

HIPEC

Varmt kemobad i forbindelse med en operation

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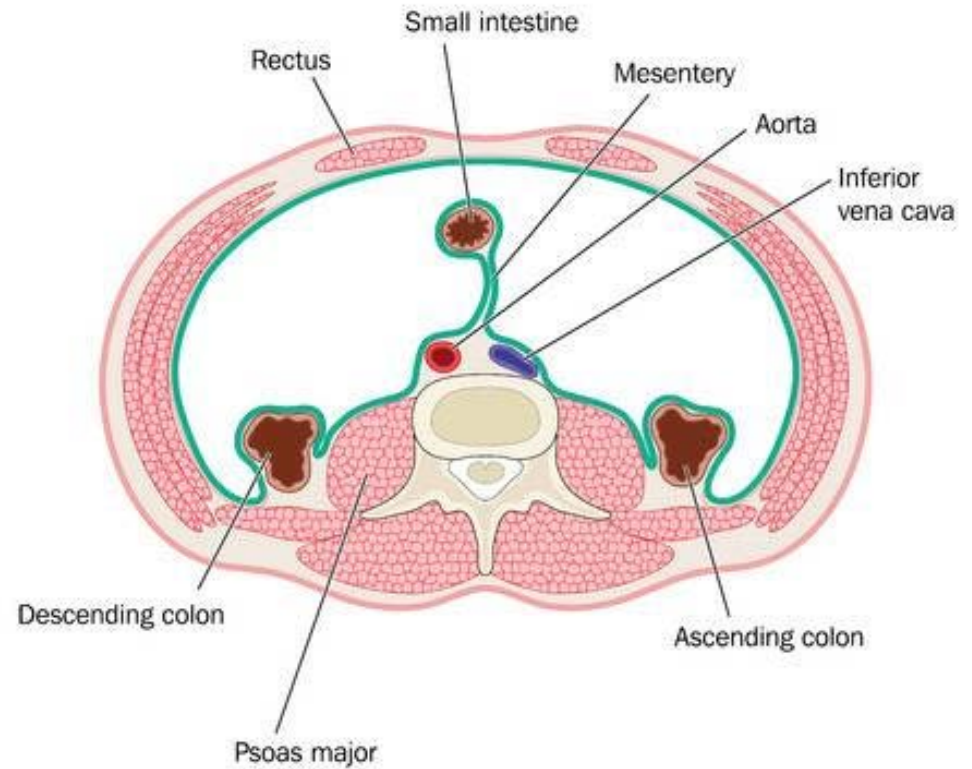
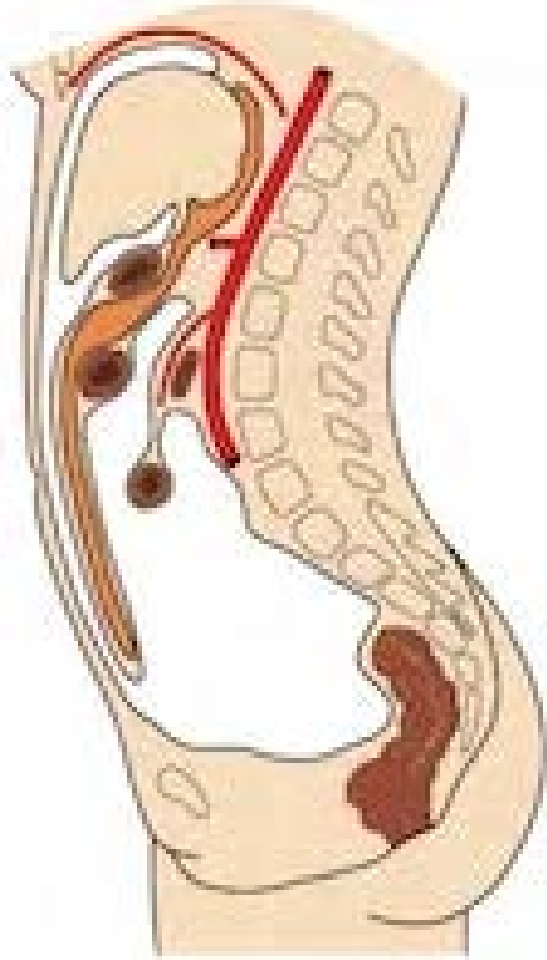
Aarhus Universitetshospital

Mave- og Tarmkirurgi

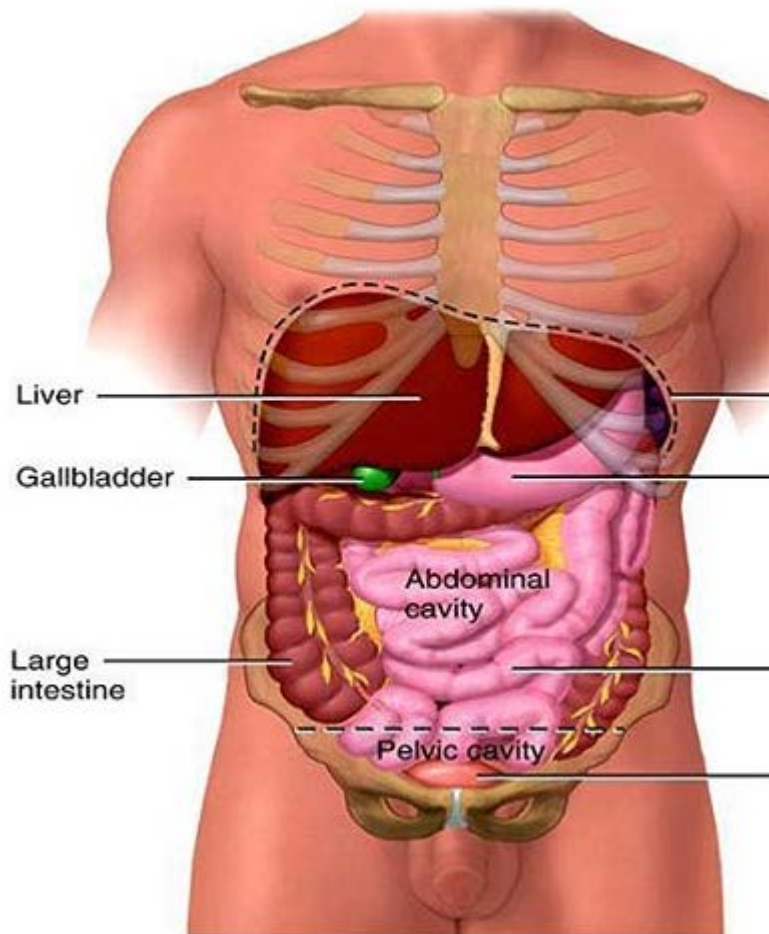
Definition: "HIPEC"

- ▶ **Behandlingsmodalitet bestående af 2 dele:**
- ▶ Cytoreductive surgery (CRS)
- ▶ Hyperthermic IntraPeritoneal Chemotherapy (HIPEC)

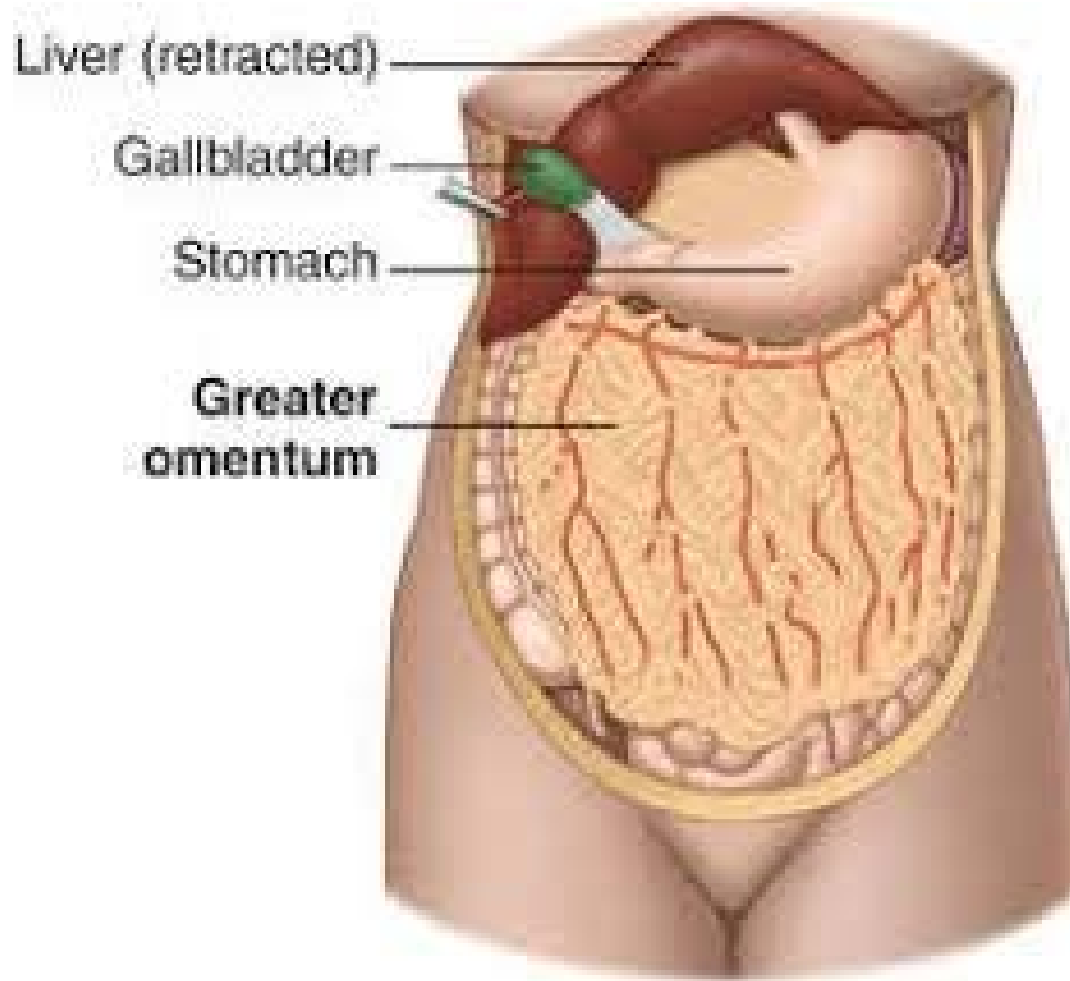
Bughinden/peritoneum – bughulen/den peritoneale kavitet



Bughulen



Omentet - fedtforklædet



CRS og HIPEC til hvad?

- ▶ **Behandling med *Kurativ intention* – helbredende øjemed**
- ▶ Internationalt anerkendt og med veldokumenteret effekt til
 - ▶ PC fra tarmkræft (KRC)
 - ▶ Pseudomyxoma peritonei (PMP)
 - ▶ PC fra blindtarmskræft (appendix cancer)
 - ▶ Primær bughindekræft (Malignt peritonealt mesotheliom)

 - ▶ Æggestokkræft (Ovariecancer) – endnu eksperimentel
 - ▶ Mavesækkkræft - eksperimentel

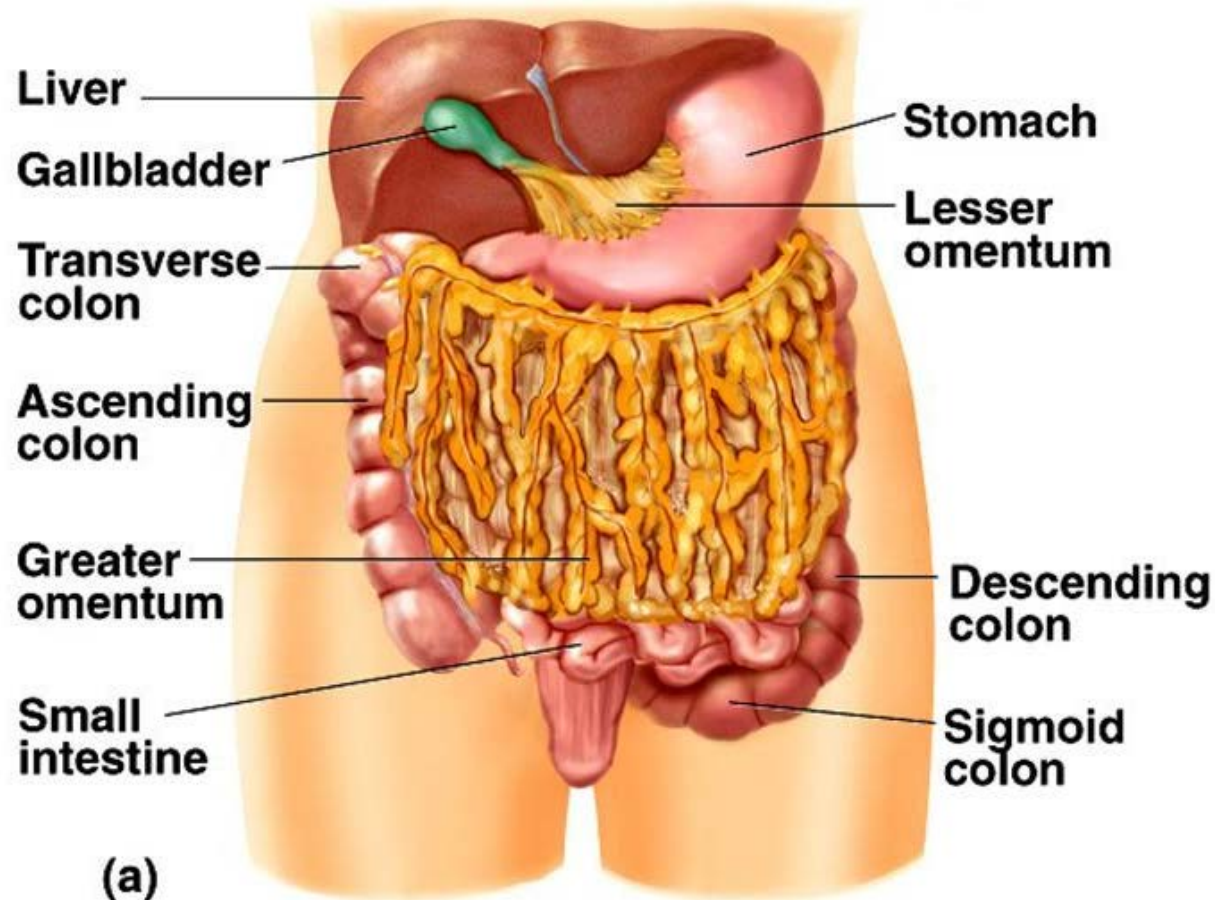
Definition: CRS + HIPEC

- ▶ CytoReductive Surgery (CRS)
- ▶ Kirurgisk fjernelse af **AL** synlig tumorvæv >2 mm
 - Organer med PC/udsæd (excision/resektion)
 - Bughinden (de dele som er sygdomsramt)
 - "Skrælning af bughinden" → store sårflader
 - Ofte ganske omfattende resektioner !
- ▶ Altid fjernelse af
 - Fedtforklædet (langs mavesækkens kant)
 - Navle
 - Æggestokke
 - Lig. Falciforme/lig. teres hepatis

Excision af peritoneum parietale



Lille sæk og omentet/fedtforklædet



Definition: CRS + HIPEC

- ▶ “Skylning”- Hyperthermic IntraPeritoneal Chemotherapy (HIPEC)
- ▶ Bughulen skylles/perfunderes med
 - ▶ Dialysevæske + heparin + KCl
 - ▶ Mitomycin C / oxaliplatin / cisplatin
- ▶ Opvarmet til 41-42°C i 1½ time/30 min/1½ time
 - Forstærket virkning af kemo
 - Ekstra effekt af hyperthermi
 - Væv og celler bliver ”utætte”
- ▶ Virkningsmekanisme
 - Diffusion
 - Max. 2-3 mm !!
 - 5-10 højere kemo-koncentration i bughinden end ved systemisk indgift



HIPEC "Skyllning med opvarmet kemo"

- ▶ Væsken perfunderer i et **lukket system** via
 - ▶ simpel hjerte-lunge-maskine
 - ▶ indsat en opvarmer

- ▶ En "**perfundør**" passer denne maskine



Postoperativ forebyggende kemoterapi

- ▶ Behandling efterfølges med
 - ▶ Postoperativ forebyggende kemo (ikke low-grade PMP)
 - ▶ Indhold og varighed kan variere



Hvorfor tilbyde patienten CRS+HIPEC ?

- ▶ Alternativet – traditionel behandling – Pallierende/livsforlængende
 - ▶ Debulking (PMP)
 - ▶ Pallierende kemo
- ▶ CRS+HIPEC øger langtidsoverlevelsen markant (KRC-PC)
 - ▶ Medianoverlevelse $\geq x 2$
 - ▶ Behandling med kurativ intention
 - ▶ Langtidsoverlevende
 - ▶ 5 års overlevelse $\geq x 3-6$

CRS+HIPEC vs. palliativ kemoterapi

PC fra KRC

| Regime | CRS + HIPEC [#] | Livsforlængende 5-FU, LV, OX/IRI, biologisk* |
|-----------------------|--------------------------|--|
| Median overlevelse | ≈ 3 år 20 – 63 mdr. | ≈ 1½ (- 2) år 15 – 23 mdr. |
| 5 års overlevelse (%) | (7) 21 – 45 (51) | 0 - 5 |

Beregnet fra operation * Beregnet fra diagnosetidspunkt

Outcome: PC vs. non-PC and palliative chemotherapy

CAIRO 1 og CAIRO 2 studies: Worse prognosis for PC

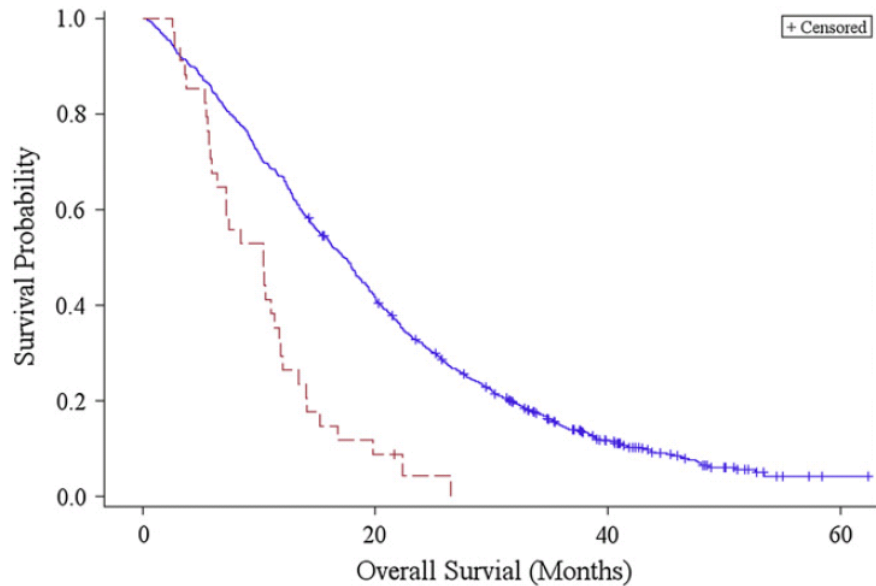


Figure 1. Kaplan–Meier curve for overall survival of metastatic CRC with and without PC at time of inclusion in the CAIRO trial. — Patients without PC. - - Patients with PC. Median overall survival was 10.4 months for patients with PC versus 17.3 months in patients without PC ($p \leq 0.001$).

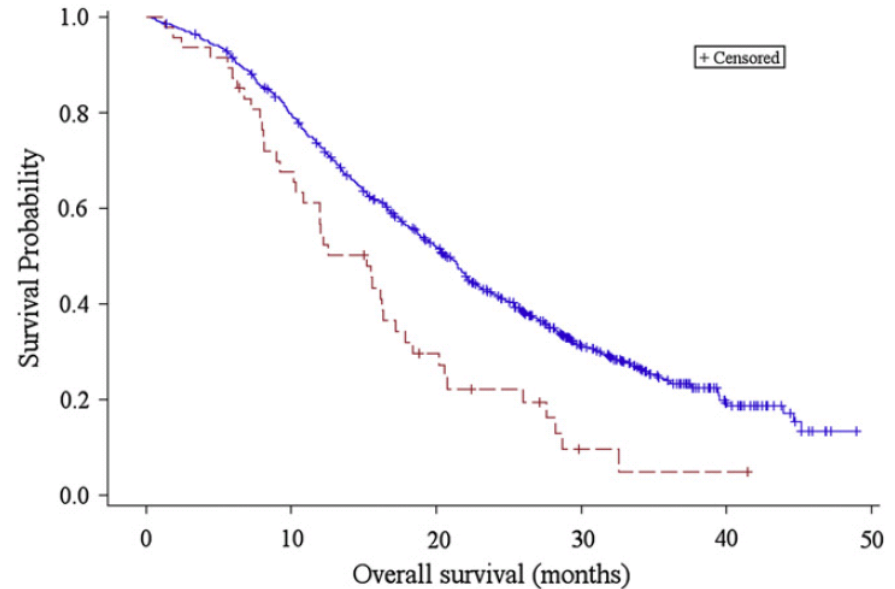


Figure 2. Kaplan–Meier curve for overall survival of metastatic CRC with and without PC at time of inclusion in the CAIRO2 trial. — Patients without PC. - - Patients with PC. Median overall survival was 15.2 months for patients with PC versus 20.7 months in patients without PC ($p \leq 0.001$).

First-line chemo (ARCAD)

14 fase-3 studier

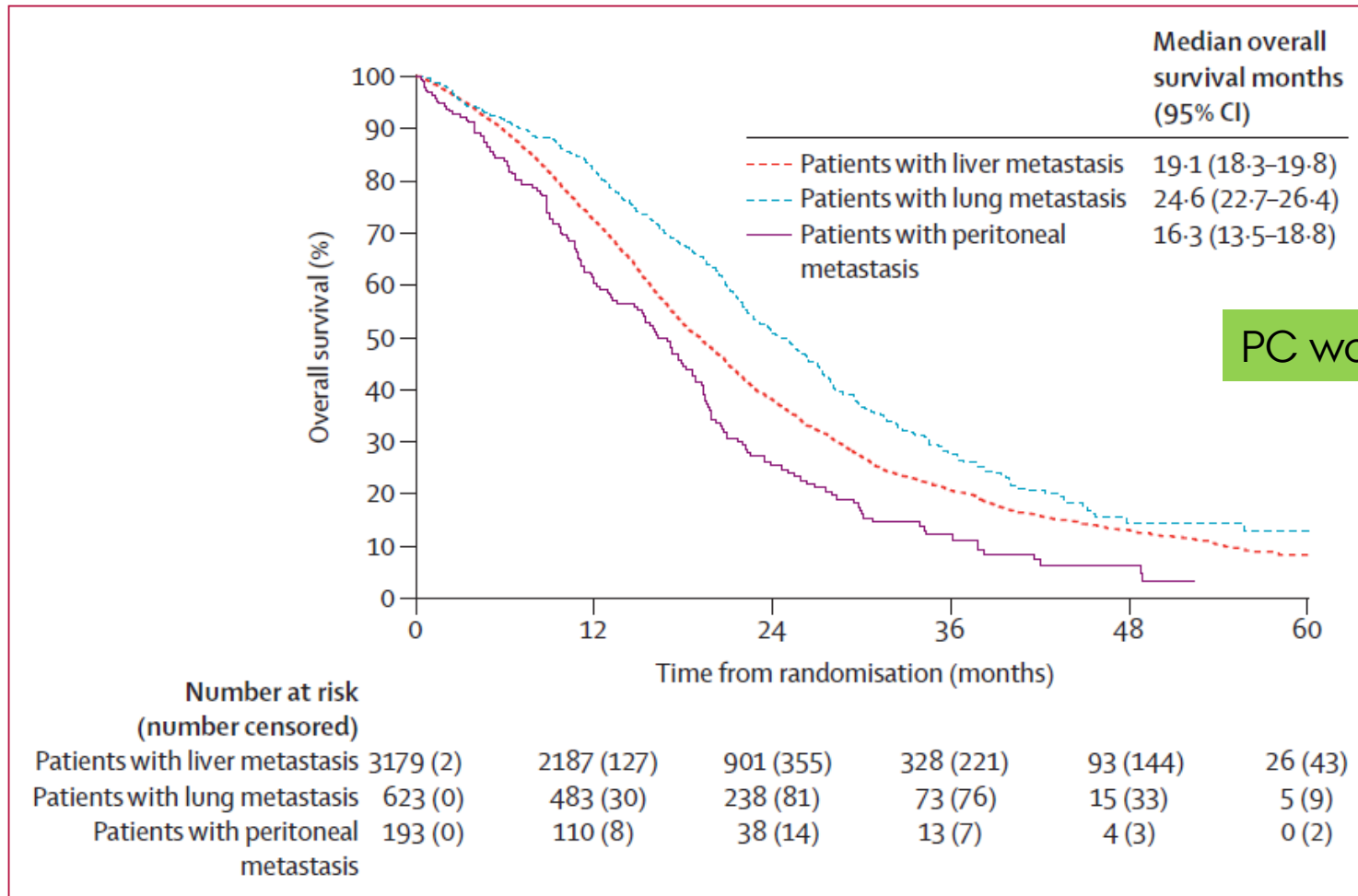


Figure 1: Overall survival in patients with metastatic colorectal cancer with metastases in a single organ

First-line chemo (ARCAD)

14 fase-3 studier

| | Events/total | Median overall survival (months)* | Hazard ratio† | p value* | Adjusted events/total‡ | Adjusted hazard ratio†‡ | Adjusted p value*‡ |
|---|--------------|-----------------------------------|------------------|----------|------------------------|-------------------------|--------------------|
| All patients | | | | | | | |
| Peritoneal status | | | | <0.0001§ | | | <0.0001§ |
| Peritoneal metastasis only | 159/193¶ | 16.3 (13.5-18.8) | 1.42 (1.21-1.66) | <0.0001 | 119/147 | 1.33 (1.10-1.60) | 0.0030 |
| Peritoneal metastasis and ≥1 other site of metastasis | 999/1181 | 12.6 (12.0-13.1) | 1.79 (1.67-1.93) | <0.0001 | 812/967 | 1.71 (1.57-1.86) | <0.0001 |
| Isolated non-peritoneal metastasis | 3068/4385 | 20.0 (19.4-20.6) | Reference | .. | 2127/3120 | Reference | .. |
| Multiple non-peritoneal metastases (≥2 disease sites) | 3758/4790 | 15.7 (15.2-16.3) | 1.37 (1.30-1.44) | <0.0001 | 2956/3849 | 1.38 (1.30-1.46) | <0.0001 |

RCT: CRS+HIPEC vs. pall. chemo

- ▶ PC from CRC (n = 87) and appendix cancer (n = 18)

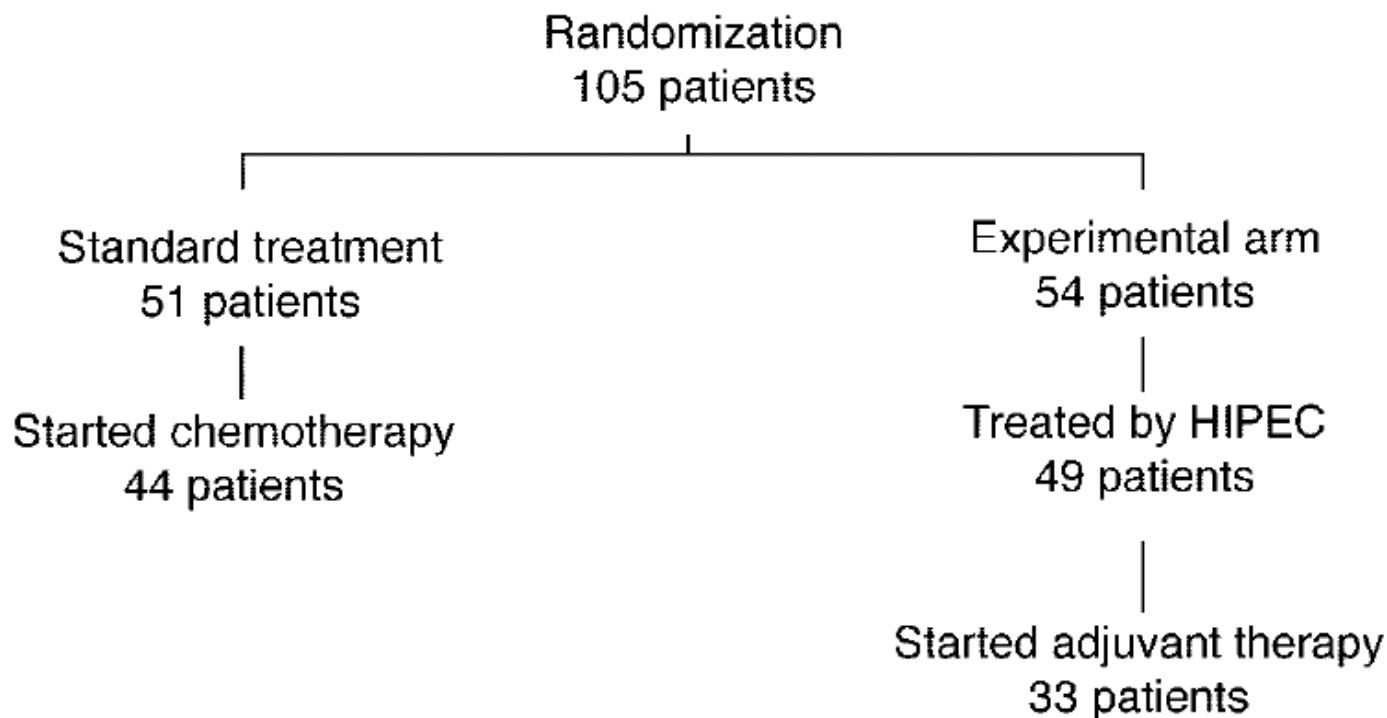


Fig 1. Trial profile of all 105 randomly assigned patients. HIPEC, hyperthermic intraperitoneal chemotherapy.

Median survival: 22.4 vs. 12.6 months

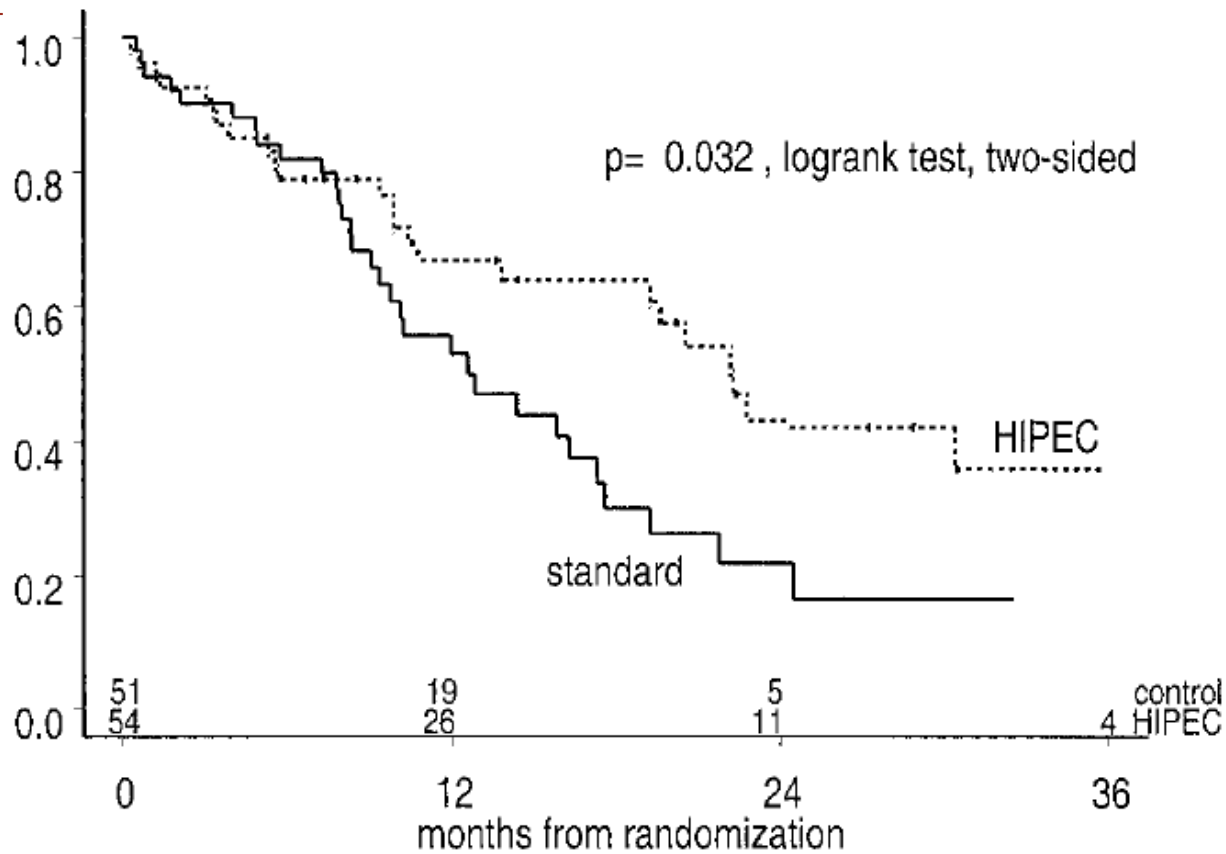


Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).

verwaal v. JCO 2003,21:3737-43



RCT: PC_CRC CRS+IP vs. systemic chemo

- ▶ Stopped prematurely (n=24 vs n=24)
- ▶ Exp. Arm:
 - ▶ IP: 5-FU every 4 wks x 6
 - ▶ Leucovorin i.v.
- ▶ Standard arm:
 - ▶ Oxa+5-FU

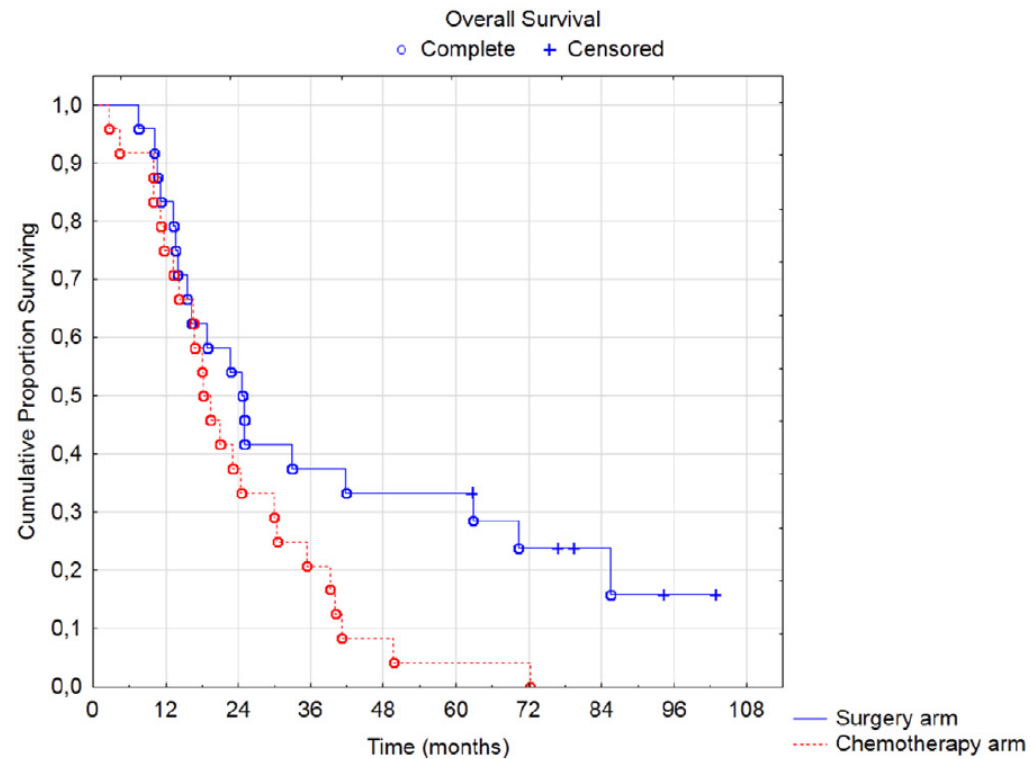


Fig. 2. Overall survival after cytoreductive surgery combined with intraperitoneal chemotherapy compared to systemic chemotherapy only in peritoneal metastases of colorectal origin,

Prodige 7 – ikke publiseret!

- ▶ Prodige 7

- ▶ CRS +/-HIPEC (oxaliplatin 460 g/m²ip+folinsyre iv+5FUiv)

- ▶ PC fra CRC

- ▶ PCI<25

- ▶ Adjuverende kemo 6 mdr.

- ▶ Endpoint: overall overlevelse

- ▶ Hypotese: median OS stige fra 30 til 48 mdr.

- ▶ 264 pt.

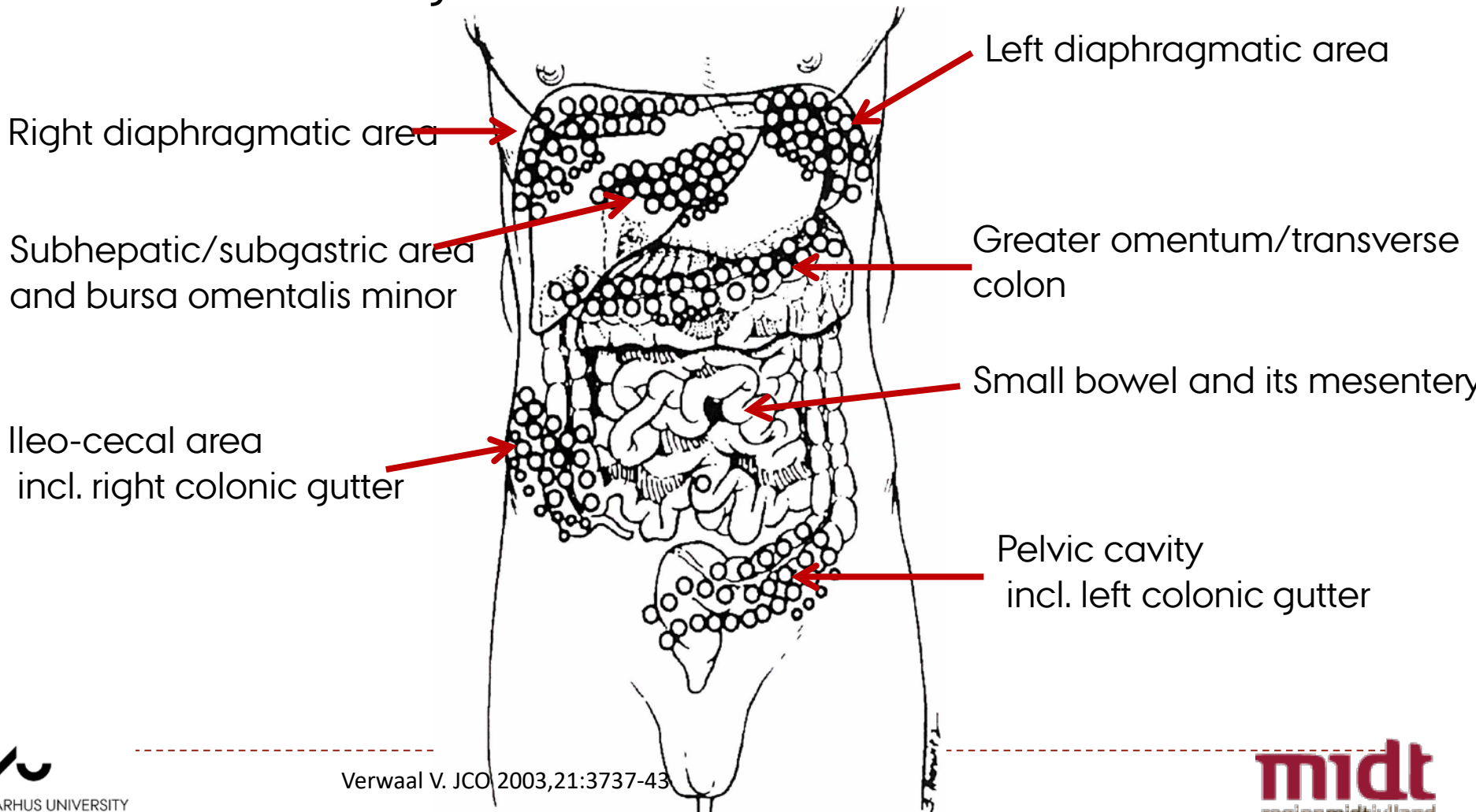
Quenet 2018

Outcome – langtids-overlevelse

- ▶ Afhænger af
 - ▶ Udbredning af PC (*Hvor meget?*)
 - ▶ Clearance af PC – kompletheden af cytoreduktion
(hvor gode er vi til at fjerne det?)

Udbredning af PC

▶ Dutch 7 Region Count Score



PC extent and survival

Median survival: 5.4 months vs. >29 months

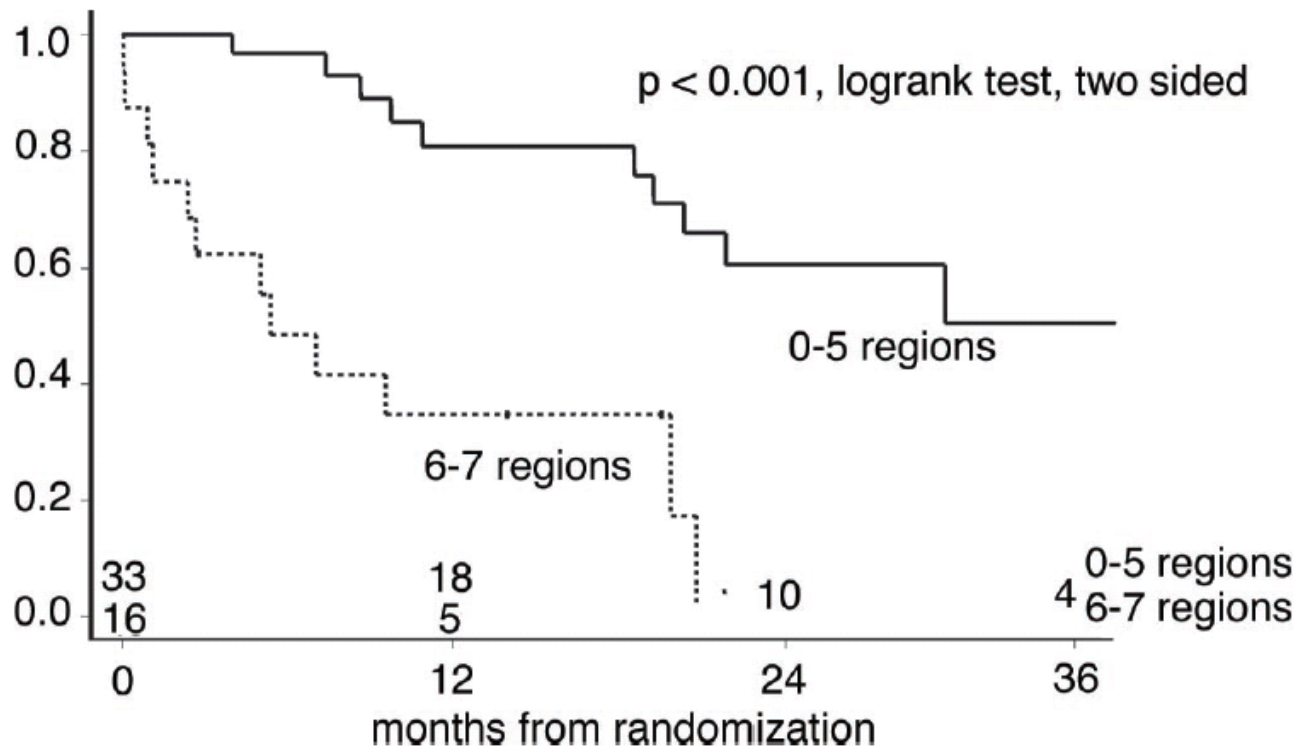


Fig 5. Kaplan-Meier survival curve of 49 patients with peritoneal carcinoma treated by cytoreduction followed by HIPEC, comparing the number of regions with residual tumor.

PC udbredning og overlevelse

FU: 45 months

PC from CRC, n = 523 (16% EPIC)

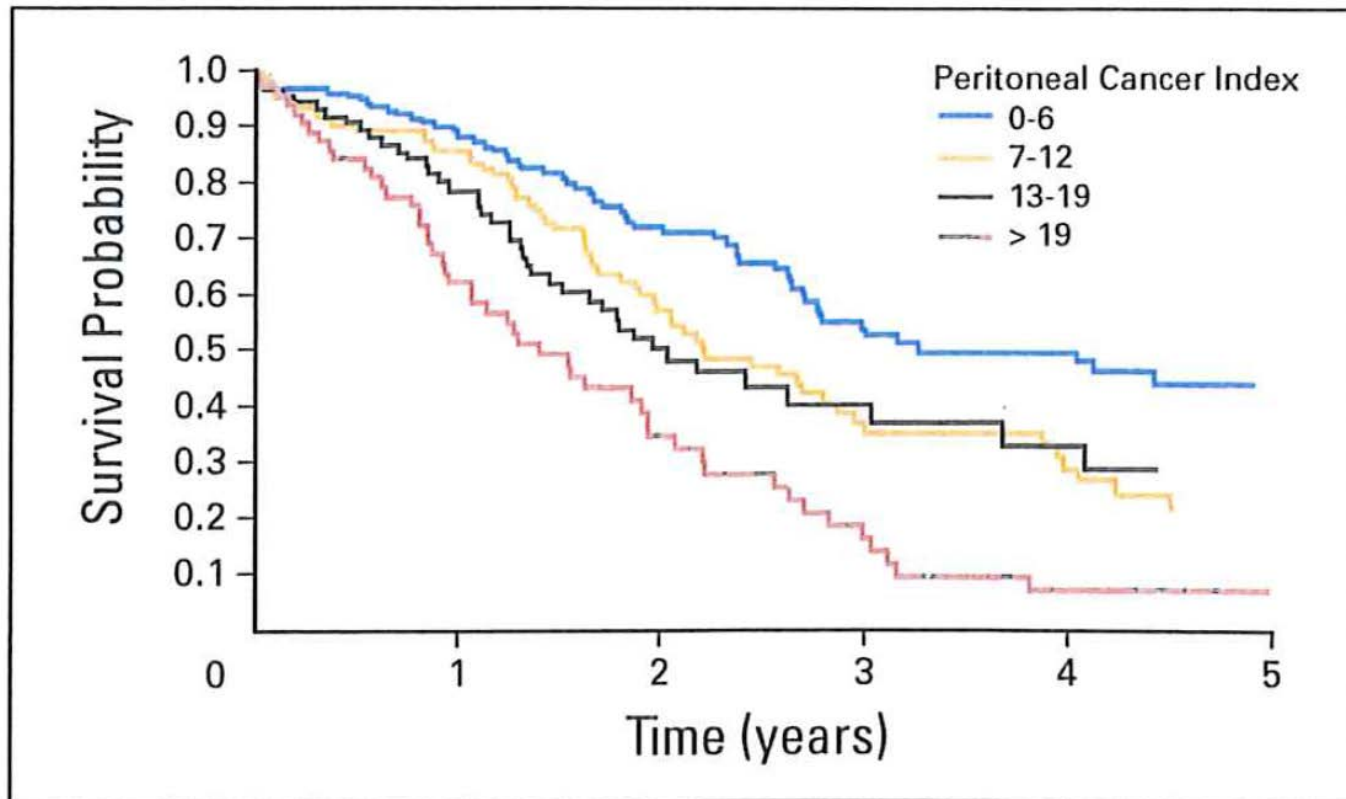


Fig 2. Prognostic impact of the extent of carcinomatosis (ie, peritoneal cancer index; $P < .001$) on overall survival.

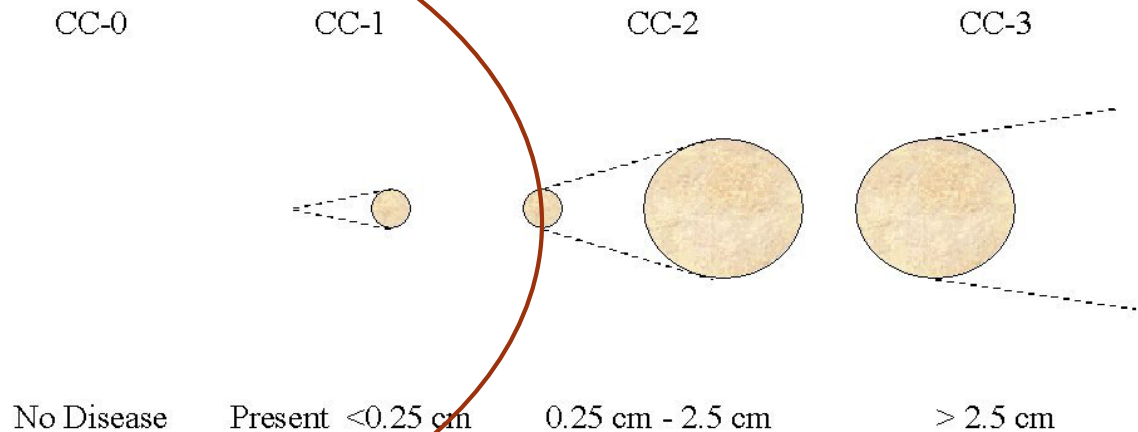
Completeness of cytoreduction

▶ Completeness of Cancer Resection score

- ▶ CCR-0 no tumor left behind (= R-1)
- ▶ CCR-1 residual tumor < 2.5 mm (= R-2a)
- ▶ CCR-2 residual tumor 2.5 mm – 2.5 cm
- ▶ CCR-3 residual tumor >2.5 cm

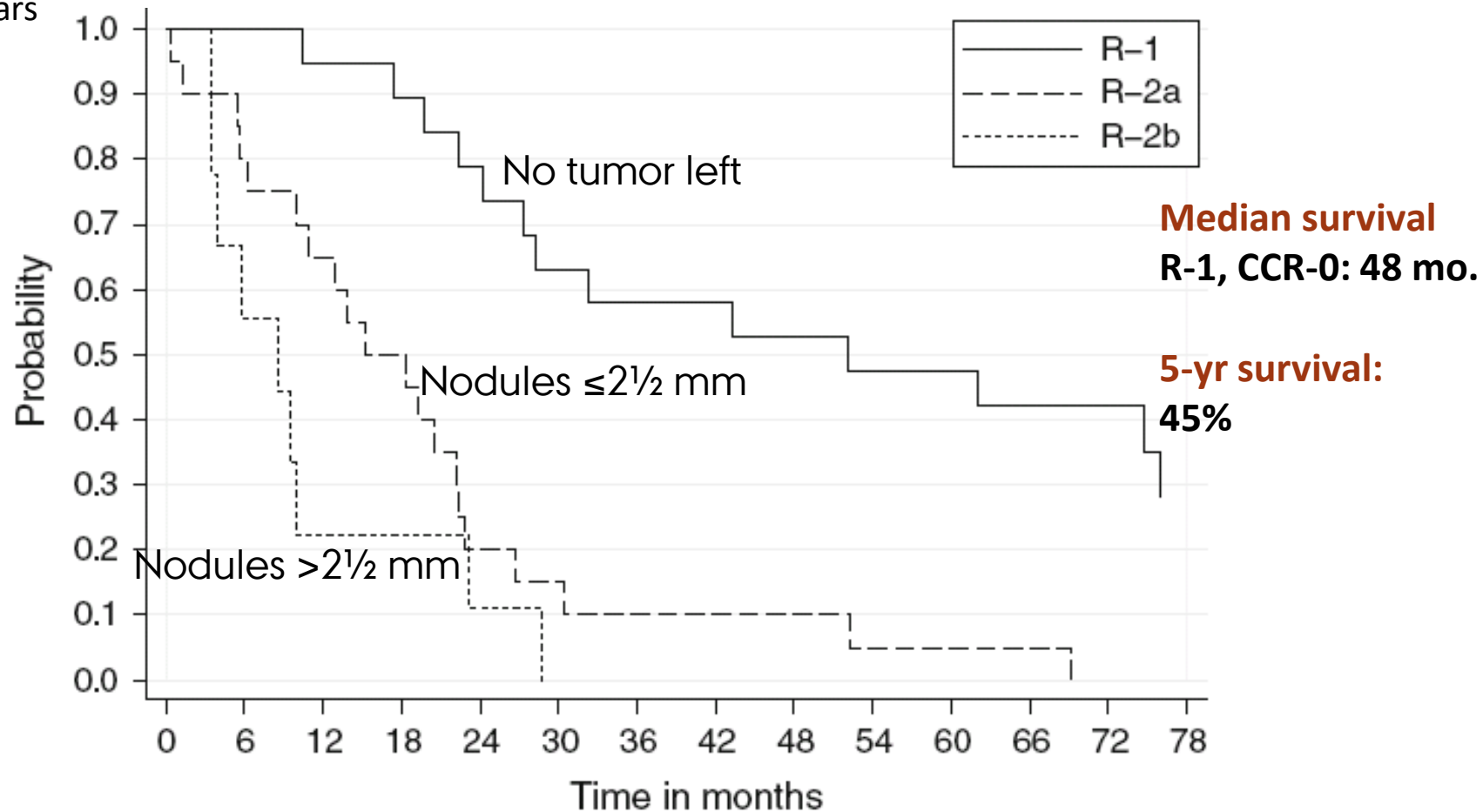
▶ Complete

- ▶ CCR-0 (+CCR-1)



Completeness and survival - CRC

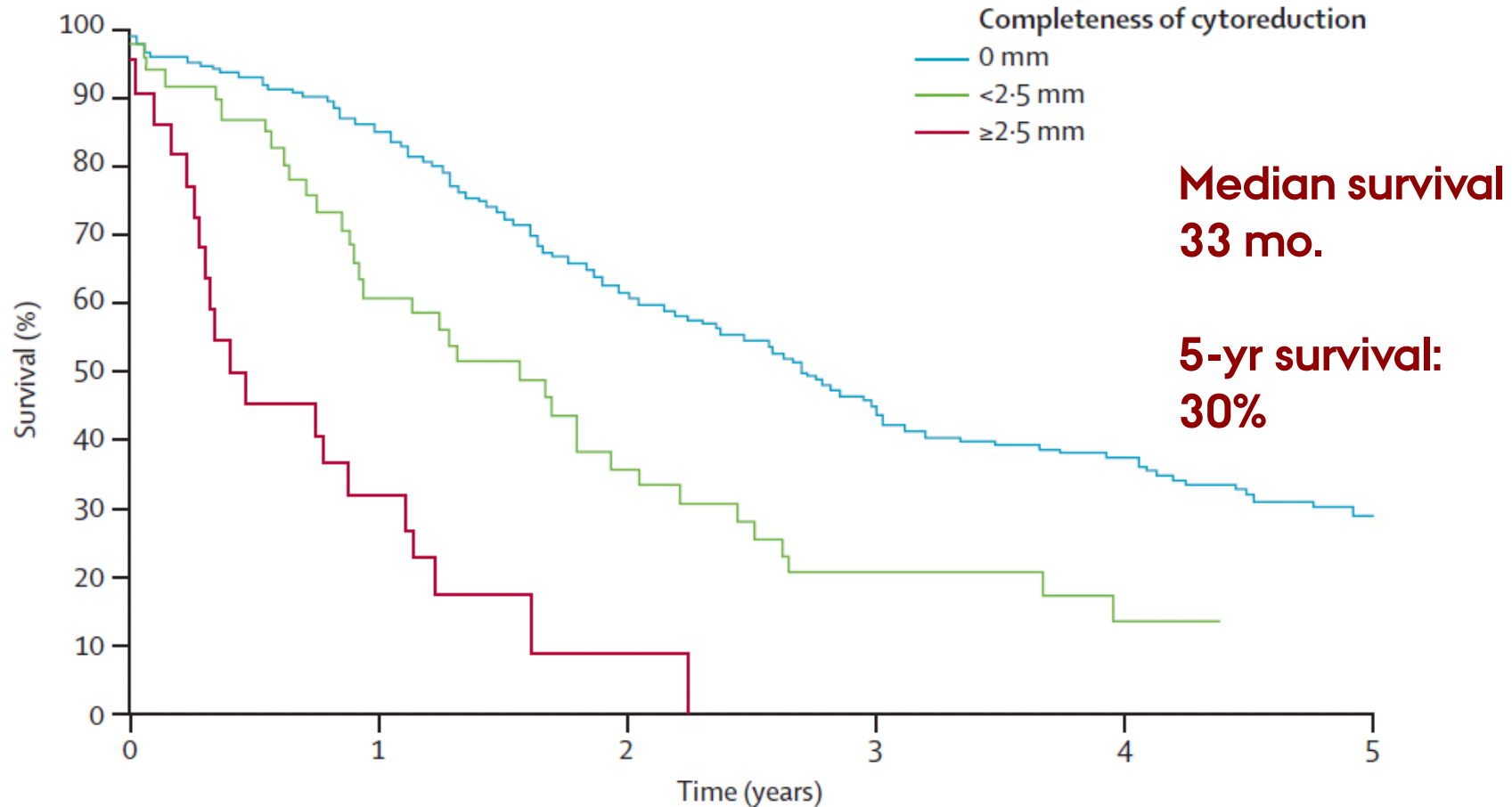
FU: 7.8 years



Completeness and survival - CRC

FU: 45 months

PC from CRC, n = 523 (16% EPIC)



Indikationer for CRS+HIPEC - Aarhus

- ▶ Begrænset og resecerbar PC udgået fra tarmkræft og tyndtarmskræft
- ▶ Pseudomyxoma peritonei
- ▶ Begrænset og resecerbar PC udgået fra blindtarmskræft
 - ▶ Incl. goblet cell carcinoid
- ▶ Malignant peritoneal mesothelioma/bughindekræft

Criteria for exclusion - Aarhus

- ▶ Fysiologisk alder >70-75 år
- ▶ ASA \geq III, performance \geq 2
- ▶ Fjernmetastaser
 - ▶ \geq 4 levermetastaser
 - ▶ >3 cm levermetastaser
 - ▶ >2 lungemetastaser
 - ▶ Andre fjernmetastaser (excl sår)
- ▶ Diffus involvering af tyndtarm/dets krøs

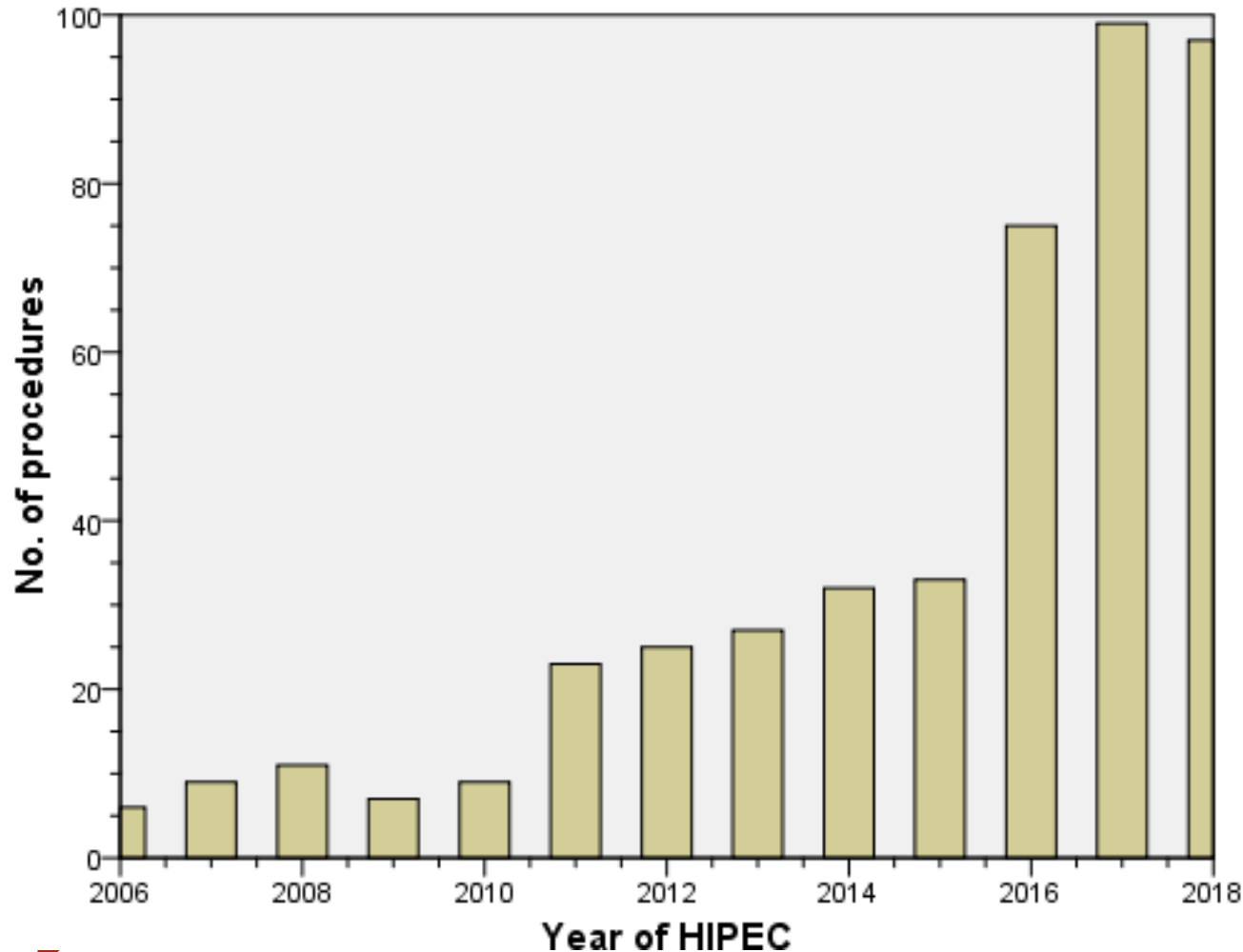


Criteria for exclusion ct. - Aarhus

- ▶ Non-resecerbar PC
 - ▶ Portårene – galdevejsobstruktion
 - ▶ Bugspytkirtel (caput (corpus))
- ▶ For PC udgået fra tarmkræft eller blindtarmskræft
 - ▶ PCI >15 (17) (≥ 12 hvis levermetastaser)
 - ▶ PC udbredning ≥ 6 of 7 regioner (Hollandske 7 regions score)

Antal gennemførte CRS+HIPEC per år over tid Aarhus

Årlig antal CRS+HIPEC



Antal kirurger:
(2) - 3 - 4

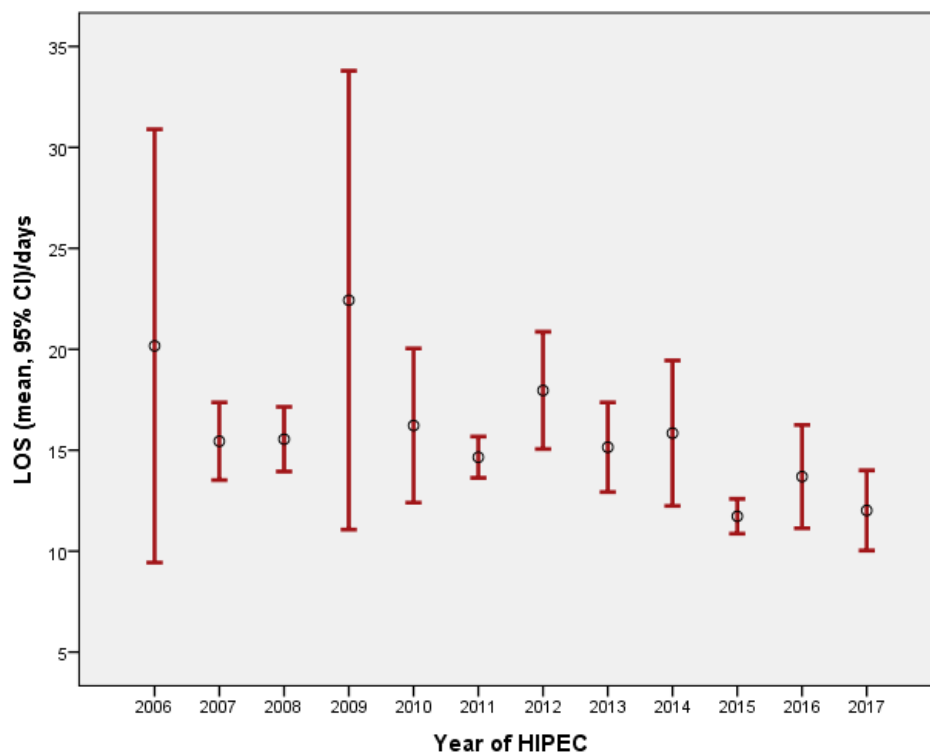
Morbidity - Aarhus experience

- ▶ Postoperative complications (in-hospital)
 - ▶ 42% had any complication

Opgjort august 2017

Indlæggelsesvarighed

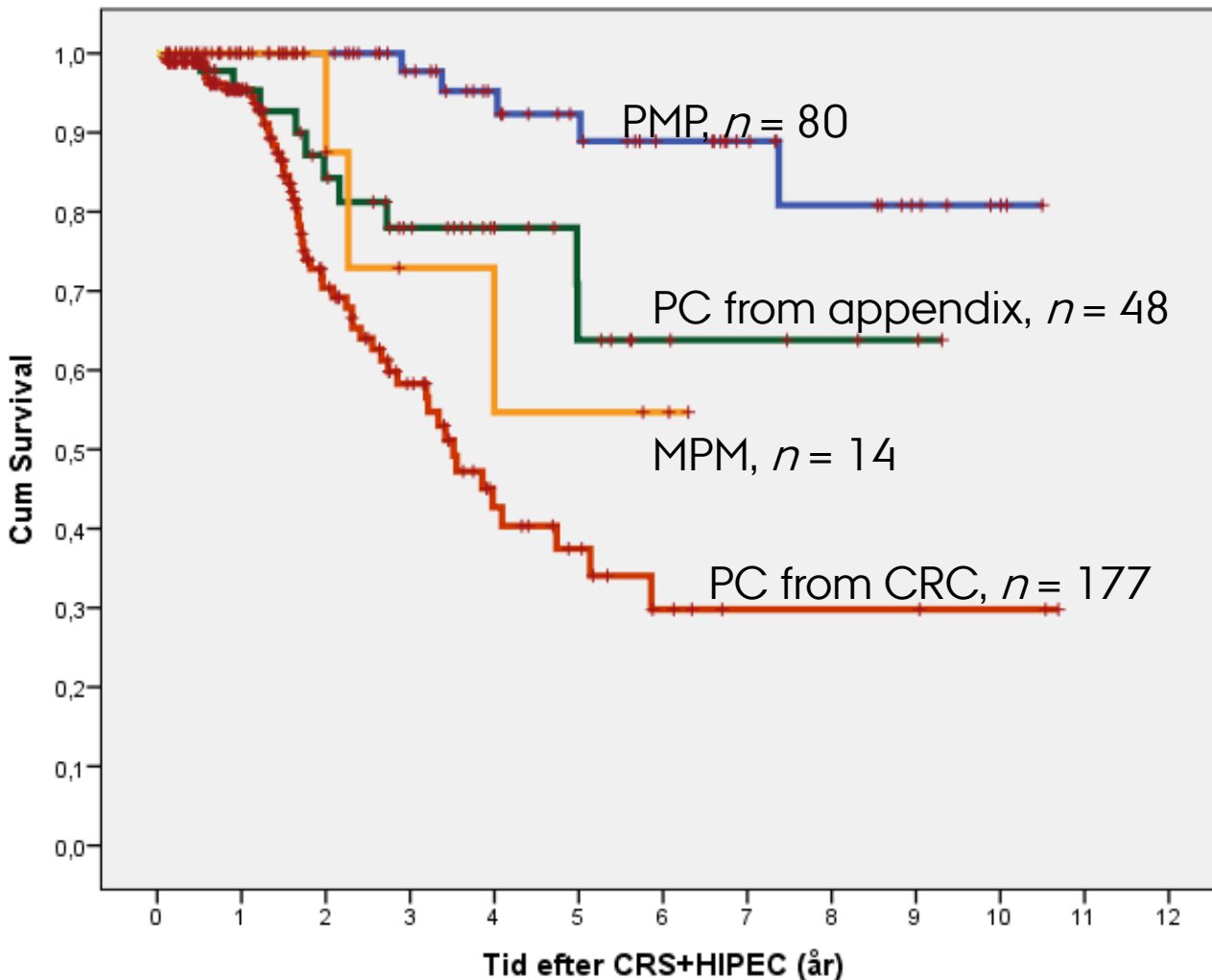
- Median (range) 13 dage (5-84)
- Overflyttet til hjemsygehus 27,8%



Mortalitet efter CRS+HIPEC

- ▶ 30-dages mortalitet: 0,3% (1/320)
- ▶ 90-dages mortalitet: 0,7% (2/305)

Overlevelse – Aarhus ($n = 320$)



| | Median overlevelse (95% CI) | 5 års overlevelse (95% CI) |
|---------------|-----------------------------|----------------------------|
| PMP | >10,5 år | 93% (84; 100) |
| PC-App | >9,3 år | 64% (43; 85) |
| MPM | >6,3 år | 55% (15; 94) |
| PC-KRC | 3,5 år (2,9; 4,2) | 38% (25; 50) |

Opgjort okt. 2017

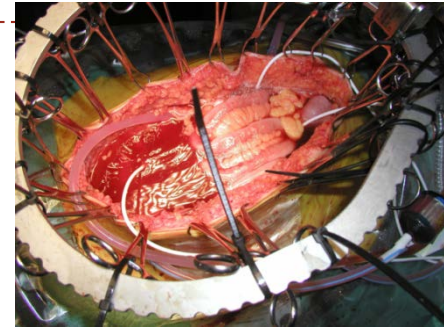
Take home messages

- ▶ CRS+HIPEC er forbundet med
 - ▶ Moderat-høj morbiditet/sygelighed (42%) MEN
 - ▶ Lav 30 dages dødelighed (0.3%)

- ▶ Det kan opnås god langtidsoverlevelse for patienter med patients med PC-CRC:
 - ▶ 2 års overlevelse 71% og 5 års overlevelse 38%

- ▶ CRS+HIPEC for PMP giver fremragende langtidsresultater
 - ▶ 5 års overlevelse 93%

- ▶ En effektiv og værdifuld behandling MED HELBREDENDE ØJEMED til udvalgte patienter



Litteratur: Danske resultater

“Incisional hernia and its impact on health-related quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: A national prospective cohort study”, S Ravn, HV Thaysen, S Harsløf, MM Sørensen, and LH Iversen, WJSO 2018, 16:85

“Effects of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of goblet cell carcinoma – a prospective cohort study”, AH Madsen, M Ladekarl, GE Villadsen, H Grønbaek, MM Sørensen, K Stribolt, VJ Verwaal, and LH Iversen, Ann Surg Oncol 2018, 25:422-430

“Palliative surgery for pseudomyxoma peritonei”, JA Funder, KV Jepsen, K Stribolt, and LH Iversen, Scand J Surg 2016, 105:84-89

“Clinical course for patients with peritoneal carcinomatosis excluded from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy”, AP Rodt, RO Svarrer, and LH Iversen, WJSO 2013, 16: 232

“Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis (HIPEC): the Danish experience”, LH Iversen, PC Rasmussen, R Hagemann-Madsen, and S Laurberg, Colorectal Dis 2013, 15: e365-e372.

“Value of laparoscopy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis”, LH Iversen, PC Rasmussen, and S Laurberg, Br J Surg 2013, 100: 285-292.

“Ny behandling af peritoneal karcinose fra kolorektal cancer: Cytoreduktiv kirurgi og hyperterm intraperitoneal kemoterapi”, LH Iversen, PC Rasmussen og S Laurberg, UFL 2007, 38: 3179-3181.

“Ekstensiv peritonektomi. Ny behandling af pseudomyxoma peritonei”, LH Iversen, PC Rasmussen, P Wara, L Buhl, NS Ambrose, and S Laurberg, UFL 2004, 35: 2981-2984.

“Pseudomyxoma peritonei”, LH Iversen, PC Rasmussen, P Wara, NS Ambrose, and S Laurberg, UFL 2004, 35: 2979-2981