Management Algorithms for Pancreatic Cysts and Intraductal Papillary mucinous Neoplasms:

The Surgeon's Perspective

PRESENTED BY

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USCAP 108TH ANNUAL MEETING
2020 EYES ON YOU
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Content

- Background (Changing concept)
- Comparison of Guidelines
- Consideration Points in Decision of Treatment
- Optimal Indication for Surgery
  (Management Algorithm)

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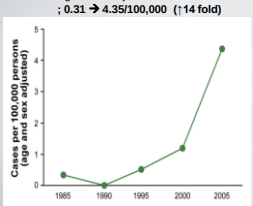
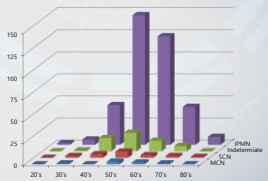
Changes in Epidemiology of Pancreatic Cyst

Age & sex-adjusted incidence
; 0.31 → 4.35/100,000 (↑14 fold)



Klibansky DA, et al.,
Clin Gastroenterol Hepatol 2012

2.2% of normal population



Chang and Jang, Medicine 2016

Patients Number and Types/Size of IPMN

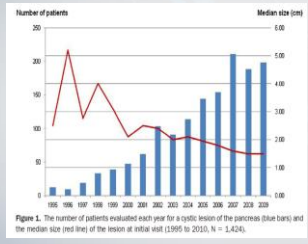
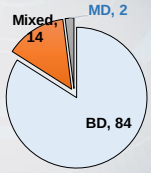


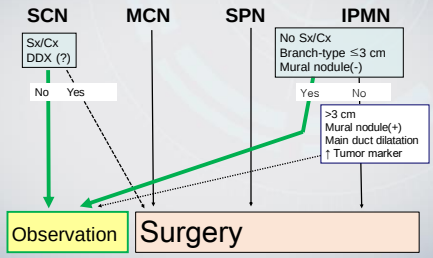
Figure 1. The number of patients evaluated each year for a cystic lesion of the pancreas (blue bars) and the median size (red line) of the lesion at initial visit (1995 to 2010, N = 1,424).

Gaujoux S et al. J Am Coll Surg 2011;212:590–600



SNUH (Unpublished data)
N=2,834

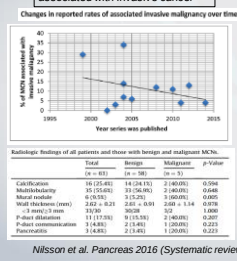
Surgical Indication



Malignancy Potential and Survival

MCN

0~34% of resected MCNs are associated with invasive cancer

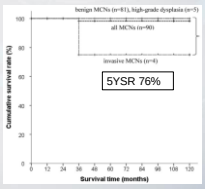


Radiologic findings of all patients and those with benign and malignant MCNs.

	Total (n = 63)	Benign (n = 58)	Malignant (n = 5)	p-Value
Calcification	16 (25.4%)	14 (24.1%)	2 (40.0%)	0.594
Multilobularity	35 (55.6%)	33 (56.9%)	2 (40.0%)	0.648
Mural nodule	6 (9.5%)	3 (5.2%)	3 (60.0%)	0.005
Wall thickness (mm)	2.62 ± 0.21	2.61 ± 0.91	2.64 ± 1.14	0.978
≤ 3 mm/> 3 mm	33/30	30/28	3/2	1.000
P-duct dilatation	11 (17.5%)	9 (15.5%)	2 (40.0%)	0.207
P-duct communication	3 (4.8%)	2 (3.4%)	1 (20.0%)	0.223
Pancreatitis	3 (4.8%)	2 (3.4%)	1 (20.0%)	0.223

Nilsson et al. Pancreas 2016 (Systematic review),

Lesions <4cm: malignancy 0.03%
Goh et al. World J Surg 2006



5YSR 76%

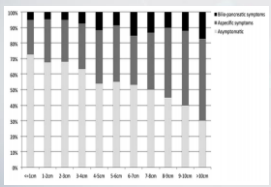
Park & Jang. Pancreatology 2014

Clinical Characteristics

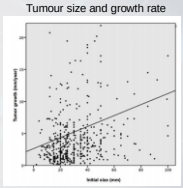
SCN

N=2,622 from 71 multicenters, 23 nations

Three serous cystadenocarcinomas (0.1%)



Tumour size and growth rate



Growth rate

<4 cm: 1.25 mm/yr
≥4 cm : 2.7mm/yr

Jais et al. Gut 2016

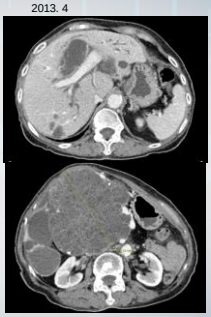
Case

SCN

- F/71
- Indigestion

2008.9

2013. 4



Malignancy Potential and Survival

SPN

N=351, Korean multi-centers study

Malignant features (28%)
- invasion to adjacent tissues, perineural/lymphovascular invasion, -
- metastasis (4%)

TABLE 2. Chronological Changes of SPTs of the Pancreas

Variables	Time Period, yr: 1990–1994 (N = 15, 4.3%)	1995–1999 (N = 72, 20.5%)	2000–2004 (N = 97, 27.6%)	2005–2008 (N = 167, 47.6%)	P
Symptoms					
No	1 (6.7)	16 (22.2)	40 (41.2)	97 (58.1)	
Yes	14 (93.3)	56 (77.8)	57 (58.8)	70 (41.9)	<0.001
Surgery mode II					
Limited surgery	5 (33.3)	12 (16.7)	26 (26.8)	60 (35.9)	
Conventional surgery	10 (66.7)	60 (83.3)	71 (73.2)	107 (64.1)	0.016
Surgery mode III					
Minimally invasive	—	—	1 (1)	51 (30.5)	
Open	15 (100)	72 (100)	96 (99)	116 (69.5)	<0.001

DP indicates distal pancreatectomy.

Kang et al. Ann Surg 2014

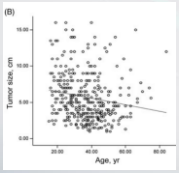
Malignancy Potential and Survival

SPN

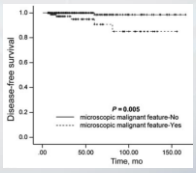
N=351, Korean multi-centers study

Malignant features (28%)

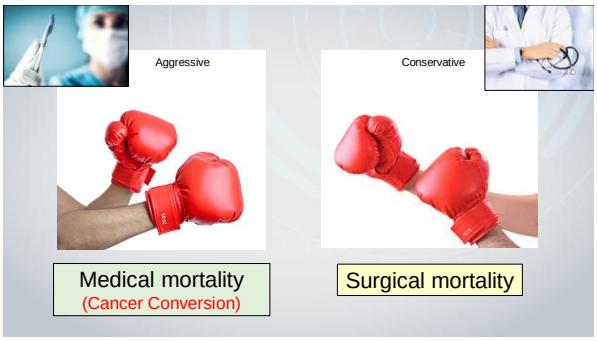
Tumor size and age



Survival according to malignancy



Kang et al. Ann Surg 2014



International Consensus (15 years ago)

- W. Traverso : The survival curves between invasive IPMN and ductal adenocarcinoma are the same!! We should resect IPMN before they become invasive.
- M. Buchler: We operate all, branch type IPMN except malignancy with nonresectable situation or metastasis....
- C.Yeo : We have been resecting healthy folks with presumed side branch IPMNs. less than 20% are observed.

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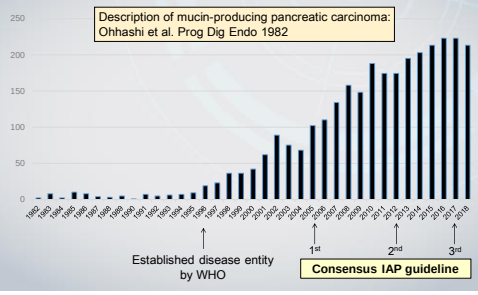
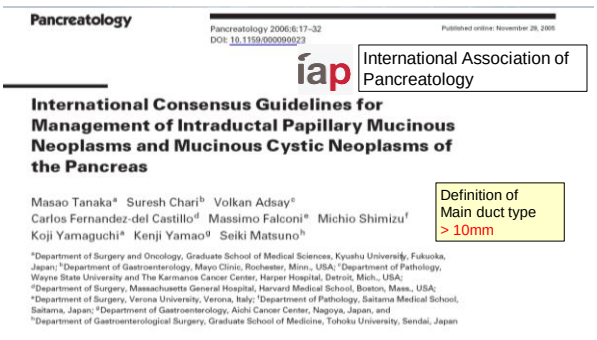
  (Management Algorithm)

Numbers of Publication on IPMN





◆ Surgical Indication of IPMN

Expert opinion

Reference (first author)	Year published	Patients	Malignant including CIS, %	Invasive malignancy, %
Kobari [16]	1999	17	31	6
Terris [17]	2000	13	15	0
Doi [18]	2002	26	46	Not stated
Matsumoto [19]	2003	16	6	Not stated
Choi [20]	2003	12	25	Not stated
Kitagawa [21]	2003	26	35	31
Sugiyama [22]	2003	32	40	9
Sohn [23]	2004	60	Not stated	30
Mean of all series			25	15

Tanaka et al. Pancreatology 2006

Key Roles in International Consensus Guidelines on IPMN

2012 — International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Volkan Adsay[c], Suresh Chari[d], Massimo Falconi[e], Jin-Young Jang[f], Wataru Kimura[g], Philippe Levy[h], Martha Bishop Pitman[i], C. Max Schmidt[j], Michio Shimizu[k], Christopher L. Wolfgang[l], Koji Yamaguchi[m], Kenji Yamao[n]

ANNALS OF SURGERY

2016 — Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract: Recommendations of Verona Consensus Meeting

2017 — Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas

Masao Tanaka[a,*], Carlos Fernández-del Castillo[b], Terumi Kamisawa[c], Jin Young Jang[d], Philippe Levy[e], Takao Ohtsuka[f], Roberto Salvia[g], Yasuhiro Shimizu[h], Minoru Tada[i], Christopher L. Wolfgang[j]

Treatment Guidelines on IPMN

Authors (Organization)	Year	Titles or Subject
Hruban	2004	Pathologic consensus
Tanaka (IAP)	2006	Guideline on Diagnosis & Treatment
SSAT	2007	Guidelines on Cystic neoplasms of the pancreas
Tanaka (IAP)	2012	2nd Guideline
Del Chiaro	2013	European experts consensus
Buscarini	2014	Italian guideline
Vege (AGA)	2015	American Gastroenterological Association
Adsay	2016	Revision on pathologic consensus guideline
Tanaka (IAP)	2017	3rd Guideline
Del Chiaro	2018	2nd European Guideline

Comparison of Guidelines on IPMN

Guideline	Absolute indication for Surgery	Relative indication for Surgery
European 2018	• Jaundice • Enhancing nodule ≥ 5mm • MPD ≥ 10mm • Positive Cytology	• pancreatitis • Cyst size >4cm • 5 ≤ MPD ≤ 9mm • New DM • Enhancing mural nodule (<5mm) • Rapid growing cyst • Elevated serum CA19-9
IAP 2012/2017	• Jaundice • Enhancing nodule ≥ 5mm • MPD ≥ 10mm • Positive Cytology	• Cyst ≥ 3cm • Thickened/enhancing cyst wall • 5 ≤ MPD ≤ 9mm • Non-enhancing mural nodule • Abrupt change in p-duct • Rapid growing cyst • Elevated serum CA19-9
AGA 2015	• Symptomatic • Solid component and MPD >5mm • Positive Cytology	• Cyst≥ 3cm • MPD dilatation • Mural nodule

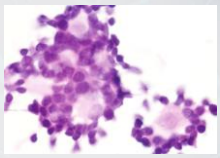
Require 2 features for EUS

Conservative

Cystic Fluid Cytology

- Specificity 83%
- Sensitivity 35%
- Accuracy 59%

Brugge et al. Gastroenterol 2004



- 33% Inadequate or non-diagnostic

Data from Mount Sinai (Scapel et al.)

Needs Invasive procedures

Comparison of Guidelines on IPMN

Guideline	Absolute indication for Surgery	Relative indication for Surgery
European 2018	• Jaundice • Enhancing nodule ≥ 5mm • MPD ≥ 10mm • Positive Cytology	• pancreatitis • Cyst size >4cm • 5 ≤ MPD ≤ 9mm • New DM • Enhancing mural nodule (<5mm) • Rapid growing cyst • Elevated serum CA19-9
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AGA 2015	• Symptomatic • Solid component and MPD >5mm • Positive Cytology	• Cyst≥ 3cm • MPD dilatation • Mural nodule

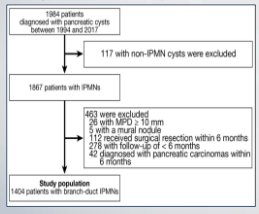
Require 2 features for EUS

Conservative

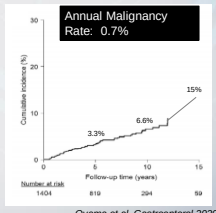
Discontinuation of surveillance after 5 year if there is no change

Long-term risk of malignancy in BD-IPMN

- Jan. 1994 ~ Dec. 2017 (20 years)
- Single institution (Univ. of Tokyo)



Cumulative Malignancy Rate



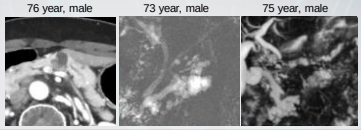
Oyama et al. Gastroenterol 2020

Sensitivity and Specificity of Clinical Guidelines on IPMN

	Sensitivity %	Specificity %
AGA with required cytology	7.3	88.2
IAP	73.2	45.6

Xu et al. Medicine 2017

Examples



Tumor size (mm)	16	42	42
MPD (mm)	4	2	9
Mural nodule	+	-	-
CA19-9	45	17	12
European	Resection	Resection	Resection
IAP	Resection	Observation	Resection
AGA	Observation	Observation	EUS/Observation

Content

- Background (Changing concept)
- Comparison of Guidelines
- **Consideration Points in Decision of Treatment**
- Optimal Indication for Surgery (Management Algorithm)

Observation

Interval
Method
How long ?

Resection

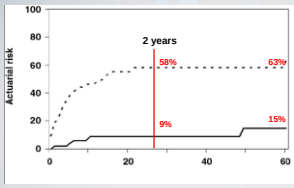
Extent
- Limited (organ preserving)
- Conventional

Method
- Open
- Laparoscopic

Considering factors

[Disease factors]	[Host factors]	[ETC]
Natural history	Age	Efficacy
Malignant potential	Co-morbidity	Mobidity/Mortality
Symptom/sign	Life expectancy	Safety
Extent of the disease	Op. risk	Longterm effect
Location	Pancreas function	Medical cost
	Medical accessibility	Opportunity cost

Natural History of IPMN



Malignancy rate according to the type

Main duct type: 45-92% (60%)
→ The majority are **candidates for resection**

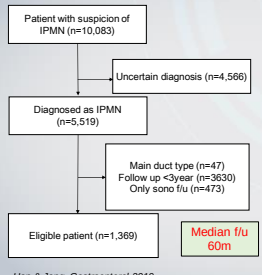
Branch duct type: 5-50% (20%)
→ Observation vs Surgery (optimal indication?)

Annual Malignancy Rate: 2~3%

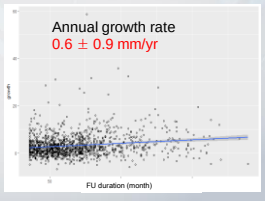
- Longitudinal risk of at least HGD or IC is time-dependent.
- Patients with branch duct IPMN present a much lower risk, justifying a nonoperative surveillance.

LEVY et al. Clin Gastroenterol Hepatol. 2006

Natural History & Surveillance of IPMN

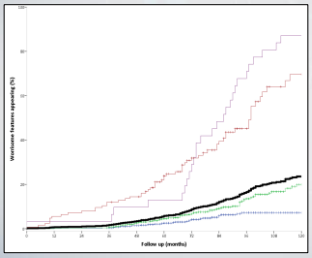


- 2001-2016
- Followed up duration over 3 yrs
- CT/MRI or EUS
  -a pleomorphic cyst
  -a clubbed, finger-like cyst
  -duct communication (+)
- Supervised by Radiologist



Han & Jang. Gastroenterol 2019

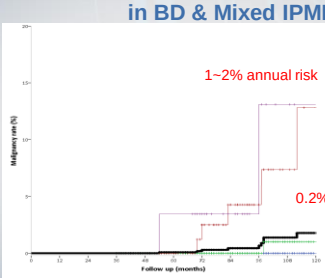
Appearance of Worrisome Features During Surveillance in BD & Mixed IPMN



Size	10Y worrisome feature (+)
≥3cm	83.1%
2≤ <3	69.6%
Total	**23.2%**
1≤ <2	20%
< 1cm	7.3%

Han & Jang. Gastroenterol 2018

Malignancy Rate During Surveillance in BD & Mixed IPMN



Size	10Y Malignancy Rate (%)
≥3cm	13.1%
2≤ <3	12.8%
Total	**1.8%**
1≤ <2	1%
< 1cm	0%

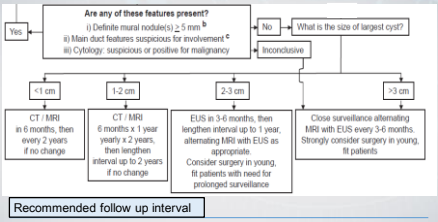
Han & Jang. Gastroenterol 2018

Optimal Surveillance Interval Based on Growth Rate & Cyst Size

	G1 (0-9.9mm)	G2 (10-19.9mm)	G3 (20-29.9mm)	G4 (over 30mm)
N	667	608	84	10
Cyst size(mm)	7.0 ± 1.9	13.4 ± 2.6	23.3 ± 2.7	34.1 ± 9.4
Growth rate (mm/yr) Max. growth rate 95% CI	0.6 ± 0.7 6.9 2	0.5 ± 0.9 7.3 2.3	1.0 ± 1.5 9.3 3.9	1.0 ± 1.2 3.3 3.3
Doubling time (yr) Shortest doubling time 95% CI	11 1 3.6	26 1.8 5.8	23 2.5 5.9	34 11.2 11
50% increasing time (yr) **Shortest 50% inc.** **95% CI**	5 0.5 (6month) 1.9	13 0.9 (10month) 2.9	11 1.3 3.0	17 5.6 5.5
Time for being 3cm cyst **Shortest time(yr)** **95% CI**	38 3.3 11.6	33 2.3 7.1	6 0.7 1.7	
Recommended follow up (yr)	6month -> 2yr	6month x2 -> 2yr	6month x 2 -> 1yr	

Han & Jang. Gastroenterol 2018

Revised Surveillance Program by IAP 2017

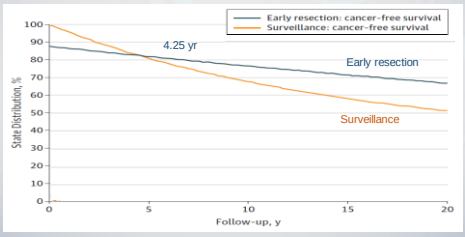


Recommended follow up interval			
6month -> 2yr	**6month x2 -> 2yr**	**6month x 2 -> 1yr**	**6month**

Tanaka et al. Pancreatology 2017

JAMA Surgery | Original Investigation

Comparative Effectiveness of Resection vs Surveillance for Pancreatic Branch Duct Intraductal Papillary Mucinous Neoplasms With Worrisome Features

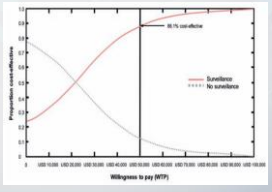


Hu et al. JAMA Surgery 2019

The Clinical and Socio-Economic Relevance of Increased IPMN Detection Rates and Management Choices

- Surveillance Strategy
must spend >$20,000 /patient to improve quality adjusted life year (QALY)

- Surgery Strategy
$132,436/QALY
Least deaths from PDAC (5.4%),
but 4.7% died due to the surgery



Budde et al. Visceral Medicine 2015

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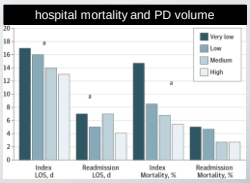
Least deaths from PDAC (5.4%),
but 4.7% died due to the surgery

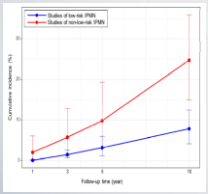


Budde et al. Visceral Medicine 2015

Hyder et al. JAMA Surgery 2013

Malignancy Potential and Survival

Meta-analytic estimates of the cumulative incidence of malignancy during follow-up

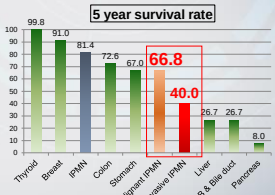


Choi et al. Clin Gastroenterol Hepatol. 2017

-AGA systematic review-
5YSR of invasive IPMN: 40%

Vege et al, Gastroenterol 2015

5 year survival rate

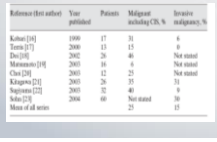


National Cancer Center, Korea, 2013

Criteria for Resection in BD-IPMN

1st Consensus Guideline (2006)

- >3cm
- Mural nodule (+)
- Duct dilatation
- Cytology (+)
- Symptomatic



2nd Consensus Guideline (2012) worrisome feature

- >3cm
- Mural nodule (+)
- Duct dilatation > 5 mm
- Thickened enhanced cyst walls
- Abrupt change in the MPD caliber with distal pancreatic atrophy
- Lymphadenopathy
- Cytology (+)

High-risk stigmata
- MPD ≥10 mm
- Enhanced solid component

Tanaka et al. Pancreatology 2006, 2012

Revised Criteria for Malignancy Predicting Factors

2nd Consensus Guideline (2012)

High-risk stigmata
- Obstructive jaundice
- MPD ≥10 mm
- Enhanced mural nodule

Worrisome features
- >3cm
- Mural nodule (+)
- Duct dilatation > 5 mm
- Thickened enhanced cyst walls
- Abrupt change in the MPD caliber with distal pancreatic atrophy
- Lymphadenopathy

Revised Consensus Guideline (2017)

High-risk stigmata
- Obstructive jaundice
- MPD ≥10 mm
- Enhanced mural nodule >5mm

Worrisome feature
- >3cm
- Mural nodule (+)
- Duct dilatation > 5 mm
- Thickened enhanced cyst walls
- Abrupt change in the MPD caliber with distal pancreatic atrophy
- Lymphadenopathy
- Increased serum CA19-9
- Cyst growth rate >5mm/2 yrs

Tanaka et al. Pancreatology 2012, 2017

Clinical Validation of the 2017 International Consensus Guidelines on IPMN

	P value	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)	Accuracy(%)	HR	95% CI	P value
Cyst size (≥3cm)	0.057	56.1	53.7	37.4	71.2	54.5			
MPD (>5mm)	0.001	54.7	78.0	55.1	77.7	70.3	5.32	2.67 – 10.60	0.001
Mural nodule	0.001	62.8	87.3	71.0	82.7	79.2	9.12	4.60 – 18.09	0.001
Thickened cystic wall	0.001	38.5	89.7	65.0	74.5	72.7	3.40	1.51 – 7.63	0.003
Abrupt change in MPD diameter	0.001	19.3	95.9	70.3	70.5	70.4	2.45	0.78 – 7.94	0.124
Lymphadenopathy	0.002	5.2	99.6	87.5	67.8	68.2	3.79	0.31 – 46.74	0.298
CEA (>5ng/mL)	0.046	6.8	97.7	60.0	67.6	67.3	2.90	0.80 – 10.45	0.104
CA 19-9 (>37 U/mL)	0.001	34.9	92.3	69.9	73.5	72.9	5.25	2.05 – 13.42	0.001
Cyst growth rate (>5mm/2year)†	0.012	60.9	70.3	42.4	83.3	67.8	3.68		0.001

Comparison of diagnostic performance between 2017 and 2012 ICG

AUC	LR	SVM1	SVM2	SVM3	RF
2012 IAP	0.746	0.650	0.650	0.650	0.758
2017 IAP	0.784	0.680	0.686	0.684	0.787

Kang & Jang. Ann Surg Treat & research 2019

Ricci et al. Pancreas 2016

Biomarkers Predicting Malignancy

A Combination of Molecular Markers and Clinical Features Improve the Classification of Pancreatic Cysts

Simeon Springer, Yuxuan Wang, Marco Dal Molin, David L. Masica, et al.

Table 4. Identification of Cysts That Required Surgery[a]

	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Composite molecular marker	75	92	88	83
Composite clinical marker	77	75	70	81
Composite molecular/clinical marker	89	69	69	88

Table 2. Frequency of Molecular Features in Different Cyst Types

	IPMN[b] (n = 96)	MCN (n = 12)	SCA (n = 12)	SPN (n = 10)
KRAS	75 (78)	6 (50)	0 (0)	0 (0)
GNAS	56 (58)	0 (0)	0 (0)	0 (0)
RNF43	36 (38)	1 (8)	0 (0)	0 (0)
CDKN2A	3 (3)	0 (0)	0 (0)	0 (0)
CTNNB1	6 (6)	0 (0)	0 (0)	10 (100)
SMAD4	5 (5)	0 (0)	0 (0)	0 (0)
TP53	9 (9)	0 (0)	0 (0)	1 (10)
VHL	0 (0)	0 (0)	5 (42)	0 (0)
BRAF	1 (1)	0 (0)	0 (0)	0 (0)
NRAS	0 (0)	0 (0)	0 (0)	0 (0)
PIK3CA	0 (0)	0 (0)	0 (0)	2 (20)
LOH chr3 (*VHL*)	4 (4)	0 (0)	7 (64)	0 (0)
LOH chr9 (*CDKN2A*)	8 (8)	0 (0)	0 (0)	0 (0)
LOH chr17 (*RNF43*)	11 (11)	0 (0)	1 (9)	0 (0)
LOH chr17 (*TP53*)	5 (5)	0 (0)	0 (0)	0 (0)
LOH chr18 (*SMAD4*)	10 (10)	1 (8)	0 (0)	0 (0)
Aneuploidy[c]	48 (50)	2 (17)	6 (50)	6 (60)

Springer et al. Gastroenterology 2015

Content

- Background (Changing concept)
- Comparison of Guidelines
- Consideration Points in Decision of Treatment
- Optimal Indication for Surgery
  (Management Algorithm)

Hazard Ratio of Malignancy Predicting Factors

Variables	Hazard ratio	95% CI	p-value
MPD>5mm	4.538	2.449-8.408	<0.001
Mural nodule	6.267	3.271-12.009	<0.001
Thickened cyst wall	1.549	0.756-3.170	0.231
Lymphadenopathy	4.966	0.478-51.623	0.180
CA19-9>37U/mL	4.032	1.826-8.903	0.001

Additive Effect of Malignancy Predicting Factors

Number Of Risk Factors	Benign (n=253)	Malignant (n=97)	Accuracy (%)
0	71	3 (4%)	
1	122	29 (19%)	44.4
2	41	22 (35%)	67.9
3	11	22 (67%)	86.9
≥4	8	21 (72%)	89.3

Jang et al. Br J Surg 2014

Personalized approach for IPMN

Diagnostic tools (Nomogram) is needed

to predict malignancy risk quantitatively in BD-IPMN considering different statistical value of several variables

Individual findings
- Duct diameter
- Mural nodule
- Tumor marker
- Symptoms, etc

Malignancy Risk Score

ANNALS OF SURGERY — A MONTHLY REVIEW OF SURGICAL SCIENCE — Ann Surg 2017;266:1062 — Wolters Kluwer

Proposed Nomogram Predicting the Individual Risk of Malignancy in the Patients With Branch Duct Type Intraductal Papillary Mucinous Neoplasms of the Pancreas

Conclusion: A nomogram predicting malignancy in patients with BD-IPMN was constructed using a logistic regression model. This nomogram may be useful in identifying patients at risk of malignancy and for selecting optimal treatment methods. The nomogram is freely available at http://statgen.s-nu.ac.kr/software/nomogramIPMN.

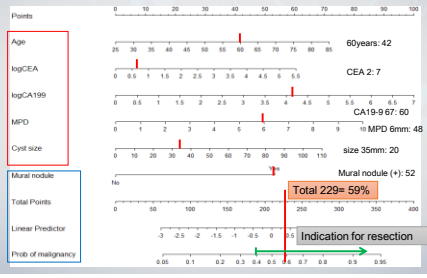
Korea-Japan 1st International collaboration study

Initial enrolled patients (n=2,488)

- Main duct diameter >10mm (n=225)
- Insufficient/incorrect data (n=5)

BD-IPMN (n=2,258)

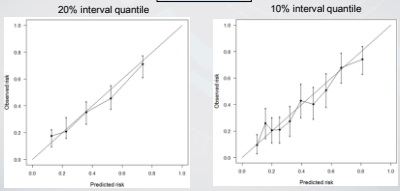
Model development – Internal validation



Evaluate performance – External validation

- 1,000 times boot-strapped Calibration

Calibration plot



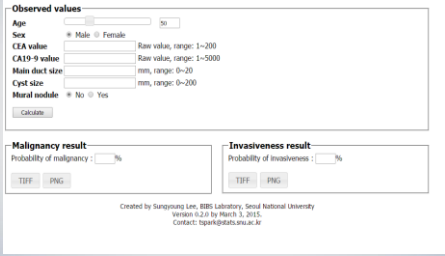
Hosmer-Lemeshow p-value : 1.31e-01

Hosmer-Lemeshow p-value : 2.22e-01

Jang et al. Ann Surg 2017

http://statgen.snu.ac.kr/software/nomogramIPMN

Pancreatic cancer IPMN malignancy & invasiveness calculator

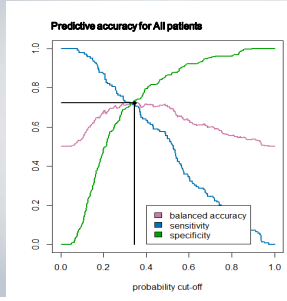


Jang et al. Ann Surg 2017

Global Validation of Nomogram Predicting Malignancy

Europe	China	Taiwan	USA
- Karolinska U - Academic Medical Center - Verona U	- Peking U - Fudan U	- National Taiwan U - Taipei Veterans H	- Johns Hopkins - Columbia U

External Validation - Malignancy prediction



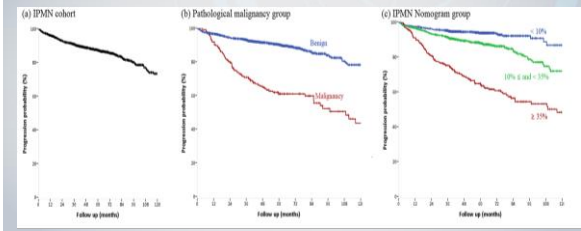
	All
AUC	0.776

Cf) AUC : 0.783
(Previous validation)

	All
Cut-off	0.346
Sensitivity	0.712
Specificity	0.736
Balance	0.724

Jung et al. Br J Surg 2019

Survival according to Pathology and Nomogram



Han and Jang. NEJM (Submitted)

Life Expectancy and Quality Adjusted Life Year according to treatment (Surgery vs Surveillance) Using Nomogram

Age	Malignancy risk	Life Expectancy				QALY			
		Surveillance	Surgery (Mortality 1%)	Surgery (Mortality 3%)	Surgery (Mortality 5%)	Surveillance	Surgery (Mortality 1%)	Surgery (Mortality 3%)	Surgery (Mortality 5%)
<65	<10%	13.29	12.43	12.06	11.81	13.29	12.08	12.00	11.75
	10~35%	10.98	12.13	11.76	11.52	10.98	11.51	11.70	11.46
	>35%	5.79	12.61	12.23	11.98	5.31	12.54	12.17	11.91
65≤Age<75	<10%	11.27	12.56	12.18	11.93	11.27	12.44	12.02	11.77
	10~35%	8.33	10.46	10.15	9.94	8.33	10.32	10.07	9.86
	>35%	6.96	8.65	8.39	8.22	6.38	8.14	8.33	8.16
≥75	<10%	9.25	10.18	9.86	9.72	9.25	10.09	9.77	9.43
	10~35%	7.41	8.07	7.83	7.67	7.41	7.95	7.83	7.67
	>35%	4.06	5.30	5.14	5.03	3.72	5.00	5.08	4.97

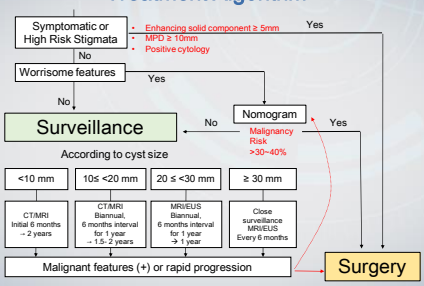
Less than 1 year
Less than 1.5 years
More than 1 year
More than 1.5 years

Han and Jang. NEJM (Gastroenterol)

Examples

	76 year, male	73 year, male	75 year, male
Tumor size (mm)	16	40	42
MPD (mm)	4	2	10
Mural nodule	+	-	-
CA19-9	45	17	12
Malignancy risk	**47.5%**	**17.9%**	**44.4%**
Invasive risk	21.6%	6.3%	15.2%
Final pathology	T1N0 invasive	Low grade dysplasia	T2N1 invasive

Treatment Algorithm



Summary & Conclusion

❖Detection of small IPMN has been increasing.

→Most of BD-IPMN are dormant. Annual malignancy conversion rate 0.2~0.6%.

→But large cyst over 3cm or growing BD-IPMN must be carefully monitored due to the increasing risk of malignancy.

❖Three guidelines have controversies on some issues due to lack of evidences.
→ needs more evidences in a future.

❖Tailored approach is needed in selection of surgery or surveillance considering malignancy potential and patient's factors. → Nomogram could be a valuable tool in selecting treatment methods as customized approach for IPMN