PANCREATIC CLUB RUSSIA

По следам 49 съезда Европейского панкреатического клуба
Июнь 28 – Июль 1, 2017, Будапешт

Обзор докладов по опухолям поджелудочной железы

EPC 2017, Егоров В.И.

11.07.2016

Heidelberg University Hospital

Management of branch duct IPMN:
Single-center experience with 543 patients selected for resection or observation.

European Pancreatic Club
Meeting 2017 - Budapest

J. Kaiser[1], J. Lebert[1], O. Strobel[1], W. Niesen[1], T. Hank[1], M. Heckler[1], C.W. Michalski[1], M.W. Büchler[1], T. Hackert[1]

Aims

- The present study compared the histological outcome of resected BD-IPMN with the indications for resection according to the current ICG of Fukuoka.
- Evaluation of the current ICG of Fukuoka

ICG of Fukuoka
Management BD-IPMN

High risk stigmata (HRS)

- Obstructed common bile duct associated with a lesion of the pancreatic head
- Enhanced solid component within the cyst
- Main pancreatic duct ≥10mm

→ Consider surgery
if clinically appropriate

Worrisome features (WF)

- Clinical evidence of pancreatitis
- Cyst size >3cm
- Thickened/enhanced cyst walls
- Main pancreatic duct size 5-9mm
- Non-enhanced mural nodules
- Abrupt change in main pancreatic duct caliber with distal pancreatic atrophy
- Regional lymphadenopathy

→ Endoscopic Ultrasound
- → Consider surgery if..
  - → "mural nodules"
  - → Main duct involvemen
  - → Cytology: suspicious/positive malignancy
- → Follow-up

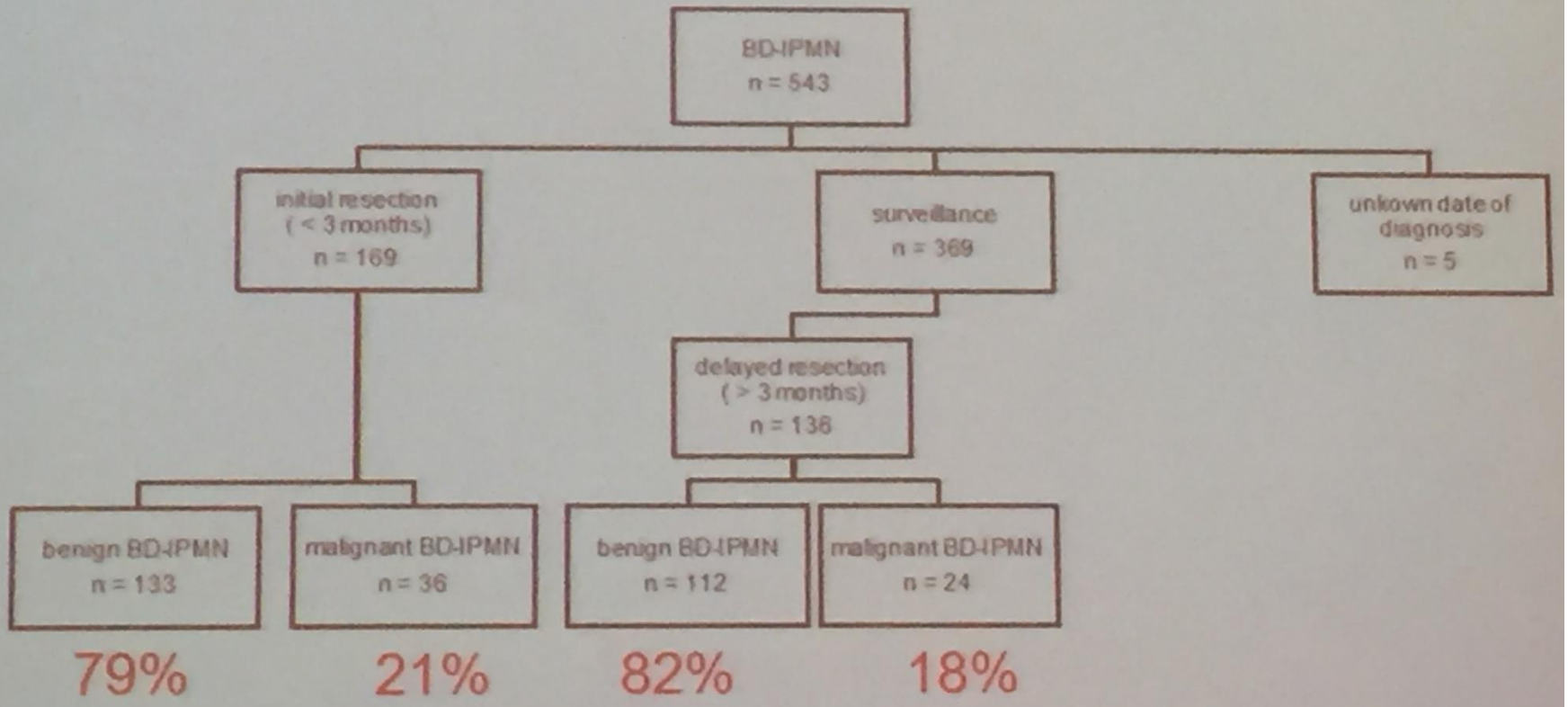
Patients and Methods

- All patients treated for the diagnosis of IPMN between 2004 and 2015 were included (n=1057)

- Patients with BD-IPMN were divided into two groups based on treatment type:
  1. initial resection (<3 months)
  2. Observation
     1. delayed resection (>3 months)
     2. Ongoing surveillance

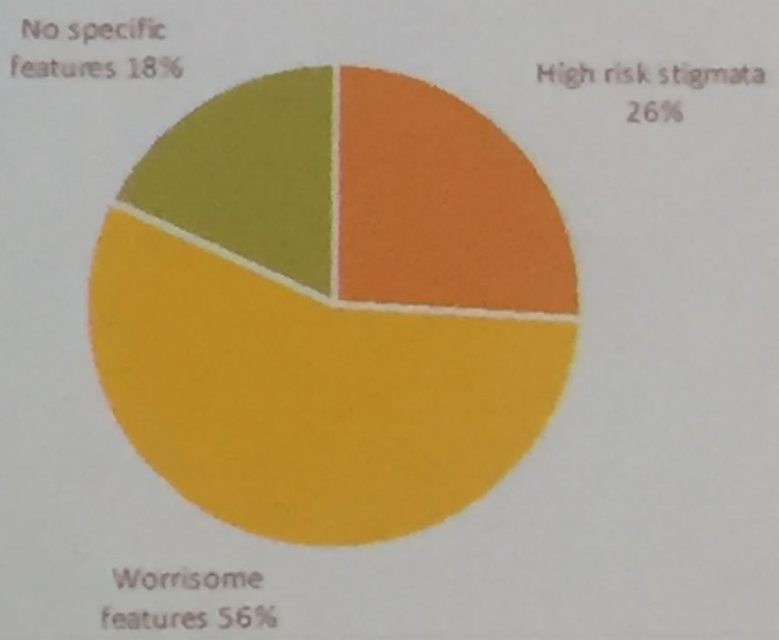
- Resected BD-IPMN were classified as bearing:
  1. high risk stigmata (HRS)
  2. worrisome features (WF)
  3. no suspicious features

Results

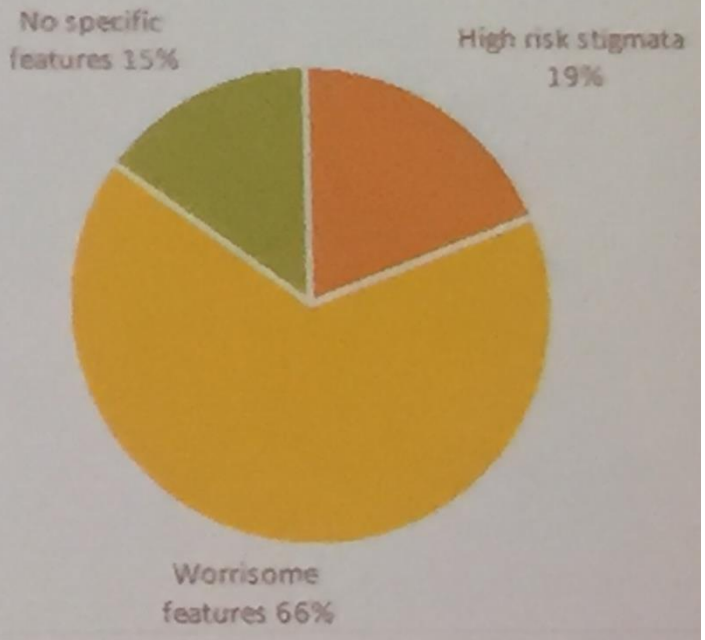

BD-IPMN
n = 543
initial resection
(< 3 months)
n = 169
surveillance
n = 369
unkown date of
diagnosis
n = 5
delayed resection
(> 3 months)
n = 136
benign BD-IPMN
n = 133
malignant BD-IPMN
n = 36
benign BD-IPMN
n = 112
malignant BD-IPMN
n = 24
79%
21%
82%
18%

Evaluation of ICG of Fukuoka

Initially resected (<3months)



Delayed resected (>3months)



Conclusion

- The management strategy advocated by the ICG of Fukuoka to classify BD-IPMN lesions shows a high accuracy (83%, 84%) with regard to "high risk stigmata".

- The accuracy of "worrisome features" is low (25%, 27%).
- Differentiation between malignant and benign lesions cannot be done sufficiently by "worrisome features".

- "Worrisome features" are present in benign and malignant BD-IPMN disease.

- "Worrisome features" offer little help in clinical decision making.

Pancreatic Cancer UK

EUROPAC

Risk independence for the identification of cystic lesions in Familial Pancreatic Cancer (FPC) kindreds

A.R.G Sheel, S. Harrison, I. Sarantitis , J.A. Nicholson, M. Raraty, P. Ghaneh, J. Ramesh, A. Farooq, E. Costello, M. Chapman, A. Smith, R. Carter, C. Mckay, Z. Hamady, G.P. Aithal, P. Hammel, M. M. Lerch, D. K. Bartsch, C. Halloran, S. P. Pereira, J.P. Neoptolemos, W. Greenhalf* on behalf of EUROPAC study group.

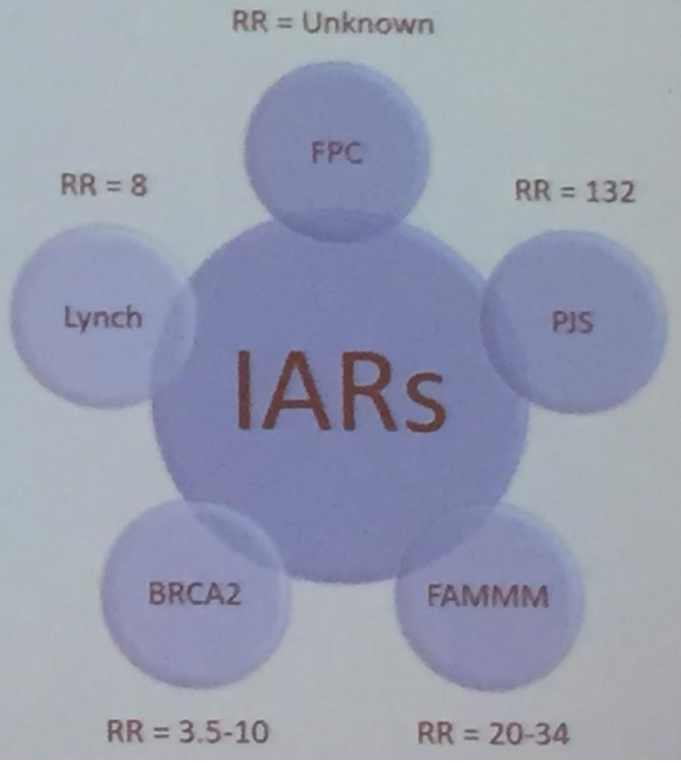
Royal College of Surgeons
ADVANCING SURGICAL CARE

Royal Liverpool & Broadgre
University Hospitals NHS Tr

Screening for pancreatic cancer

- Screening:
  - Why?
  - Who?
  - What?
  - How?
  - When?
  - Where?

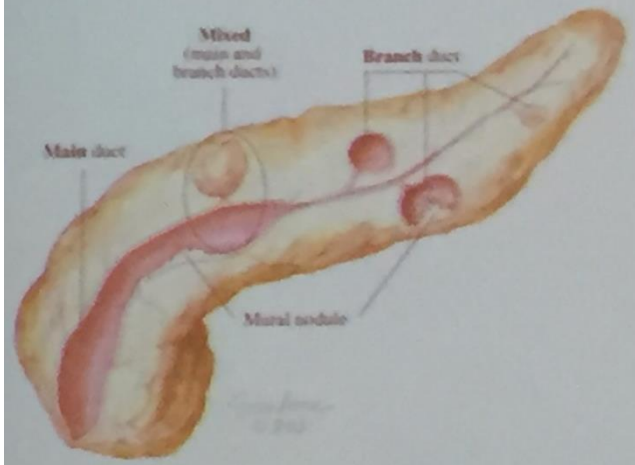
Who? Individuals at risk (IARs)



Pilot screening studies

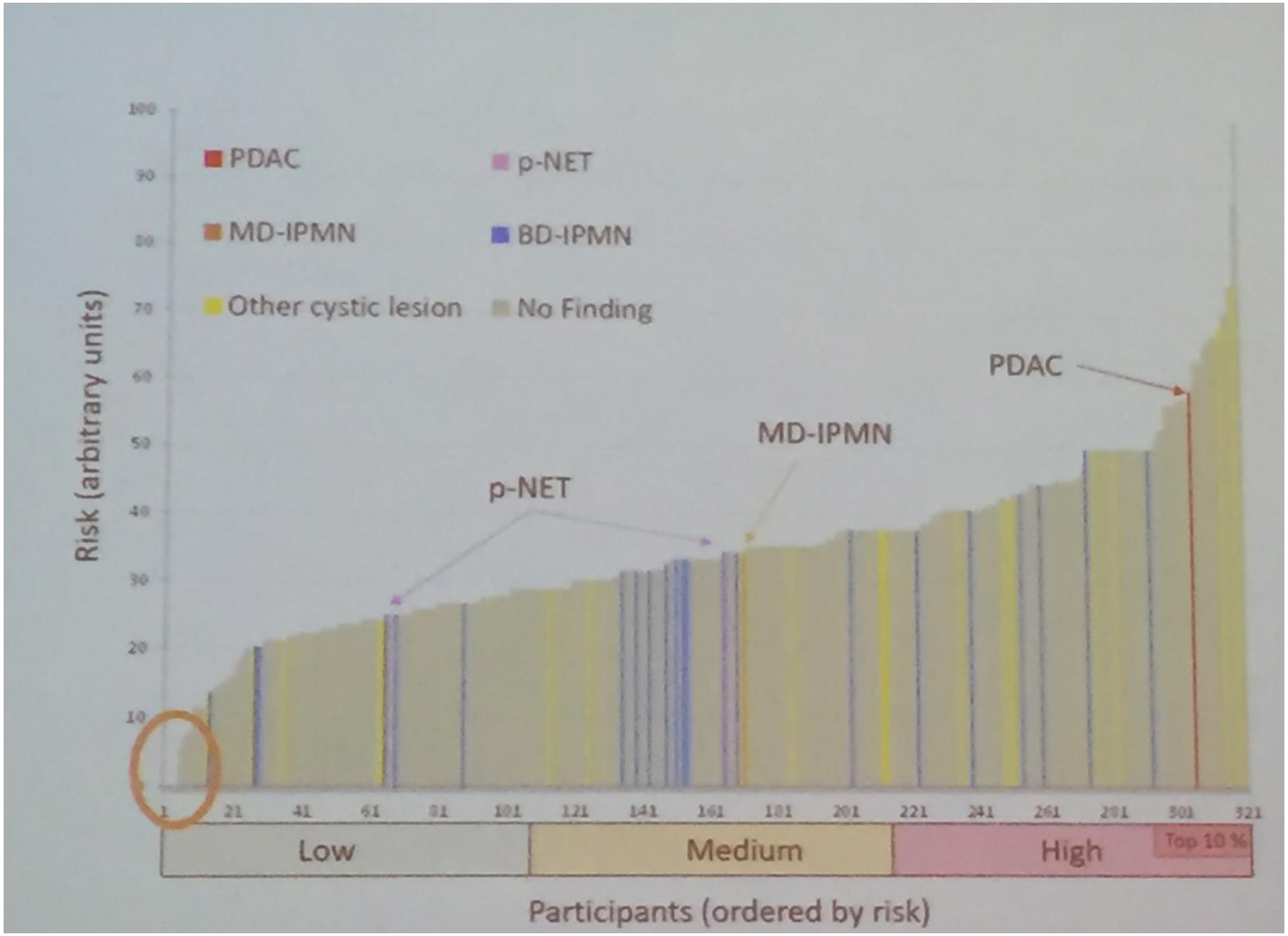
- 20 publications (1999-2016)
- **30 PDAC**
- 6 MD-IPMNs
- 60 BD-IPMNs
- 131 surgical resections as a result of screening

Intraductal papillary mucinous neoplasia (IPMN)



- Precursor lesions – more frequently in high risk individuals
- IPMNS should only be considered a genuine positive screening event if this is true

Aim: We assessed if familial risk correlates with a higher incidence of IPMNs in our **FPC** kindreds


PDAC
p-NET
MD-IPMN
BD-IPMN
Other cystic lesion
No Finding
Risk (arbitrary units)
PDAC
MD-IPMN
p-NET
Low
Medium
High
Top 10 %
Participants (ordered by risk)

Conclusion: BD-IPMN are incidental screening findings

- This screening study has identified 4 positive events
- The PDAC occurred in the highest risk group
- The MD-IPMN in the middle risk category

- The 22 BD-IPMNs were identified with equal probability in individuals of all risk categories.

- These data do not support the idea that BD-IPMN are a positive finding in screening programmes

LMU KLINIKUM

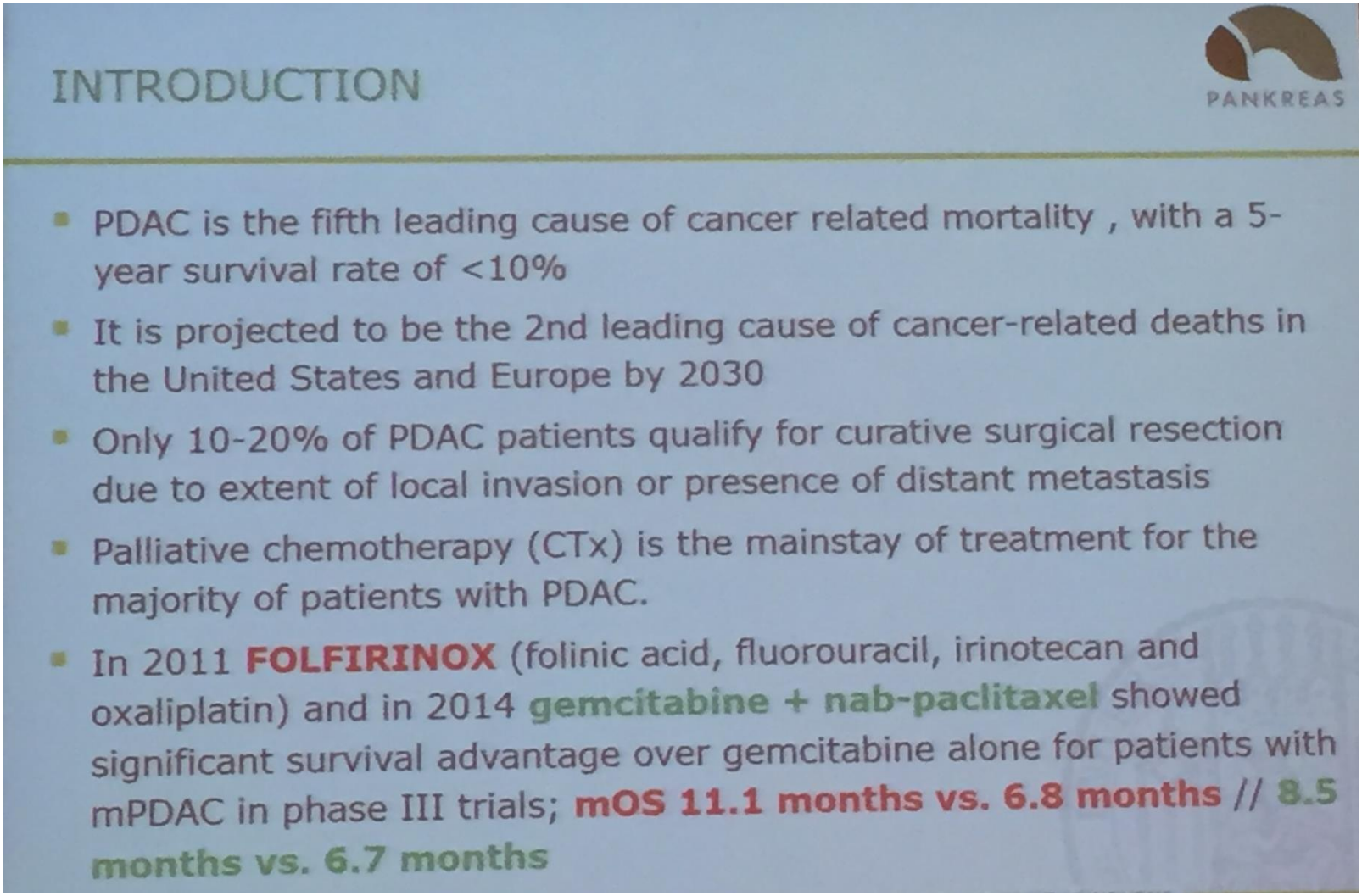
INTENSIFIED CHEMOTHERAPY IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) IN CLINICAL ROUTINE: A EUROPEAN RETROSPECTIVE MULTICENTER STUDY

G Beyer, MA Javed, NNH Le, A Vinci, H Wong, DH Palmer, R Morgan, A Lamarca, R Hubner, JW Valle, S Alam, S Chowdhury, YT Ma, L Archibugi, G Capurso, P Maisonneuve, A Neesse, M Sund, M Schober, S Krug

Pancreas 2000

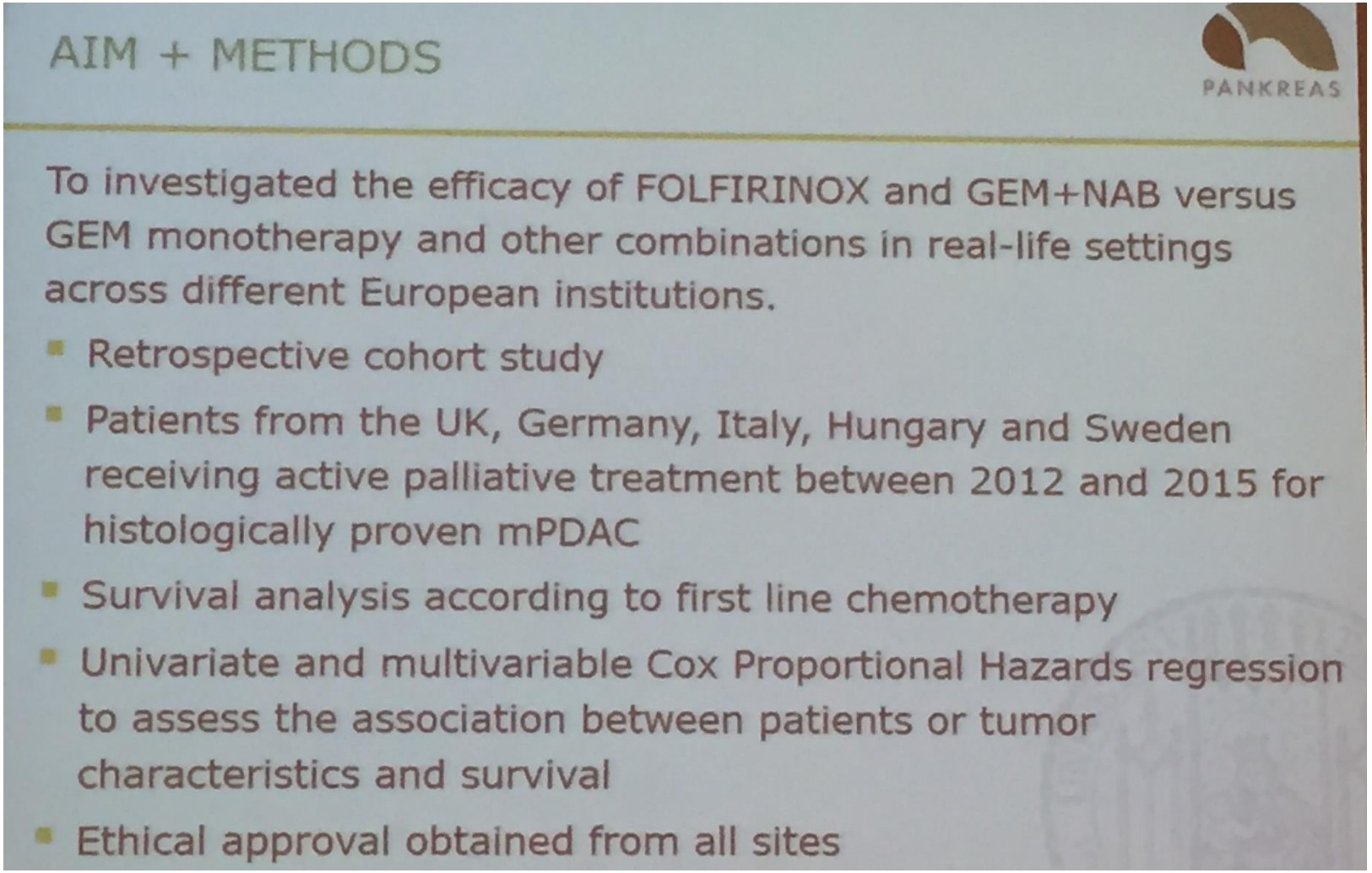
FOLFIRINOX and GEM+NAB vs GEM for mPDAC

G.Beyer, Germany



FOLFIRINOX and GEM+NAB vs GEM for mPDAC

G.Beyer, Germany



COHORT AND PATIENT FLOW

1090 patients included

34 patients excluded (unknown therapy)

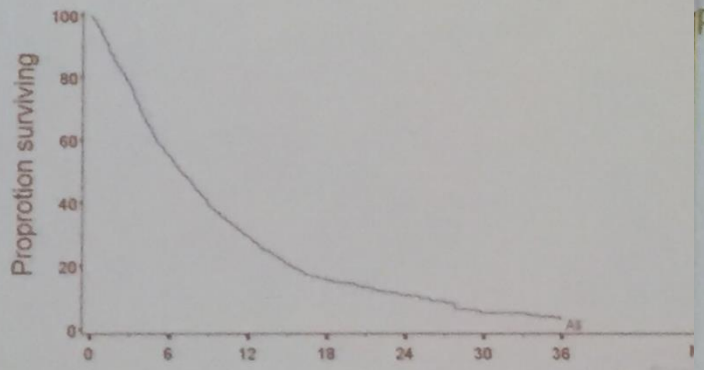
1056 patients for descriptive analysis

26 patients excluded (incomplete follow-up)

1030 patients for survival analysis

KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK II

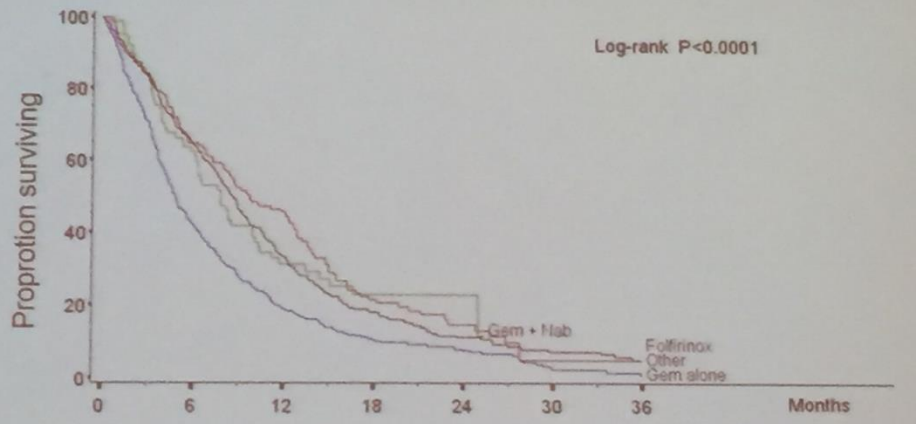
OVERALL SURVIVAL FOR ALL PATIENTS



Patients at risk								Medi (95
All CTx regimens	1030	526	252	111	55	21	8	6.9 (6

KLINIKUM DER UNIVERSITÄT MÜNCHE

OVERALL SURVIVAL ACCORDING TO MAJOR CT REGIMENS



Patients at risk								Median OS (95% CI)
Gem alone	429	170	72	34	19	5	1	4.9 (4.4- 5.6)
Gem plus Nab	78	47	18	10	2	0	0	7.9 (6.2-10.0)
Folfirinox	182	105	64	24	10	2	1	9.9 (8.1-12.6)
Any Other	327	197	95	42	24	14	6	8.7 (7.7- 9.4)

CONCLUSION

PANKREAS

- The use of FOLFIRINOX and GEM+NAB in clinical routine is variable in Europe.
- Compared to GEM-monotherapy, FOLFIRINOX and GEM+NAB were associated with improved survival, thus confirming data from randomized trials.
- Other gemcitabine or 5-FU based combinations were also associated with better outcome, however this needs to be further investigated in a prospective setting.
- Female gender, previous curative surgery and good performance status are associated with improved survival.

UniversitätsKlinikum Heidelberg

Validation of the New R-Status Definitions (1mm margin) for Pancreatic Adenocarcinoma resected by Distal or Total Pancreatectomy

T. Hank, MD[1]; U. Hinz, MSc[1]; J. Kaiser, MD[1]; W. Niesen, MD[1]; F. Bergmann, MD[2]; T. Hackert, MD[1]; M. W. Büchler, MD[1]; O. Strobel, MD[1]

[1] Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg

[2] Institute of Pathology, University of Heidelberg, Heidelberg

Background:

- Several definitions of margin clearance in pancreatic cancer
- New protocols of pathologic workup with consideration of the circumferential margins*
- Heterogenous R0/R1 rates and associated survival in pancreatic cancer
- No data for strict R-definitions in distal- or total pancreatectomy

„Old" R1-definition:

Tumor cells infiltrate transsection or circumferential margins

(R1)

„New" R1-definition*:

Tumor cells infiltrate transsection or circumferential margins

(R1 direct)

\+

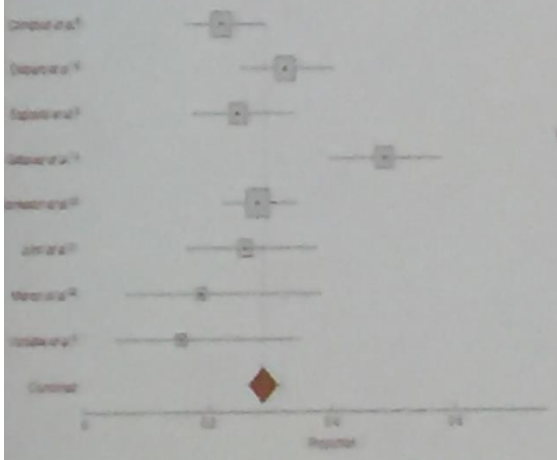
Tumor free margin <1mm (R1<1mm)

*Verbeke et al., Br J Surg 2006
*Esposito et al., Ann Surg Oncol 2008

High variability of R0/R1 rates

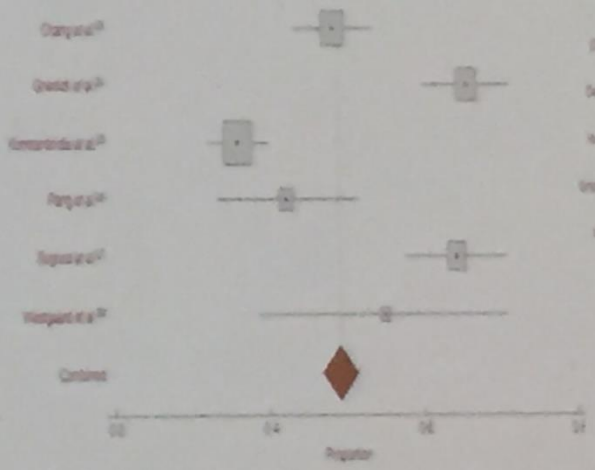
Systematic review

Meta-analysis of radical resection rates and margin assessment in pancreatic cancer



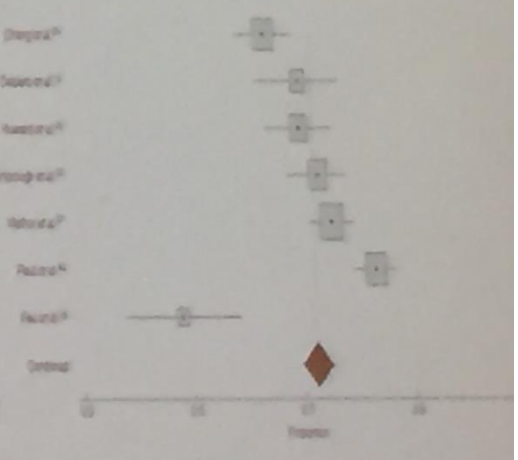
R0-rate (>1mm margin)
axial slicing technique

R0 = 29%



R0-rate (>1mm margin)
different slicing technique

R0 = 49%



R0-rate (0mm margin)

R0 = 72%

Chandrasegaram et al., BJS 2015

Results

Parameter		Total 455 (100%)	R0 197 (23.5%)	R1 (<1 mm) 194 (22.9%)	R1 (direct) 244 (53.6%)	p
Sex						0.2244
	Male	244 (53.6%)	53 (49.5%)	91 (49%)	140 (57.4%)	
	Female	211 (46.4%)	54 (50.5%)	53 (51%)	104 (42.6%)	
Age [yrs]*		64.5 (6.1-87.4)	63.6 (36.1-84.3)	64.6 (30.3-87.4)	64.6 (39.2-86.4)	0.7482
	<65	35 (7.7%)	9 (8.4%)	9 (8.7%)	17 (7%)	0.3151
	65-70	275 (60.4%)	72 (67.3%)	67 (64.8%)	146 (59.8%)	
	>70	146 (31.9)	26 (24.3%)	38 (36.5%)	91 (33.2%)	
ASA Score						0.7410
	ASA I	10 (2.2%)	2 (1.9%)	2 (1.9%)	6 (2.5%)	
	ASA II	261 (58.1)	66 (61.7%)	65 (62.1%)	130 (54.4%)	
	ASA III	177 (39.4)	39 (36.5%)	36 (36%)	102 (42.7%)	
	ASA IV	1 (0.2)	0 (0%)	0 (0%)	1 (0.4%)	
BMI [kg/m²]*		26.2 (16.4-43.7)	24.6 (16.6-38.6)	26.3 (17.8-41.4)	26.4 (16.4-43.7)	0.4636
CA 19-9						<0.0001
	< 37 [U/mL]	153 (31.1%)	52 (52.6%)	33 (33.3%)	48 (20.9)	
	≥ 37 [U/mL]	295 (68.9%)	47 (47.6%)	66 (66.7%)	182 (79.1%)	
Type of surgery						0.0013
	TP (pp)	92	23 (21.50%)	15 (14.4%)	55 (22.13%)	
	TP stomach	130	17 (15.9%)	30 (28.5%))	83 (34.02%)	
	TP (pr)	16	4 (3.7%)	1 (1.0%)	10 (4.1%)	
	DP	218	63 (58.9%)	58 (56.6%)	97 (39.8%)	
Histology						<0.0001
	PDAC	333 (73.2%)	62 (59%)	69 (92.7%)	186 (75.6%)	
	IPMN-associated PDAC	73 (16%)	21 (19.6%)	13 (12.8%)	39 (16%)	
	IPMC	21 (4.6%)	10 (10%)	1 (1%)	4 (1.6%)	
			(2.8%)	4 (3.9%)	8 (3.3%)	
			(2.8%)	0 (0%)9	6 (2.1%)	
			(1.9%)	0 (0%)	0 (0%)	
			(0%)	0 (0%)	3 (1.2%)	
						<0.0001
			(24.3%)	0 (0%)	0 (0%)	
			(8.4%)	0 (0%)	0 (0%)	
			(66.4%)	102 (99.1%)	227 (93%)	
			(0.9%)	2 (1.9%)	17 (7%)	
						<0.0001
			(62.6%)	15 (14.4%)	28 (11.5%)	
			(37.4%)	89 (85.6%)	216 (88.5%)	
						<0.0001
			(4.7%)	1 (1%)	1 (0.4%)	
			(67%)	75 (72.8%)	139 (56.6%)	
			(25.8%)	27 (26.2%)	100 (41%)	
			(2.6%)	0 (0%)	5 (2.1%)	
						0.0002
			(16.6%)9	28 (26.9%)	36 (14.8%)	
			(36.6%)	25 (24%)	42 (17.2%)	
			(15%)	15 (14.4%)	32 (13.1%)	
			(29.9%)	32 (30.8%)	121 (49.6%)	

CA 19-9

Histol. Typ

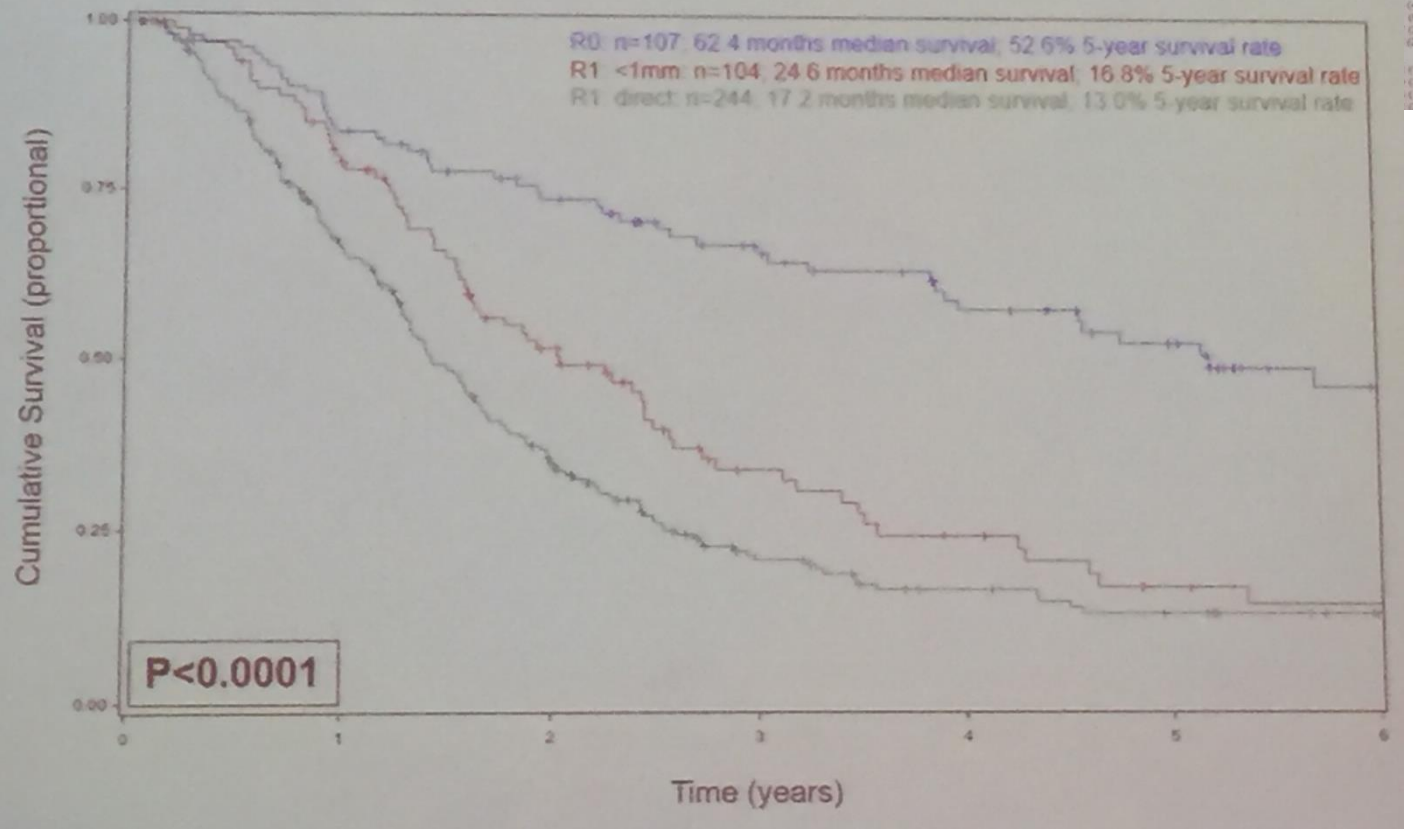
pT stage

pN stage

Grading

Results

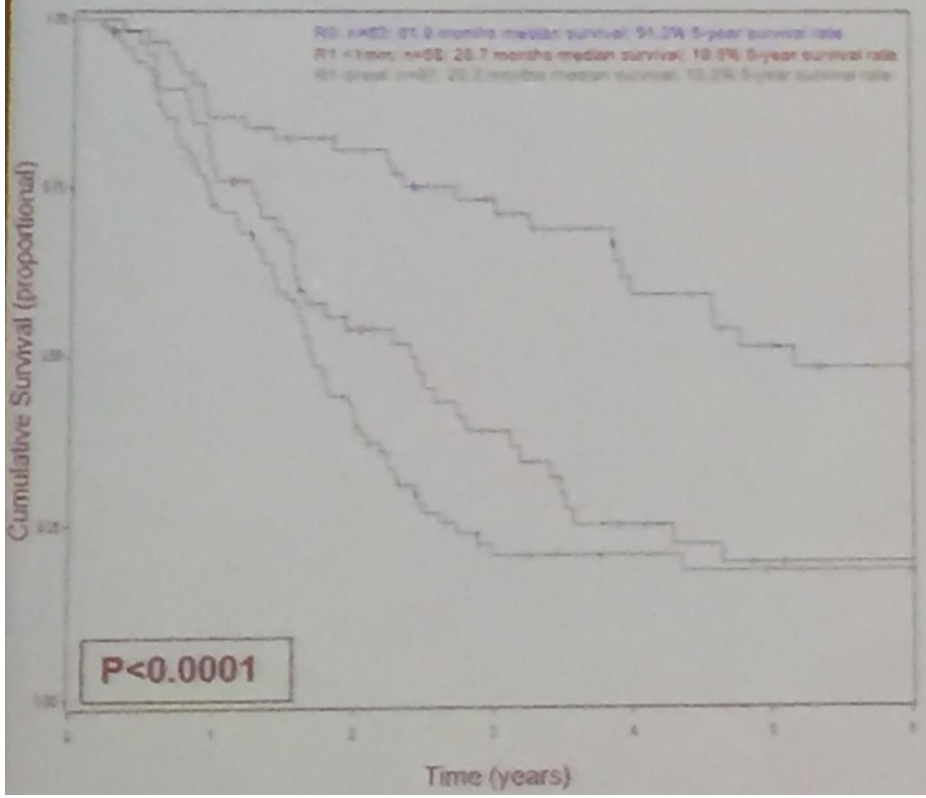
Survival – 455 patients (DP & TP)



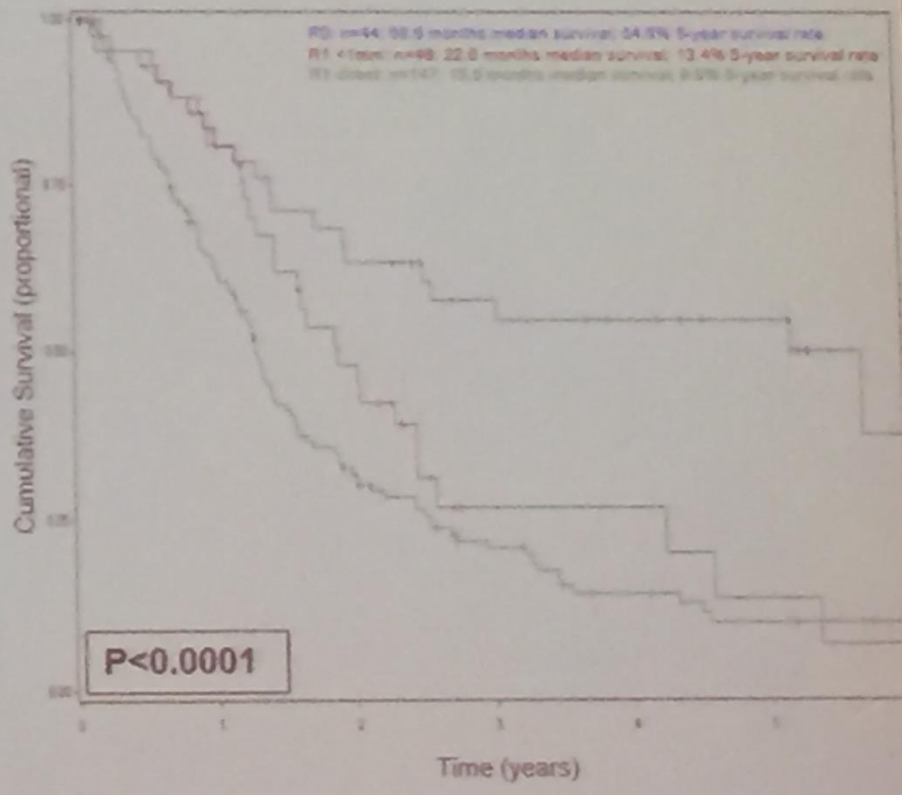
Results

Survival

Distal pancreatectomy



Total pancreatectomy



Conclusions:

- The new R-status (1mm margin) is validated as independent prognostic factor for pancreatic cancers in the body and tail.

- Current nomenclature in Germany:*
  - R0 wide (CRM-) >1mm
  - R0 narrow (CRM+) <1mm
  - R1

*Updated S3-Leitlinie zum exokrinen Pankreaskarzinom, Version 1.0, 2013

49th Annual **EPC** Meeting
June 28 - July 2017
Budapest, HungaryC

NON-OPERATIVE MANAGEMENT OF LOW-RISK BRANCH-DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS IS SAFE IN THE LONG-TERM (>5 YEARS) FOLLOW-UP

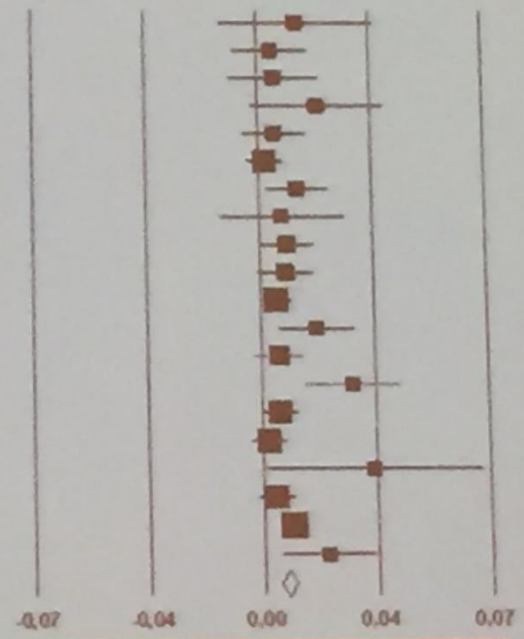
Alessandra N. Piccioli MD,
Division of Pancreatic Surgery
Pancreas Translational & Clinical Research Center
San Raffaele Scientific Institute
Vita-Salute University
Milan, Italy

Chirurgia del Pancreas

Meta-analysis & Systematic Review low risk BD-IPMNs under surveillance

Development of overall pancreatic malignancy

Study name	Statistics for each study							Relative weight
	Rate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Wakabayashi	0.012	0.012	0.000	-0.012	0.036	1.000	0.317	0.90
Sai	0.004	0.005	0.000	-0.007	0.016	0.707	0.480	3.32
Ise	0.005	0.007	0.000	-0.009	0.019	0.707	0.480	2.44
Kobayashi	0.018	0.011	0.000	-0.002	0.039	1.732	0.083	1.19
Pelaez-Luna	0.005	0.005	0.000	-0.005	0.015	1.000	0.317	4.24
Salvia	0.002	0.003	0.000	-0.004	0.008	0.707	0.480	8.73
Sawai	0.012	0.005	0.000	0.002	0.021	2.449	0.014	4.54
Shin	0.007	0.010	0.000	-0.012	0.025	0.707	0.480	1.34
Tanno	0.008	0.004	0.000	0.000	0.017	2.000	0.046	6.53
Bae	0.008	0.004	0.000	-0.001	0.016	1.732	0.083	5.10
Uehara	0.005	0.002	0.000	0.000	0.010	2.000	0.046	10.09
Kang	0.017	0.006	0.000	0.005	0.028	2.828	0.005	3.19
Khanoussi	0.005	0.004	0.000	-0.002	0.013	1.414	0.157	6.32
Ohno	0.028	0.007	0.000	0.013	0.042	3.742	0.000	2.25
Cauley	0.006	0.003	0.000	0.000	0.011	2.000	0.046	8.96
Adix	0.002	0.003	0.000	-0.003	0.007	0.707	0.480	9.08
Othman	0.034	0.017	0.000	0.001	0.068	2.000	0.046	0.48
Mori	0.004	0.003	0.000	-0.002	0.010	1.414	0.157	8.63
Sahora	0.009	0.002	0.000	0.005	0.013	4.359	0.000	11.39
Kamata	0.020	0.007	0.000	0.005	0.034	2.646	0.008	2.27
	0.007	0.001	0.000	0.005	0.010	6.018	0.000	



Risk of pancreatic malignancy 82/2177 = 3.7% - 7/1000 pyrs

Crippa. Dig Liver Disease 2016;48:473

Gastroenterology 2015;148:819–822

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee

When Can Pancreatic Cyst Surveillance Be Discontinued?

6. The AGA suggests against continued surveillance of pancreatic cysts if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate. *(Conditional recommendation, Very low quality evidence)*

Background

- ✓ Natural history of IPMNs is unknown
- ✓ Few data on long-term follow-up (> 5 years) of BD-IPMNs undergoing surveillance
  - ✓ Risk of IPMN progression
  - ✓ Risk of development of PDAC (1.5-11%)

Methods

- ✓ Study design: multicenter retrospective study (Negrar/Milan, Bologna and Rome)
- ✓ Pts with clinico-radiological diagnosis of BD-IPMNs without WF and HRS with a minimum follow-up of 5 years
  - ✓ Cyst size < 30 mm
  - ✓ MPD < 5 mm
  - ✓ No solid components
  - ✓ No symptoms
  - ✓ No atypical cytology
- ✓ Work-up
  - ✓ initial workup and subsequent follow up with MRCP
  - ✓ (uncertain diagnosis → secretin-enhanced MRCP/EUSP-FNA)

Changes during follow-up

- ✓ Worrisome features and high-risk stigmata
  - ✓ Late diagnosis during the surveillance
    - ✓ WF onset after a **median of 71 months**
    - ✓ HRS onset after a **median of 77.5 months**
  - ✓ Pattern of onset
    - ✓ After minor changes: 7 patients (27%)
    - ✓ No previous modifications: 19 patients (73%)

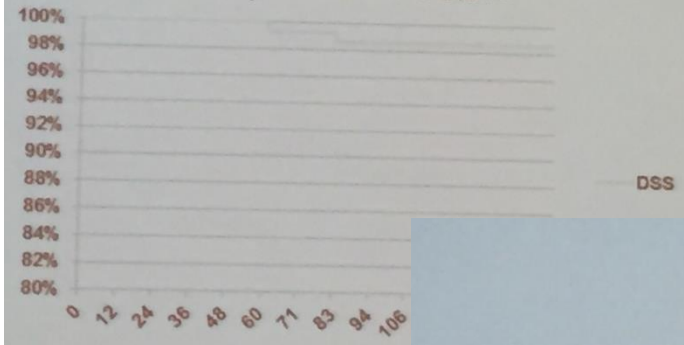
Surgery during follow-up

- ✓ **8 pts** (5%) including: - 5/6 HRS (83%)
  - 3/20 WF (15%)

PZ	HRS/WF	Indication	Previous change	Time from diagnosis	Operation	Pathology
1	HRS	MPD > 10 mm Cyst size 60 mm	Increase in MPD Increase in cyst size	84 months	LP	Mixed IPMN - HGD
2	HRS	Jaundice: solid nodule	No	64 months	PD	IPMN distinct PDAC BD-IPMN - LGD

Disease-Specific Survival

12-year **DSS** : 98.5%



- ✓ Two patients died of disease:
  - ✓ Liver metastases in pt with
  - ✓ Liver metastases after Whi

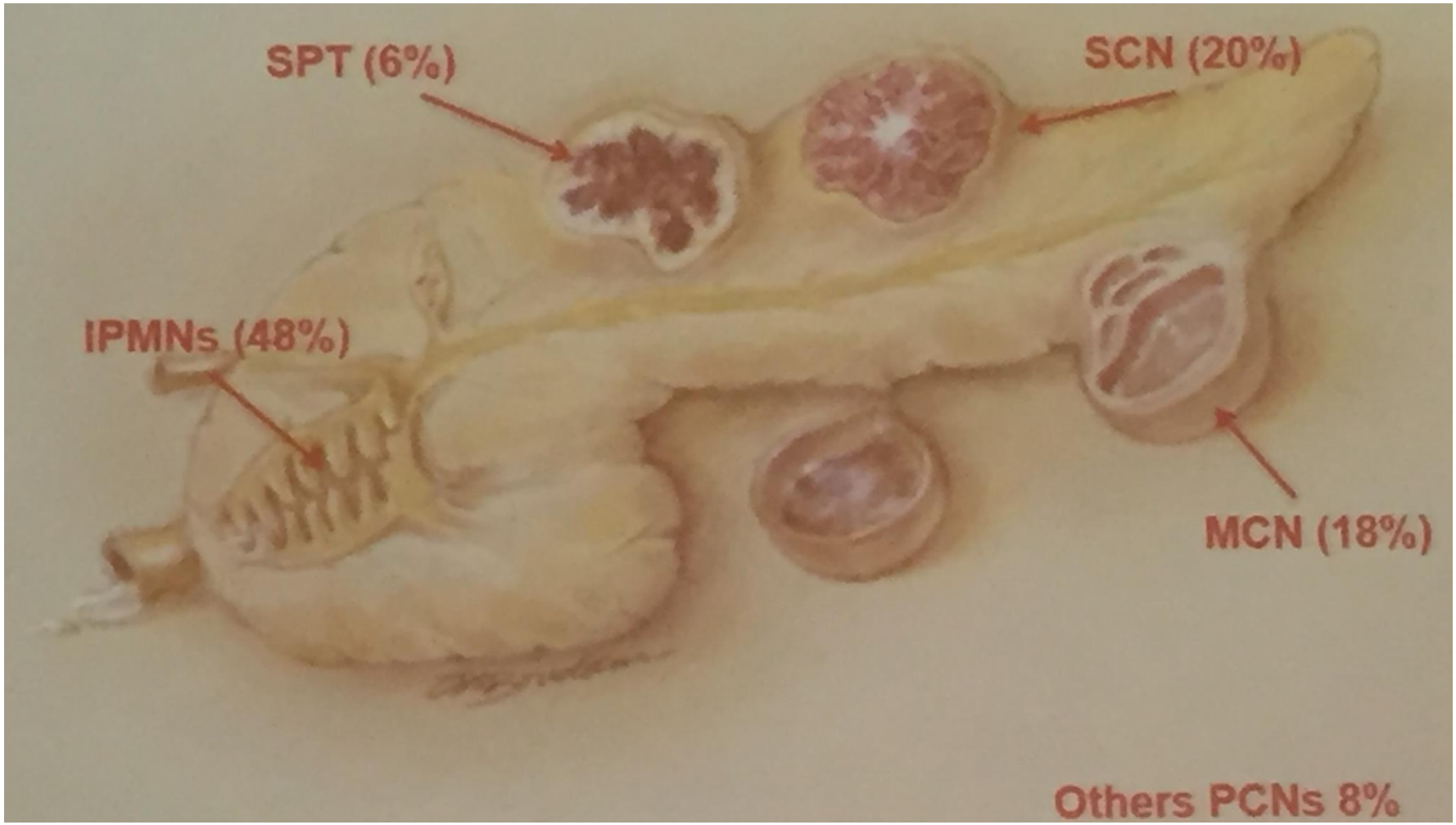
Invasive pancreatic mal

Conclusions

- ✓ Surveillance of "low-risk" BD-IPMNs is safe
- ✓ Mortality related to pancreatic malignancy of 1.5%
- ✓ Frequent changes in BD-IPMNs (48%) but....
  - ✓ Clinically-relevant changes (WF+HSR) in 18%
  - ✓ HRS rare
  - ✓ AFTER 5 years of follow-up
- ✓ Surveillance should not be discontinuated especially in BD-IPMNs > 15 mm at diagnosis
- ✓ An intensification of follow up should be considered after 5 years

Pancreatic cysts and IPMN

M.del Chiaro



Clinical relevance PCNs

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✓ PCNs are a common diseases with an estimated prevalence in the general population of 20-30%.

Del Chiaro M et al. DLD 2013

✓ Someone of the PCNs can progress from adenoma for to cancer (i.e. IPMN and MCN)

✓ Other lesions have a benign attitude (i.e. SCN)

Jalis B,....Del Chiaro M et al. GUT 2016

✓ PCNs represents a terrific opportunity for preemptive pancreatic surgery, but in the other hands a risk for patients over-treatment.

Del Chiaro M et al. WJG 2014

✓ The accuracy of pre-operative diagnostic modalities is low, even in tertiary high specialized centers (around 60%)

Del Chiaro M et al. Annals Surg Oncol 2014

IPMNs: prognosis

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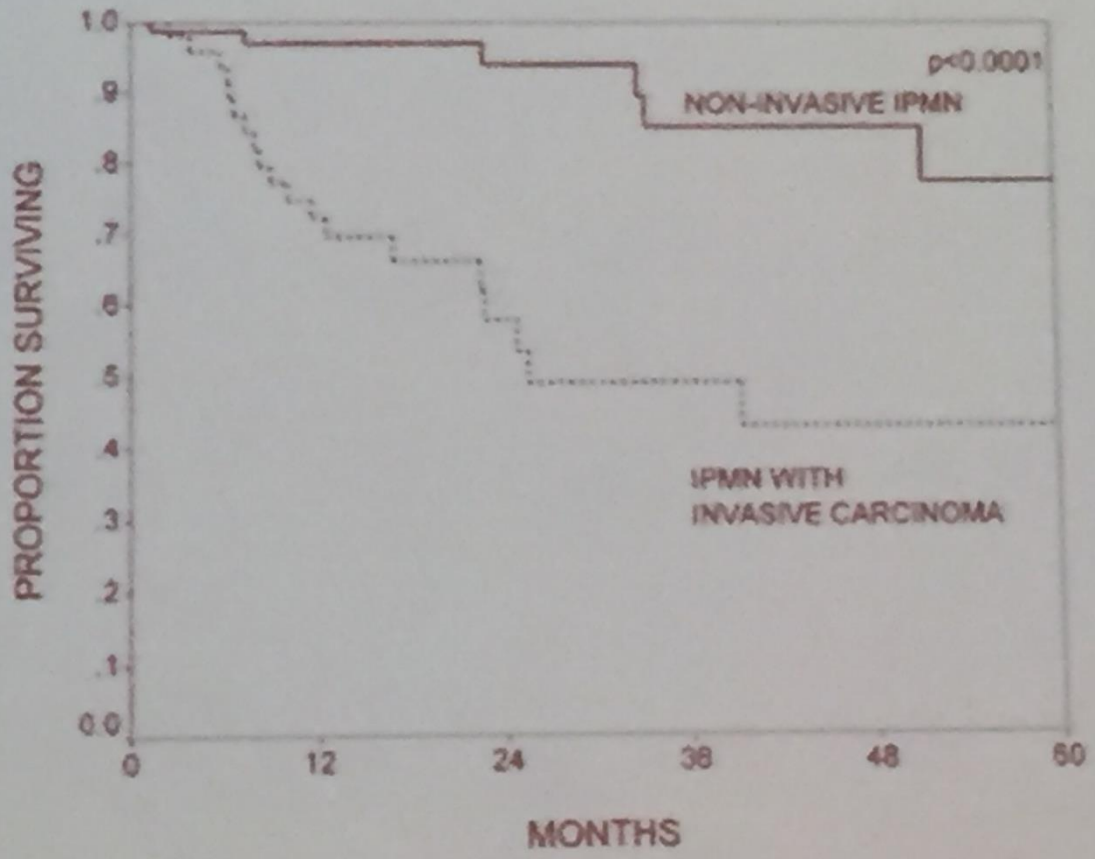
Actuarial survival curves of IPMNs



Sohn et al. Ann Surg. 2004

MD and mixed type should be always resected

What is it the cut-off of MPD for surgical approach?

Studies with a dimensional MPD cut-off to segregate groups according to their risk of malignancy			
Reference	Cut-off (mm)	Sens/Spec (%)	Accuracy (%)
Seo N et al	7	65.9/92	-
Harima H et al	8	100/86	94
Kawada N et al	10	50/99	93
Tawada K et al	7	66.7/82.1	-
Shimizu Y et al	7	74/72	-
Hirono S et al	5	74.4/80.4	76.9
Zhang HM et al	8	PPV 86%	-
Hirono S et al	5	72/83	78
Satoshi N et al	3	70/59	66
Chiu S et al	3	56/87	79
Okabayashi T et al	5	83/100	90
Kawai M et al	5	85/71	81
Kubo H et al	10	78/94	88

And…our aim is not to remove cancer, but to remove HGD

BD-IPMNs

Risk of malignancy according to cyst size in IPMN		
Reference	Cyst size	% of malignancy (HGD/IC)
Masica et al 2016	>40mm	88% sensitivity 40% specificity
Sahora et al 2013	>30mm	12%
Hirono et al 2012	>30mm	47.4%
Ohtsuka et al 2012	>30mm	29.2%
Sadakari et al 2010	>30mm	3.6%
Woo et al 2009	> 30mm	28.5%

Which kind of surgery?

In the large majority of the cases radical resection

Enucleations

126 consecutive patients (30% IPMNs)

Mortality: 0.8% Morbidity: 63%

Faltot F et al. Surgery 2015

Central pancreatectomy

100 consecutive patients (65% PCNs)

Mortality: 3% Morbidity: 72%

Goudard Y et al. JAMA Surg 2014

Be careful with parenchyma sparing procedures

- Oncologic Risk
- Peri-Operative Risks
- No evidence of benefits

Del Chiaro M. JAMA Surg 2014

BD-IPMNs

Karolinska Institutet

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Progress Report

European experts consensus statement on cystic tumours of the pancreas

Marco Del Chiaro[a,*], Caroline Verbeke[b], Roberto Salvia[c], Gunter Klöppel[d], Jens Werner[e], Colin McKay[f], Helmut Friess[g], Riccardo Manfredi[h], Eric Van Cutsem[i], Matthias Löhr[a], Ralf Segersvärd[a], the European Study Group on Cystic Tumours of the Pancreas

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Review article

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[a], Christopher L. Wolfgang[j], Koji Yamaguchi[aa], Kenji Yamao[ab]

Lifelong follow-up

VS

Gastroenterology 2015;148:819–822

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege,[1] Barry Ziring,[2] Rajeev Jain,[3] Paul Moayyedi,[4] and the Clinical Guidelines Committee

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [2]Division of Internal Medicine, Sidney Kimmel College of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania; [3]Texas Digestive Disease Consultants, Dallas, Texas; [4]Division of Gastroenterology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada

5 yrs follow-up

IPMNs follow-up: Is it safe according with EU guidelines?

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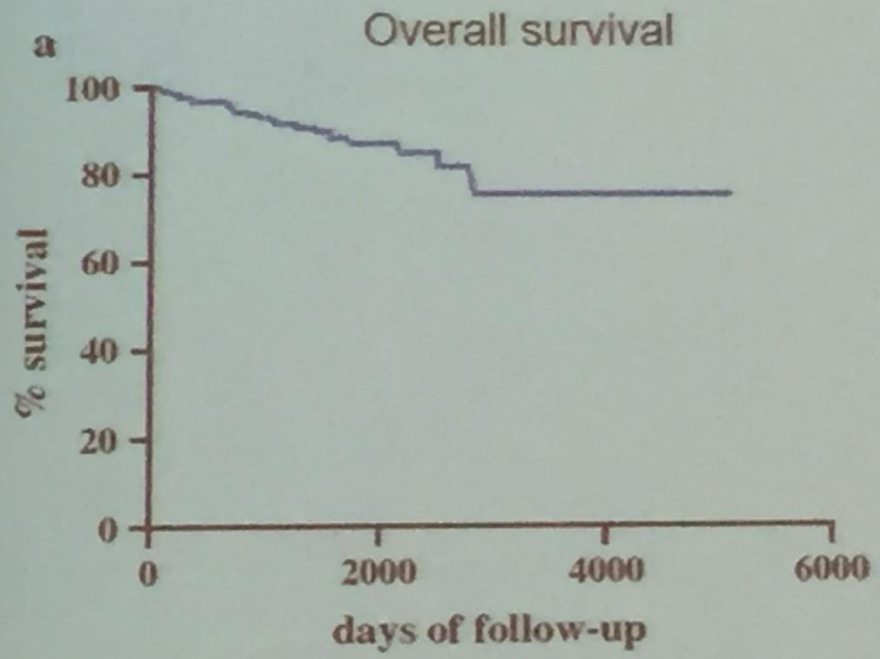
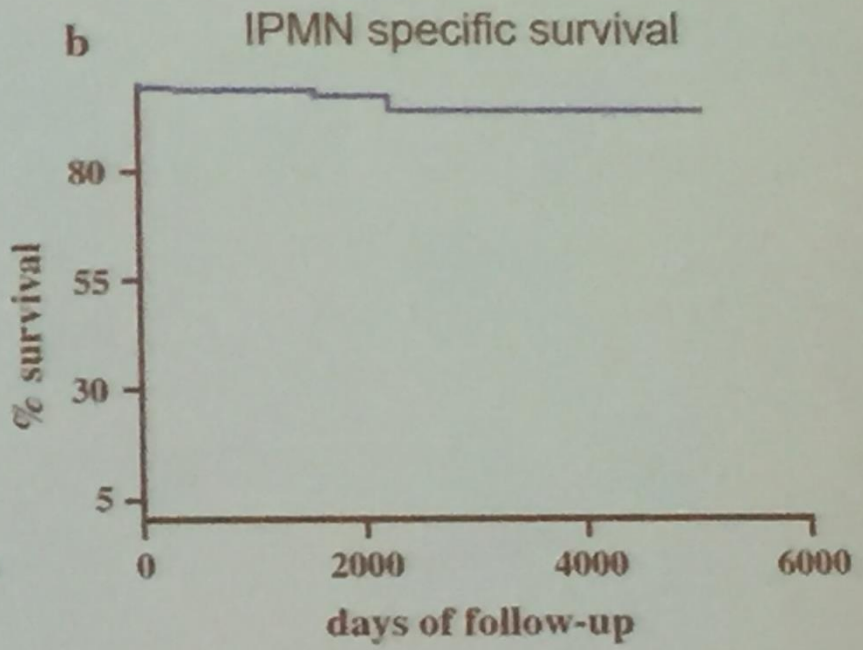
400 pts under surveillance





	# pts	%
Overall mortality	33	8.3
IPMN related mortality	4	1
Extra pancreatic tumors	5	1.3
Other causes	24	6

Del Chiaro M et al. Ann Surg Oncol 20

Can we stop surveillance after 5 yrs?

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NO

This first study comparing the 3 current guidelines for surgically removed pancreatic cysts demonstrated that although (12%-13%) fewer patients will undergo unnecessary surgery with the AGA guideline; 12% of pancreatic cysts with high-grade dysplasia or malignancy would have been missed when compared with none with the IAP or European guidelines.

Lekkerkerker SJ et al. GIE 2016

Should IPMNs patients followed for other neoplasia?

1340 consecutive patients observed for IPMNs (Pancreas 2000 project)

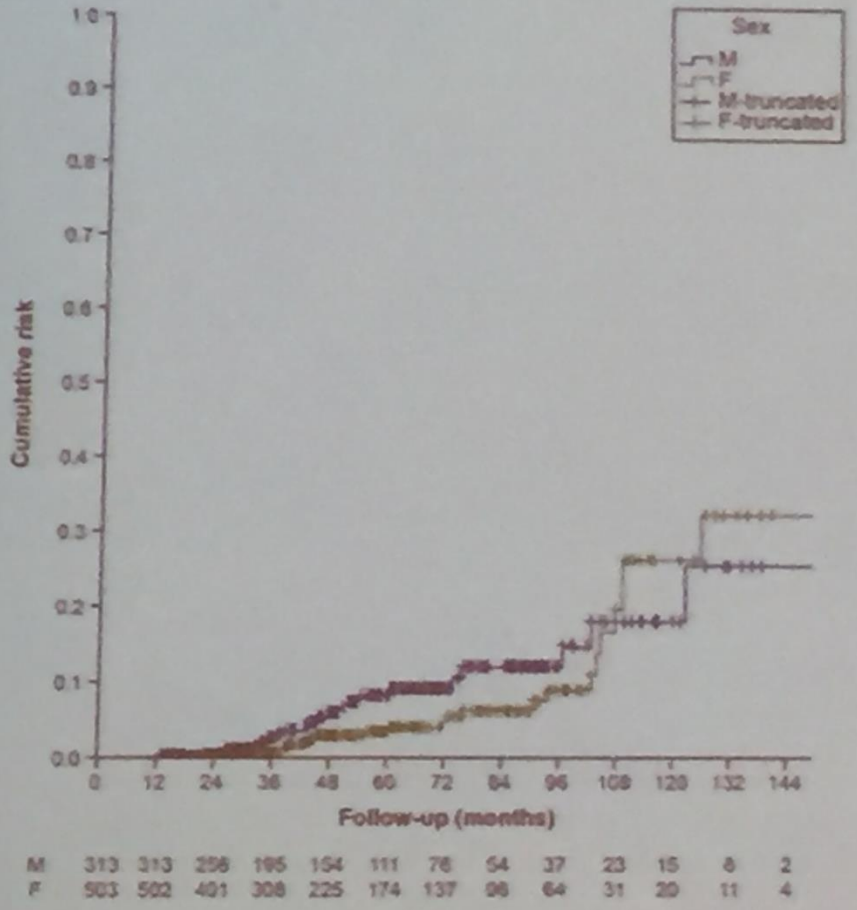

Table 3. Observed and Expected Number of Extrapancreatic Neoplasms During IPMN Follow-Up Evaluation

Cancer site	Observed cases*	Expected cases	SIR	95% CI
Males (N = 313)	23	15.52	1.48	0.94–2.22
Females (N = 503)	25	16.63	1.39	0.90–2.05
Males				
Prostate	5	2.55	1.96	0.63–4.57
Lung	3	2.03	1.47	0.30–4.31
Colorectal	4	1.61	2.48	0.67–6.36
Kidney	4	0.43	9.10	2.45–23.30‡
Gastric	3	0.57	5.19	1.04–15.17‡
Non-Hodgkin lymphoma	1	0.48	2.08	0.03–11.59
Melanoma	1	0.33	2.96	0.04–16.47
Esophagus	1	0.15	6.47	0.08–35.98
Breast	1	0.02	35.11	0.46–195.34
Females				
Breast	9	5.10	1.76	0.81–3.35
Colorectal	5	1.64	3.03	0.98–7.08
Lung	1	0.82	1.21	0.02–6.75
Corpus uteri	1	0.81	1.23	0.02–6.86
Melanoma	5	0.53	9.32	3.01–21.76‡
Thyroid	1	0.86	1.15	0.02–6.40
Kidney	1	0.32	3.12	0.04–17.36
Head-neck	1	0.28	3.56	0.05–19.79
Gallbladder	1	0.18	5.46	0.07–30.39

Marchegiani G et al, CGH 2015

IPMNs follow-up: costs

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Eur Radiol
DOI 10.1007/s00330-016-4377-4

HEPATOBILIARY-PANCREAS

Pancreatic MRI for the surveillance of cystic neoplasms: comparison of a short with a comprehensive imaging protocol

Raffaella Maria Pozzi-Mucelli[1] · Irina Rinta-Kiikka[2] · Katharina Wünsche[3] · Johanna Laukkarinen[4] · Knut Jørgen Labori[5] · Kim Ånonsen[6] · Caroline Verbeke[7,8] · Marco Del Chiaro[9] · Nikolaos Kartalis[1]

498 patients

↓

Same accuracy even in Inter-observer analysis

↓

1.8 milion USD saved

- It Reduces the costs of surveillance.
- It can´t be used "alone"
- It can´t be recommended yet

IPMNs: assesment of resection margins

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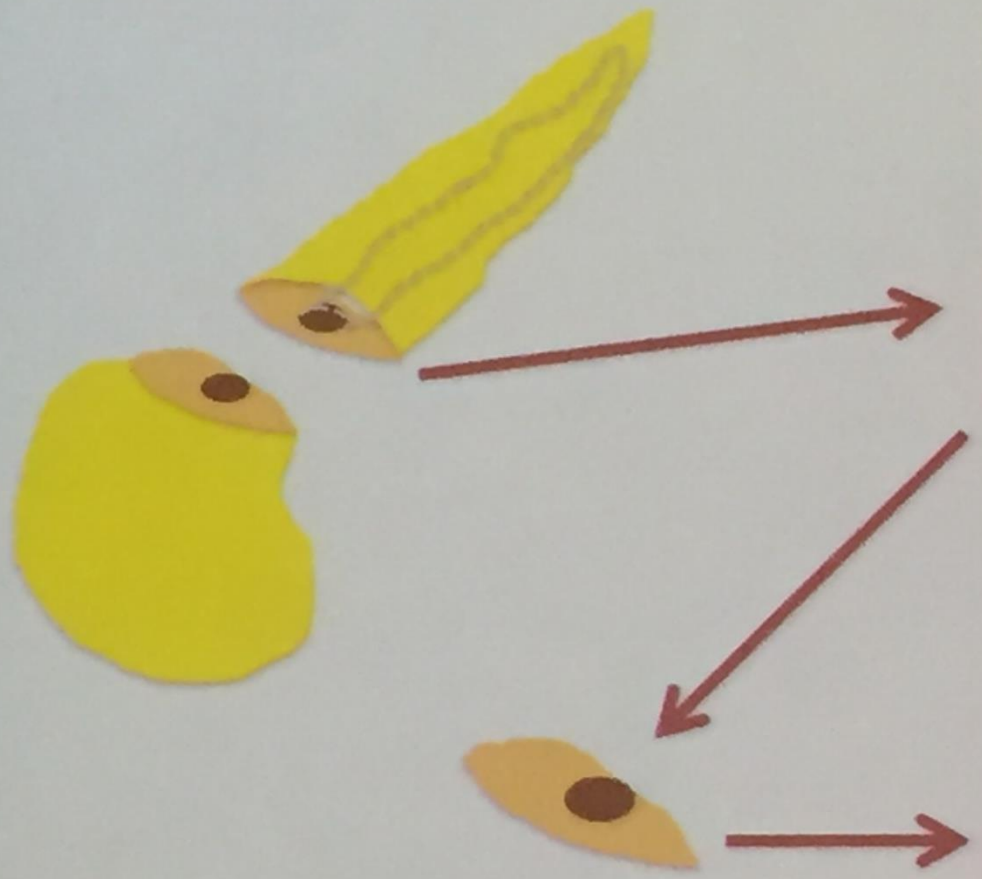

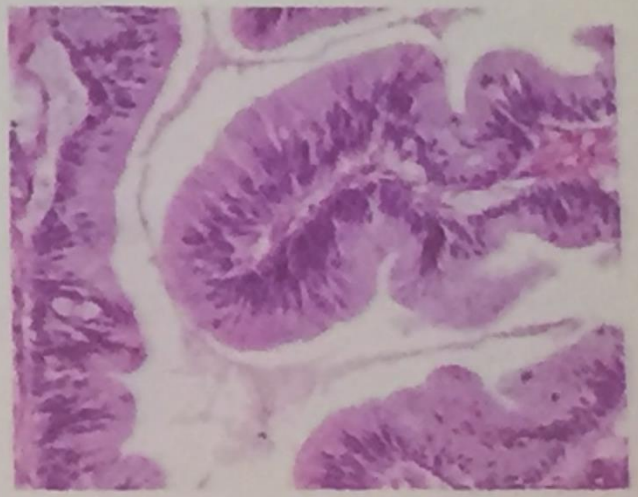

- Low-grade dysplasia
- Medium-grade dysplasia
- High-grade dysplasia
- Denuded duct

Del Chiaro M et al. DLD 2013

IPMNs: assesment of resection margins

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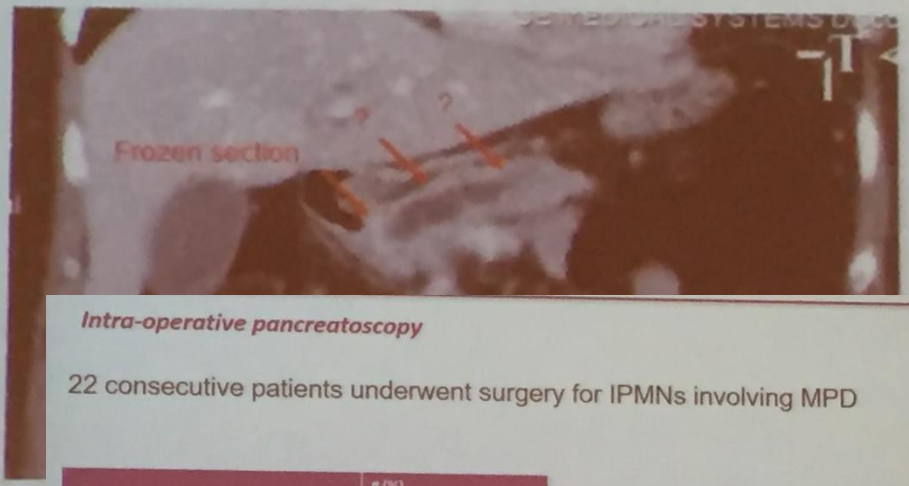
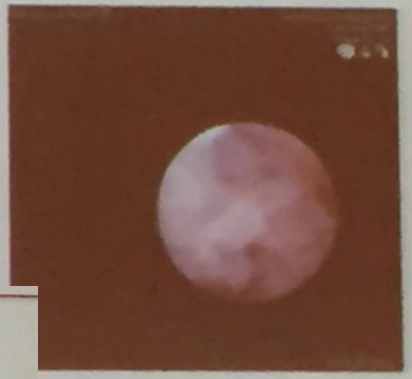
Intra-operative pancreatoscopy





Intra-operative pancreatoscopy

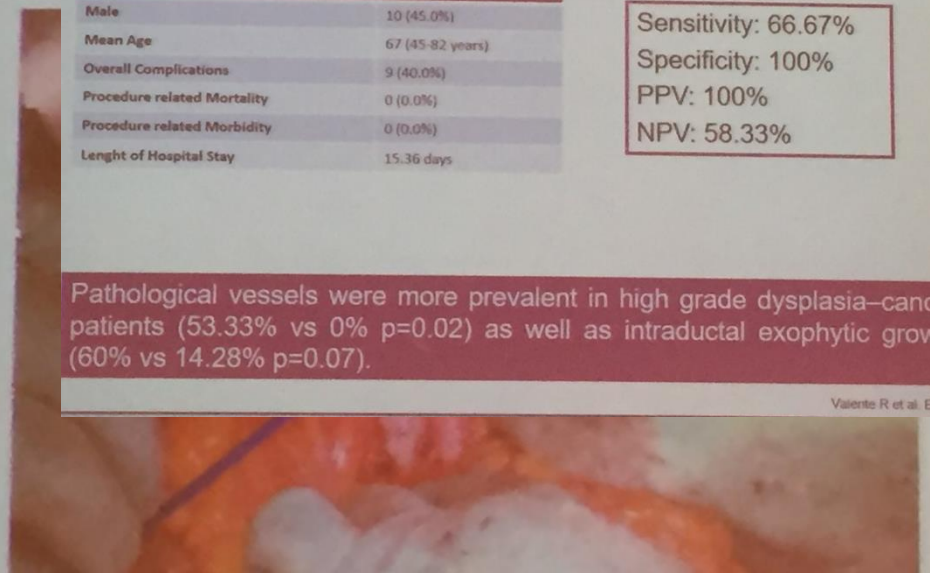
22 consecutive patients underwent surgery for IPMNs involving MPD

	# (%)
Male	10 (45.0%)
Mean Age	67 (45-82 years)
Overall Complications	9 (40.0%)
Procedure related Mortality	0 (0.0%)
Procedure related Morbidity	0 (0.0%)
Lenght of Hospital Stay	15.36 days

Sensitivity: 66.67%
Specificity: 100%
PPV: 100%
NPV: 58.33%

Pathological vessels were more prevalent in high grade dysplasia–cancer patients (53.33% vs 0% p=0.02) as well as intraductal exophytic growth (60% vs 14.28% p=0.07).

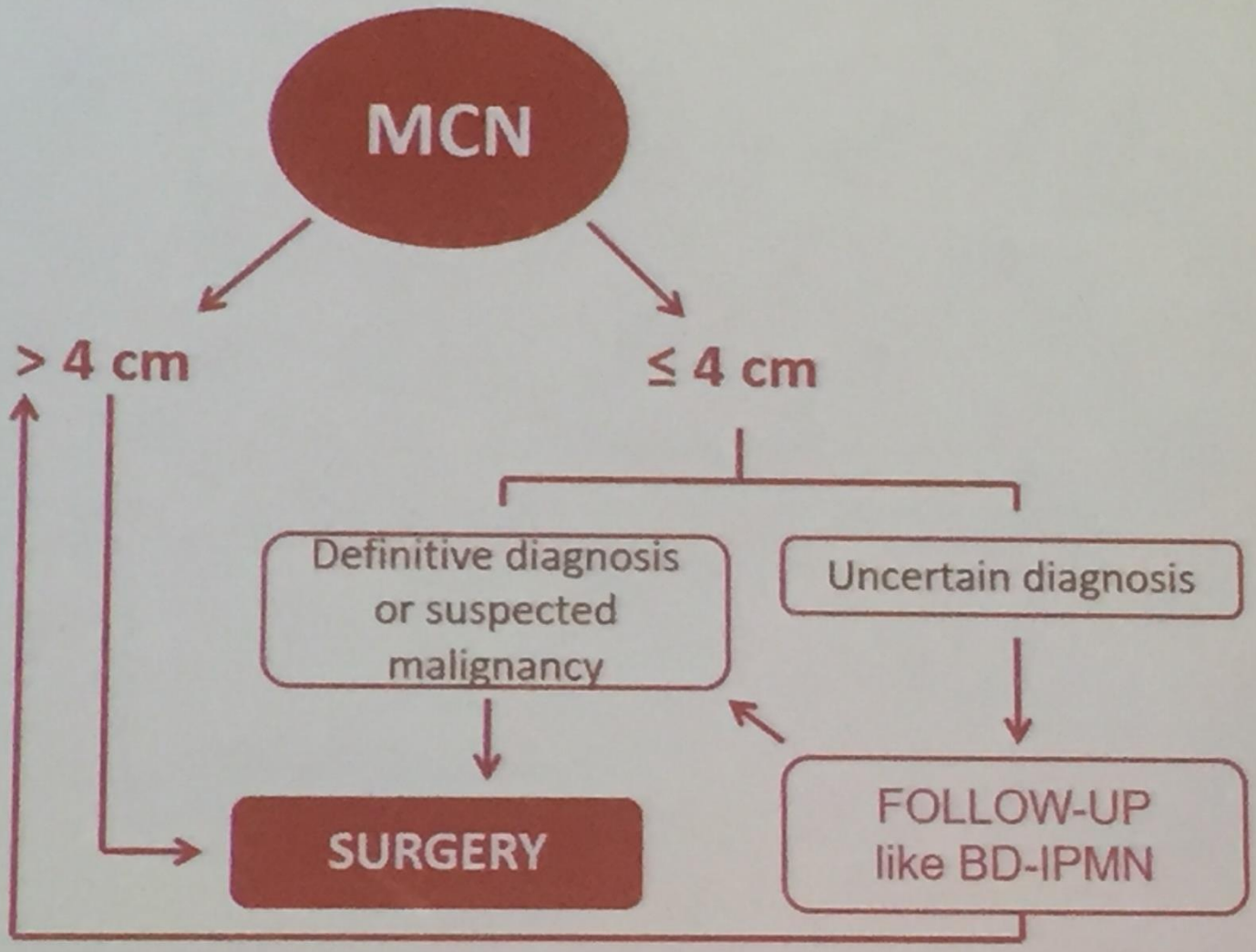
Valente R et al. EPC 201



- ✓ It is not the standard of care
- ✓ Prespective studies are recommended.
- ✓ Pancreatoscopy seems to be more accurate than EUS in assessing duct involvment

Del Chiaro M et al. Am J Gastroent. 2017

MCNs



Del Chiaro M et al, DLD 2013

SCNs

Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of International Association of Pancreatology and European Pancreatic Club and European study Group on Cystic Tumors of the Pancreas

Jais B[1], Rebours V[2], Malleo G[2], Salvia R[2], Fontana M[2], Maggino L[2], Bassi C[3], Manfredi R[3], Moran R[3], Lennon AM[3], Zaheer A[3], Wolfgang C[3], Hruban R[3], Marchegiani G[4], Fernández Del Castillo C[4], Brugge W[4], Ha Y[5], Kim MH[5], Oh D[6], Hirai I[6], Kimura W[6], Jang JY[7], Kim SW[7], Jung W[7], Kang H[8], Song SY[8], Kang CM[9], Lee WJ[9], Crippa S[10], Falconi M[10], Gomatos I[11], Neoptelomos J[11], Milanetto AC[12], Sperti C[12], Ricci C[13], Casadei R[13], Bissolati M[14], Balzano G[14], Frigerio I[15], Girelli R[15], Delhaye M[16], Bernier B[16], Wang H[17], Jang KT[18], Song DH[19], Huggett MT[20], Oppong KW[20], Pererva L[21], Kopchak KV[21], Del Chiaro M[22], Segersvard R[22], Lee LS[23], Conwell D[23], Osvaldt A[24], Campos V[24], Aguero Garcete G[25], Napoleon B[25], Matsumoto I[26], Shinzeki M[26], Bolado F[27], Urman Fernandez JM[27], Keane MG[28], Pereira SP[28], Araujo Acuna I[29], Vaquero EC[29], Angiolini MR[30], Zerbi A[30], Tang J[31], Leong RW[31], Faccinetto A[32], Morana G[32], Petrone MC[33], Arcidiacono PG[33], Moon JH[34], Choi HJ[34], Gill RS[35], Pavey D[35], Ouaissi M[36], Sastre B[36], Spandre M[37], De Angelis CG[37], Rios Vives MA[38], Concepcion-Martin M[38], Ikeura T[39], Okazaki K[39], Frulloni L[40], Messina O[40] and Lévy P[4]

Gut 2010

- ✓ SCNs are (always) benign
- ✓ If the diagnosis is clear surgery and follow up are almost never needed
- ✓ In case with unclear diagnosis (olygocystic) follow-up or surgery is recommended
- ✓ In young patients a “mild” follow-up is maybe recommended in order to prevent local complications

The problem of differential diagnosis

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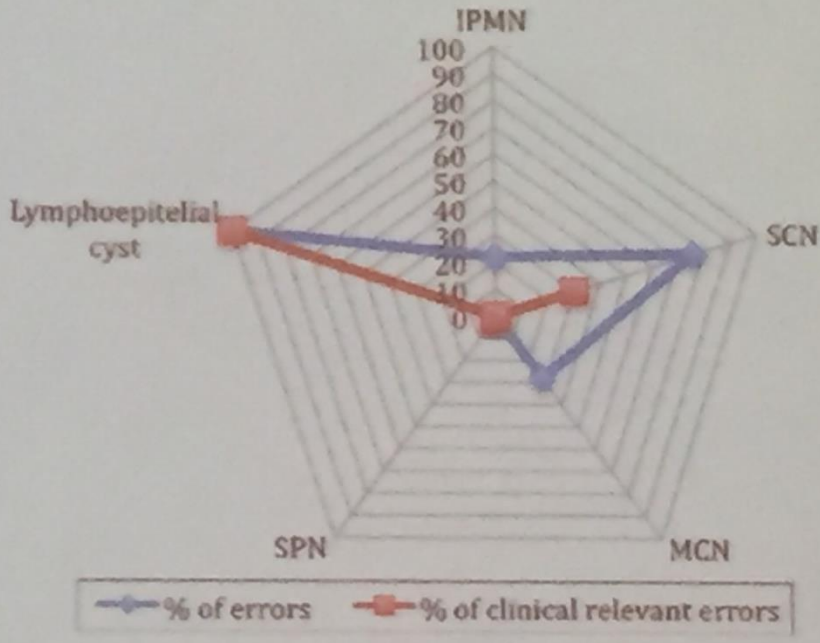
Variable	Correct diagnosis	Incorrect diagnosis	p
Sex			0.7
Male (n = 60)	38 (63.3 %)	22 (36.7 %)	
Female (n = 81)	48 (59.2 %)	33 (40.8 %)	
Mean age (years ± SD)	65.6 ± 13.5	59.2 ± 23.2	0.2
Presence of symptoms			0.6
Yes	62 (59.1 %)	39 (40.9 %)	
No	44 (62.8 %)	26 (37.2 %)	
Kind of symptom			0.5
Abdominal pain	27 (60 %)	18 (40 %)	
Pancreatitis	9 (75 %)	3 (25 %)	
Jaundice	5 (42.8 %)	4 (57.2 %)	
Weight loss	2 (66.7 %)	1 (33.3 %)	
Pancreatic exocrine insufficiency	1 (100 %)	0 (0 %)	
Cholangitis	1 (100 %)	0 (0 %)	
Localization of lesion			<0.001
Head	31 (56.4 %)	24 (43.6 %)	
Body-tail	33 (54.1 %)	28 (45.9 %)	
Diffuse or whole gland	22 (88 %)	3 (12 %)	
Histology			<0.001
IPMN	57 (78.1 %)	16 (21.9 %)	
SCN	8 (24.2 %)	25 (75.7 %)	
MCN	6 (72 %)	7 (28 %)	
SPN	3 (37.5 %)	5 (62.5 %)	
Lymphoepithelial cyst	0 (0 %)	2 (100 %)	
Mucinous neoplasia (IPMN + MCN)			<0.001
Yes	75 (76.5 %)	23 (23.5 %)	
No	11 (25.6 %)	32 (74.4 %)	
Malignancy at histology			0.2
Yes	20 (66.7 %)	10 (33.3 %)	
No	66 (78.7 %)	20 (25.3 %)	
Imaging modality			0.8
CT scan	83 (68.1 %)	39 (31.9 %)	
MRI	54 (63.5 %)	31 (36.5 %)	
EUS + FNA	18 (58.1 %)	13 (41.9 %)	
Single imaging modality			0.9
Yes	30 (61.2 %)	19 (38.8 %)	
No	96 (68.6 %)	44 (31.4 %)	
Period of diagnosis			0.6
2004–2006	19 (54.5 %)	15 (45.5 %)	
2007–2009	21 (61.7 %)	13 (38.3 %)	
2010–2012	47 (63.5 %)	27 (36.5 %)	
Median diameter of cystic lesion (mm ± SD)	55.6 ± 42.7	44.3 ± 38	0.07



Del Chiaro M et al. Ann Surg Oncol 2014

Differential diagnosis

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State of the Art

Diagnosis: MRI, CT-scan, EUS (+/-FNA)

Follow-up: MRI (EUS?)

New technologies

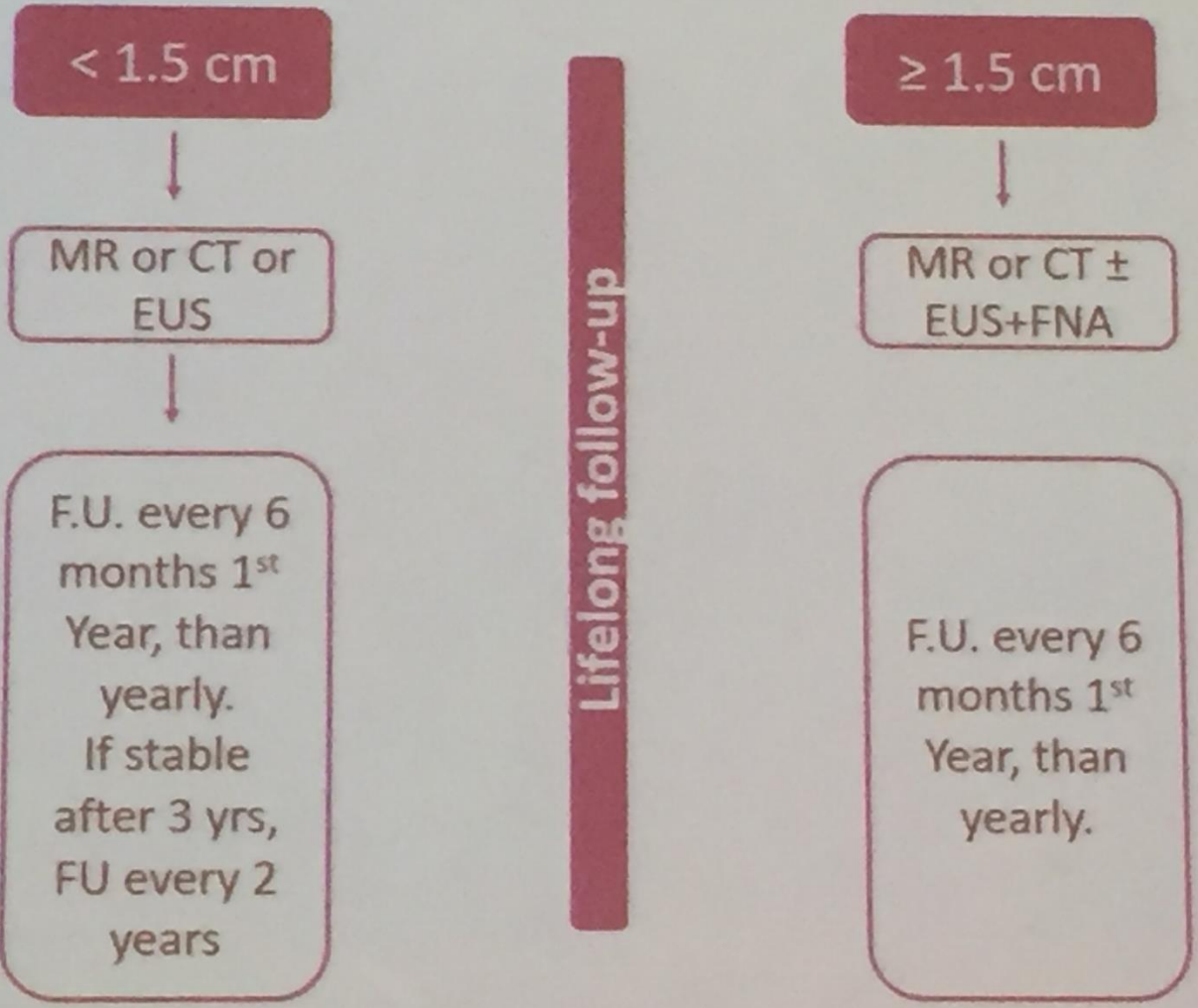
Pancreatoscopy

Confocal laser microscopy

Enucleation

Del Chiaro et al, 2013

Undefined small PCNs



Revision of the European Guidelines 2017, unpublishe

Conclusions

- ✓ The current European Guidelines are safe and trustable.
- ✓ The new guidelines will (hopefully) improve the clinical practice in the management of PCNs.
- ✓ New data coming from large multi-institutional studies (i.e. European Study Group on Cystic Tumors of the Pancreas) are increasing the level of evidence in this field.
- ✓ The level of evidence in PCNs management remain low. "Pure" evidence based guidelines can be dangerous and the expert opinion remains an important guide for clinicians.
- ✓ More work (all together) remains the only way to improve our knowledge in this crucial and complicated topic

EPC 2017

Budapest, 29th June 2017

NEOADJUVANTS IN PANCREATIC CANCER

Prof. Claudio Bassi FRCS, FACS, FEBS
The Pancreas Institute Verona - Italy

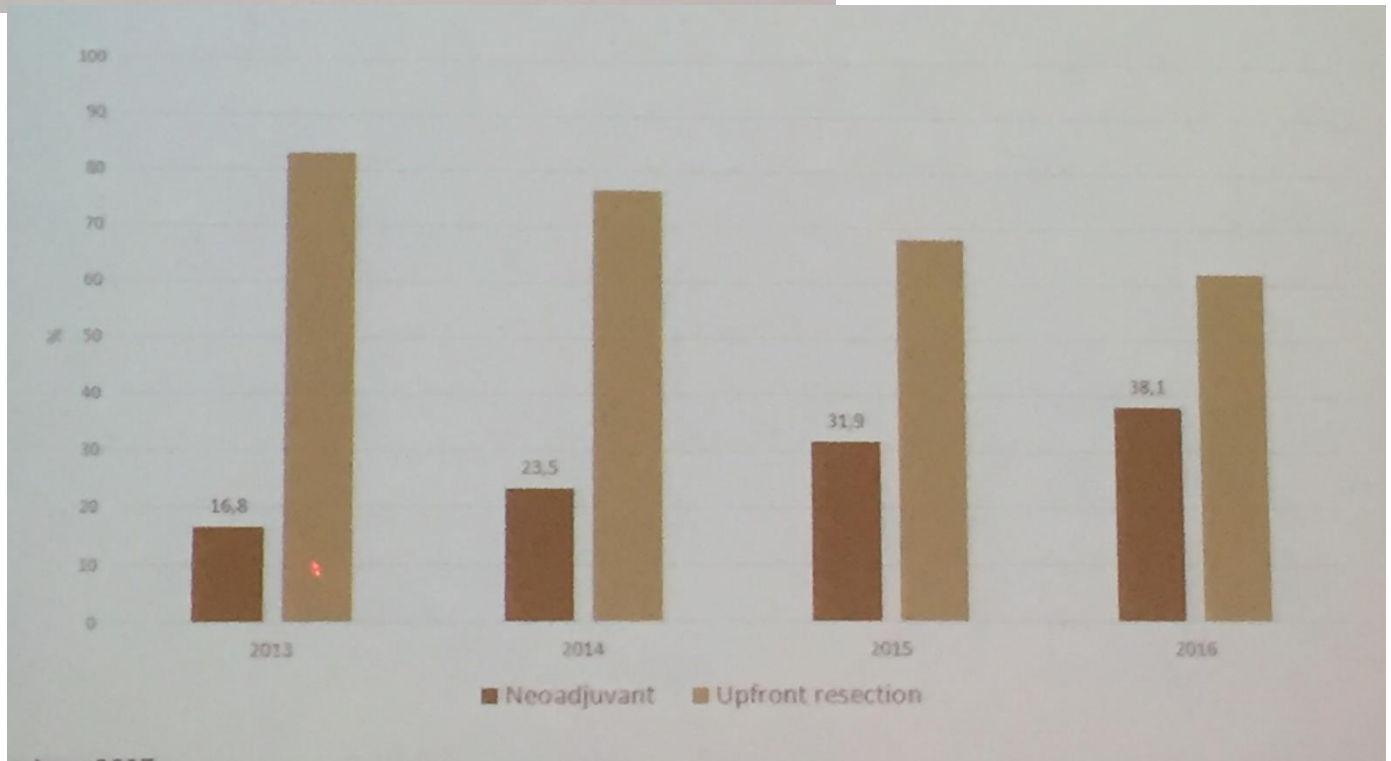
No evidence based data available
Just "clinical experiences" with no RCT

The Verona Experience 1

422 patients undergoing pancreatic resection for PDAC (2013-2015)

UPFRONT SURGERY 318 (75.4%)

NEOADJUVANT THERAPY 104 (24.6%)



104 (65%) resected out of 162 post Neo ADJ explorations

1

Confounding factors on re staging:

- Inter-observer difference in interpretation
- **Neoadjuvant chemotherapy**

Radiological and Surgical Implications of Neoadjuvant Treatment With FOLFIRINOX for Locally Advanced and Borderline Resectable Pancreatic Cancer

Cristina R. Ferrone, MD, Giovanni Marchegiani, MD,* Theodore S. Hong, MD,† David P. Ryan, MD,‡ Vikram Deshpande, MD,‡ Erin I. McDonnell,‡ Francesco Sabbatino, PhD,* Daniela Dias Santos, MD,* Jill N. Allen, MD,‡ Lawrence S. Blaszkowsky, MD,‡ Jeffrey W. Clark, MD,‡ Jason E. Faris, MD,‡ Lipika Goyal, Andrew X. Zhu,*

NAT was associated with smaller tumor size at gross pathology (23 vs 28 mm), and lower rates of lymphovascular (73.1% vs 96.9%), perineural (80.8% vs 98.1%) and peripancreatic fat invasion (71.2% vs 91.2%) all p≤0.001

Size	15 mm (15-30 mm)
Neural invasion	[illegible]
Vascular/lymphatic invasion	72 (69.2%)
[illegible]	63 (60.6%)
LNR	0.04 (0-0.11)
R0	65 (62.5%)

R1 resection was associated with higher rate of nodal involvement (p = 0.017), vascular invasion and neuronal invasion (p = 0.03 and p = 0.047)

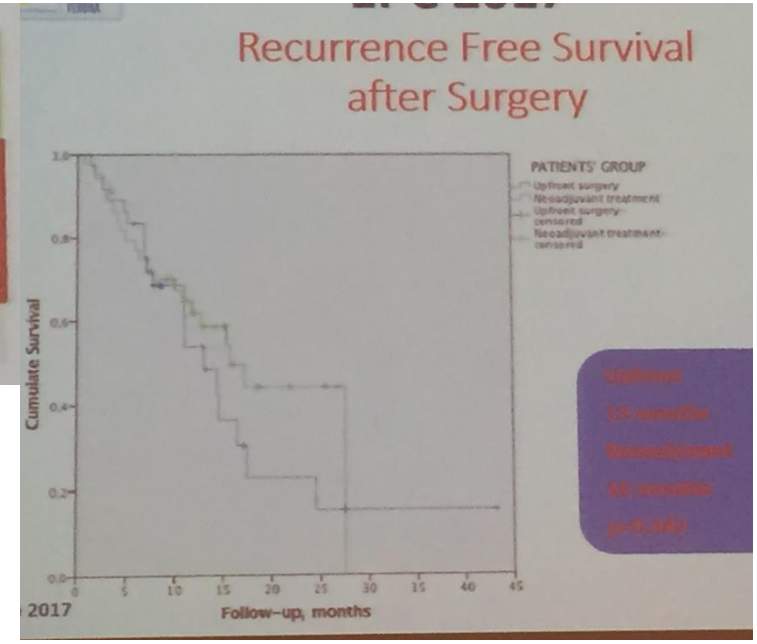
In the 113 BR the resection rate was 73% (64% R0)

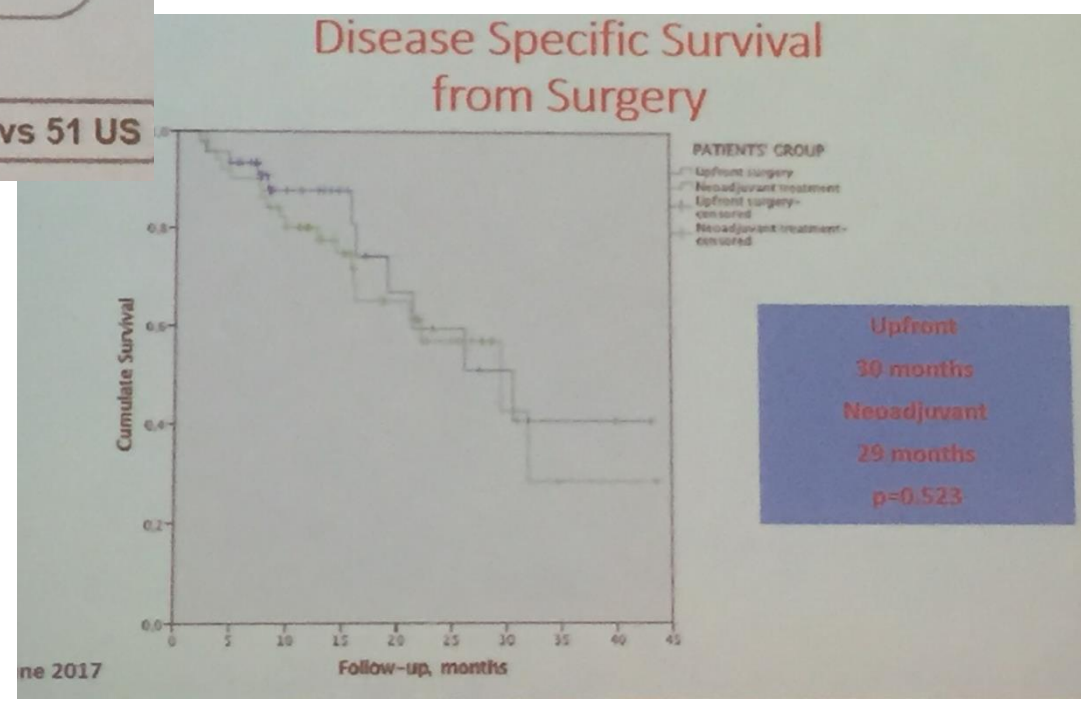
VARIABLE	UPFRONT SURGERY 318 (75,4 %)	NEOADJUVANT THERAPY 104 (24,6 %)	p-value
Median n° harvested lymph nodes	42 (11 – 119)	41 (10 – 80)	0,711
Median n° positive lymph nodes	4 (0 – 34)	1 (0 – 18)	0,000
Median lymph node ratio	0,09 (0,00 – 0,59)	0,03 (0,00 – 0,42)	0,000

Propensity score matching using as variables:

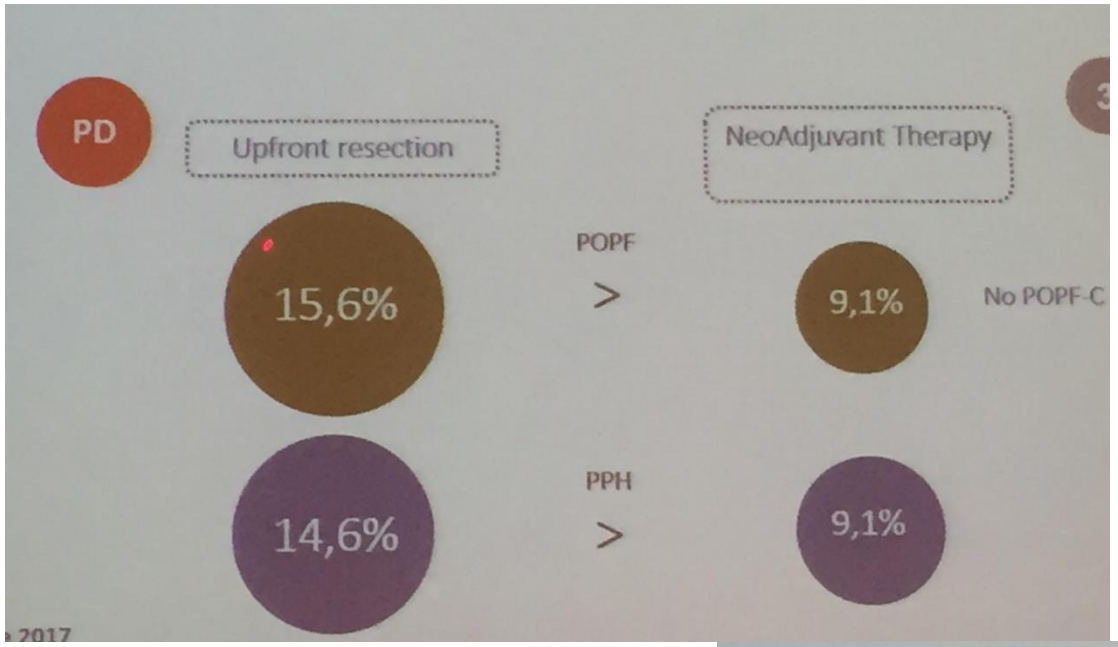
-resectable/BR
-Age
-Size
-Ca19.9
-Adjuvant chemotherapy

51 NAT vs 51 US





Therefore the neoadjuvant group had less complications. But the average complication burden was higher in the neoadjuvant group.



EPC 2017

Take Home messages:

- **The NAT perspective is more and more frequent despite the lack of EB data coming from RCT**
- According to our experience so far in the NAT group there was a **higher N0 rate**
- Although not significant, we found a difference in **OS** (from diagnoasis) between the NAT and US groups. To better assess this possible differences longer FU is needed
- After resection the NAT group had **less complications** than the US group. But when complicated the NAT had a **higher ACB**

E·P·C

49th Meeting of European Pancreatic Club in 2017

What is the optimal treatment for borderline resectable pancreatic cancer?

- A multi-institutional analysis in the Japanese Society of Pancreatic Surgery-

Y. Nagakawa[1], Y. Hosokawa[1], Y. Sahara[1], Y. Murakami[2], H.Yamaue[3], S. Satoi[8], T. Fujii[9], H. Unno[4], M. S. Isaji[5], I. Endo[6], M. Sho[7], Y. Hijikata[1], C. Takishita[1], K. Kasuya[1], K. Katsumata[1], T. Ohta[10], T. Nagakawa[10], A. Tsuchida[1].

1. Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University, Tokyo
2. Department of Surgery, Division of Clinical Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima
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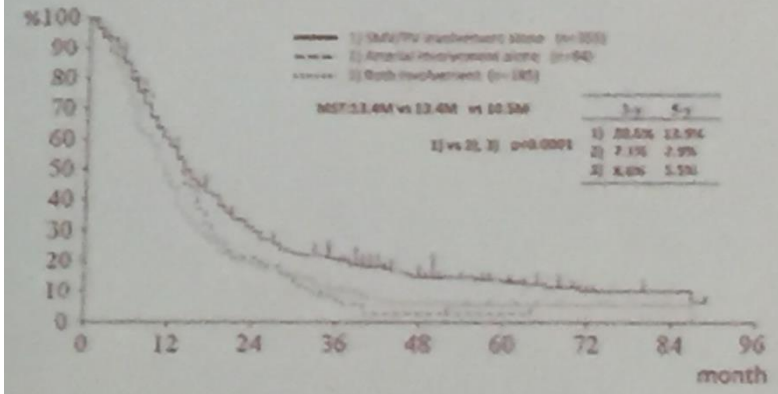
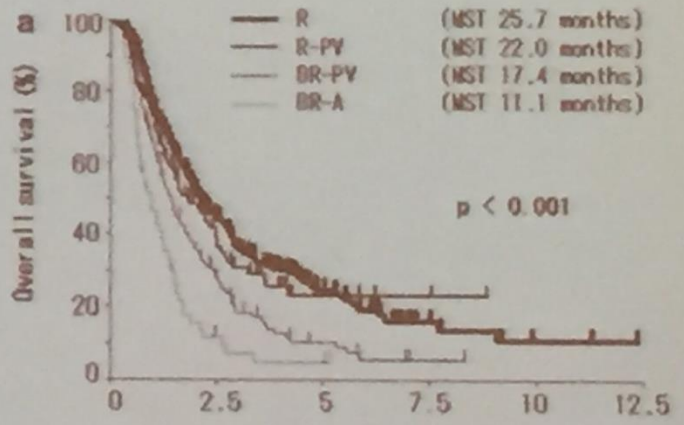
6. Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Yokohama
7. Department of Surgery, Nara Medical University, Nara
8. Department of Surgery, Kansai Medical University, Osaka
9. Department of Surgery and Science, Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama, Toyama
10. Department of Gastroenterological Surgery, Kanazawa University Graduate School of Medical Science, Kanazawa

BR-PV has a better prognosis than BR-A following upfront surgery.

Clinical features and treatment outcome of borderline resectable pancreatic head/body cancer: a multi-institutional survey by the Japanese Society of Pancreatic Surgery



National Comprehensive Cancer Network Resectability Status for Pancreatic Carcinoma Predicts Overall Survival



BR-PV: patients with only portal or superior mesenteric vein involvement.
BR-A: patients with arterial involvement (BR-A).

BR-PV: R0 resection seems to be possible without preoperative treatment.
BR-A: It is difficult to achieve R0 resection without preoperative treatment .

Clinical questions

1) For BR-PV patients, neoadjuvant therapy improves survival outcome or not?

2) In the treatment for BRPC, combining radiotherapy as neoadjuvant therapy is effective or not?

3) What is the prognostic factor of patients who underwent neoadjuvant therapy?

➡ These factors may indicate the optimal management for BRPC.

Aim

To clarify appropriate management for BRPC in analysis dividing patients with BR-PV and BR-A.

Material and Methods

Total 63 Japanese institutions participated to this study.

Patients receiving treatment for BRPC between 2011 and 2013 were registered in common database.

BRPC was defined according to the Japanese general rules for the study of pancreatic cancer.

Definition: Resectability status

Japanese General Rules for the Study of Pancreatic Cancer The 7th edition

Resectable (R)

There is no contact of tumor with SMV/PV, or contact/infiltration is seen at less than 180 degrees, but no obstruction is confirmed.

Clear adipose tissue was observed between SMA, CA, CHA and the tumor, and contact and invasion was not observed.

Borderline resectable (BRPC)

BR-PV

Although there is no contact and infiltration of tumor with SMA, CA, contact with the SMV / PV at 180° or more and Invasion or obstruction is observed, and its range does not exceed the duodenum lower border

BR-A

SMA or CA has contact / infiltration of less than 180° with tumor, but no stenosis / deformity.

Tumor contact or invade to CHA, although there is no contactor invasion to PHA or CA.

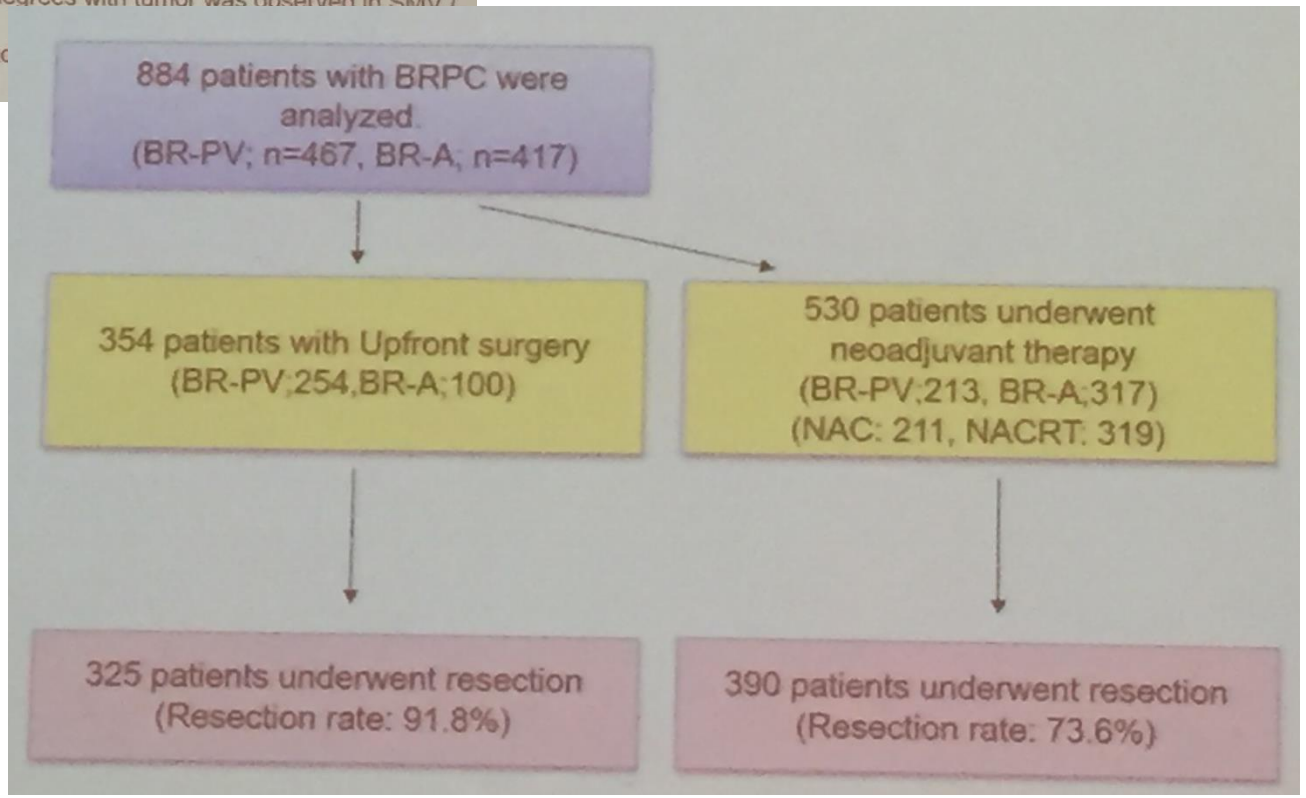
*Even though invasion to CA or CHA,DP-CAR is possible

Unresectable locally advanced (UR-LA)

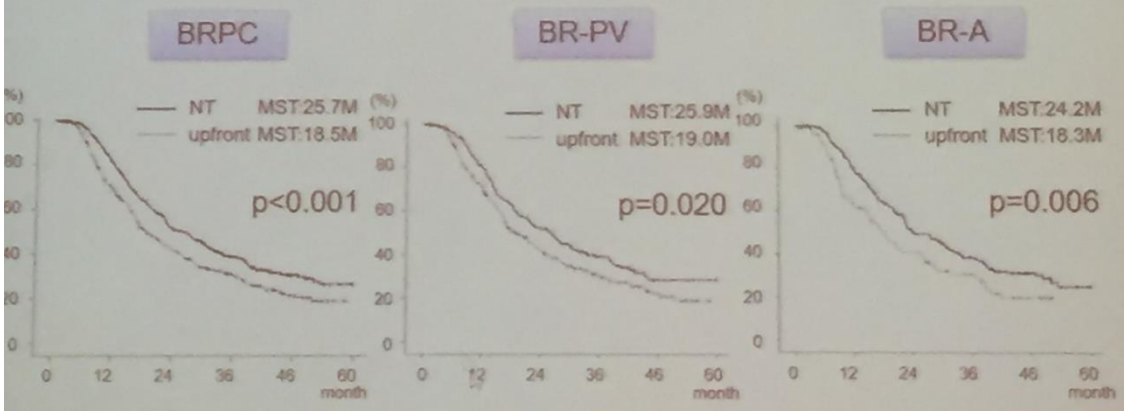
Contact / invasion or obstruction of more than 180 degrees with tumor was observed in SMV / PV, and its range exceeds the lower duodenum.

Tumor contact or invade to CHA and contact or invac

Tumor contact or invade to the aorta.

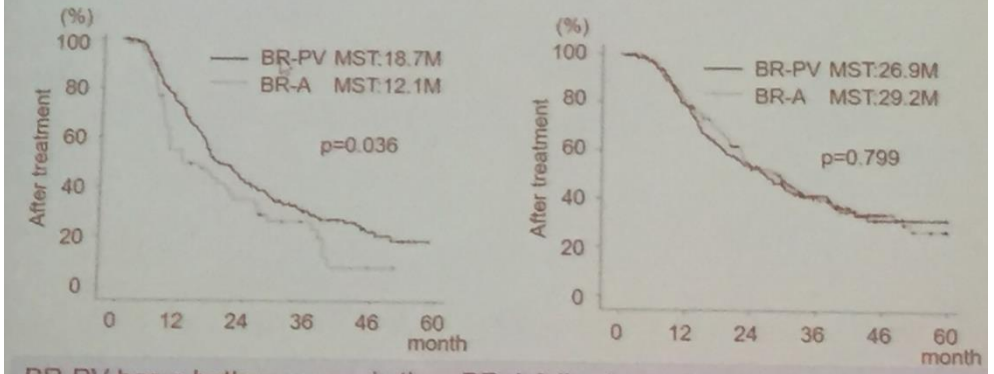


Overall survival
(Upfront Surgery vs Neoadjuvant therapy)



Neoadjuvant therapy significantly improved overall survival in either BR-PV and BR-A.

Overall survival
(Pancreatic head cancer)



BR-PV has a better prognosis than BR-A following upfront surgery.
However, there was no difference in patients with neoadjuvant therapy.

Neoadjuvant therapy and treatment effectiveness (NACRT vs NAC)

	Total (n=530)	NAC (n=211)	NACRT (n=319)	p value
Response rate				
CR/PR	122 (23.0%)	51 (24.2%)	71 (22.3%)	0.609
SD/PD	408 (77.0%)	160 (75.8%)	248 (77.7%)	
Post-NT CA19-9 levels (U/ml)				
≥ 40	306 (57.7%)	121 (57.3%)	185 (58.0%)	0.883
< 40	224 (42.3%)	90 (42.7%)	134 (42.0%)	
Resection rate				
Resection	390 (73.6%)	170 (80.6%)	220 (69.0%)	0.003
Non-resection	140 (26.4%)	41 (19.4%)	99 (31.0%)	

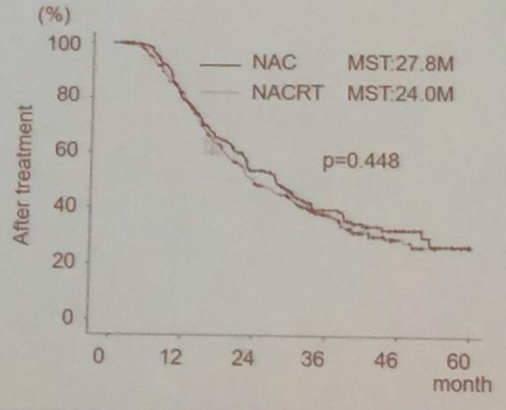
Resection rate of NACRT was significantly lower than that of NAC.

Neoadjuvant therapy and treatment effectiveness (NACRT vs NAC)

	Total (n=530)	NAC (n=211)	NACRT (n=319)	p value
Curability				
R0	329 (84.4%)	140 (82.4%)	189 (85.9%)	0.338
R1	61 (15.6%)	30 (17.6%)	31 (14.1%)	
Lymph node metastasis				
negative	192 (49.2%)	53 (31.2%)	139 (63.2%)	<0.001
positive	198 (50.8%)	117 (68.8%)	81 (36.8%)	
Portal vein involvement				
negative	240 (61.5%)	95 (55.9%)	145 (65.9%)	0.044
positive	150 (38.5%)	75 (44.1%)	75 (34.1%)	
Stage				
stage 0-IB	43 (11.0%)	8 (4.7%)	35 (15.9%)	<0.001
stage IIA-IV	347 (89.0%)	162 (95.3%)	185 (84.1%)	

Lymph node metastasis rate, portal vein involvement rate, pathological stage in patients with NACRT was significantly lower than these of NAC.

The Neoadjuvant therapy for BRPC patients NAC vs NACRT



There was no significant difference between NACRT and NAC in overall survival.

Post-NT, operative serum albumin and CA19-9 level are a predictive biomarker for prognosis. R0 is also needed to improve survival.

Prognostic factors in patients with neoadjuvant therapy

	Univariate analysis			Multivariate analysis		
	number of patients	MST (month)	p value	Hazard ratio	95% CI	p value
Neoadjuvant therapy						
NAC	211	27.8	0.448			
NACRT	319	24.0				
Post-NT serum albumin (g/dl)						
≥3.9	251	32.0	<0.001	1.402	1.120-1.756	0.003
<3.9	279	22.5				
Post-NT CA19-9 levels (U/ml)						
≥40	306	38.1	<0.001	0.556	0.440-0.703	<0.001
<40	224	20.0				
Response rate (RECIST)						
PR/CR	122	38.6	<0.001	1.473	1.105-1.963	0.008
SD/PD	408	22.7				

NT: neoadjuvant therapy

Prognostic factor in patients with resection after neoadjuvant therapy

	Univariate analysis			Multivariate analysis		
	number of patients	MST (month)	p value	Hazard ratio	95% CI	p value
Lymph node metastasis						
positive	198	27.5	<0.001	0.696	0.519-0.934	0.016
negative	192	50.5				
Portal vein involvement						
positive	150	27.3	<0.001	0.702	0.524-0.942	0.018
negative	240	39.1				
UICC-stage						
stage 0-IIB	66	36.5	0.002	0.77	0.535-1.108	0.159
stage III-IV	324	24.6				
Curability						
R0	329	36.5	<0.001	0.631	0.438-0.911	0.014
R1	61	22.6				
Post-operative albumin (g/dl)						
≥3.9	195	39.2	0.006	1.387	1.047-1.839	0.023
<3.9	195	27.9				
Post-operative CA19-9 levels U/ml)						
≥40	111	18.4	<0.001	0.366	0.274-0.491	<0.001
<40	279	42.4				
djuvant therapy after resection						
Yes	333	33.3	0.013	0.453	0.299-0.688	<0.001
No	57	19.1				

Conclusion

Neoadjuvant therapy significantly improved survival outcome in either BR-PV and BR-A.

These results suggested that effective neoadjuvant systemic chemotherapy and preoperative nutrition support are important to improve survival outcome for BRPC.

Philipps Universität Marburg

KF0325 DFG

UKGM UNIVERSITÄTSKLINIKUM GIESSEN UND MARBURG

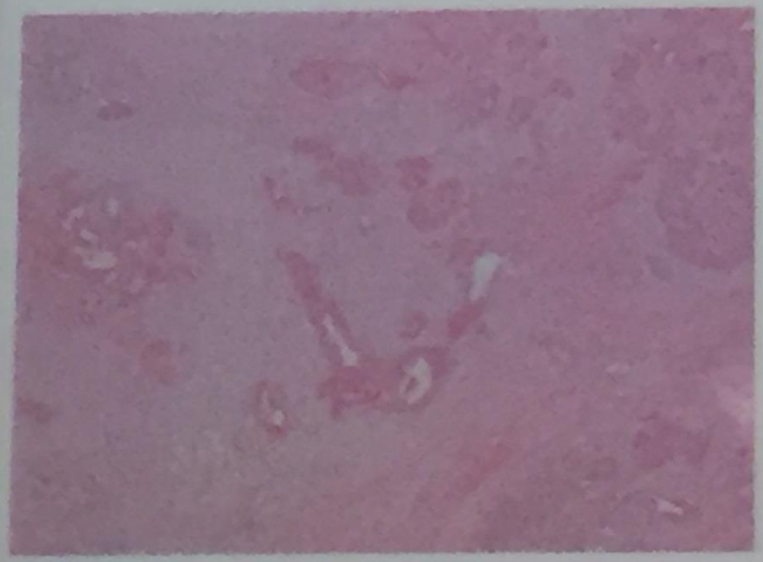
Molecular mechanisms of cancerogenesis and therapeutic targeting in the pancreas

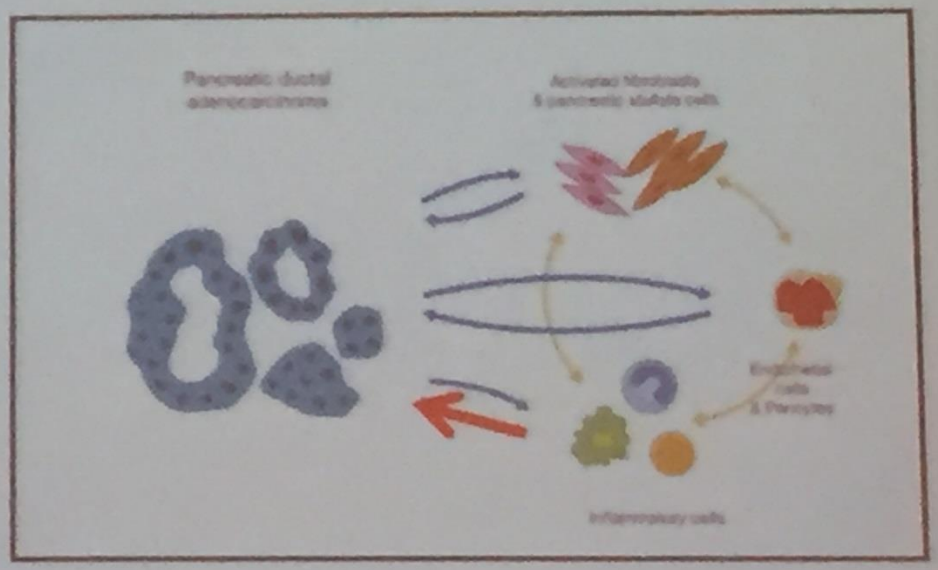
EPC 2017

T.M.Gress
Klinik für Gastroenterologie, Endokrinologie, Stoffwechsel and Infektiologie
Philipps-Universität Marburg

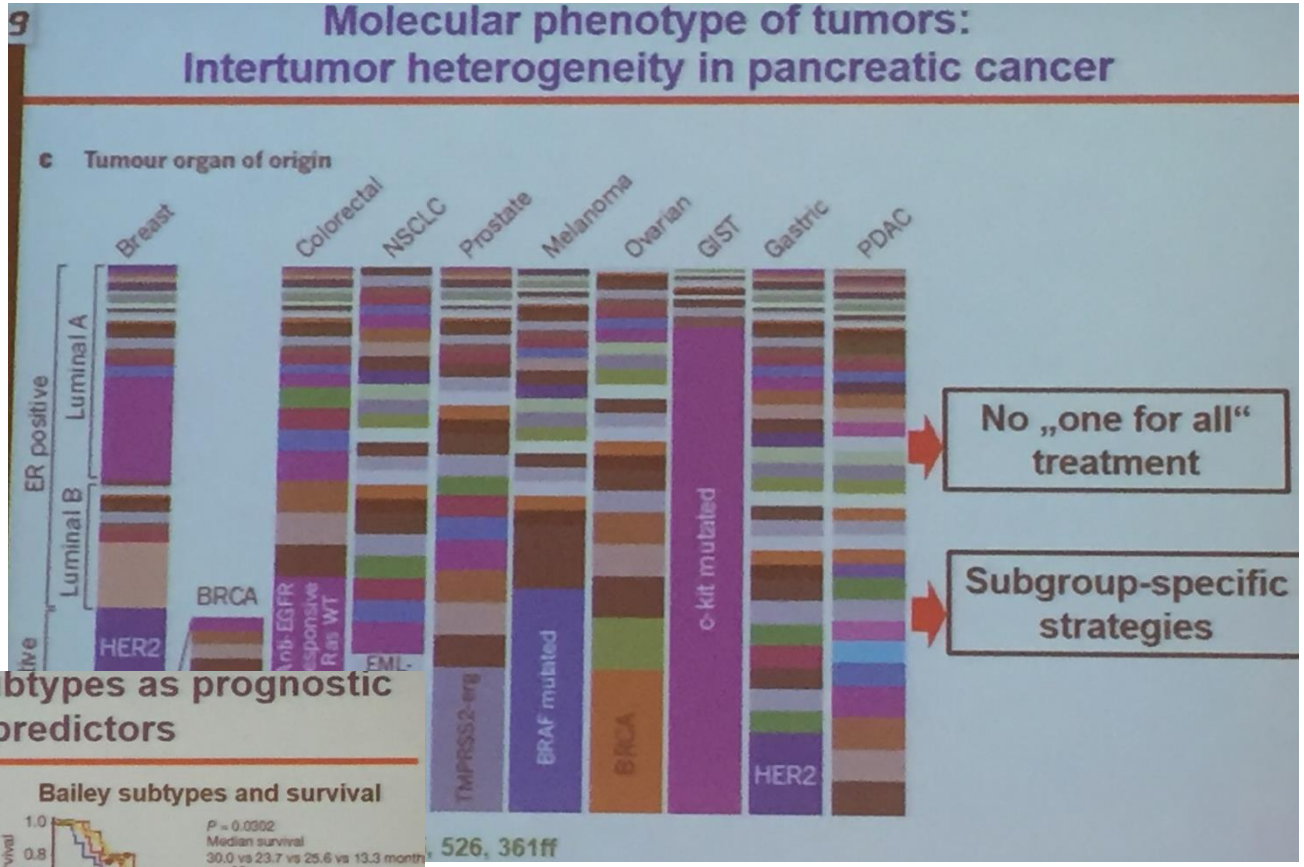
Reasons for the failure of medical treatments in PDAC?

- **intertumor molecular heterogeneity**
- **tumor microenvironment**
  - extensive stromal reaction (desmoplasia)
  - impaired immune defense

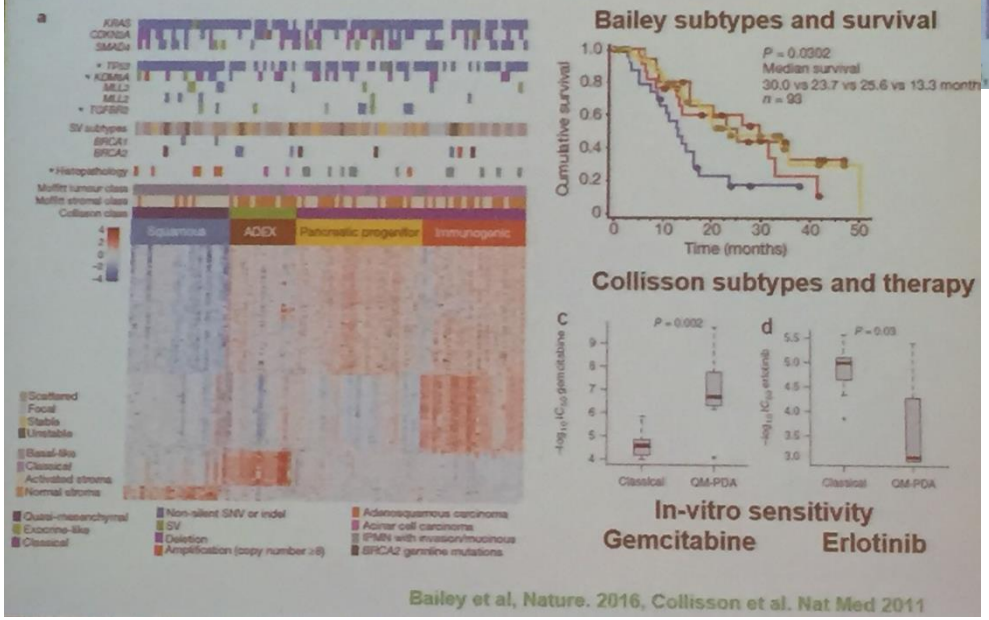




Molecular phenotype of tumors: Intertumor heterogeneity in pancreatic cancer



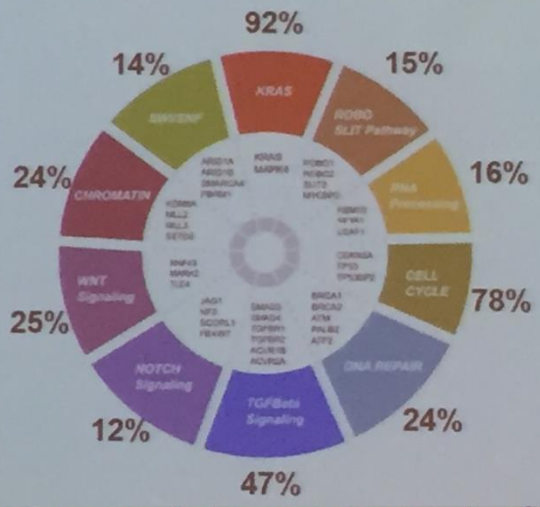
Transcriptional molecular subtypes as prognostic and therapeutic predictors



Bailey et al, Nature. 2016, Collisson et al. Nat Med 2011

Comprehensive integrated genomic analyses of 457 PDAC

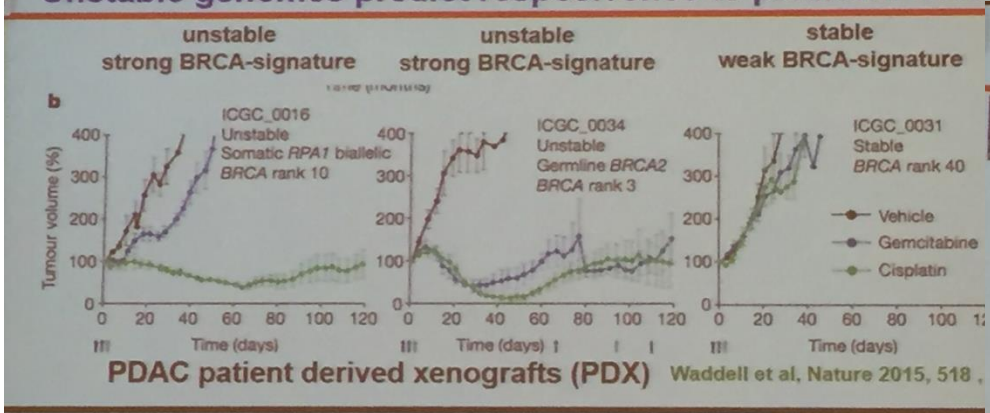
- 32 recurrently mutated genes
- aggregated into 10 molecular mechanisms/pathways



Subgroups of PDAC based on the frequency and distribution of structural rearrangements

4 subtypes: stable, locally rearranged, scattered and unstable

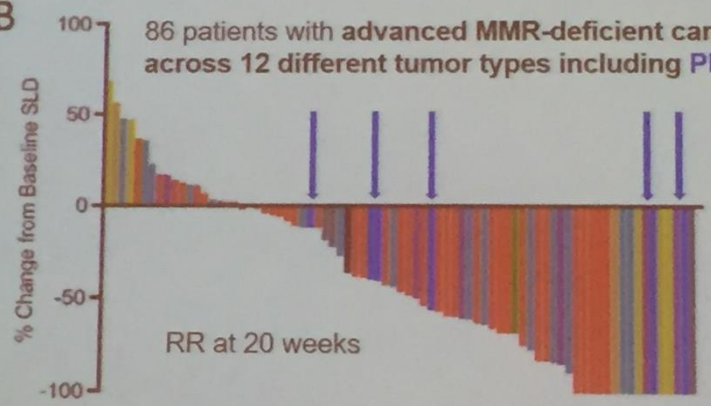
Unstable genomes predict resposivenes to platinum CTX



PDAC patient derived xenografts (PDX) Waddell et al, Nature 2015, 518 ,

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade with pembrolizumab

1% MMR deficiency/ hypermutated genotypes in PDAC
(Humphries et al. Gastroenterol. 2017)



- Objective radiographic responses in 53% of patients and complete responses in 21% of patients
- Response rate for non-CRC solid tumors including PDAC 52%

BRCA2-defective tumors respond to PARP-1 inhibitors

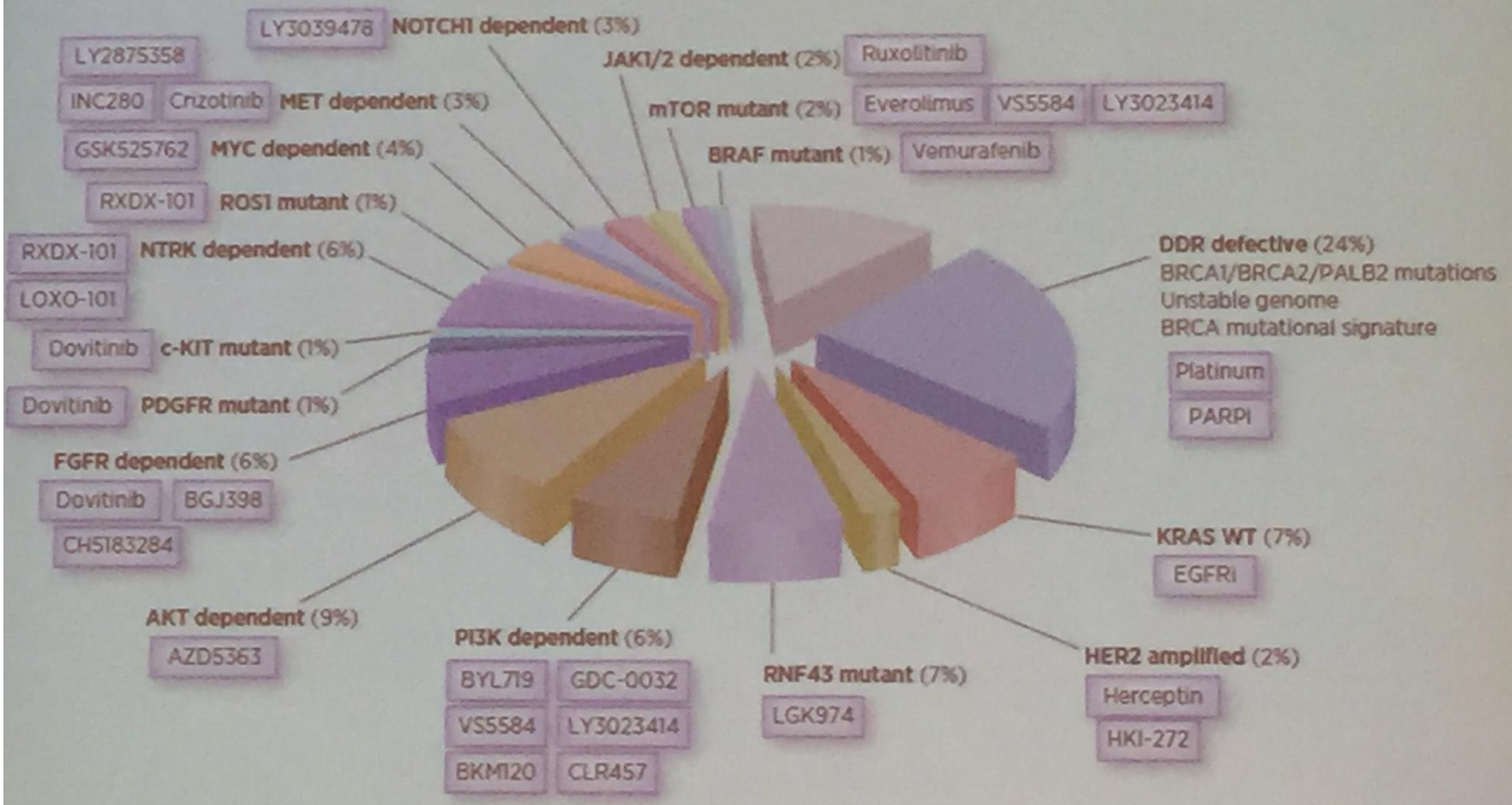
Multicenter Phase II study of **Olaparib monotherapy** in 298 **pretreated patients *BRCA*1/2-mutated tumors (PDAC 3rd line)**

Kaufman B, et al. J Clin Oncol. 2015

Response	Ovar (n = 193)	Breast (n = 62)	Pancreas (n = 23)	Prostate (n = 8)
Tumor Response %	31	13	22	50
SD ≥ 8 wks	40	47	35	25
PD	21	37	39	25

PDAC:
- Med. PFS: 4.6 month
- Med. OS: 9.8 month

Opportunities for personalized therapeutic strategeies based on the PDAC actionable genome



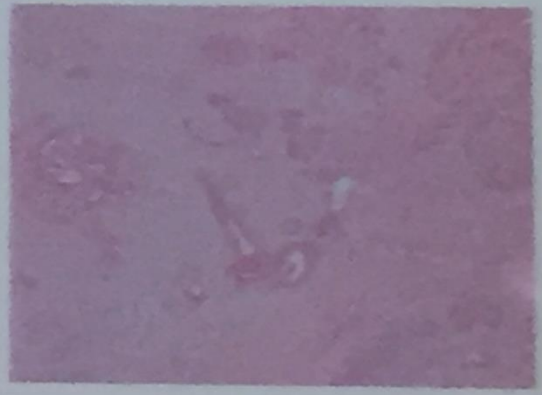
Dreyer et al, Clin Cancer Res; 23(7) April 1, 2017, Waddell et al, Nature 518 , 495ff, 2015, Bailey et al, Nature. 2016

If intertumor heterogeneity is the major reason for treatment failure, then....

- **Why do virtually all PDACs have the same 4 driver mutations kRAS, p53, CDKN2A, SMAD4?**

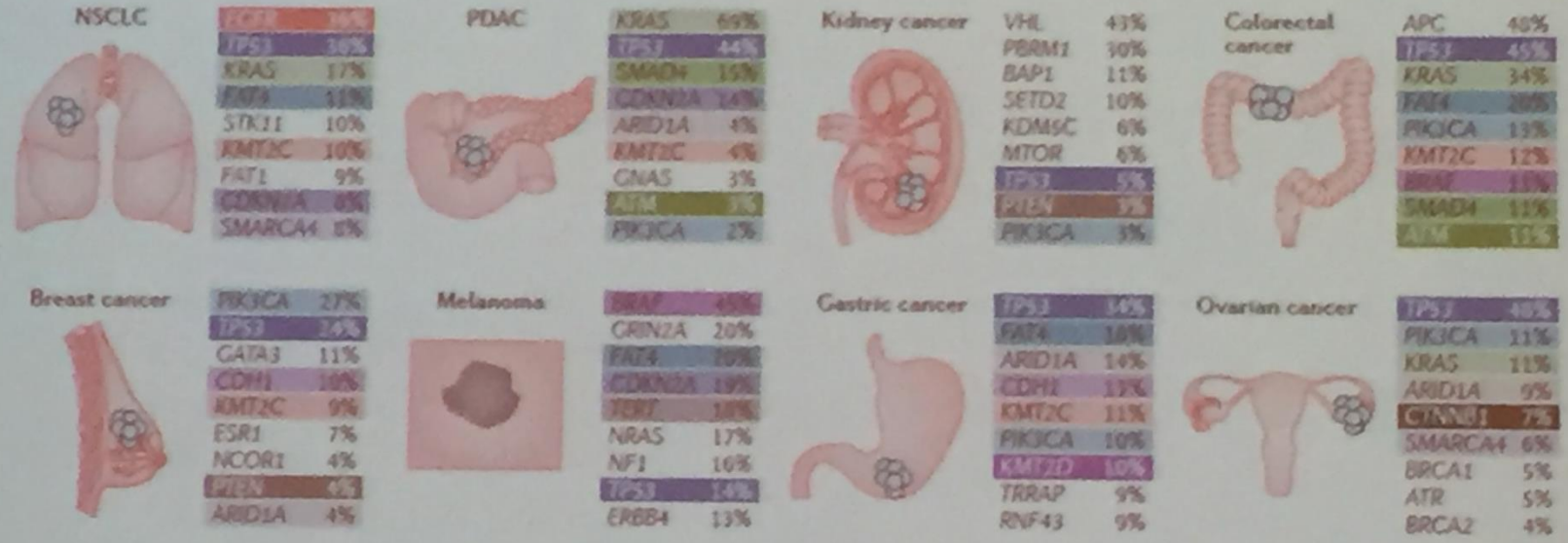
Why do all tumors virtually have the same phenotype?

- Metastases
- Resistance to Radio- and Chemotherapy
- Avascularity
- High degree of desmoplasia
- Strong inflammatory infiltrate



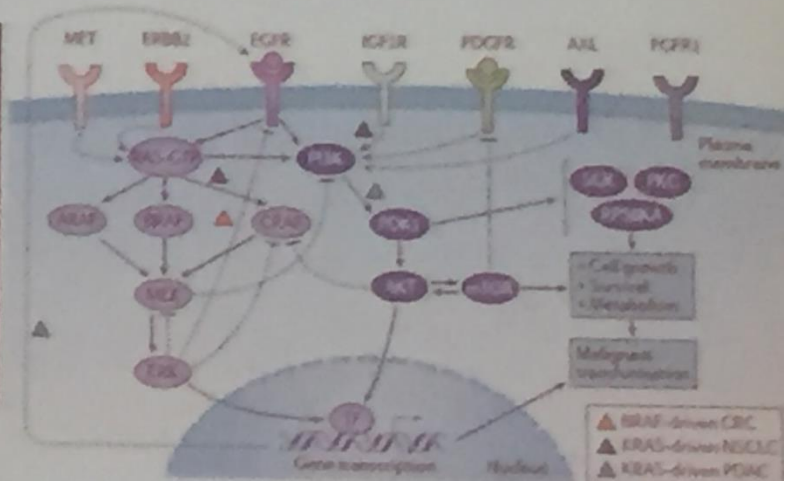
- **Why do other tumor types with mutations in the same driver genes have a different phenotype?**

Effects of driver genes and their inhibitors may differ from in one tumor to the other: *The tissue context matters*



driver gene mutations **exert oncogenic signalling in a tissue-specific manner** including:

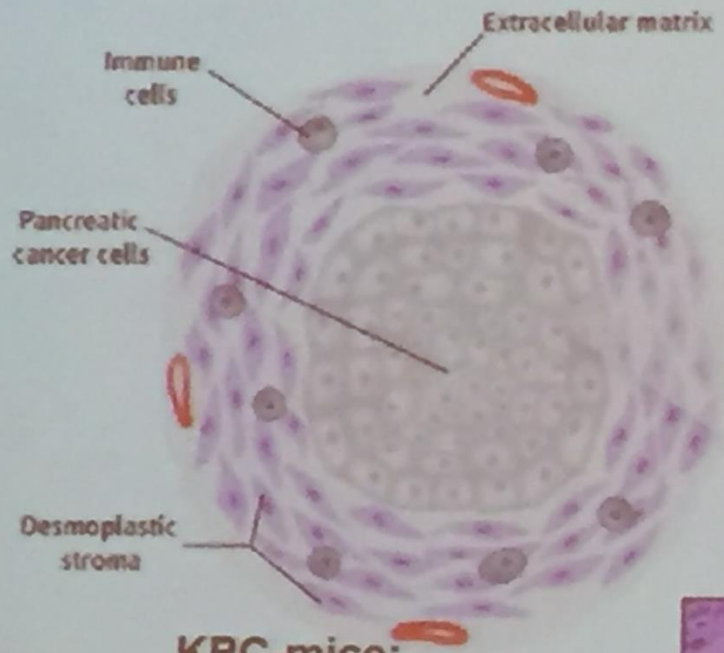
- **feed-back loops**
- **signalling cross-talk**
- **differences in cellular environment**

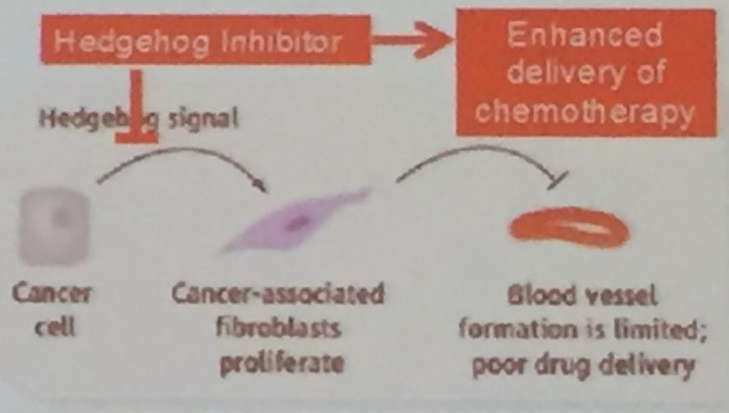


Schneider et al Nature Rev.Cancer, 17, 239, 2017

Tumor stroma as „fortress“ with reduced vascularisation, impaired „drug delivery“ and response to treatment

Olson & Hanahan Science 2009, Olive et al, Science 2009



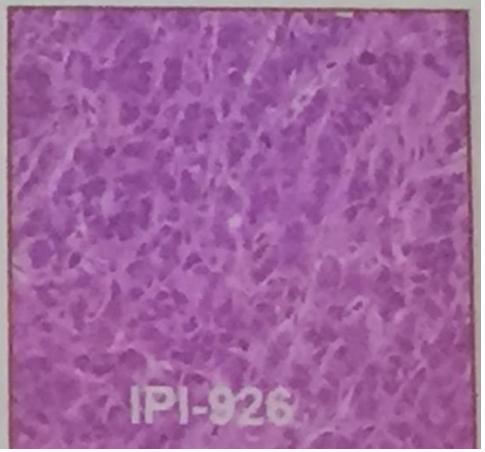


KPC-mice:

SHH-inhibitor IPI-926 depletes stroma

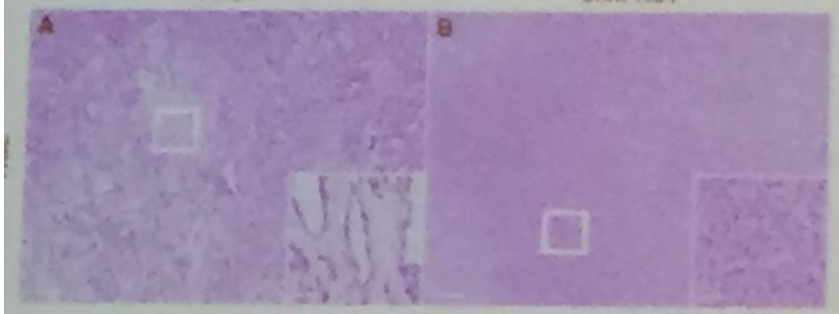
IPI-926 + Gem prolongs survival

IIb clinical trial stopped due to inferiority to Gem alone

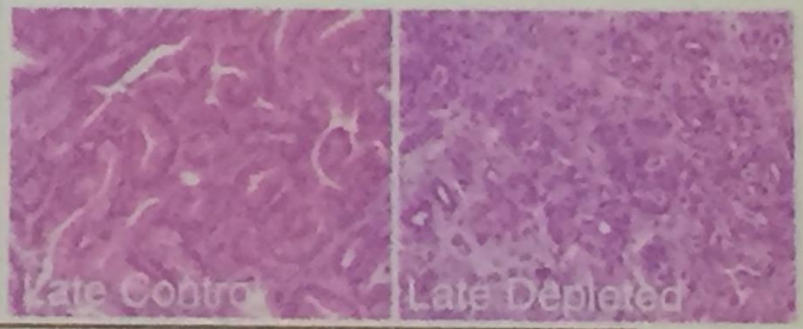


Stroma depletion by genetic ablation of SHH or CAF depletion leads to undifferentiated tumors with decreased survival

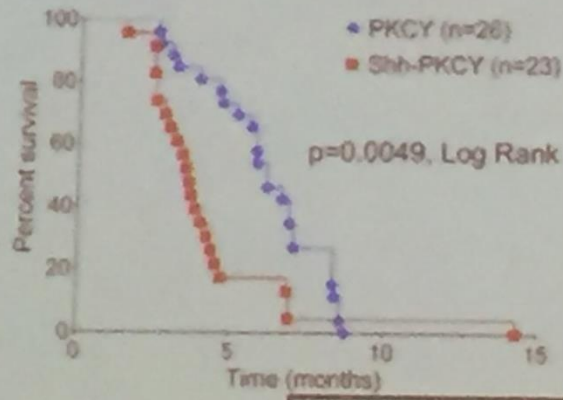
Genetic ablation of SHH in KPC-mice:

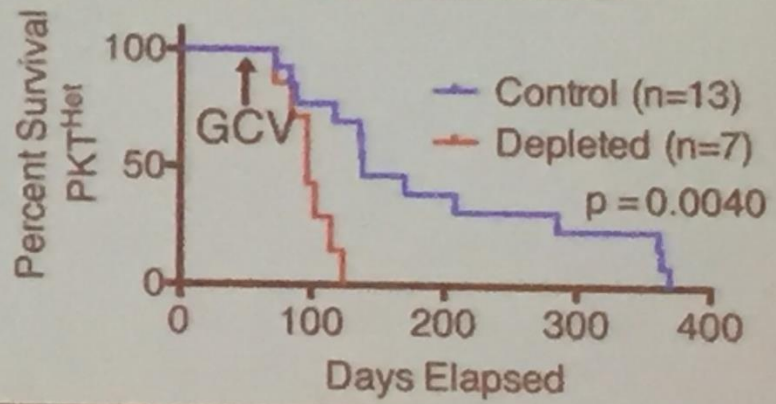


CAF depletion in KTC-mice:



reduced stroma content, **undifferentiated histology**, **EMT**, altered **immune cell** composition, increased **vascularity** and **proliferation**





Tumors develop earlier and **survival is reduced**

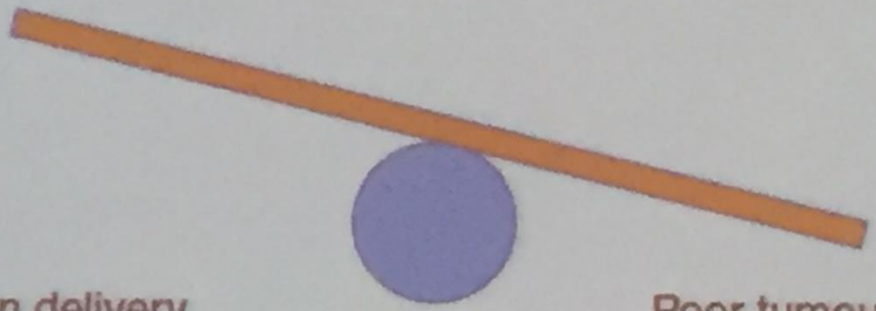
Rhim et al. Cancer Cell 25, 1–13, 2014

Stromal depletion approaches can tip the balance from tumour-suppressive towards tumour-promoting effects

Stromal depletion approaches

Tumour suppressive

Tumour promoting



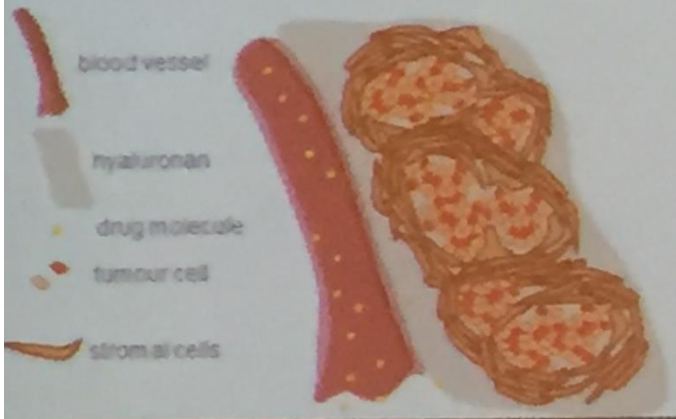
Increased oxygen delivery
Increased drug delivery
Pro-apoptotic effects
Altered immune competence

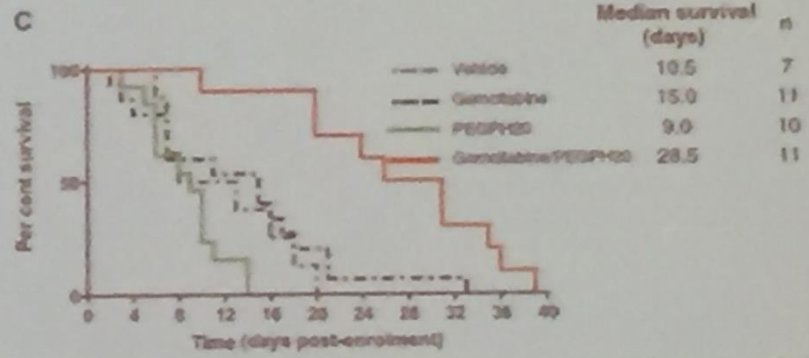
Poor tumour cell differentiaion
Increased EMT
increased Stemmness
Increased Invasion

Neesse A, Algul H, Tuveson DA, Gress TM. Gut 2015;64:1476–1484.

Stroma remodeling to change stroma composition in KPC-mice

Depletion of hyaluronic acid using hyaluronidase (PEGPH20) **reduces interstitial pressure,** increases **intratumoral drug concentration** and **prolongs survival** with Gem

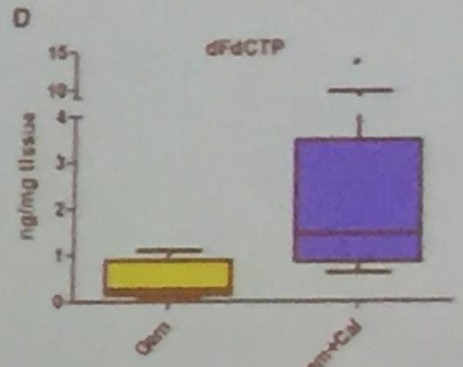




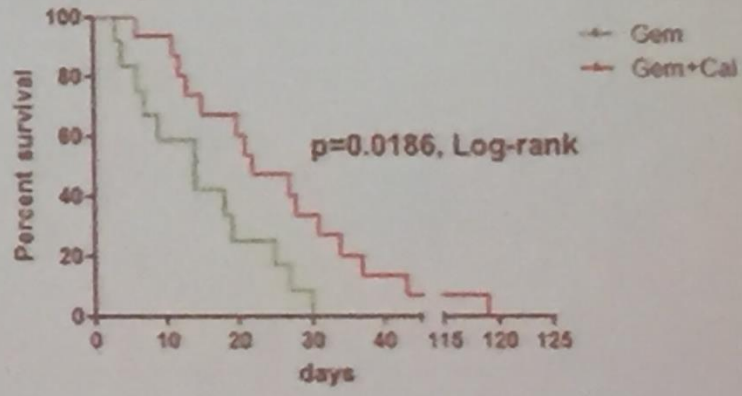
Jacobetz et al Gut 2012, Provencano et. al Cancer Cell 2012

VDR-Ligands drive PSC into a quiescent phenotype and enhances Gem delivery and efficacy

Sherman et al. Cell 159, 80-93, 2014

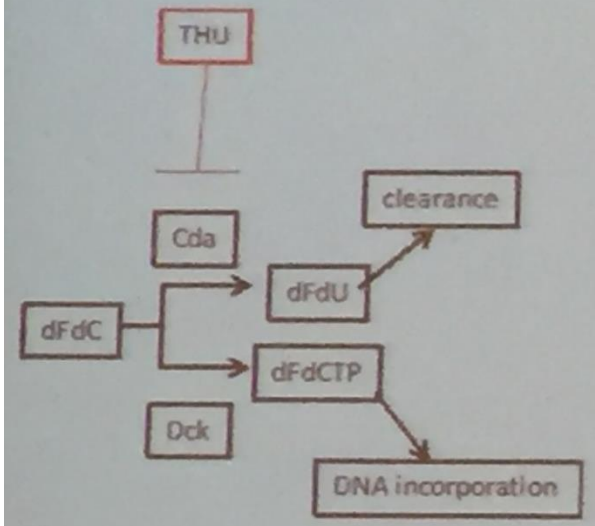


intratumoral active gemcitabine (dFdCTP)



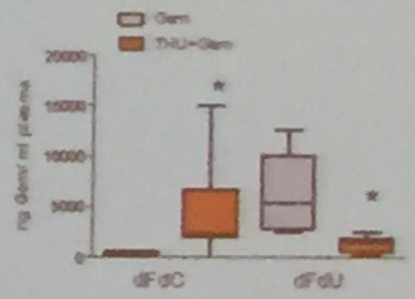
Survival Gem vs Gem+Cal

Is it enough just to increase the concentrations of CTX-agents to improve response rates?



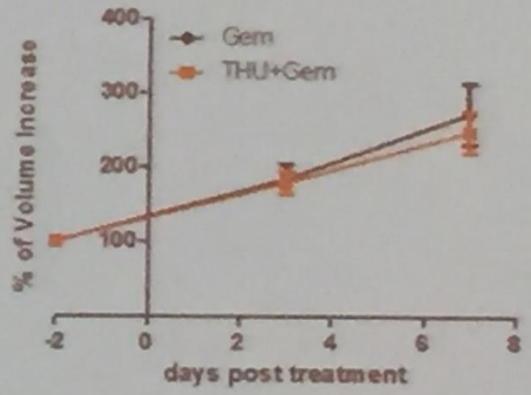
Inhibition of Gem clearance

Gem plasma

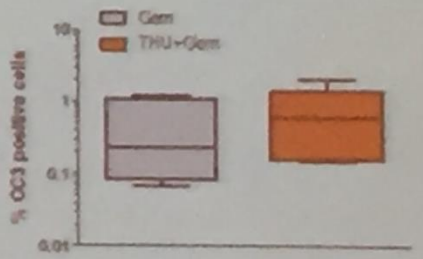


Gem tumor tissue

tumor volume



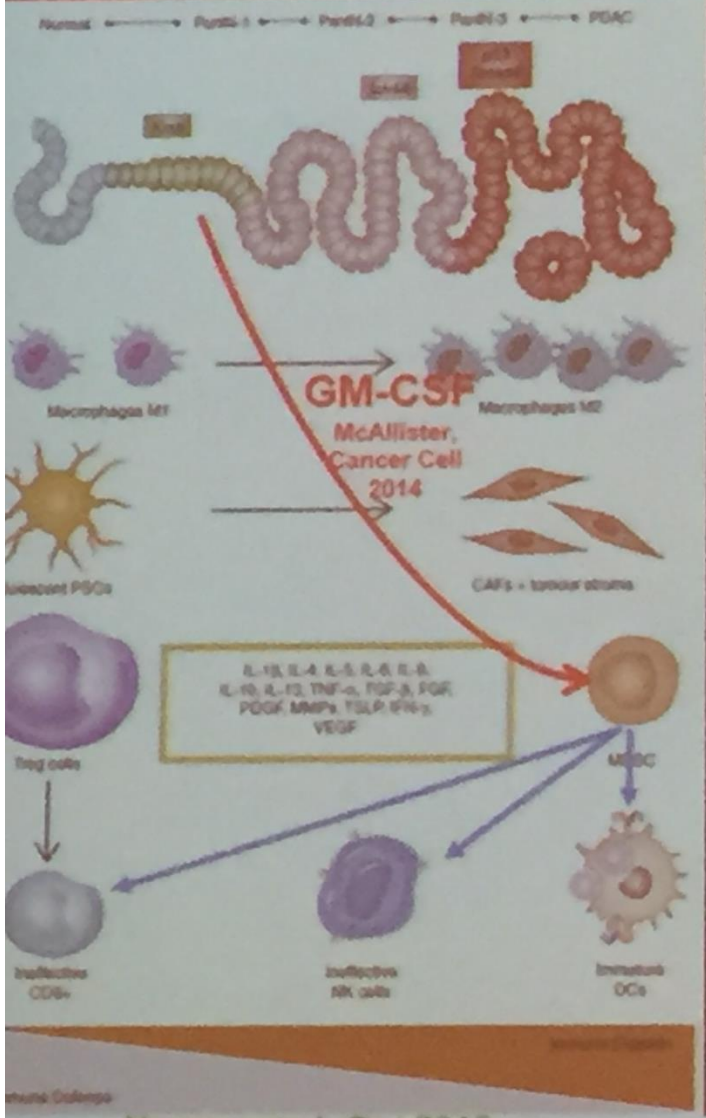
apoptotic tumor cells



- Just increasing CTX concentrations alone is not enough
- Additional ECM modulation/degradation appear necessary to sensitize tumors to chemotherapy

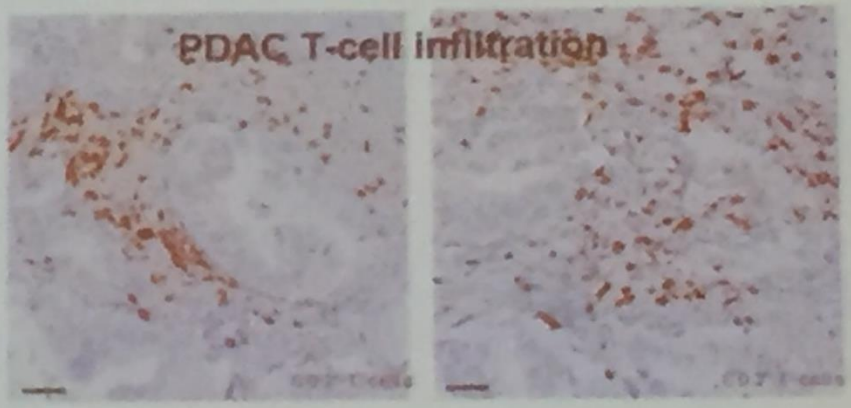
Neesse et al. PNAS 2013

Oncogenic Kras ductal cells initiates a cascade of stromal cell-autonomous and non-cell-autonomous alterations



Neesse et al Gut 2015

Immune infiltrating cells (IIC) in PDAC stroma

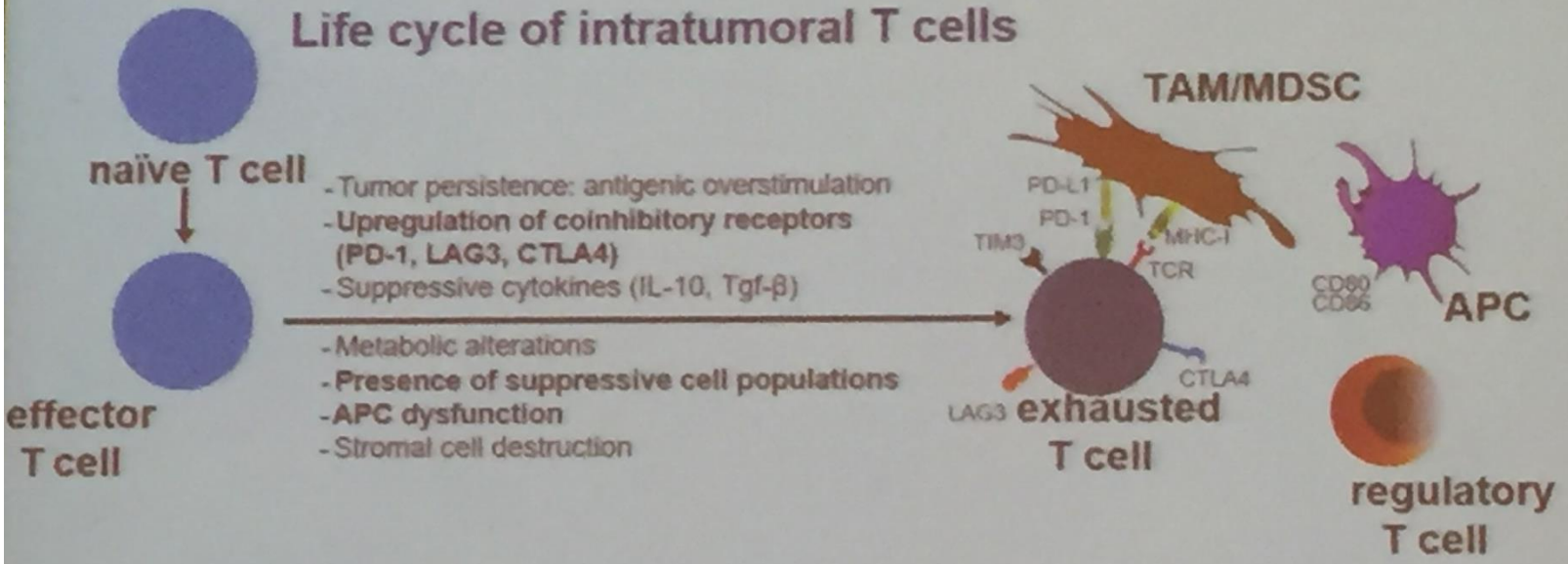


- **≈50% of cells** in PDAC **CD45+ leucocytic**
- leucocytic infiltration **starts early**
- immunosuppressive **TAMs, MDSC, Tregs** are **abundant**
- **T effector, NK and dendritic cells** are **exhausted or absent**
- **„immune priveliged area" of PDAC immune evasion**

Bauer et al, *Cancer letters* 2016

Intratumoral effector T-cell dysfunction in PDAC

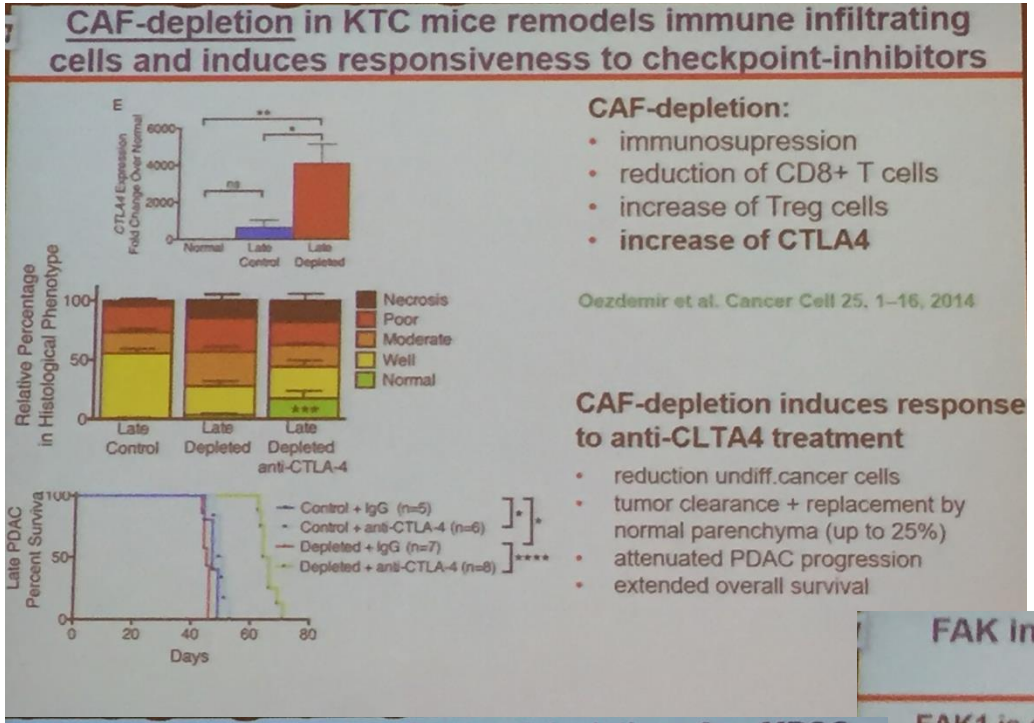
Life cycle of intratumoral T cells

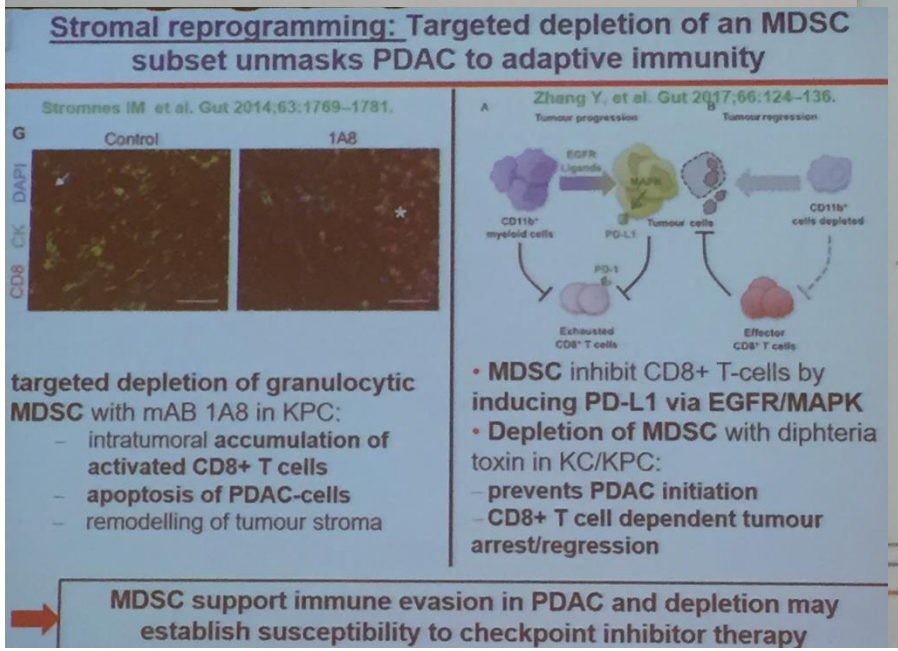


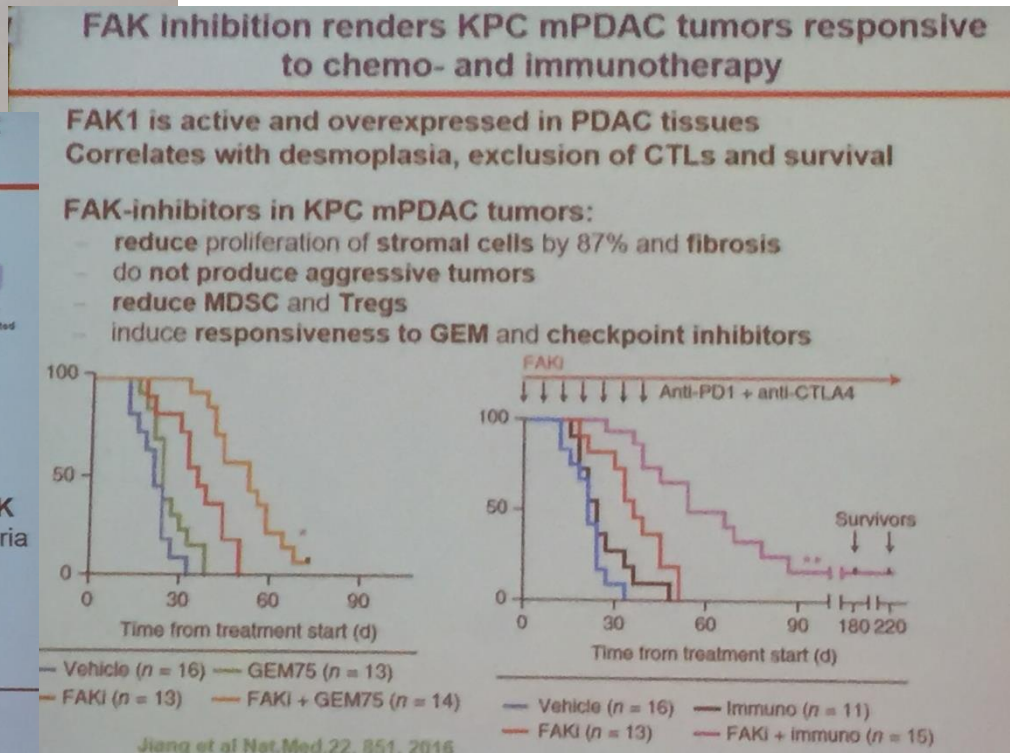
MDSC, TAMs, Treg and dysfunctional APC lead to „exhausted intratumoral effector T-cells“

Bauer et al, *Cancer letters* 10;381(1):259-68, 2016

Воздействие на строму для улучшения ответа на химио- и иммунотерапию







Inserm CRCM LA LIGUE

Novel therapeutic targets for pancreatic adenocarcinoma revealed by a multi-omics analysis of patient-derived xenografts

Rémy Nicolle
Programme Carte d'Identité des Tumeurs® (CIT)
Ligue contre le cancer, Paris FRANCE

LMU KLINIKUM

A comprehensive prognostic signature based on interaction of immune cell infiltration with stromal composition for resected pancreatic ductal adenocarcinoma

U. M. Mahajan[1,2], E. Langhoff[2], E. Costello[3], W. Greenhalf[3], C. Halloran[3], G. Beyer[1,2], F.-U. Weiss[1], J. P. Neoptolemos[3], M. W. Büchler[4], T. Kohlmann[5], M.M. Lerch[1], J. Mayerle[1,2]

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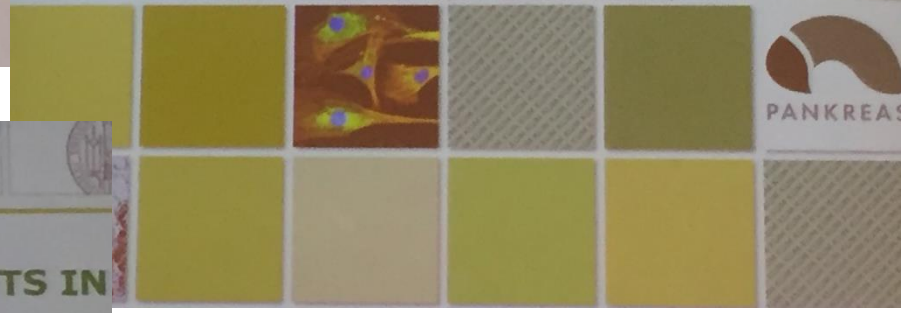
[3]NIHR Liverpool Pancreas Biomedical Research Centre, University of Liverpool, UK
[4]Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany
[5]Department of Community Medicine, University Medicine Greifswald, Greifswald, Germany

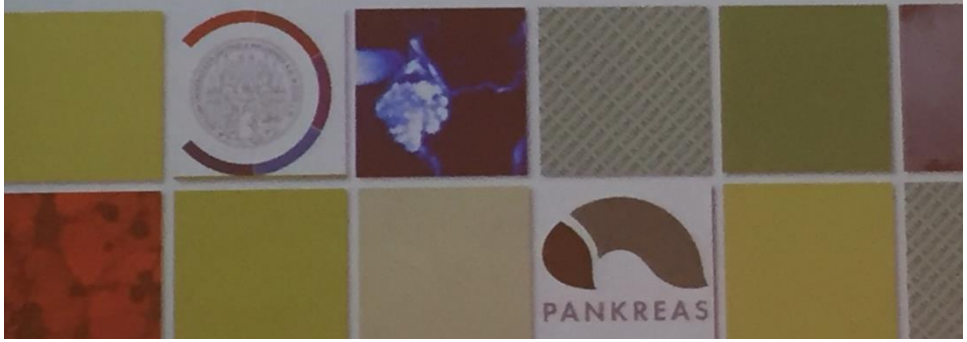


LMU KLINIKUM MEDIZINISCHE KLINIK UND POLIKLINIK II · DIREKTORIN PROF. DR. JULIA MAYERLE

POTENTIAL TRANSPORT PROCESS TARGETS IN PANCREATIC CANCER

Joint UEG/EPC Research Meeting, June 2017, Budapest

JULIA MAYERLE



SUMMARY AND CONCLUSION

PANKREA

- Chemoresistance in pancreatic cancer is multifactorial and a big issue for successful treatment of the disease.
- Possible strategies to overcome treatment resistance are:
  - drug transport by nanocarriers (Nab-Paclitaxel)
  - targeted transport via surface specific carriers (MUC1, EGFR1)
  - modulation of microenvironment such as in PEGPH20 or S1
  - modulation of enzymatic activity in bystanders (CAFs or CAMs)
- Treatment stratification with respect to predictive markers such as hENT1, hyaluronic acid, Ca19.9 or cathepsin D might pave our way towards precision medicine.

PANCREATIC CLUB RUSSIA

Спасибо за внимание