

#PCUKStudyDay

## **ESPAC-5F and Neoadjuvant Chemotherapy**

Thursday 8<sup>th</sup> October 2020, 09.00 – 10.00

**ESPAC-5F: Four arm, prospective, multicentre, international randomised phase II trial of immediate surgery compared with neoadjuvant gemcitabine plus capecitabine (GEMCAP) or FOLFIRINOX or chemoradiotherapy (CRT) in patients with borderline resectable pancreatic cancer.**

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European Study Group for Pancreatic Cancer (ESPAC)**



**ISRCTN: 89500674**

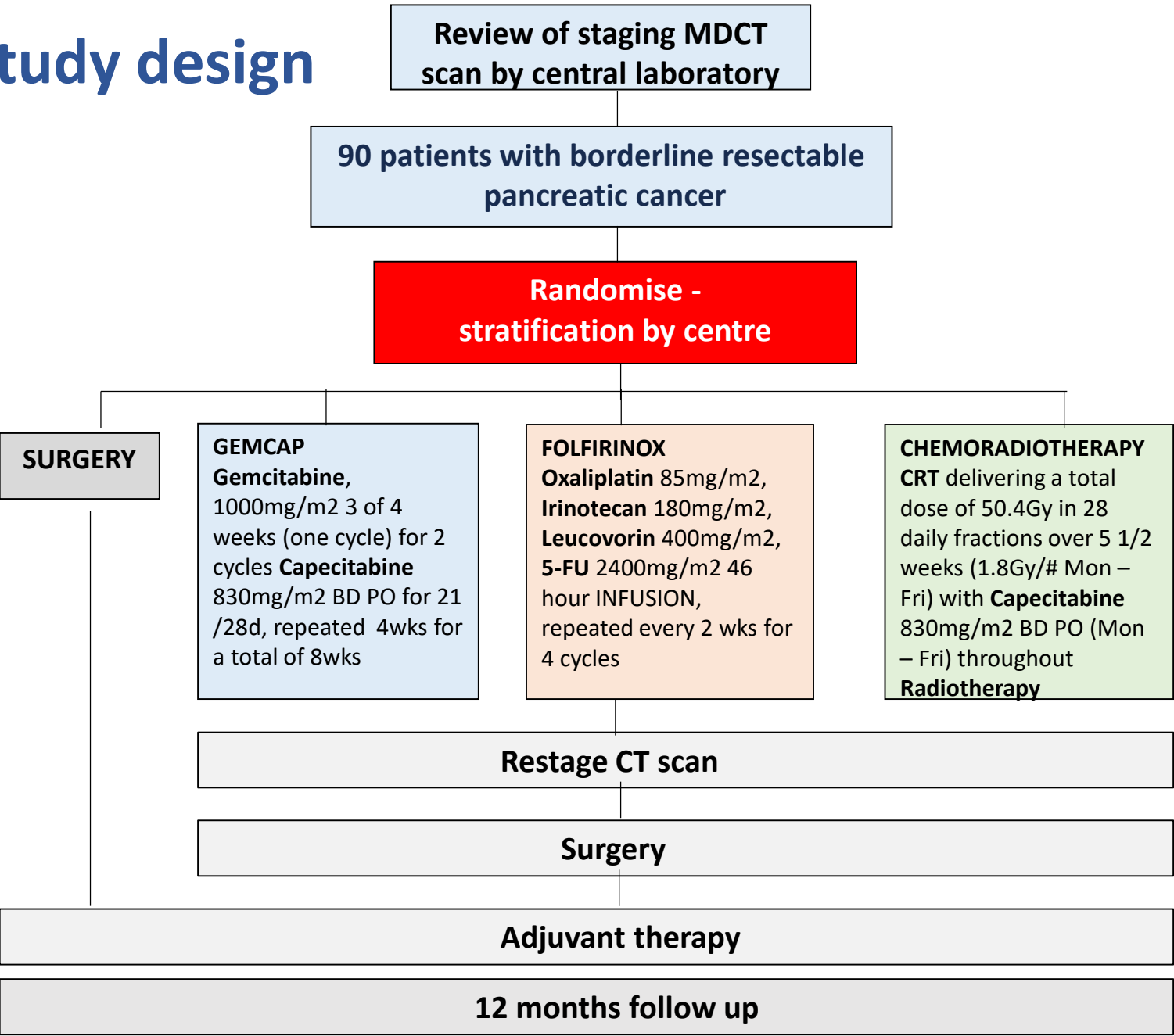
**EudraCT: 2013-003932-56**

**CRUK: C20203/A16186**

# Background

- Patients with borderline resectable pancreatic cancer have poor survival and low resection rates
- Neoadjuvant therapy may improve the outcome for these patients
- The aim of this trial was to determine the feasibility and efficacy of a comparison of immediate surgery versus neoadjuvant GEMCAP or FOLFIRINOX or CRT

# Study design



## Primary

1. Recruitment rate
2. Resection rate (R1 + R0)

## Secondary

1. R0 resection margin rate
2. Toxicity
3. Overall survival
4. Post operative complication rate
5. Post operative mortality rate
6. Response rate
7. Disease free survival rate
8. Local disease free survival rate
9. Quality of life

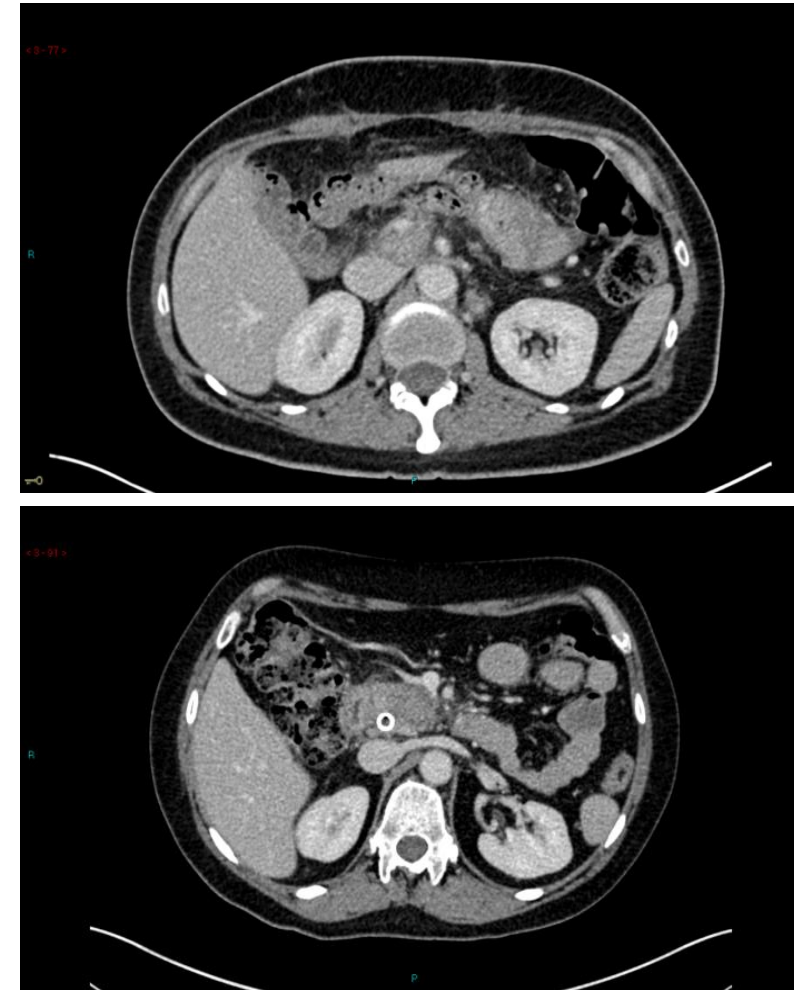
- Two patients excluded from the Full Analysis Set (one Immediate surgery, one CRT)
- Some data cleaning ongoing

# Eligibility criteria

1. Borderline resectable mass in the pancreatic head as defined by CT criteria.
2. Histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants).
3. Able to undergo biliary drainage using a covered, partially covered self-expanding metal or uncovered metal stent.
4. Age  $\geq 18$  years.
5. WHO performance status 0, 1.
6. Platelets  $>100 \times 10^9/l$ ; WBC  $> 3 \times 10^9/l$ ; neutrophils  $> 1.5 \times 10^9/l$ .
7. Serum bilirubin  $<1.5$  ULN.
8. Glomerular filtration rate estimated  $>50\text{ml/min}$  according to Cockcroft & Gault (or equivalent value following local scale/formula).
9. Able to comply with protocol requirements and deemed fit for surgical resection, chemotherapy and radiotherapy.
10. Written informed consent.

# Borderline resectable criteria

	Features	Requirements
<b>Resectable (RS)</b>	<ul style="list-style-type: none"> <li>a. Normal tissue plane between tumour and vessels.</li> <li>b. No evidence of metastatic disease.</li> </ul>	a and b
<b>Borderline resectable (BR)</b>	<ul style="list-style-type: none"> <li>a. Loss of normal tissue plane between tumour and vessels.</li> <li>b. Venous involvement (contact and or distortion) of the SMV, PV or SMV-PV confluence – allowing surgical reconstruction.</li> <li>c. Tumour abutment <math>&lt;180^\circ</math> of the SMA or coeliac axis.</li> <li>d. No evidence of metastatic disease.</li> </ul>	a and or b or c and d
<b>Unresectable</b>	<ul style="list-style-type: none"> <li>a. Encasement/contact of SMA or coeliac axis of <math>&gt;180^\circ</math>.</li> <li>b. Long segment involvement/occlusion of the SMV, PV or SMV-PV confluence with no reconstruction possible.</li> <li>c. Encasement of the hepatic artery.</li> <li>d. Confirmed metastatic disease.</li> </ul>	one or more of a, b, c,d.



# Baseline patient characteristics

		Immediate Surgery n=32	GEMCAP n=20	FOLFIRINOX n=20	CRT n=16
Age (yrs), median (IQR)		61 ( 54 , 66 )	64 ( 59 , 70 )	64 ( 63 , 70 )	66 ( 59 , 69 )
Sex, n (%)	Female	19 ( 59 % )	11 ( 55 % )	10 ( 50 % )	9 ( 56 % )
	Male	13 ( 41 % )	9 ( 45 % )	10 ( 50 % )	7 ( 44 % )
Smoking Status, n (%)	Current	7 ( 22 % )	4 ( 20 % )	2 ( 10 % )	3 ( 19 % )
	Past	11 ( 34 % )	8 ( 40 % )	3 ( 15 % )	8 ( 50 % )
	Never	14 ( 44 % )	8 ( 40 % )	15 ( 75 % )	5 ( 31 % )
Diabetic Status, n (%)	No	23 ( 72 % )	14 ( 70 % )	7 ( 35 % )	12 ( 75 % )
	Type II	5 ( 16 % )	4 ( 20 % )	8 ( 40 % )	3 ( 19 % )
	Type II (on insulin)	4 ( 12 % )	2 ( 10 % )	5 ( 25 % )	1 ( 6 % )
WHO PS, n (%)	0	16 ( 50 % )	7 ( 35 % )	8 ( 40 % )	9 ( 56 % )
	1	16 ( 50 % )	13 ( 65 % )	12 ( 60 % )	7 ( 44 % )
CA19-9 (kU/L), median (IQR)		859 ( 200 , 1847 )	493 ( 181 , 1298 )	659 ( 130 , 1366 )	322 ( 67 , 717 )
	No. Unknown	2	1	2	0

# Surgical characteristics

		Immediate Surgery n=32	GEMCAP n=20	FOLFIRINOX n=20	CRT n=16
Type of operation (n%)	Pylorus preserving whipples	15 ( 47 % )	6 ( 30 % )	11 ( 55 % )	6 ( 38 % )
	Standard Whipples	2 ( 6 % )	5 ( 25 % )	0 ( 0 % )	1 ( 6 % )
	Total pancreatectomy	4 ( 13 % )	1 ( 5 % )	0 ( 0 % )	1 ( 6 % )
	Bypass	6 ( 19 % )	0 ( 0 % )	5 ( 25 % )	2 ( 13 % )
	Open and close	1 ( 3 % )	2 ( 10 % )	1 ( 5 % )	0 ( 0 % )
Reason no surgery attempted (n%)	Progression	4 ( 12 % )	5 ( 25 % )	2 ( 10 % )	5 ( 31 % )
	Death	0 ( 0 % )	1 ( 5 % )	1 ( 5 % )	1 ( 6 % )



# Resection details: resected patients n=52

		Immediate Surgery n=21	GEMCAP n=12	FOLFIRINOX n=11	CRT n=8
Extent of resection, n(%)	Resection with extended lymphadenectomy	5 ( 24 % )	5 ( 42 % )	1 ( 9 % )	2 ( 25 % )
	Standard resection	16 ( 76 % )	7 ( 58 % )	10 ( 91 % )	6 ( 75 % )
Vein resection, n(%)	Yes	14 ( 67 % )	6 ( 50 % )	6 ( 55 % )	6 ( 75 % )
	No	7 ( 33 % )	6 ( 50 % )	5 ( 45 % )	2 ( 25 % )
R Status, n(%)	R0	3 ( 14 % )	2 ( 17 % )	2 ( 18 % )	3 ( 37 % )
	R1	17 ( 81 % )	10 ( 83 % )	9 ( 82 % )	5 ( 63 % )
	R2	1 ( 5 % )	0 ( 0 % )	0 ( 0 % )	0 ( 0 % )
Adjuvant therapy, n(%)	Yes	17 ( 81 % )	10 ( 83 % )	9 ( 82 % )	7 ( 87 % )
	No	4 ( 19 % )	2 ( 17 % )	2 ( 18 % )	1 ( 13 % )

# Tumour characteristics: resected patients n=52

		Immediate Surgery n=21	GEMCAP n=12	FOLFIRINOX n=11	CRT n=8
Tumour, n(%)	pT1	0 ( 0 % )	0 ( 0 % )	3 ( 27 % )	2 ( 25 % )
	pT2	4 ( 19 % )	4 ( 33 % )	0 ( 0 % )	2 ( 25 % )
	pT3	17 ( 81 % )	8 ( 67 % )	8 ( 73 % )	4 ( 50 % )
Nodes, n(%)	Negative	2 ( 10 % )	5 ( 42 % )	3 ( 27 % )	6 ( 75 % )
	Positive	19 ( 90 % )	7 ( 58 % )	8 ( 73 % )	2 ( 25 % )
Grade, n(%)	Undifferentiated	0 ( 0 % )	1 ( 8 % )	0 ( 0 % )	0 ( 0 % )
	Poor	5 ( 24 % )	1 ( 9 % )	4 ( 36 % )	2 ( 25 % )
	Moderate	15 ( 71 % )	4 ( 33 % )	6 ( 55 % )	2 ( 25 % )
	Well	0 ( 0 % )	2 ( 17 % )	1 ( 9 % )	1 ( 13 % )
	Not reported	0 ( 0 % )	4 ( 33 % )	0 ( 0 % )	3 ( 37 % )
	Unknown	1 ( 5 % )	0 ( 0 % )	0 ( 0 % )	0 ( 0 % )
Maximum Tumour Dimension (mm), median (IQR)		36 ( 32 , 45 )	30 ( 30 , 42 )	30 ( 22 , 35 )	32 ( 22 , 43 )

# Neo-adjuvant treatment received

## GEMCAP

- 18 (90%) of 20 patients received 2 cycles of treatment; 2 (10%) did not receive any treatment
- % protocol GEM dose: Median = 94 [ IQR: 70 - 99 ]
- % protocol Capecitabine dose: Median = 90 [ IQR: 80 - 99 ]

## FOLFIRINOX

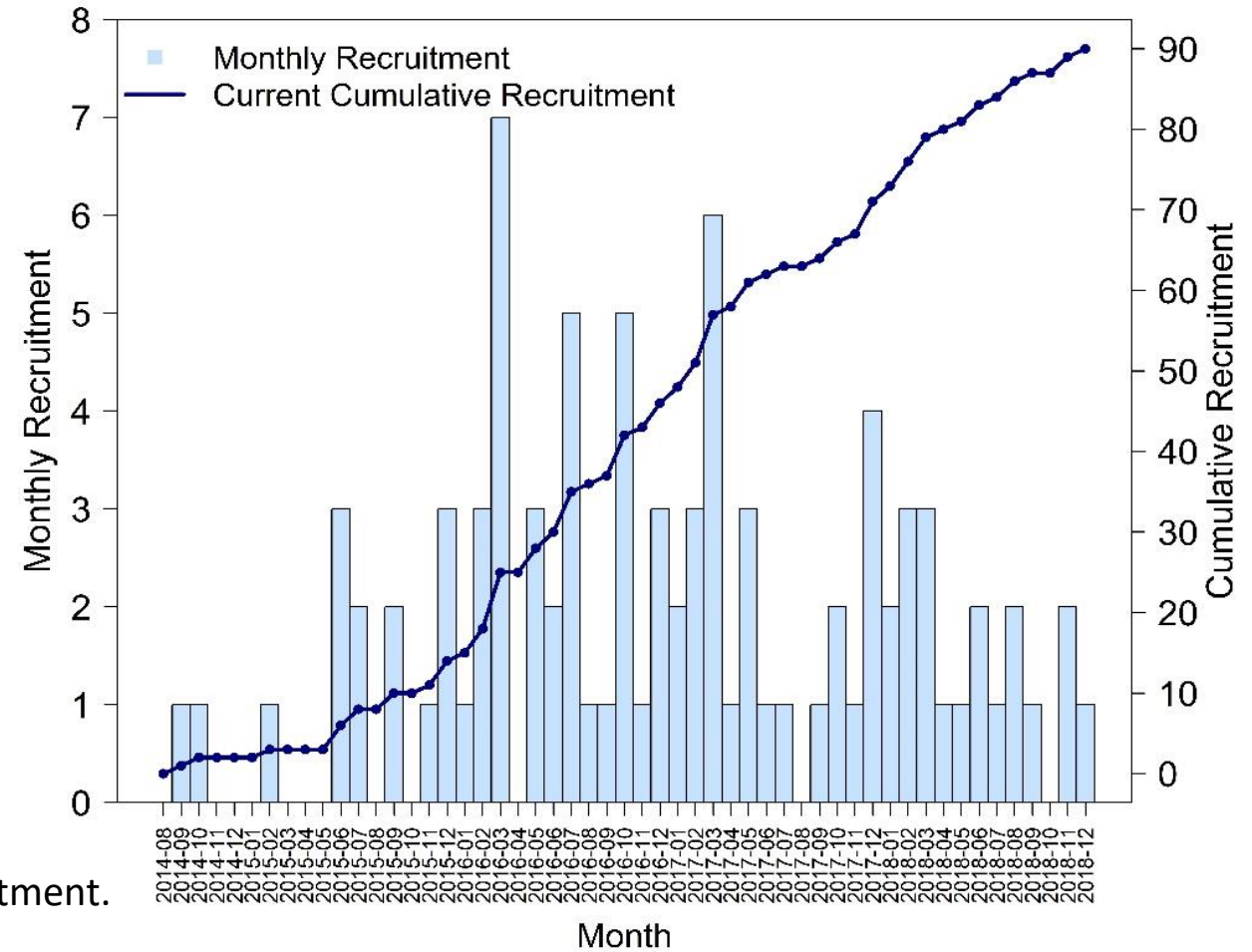
- 15 (75%) of 20 patients received 4 cycles of treatment; 1 (5%) did not receive any treatment
- % protocol Oxaliplatin dose: Median = 96 [ IQR: 75 - 99 ]
- % protocol Irinotecan dose: Median = 96 [ IQR: 77 - 100 ]
- % protocol 5-FU dose: Median = 98 [ IQR: 82 - 100 ]

## CRT

- 12 (75%) of 16 patients received 5<sup>1</sup>/<sub>2</sub> weeks of treatment; 2 (12%) did not receive any treatment
- % protocol Radiotherapy dose: Median = 100 [ IQR: 100 - 100 ]
- % protocol Capecitabine dose: Median = 84 [ IQR: 53 - 93 ]

# Primary outcome – recruitment rate

Date of study greenlight	29/08/2014
Date of first randomisation	03/09/2014
Date of last randomisation	20/12/2018
Number of pts recruited	90
<b>Recruitment rate (95% CI)*</b>	<b>20.74 ( 16.68 , 25.49 )</b>



\*Defined as patients recruited divided by time (years) open to recruitment.

# Primary outcome - resection rate (R0 + R1)

	No of resections	No of patients	Rate* (95% CI)	P-value
Immediate Surgery	20	32	62% ( 44% , 79 %)	0.668
Neoadjuvant treatment	31	56	55% ( 41% , 69% )	
Overall	51	88	58% ( 47% , 68% )	

\*Defined as R0 + R1 resections in patients included in the Full Analysis Set

## Secondary outcomes - resection rate (R0)

	No of R0 resections	No of resected patients	Rate** (95% CI)	P-value
Immediate Surgery	3	20	15% ( 3% , 38% )	0.721
Neoadjuvant treatment	7	31	23% ( 10% , 41% )	
Overall	10	51	20% ( 10% , 33% )	

\*\*Defined as R0 resections in (R0 + R1) resected patients

# Secondary outcomes - toxicity

9 (18%) neoadjuvant patients in the safety set reported 12 SAEs of Grade 3 or above

1 (6%) GEMCAP patients  
reported 1 SAE

5 (26%) FOLFIRINOX patients  
reported 6 SAEs

3 (21%) CRT patients  
reported 5 SAEs

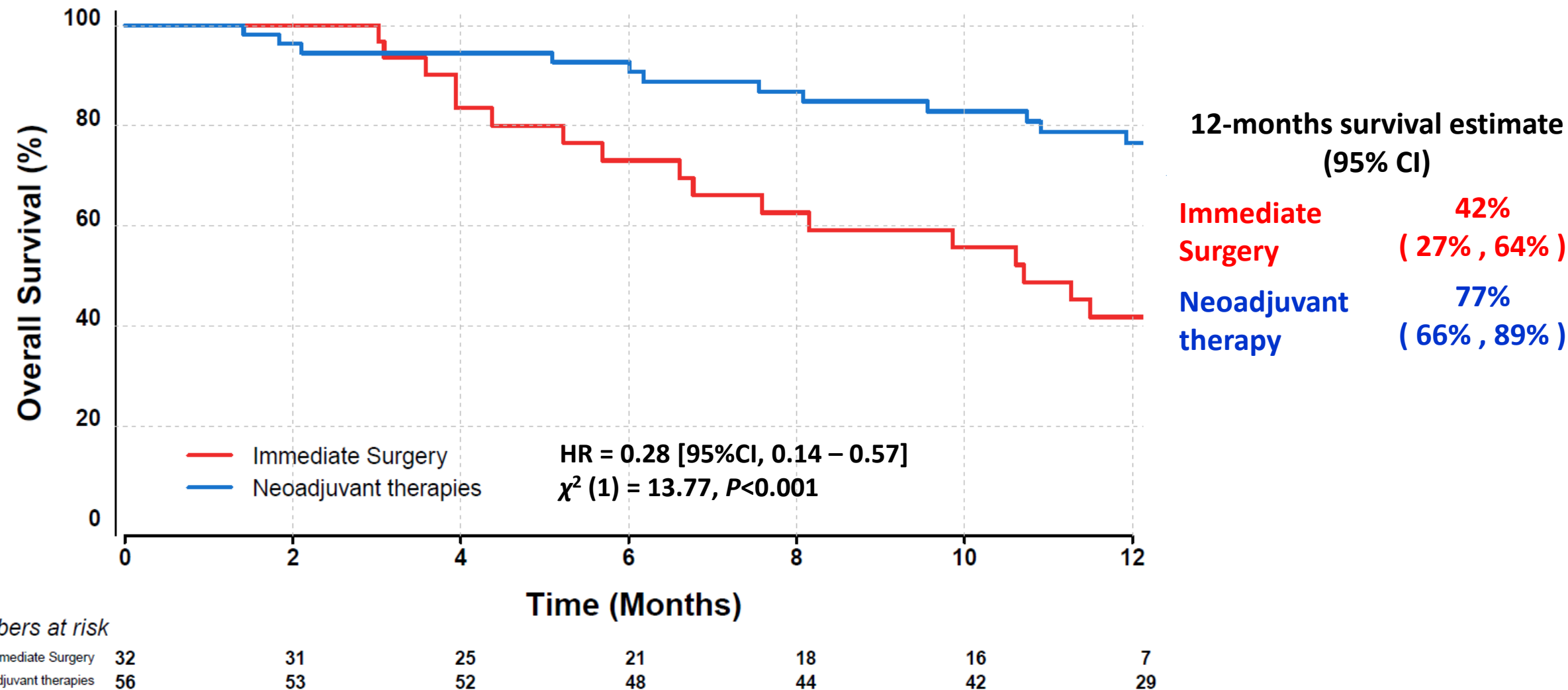
CTCAE Event Name	GEMCAP	FOLFIRINOX	CRT
Grade 3-4			
Febrile neutropenia	0	1	0
Diarrhea	0	1	0
Gastritis	0	1	0
Nausea	0	1	1
Hepatic infection	1	0	0
Infections and infestations – Other <sup>1</sup>	0	0	1
Sepsis	0	1	0
Wound dehiscence	0	0	1
Metabolism and nutrition disorders – Other <sup>2</sup>	0	0	1
Grade 5			
Sepsis	0	1 <sup>3</sup>	1

<sup>1</sup>Neutropenic sepsis

<sup>2</sup>Diabetic ketoacidosis

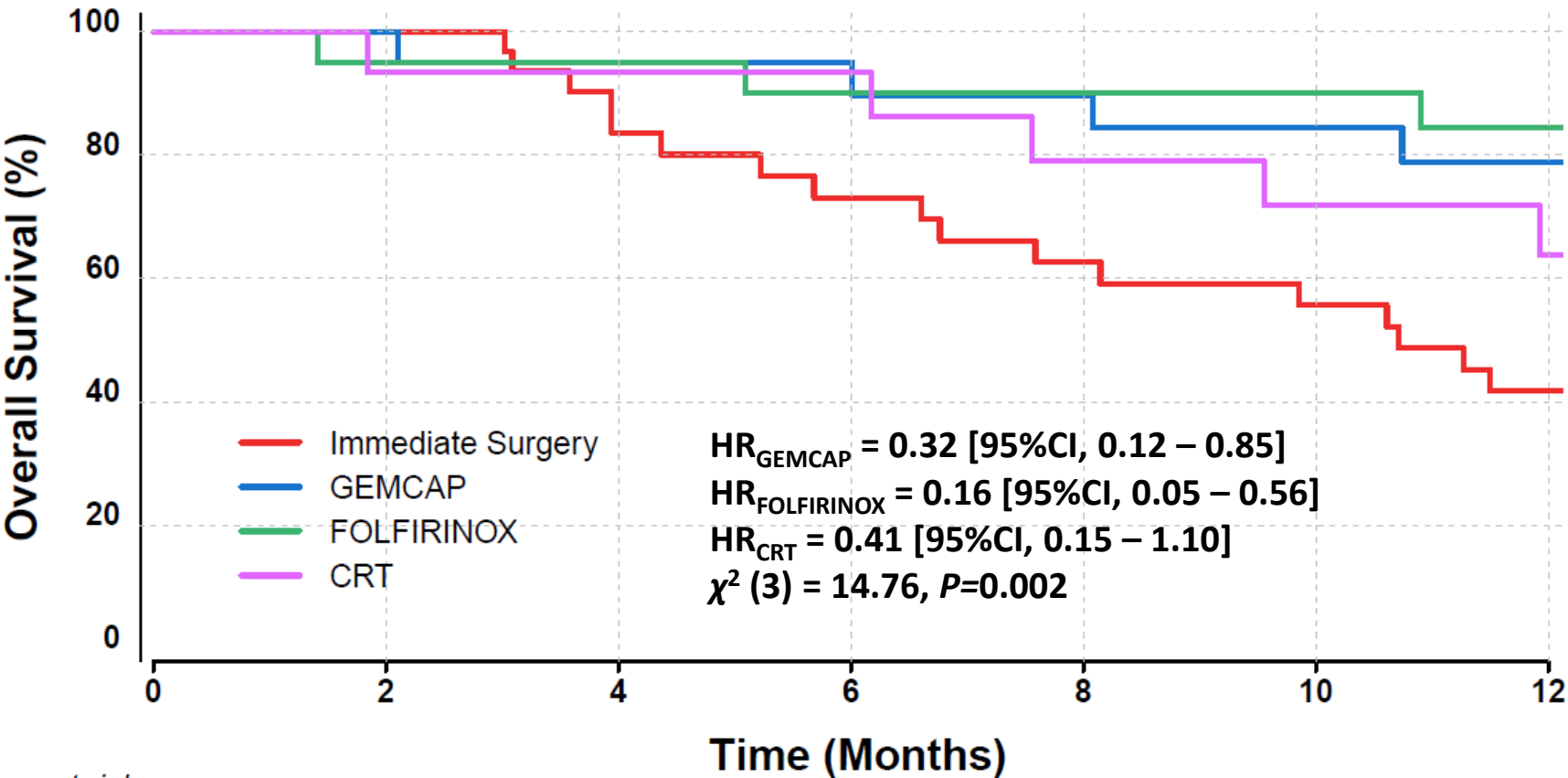
<sup>3</sup>SUSAR

# Secondary outcomes - overall survival (I)





# Secondary outcomes - overall survival (II)



12-months survival estimate  
(95% CI)

Immediate Surgery	42% ( 27% , 64% )
GEMCAP	79% ( 62% , 100% )
FOLFIRINOX	84% ( 70% , 100% )
CRT	64% ( 43% , 95% )

Numbers at risk

Immediate Surgery	32	31	25	21	18	16	7
GEMCAP	20	20	19	18	17	16	7
FOLFIRINOX	20	19	19	17	16	16	14
CRT	16	14	14	13	11	10	8

# Conclusions

- There was no statistical significant difference (p-value=0.668) in resection rate for immediate surgery (62%, [95% CI 44-79%]) versus neoadjuvant therapy (55%, [95% CI 41-69%])
- There was a significant survival advantage at one year for neoadjuvant therapy (77%, [95% CI 69-89%]) compared with immediate surgery (42%, [95% CI 22-64%])
- Among the neoadjuvant treatments, FOLFIRINOX demonstrated the best survival at one year versus immediate surgery (84%, [95% CI 70-100%]) compared with GEMCAP (79%, [95% CI 63-100%]) and CRT (64%, [95% CI 43-95%])
- Toxicity was higher in the FOLFIRINOX arm but overall was manageable.
- Neoadjuvant therapy should be considered for patients with borderline resectable pancreatic cancer

# Acknowledgements



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# Acknowledgements

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## Investigators:

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