ORDINE
MEDICI CHIRURGHI
E ODONTOIATRI
DELLA PROVINCIA
DI BRESCIA

COMMISSIONE CULTURA
Coordinatore: Dott. Germano Bettoncelli

In collaborazione con

Fondazione
Nadia Valsecchi

Convegno

DIAGNOSI E CURA DEI TUMORI PANCREATICI

Sala Conferenze Ordine Medici ed Odontoiatri - Via Lamarmora n. 167 (Palazzo il Diamante) - Brescia

19 maggio 2018 - ore 8.00

ESMO
Designated Centre of Integrated Oncology and Palliative Care

FONDAZIONE GISCAD
SOCIO FONDATORE

Organization Accredited
by Joint Commission International

Chemio prima o chemio dopo l'intervento chirurgico?

Alberto Zaniboni

Oncologia Medica
Fondazione Poliambulanza - Brescia

Le mie disclosures

Research grants:

Roche, Novartis, Pfizer, Astra Zeneca, Janssen, Boheringer

Advisory boards / Speaker Bureau:

Amgen, Merk Serono, Bayer, Servier, BMS, Lilly, Sanofi

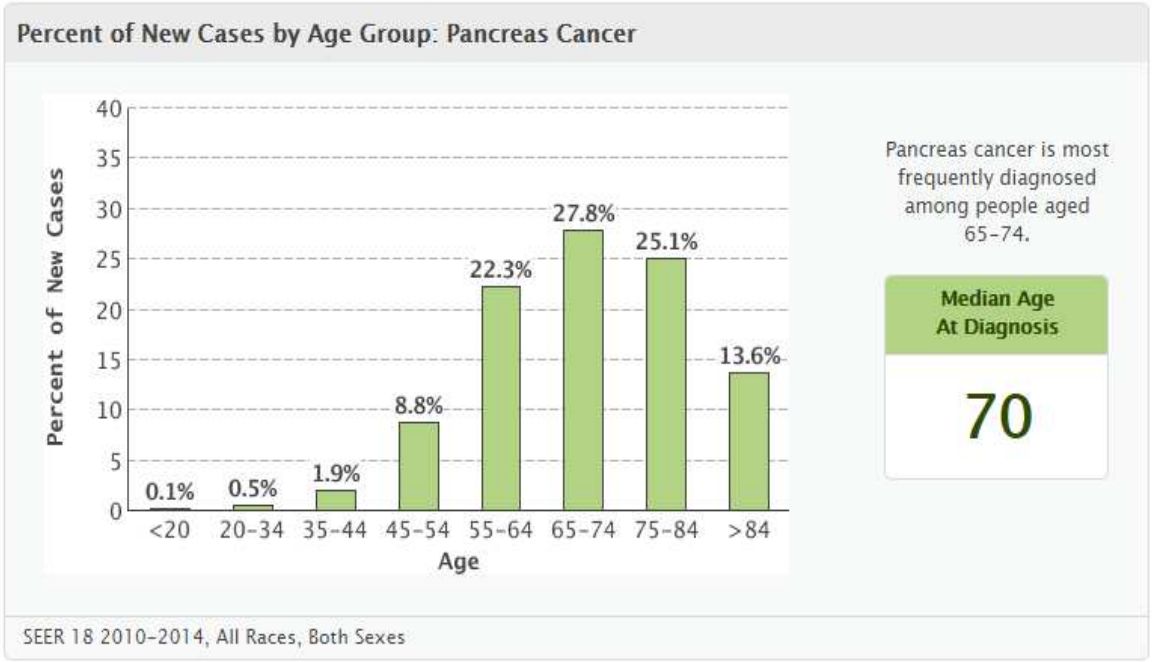
Pancreatic Adenocarcinoma: A Very Tough Disease!

- **~ 85% of patients are diagnosed with advanced unresectable disease**
- **~ 80% of patients who have resection and adjuvant therapy relapse**
- **“Cure” rate is only ~5%**
- **Median survival of patients with metastases without treatment is only about three months**
- **Incidence numbers and numbers of deaths are almost identical**

Pancreatic cancer epidemiology: 12.000/year in Italy

Stage	Incidence (%)	5 year survival (%)	N° of cases
Resectable	20%	20%	2400
Borderline resectable	10%	0-5%	1200
Locally advanced/ unresectable	30%	0%	3600
Metastatic	40%	0%	4800

Major Unmet Need: Unfavorable PS & Elderly



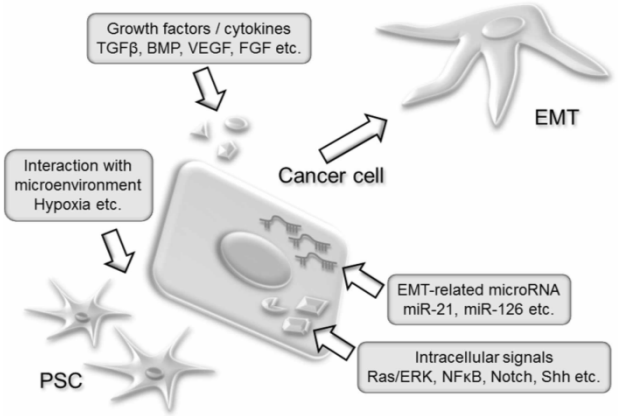
Majority of patients with advanced pancreatic cancer have PS of 2-3

- Clinical trials accrue PS 0-1 and median age 60-62 years
- **Fatigue** is *the* most important limiting factor with gemcitabine/*nab*-paclitaxel or FOLFIRINOX

National Cancer Institute. SEER Cancer Stat Facts: Pancreas Cancer

Pancreatic cancer is a systemic disease from the onset

- High frequency of systemic failures of disease even after curative resections
- Subclinical metastases present at the outset



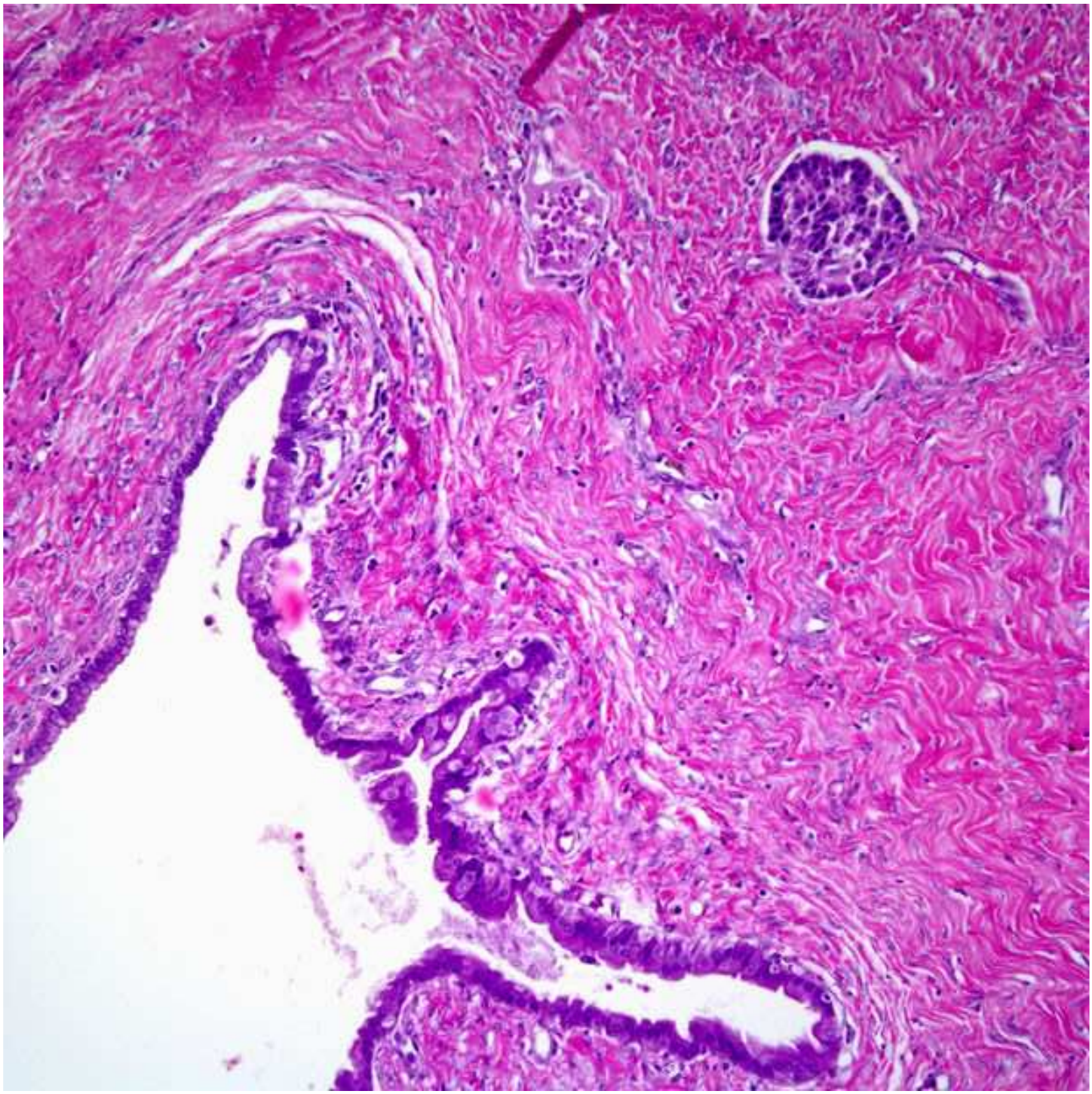
Cell

EMT and Dissemination Precede Pancreatic Tumor Formation

Rhim AD et al. Cell 2012

1 cm: 30% of probability of metastases

3 cm: 90% of probability of metastases



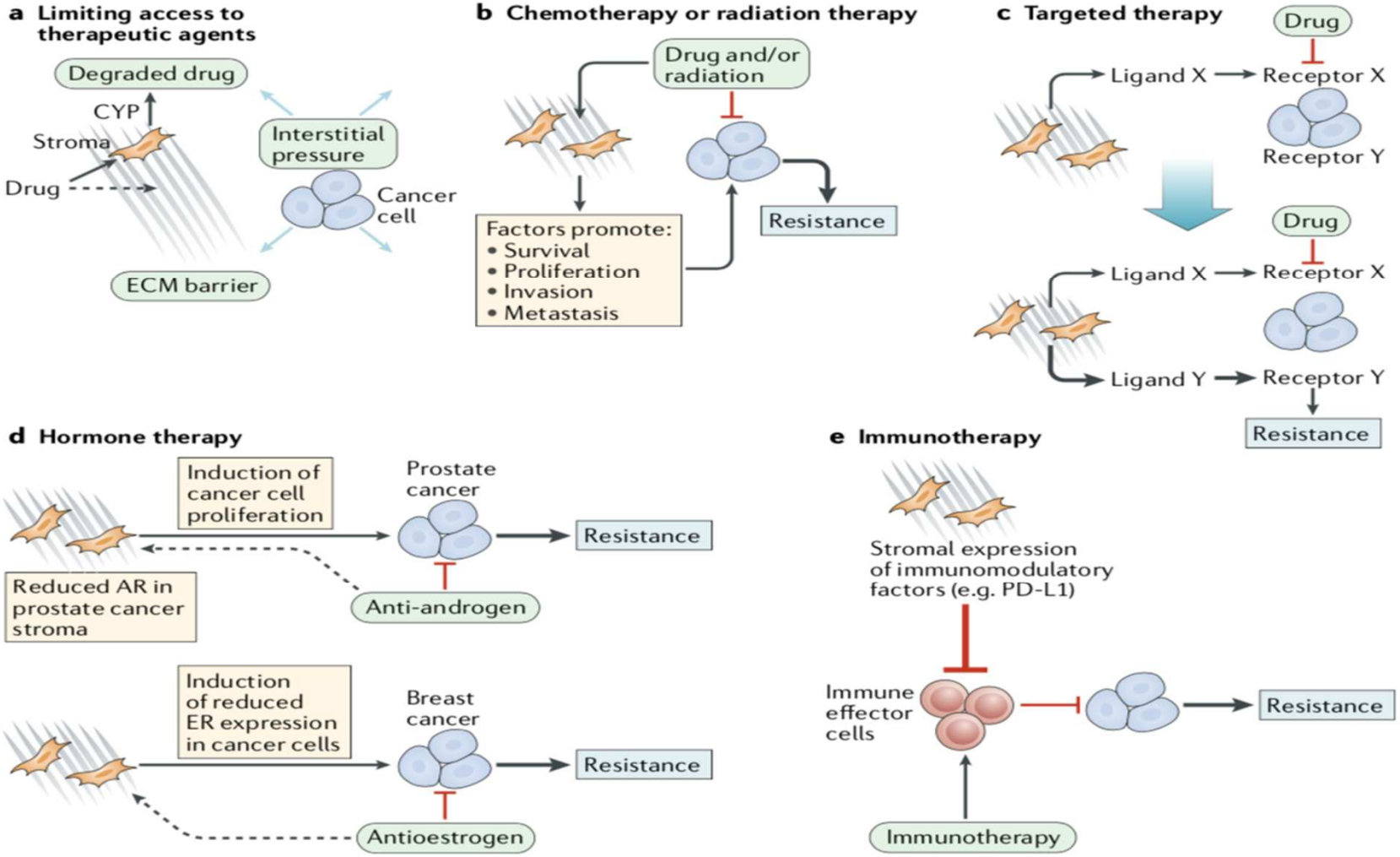


Fig. 2 | **Tumour-stroma-mediated chemoresistance.** In response to anticancer therapy, the tumour stroma mediates resistance to therapy and disease recurrence. **a** | Dense fibrosis causes limited access of cancer cells to therapeutic agents in three ways: creating an extracellular matrix (ECM) barrier that such agents cannot diffuse through; promoting stromal cytochrome P450 (CYP)-mediated degradation of drugs; and increasing interstitial pressure that prevents therapeutic agents from entering the tumour. **b** | In response to chemotherapy or radiation therapy, cancer-associated fibroblasts (CAFs) and mesenchymal stromal cells (MSCs) secrete different growth factors, cytokines, and chemokines that promote cancer cell survival, proliferation, invasion, and metastasis, leading to resistance. **c** | Targeted inhibition of a specific pathway (ligand X–receptor X) results in the stromal secretion of new ligands (ligand Y–receptor Y), resulting in survival and resistance. **d** | In prostate cancer, decreased androgen receptor (AR) expression in the stroma leads to resistance to androgen-deprivation therapies. In breast cancer, the stroma promotes decreased oestrogen receptor (ER) expression in cancer cells, leading to resistance to antihormonal therapies. **e** | CAFs, MSCs, and ECM suppress effector immune cell activation and tumour infiltration. PD-L1, programmed cell death 1 ligand 1.

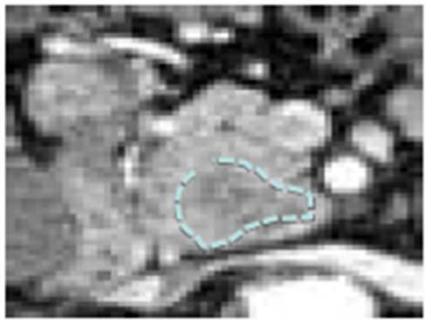
Ann Surg Oncol (2009) 16:1725–1726
DOI 10.1245/s10434-009-0409-5

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

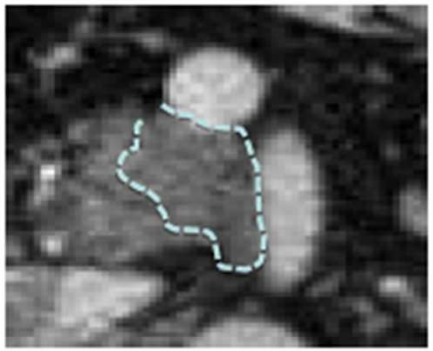
ORIGINAL ARTICLE – CONSENSUS REPORT: RESECTABLE AND BORDERLINE RESECTABLE PANCREAS CANCER

AHPBA/SSO/SSAT Consensus Conference on Resectable and Borderline Resectable Pancreatic Cancer: Rationale and Overview of the Conference

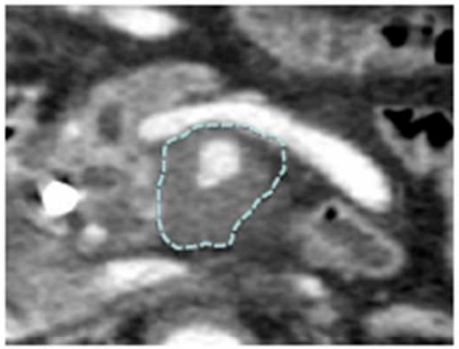
The "concept" of surgical resectability



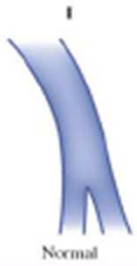
No metastases
No vascular contact



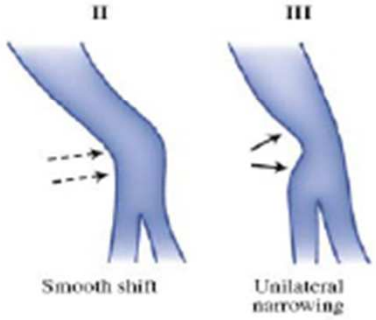
Portal/SMV
Or SMA < 180°



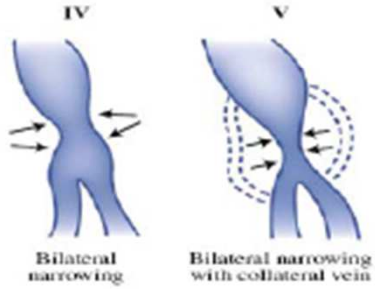
SMA > 180°
Celiac trunk abutment
SMV or portal occlusion
Vena cava/aorta



Resection R0 possible



Resection ≥ R1



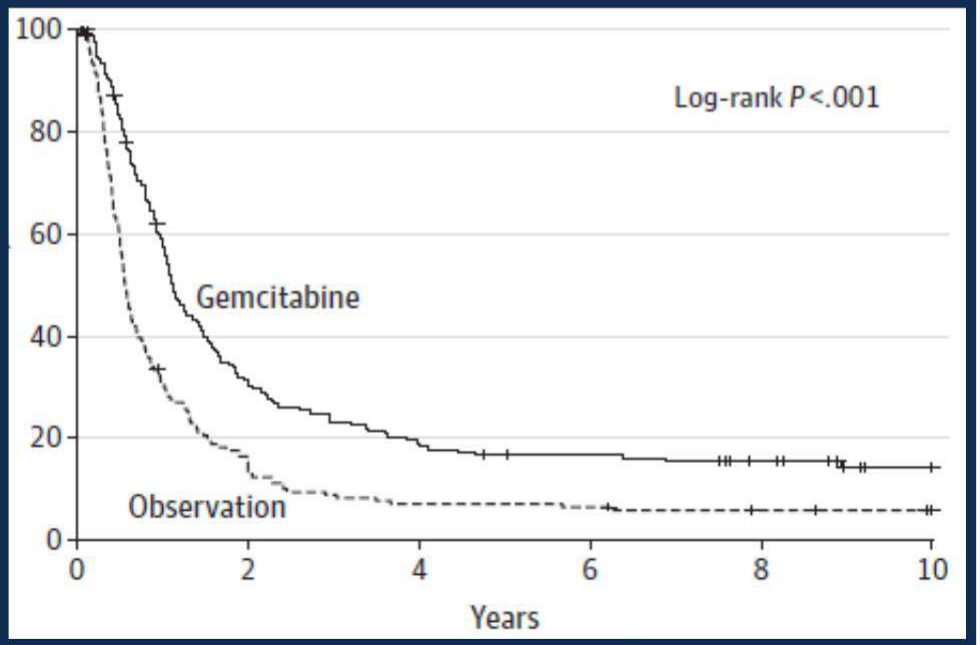
No resection

Tempero M, J Natl Compr Canc Netw 2014
He J, W J Gastroenterol 2014

Evidence for Chemotherapy

CONKO-001

- Adj Gem vs. Sx alone
- N = 368, 1998-2004
- 1^0: DFS (13.4 vs. 6.7 mths)

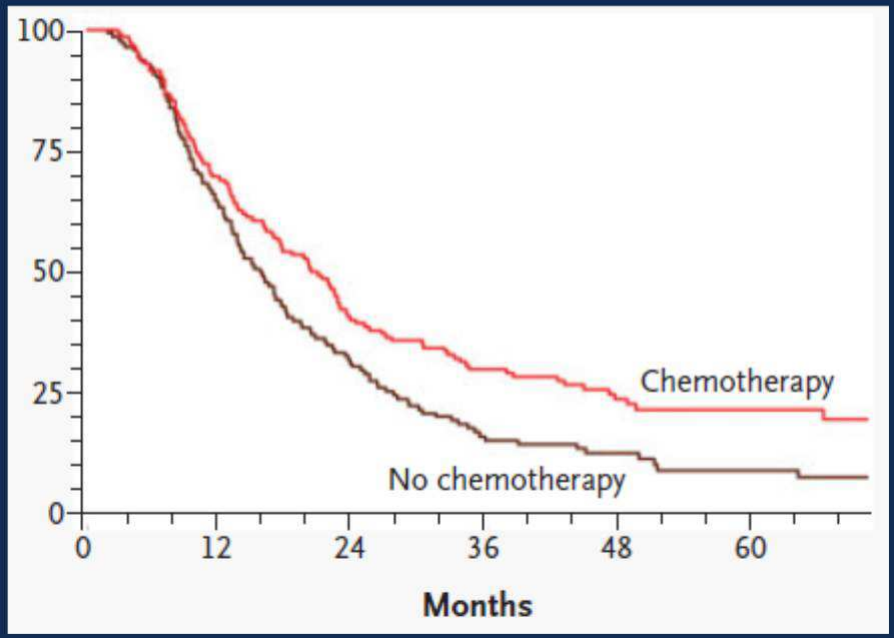


Oettle H. *JAMA*. 2013

Evidence for Chemotherapy

ESPAC-1

- 2x2 Design, 5-FU
- N = 289, 1994-2000
- 1^0: OS (20.1 vs. 15.5 mths)



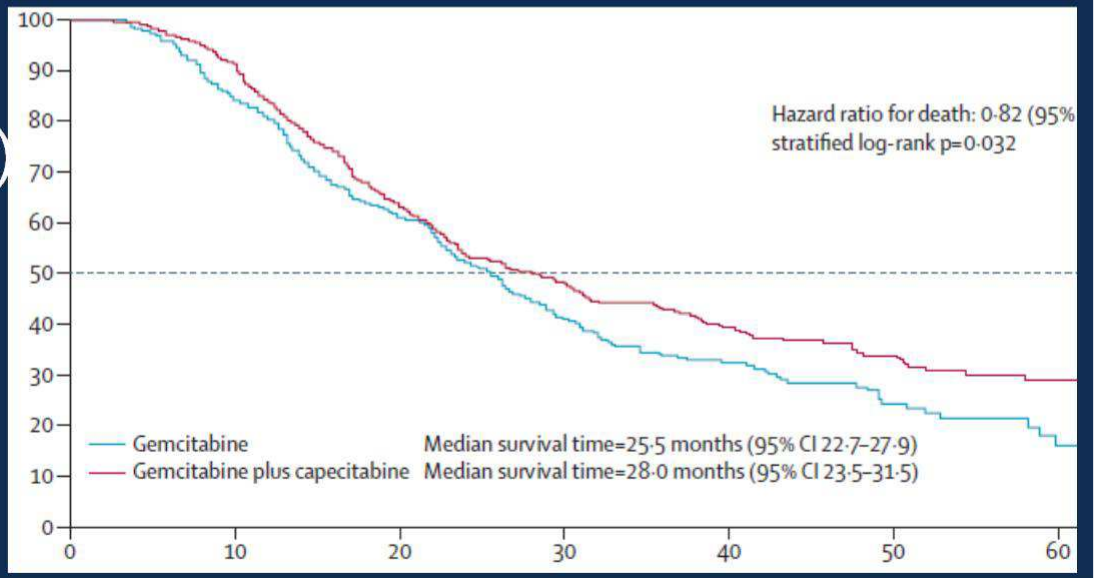
Neoptolemos J. *NEJM*. 2004.

Latest Evidence for Chemotherapy

ESPAC-4

- Gem/Cape vs. Gem alone
- N = 730, 2008-2014
- 1^0: OS (28 vs. 25.5 mths)

Emerging standard of care



Neoptolemos J. *Lancet*. 2017.

Stadio 2B: cosa significa?

Il chirurgo tecnicamente potrebbe resecare, ma deve:

- ✓ Resecare porzioni o tratti di vaso
- ✓ Deve esserne capace
- ✓ Aumenta il rischio operatorio, anche se non in modo significativo in centri esperti

Locally advanced pancreatic cancer: how to treat

1. Chemotherapy
2. Radiotherapy
3. Chemoradiotherapy
4. Induction chemotherapy followed by chemoradiotehrapy

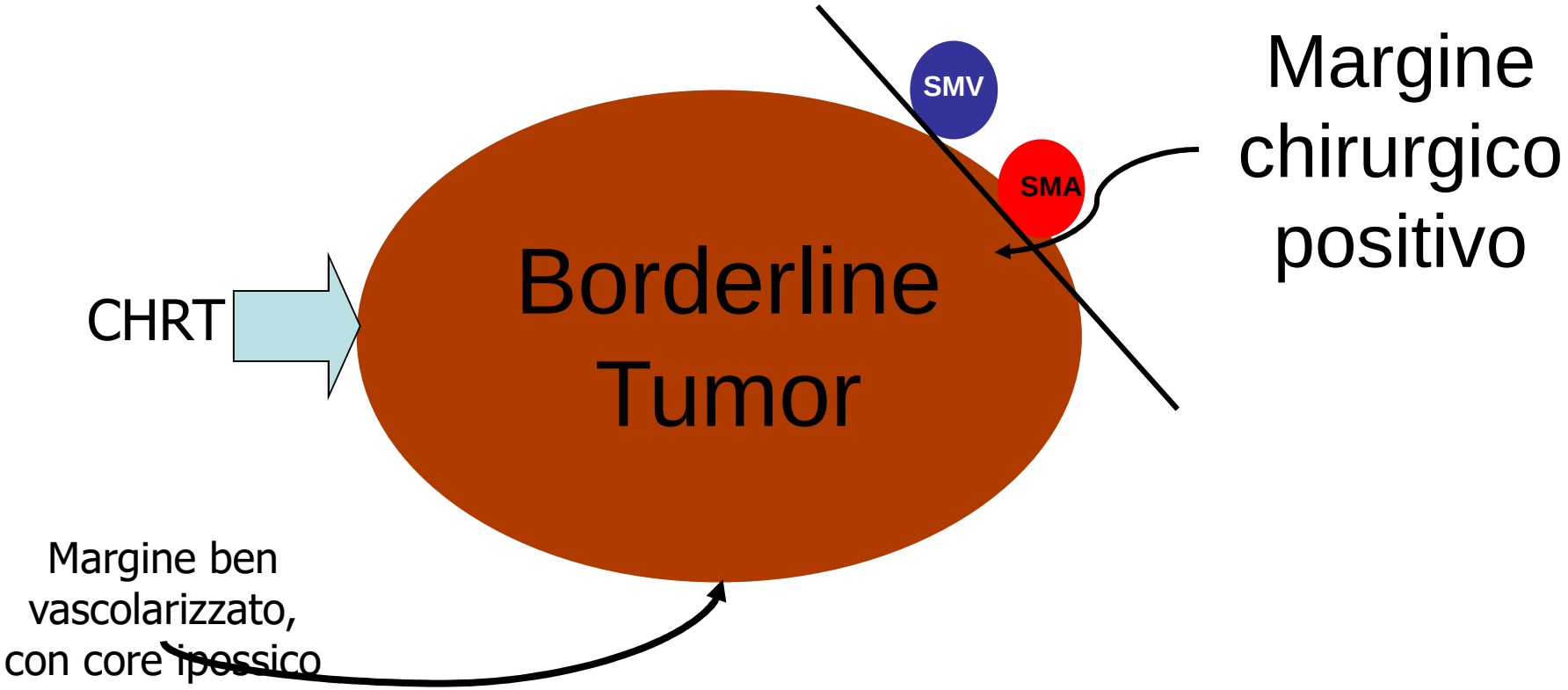
Il tentativo di una visione diversa delle cose

Due filosofie a confronto: Borderline Disease

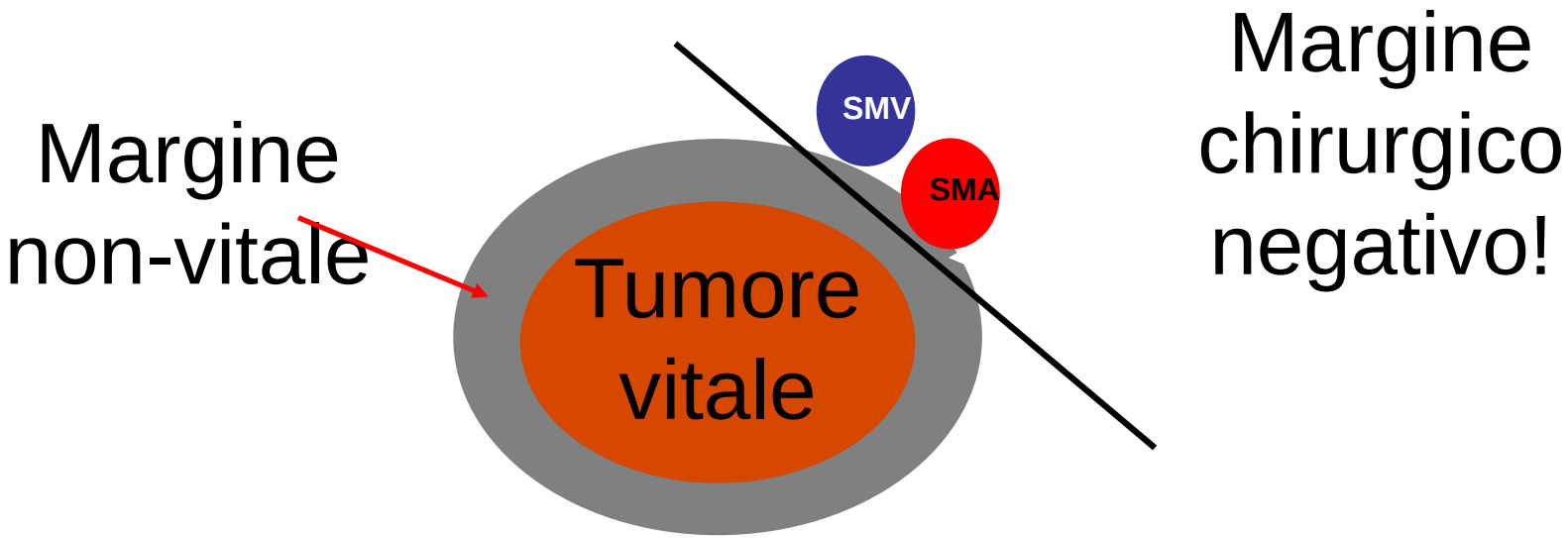
“Il tumore ***non è indisputabilmente non resecabile,*** perciò io provo a resecarlo”

“Il tumore non è ***indisputabilmente non resecabile***, perciò faccio una terapia preoperatoria”

Carcinoma duttale borderline resectable



Dopo chemio e chemioradioterapia preoperatoria



I risultati della neoadiuvante

- ✓ Circa 1/3 dei pazienti giudicati BL-R o NR potranno essere resecati dopo terapia neoadiuvante
- ✓ Se resecati, la loro sopravvivenza è sovrapponibile a quella dei pazienti giudicati come resecabili ab-initio

Chemotherapy as First Choice: Which Drug or Regimen?

	Gemcitabine[1]	Gem + Cape[2]	Gem + Cisplatin[3]	Gem + Oxaliplatin[4]	Gem + *nab*-Paclitaxel	FOLFIRINOX[6]
RR, %	7-17.3	19.1	12.9	26.8	23	31
mPFS, months	2.33-3.9	5.3 HR 0.78	3.8 HR 0.97	5.8 HR 1.287	5.5 HR 0.69	6.4 HR 0.47
mOS, months	5.65-10	7.1 HR 0.86	7.2 HR 1.10	8.8 HR 1.18 ns	8.5 HR 0.72	11.1 HR 0.57

mPFS, median progression free survival; ns, not significant; RR, response rate

1. Burris HA 3rd, et al. *J Clin Oncol.* 1997;15(6):2403-2413. 2. Lim JY, et al. *Cancer Res Treat.* 2015;47(2): 266-273. 3. Colucci G, et al. *J Clin Oncol.* 2010;28:1645-1651. 4. Louvet C, et al. *J Clin Oncol.* 2005;23(15):3509-3516. 5. Von Hoff DD, et al. *N Engl J Med.* 2013;369(18):1691-1703. 6. Conroy T, et al. *N Engl J Med.* 2011;364(19):1817-1825.

Digestive and Liver Disease

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

Progress Report

Borderline resectable pancreatic cancer: More than an anatomical concept

Borderline Resectable *Patients*

Two different entities (or may be not?)

- **Technical borderline:** tumors involving vessels to a limited extent and for which resection would likely be compromised by positive surgical margins

- **Biological borderline:** tumors that, despite technical resectability, have an unfavorable biology leading to an early relapse or death

Petrelli F et al
Digestive and Liver Disease 2016

Fattori associati ad “early death”

TABLE 3 Significant predictors of early death in 224 patients resected for pancreatic cancer[a]

Predictor	OR	95% CI	*P* value
Duration of symptoms (d)			
≤40	1		
>40	4.40	1.81–10.73	.001
CA 19-9 (U/mL)			
≤200	1	–	–
>200	3.00	(1.26–7.14)	.01
Grade			
G1–G2	1		
G3–G4	8.55	(3.41–21.45)	<.0001
Resection margin			
R0	1	–	–
R1	2.01	(0.76–5.55)	.16
R2	9.77	(1.97–19.10)	.002

OR odds ratio, *95% CI* 95% confidence interval

Barugola G, et al. Ann Surg Oncol. 2009 Dec;16(12):3316-22.

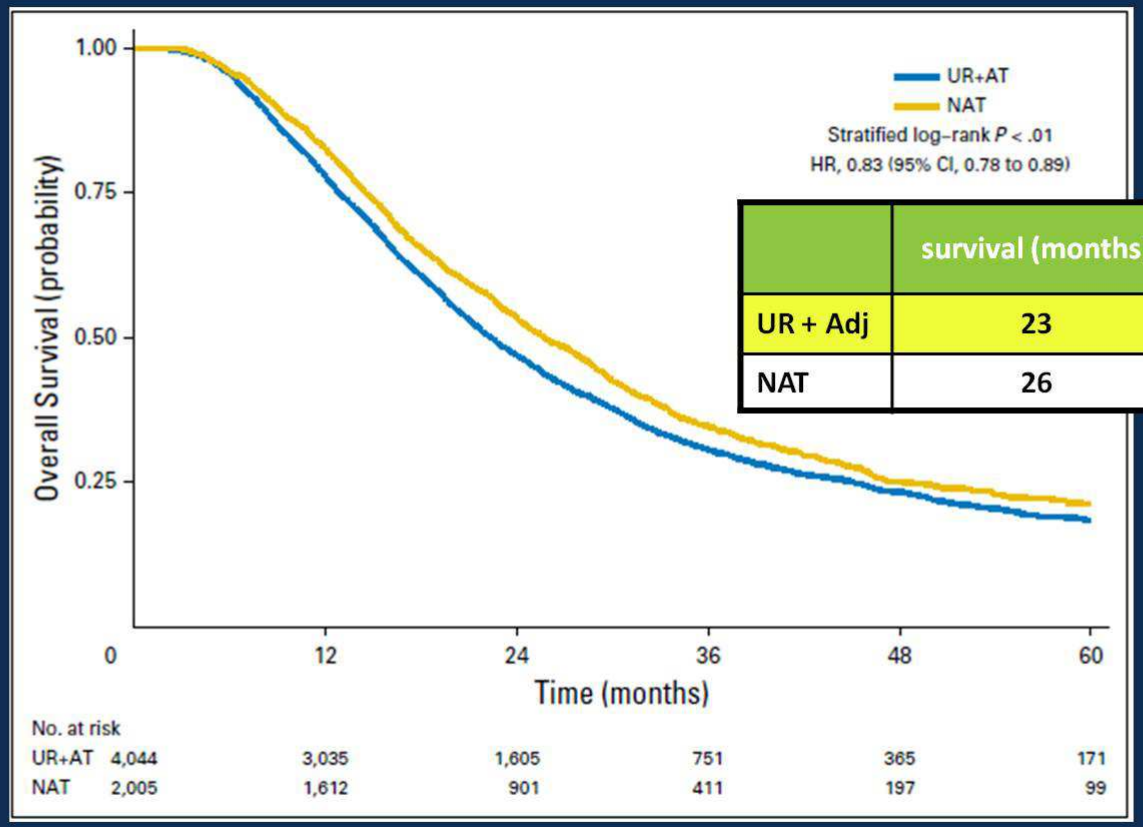
Una cosa brutta a dirsi

il risultato vero sembra purtroppo solo di selezione

Neoadjuvant treatment

- Pancreatic cancer as a systemic disease ab initio.
- More patients may receive “neo” in comparison with adjuvant therapy (25% of patients do not receive adjuvant treatment)
- Better tolerance
- Increase of radical surgery
- Sparing useless surgery to patients rapidly progressing

OS (stage I & II): NAT vs. UR + adjuvant TX



	survival (months)	P
UR + Adj	23	< .01
NAT	26	

Mokdad AA, et al. J Clin Oncol 2017; 35:515-522

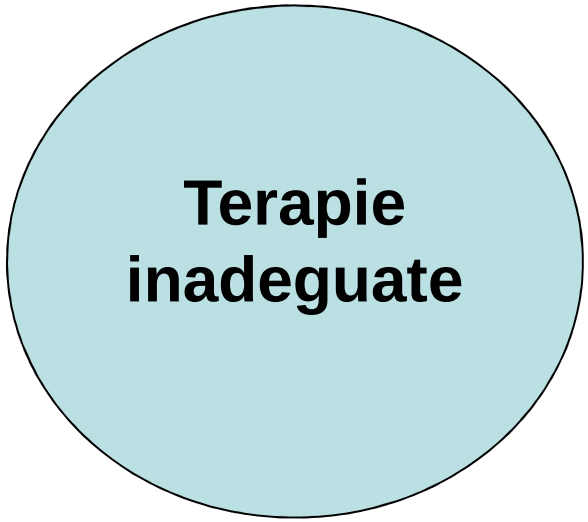
Presented By Massimo Falconi at 2017 ASCO Annual Meeting

Perchè facciamo solo piccoli progressi?

☹ **Inadeguato utilizzo di un high-quality imaging per definire la resecabilità**

☹ **Non vengono riconosciute le situazioni borderline**

☹ **Sono frequenti le resezioni con margini positivi**



💣 **Farmaci solo parzialmente efficaci**

💣 **Ruolo della radioterapia rimane controverso**

💣 **Assenza di interesse nel riconsiderare le sequenze terapeutiche**

I fattori condizionanti una giusta scelta

1. Un imaging di qualità
2. Una valutazione attenta di tutti i parametri che concorrono ad una corretta stadiazione (oltre all'imaging, clinica e markers)
3. Un lavoro di equipe con una cultura ed una expertise condivisa

Nel regno della chirurgia oncologica

La biologia è il Re

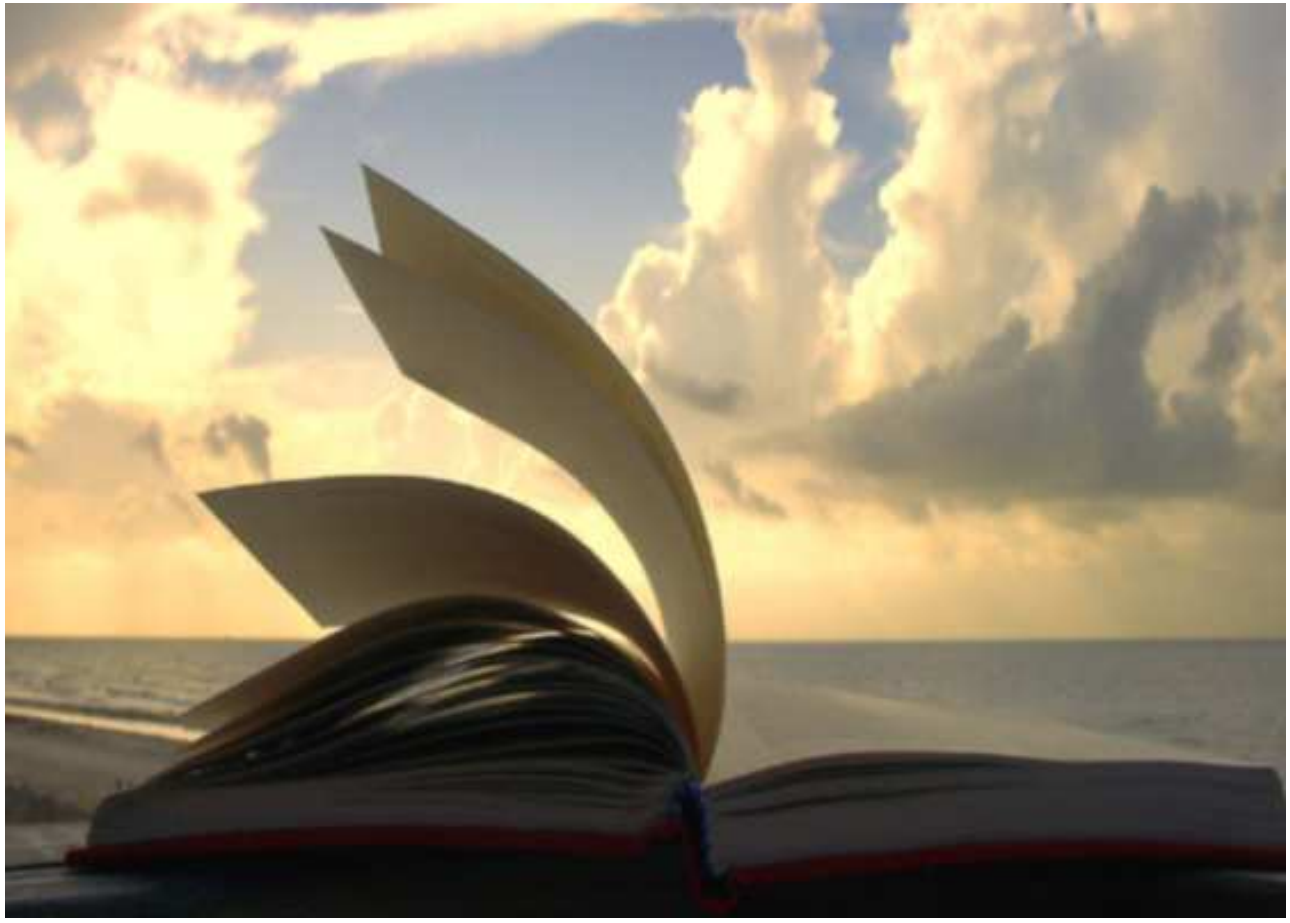
La selezione è la Regina

Le manovre tecniche sono il Principe e la Principessa

Talvolta il Principe e la Principessa cercano di strappare il potere al Re ed alla Regina raggiungendo una temporanea apparente vittoria, abitualmente, però, di corto respiro.

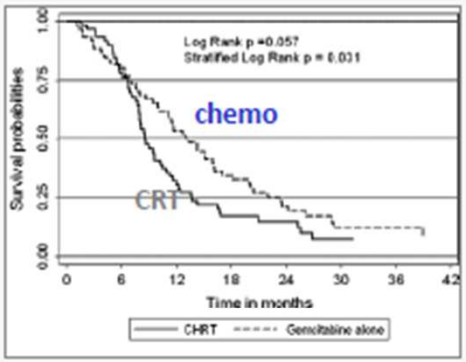
Blake Cady

Ed è già tempo di cambiare

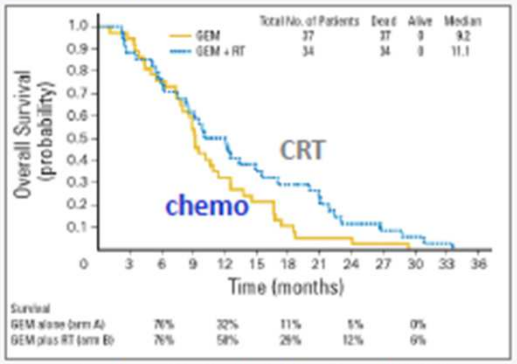


Locally advanced pancreatic cancer: radiotherapy, chemotherapy or chemoradiotherapy?

Frontline CRT (prospective)



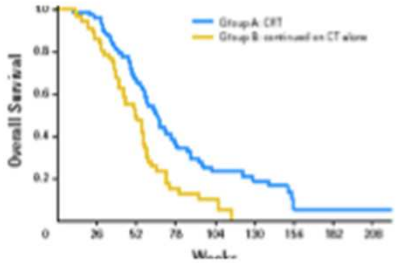
Chauffert B et al, Ann Oncol 2008



Loehrer P et al, J Clin Oncol 2011


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

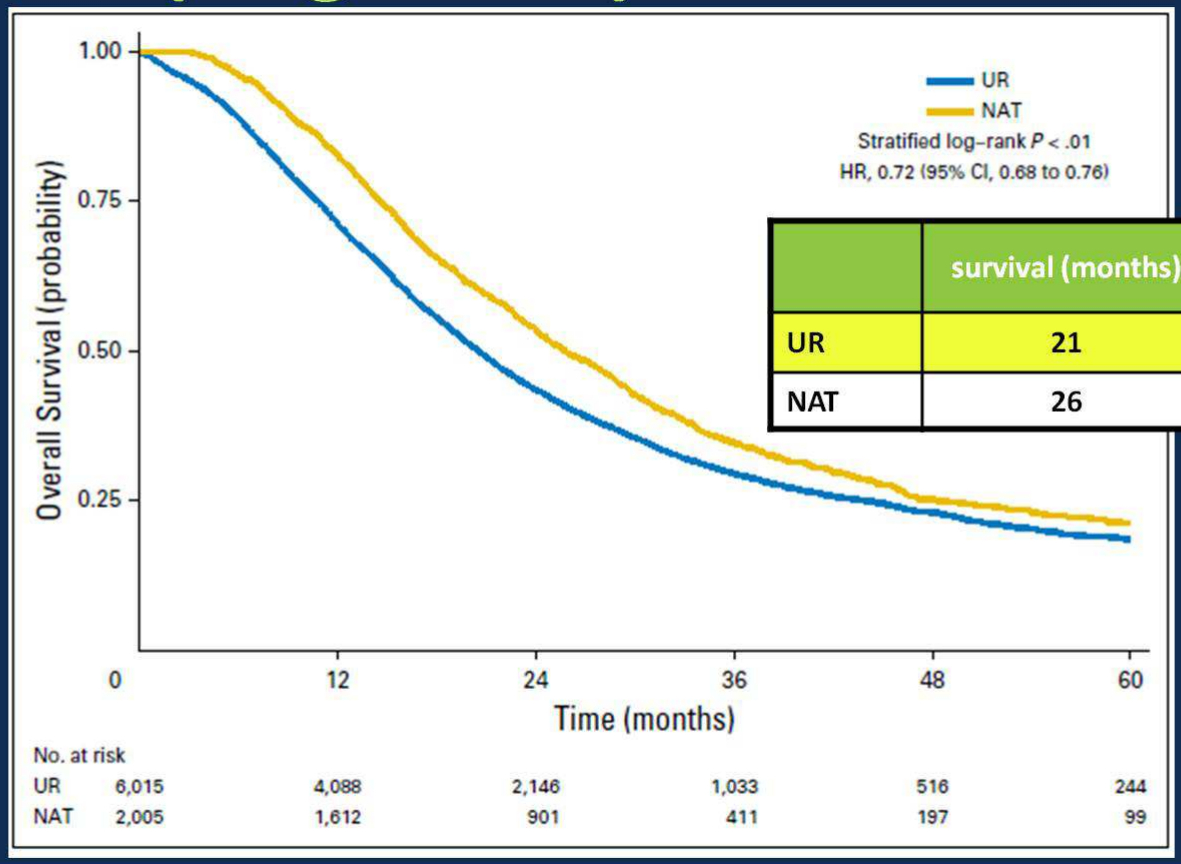
Impact of Chemoradiotherapy After Disease Control With Chemotherapy in Locally Advanced Pancreatic Adenocarcinoma in GERCOR Phase II and III Studies



Start with chemotherapy.

Consider the addition of radiotherapy after 3 months of chemotherapy without progressive disease in patients with a good PS

OS (stage I & II): NAT vs. UR



	survival (months)	P
UR	21	< .01
NAT	26	

Mokdad AA, et al. J Clin Oncol 2017; 35:515-522

Presented By Massimo Falconi at 2017 ASCO Annual Meeting

Resectable Pancreatic Cancer

- Emerging consensus on definition
- Intergroup/NCTN criteria favored: based on INTERFACE
- Arteries (celiac, common hepatic, superior mesenteric)
  - No involvement
- Veins (portal, superior mesenteric)
  - No involvement, or < 180°interface
- Nodes, organs
  - No metastatic disease
  - No nodes outside the surgical basin

30-40% of PDAC pts dies of LA disease w/o ever developing metastases!

Table 2. Relationship of Metastatic Burden at Autopsy to Clinicopathologic Features

Characteristic	None (n = 9)		1 to 10 (n = 13)		11 to 99 (n = 26)		100s to 1,000s (n = 26)		P
Mean (± SD) age, years	62.0 ± 15.0		66.3 ± 8.5		61.3 ± 9.4		62.0 ± 13.1		.81
Male:female	4:5		10:3		17:9		11:15		.12
Smoking history									
Never	4	44	3	23	10	38	12	46	.37
Former	2	22	7	54	11	42	7	27	
Current	3	33	1	8	4	15	3	12	
Unknown	0		2	15	1	4	4	15	
Stage at diagnosis									
I-II	3	33	3	23	8	31	6	23	.09
III	5	55	5	38	4	15	4	15	
IV	1	11	5	38	14	54	16	62	
Tumor location									
Head/body	7	77	12	92	20	77	21	81	.80
Tail	1	11	1	8	3	12	4	15	
Not specified	1	11	0		3	12	1	4	
Mean (± SD) tumor size, cm (stage III/IV carcinomas only)	5.3 ± 2.8		6.9 ± 3.8		5.5 ± 1.7		6.0 ± 3.0		.58
Tumor differentiation									
Well	0		1	8	0		0		.19
Moderate	3	33	8	62	9	35	6	23	
Poor	6	66	4	31	16	62	18	69	
Anaplastic	0		0		1	4	2	8	
Histology									
Duct adenocarcinoma	7	77	11	85	22	85	22	85	.76
Colloid (mucinous noncystic) carcinoma	1	11	1	8	2	8	1	4	
Adenosquamous carcinoma	1	11	1	8	0		0		
Signet ring carcinoma	0		0		1	4	1	4	
Anaplastic carcinoma	0		0		1	4	2	8	
Treatment									
None	2	22	4	31	2	8	3	12	< .02
Chemoradiation	6	66	7	54	8	31	7	27	
Chemotherapy	1	11	2	15	16	62	16	62	
Median overall survival, months	17.0		10.0		11		8		
Range	3-53		1-48		1-62		2-27		.69

Abbreviation: SD, standard deviation.

J Clin Oncol 27:1806-1813. © 2009

Phase III Adjuvant Studies in Resected Pancreatic Cancer

Study	Question	Treatment	Projected number	NCT number
APACT	Gemcitabine/ *nab*-paclitaxel	Gemcitabine vs gemcitabine/ *nab*-paclitaxel	800	02301143 (completed)
ACCORD24	FOLFIRINOX	mFOLFIRINOX vs gemcitabine	490	01526135 (completed)
RTOG-80408	C-RT role	Any chemo x 6 months +/-C-RT	950	01013649

FOUNDATIONONE

Patient Name	Report Date	Tumor Type
6703870356, IT	06 November 2017	Pancreas ductal adenocarcinoma

Date of Birth	31 July 1948	**Medical Facility**	Fondazione Poliambulanza		
Sex	Male	**Ordering Physician**	Zani Boni, Alberto	**Specimen Received**	20 October 2017
FMI Case #	TRF281397	**Additional Recipient**	Not Given	**Specimen Site**	Lung
Medical Record #	Not Given	**Medical Facility ID #**	205195	**Date of Collection**	05 October 2017
Specimen ID	12703/17 1-1	**Pathologist**	Albert Zaniboni	**Specimen Type**	Block

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS[1]

7 genomic findings

2 therapies associated with potential clinical benefit

0 therapies associated with lack of response

8 clinical trials

[1] Reduced sensitivity due to sample quality – See Appendix: Performance Specifications for details.

TUMOR TYPE: PANCREAS DUCTAL ADENOCARCINOMA

Genomic Alterations Identified[†]

KRAS G12D
CDKN2A p16INK4a R80* and p14ARF P94L
MYST3 A190ST
SF3B1 G740E
TP53 R196*

Additional Findings[†]

Microsatellite status MS-Stable
Tumor Mutation Burden TMB-Low; 4 Muts/Mb

[†] For a complete list of the genes assayed and performance specifications, please refer to the Appendix

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
KRAS G12D	None	Cobimetinib Trametinib	Yes, see clinical trials section
CDKN2A p16INK4a R80* and p14ARF P94L	None	None	None
Microsatellite status MS-Stable	None	None	None
MYST3 A190ST	None	None	None
SF3B1 G740E	None	None	None
TP53 R196*	None	None	None

For further information and assistance please call Roche Customer Care: +49 7624 14 2098 or email at europe.foundationmedicine@roche.com

Electronically Signed by Suggarth Daniel, M.D. | Jeffrey S. Ross, M.D., Medical Director | 06 November 2017

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 / CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 / CLIA: 22D2027531

A New Approach: Neoadjuvant

- Systemic disease from the outset
- Preclinical and clinical evidence

Need Fisher, not Halsted!

- Neoadjuvant therapy allows:
  - Early control of systemic disease
  - Use of aggressive chemotherapy regimens
  - Drop-out of resistant biology
  - On therapy evaluation of biomarkers

Sohal D. *JNCI*. 2014.