Neoadjuvant treatment concepts: chemo versus chemo followed by chemoradiation

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Presentation of Pancreatic Adenocarcinoma

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;9:281-292; Siegel RL, Miller KD, Jemal A. CA Cancer J Clin. 2017;67:7-30.

Owing to the difficulty of relying on strict criteria for unresectability, it should be recommended that all cases with nonmetastatic tumours and discussed by a multidisciplinary board in a high-volume centers, and these evaluations are repeated after treatment induction to confirm definitive unresectability.

What Are the Objectives of Neoadjuvant Treatment in Borderline/LA Tumors?

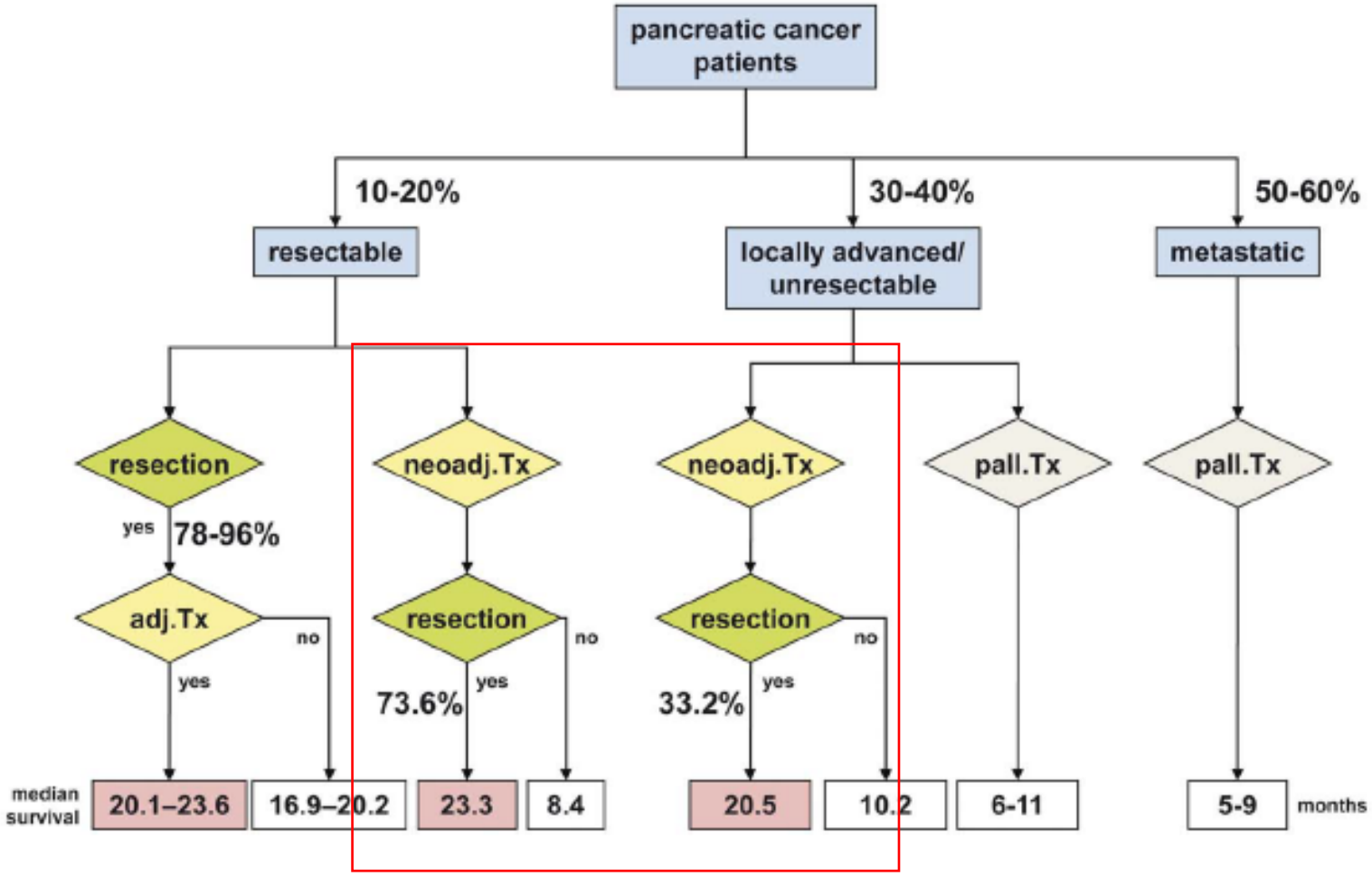
- Increase rate R0 resections
- Increase OS of these patients 
- Early treatment of micrometastatic disease
- Unnecessary surgical resection in patients with aggressive disease that develop early recurrence

however...

- We need tumor tissue before treatment; sometimes difficult 
- Biliary drainage if it is necessary with metal stent

Any option **surgery first**? My answer is **NO**

Neoadjuvant therapy in PDAC and resection rate associated with OS



-Trials from 1980-2009
-111 Trials
-4394 patients
-Old QTA
-RT associated to QTA in 93% trials
-**33.2% of unresectable tumours (borderline and LA) can be resected with comparable survival as initially resectable tumours.**

Gillen et al, PloS Medicine 2010;7:e10000267

Downsizing and downstaging effect: a systematic literature review and meta-analysis

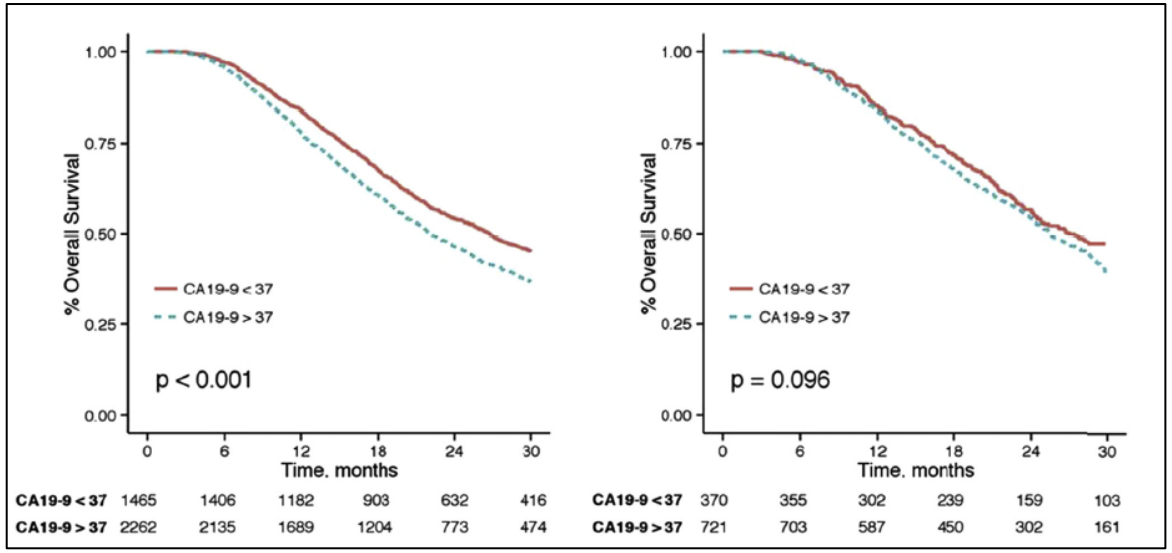
Review of studies evaluating the effect of neoadjuvant therapy (CRT, CT + CRT) on histopathological outcome in LA and BRD PDAC in comparison to upfront surgery

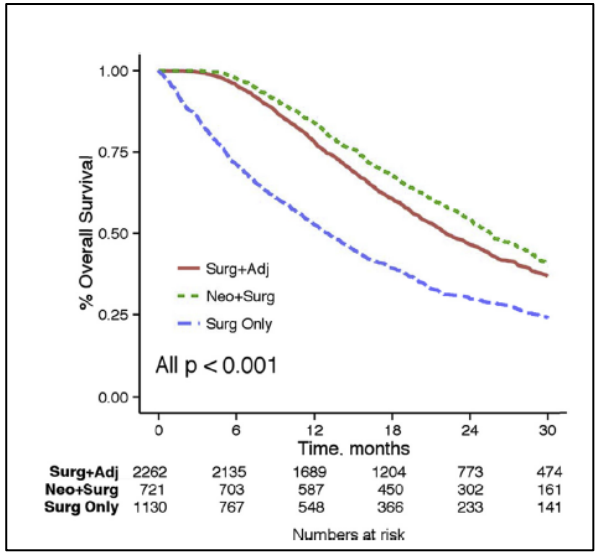
	Upfront surgery	Neoadjuvant	p
pT3/pT4 or yT3/T4	88%	75%	0.0002
pN0 or yN0	35%	58%	<0.00001
R0 resection*	73%	83%	<0.00001
Perineural invasion	79%	65%	<0.00001
Lymphatic vessel inv	63%	34%	<0.00001

*No precision on R0 resection margin definitions in the reviewed studies

Schorn S, et al. *Cancer Treat Rev.* 2017;55:96-106.

Poor OS associated with elevation in CA 19.9 can be mitigated by neoadjuvant treatment





Surgery and adjuvant therapy and neoadjuvant therapy and surgery

-The only treatment strategy that completely mitigates the increase mortality related to CA 19.9 elevation is neoadjuvant treatment.

-Patients with elevation in CA 19.9 above normal should be considered biologically borderline resectable tumours and have to be treated with neoadjuvant treatment.

Berquist et al. J Am Coll Surg 2016; 223:52-65.

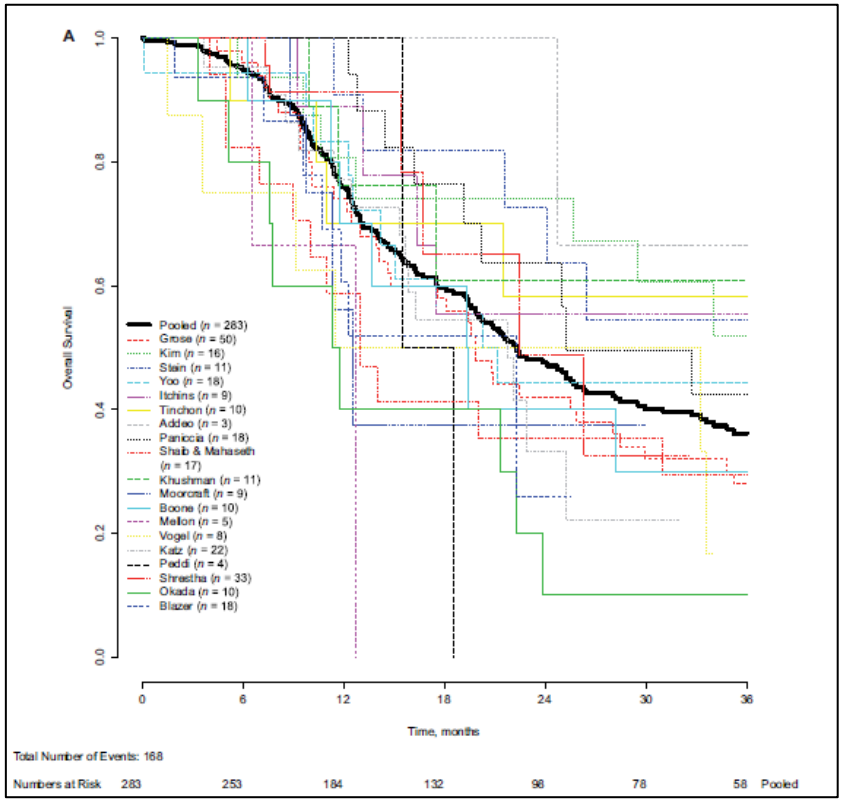
Neoadjuvant treatment with chemotherapy followed by surgery

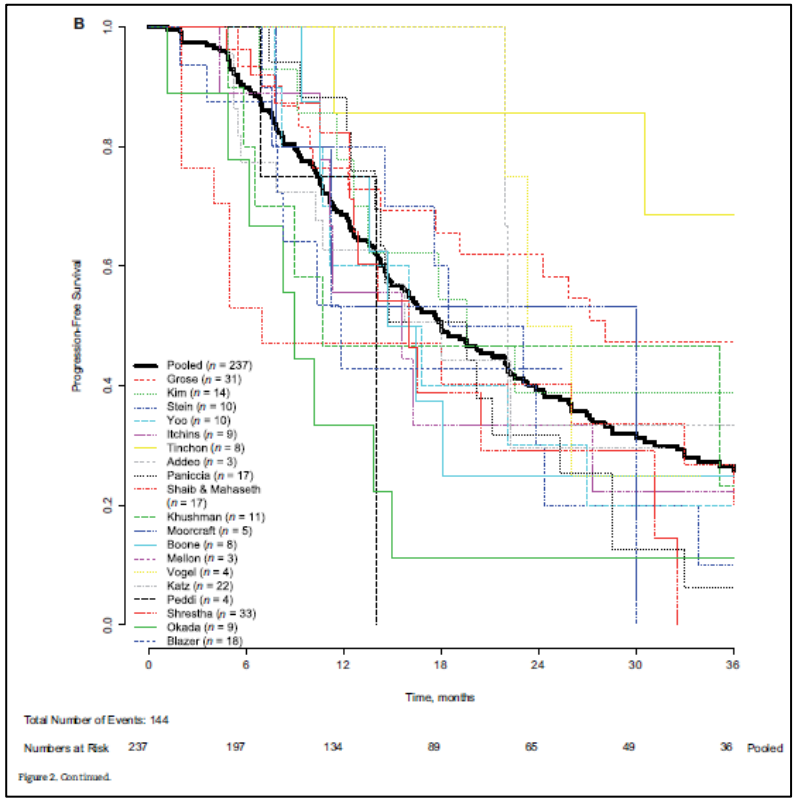
Neoadjuvant FOLFIRINOX in patients with borderline PDAC: A systemic review and patient-level meta-analysis

- Studies with BRPC treated with FOLFIRINOX as neoadj treatment
- Primary endpoint: OS
- N: 24 studies (8 prospective, 16 retrosp), 283 patients
- The use of RT after FOLFIRINOX varied across studies.
- No correlation between RT and OS
- Median number of cycles: 4-9
- Resection rate: 67.8%
- R0 resection rate: 83.9%
- Pooled event rates: Neutropenia, diarrhea, and fatigue

Janssen et al, JNCI 2019; 111(8)

Neoadjuvant FOLFIRINOX in patients with borderline PDAC: A systemic review and patient-level meta-analysis



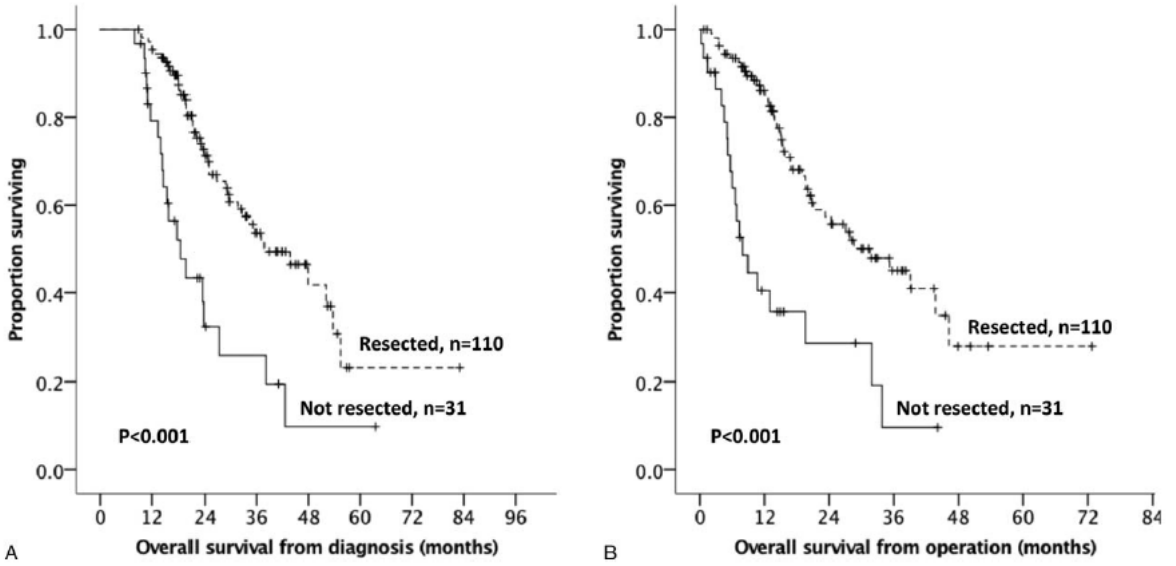


Median OS 11 to 34.2 months. The patient-level **median OS was 22 months**
Patients median PFS was 18 months

Janssen et al, JNCI 2019; 111(8)

Predictors of Resectability and Survival in Patients With Borderline and Locally Advanced Pancreatic Cancer who Underwent Neoadjuvant Treatment With FOLFIRINOX

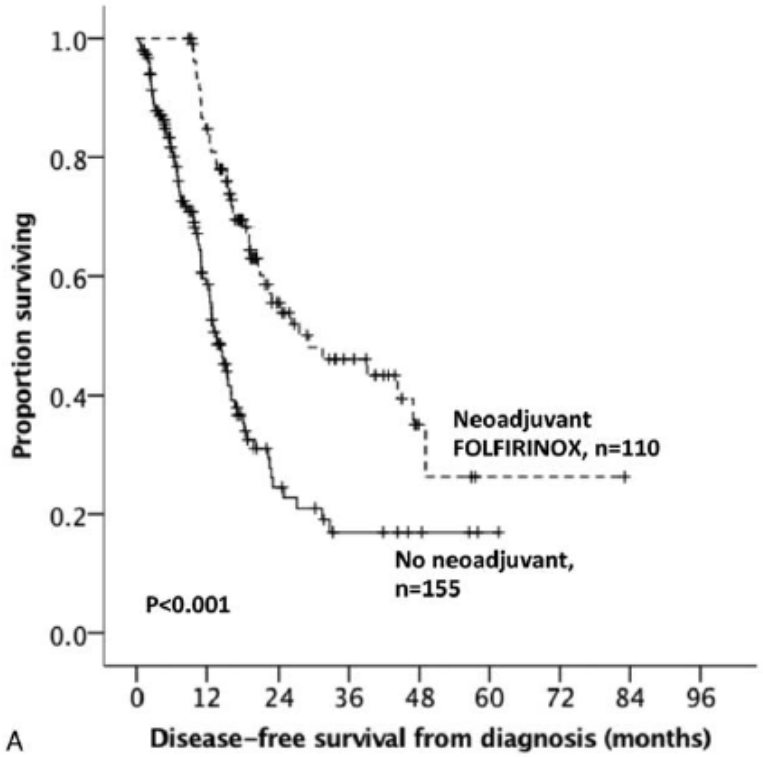
- Clinicopathologic data of PDAC patients surgically explore (4.11-11.16) in a single institution were retrospective collected.
- 141 pts were surgically explored (BR 49%, LA 51%), after FOLFIRINOX treatment, 78% were resected.
- Charlson comorbidity index>1, preop CA 19.9 >100 and tumour size predicted decreased OS



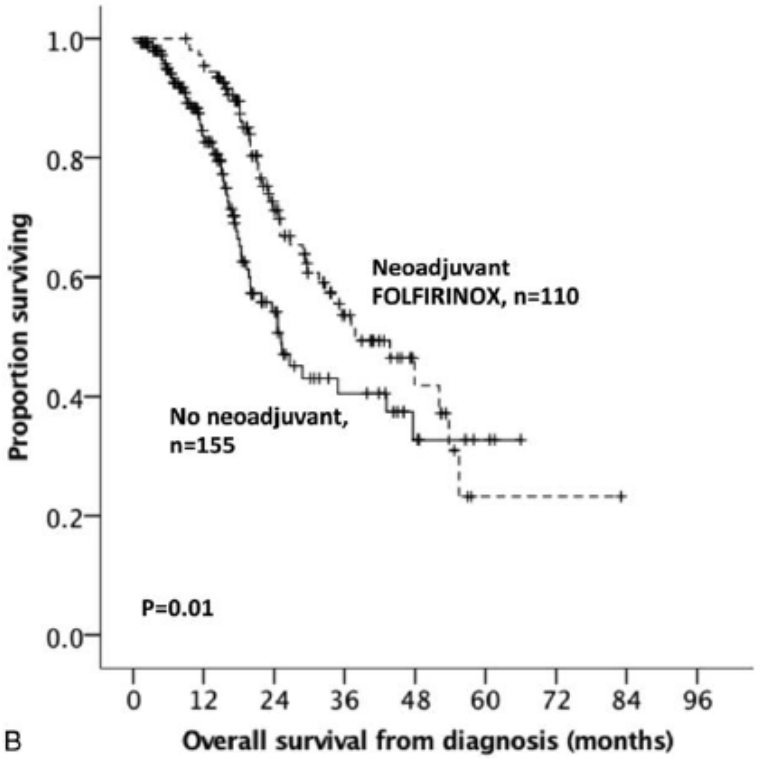
A: OS 18.6 m vs 37.7 m
B: OS 8 m vs 31.7 m

Michelakos et al, Ann Surg 2019;269 (4):733-740

Predictors of Resectability and Survival in Patients With Borderline and Locally Advanced Pancreatic Cancer who Underwent Neoadjuvant Treatment With FOLFIRINOX



A



B

A: DFS 29.1 m vs 13.7 m, p< 0.001
B: OS 37.7 m vs 25.1 m, p=0.01

Michelakos et al, Ann Surg 2019;269 (4):733-740

Neoadyuvant treatment with FOLFIRINOX vs Gemcitabine and nab-paclitaxel

- **Retrospective study in Syracuse, NY and Pittsburgh, PA (6/2011 → 5/2017)**
- **Median follow-up: 27.5 months**

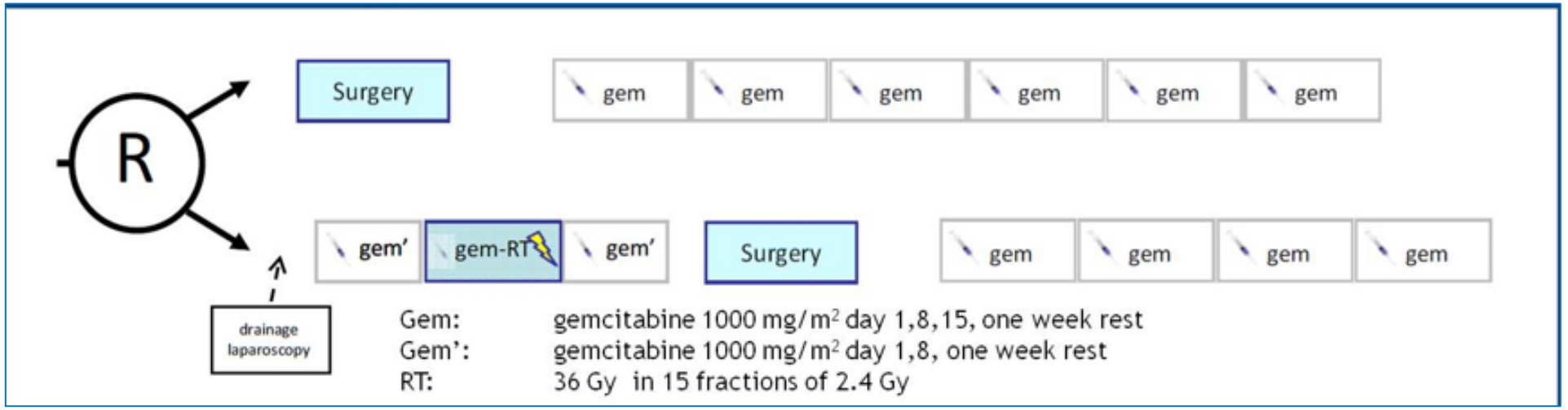
	Folfirinox	G-nP	p
n	73	120	
BRPC/resectable	79 %/21%	59 %/41%	0.004
Vessel involvement	80%	59%	0.026
Tumor size	2.9 cm	2.7 cm	0.023
CA 19.9 decrease	80 %	80 %	ns
Lymphovascular invasion	61 %	81 %	0.003
ypN1	62 %	86 %	0.028

- **Not significant trend toward improved OS with Folfirinox (OR 0.674 ; 95 %CI 0.38-1.2; p=0.183)**
- **Ongoing SWOG S1505 will evaluated Folfirinox vs G-nP**

Dhir et al. Ann Surg Oncol 2018;25:1896-1903

Neoadjuvant treatment with chemotherapy followed by chemoradiation

Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC)



Primary objective: **Overall Survival**
Borderline resectable 46%/53%

DPCG
Dutch Pancreatic Cancer Group

Van Tienhoven G, et al. ASCO 2018. Abstract LBA4002.

Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC)

DPCG Dutch Pancreatic Cancer Group	Arteries			Veins
	Superior Mesenteric	**Celiac Trunk**	**Common Hepatic**	Superior Mesenteric Portal
Resectable (all four required)	no contact	no contact	no contact	≤ 90° contact
Borderline resectable (minimally one required)	≤ 90° contact	≤ 90° contact	≤ 90° contact	90°-270° contact, and no occlusion

Van Tienhoven G, et al. ASCO 2018. Abstract LBA4002.

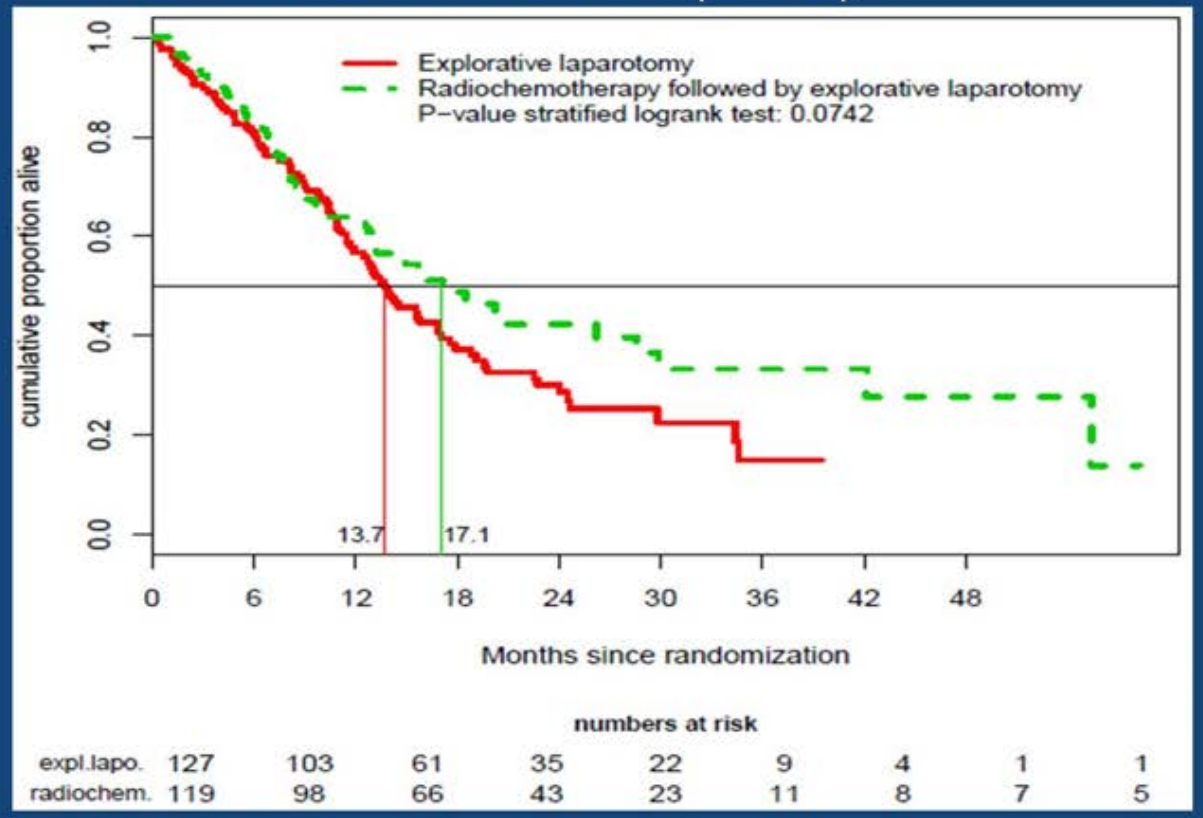
Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC)

	Immediate surgery N=127	Preop. radiochemotherapy N=119	p value
Resection rate	91/127 (72%)	72/119 (60%)	.065
R0 resection rate PP	28/91 (31%)	45/72 (63%)	<.001
Serious Adverse Events	49 (39%)	55 (46%)	.28

Van Tienhoven G, et al. ASCO 2018. Abstract LBA4002.

Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC)

Overall survival (ITT)



Preliminary: 149/176 events

Median survival:

13.7 vs 17.1 months

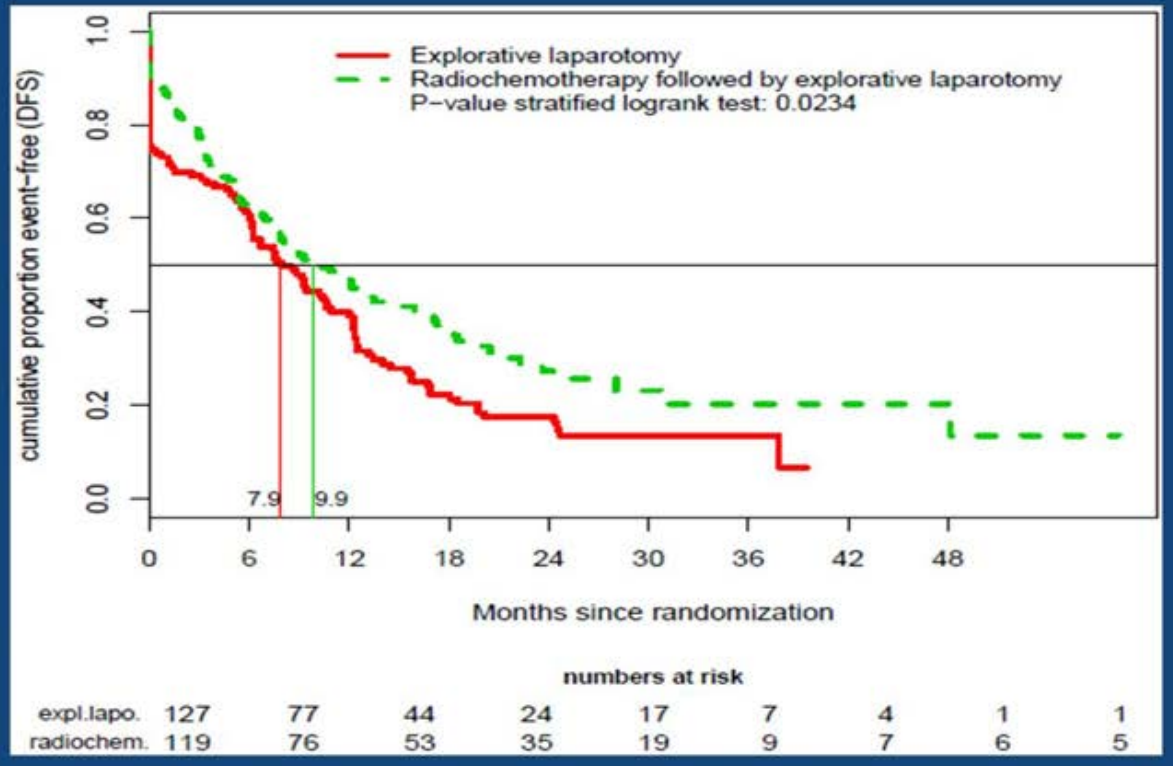
HR 0.74

p=0.074

Van Tienhoven G, et al. ASCO 2018. Abstract LBA4002.

Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC)

Disease free survival



Median DFS:

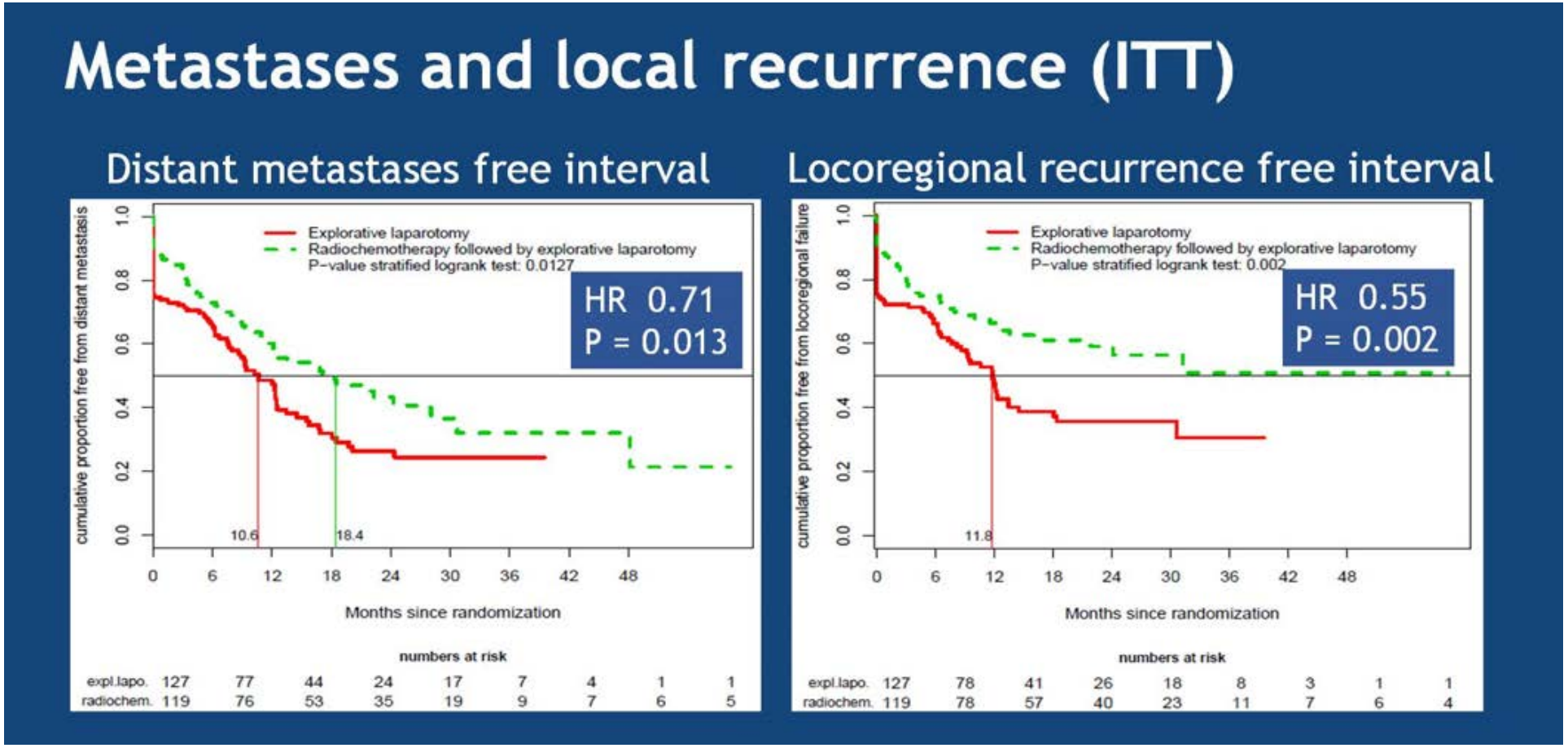
7.9 vs 9.9 months

HR 0.71

p=0.023

Van Tienhoven G, et al. ASCO 2018. Abstract LBA4002.

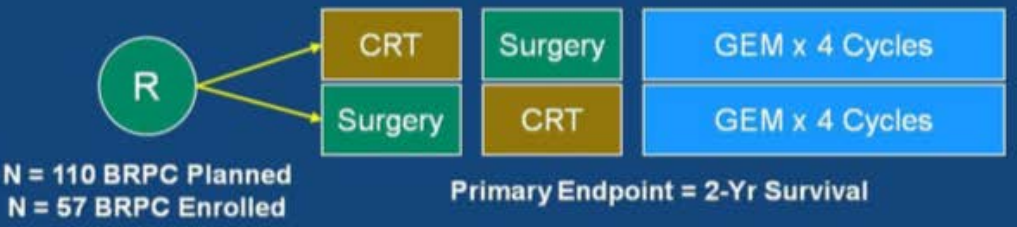
Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC)



Van Tienhoven G, et al. ASCO 2018. Abstract LBA4002.

What Is the Best Treatment Option for BRPC patients?

Neoadjuvant Versus Adjuvant – Chemoradiation (CRT)



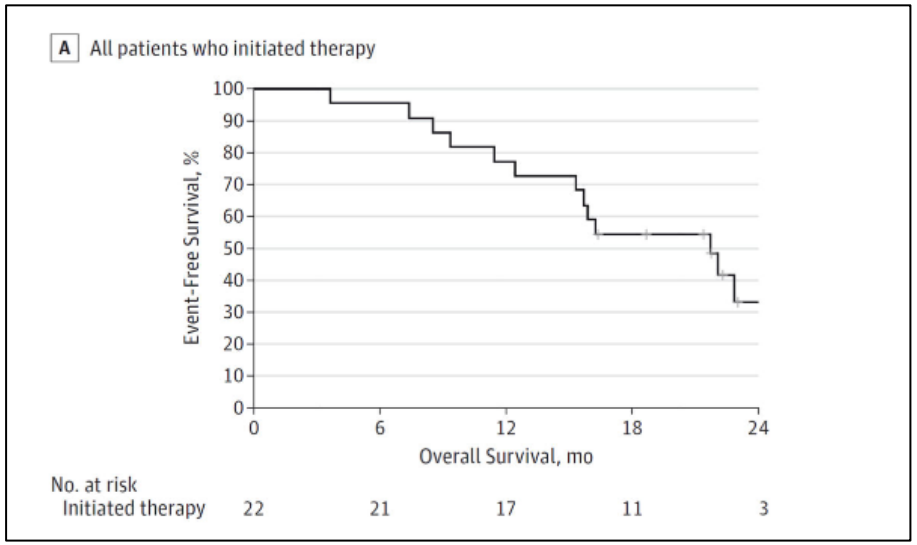
N = 110 BRPC Planned
N = 57 BRPC Enrolled

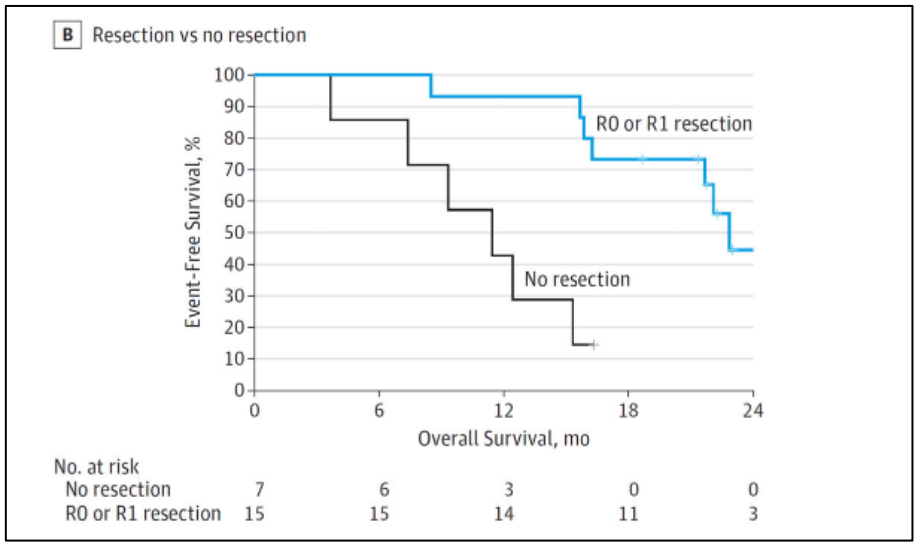
Primary Endpoint = 2-Yr Survival

	Neoadjuvant CRT	Adjuvant CRT	
2 year survival - ITT	**40%**	26%	p = 0.004
Median OS (months) – ITT	**21**	12	HR 1.97; p = 0.028
R0 Resection Rate - ITT	**51%**	26%	p = 0.004
R0 Resection Rate - Resected	**82%**	33%	p = 0.010
Positive Lymph Nodes	**0.5 ± 0.9**	1.9 ± 1.6	p = 0.004

Jang JY, et al. *Ann Surg.* 2018;268:215-222.

Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for BRPC: A021101

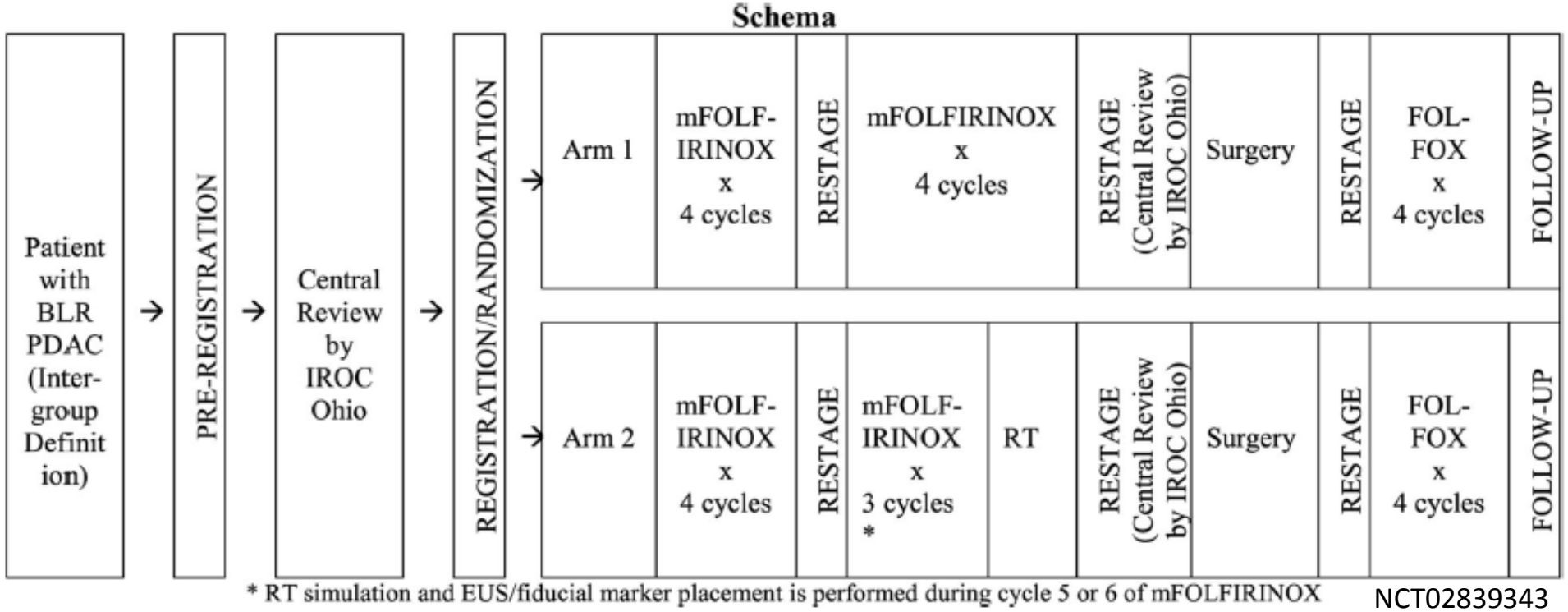




-N 23 BRPC
-64% grade 3 or higher AE
-68% underwent surgery (80% vascular resection)
-93% microscopically negative margins
-13% pathological complete response
-mOS: 21.7 months
-18 m OS resected vs non resected: 67% vs 43%

Katz et al. JAMA Surg 2016; 151(8): e161137

A021501: Preoperative chemotherapy vs chemotherapy plus RT for borderline resectable PDAC

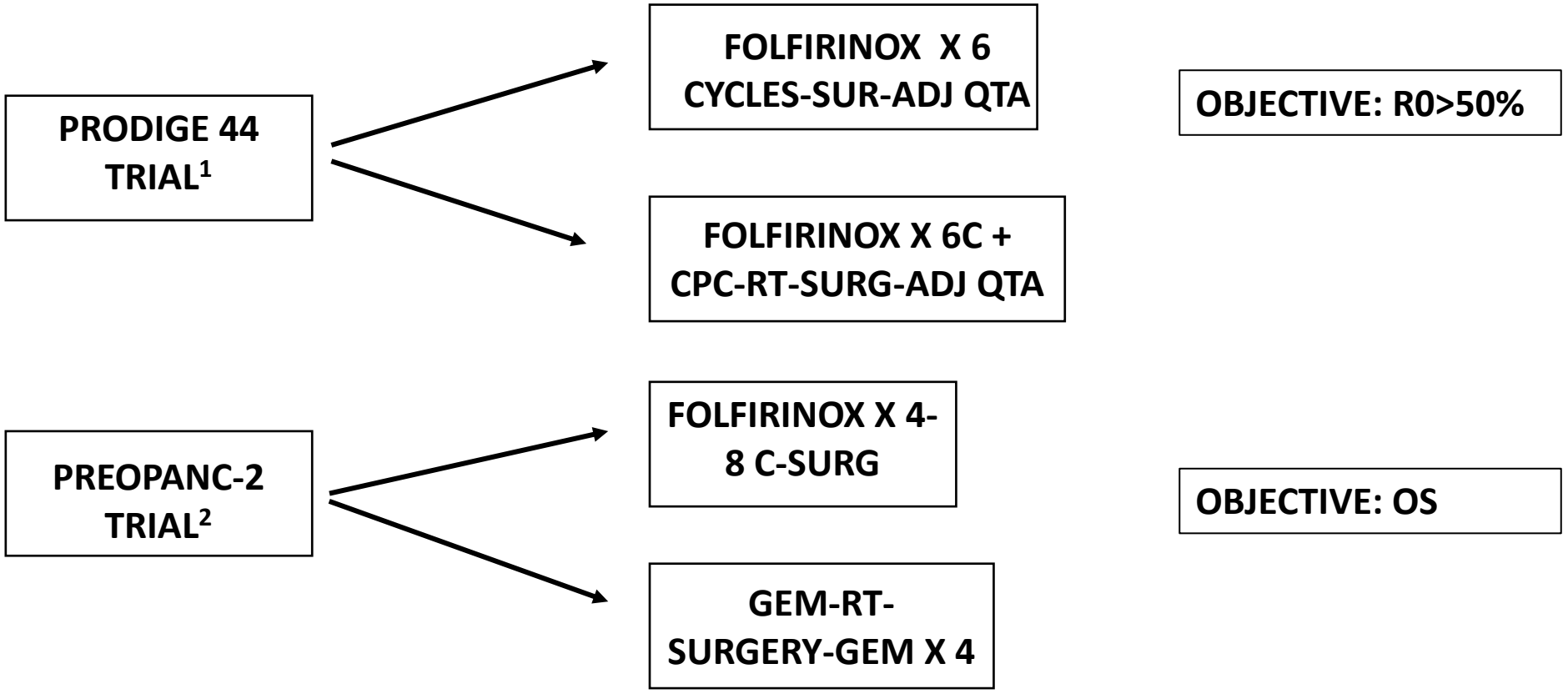


NCT02839343

R phase II trial. N 134 patients
Objective: 18 m OS
RT: Stereotactic body radiation therapy (33-40 Gy in 5 fractions)
R0 resection rate to asses treatment futility after accrual of 30 patients

Katz et al, BMC Cancer 2017; 17:505

Ongoing clinical trials for BRPC testing neoadjuvant strategy



- These trials will hopefully answer two important questions
  - Is induction therapy a strategy to improve OS in BRPC?
  - Should we use QTA or QTA followed by RT?

1-NCT02839343
2-NTR7292

Conclusions neoadjuvant treatment with chemotherapy

- Multidisciplinary approach and surgical pancreatic expertise are essential for successfully treating these patients.
- Promising data with Folfirinox, mFolfirinox and gem-nab are available from retrospective and prospective studies, mainly monoinstitutional studies
- Folfirinox as neoadjuvant regimen is safe and may have significant survival benefit, without increase of the surgical morbidity and mortality. It has be to demonstrated in ongoing randomized studies
- Consultation in a high-volume center and enrollment in a clinical trial are recommended

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Conclusions neoadjuvant treatment with chemotherapy followed chemo-radiotherapy

- During conventional chemoradiotherapy systemic micrometastasis disease may be suboptimal treated for as many as 3 months prior to resection.
- The systemic regimens now in routine use for localized disease are associated with higher RR. The use of RT are controversial in this setting.
- Chemotherapy followed by SBRT may also be safe and feasible in the neoadjuvant setting, and may improve the potential for resection in patients with borderline resectable or locally advanced disease.
- However, further studies are needed before SBRT is recommended as a treatment option for patients with borderline resectable disease.

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Thank you for your attention

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