Cancer pancreatis

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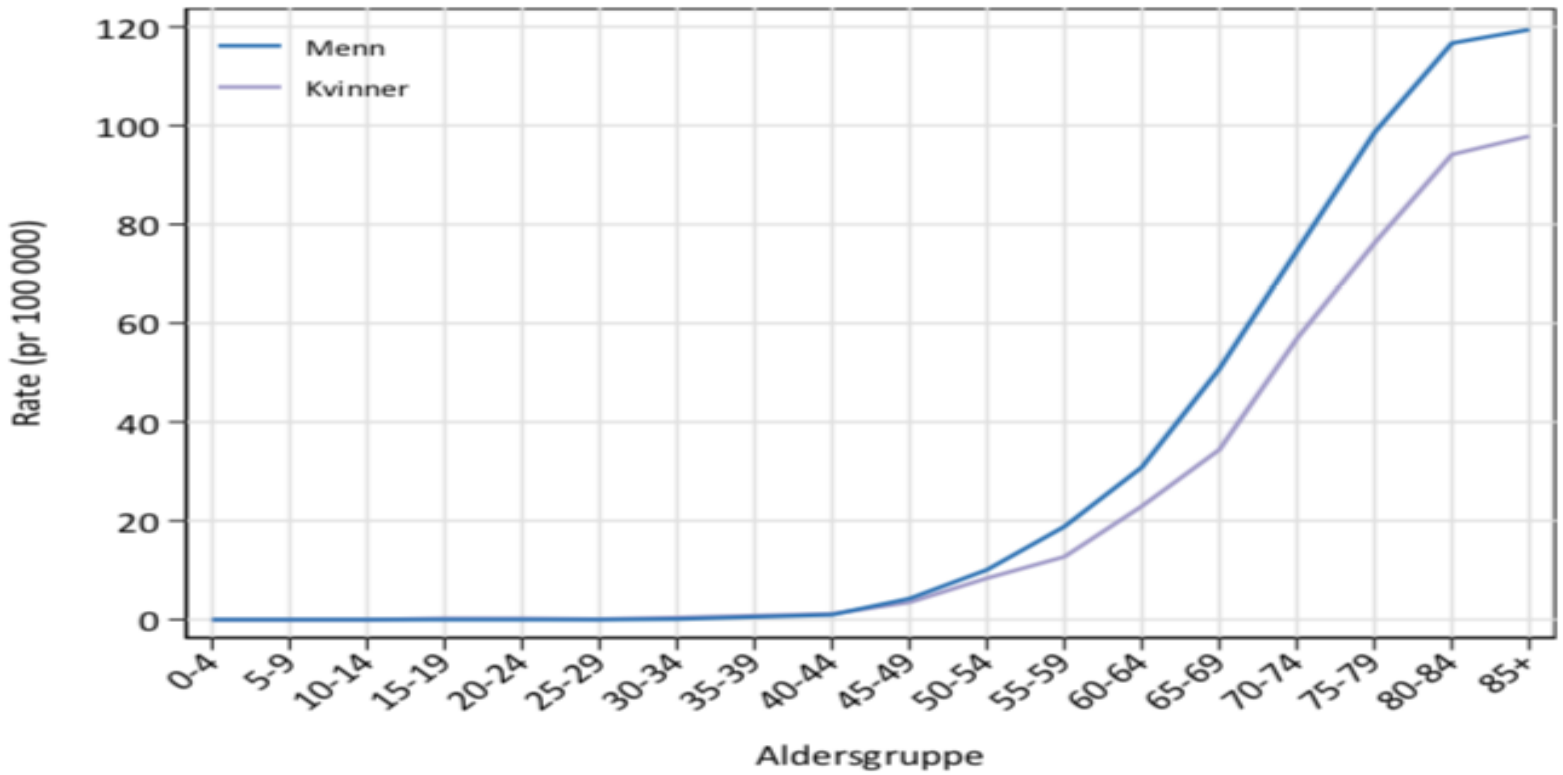
Epidemiologi pancreascancer

- Fjerde vanligste cancerrelaterte dødsårsak globalt
- Insidens Norge: 16:100 000
  - Ca 800 nye krefttilfeller årlig
- Reseksjonsrate: Ca 15-20 %
  - Relativ 5-års overlevelse 5 %
- Median OS: 6 mnd (hele kohorten)

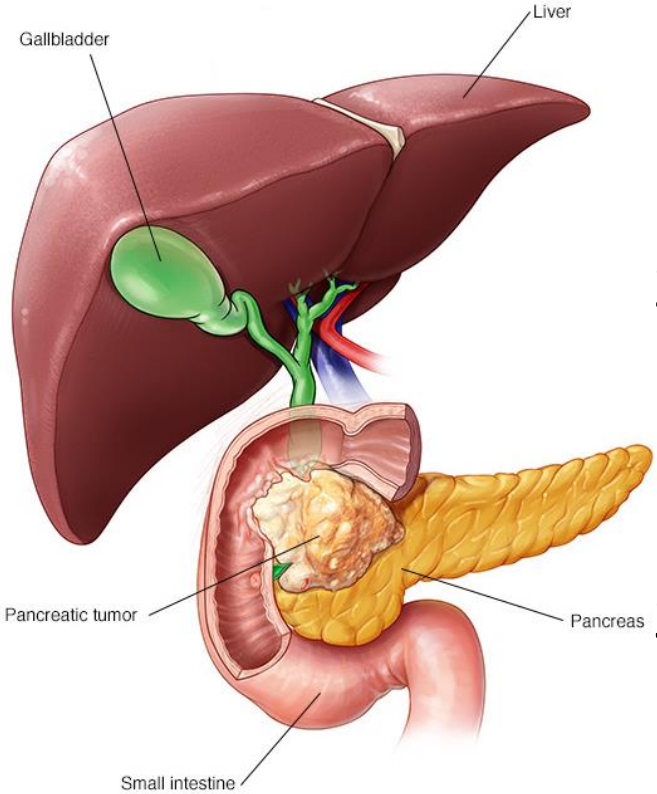
Insidens pancreascancer



Samlet insidens: 14/100.000

3.2: Insidensrater fordelt på 5-års aldersgrupper og kjønn.

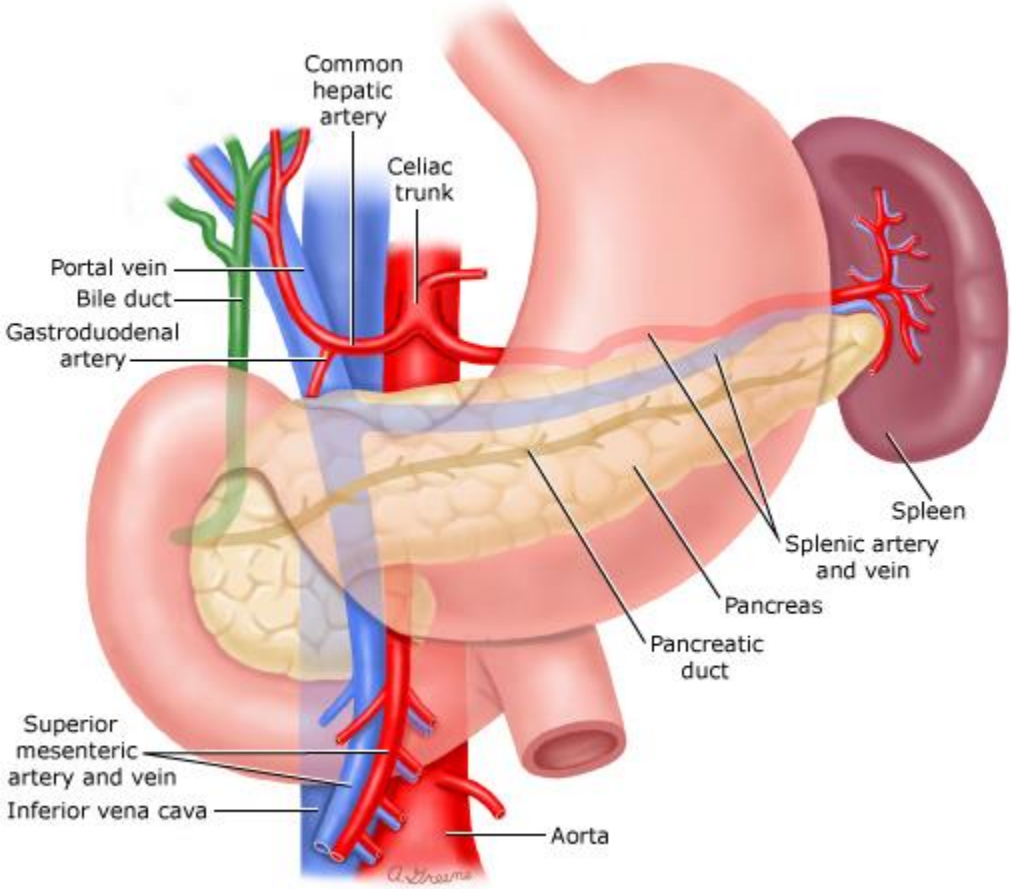
Maligne svulster i pancreas



1. Primære svulster
   - Eksokrine (ductalt og acinært)
   - Endokrine
2. Periampullære svulster
   - Cholangiocarcinomer
   - Papilla Vateri
   - Duodenalcancer
3. Metastaser
   - Eks fra nyre, mamma, lunge

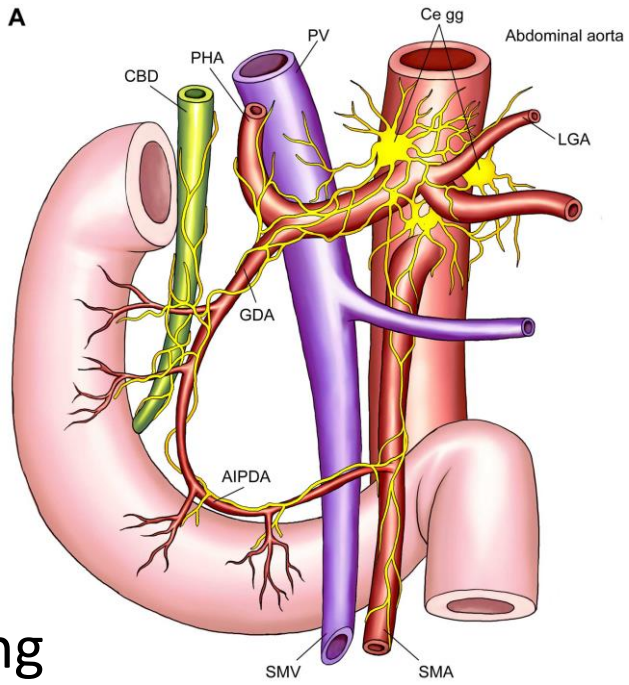
Forstadier til cancer, cystiske pancreastumores

Pancreas anatomi



Tumor karakteristika

- ¾ tumores beliggende i caput
- Aggressiv lokal vekst
  - T1 ➔T4 ca 1 år
  - Perineural innvekst hos 70-80 %
  - Tidlig lymfeknutespredning
  - Karinnvekst
- Tidlig fjernspredning
  - Tumor < 1 cm: 10 % fjernspredning
  - ¾ metastaser ved diagnosetidspunktet



Liang DK et al, BBA Reviews (2016) Yu et al, Gut (2015)

Risikofaktorer

- Kronisk pancreatitt
- Overvekt
- Røyking
- Alkoholoverforbruk
- Diabetes mellitus type 1 og 2
- Arv

Symptomer/funn ved pancreascancer

• Gulsott/Icterus	70 %
• Vekttap	50 - 90 %
• Ernæringssvikt	50 - 75 %
• Smerter	75 - 80 %
• Diabetes	15 - 40 %

Nasjonalt handlingsprogram for pancreaskreft 2017

Pakkeforløp pancreaskreft

Kriterier for henvisning pakkeforløp
Stille icterus
Radiologisk verifisert tumor i pancreas

Pakkeforløp pancreaskreft

Forløpsbeskrivelse		Forløpstid
Fra henvisning mottatt til første fremmøte utredende avdeling		8 kalenderdager
Fra første fremmøte i utredende avdeling til avsluttet utredning (beslutning tas)		14 kalenderdager
Fra avsluttet utredning til start behandling	Kirurgisk behandling	14 kalenderdager
Fra avsluttet utredning til start behandling	Medikamentell behandling	14 kalenderdager
Fra henvisning mottatt til start behandling	Kirurgisk behandling	36 kalenderdager
Fra henvisning mottatt til start behandling	Medikamentell behandling	36 kalenderdager

Multidisplinært team (MDT)

Kirurg

Onkolog

Radiolog

Patolog

Målsetning ved utredning

- **Tumordiagnostikk**
  - Benign/premalign/malign

CT, MR, EUS, UL/CEUS, evt biopsi

- **Resektabilitet**
  - Tumorutbredelse lokalt
    - Innvekst/ karaffeksjon
    - Resektabel – ikke reseketabel – borderline?
  - Metastasering

CT, MR

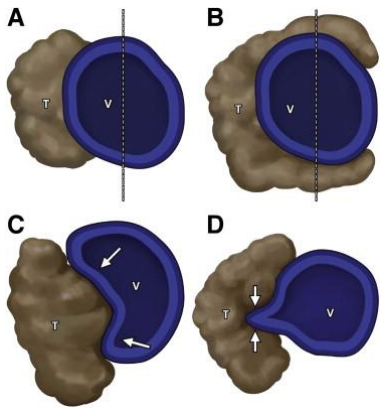
- **Operabilitet**
  - komorbiditet, alder, frailty?

CT- utredning

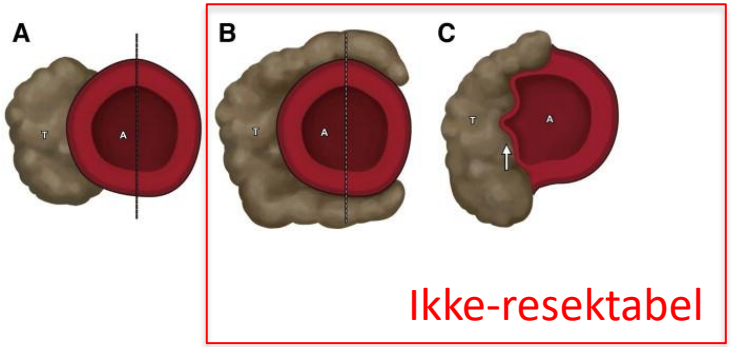
- CT-pancreas (tynnsnittserie)
  - Tidlig arteriell etter 20 sek.
  - Sen arteriell/parenkym etter 40 sek.
    - Ductalt adenocarc: hypovaskulære
    - NET: Tidlig oppladende, hypervaskulære
  - Portovenøs fase/lever parenkym etter 80 sek.
    - Levermetastaser
- CT abdomen/thorax

Al-Hawary et al, Gastroenterology (2014)
Wong et al. Abdom Imaging (2010)

Staging med CT: vene og arterie innvekst / encasement



A: < 180 grader
B: > 180 grader
C: < 180 grader med deformert vegg
D: ”Tear-drop” deformitet

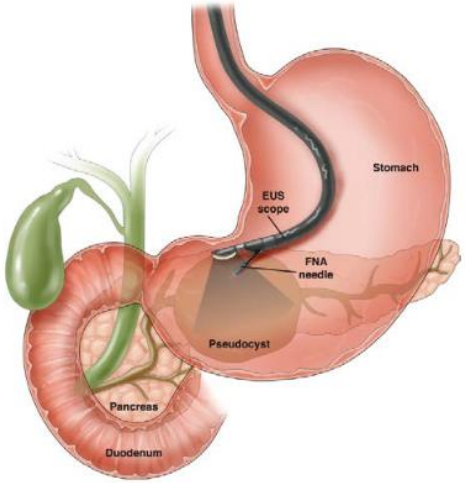


A: < 180 grader
B: > 180 grader
C: Affeksjon med deformert karvegg

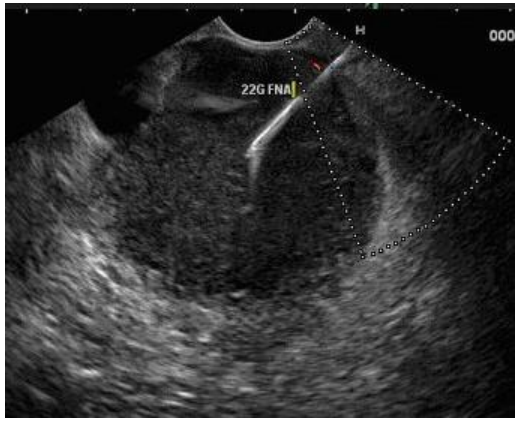
Al-Hawary et al, Gastroenterology (2014)

Endoskopisk ultralyd

- Små (< 2 cm) og uavklarte lesjoner
- Histologisk diagnose
  - Neoadjuvant kjemoterapi
  - Palliativ kjemoterapi

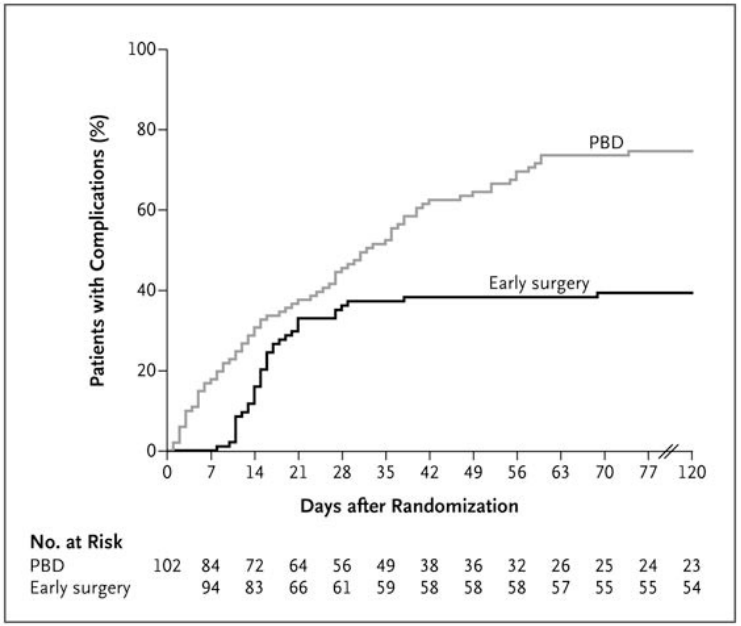


- FNA/FNB
  - Kun positive funn er konklusive



Endoskopisk retrograd cholangiografi

- Sjelden diagnostisk indisert
  - Eks Icterus uten påvist tumor
- Preoperativ stentbehandling ved icterus - omdiskutert
  - Symptomer (cholangitt, kløe)
  - Økt risiko for postopr komplikasjoner ved stenting
  - Høy Bilirubin – postop leversvikt
- Palliativ stentbehandling



van der Gaag et al, New Engl J og Medicine (2010)

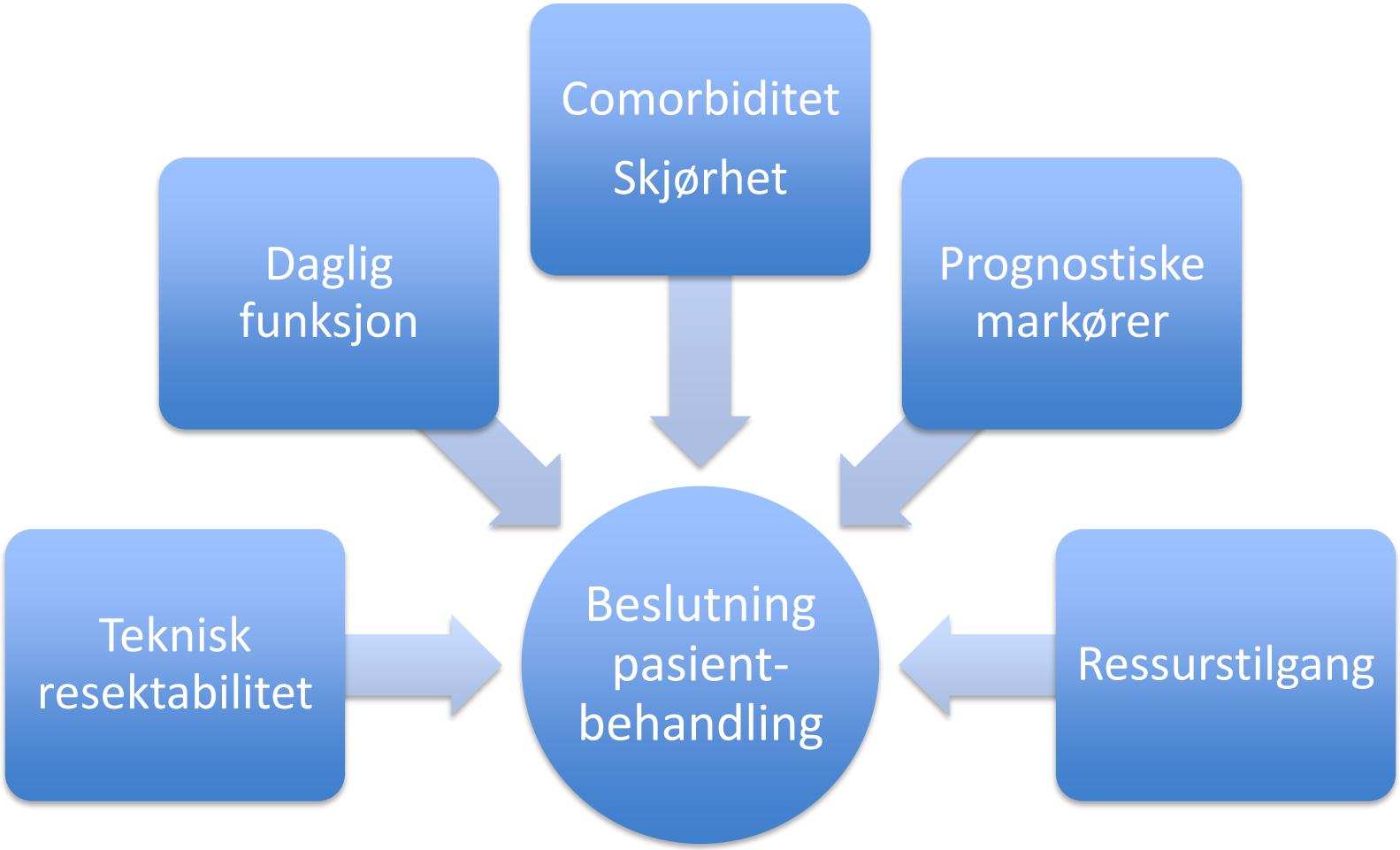
Andre tester

- CA 19-9
- CEA
- Mutasjonsanalyser p.t. ingen terapeutisk relevans
  - KRAS, p53 etc

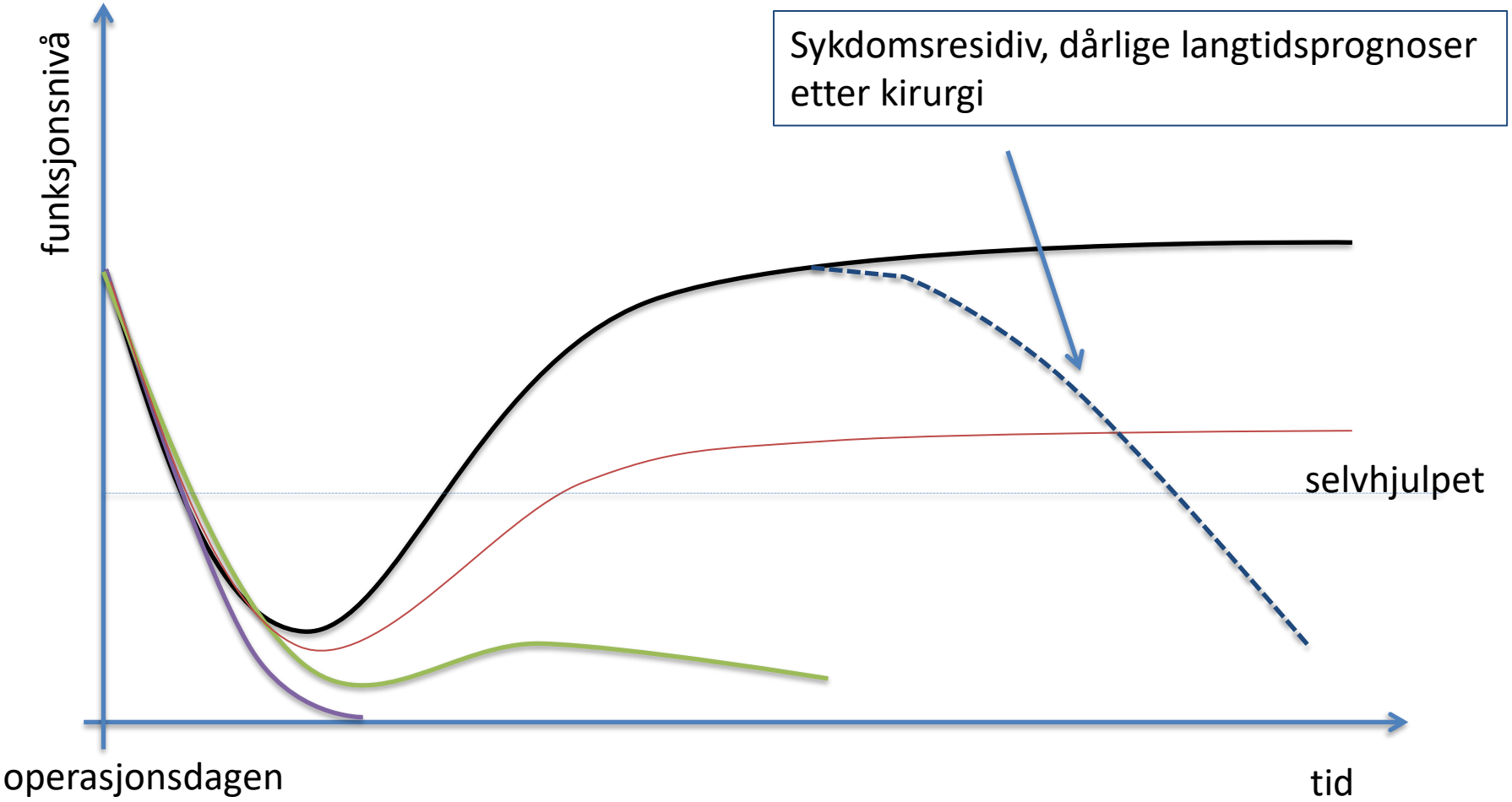
- Perkutan biopsi **ikke** indisert ved resektabel tumor

Utvelgelse til kirurgi

Utvelgelse til kirurgi



Funksjonsnivå før og etter operasjon



Modified Frailty Score og pancreaskirurgi

Frailty Index /CCI	Non-frail (0) n = 2797	Mild (1-2) n = 4496	Alvorlig (3-4) n = 107	p
Morbiditet (Clavien 4)	6.3 %	9.7 %	26.2 %	p < 0.001
Mortalitet	1.9 %	3.8 %	4.7 %	p < 0.001
Overlevelse (median, mnd)	23	19	15	p < 0.001

- Hele cohorten: Clavien IV: 8.7 %, mortalitet 3.1 %
- Modifed Frailty score: hjertesykdom, lungesykdom, nevrologisk sykdom, mental status, diabetes, funksjonsnivå++

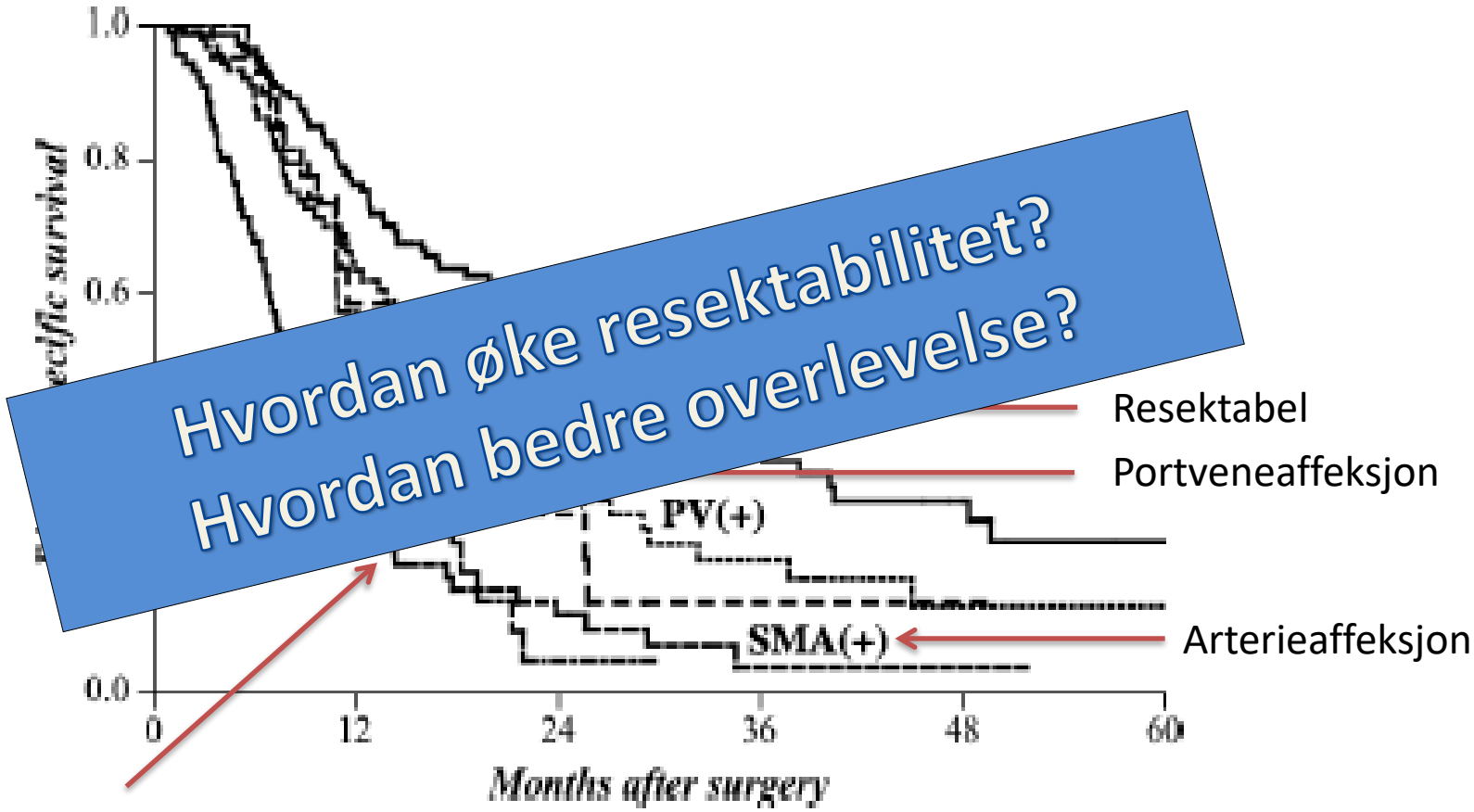
Konstantinidis I et al, abstract, J Clin Onc (2017)

Resektabilitetsvurdering

Status	Arterie	Vene
Resektabel	Ingen kontakt mellom tumor og arterier	Ingen eller < 180° kontaktflate mellom tumor og vene
Borderline resektabel	< 180° kontaktflate mot arterie	180° kontaktflate mot vene med mulighet for rekonstruksjon
Ikke-resektabel	Fjernspredning > 180° tumorkontakt mot arterie	Ikke rekonstruerbare vener

National comprehensive cancer network (NCCN)- 2015
International Study Group of Pancreatic Surgery (ISGPS) -2014

Sykdomsspesifikk overlevelse jfr NCCN-kriteriene



Hvordan øke resektabilitet?
Hvordan bedre overlevelse?

Yamada S et al, Pancreas (2013)

Neoadjuvant kjemoterapi

- Metastudier og retrospektive studier:
  - Økt andel frie reseksjonsmarginer (R0) ?
  - Mindre perinevral innvekst ?
  - Lavere andel positive lymfeknuter ?
  - Antatt forbedret overlevelse
    - Bordeline resektable - venereseksjon
- Ekskludere pasienter med rask sykdomsprogress

Schorn et al, Cancer treatment reviews (2017)
Papalezova et al, Journal of Surgical Oncology (2012)
Katz MH et al, Cancer (2012)
Ferrone et al, Ann Surg (2015)
Delpero et al, Ann Surg Onc (2015)

Kontroverser neoadjuvant kjemoterapi

- Marginal objektiv (radiologisk) respons på CT
  - Downsizing sjelden (<1 %)
  - Stable disease vanligst (ca 70 %)
    - Nye RECIST (respons) kriterier må utarbeides? Bruk av MR?
- Alle resektable eller bare borderline pasienter?
- 1/3 av pasientene ekskluderes for kirurgi
- Høy andel R0- Underestimering?

Katz MH et al, Cancer (2012)
Laurence et al J Gastrointes Surg. (2012)
Chiaro et al, Jama Surg (2017)

Neoadjuvant kjemoterapi

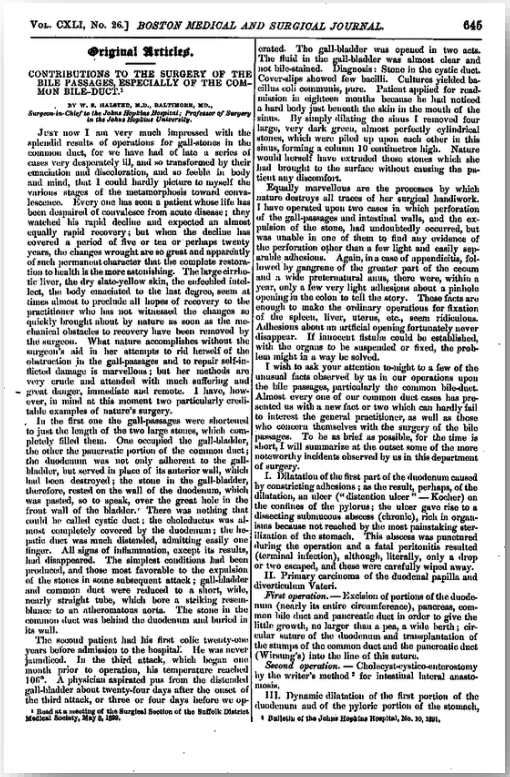
STUDY PROTOCOL Open Access

Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) – study protocol for a national multicentre randomized controlled trial

Knut Jørgen Labori[1*], Kristoffer Lassen[1], Dag Hoem[2], Jon Erik Grønbech[3,4], Jon Arne Søreide[5,6], Kim Mortensen[7], Rune Smaaland[8], Halfdan Sorbye[9,10], Caroline Verbeke[11,12] and Svein Dueland[13]

Kirurgisk metode

William Halsted (1852-1922)



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Original Articles.

CONTRIBUTIONS TO THE SURGERY OF THE BILE PASSAGES, ESPECIALLY OF THE COMMON BILE-DUCT.[1]

BY W. S. HALSTED, M.D., BALTIMORE, MD.,
Surgeon-in-Chief to the Johns Hopkins Hospital; Professor of Surgery in the Johns Hopkins University.

Just now I am very much impressed with the splendid results of operations for gall-stones in the common duct, for we have had of late a series of cases very desperately ill, and so transformed by their emaciation and discoloration, and so feeble in body and mind, that I could hardly picture to myself the various stages of the metamorphosis toward convalescence. Every one has seen a patient whose life has been despaired of convalesce from acute disease; they watched his rapid decline and expected an almost equally rapid recovery; but when the decline has covered a period of five or ten or perhaps twenty years, the changes wrought are so great and apparently of such permanent character that the complete restoration to health is the more astonishing. The large cirrhotic liver, the dry slate-yellow skin, the enfeebled intellect, the body emaciated to the last degree, seem at times almost to preclude all hopes of recovery to the practitioner who has not witnessed the changes so quickly brought about by nature as soon as the mechanical obstacles to recovery have been removed by the surgeon. What nature accomplishes without the surgeon's aid in her attempts to rid herself of the obstruction in the gall-passages and to repair self-inflicted damage is marvellous; but her methods are very crude and attended with much suffering and great danger, immediate and remote. I have, however, in mind at this moment two particularly creditable examples of nature's surgery.

In the first one the gall-passages were shortened to just the length of the two large stones, which completely filled them. One occupied the gall-bladder, the other the pancreatic portion of the common duct; the duodenum was not only adherent to the gall-bladder, but served in place of its anterior wall, which had been destroyed; the stone in the gall-bladder, therefore, rested on the wall of the duodenum, which was pasted, so to speak, over the great hole in the front wall of the bladder. There was nothing that could be called cystic duct; the choledoctus was almost completely covered by the duodenum; the hepatic duct was much distended, admitting easily one finger. All signs of inflammation, except its results, had disappeared. The simplest conditions had been produced, and those most favorable to the expulsion of the stones in some subsequent attack; gall-bladder and common duct were reduced to a short, wide, nearly straight tube, which bore a striking resemblance to an atheromatous aorta. The stone in the common duct was behind the duodenum and buried in its wall.

The second patient had his first colic twenty-one years before admission to the hospital. He was never jaundiced. In the third attack, which began one month prior to operation, his temperature reached 106°. A physician aspirated pus from the distended gall-bladder about twenty-four days after the onset of the third attack, or three or four days before we operated. The gall-bladder was opened in two acts. The fluid in the gall-bladder was almost clear and not bile-stained. Diagnosis: Stone in the cystic duct. Cover-slips showed few bacilli. Cultures yielded bacillus coli communis, pure. Patient applied for readmission in eighteen months because he had noticed a hard body just beneath the skin in the mouth of the sinus. By simply dilating the sinus I removed four large, very dark green, almost perfectly cylindrical stones, which were piled up upon each other in this sinus, forming a column 10 centimetres high. Nature would herself have extruded these stones which she had brought to the surface without causing the patient any discomfort.

Equally marvellous are the processes by which nature destroys all traces of her surgical handiwork. I have operated upon two cases in which perforation of the gall-passages and intestinal walls, and the expulsion of the stone, had undoubtedly occurred, but was unable in one of them to find any evidence of the perforation other than a few light and easily separable adhesions. Again, in a case of appendicitis, followed by gangrene of the greater part of the cecum and a wide preternatural anus, there were, within a year, only a few very light adhesions about a pinhole opening in the colon to tell the story. These facts are enough to make the ordinary operations for fixation of the spleen, liver, uterus, etc., seem ridiculous. Adhesions about an artificial opening fortunately never disappear. If innocent fistulæ could be established, with the organs to be suspended or fixed, the problem might in a way be solved.

I wish to ask your attention to-night to a few of the unusual facts observed by us in our operations upon the bile passages, particularly the common bile-duct. Almost every one of our common duct cases has presented us with a new fact or two which can hardly fail to interest the general practitioner, as well as those who concern themselves with the surgery of the bile passages. To be as brief as possible, for the time is short, I will summarize at the outset some of the more noteworthy incidents observed by us in this department of surgery.

I. Dilatation of the first part of the duodenum caused by contracting adhesions; as the result, perhaps, of the dilatation, an ulcer ("distention ulcer" — Kocher) on the confines of the pylorus; the ulcer gave rise to a dissecting submucous abscess (chronic), rich in organisms because not reached by the most painstaking sterilization of the stomach. This abscess was punctured during the operation and a fatal peritonitis resulted (terminal infection), although, literally, only a drop or two escaped, and these were carefully wiped away.

II. Primary carcinoma of the duodenal papilla and diverticulum Vateri.

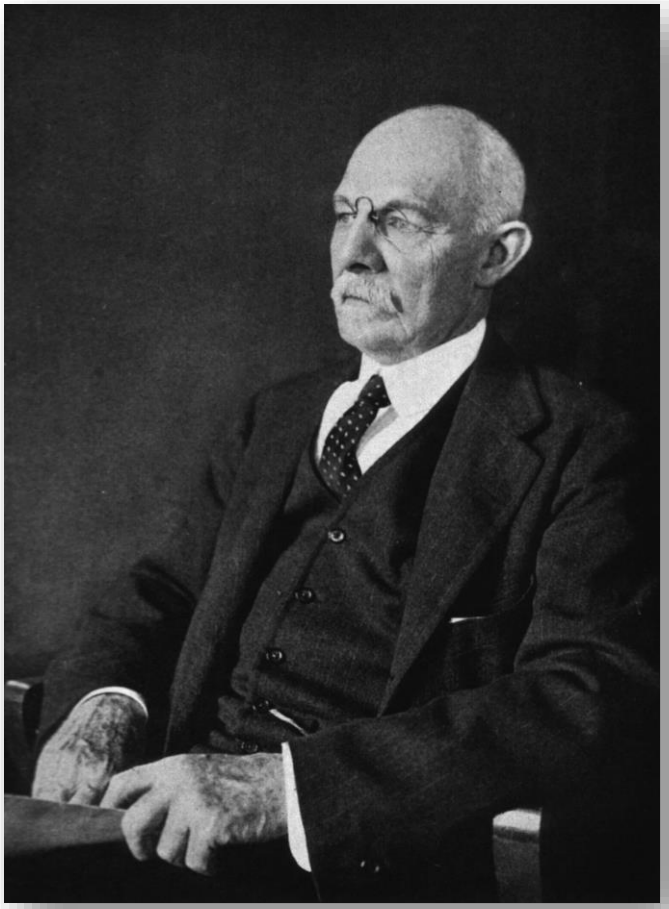
First operation. — Excision of portions of the duodenum (nearly its entire circumference), pancreas, common bile duct and pancreatic duct in order to give the little growth, no larger than a pea, a wide berth; circular suture of the duodenum and transplantation of the stumps of the common duct and the pancreatic duct (Wirsung's) into the line of this suture.

Second operation. — Cholecyst-cystico-enterostomy by the writer's method[2] for intestinal lateral anastomosis.

III. Dynamic dilatation of the first portion of the duodenum and of the pyloric portion of the stomach,

[1] Read at a meeting of the Surgical Section of the Suffolk District Medical Society, May 3, 1899.

[2] Bulletin of the Johns Hopkins Hospital, No. 10, 1891.



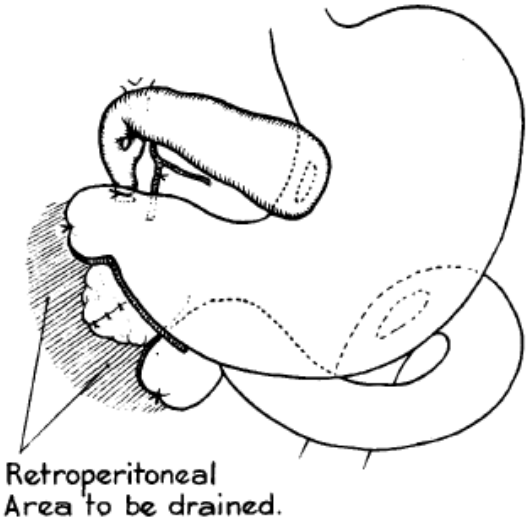
Contributions to the surgery of the bile passages, especially of the common bile-duct.
Halsted W. Boston Med Surg J. 1899

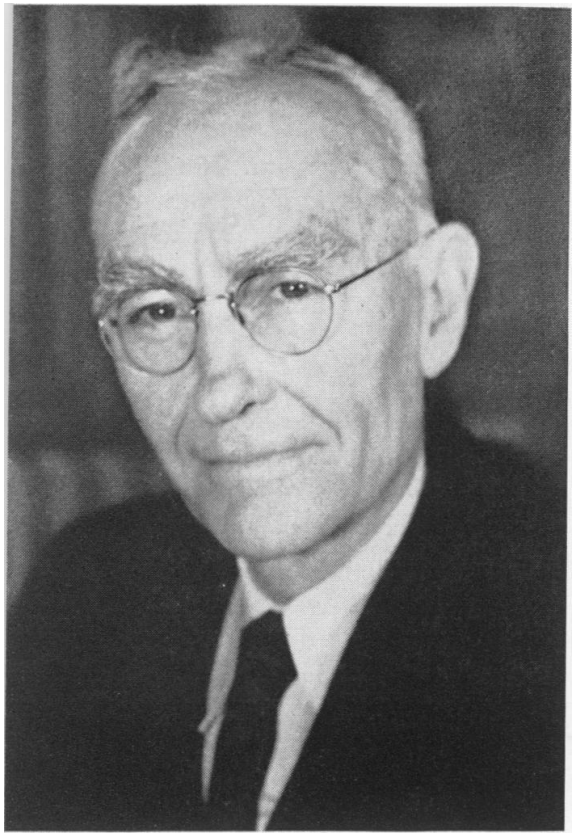
Allen Whipple (1881-1963)

TREATMENT OF CARCINOMA OF THE AMPULLA OF VATER

ALLEN O. WHIPPLE, M.D., WILLIAM BARCLAY PARSONS, M.D.,
AND CLINTON R. MULLINS, M.D.
NEW YORK, N. Y
FROM THE DEPARMENT OF SURGERY, COLUMBIA UNIVERSITY

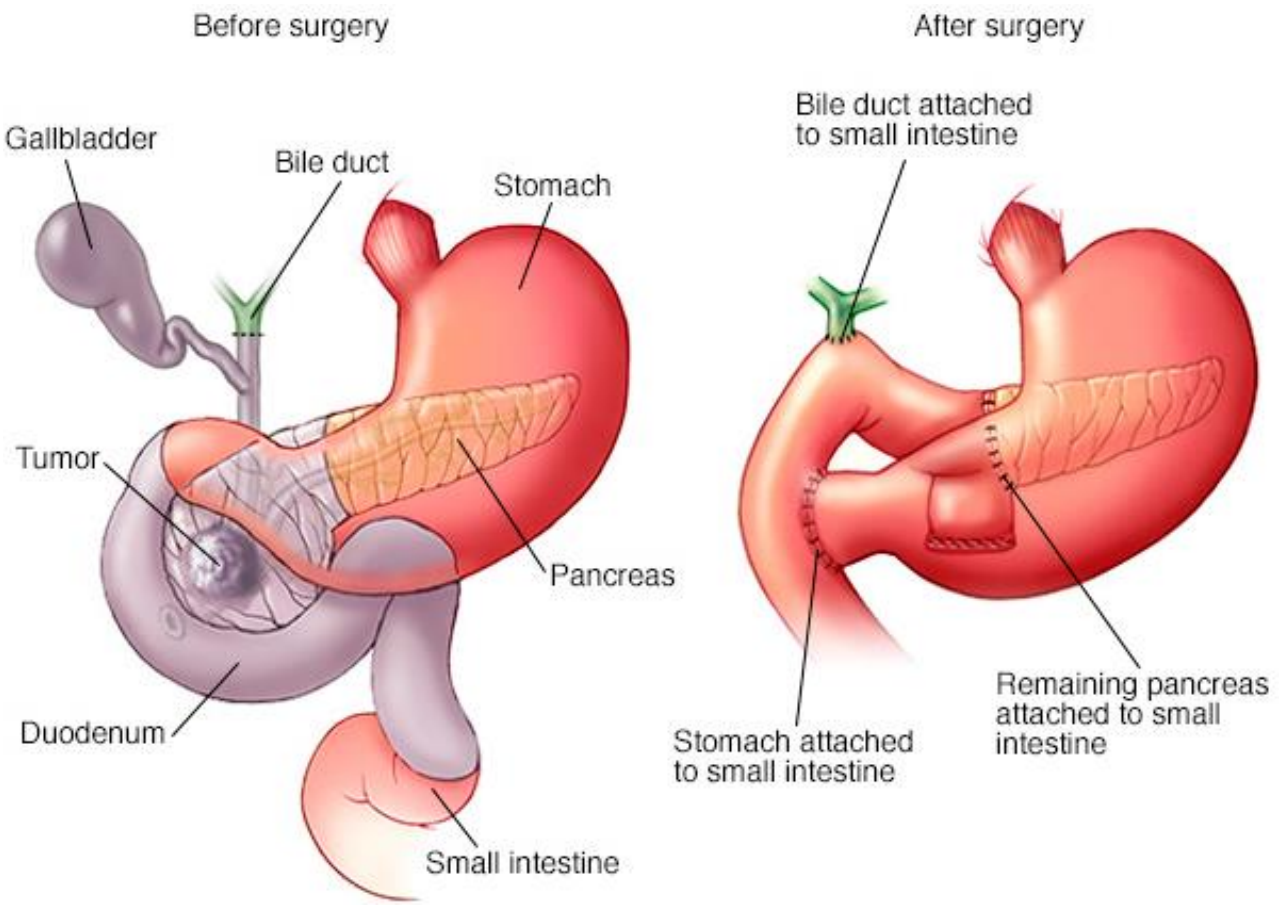
Annals og Surgery 1935





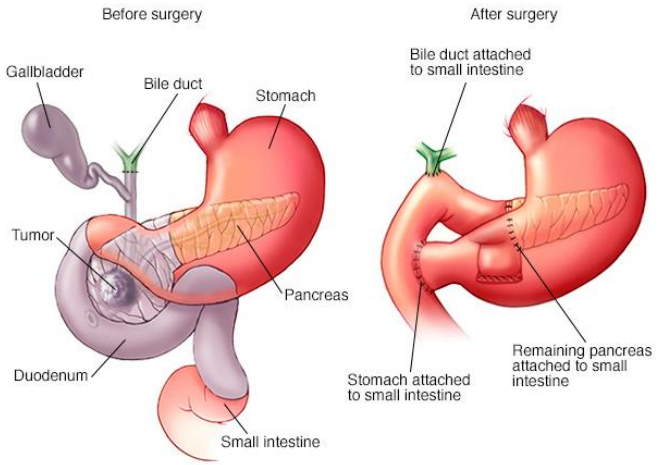
Chandrcanth A et al, HPB (2011)

Whipples prosedyre (WP) eller Pylorusbevarende pancreatoduodenectomi (PPPD)



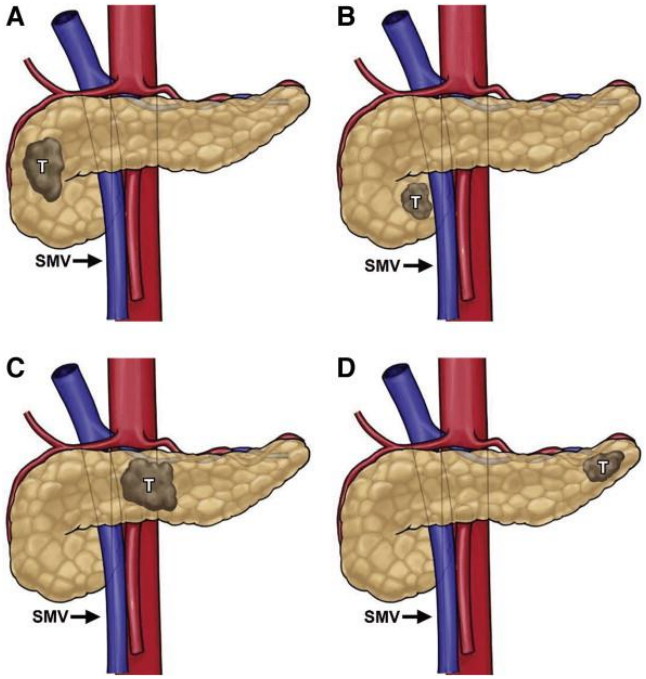
Pylorusbevarende pancreatoduodenectomi

- Foretrukket metode foran Whipple
  - Antatt bedre fysiologisk rekonstruksjon
    - Mindre gastric dumping og gallerefluks
- Mortalitet: 2-4 %
- Morbiditet: ≈ 30 %
- RCT: WP ≈ PPPD
  - Liggetid, blodtap, vekttap,
  - Morbiditet og mortalitet
  - Langtidsoverlevelse



Büchler et al, Arch Surg (2003)
Tran et al, Annals og Surgery (2004)
Hoem, ESJO (2012)

Valg av operasjonsmetode

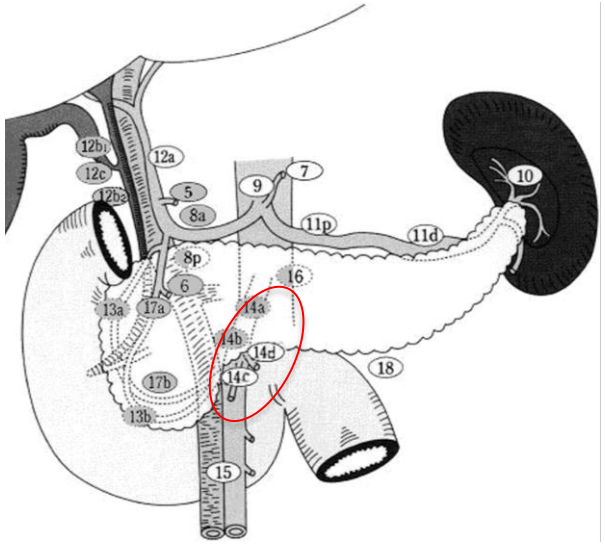


- <u>Lesjoner A og B:</u>
  - Whipples/PPPD (86 %)
- <u>Lesjon C:</u>
  - Distal eller total pancreatectomi (7 %)
- <u>Lesjon D:</u>
  - Distal pancreasreseksjon (7 %)

Hoem, ESJO (2012)

Lymfeknutedisseksjon ved PPPD/WP

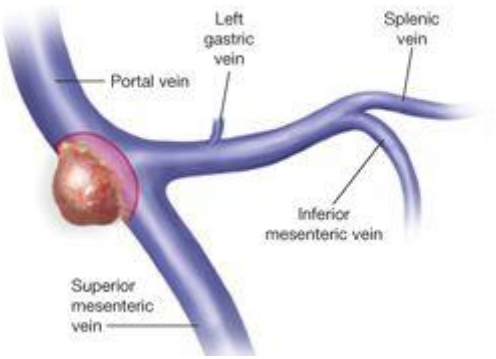
- Utvidet LK disseksjon
  - Bedrer ikke langtidsresultater
  - Øker komplikasjonsfaren
- Anbefalt > 15 LK totalt
- 70 % LK pos

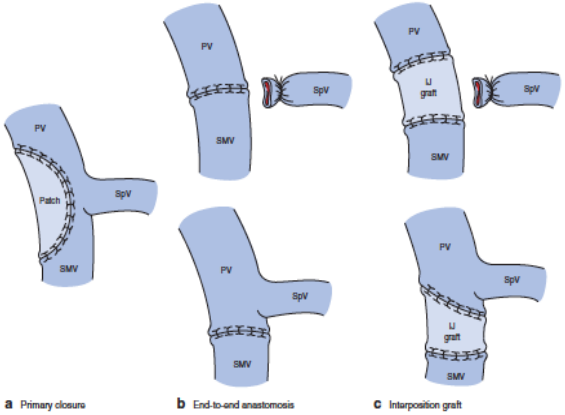


Iqbal et al, ESJO 2009
ISGPS consensus statement 2014
Hoem 2012

Venereseksjon (VR)

- Postoperative komplikasjoner:
  - Øker ved VR (?)
  - Uavhengig av type VR
- Overlevelse
  - Divergerende resultater
  - VR ≈ Ikke-VR





Kleive et al, Br J Surg (2017)
Delpero et al, Ann Surg Onc (2015)
Worni M, JAMA Syrgery (2013)
Ravikumar R et al, Am Coll Surg (2013) og BJS (2017)

Peri- og postoperativ behandling

- Preoperativ antibiotikaprofylakse
- Tromboseprofylakse
- Eksokrin enzymsubstitusjon
- Ernæring (ERAS)

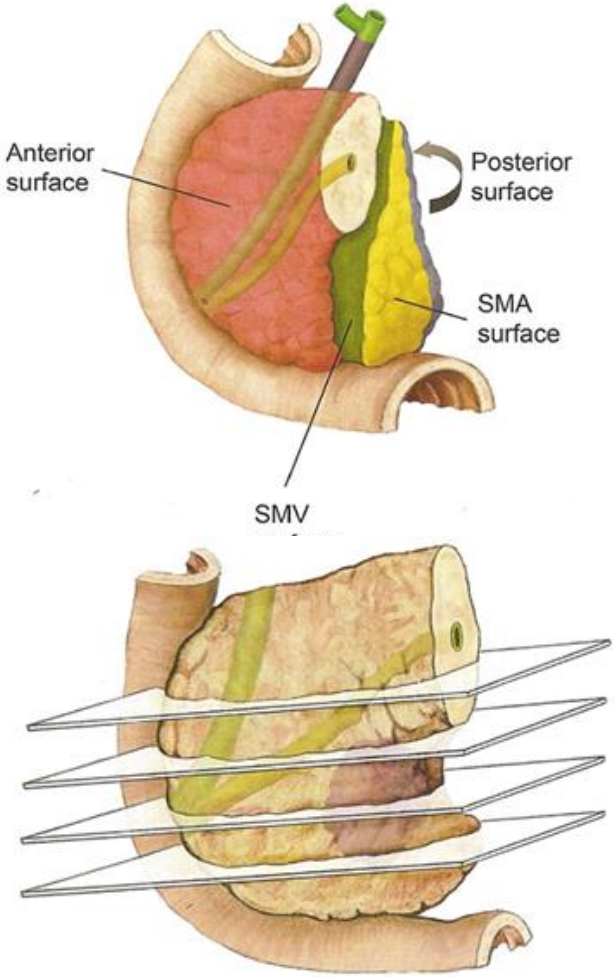
- Vurdere adjuvant kjemoterapi
- Poliklinisk kontroll

Nasjonalt handlingsprogram pancreascancer- 2017

Patologisk vurdering av preparat

- Anbefalt felles mal for besvarelse
  - Standardiserte reseksjonsflater
    - R0/R1 klassifiseringer
  - LK evaluering
  - Kar- og perinevral innvekst

- R0 - ulike klassifiseringer
  - Store variasjoner R1 (0 - 83 %)



ISGPS consensus statement 2014

Oppsummering

- Utredning
  - CT og MR, (EUS)
- Utvelgelse
  - Operabilitet/komorbiditet
  - Resektabilitetskriterier
- Kirurgisk metode
  - PPPD, venereseksjon
  - Neoadjuvant kjemoterapi?

Videre lesing

- Pancreaskreft (bukspyttkjertelkreft) – handlingsprogram - Helsedirektoratet