Das Pankreaskarzinom

INSELSPITAL
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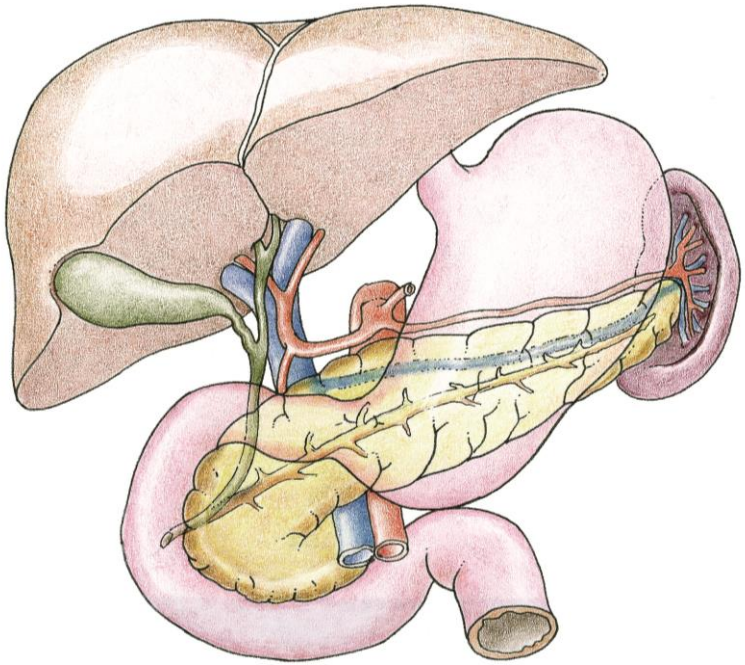
Die Bauchspeicheldrüse - das Pankreas

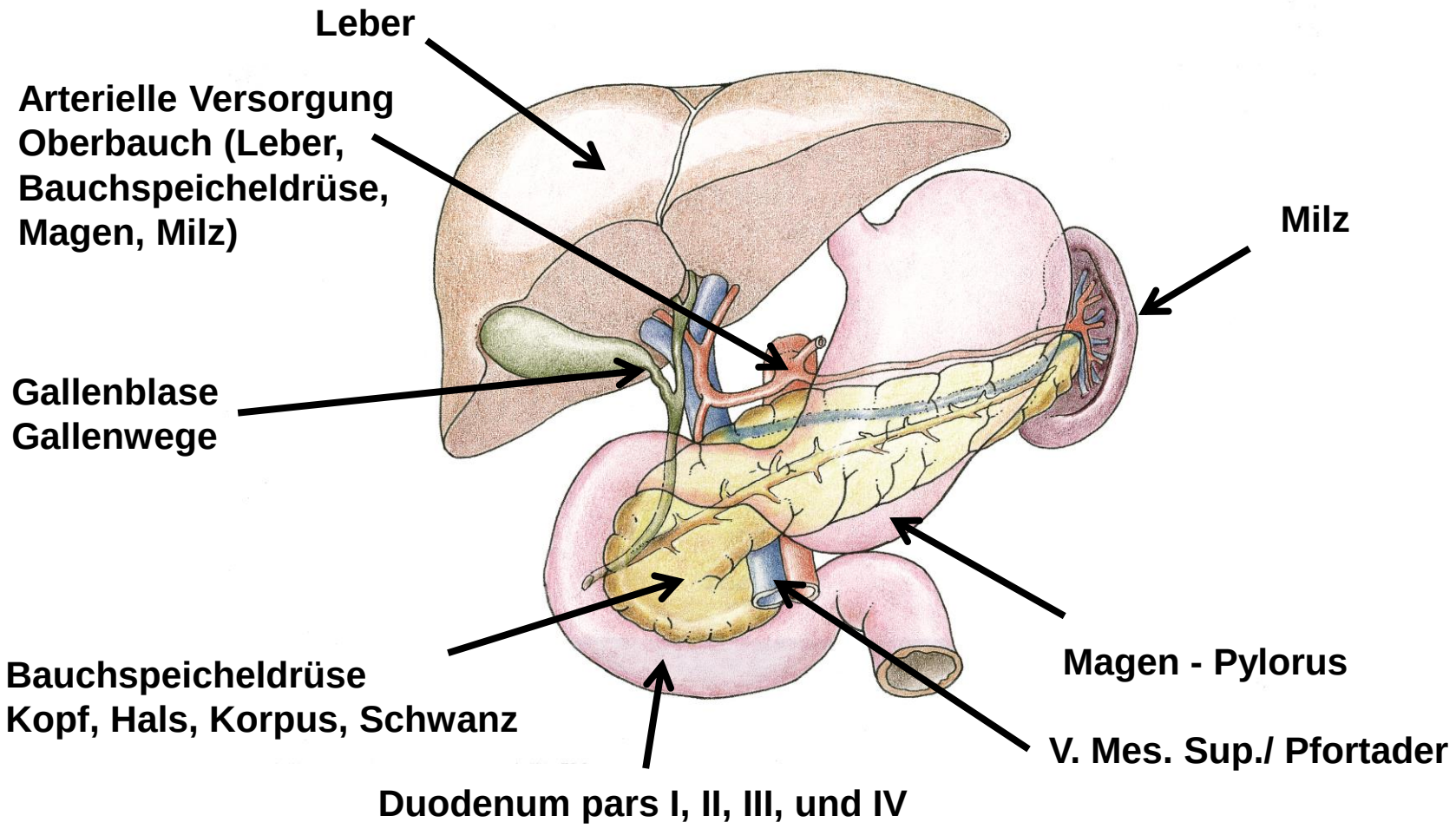
griechisch: πάνκρεας, *pánkreas*,
***pán* für „alles“, *kréas* für „Fleisch“**
Fleischige Konsistenz…

2 wichtige Funktionen:

- **Verdauung**
- **Zuckerstoffwechsel - Insulin**



Normale Anatomie der Bauchspeicheldrüse



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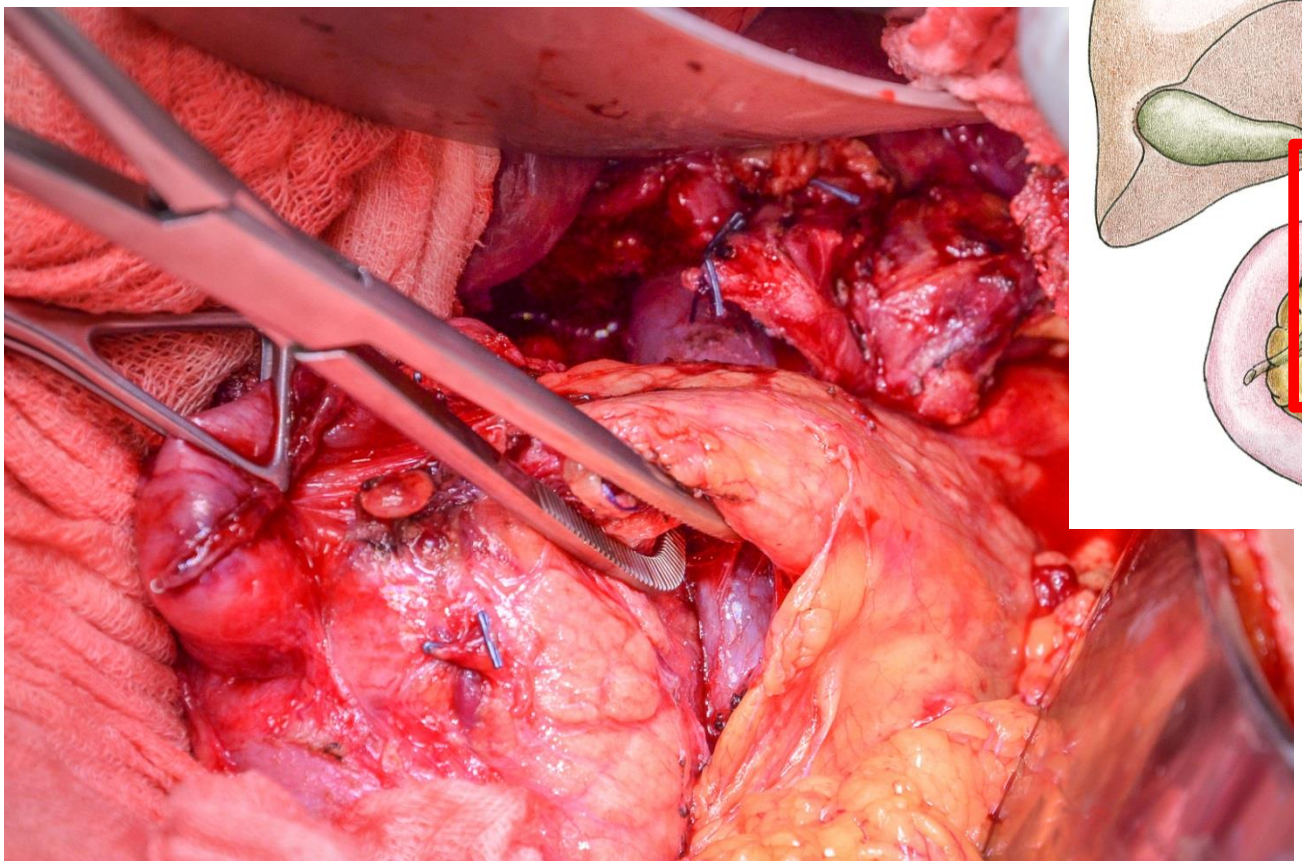
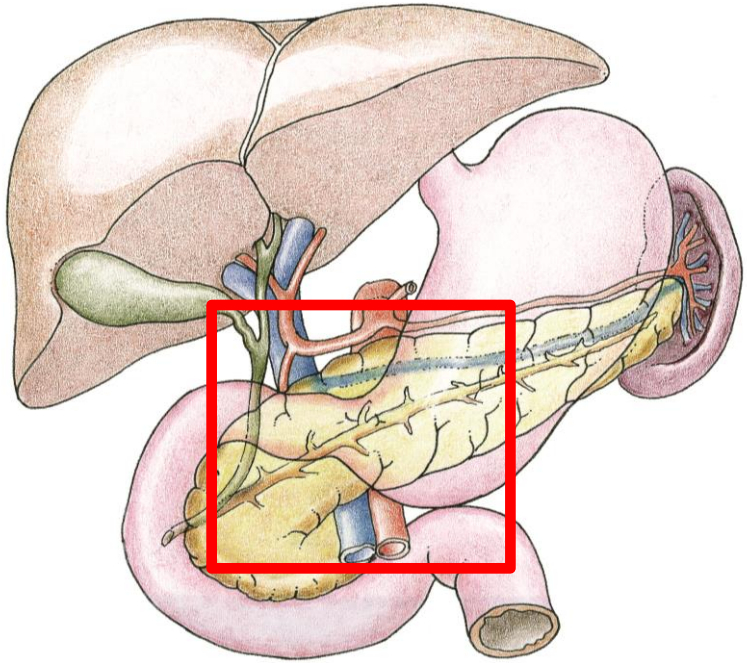
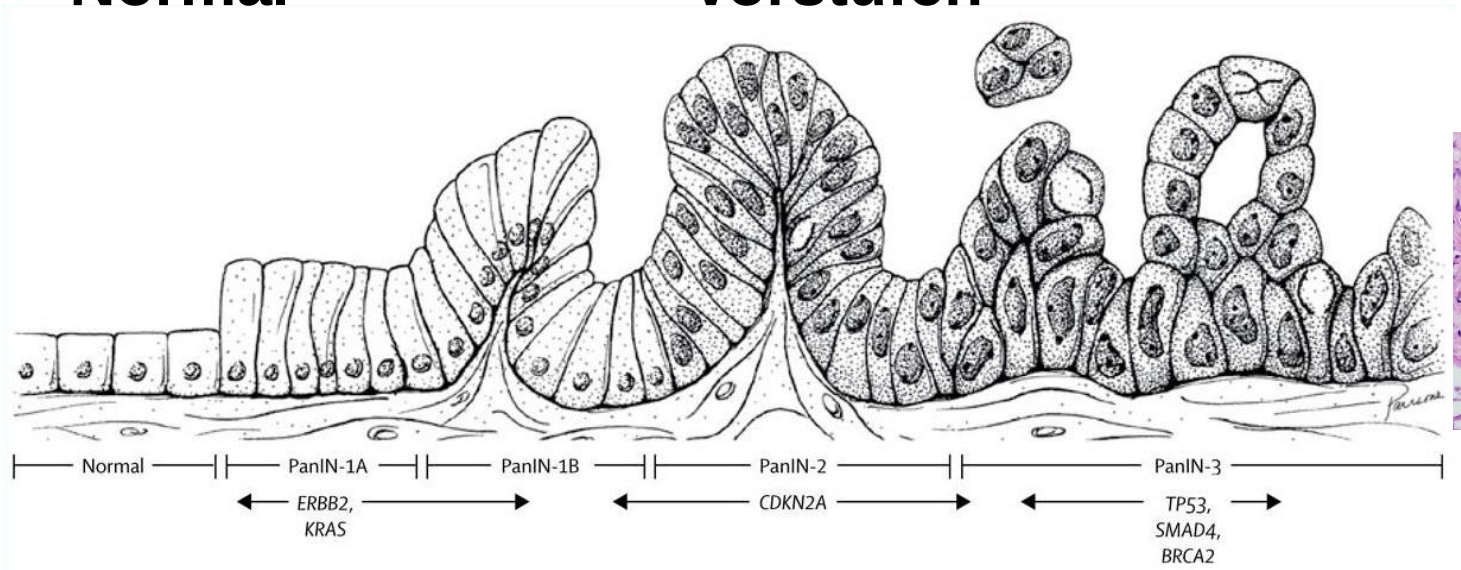
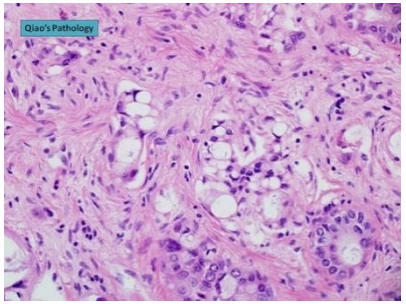




Der Weg zum Pankreaskarzinom…

Normal **Vorstufen** **Karzinom**





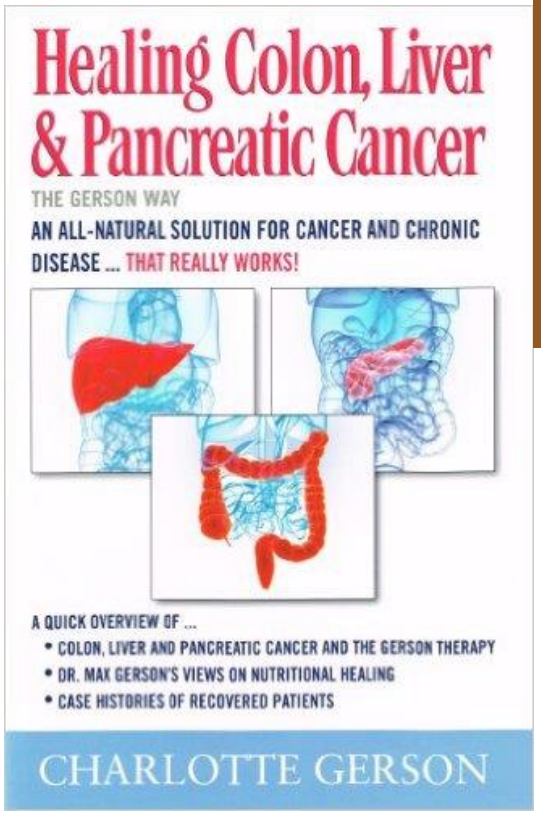
Vincent 2011, Lancet

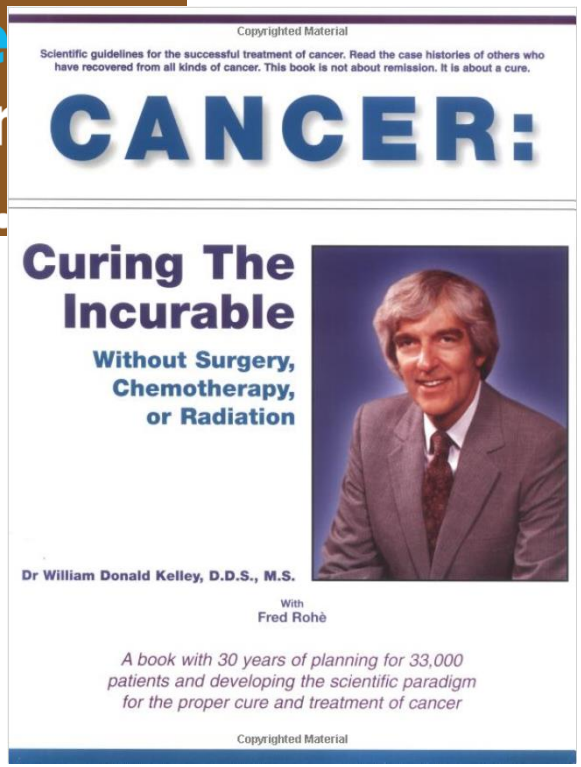
Symptome

Meist keine Frühsymptome…

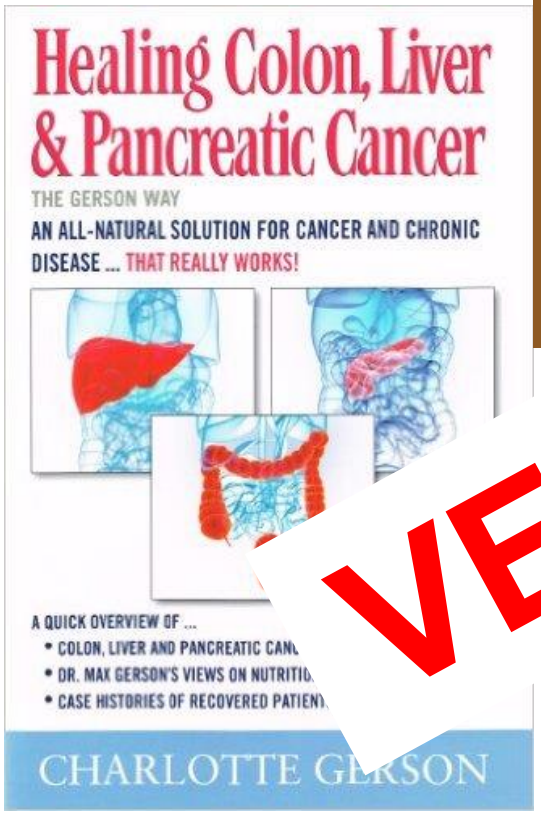
Ikterus
Schmerzen
Gewichtsverlust
Diabetes mellitus (endokrine Pankreasinsuffizienz)
Exokrine Pankreasinsuffizienz
Nausea/Erbrechen

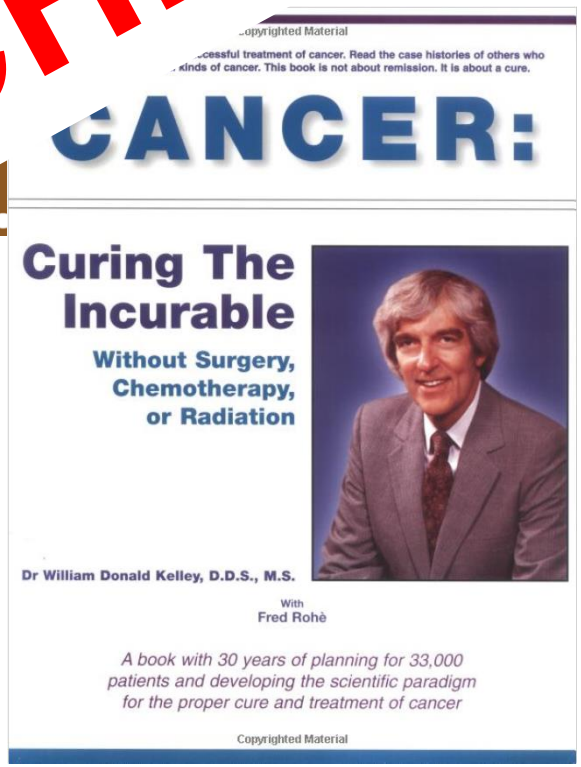
Pankreaskarzinom
Heilung – na klar!





Pankreaskarzinom
Heilung – na klar!





VERSPRECHEN

Pankreaskarzinom: der tödlichste Krebs des Bauchraums

2016 USA

Neue Fälle pro Jahr: ~53,000

Davon sterben: ~42,000

Estimated New Cases

Males			Females		
Prostate	180,890	21%	Breast	246,660	29%
Lung & bronchus	117,920	14%	Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%	Colon & rectum	63,670	8%
Urinary bladder	58,950	7%	Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%	Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%	Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%	Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%	Leukemia	26,050	3%
Leukemia	34,090	4%	Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%	Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**	**All Sites**	**843,820**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	85,920	27%	Lung & bronchus	72,160	26%
Prostate	26,120	8%	Breast	40,450	14%
Colon & rectum	26,020	8%	Colon & rectum	23,170	8%
Pancreas	21,450	7%	Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%	Ovary	14,240	5%
Leukemia	14,130	4%	Uterine corpus	10,470	4%
Esophagus	12,720	4%	Leukemia	10,270	4%
Urinary bladder	11,820	4%	Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%	Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%	Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**	**All Sites**	**281,400**	**100%**

Siegel et al. CA, 2016

Pankreaskarzinom: der tödlichste Krebs des Bauchraumes

2016 USA

Neue Fälle pro Jahr:

~53,0

Da

REALITÄT

Estimated New Cases

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Siegel et al. CA, 2016

Pankreaskarzinom: der tödlichste Krebs des Bauchraums

2016 USA

Neue

Da

Schweiz:

ca. 1’100 neue Fälle

Estimated New Cases

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Lung & bronchus	117,920	14%			13%
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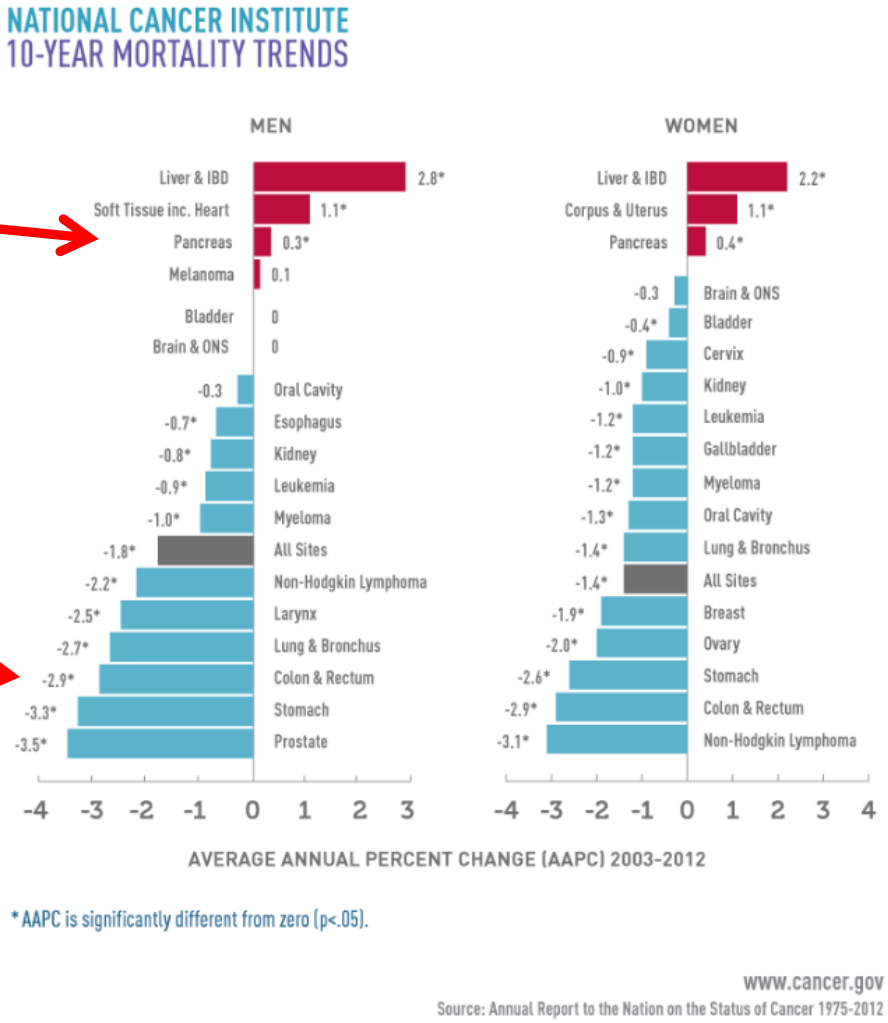
Siegel et al. CA, 2016

Therapie-Erfolg im Vergleich: 10-Jahres “Sterblichkeits”-Trend

Pankreas:
+ 0.3% pro Jahr

Dickdarm:
- 2.9% pro Jahr



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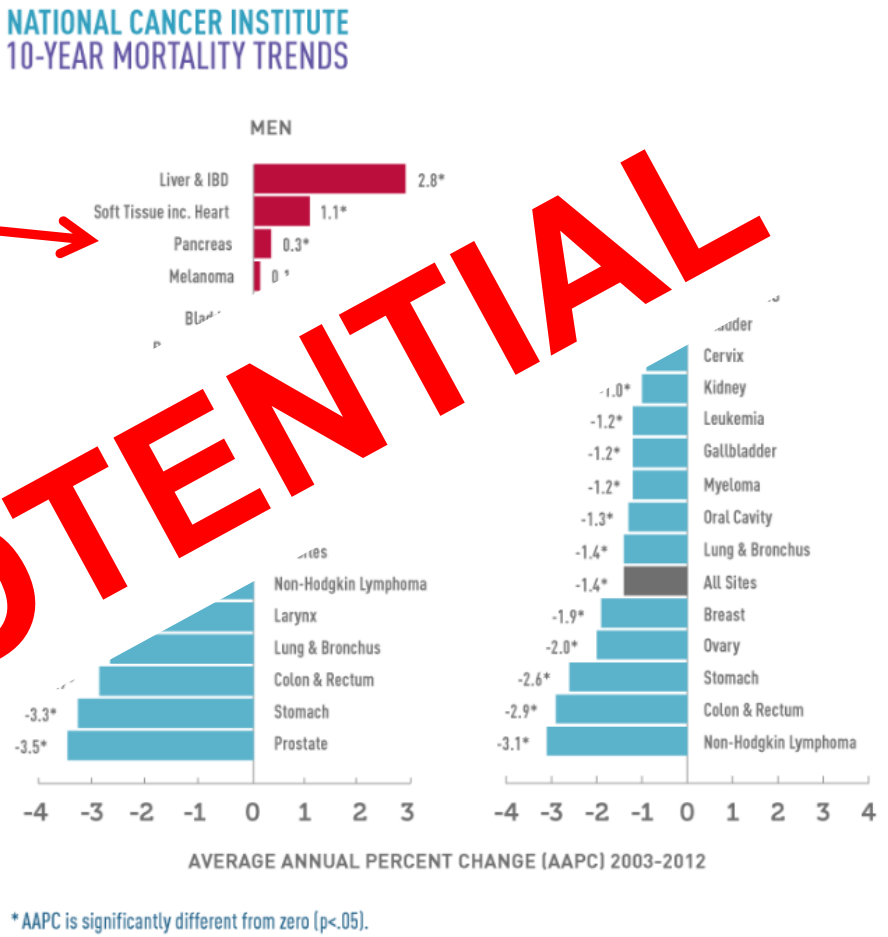
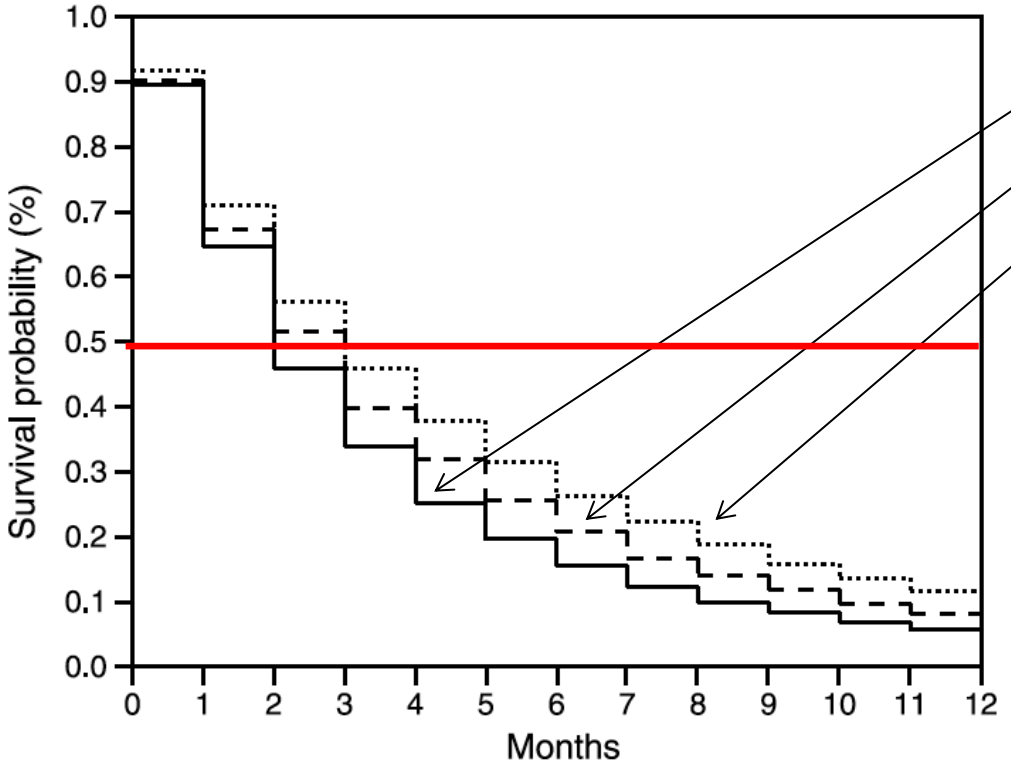


Worni et al Pancreas • Volume 42, Number 7, October 2013

Modest Improvement in Overall Survival for Patients With Metastatic Pancreatic Cancer

A Trend Analysis Using the Surveillance, Epidemiology, and End Results Registry From 1988 to 2008

Mathias Worni, MD, MHS,† Ulrich Guller, MD, MHS,†‡ Rebekah R. White, MD,* Anthony W. Castleberry, MD,* Ricardo Pietrobon, MD, PhD,* Thomas Cerny, MD,‡ Beat Gloor, MD,† and Dieter Koeberle, MD‡*



- 1988-1994
- 1995-2001
- 2002-2008

Medianes Überleben 1988:
2 months (CI: 2-2)
Medianes Überleben 2008:
3 months (CI: 3-4)

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Pancreatic Adenocarcinoma

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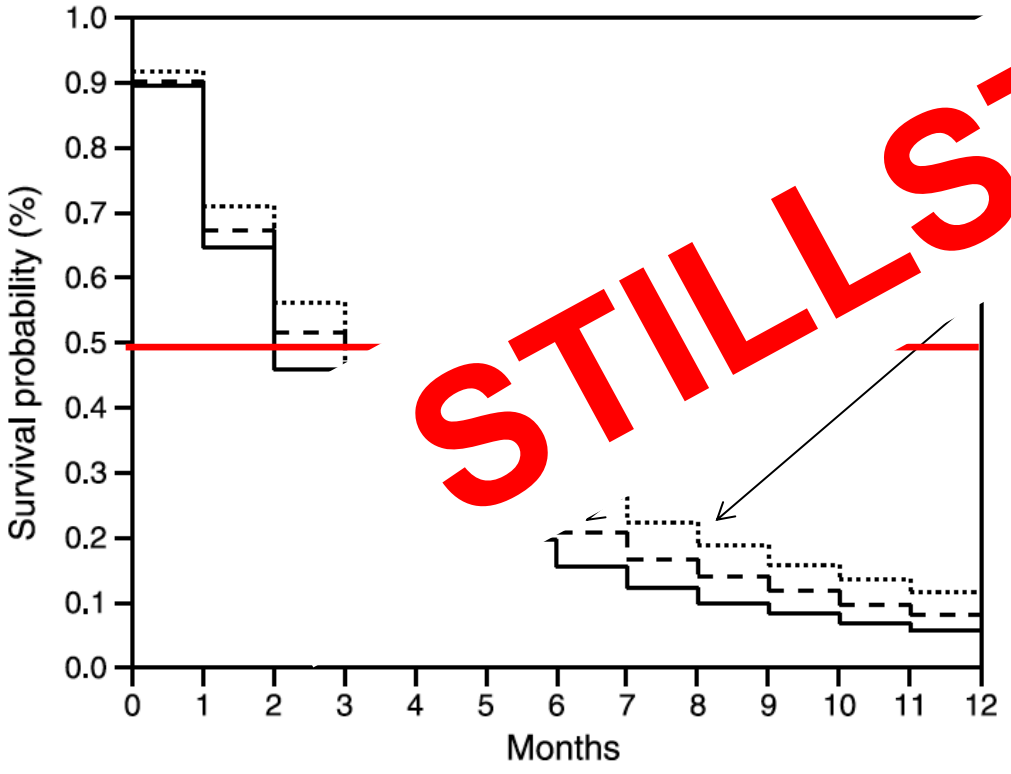

STILLSTAND

94
-2001
2002-2008

Medianes Überleben 1988:
2 months (CI: 2-2)
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3 months (CI: 3-4)

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Ann Surg Oncol (2012) 19:1316–1323
DOI 10.1245/s10434-011-2088-2

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

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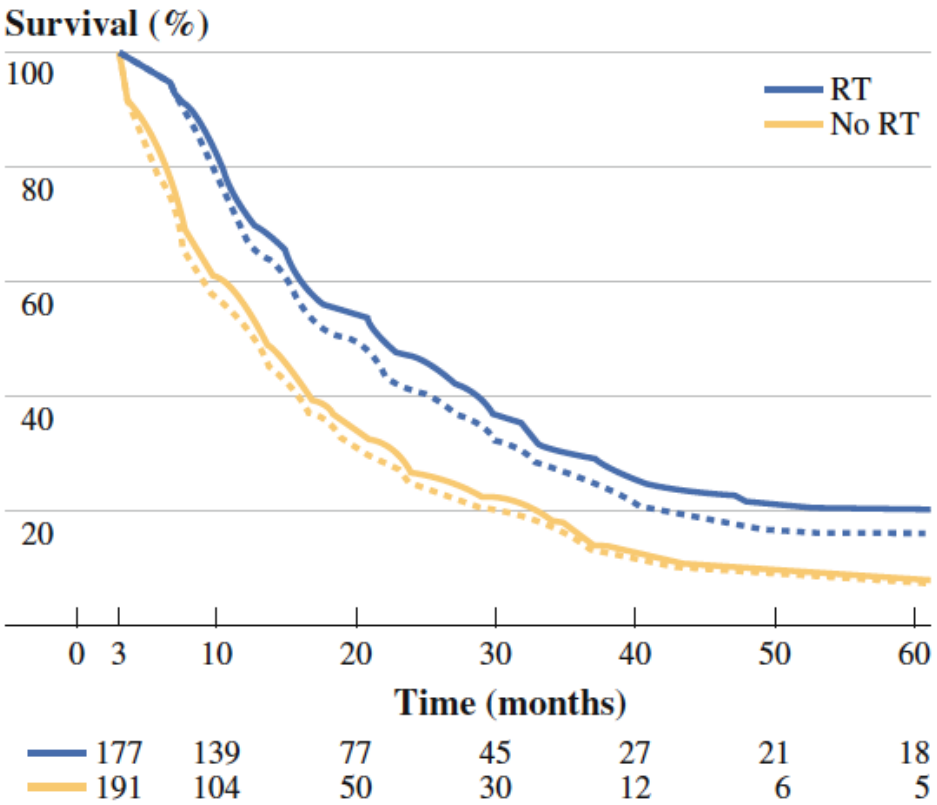

Chirurgisch angehbare Tumoren

5-Jahres-Überleben

Insgesamt: 20-25%

Tumor vollständig entfernt:
JA: 35% 5-Jahres-Überleben
NEIN: 15% 5-Jahres-Überleben

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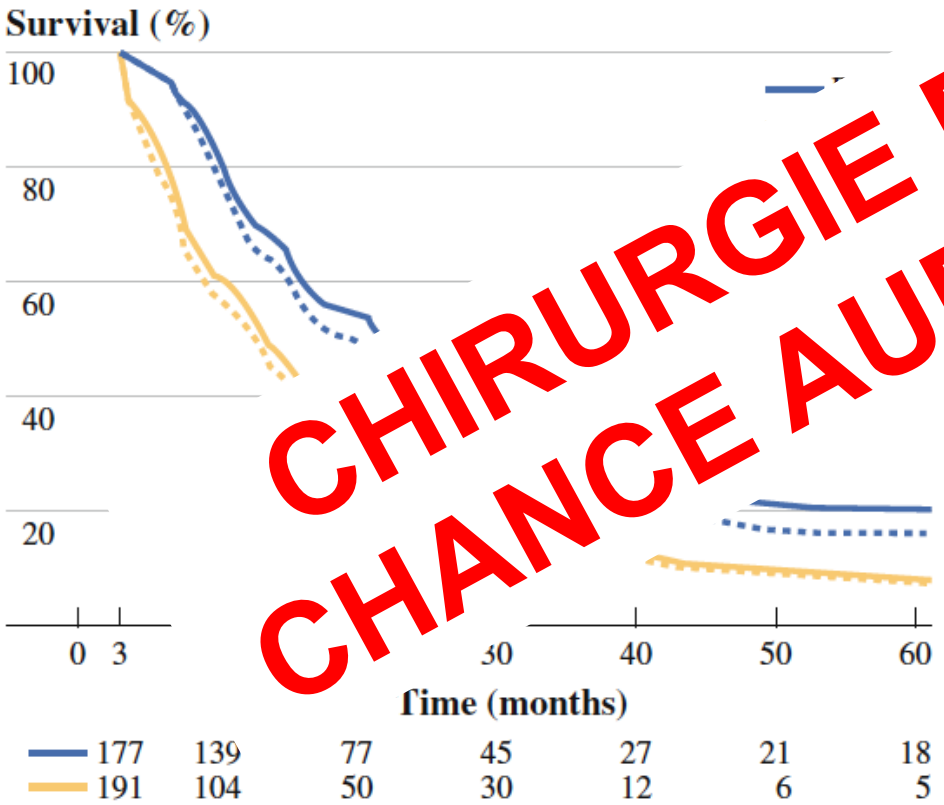


CHIRURGIE EINZIGE CHANCE AUF HEILUNG

…noren

…nres-Überleben

Insgesamt: 20-25%

Tumor vollständig entfernt:

JA: 35% 5-Jahres-Überleben

NEIN: 15% 5-Jahres-Überleben

Realität: schlechte Prognose
Gründe?

1. Frühstadium meist asymptomatisch
2. Früh Systemerkrankung
3. Fehlen von Screening-Tests
4. Schlechtes Ansprechen auf Chemotherapie

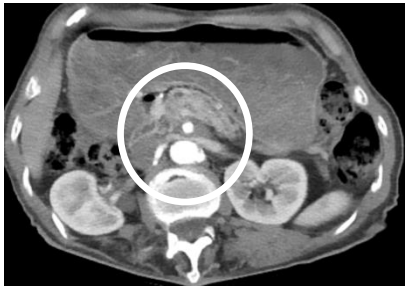
Klinische Tumoreinteilung

Resezierbar / «borderline» resezierbar

20%

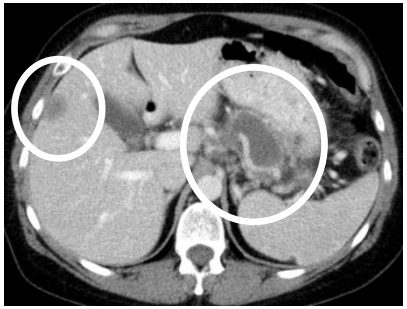
Lokal fortgeschritten

30%



Metastasiert

50%

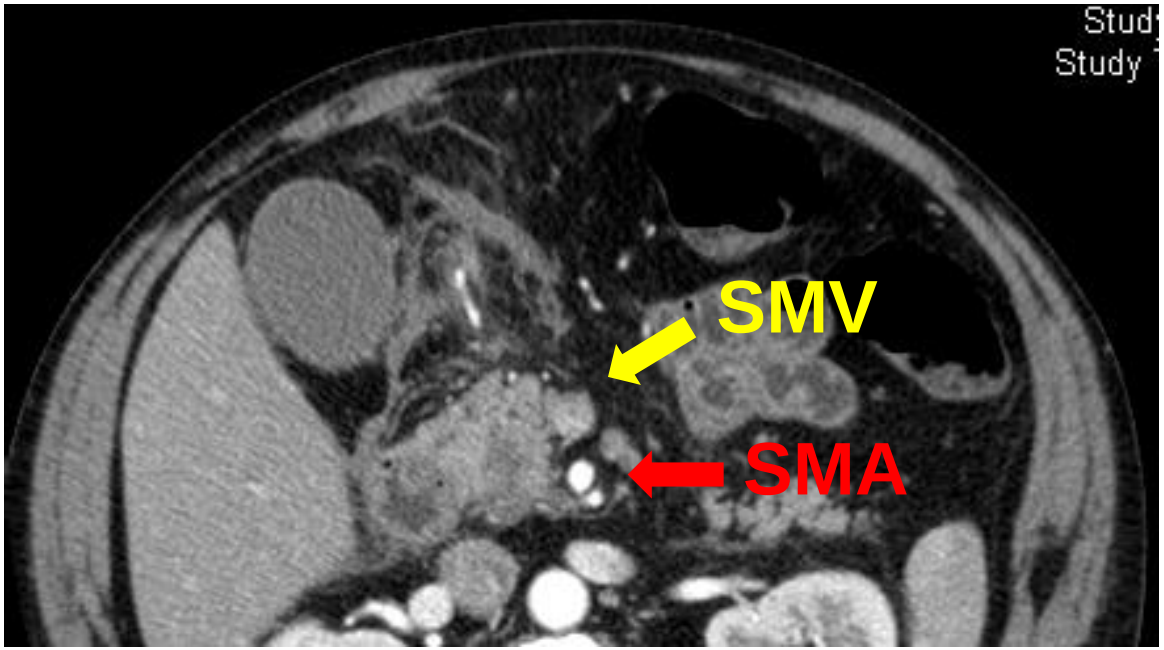


Definitionen

"Potentially resectable" =

Kein arterieller Kontakt mit Tumor UND

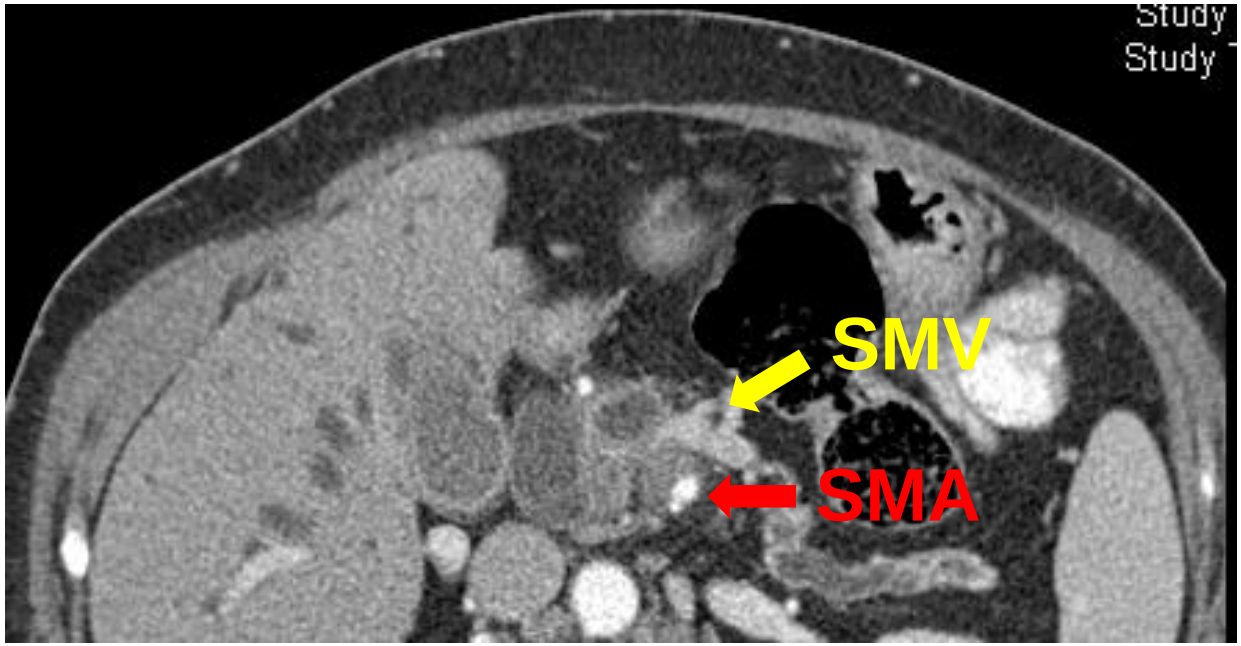
SMV/PV offen (vein abutment OK)



Definitionen

“Borderline resectable” =

Arterie (SMA, Leberarterie) max 180° ODER rekonstruierbare Venenbeteiligung



Definitionen

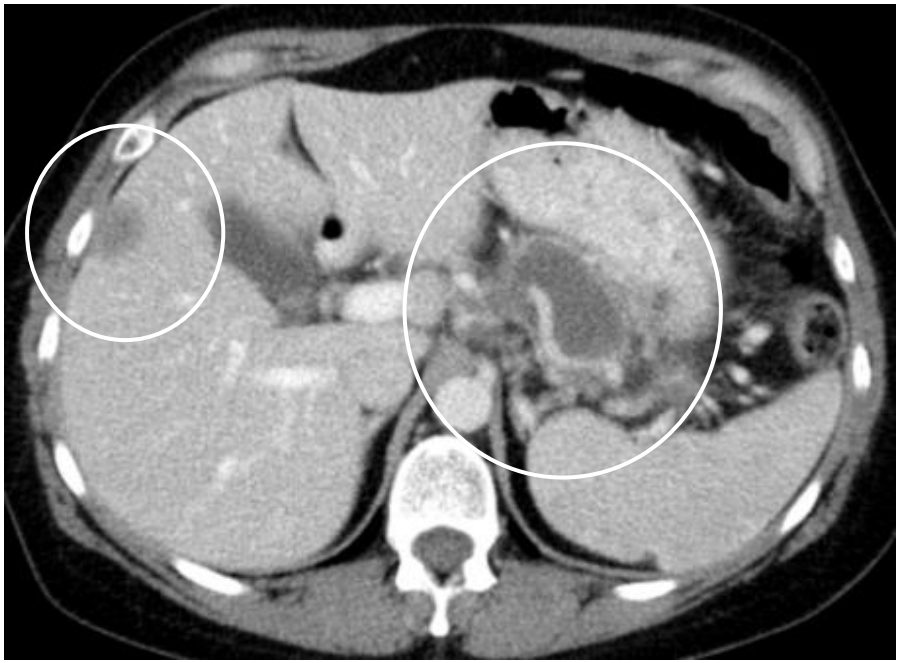
"Locally advanced" =

Arterie (SMA, Leberarterie) ummauert ODER nicht rekonstruierbare venöse Beteiligung

Definitionen

“Metastataic” =

Meist Lebermetastasen, selten Lungenmetastasen



Therapie:
Aktuell: State of the Art

Resezierbar / «borderline» resezierbar

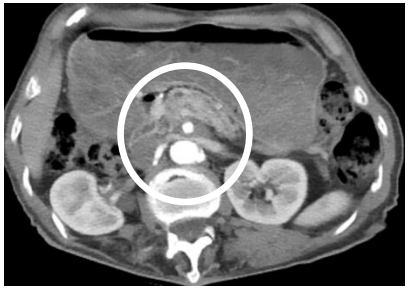
→ Chirurgische Resektion mit adjuvanter Chemotherapie

20%

Lokal fortgeschritten

→ Chemotherapie (+/- Bestrahlung)

30%



Metastasiert

→ Chemotherapie

50%

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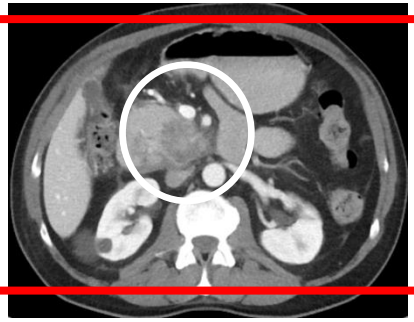
20%



Lokal fortgeschritten
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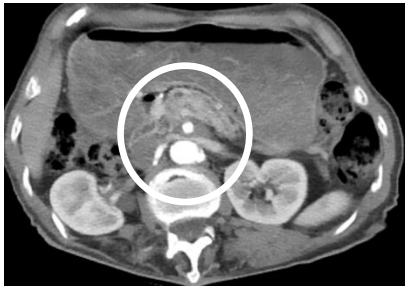

Metastasiert
→ Chemotherapie

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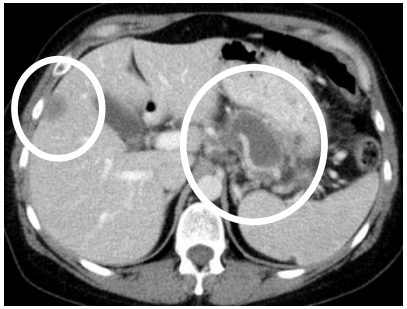
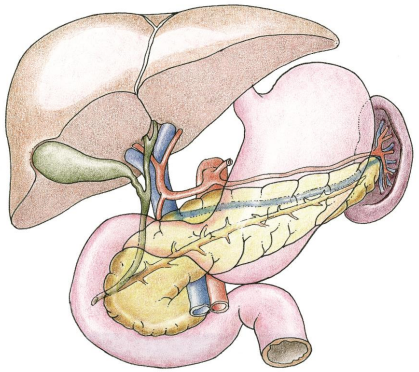


Vorbereitung auf die Operation

Tumorstaging

- Computertomographie
- Magnetresonanztomographie (mit Diffusion)
- Endoskopischer Ultraschall +/- FNP
- (PET-CT)



Vorbereitung auf die Operation

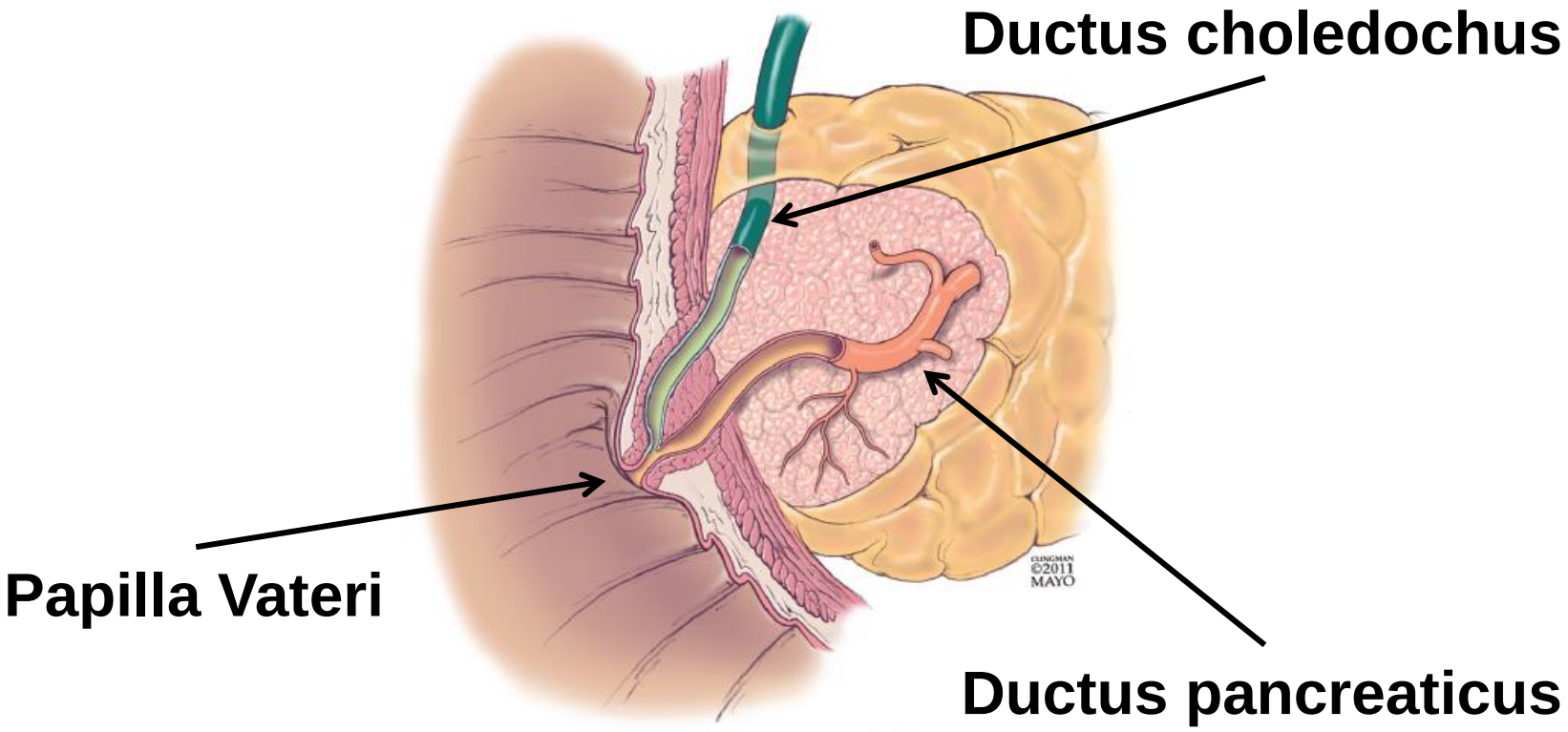
Ernährungssituation und Performance Status des Patienten

→ Alter alleine ist kein absoluter Wegweiser

→ Zusatznahrung?
Nasojejunale Sode?
TPN?
Oral impact?
→ Ziel anabole Stoffwechsellage

Vorbereitung auf die Operation

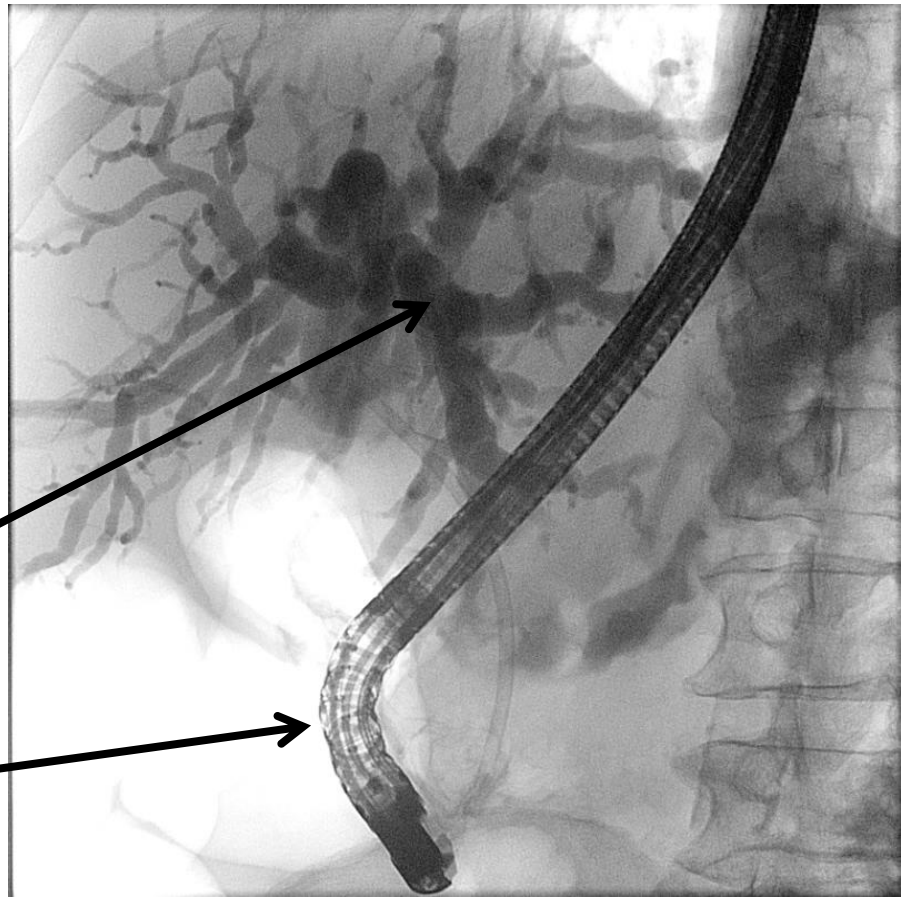
Sicherstellung des Galleabflusses



Vorbereitung auf die Operation

ERCP (endoskopisch retrograde cholangio-pancreatographie)

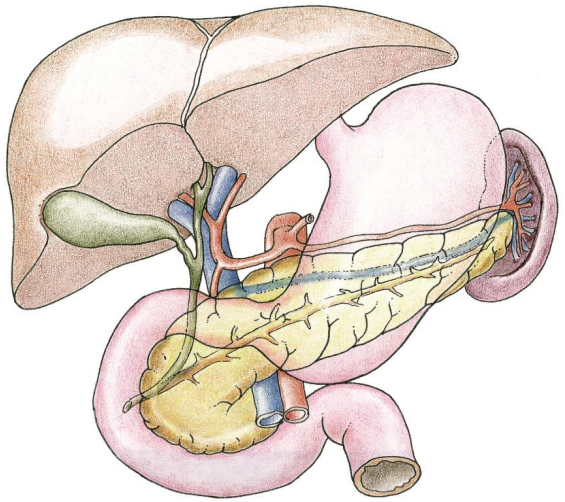
Alternative: PTCD



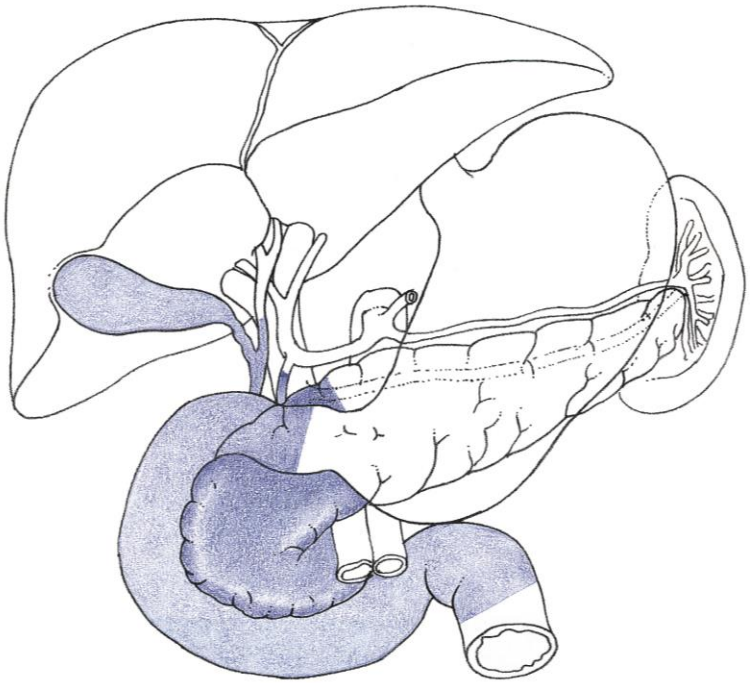
Pankreaschirurgie

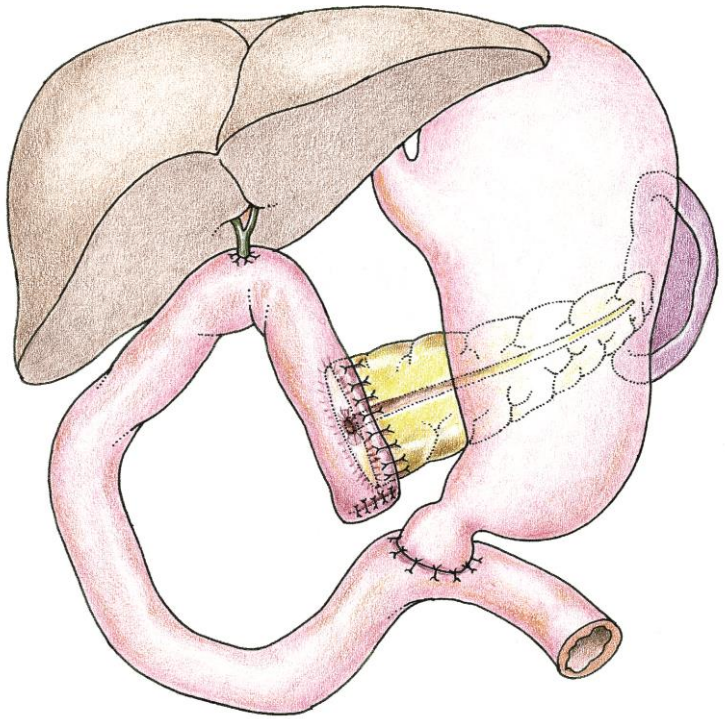
Operationsstrategie hauptsächlich abhängig von:

- **Tumortyp**
- **Tumorlokalisation**
- **Lokaler Ausdehnung des Tumors**

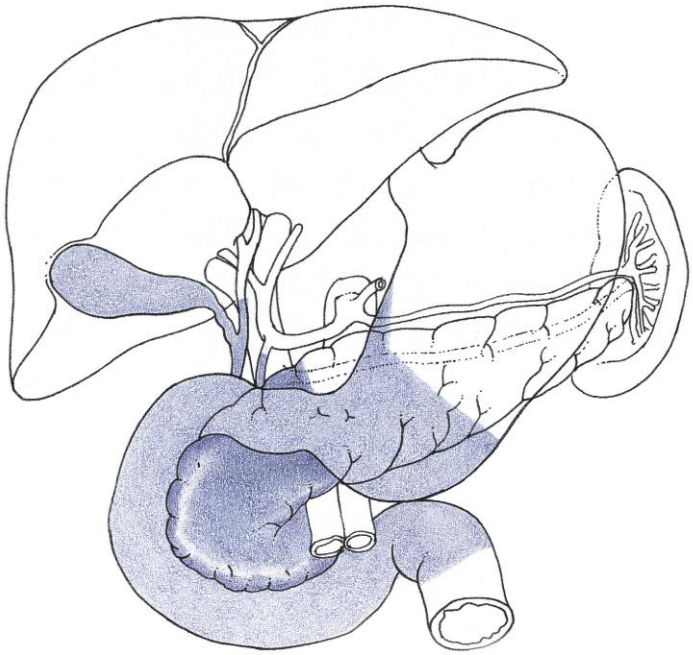


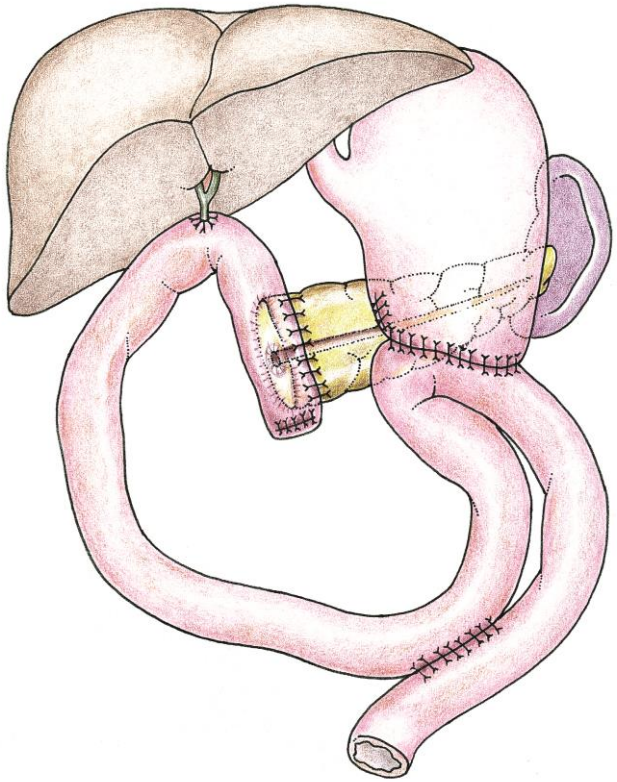
Pankreaskopfkarzinom
pp-Whipple (Duodeno-Pankreatektomie)



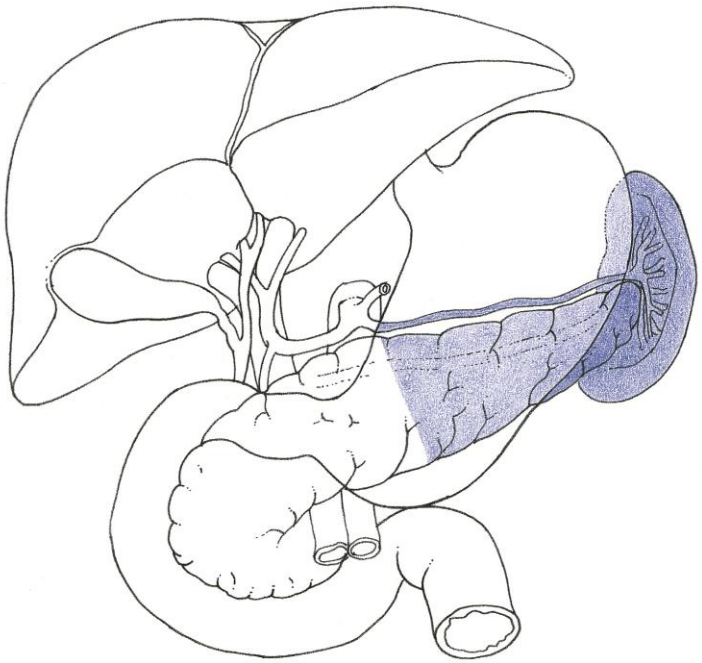


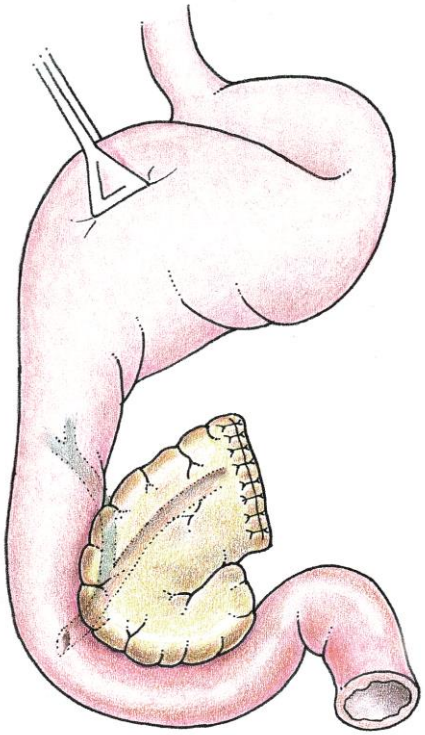
Pankreaskopf-Karzinom
Klassische Whipple-OP





Pankreasschwanz-Karzinom
Distale Pankreatektomie mit Splenektomie





Postoperativ

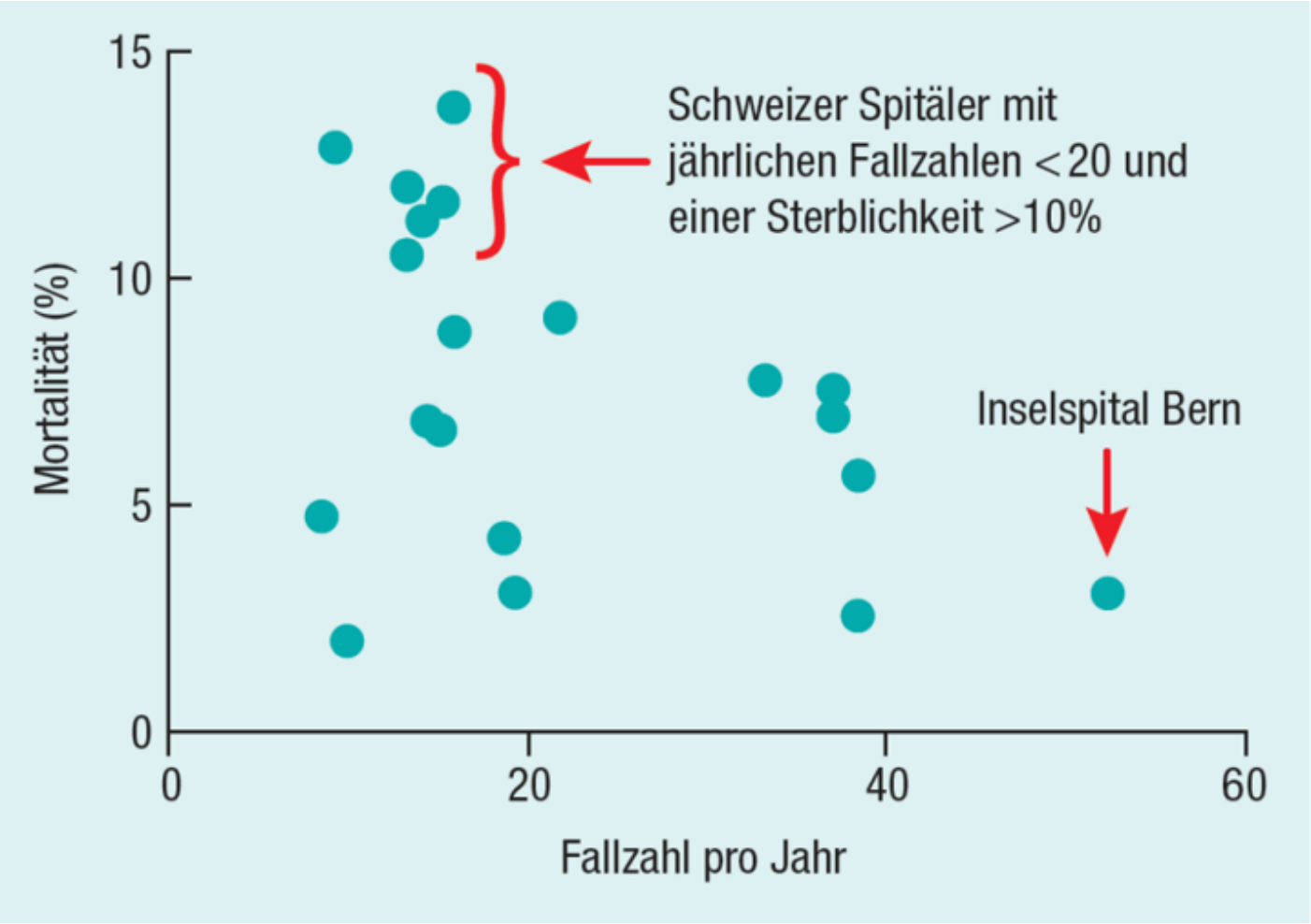
1. Naso-Jejunalsonde – Start feeding 6 Stunden postoperativ
2. TPN – nur in Ausnahmesituationen
3. Sandostatin/Pasireotide bei weichem Pankreas / kleinem Gang
4. PDA - DK
5. Mobilisation frühzeitig möglich / Atemtherapie
6. Drainagen für mindestens 3 Tage (Zug wenn Amylase/Lipase in Drainage < 3x Serumwert, Fördermenge < 200 ml)

Mögliche Folgen des Eingriffes

- **Allgemeine Komplikationen**
  - Blutung, Thrombose, Embolien, Infektion (Abszesse, Wundinfektion, Pneumonie), Lungenödem, Narbenhernie

- **Pankreaschirurgie-spezifische Komplikationen**
  - Anastomoseninsuffizienz
  - Anastomosenstenosen
    → Dilatation, Endoskopie, PTCD
  - verzögerte Magenentleerung (delayed gastric emptying)
  - Diabetes mellitus, exokrine Pankreasinsuffizienz

Mortalität


15
10
5
0
Mortalität (%)
0
20
40
60
Fallzahl pro Jahr
Schweizer Spitäler mit
jährlichen Fallzahlen <20 und
einer Sterblichkeit >10%
Inselspital Bern

State of the Art Therapie- resektable Tumoren - Gedanken

Hohe Rate an positivem Resektionsrand (R1 → 50-80%, Überleben reduziert im Vergleich zu R0 – 35% vs 15%)

Langzeitüberleben (>5-year) nach chirurgisch kompletter Resektion 20-25%

Adjuvante Chemotherapie verbessert Überleben ABER ¼ to ½ der resezierten Patienten kriegen NIE adjuvante Systemtherapie

Esposito et al, Ann Surg Onc 2008
Rau et al, Surgery 2012
Klinkenbijl et al., Ann Surg 1999
Neoptolemos et al., Lancet 2001
Oettle et al., JAMA 2007
Herman et al., JCO 2008

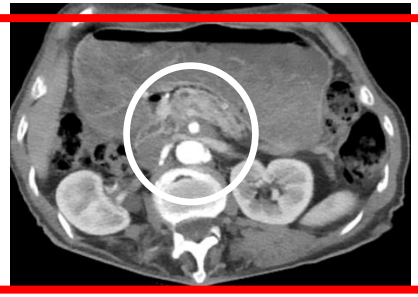
Therapie:
Aktuell: State of the Art

Resezierbar / «borderline» resezierbar
→ Chirurgische Resektion mit adjuvanter Chemotherapie

20%

Lokal fortgeschritten
→ Chemotherapie (+/- Bestrahlung)

30%



Metastasiert
→ Chemotherapie

50%

FACTS?

- Chemotherapie → sehr limitiert
- Bestrahlung in Europa selten, USA häufig
- Mittleres Überleben ca. 1 Jahr

Thermale Ablation
RFA, MVA, cryotherapy

- Anwendung bei Pankreaskarzinomen sehr eingeschränkt:
  - Komplexe anatomische Verhältnisse
  - Vielzahl lebenswichtiger Gefässe (SMA, Trunkus zöliakus/Leberarterie, VMS/Portalvene)
  - “Heat sink effect”

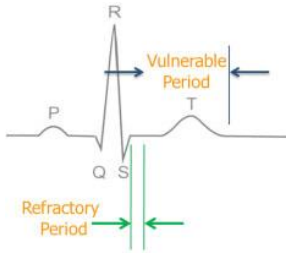
Spiliotis et al, Langenbecks Arch Surg 2007
Wu et al, J Surg Oncol 2006
Frigerio et al, J Hepatobiliary Pancreat Sci 2013
Xu et al, J Dig Dis 2008
Lygidakis et al, Hepatogastroenterology 2007

Neue Hoffnung?
Irreversible electroporation

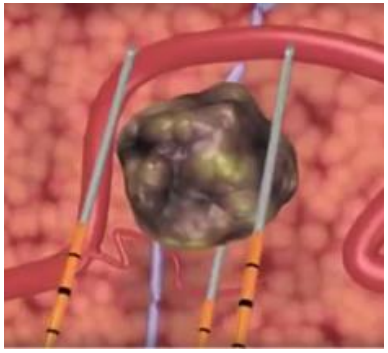
- Erstmals angewandt 1898
- Erstmals beim Menschen therapeutisch angewendet zur Ablation von Weichteilgewebe 2005
- Erstmals angewendet bei lokal fortgeschrittenem Pankreaskarzinom 2009

Irreversible electroporation

- Elektrischer Strom
- Kurze Impulse (70-90 us)
- Hohe Spannung (max. 3000 Volt)
- Appliziert während der refraktären Periode des Herzzyklus (50ms after the R wave on ECG)



→ Mikroporen (Nanometer Bereich) im Bereiche der Zellmembranen → Hämostasestörung → Apoptose



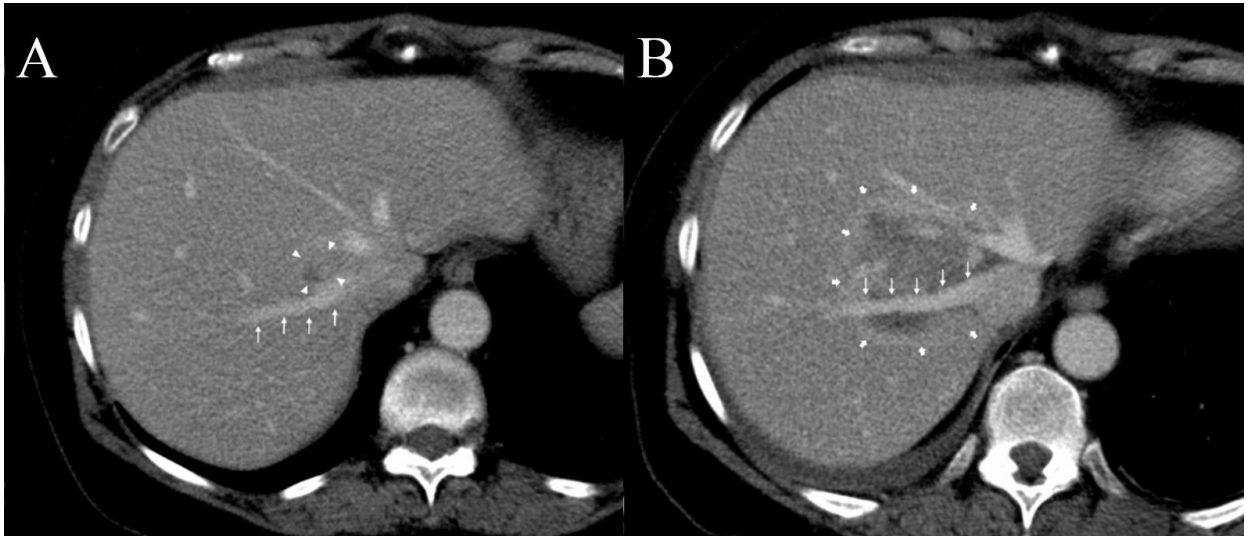
Irreversible electroporation

Kontraindikationen:

- Herz-Reizleitungsstörungen (AV-)
- Epilepsie
- Kürzlich stattgehabter Herzinfarkt (<2 months)
- Metallstent (nicht entfernbar) im Ablationsgebiet

Vorteile der IRE

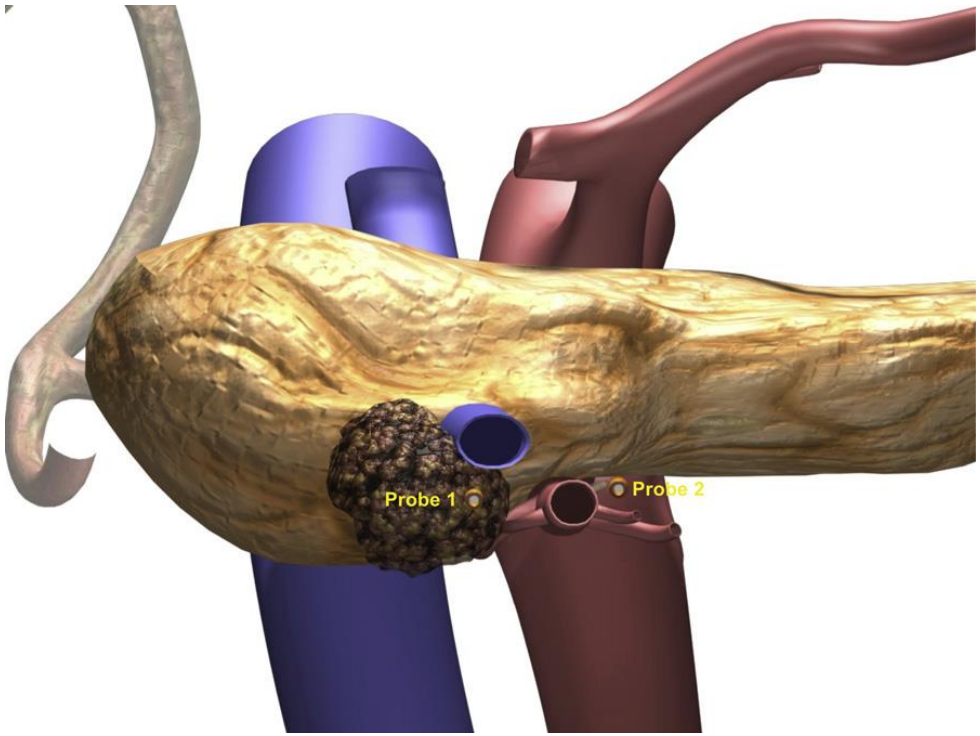
- → Elastin, Kollagen und weitere strukturelle Komponenten werden nicht zerstört
  → Gefässe – Gänge werden geschont
- → Kein “heat sink effect”



Dollinger et al, PLOS one 2015

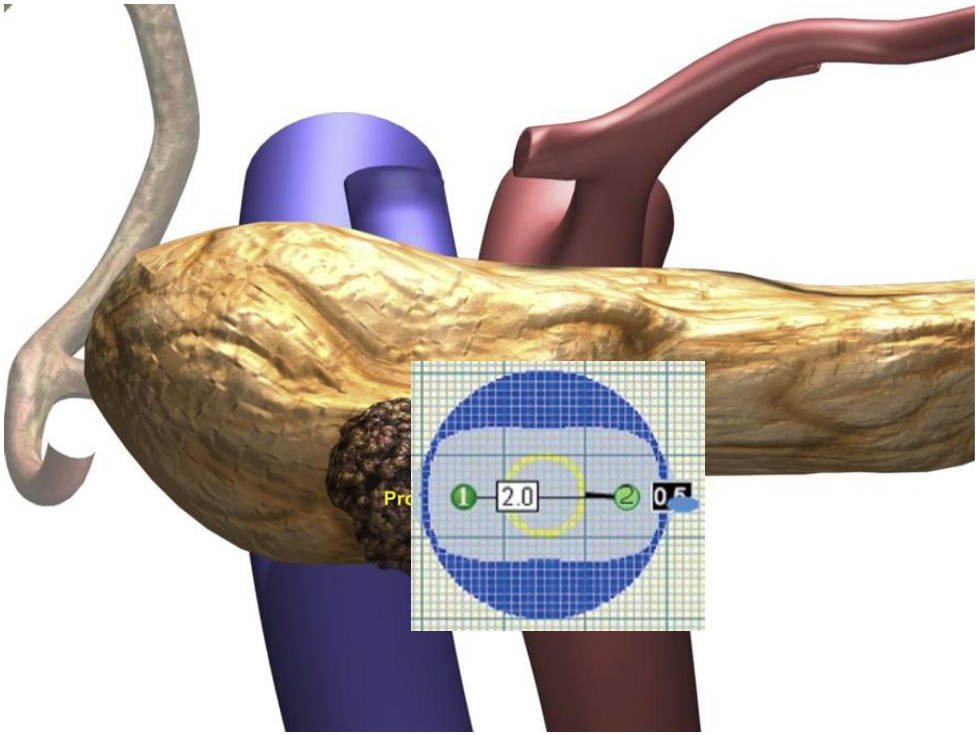
Wann wird IRE beim Pankreaskarzinom angewendet?

“Margin accentuation” für Karzinome, welche eine hohe Wahrscheinlichkeit haben, R1 reseziert zu werden (-80% der Tumore)



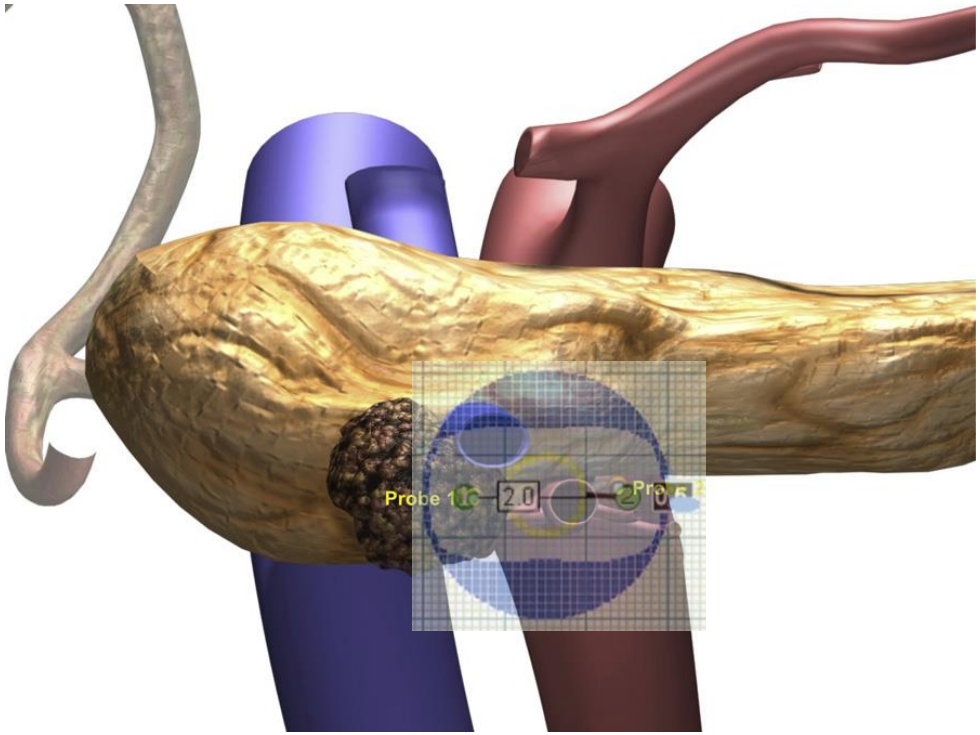
Kwon et al, Surgery 2014

Wann wird IRE beim Pankreaskarzinom angewendet?



Kwon et al, Surgery 2014

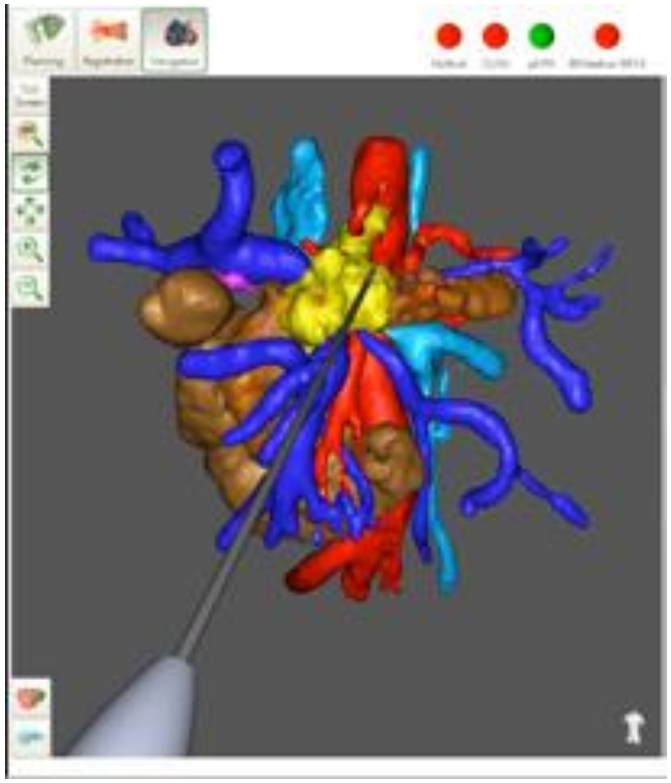
Wann wird IRE beim Pankreaskarzinom angewendet?



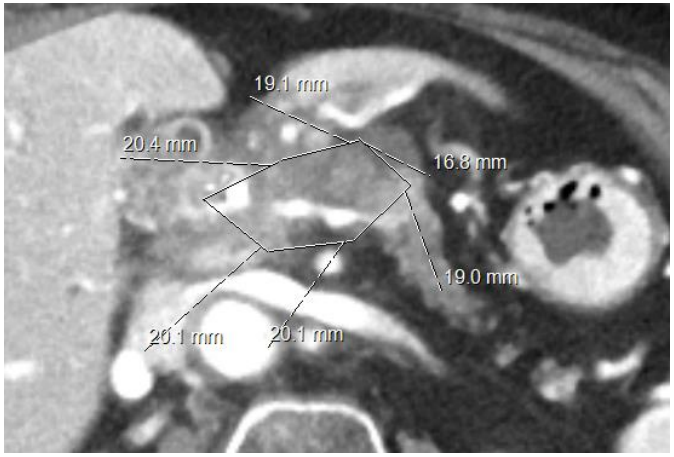
Kwon et al, Surgery 2014

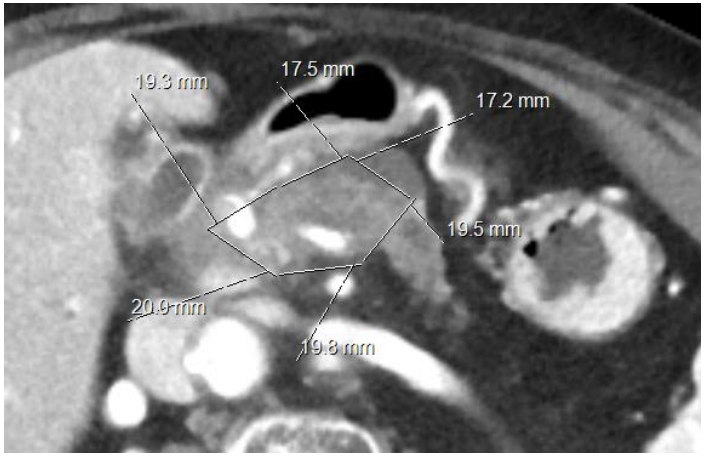
Wann wird IRE beim Pankreaskarzinom angewendet?

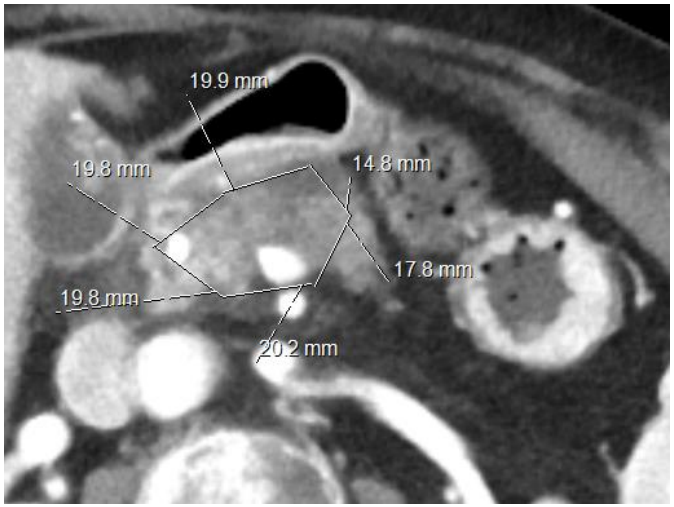
- In situ IRE bei lokal fortgeschrittenen Pankreaskarzinomen

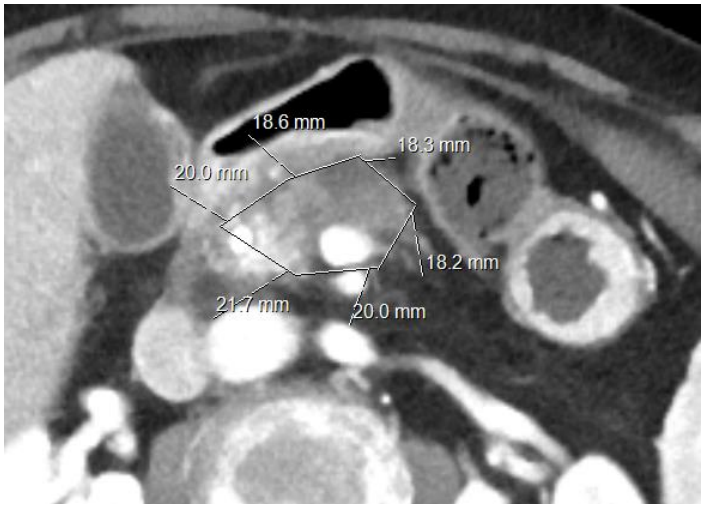


Wann wird IRE beim Pankreaskarzinom angewendet?









Stand des Wissens

- Keine randomisierte Studie
- Multiple “case series” mit/ohne Vergleichsgruppe, “case reports”

Current evidence

Ann Surg Oncol (2013) 20:S443–S449
DOI 10.1245/s10434-012-2736-1

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

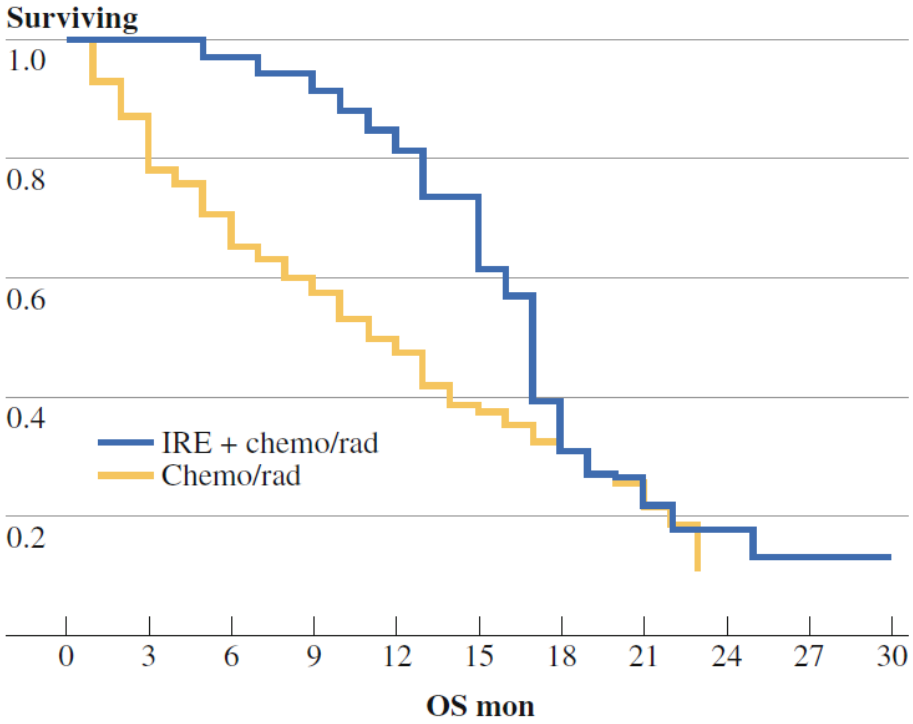
ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

Irreversible Electroporation in Locally Advanced Pancreatic Cancer: Potential Improved Overall Survival

Robert C. G. Martin II, MD, PhD, FACS[1], Kelli McFarland, MD[2], Susan Ellis, OCN[1], and Vic Velanovich, MD, FACS[2]

- Propensity-score matched nach 4 Monaten “neo-adjuvanter” Chemo/XRT
- Gruppe 1: Chemo/XRT (85 pts)
- Gruppe 2: IRE + Chemo/XRT (54 pts, 19 pts mit gleichzeitiger Pankreasresektion)

Current evidence



- Local progression-free survival: 14 vs. 6 Monate p=0.01
- Distant progression-free survival: 15 vs. 9 Monate p=0.02
- Overall survival: 20.2 vs. 11 Monate p=0.03

Current evidence

PAPERS OF THE 135TH ASA ANNUAL MEETING

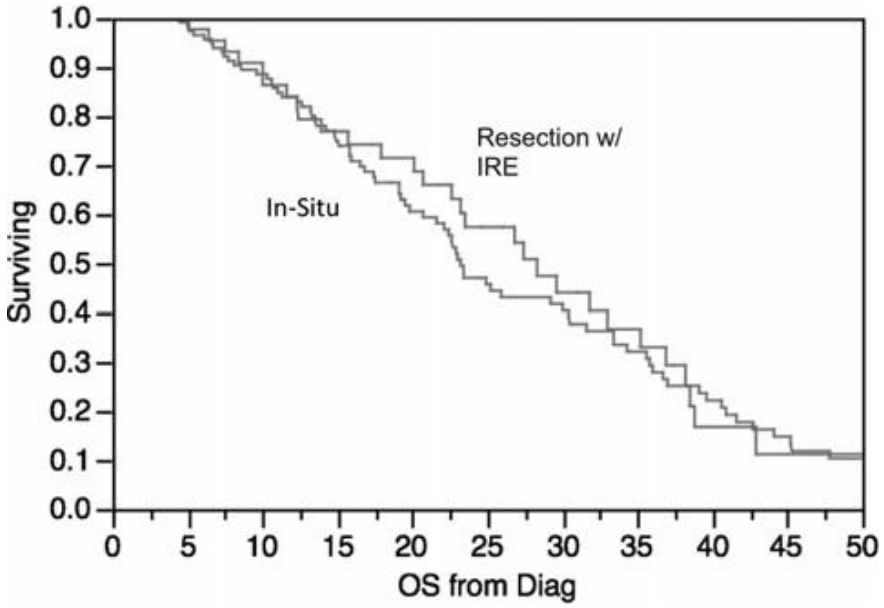
Treatment of 200 Locally Advanced (Stage III) Pancreatic Adenocarcinoma Patients With Irreversible Electroporation

Safety and Efficacy

Robert C. G. Martin, II, MD, PhD, FACS, David Kwon, MD, FACS,† Sricharan Chalikonda, MD, FACS,‡ Marty Sellers, MD, MPH, FACS,§ Eric Kotz, MD,¶ Charles Scoggins, MD, MBA, FACS,* Kelly M. McMasters, MD, PhD, FACS,* and Kevin Watkins, MD, FACS||*

- Grösste Studie mit insgesamt 200 Patienten (150 mit in situ IRE, 50 mit margin-accentuation IRE)
- Juli 2010 – Oktober 2014

Current evidence



- Median f/u 29 Monate
- Median PFS: 12.4 Monate, distant PFS 16.8 Monate
- Median overall survival: 28.3 Monate für margin accentuation IRE, 23.2 Monate für in situ IRE vs. < 12 Monate bei Patienten mit Chemo-(XRT)

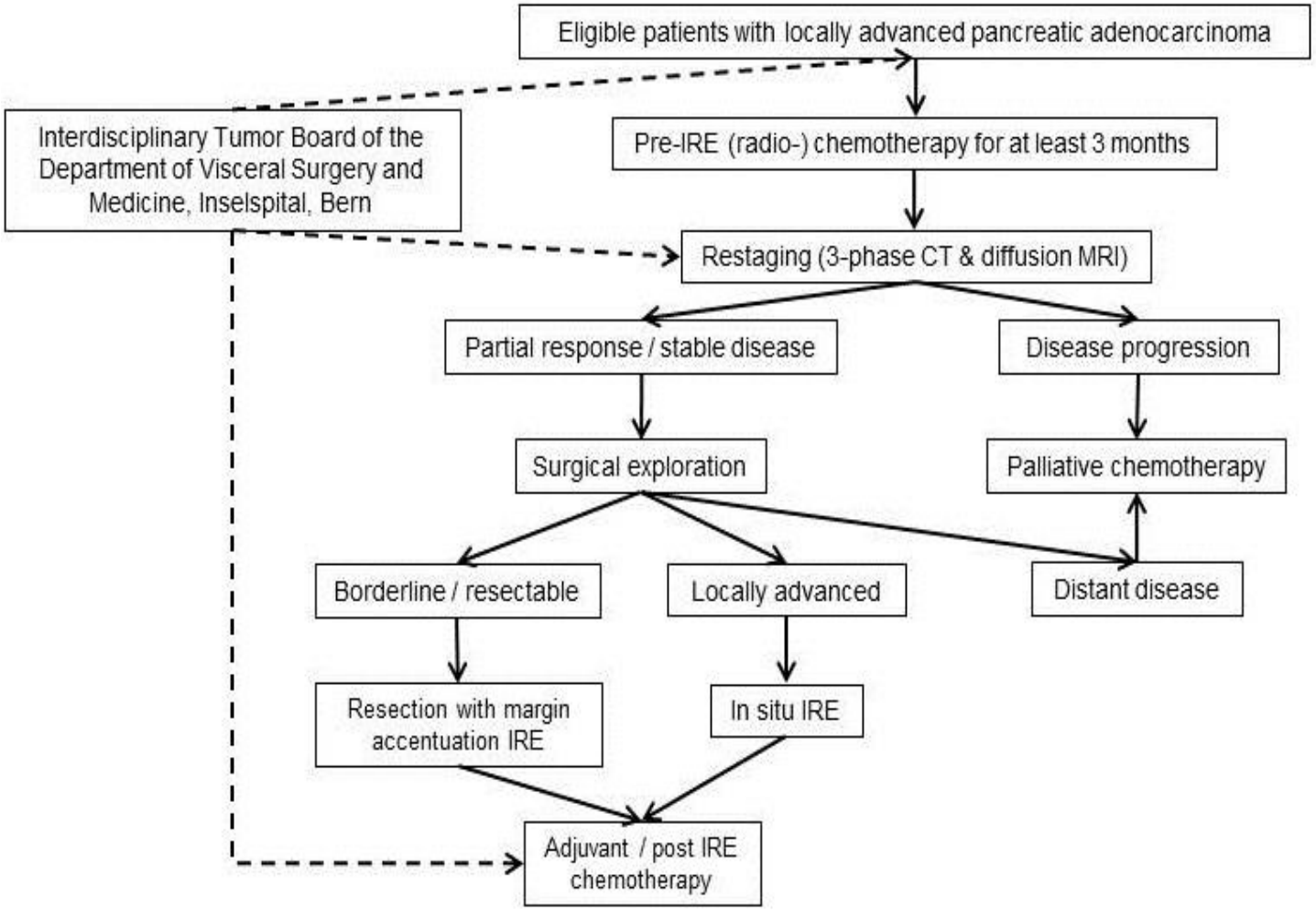
Komplikationen

- Herzrhythmusstörungen
- Gastro-intest. Ulzera
- Blutung
- Infektion

In situ: 33%
Margin accentuation: 40%

- Mortality (2%) – Blutung aus Ulkus, Leberversagen, Lungenembolie

Bern – locally advanced PC



Bern – grenzwertig resezierbare PC?

- Gleiche Chirurgie wie zuvor – aber margin accentuation IRE nach chirurgischer Exploration mit dem Ziel, die R0 Resektionsrate zu erhöhen

Forschung

- Effect of ***margin accentuation IRE*** among patients with pancreatic cancer on short- and long-term outcomes

CTU[1]-Forschungs-Grants der Insel Gruppe für Nachwuchsforschende

- Impact of IRE on ***quality of life*** for patients with locally advanced pancreatic cancer

Life 2017
SAKK/CELGENE Grant
FOR RESEARCH ON PANCREATIC CANCER CARE

- ***Differential immunologic signature*** after pancreatic cancer treatment: does IRE lead to a prolonged and potent T-cell mediated immune response compared to surgical resection?

bernische krebsliga
ligue bernoise contre le cancer

Bitte bei lokal fortgeschrittenen Pankreaskarzinom-Patienten an die IRE/mich denken

Auch bei allen anderen Fragen…

Mathias Worni

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031 632 60 68
031 632 21 11 → Sucher: 7562

?

Thank you