D	Indeterminate
4) 45, m	yes	Whipple	BD – IPMN LGD	*KRAS* p.G12D *GNAS* p.R201C	neg	/	103	PDAC G2	*KRAS* p.G12V *SMAD4* p.Y95N	Likely independent
5) 58, f	no	Whipple	BD – IPMN LGD	*KRAS* p.G12D	neg	/	13	BD – IPMN LGD	*KRAS* p.G12D	Indeterminate
6) 57, m	yes	Whipple	MIXED – IPMN LGD	*KRAS* p.G12V	neg	/	48	BD – IPMN LGD CYST 1 BD – IPMN LGD CYST 2 BD – IPMN LGD CYST 3	*KRAS* p.G12D *GNAS* p.R201C *KRAS* p.G12V *KRAS* p.G12D *GNAS* p.R201H	Likely independent
7) 67, f	no	Whipple	MIXED – IPMN HGD	*KRAS* p.G13D *GNAS* p.R201H *SMAD4* p.C347Y	neg	/	53	MIXED– IPMN HGD INV	*KRAS* p.Q61H *GNAS* p.R201H *KRAS* p.G12V p.Q120 *GNAS* p.R201H	Likely independent
8) 64, f	no	Whipple	MIXED – IPMN HGD	*KRAS* p.G12D *GNAS* p.R201C	neg	/	134	MIXED– IPMN HGD	*KRAS* p.G12V *GNAS* p.R201H	Likely independent
9) 68, m	no	Whipple	MIXED – IPMN HGD	*KRAS* p.G12V *GNAS* p.R201C p.R201H *RNF43* p.G659T	IPMN LGD	*KRAS* p.G12V	13	MIXED– IPMN LGD	*KRAS* p.G12D *GNAS* p.R201C *TP53* p.G245D	Likely independent
10) 66, f	no	Whipple	MIXED – IPMN HGD	*KRAS* p.G12C	IPMN LGD	*KRAS* p.G12D	50	MIXED– IPMN HGD	*KRAS* p.G12V *GNAS* p.R201H	Likely independent
11) 77, f	yes	Whipple	MD – IPMN HGD INV	*KRAS* p.G12V *KRAS* p.G12V	IPMN INV	*KRAS* p.G12D	90	PDAC	*KRAS* p.G12D	Indeterminate
12) 80, f	no	Whipple	MD-IPMN HGD INV	*KRAS* p.G12D *TP53* p.C176Y *SMAD4* p.E330K *KRAS* p.G12D *TP53* p.C176Y	IPMN HGD	*KRAS* p.G12D *TP53*: p.C176Y	53	MD-IPMN HGD INV	*KRAS* p.G12D *TP53*: p.C176Y *SMAD4* p.E330K *KRAS* p.G12D *TP53*: p.C176Y *SMAD4* p.E330K	Likely related
13) 66, m	no	Distal p	MD-IPMN HGD (0.4 cm lesion of cancer)	*KRAS* p.G12D *CDKN2A*: p.R58* *ENO1*: p.W386X	IPMN HGD	N/A	34	MD-IPMN HGD	*KRAS* p.G12D *CDKN2A*: p.R58* *RNF43*: p.W386X	Likely related

BD indicates branch-duct IPMN; distal p, distal pancreatectomy/HGD; high-grade dysplasia; LGD, low-grade dysplasia; MD, main duct IPMN; MIXED, mixed-type IPMN; *Mutation with the highest concentration.

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Clinicopathologic characteristics of 260 patients who underwent resection of noninvasive IPMNs

Radiologic Pattern of Progression in Noninvasive IPMNs

	No Progression 210 (81%)	BD Progression 32 (12%)	MD Progression 7 (3%)	Progression With Separate Solid Mass/Systemic 11 (4%)	*P*
Characteristics of the primary IPMN					
IPMN duct type					
BD-IPMN	131 (81%)	22 (14%)	1 (1%)	7 (4%)	0.060
MD/Mixed-type IPMN	79 (80%)	10 (10%)	6 (6%)	4 (4%)	
Dysplasia					
Low grade	147 (84%)	24 (14%)	1 (1%)	3 (1%)	**0.001**
High grade	63 (75%)	8 (10%)	5 (6%)	8 (10%)	
Resection margin					
Negative	178 (82%)	27 (12%)	5 (2%)	8 (4%)	0.183
LGD	28 (80%)	5 (14%)	1 (3%)	1 (3%)	
HGD*	4 (57%)	0	1 (14%)	2 (29%)	
Family history	20 (61%)	8 (24%)	2 (6%)	3 (9%)	0.36
Time to progression	—	27 (14–53)	52 (38–69)	49 (32–78)	
Median (IQR)					
Completion pancreatectomy	0	4 (28%)	6 (42%)	4 (28%)	—
Pathology of disease progression in second operation					
IPMN low grade	—	3 (60%)	2 (40%)	0	
IPMN high grade	—	1 (25%)	3 (75%)	0	
IPMN with invasive carcinoma	—	0	1 (100%)	0	
Conventional PDAC	—	0	0	4 (100%)	

*Seven patients had a resection margin positive for HGD at the final histological examination. In 3 cases, the surgeon decided not to proceed with a completion pancreatectomy based on the patients' advanced age and medical problems, balancing the risk of residual neoplasia with potential disability from brittle diabetes following completion pancreatectomy. In 4 cases, although the definitive margin status on the final pathological report was positive for HGD, the intraoperative margin was called negative, precluding additional resection.

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Risk factors of development of high-grade IPMN or invasive carcinoma in remnant pancreas

	Univariate			Multivariate		
	Progression to PDAC - HGD	No Progression to PDAC -HGD	*P*	OR	95% CI	*P*
	16 (6%)	244 (94%)				
Age, Median (IQR)	68 (56–75)	69 (61–76)	0.593	—	—	—
Male gender	9 (56%)	122 (50%)	0.628	—	—	—
Family history	5 (33%)	28 (12%)	0.029	5.82	1.49–22.78	0.011
IPMN duct-type						
Main/Mixed-type	7 (44%)	92 (38%)	0.608	—	—	—
IPMN						
LGD IPMN	5 (31%)	171 (70%)	0.004	9.22	2.76–20.71	<0.001
HGD IPMN	11 (69%)	73 (30%)				
Positive margin*	6 (38%)	37 (15%)	0.032	3.10	0.94–10.88	0.064
HGD at the margin	3 (18%)	4 (2%)	0.006			

HGD, high-grade dysplasia; LGD, low-grade dysplasia.
*Any grade of dysplasia.

Patients with a primary IPMN with HGD or with positive family history are at an increased risk to develop subsequent high-risk neoplasms in the remnant pancreas

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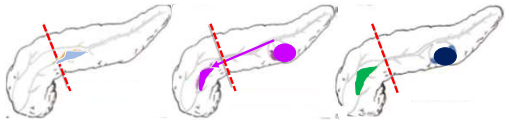
Metachronous

Mechanisms of local progression after resection of IPMNs



Residual IPMN at margin

Preoperative IPMN spreading

Genetically related

Two independent IPMNs

Genetically distinct

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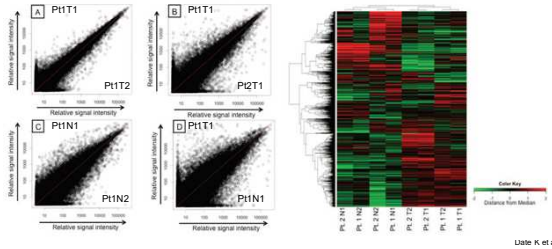
Main duct type

Metachronous

Scattered plots and heat map comparing different samples

Whole genome microarray from 2 patients with metachronous MD-IPMNs



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Main duct type

GNAS/KRAS mutational status and immunohistochemistry from 28 distinct IPMNs from 12 patients

No.	Lesion	Type	Histologic Grade	Histologic Subtype	*KRAS* Status	*GNAS* Status	S100P	CLDN18	HH	AGR2	HPSE	Monoclonal*	Polyclonal*
1	T1	MD	Inv-Ca	Gastric	G12V	Wt	+	+	+	+	+	T1–T2 (5/5)	–
	T2	MD	HGD	Pancreatobiliary	G12V	Wt	+	+	+	+	+		
2	T1	MD	HGD	Intestinal	Wt	R201H	+	+	+	+	+	T1–T2 (5/5)	–
	T2	MD	Inv-Ca	Intestinal	Wt	R201H	+	+	+	+	+		
3	T1	MD	HGD	Intestinal	G12V	Wt	+	+	–	+	+	T1–T2 (4/5)	–
	T2	MD	HGD	Intestinal	G12V	Wt	+	+	+	+	+		
4	T1	MD	HGD	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†		–
	T2	MD	HGD	Pancreatobiliary	G12D	Wt	+	+	+	+	–	T2–T3 (4/5)	
	T3	MD	HGD	Pancreatobiliary	G12D	Wt	+	+	+	+	+		
5	T1	MD	HGD	Intestinal	G12R	R201C	+	+	+	+	+	T1–T2 (5/5)	–
	T2	MD	IGD	Intestinal	G12R	R201C	+	+	+	+	+		
6	T1	MD	Inv-Ca	Pancreatobiliary	Wt	R201H	+	+	–	+	+	T1–T2 (5/5)	T1–T3 (5/5)
	T2	MD	Inv-Ca	Pancreatobiliary	Wt	R201C, H	+	+	–	+	+		T2–T3 (5/5)
	T3	BD	HGD	Intestinal	Wt	R201C	+	+	–	+	+		
7	T1	MD	HGD	Gastric	G12V	R201H	+	+	+	+	+	T1–T2 (5/5)	–
	T2	MD	Inv-Ca	Pancreatobiliary	G12V	R201H	+	+	+	+	+		
8	T1	MD	HGD	Intestinal	G12D	R201H	+	+	+	+	+	T1–T2 (5/5)	T1–T3 (5/5)
	T2	MD	HGD	Intestinal	G12D	R201H	+	+	+	+	+		T2–T3 (5/5)
	T3	BD	LGD	Gastric	G12V, D	R201H	+	+	+	+	+		
9	T1	MD	LGD	Gastric	G12V	R201H	+	+	–	+	–	–	T1–T2 (4/5)
	T2	BD	LGD	Gastric	G12D	R201C	+	+	–	+	+		
10	T1	MD	HGD	Intestinal	G12D	R201C	+	+	+	+	–	–	T1–T2 (4/5)
	T2	BD	LGD	Gastric	Wt	Wt	+	+	–	+	+		
11	T1	BD	LGD	Gastric	G12D	R201C	+	+	–	+	–	–	T1–T2 (4/5)
	T2	BD	LGD	Gastric	Wt	R201H	+	+	–	+	–		
12	T1	BD	LGD	Gastric	G12V	Wt	+	+	+	+	+	–	T1–T2 (4/5)
	T2	BD	Inv-Ca	Intestinal	Wt	R201C	+	+	+	+	+		T1–T3 (5/5)
	T3	BD	IGD	Gastric	G12D	R201C	+	+	+	+	+		T1–T4 (5/5)
	T4	BD	LGD	Gastric	G12D	R201H	+	+	+	+	+		T2–T3 (4/5)
													T2–T4 (4/5)
													T3–T4 (5/5)

Date K et al. Ann Surg 2017

Main duct type

Metachronous IPMN

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- Incidence: 8~12% in non-invasive IPMN
- Recurrence of primary tumors or independent tumors associated with polyclonal tumor initiation?
  - Polyclonal tumors
  - Monoclonal skip progression in a subset of main duct type tumors

Izawa T et al. Cancer 2001
Matthaei H et al. Ann Surg 2012

- Issues of management of metachronous IPMNs
  - Feasibility of total pancreatectomy
  - Significance of surgical margin
  - Requirement of surveillance after surgical resection

Tamura K et al. Ann Surg 2014
Tamura K et al. Surgery 2015
Date K et al. Ann Surg 2017

Nagai K et al. Mod Pathol 2020

Main duct type

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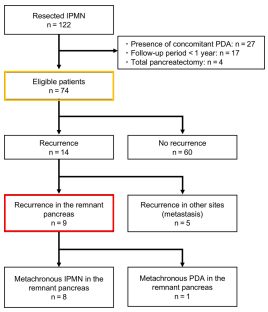

Table 1 Univariate and multivariate analyses of risk factors for metachronous neoplasms in the remnant pancreas

Characteristic	Univariate				Multivariate			
	Metachronous IPMN/PDA in remnant pancreas (n = 9)	No recurrence in remnant pancreas (n = 60)	OR	95% confidence interval	p value	OR	95% confidence interval	p value
Age, median (quantile)	66 (57–74)	66 (59–71)	1.02	0.94–1.10	0.70			
Men	5 (56%)	27 (45%)	0.66	0.16–2.68	0.56			
Location of IPMN								
Pancreas body to tail	8 (89%)	20 (33%)	16.00	1.87–137	0.01	14.6	1.62–131	0.02
MPD diameter ≥5 mm	7 (78%)	46 (77%)	1.07	0.20–5.72	0.94			
Serum CA 19-9 level								
Abnormal (≥37 U/mL)	1 (11%)	8 (13%)	0.86	0.09–7.93	0.89			
Histology of the primary tumor								
LGD	1 (11%)	17 (28%)	0.32	0.04–2.72	0.30			
HGD	5 (56%)	32 (53%)	1.09	0.27–4.48	0.90			
IPMN-associated carcinoma	3 (33%)	11 (18%)	2.23	0.48–10.30	0.31			
Epithelial types								
Intestinal	3 (33%)	28 (47%)	0.57	0.13–2.50	0.46			
Gastric	2 (22%)	23 (38%)	0.46	0.08–2.41	0.36			
Pancreatobiliary	4 (44%)	6 (10%)	7.20	1.51–34.3	0.01	6.13	1.05–35.7	0.04
Positive surgical margin*	2 (22%)	10 (17%)	1.43	0.26–7.91	0.68			

MPD main pancreatic duct, *LGD* low-grade dysplasia, *HGD* high-grade dysplasia, *OR* odds ratio
*Dysplasia of any grade

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Main duct type

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Table 2 Clinical and pathological characteristics of metachronous recurrent IPMNs

Patient	Primary IPMNs								Recurrent lesions	
	Age/Sex	Cyst size (mm)	MPD diameter (mm)	Operation	Histology	Depth of invasion (mm)	LVI	Resection margin	Histology	Time to second operation (years)
1	81/M	20	10	DP	HGD	0	–	Negative	INV	2.1
2	74/F	20	6	DP	INV	2	Negative	Negative	HGD	1.9
3	74/M	60	3	DP	HGD	0	–	LGD	HGD	2.5
4	73/M	30	8	Whipple	INV	1	Negative	Negative	INV	1.3
5	65/F	12	9	DP	LGD	0	–	LGD	INV	4.5
6	57/F	35	6	DP	HGD	0	–	Negative	INV	2.8
7	54/F	60	7	DP	HGD	0	–	Negative	INV	0.9
8	55/M	35	2	DP	INV	8	Negative	Negative	HGD	2
9	66/M	26	6	MP	HGD	0	–	Negative	Concomitant PDA[a]	4.4

DP distal pancreatectomy, *MP* middle pancreatectomy, *INV* invasive carcinoma (IPMN-associated carcinoma), *HGD* high-grade dysplasia, *LGD* low-grade dysplasia, *PDA* pancreatic ductal adenocarcinoma, *LVI* lymphovascular invasion
[a]PDA independently developed from the primary IPMN

Mean: 2.4 months

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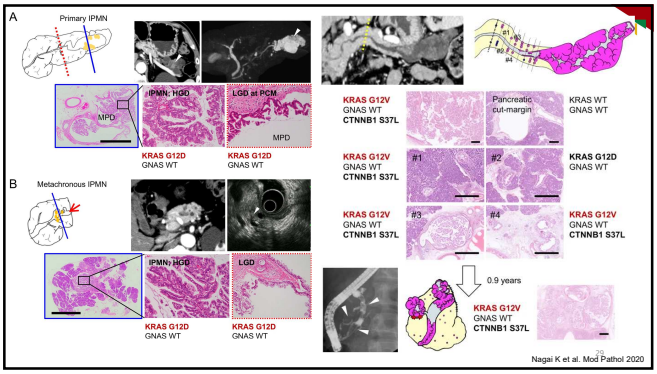

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Main duct type

Multifocal IPMN

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- Median follow-up period: 52 months
- Metachronous tumors developed in 9 patients (12%)
- Risk factors for metachronous tumor development
  - Location: body/tail
  - Pancreatobiliary subtype
- Eight cases shared molecular aberrations between their primary and metachronous tumors
- Suggesting migrations from the primary tumor to the pancreatic duct as the cause of metachronous tumor development
- Post-resection **metachronous tumors** develop by **skip dissemination** of the **primary tumor**, potentially **via the pancreatic duct**

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Significance of surgical margin evaluation

- Since metachronous tumors develop by skip dissemination of the primary tumor, evaluation of resection margin can not be predicted residual tumor
- Possible scenario of resection margin evaluation
  - Presence of carcinomas: more resection
  - Presence of high grade IPMN: may be more resection
  - Absence of IPMN: No guarantee of tumor free

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Requirement of surveillance after surgical resection

- Careful clinical follow-up after the resection is warranted regardless of recurrence or growth of separate lesion

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Summary of multifocal IPMN

- **Synchronous**
- **Branch duct type**
- Low grade dysplasia
- Gastric subtype
- Clonal heterogeneity and distinct molecular alterations
- **Independent lesions**

- **Metachronous**
- **Main duct type**
- Location: body/tail
- High grade dysplasia
- Pancreatobiliary subtype
- **Skip dissemination** of the primary tumor, potentially via the pancreatic duct

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Thank you for attention!

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