ESMO
Designated Centre of Integrated Oncology and Palliative Care

FONDAZIONE GISCAD
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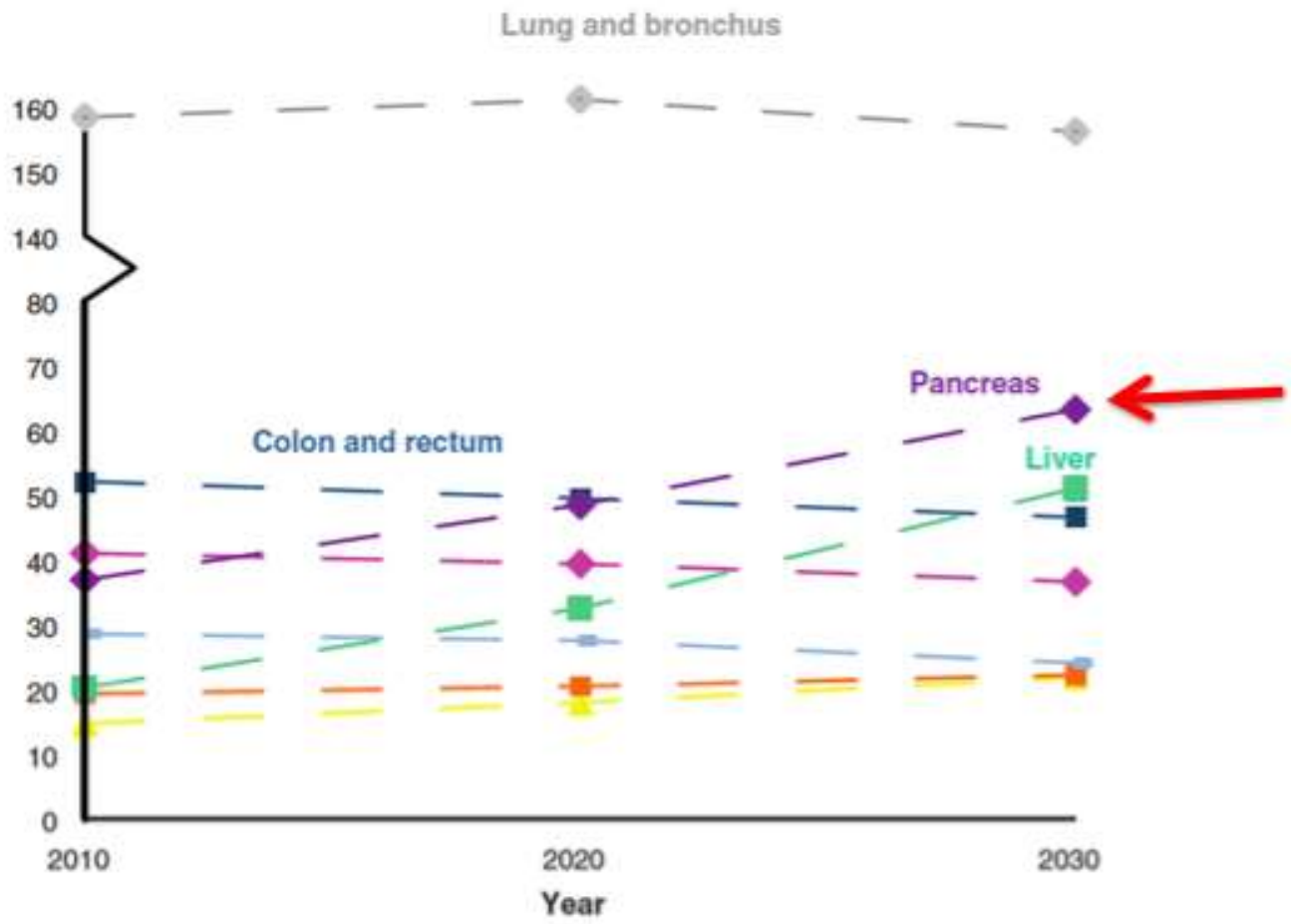
COME TRATTARE LA NEOPLASIA LOCALMENTE AVANZATA BORDERLINE PER RESECABILITÀ

L'oncologo

Alberto Zaniboni

Oncologia Medica
Fondazione Poliambulanza - Brescia

Pancreatic cancer deaths in 2030

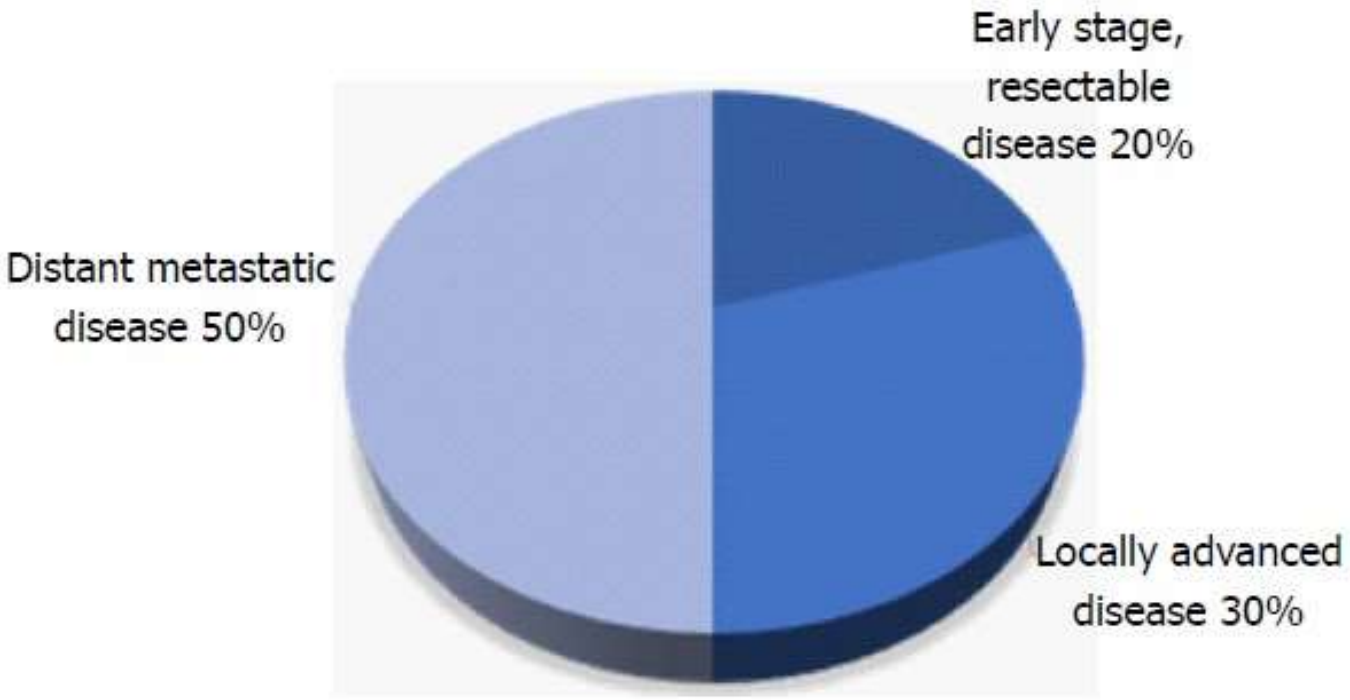


Rahib et al (PanCan), Cancer Research, 2014

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

Stage at Time of Diagnosis



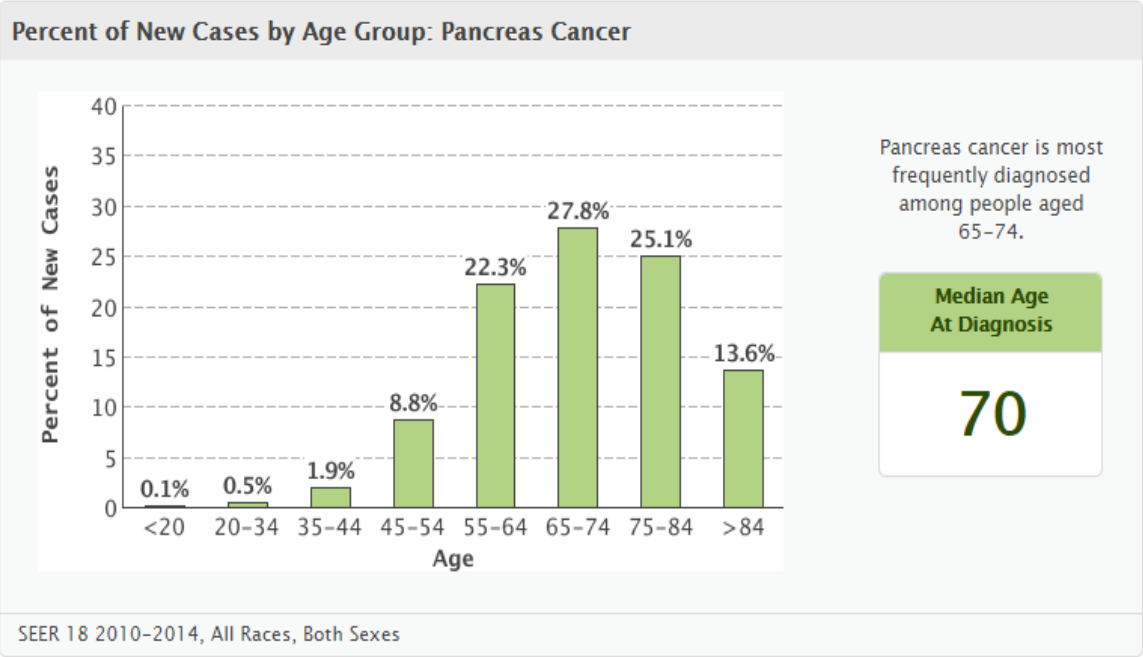
Lau SC, Cheung WY. *World J Gastrointest Oncol*. 2017;9(7):281-292

Pancreatic Cancer Survival Rates By Stage

Stage	Incidence	5-Year Survival
Resectable	20%	20%
Borderline resectable	10%	0-5%
Locally advanced/ unresectable	30%	0%
Metastatic	40%	0%

Lau SC, Cheung WY. World J Gastrointest Oncol. 2017;9(7):281-292. Siegel RL, et al. *Ca Cancer J Clin.* 2017;67(1):7-30.

Major Unmet Need: Unfavorable PS & Elderly

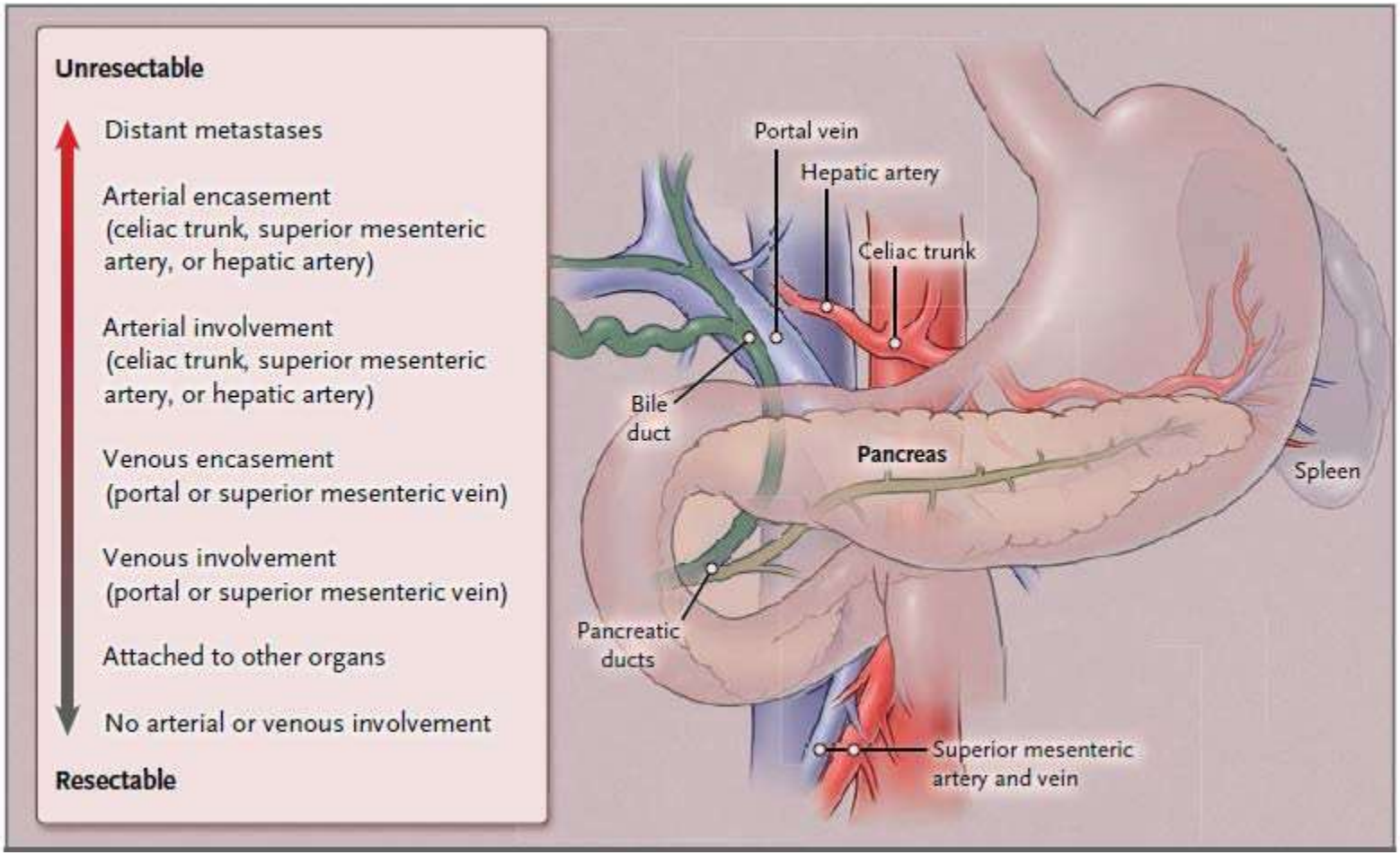


Majority of patients with advanced pancreatic cancer have PS of 2-3

- 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

Anatomy of Pancreatic Cancer



Ryan DP, et al. *N Engl J Med*. 2014;371(11):1039-1049.

Table 1. Criteria of borderline and locally advanced tumor of pancreas according to the National Comprehensive Cancer Network and Americas Hepato-Pancreato-Biliary Association classifications

Vascularization	Resectable	Borderline	Locally advanced pancreatic carcinoma
Superior mesenteric vein or portal vein	Abutment or no contact[a]	Abutment, encasement or occlusion	Not reconstructable
Superior mesenteric artery	No contact	Abutment	Encasement
Common hepatic artery	No contact	Abutment or short segment encasement	Long segment encasement
Celiac axis	No contact	Abutment	Encasement

[a]Abutment means contact between tumor and vessel wall of less than 180° of the circumference.

Ann Oncol. 2017;28(7):1473-1483.

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

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Sohal D. *JNCI*. 2014.

Short Communication

The concept of 'borderline resectable' pancreatic cancer: limited foundations and limited future?

John A. Windsor[1,2], Savio George Barreto[3]

J Gastrointest Oncol 2017;8(1):189-193

Borderline Resectable?

- Praticamente tutti i pazienti con PADC hanno malattia sistemica all'esordio
  - 85% dei resecati sviluppa metastasi
  - Ø 1 cm = 30% Ø 3 cm = 90%
- Somministrare NACT presuppone corretta e precisa identificazione dei pazienti BR
  - 7 definizioni di BR: termini ambigui, parametri arbitrari
  - Casistiche piccole e retrospettive
- La selezione dei pazienti BR si basa su criteri anatomici
  - Unico criterio: CT e rapporti vascolari
  - Invasione microscopica dell'intima venosa?
  - Criteri di aggressività biologica?
  - Analisi genomica?
- La NACT aumenta percentuali di R0?
  - Dati contrastanti!!
- Non è noto se NACT migliora l'outcome
  - Nessun dato da studi randomizzati
- Incapacità di ristadiare i BR dopo NACT
- Perché non fare NACT ai resecabili?

Windsor JA, J Gastr Oncol 2017

ELSEVIER

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

Continuum Between Technically Resectable and Unresectable Disease

RESECTABLE tumor

- ✓ No distant metastasis
- ✓ No tumor contact with CA, SMA or CHA
- ✓ No tumor contact with SMV or PV or contact ≤ 180°

BORDERLINE resectable tumor

- ✓ No distant metastasis
- ✓ Solid tumor contact with SMV/PV >180°
- ✓ Solid tumor contact with CHA or with SMA or CA ≤ 180°

Locally Advanced UNRESECTABLE tumor

- ✓ Distant metastasis
- ✓ Unreconstructible SMV/PV involvement or occlusion
- ✓ Solid tumor contact of >180° with the SMA or CA

Callery MP, et al. *Ann Surg Oncol.* 2009;16(7):1727-1733. National Comprehensive Cancer Network 2016. www.nccn.org. Accessed 02 October 2017.

NCCN But Not ESMO Guidelines for LAPC Evolved to Mirror MPC

NCCN (v3.2017)

Good PS

Preferred: Clinical trial

Category 2A:
- FOLFIRINOX (ECOG 0-1)
- **Gem + *nab*-paclitaxel** (KPS ≥70)
- Gem mono
- Gem-based therapy

Category 2B:
- Capecitabine
- 5-FU +/- oxaliplatin

ChemoRT in select patients following an adequate course of chemo → no clear survival benefit

Recommendation for Gem + nab-paclitaxel and FOLFIRINOX based on extrapolation from RCTs in MPC

Poor PS

- Gem mono (cat. 1)
- Palliative and best supportive care

ESMO (2015)

Standard of Care:
- Gem monotherapy (6 months)

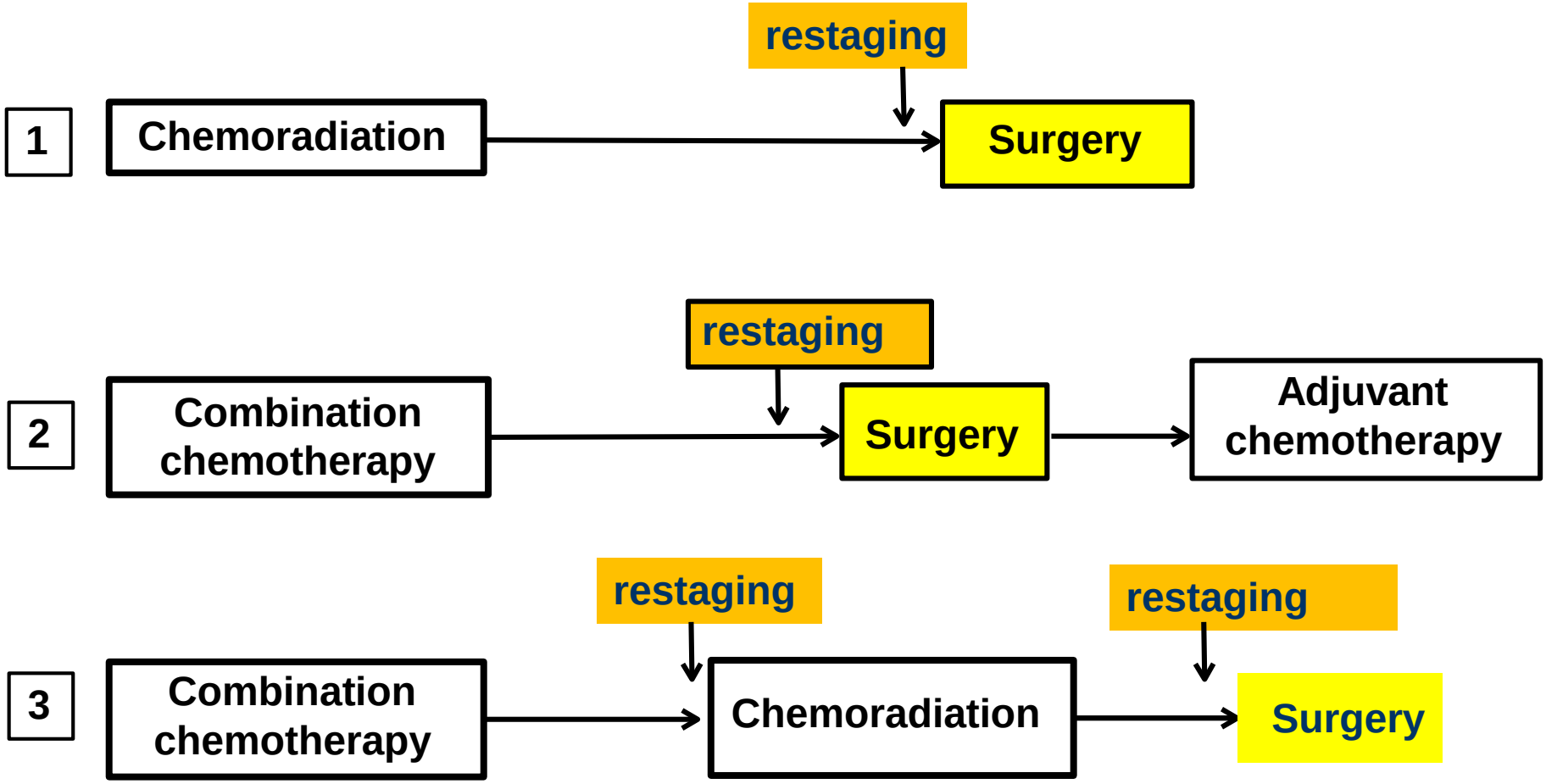
Other options:
- Chemoradiation (Cap/RT recommended)

"Small retrospective and prospective studies suggest FOLFIRINOX may have rendered some patients with LAPC resectable. However, it is too early to recommend FOLFIRINOX."

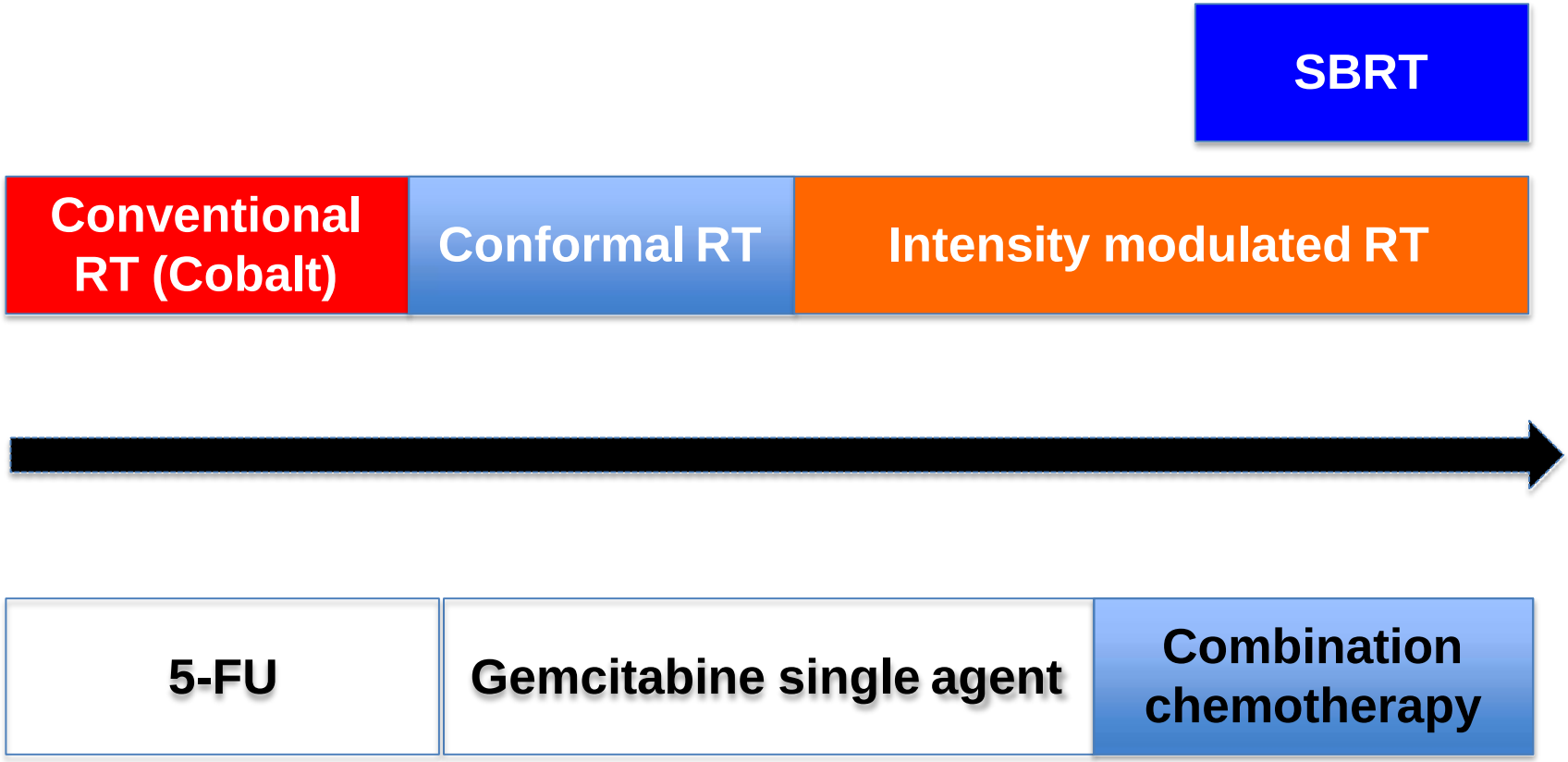
MPC, metastatic pancreatic cancer; RCTs, randomized clinical trials

Currently Available Induction Strategies

Staging: Borderline Resectable Pancreatic Cancer



We Need Parallel Improvements in Systemic and Locoregional Therapies



SBRT, stereotactic body radiation therapy; RT, radiotherapy

Pancreas. 2015 May;44(4):515-21. doi: 10.1097/MPA.0000000000000314.

FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies.

Petrelli F[1], Coinu A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Aitini E, Barni S; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD).

⊕ **Author information**

Abstract

OBJECTIVE: The use of neoadjuvant chemotherapy can enable surgical resection of borderline resectable or unresectable pancreatic cancer (PC). The aim of this study was to evaluate the effectiveness of the multiagent 5-fluorouracil + oxaliplatin + irinotecan + leucovorin (FOLFIRINOX) regimen as a neoadjuvant treatment for PC.

METHODS: Studies in which FOLFIRINOX with or without radiotherapy was given before surgery to patients with borderline resectable or unresectable PC were analyzed using a meta-analytical approach. The primary outcomes were resection rate and radical (R0) resection rate. Data were expressed as weighted pooled proportions with 95% confidence intervals (CIs).

RESULTS: Thirteen studies, with a total of 253 patients, were included in this meta-analysis. After undergoing the treatment, 43% (95% CI, 32.8-53.8) of patients were resected and 39.4% (95% CI, 32.4-46.9) underwent R0 resection (85% of surgical specimens). In particular, among borderline resectable PCs, R0 resection was possible in 63.5% (95% CI, 49%-76%) of the cases. The rate of R0 resection in unresectable PCs was 22.5% (95% CI, 13.3-35.4).

CONCLUSIONS: This meta-analysis shows that down-staging after neoadjuvant FOLFIRINOX-based therapy is noticeable in patients with borderline resectable/unresectable PC, with a total R0 resection rate of 40%.

Cancer Res Treat. 2017 Jun 9 [Epub ahead of print] https://doi.org/10.4143/crt.2017.105

Original Article

Open Access

The Role of Consolidation Chemoradiotherapy in Locally Advanced Pancreatic Cancer Receiving Chemotherapy: An Updated Systematic Review and Meta-Analysis

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Yen-Feng Chiu, PhD[2]
Jih-Chang Yu, PhD[2]
Li-Tzong Chen, MD, PhD[1,3,4]
Hui-Ju Ch'ang, MD[1,5,6]

Purpose

The role of consolidation chemoradiation (CCRT) after systemic chemotherapy in locally advanced pancreatic cancer (LAPC) is still controversial. We aim to evaluate the effectiveness of CCRT in LAPC using systematic review and meta-analysis of prospective studies.

Materials and Methods

Prospective clinical trials of LAPC receiving chemotherapy with or without subsequent CCRT were included in the analysis. We systematically searched in PubMed, MEDLINE, Embase, and Web of Science. The primary outcome of interest was 1-year survival. Secondary endpoints were median overall survival, progression-free survival, toxicity, and resection rate.

Results

Forty-one studies with 49 study arms were included with a total of 1,018 patients receiving CCRT after induction chemotherapy (ICT) and 954 patients receiving chemotherapy alone. CCRT after ICT did not improve 1-year survival significantly in LAPC patients compared with chemotherapy alone (58% vs. 52%). ICT lasted for at least 3 months revealed significantly improved survival of additional CCRT to LAPC patients compared to chemotherapy alone (65% vs. 52%). A marginal survival benefit of consolidation CCRT was noted in studies using maintenance chemotherapy (59% vs. 52%), and fluorouracil-based CCRT (64% vs. 52%), as well as in studies conducted after the 2010 (64% vs. 55%).

Conclusion

The survival benefit of ICT+CCRT over chemotherapy alone in treating LAPC was noted when ICT lasted for at least 3 months. Fluorouracil-based CCRT, and maintenance chemotherapy were associated with improved clinical outcomes.

A

Study	No. of events	No.	Proportion	95% CI
1985 Klaassen	12	44	0.27	0.15-0.43
1988 GITSG	4	21	0.19	0.05-0.42
1998 Todd	27	38	0.71	0.54-0.85
2007 Isacoff	29	54	0.54	0.40-0.67
2008 Chauffert	32	60	0.53	0.40-0.66
2010 Ishii	32	50	0.64	0.49-0.77
2011 Loehrer	12	37	0.32	0.18-0.50
2011 Sahora	10	25	0.40	0.21-0.61
2011 Sahora	15	33	0.45	0.28-0.64
2012 Lee	30	43	0.70	0.54-0.83
2012 Ozaka	7	18	0.39	0.17-0.64
2012 Ozaka	8	13	0.62	0.32-0.86
2012 Ueno	34	66	0.52	0.39-0.64
2013 Heinemann	11	31	0.35	0.19-0.55
2013 Heinemann	13	31	0.42	0.25-0.61
2013 Heinemann	17	33	0.52	0.34-0.69
2013 Ueno	39	68	0.57	0.45-0.69
2013 Ueno	42	68	0.62	0.49-0.73
2016 Hammel	94	136	0.69	0.61-0.77
2015 Stein	27	31	0.87	0.70-0.96
Random-effects model estimate:			**0.52**	**0.45-0.60**

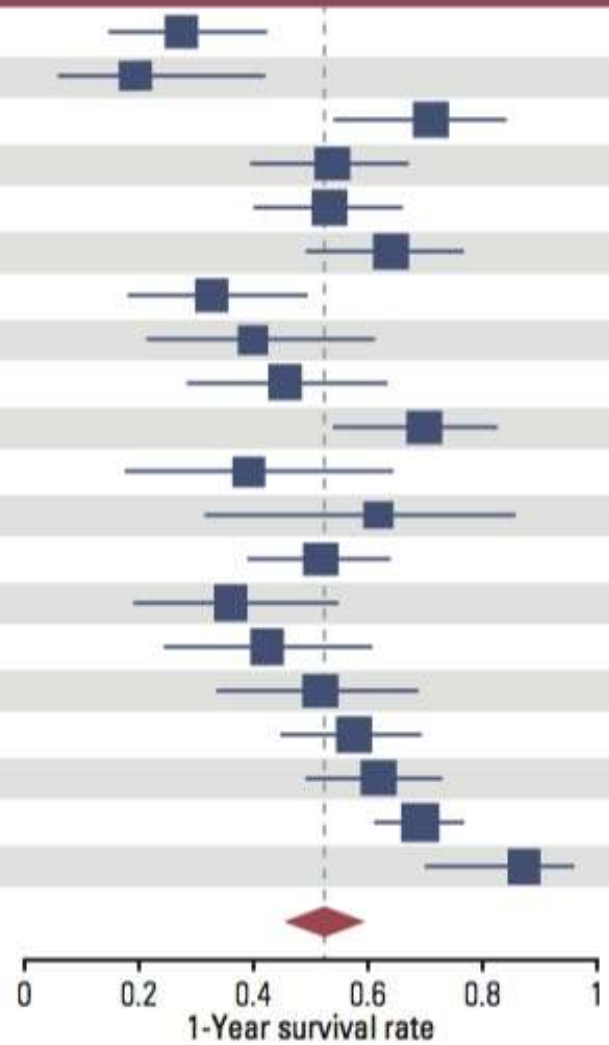


Fig. 2. Forest plot of 1-year survival [19-21,23-29,31-58]. (A) Chemotherapy groups. (B) ICT+CCRT groups. CI, confidence interval; ICT, induction chemotherapy; CCRT, chemoradiation. *(Continued to the next page)*

B

Study	No. of events	No.	Proportion	95% CI
1989 Wagener	10	19	0.53	0.29-0.76
1996 Wagener	26	53	0.49	0.35-0.63
2002 Epelbaum	6	20	0.30	0.12-0.54
2003 Al-Sukhun	10	20	0.50	0.27-0.73
2005 Mishra	4	20	0.20	0.06-0.44
2006 Kurt	8	24	0.33	0.16-0.55
2007 Goldsteing	19	41	0.46	0.31-0.63
2007 Ko	16	25	0.64	0.43-0.82
2008 Marti	12	26	0.46	0.27-0.67
2008 Moureau-Zabotta	31	59	0.53	0.39-0.66
2010 Nakachi	11	20	0.55	0.32-0.77
2010 Landry	7	11	0.64	0.31-0.89
2011 Ch'ang	34	50	0.68	0.53-0.80
2011 Crane	46	69	0.67	0.54-0.78
2011 Goldsteing	34	48	0.71	0.56-0.83
2011 Milandri	21	33	0.64	0.45-0.80
2012 Kim	26	37	0.70	0.53-0.84
2013 Leone	25	39	0.64	0.47-0.79
2013 Mukjerjee	24	38	0.63	0.46-0.78
2013 Mukjerjee	28	36	0.78	0.61-0.90
2013 Youl	42	78	0.54	0.42-0.65
2014 Esnaola	18	37	0.49	0.32-0.66
2014 Ke	24	32	0.75	0.57-0.89
2015 Herman	29	49	0.59	0.44-0.73
2016 Hammel	86	133	0.65	0.56-0.73
Random-effects model estimate:			**0.58**	**0.53-0.62**

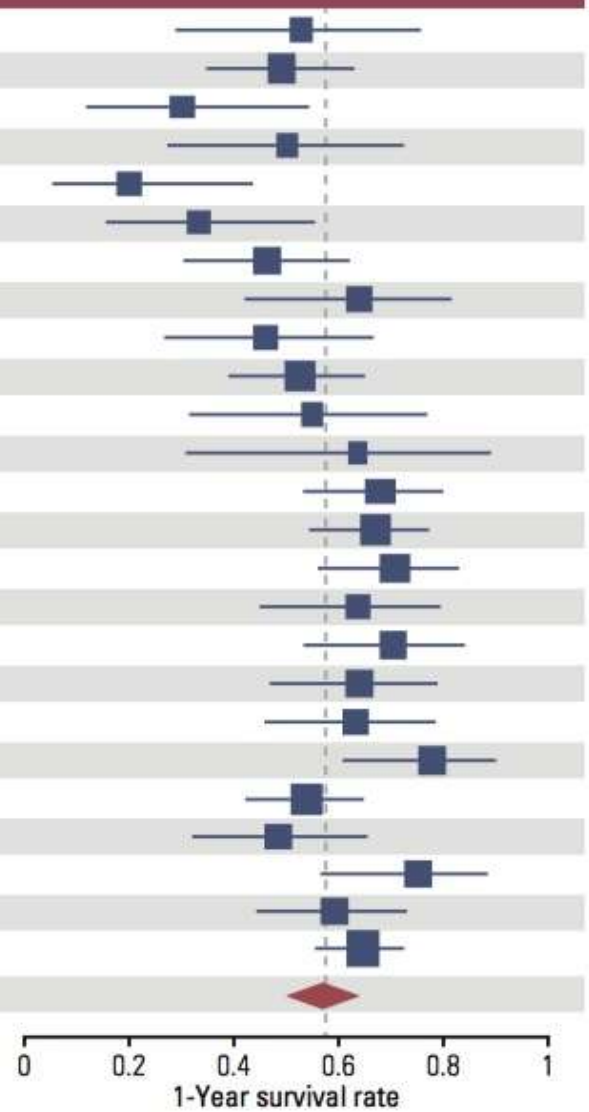


Fig. 2. Forest plot of 1-year survival [19-21,23-29,31-58]. (A) Chemotherapy groups. (B) ICT+CCRT groups. CI, confidence interval; ICT, induction chemotherapy; CCRT, chemoradiation. *(Continued to the next page)*

Guess the right question, then, is not
"*should we employ* loco-regional therapies in LA-PDAC",

but rather

"*in which pts* with LA-PDAC should we use loco-regional theraputic approaches"???

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

Could we identify them???

Table 4 Factors associated with the risk of metachronous liver metastasis for stage III pancreatic cancer (univariate and multivariate cox regression model) ($N = 707$)

Variable	Univariate analysis			Stepwise multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (≥60 vs. <60)	0.78	0.60–1.02	0.0736	0.77	0.58–1.01	0.0555
Sex (male vs. female)	0.82	0.63–1.08	0.1534			
Smoking (yes vs. no)	0.98	0.75–1.29	0.8878			
Alcohol (yes vs. no)	0.93	0.63–1.39	0.7288			
Location (body/tail vs. head/neck)	0.81	0.62–1.07	0.1367			
Diameter (≥20 vs. <20)	1.62	1.02–2.59	0.0413	1.58	0.99–2.52	0.0542
ALT or AST (elevated vs. normal)	1.02	0.67–1.55	0.9162			
ALB (low vs. normal)	1.03	0.72–1.47	0.8848			
CA19-9 (elevated vs. normal)	1.15	0.81–1.62	0.4381			

World Journal of Surgical Oncology (2017) 15:120

...not on clinical grounds!!!

Maybe biology will help…

Table 3. Relationship of Genetic Features to Patterns of Failure in Advanced Stage Pancreatic Cancer

Metastatic Burden by Gene for Primary Carcinoma	Locally Destructive				Locally Confined				
	0		1-10		11-99		100s-1,000s		
	No.	%	No.	%	No.	%	No.	%	*P*
KRAS2 (n = 59)	6/7	86	11/11	100	19/21	90	20/20	100	.283
	17/18; 94%				39/41; 95%				.672
TP53 (n = 58)	6/6	100	6/11	54	16/21	76	18/20	90	.083
	12/17; 71%				34/41; 83%				.037
DPC4 (n = 65)	2/9	22	5/11	45	17/24	71	16/22	73	.032
	7/20; 35%				33/46; 72%				.007

J Clin Oncol 27:1806-1813. © 2009

Extended Surgery: Vascular Resection

- **Venous resection[1]**
  - 28 studies (retrospective), 1458 patients
    - Median mortality rate: 4%
    - Median average length of stay: 17 days
    - 75% chance of a clear margin

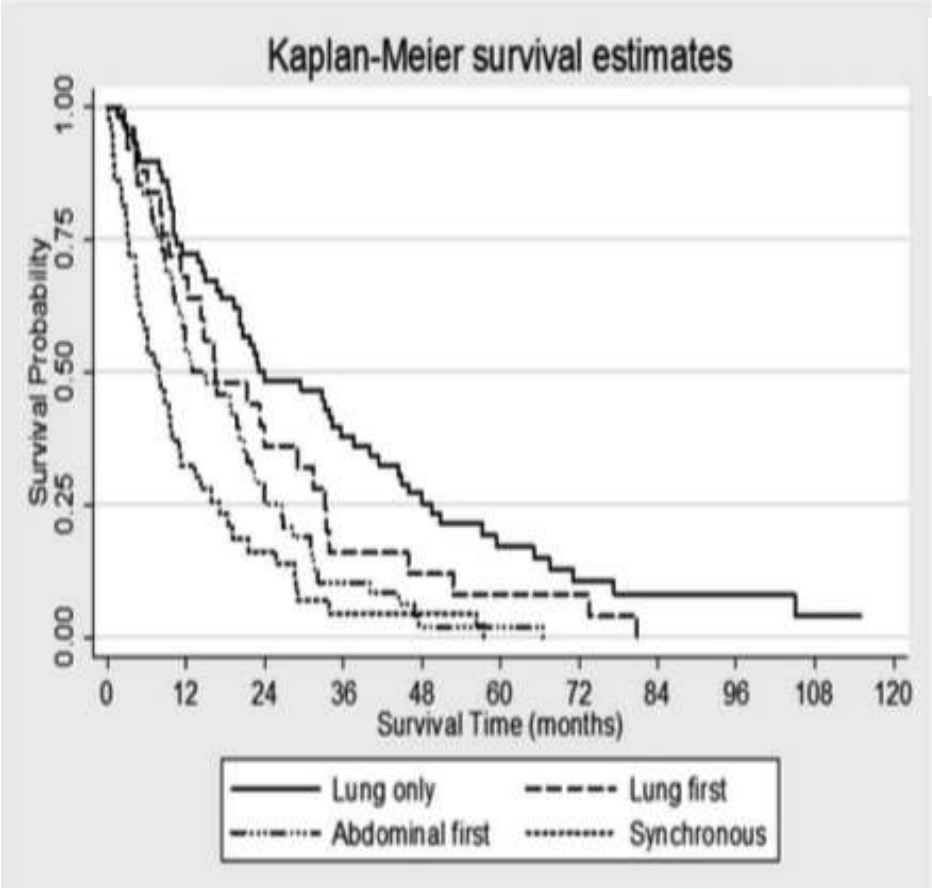
- **Arterial resection (AR)[2]**
  - 26 studies (retrospective)
    - No AR: 2243 patients
    - AR: 336 patients
  - Increase in perioperative mortality OR: 5.04 (95% CI: 2.69-9.45)
  - Poor survival
    - 1 year OR: 0.49 (95% CI: 0.31-0.78)
    - 3 year OR: 0.38 (95% CI: 0.17-0.86)

1. Chua TC, et al. *J Gastrointest Surg.* 2010;14(9):1442-1452. 2. Mollberg N, et al. *Ann Surg.* 2011;254(6):882–893.

J Surg Oncol. 2015 July ; 112(1): 80–85. doi:10.1002/jso.23943.

THE INDOLENT NATURE OF PULMONARY METASTASES FROM DUCTAL ADENOCARCINOMA OF THE PANCREAS

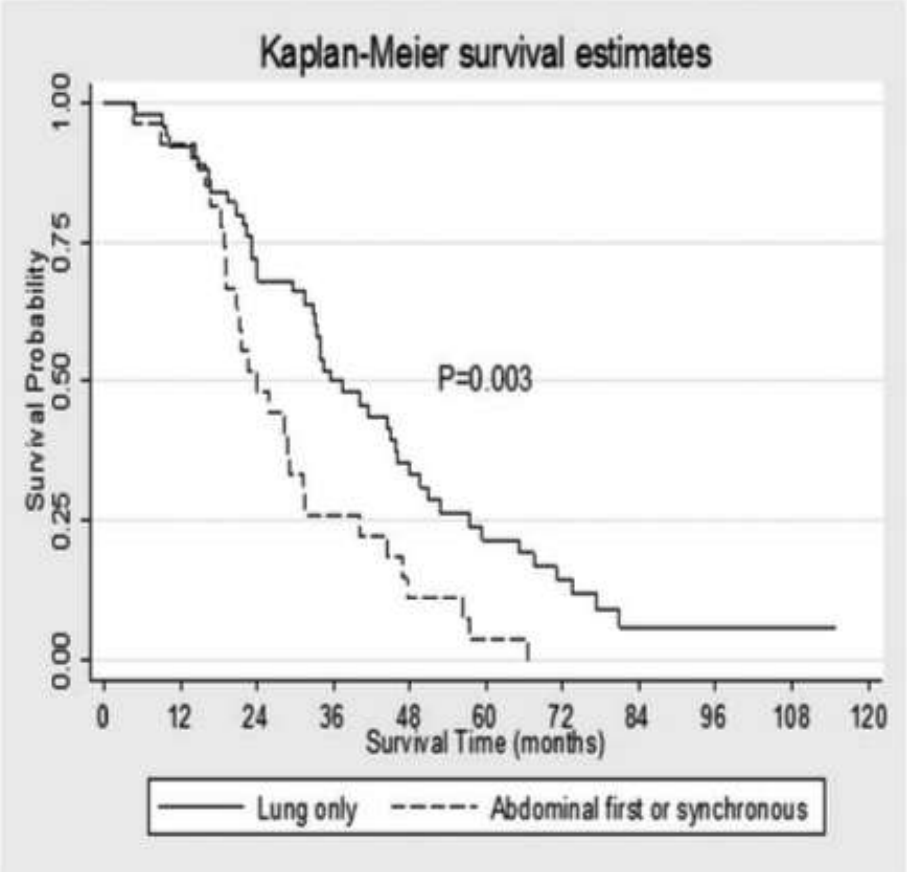
Stephanie Downs-Canner, MD[1], **Mazen Zenati, MD**[2], **Brian A. Boone, MD**[1], **Patrick R. Varley, MD**[1], **Jennifer Steve, BA**[1], **Melissa E. Hogg, MD**[1], **Amer Zureikat, MD**[1], **Herbert J. Zeh, MD**[1], and **Kenneth K.W. Lee, MD**[1]



J Surg Oncol. 2015 July ; 112(1): 80–85. doi:10.1002/jso.23943.

Figure 1. Median survival in all patients with pulmonary metastases from PDAC grouped by site of first metastases

Among those with lung as a first and only site of metastases, median survival was 23.1 months compared to 16.5 months for those with lung first but not only metastases, 12.9 months for those with abdominal metastases before lung metastases, and 7.3 months for those with synchronous intra-abdominal and lung metastases. Using patients with lung only metastases as a reference for comparison, the hazard ratios of death are 1.5 (95% C.I. 0.94-2.45, p=0.091) for patients with lung first but not only metastases, 2.2 (95% C.I. 1.43-3.23, p<0.0001) for patients with abdominal first metastases, and 3.3 (95% C.I. 2.2-5.1, p<0.0001) for patients with synchronous abdominal and lung metastases.



J Surg Oncol. 2015 July ; 112(1): 80–85. doi:10.1002/jso.23943.

Figure 2. Median survival in patients who underwent resection of primary PDAC

Among those patients who underwent resection of their primary PDAC, the median survival of those with lung as a first recurrence was 35.6 months compared to 23.8 months among those with abdominal first or synchronous recurrence (p= 0.003).

Research

JAMA Oncology | Brief Report

Association of Alterations in Main Driver Genes With Outcomes of Patients With Resected Pancreatic Ductal Adenocarcinoma

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JAMA Oncol. doi:10.1001/jamaoncol.2017.3420
Published online November 2, 2017.

Table 2. Disease-Free Survival and Overall Survival by *KRAS* Codon Mutation and Combined *KRAS, CDKN2A, SMAD4*, and *TP53* Gene Alterations

Driver Gene Alteration	Disease-Free Survival (n = 335)			Overall Survival (n = 338)		
	Patients, No. (%)	HR (95% CI)[a]	*P* Value[b]	Patients, No. (%)	HR (95% CI)[a]	*P* Value[b]
KRAS mutation[c]						
G12D	122 (36.4)	1 [Reference]		123 (36.4)	1 [Reference]	
G12V	104 (31.0)	0.57 (0.41-0.79)	<.001	105 (31.1)	0.63 (0.46-0.87)	.005
G12R	44 (13.1)	0.67 (0.43-1.05)	.08	45 (13.3)	0.82 (0.54-1.25)	.35
Other codon	25 (7.5)	0.63 (0.37-1.10)	.10	25 (7.4)	0.83 (0.50-1.39)	.48
2 Codon mutations	11 (3.3)	0.27 (0.11-0.69)	.006	11 (3.3)	0.55 (0.26-1.15)	.11
Wild-type	27 (8.1)	0.38 (0.22-0.65)	<.001	27 (8.0)	0.50 (0.30-0.83)	.008
No. of altered genes						
0-2 Genes	126 (37.6)	1 [Reference]		127 (37.6)	1 [Reference]	
3 Genes	135 (40.3)	1.37 (1.01-1.86)	.05	136 (40.2)	1.22 (0.91-1.64)	.18
4 Genes	74 (22.1)	1.79 (1.24-2.59)	.002	75 (22.2)	1.38 (0.98-1.94)	.06
Gene combinations[d]						
0-2 Genes	126 (37.6)	1 [Reference]		127 (37.6)	1 [Reference]	
3 Genes						
KRAS, SMAD4, TP53	35 (10.4)	1.16 (0.74-1.82)	.53	35 (10.4)	1.08 (0.69-1.69)	.75
KRAS, CDKN2A, TP53	64 (19.1)	1.51 (1.04-2.20)	.03	64 (18.9)	1.38 (0.96-1.98)	.08
KRAS, CDKN2A, SMAD4	34 (10.1)	1.27 (0.79-2.05)	.32	35 (10.4)	1.28 (0.80-2.06)	.30

Abbreviation: HR, hazard ratio.

[a] Cox proportional hazards regression model adjusted for age, sex, pathologic N stage, tumor grade, lymphovascular invasion, receipt of perioperative treatment, resection margin status, and institution.

[b] *P* value for multivariable-adjusted Cox proportional hazards regression.

[c] Data not reported for patients with *KRAS* G12C mutations due to the small sample size (n = 2).

[d] Data not reported for patients with combination of *CDKN2A*, *SMAD4*, and *TP53* alterations due to the small sample size (n = 2). Percentages do not add up to 100% in *KRAS* mutation analysis because we do not present data for 2 patients with G12C mutations.

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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

Outcomes With FOLFIRINOX and Gemcitabine + *nab*-Paclitaxel in Unresectable LA Pancreatic Cancer

- **All patients who started first-line FOLFIRINOX, gemcitabine + *nab*-paclitaxel or gemcitabine for uLAPC between April 2015 and March 2016 were identified in Cancer Care Ontario's New Drug Funding Program database**

Regimen	Number Patients	6-Months OS	Resection
FOLFIRINOX	90	87.8	12
nab-Paclitaxel	40	75.1	10
GEM	17	76.4	2

- **Surgical resection after initial chemotherapy was not associated with better OS in multivariable analysis (HR 0.26, 95%CI 0.03-1.98, *P* = .19)**

LA, locally advanced; uLAPC, unresectable locally advanced pancreactic cancer

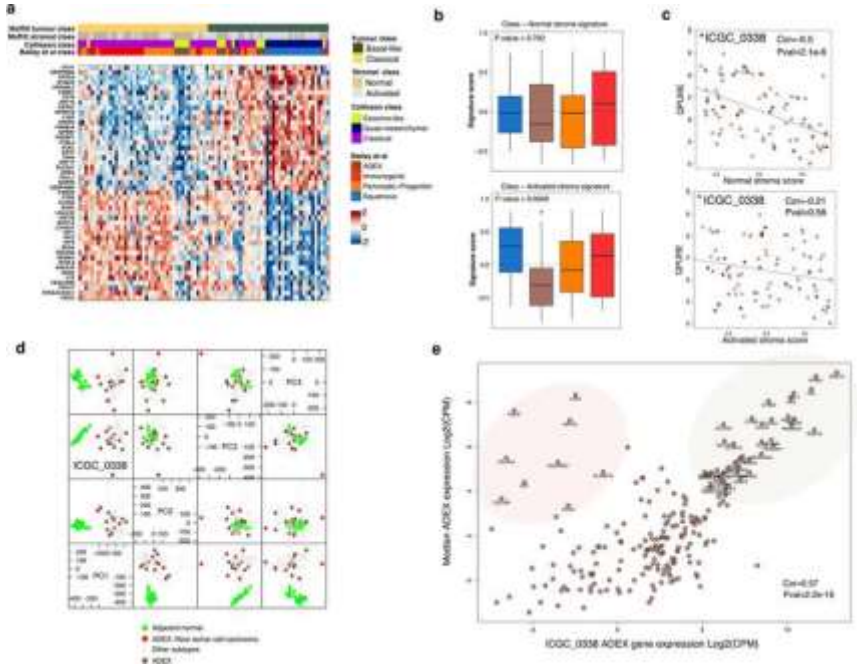
Chen KK, et al. *J Clin Oncol*. 2017;4(suppl):Abstract 394.

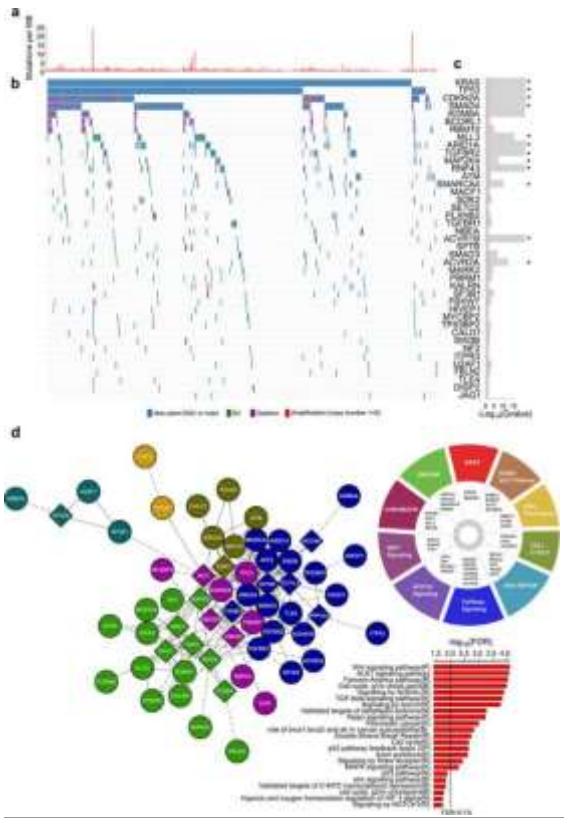
Unresectable PDAC: Take Home Messages

- **First approach:** **Chemotherapy**
- **Which regimen?:** **Wait for randomized trials. Gemcitabine alone may be reasonable, but it is understandable to use a combination—especially GEM/*nab*-paclitaxel (see LAPACT study, Philip P, et al)**
- **Radiotherapy:** **Possible in well-selected patients not progressing for more than 4 to 6 months, preferably in combination with capecitabine**
- **Consider surgery:** **In case of a response to systemic treatment, but be cautious with extended surgery**
- **Future perspectives:**
  - **CRT or SBRT (new radiation techniques trials)**
  - **New local modalites such as irreversible electroporation (NanoKnife), TTF field in combination with chemotherapy**

But, they are experimental and should be offered only in clinical trials!

There is Not ONE Pancreatic Cancer, But SEVERAL (at least 4) Types With Different Behavior





4 subtypes:

1. **Squamous:** More aggressive and spread more quickly
2. **Pancreatic progenitor:** Triggered by errors in the cells that should guide the development of the pancreas
3. **Immunogenic**
4. **Aberrantly differentiated endocrine exocrine (ADEX):** Subtype of pancreatic progenitor tumors, where specific genes are upregulated

Subtypes correlate with histopathologic characteristics and may provide rationale for therapeutic strategies

Bailey P, et al. *Nature.* 2016;531(7592):47-52.

LAP07 Conclusions

- LAP07 prospectively confirmed the value of frontline chemotherapy in patients with LAPC
- Overall survival in CRT arm is not superior to chemotherapy arm in patients with LAPC with tumor controlled after 4 months of chemotherapy
- However, trend for PFS in favor of CRT
- In the CRT arm, patients had a significantly less local tumor progression and a longer period without chemotherapy

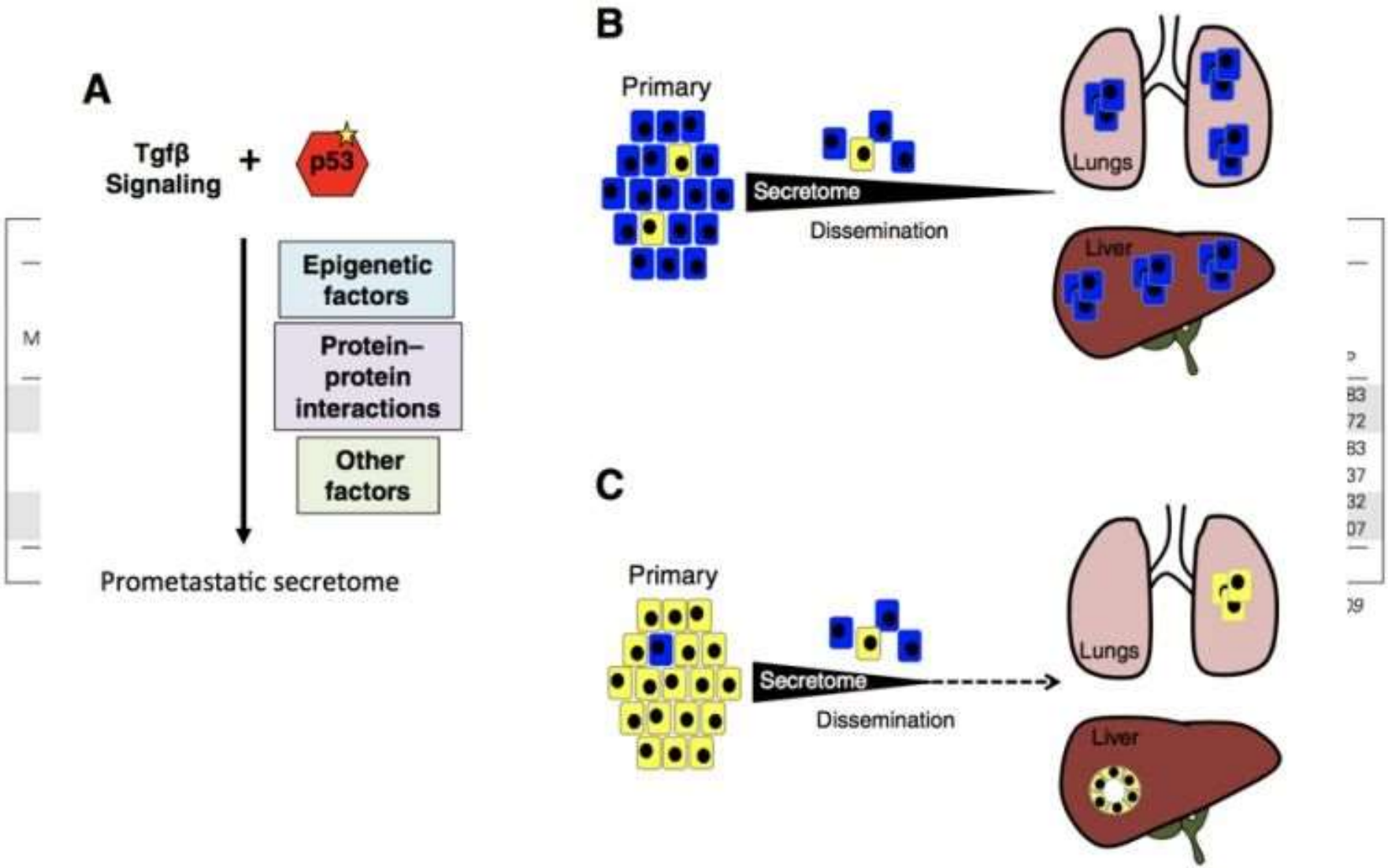
Hammel P, et al, *JAMA*. 2016;315(17):1844-1853.

Evolution of Neoadjuvant Therapy in Resectable and Borderline Resectable

- **Development of optimal neoadjuvant/perioperative combination chemotherapy platforms**
  - **SWOG 1505**
  - **ESPAC-5**

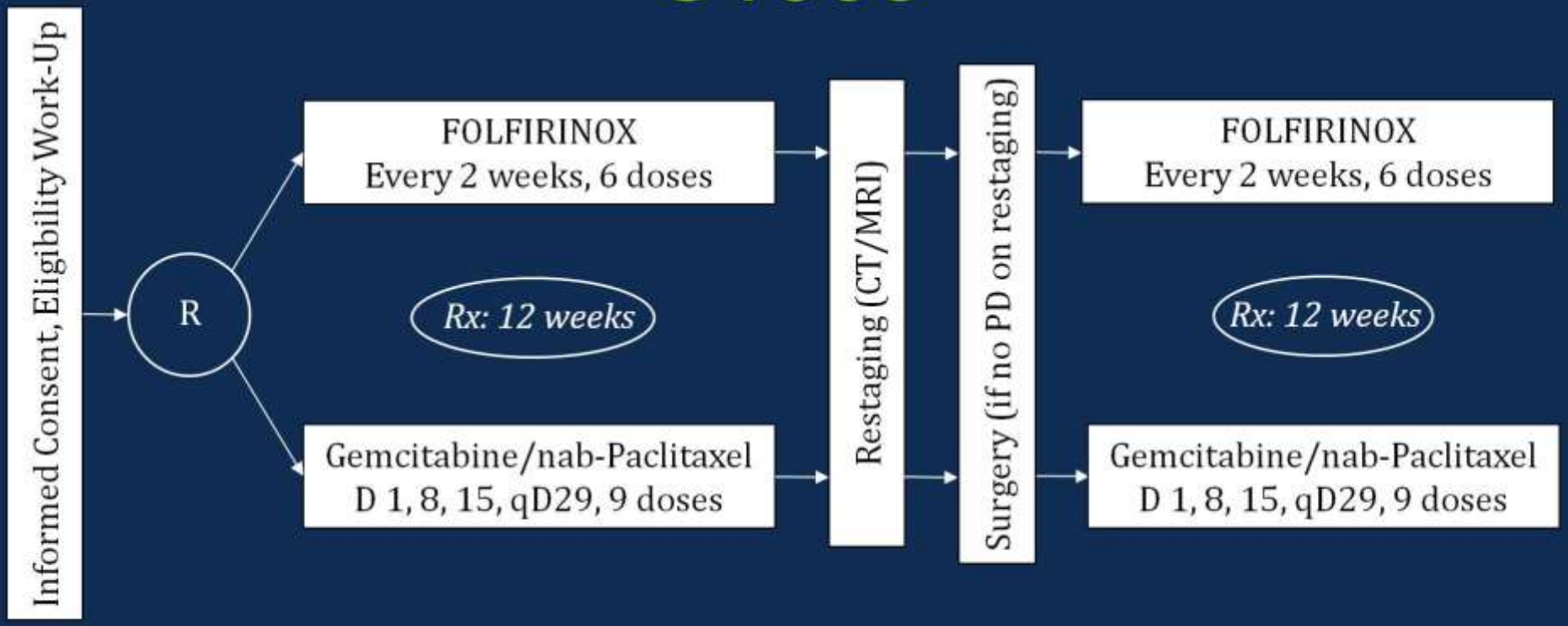
- **Role of radiotherapy in borderline resectable disease**
  - **Alliance A021501**
  - **ESPAC-5**

Maybe biology will help…



Clin Cancer Res; 23(6); 1607–20. ©2016

Testing A New Approach: SWOG S1505



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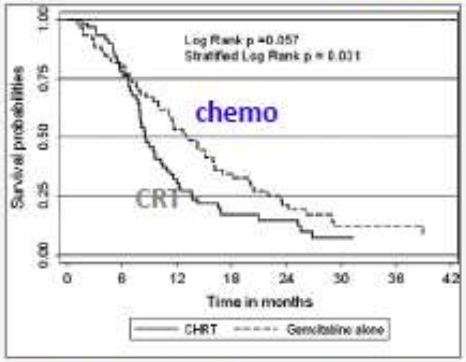
Sohal D. TPS4152, ASCO. 2017.

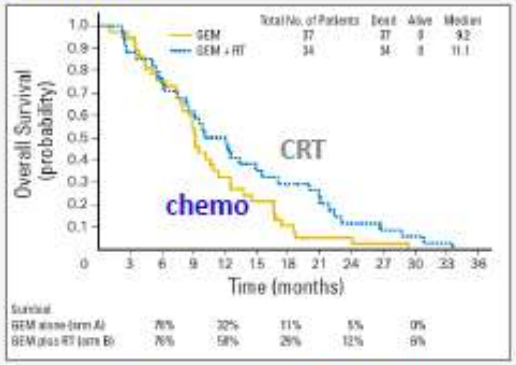
Presented By Davendra Sohal at 2017 ASCO Annual Meeting

Locally advanced pancreatic cancer: radiotherapy, chemotherapy or chemoradiotherapy?

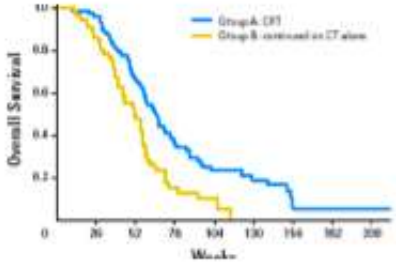
Frontline CRT (prospective)



Chauffert B et al, Ann Oncol 2008



Loehrer P et al, J Clin Oncol 2011



Start with chemotherapy.

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

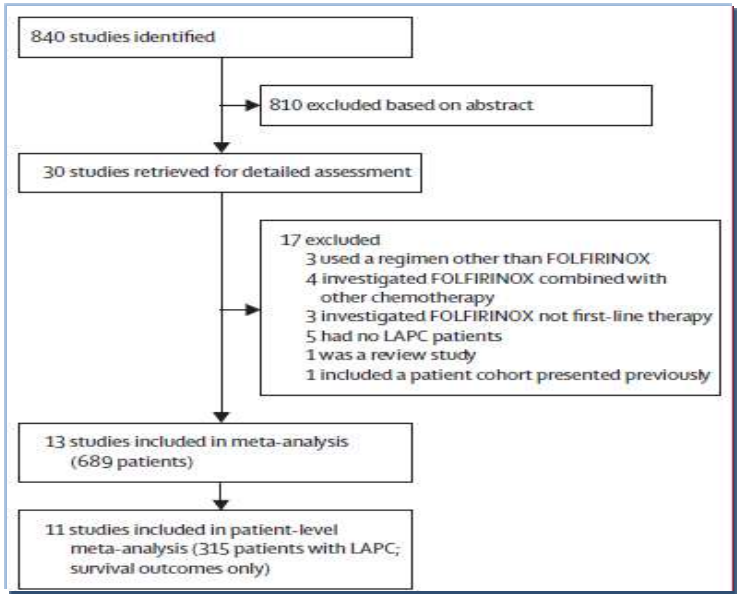
FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis

THE LANCET Oncology

Published online May 6, 2016

Our primary outcome was overall survival. Secondary outcomes were progression-free survival; rates of grade 3 or 4 adverse events; and the proportion of patients who underwent radiotherapy or chemoradiotherapy, surgical resection after FOLFIRINOX, and R0 resection. We evaluated survival outcomes with the Kaplan–Meier method with patient-level data.

Findings



mOS: *24·2 months*

mPFS: *15 months*

R0 resection: *78.4%*

Interpretation Patients with locally advanced pancreatic cancer treated with FOLFIRINOX had a median overall survival of 24·2 months—longer than that reported with gemcitabine (6–13 months). Future research should assess these promising results in a randomised controlled trial, and should establish which patients might benefit from radiotherapy or chemoradiotherapy or resection after FOLFIRINOX.

Folfirinox and LAPC in true life : be careful

	Group 1 (n=241) Conroy's criteria OK	Group 2 (n=26) Deviations to criteria	Group 3 (n=59) LAPC
Age ≤ 75	241 (100%)	18 (69%)	55 (93%)
PS0-1	241 (100%)	17 (65%)	55 (93%)
Subnormal bilirubin level (<1.5 N)	241 (100%)	17 (65%)	51 (86%)
Overall Response Rate (ORR)	95 (39%)	4 (16%)	23 (39%)
Complete Response (CR)	6 (2%)	0	0
Partial Response (PR)	89 (37%)	4 (16%)	23 (39%)
Stable Disease (SD)	63 (26%)	10 (40%)	25 (42%)
Dose adjustment at C1	98 (41%)	13 (50%)	29 (49%)
Dose adjustment after C1	98 (40%)	6 (24%)	20 (34%)
Grade III/IV toxicity	77 (32%)	10 (40%)	20 (34%)
PFS (months)	6.54 [5.98-7.29]*	4.14 [1.68-6.21]*	9.49 [8.74-11.47]
OS (months)	10.91 [8.94-12.02]**	7.00 [4.01-11.20]**	11.24 [9.95-15.01]

- Conroy's criteria not respected: ↘ PFS and OS

Metges JP et al., ASCO 2014

- **CT-guided biopsy of the pancreatic mass confirmed the diagnosis of a poorly differentiated pancreatic adenocarcinoma**

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ1**
- T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis