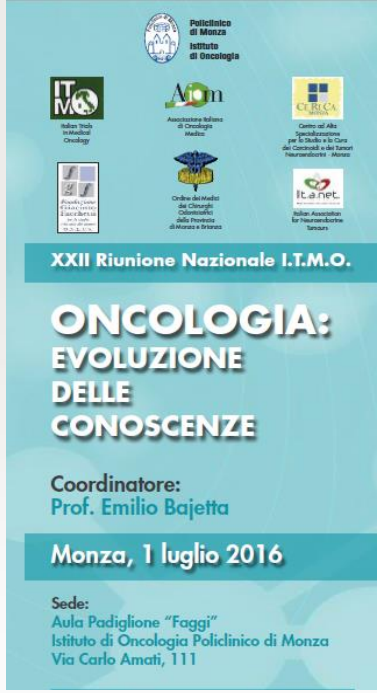
TRATTAMENTO NEOADIUVANTE PER PAZIENTI BORDERLINE RESECTABLE

Laura Catena



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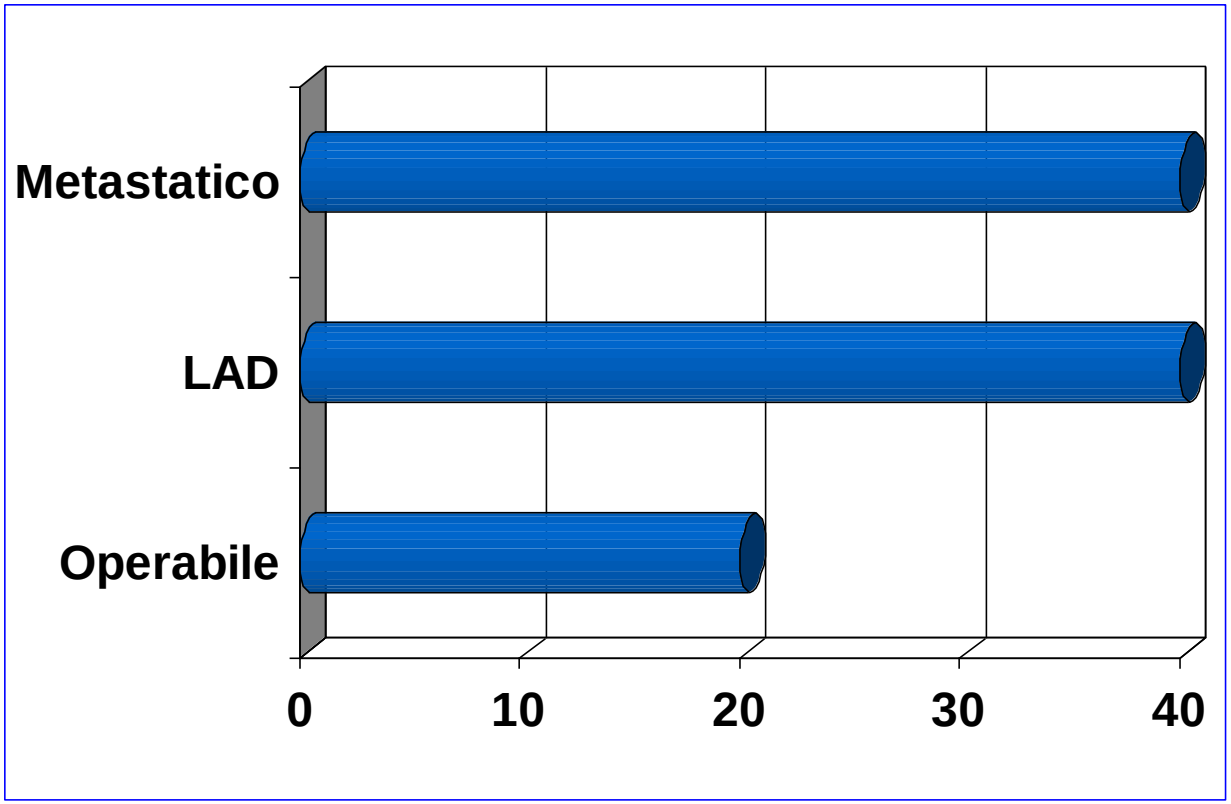
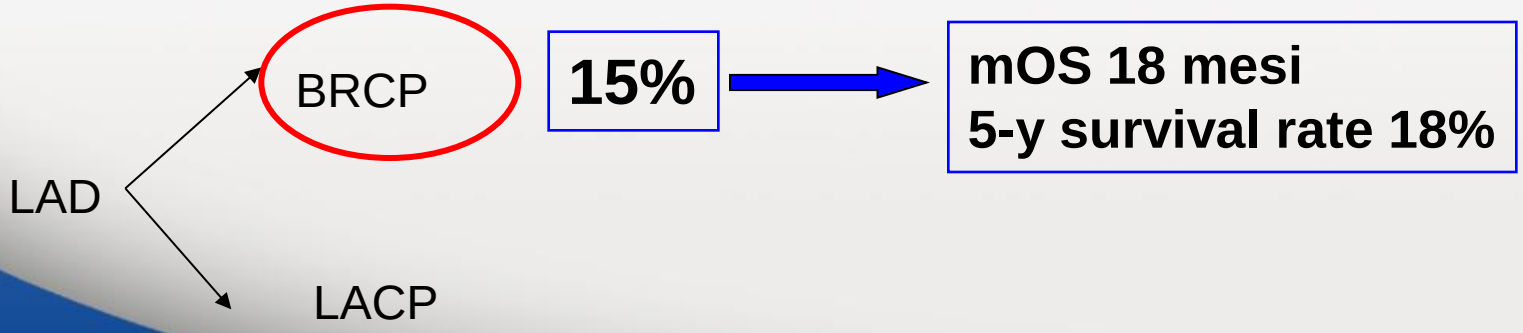

Metastatico
LAD
Operabile
0
10
20
30
40


BRCP
LAD
LACP
15%
mOS 18 mesi
5-y survival rate 18%

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BORDERLINE RESECTABLE= resecabili con RV ma ad alto rischio di R1/R2 e di recidiva

Table 1 Criteria for resectability

	NCCN	AHPBA/ SSAT/SSO	MD Anderson	Intergroup (Alliance)
Celiac artery	No abutment for pancreatic head cancer. For body/tail, ≤ 180° contact	No abutment or encasement	Abutment	Tumor-vessel interface < 180° of vessel wall circumference
CHA	Solid tumor contact ≤ 180° allowing for reconstruction	Abutment or short segment encasement	Abutment or short-segment encasement	Reconstructable short-segment interface of any degree
SMA	Solid tumor contact ≤ 180°	Abutment	Abutment	Tumor-vessel wall interface < 180° of vessel wall circumference
SMV/PV	Solid tumor contact > 180° or contact of ≤ 180° with contour irregularity or thrombosis allowing for safe reconstruction	Occlusion	Occlusion	Tumor-vessel interface ≥ 180° of vessel wall circumference and/or reconstructible occlusion

CHA: Common hepatic artery; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; PV: Portal vein; NCCN: National Comprehensive Cancer Network; AHPBA/SSAT/SSO: Americas Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology.

World J Gastrointest Oncol 2015 October 15; 7(10): 241-249

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NCCN Guidelines

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head /uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

Resecabilità NPL corpo/coda

December 2011, Volume 18, Issue 13, pp 3608-3614

First online: 17 May 2011

Splenic Artery Invasion in Pancreatic Adenocarcinoma of the Body and Tail: A Novel Prognostic Parameter for Patient Selection

Stefano Partelli, Stefano Crippa, Giuliano Barugola, Domenico Tamburrino, Paola Capelli, Mirko D'Onofrio, Paolo Pederzoli, Massimo Falconi

RESULTS: Postoperative morbidity was 31% with no mortality. The 1-, 3-, and 5-year overall survival rates were 77%, 48%, and 24.5%, respectively. Invasion of the splenic artery (SA) was observed in 19 patients (22%). Patients with SA invasion had a significantly poorer prognosis compared with those without SA invasion (median survival: 15 vs. 39 months, P = 0.014). On multivariable analysis, adjuvant therapy, poor differentiation (G3/G4), R2 resection, the presence of lymph node metastases, and SA invasion were independent predictors of survival.

Ann Surg. 2010 Mar;251(3):483-7. doi: 10.1097/SLA.0b013e3181cf9171.

Invasion of the splenic artery is a crucial prognostic factor in carcinoma of the body and tail of the pancreas.

Kanda M[1], Fujii T, Sahin TT, Kanzaki A, Nagai S, Yamada S, Sugimoto H, Nomoto S, Takeda S, Kodera Y, Morita S, Nakao A.

CONCLUSIONS: Our results indicated that the invasion of the SA, but not that of the SV, is a crucial prognostic factor in pancreatic body and tail cancer.

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Resecabilità Biologica

- Sintomi > 40 gg
- Ca 19.9 > 200 U/ML
- G3/G4

	R0	**R1**	**R2**
Mortalità a 12 m (%)	60	75	90

Barugola G, Ann Surg Oncol. 2009

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Annals of Surgical Oncology
December 2014, Volume 21, Issue 13, pp 4351-4358

First online: 05 August 2014

Serum CA 19-9 Response to Neoadjuvant Therapy is Associated with Outcome in Pancreatic Adenocarcinoma

Brian A. Boone, Jennifer Steve, Mazen S. Zenati, Melissa E. Hogg, Aatur D. Singhi, David L. Bartlett, Amer H. Zureikat, Nathan Bahary, Herbert J. Zeh III

BRPC

	↓ Ca 19.9 > 50%	↑ Ca 19.9
R0 (%)	80	0

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CRITICITA’ del BRPC

- Alto rischio di malattia metastatica occulta
- Alto rischio di chirurgia non radicale (R0 fattore prognostico più importante)
- Maggior complessità chirurgica per resezione e ricostruzione vascolare
- Rischio di assenza di BENEFICIO ONCOLOGICO

Fathi A, J Gastrointest Oncol, 2015

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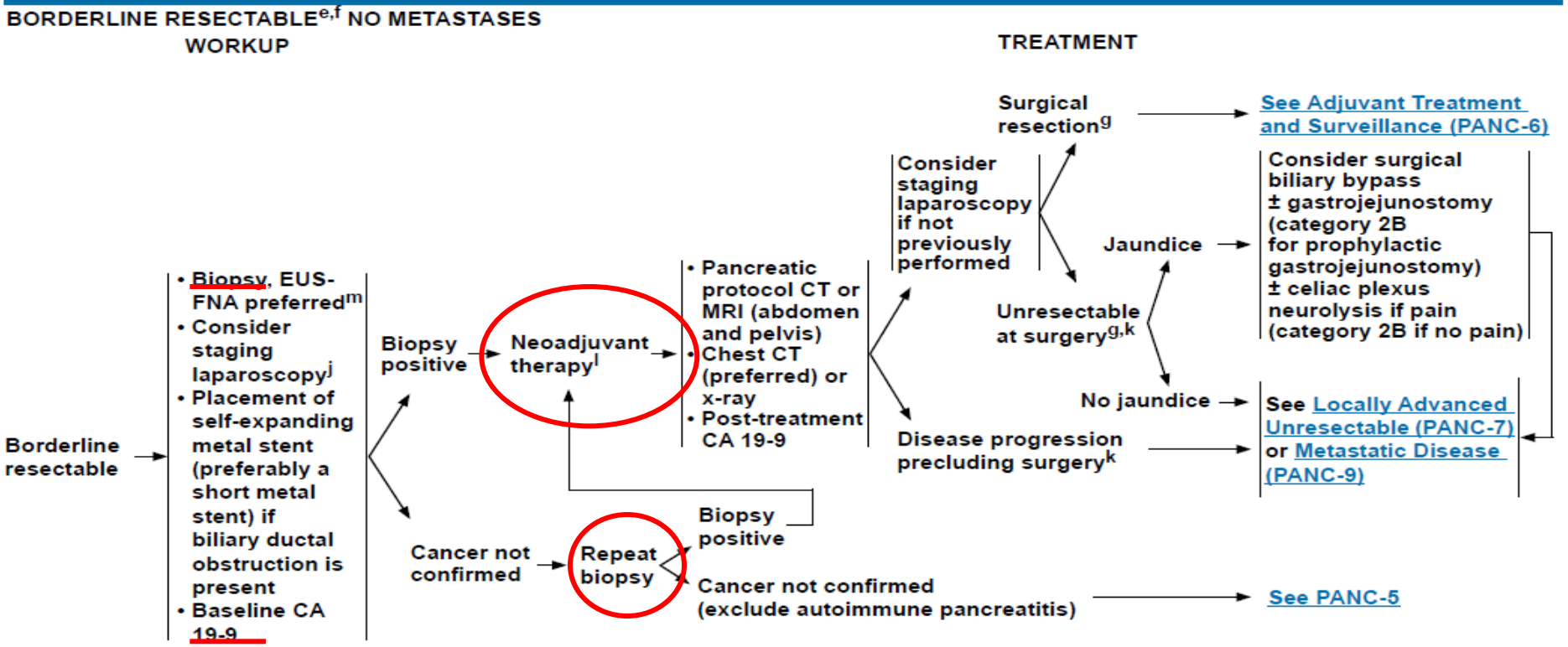

Neoadjuvant

- There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center.

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
C	Nei tumori "borderline resectable" è raccomandabile una strategia terapeutica con trattamento neoadiuvante seguito da ristadiazione ed eventuale resezione chirurgica[107,108,112]	Positiva debole

Obiettivi

- Downstaging
- Aumentare tasso R0
- Identificare i pazienti con malattia biologicamente aggressiva

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Gemcitabine-based chemotherapy

RESPONSE RATE 20-30%
Maggior efficacia delle combinazioni

Ref.	CT	Phase	ORR(%)	Resection Rate (%)	mOS
Louvet	GEMOX *vs* GEM	III	27,3 *vs* 14,9	n.d	10,3 *vs* 10,3
Rocha Lima	CPT 11 + GEM *vs* GEM	III	25,9 *vs* 4,2	nd	9,8 *vs* 11,7
Kindler	Bevacizumab + GEM *vs* GEM	III	nd	nd	9,9
Lee	GEM + CAP	II	nd	24	23,1
Sahora	GEM + Docetaxel	II	nd	12	16

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Radio-chemioterapia neoadiuvante

Table 2 Selected neoadjuvant studies for borderline resectable pancreatic cancer

Ref.	Study type	*n*	Regimen	Resection	R0 resection	Median OS (resected patients)	Median OS (all patients)	Definition
Katz *et al*[40]	Retrospective	84	5-FU, paclitaxel, gemcitabine	38%	97%	40 mo	21	MDA
			or capecitabine + RT; Gem or 5-FU or capecitabine + RT					
Mellon *et al*[45]	Retrospective	110	GTX X 3 cycles followed by SBRT	51%	96%	19	34	NCCN
Landry *et al*[39]	Randomized phase II	21	Gem + RT; Gem/cis/5-FU followed by 5-FU/RT	24%	100%	26	19.4 mo; 13.4 mo	Other
Lee *et al*[44]	Prospective trial	18	Gem/capecitabine X 3-6 cycles	61%	82%	23	16	NCCN
Kim *et al*[42]	Phase II study	39	Gem/Ox + RT	63%	84%	25	18	NCCN
Motoi *et al*[43]	Phase II study	16	Gem/S1 X 2 cycles	NA	87%	NA	18	MDA
Takahashi *et al*[46]	Prospective	80	Gem + RT followed by Gem	54%	98%	NA	NA	Other

NCCN: National Comprehensive Cancer Network; MDA: MD Anderson; 5-FU: 5-flurouracil; NA: Not available; RT: Radiation therapy.

- Dose di RT
- Scelta della CT radiosensibilizzante
- Schema di CT associato

Studio	Trattamento
PREOPANC	CH + ADV GEM *vs* GEM + RT→CH → ADV GEM
Alliance A021501	Folfirinox (8) →CH → ADV *vs* Folfirinox (7) + SBRT →CH → AD
NCT00557492	GEM + BEV + RT → CH
NCT01458717, Seoul	RT + GEM → CH →GEM ADV *vs* CH →GEM ADV
Japan Adjuvant Study Group of Pancreatic Cancer	RT+S1 →CH
University of Pittsburgh	GEM + Nab-PAC + SBRT *vs* Folfirinox + SBRT
PANDAS-PRODIGE 44	Folfirinox + RT →CH →ADV *vs* Folfirinox →CH →ADV
Duke University	GEM + Nab-PAC + IMRT/IGRT →CH →ADV

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Localized Pancreatic Cancer: Multidisciplinary Management

Andrew L. Coveler, MD, Joseph M. Herman, MD, MSc, Diane M. Simeone, MD, and E. Gabriela Chiorean, MD

KEY POINTS

- Neoadjuvant multimodality therapy should be considered for patients with borderline resectable and locally advanced unresectable pancreatic cancer.
- Induction chemotherapy for at least 2 to 3 months selects patients without rapid disease metastasis who may benefit most from the addition of radiotherapy.
- Ongoing clinical trials will help define the role of adjuvant radiotherapy for resectable patients (RTOG0848), as well as for locally advanced unresectable patients (RTOG1201).
- Select patients with initially localized but unresectable disease may undergo potentially curable surgical resection after neoadjuvant therapy and have outcomes comparable to patients with initially resectable disease.
- Radiologic RECIST response does not adequately predict resectability for patients with borderline resectable or locally advanced unresectable pancreatic cancer.
- Pathologic complete or near-complete response (often defined as < 5% viable cells) to neoadjuvant therapy may predict increased survival.
- It is currently unknown whether borderline resectable or locally advanced unresectable patients undergoing induction (neoadjuvant) multi-agent chemotherapy will derive additional benefit with the addition of radiotherapy.
- Novel combinations of systemic treatment and radiotherapy modalities such as SBRT and IMRT may provide superior resectability and local control.
- Blood and tissue biomarkers may assist in determining optimal neoadjuvant strategies.

FOLFIRINOX-Based Neoadjuvant Therapy in Borderline Resectable or Unresectable Pancreatic Cancer

A Meta-Analytical Review of Published Studies

Fausto Petrelli, MD, Andrea Coinu, MD,* Karen Borgonovo, MD,* Mary Cabiddu, MD,* Mara Ghilardi, MD,* Veronica Lonati, Biologist,* Enrico Aitini, MD,† and Sandro Barni, MD,* on behalf of Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD)*

TABLE 1. Characteristics of Included Trials

Author, y	Type of Study/ Study Period	No. Pts	Median Age/PS 0–1	Stage: Borderline/ Unresectable % (Criteria)	Schedule (Median No. Cycles)	CT-RT %/ Radiosensitizer	Resection (%/All Pts)	R0 resection (%/All Pts)	ORR, %	Median OS, mo	G3-G4 Toxicity, %
Mahaseth et al,[16] 2013	Cohort/2010–2012	24	63/98*	17 stage II/83 stage III (NR)	m-FOLFIRINOX (3)	58/7 CAP 78%, GEM 22%	42.8†	35.7†	33	17.8	57
Boone et al,[9] 2013	Retrospective series/ 2011–2012	25	59/100	48/52 (AHPBA/SSO/SSAT)	FOLFIRINOX (5)	24 SBRT alone (36 Gy in 3 fractions)	43‡	33‡	NR	NR	60
Gunturu et al,[17] 2013	Retrospective series/ 2010–2011	16	60/100	0/100 (NR)	FOLFIRINOX (11)§	No	12.5	12.5	50	Not reached	28.7§
Peddi et al,[18] 2012	Retrospective series/ 2009–2012	23	58/86.9§	17/83 (NR)	FOLFIRINOX (4)§	No	34.7	34.7	33.4	NR	55.8§
Hosein et al,[19] 2012	Retrospective series/ 2008–2011	18	57.5/100	23/77 (AHPBA/SSO/SSAT)	FOLFIRINOX (6)	16/GEM 100%	55	44	NR	Not reached	44
Tinchon et al,[25] 2013	Cohort/2010–2012	12	NR/100	100/0 (AHPBA/SSO/SSAT)	FOLFIRINOX (4)	No	83	NR	33.3‖	Not reached	41.6
Christians et al,[15] 2014	Retrospective series/ 2010–2012	18	59/NR	100/0 (Katz criteria)	FOLFIRINOX	100/CAP 50%, GEM 50%	67	67	NR	Not reached	75
Faris et al,[8] 2013	Retrospective series/ 2010–2012	22	63/91	0/100 (NCCN)	FOLFIRINOX (8)	91/5FU or CAP 100%	22.7	22.7	36.4**	Not reached	7††
James et al,[20] 2014	Prospective phase 2/NR	22	62§/100	0/100 (NR)	m-FOLFIRINOX (8)§	No	46	NR	NR	NR	71.8
Hazariwala et al,[21] 2013	Retrospective series/NR	14	NR	43/57 (NR)	FOLFIRINOX (NR)	100/CAP 78%, GEM 22%	50	42.8	NR	NR	NR
Vasile et al,[22] 2013	Prospective phase 2/NR	32	60/100	NR	m-FOLFIRINOX (6)	15.6/NR	41	41	37	24.2	NR
Kharofa et al,[23] 2012	Retrospective series/ 2009–2011	12	NR	100/0 (NR)	FOLFIRINOX (4)	100/CAP 33%, GEM 67%	58	58	NR	Not reached	NR
Lowery et al,[24] 2012	Retrospective series/ 2010–2011	19	58/NR	0/100 stage III	FOLFIRINOX (6)	53% (without surgery)/NR	5	NR	21	13.7	NR

Risultati

- 13 studi pubblicati tra 2012 e 2014
- 253 pazienti
- Resection Rate: 43%
- Resection Rate senza RT: 42,3%
- R0: 39,4%
- Response rate: 35,4%
- mOS: 13,7-24,2 m
- In BRCP Resection Rate 68,5%, R0 63,5%

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Tossicità G3/G4

- Cumulative rate G3/G4: 28,7-75%
- Neutropenia: 3-22%
- Uso di fattori di crescita a scopo profilattico
- Diarrea: 0-18%
- Riduzione di dose: 17-83%

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Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial

Timothy M Nywening, Andrea Wang-Gillam*, Dominic E Sanford, Brian A Belt, Roheena Z Panni, Brian M Cusworth, Adetunji T Toriola, Rebecca K Nieman, Lori A Worley, Motoyo Yano, Kathryn J Fowler, A Craig Lockhart, Rama Suresh, Benjamin R Tan, Kian-Huat Lim, Ryan C Fields, Steven M Strasberg, William G Hawkins, David G DeNardo, S Peter Goedegebuure, David C Linehan*

- Blocco di CCR2 ristabilisce la risposta immunitaria al tumore in modelli pre-clinici
- PF-04136309, piccola molecola orale inibitore di CCR2
- Studio Fase Ib (Folfirinox e Folfirinox + PF-04136309)
- Dose raccomandata in associazione a Folfirinox 500 mg 2 volte/die
- RR 0% vs 49%

Lancet Oncol, 2016 17:651-662

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Treatment of borderline resectable (BR) and locally advanced (LA) pancreatic cancer in the era of FOLFIRINOX and gemcitabine plus *nab*-paclitaxel: A multi-institutional study.

- 86 pts (***67% BRPC***)
- 69% Folfirinox
- ***31% Gem + nab-paclitaxel***
- **R0 86%** (no diff. X tipo di CT)
- Marked PR 13,6 vs 15,4
- OS marked PR *vs* Non marked PR: 53 vs 25m

Idrees K, ASCO GI 2016

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Neoadjuvant *nab*-paclitaxel and gemcitabine (AG) in borderline resectable (BR) or unresectable (UR) locally advanced pancreatic adenocarcinoma (LAPC) in patients ineligible for FOLFIRINOX.

- 20 pts non candidabili a Folfirinox (14 BRCP)
- **R0 29%**
- Tossicità come nella malattia M+
- Frequenti riduzioni di dose
- Pazienti unfit

Peterson S, ASCO GI 2016

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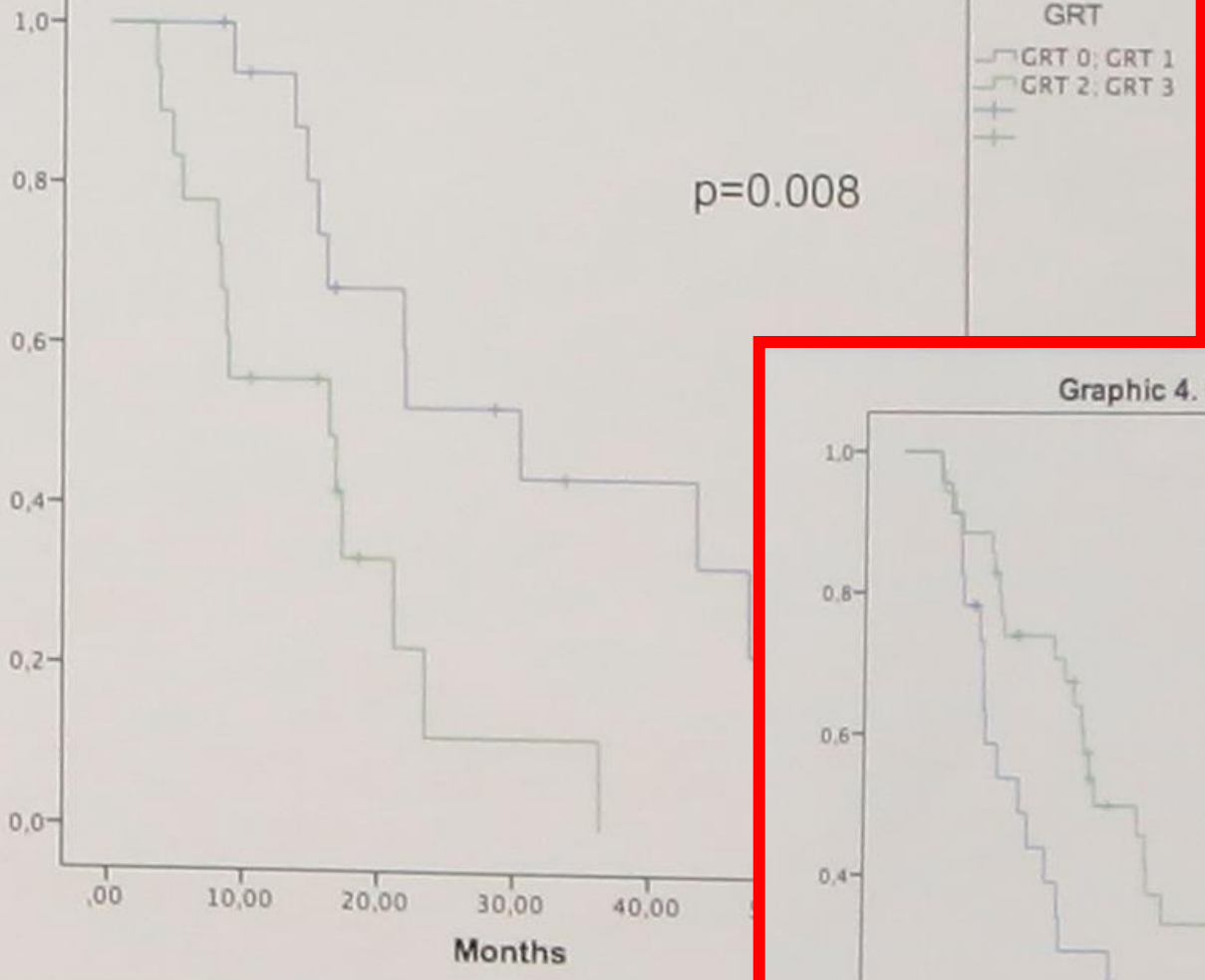
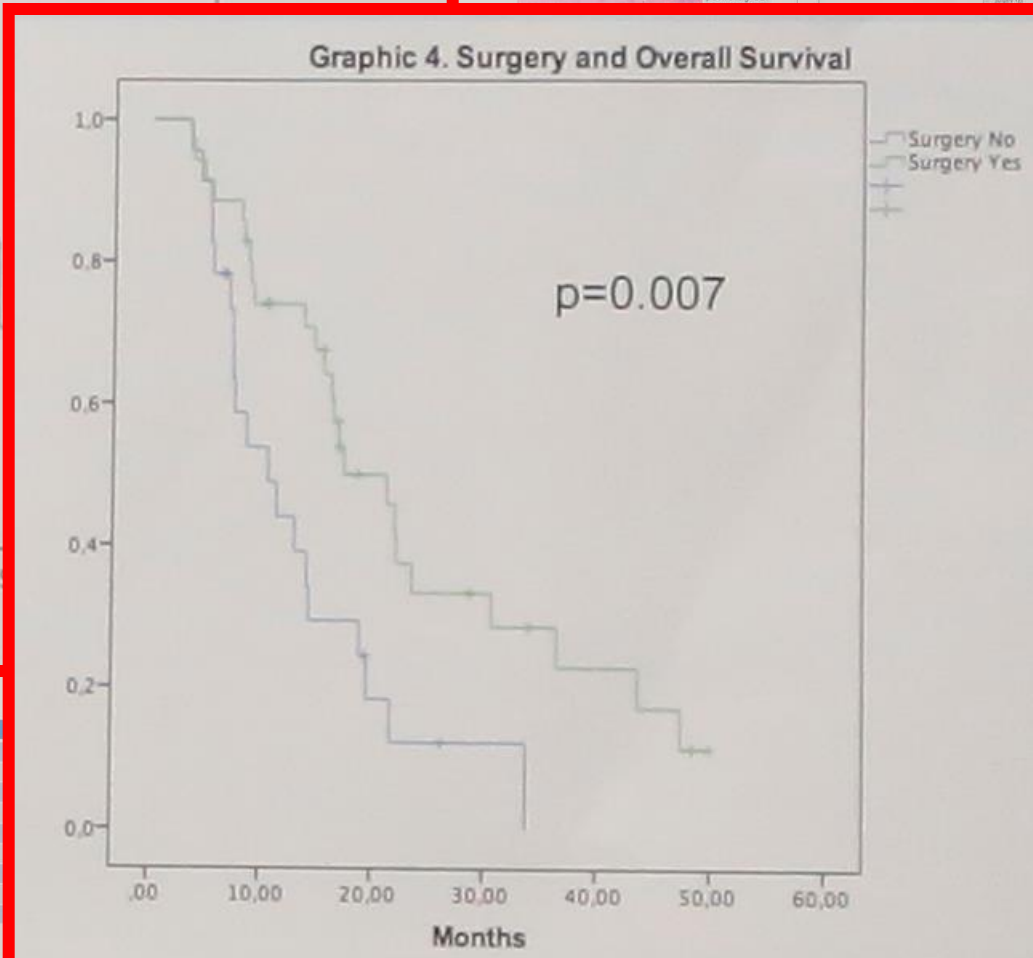
Graphic 5. Histopathological response and Overall Survival

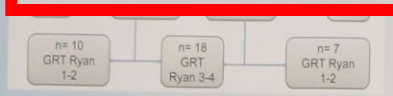


Graphic 4. Surgery and Overall Survival



plus nabpaclitaxel in improved survival.

bio C[1], Hernando O[1], Lopez-Rios G[2] , Plaza C[2], Hidalgo M[4]
éuticas. Hospital Universitario Madrid Norte Sanchinarro, Madrid, Spain.
adrid, Spain.



We evaluated the surgical specimen in order to define the Grade of Tumor Regression(GRT) by adapted Ryan criteria[1]. Defining GRT 0-1 is a complete response or only few groups of cells tumor and GRT 2-3 as a limited response with profuse residual tumor.

Table 2. Grade III- IV Toxicities

	N	%
Neutropenia	15	25,9
Thrombocytopenia	5	8,6
Anaemia	3	5,2
Neutropenic Fever	0	0
Neuropathy	1	1,7
Infection	1	1,7
Colangitis (in patients with stent)	2	3,4
Other	3	5,2

Abstract ID: 4109

1. Ryan R et al. Histopathology. 2005 Aug;47(2):141-6.

Trattamenti in studio

FIRINOX
Pembrolizumab
CAPOXIRI
GEM + Capecitabina
GMCI+mFolfirinox
Gemcitabina + Oxaliplatino + Tarceva

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Chemioterapia

CT + RT

Valutazione di estensione e risposta

Impatto su OS

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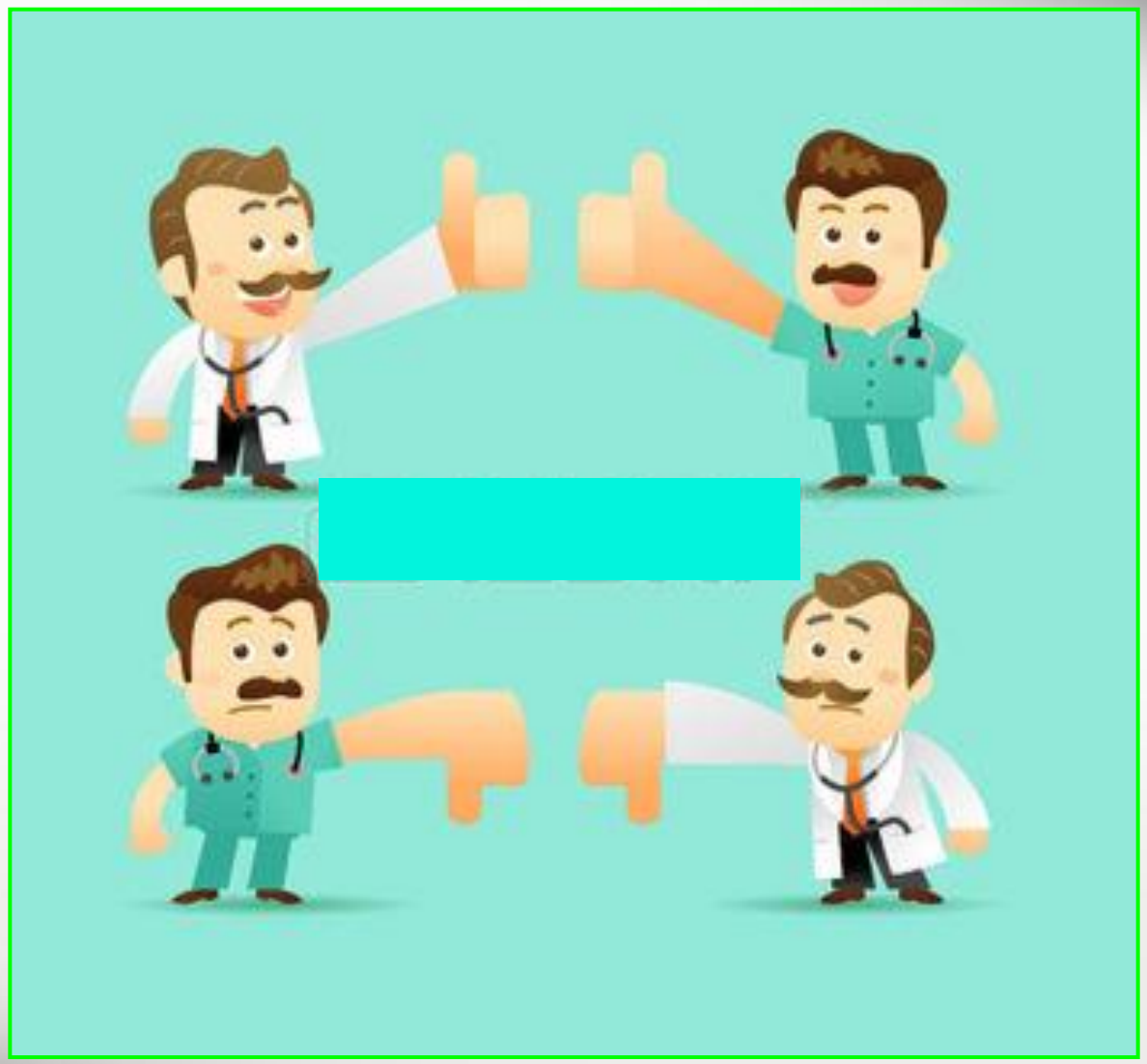

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