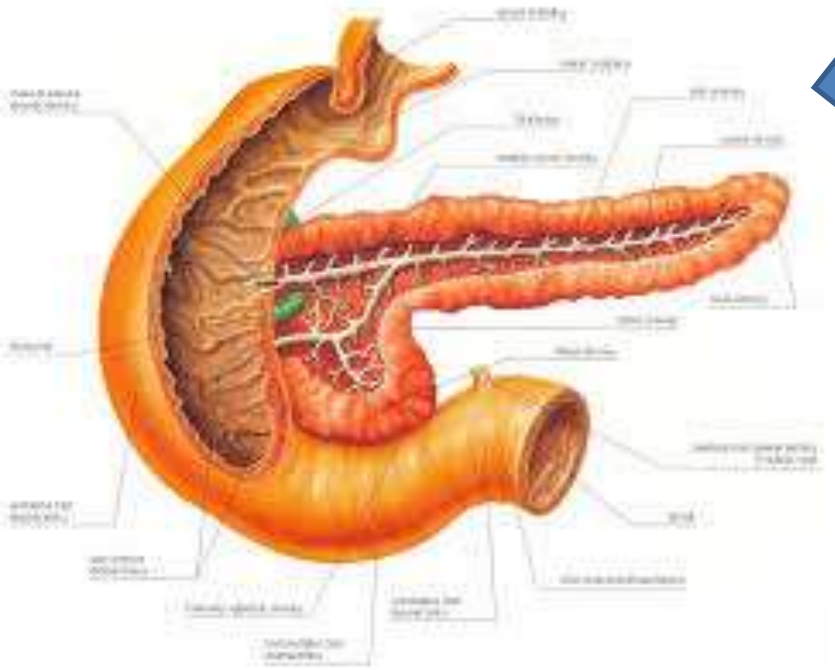
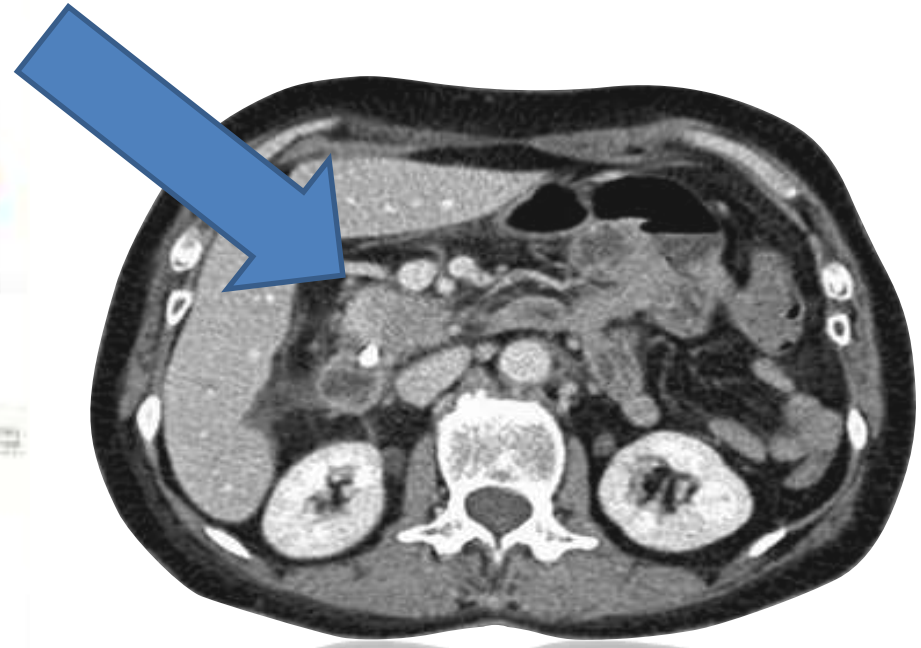
Systémová léčba lokalizovaného a lokálně pokročilého karcinomu pankreatu

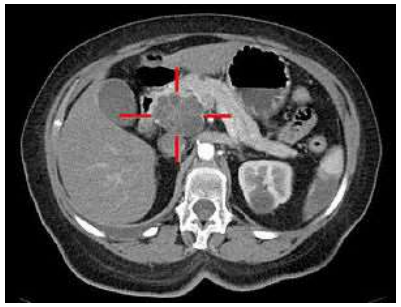
Radim Němeček

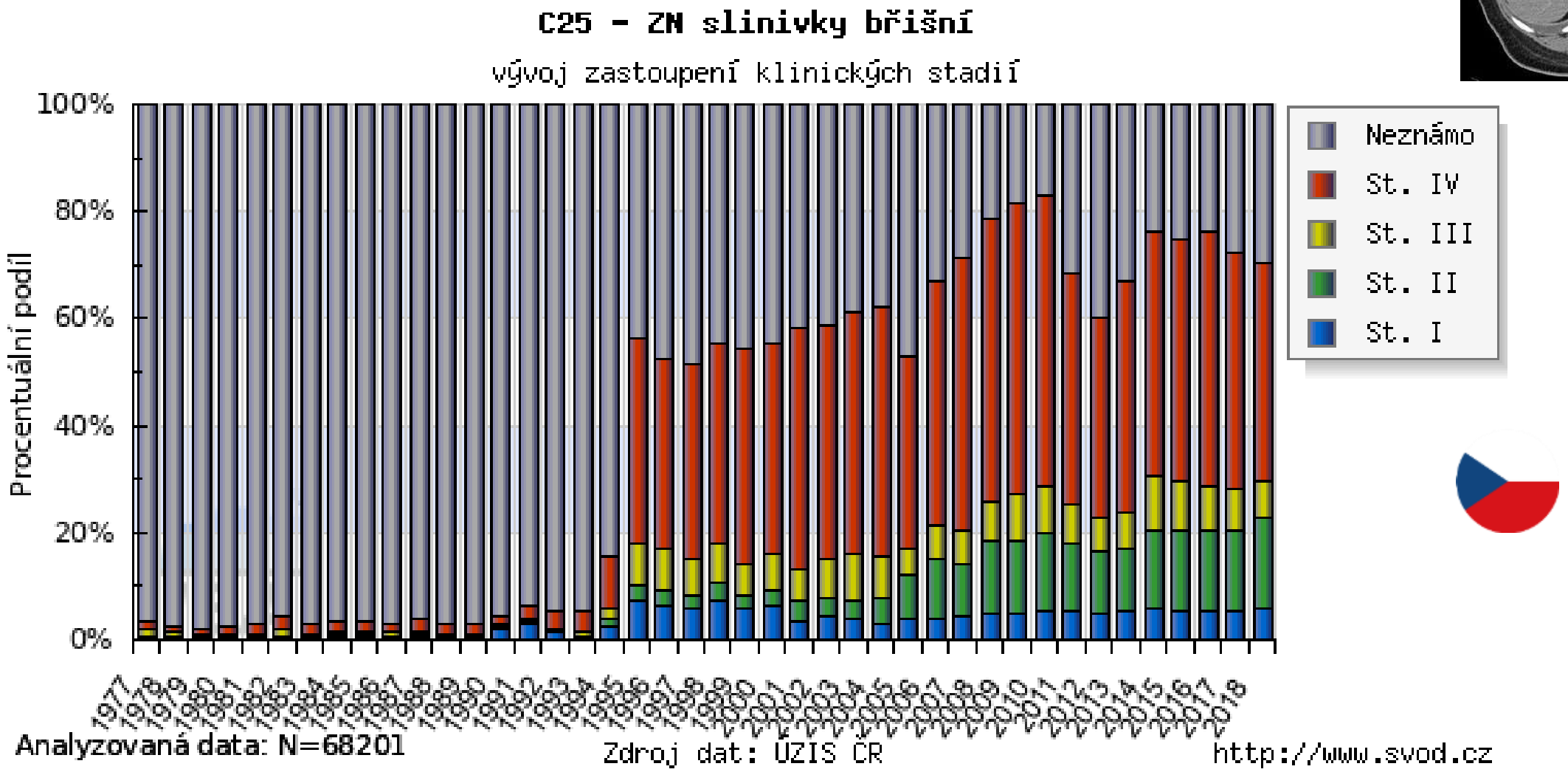
XXIV. setkání KMO - Medlov 24.-26.6.2022





C25 – zastoupení klinických stádií



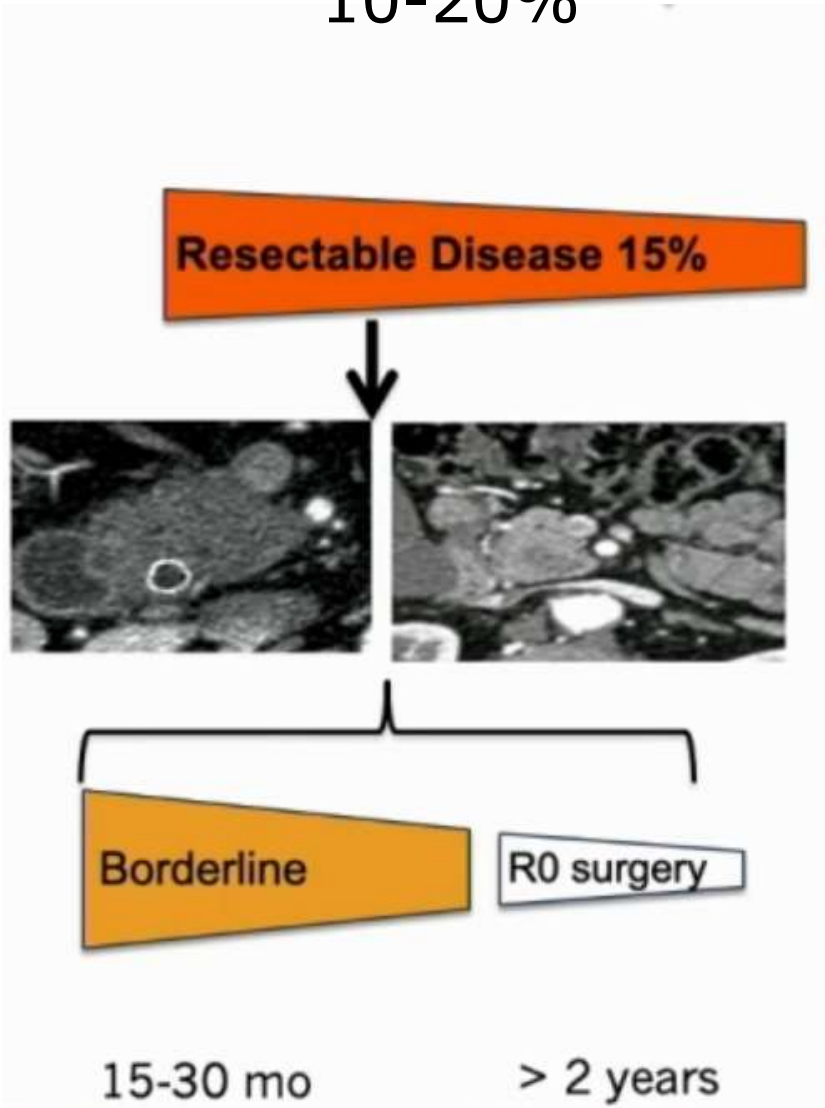


MUNI MED

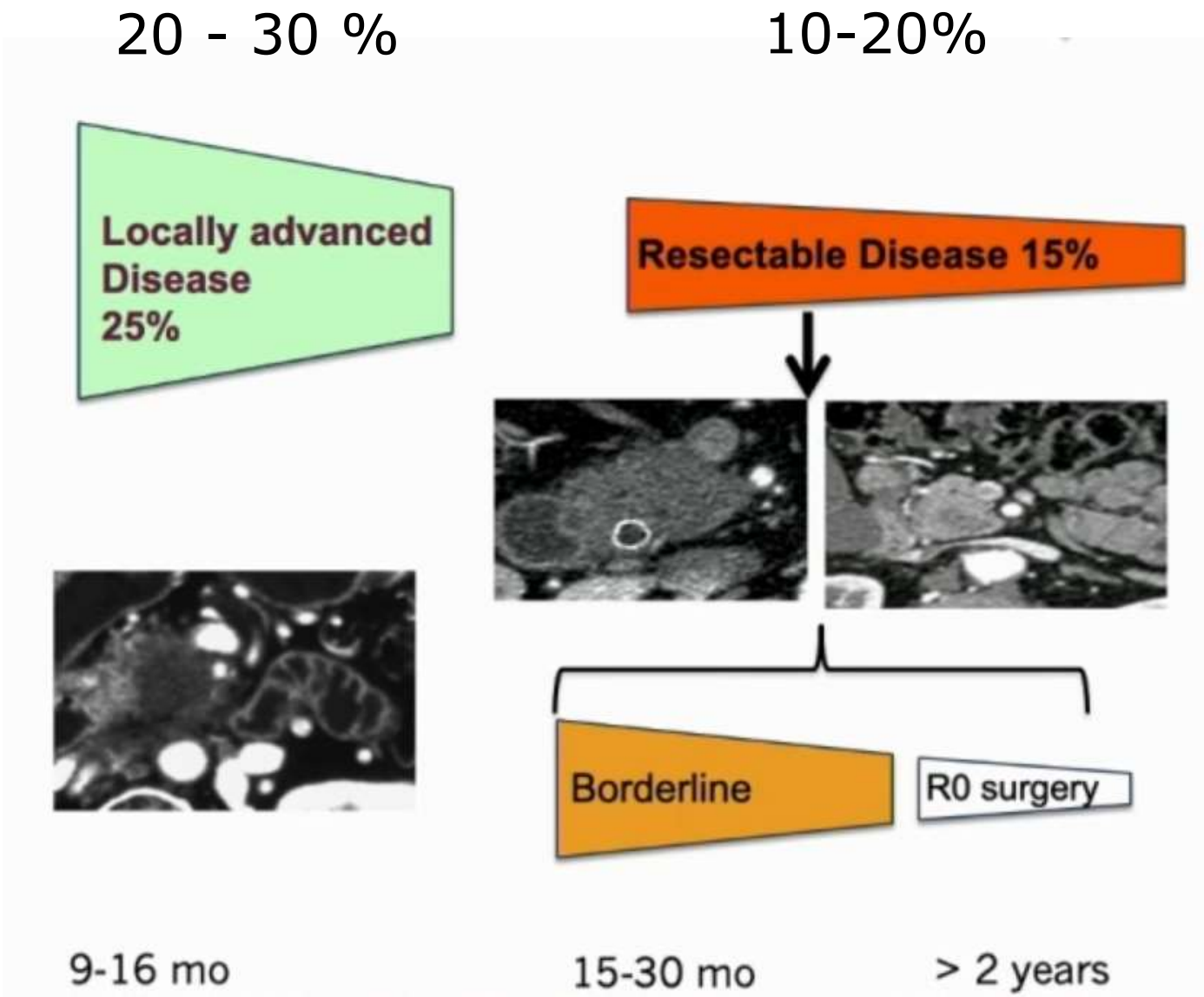
Masarykův onkologický ústav

Karcinom pankreatu v době dg:

10-20%



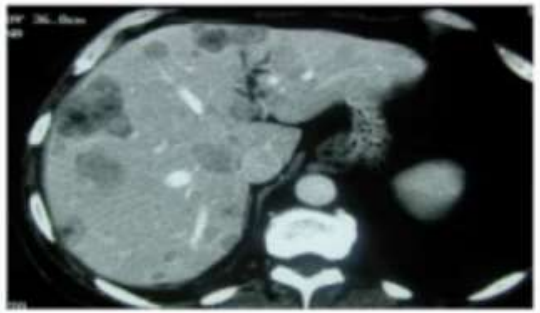
Karcinom pankreatu v době dg:



Karcinom pankreatu v době dg:

50-60 %

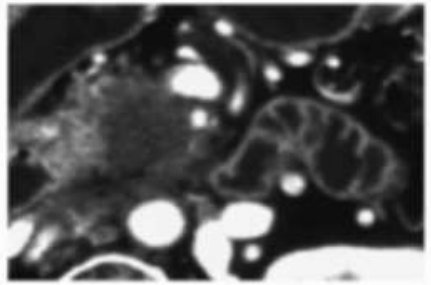
Metastatic Disease 60%



Overall survival 5-11 mo

20 - 30 %

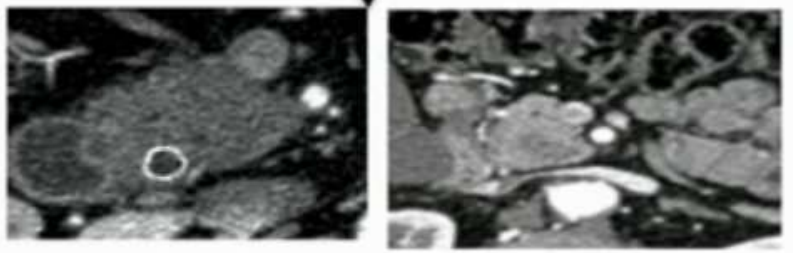
Locally advanced Disease 25%



9-16 mo

10-20%

Resectable Disease 15%



Borderline

R0 surgery

15-30 mo

> 2 years

Resekabilita ca pankreatu:

Unresectable

Distant metastases

Arterial encasement (celiac trunk, superior mesenteric artery or hepatic artery)

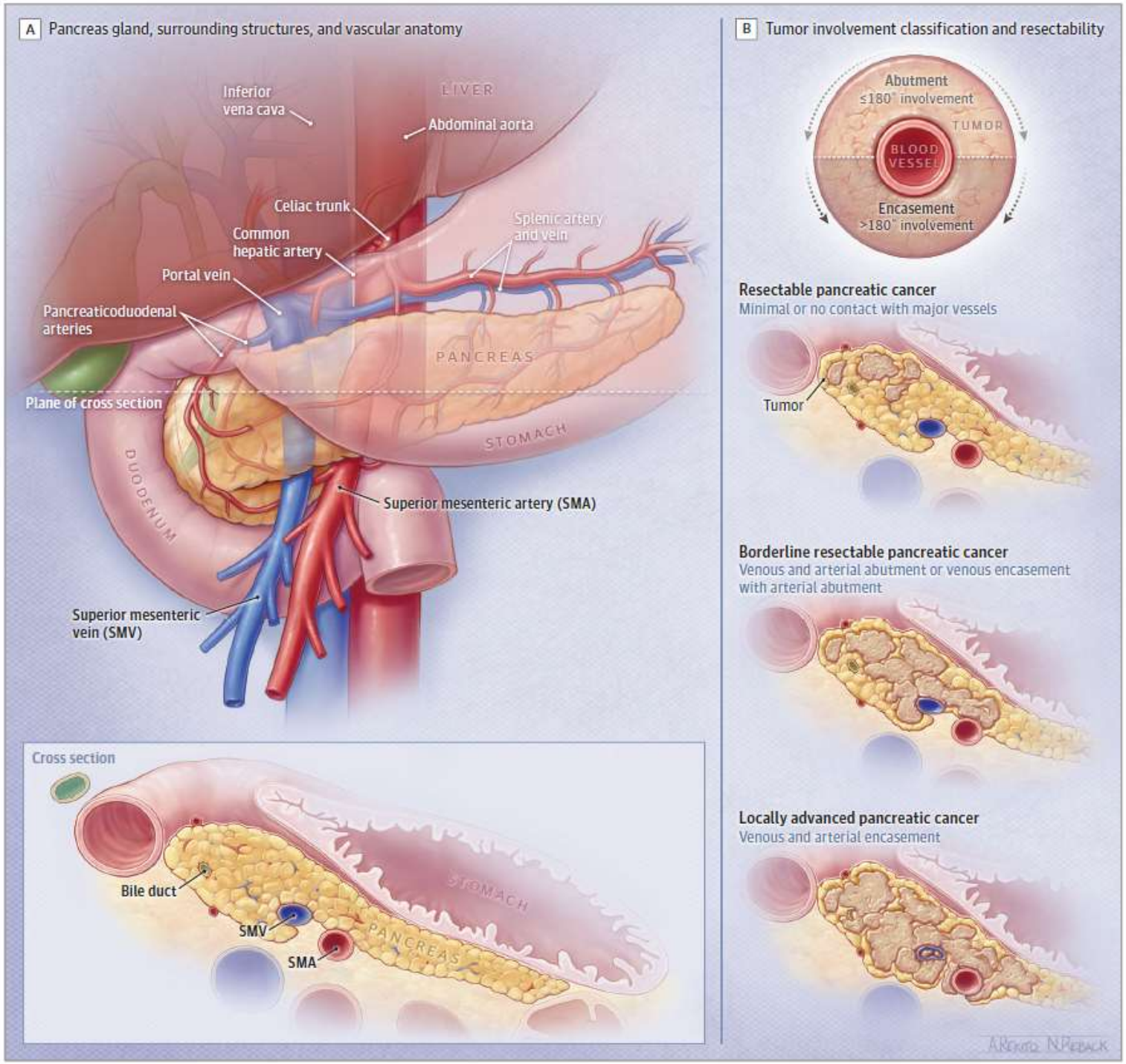
Venous encasement (portal or superior mesenteric)

Venous involvement (portal or superior mesenteric)

Attached to other organs

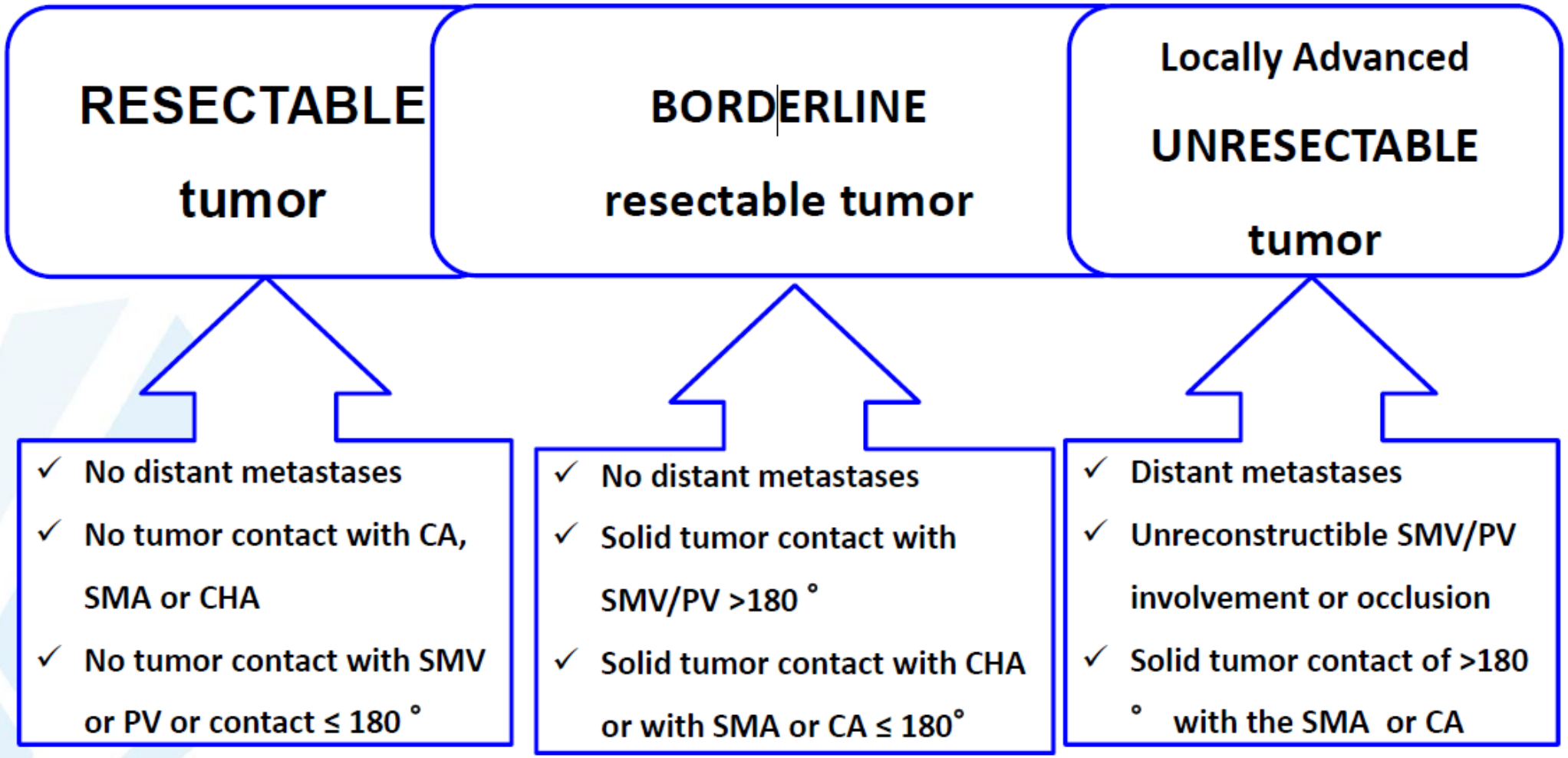
No arterial or venous involvement

Resectable



Ryan DP, et al. N Engl J Med. 2014;371(11):1039–49
Park W et al. JAMA. 2021;326(9):851-862

Kontinuum mezi technicky resekabilním a neresekabilním KP:



Ryan DP, et al. N Engl J Med. 2014;371(11):1039–49
Park W et al. JAMA. 2021;326(9):851-862

Definition of borderline PDAC

Type of definition	Anatomical	Biological	Conditional
Resectable	R-Type A	No: R-Type A	No: R-Type A
Borderline resectable	BR-Type A	Yes: BR-Type B No: BR-Type A Yes: BR-Type AB	Yes: BR-Type C No: BR-Type A Yes: BR-Type AC
Locally advanced	LA-Type A	No: LA-Type A Yes: LA-Type AB	No: LA-Type A Yes: LA-Type AC

Biological definition:

- **CA19-9** more than **500 IU/mL**
- Regional lymph node metastasis (biopsy or PET-CT)

Conditional host-related definition:

- Depressed performance status (PS: 2 or more)

Tumour is classified based on combination of A, B, and C
(for example, a patient with both Type B and C features would be classified as Type ABC)

- There are different anatomical definitions (arterial <180º, venous >180º)
- Patients with low probability of R0 resection margin

BR, borderline resectable; CA, cancer antigen; LA, locally advanced; PDAC, pancreatic ductal adenocarcinoma; PET-CT, positron emission tomography–computed tomography; PS, performance status; R, resectable; R0, no evidence of residual tumour at resection margins.

Isaji S, et al. Pancreatology. 2018;18(1):2–11.

Stanovení resekability karcinomu pankreatu:

Onkolog

Radioterapeut

Gastroenterolog

Patolog

Radiolog

Chirurg

Vzhledem k absenci zcela jednoznačných a jednotných kritérií resekability je doporučováno, aby
KAŽDÝ PACIENT s nemetastatickým KP byl zhodnocen mezioborovou indikační komisí v rámci high-volume centra !

NCCN Guidelines. Pancreatic Adenocarcinoma. Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf (Accessed March 2020).

SOUHRN léčby adenokarcinomu pankreatu:

„Kurativní"

Perioperační léčba

Kombinace neoadjuvantní a adjuvantní léčby před a po operaci

Neoadjuvantní léčba

Cíl:

- downstaging
- zvýšení šance na dosažení R0 resekce

OPERACE

Cíl:

- **R0 resekce**

Adjuvantní léčba

Cíl:

- likvidace mikrometastáz
- prodloužení přežití (mOS)

Paliativní

Paliativní léčba

I. a II. linie chemoterapie

Cíl:

- **prodloužení života (mOS)**
- **zlepšení kvality života (QoL)**
- **zmírnění symptomů**

Adjuvantní léčba u ca pankreatu – proč ??

- při samotné resekci zrelabuje do 5ti let 85-95 % pacientů (většina do 3 let)
- adjuvantní léčba s cílem zlikvidování reziduálních nádorových buněk (mikrometastáz) zásadně zlepšuje výsledky:

Studie /počet pacientů	Přínos studie	Léčebná ramena	Medián DFS (měsíce)	Hodnota „p“	Medián OS (měsíce)	Hodnota „p“	Četnost dokončení studie (%)
CONKO-001 2007 (n=354)[8]	Practice changing pro gemcitabin	Observace	6,7	< 0,001	20,2	0,01	-
		gemcitabin	13,4		22,8		62,0
ESPAC-3 2010 (n=1088)[9]	Potvrzení gemcitabinu jako standardu léčby	FU/FA	14,1	0,53	23,0	0,39	55,0
		Gemcitabin	14,3		23,6		60,0
ESPAC-4 2017 (n=730)[10]	Trend upřednostňující gem+cape	Gemcitabin	13,1	0,082	25,5	0,032	65,0
		Gemcitabin + capecitabin	13,9		28,0		54,0
PRODIGE-24 -PA6 2018 (n=493)[11]	Practice changing pro mFOLFIRINOX u fit pacientů	Gemcitabin	12,8	< 0,0001	35,0	0,003	79,0
		mFOLFIRINOX	21,6		54,4		66,4
APACT 2019 (n=866)[12]	Selhání gem+nab-pakli v adjuvanci	Gemcitabin	18,8	0,18	36,2	0,045	71,0
		Gemcitabin +nab-paklitaxel	19,4		40,5		66,0

20-letý vývoj adjuvantní léčby ca pankreatu:

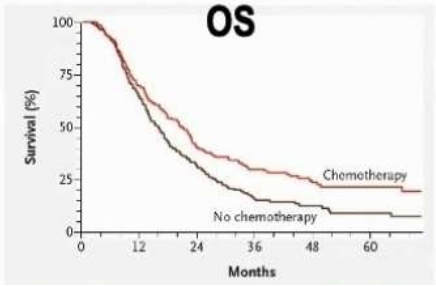
Studies: ESPAC-1 :
5FU > observation.
Neoptolemos et al, N Engl J Med 2004

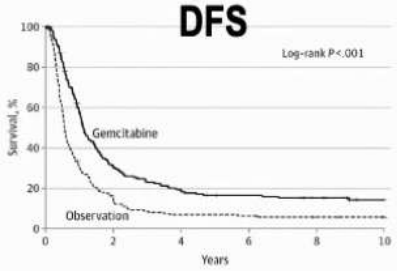
CONKO-001 :
Gemcitabine > obs.
Oettle H et al, JAMA 2007 & 2013

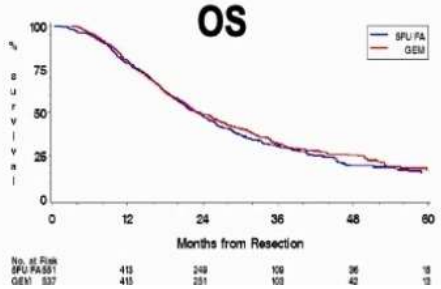
ESPAC-3 :
Gemcitabine = 5FU
Neoptolemos JP et al, JAMA 2010

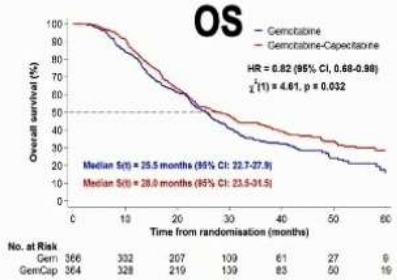
ESPAC-4 :
Gem+Capecitabine > **Gem**
Neoptolemos JP et al, Lancet 2017

2001 2004 2007 2010 2013 2016



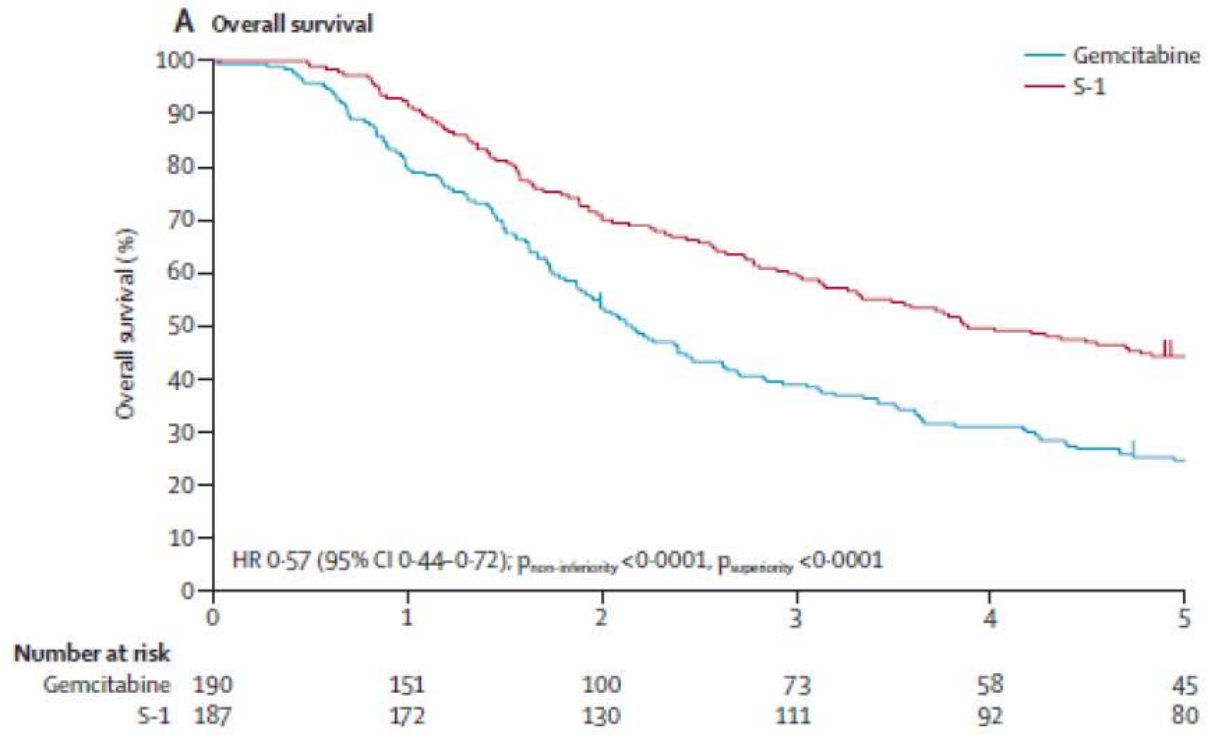


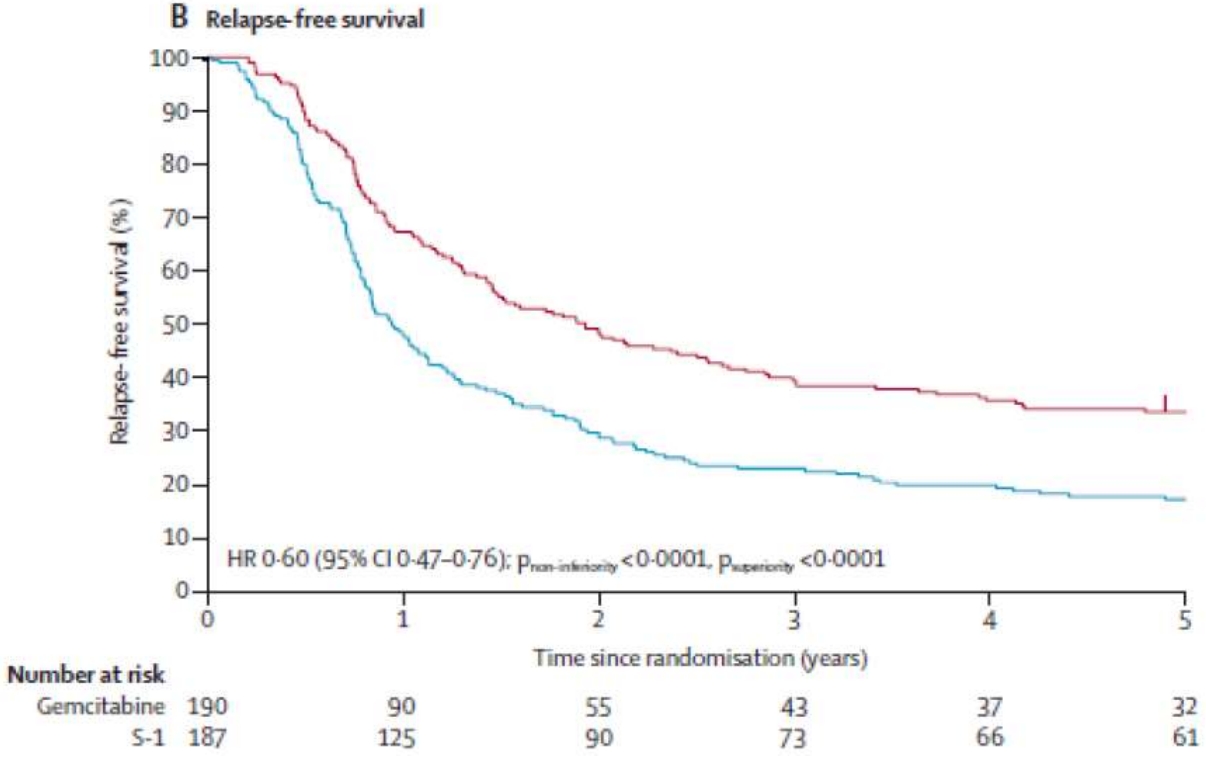




Taieb J, PanCan Academy 17.2.2021

Adjuvantní **S1** vs gemcitabin po resekci KP – randomizovaná otevřená non-inferiorní studie **JASPAC 01** (asijská populace)





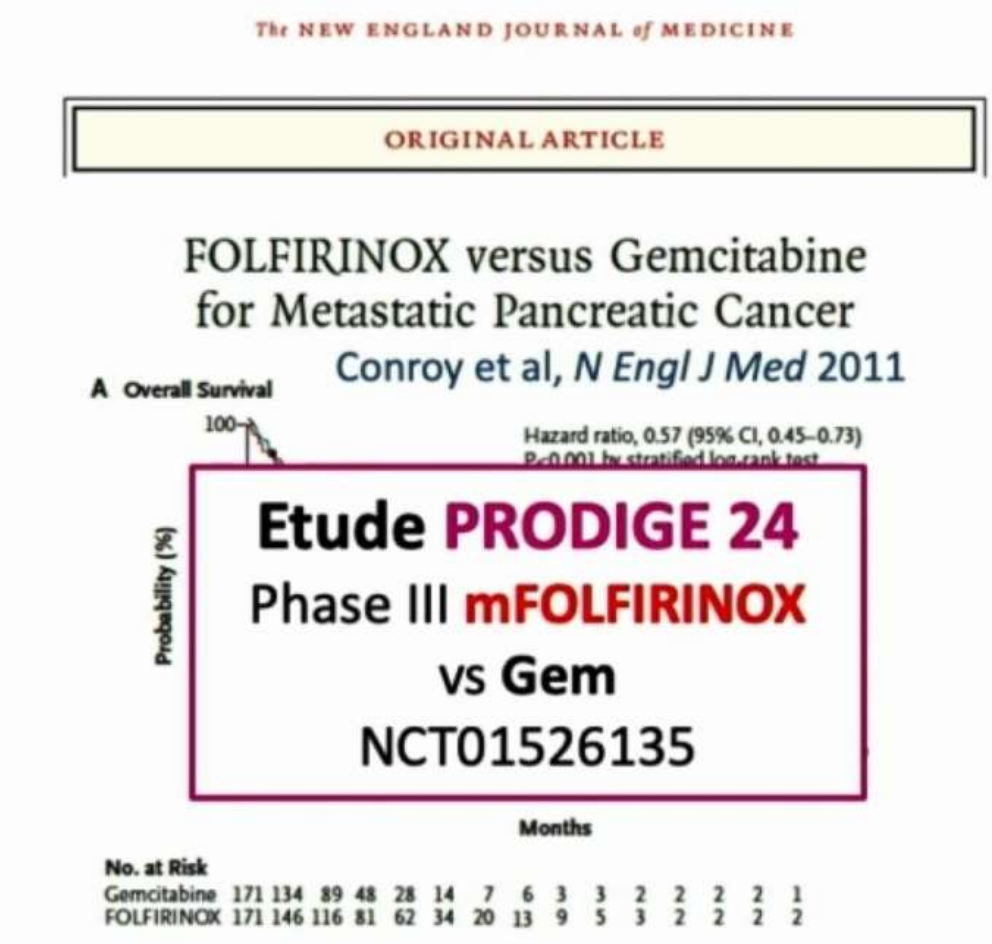
- N = 385
- S1 40-60 mg 2xD podávaný 4t + 2t pauza
- HR pro S1 0,57

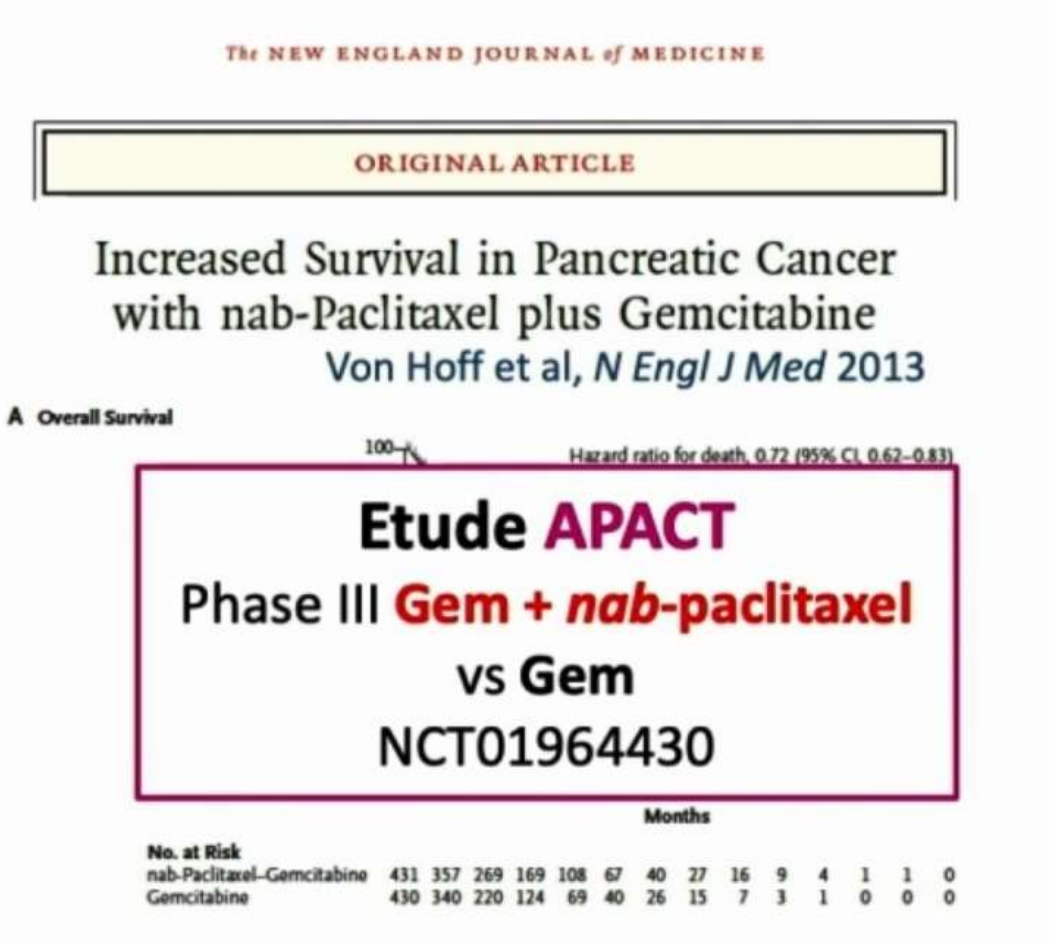
- 5yOS 43,6 vs 24,2 %
- G3/4 toxicita menší u S1

The Lancet, June 2016

Pokrok v adjuvanci ca pankreatu

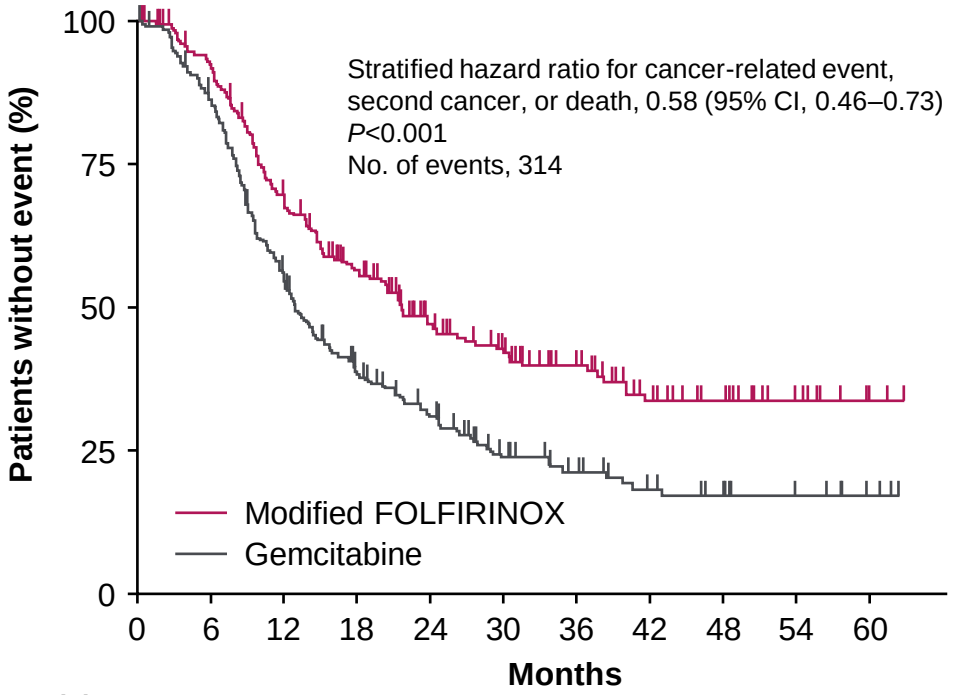
- **po publikaci 2 pozitivních studií u metastatického KP byly režimy FOLFIRINOX i gemcitabine/nab-paklitaxel testovány i v adjuvantní indikaci:**





Průlom v adjuvanci u ca pankreatu – studie PRODIGE24:

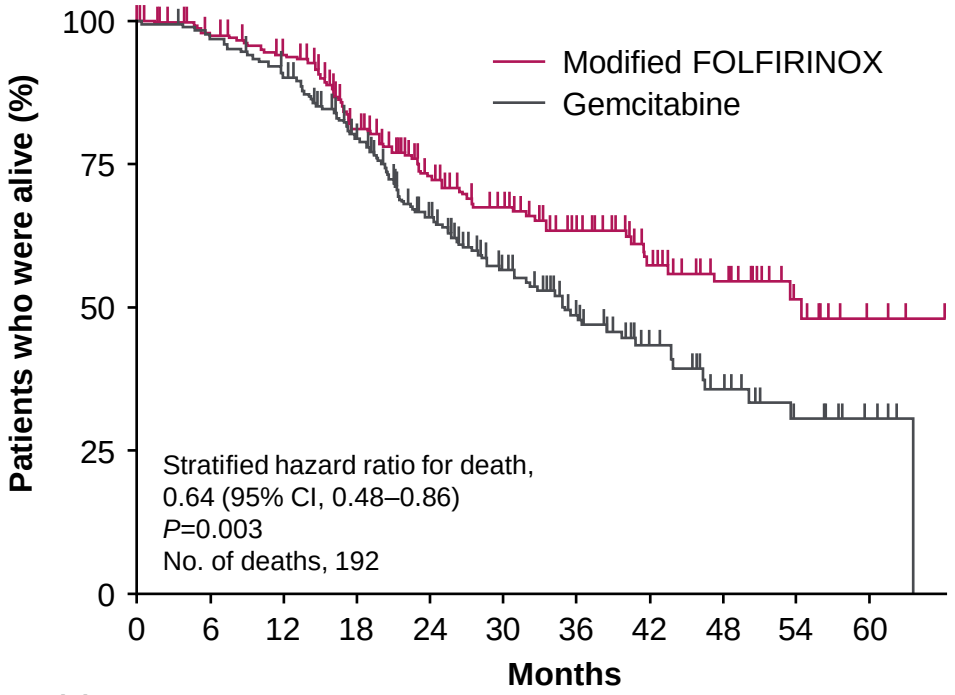
A. Disease-free Survival



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

mDFS: 12.8 months vs **21.6** months, *P*<0.0001
3y DFS 39,7 % vs 21,4 %

B. Overall Survival



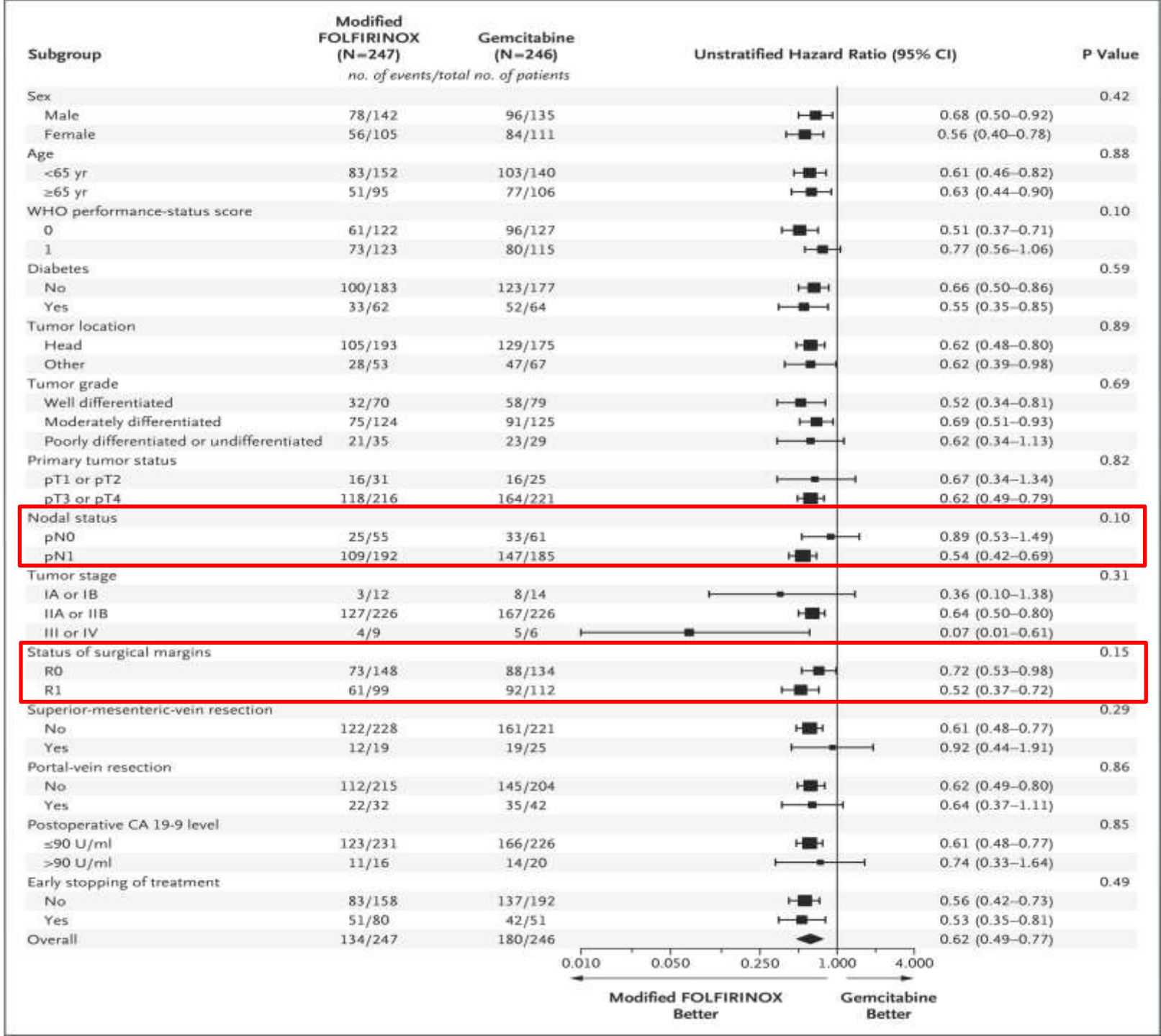
No. at risk											
Modified FOLFIRINOX	247	223	210	165	119	91	68	46	32	16	4
Gemcitabine	246	233	215	171	120	81	55	33	18	9	4

mOS: 35 months vs **54.4** months, *P*=0.003
3yOS 66,2 % vs 51,2 %

CI, confidence interval; mDFS, median disease-free survival; mOS, median overall survival.

Conroy T, et al. N Engl J Med. 2018;379(25):2395–406.

FOLFIRINOX lepší ve všech podskupinách:



Subgroup	Modified FOLFIRINOX (N=247)	Gemcitabine (N=246)	Unstratified Hazard Ratio (95% CI)	P Value
	no. of events/total no. of patients			
Sex				0.42
Male	78/142	96/135	0.68 (0.50–0.92)	
Female	56/105	84/111	0.56 (0.40–0.78)	
Age				0.88
<65 yr	83/152	103/140	0.61 (0.46–0.82)	
≥65 yr	51/95	77/106	0.63 (0.44–0.90)	
WHO performance-status score				0.10
0	61/122	96/127	0.51 (0.37–0.71)	
1	73/123	80/115	0.77 (0.56–1.06)	
Diabetes				0.59
No	100/183	123/177	0.66 (0.50–0.86)	
Yes	33/62	52/64	0.55 (0.35–0.85)	
Tumor location				0.89
Head	105/193	129/175	0.62 (0.48–0.80)	
Other	28/53	47/67	0.62 (0.39–0.98)	
Tumor grade				0.69
Well differentiated	32/70	58/79	0.52 (0.34–0.81)	
Moderately differentiated	75/124	91/125	0.69 (0.51–0.93)	
Poorly differentiated or undifferentiated	21/35	23/29	0.62 (0.34–1.13)	
Primary tumor status				0.82
pT1 or pT2	16/31	16/25	0.67 (0.34–1.34)	
pT3 or pT4	118/216	164/221	0.62 (0.49–0.79)	
Nodal status				0.10
pN0	25/55	33/61	0.89 (0.53–1.49)	
pN1	109/192	147/185	0.54 (0.42–0.69)	
Tumor stage				0.31
IA or IB	3/12	8/14	0.36 (0.10–1.38)	
IIA or IIB	127/226	167/226	0.64 (0.50–0.80)	
III or IV	4/9	5/6	0.07 (0.01–0.61)	
Status of surgical margins				0.15
R0	73/148	88/134	0.72 (0.53–0.98)	
R1	61/99	92/112	0.52 (0.37–0.72)	
Superior-mesenteric-vein resection				0.29
No	122/228	161/221	0.61 (0.48–0.77)	
Yes	12/19	19/25	0.92 (0.44–1.91)	
Portal-vein resection				0.86
No	112/215	145/204	0.62 (0.49–0.80)	
Yes	22/32	35/42	0.64 (0.37–1.11)	
Postoperative CA 19-9 level				0.85
≤90 U/ml	123/231	166/226	0.61 (0.48–0.77)	
>90 U/ml	11/16	14/20	0.74 (0.33–1.64)	
Early stopping of treatment				0.49
No	83/158	137/192	0.56 (0.42–0.73)	
Yes	51/80	42/51	0.53 (0.35–0.81)	
Overall	134/247	180/246	0.62 (0.49–0.77)	

Conroy T, et al. N Engl J Med. 2018;379(25):2395–406.

Toxicita:

- podobné procento hematologické G3/4 toxicity při použití G-CSF (60 % pac.)

- U FOLFIRINOXu:
  - více **G3/4 mukositid a GIT toxicity**
  - více **neuropatií**

- FOLFIRINOX je zvládnutelný
- žádné protrahované pozdní NUL kromě neuropatie u malé podskupiny pacientů (2,9 %)

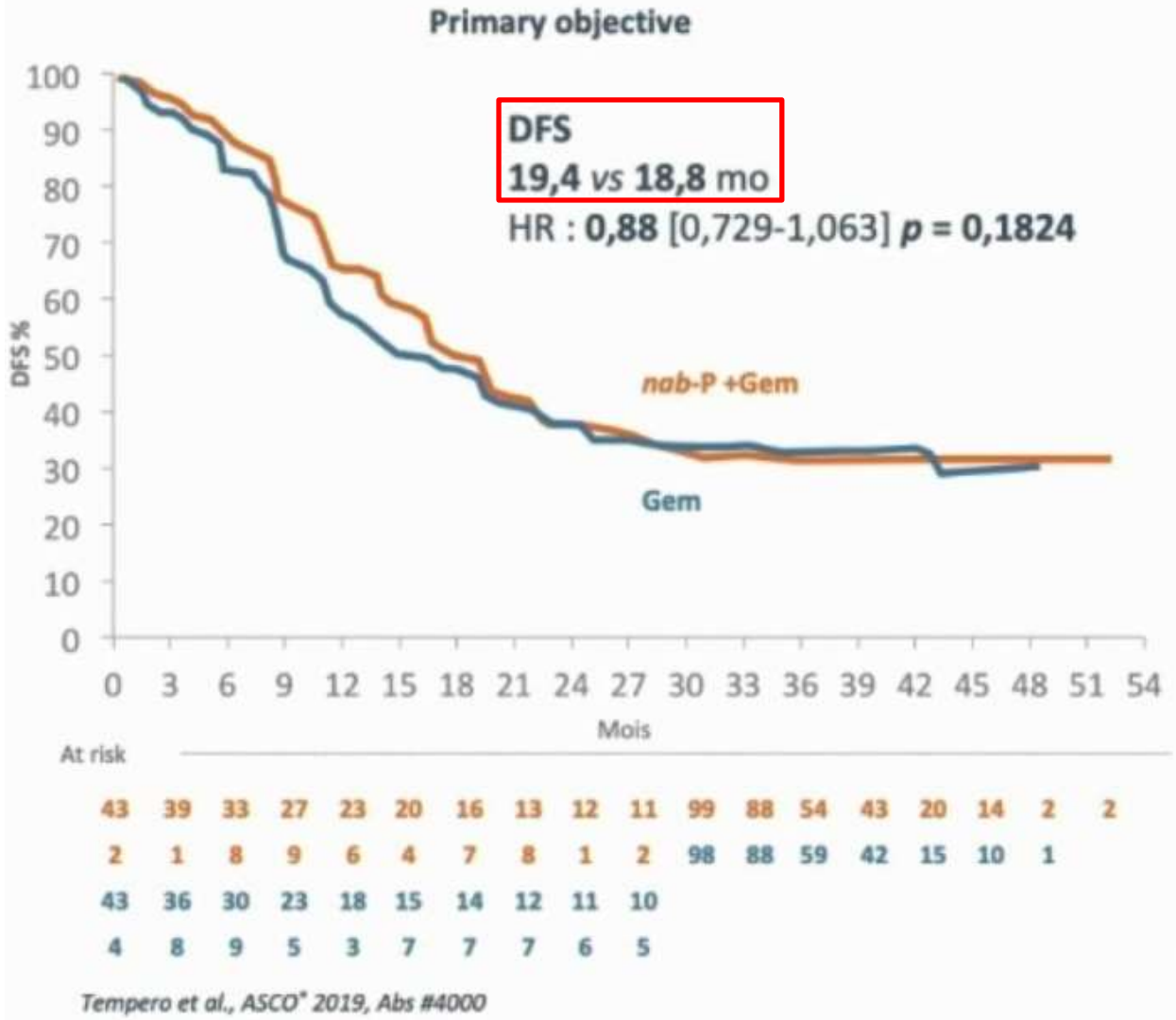
Conroy T, et al. N Engl J Med. 2018;379(25):2395–406.

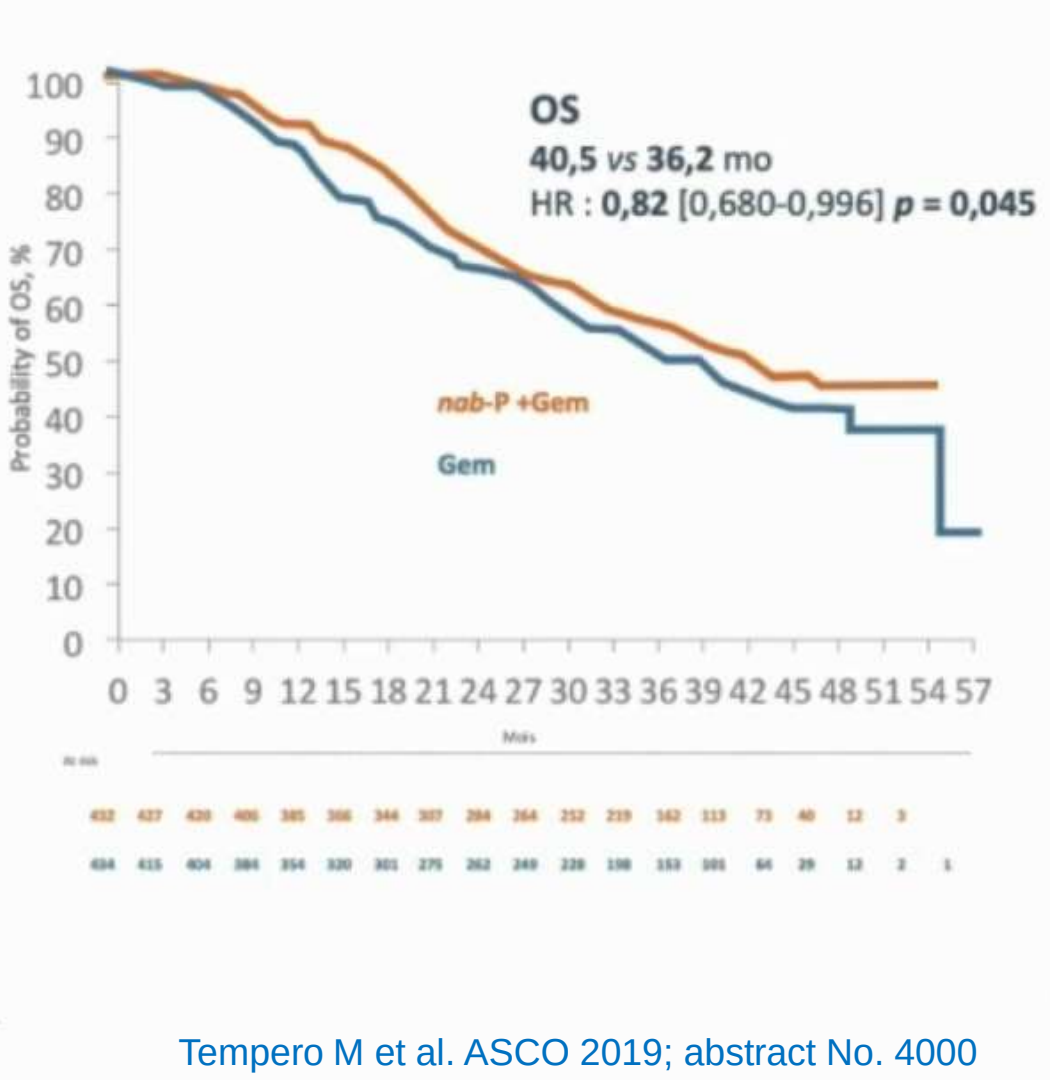
Table 2. Adverse Events during Treatment (Safety Population).*

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

Gemcitabine/nab-paklitaxel v adjuvanci selhal …

APACT = negativní studie !!!





Tempero M et al. ASCO 2019; abstract No. 4000

Toxicita:

- G3/4 u 86 vs 68 % pac.
- více G3/4 hematologické toxicity a únavy
- více závažné neuropatie 15 vs 0 %
- toxické úmrtí u 2 pacientů v obou ramenech

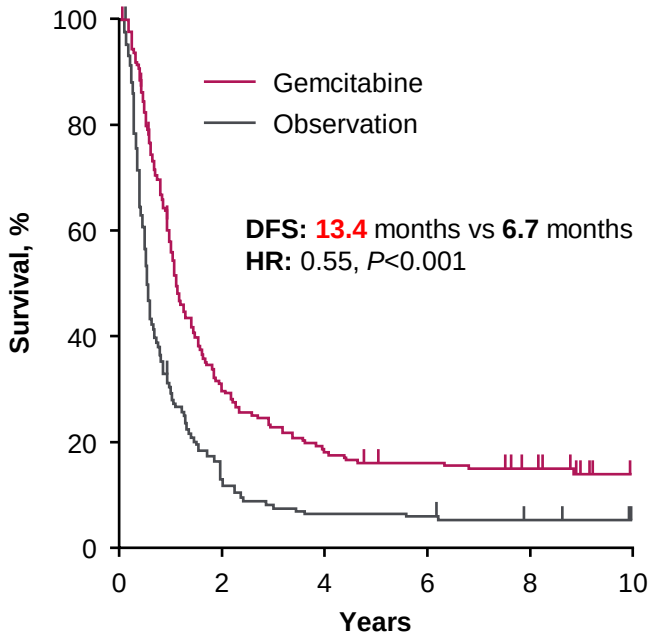
Evénements, n (%)		*NAB-P* + Gem (N=429)	Gem (N=423)
Safety summary	Patients with ≥1 grade ≥ 3 TEAE	**371** (8)	**286** (68)
	Patients with ≥1 serious TEAE	**176** (41)	**96** (23)
Grade ≥3 hematologic TEAEs (occuring in ≥5% of patients in eiteher treatment arm)	Any hematologic TEAEs	**250** (58)	**204** (48)
	Neutropenia	212 (49)	184 (43)
	Anemia	**63** (15)	**33** (8)
	Leukopenia	**36** (8)	**20** (5)
	Febrile neutropenia	**21** (5)	**4** (1)
Grade ≥3 nonhematologic TEAEs (occuring in ≥5% of patients in eiteher treatment arm)	Peripheral neuropathy (SMQ)	64 (15)	**0**
	Fatigue	**43** (10)	**13** (3)
	Diarrhea	**22** (5)	**4** (1)
	Asthenia	**21** (5)	**8** (2)
	Hypertension	**17** (4)	**27** (6)

Tempero M et al. ASCO 2019; abstract No. 4000

Adjuvantní chemoterapie **u ostatních pacientů** (neschopných tolerovat režim mFOLFIRINOX):

CONKO-001 Trial[1]

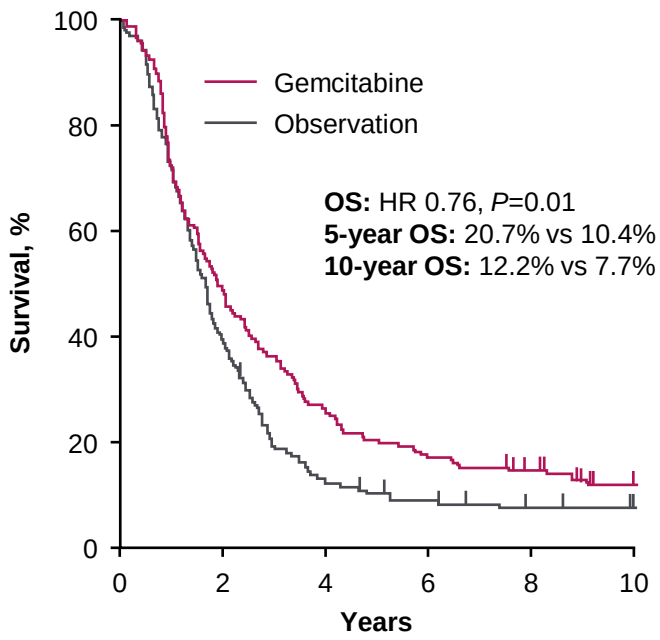
Disease-free Survival



No. at risk						
Gemcitabine	179	52	32	26	20	12
Observation	175	26	12	11	8	6

Follow-up time: 136 months

Overall Survival

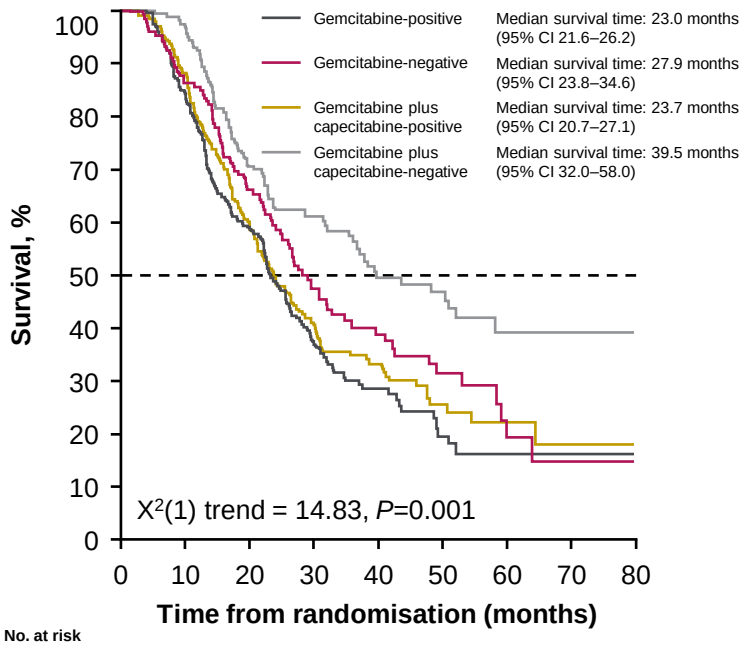


No. at risk						
Gemcitabine	179	87	47	31	24	14
Observation	175	70	22	14	9	7

mOS: 22.8 months vs 20.2 months in the observation group

ESPAC-4 Trial[2]

Overall Survival



No. at risk									
Gemcitabine-positive	219	178	118	58	31	12	3	1	0
Gemcitabine-negative	147	124	89	51	30	15	6	2	0
Gemcitabine plus capecitabine-positive	221	193	124	71	42	20	6	3	1
Gemcitabine plus capecitabine-negative	143	135	95	68	41	30	13	7	0

mOS in R0 patients: 27.9 months (gemcitabine arm) vs 39.5 months (gemcitabine plus capecitabine arm)

DFS, disease-free survival; HR, hazard ratio; mOS, median overall survival; OS, overall survival; R0, no evidence of residual tumour at resection margins.

1. Oettle H, et al. JAMA. 2013; 310(14):1473–81;
2. Neoptolemos JP, et al. Lancet. 2017:389(10073);1011–24.

Adjuvance u ca pankreatu – SOUHRN:

- **mFOLFIRINOX novým standardem** adjuvantní léčby u pacientů ve velmi dobrém celkovém stavu s PS 0-1 (ESMO,[1] NCCN[2] a ASCO[3] guidelines)
  - zdvojnásobení 3-letého DFS (39.7% vs 21.4%)[4]
  - efektivní rovněž u nádorů s: **N1** (HR 0.54) a **R1** resekcí (HR 0.52)[4]

- **gemcitabin** nebo **gemcitabin+capecitabin** u pacientů s PS 2

- **zahájit nejpozději do 3 měsíců od operace** (ale ne dříve než za 6 týdnů) !!

- **podávat po dobu celých 6 měsíců (12 sérií)**

ASCO, American Society of Clinical Oncology; DFS, disease-free survival; ESMO, European Society for Medical Oncology; HR, hazard ratio; N1, evidence of tumour in lymph nodes; NCCN, National Comprehensive Cancer Network; R1, microscopic residual tumour at resection margins.

1. Ducreux M, et al. Ann Oncol. 2015;26(suppl_5):v56–68;
2. NCCN Guidelines. Pancreatic Adenocarcinoma. Version 1.2022. Available at https://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf (Accessed March 2022);
3. Khorana AA, et al. J Clin Oncol. 2019;37(23):2082–8;
4. Conroy T, et al. N Engl J Med. 2018;379(25):2395–406.

ALE:

- výsledky adjuvantních studií představují **selektovanou populaci**
- v běžné klinické praxi téměř **každý druhý pacient (50 %) nedostane** žádnou adjuvantní CHT !!
- **ne každý snese FOLFIRINOX** (toxicita gr. 3/4 u 75.9% pac.)
- resekce indukuje mortalitu 3-9 %, morbiditu 20-60 % (včetně píštělí 7-40 %)

A navíc - výsledky stále ještě nejsou ideální:

- **R1 resekce u 60-70 % pac.**
- **N+ u 70-80 % pac.**
- **3-letý DFS ≤ 40 %**

Conroy T, et al. N Engl J Med. 2018; Bakens et al. Cancer Med 2016;
Mayo et al. J Am Coll Surg 2012; Merkow et al. Ann Surg 2014; Nussbaum et al. Ann Surg Oncol 2016

Co s tím ?? → NEOADJUVANTNÍ LÉČBA (NAT) !!!

PROČ ??

- standardní postup u ca rekta, jícnu, žaludku, jaterních metastáz mCRC…
- **vyšší compliance** k CHT (více pacientů schopných podstoupit NAT než AT)
- **downstaging + zvýšení pravděpodobnosti / četnosti R0 resekcí**
- časná léčba (mikro)metastáz - **M1** onemocnění již **iniciálně ??**
- otestování senzitivity nádoru k CHT

- **NAT může zlepšit výsledky (zejména celkové přežití - mOS)**

SOUHRN léčby adenokarcinomu pankreatu:

Kurativní

Neoadjuvantní léčba

Cíl:

- downstaging
- zvýšení šance na dosažení R0 resekce

OPERACE

Cíl:

- **R0 resekce**

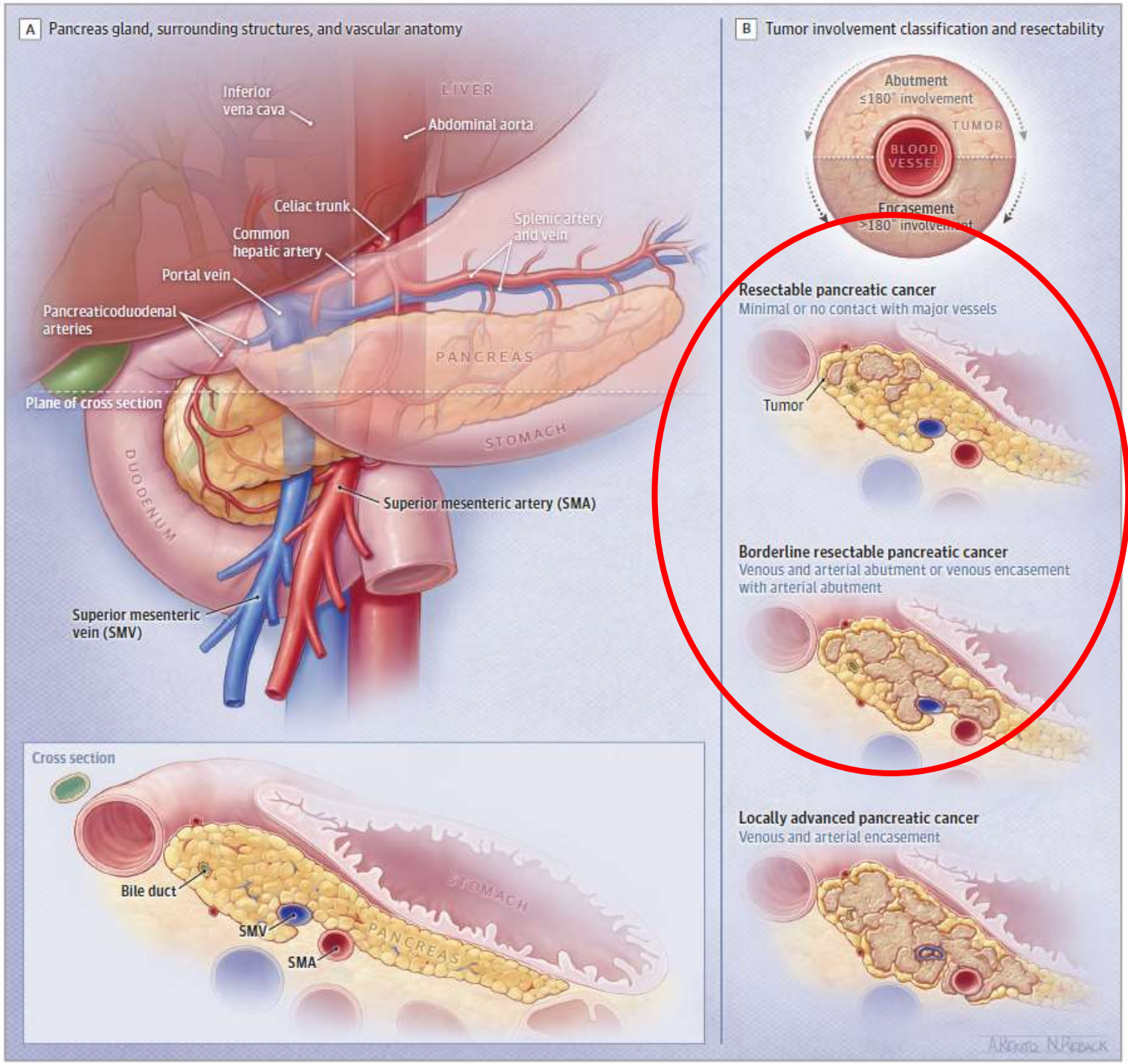
Adjuvantní léčba

Cíl:

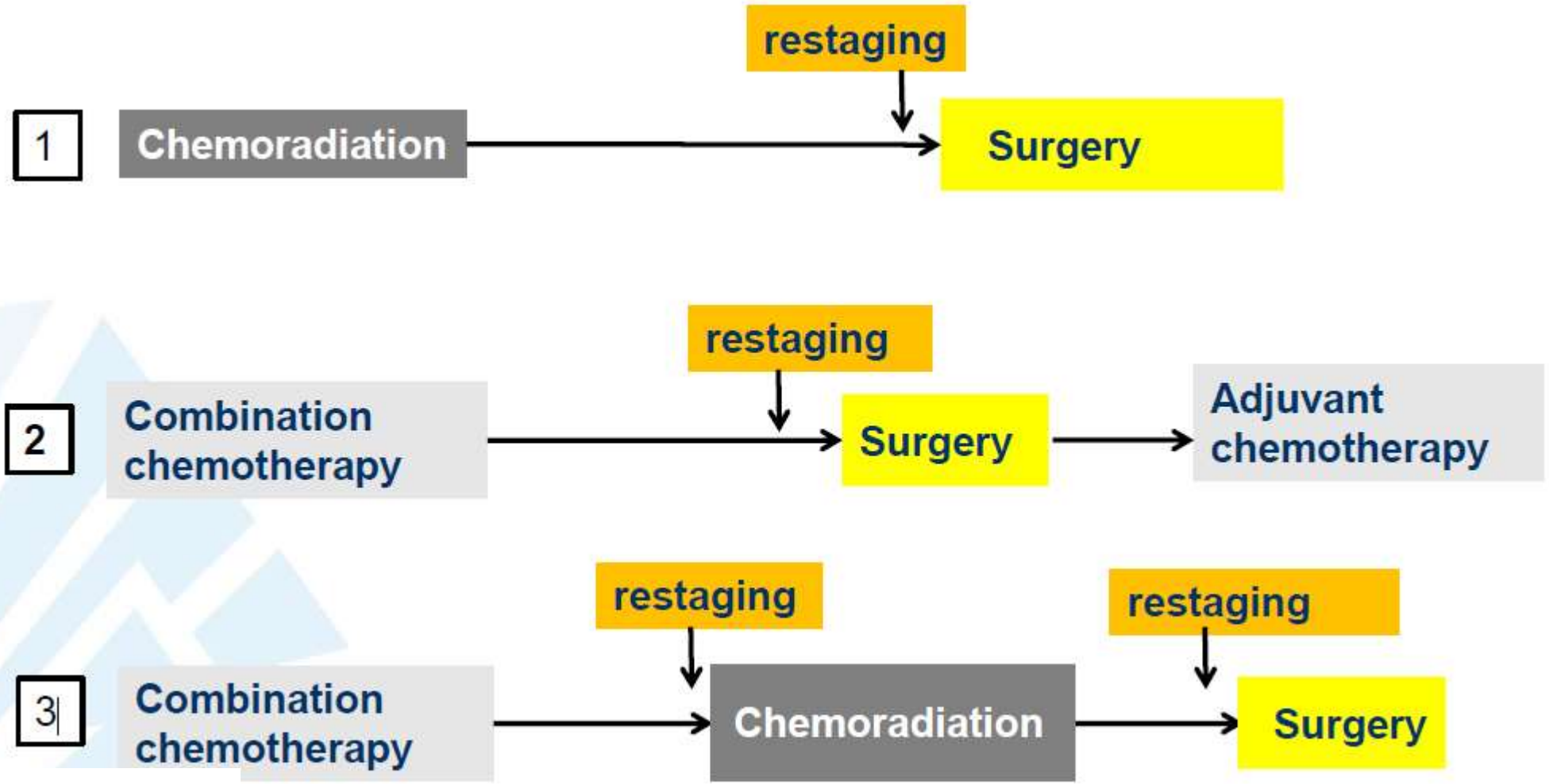
- likvidace mikrometastáz
- prodloužení přežití (mOS)

NEOADJUVANTNÍ LÉČBA

BORDERLINE-RESEKABILNÍHO A PRIMÁRNĚ RESEKABILNÍHO CA PANKREATU



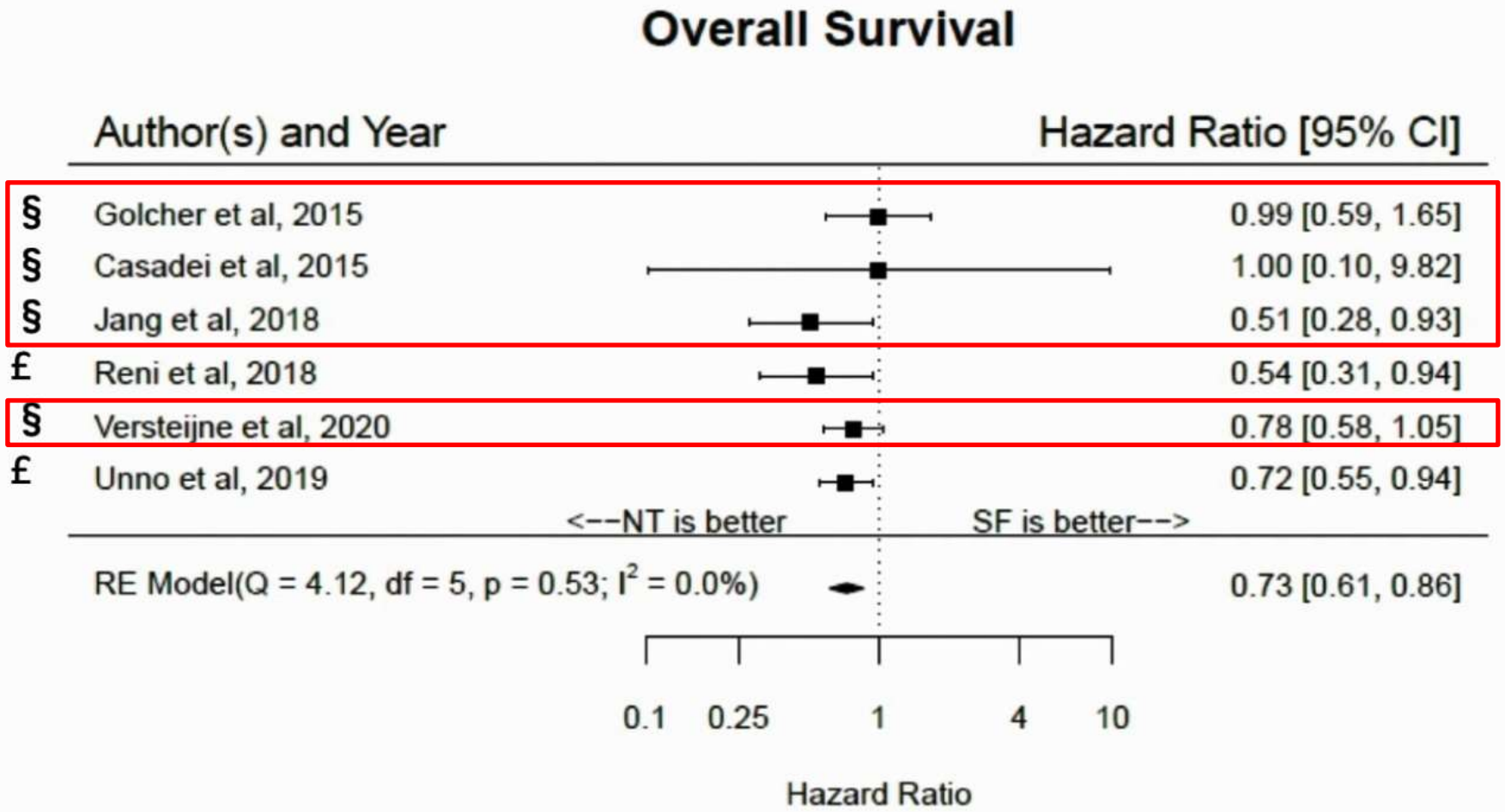
Současné strategie indukční / neoadjuvantní léčby u hraničně resekabilního ca pankreatu:



Cutsem E. CECOG Pancreatic Cancer Academy April 2022

Operable and border-line
Meta-analysis

§ CRT
£ chemo

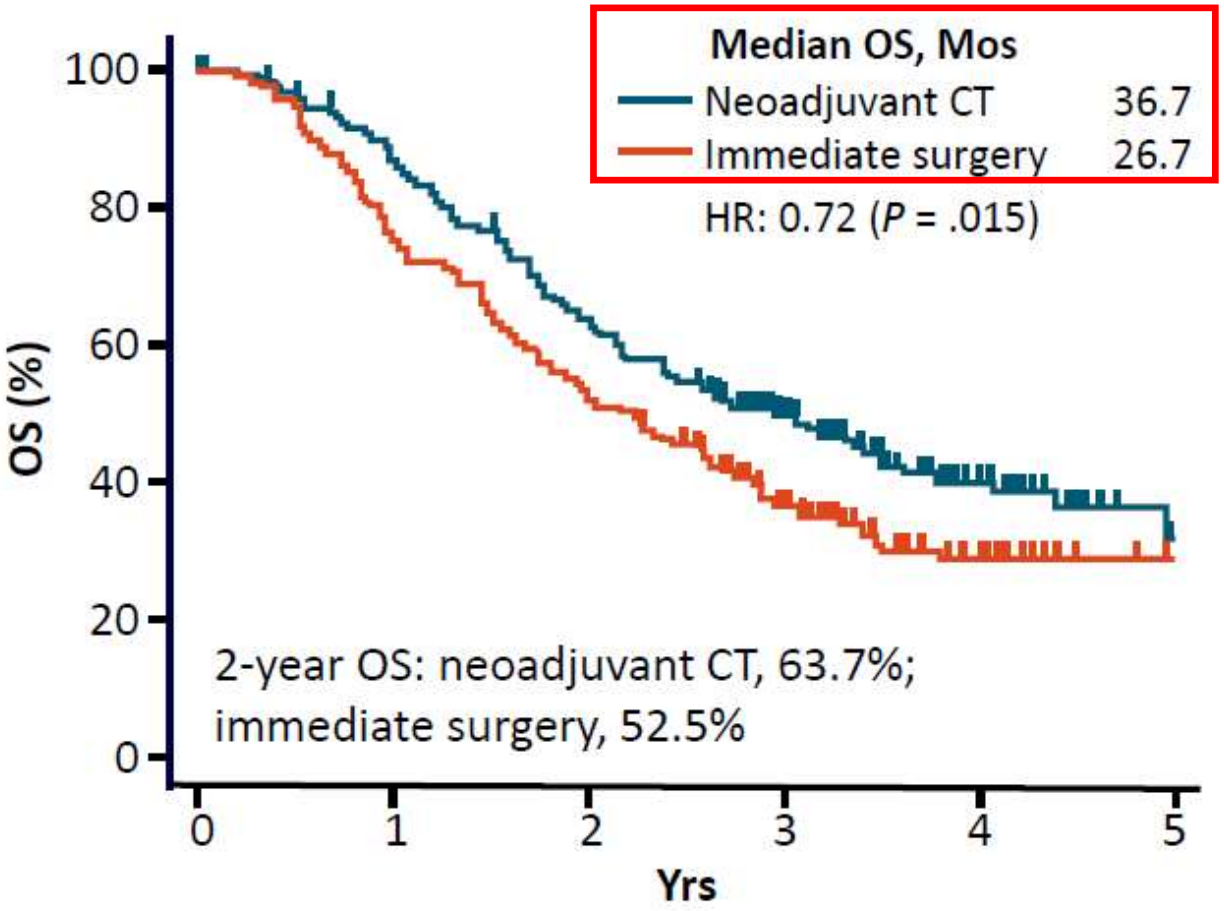


Cloyd JM et al, J Clin Med 2020

PREP-02/JSAP-05: neoadjuvantní CHT vs primární operace - resekabilní

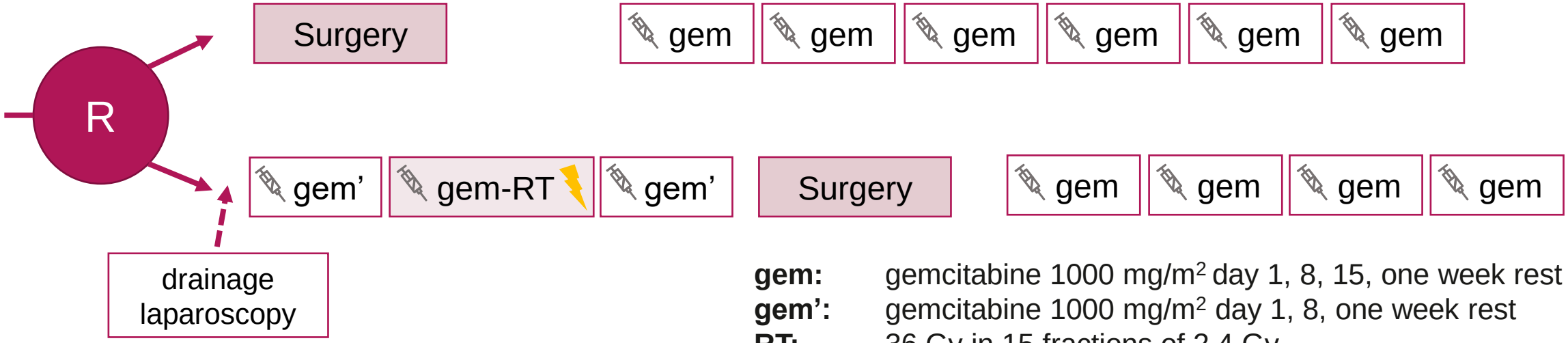
- Randomized phase II/III trial

*Gemcitabine: 1 g/m² on Days 1, 8; oral S-1: 40 mg/m² BID on Days 1-14.



Unno M et al. ASCO GI 2019; abstract 189

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)



gem: gemcitabine 1000 mg/m^2 day 1, 8, 15, one week rest
gem': gemcitabine 1000 mg/m^2 day 1, 8, one week rest
RT: 36 Gy in 15 fractions of 2.4 Gy

Primární cíl: **overall survival** **Borderline resectable 46%**/53%

Dospělí pacienti s PS 0/1 a resekabilním* nebo hraničně resekabilním KP (n=246)

*No contact with superior mesenteric, celiac trunk, or common hepatic arteries and ≤ 90° contact with superior mesenteric portal vein.
†≥ 1 of the following required: ≤ 90° contact with superior mesenteric, celiac trunk, or common hepatic arteries or 90° to 270° contact with superior mesenteric portal vein and no occlusion.

Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

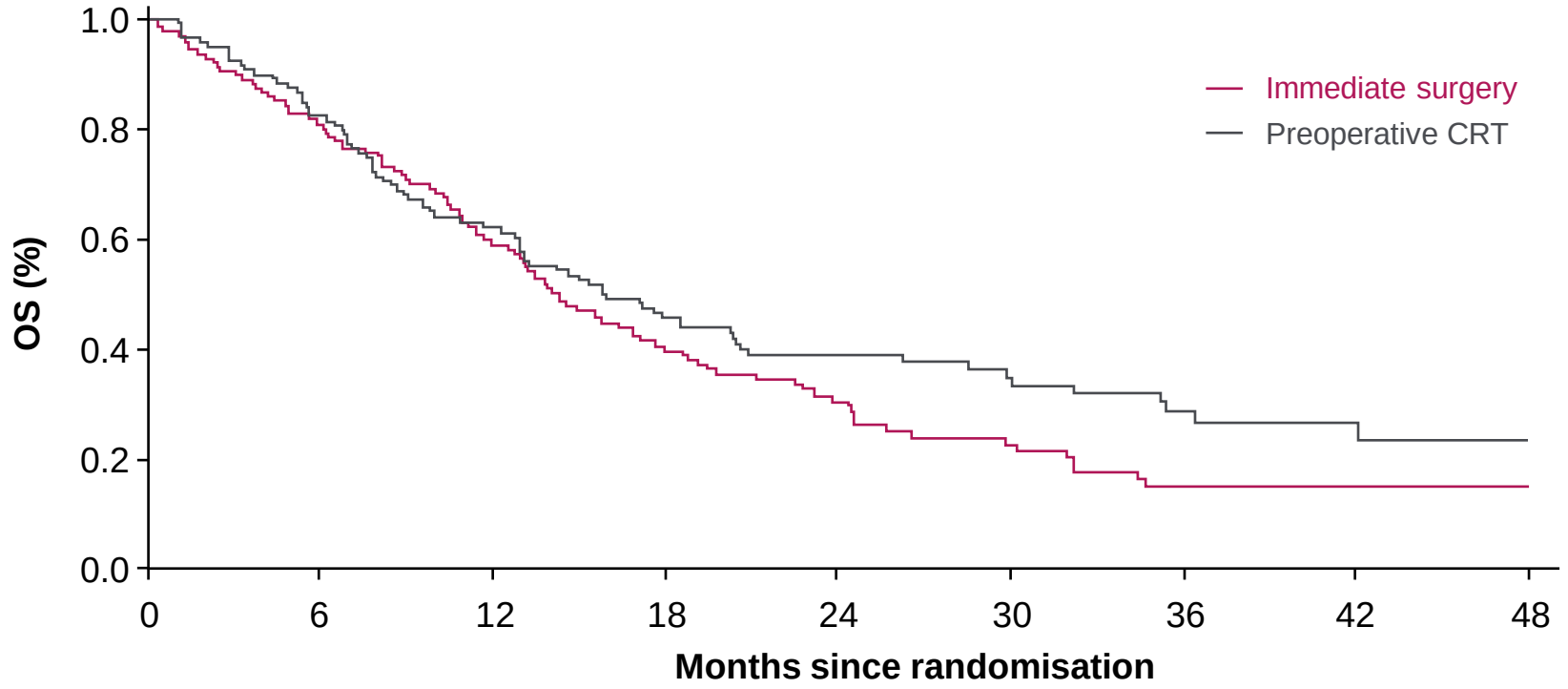
	Immediate surgery (N=127)	Preoperative radiochemotherapy (N=119)	*P* value
Resection rate	91/127 (72%)	72/119 (61%)	0.058
R0 resection rate PP	37/92 (40%)	51/72 (71%)	<0.001
Serious adverse events	52 (41%)	62 (52%)	0.096
Pathological Lymph nodes	78%	33%	<0.001
Venous invasion	65%	35%	<0.001
Perineural invasion	85%	45%	<0.001

PP, per protocol; R0, no evidence of residual tumour at resection margins.

Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Overall Survival (ITT)



No. at Risk									
Immediate surgery	119	99	74	54	37	26	16	9	7
Preoperative CRT	127	104	76	49	31	2	11	3	2

Median survival:
16 vs 14.3 months
HR 0.78
***P*=0.0960**

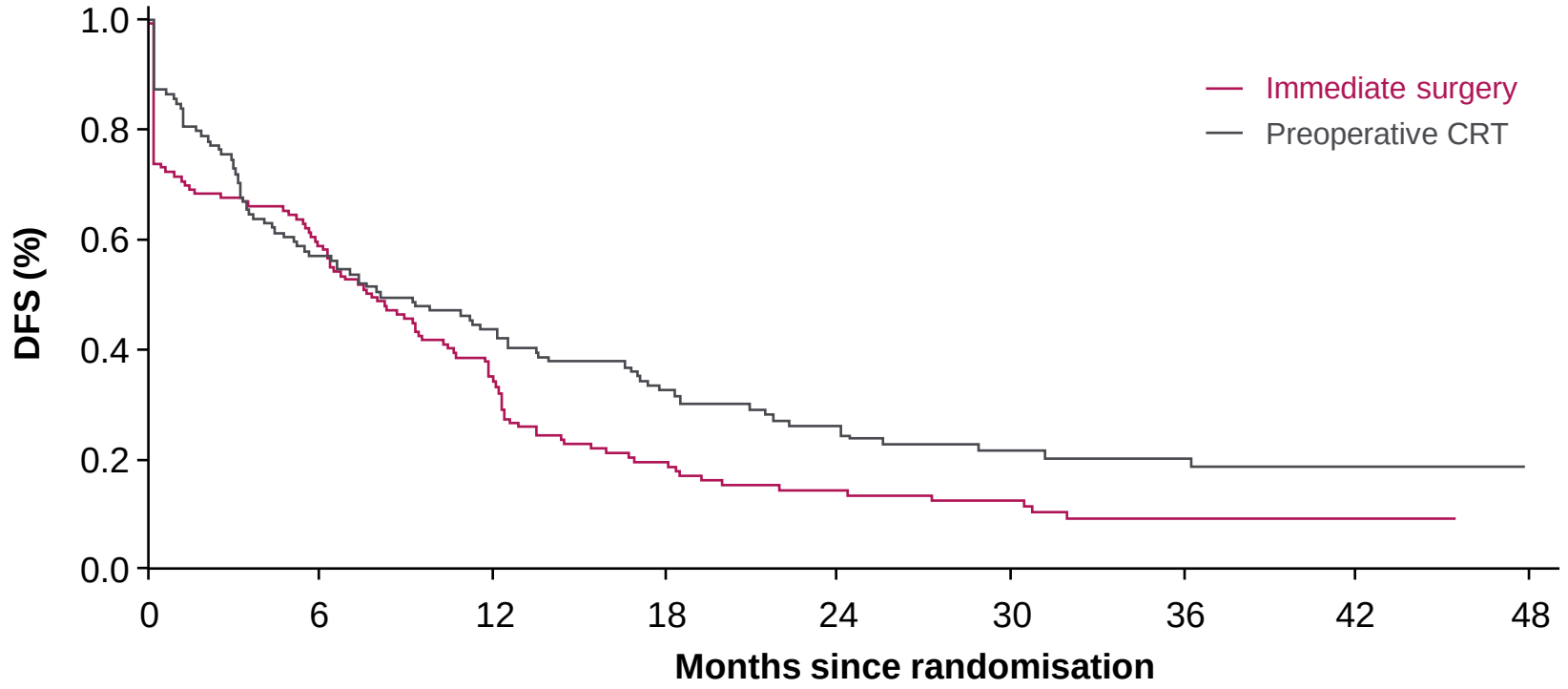
negativní studie

HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Disease-free Survival



Median DFS:
8.1 vs 7.7 months
HR 0.73
***p*=0.0320**

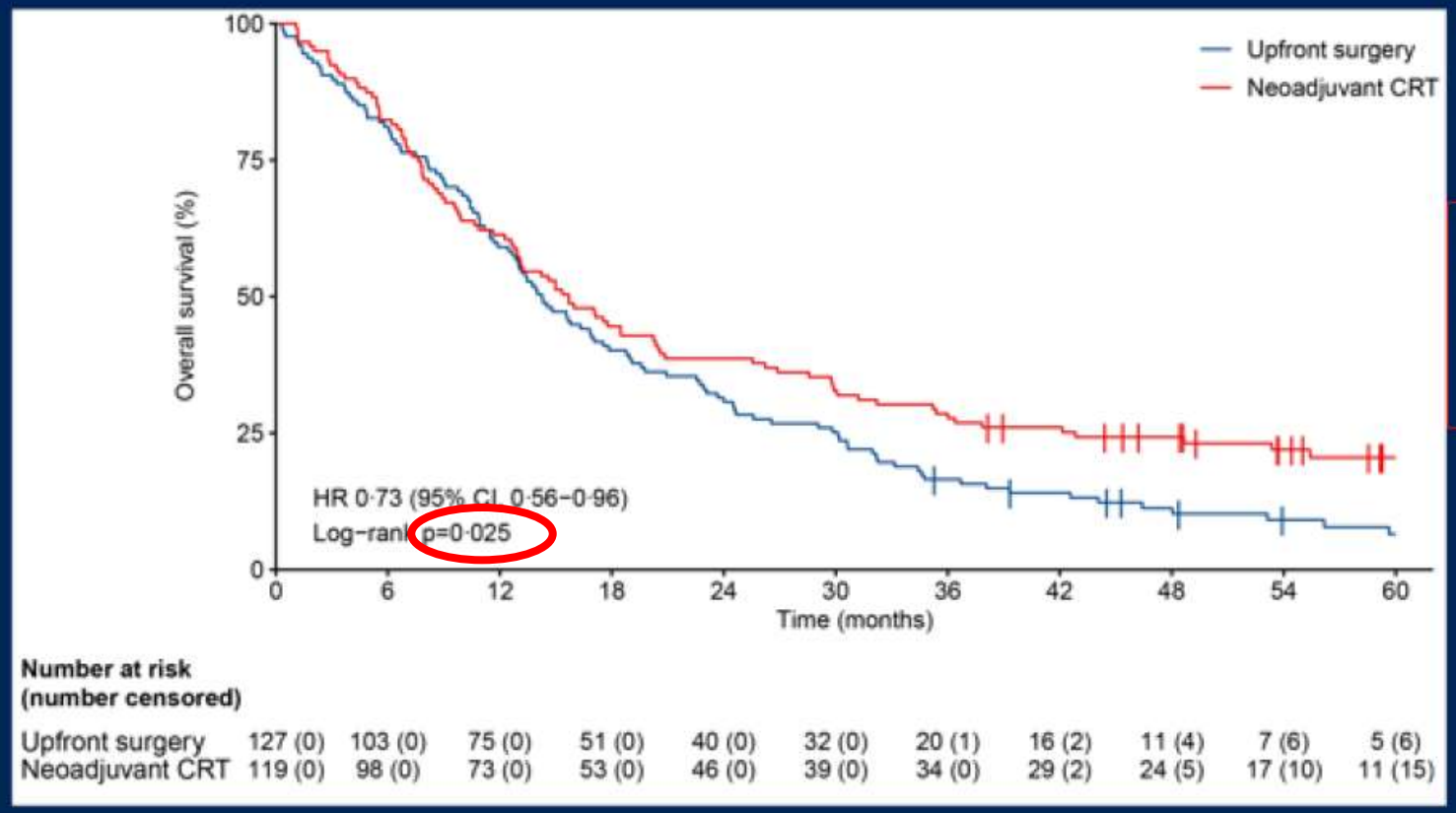
No. at Risk									
Immediate surgery	119	69	53	39	26	19	13	7	6
Preoperative CRT	127	75	48	25	17	13	7	2	1

DFS, disease-free survival; HR, hazard ratio.

Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Results – Overall survival by intention-to-treat



Median overall survival:
Upfront surgery: 14.3 mo
Neoadjuvant CRT: 15.7 mo

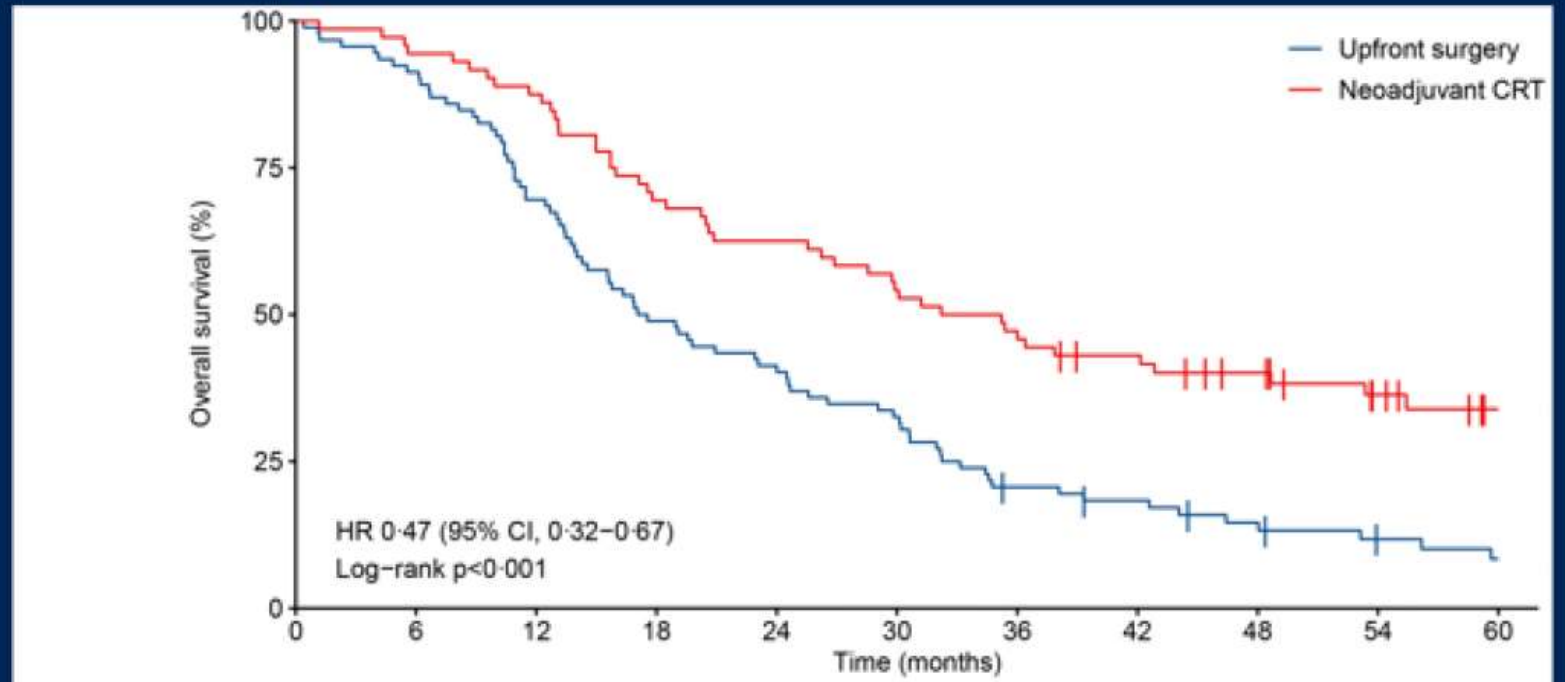
5-year survival:
Upfront surgery: 6.5%
Neoadjuvant CRT: 20.5%

Follow up 59 months

Casper Van Eijck et al. ASCO 2021; Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Results – Patients that underwent resection



Number at risk (number censored)

Upfront surgery	92 (0)	84 (0)	64 (0)	45 (0)	38 (0)	30 (0)	18 (1)	15 (2)	11 (3)	7 (5)	5 (5)
Neoadjuvant CRT	72 (0)	68 (0)	63 (0)	50 (0)	45 (0)	39 (0)	34 (0)	29 (2)	24 (5)	17 (10)	11 (15)

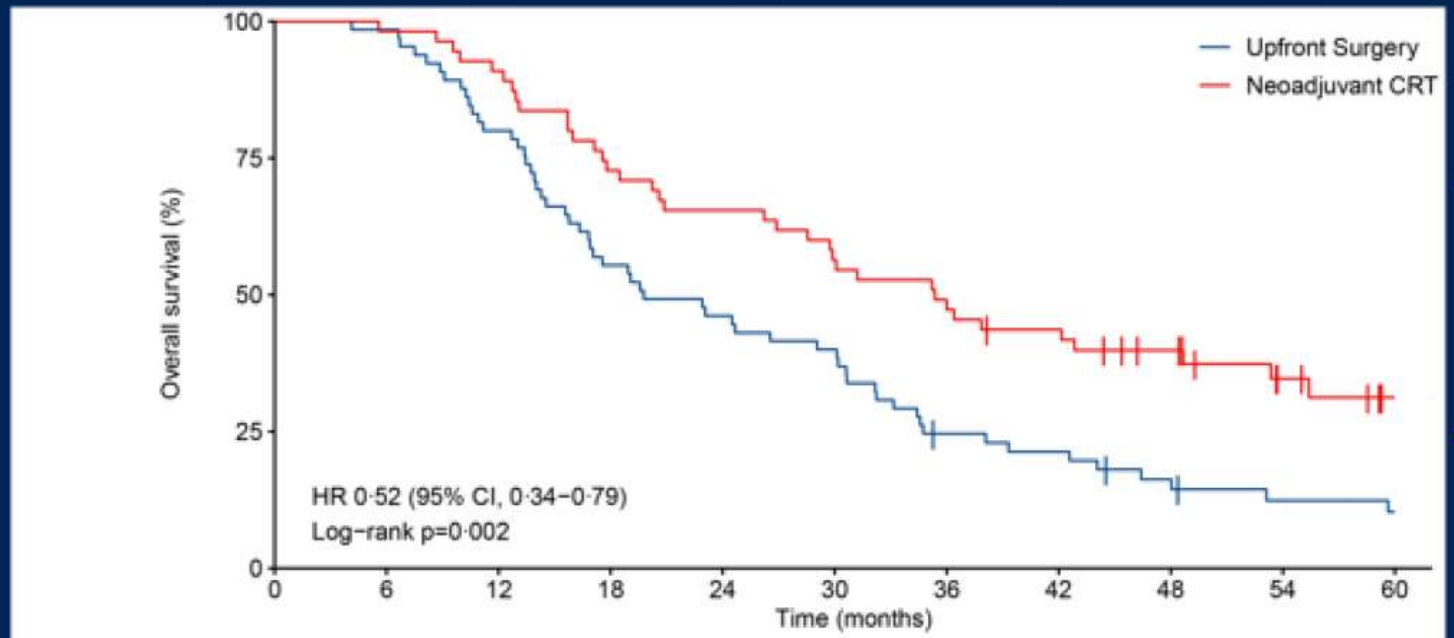
Median overall survival:
Upfront surgery: 17.3 mo
Neoadjuvant CRT: 33.7 mo

5-year survival:
Upfront surgery: 8.4%
Neoadjuvant CRT: 33.9%

Casper Van Eijck et al. ASCO 2021; Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Results – Patients that started adjuvant therapy



Number at risk (number censored)

Upfront Surgery	65 (0)	64 (0)	52 (0)	36 (0)	30 (0)	26 (0)	15 (1)	13 (1)	9 (2)	6 (3)	5 (3)
Neoadjuvant CRT	55 (0)	54 (0)	50 (0)	40 (0)	36 (0)	31 (0)	27 (0)	23 (1)	18 (4)	11 (9)	6 (13)

Median overall survival:
Upfront surgery: 19.8 mo
Neoadjuvant CRT: 35.4 mo

5-year survival:
Upfront surgery: 10.3%
Neoadjuvant CRT: 31.2%

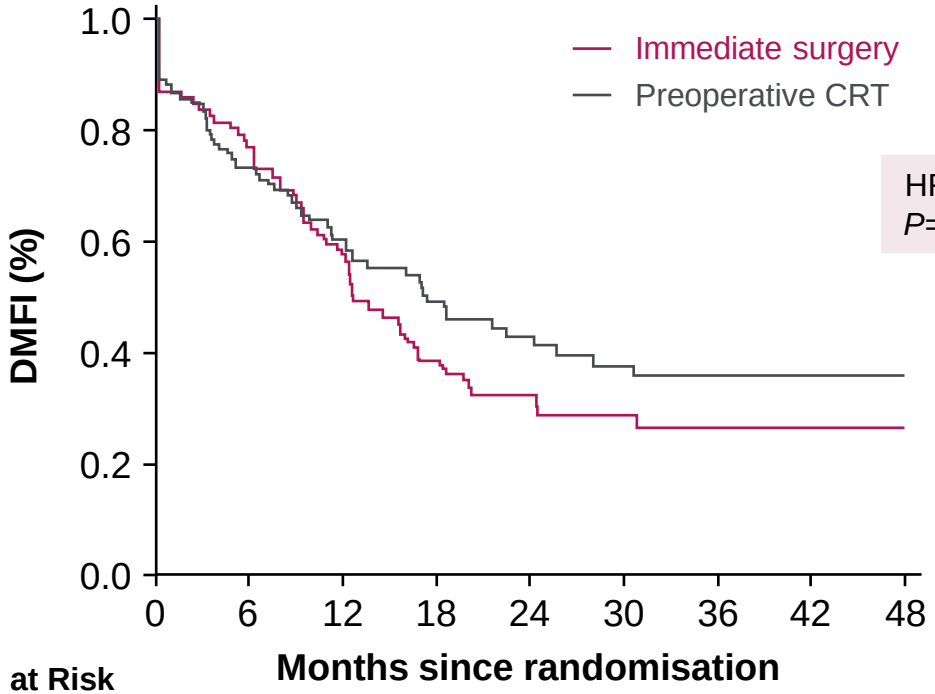
79 % vs. 81 % pac. (upfront surgery vs NAT) zahájilo adjuvantní léčbu – více než obvykle !!

Casper Van Eijck et al. ASCO 2021; Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

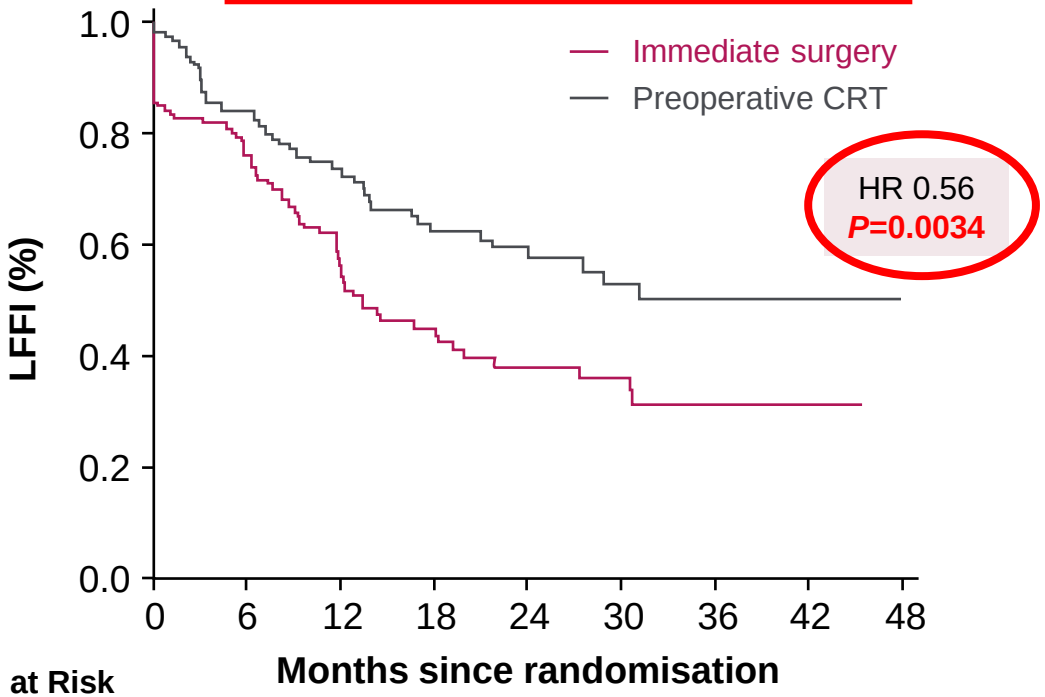
Metastases and Local Recurrence (ITT)

Distant metastases-free Interval



No. at Risk									
Immediate surgery	119	76	57	44	28	21	15	8	7
Preoperative CRT	127	87	59	34	20	14	8	3	2

Locoregional failure-free Interval

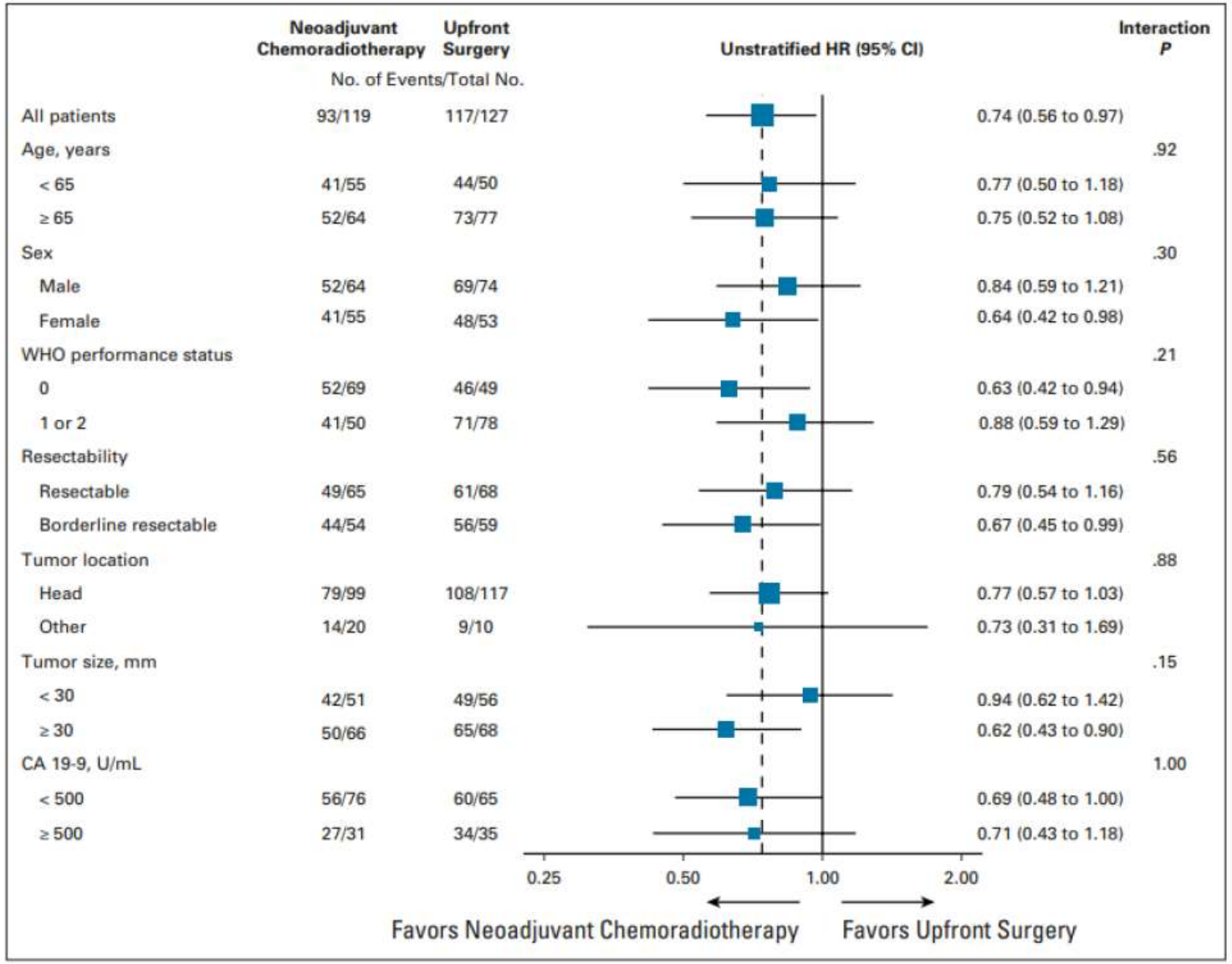


No. at Risk									
Immediate surgery	119	86	66	48	35	23	14	8	6
Preoperative CRT	127	86	53	35	22	17	9	2	1

DMFI, distance metastases-free interval; HR, hazard ratio; ITT, intent-to-treat; LFFI, locoregional failure-free interval.

Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)



Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Outcome	Resectable Pancreatic Cancer (n = 133)				Borderline Resectable Pancreatic Cancer (n = 113)			
	Preoperative CRT (n = 65)	Immediate Surgery (n = 68)	HR (95% CI)	*P*	Preoperative CRT (n = 54)	Immediate Surgery (n = 59)	HR (95% CI)	*P*
Primary								
Median OS, months	14.6	15.6	0.96 (0.64 to 1.44)	.830	17.6	13.2	0.62 (0.40 to 0.95)	.029
Secondary								
Median DMFI, months	17.0	13.5	0.93 (0.59 to 1.47)	.770	21.5	12.2	0.69 (0.42 to 1.15)	.150
	No. (%)	No. (%)	OR (95% CI)		No. (%)	No. (%)	OR (95% CI)	
Resection rate	44 of 65 (68)	54 of 68 (79)	0.54 (0.25 to 1.19)	.170	28 of 54 (52)	38 of 59 (64)	0.60 (0.28 to 1.27)	.190
R0 rate	29 of 44 (66)	32 of 54 (59)	1.33 (0.58 to 3.04)	.540	22 of 28 (79)	5 of 38 (13)	24.20 (6.57 to 89.12)	< .001
Safety								
Patients with SAEs (all grades)	35 of 65 (54)	31 of 68 (46)	1.39 (0.70 to 2.76)	.390	27 of 54 (50)	21 of 59 (36)	1.81 (0.85 to 3.85)	.130

PP, per protocol; R0, no evidence of residual tumour at resection margins.

Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

RES:

- Primárně resekabilní pacienti – bez rozdílu mezi oběma rameny
- Borderline: benefit v četnosti R0 resekcí, DFS a OS (lokální a distální rekurence)

Preoperative radiochemotherapy vs immediate surgery for **resectable and borderline resectable** pancreatic cancer (PREOPANC-1)

Pozitiva:

- **první randomizovaná studie validující neoadjuvantní strategii u lokalizovaného PDAC**

Otazníky?

- **je skutečně NAT založená na gemcitabinu novým standardem ??**

(gemcitabin v monoterapii aktuálně považován za CHT (adjuv. i neoadjuv.) pro pacienty v horším celkovém stavu)

- **jaký je přínos CH-RT ??**

DPCG
Dutch Pancreatic Cancer Group

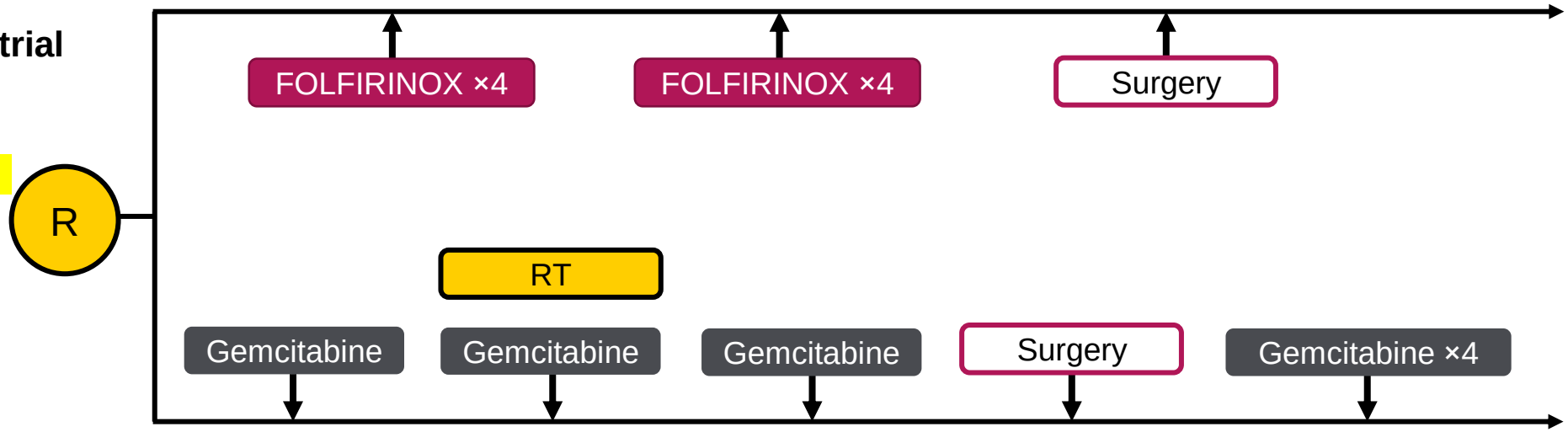
Casper Van Eijck et al. ASCO 2021; Versteijine E, et al. J Clin Oncol. 2020; 38:1763–73.

PREOPANC-2 trial

Phase 3 randomised controlled multicentre trial

Key inclusion criteria:
(Borderline) resectable pancreatic cancer
WHO PS 0–1

352/369 accrual
Primary objective: OS

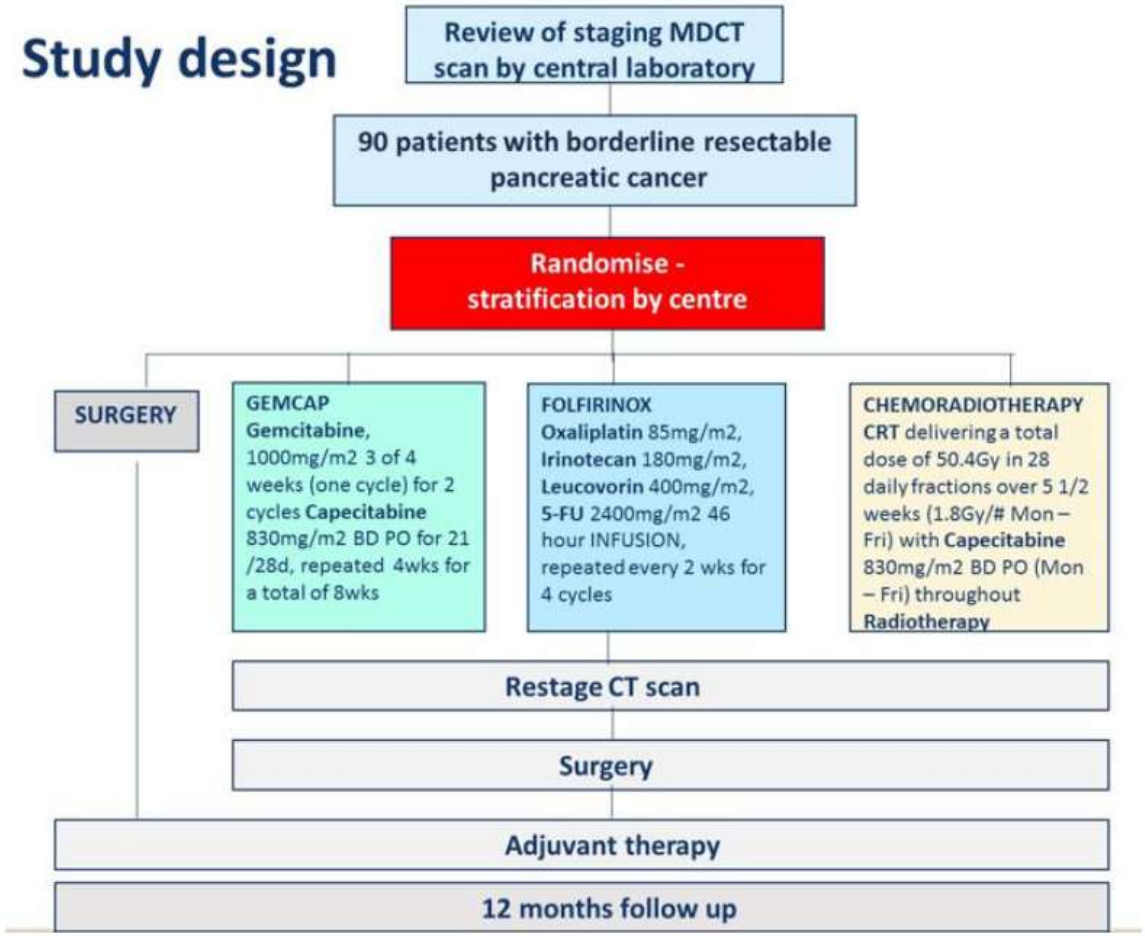


DPCG
Dutch Pancreatic Cancer Group

OS, overall survival; PS, performance status; RT, radiotherapy; WHO, world health organisation.

NTR7292; available at https://www.trialregister.nl/trial/7094.

ESPAC-5F - jaká je nejlepší léčba pro BRPC ??



Primary objective:
-Recruitment Rate
-Resection Rate (R1+R0)

	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%)	

	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%)	

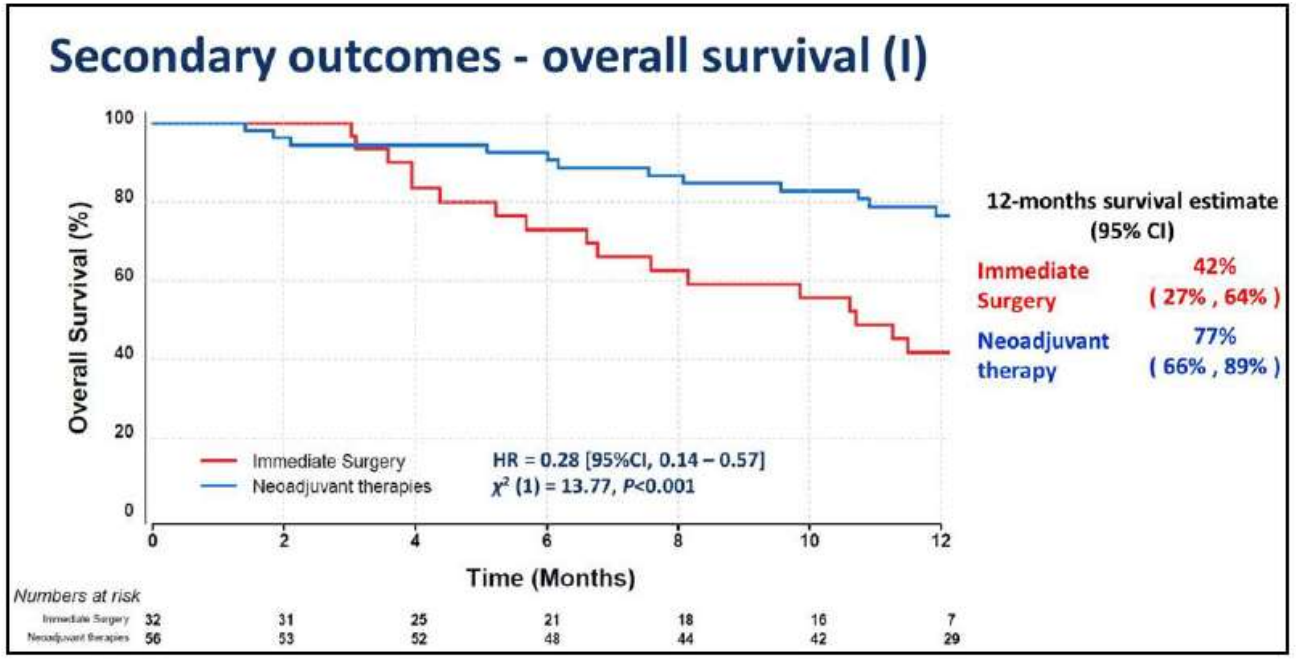
*R0+R1** R0

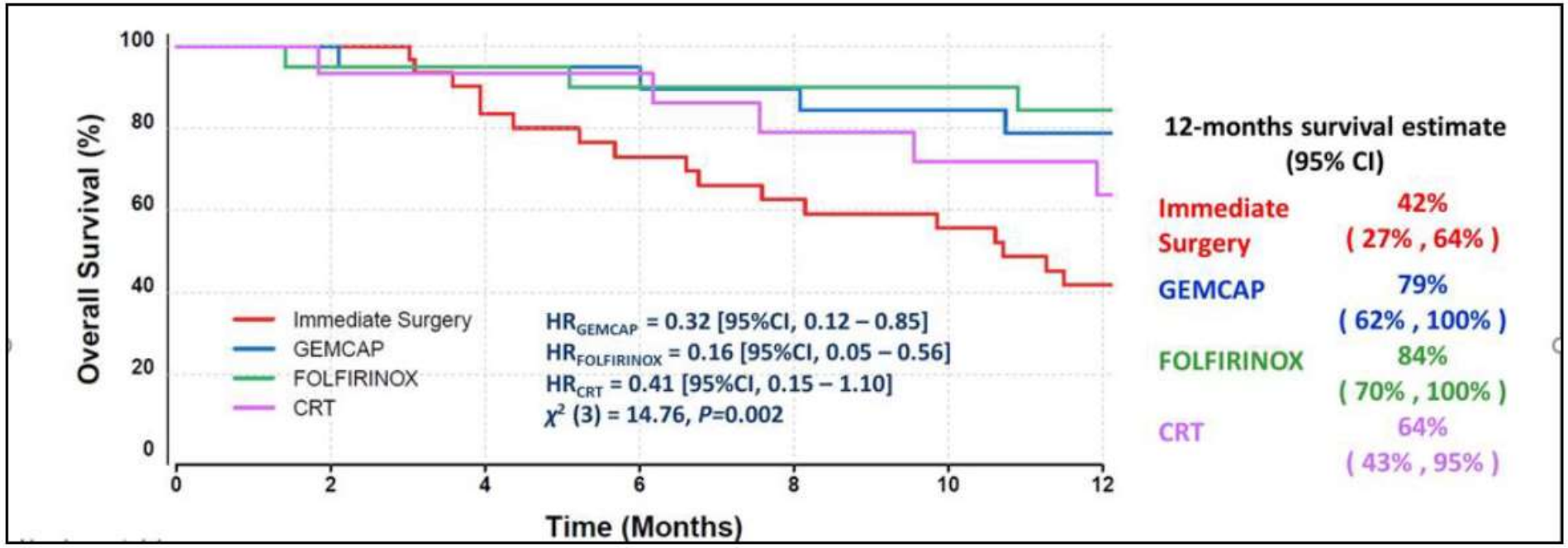
N 32, 20, 20, 16

- jen pacienti s BRPC

Ghaneh P et al. ASCO 2020

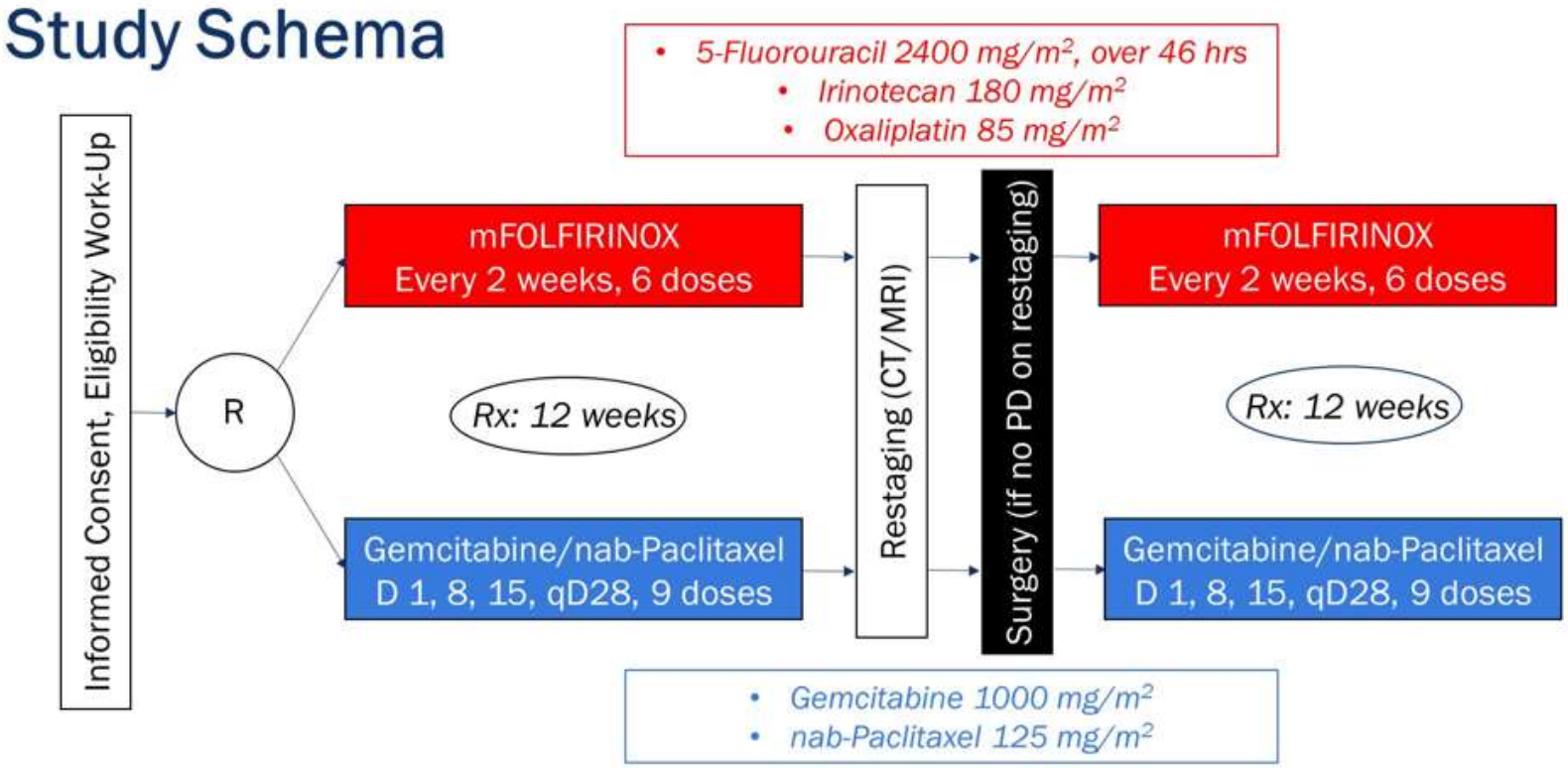
Nejlepší léčba pro BRPC ?? - studie ESPAC-5F





Ghaneh P et al. ASCO 2020

SWOG1505: Results of perioperative chemotherapy with mFOLFIRINOX versus gemcitabine/nab-paclitaxel for **resectable** pancreatic ductal adenocarcinoma



Inclusion criteria:
- no interface w/celiac, common hepatic, or superior mesenteric arteries
- <180º interface w/ portal and superior mesenteric veins

Primary objective 2y-OS

CT, computed tomography; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; R, randomised; Rx, treatment.

Sohal D et al . JAMA Oncol 2021 .

Perioperative chemotherapy in **resectable** disease: **SWOG1505 trial**

2Y OS

	mFOLFIRINOX (N=40)	Gem/nab-P (N=33)
R0 Resection	34 (85%)	28 (85%)
Complete or Major Pathologic Response	10 (25%)	14 (42%)
Total Nodes Resected, median (range)	19 (1-56)	18 (3-45)
Node Negative Resection	16 (40%)	15 (45%)
Disease-Free Survival after Resection	10.9 mths	14.2 mths

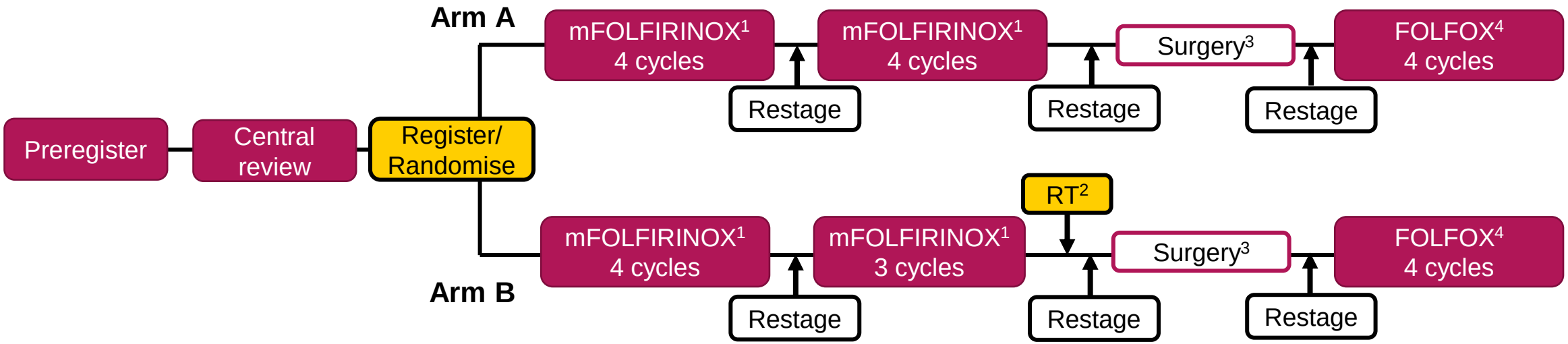
Perioperative mFOLFIRINOX and Gem/nab-P appear to have similar efficacy with acceptable safety and resectability rates

Sohal D et al . JAMA Oncol 2021 .

ROLE RADIOTERAPIE V PŘEDOPERAČNÍ LÉČBĚ BRPC ??

Alliance A0121501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy for **borderline resectable** adenocarcinoma of the pancreas

Patients with borderline resectable PDAC*
Primary objective: **18 month OS rate**
Quality control: Imaging, RT, surgery, pathology



*Intergroup definition. 1. Oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, infusional 5-fluorouracil 2400 mg/m^2 over 46 hours;
2. **Stereotactic Body RT, 33–40 Gy in 5 fractions or hypofractionated image guided RT, 25 Gy in 5 fractions**;
3. Segmental pancreatectomy with regional lymphadenectomy ± vascular resection;
4. Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and infusional 5-fluorouracil 2400 mg/m^2 over 46 h.
OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; RT, radiotherapy.

Katz et al, presented in 2021 ASCO-GI meeting.

Alliance A0121501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy for **borderline resectable** adenocarcinoma of the pancreas

Arm A: mFOLFIRINOX (n=70)

18 month OS rate (KM): 66.4%

EFS: 15.0 months
Resection rate: 49%
pCR rate: 0%
Preoperative grade ≥3 AE rate: 57%

Efficacious ✓

Arm B: mFOLFIRINOX → RT (n=56)

18 month OS rate (KM): 47.3%

EFS: 10.2 months
Resection rate: 35%
pCR rate: 11%
Preoperative grade ≥3 AE rate: 64%

Did not meet requirements to conclude efficacy ✗

AE, adverse event; EFS, event-free survival; KM, Kaplan Meier; OS, overall survival; pCR, pathological complete response; RT, radiotherapy.

Katz et al, presented in 2021 ASCO-GI meeting.

Preoperative radiochemotherapy

Retrospective analysis of prospective consecutive surgical BR or LA PAC patients after induction FLX in 23 French centers between November 2010 and December 2015, treated with or without preoperative additional CRT (FLX vs FLX + CRT groups)

Ann Surg Oncol (2019) 26:109–117
https://doi.org/10.1245/s10434-018-6931-6

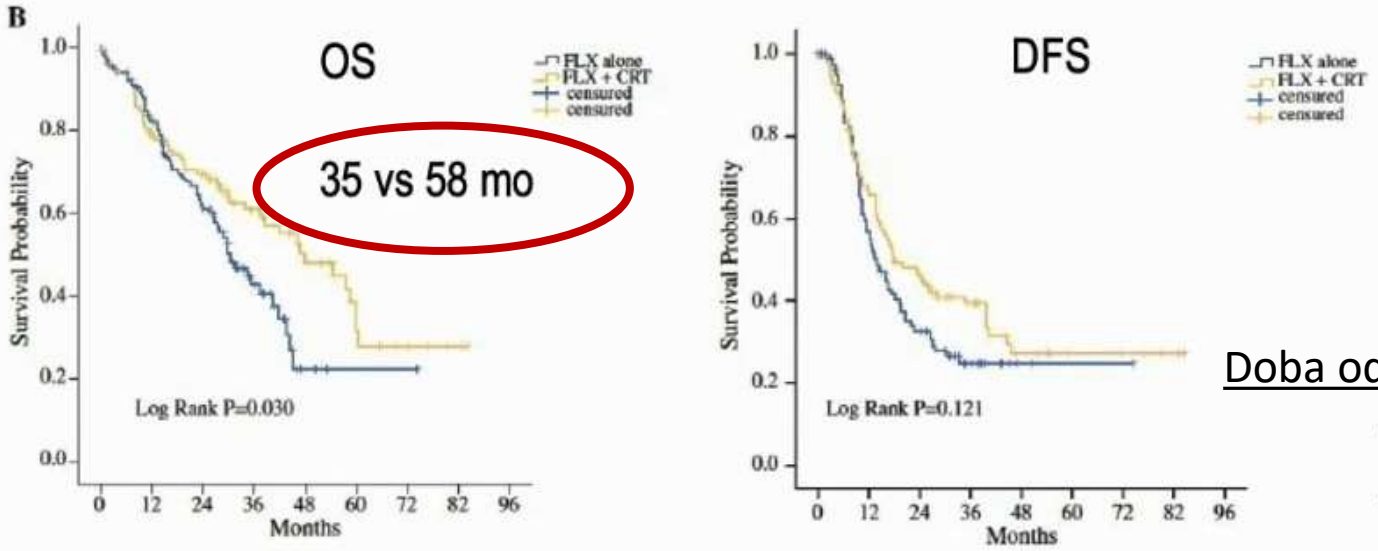
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – PANCREATIC TUMORS

How Does Chemoradiotherapy Following Induction FOLFIRINOX Improve the Results in Resected Borderline or Locally Advanced Pancreatic Adenocarcinoma? An AGEO-FRENCH Multicentric Cohort

Daniel Pietrasz, MD[1,2], Olivier Turrini, MD, PhD[3], Véronique Vendrely, MD[4], Jean-Marc Simon, MD[5], Olivia Hentic, MD[6], Romain Coriat, MD, PhD[7], Fabienne Portales, MD[8], Bertrand Le Roy, MD[9], Julien Taieb, MD, PhD[10], Nicolas Regenet, MD[11], Diane Goere, MD, PhD[12], Pascal Artru, MD[13], Jean-Christophe Vaillant, MD, PhD[2], Florence Huguet, MD, PhD[14], Christophe Laurent, MD, PhD[15], Alain Sauvanet, MD, PhD[16], Jean-Robert Delpero, MD[3], Jean Baptiste Bachet, MD, PhD[17], and Antonio Sa Cunha, MD, PhD[1]



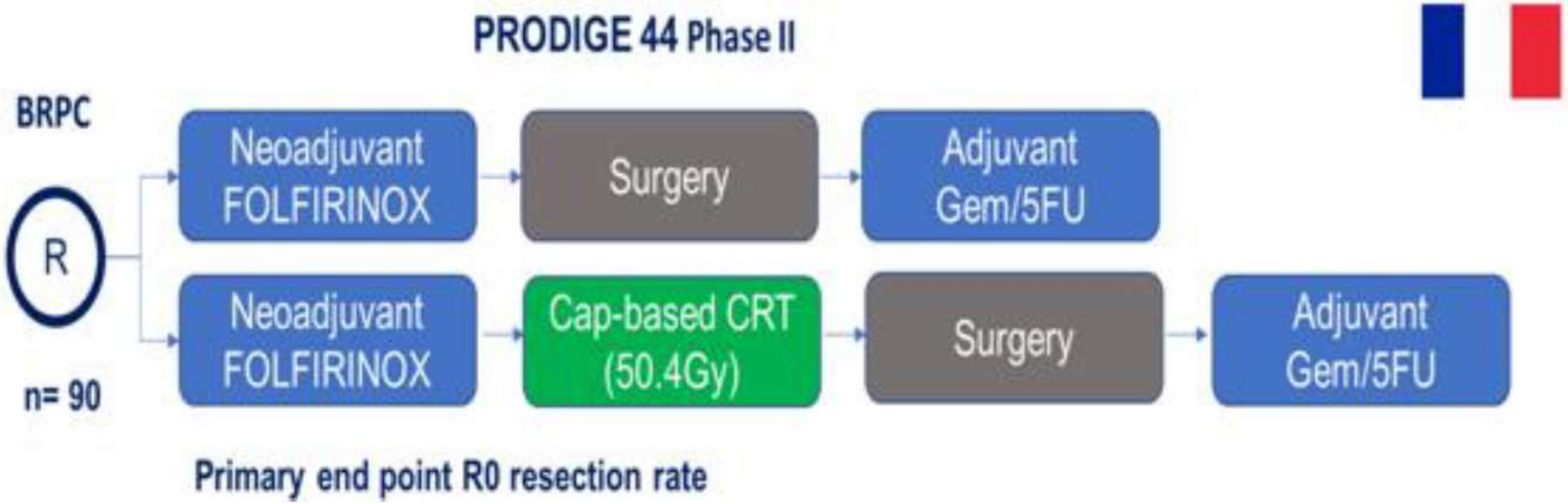
	FLX	FLX + RCT	p
Résection R0	76%	89%	0,017
ypN0	48%	76%	<0,001
Réponse pathologique majeure	13%	33%	0,001
Rechute locorégionale	51%	28%	0,004
SG médiane	35,5 mois	57,8 mois	0,007

- **N=203 patients (106 BR, 97 LA)**
- **FOLFIRINOX (n=101) ± RCT (n=102)**

Doba od dg po operaci:

- FOLFIRINOX : **5,4** mo (3,0-16,6)
- FOLFIRINOX + RCT : **8,7** mo (4,5-20,8)

Neoadjuvant FOLFIRINOX with or without Preoperative Concomitant Chemoradiotherapy in Patients With Borderline Resectable Pancreatic Carcinoma (PANDAS-PRODIGE 44) – phase II



NCT02676349

ongoing

Katz et al, presented in 2021 ASCO-GI meeting.

EXISTUJÍ BIOMARKERY VYUŽITELNÉ V LÉČBĚ LOKALIZOVANÉHO PDAC ??

DDR Mutations in Pancreatic Cancer

JOHNS HOPKINS MEDICINE

- 17 – 25% of pancreatic adenocarcinomas harbor mutations in the DDR genes
  - DNA damage response and repair (DDR) mutations
  - *BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51*, and others

- **5-7 % jsou germinální BRCA mutace**

KYT Dataset (16.5% DDR)

Gene	n, % (N = 616)
ATM	28 (4.5)
BRCA2	18 (2.9)
SMARC4	10 (1.6)
BAP1	8 (1.3)
BRCA1	8 (1.3)
BRIP1	6 (1.0)
PALB2	5 (0.8)
CHEK2	4 (0.6)
FANCA	4 (0.6)
FANCC	3 (0.5)
RAD50	3 (0.5)
STAG2	2 (0.3)
BARD1	1 (0.2)
CHEK1	1 (0.2)
FANCG	1 (0.2)

Caris Dataset (17.4% DDR)

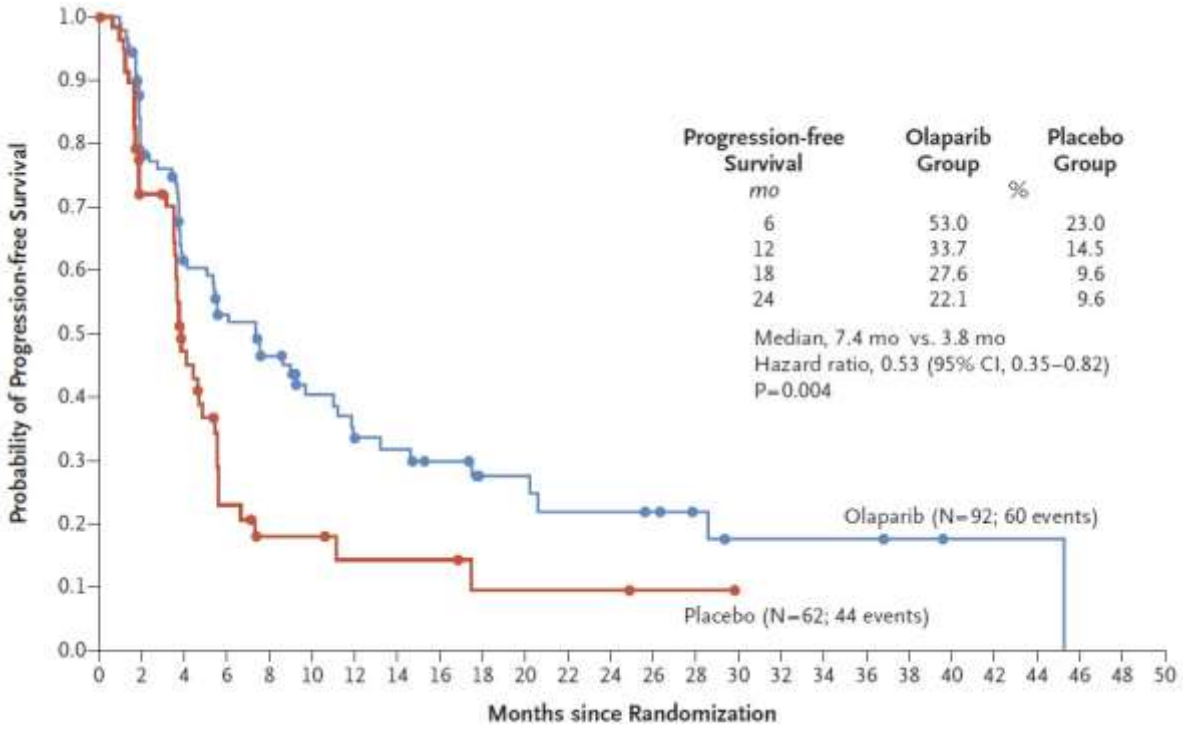
Pancreas Gene	% (N = 833)
ATM	3.60%
BRCA2	3.33%
BRCA1	1.41%
PALB2	1.20%
CHEK2	0.60%
BAP1	0.48%
BRIP1	0.48%
NBN	0.12%
WRN	0.12%
ATRX	0%
BLM	0%
FANCC	0%
MRE11A	0%
RAD50	0%
ARID1A	5.54%

Pishvaian, et al, Clinical Cancer Research, 2018; Heeke, et al, JCO Precision Oncology, 2018; Aguirre, et al, Cancer Discovery, 2018; Witkiewicz, et al, Nat Commun, 2015; Lowery, et al, Clinical Cancer Research, 2017; Waddell, et al, Nature, 2015; Bailey, et al, Nature, 2016; Biankin, et al, Nature, 2012; Collisson, et al, Nat Med, 2011

Mutace BRCA1/2:

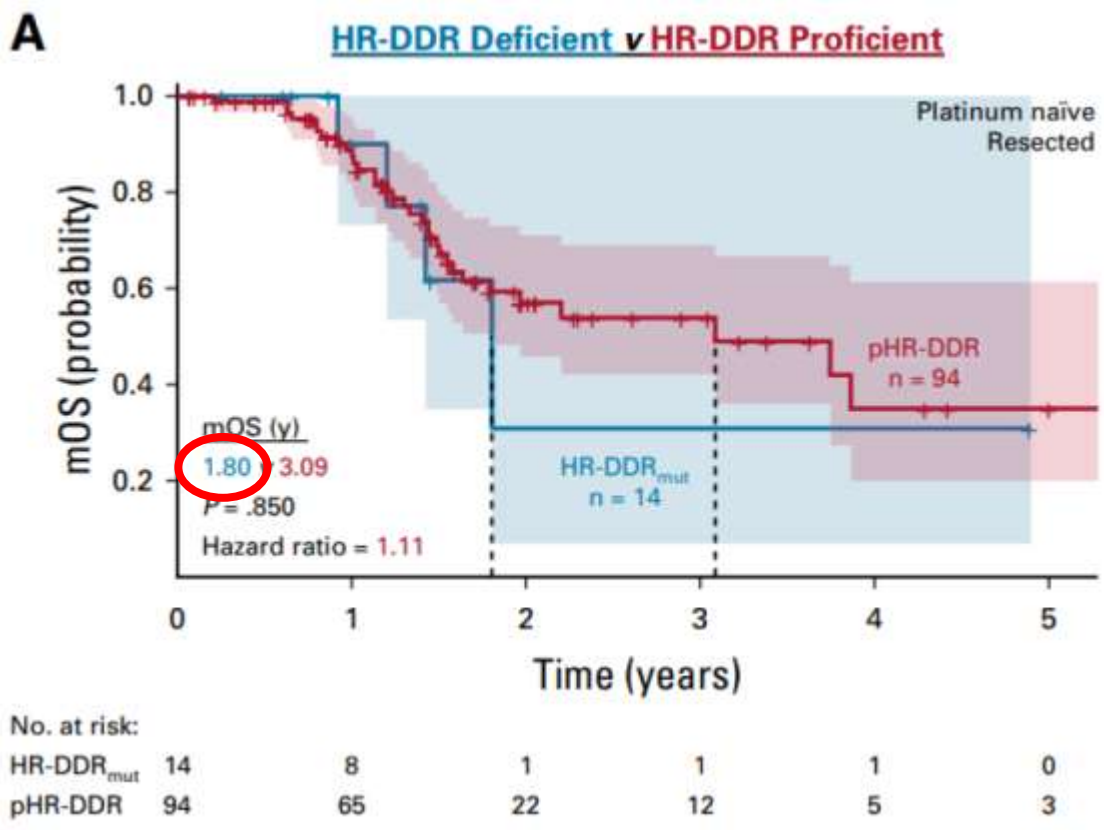
Pacienti s **germinální mutací v nádorově supresorovém genu BRCA1 nebo 2 (5-7 %)**

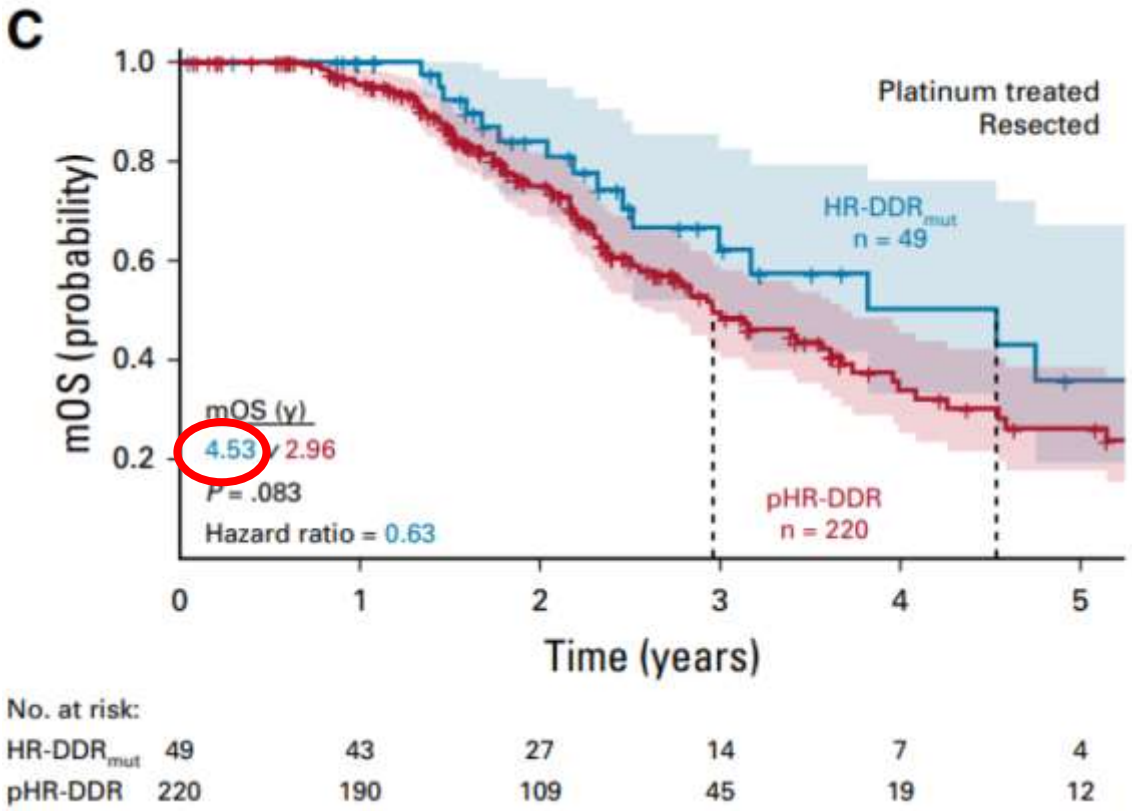
- predispozice ke vzniku ca **prsu, ovaria a pankreatu**
- efektivita režimů na bázi **platiny** a **PARP inhibitorů**
- po min. 4 měsících CHT mFOLFIRINOX přechod na udržovací terapii PARP inhibitorem **olaparibem**
- zdvojnásobení času do progrese onemocnění (z **3,8** na **7,4** měsíců) - studie POLO



Golan et al. NEJM 2019; 381 (4): 317-327.

Prediktivní biomarkery u BRPC ovlivňující léčebná rozhodnutí - DDR





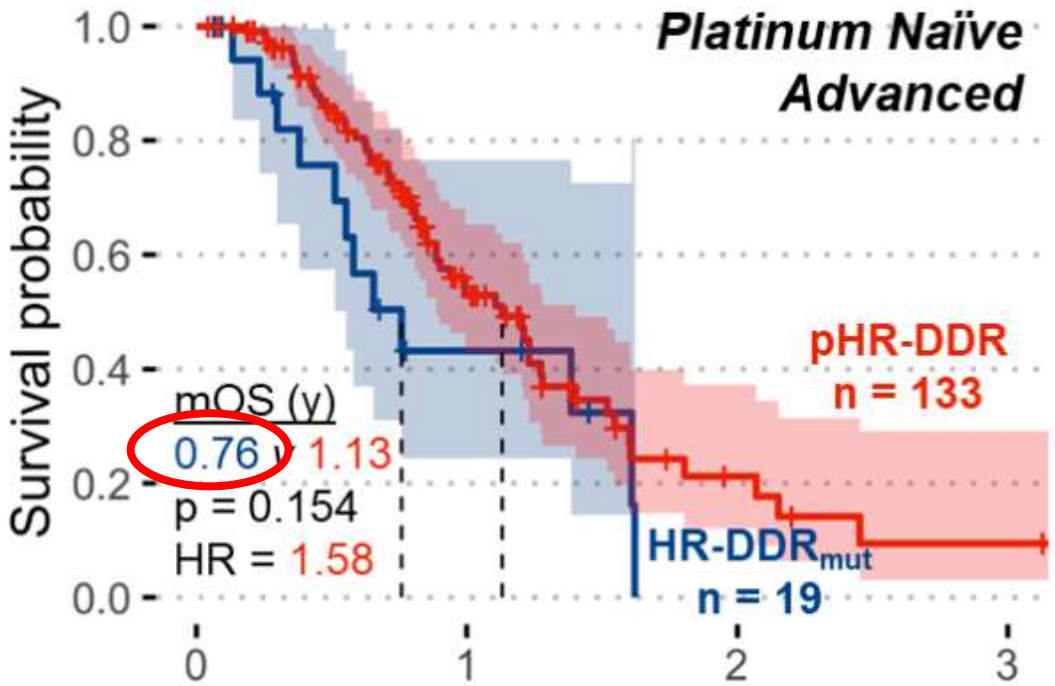
- **resekabilní onemocnění**
- **retrospektivní data**

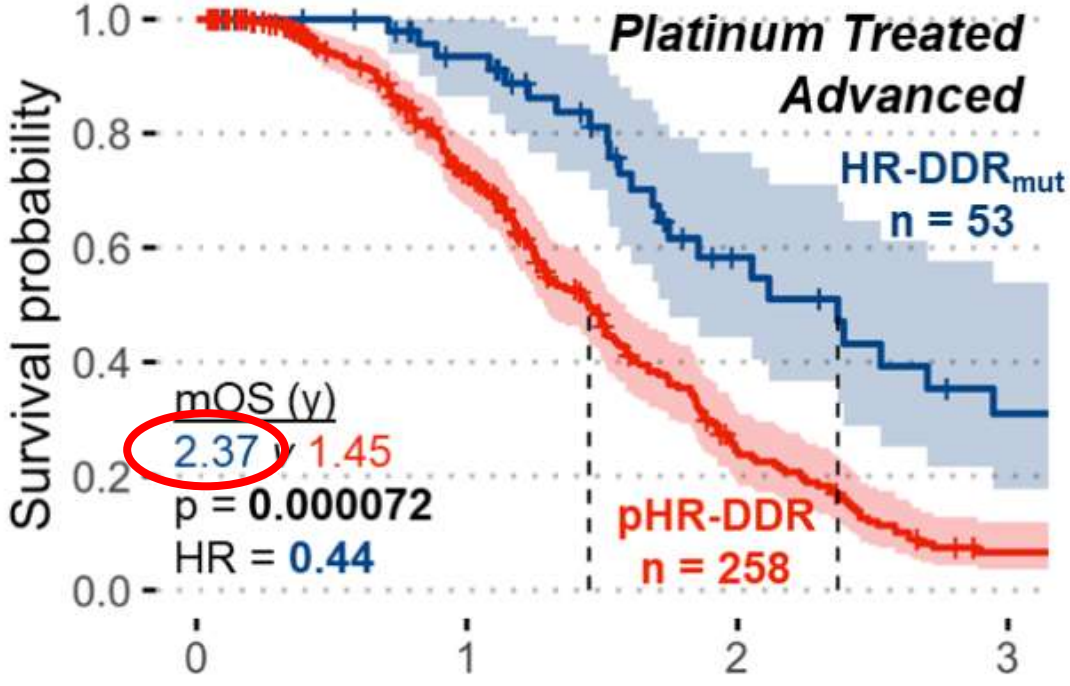
Pishvaian JCO Precis Oncol 2019

DDR Mutated Pancreatic Cancers Should be Treated with Platinums

JOHNS HOPKINS MEDICINE

- For patients with DDR mutated tumors, treatment with platinum-based Tx improves OS
  - One YEAR improvement in overall survival compared to DDR proficient patients
  - More than one year improvement compared to NON-platinum-based therapy
- 50% of patients with pancreatic adenocarcinomas are treated with NON-platinum-based chemo
  - It is critical to know who these patients are as treatment decisions are made





Pishvaian, et al, JCO Precision Oncology, October, 2019

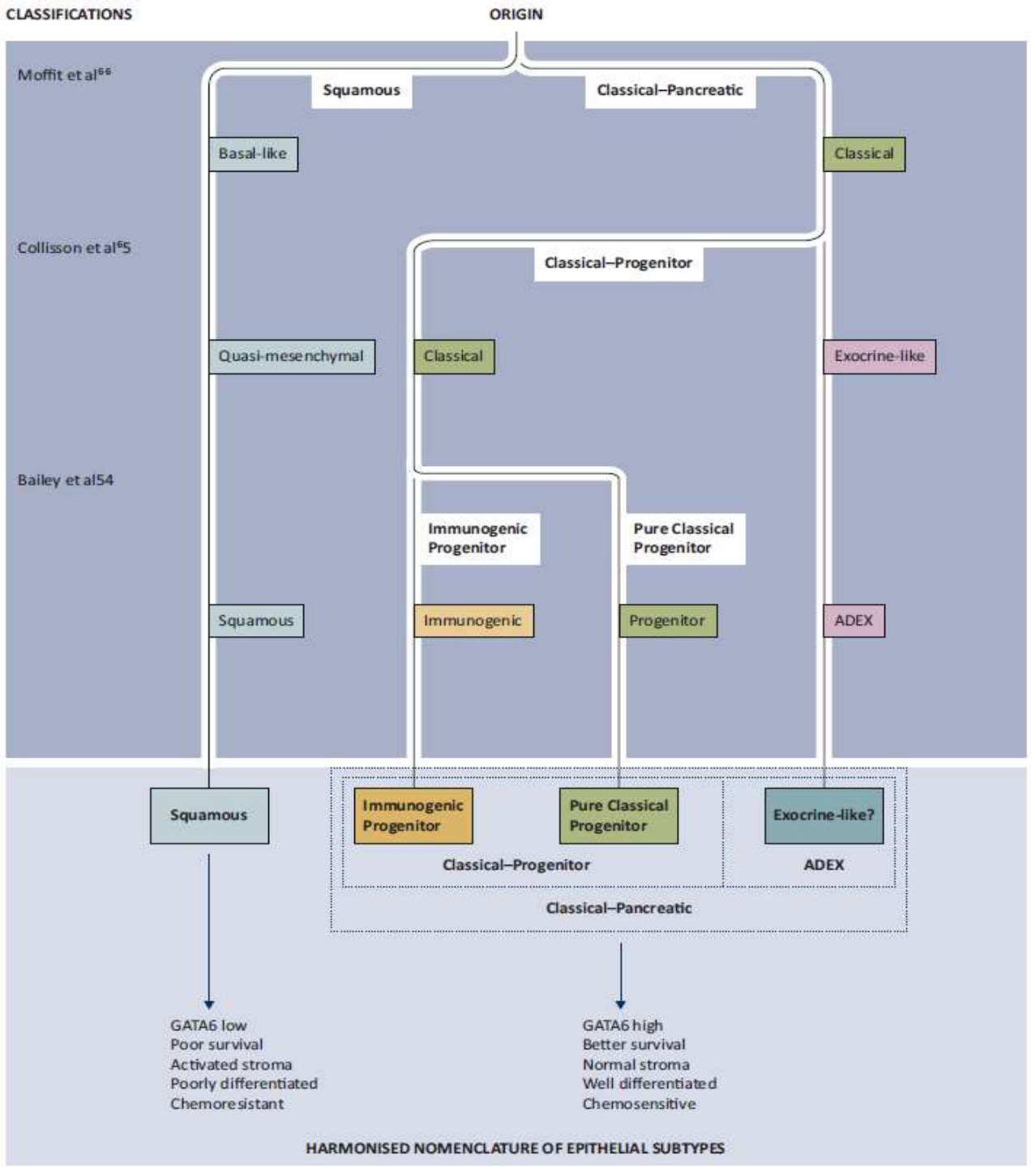
Syntézou rozdílných klasifikací identifikovány **2 základní klinicky relevantní podtypy KP:**

1/ skvamózní (basal-like, quasi-mesenchymal)
– high grade nádory s většinou meta onem., aktivovaným stromatem, rezistencí k CHT a špatnou prognózou.

2/ klasický - prognosticky **příznivější** onem. s normálním stromatem a dobře diferencovaným, relativně chemosenzitivním nádorem.

Klinická studie **COMPASS** u pokročilých KP potvrdila u obou skupin odlišný RR (10 % u basal-like vs. 33 % u klasických KP) i medián OS (5,9 m vs. 9,3 m).

Hlavním rozlišovacím biomarkerem mezi oběma podtypy se zdá být **exprese GATA6** (nízká exprese u basal-like versus vysoká exprese u klasických KP).

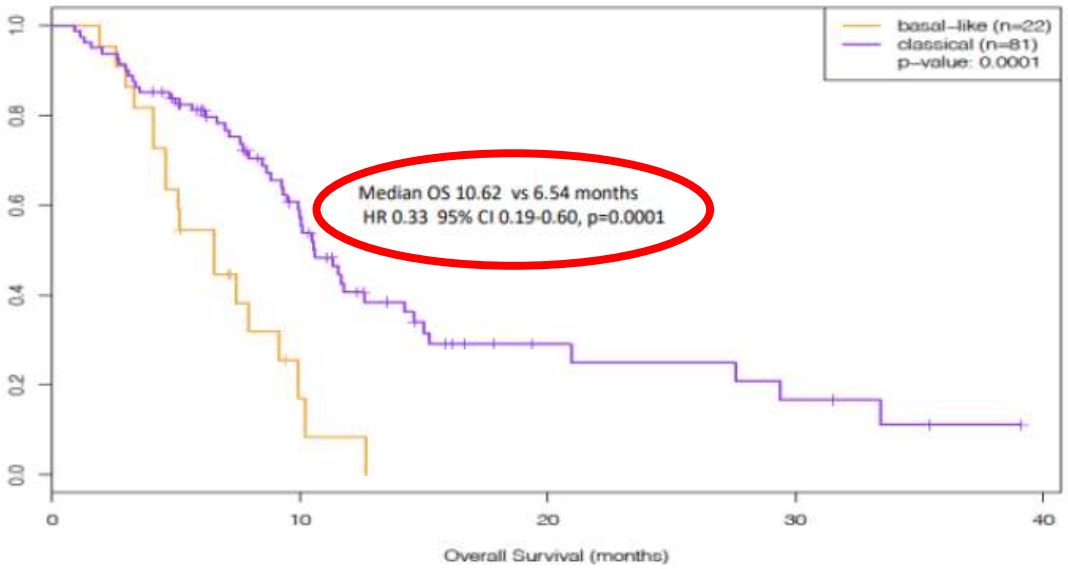


Casolino R et al. Ann Oncol. 2021 Feb;32(2):183;
O'Kane GM et al. Clin Cancer Res. 2020; 26: 4901-4910

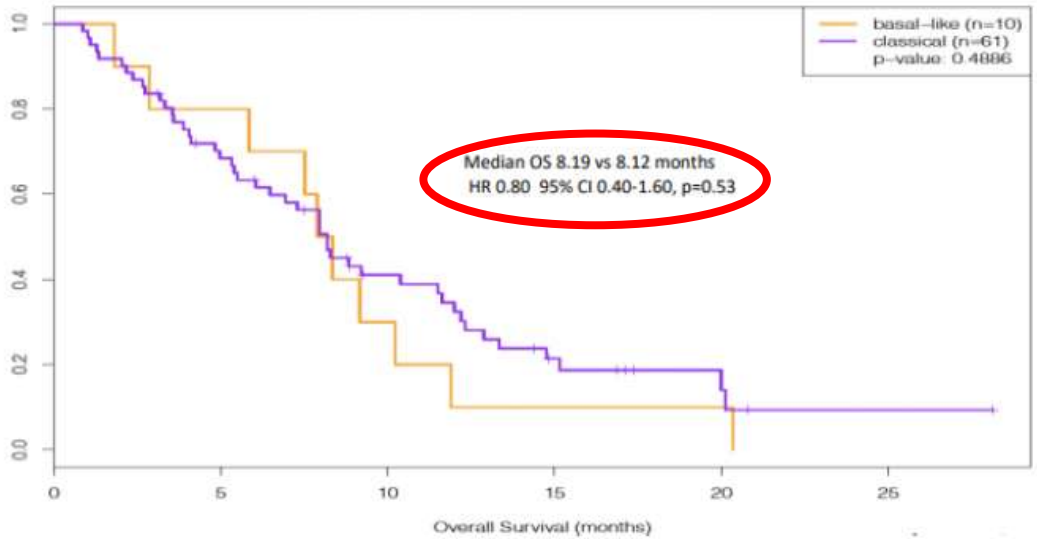
Prediktivní biomarkery u BRPC ovlivňující léčebná rozhodnutí - GATA6

- pokročilé onemocnění
- retrospektivní data

OS in patients receiving mFFX



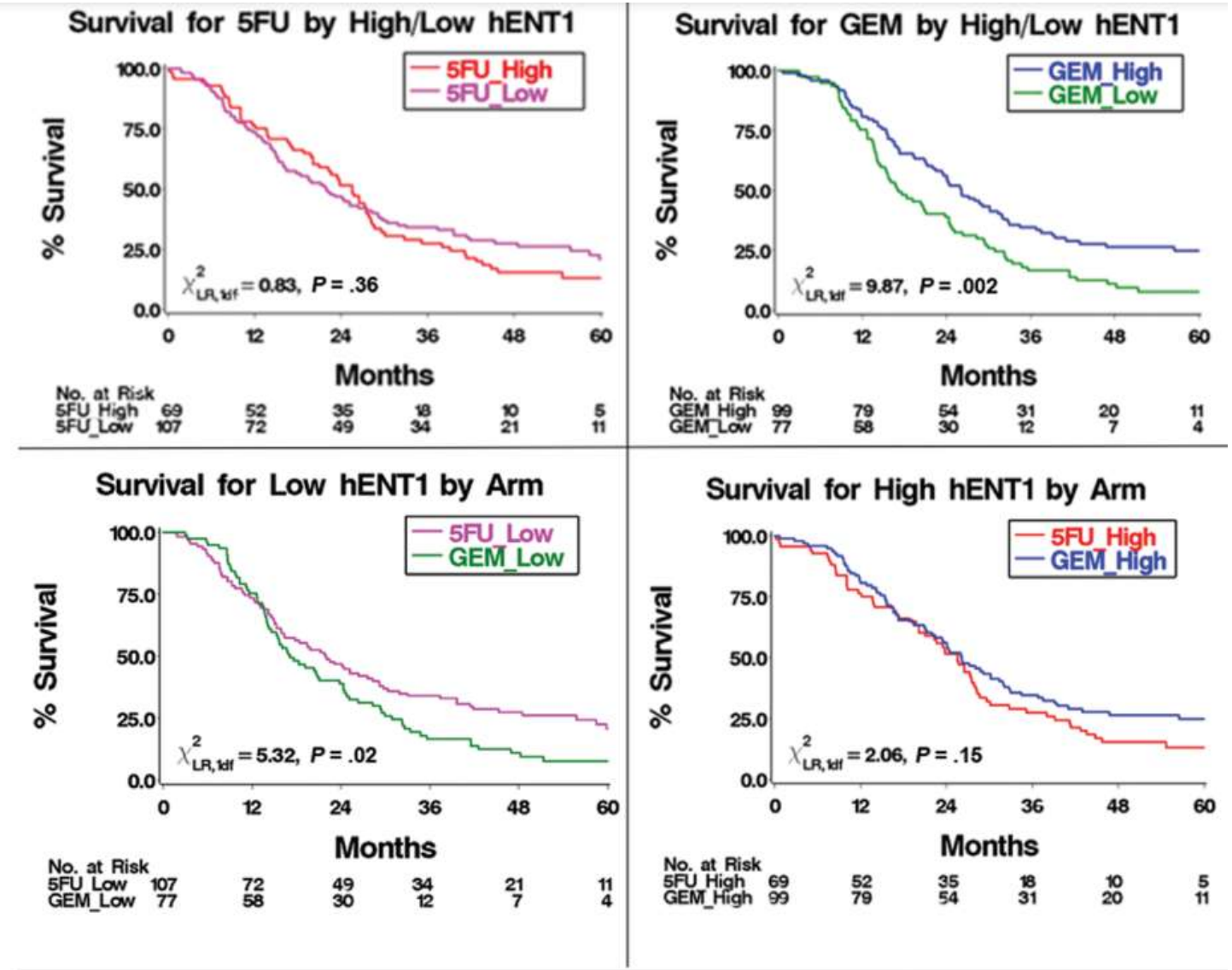
OS in patients receiving G+N



- **FFX efektivnější u klasického podtypu, bez výraznějšího rozdílu v efektivitě u basal-like**
- **rozlišení dle exprese GATA6 (přítomná u klasického podtypu PDAC)**
- studie PASS-01, NCT04469556

Aung K et al. Clin Cancer Res 2018; O´Kane G et al. Clin Cancer Res 2020

Prediktivní biomarkery u BRPC ovlivňující léčebná rozhodnutí – hENT1



Human equilibrative nucleoside transporter 1 (hENT1) levels in pancreatic adenocarcinoma may predict survival in patients who receive adjuvant gemcitabine after resection.

Median survival for patients treated with **gemcitabine** was **17.1** (95% CI = 14.3 to 23.8) months for those with **low hENT1 expression** vs **26.2** (95% CI = 21.2 to 31.4) months for those with **high hENT1 expression** ($\chi(2)_1 = 9.87$; P = .002).

For the 5-fluorouracil group, median survival was **25.6** (95% CI = 20.1 to 27.9) and **21.9** (95% CI = 16.0 to 28.3) months for those with low and high hENT1 expr.

Gemcitabine should not be used for patients with low tumor hENT1 expression.

Greenhalf W et alJ Natl Cancer Inst. 2014 Jan;106(1):djt347.

CLINICAL PRACTICE GUIDELINES

Borderline resectable disease:

treatments

Summary of recommendations
All patients with localized disease should be evaluating in MDTB meetings in expert centers
A borderline tumour is defined when one of the following criteria is present: solid tumour contact with the CA or the SMA of ≤180°, solid tumour contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity or thrombosis of the vein but allowing for vein reconstruction
Patients with BRPC have a high probability of an R1 resection and should be considered for induction treatment prior to surgery
Patients should be included in clinical trials wherever possible. If not feasible, a period of induction chemotherapy (FOLFIRINOX or gemcitabine and nab-paclitaxel), followed by chemoradiation, and then surgery appears to be the best option
Following induction therapy, unless a contra-indication exists, medically fit patients without disease progression and with a decrease in CA 19.9 should undergo surgical exploration unless contra-indication

ESMO

ESMO guidelines 2022 – in press

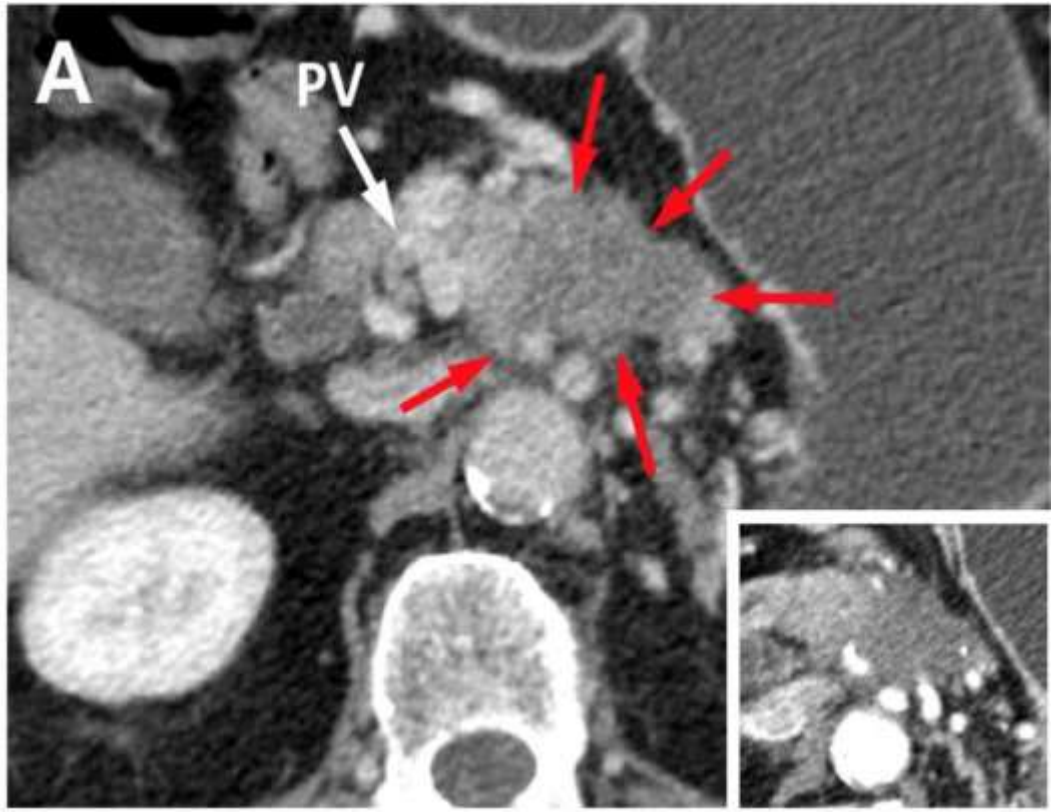
Efficacy of neoadjuvant therapy in BRPC

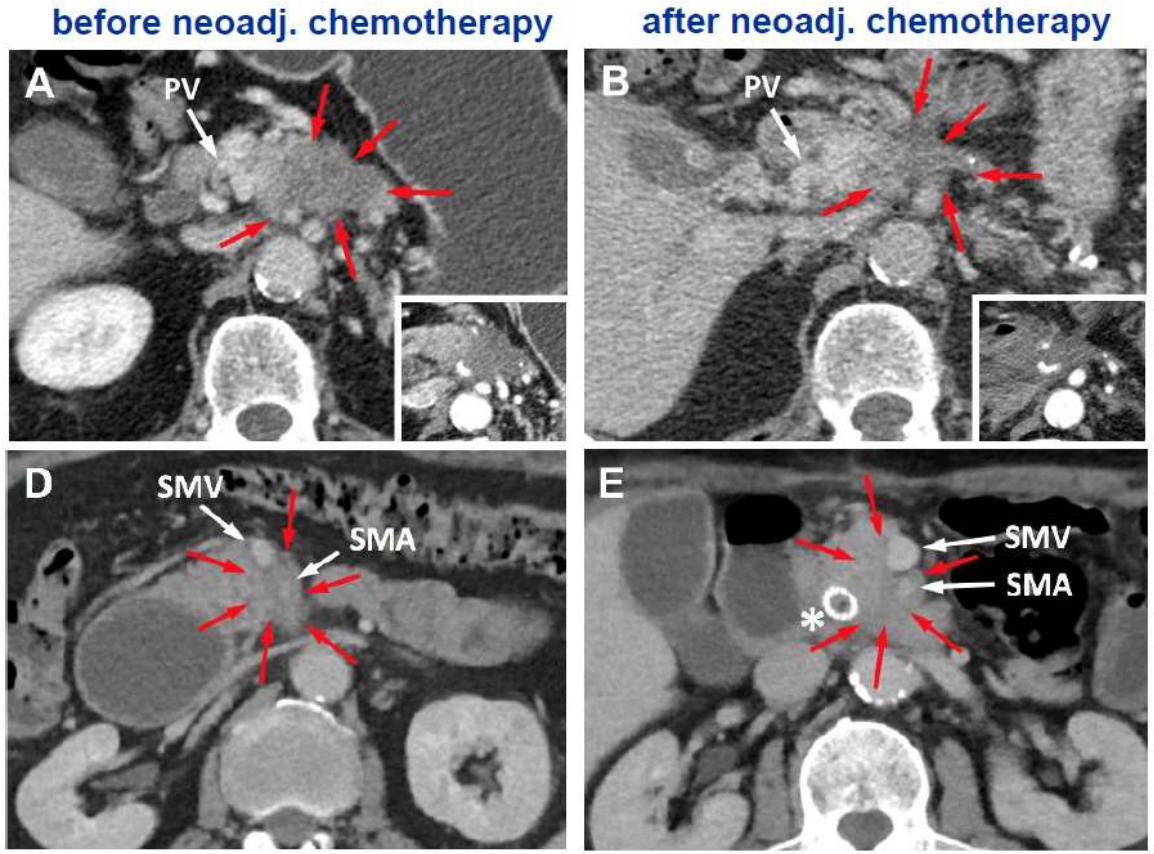
First author	Stage	Therapy	n	R0	mOS	HR
Jang 2018	BRPC	Surgery	23	26%	12 m	HR 1.495 *P* = 0.028
		CRT⇨Surgery	27	52%	21 m	
Versteijne 2021	BRPC	Surgery⇨Gem	54	8.5%	13.2 m	HR 0.67; *P* = 0.045
		CRT(gem) ⇨S⇨Gem	59	40.7%	17.3 m	
Unno 2019*	Resectable + BRPC	Surgery⇨S1	180	72%	26.7 m	HR 0.75
		Gem + S1⇨Surg⇨S1	182	77%	36.7 m	*P*= 0.015
Katz 2021*	BRPC	FFX⇨Surg ⇨Folfox	70	42%	30.0 m	-
		FFX ⇨SBRT⇨Surgery ⇨Folfox	56	25%	17.1 m	-

*ASCO abstracts

ESMO guidelines 2022 – in press

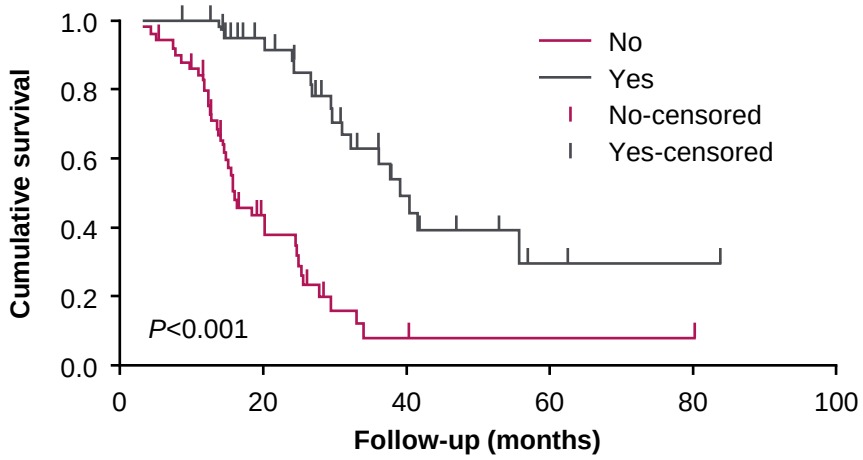
SYSTÉMOVÁ
(INDUKČNÍ / NEOADJUVANTNÍ) LÉČBA
LOKÁLNĚ POKROČILÉHO
CA PANKREATU



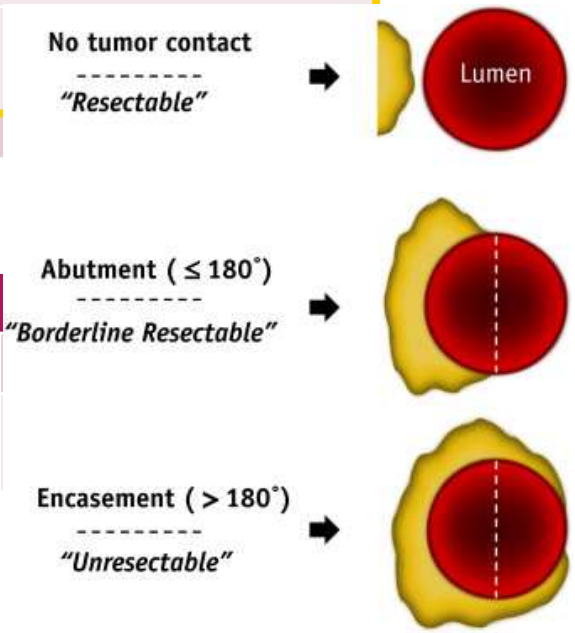


Lokálně pokročilý ca pankreatu (LAPC)

Vascular structures, any one of which, determine the stage of disease for localised PC		Borderline resectable	Locally advanced	
			Type A	Type B
Tumour-artery anatomy	SMA (usually pertains to a tumour of the head or uncinate process)	≤180° (abutment)	>180° encasement but ≤270°	>270° degree encasement
	Coeliac artery (usually pertains to a tumour of the pancreatic body)	≤180° (abutment)	>180° encasement but does not extend to the aorta and amenable to coeliac resection (with or without reconstruction)	>180° and abutment/encasement of the aorta
	HA (usually pertains to a tumour of the pancreatic neck/head)	Short segment abutment/encasement without extension to coeliac artery or HA bifurcation	>180° encasement with extension to coeliac artery and amenable to vascular reconstruction	>180° encasement with extension beyond bifurcation of proper HA into right and left hepatic arteries
Tumour-vein anatomy	SMV-PV	>50% narrowing of SMV, PV, SMV/PV with a distal and proximal target for reconstruction	Occlusion without option for reconstruction	
Traditionally considered for resection after neoadjuvant therapy		Yes	No	



Median overall survival		
Resection	Estimate	Standard error
No	**15.800**	1.770
Yes	**38.900**	2.949



CI, confidence interval; HA, hepatic artery; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PV, portal vein; SMA, super mesenteric artery; SMV, superior mesenteric vein.

Chatzizacharias NA, et al. Surgery. 2018;163(5):1053–62.

Cancer Treatment Reviews 77 (2019) 1–10

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-Tumour Treatment

Optimizing the management of locally advanced pancreatic cancer with a focus on induction chemotherapy: Expert opinion based on a review of current evidence

Thomas Seufferlein[a,*], Pascal Hammel[b], Jean Robert Delpero[c], Teresa Macarulla[d], Per Pfeiffer[e], Gerald W. Prager[f], Michele Reni[g], Massimo Falconi[h], Philip A. Philip[i], Eric Van Cutsem[j]

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[b] Hôpital Beaujon (AP-HP), Clichy, and Université Paris VII-Denis Diderot, France
[c] Aix Marseille Université, Marseille, France
[d] Vall d'Hebron University Hospital, Barcelona, Spain
[e] Odense University Hospital, Odense, Denmark
[f] Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University Vienna, Austria
[g] Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
[h] Pancreas Translational and Clinical Research Centre, San Raffaele Scientific Institute, "Vita-Salute" University, Milan, Italy
[i] Department of Oncology, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA
[j] Digestive Oncology, University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

ABSTRACT

Surgical resection of pancreatic cancer offers a chance of cure, but currently only 15–20% of patients are diagnosed with resectable disease, while 30–40% are diagnosed with non-metastatic, unresectable locally advanced pancreatic cancer (LAPC). Treatment for LAPC usually involves systemic chemotherapy, with the aim of controlling disease progression, reducing symptoms and maintaining quality of life. In a small proportion of patients with LAPC, primary chemotherapy may successfully convert unresectable tumours to resectable tumours. In this setting, primary chemotherapy is termed 'induction therapy' rather than 'neoadjuvant'. There is currently a lack of data from randomized studies to thoroughly evaluate the benefits of induction chemotherapy in LAPC, but Phase II and retrospective data have shown improved survival and high R0 resection rates. New chemotherapy regimens such as *nab*–paclitaxel + gemcitabine and FOLFIRINOX have demonstrated improvement in overall survival for metastatic disease and shown promise as neoadjuvant treatment in patients with resectable and borderline resectable disease. Prospective trials are underway to evaluate these regimens further as induction therapy in LAPC and preliminary data indicate a beneficial effect of FOLFIRINOX in this setting. Further research into optimal induction schedules is needed, as well as guidance on the patients who are most suitable for induction therapy. In this expert opinion article, a panel of surgeons, medical oncologists and gastrointestinal oncologists review the available evidence on management strategies for LAPC and provide their recommendations for patient care, with a particular focus on the use of induction chemotherapy.

REVIEW

Reshaping preoperative treatment of pancreatic cancer in the era of precision medicine

R. Casolino[1,2], C. Braconi[1], G. Malleo[3], S. Paiella[3], C. Bassi[3], M. Milella[4], S. B. Dreyer[1,5], F. E. M. Froeling[6], D. K. Chang[1,5], A. V. Biankin[1,5,7*] & T. Golan[8]

[1]Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Bearsden, Glasgow, Scotland, UK; Departments of [2]Medicine; [3]Surgery; [4]Medicine, Medical Oncology, University and Hospital Trust of Verona, Verona (VR), Italy; [5]West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow; [6]Edinburgh Cancer Centre, Western General Hospital, NHS Lothian, Edinburgh, UK; [7]South Western Sydney Clinical School, Faculty of Medicine, University of NSW, Liverpool, NSW, Australia; [8]Oncology Institute, Sheba Medical Center, Tel Hashomer, Israel

Available online 26 November 2020

This review summarises the recent evidence on preoperative therapeutic strategies in pancreatic cancer and discusses the rationale for an imminent need for a personalised therapeutic approach in non-metastatic disease. The molecular diversity of pancreatic cancer and its influence on prognosis and treatment response, combined with the failure of 'all-comer' treatments to significantly impact on patient outcomes, requires a paradigm shift towards a genomic-driven approach. This is particularly important in the preoperative, potentially curable setting, where a personalised treatment allocation has the substantial potential to reduce pancreatic cancer mortality.

Key words: Pancreatic cancer, preoperative, neoadjuvant, precision medicine, prognostic biomarkers, predictive biomarkers

Obecné principy léčby LAPC:

- neresekabilní onem. - systémová (paliativní) CHT s neoadjuvantním záměrem
- režimy **mFOLFIRINOX** nebo **gemcitabine/nab-paklitaxel**
- podání min. 3 měsíce + následné přešetření (vyloučení pacientů s rychlou progresí):
  - **progrese** - změna režimu paliativní CHT
  - **regrese** - opakované projednání na MDT a zvážení resekce
  - **stabilizace či mírná regrese** (není diseminace, ale inoperabilita trvá)

    → pokračování v systémové CHT stejným režimem (případně maintenance)

    + snaha o dosažení lokální kontroly:
      - **konkomitantní chemo-radioterapie (CHRT)**
      - **STX RT (SBRT)**

Metody k navýšení lokální kontroly:

1/ konkomitantní chemo-radioterapie (CHRT)

- tradiční postup s minimální efektivitou
- více v USA, v Evropě často zavrhovaný…
- délka cca 5 týdnů
- konkomitantně nízké dávky 5-FU nebo gemcitabinu – nedostatečné k zabránění systémové diseminace !!

Lineární urychlovač VARIAN Truebeam STX

2/ STX RT (SBRT)

- technicky náročná metoda, zatím nedostatečná evidence, nutnost zavedení **klipů do nádoru**
- krátká (**3-5 frakcí**) cílená RT na oblast tumoru
- minimální přerušení systémové léčby – snížení rizika vzdálené diseminace
- dobrá tolerance (při pečlivém naplánování a ochraně OaR jen minimum NUL)
- signifikantní snížení četnosti lokálního relapsu onem.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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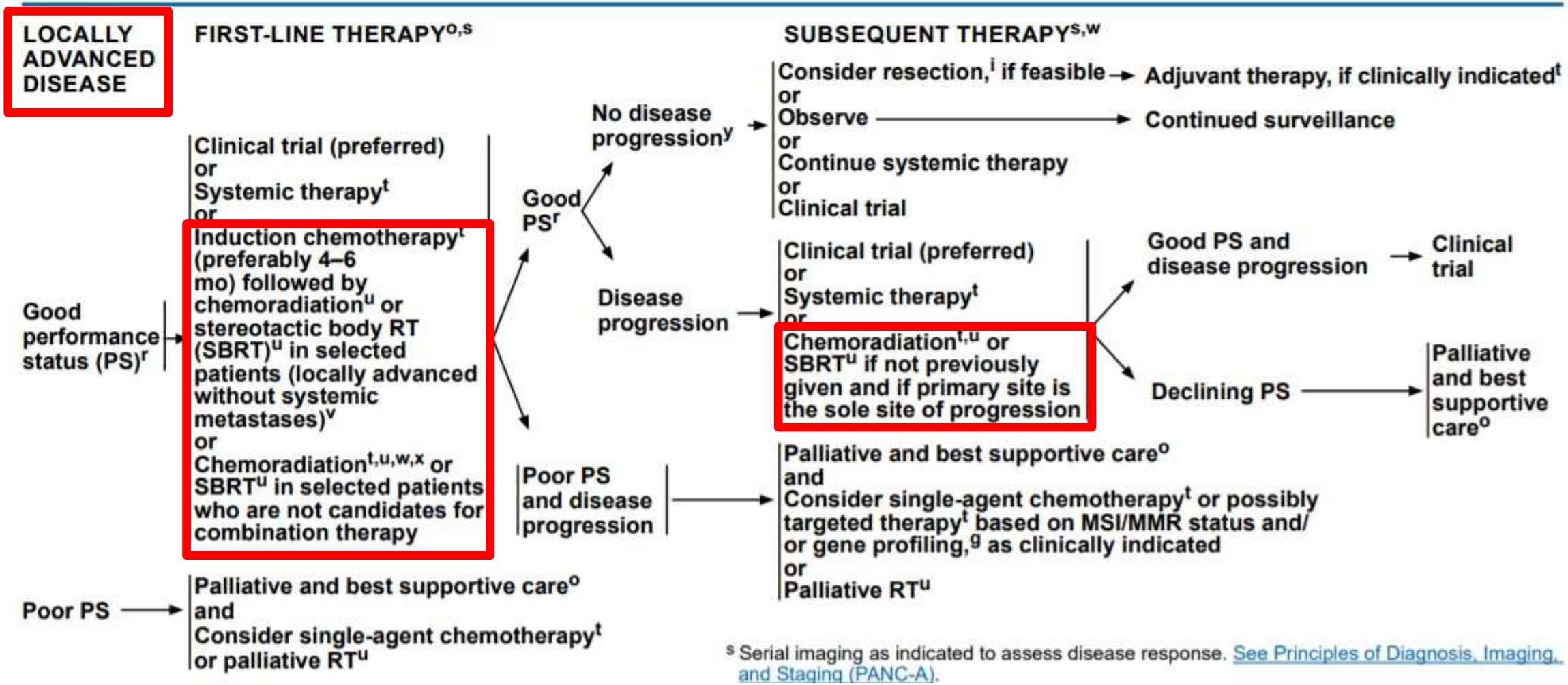
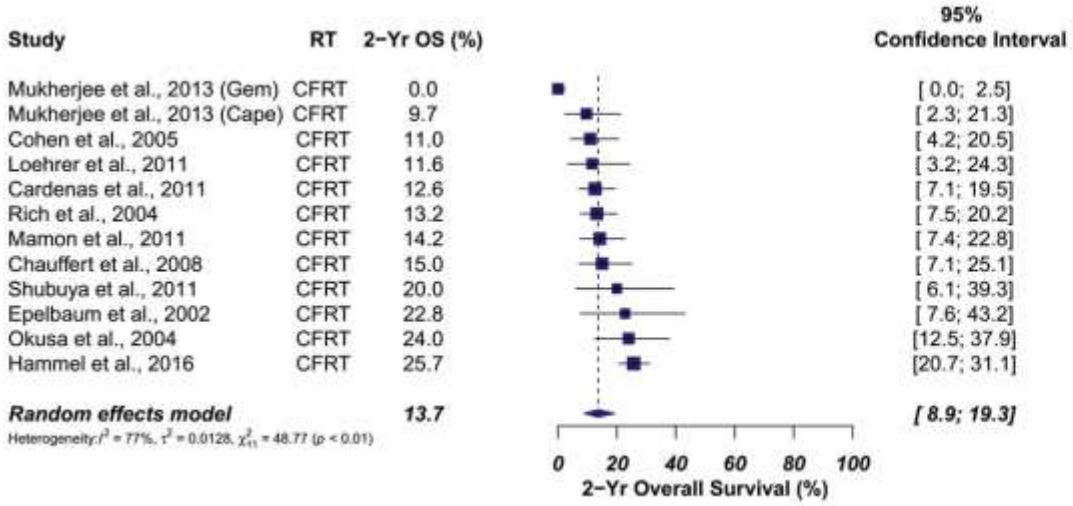
Discussion

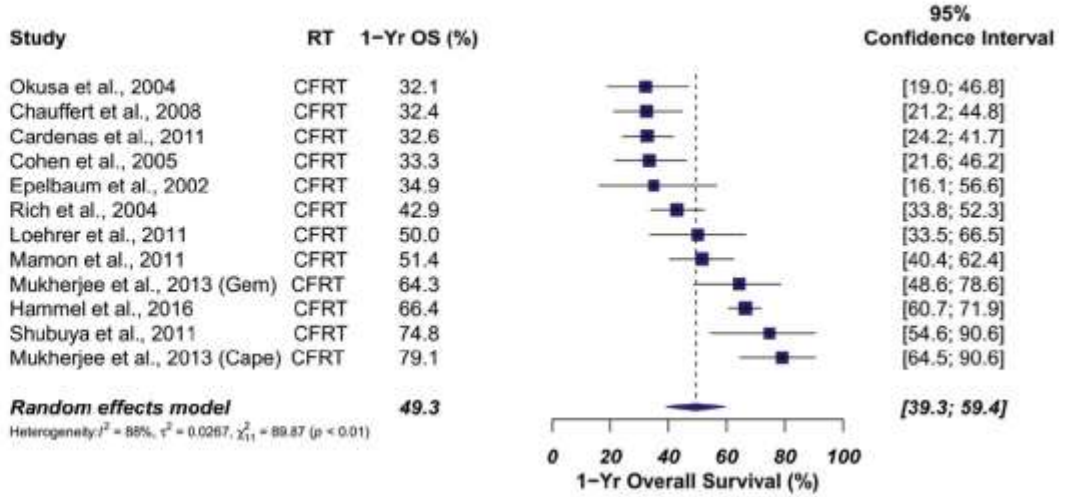


[s] Serial imaging as indicated to assess disease response. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

Recentní (2020) metaanalýza porovnávající 9 studií se SBRT vs 11 studií s CHRT:

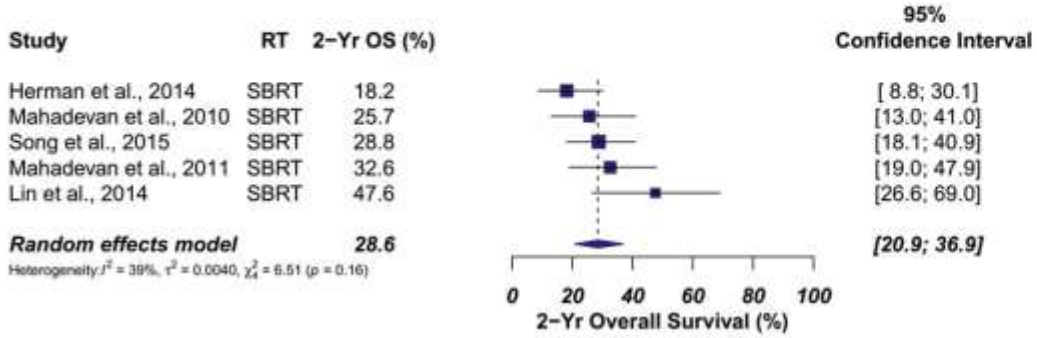
- u SBRT nejčastější LD 5x6Gy (méně než je doporučováno v MOU), u CHRT obvyklé dávky 45-50Gy á 1,8-2Gy
- **2y-OS významně vyšší při léčbě SBRT (28,6 % vs 13,7 %**, p=0,003)

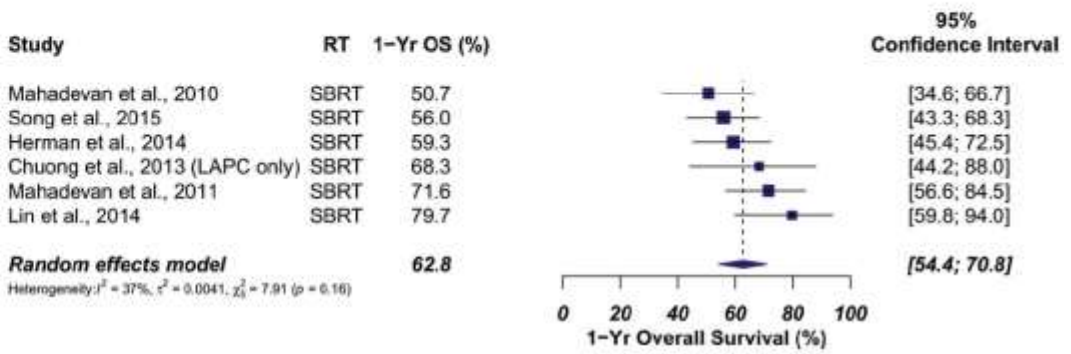




2-yr OS: 13.7% (CFRT) vs 28.6% (SBRT), p=0.003

1-yr OS: 49.3% (CFRT) vs 62.8% (SBRT), p=0.08

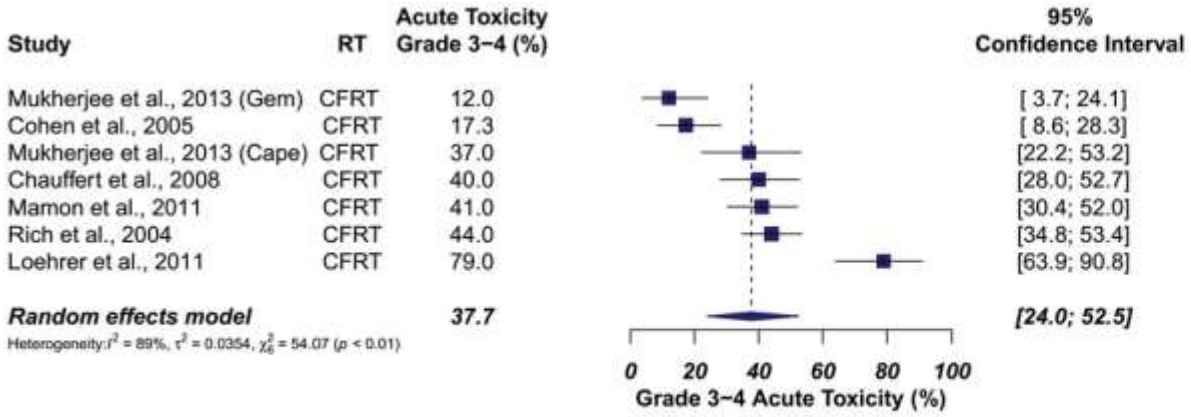


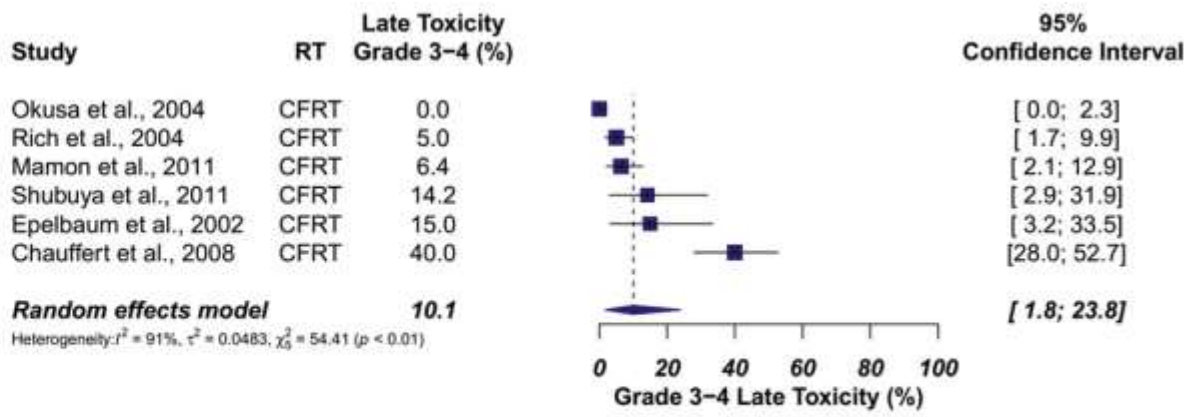


Tchelebi TL et al. Cancer 2020; 126(10):2120-2131

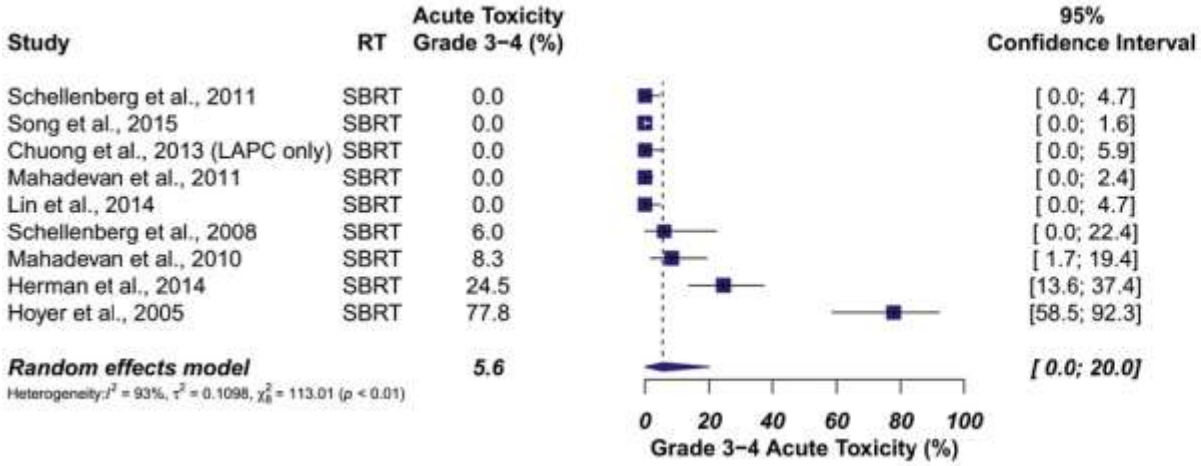
Recentní (2020) metaanalýza porovnávající 9 studií se SBRT vs 11 studií s CHRT:

- akutní toxicita u SBRT významně nižší
- rozdíl v pozdní toxicitě statisticky nesignifikantní

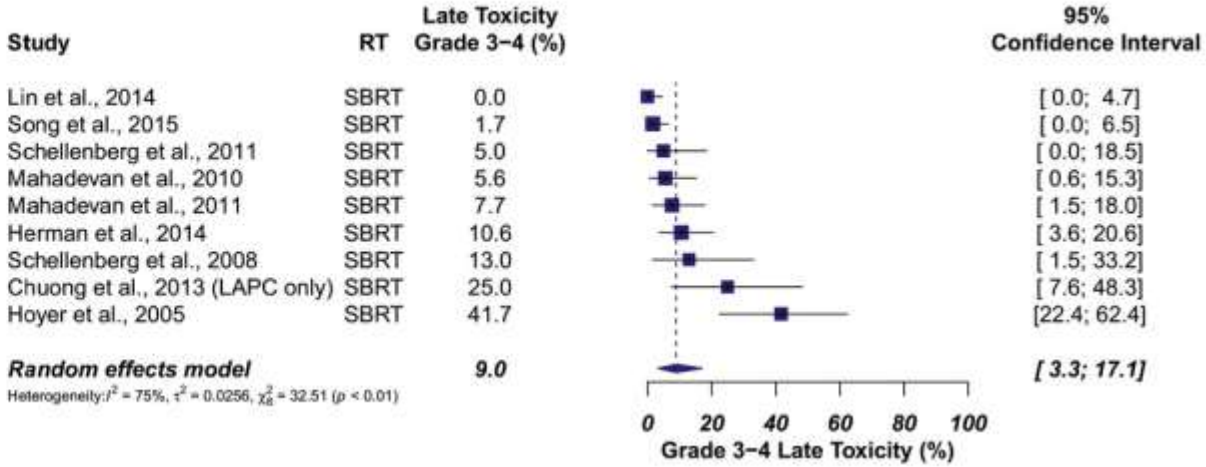




Grade 3-4 Acute Tox 37.7% (CFRT) vs 5.6 % (SBRT), p=0.013



Grade 3-4 Late Tox 10.1% (CFRT) vs 9.0 % (SBRT), p=0.85



Tchelebi TL et al. Cancer 2020; 126(10):2120-2131

Practical Radiation Oncology
Volume 9, Issue 5, September–October 2019, Pages 322-332

ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a], Devon Godfrey PhD [a], Karyn A. Goodman MD [b], Sarah Hoffe MD [c], Laura A. Dawson MD [d, e], David Dessert [f], William A. Hall MD [g], Joseph M. Herman MD, MS [h], Alok A. Khorana MD [i], Nipun Merchant MD [j], Arti Parekh MD [k], Caroline Patton MA [l], Joseph M. Pepek MD [m], Joseph K. Salama MD [a, n], Richard Tuli MD, PhD [o], Albert C. Koong MD, PhD [h]

Základní doporučení pro:

- dávkování
- frakcionaci
- indikaci konvenční RT vs. SBRT
- plánování
- otázky sekvence s chemoterapií

→ **používáme v MOÚ**

Klíčový aspekt - nutnost **kontroly pohybu tumoru** (nejvýraznější v kranio-kaudálním směru … 24 +/- 16mm)
a okolních orgánů v riziku (duodenum, žaludek, tenké střevo, ledviny, játra, mícha)

Cíl – snaha **zredukovat lemy** a tím i možnou toxicitu léčby.

Strategie - techniky aktivního zadržení dechu, abdominální komprese, end-expirační gating, tumor tracking …
- nutnost **zavedení lokalizačních klipů do nádoru** – většinou cestou endosonografie

ELSEVIER

Practical Radiation Oncology

Volume 10, Issue 3, May–June 2020, Pages e136-e146

Basic Original Report

Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) Guidelines for Pancreatic Stereotactic Body Radiation Therapy (SBRT)

Andrew Oar MBBS, MIPH, FRANZCR [a, b], Mark Lee MBBS, MSc, FRANZCR [a], Hien Le MBBS, FRANZCR [c], George Hruby BHB, MBChB, FRANZCR [d, e], Raymond Dalfsen BMRSc [c], David Pryor MBBS, FRANZCR [f], Dominique Lee MBChB, FRANZCR [f], Julie Chu MBBS, FRANZCR [g], Lois Holloway PhD [b, h, i, j], Adam Briggs MSc [d], Andrew Barbour PhD, FRACS [f, k], Sarat Chander MBBS, FRANZCR [g], Sweet Ping Ng MBBS, FRANZCR [g], Jas Samra D Phil, FRACS [d, e], John Shakeshaft MA, PhD [a], David Goldstein MBBS, FRACP [l, m], Nam Nguyen MBBS, PhD, FRACP [n], Karyn A. Goodman MD, MS [o] ... Andrew Kneebone MBBS, FRANZCR [d, e]

- konsenzus stran dávky a řešení dýchacích pohybů
- **40 Gy v 5 frakcích**
- RT ve výdechové fázi cyklu nebo aktivní kontrola dechu
- v MOU DIBH + zajištění stejného nádechu kontrolou dechové křivky pacienta

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NCCN guidelines – v. 2.2021:

SBRT pankreatu je možná pouze v tzv. „high volume experienced centres“, disponujících možnostmi moderních technik aplikace dávky + lokalizace tumoru a vyřešeným “motion management“ - klipy, IGRT, VMAT atd.

Probíhající studie:

SBRT in locally advanced pancreatic cancer with different biological effective doses

- konkomitance SBRT + CHT gemcitabin/nab-paklitaxel
- dávka SBRT **60-70 Gy** nebo **více než 70 Gy**
- cíle: 1-y PFS, 1-y local control rate, OS, pravděpodobnost GI toxicity

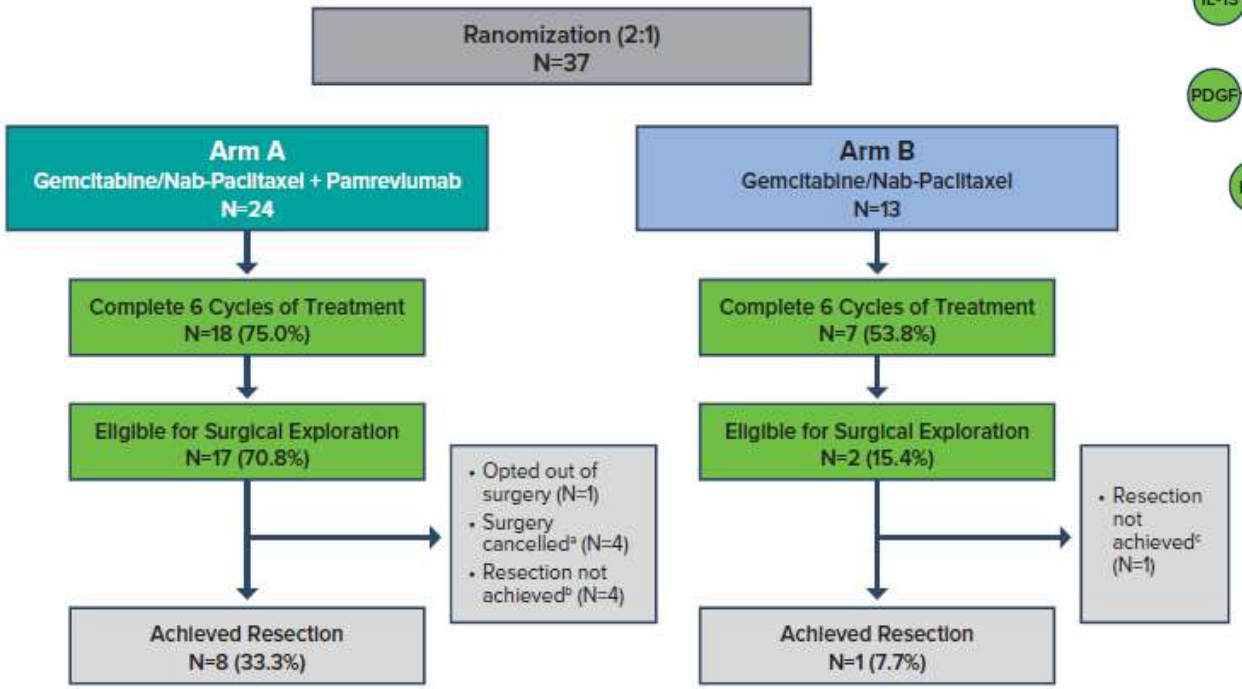
Phase III FOLFIRINOX (mFFX) +/- SBRT in LAPC

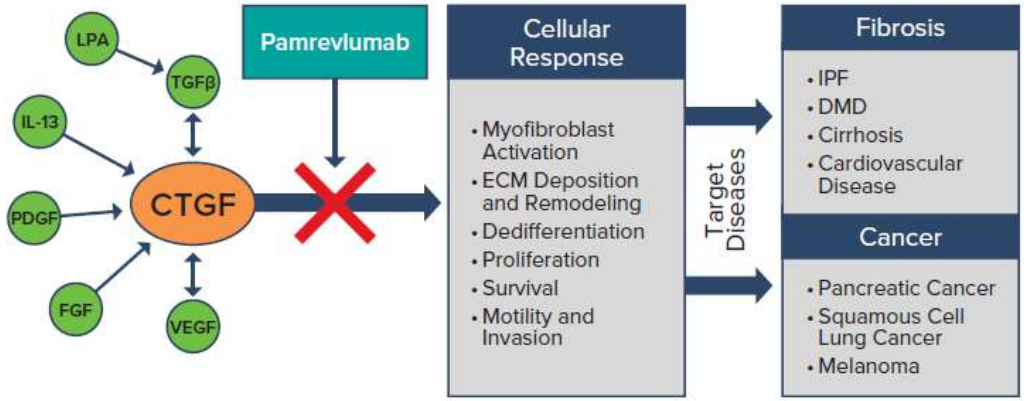
Endpoints:

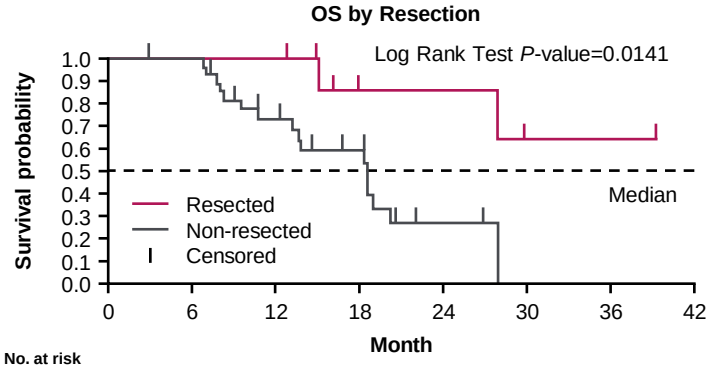
- Progression free survival for mFFX +/- SBRT
- Metastasis free survival for mFFX +/- SBRT
- Local progression-free survival
- Evaluation acute toxicity
- Evaluate the quality of life of patients before and after either chemotherapy or chemotherapy and SBRT

Participating Institutions:
Stanford, UCSF, UCLA, Loyola, BC Cancer Agency, Duke, UTSW

Pamrevlumab: New strategies in locally advanced PDAC







No. at risk								
Non-resected	28	27	17	10	2	0		
Resected	9	9	9	4	4	1	1	0

	N	Event	Censored	Median (95% CI)
Non-resected	28	16 (57.1%)	12 (42.9%)	18.56 (13.27, 20.21)
Resected	9	2 (22.2%)	7 (77.8%)	NE (15.01, NE)

CI, confidence interval; CTGF, connective tissue growth factor; DMD, Duchenne muscular dystrophy; ECM, extracellular matrix; FGF, fibroblast growth factor; IL-13, interleukin 13; IPF, idiopathic pulmonary fibrosis; LPA, lysophosphatidic acid; NE, not evaluable; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor.

Picozzi VJ, et al. J Clin Oncol. 2018;36(no. 15_suppl):4016 (abstract and poster presentation).

CLINICAL PRACTICE GUIDELINES

Locally advanced disease: treatments

Summary of recommendations
In LAPC, the purpose of conversion therapy is to induce down-sizing to facilitate resection in patients with initial non-resectable disease. Several meta-analyses have demonstrated that neoadjuvant therapy increases the possibility of an R0 resection and that OS is prolonged
When a conversion surgery strategy is chosen, the standard of care is (up to) 6 months of combination chemotherapy (FOLFIRINOX or nab-paclitaxel plus gemcitabine).
All patients must be evaluated by the local MDTB for resectability every 2-3 months
Patients with LAPC should be included in clinical trials when possible

ESMO

ESMO guidelines 2022 – in press

Take home messages I. - resekabilní onem.:

- primárně **resekabilní** pacienty doporučeno prozatím primárně **resekovat** !
- po operaci **adjuvantní CHT u všech** pacientů schopných CHT podstoupit
- PS 0-1 - mFOLFIRINOX po dobu 6m
- PS 2 – gem nebo gem/cape případně jen observace
- léčbu zahájit **do 6-12 týdnů** (ne dříve a ne později !) a podávat **celých 6m**
- adjuvantní RT spíše nedoporučována
- při minimálních známkách BRPC (infiltrace cév) zvážit neoadjuvanci !!

Take home messages II. - BRPC:

- definice BRPC by měla zahrnovat nejen **anatomická**, ale i **biologická** a **výkonnostní** kritéria
- **perioperační léčba** důrazně doporučována (PREOPANC-1, ESPAC F)
- standardem je **kombinovaná CHT**, případně následovaná CHRT

Otevřené otázky:

- délka trvání NAT ?? (4 měsíce)
- role RT ??
- role a délka pooperační léčby ??

Take home messages III. - LAPC:

- cílem neoadjuvantní léčby:
    - dosažení downstagingu
    - zvýšení šance na R0 resekci
    - prodloužení OS (zejména při konverzi NR→R)
- standardem je **kombinovaná CHT (FFX nebo gem/nab-pakli)** po dobu **až 6m**
- reevaluace resekability **á 2-3 m**
- pokud nedošlo k diseminaci, ale inoperabilita trvá, pak STX RT nebo CHRT


Děkuji za pozornost