Non surgical treatment for pancreatic cancer

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Objectives

- Localised pancreatic cancer: resectable versus unresectable
- -> chemotherapy (neoadjuvant/adjuvant)
- -> chemoradiotherapy
- -> Radiotherapy techniques including SABR

- Metastatic pancreatic cancer

Resectable (10-20%)

- Surgical resection is the only potentially curative treatment.
- Furthermore, prognosis is poor, even after a complete (R0) resection.
- Even though it looks like tumour completely resected, a high proportion of patients relapse which must mean microscopic cells (not visible on scan) left behind

Adjuvant chemotherapy

- Chemotherapy is the use of cytotoxic medications to destroy rapidly growing cells
- Adjuvant refers to giving it following definitive treatment to improve the odds of cure/long term DFS
- Comes with significant risks: life threatening neutropenic sepsis and thromboembolism, and other risks can be specific to particular chemotherapy

Journal of Clinical Oncology > List of Issues > Volume 26, Issue 15_suppl >

GASTROINTESTINAL (NONCOLORECTAL) CANCER

CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (PC)

P. Neuhaus , H. Riess , S. Post , K. Gellert , K. Ridwelski , H. Schramm...

- 368 patients randomised following Whipple's for pancreatic adenocarcinoma (R0/R1) **(2007)**
- 6 months Gemcitabine versus observation
- DFS 13.4 months gemcitabine versus 6.9 months observation
- DFS at 3 years gemcitabine = 23.5% versus DFS at 3 years observation = 8.5%
- Median OS 22.8 months Gemcitabine versus 20.2 months observation

September 8, 2010

Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer Resection

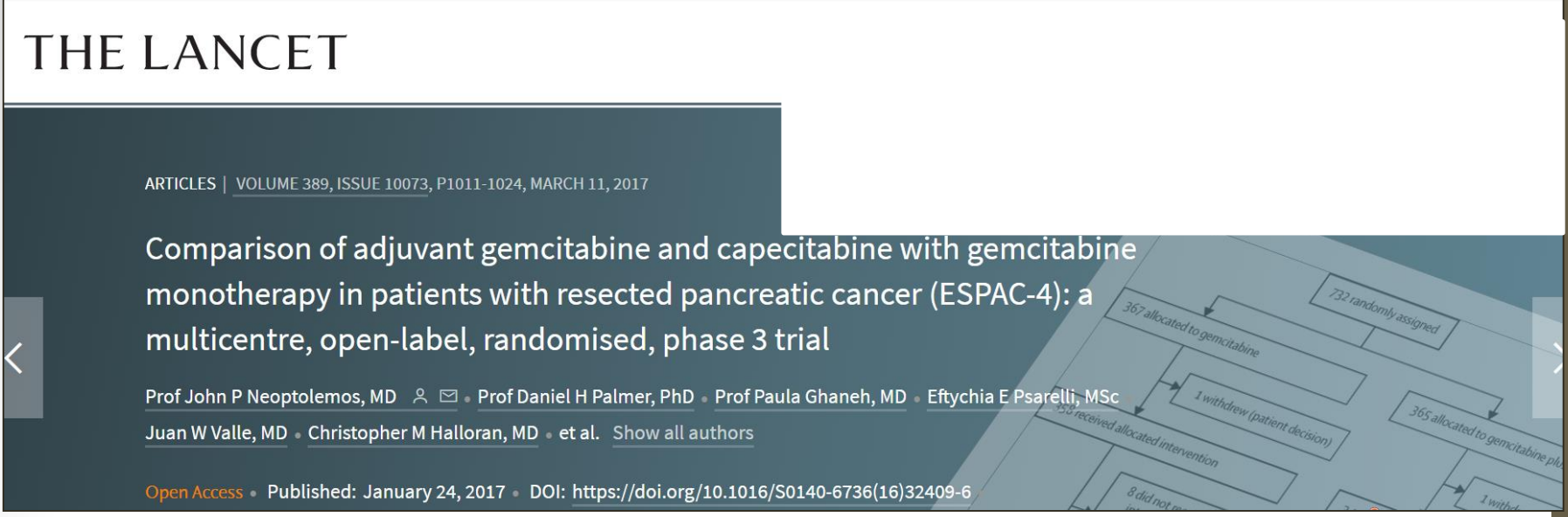
A Randomized Controlled Trial

John P. Neoptolemos, MD; Deborah D. Stocken, PhD; Claudio Bassi, MD; et al

» Author Affiliations | Article Information

JAMA. 2010;304(10):1073-1081. doi:10.1001/jama.2010.1275

- Median OS 23 months 5FU versus 23.6 months with Gemcitabine = no statistically significant difference
- 14% 5FU versus 7.5% Gemcitabine experienced serious treatment related adverse events (p=0.001)



- 6 cycles Gem Cap versus 6 cycles Gem: median OS 28 months versus 25.5 months
- Higher toxicity for Gem Cap arm of study but considered acceptable, therefore became new standard of care in 2017

ORIGINAL ARTICLE

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

Thierry Conroy, M.D., Pascal Hammel, M.D., Ph.D., Mohamed Hebbar, M.D., Ph.D., Meher Ben Abdelghani, M.D., Alice C. Wei, M.D., C.M., Jean-Luc Raoul, M.D., Ph.D., Laurence Choné, M.D., Eric Francois, M.D., Pascal Artru, M.D., James J. Biagi, M.D., Thierry Lecomte, M.D., Ph.D., Eric Assenat, M.D., Ph.D., et al., for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

December 20, 2018
N Engl J Med 2018; 379:2395-2406
DOI: 10.1056/NEJMoa1809775

Chinese Translation 中文翻译

- 493 patients randomised between gemcitabine vs mFolfirinox for 24 weeks after pancreatic adenocarcinoma resection (R0/R1), PS0/1
- N0/N1 both allowed in trial but stratified between groups

Table 1. **Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).***

Characteristic	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)
Age		
Median (range) — yr	63 (30–79)	64 (30–81)
≥70 yr — no. (%)	47 (19.0)	54 (22.0)
Male sex — no. (%)	142 (57.5)	135 (54.9)
WHO performance-status score — no./total no. (%)†		
0	122/245 (49.8)	127/242 (52.5)
1	123/245 (50.2)	115/242 (47.5)
Status of surgical margins — no. (%)‡		
R0	148 (59.9)	134 (54.5)
R1	99 (40.1)	112 (45.5)
Tumor histologic findings — no./total no. (%)		
Ductal adenocarcinoma	244/247 (98.8)	242/245 (98.8)
Nonductal carcinoma	3/247 (1.2)	3/245 (1.2)
Tumor stage — no. (%)§		
I	12 (4.9)	14 (5.7)
IIA	43 (17.4)	47 (19.1)
IIB	183 (74.1)	179 (72.8)
III	1 (0.4)	1 (0.4)
IV	8 (3.2)	5 (2.0)
Lymphovascular invasion — no./total no. (%)	154/209 (73.7)	135/214 (63.1)
Perineural invasion — no. (%)	205/221 (92.8)	207/231 (89.6)
Surgery		
Venous resection — no./total no. (%)	53/245 (21.6)	69/245 (28.2)
Portal-vein resection — no. (%)	32 (13.0)	42 (17.1)
Superior-mesenteric-vein resection — no. (%)	19 (7.7)	25 (10.2)
Arterial resection — no./total no. (%)	8/247 (3.2)	7/245 (2.9)

Patients in the modified-FOLFIRINOX group received fluorouracil (without bolus), leucovorin, irinotecan, and oxaliplatin. There were no significant differences between the two treatment groups, except for lymphovascular invasion (P=0.02).
Scores for the World Health Organization (WHO) performance status are assessed on a 5-point scale, with higher numbers indicating greater disability; a score of 0 indicates that the patient is fully active and able to carry on activities without restriction, and a score of 1 that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out light work.
A surgical margin of R0 indicates that no cancer cells were present within 1 mm of all resection margins, and R1 the presence of cancer cells within 1 mm of one or more resection margins.
Tumor stage was assessed according to the 2009 tumor–node–metastasis (TNM) classification, 7th edition.[19]

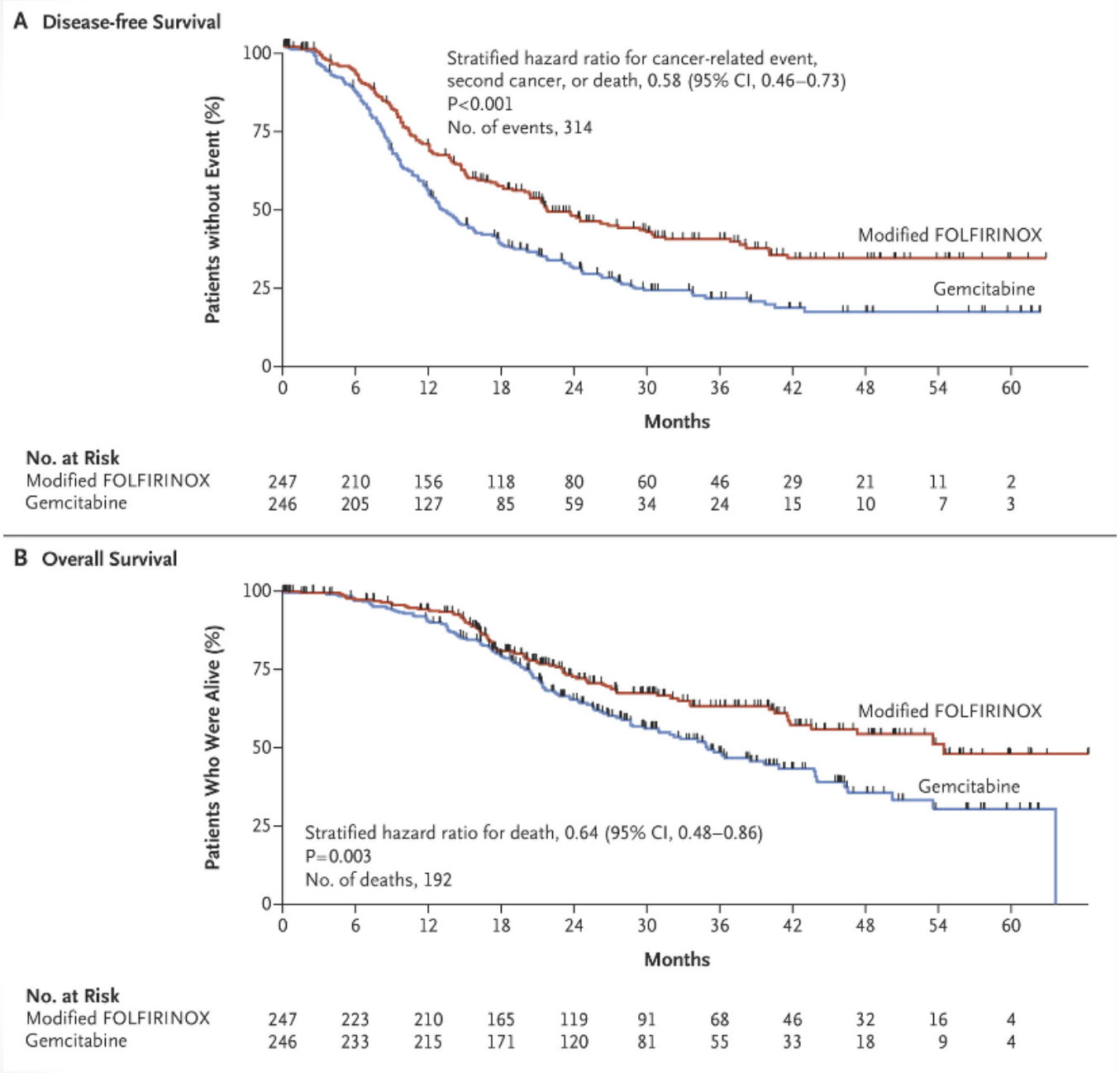

A Disease-free Survival
Patients without Event (%)
100
75
50
25
0
Stratified hazard ratio for cancer-related event, second cancer, or death, 0.58 (95% CI, 0.46–0.73)
P<0.001
No. of events, 314
Modified FOLFIRINOX
Gemcitabine
0 6 12 18 24 30 36 42 48 54 60
Months
No. at Risk
Modified FOLFIRINOX 247 210 156 118 80 60 46 29 21 11 2
Gemcitabine 246 205 127 85 59 34 24 15 10 7 3
B Overall Survival
Patients Who Were Alive (%)
100
75
50
25
0
Modified FOLFIRINOX
Gemcitabine
Stratified hazard ratio for death, 0.64 (95% CI, 0.48–0.86)
P=0.003
No. of deaths, 192
0 6 12 18 24 30 36 42 48 54 60
Months
No. at Risk
Modified FOLFIRINOX 247 223 210 165 119 91 68 46 32 16 4
Gemcitabine 246 233 215 171 120 81 55 33 18 9 4

Table 2. Adverse Events during Treatment (Safety Population).*

Event	Modified FOLFIRINOX (N=238)			Gemcitabine (N=243)			P Value
	Any Grade	Grade 3 or 4	Grade 4	Any Grade	Grade 3 or 4	Grade 4	
	number of patients with event (percent)						
Hematologic event†							
Low hemoglobin level	200 (84.7)	8 (3.4)	0	216 (89.3)	6 (2.5)	0	0.56
Neutropenia	157 (66.5)	67 (28.4)	14 (5.9)	154 (63.6)	63 (26.0)	14 (5.8)	0.56
Febrile neutropenia	7 (3.0)	7 (3.0)	2 (0.8)	10 (4.1)	9 (3.7)	1 (0.4)	0.64
Hyperleukocytosis	110 (46.6)	11 (4.7)	2 (0.8)	134 (55.4)	17 (7.0)	1 (0.4)	0.27
Thrombocytopenia	111 (47.0)	3 (1.3)	0	122 (50.4)	11 (4.5)	3 (1.2)	0.03
Lymphopenia	87 (36.9)	3 (1.3)	0	117 (48.3)	7 (2.9)	1 (0.4)	0.34
Nonhematologic event‡							
Fatigue	199 (84.0)	26 (11.0)	0	187 (77.6)	11 (4.6)	0	0.009
Diarrhea	200 (84.4)	44 (18.6)	3 (1.3)	118 (49.0)	9 (3.7)	0	<0.001
Nausea	187 (78.9)	13 (5.5)	0	133 (55.2)	2 (0.8)	0	0.004
Abdominal pain	111 (46.8)	8 (3.4)	0	114 (47.3)	1 (0.4)	0	0.02
Vomiting	108 (45.6)	12 (5.1)	0	70 (29.0)	3 (1.2)	0	0.02
Anorexia	106 (44.7)	6 (2.5)	0	60 (24.9)	3 (1.2)	0	0.34
Sensory peripheral neuropathy	145 (61.2)	22 (9.3)	2 (0.8)	21 (8.7)	0	0	<0.001
Paresthesia	136 (57.4)	30 (12.7)	0	13 (5.4)	0	0	<0.001
Weight loss	90 (38.0)	3 (1.3)	0	49 (20.3)	1 (0.4)	0	0.37
Fever	39 (16.5)	1 (0.4)	0	78 (32.4)	1 (0.4)	0	1.00
Mucositis	80 (33.8)	6 (2.5)	0	36 (14.9)	0	0	0.01
Alopecia§	64 (27.0)	0	—	47 (19.5)	0	—	—
Hand–foot syndrome	12 (5.1)	1 (0.4)	0	2 (0.8)	0	0	0.50
Thrombosis or embolism	14 (5.9)	6 (2.5)	0	19 (7.9)	1 (0.4)	0	0.07
Constipation	49 (20.7)	0	0	52 (21.6)	0	0	—
Biochemical event¶							
Increased alanine aminotransferase level	151 (64.0)	10 (4.2)	0	178 (73.6)	12 (5.0)	0	0.71
Increased aspartate aminotransferase level	158 (66.9)	9 (3.8)	1 (0.4)	167 (69.0)	8 (3.3)	0	0.76
Increased alkaline phosphatase level	173 (73.6)	5 (2.1)	0	111 (45.9)	5 (2.1)	0	1.00
Increased γ-glutamyltransferase level	150 (65.2)	42 (18.3)	6 (2.6)	110 (46.0)	20 (8.4)	3 (1.3)	0.002
Hyperglycemia	59 (24.9)	7 (3.0)	0	59 (24.4)	5 (2.1)	0	0.53

Radiotherapy

- Ionising radiation usually delivered using a linear accelerator
- Cause ionisation of atoms leading to DNA damage within cell nuclei
  - Some damage is repairable and other cells die
- Aim: to kill the cancer cells but cause only repairable damage to normal tissue (or no damage at all)

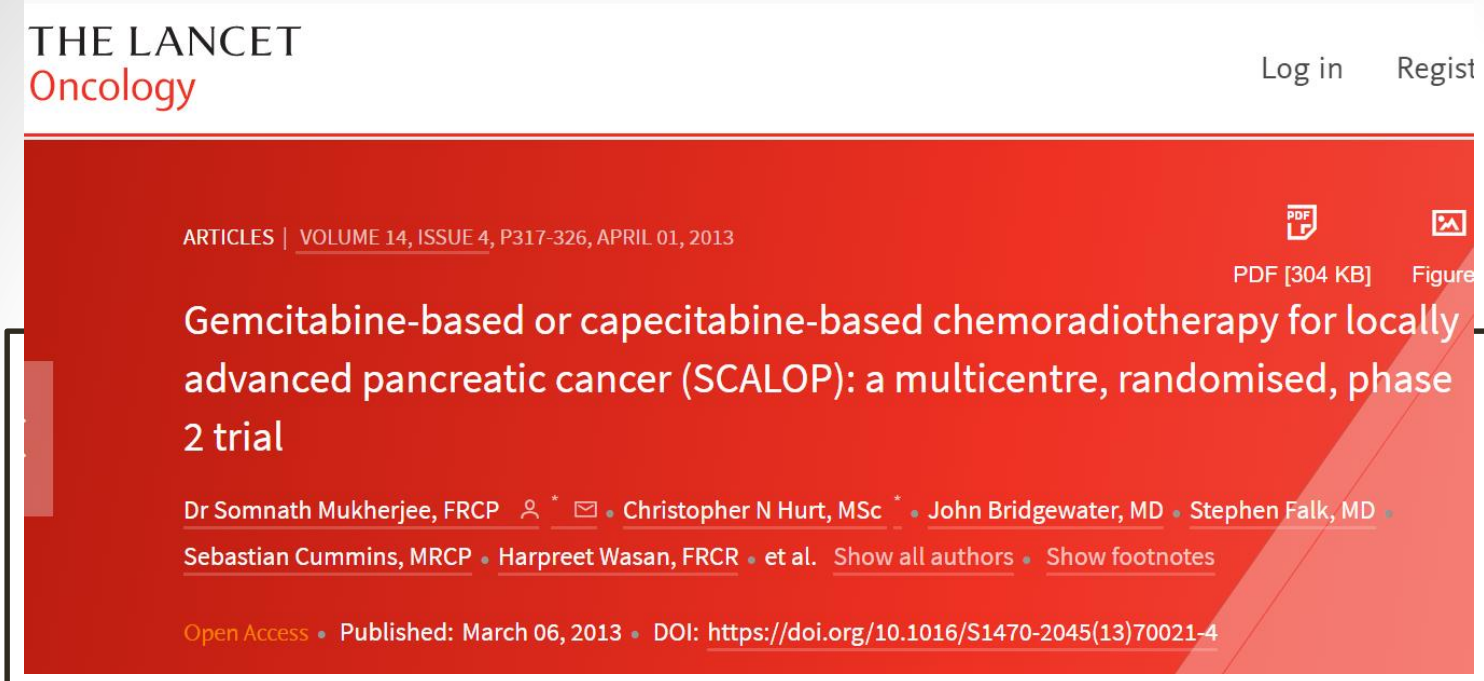
Radiotherapy for pancreatic cancer

- Conventionally fractionated radiotherapy
- Significant OARs: duodenum, kidneys (functioning renogram), spinal cord, small bowel, liver

Chemoradiotherapy

- Chemotherapy and radiotherapy used together to increase radiation sensitivity and improve cancer cell death
- Also increases side effects

Locally advanced (unresectable) pancreatic cancer (30-40%)



- Locally advanced unresectable pancreatic cancer: Primary < 7cm, PS0-1, eGFR >50 (need EDTA or functioning renogram)

- **Induction chemo Gem/Cap x 3** -> Restage with 4th cycle gem/cap while planning -> Randomised 1:1 between concurrent CRT 50.4Gy/28# + capecitabine 830mg/m2 versus CRT with gemcitabine

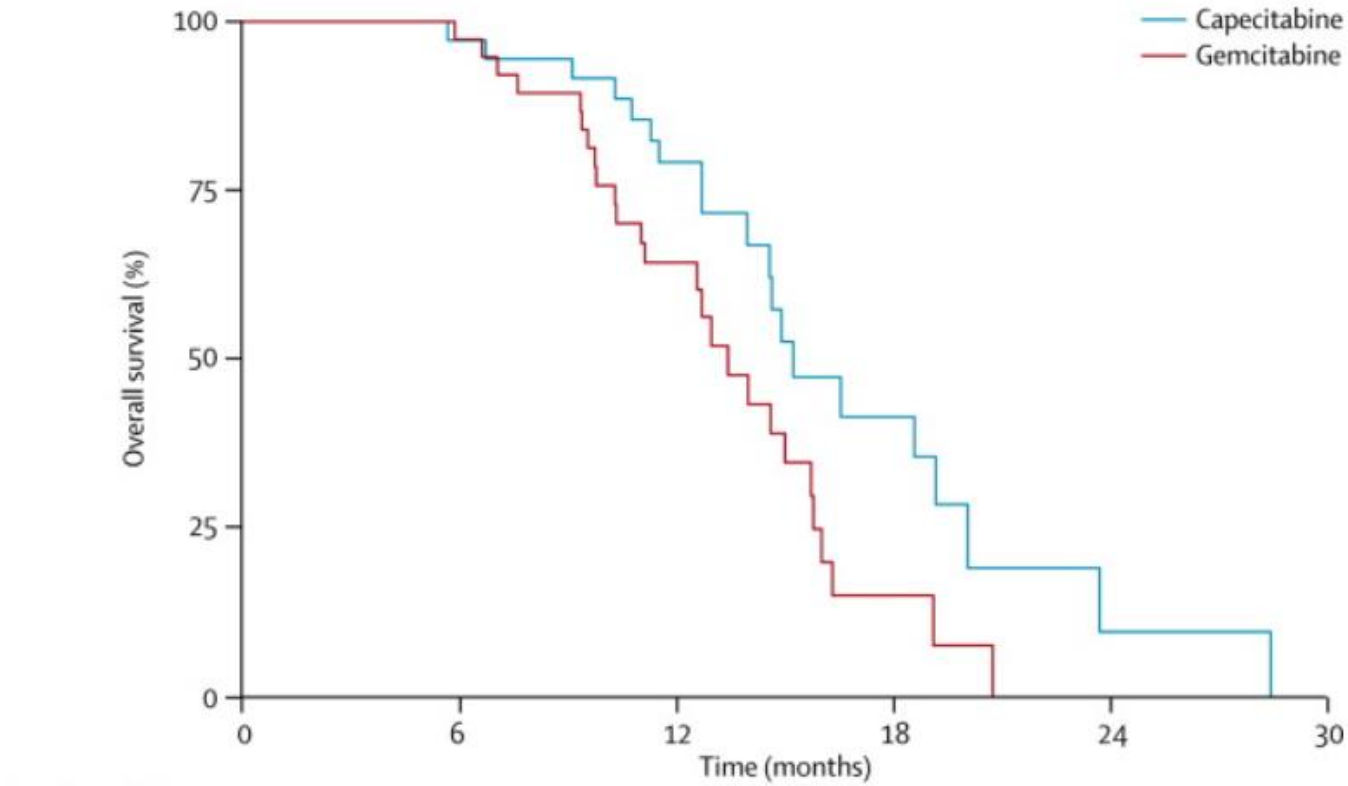


Figure 3 Kaplan–Meier estimates of overall survival, by treatment group

Neoadjuvant FOLFIRINOX in Patients With Borderline Resectable Pancreatic Cancer: A Systematic Review and Patient-Level Meta-Analysis

Quisette P Janssen, Stefan Buettner, Mustafa Suker, Berend R Beumer, Pietro Addeo, Philippe Bachellier, Nathan Bahary, Tanios Bekaii-Saab, Maria A Bali, Marc G Besselink ... Show more

JNCI: Journal of the National Cancer Institute, Volume 111, Issue 8, August 2019, Pages 782–794, https://doi.org/10.1093/jnci/djz073

Published: 14 May 2019 **Article history** ▾

- Big meta-analysis of neoadjuvant mFolfirinox in BRPC: showed favourable median OS 22.2 months
- Resection rate = 67.8%

Neoadjuvant mFolfirinox: RCT

Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial

Q. P. Janssen, J. L. van Dam, B. A. Bonsing, H. Bos, K. P. Bosscha, P. P. L. O. Coene, C. H. J. van Eijck, I. H. J. T. de Hingh, T. M. Karsten, M. B. van der Kolk, G. A. Patijn, M. S. L. Liem, H. C. van Santvoort, O. J. L. Loosveld, J. de Vos-Geelen, B. M. Zonderhuis, M. Y. V. Homs, G. van Tienhoven, M. G. Besselink, J. W. Wilmink & B. Groot Koerkamp ✉ for the Dutch Pancreatic Cancer Group

BMC Cancer **21**, Article number: 300 (2021) | Cite this article

Do these patients need adjuvant chemo after?

- Only if Node positive (median OS 26/12 with adjuvant chemo versus 13/12 without adjuvant chemo)
- If node negative adjuvant chemotherapy offers no survival benefit in those who have received neoadjuvant chemotherapy

September 10, 2020

Evaluation of Adjuvant Chemotherapy in Patients With Resected Pancreatic Cancer After Neoadjuvant FOLFIRINOX Treatment

Stijn van Roessel, MD, MSc[1]; Eran van Veldhuisen, BSc[1]; Sjors Klompmaker, MD, MSc, PhD[1,2]; et al

SABR

- Highly precise form of hypofractionated radiotherapy (high dose delivered in a single fraction), initially developed to treat small brain tumours and functional abnormalities of the brain.

- SABR = stereotactic ablative body radiotherapy: ablative radiation doses delivered in a single or few (up to 5 fractions)

SABR for pancreatic cancer

- Can be used as alternative to conventionally fractionated radiotherapy for consolidation or retreatment (alternative to surgery)
- 18-36Gy/3#
- Rapid dose fall off outside of target volume, meaning radiation doses to organs at risk can be optimised

Stereotactic ablative radiotherapy (SABR) as primary, adjuvant, consolidation and re-treatment option in pancreatic cancer: scope for dose escalation and lessons for toxicity

Christy Goldsmith ✉, P. Nicholas Plowman, Melanie M. Green, Roger G. Dale & Patricia M. Price

Radiation Oncology **13**, Article number: 204 (2018) | Cite this article

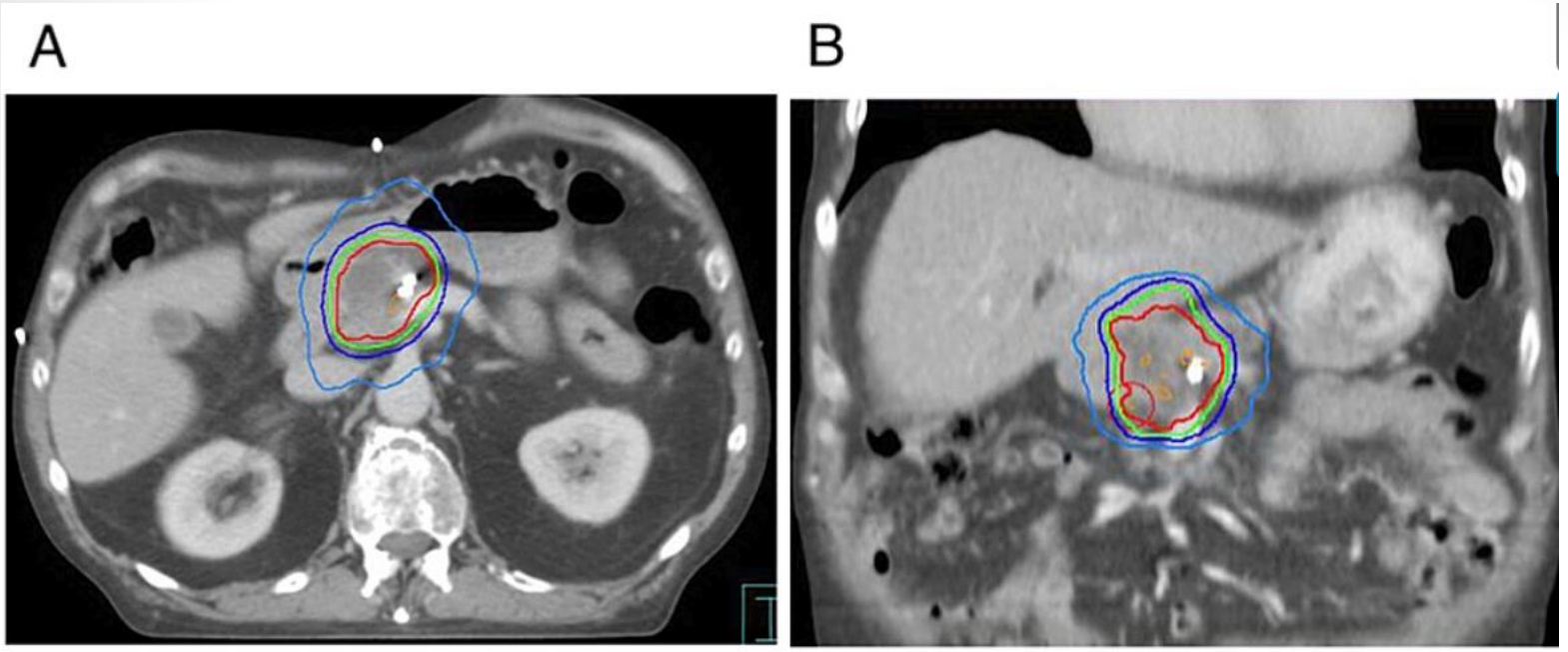


Figure 2: Dose distribution of pancreas stereotactic body radiotherapy plan on axial (A) and coronal (B) computed tomography simulation scan (prescription: 27 Gy in three fractions)

Isodose lines: Orange: 27.81 Gy (103% of prescription); red: 27.0 Gy (100% of prescription); green: 25.65 Gy (95% of prescription); dark blue: 21.6 Gy (80% of prescription); light blue: 13.5 Gy (50% of prescription)

Cite this article as: Glicksman R M, Chung H, Myrehaug S, et al. (September 23, 2020) Stereotactic Radiotherapy for Pancreatic Cancer: A Single-Institution Experience. Cureus 12(9): e10618. doi:10.7759/cureus.10618

Metastatic pancreatic cancer: 3 x chemo choices

- **Folfirinox:** PS0/1: fortnightly IV chemo; ORR 30%,
- median OS = 11/12

- **Gemcitabine + Abraxane:** (PS0/1): ORR 20%, median OS = 8/12

- **Weekly Gemcitabine**: Ps2+: ORR 10%,
- median OS 6/12 (NB max bili = 1.5x above ULN)

- 2nd line = something on list above haven't already used, or single agent cape (NB can only use gem/abraxane 1st line)

For chemotherapy

- Need to have good performance status
- Need to have good renal and liver function
- Regular visits to hospital, blood tests etc
- Chemotherapy side effects

- Supportive measures: analgesia, Creon

New directions for systemic treatment

- Investigating PARP inhibitors for BRCA patients with metastatic pancreatic cancer
- Nimotuzumab + gem versus placebo + gem for KRAS mutated pancreatic cancer
- Stroma targeting agents in addition to chemotherapy
- Immunotherapy for pancreatic cancer

Questions?