Quoi de neuf
en pathologie pancréatique…

13ème journée de Gastro-entérologie de Cochin
28 janvier 2017

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Conflit d'intérêt

aucun

Quoi de neuf…

24.6 millions d'articles référencés
... et 500000 de plus chaque année

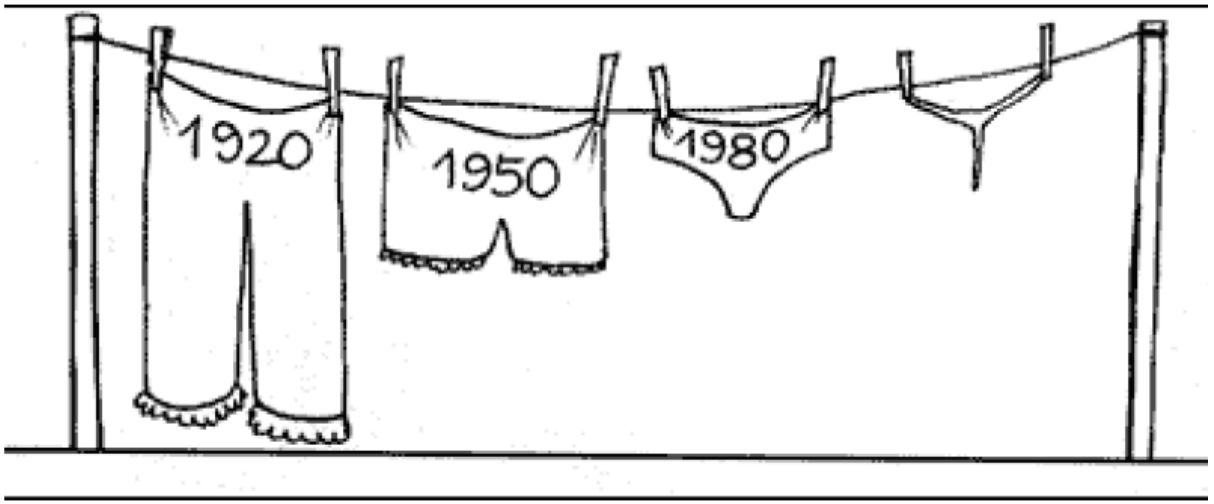
Qui opérer ? | **Comment ?** | **Et après ?**

Qui opérer ? *les tumeurs kystiques*

recouvrent un large éventail histologique de lésions…

jusqu'à 30% des indications chirurgicales

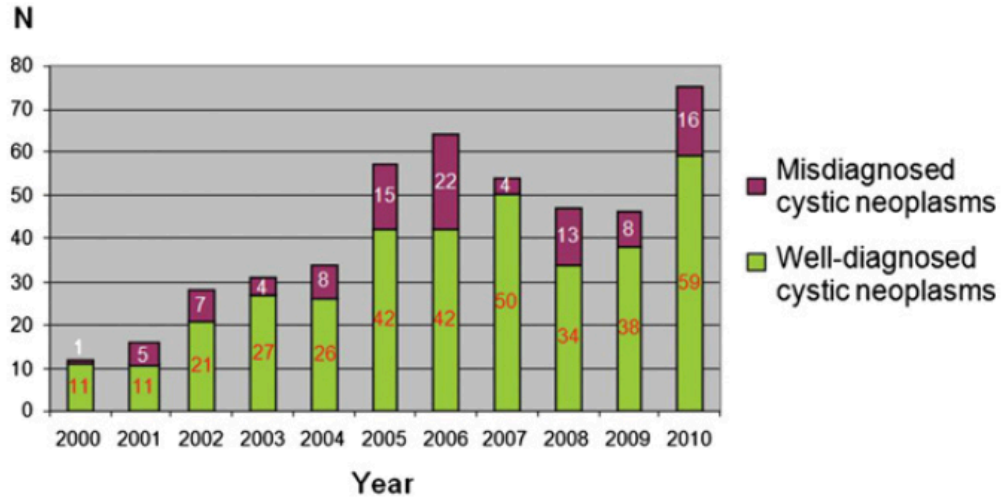
… de plus en plus petite au diagnostic



Lee, Am J Gastroenterol, 2010
Kimura, Int J Pancreatol 1995

les tumeurs kystiques

Pancreatic resections for cystic neoplasms: From the surgeon's presumption to the pathologist's reality



Diagnosis	n (%)
Well-diagnosed cystic neoplasms	373 (78.4)
Misdiagnosed cystic neoplasms	103 (21.6)
Serous cystic neoplasms (n = 69)	
Well diagnosed	51 (73.9)
Misdiagnosed	18 (26.1)
Mucinous cystic neoplasms (n = 123)	
Well diagnosed	98 (79.7)
Misdiagnosed	25 (20.3)
Main duct/mixed-IPMN (n = 156)	
Well diagnosed	126 (80.7)
Misdiagnosed	30 (19.3)
Branch duct-IPMN (n = 75)	
Well diagnosed	54 (72.0)
Misdiagnosed	21 (28.0)
Cystic neuroendocrine neoplasms (n = 15)	
Well diagnosed	8 (53.3)
Misdiagnosed	7 (46.7)
Solid pseudopapillary neoplasms (n = 38)	
Well diagnosed	36 (94.7)
Misdiagnosed	2 (5.3)

Même dans des centres experts

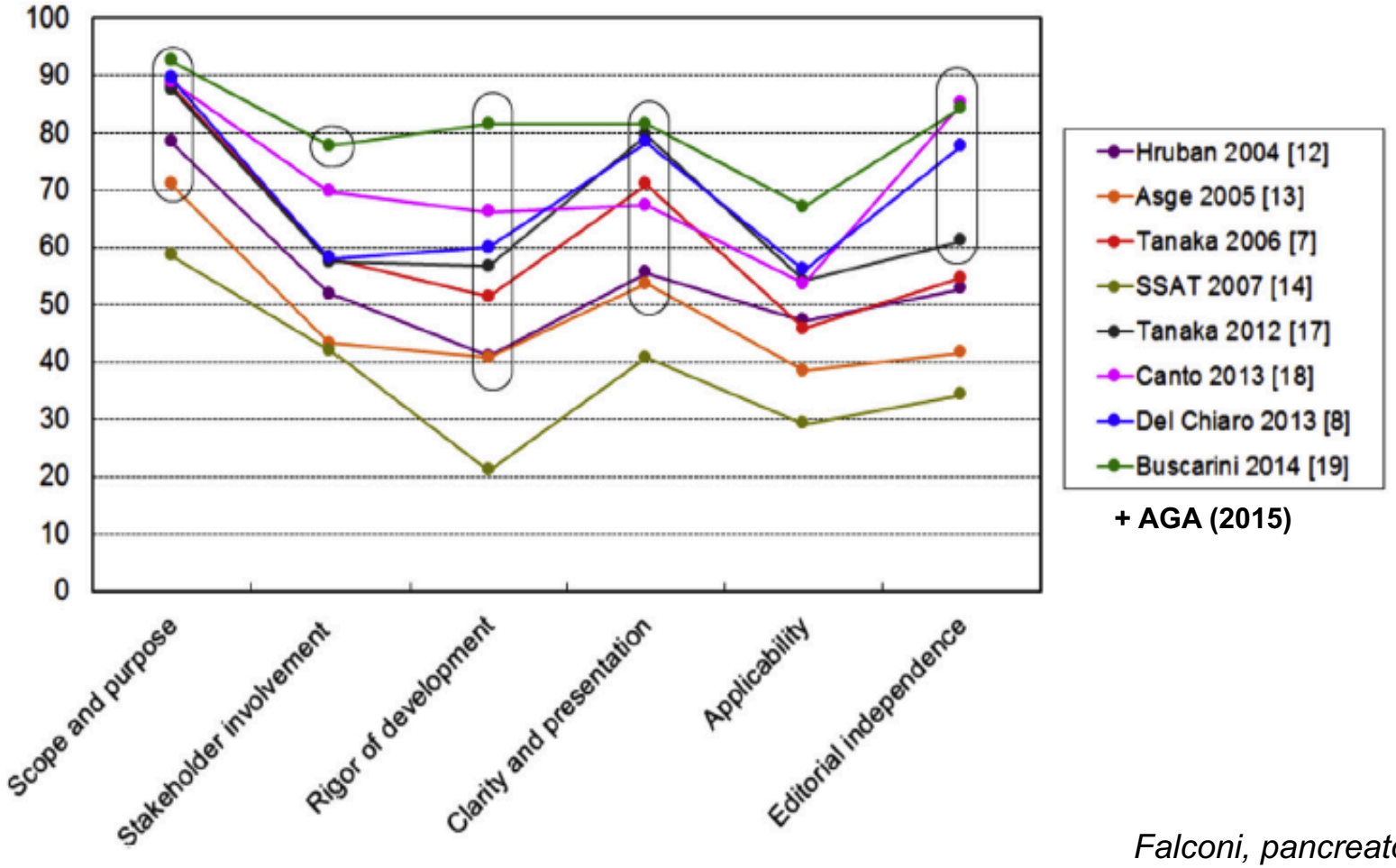
+/- 20% d'erreur diagnostique!!!

9% de resection pour lésions non tumorales

Salvia, Surgery, 2012

les tumeurs kystiques

Nombreuses (+/- 9)
« *guidelines* » ou « recommandations »



+ AGA (2015)

Falconi, pancreatology, 2015

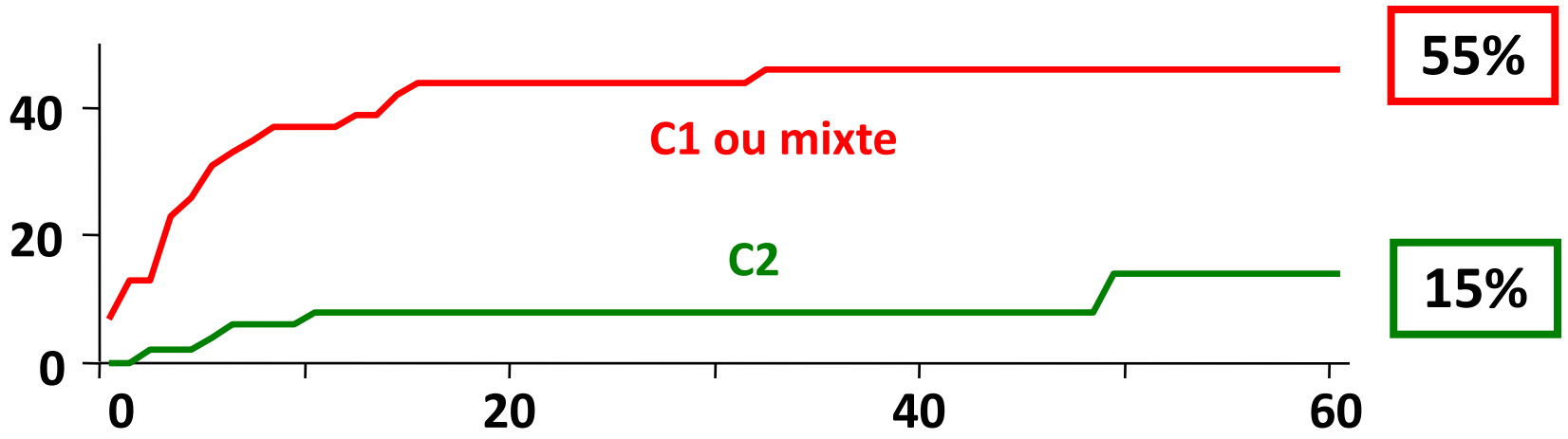
les tumeurs kystiques - TIPMP

Worrisome features

- taille> 3 à 4 cm
- CPP >5-9 mm
- Paroi épaissie ou IV+
- Nodules muraux IV-
- Changement de calibre
- Cellule atypique / cyto
- N+ Rx
- Croissance

High risk stigmatas

- Ictère
- CPP ≥ 10 mm
- Nodule IV+
- Cytologie positive (haut grade ou adk)
- CA 19.9 élévé



Tanaka, Pancreas, 2012

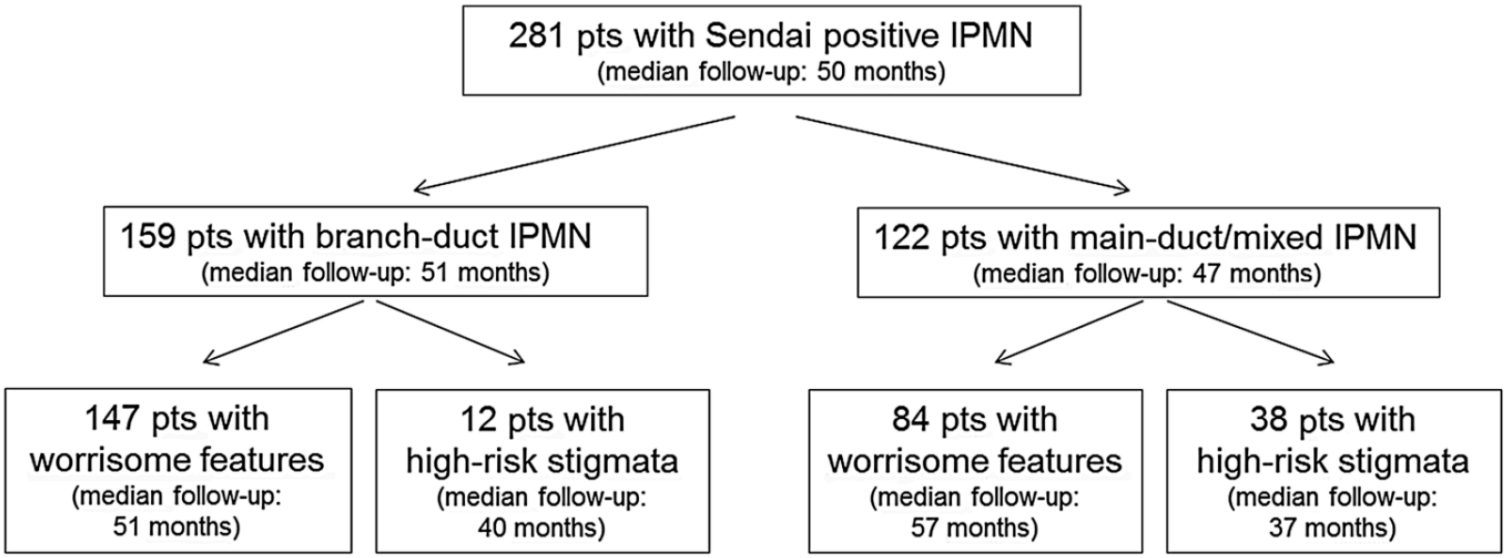
les tumeurs kystiques - TIPMP

Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis

Gut

R: Les critères actuellement retenus sont-ils trop « sévères »?

MM: Etude rétrospective multicentrique internationale

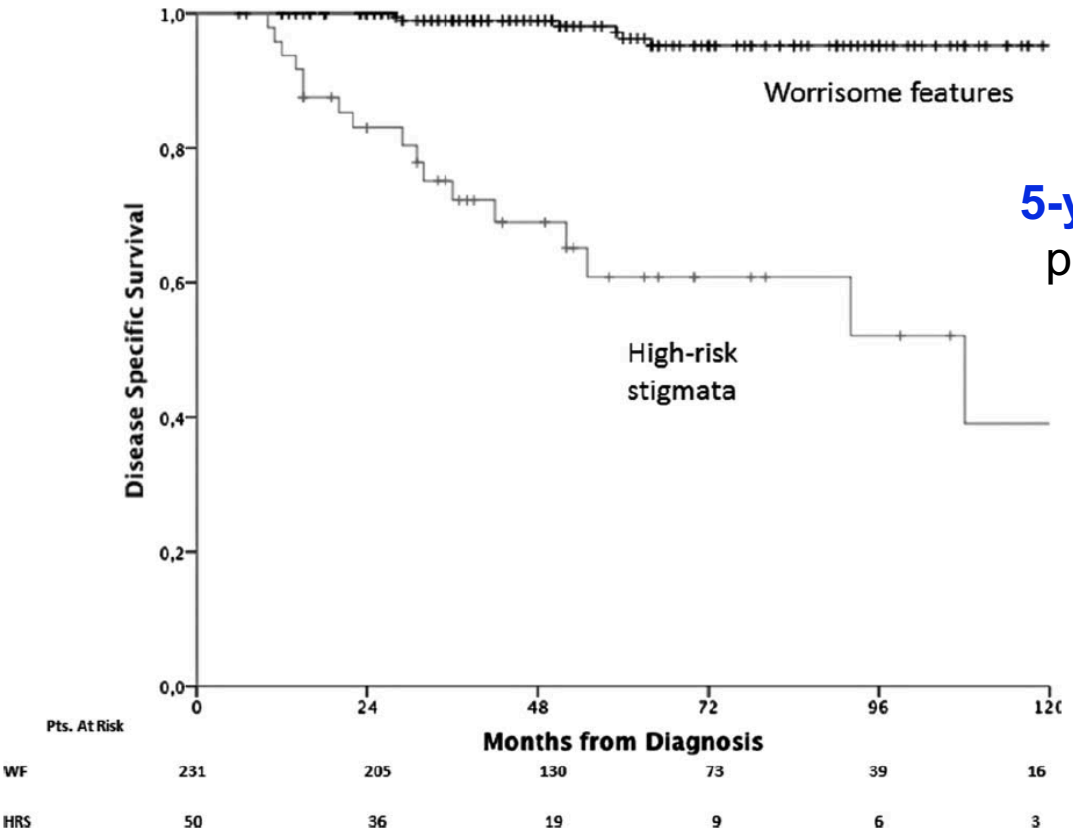


Crippa, Gut, 2016

les tumeurs kystiques - TIPMP

Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis

Gut



96.2%

5-year DSS
p<0.0001

60.2%

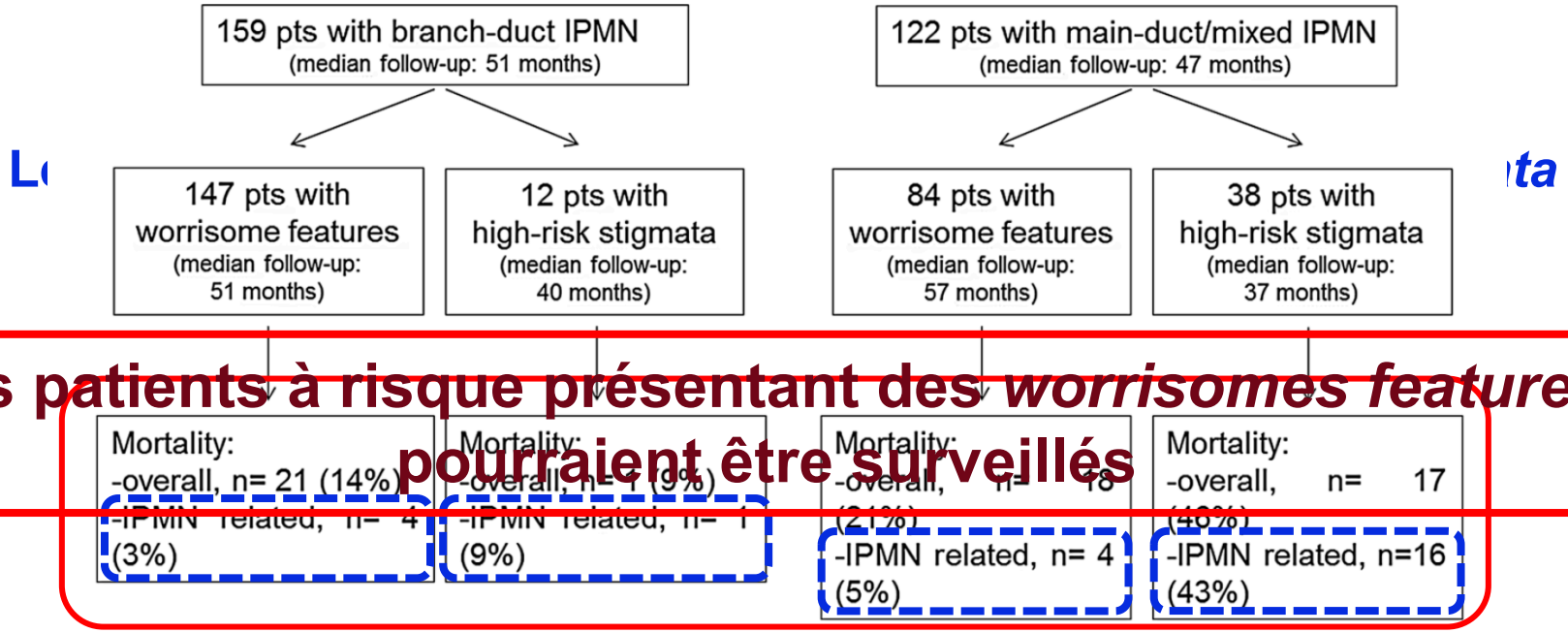
Age > 70 ans
Ictère
CPP > 15 mm
Cellules atypiques

Crippa, Gut, 2016

les tumeurs kystiques - TIPMP

Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis

Gut



Les patients à risque présentant des *worrisomes features* pourraient être surveillés

Crippa, Gut, 2016

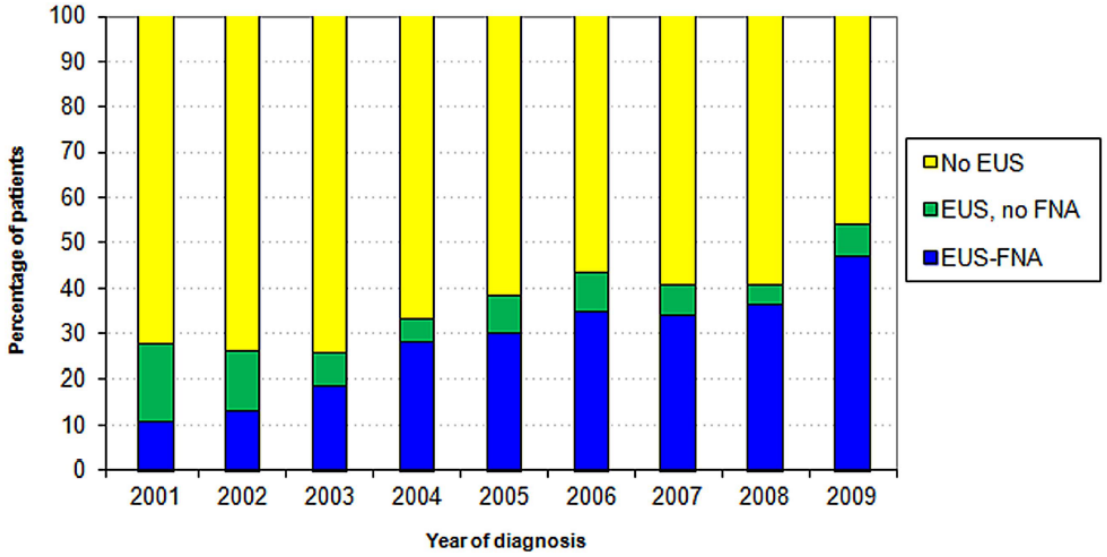
adénocarcinomes

Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer

Gut

R: Quelle conséquence d'un biopsie pré-opératoire ?

MM: Etude rétrospective multicentrique NA - *Surveillance, Epidemiology, and End Results (SEER) – Medicare data* - 2034 patients de 1998 à 2009



Ngamruengphong, Gut, 2015

adénocarcinomes

Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer

Gut

Table 5 Overall survival and pancreatic cancer-specific survival by tumour location in multivariable analyses: EUS-FNA group vs non-EUS-FNA group (reference group)

	Patients (n)	Overall survival		Cancer-specific survival	
		HR* (95% CI)	p Value	HR* (95% CI)	p Value
Head disease	1489	0.86 (0.73 to 1.01)	0.07	0.89 (0.75 to 1.07)	0.23
Body/tail disease	307	0.80 (0.51 to 1.26)	0.33	0.86 (0.54 to 1.39)	0.55

Ngamruengphong, Gut, 2015

adénocarcinomes

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

Locally Advanced Pancreatic Cancer

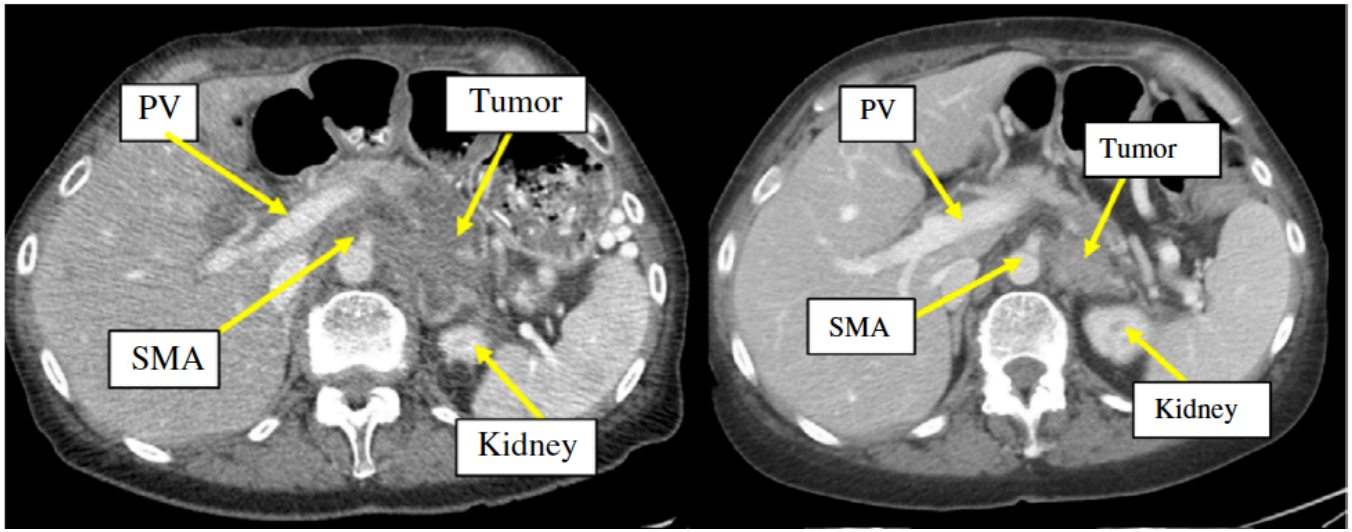
Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients

R: Quelle place du FOLFIRINOX en néoadjuvant?

MM: Etude rétrospective unicentrique – Heidelberg –2001 à 2015 - 575 patients

R: Taux de résection FOLFIRINOX=61% vs GEM+Rxttt=46%, p=0.026

En MV, FOLFIRINOX, associé à un bénéfice en terme de survie

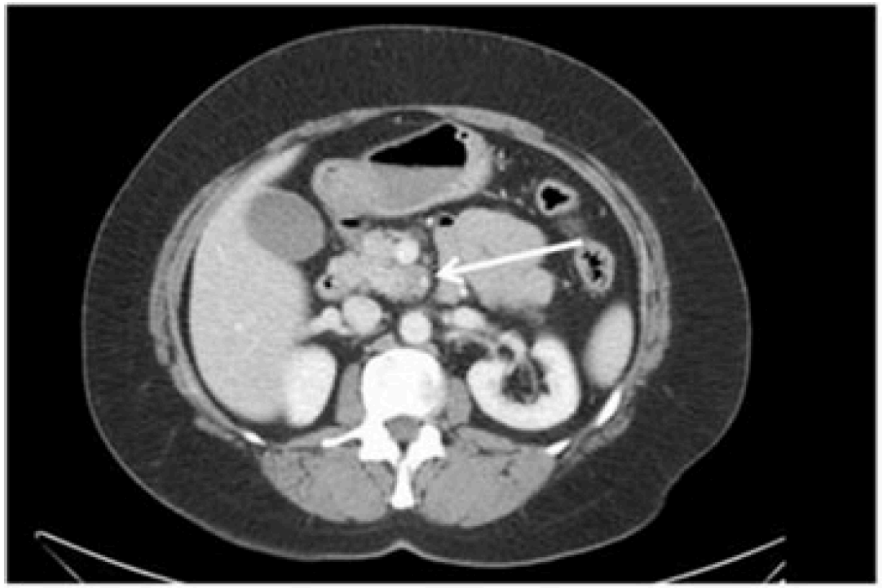


Hackert, Ann Surg, 2016

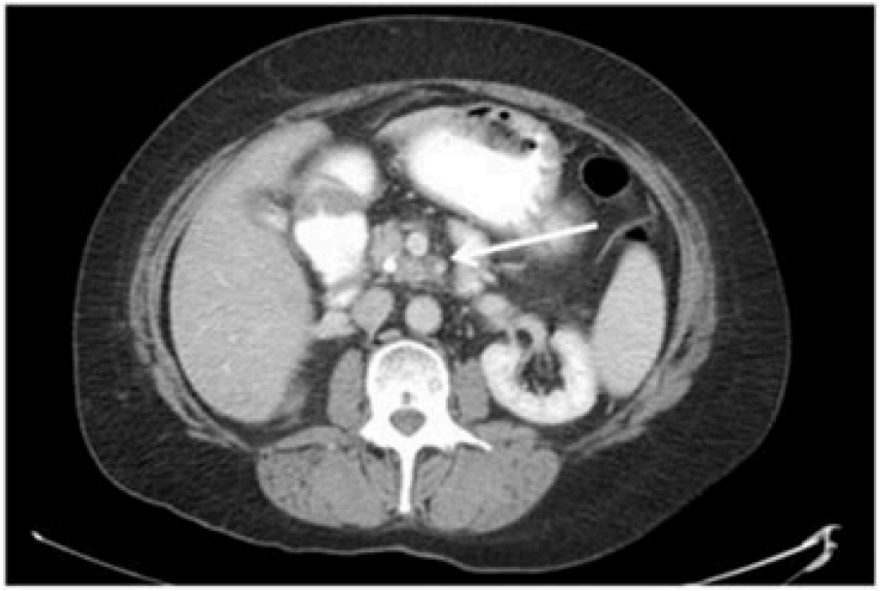
adénocarcinomes

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

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



Pre FOLFIRINOX



Post FOLFIRINOX

Difficulté de l'évaluation radiologique de la réponse

Ferrone, Ann Surg, 2015

adénocarcinomes

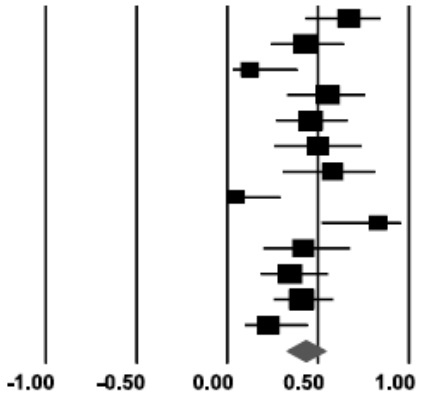
FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis

THE LANCET

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Christians	0.670	0.432	0.844	1.413	0.158
Boone	0.430	0.241	0.642	-0.639	0.523
Gunturu	0.125	0.031	0.386	-2.574	0.010
Hosein	0.555	0.330	0.760	0,466	0.641
James	0.460	0.269	0.663	-0.375	0.708
Hazariwala	0.500	0.260	0.740	0.000	1.000
Kharofa	0.580	0.305	0.813	0.552	0.581
Lowery	0,050	0.007	0.293	-2.797	0.005
Tinchon	0.830	0.520	0.957	2.063	0.039
Mahaseth	0.420	0.200	0.677	-0.596	0.551
Peddi	0.347	0.184	0.556	-1.443	0.149
Vasile	0.410	0.256	0.584	-1.013	0.311
Faris	0.227	0.098	0.443	-2.408	0.016
	0.430	0.328	0.538	-1.269	0.204

Statistics for each study

Event rate and 95% CI



Taux de résection R0 après FOLFIRINOX pour borderline ou LA

50%
avec 75% de R0

Survie médiane

24 mois

FOLFIRINOX
CHIMIOTHERAPIE DE REFERENCE EN NEOADJUVANT

Suker, Lancet, 2016

adénocarcinomes

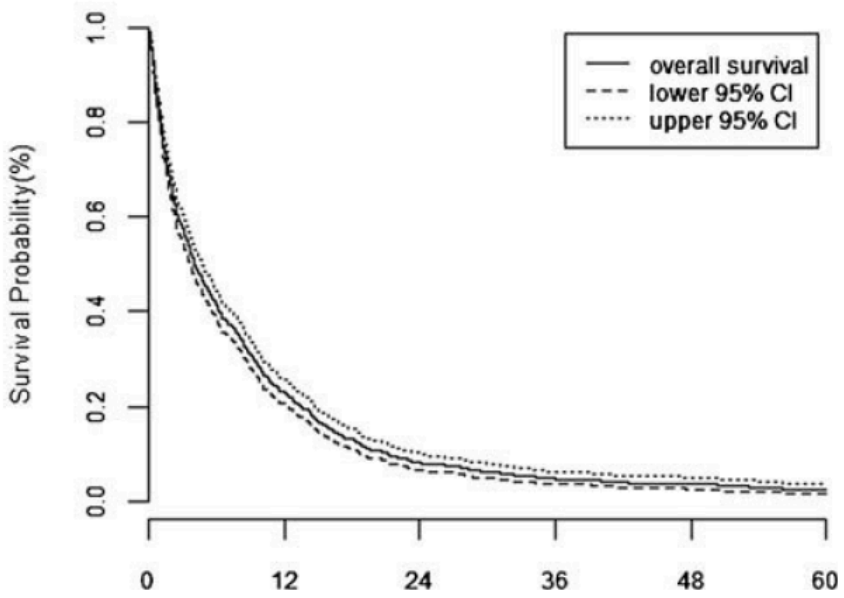
Pancreatic Adenocarcinoma in the Finistère Area, France, Between 2002 and 2011 (1002 Cases)

Population Characteristics, Treatment and Survival

60% M+ au diagnostic

10% ont une chirurgie R0

OS mediane 4,1 mois



Arnacheluum, Pancreas , 2016

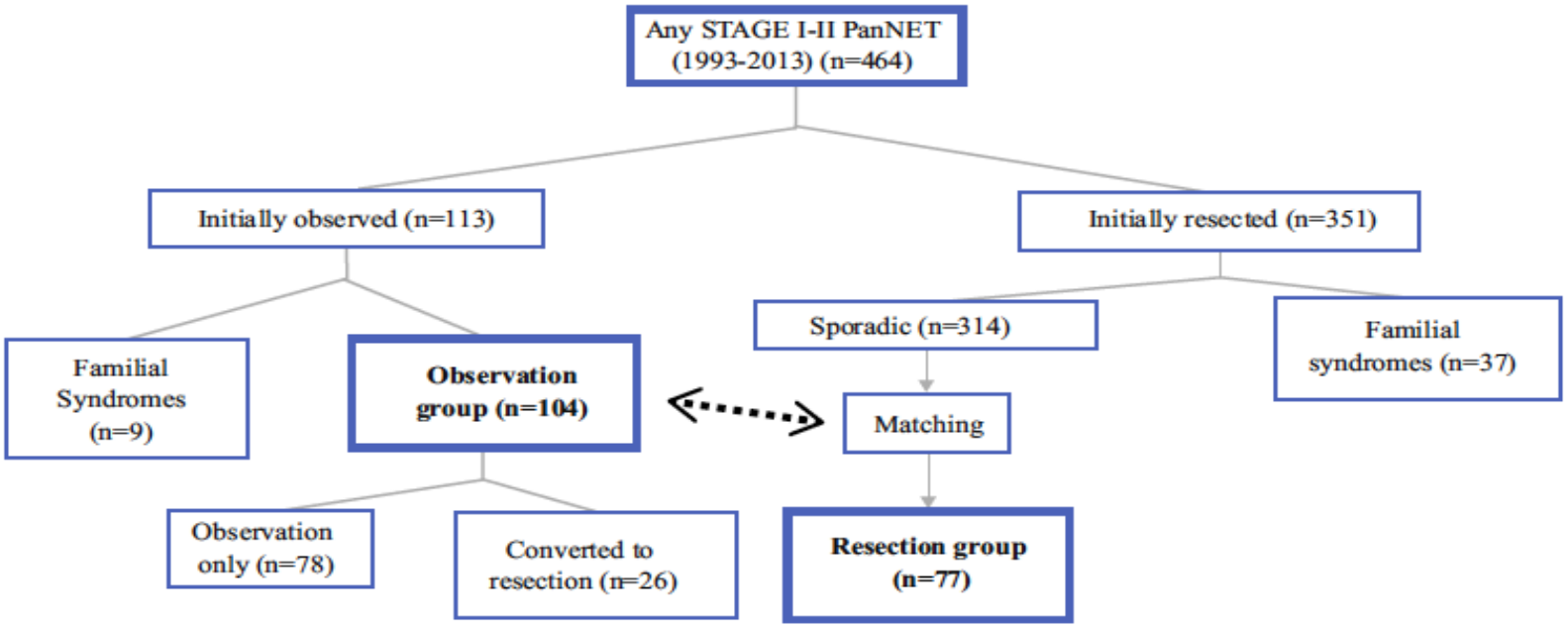
tumeurs neuroendocrines

Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case–Control Study

R: Prise en charge des TNE < 3 cm

MM: Etude rétrospective unicentrique – *MSKCC*

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY



Sado, ASO, 2015

tumeurs neuroendocrines

Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case–Control Study

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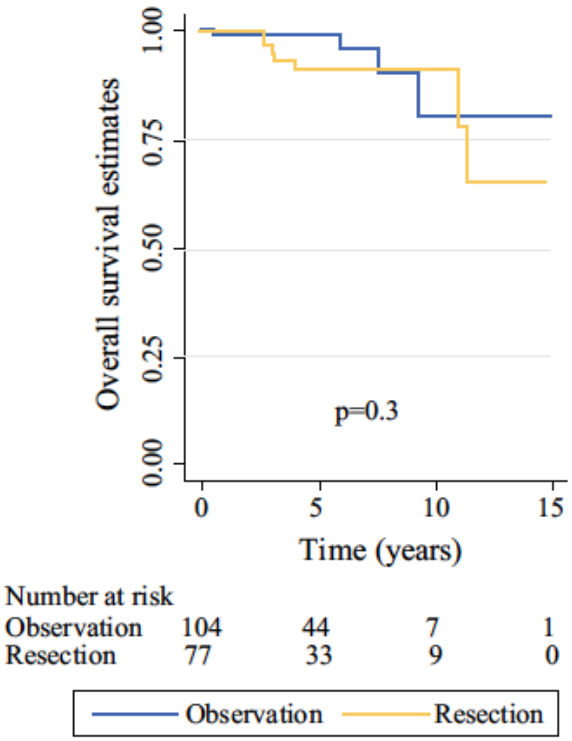


Characteristics	Observation only group ($n = 78$)	Resection group ($n = 77$)	P value
5Y overall survival, % (95 % CI)	99 (95–100)	91 (84–97)	0.3
5Y metastasis-free survival, % (95 % CI)	99 (95–100)	88 (79–96)	0.08
Recurrence[c]	0	5 (6 %)	NA

FU 44 mois

PAS d'apparition de métastases
PAS de décès liés à la TNE
Croissance lente chez 50% des patients

SURVEILLER DES TNE NF < 2 cm ASYMPTOMATIQUES EST UNE OPTION

Sado, ASO, 2015

Comment les opérer ?

Nationwide In-hospital Mortality Following Pancreatic Surgery in Germany is Higher than Anticipated

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

R: Quels résultats pour la chirurgie pancréatique

MM: Etude rétrospective allemande – 2009-2013 - 58003 patients

Mortalité 10,1%
Réoperation 16%
Transfusion > 6 CGR 20%

Mortalité 7,8%
(source PMSI)

Nimpitsch, Ann Surg, 2016

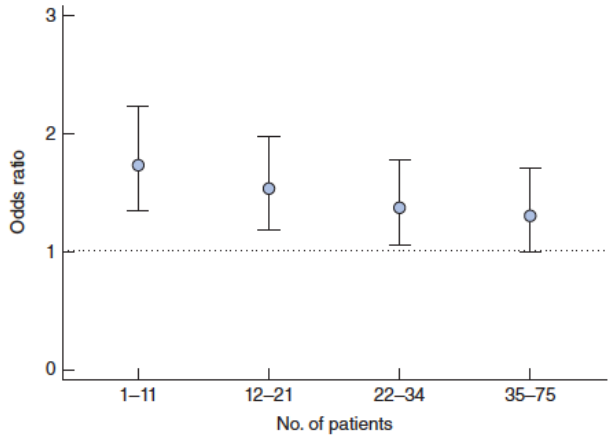
Comment les opérer ?

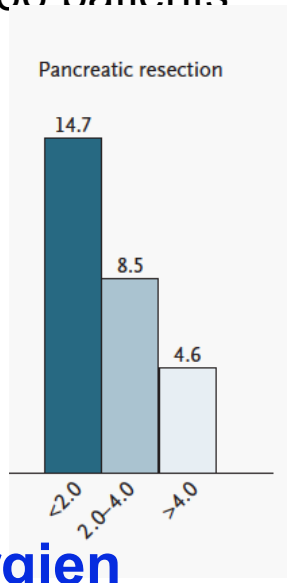
Volume–outcome relationship in pancreatic surgery

BJS British Journal of Surgery

R: Quels résultats pour la chirurgie pancréatique

MM: Etude rétrospective allemande – 2008 à 2010 - 9566 patients





Effet centre / effet chirurgien

BENEFICE A LA CENTRALISATION

Alsfasser, BJS, 2015

Comment les opérer ?

A Randomized Prospective Multicenter Trial of Pancreaticoduodenectomy With and Without Routine Intraperitoneal Drainage

ANNALS OF SURGERY
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R: Le drainage après DPC est-il nécessaire?

MM: Etude prospective randomisée multicentrique USA

TABLE 4. Mortality 30, 60, and 90 days after pancreaticoduodenectomy

N (%)	All (137)	Drain (68)	No Drain (69)	*P*
30-d mortality	4 (3)	0 (0)	4 (6)	0.120
60-d mortality	7 (5)	1 (1)	6 (9)	0.115
90-d mortality	10 (7)	2 (3)	8 (12)	0.097

Fisher exact test for all.

Arrêt précoce de l'étude pour sur-morbidité dans le bras sans drain

LE DRAINGE APRES DPC RESTE LA REGLE

Van Buren, Ann Surg, 2015

Comment les opérer ?

No Need for Routine Drainage After Pancreatic Head Resection: The Dual-Center, Randomized, Controlled PANDRA Trial (ISRCTN04937707)

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

R: Le drainage après DPC est-il nécessaire?

MM: Etude prospective randomisée bi-centrique allemande

Non infériorité de l'absence de drain….
***MAIS* 25% des patients randomisés sans drain en ont eu un...**

MAIS UN SOUS-GROUPE DE PATIENT POURRAIT NE PAS ETRE DRAINE

Witzigmann, *Ann Surg, 2015*

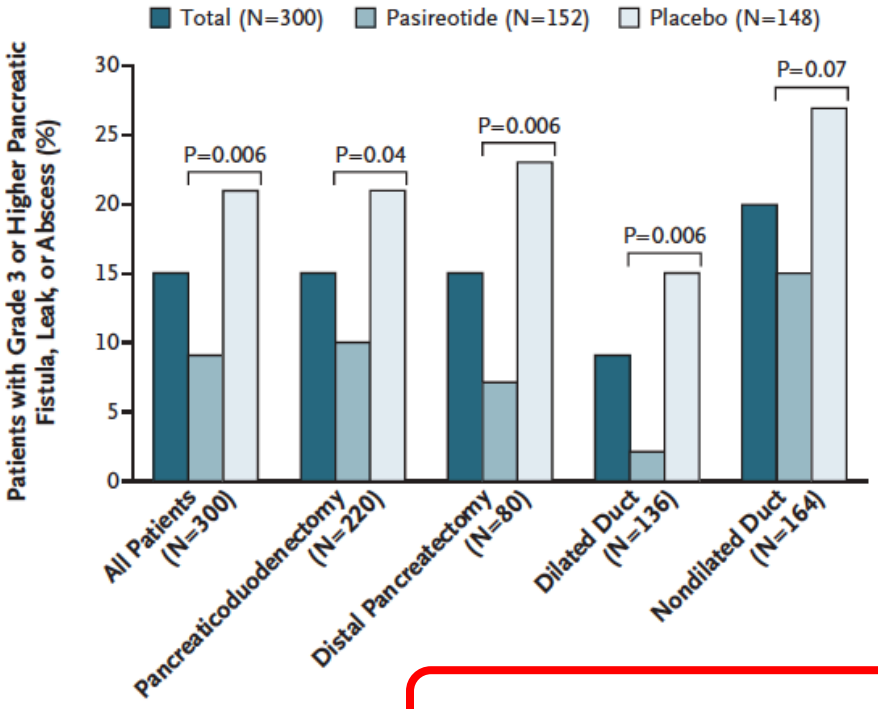
Comment les opérer ?

Pasireotide for Postoperative Pancreatic Fistula

The NEW ENGLAND JOURNAL of MEDICINE

R: Les analogues de la somatostatine réduisent-ils le risque de fistule

MM: Etude prospective randomisée unicentrique MSKCC



Le pasiréotide permet de réduire de moitié le risque de survenue d'une fistule pancréatique

ET LA SOMATOSTATINE ???

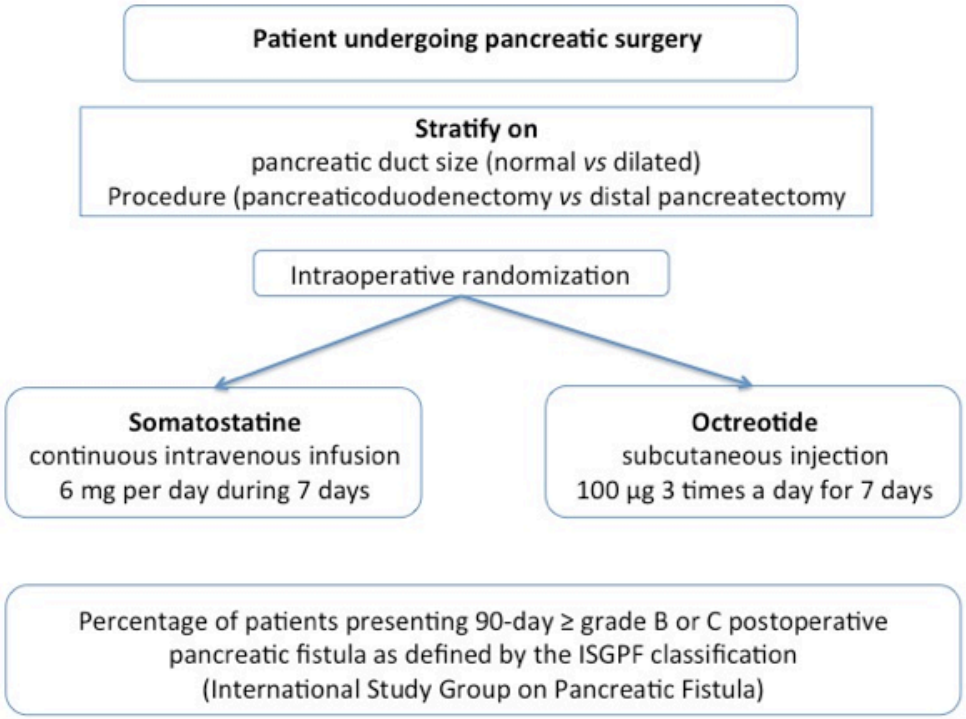
Allen, NEJM, 2014

Comment les opérer ?

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ

Les Programmes Hospitaliers de Recherche Clinique (PHRC)

R: la somatostatine réduisent-ils le risque de fistule
MM: Etude prospective randomisée multicentrique française



Gaujoux, PHRC 2015

Comment les opérer ?

Early Enteral Versus Total Parenteral Nutrition in Patients Undergoing Pancreaticoduodenectomy

A Randomized Multicenter Controlled Trial (Nutri-DPC)

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885

R: Comment réalimenter les patients en post-opératoire?
MM: Etude prospective randomisée multicentrique française

R: mortalité 10% vs 5%
morbidité 77% vs 64% (p=0.04)
fistule 48% vs 27% (p=0.007)

La nutrition entérale précoce est à éviter

Perinel, Ann Surg, 2016

Comment les opérer ?

Minimally Invasive Versus Open Pancreaticoduodenectomy for Cancer

Practice Patterns and Short-term Outcomes Among 7061 Patients

ANNALS OF SURGERY
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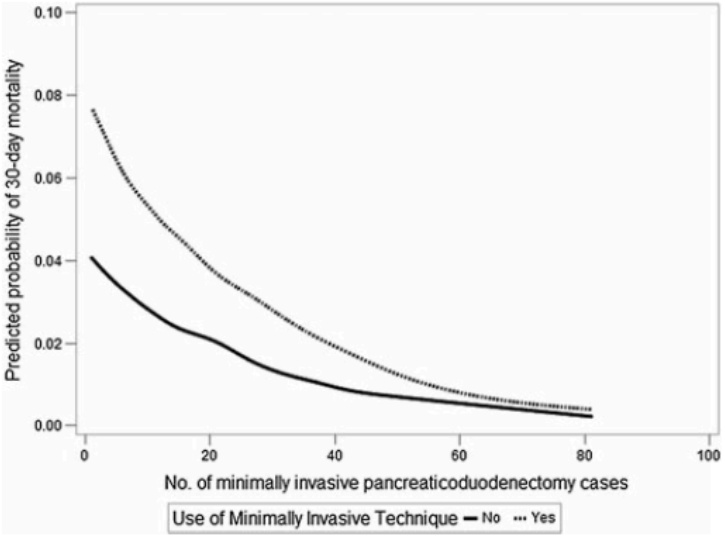
R: La DPC coeliosocopique est elle souhaitable?
MM: Etude de registre USA



La DPC par coelioscopie est associée à un mortalité à 30 jours plus élevées

LA DPC PAR LAPAROTOMIE RESTE LE GOLD-STANDARD

Adam, Ann Surg, 2015

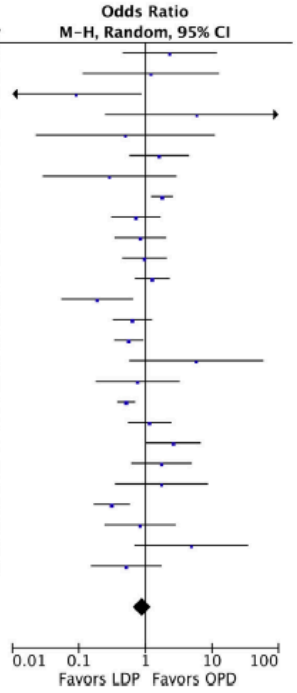
Comment les opérer ?

A systematic review and meta-analysis of laparoscopic versus open distal pancreatectomy for benign and malignant lesions of the pancreas:

SURGERY

Study or Subgroup	LDP Events	LDP Total	OPD Events	OPD Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Velanovic (2006)	3	15	4	41	2.5%	2.31 [0.45, 11.83]	2006
Thaker (2007)	1	7	4	33	1.4%	1.21 [0.11, 12.81]	2006
Teh (2007)	1	12	8	16	1.5%	0.09 [0.01, 0.88]	2007
Tang (2007)	3	9	0	5	0.8%	5.92 [0.25, 141.48]	2007
Bruzoni (2008)	1	7	1	4	0.9%	0.50 [0.02, 11.09]	2008
Eom (2008)	8	31	11	62	4.2%	1.61 [0.57, 4.54]	2008
Matsumoto (2008)	1	14	4	19	1.5%	0.29 [0.03, 2.92]	2008
Kooby (2008)	60	159	129	508	7.1%	1.78 [1.22, 2.60]	2008
Kim (2008)	23	93	11	35	4.9%	0.72 [0.30, 1.69]	2008
Baker (2009)	10	27	35	85	4.8%	0.84 [0.34, 2.05]	2009
Finan (2009)	31	44	74	104	5.3%	0.97 [0.45, 2.10]	2009
Vijan (2010)	34	100	29	100	6.1%	1.26 [0.69, 2.29]	2010
Aly (2010)	4	40	13	35	3.5%	0.19 [0.05, 0.65]	2010
Di Norcia (2010)	13	71	50	192	5.7%	0.64 [0.32, 1.26]	2010
Jayaraman (2010)	29	107	94	236	6.6%	0.56 [0.34, 0.93]	2010
Kang (2010)	4	5	11	27	1.4%	5.82 [0.57, 59.32]	2010
Waters (2010)	4	18	6	22	2.9%	0.76 [0.18, 3.26]	2010
Cho (2011)	100	254	253	453	7.4%	0.51 [0.38, 0.70]	2011
Butturini (2011)	21	43	33	73	5.4%	1.16 [0.54, 2.46]	2011
Fox (2011)	12	42	10	76	4.6%	2.64 [1.03, 6.78]	2011
Mehta (2012)	20	30	16	30	4.2%	1.75 [0.62, 4.97]	2012
Soh (2012)	7	10	12	21	2.5%	1.75 [0.35, 8.71]	2012
Stauffer (2012)	27	82	55	90	6.0%	0.31 [0.17, 0.58]	2012
Limongelli (2012)	7	16	14	29	3.5%	0.83 [0.24, 2.84]	2012
Corey (2012)	4	7	3	14	1.9%	4.89 [0.68, 34.96]	2012
Abu Hilal (2012)	10	35	7	16	3.5%	0.51 [0.15, 1.76]	2012
Total (95% CI)		**1278**		**2326**	**100.0%**	**0.90 [0.66, 1.22]**	
Total events	438		887				

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 69.67$, df = 25 ($P < 0.00001$); $I^2 = 64\%$
Test for overall effect: Z = 0.68 (P = 0.50)



PAS DE DIFFÉRENCE
FISTULE
MORBIDITE

SUPERIORITE LAPAROSCOPIE
PERTE SANGUINE
DMS

RESULTATS ONCOLOGIQUES
A MIEUX EVALUER

PG/SPG COELIOSCOPIQUE POUR PATHOLOGIE BENIGNE EST VALIDEE

Mehrabi, Surgery, 2015

Et après?

Time to the Initiation of Adjuvant Chemotherapy Does Not Impact Survival in Patients With Resected Pancreatic Cancer

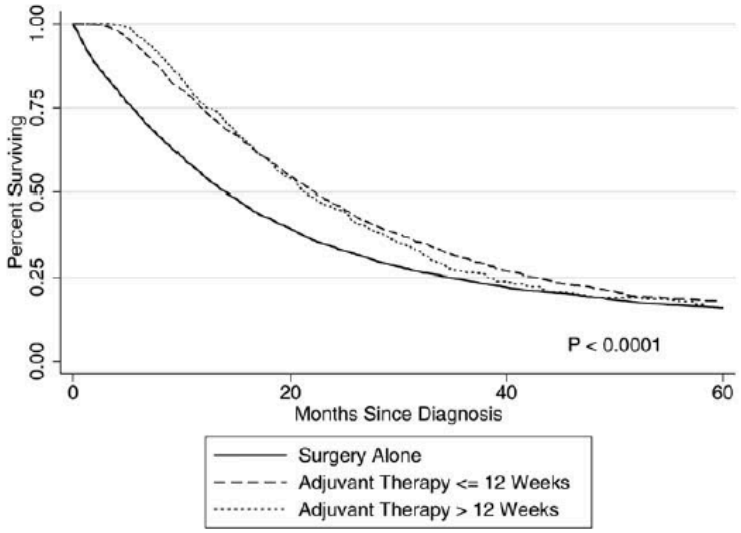


Figure 1. Overall 5-year survival of the current study cohort.

Plus que la précocité de mise en route, c'est l'administration de la totalité du traitement adjuvant qui importe

Mirkin, Cancer, 2016

Et après?

ESPAC-4

Gemcitabine +/- capecitabine en adjuvant

ASCO, 2016

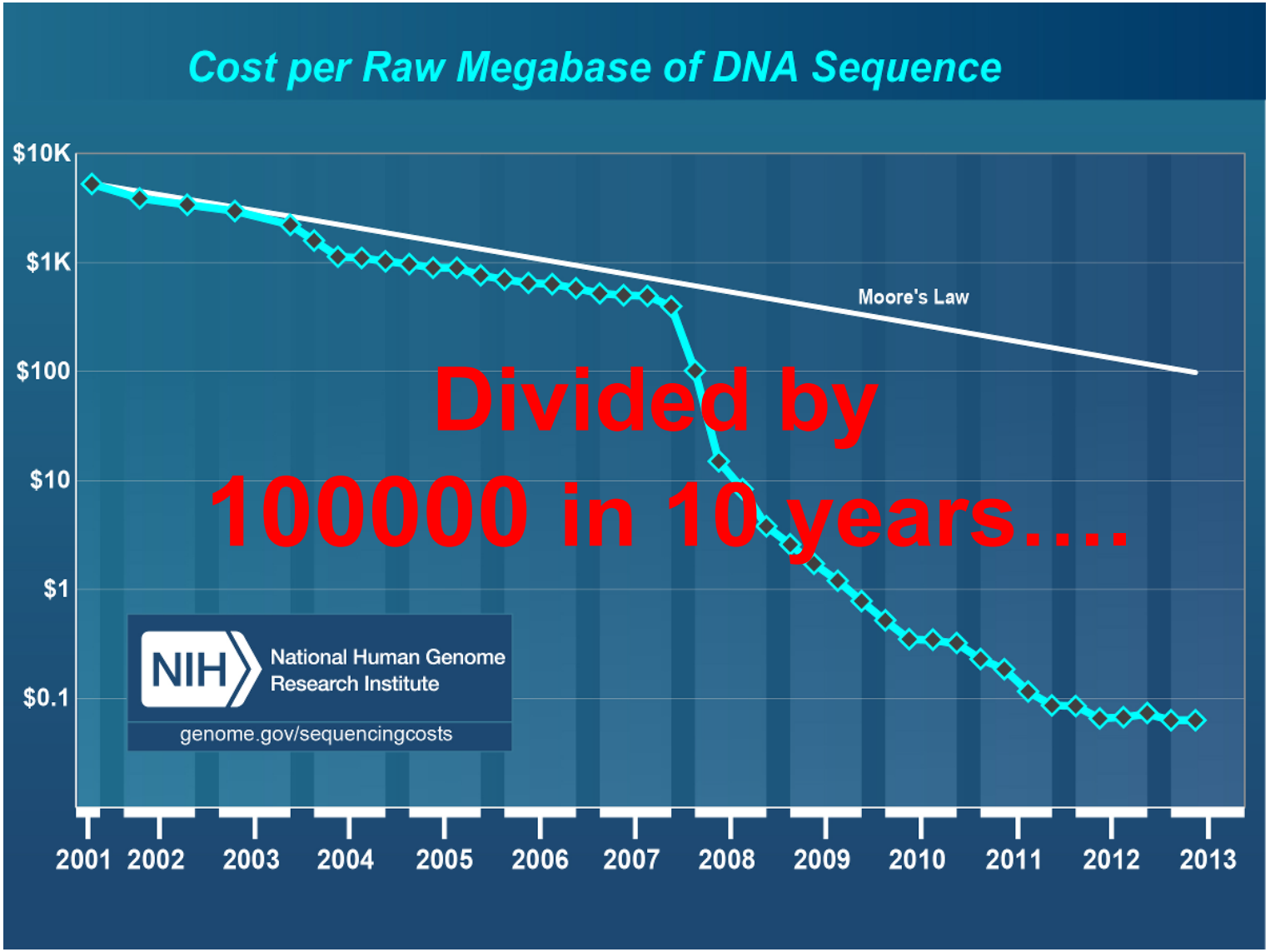
What is next ?

Next Generation Sequencing

massively parallel DNA sequencing

is becoming a daily clinical tool

What is next ?


Cost per Raw Megabase of DNA Sequence
$10K
$1K
$100
$10
$1
$0.1
Moore's Law
Divided by
100000 in 10 years….
NIH
National Human Genome
Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
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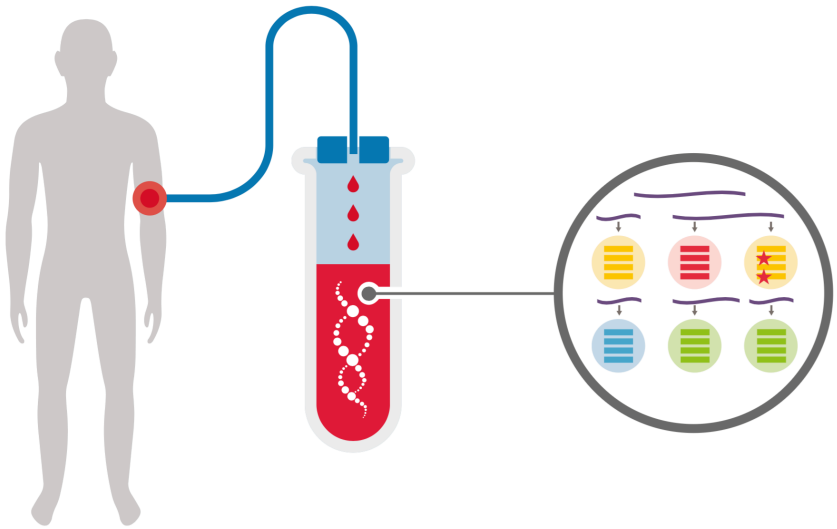
2012
2013

Liquid biopsy



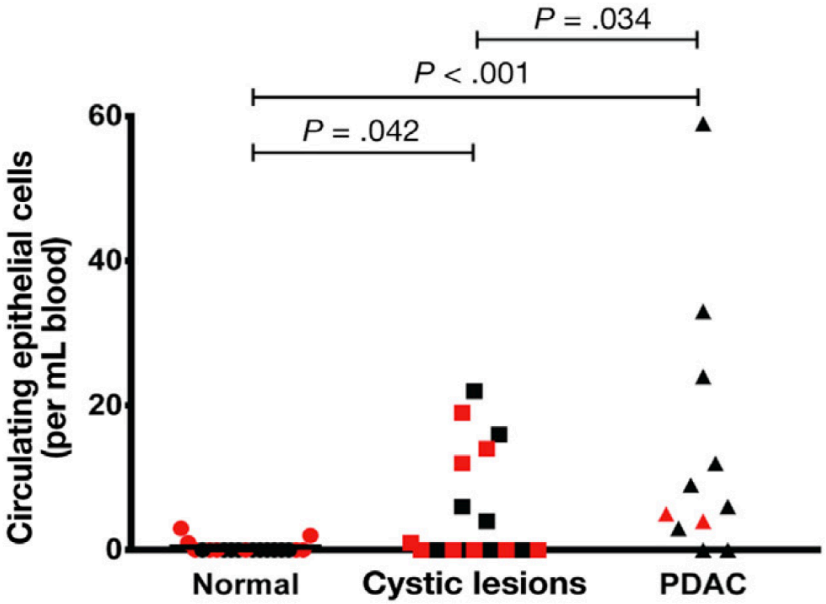
Circulating tumor cells

Circulating cell-free DNA

Liquid biopsy in IPMN

Detection of Circulating Pancreas Epithelial Cells in Patients With Pancreatic Cystic Lesions

Andrew D. Rhim,[1,2,3] Fredrik I. Thege,[4] Steven M. Santana,[5] Timothy B. Lannin,[5] Trisha N. Saha,[1,2] Shannon Tsai,[2,3] Lara R. Maggs,[2,3] Michael L. Kochman,[2,3,8] Gregory G. Ginsberg,[2,3,8] John G. Lieb,[2,3] Vinay Chandrasekhara,[2,3] Jeffrey A. Drebin,[3,6] Nuzhat Ahmad,[2] Yu–Xiao Yang,[2] Brian J. Kirby,[5,7] and Ben Z. Stanger[2,3,8]

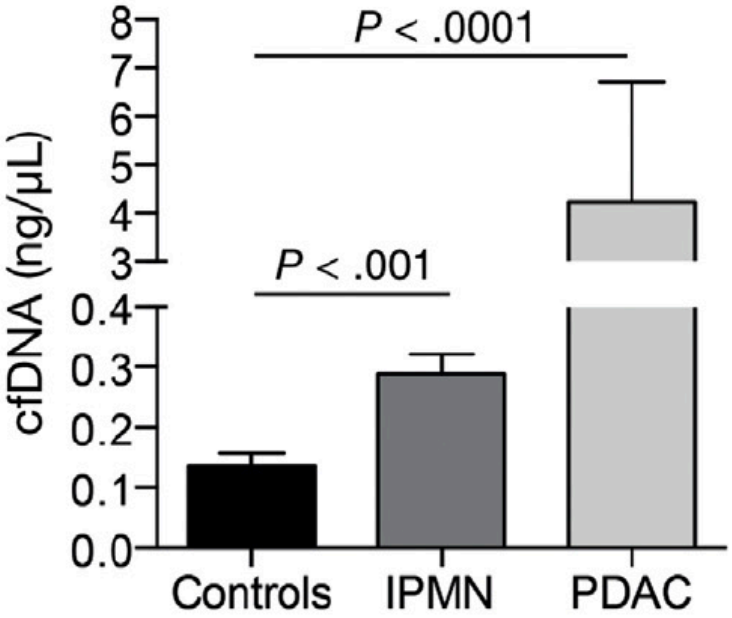


Rhim, Gastroenterology, 2014

Liquid biopsy in IPMN

Detection of Hot-Spot Mutations in Circulating Cell-Free DNA From Patients With Intraductal Papillary Mucinous Neoplasms of the Pancreas

Andreas W. Berger,[1,*] **Daniel Schwerdel**,[1,*] Ivan G. Costa,[2] Thilo Hackert,[3] Oliver Strobel,[3] Sandra Lam,[1] Thomas F. Barth,[4] Bernd Schröppel,[1] Alexander Meining,[1] Markus W. Büchler,[3] Martin Zenke,[5] Patrick C. Hermann,[1] Thomas Seufferlein,[1] and Alexander Kleger[1]

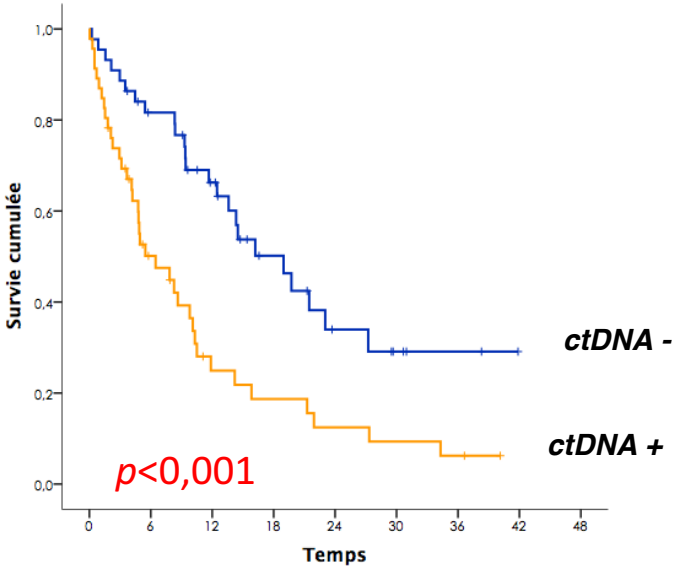


Berger, Gastroenterology, 2016

Liquid biopsy in pancreatic cancer

Prognostic value of ctDNA in advanced pancreatic cancer

	All patients n=90	ctDNA + n=46 (51%)	ctDNA - N=44 (49%)
Overall survival$^{\alpha}$ (months)	10.5	6.5	18.9
Death	61 (68%)	37 (80%)	24 (54%)



18.9 *vs* 6.5 months

Pietrasz D et al Clin cancer Res 2016

Conclusions

Une meilleure sélection des patients

Une chirurgie qui reste complexe

Un raffinement des stratégies néo/adjuvantes

Quoi de neuf
en pathologie pancréatique…

13ème journée de Gastro-entérologie de Cochin
28 janvier 2017

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Hôpital Cochin - Paris