

Bukspottkörtelcancer – biologi och selektion, att välja rätt patient för rätt behandling

Asif Halimi, MD, FACS

Överläkare

Medicinskchef ÖGI

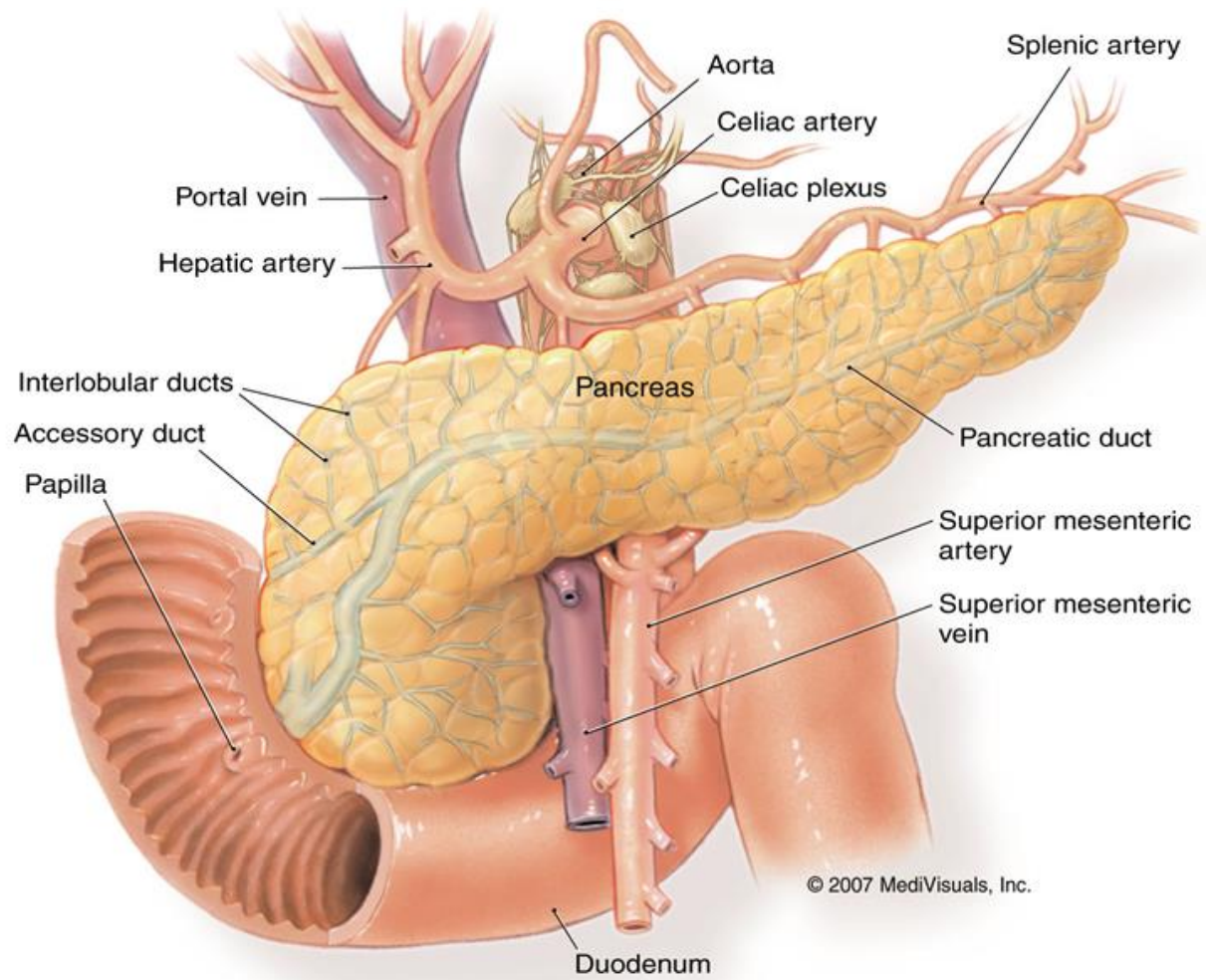
Kirurgcentrum

Norrlandsuniversitetssjukhus



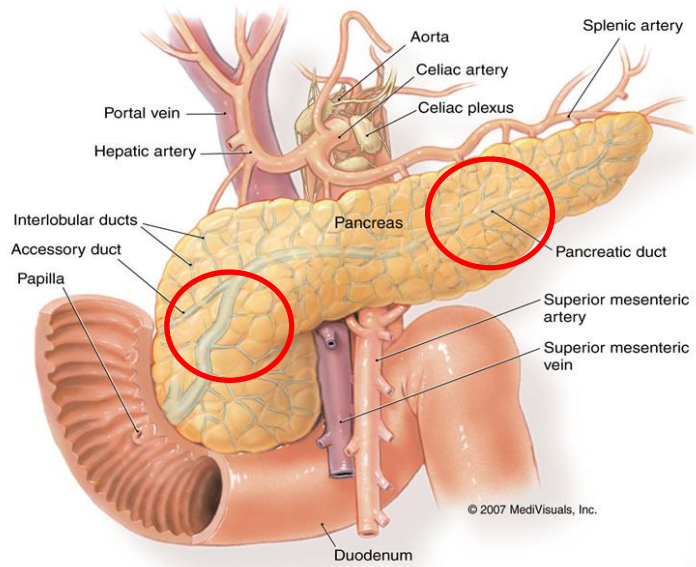
- ingen intressekonflikt



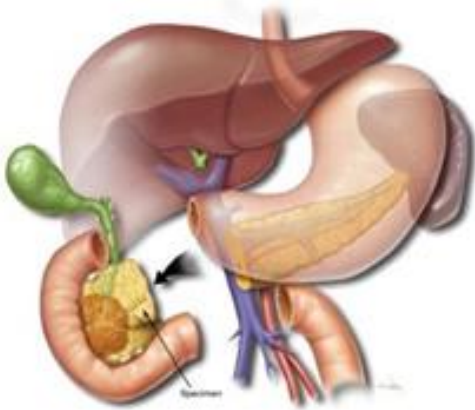


© 2007 MediVisuals, Inc.

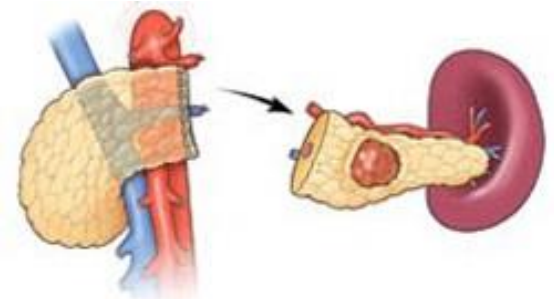
PANKREASKIRURGI



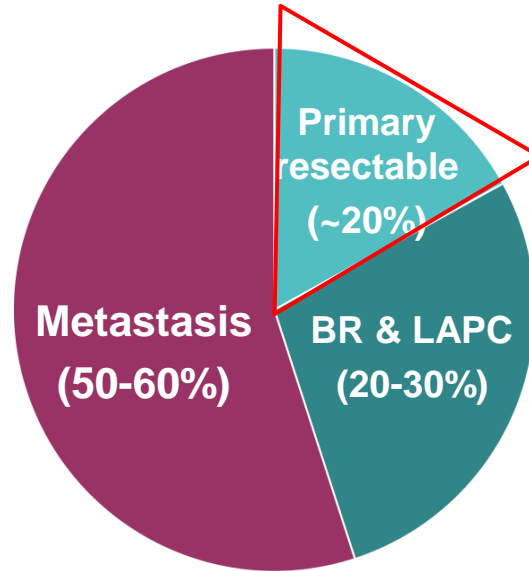
Whipple



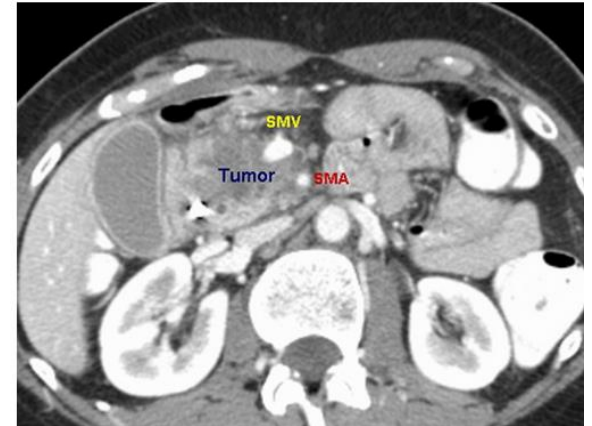
Distal pankreatektomi



BUKSPOTTKÖRTELCANCER

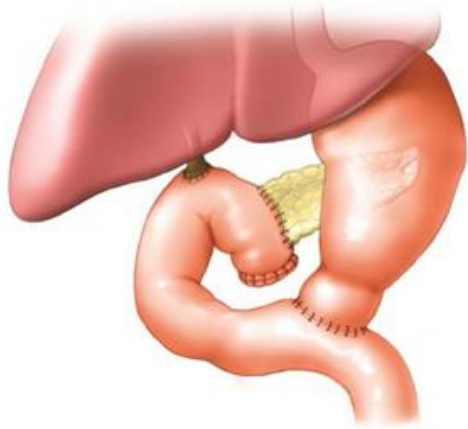


1 : 5



SURGERY IS CRUCIAL

Surgery + chemotherapy treatment gives the best survival chance



Abraxane
Nab-Paclitaxel



ESPAC TRIALS

Trial	Treatment	Pts, n (N = 2092)	5-Yr OS, % (95% CI)	Stratified Log-Rank χ^2	P Value
ESPAC-1	5-FU/ leucovorin	149	21 (14.6-28.5)	7.03	.030*
	No chemotherapy	143	8.0 (3.8-14.1)		
	CRT (5-FU/RT)	145	10.8 (6.1-17.0)		
ESPAC-3	GEM	539	17.5 (14.0-21.2)	0.74	.390*
	5-FU/ leucovorin	551	15.9 (12.7-19.4)		
ESPAC-4	GEM	366	16.3 (10.2-23.7)	4.61	.032†
	GEMCAP	364	28.8 (22.9-35.2)		

Fluorouracil
Leucovorin
Irinotecan
Oxaliplatin

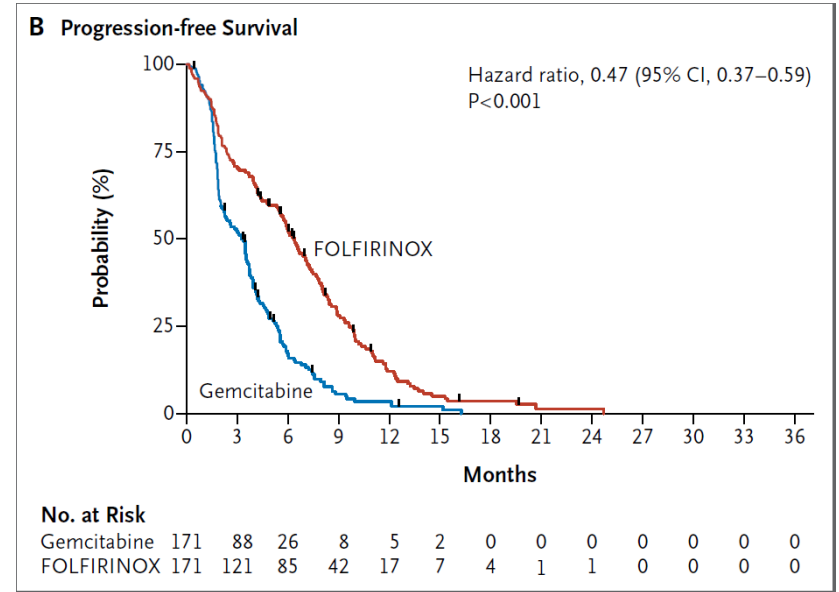
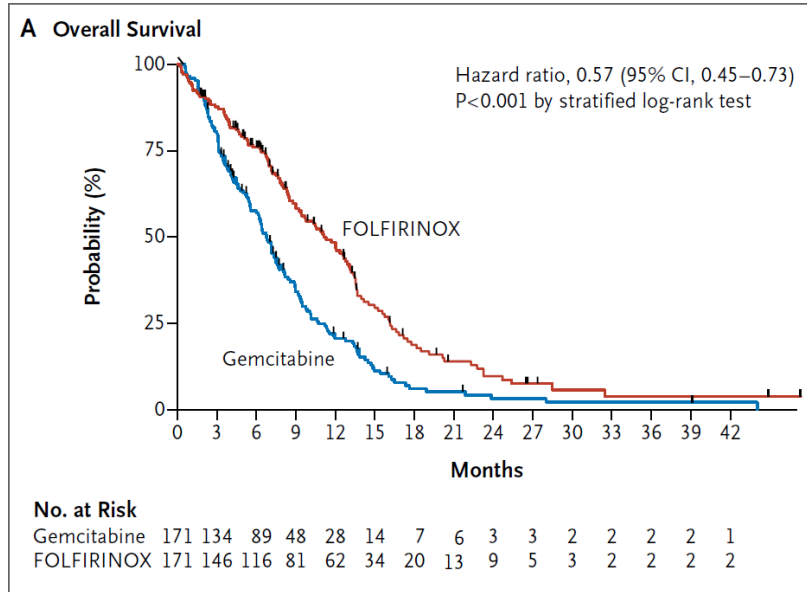
ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

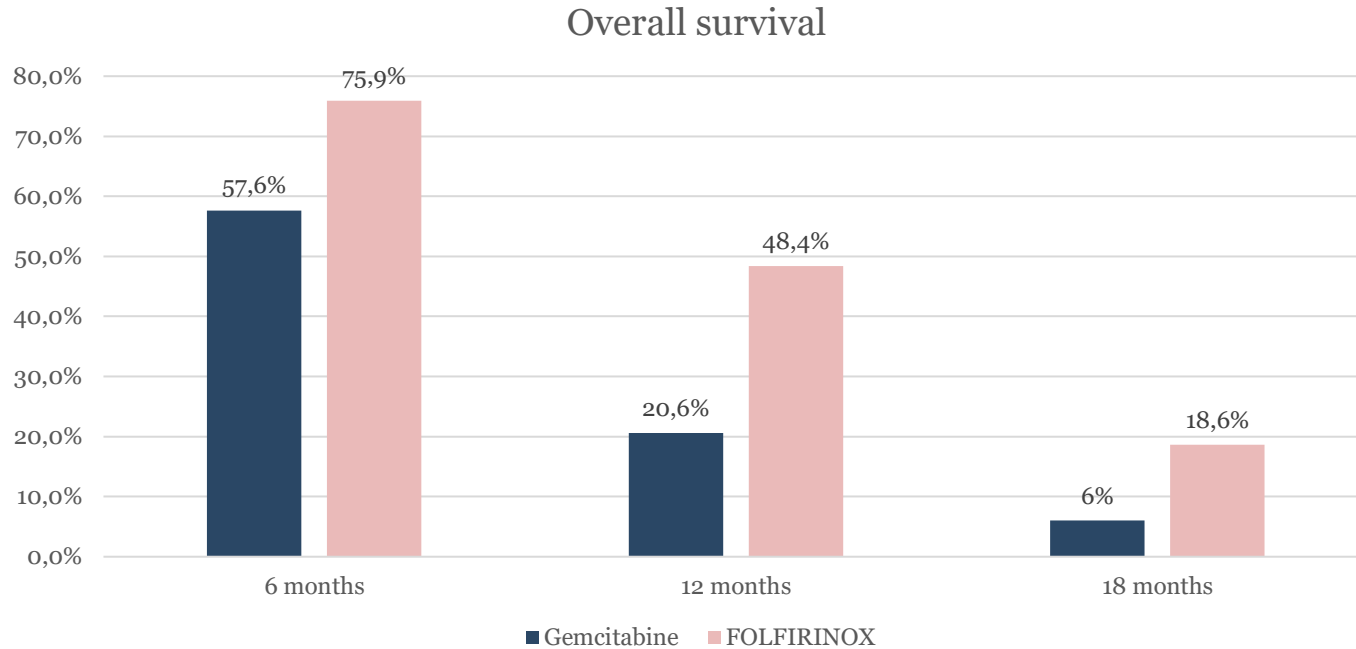
Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D.,
Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D.,
Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D.,
Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D.,
Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D.,
Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D.,
Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D.,
Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D.,
for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*



FOLFIRINOX ERA



FOLFIRINOX ERA



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

DECEMBER 20, 2018

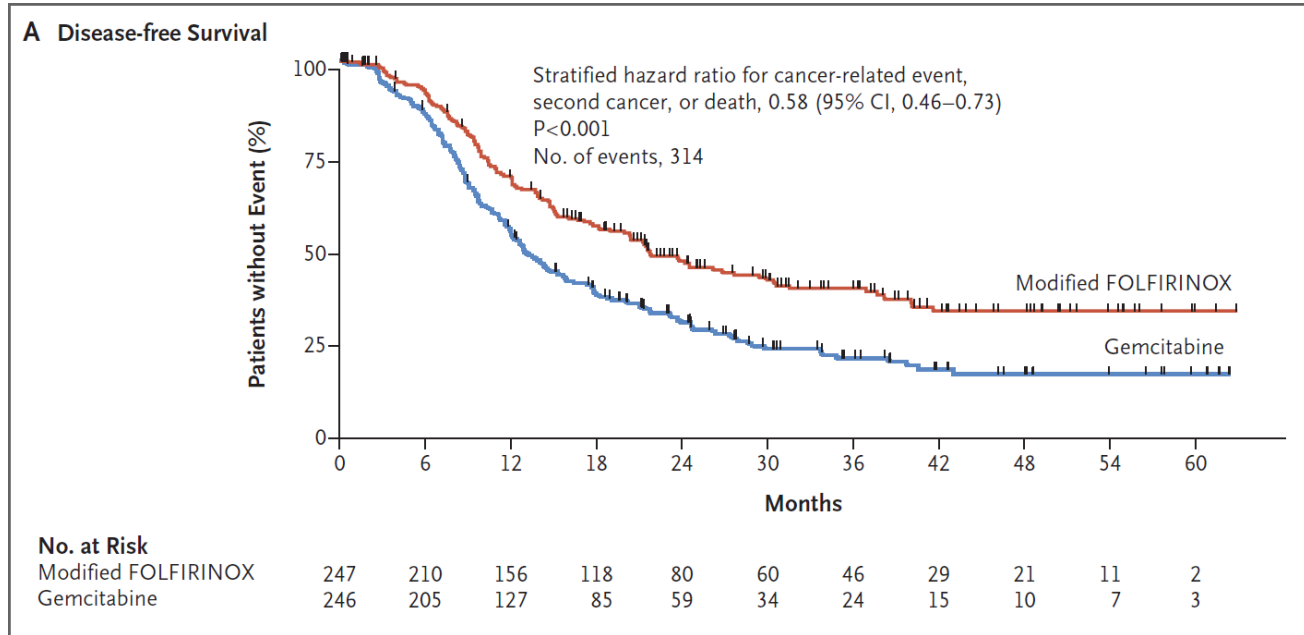
VOL. 379 NO. 25

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group*

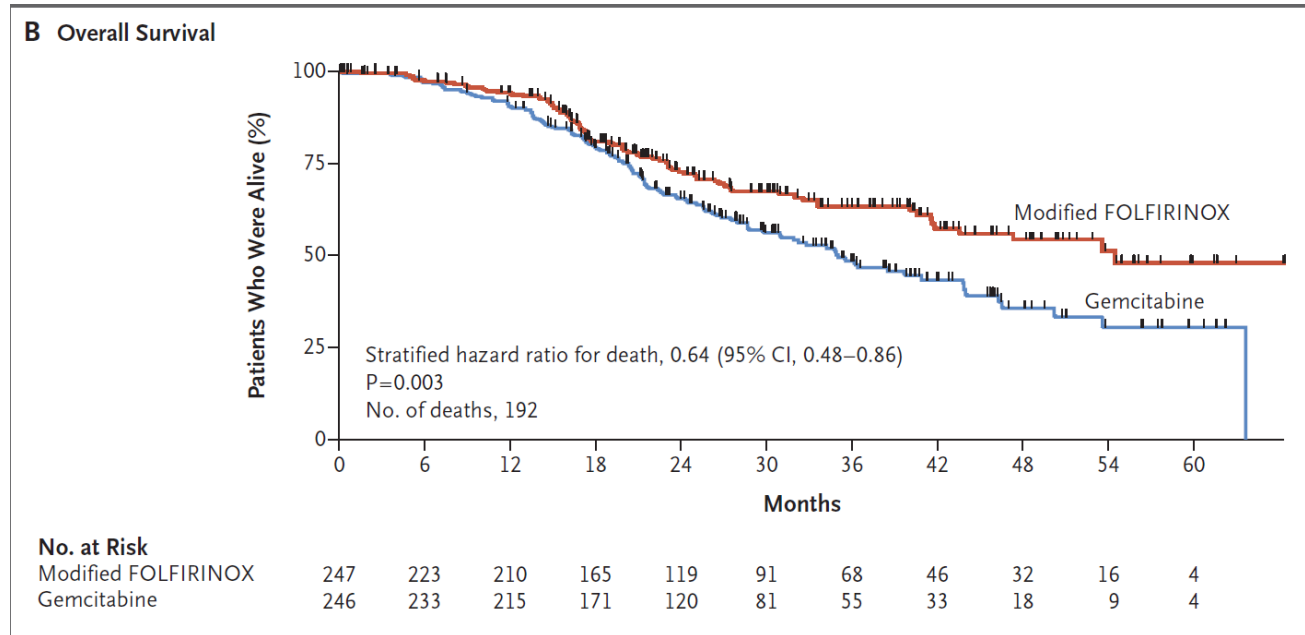


FOLFIRINOX ERA



Median disease-free survival:
21,6 months with mod-FOLFIRINOX vs **12,8 months** with Gemcitabine

FOLFIRINOX ERA

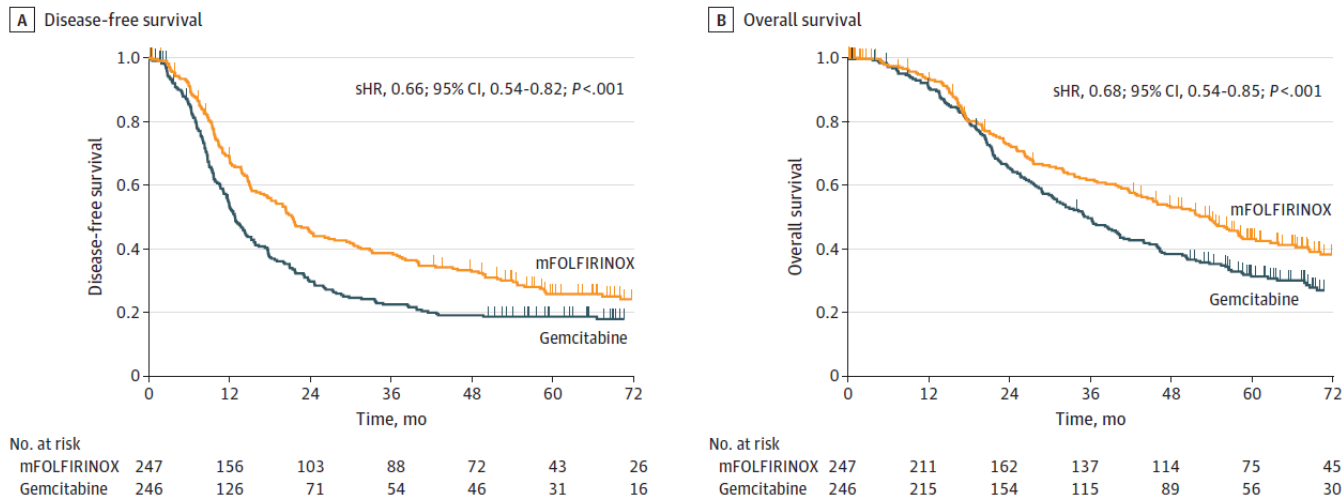


Median overall survival:
54,4 months with mod-FOLFIRINOX vs **35 months** with Gemcitabine



FOLFIRINOX ERA – 5-YEAR FOLLOW-UP

Figure 1. Kaplan-Meier Analysis of Survival in the Intention-to-Treat Population



Median overall survival:

53,5 months with mod-FOLFIRINOX vs **35,5 months** with Gemcitabine

5-year Overall survival:

43,2 % with mod-FOLFIRINOX vs **31,4 %** with Gemcitabine



Table 3. Five-Year Outcomes From Randomized Clinical Trials of Adjuvant Chemotherapy in Patients With Resected PDAC

Source	Patients, No.	Adjuvant therapy	Median follow-up, mo (IQR)	DFS		OS	
				Median, mo (95% CI)	5-y, %	Median, mo (95% CI)	5-y, %
ESPAC-1 ⁹	147	FU + leucovorin	47.0 (33-62)	15.3 (10.5-19.2)	NA	20.1 (16.5-22.7)	21.1 ^a
	142	Observation	47.0 (33-62)	9.4 (8.4-15.2)	NA	15.5 (13.0-17.7)	8.0 ^a
CONKO-001 ¹⁰	179	Gemcitabine	136 (104-144)	13.4 (11.6-15.3)	16.6	22.8 (NA)	20.7
	175	Observation	136 (104-144)	6.7 (6.0-7.5)	7.0	20.2 (NA)	10.4
JSAP-02 ¹³	58	Gemcitabine	60.4 (40.6-77.1)	11.4 (8.0-14.5)	NA	22.3 (16.1-30.7)	23.9
	60	Observation	60.4 (40.6-77.1)	5.0 (3.7-8.9)	NA	18.4 (15.1-25.3)	10.6
ESPAC-3 ¹²	537	Gemcitabine	34.2 (27.1-43.4)	14.3 (13.5-15.6) ^b	NA	23.6 (21.4-26.4)	17.5 ^a
	551	FU + leucovorin	34.2 (27.1-43.4)	14.1 (12.5-15.3) ^b	NA	23.0 (21.1-25.0)	15.9 ^a
JASPAC-01 ²⁰	187	S-1	79.3 (72.0-89.0)	22.9 (NA) ^c	33.3	46.5 (37.8-63.7)	44.1 ^a
	190	Gemcitabine	83.2 (71.8-88.5)	11.3 (9.7-13.6) ^c	16.8	25.5 (22.5-29.6)	24.4 ^a
ESPAC-4 ¹¹	364	Gemcitabine + capecitabine	43.2 (39.7-45.5)	13.9 (12.1-16.6)	18.6	28.0 (23.5-31.5)	28.8 ^a
	366	Gemcitabine	43.2 (39.7-45.5)	13.1 (11.6-15.3) ^c	11.9	25.5 (22.7-27.9)	16.3 ^a
APACT ²¹	432	Gemcitabine + nab-paclitaxel	63.2 (NA) ^c	16.6 (NA)	NA	41.8 (NA) ^d	38 ^d
	434	Gemcitabine	63.2 (NA) ^c	13.7 (NA)	NA	37.7 (NA) ^d	31 ^d
PRODIGE 24	247	mFOLFIRINOX	69.7 (59.4-84.1)	21.4 (17.5-26.7)	26.1	53.5 (22.4-NE)	43.2
	246	Gemcitabine	69.7 (59.4-84.1)	12.8 (11.6-15.2)	19.0	35.5 (20.3-80.8)	31.4

Abbreviations: DFS, disease-free survival; FU, fluorouracil; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; NA, not available; NE, nonestimable; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma.

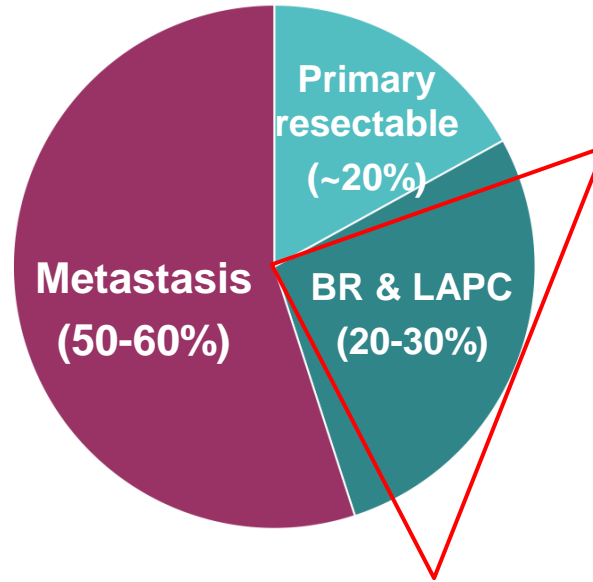
^a Estimated 5-year survival.

^b Progression-free survival.

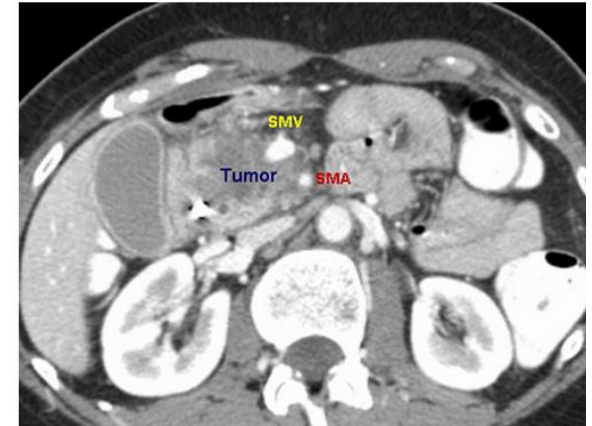
^c Recurrence-free survival.

^d Post hoc analysis; data cutoff date of April 9, 2021 (88% mature).

BUKSPOTTKÖRTELNCANCER



1 : 5



Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180^\circ$ contact without vein contour irregularity.
Borderline Resectable ²	<p><u>Pancreatic head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of $\leq 180^\circ$ • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of $\leq 180^\circ$ • Solid tumor contact with the CA of $> 180^\circ$ without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category]. 	<ul style="list-style-type: none"> • Solid tumor contact with the SMV or PV of $> 180^\circ$, contact of $\leq 180^\circ$ with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
<u>Unresectable²</u>	<ul style="list-style-type: none"> • Distant metastasis (including non-regional lymph node metastasis) <p><u>Head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with SMA $> 180^\circ$ • Solid tumor contact with the CA $> 180^\circ$ • Solid tumor contact with the first <u>jejunal SMA branch</u> <p><u>Body and tail</u></p> <ul style="list-style-type: none"> • Solid tumor contact of $> 180^\circ$ with the SMA or CA • Solid tumor contact with the CA and aortic involvement 	<p><u>Head/uncinate process</u></p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining <u>jejunal branch</u> into SMV <p><u>Body and tail</u></p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)



CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS^a

- Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

Resectability Status	Arterial	Venous
Resectable	<ul style="list-style-type: none"> • No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). 	<ul style="list-style-type: none"> • No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180^\circ$ contact without vein contour irregularity.
Borderline Resectable ^b	<p><u>Pancreatic head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of $\leq 180^\circ$. • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of $\leq 180^\circ$. 	<ul style="list-style-type: none"> • Solid tumor contact with the SMV or PV of $>180^\circ$, contact of $\leq 180^\circ$ with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced ^{b,c}	<p><u>Head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact $>180^\circ$ with the SMA or CA. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact of $>180^\circ$ with the SMA or CA. • Solid tumor contact with the CA and aortic involvement. 	<ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).

Prognosis Based Definition of Resectability in Pancreatic Cancer

A Road Map to New Guidelines

Atsushi Oba, MD, PhD,† Chiara Croce, MD, PhD,* Patrick Hosokawa, MS,‡ Cheryl Meguid, DNP,*
Robert J. Torphy, MD,* Mohammed H. Al-Musawi, MD, MBChB, MSc, FIBMS, FRCS,§
Steven Ahrendt, MD,*¶ Ana Gleisner, MD, PhD,*¶ Richard D. Schulick, MD, MBA, FACS,*¶✉ and
Marco Del Chiaro, MD, PhD, FACS*¶*

7 849 operated patients between 2010 – 2016, **1500** hospitals in USA

TABLE 2. Univariate and Multivariate Cox Models

Variable	Multivariate		Univariate	
	HR (CI)	P-value	HR (CI)	P-value
CA19-9 (U/mL)		<0.0001		<0.0001
0-2.0	1.04 (0.94-1.16)		1.06 (0.95-1.17)	
2.1-36.9	Ref		Ref	
37.0-97.9	1.08 (0.99-1.18)		1.10 (1.01-1.20)	
98.0+	1.34 (1.26-1.43)		1.38 (1.29-1.47)	
Neoadjuvant treatment	1.32 (1.23-1.41)	<0.0001	1.31 (1.22-1.39)	<0.0001
Tumor size (mm)		<0.0001		<0.0001
0-29	Ref		Ref	
30+	1.31 (1.23-1.38)		1.33 (1.26-1.40)	
Age		<0.0001		
18-50	Ref		Ref	
51-65	1.02 (0.91-1.14)		1.05 (0.93-1.18)	
66-75	1.19 (1.06-1.34)		1.25 (1.11-1.40)	
76+	1.37 (1.21-1.55)		1.44 (1.27-1.62)	
Facility type		<0.0001		<0.0001
Academic/research	Ref		Ref	
Others	1.19 (1.08-1.30)		1.23 (1.17-1.30)	
Charlson/Deyo score		<0.0001		<0.0001
0	Ref		Ref	
1	1.07 (1.01-1.13)		1.10 (1.03-1.17)	
2+	1.36 (1.24-1.48)		1.39 (1.27-1.52)	
Primary site		0.0002		0.02
Tail	Ref		Ref	
Body	1.05 (0.92-1.19)		0.95 (0.84-1.09)	
Head	1.19 (1.08-1.30)		1.08 (0.99-1.19)	
Sex		0.02		0.02
Female	Ref		Ref	
Male	1.07 (1.01-1.13)		1.06 (1.01-1.12)	
T-Stage				0.21
1-3	Ref		Ref	
4			1.09 (0.96-1.24)	

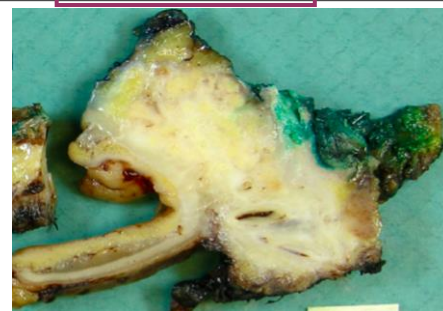
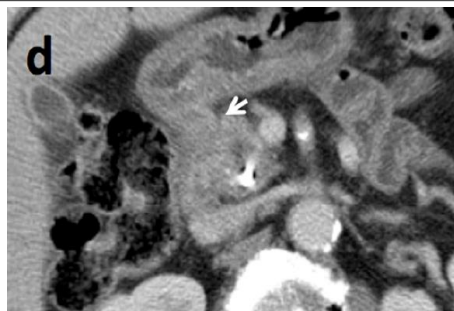
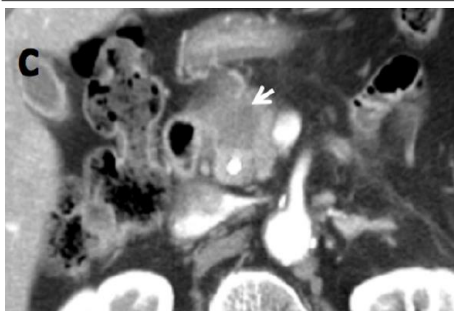
T4 stage was not independently associated with OS – tumor biology is important!



RADIOLOGY UNRELIABLE AFTER CHEMOTHERAPY

	Pre-FOLFIRINOX Treatment (n = 40)	Post-FOLFIRINOX Treatment (n = 40)	<i>P</i>
CA 19.9, median (range) ¹	169 (1–4754)	0.17 (0.01–9.81)	<0.001
CA 19.9 > 40 U ¹	26 (70.3%)	11 (28.9%)	<0.001
Tumor diameter at CT, median (range), cm	3.6 (0–6.0)	2.1 (0–5.4)	<0.001
Gastrointestinal consensus group	LAPC = 25 (62.5%) Borderline = 15 (37.5%)	Complete = 6 (15%) Partial = 30 (75%) Stable = 4 (10%) Progression = 0	
Blinded review by senior pancreatic surgeon (A.L.W.)	Resectable—0 Borderline—14 (35%) LA—26 (65%)	Resectable—12 (30%) Borderline—9 (22%) LA—19 (48%)	

Imaging unresectable:
92% R0 resection



MORBIDITY AFTER PANCREATIC SURGERY

All complications → 57%

Clavien Dindo >3 → 27%



MORTALITY AFTER PANCREATIC SURGERY

In hospital mortality:

- ❖ Germany 10,1 %
- ❖ 6,5 % in high volume, 11,5 % in low volume

90 day mortality:

- ❖ France 8,1 %, (Whipple 9,2%)

Accepted mortality in high-volume centers: 2-3 %

MORTALITY AFTER PANCREATIC SURGERY

Sweden:

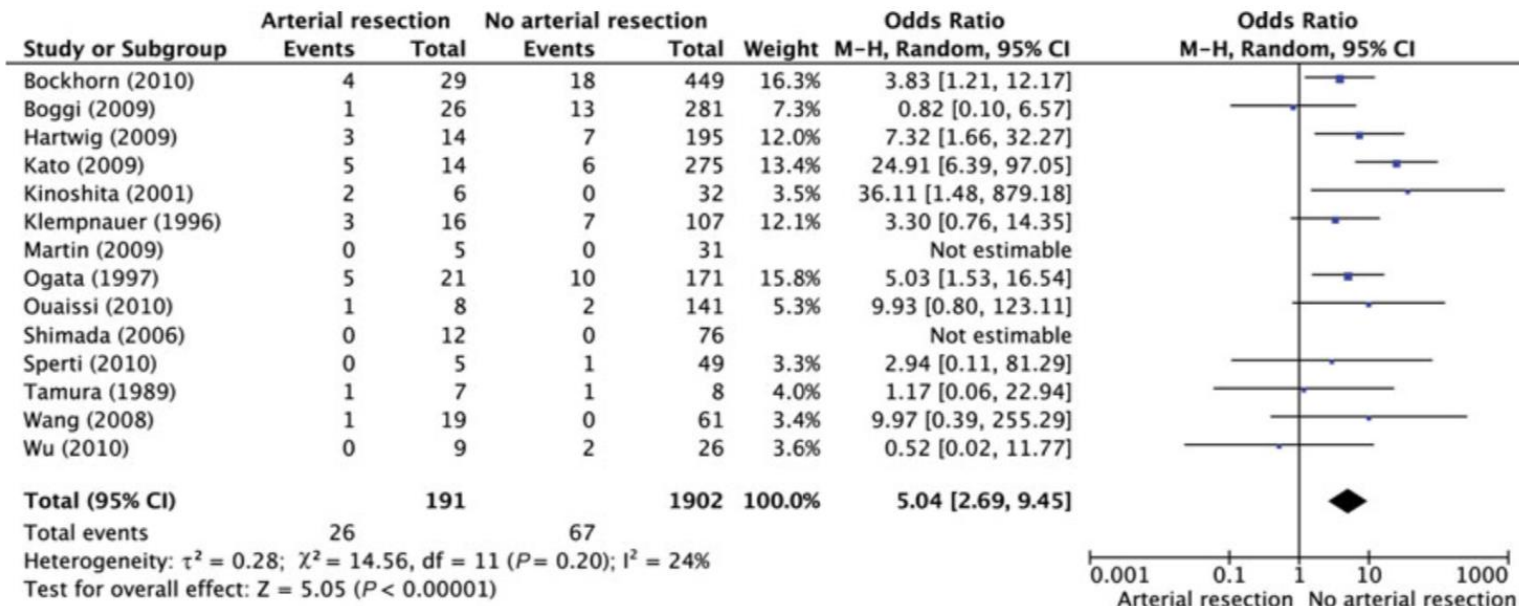
30 day mortality:

- ❖ Whipple and total pancreatectomy: 1,5%
- ❖ Distal pancreatectomy: 0,3%

90 day mortality:

- ❖ Whipple and total pancreatectomy: 3,5%
- ❖ Distal pancreatectomy: 1,8%

ARTERIAL VS STANDARD WHIPPLE



Morbidity **53.6 %** , Mortality **11.8 %**

Median blood loss range **300-4500 ml**



PANCREAS WITH VENOUS AND ARTERIAL RESECTION

- Vein + artery – 90 day 9%
 - *Kinny-Köster et al, Annals of Surg 2023*
- Vein resection – 90 day 7%
- Liver artery, Celiac trunk – 90 day 9%
- SMA resection – 90 day 14%
 - *Boggi et al, BJS 2022*



OUR EXPERIENCE

HPB (Oxford). 2018 Aug 6. pii: S1365-182X(18)32704-7. doi: 10.1016/j.hpb.2018.07.017. [Epub ahead of print]

Pancreatectomy with arterial resection is superior to palliation in patients with borderline resectable or locally advanced pancreatic cancer.

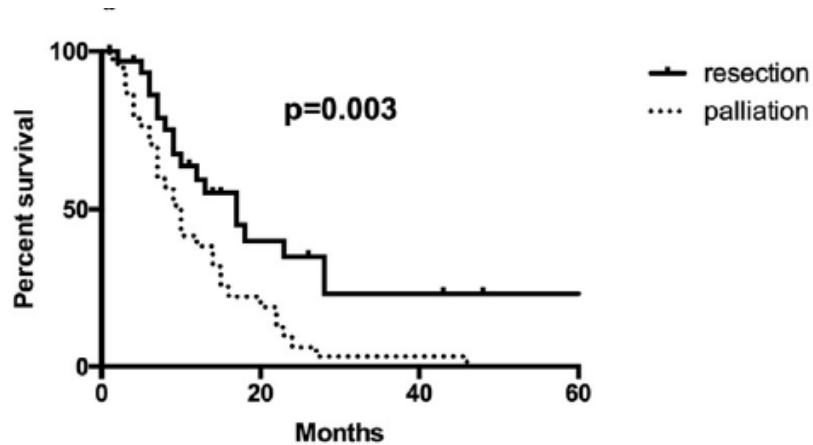
Del Chiaro M¹, Rangelova E², Halimi A², Ateeb Z², Scandavini C², Valente R², Segersvärd R², Arnelo U², Verbeke CS³.

Intra- and postoperative results	Resection group (n=34) %	Palliative Group (n=39) %	p
Mean operation time (minutes)	426 ± 14	171 ± 11	<0.0001
Mean intraoperative blood loss (ml)	613 ± 72	188 ± 21	<0.0001
Postoperative mortality (in hospital)	<u>2.9 %</u>	2.6 %	0.9
Postoperative overall morbidity	61.7%	43.5%	0.1
Postoperative overall surgical complications	<u>38.2 %</u>	25.6 %	0.2
Severe postoperative complications (Clavien-Dindo ≥ 3b)	<u>11.7 %</u>	5.1 %	0.3
Reoperation	8.8 %	-	0.058
Need for ICU stay	8.8 %	-	0.058
Mean length of hospital stay (days)	18 ± 2.4	9.3 ± 1	0.0005



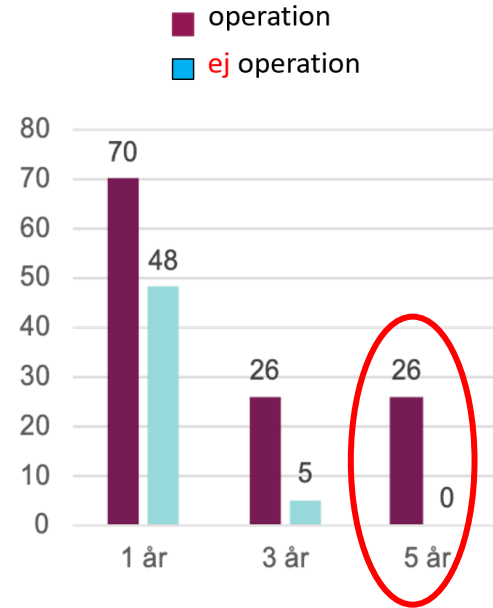
UMEÅ UNIVERSITY

OUR EXPERIENCE



patients at risk

Resection	33	9	6	3
Palliation	38	7	2	0



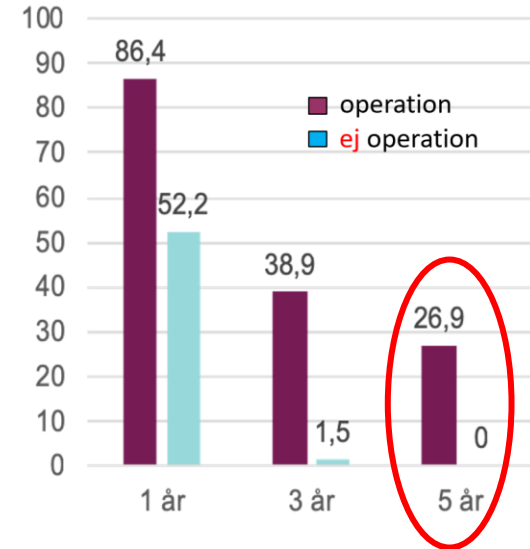
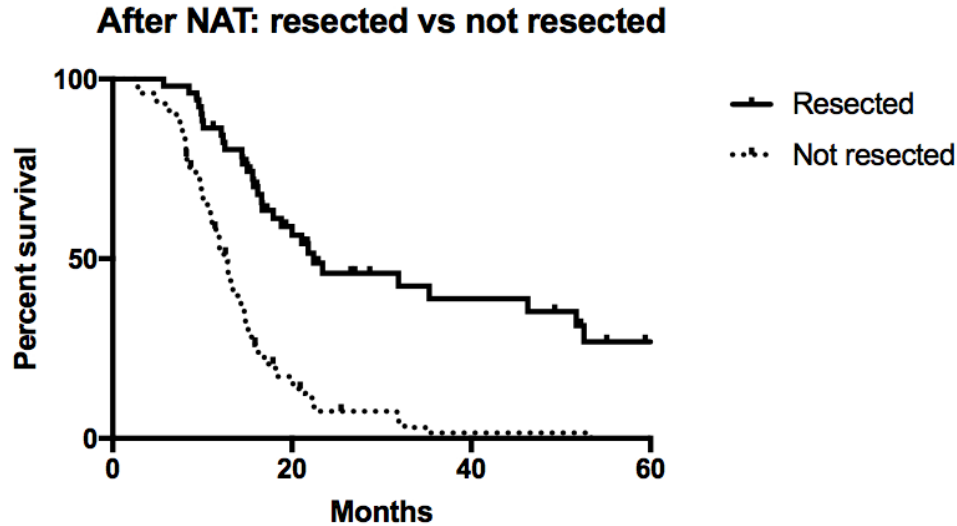
OUR EXPERIENCE

156 pts with pancreatic cancer receiving neoadjuvant treatment

Patient data	
Man : Female (n)	82 : 74
Age (yrs)	64 (32-81)
Caput: corpus: cauda	119 : 32 : 5
Resectability : BR : LAPC (<i>ISGPS</i>) (n)	2 : 22 : 132
Resectability rate: 2011-15 vs -16-17 (%)	34.7 : <u>59.5%</u> (p=0.009)

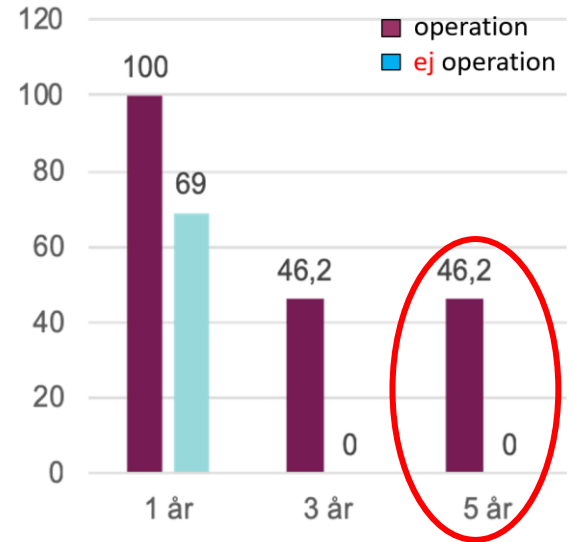
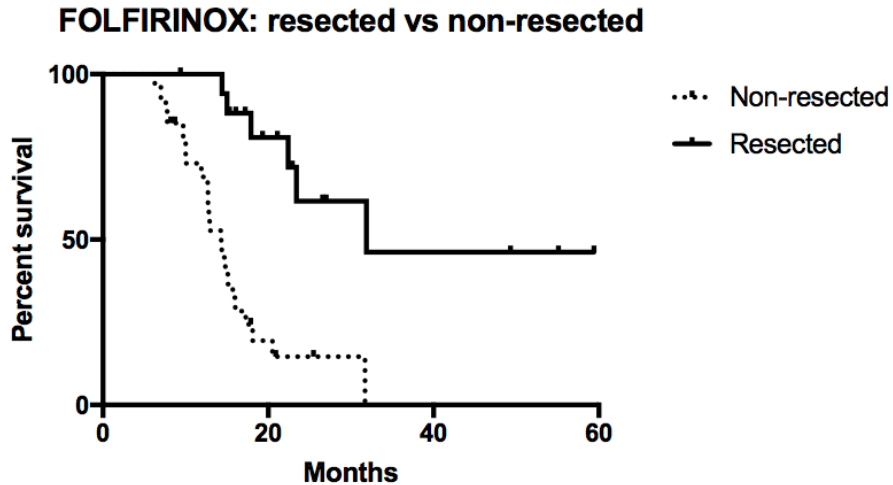
OUR EXPERIENCE

Survival after neoadjuvant: **resected** vs **unresected** patients



OUR EXPERIENCE

Survival after neoadjuvant: **resected** vs **unresected** patients



VENOUS RESECTION 2016 VS 2022

Systematic review

Meta-analysis of benefits of portal–superior mesenteric vein resection in pancreatic resection for ductal adenocarcinoma

F. Giovinazzo¹, G. Turri¹, M. H. Katz³, N. Heaton² and I. Ahmed¹

¹Hepatobiliary and Pancreatic Surgical Unit, NHS Grampian, Aberdeen, and ²Institute of Liver Studies, King's College Hospital, London, UK, and ³MD Anderson Cancer Center, Houston, Texas, USA

Correspondence to: Dr F. Giovinazzo, Department of Surgery, Aberdeen Royal Infirmary, Foresterhill Road, Aberdeen AB25 2ZN, UK (e-mail: francesco.giovinazzo@nhs.net)

- 27 studies
- ↑ mortality
- ↑ R1/R2 resections

Venous resection for pancreatic cancer, a safe and feasible option? A systematic review and meta-analysis

E.S. Zwart^{a,1}, B.S. Yilmaz^{b,1}, A. Halimi^{c,d}, R. Ahola^e, B. Kurlinkus^f, J. Laukkarinen^e, G.O. Ceyhan^{g,*}

^a Amsterdam UMC, Amsterdam, Cancer Center Amsterdam, Netherlands Department of Surgery, the Netherlands

^b Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany

^c Division of Surgery, CLINTEC, Karolinska Institute, Sweden

^d Department of Surgical and Perioperative Sciences, Umeå University Hospital, Sweden

^e Tampere University Hospital and Tampere University, Tampere, Finland

^f Clinic of Gastroenterology, Nephrourology and Surgery, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

^g Department of General Surgery, HPB Unit, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey

- 32 studies
- ↑ R1 (36,7% vs 28,6%)
- Similar 90-d mortality & OS



HOW WE DO IT IN THE NORTH

BR & LAPC → chemotherapy

- 6-8 cycles FOLFIRINOX **or** 4-6 cycles Gem-Nab paclitaxel
- 2 months radiology
- MDT → Radiology unchanged, ↓ Ca19-9, no metastasis
- **nMDT**
- Conclude the planned chemotherapy
- New radiology
- MDT → Radiology unchanged, ↓ Ca19-9, no metastasis, patients status
- Exploration

- Radiology progression, ↑ Ca19-9 → 2nd line chemotherapy (if possible, or palliation)



HOW WE DO IT IN THE NORTH

- Downsizing / downstaging rarely required
 - If there is a need for tumor shrinking and/or ↓ vascular engagement prior to resection
 - These cases usually require more chemo cycles

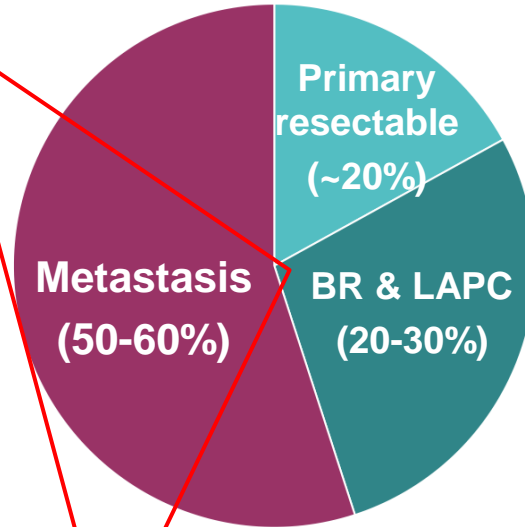


UMEÅ DATA

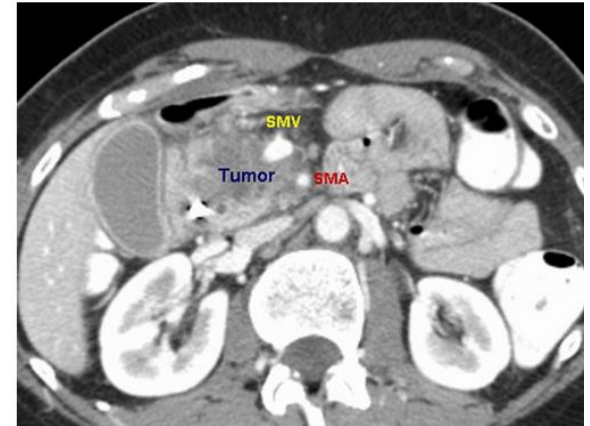
- 2020 – 2023
- 33 cases with BR and LAPC
 - 7 open & close due to metastasis
 - 26 resected
- **100 %** resection rate if no intraoperative metastasis
- Average bleeding 217 ml (range 0 – 1500 ml)
- Mortalitet:
 - 30 day 3%
 - 90 day 6%



BUKSPOTTKÖRTELNCANCER



1 : 5



METASASERAD BUKSPOTTKÖRTELCANCER

- Att operera primär tumören vid metastaserad sjukdom hjälper inte
- Viktigt att patienten får komma till bromsande palliativ cytostatika så snart som möjligt
- ScanPan-1 studien
 - Oligometastas studie
- SPEARMINT studien
 - ERCP + stent, med eller utan ablation

ATT VÄLJA RÄTT PATIENT

- Tumör faktorer, patient faktorer
- Tumör lokalisation, storlek, kärlengagemang?
- +75 årig häcklöpare eller 82 årig off-pist skidåkare, vs rullstolsbunden 50 åring
- Resektabel tumör? operabel patient?



IN SUMMARY

- Combination of Surgery + chemo gives the best survival chance.
- "New" chemotherapy regimens give us the possibility to treat patients otherwise deemed palliative.
- Tumor biology is more important than tumor staging.
- We have come far with surgery, we can do advanced procedures with acceptable complication rates, which is superior to palliation.
- "with great power comes great responsibility", just because we can, we shouldn't.
- Selection the right patient is crucial.



TACK!



UMEÅ UNIVERSITY

asif.halimi@umu.se