COME TRATTARE LA NEOPLASIA LOCALMENTE AVANZATA BORDERLINE PER RESECABILITÀ

Il chirurgo

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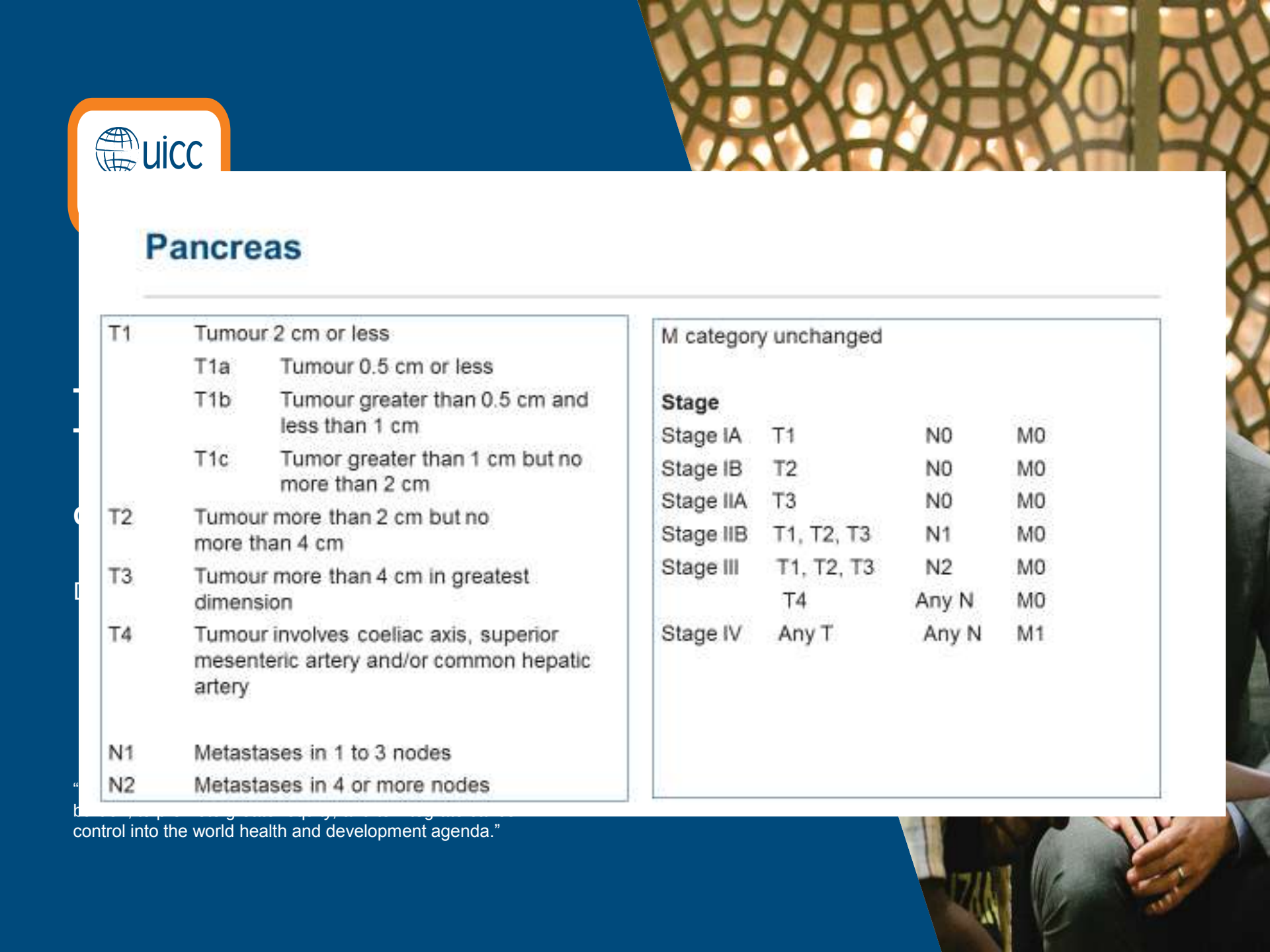
My today agenda

- The mess of definitions for either Bordeline or LAPC
- Expectation after new primary oncological therapies
- What are the surgical outcomes?
- Problems with the reassessment
- Who should be eventually operated upon?
- Toward a new comprehensive paradigm?

My today agenda

- **The mess of definitions for either Bordeline or LAPC**



Pancreas

T1	Tumour 2 cm or less	
	T1a	Tumour 0.5 cm or less
	T1b	Tumour greater than 0.5 cm and less than 1 cm
	T1c	Tumor greater than 1 cm but no more than 2 cm
T2	Tumour more than 2 cm but no more than 4 cm	
T3	Tumour more than 4 cm in greatest dimension	
T4	Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery	
N1	Metastases in 1 to 3 nodes	
N2	Metastases in 4 or more nodes	

M category unchanged

Stage			
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

control into the world health and development agenda."

Definition from surgical\oncological standpoints

Definitions

- Resectable
- Borderline
- Unresectable

According to:

- Relationship between tumor & vessels
- Technical affordability (resection & reconstruction, if needed)
- Concern of achieving
  - an R0 resection
  - an acceptable DFS (by M Falconi)

In other words

Borderline

A definition of a wide gray area which usually accounts for around 15-25% of patients in whom a diagnosis of PDAC is done.

For a proper assessment A,B, C (anatomical, biological and patient related frailty) criteria must be looked for and considered

The definition of LAPC

- No metastatic disease to liver and/or other distant organs or nodes and/or peritoneal involvement
- Vascular involvement technically not affordable

A setting where two concepts are synonymous

Anatomical definition

=

Surgical no resectability

A setting where every surgeon must say

What should be common to these two settings whichever defined?

- No upfront surgery for either oncological or technical needs
- A single (chemo) or combined (chemo + radiochemo) therapeutic approaches first
- By definition these approaches should be defined either neoadjuvant (in BL) or primary (in LAPC)
- Different rate of surgical expectation thereafter

My today agenda

- The mess of definitions for either Bordeline or LAPC
- **Expectation after new primary oncological therapies**

What already exists in the current landscape?

- FOLFIRINOX

  ± modified

  ± radio\chemoradiotherapy

- Gem + Nab-paclitaxel

  ± radio\chemoradiotherapy

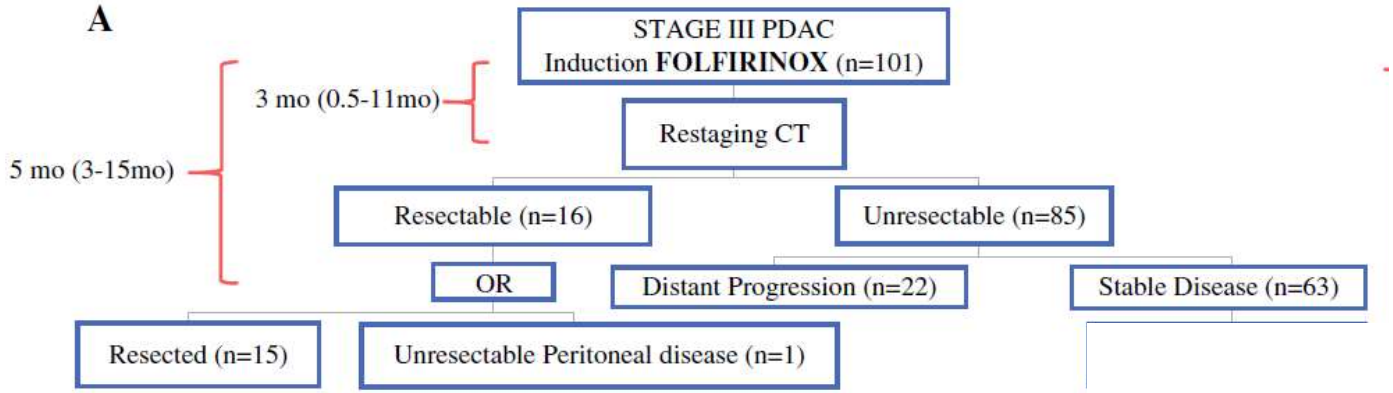
- other

FOLFIRINOX from surgical point of view

	Number of patients	Radiotherapy or chemoradiotherapy	Resection	R0 resection
Boone[22]	10	5 (50%)	2 (20%)	1 (50%)
Conroy[12]	11	NR	0	NA
Faris[21]	22	20 (91%)	5 (23%)	5 (100%)
Gunturu[24]	16	NR	2 (13%)	NR
Hohla[18]	6	2 (33%)	2 (33%)	NR
Hosein[23]	14	9 (64%)	6 (43%)	5 (83%)
Mahaseth[19]	20	10 (50%)	4 (20%)	3 (75%)
Marthey[25]	77	24 (31%)	28 (36%)	25 (89%)
Mellon[28]	21	21 (100%)	5 (24%)	5 (100%)
Moorcraft[26]	8	NR	2 (25%)	NR
Peddi[20]	19	NR	4 (21%)	NR
Sadot[29]	101	63 (62%)	31 (31%)	16 (52%)
Total	325	154 (57%)	91 (28%)	60 (74%)

Suker M, et al. Lancet Oncol 2016

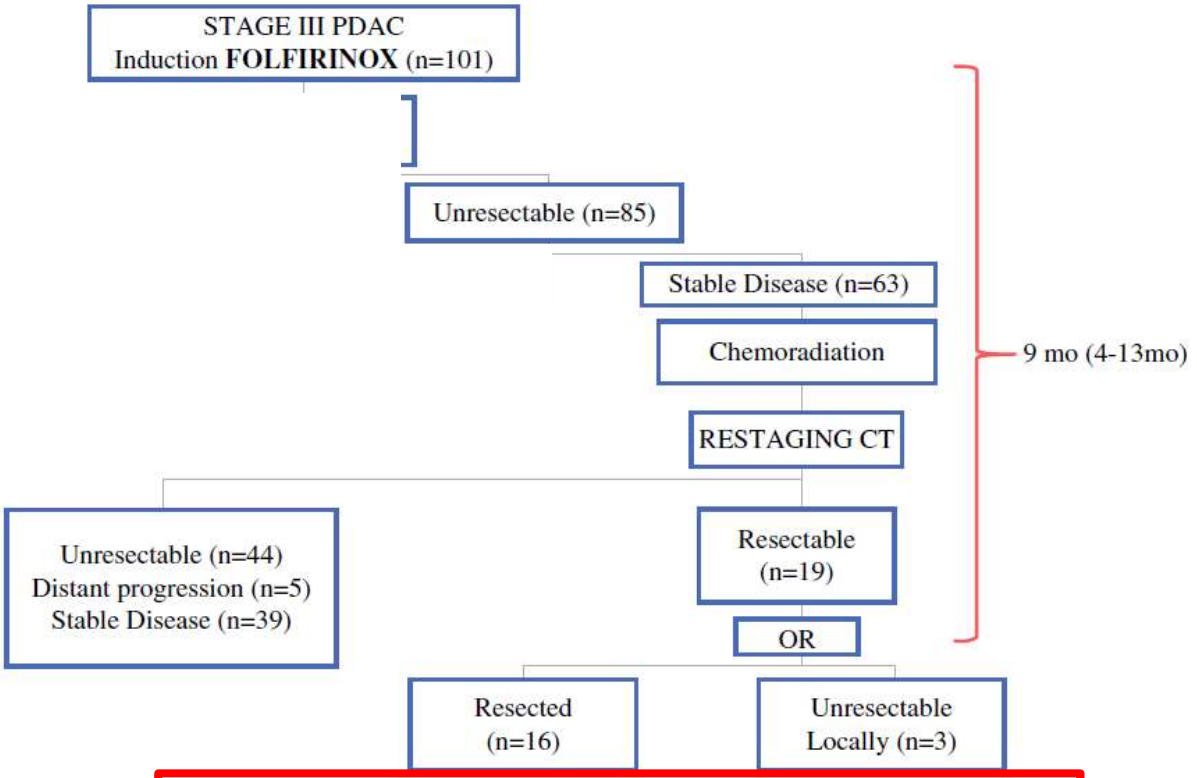
FOLFIRINOX + radio/chemoradiotherapy from surgical point of view



Achieved resection rate: 14.8%

Sadot E, et al. Ann Surg Oncol 2015

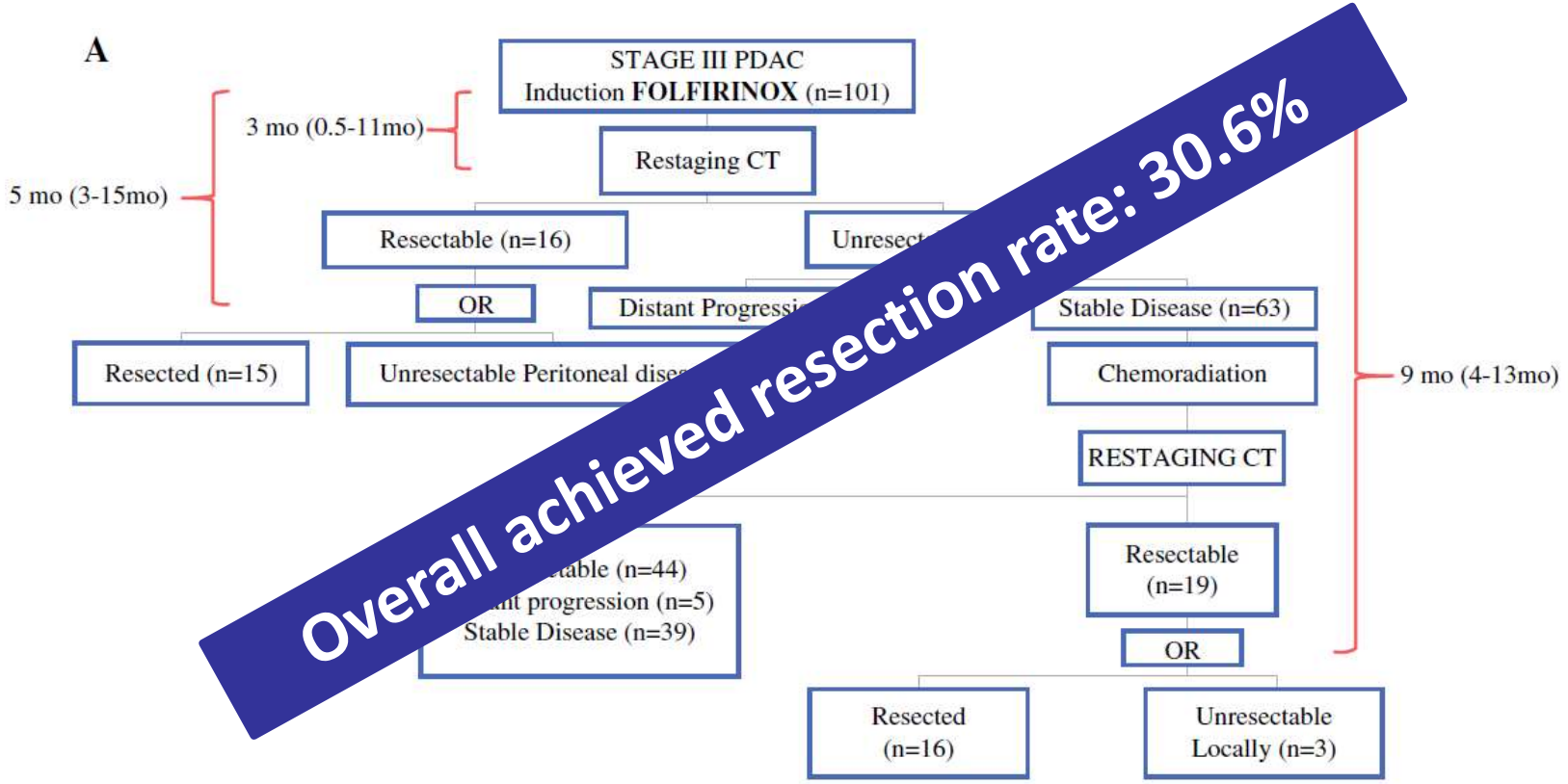
FOLFIRINOX + radio/chemoradiotherapy from surgical point of view



Additional resections rate achieved: 25.3%

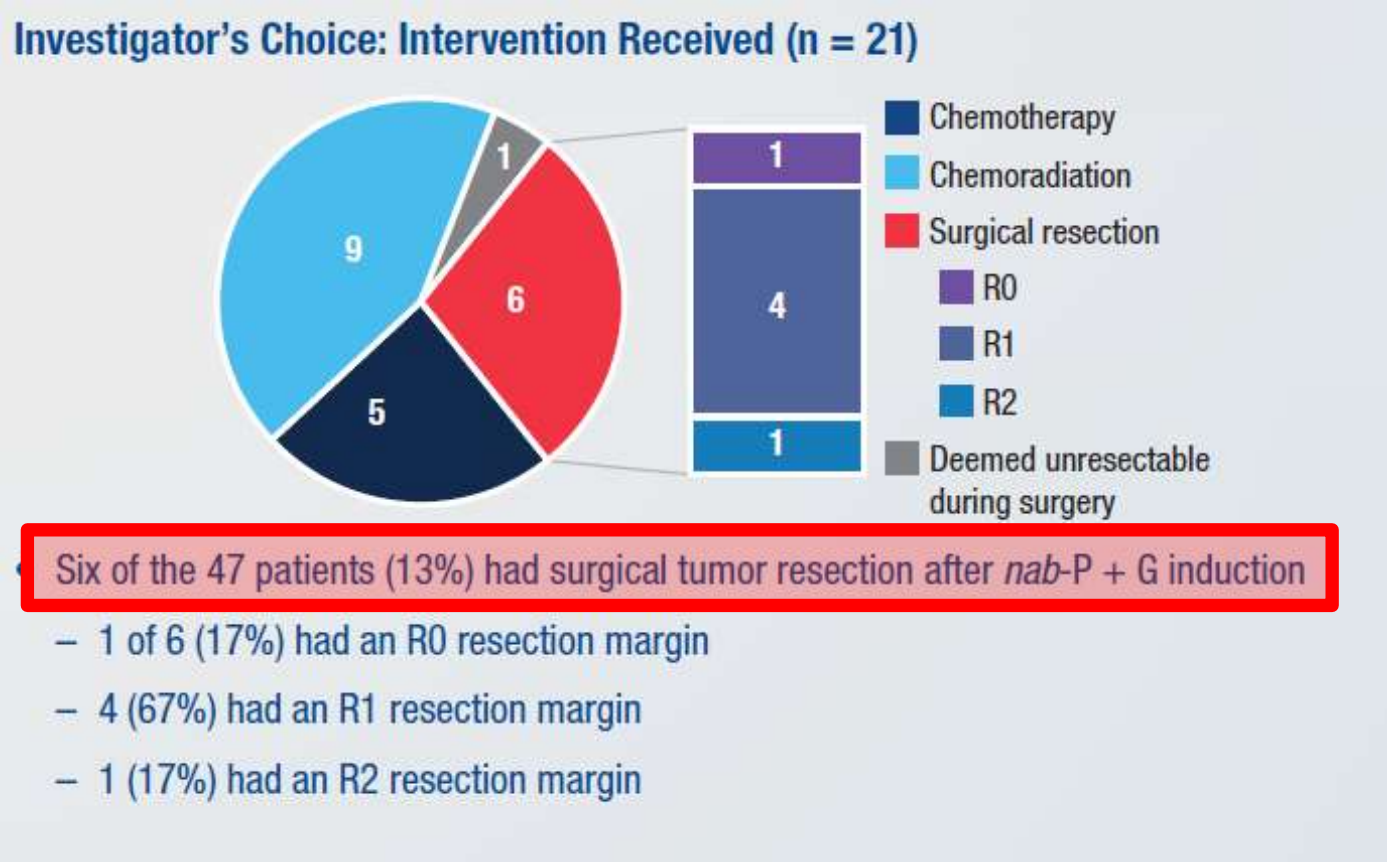
Sadot E, et al. Ann Surg Oncol 2015

FOLFIRINOX + radio/chemoradiotherapy from surgical point of view



Sadot E, et al. Ann Surg Oncol 2015

Gem+Nab-paclitaxel from surgical point of view



Jill L, et al. ASCO GI 2017

Other from surgical point of view

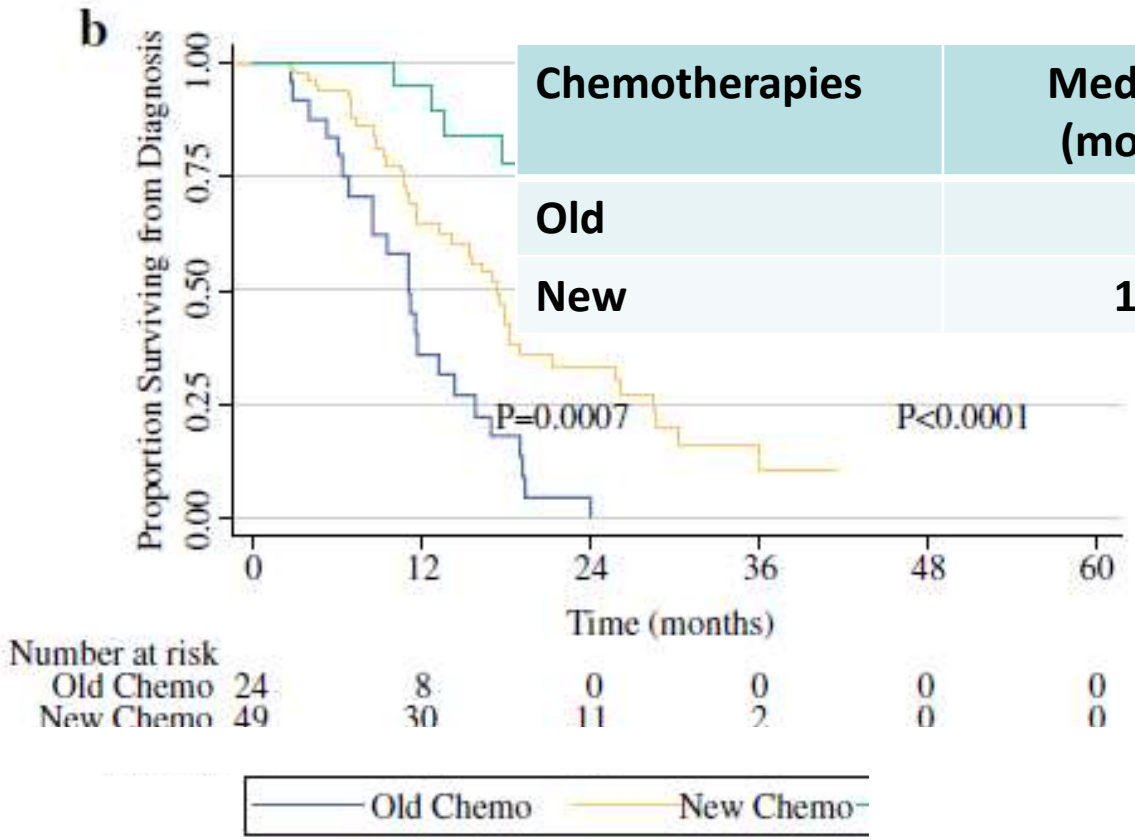
Regimen	N	resected
gem/FU-based[1-3]	134-365	26-33%
FolfIrinOx[4-5]	355	26-28%
AG/4drugs[unpubl]	223	27%

By courtesy of Michele Reni

My today agenda

- Expectation after new primary oncological therapies
- **What are the surgical outcomes?**

OS *vs.* type of treatment

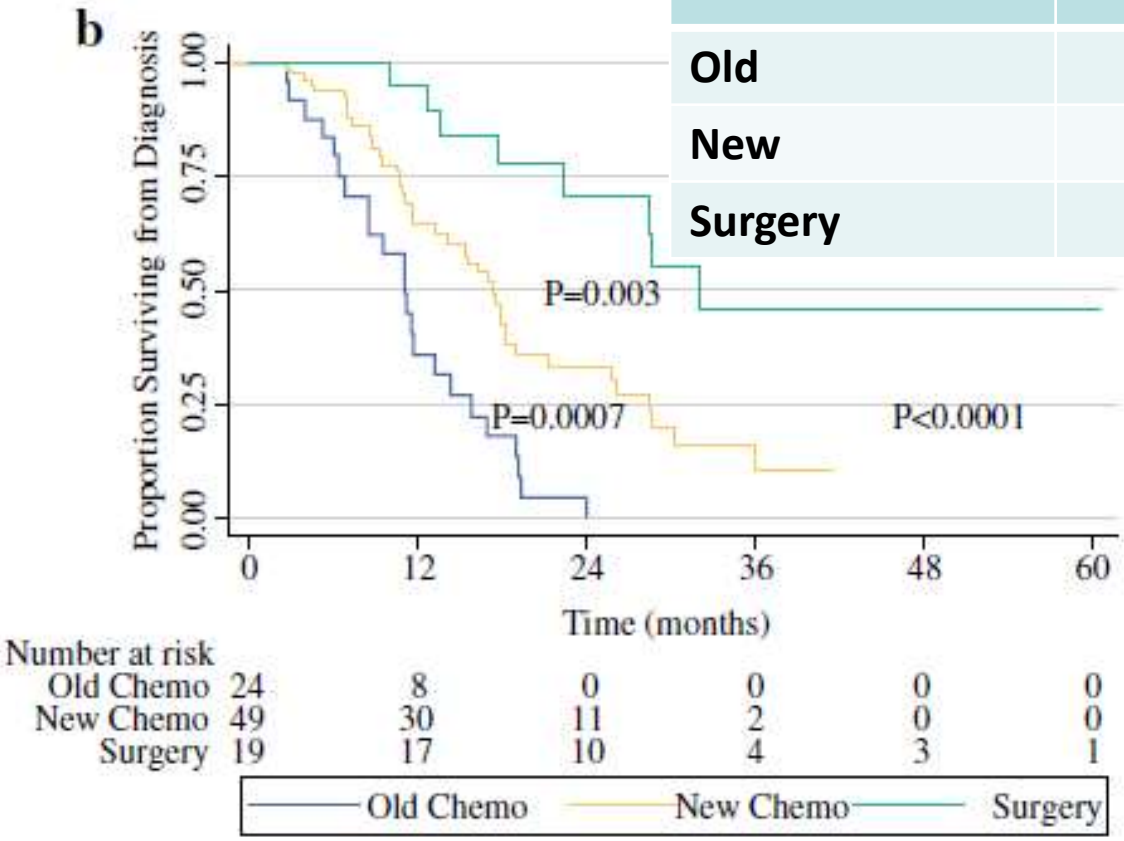


Chemotherapies	Median OS (months)
Old	11
New	17.3

Bednar F, et al. Ann Surg Oncol 2017

OS *vs.* type of treatment

Chemotherapies	Median OS (months)
Old	11
New	17.3
Surgery	32



Bednar F, et al. Ann Surg Oncol 2017

LAPC: Conversion to resectable disease, myth or new reality? A first take home message

- New therapies allow a previous unfeasible resection as possible in 1 out 3-4 patients, as overall
- The addition of radio/chemoradioterapy might have an adding value if resection is not feasible, yet
- The percentages of R0 are quite good
- Once the resection is performed OS is better rather than oncological therapies alone

My today agenda

- The mess of definitions for either Bordeline or LAPC
- Expectation after new primary oncological therapies
- What are the surgical outcomes?
- **Problems with the reassessment**

A problem already arisen some years ago

Response of Borderline Resectable Pancreatic Cancer to Neoadjuvant Therapy Is Not Reflected by Radiographic Indicators

Matthew H. G. Katz, MD[1]; Jason B. Fleming, MD[1]; Priya Bhosale, MD[2]; Gauri Varadhachary, MD[3]; Jeffrey E. Lee, MD[1]; Robert Wolff, MD[3]; Huamin Wang, MD[4]; James Abbruzzese, MD[3]; Peter W. T. Pisters, MD[1]; Jean-Nicolas Vauthey, MD[1]; Chusilp Charnsangavej, MD[2]; Eric Tamm, MD[2]; Christopher H. Crane, MD[5]; and Aparna Balachandran, MD[2]

BACKGROUND: Experience with preoperative therapy for other cancers has led to an assumption that borderline resectable pancreatic cancers can be converted to resectable cancers with preoperative therapy. In this study, the authors sought to determine the rate at which neoadjuvant therapy is associated with a reduction in the size or stage of borderline resectable tumors. **METHODS:** Patients who had borderline resectable pancreatic cancer and received neoadjuvant therapy before potentially undergoing surgery at the authors' institution between 2005 and 2010 were identified. The patients' pretreatment and post-treatment pancreatic protocol computed tomography images were rereviewed to determine changes in tumor size or stage using modified Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) and standardized anatomic criteria. **RESULTS:** The authors identified 129 patients who met inclusion criteria. Of the 122 patients who had their disease restaged after receiving preoperative therapy, 84 patients (69%) had stable disease, 15 patients (12%) had a partial response to therapy, and 23 patients (19%) had progressive disease. Although only 1 patient (0.8%) had their disease downstaged to resectable status after receiving neoadjuvant therapy, 85 patients (66%) underwent pancreatectomy. The median overall survival duration for all 129 patients was 22 months (95% confidence interval, 14-30 months). The median overall survival duration for the patients who underwent pancreatectomy was 33 months (95% confidence interval, 25-41 months) and was not associated with RECIST response ($P = .78$). **CONCLUSIONS:** Radiographic downstaging was rare after neoadjuvant therapy, and RECIST response was not an effective treatment endpoint for patients with borderline resectable pancreatic cancer. The authors concluded that these patients should undergo pancreatectomy after initial therapy in the absence of metastases. *Cancer* 2012;118:5749-56. © *2012 American Cancer Society.*

Performances of CT in resectability assessment after neoadjuvant TXs

CT accuracy for determination of resectability of pancreatic head cancer.

	Accuracy	Specificity	False positives	Negative predictive value
Control group	34/41 83%	88%	4/41 10%	91%
Neoadjuvant group	18/31 58%	52%	12/31 39%	93%
p value	0.039	0.003	0.005	ns

ns, non significant.

Cassinotto C, et al. Eur J Radiol 2013

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- **Who should be eventually operated upon?**

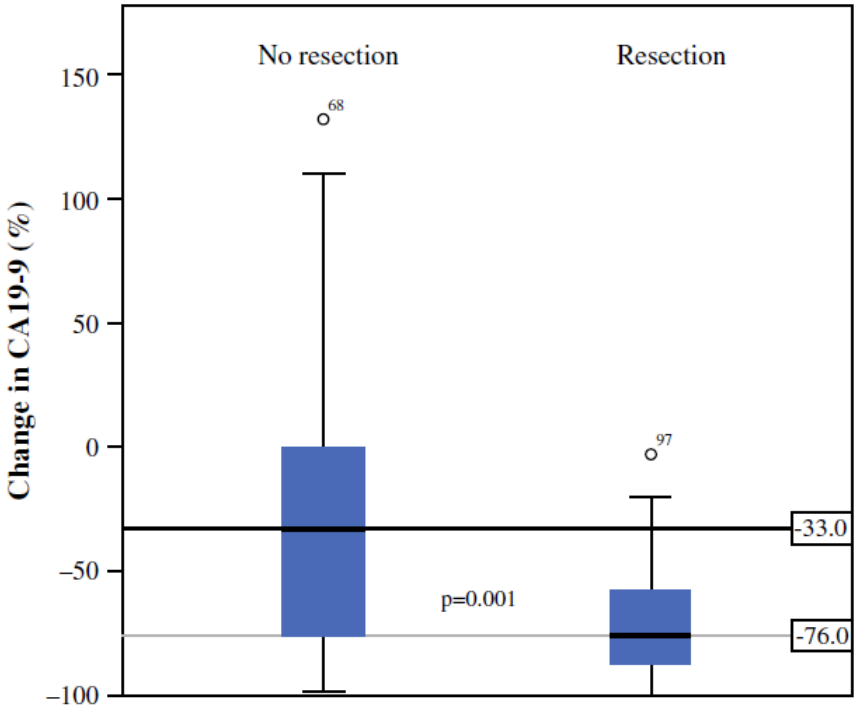
Who should be eventually operated upon?

In the absence of reliable criteria to evaluate response, the following strategy (**can be**) routinely followed:

- continuation of palliative chemotherapy in case of progressive disease (based on CT findings or tumoral marker values);
- in patients with stable, or regressing disease, treatment is based on clinical evaluation and evolution of CA 19-9:
  - patients with clinical improvement, decreased CA 19-9 serum level (<200) and if disease looks stable or regressing on CT: surgical exploration is performed to see if resection is possible,
  - in the other cases: continuation of medical treatment.

Cassinotto C, et al. Diagnostic and Interventional Imaging 2016

Ca 19-9 again!!!!
Ca 19-9 reduction after induction therapy



Sadot E, et al. Ann Surg Oncol 2015

Ca 19-9 again!!!!
Ca 19-9 as a decision driver

	N	Median OS (months)	2-yr OS	5-yr OS	p
CA19.9 responders	**140**	**19.4**	**36.2%**	**7.3%**	
CA19.9 non-responders	**40**	**11.4**	**15.9%**	**0%**	**0.0002**

Responders: more than 50% decrease

Reni M, et al. Ann Oncol 2017

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CA19.9 non-responders not resected	**31**	**11.4**	**12.9%**	**0%**	**0.28**

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CA19.9 responders not resected	**101**	**19.2**	**25.5%**	**2.7%**	**<0.00001**
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Reni M, et al. Ann Oncol 2017

BL or LAPC: the new reality of conversion to an oncological\technical resectability A 2nd take home message

- The rich desmoplastic reaction does not often allow a recognizable tumor downsizing
- This fact might impair the radiological capability to properly recognize the response to therapy
- If no progression, Ca 19.9 fall has got a substantial value both in term of resectability and outcomes

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- Who should be eventually operated upon?
- **Toward a new comprehensive paradigm?**

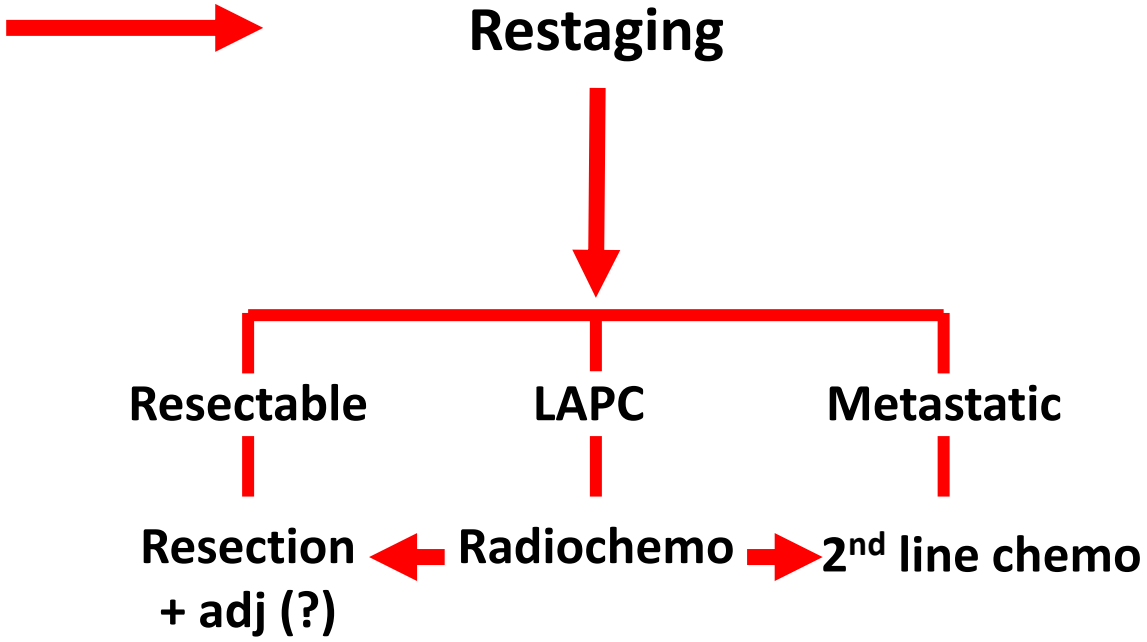
It is time for changing both the perspective and the paradigm in all settings

Upon diagnosis

Neoadjuvant

or

Primary chemotherapy



The roles in the LAPC or BL disease from the past….

by courtesy of Gianpaolo Balzano

The roles in the LAPC or BL disease from the past to present

by courtesy of Gianpaolo Balzano

Thank you

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Chirurgia del Pancreas