Pancreatic Cancer Academy

Nov. 29. – 30. 2019

NH Hotel Vienna Airport

Patient Case 2: borderline resectable PDAC

Criteria for surgical resection of pancreatic cancer

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Declaration of conflict of interest

Type	
Speaker Bureau / Honoraria	**Novartis, Ipsen, AAA, Celgene; J&J**
Consultant / Advisory Board	**AAA, Mylan, Celgene**

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The setting of my talk

- PDAC
- Assessed at diagnosis as either borderline or resectable disease
- Neoadjuvant approach
- Surgical perspective for resection after therapy

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Criteria of resectability should be clear starting from the anatomical definition

Type of definition	Anatomical
R	R-Type A
BR	BR-Type A
Locally advanced: LA	LA-Type A

Isaji et al. Pancreatology 2018

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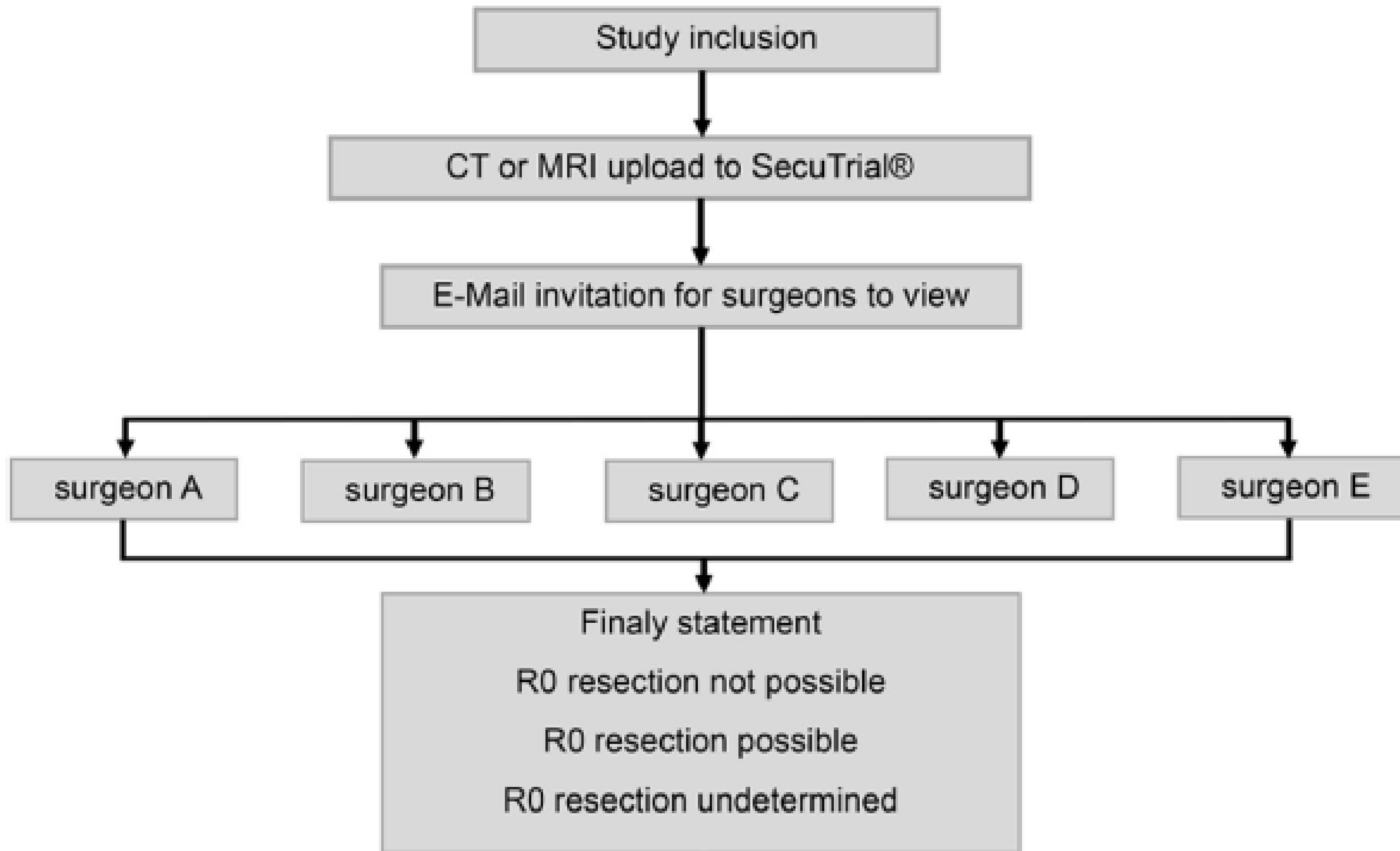
But if you take 5 experts surgeons…



Wittel et al. BCM Cancer 2018

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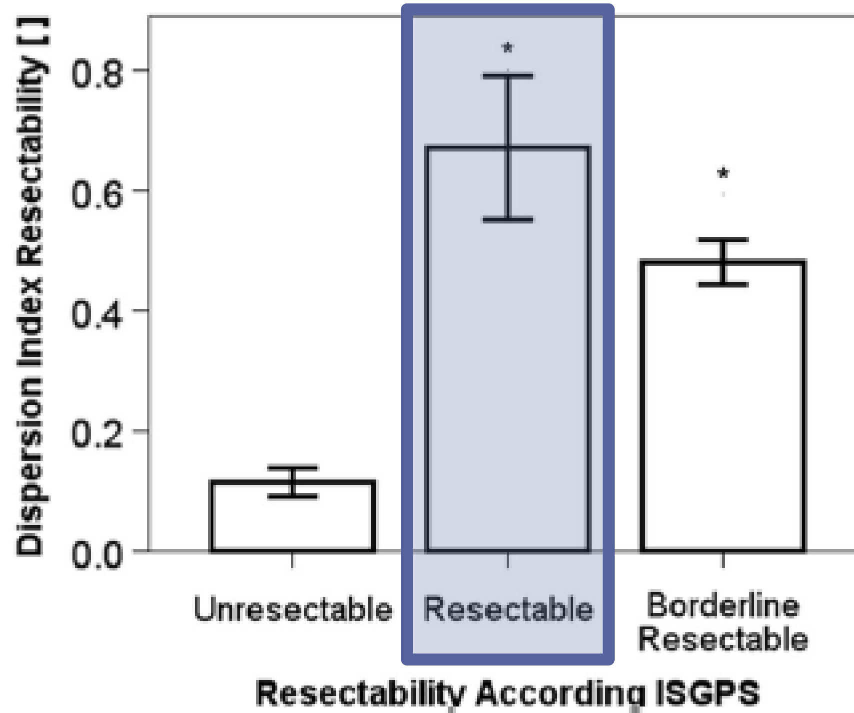
the agreement was quite low!



Wittel et al. BCM Cancer 2018

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A more difficult task: resectability criteria are nowadays multifactorial

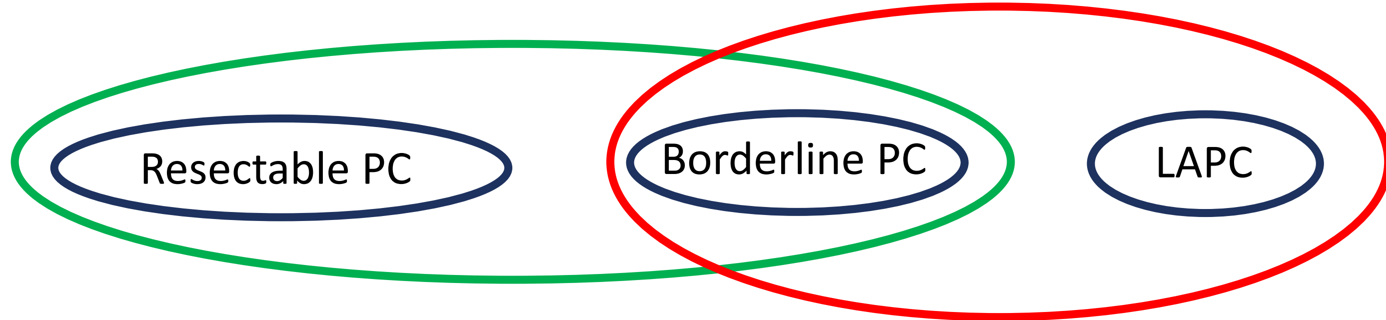
Type of definition	Anatomical	Biological	Conditional
R	R-Type A	No: R-Type A	No: R-Type A
		Yes: BR-Type B	Yes: BR-Type C
BR	BR-Type A	No: BR-Type A	No: BR-Type A
		Yes: BR-Type AB	Yes: BR-Type AC
Locally advanced: LA	LA-Type A	No: LA-Type A	No: LA-Type A
		Yes: LA- Type AB	Yes: LA-Type AC

Biological definition:	• CA 19-9 more than 500 IU/ml • Regional lymph node metastasis (biopsy or PET-CT)
Conditional host-related definition:	• Depressed performance status (PS: 2 or more)

Tumor is classified based on combination of A, B, and C
(for example, a patient with both Type B and Type C features would be classified as Type ABC).

Isaji et al. Pancreatology 2018

The literature does not help: complexity in comparing different series



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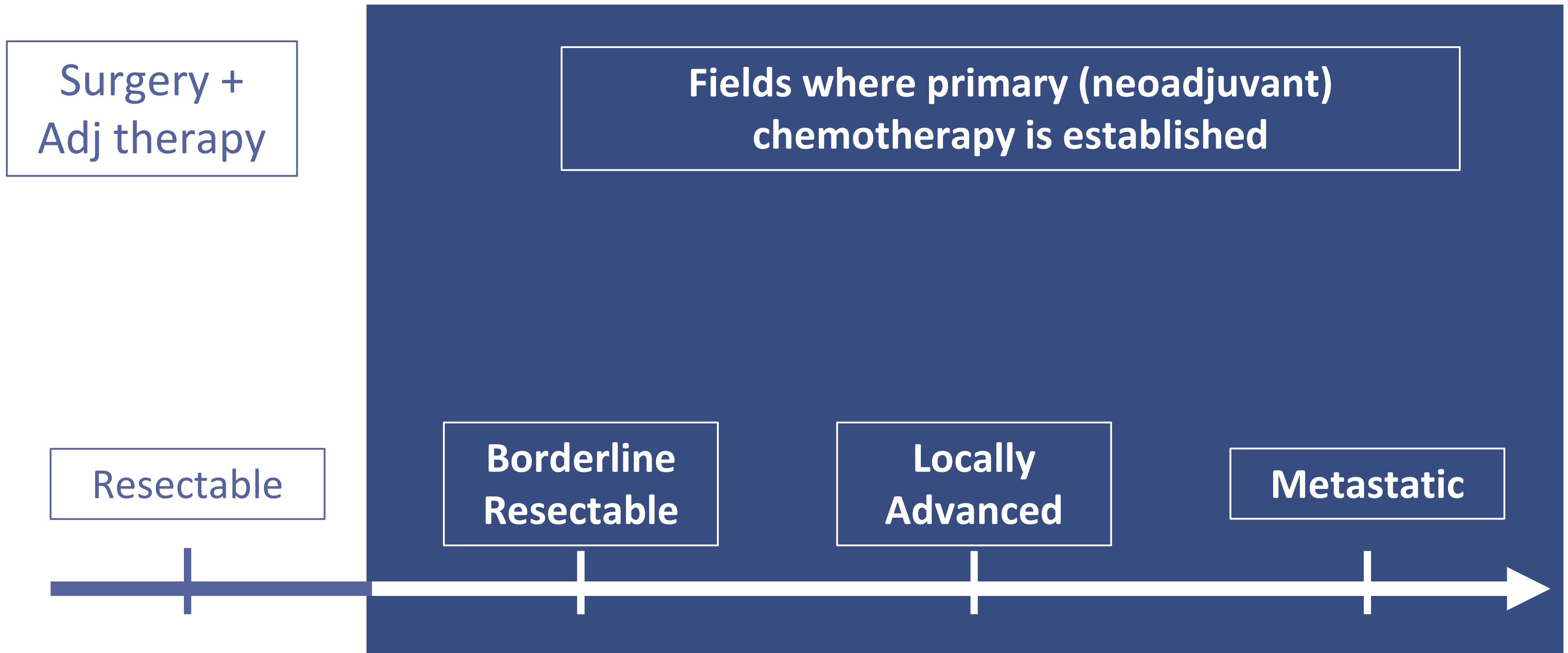
Despite some controversies on treatment strategy….



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A recent prove in favor of neoadjuvant approach at least in U.S.

Ann Surg Oncol (2019) 26:4108–4116
https://doi.org/10.1245/s10434-019-07602-6

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

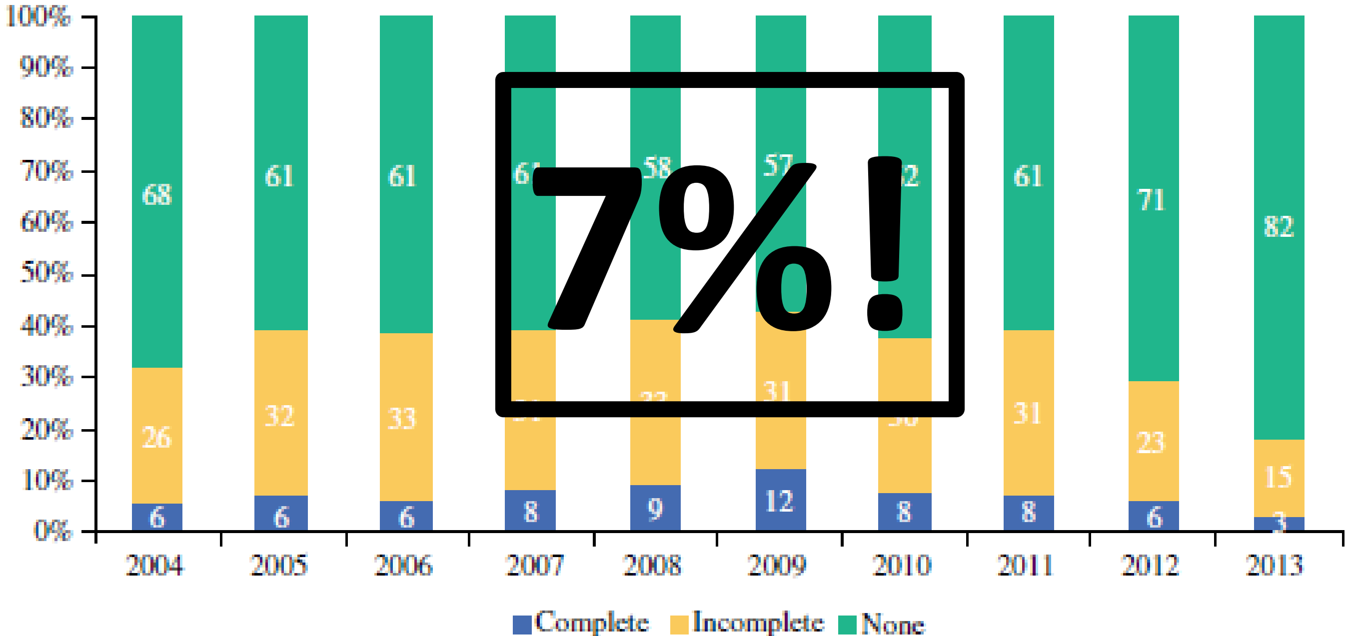
ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Completion of Adjuvant Chemotherapy After Upfront Surgical Resection for Pancreatic Cancer Is Uncommon Yet Associated With Improved Survival

Ariella M. Altman, MD[1], Keith Wirth, MD[1], Schelomo Marmor, MPH, PhD[1], Emil Lou, MD, PhD[2], Katherine Chang, MD[2], Jane Y. C. Hui, MD, MS[1], Todd M. Tuttle, MD, MS[1], Eric H. Jensen, MD[1], and Jason W. Denbo, MD[1,3]

A recent prove in favor of neoadjuvant approach: adjuvant chemotherapy completion at least in US

2,440 patients
SEER-MEDICARE 2004-2013



Altman et al. Ann Surg Oncol 2019

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Rational criteria which should favor a neoadjuvant approach

- Control of micrometastatic disease presents in around 70-80% of patients despite not recognizable

- Downsizing\staging in about 30% of patients with “modern” regimens

- To increase adjuvant therapy attrition and completion quite low due to surgical complications in a demanding surgery (morbidity 40-60% and mortality <5% even in referral centers)

- Biological selection

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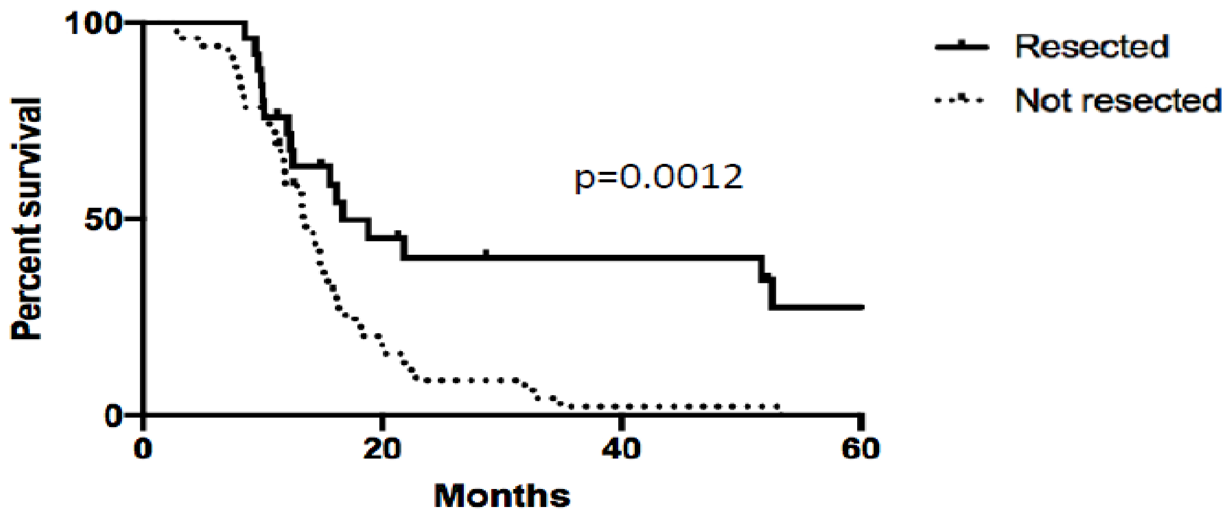
Some results are in this direction



%	Median	12 mos	36 mos	60 mos
Resected	**16.7**	**76.0**	**40.2**	**27.6**
Non-resected	13.5	58.5	2.2	0

Rangelova et al. Ann Surg 2019

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and subsequent resectability criteria are becoming….

Conclusions: All patients with BRPC/LAPC who do not progress during NAT should be considered for surgical resection, irrespective of the type or dose of NAT given. Higher levels of Ca 19-9 should not be considered an absolute contraindication for resection.

Rangelova et al. Ann Surg 2019

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One image for an increasing mood

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but …. not everything that glitters is gold

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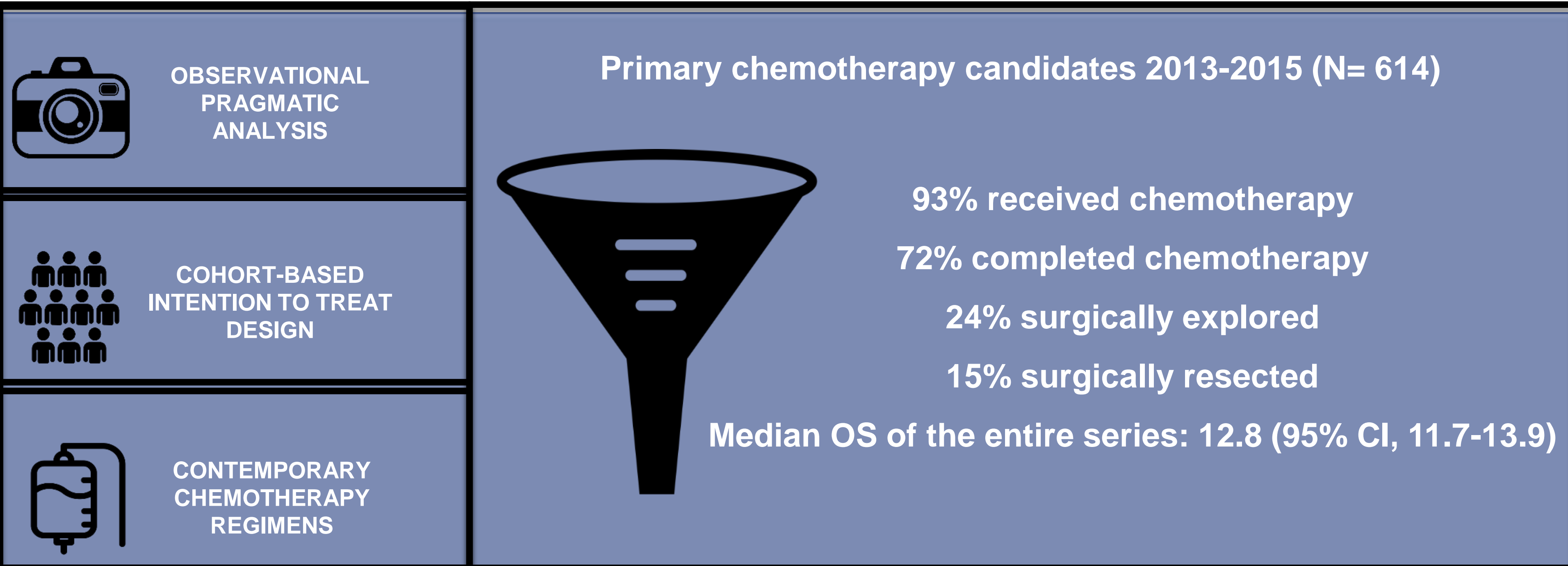
Some questions are still pending: how often does it happen?



Maggino et al. JAMA Surg 2019
to the courtesy of Prof Salvia R, Verona, Italy

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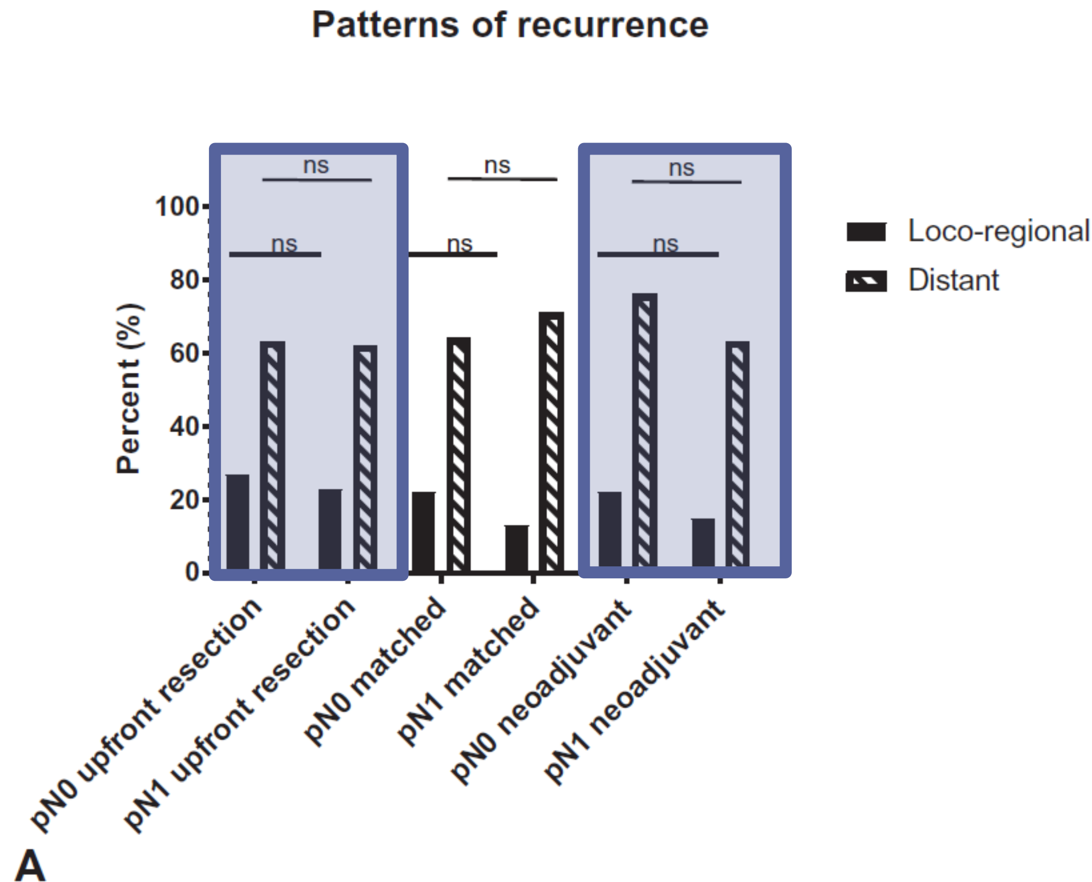
Some questions are still pending: do we change the pattern of recurrence?

(n= 546)



Honselmann et al. Ann Surg 2019

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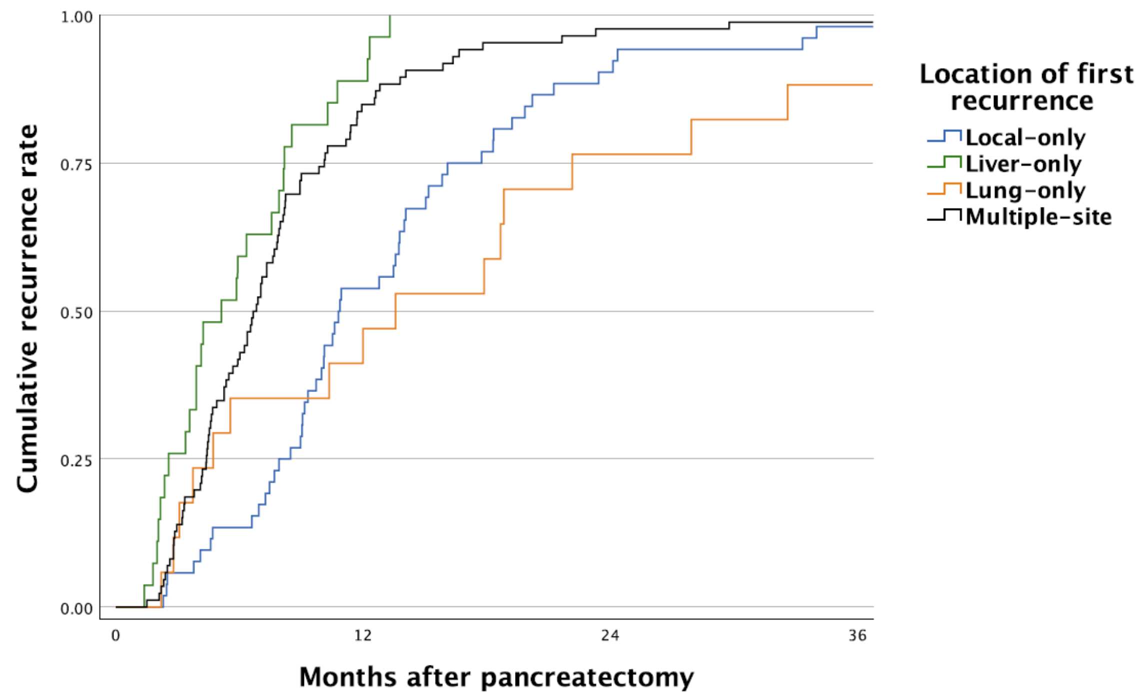
Some questions are still pending: are we able to postpone their occurrence?

(n= 231)



Recurrence patterns	*0-6 months*	*6-12 months*	*12-18 months*
Liver only (*n*=28)	60.7% (*n*=17)	89.3% (*n*=25)	100% (*n*=28)

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Groot et al. Eur J Surg Oncol 2019

Some questions are still pending: do we decrease the rate of early distant recurrences?

	SURGERY	pts	Liver recurrences <12 months
Groot V, et al. Ann Surg 2018	UPFRONT	692	95 (13.7%)
Groot V, et al Eur J Surg Oncol 2019	AFTER NEODJ	231	32 (13.8%)

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My name is biology!

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Factors associated with both RFS and OS after neoadjuvant therapy: an overview

- ***MGH:*** Charlson >1, preoperative **CA19-9** >100 U/mL, **T size** > 3.0 cm on CT scan or > 2.5 cm on pathology
- ***Verona:*** none
- ***Heidelberg:*** **CA19-9** >100 U/ml, **N+**, **M+**, **arterial/venous involvement**
- ***Stockholm:*** *not* CA19-9
- ***AGEO-FRENCH:*** CRTx, **lack of venous resection**

to the courtesy of Sven Mieog, Leiden, The Netherlands

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An additional advise: is really the resection our target or should we look at different goals?

Article

Versteijne E, et al. BJS 2018; 105: 946-958

Setting

Resectable and BL resectable

Source

Literature (38 studies):

3,484: 1,738 NAT (49.9%)

Analysis

Meta-analysis, Intention-to treat

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An additional advise: is really the resection our goal or should we look at different goals?

Type of analysis	OS (months)	p
ITT		
NAT	**18.8**	
UR	**14.8**	

Versteijne et al. BJS 2018

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An additional advise: is really the resection our goal or should we look at different goals?

Type of analysis	OS (months)	p
ITT		
NAT	18.8	
UR	14.8	
Resected		
NAT	***26.1***	
UR	***15.0***	

Versteijne et al. BJS 2018

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An additional advise: is really the resection our goal or should we look at different goals?

Type of analysis	OS (months)	p
ITT		
NAT	18.8	
UR	14.8	
Resected		
NAT	*26.1*	
UR	*15.0*	
% pts resected		
NAT	***66 (%)***	***< 0.001***
UR	***81.3 (%)***	

Versteijne et al. BJS 2018

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Some additional concern: the center, the volume and, may be, the country

Ann Surg Oncol
https://doi.org/10.1245/s10434-019-08023-1

Annals of SURGICAL ONCOLOGY
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ORIGINAL ARTICLE – PANCREATIC TUMORS

National Use of Chemotherapy in Initial Management of Stage I Pancreatic Cancer and Failure to Perform Subsequent Resection

Ryan J. Ellis, MD, MS[1,2,3], Jessie W. Ho, MD[1,2], Cary Jo R. Schlick, MD[1,2], Ryan P. Merkow, MD, MS[1,2,3], David J. Bentrem, MD, MS[1,2], Karl Y. Bilimoria, MD, MS[1,2,3], and Anthony D. Yang, MD, MS[1,2]

[1]Surgical Outcomes and Quality Improvement Center (SOQIC), Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Northwestern Institute for Comparative Effectiveness Research in Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL; [3]Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, IL

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Some additional concern: the center, the volume and, may be, the country

17,495 patients
SEER-MEDICARE 2005-2015

Preop chemotherapy	OR (95%CI)
26.6%	
More likely	
≥ 80years of age	1.64 (1.39-1.93)
T2 tumor	2.56 (2.36-2.78)
Low-volume center	2.10 (1.63-2.71)

Ellis al. Ann Surg Oncol 2019

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Some additional concern: the center, the volume and, may be, the country

17,495 patients
SEER-MEDICARE 2005-2015

Subsequent resection	OR (95%CI)
33.5%	
More likely	
T1 tumor	1.22 (1.04-1.43)
High-volume center	4.03 (2.90-5.06)

Only 20.4% of hospitals performed resection in >50% of patients after upfront chemotherapy

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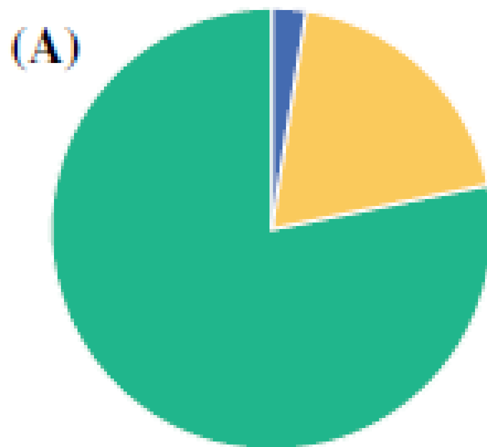
Ellis al. Ann Surg Oncol 2019

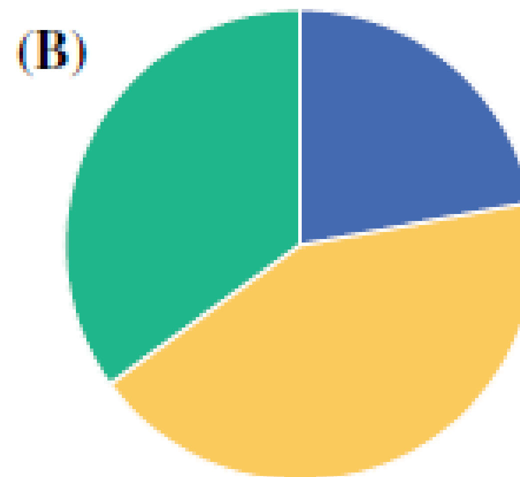
Some additional concern: the center, the volume and, may be, the country

17,495 patients
SEER-MEDICARE 2005-2015

Upfront chemotherapy



Subsequent resection



- **Individual factors: e.g. patient age, T stage**
- **Hospital factors: e.g. volume, academic status**
- **Unmeasured factors; e.g. surgeon preference**

Ellis al. Ann Surg Oncol 2019

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Criteria for surgical resection of pancreatic cancer after neoadjuvant chemotherapy

- A “neoadjuvant” approach really seems better “cover” all needs in non-metastatic setting
- “Surgical skills” is the right **USERNAME** before any indication to move to the OR (MDT approach, expert dedicated surgical team)

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Criteria for surgical resection of pancreatic cancer (II)

- “Waiting for “useful” molecular signatures that will lead to a personalized also surgical approach, results should be according an ITT basis (**“all that glitters ain't gold!”**)
- “Biological selection” remains unfortunately the right **PASSWORD** for any therapeutic choice

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Thank you

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