

Kirurgisk behandling av colon- og rectum cancer, inkl. metastasekirurgi

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Januar 2023

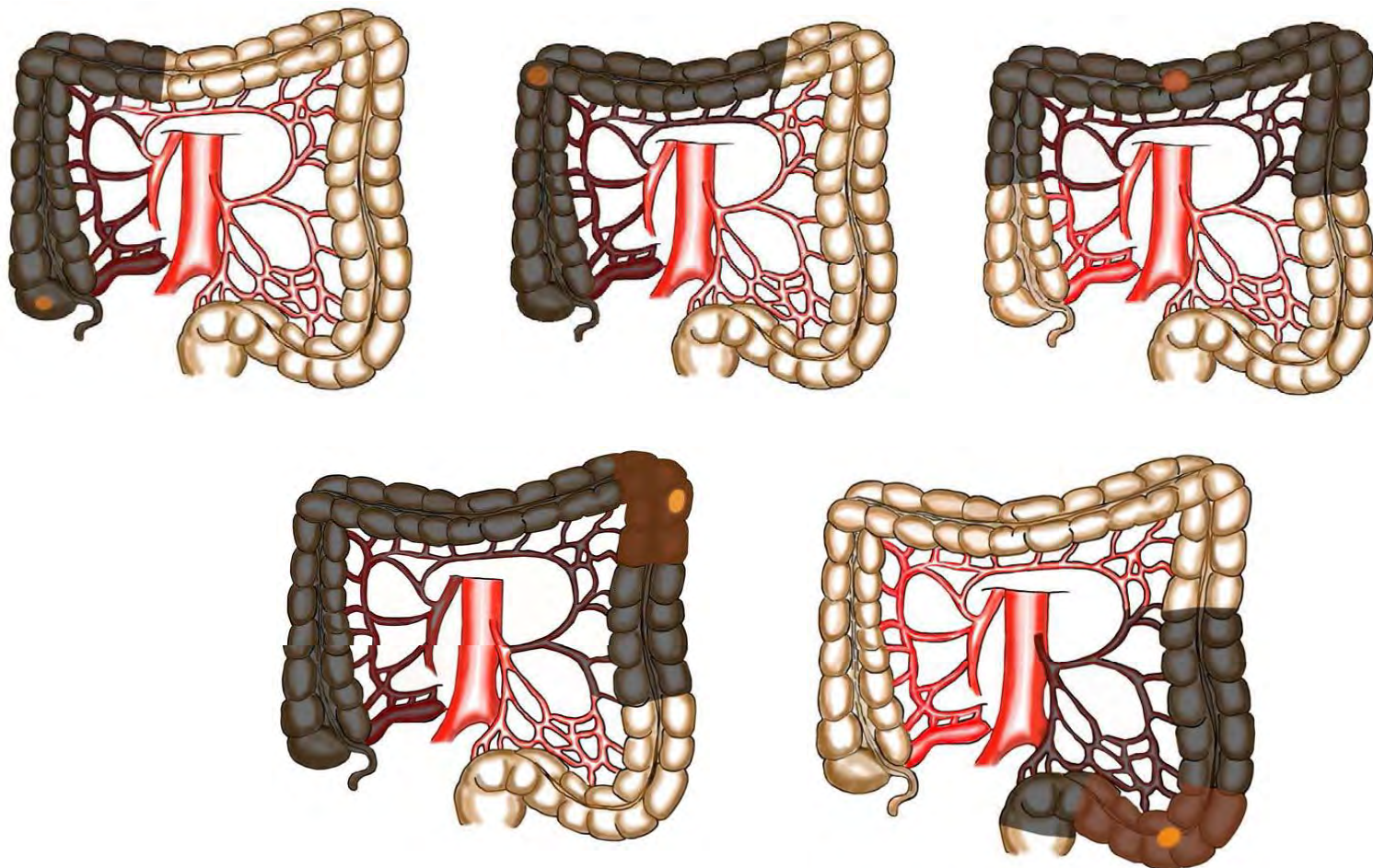
Disposisjon

- Colon cancer
- Rectum cancer
 - Resektabel
 - Lokalavansert (LARC)
 - Lokalt recidiv (LRRC)
- Levermetastaser
- Lungemetastaser
- Peritoneale metastaser

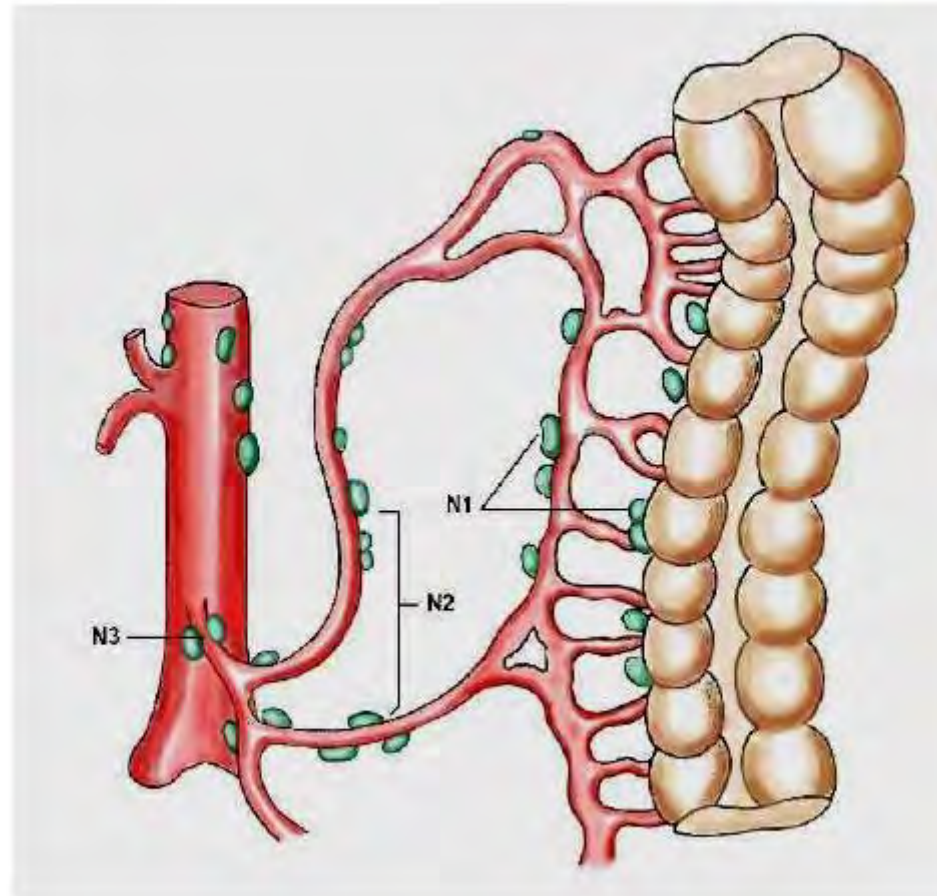
Kolorektal cancer. Diagnose

- Rammer særlig de eldre.
- 10 % er under 55 år.
- 30 % er lokalt voksende (st 1-2), 40 % har lymfeknutemetastaser (st 3), 20 % fjernmet (st 4).
- En del av svulstene er arvelige
- De fleste utvikles fra polypper, men kun 5-10% av polyppene blir maligne.

Tumor lokalisasjon og type reseksjoner

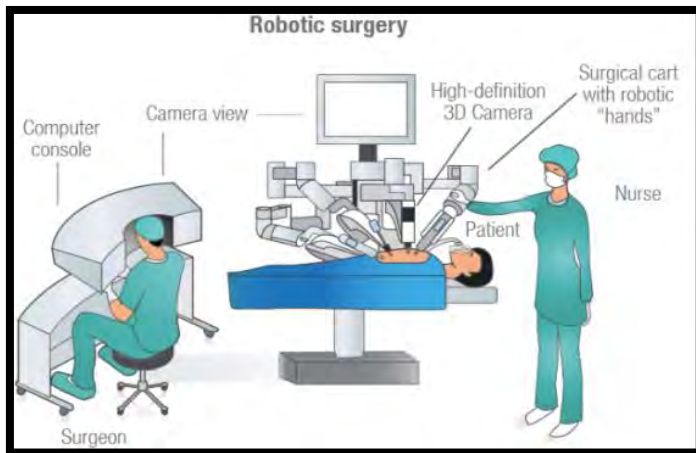


Nivå for lymfeknute fjerning

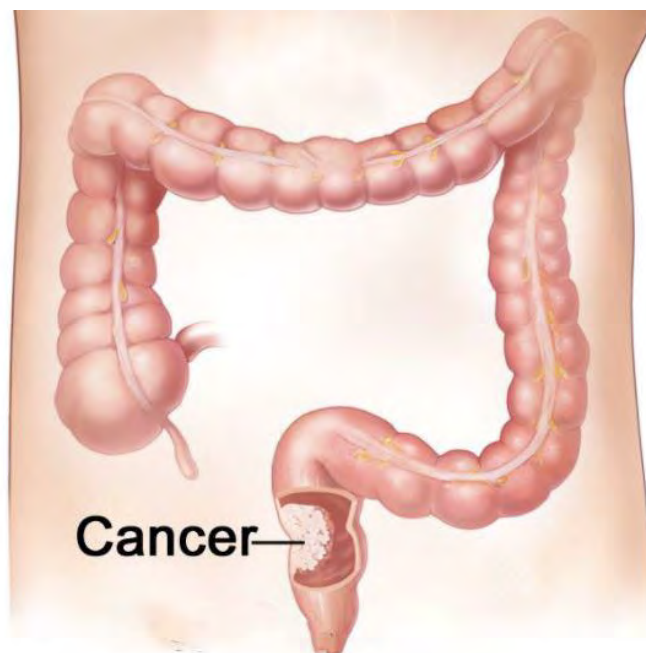


Inngrep colon (åpen, laparoscopisk eller med robot)

- Høyresidig hemicolectomi
- Venstresidig hemicolectomi
- Transversumreseksjon
(evt utvidet hø./ eller venstresidig hemicolectomi)
- Sigmoidum reseksjon

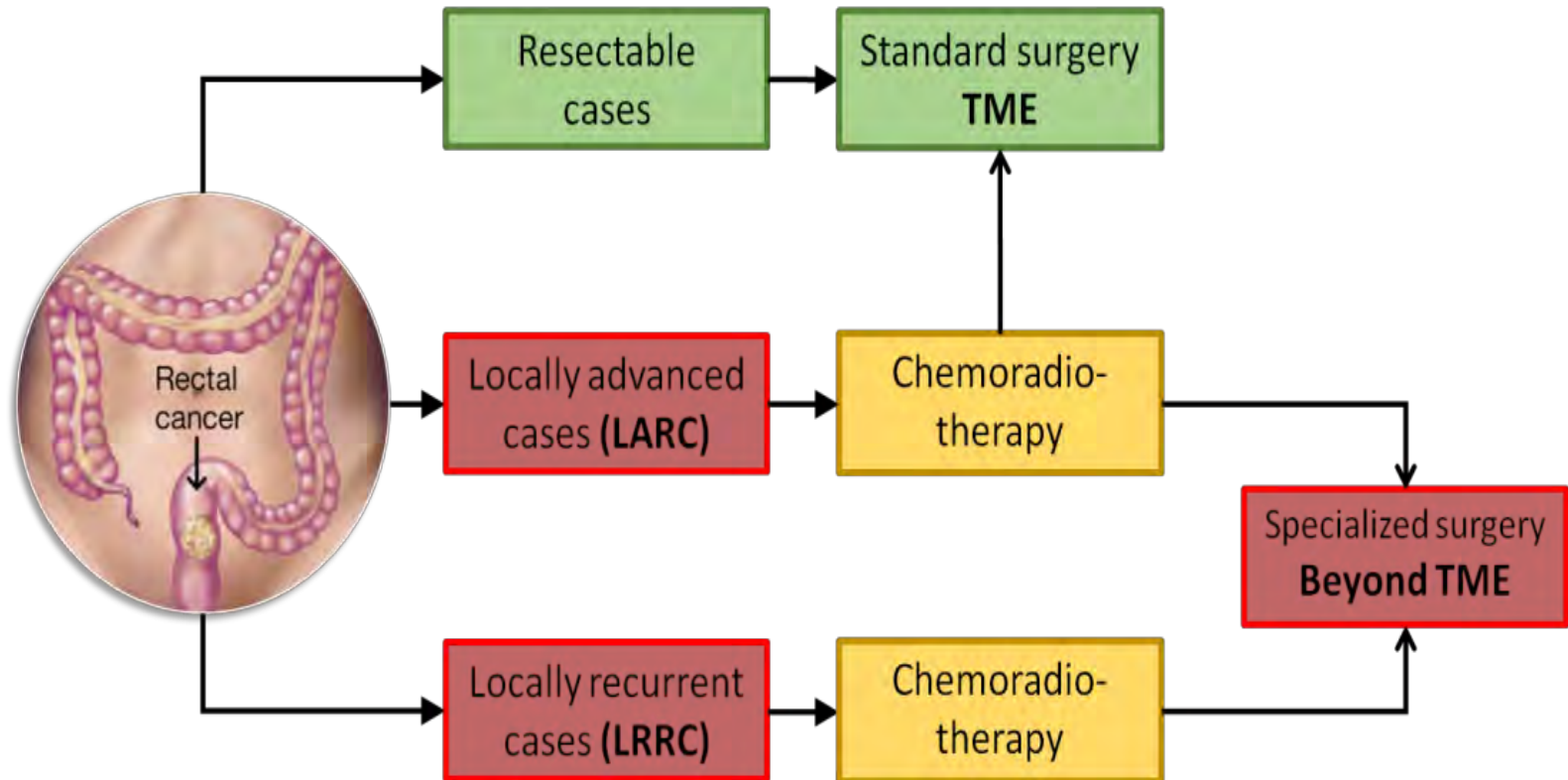


Rectal cancer

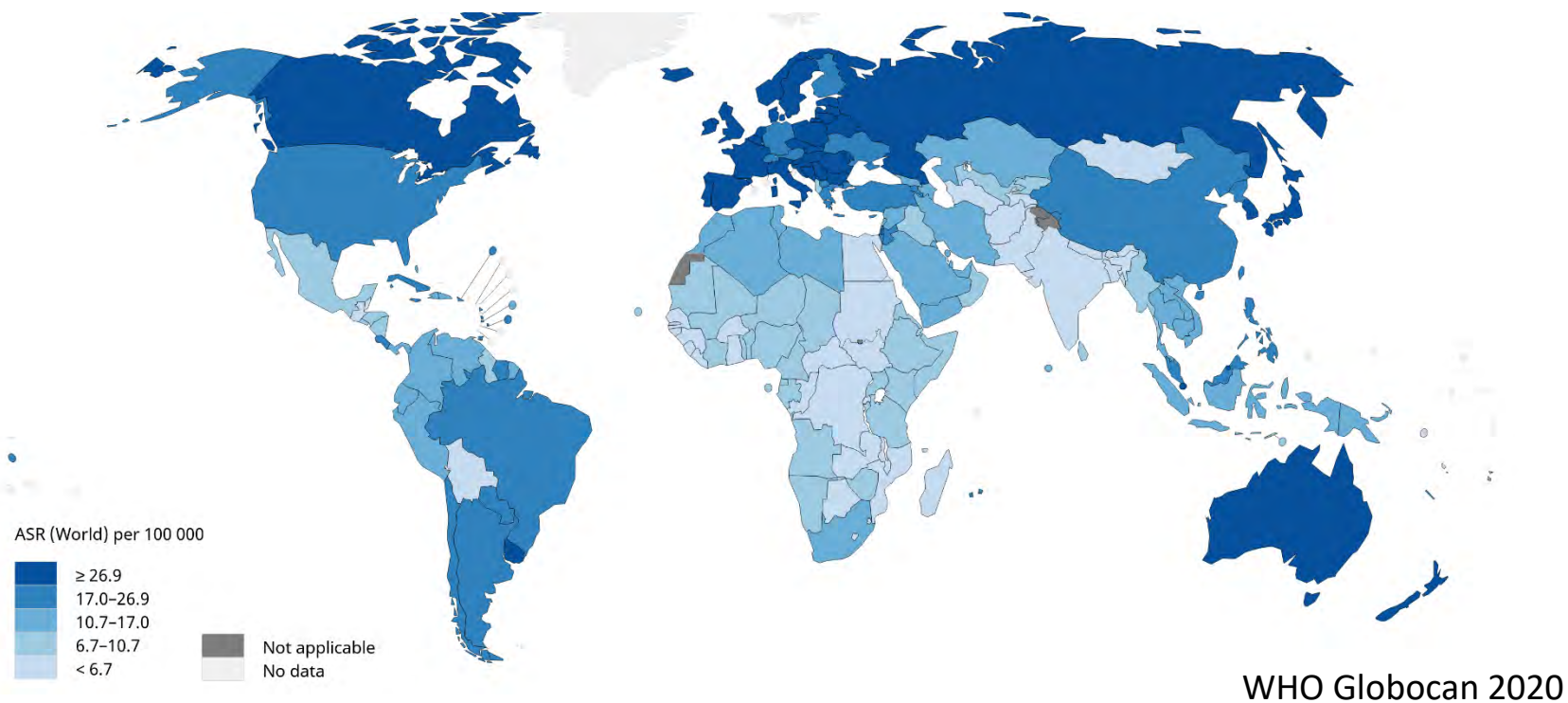


Arne M. Solbakken 300322

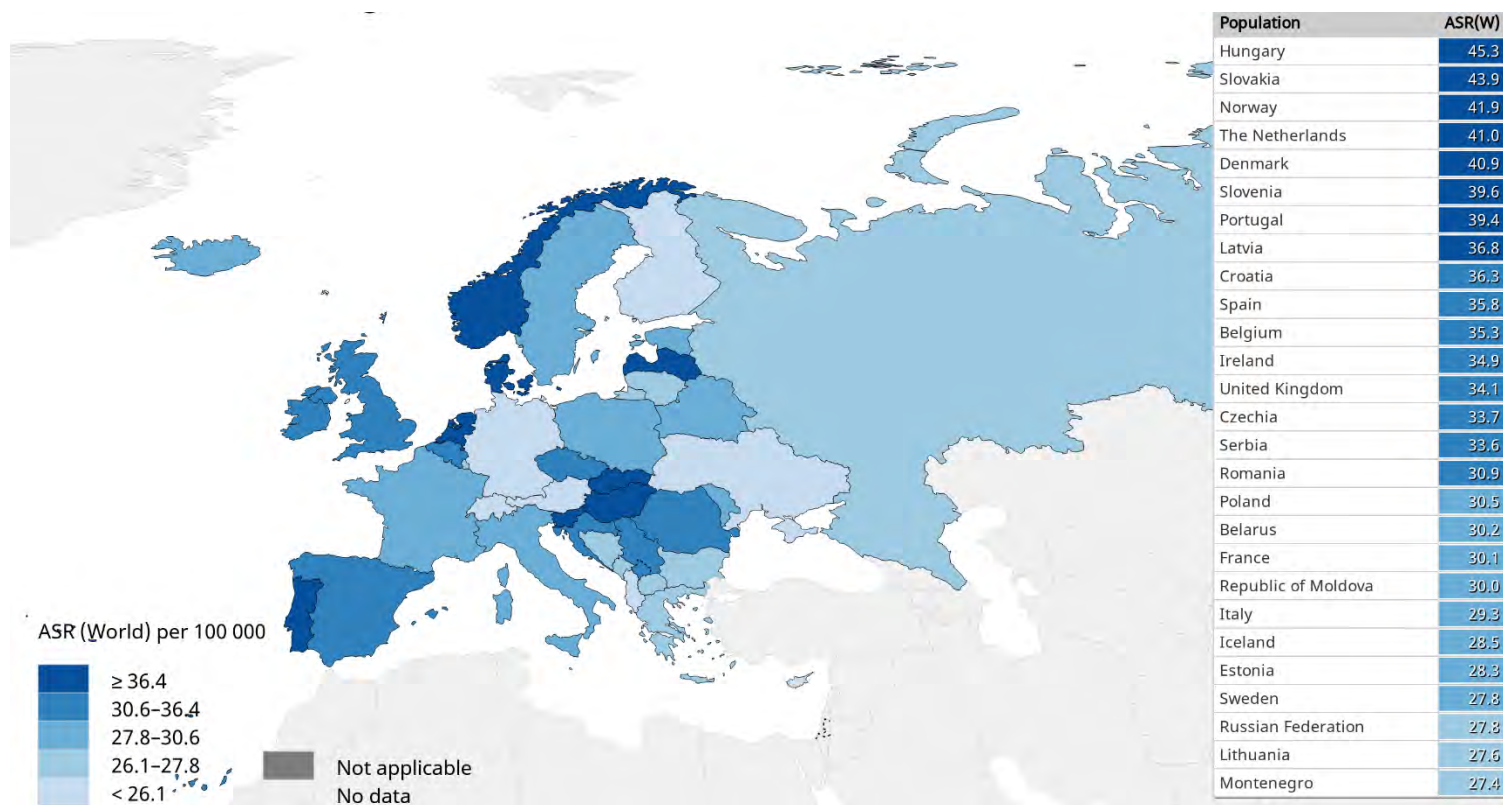
Rectum cancer



Colorectal cancer incidence 2020



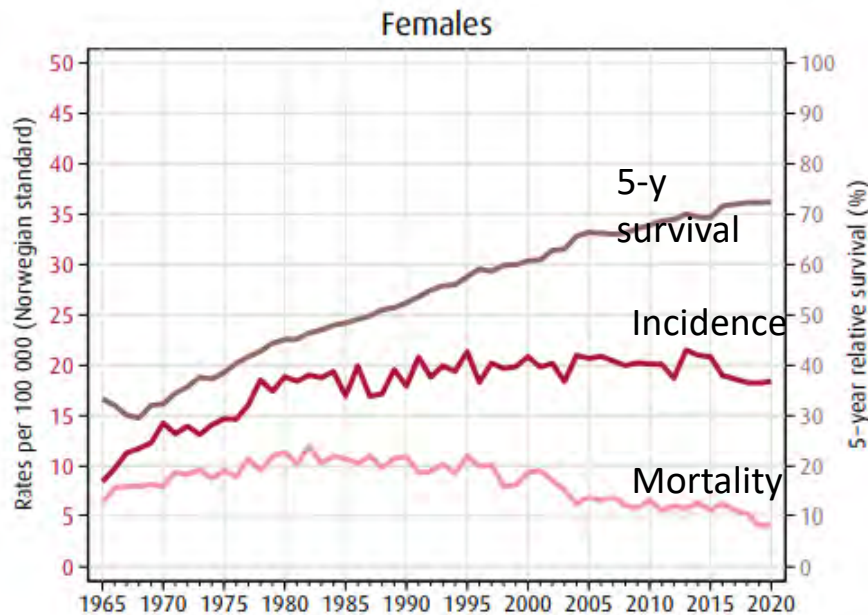
Colorectal cancer incidence Europe 2020 (age-standardized rates)



WHO Globocan 2020

Rectal cancer trends in Norway

Incidence, mortality and 5-year relative survival



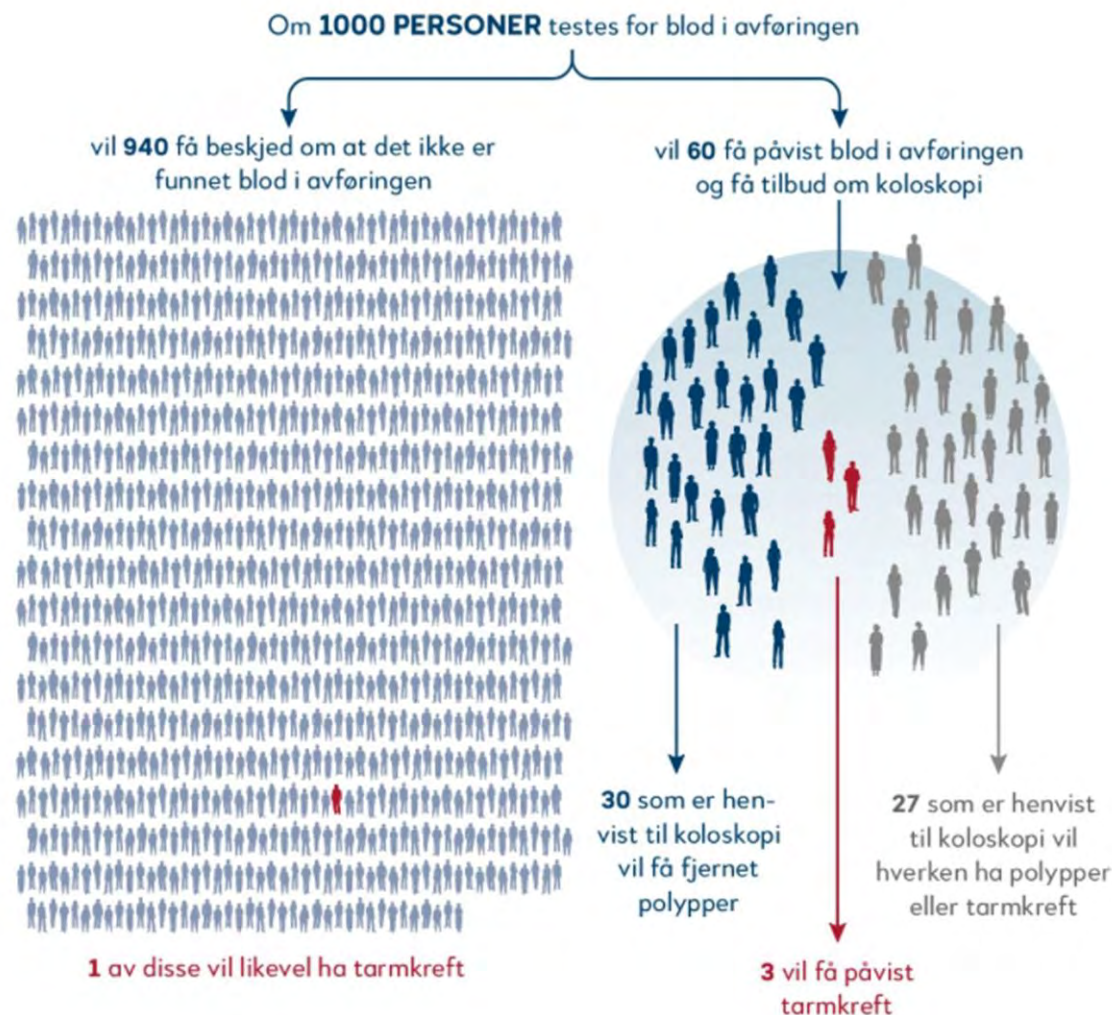
5-y rel. survival after diagnosis: 73 %

5-y rel. survival after operation: 89%

Cancer in Norway
2020

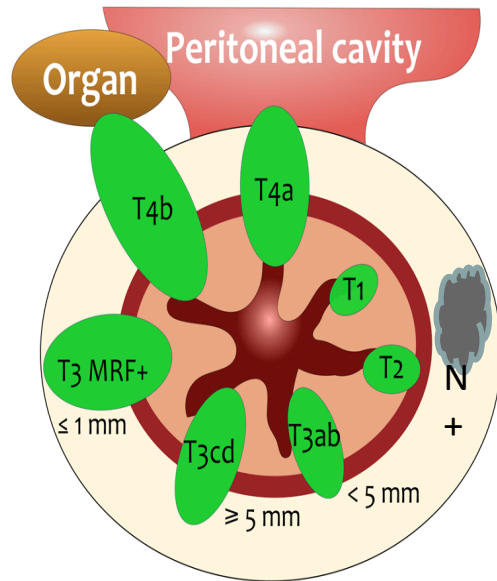
Screening for rectal cancer

- American Cancer Society
 - from 45 years
- Norway 2022
 - from 55 years
 - Fecal occult blood test x 1
 - Colonoscopy if pos.
 - In the long run: Colonosc



Cancer in Norway 2020

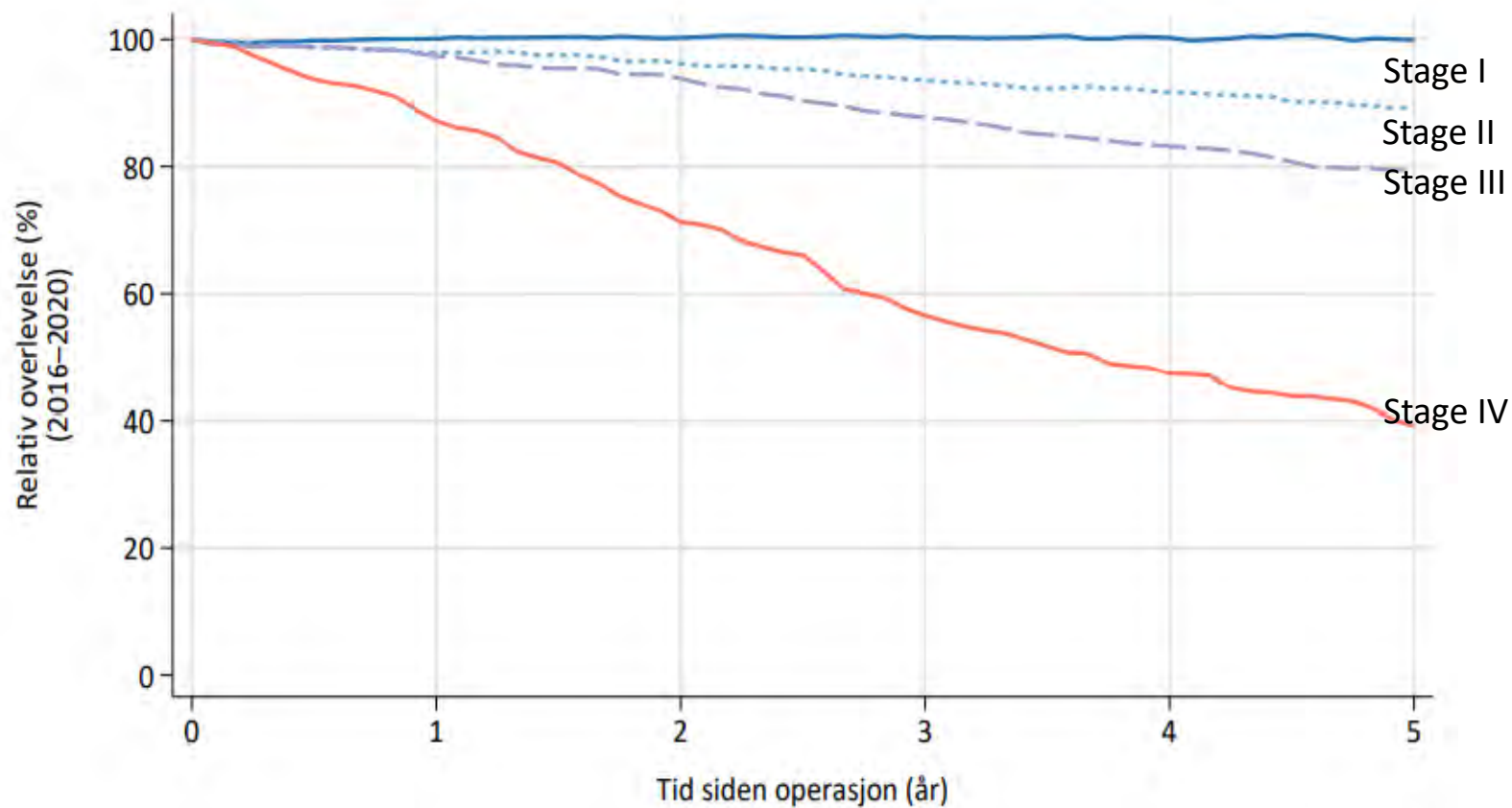
Rectal cancer AJCC stages



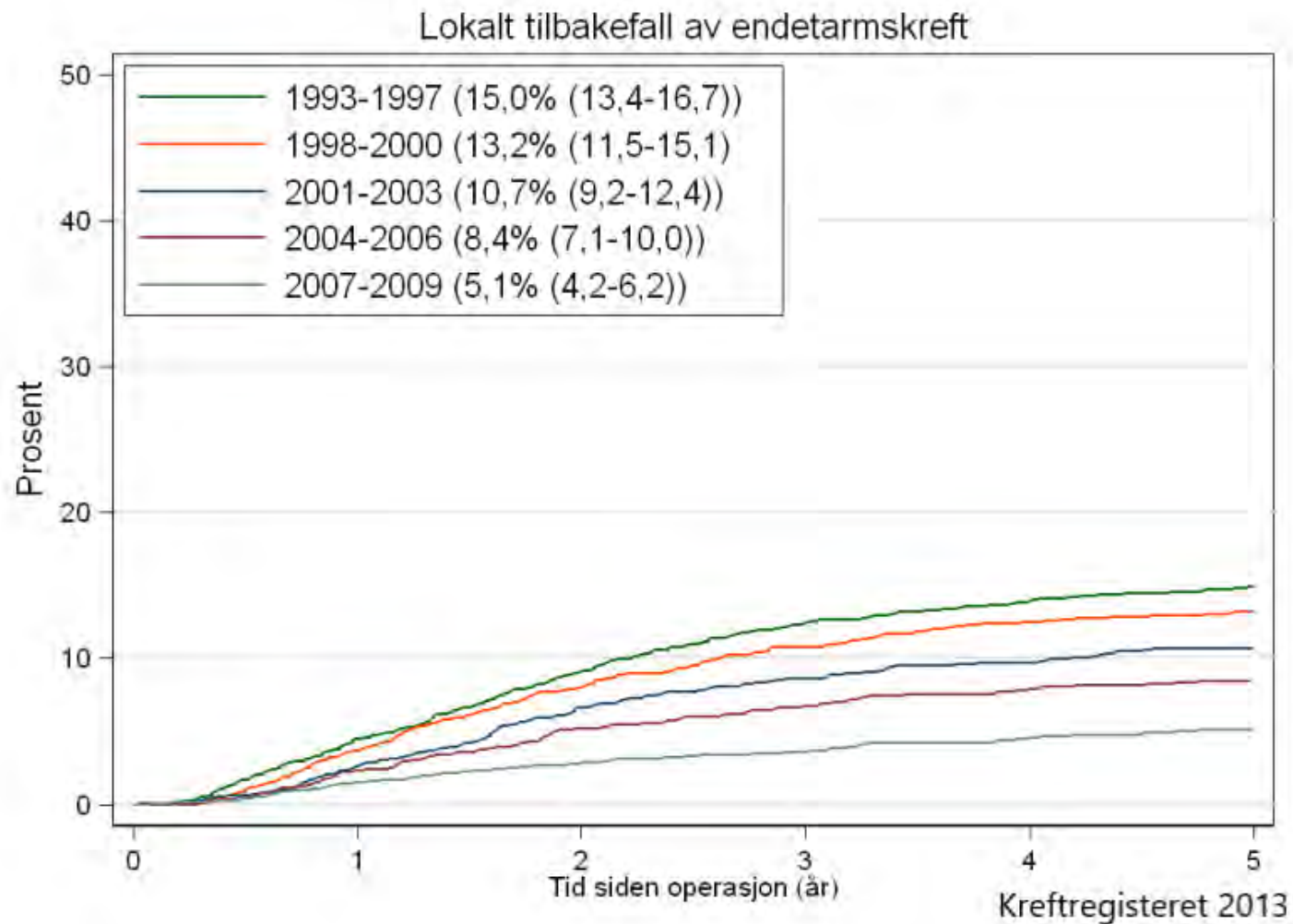
0	Tis	N0	M0
I	T1-T2		
IIA	T3		
IIB	T4a		
IIC	T4b		
IIIA	T1-T2	N1/N1c	
IIIB	T1	N2a	
	T3-T4a	N1/N1c	
	T2-T3	N2a	
IIIC	T1-T2	N2b	
	T4a	N2a	
	T3-T4a	N2b	
	T4b	N1-N2	
IVA	Any T	Any N	M1a
IVB			M1b
IVC			M1c

Source: *AJCC Cancer Staging Manual*, 8th edition. Springer International Publishing, 2017.

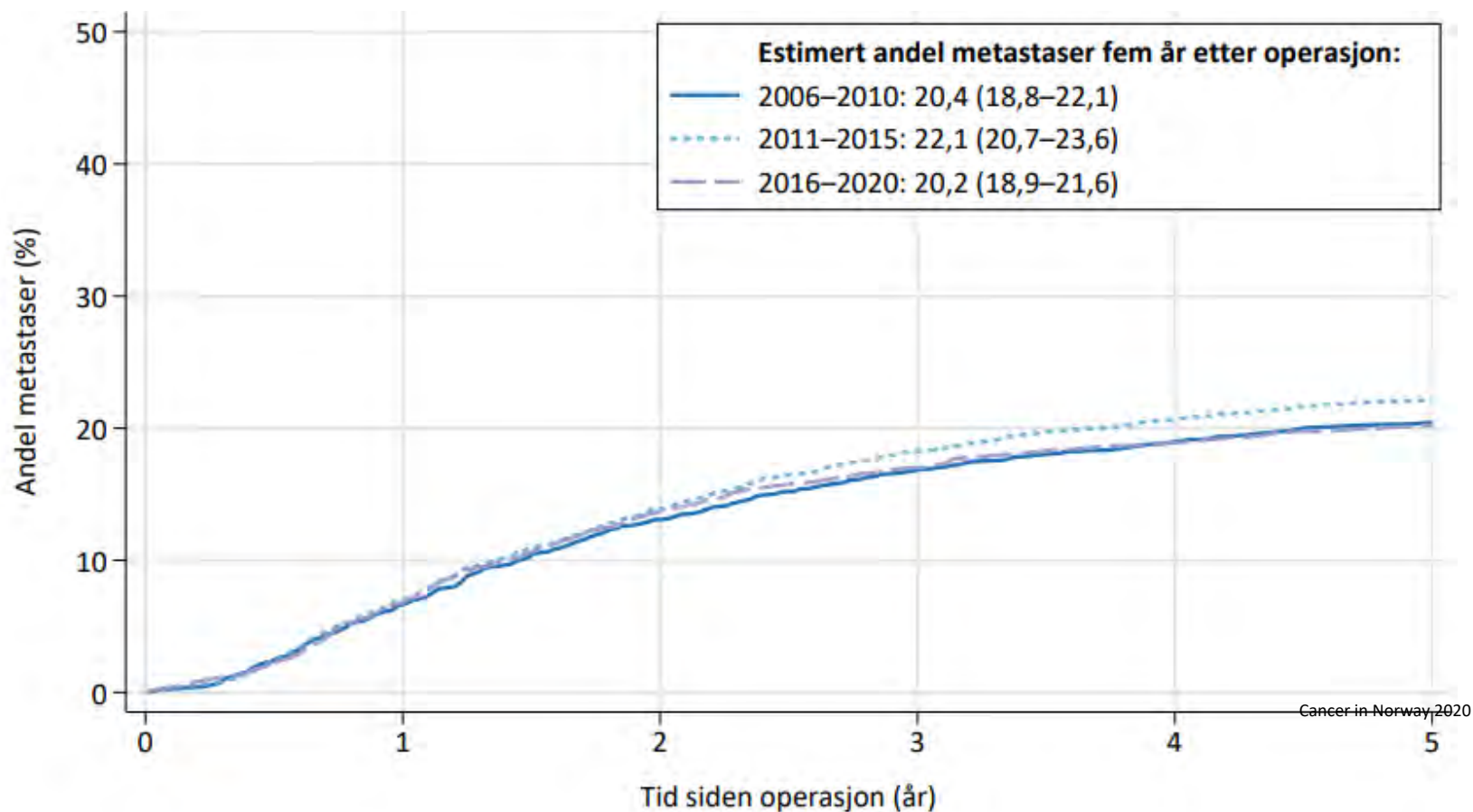
Rectal cancer stages and prognosis (operated patients)



Kontroll med lokale residiver

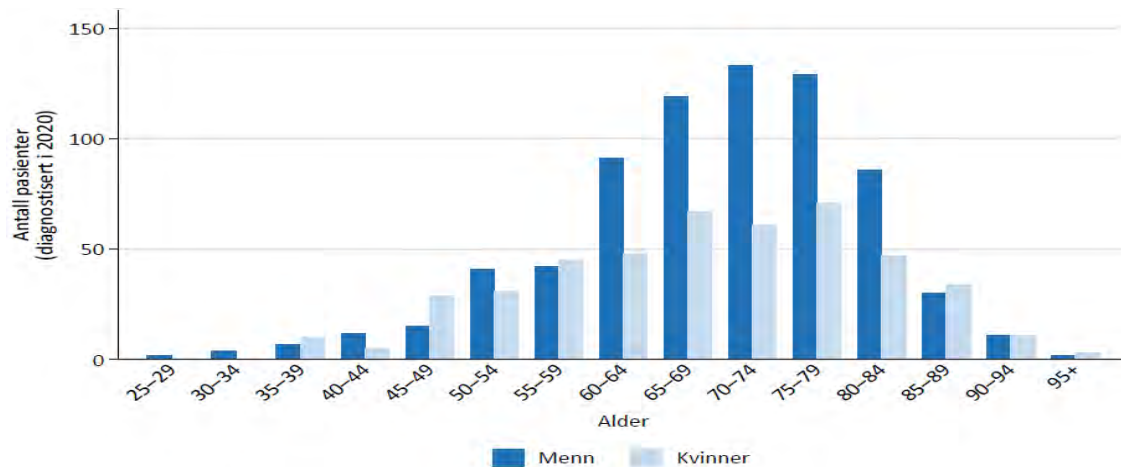


Hva med metastasene?



Inngrep rectum

- Kirurgi utføres med TME-teknikk (total mesorectal excisjon) og ved omfattende sykdom evt. utenfor dette planet (beyond-TME (bTME) eller en-bloc reseksjon
- LFR= lav fremre rectum reseksjon
- Hartmann's operasjon = (stomi + anus inntakt)
- APR= abdominoperineal rectumamputasjon



Endetarms kreft i Norge etter 1993.

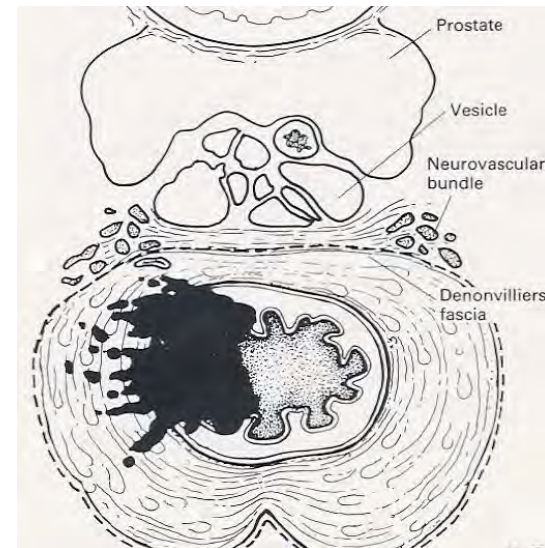
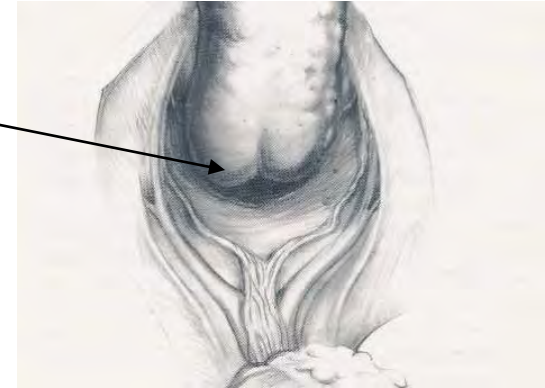
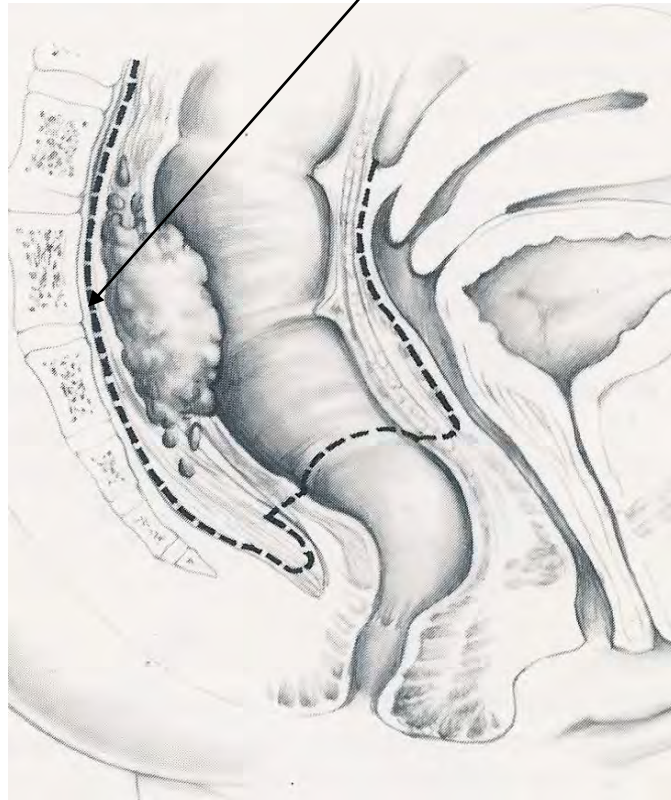
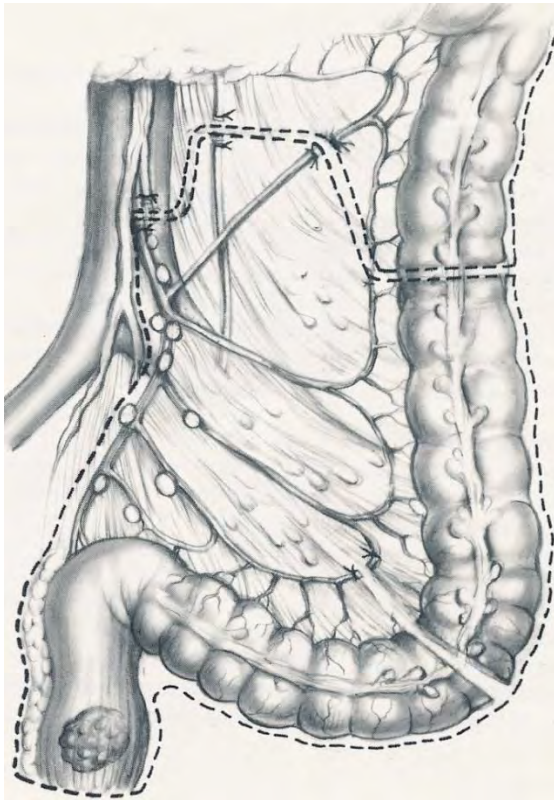


- Innføring av **TME**(total mesorectal excisjon)
- Utviklet av R J Heald, Basingstoke, publ. 1982.
- Kirurgi i "nye" anatomiske plan.
- Teknikken er innført i Norge og Sverige fra 1993. Seinere i andre land.
- **Økt volum** (fra 54 sykehus i 1993 til 25 nå).
- **Spesialisering** (knyttet til gastrokirurgene – elektivt)
- **Bedre resultat**. Fjernspredning og lokale tilbakefall

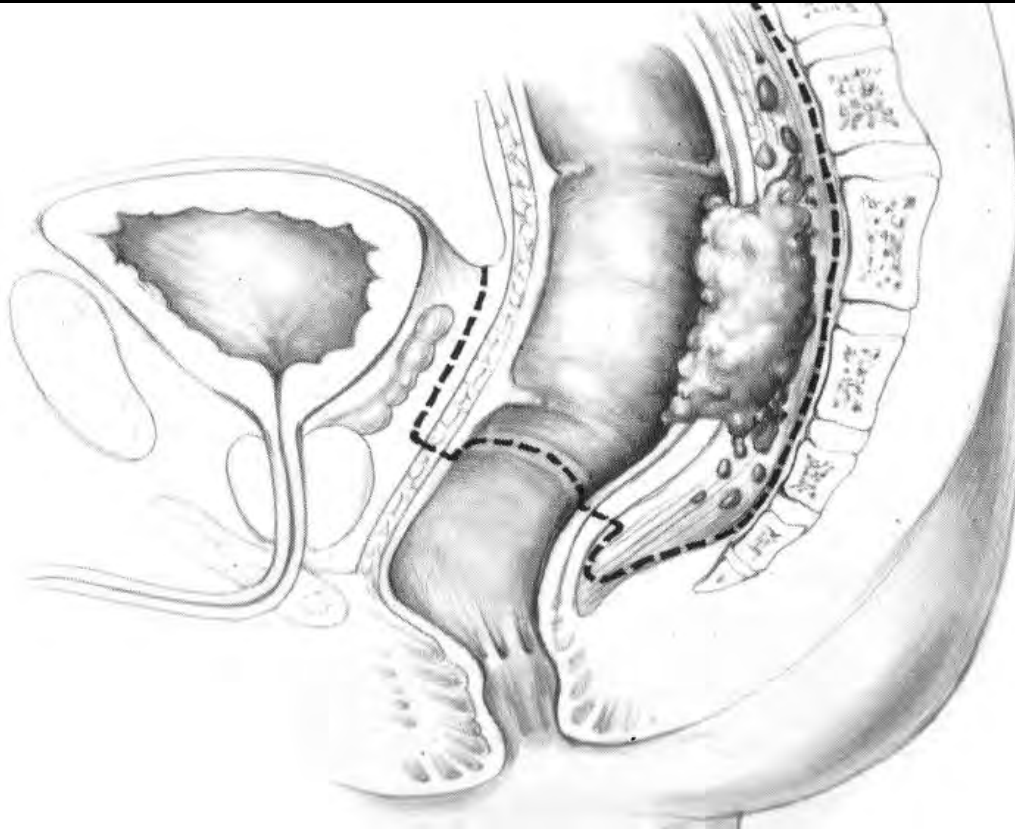
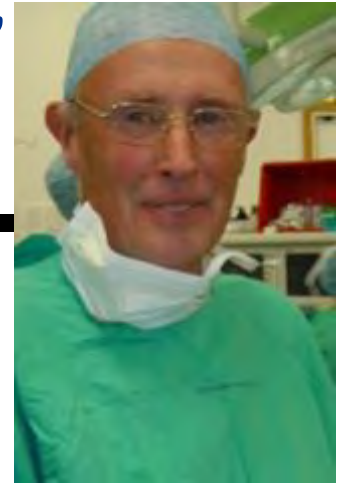
TME (total mesorectal excision)

Fra 28% recidiv rate i 1988 til 5 % i Norge i 2000

"Holy plane"

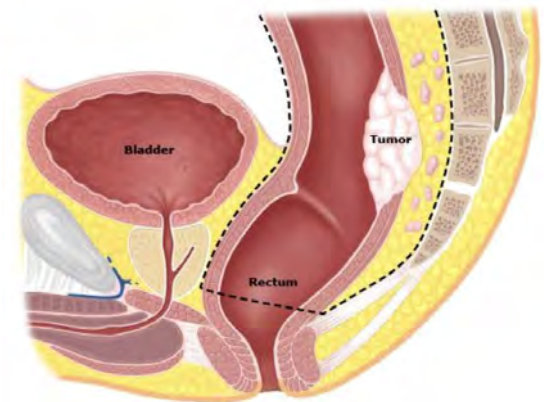
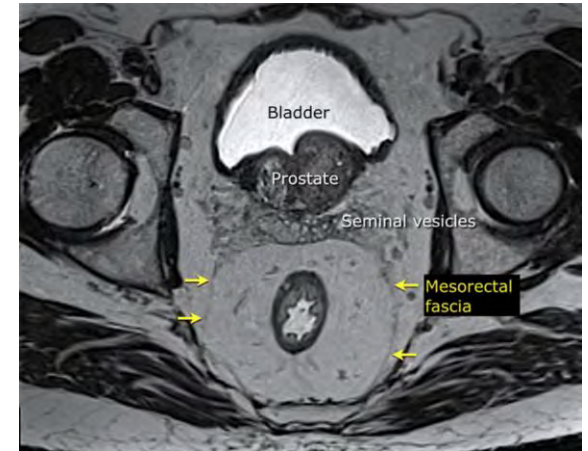
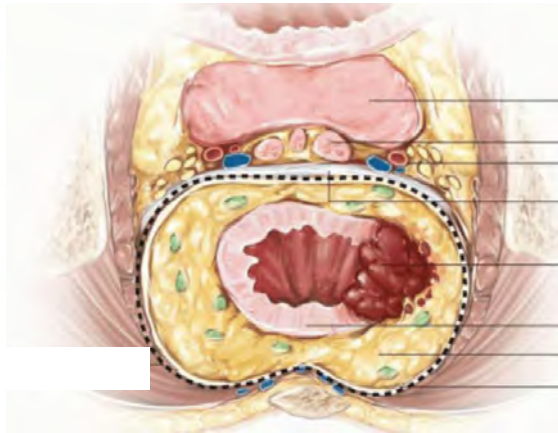
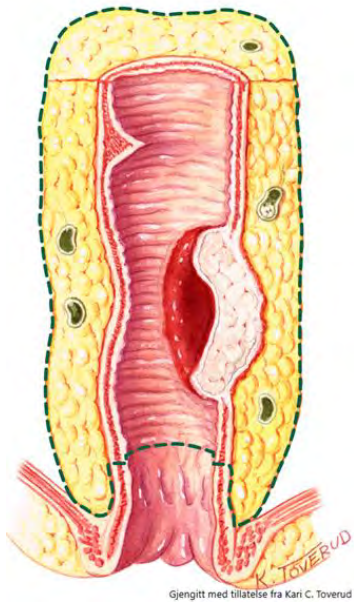


TME¹: Healds “holy plane”



TME: Total mesorectal excision. Heald, Lancet 1986. Recidivrate 4%.

Anatomy - the mesorectal fascia (MRF)



Man kan leve som man vil med stomi

Slik tar Charlotte (24) oppgjør med stomi-tabuet (VG 06.11.16)

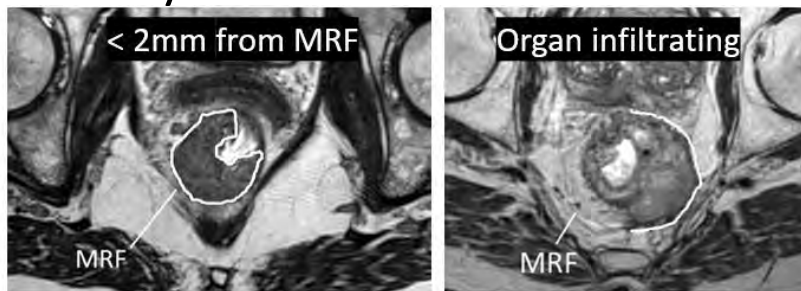


- kontaktidrett
- samliv
- turer
- svømming
- badstu



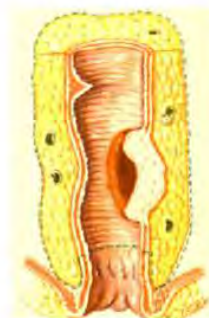
Treatment options depend on the tumours relations to the mesorectal fascia

Primary non- resectable rectal cancer

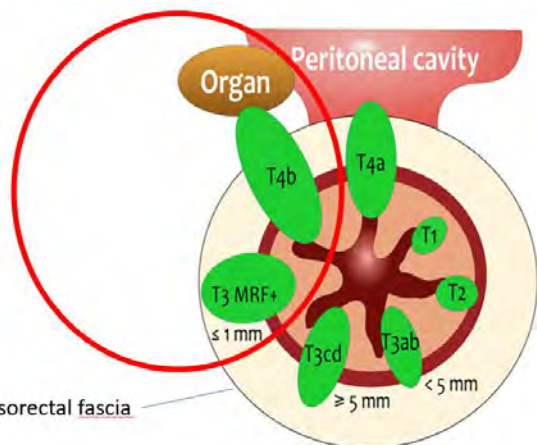


Neo-adjuvant treatment

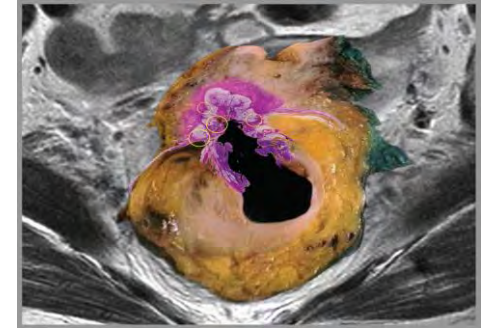
TME



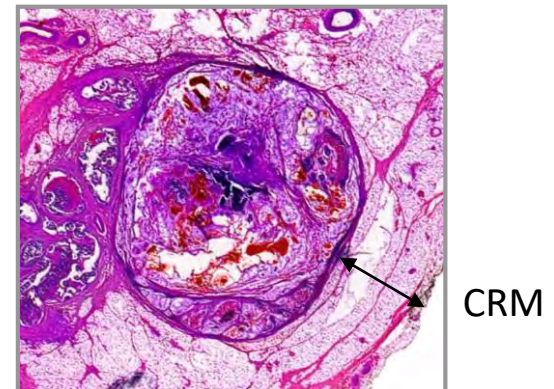
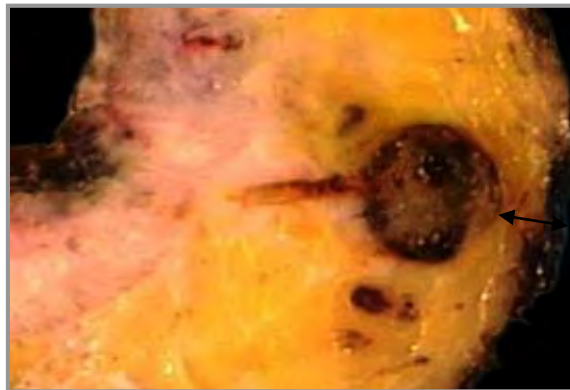
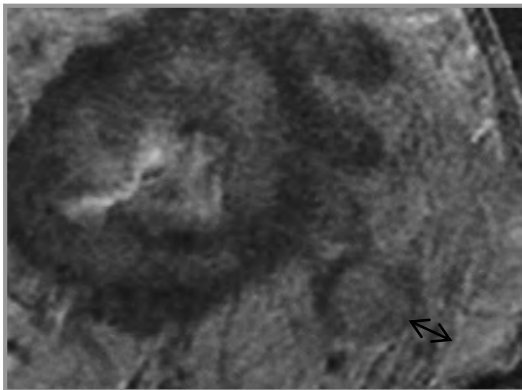
Beyond TME surgery
Radium Hospital: ~ 100/year



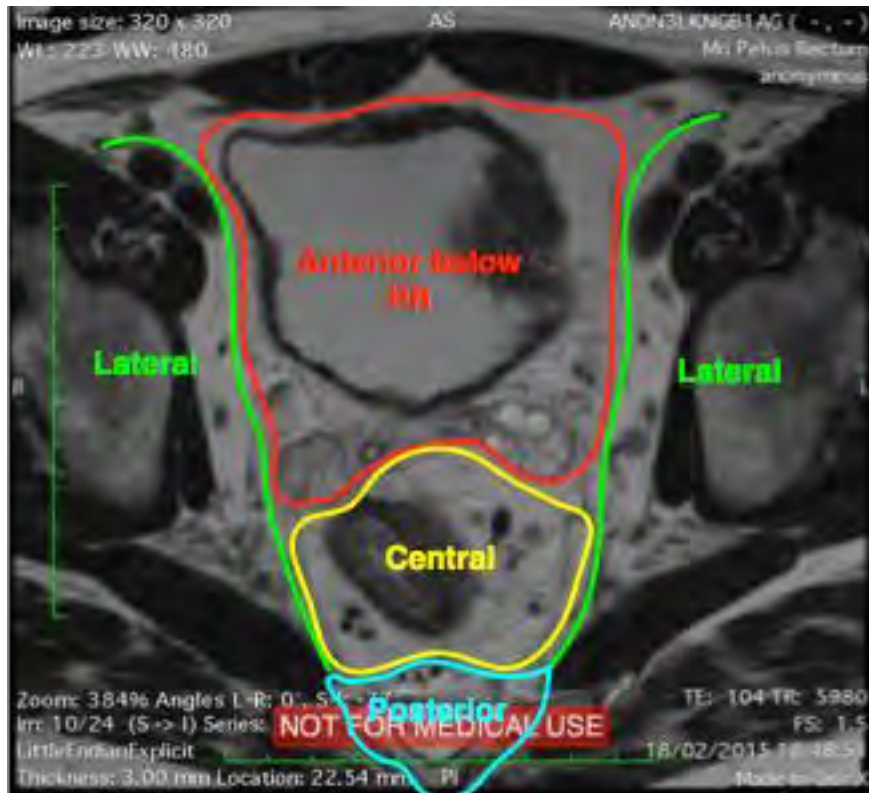
Lokalavanser rectum cancer (LARC)

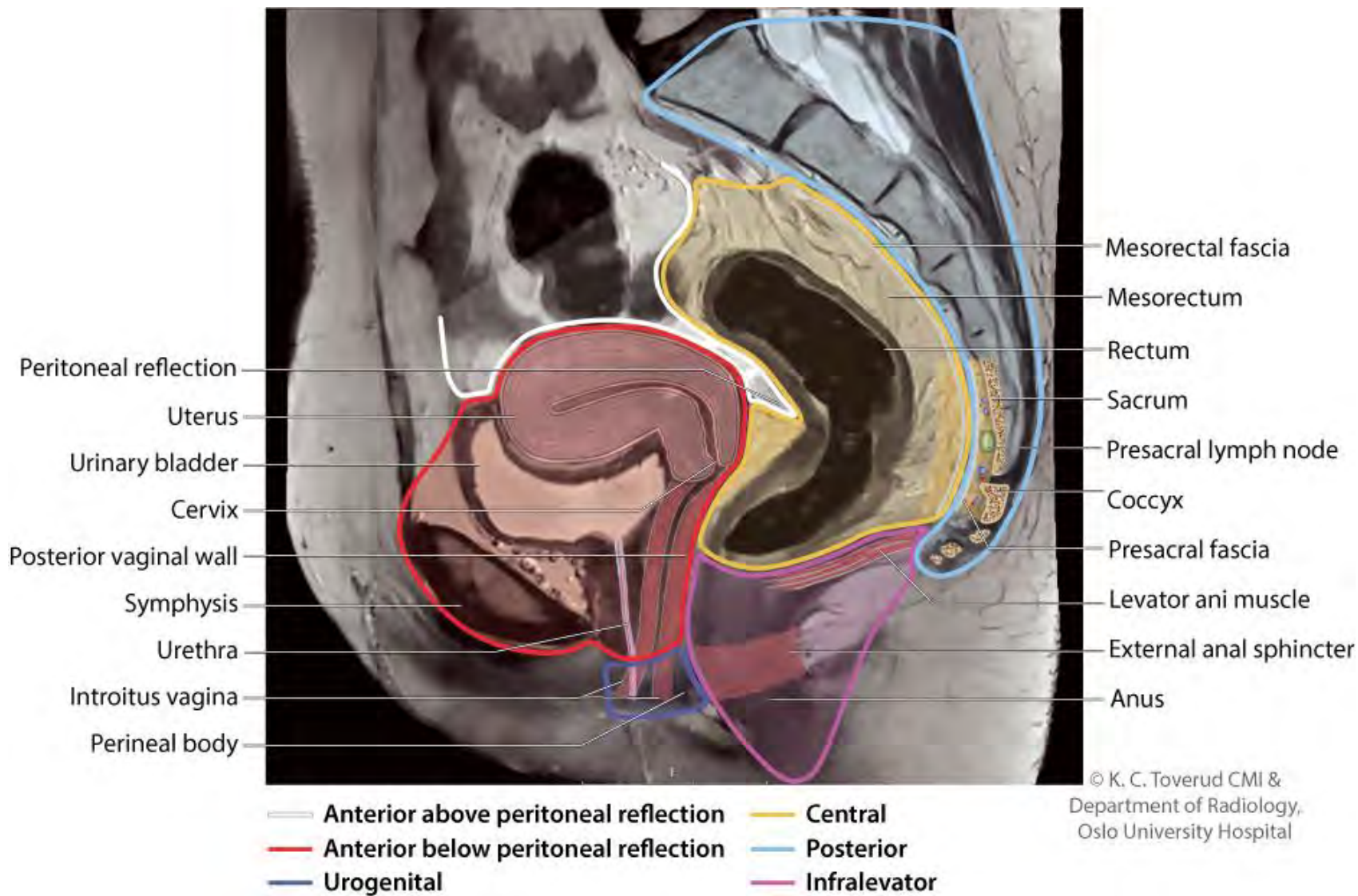


- 10%–20% har en primært inoperabel svulst pga fiksasjon i bekkenet eller innvekst i andre strukturer/ organer) (Pahlman 1985)
- 1/3 av cancer recti pasientene har truede utre marginer ved < 2 mm avstand til CRM)
- Preoperativ MR er den beste undersøkelsen for å vurdere de lokale forhold i bekkenet (MERCURY study group 2006 and 2007; Beets–Tan 2005)



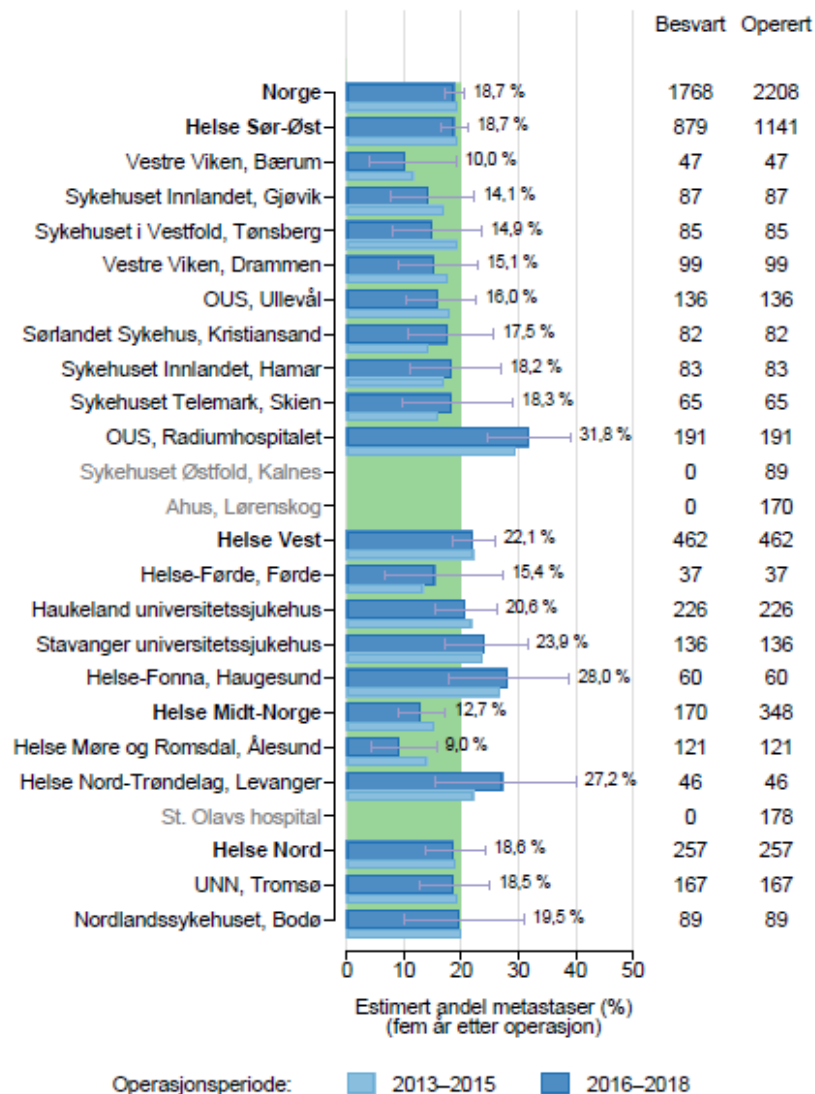
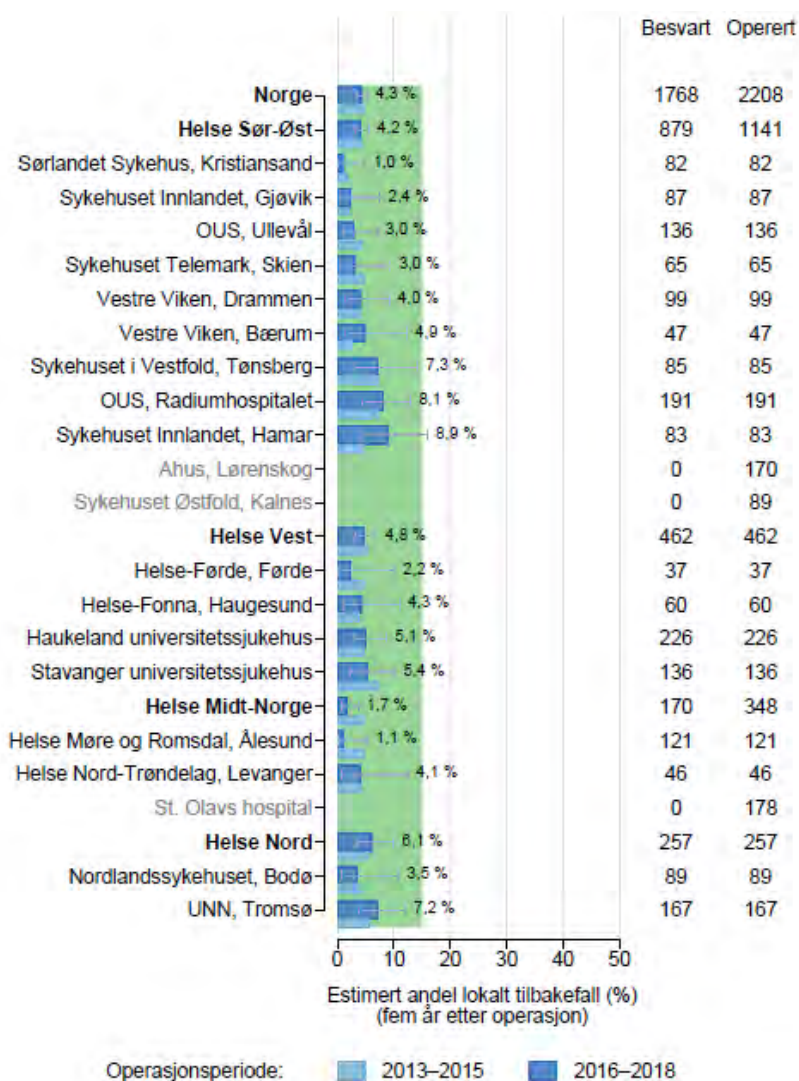
bTME = tumorvekst utenfor mesorectum



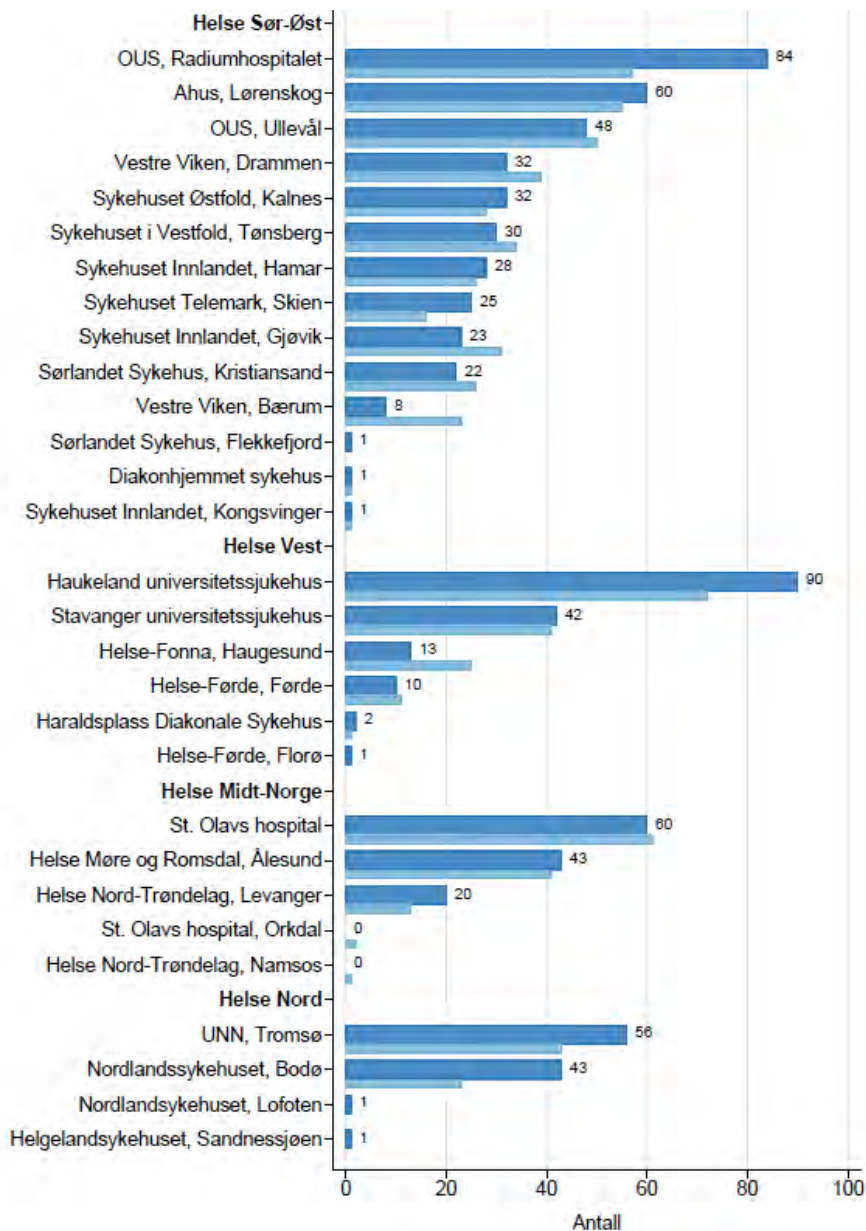


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Department of Radiology,
Oslo University Hospital

Årsrapport 2018, lokale residiv og metastaser



Økt sentralisering av avansert kirurgi



Treatment

Pre-operative oncological treatment
for some to increase chances of R0

- Primary resectable rectal cancer
- Primary non-resectable rectal cancer

Free margin

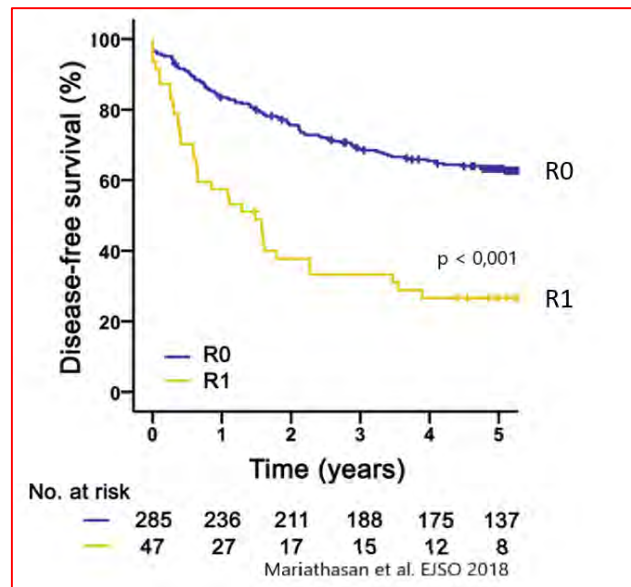


R0

Involved margin



R1



Tumour infiltration in adjacent organs

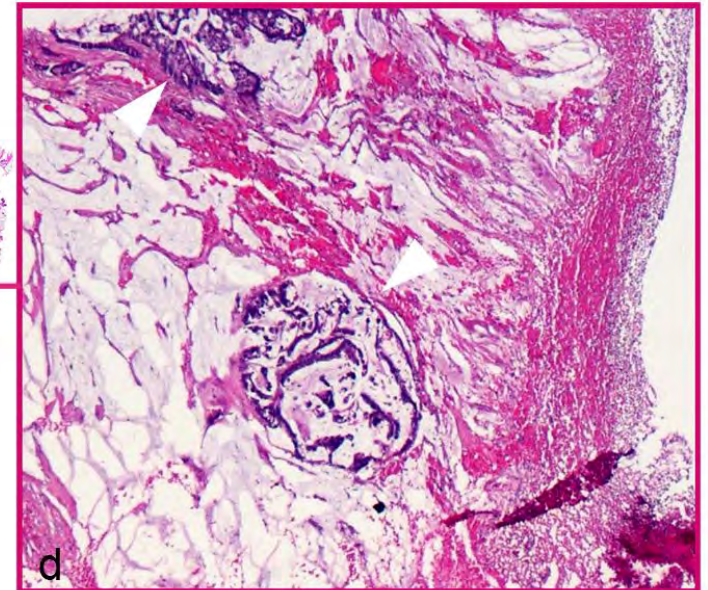
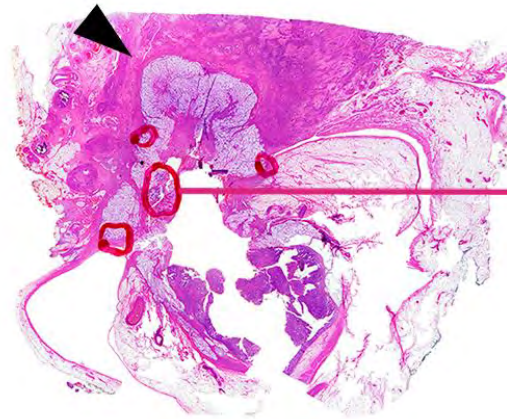
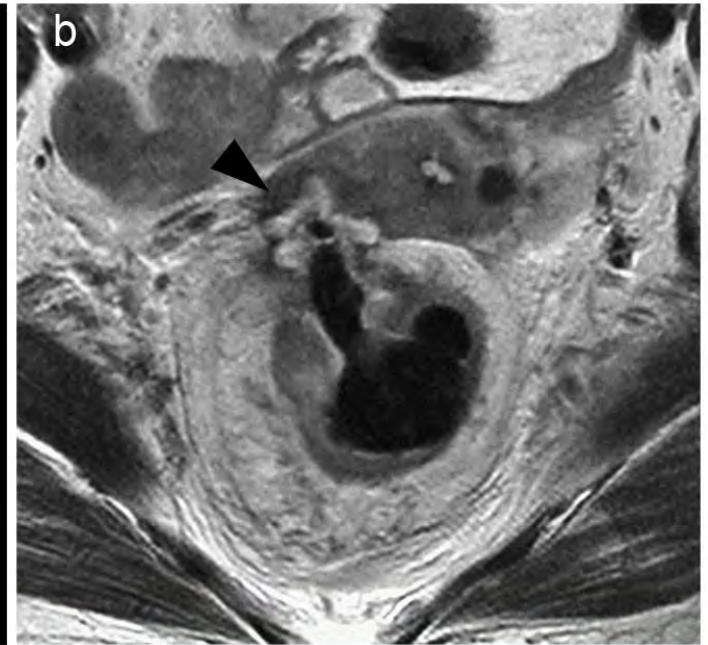
Tumour islets within mucinous infiltration (black arrowheads) of the uterine cervical stroma.

(a) Resection specimen slice.

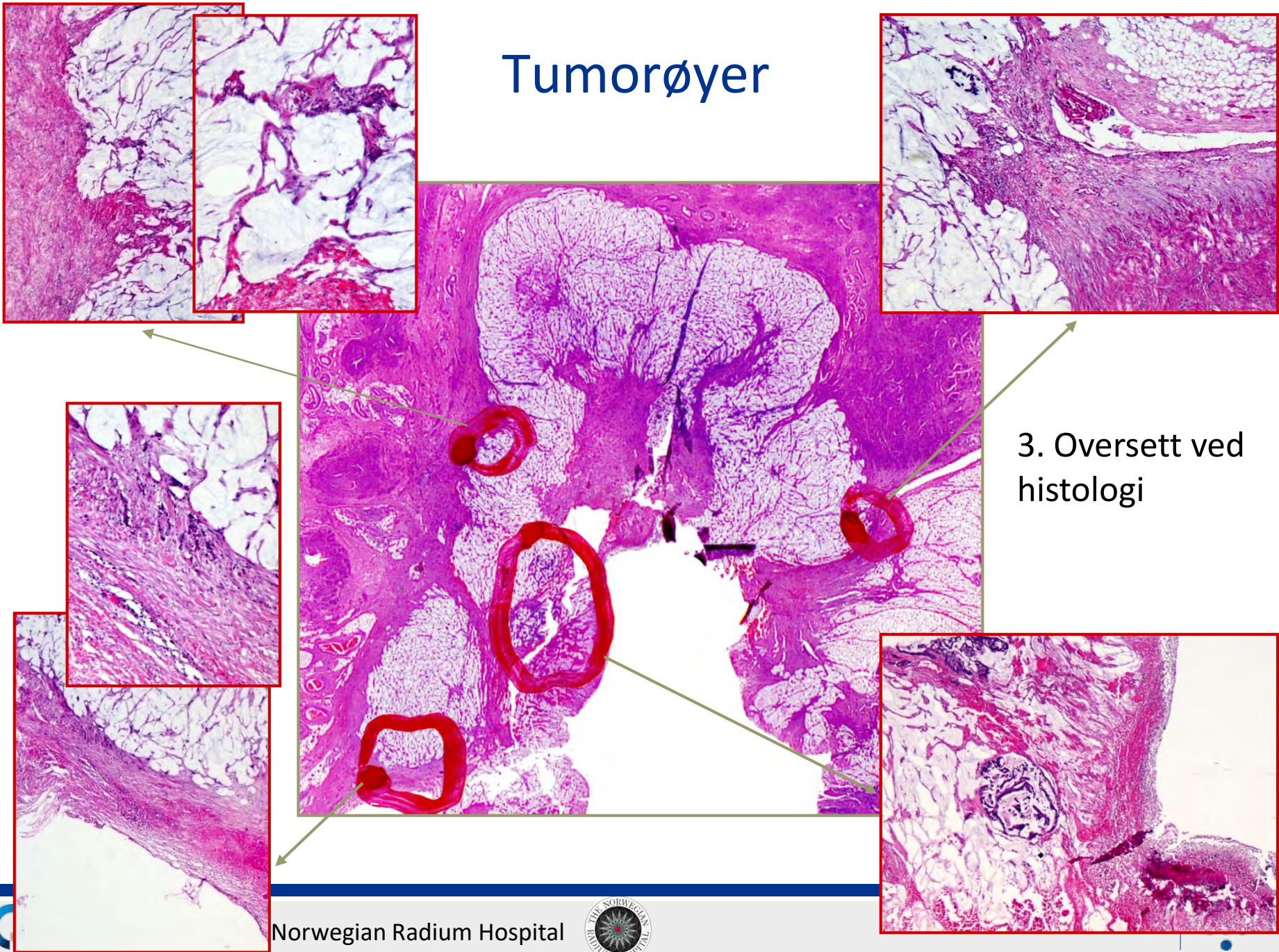
(b) Corresponding transversal T2-weighted MRI obtained after radiation therapy.

(c) Corresponding whole-mount histology (haematoxyline and eosine stained). Four islets of tumour where present (red circles).

(d) Original magnification x 25 of the largest tumour deposits (white arrowhead).

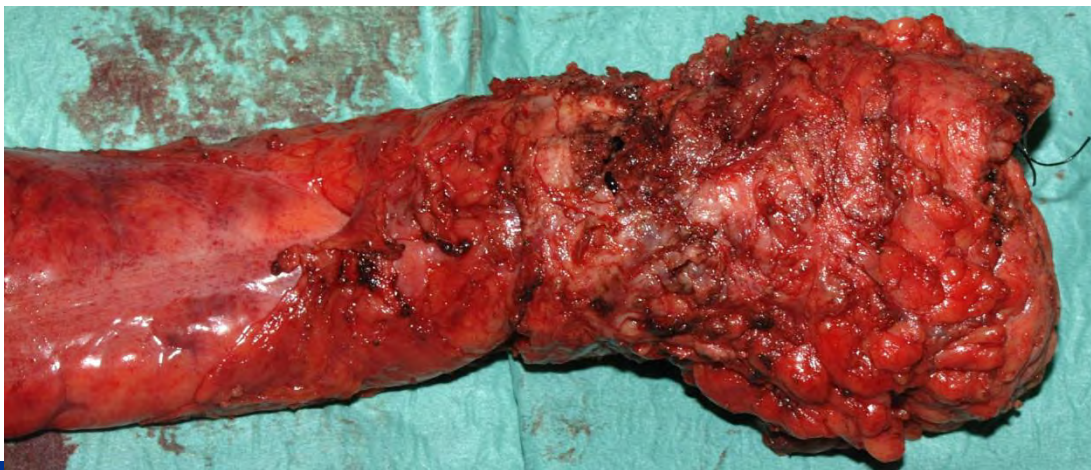
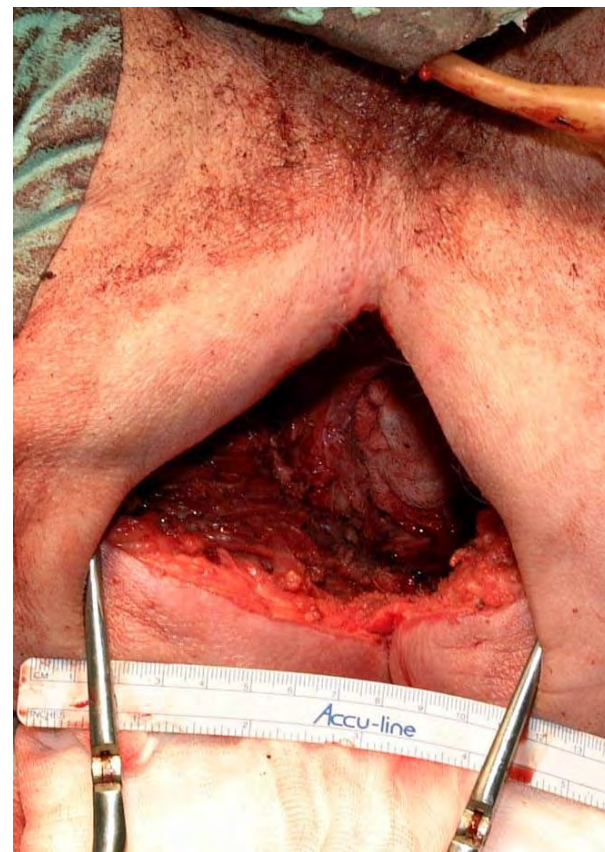
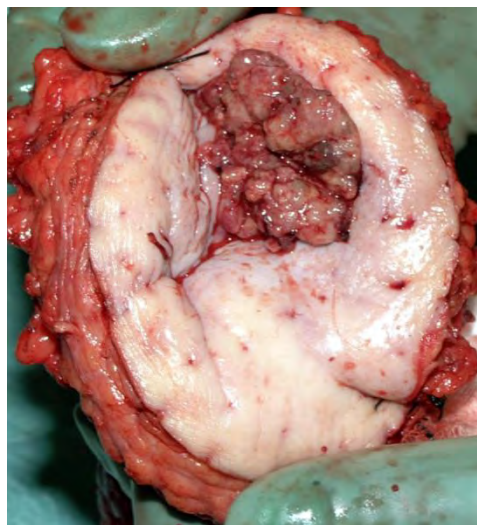
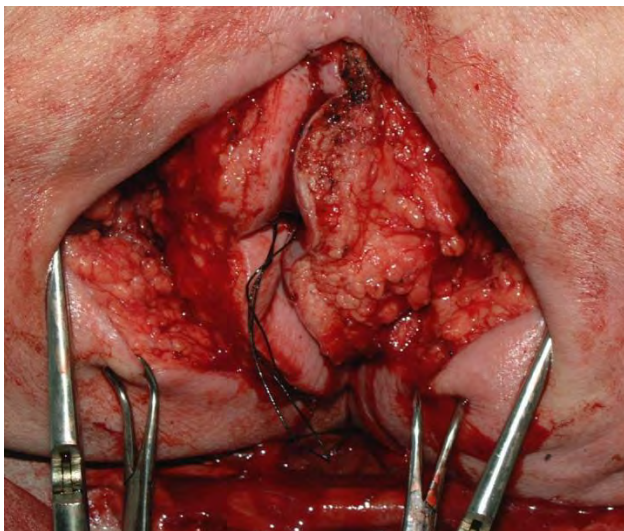


Tumorøyer



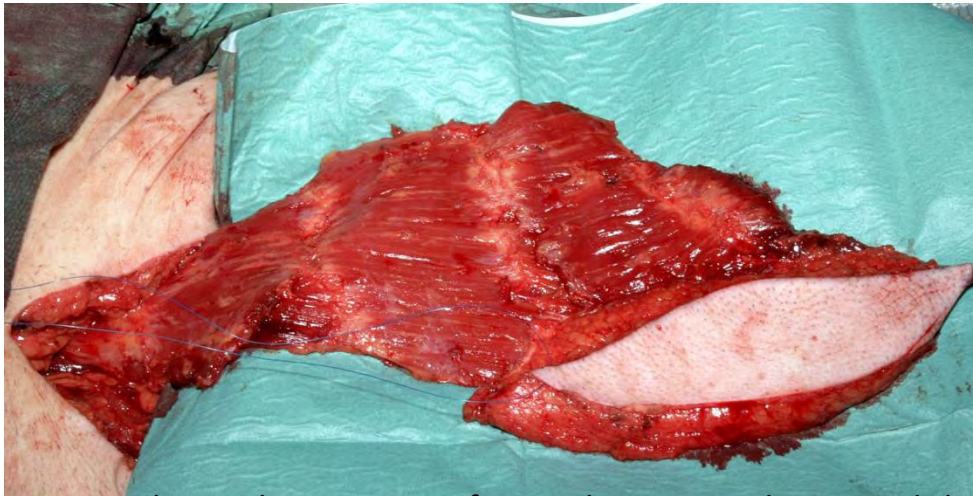
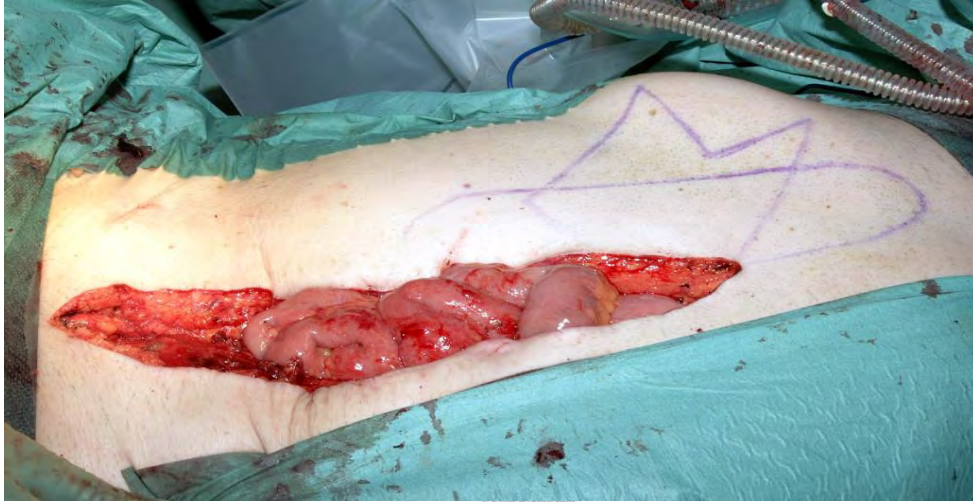
3. Oversett ved histologi

Vevsdefekter



Hva nå?

Nytte av muskellapper (for eksempel VRAM)

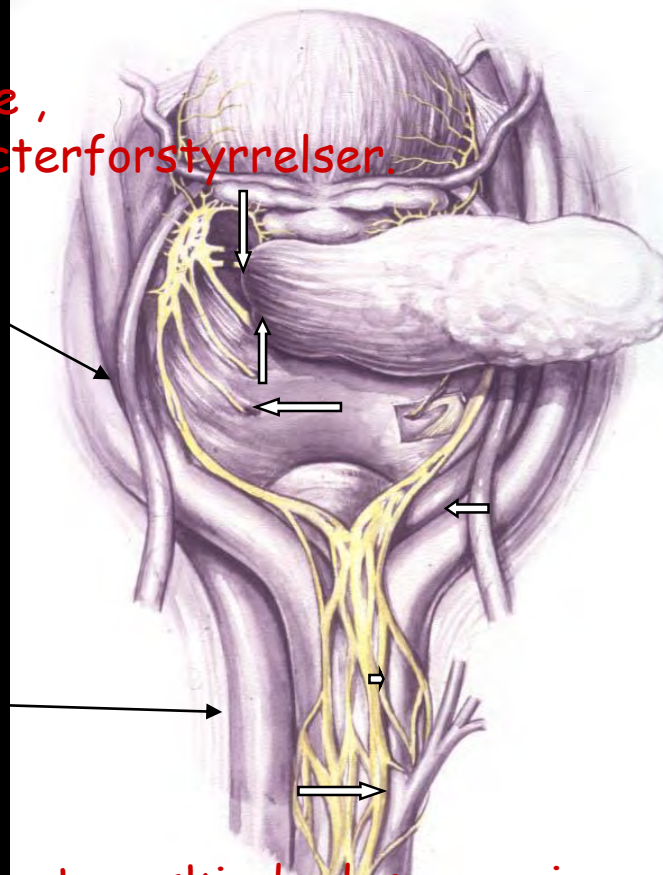


Butler et al. Outcomes of Immediate Vertical Rectus Abdominis Myocutaneous Flap Reconstruction for Irradiated Abdominoperineal Resection Defects, J Am Coll Surg, Vol. 206, No. 4, April 2008

TME: Pelvic autonomic nerves.

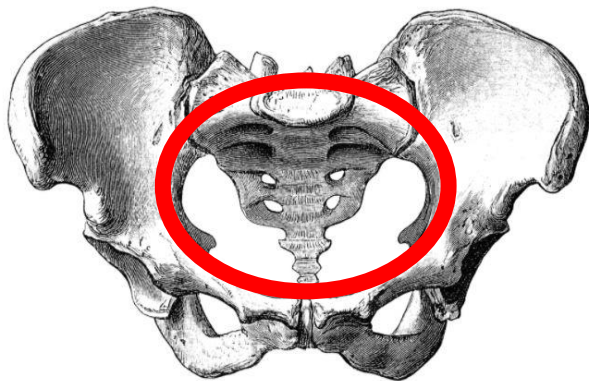
Areas of caution

Parasympathetic
ereksjonssvikt, tørr skjede,
blæreforstyrrelser, sphincterforstyrrelser.

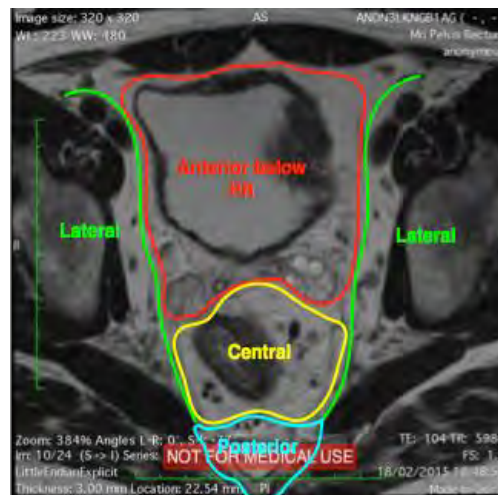
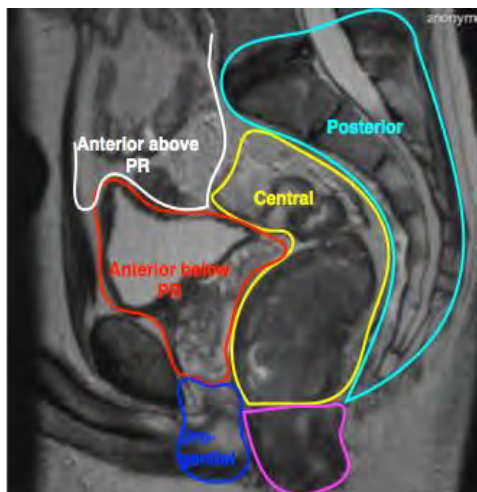


Sympathetic
Retrograd ejakulasjon, tørr skjede dysparauni,
blæreforstyrrelser (hemmet detrusor), sphincterforstyrrelser.

- LRRC:
 - Lokalt tilbakefall av kreftceller i det lille bekken etter tidligere fjerning av primær rektumcancer



- anastomoserecidiv
- ny tumor i tidl. tumorområde
- lymfeknuter bekkenvegg og lysker
- drenskanaler
- kirurgiske arr



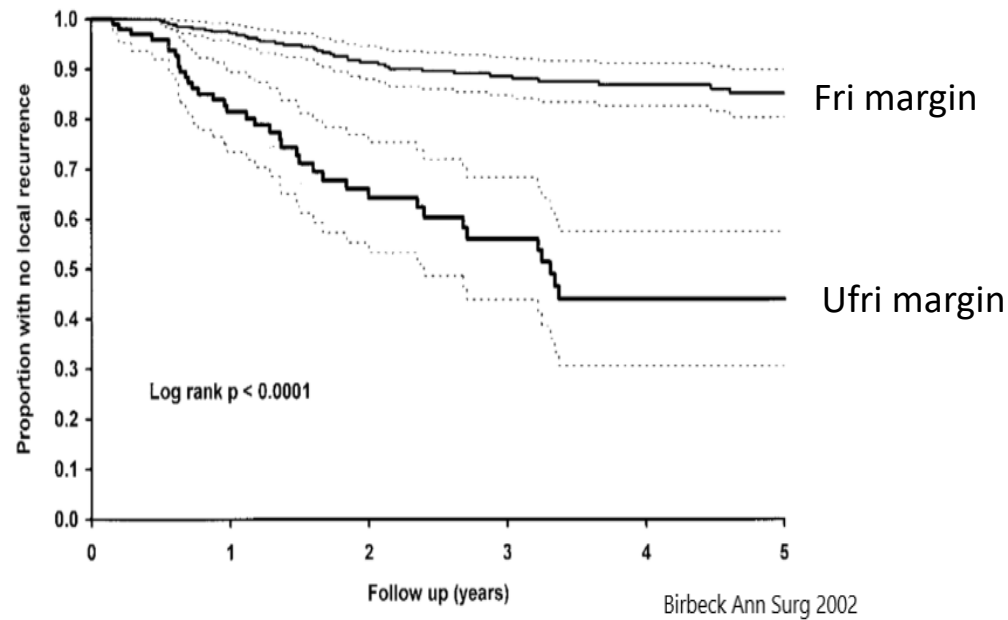
Beyond TME trial

Hvorfor får pas. LRRC?

- Gjenværende kreftceller
 - Ufri margin
 - Tumor/tarmperforasjon
 - Metastaser til lymfeknuter utenfor reseksjonen
 - Anastomoselekkasje

Hvorfor får pas. LRRC?

- Ufri margin øker risiko for LRRC



Hvorfor får pas. lokalt residiv?

- Anastomoselekkasje gir øket risiko for LRRC

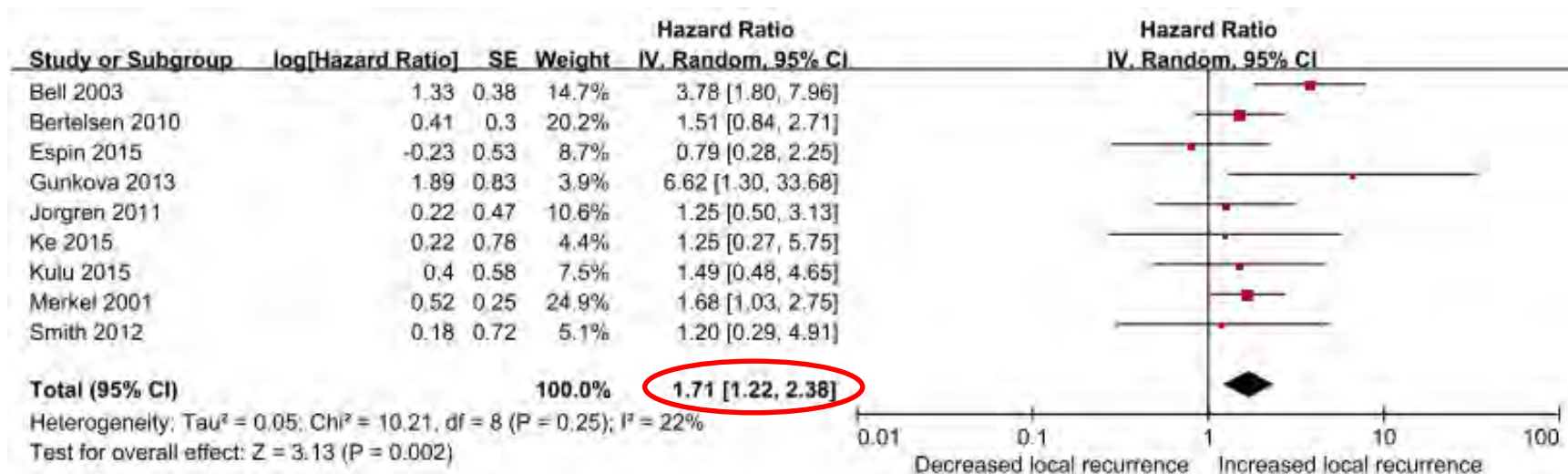


Fig. 2 Effect of anastomotic leakage on the risk of local recurrence of rectal cancer after anterior resection

Wang 2017

Hvordan håndterer vi LRRC?

- Nasjonalt handlingsprogram 2022:
 - Behandles som lokalavansert primær rektumcancer
 - Preoperativ strålebehandling
 - Re-bestråling i enkelte tilfeller
 - Tillegg av kjemoterapi før eller etter stråling kan vurderes
 - Behandlingen bør sentraliseres og registeres
 - Utføres ved sentra som har ekspertise og volum
- Helse Sør-Øst:
 - Onkologisk behandling ved Ullevål og evt. lokalsykehus
 - Neoadjuvant behandling
 - Standard: Kjemoradiasjon (2 Gy x 25 med kapecitabine)
 - Hyperfraksjonert rebestråling (1,2 Gy x 2 x 17 med kapecitabine)
 - TNT i PelvEx II?
 - Randomisering: Kjemoradiasjon vs. induksjonskjemoterapi + kjemoradiasjon
 - Kirurgi ved Radiumhospitalet

Hvor mange residiv opereres årlig?

Helse Sør-Øst: 2,9 mill innbyggere
700 opererte rektumcancere

25-30 residiv henvises til OUS

10 residiv
opereres på
Radiumhospitalet

omtrentlige tall...



Kirurgi for LRRC

- Planlegging
 - MR
- Kirurgi
 - Reseksjoner
 - Rekonstruksjoner
 - Anestesi
- Postop. oppfølging
 - Mye komplikasjoner



Kirurgi for LRRC

- Oftest multiviscerale reseksjoner

- Anteriort

- Hysterektomi
 - Vaginalreseksjon
 - Cystektomi / cystoprostatektomi

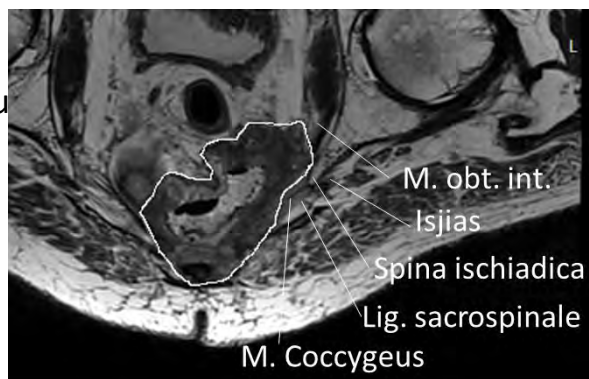
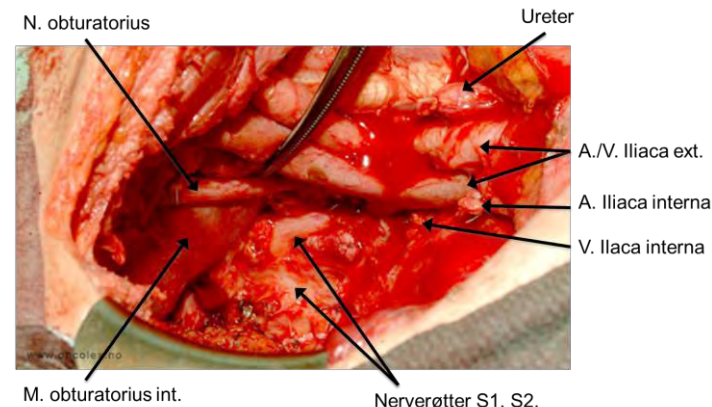
- Lateralt

- Ureteres
 - Iliaca internakar
 - Ligamenter/muskulatur
 - Bekkenben
 - Isjias

- Dorsalt

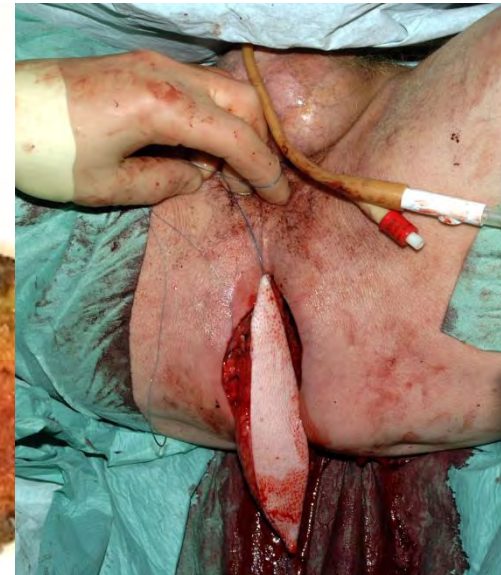
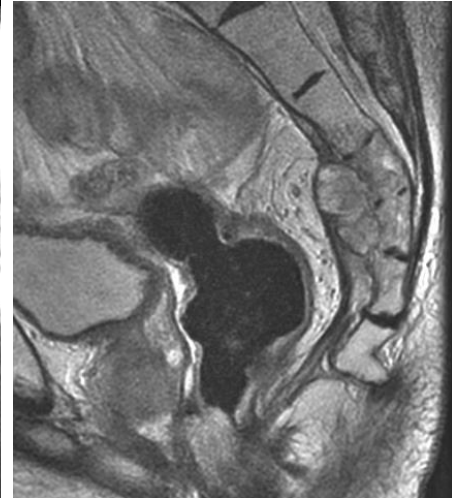
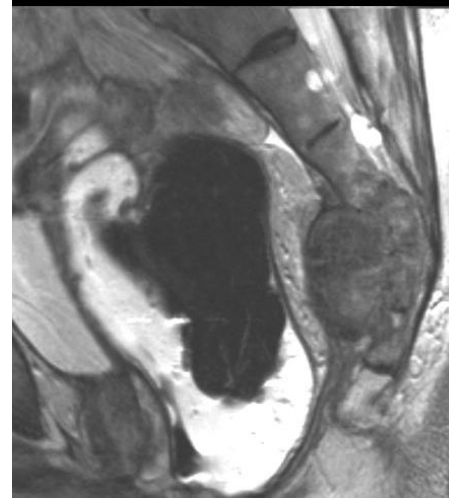
- Sakrale nerverøtter
 - Sakrumreseksjoner

Hø. Bekkenvegg e. avsatt iliaca interna



En-bloc/ multiorgan resections

- Tumours adherent to adjacent organs should be resected *en-bloc* (recurrence 18% vs. 69%) (Hunter 1987)
- Operative strategy based on TME but extended to include suspected tissue outside the mesorectum
- Whole spectre of pelvic surgery should be available
- Support from other surgical disciplines in resection and reconstruction



Hvordan går det med de som opereres for LRRC?

	År	tidsperiode	n	def. R0	R0	5-y re-residiv		5-y mets		median OS	5-y OS		Merknad	Forfatter
						R0	R1	R0	R1		R0	R1		
PelvEx	2018	2004-2014	1184	> 1mm	55 %					2,5-3 år	28 %	17 %	100 % multivisceral kirurgi	PelvEx Collaborative
Karolinska	2022		126	> 0mm	76 %		38 %		48-74 %		35 %		49 % multivisceral kirurgi	Nordkamp
Eindhoven			251	>0 mm	61 %		58 %				35 %		48 % multivisceral kirurgi	
Sverige	2018	1995-2002	121	ikke angitt	53 %	20 %	29 %	30 %	42 %		43 %	14 %		Westberg
Aarhus	2015	2001-2010	115	ikke angitt	60 %	30 %		41 %		2,8 år	40 %	16 %		Nielsen
Radiumhospitalet	2020	2007-2017	110	> 1mm	57 %		28 %		38 %	3,5 år	40 %		ikke kvalitetssikret	ikke publisert

Rad (Wiig/ Larsen)	2007)	1990-2004	150		44%	27%	63%				52%	14%		
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«40 % regelen»

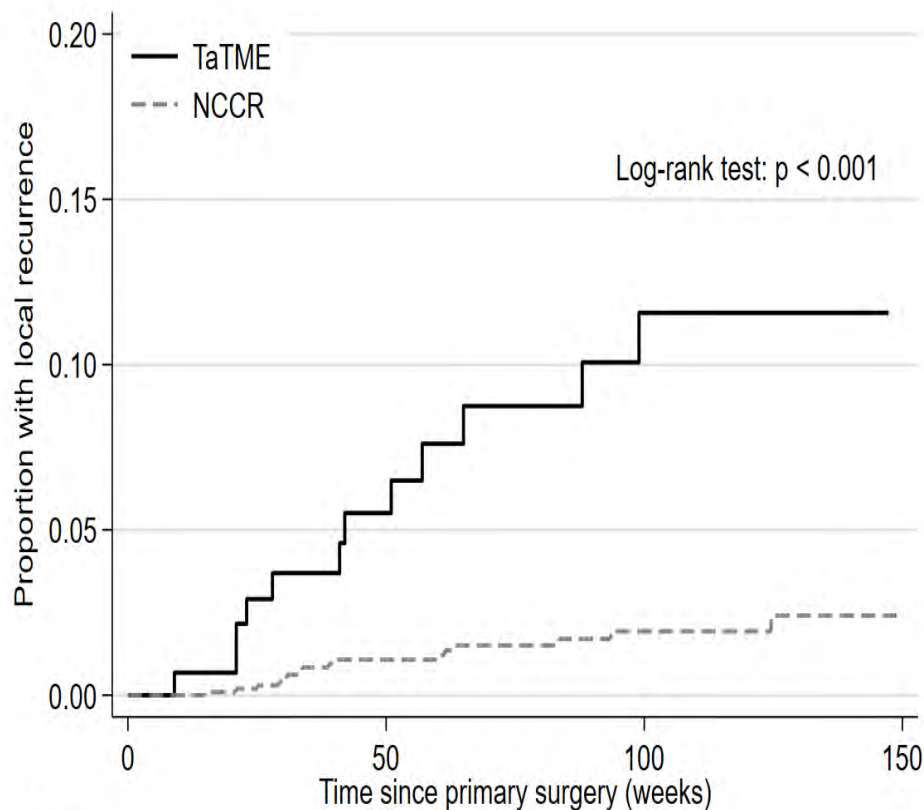
~ 40 % R1

< 40 % re-residiv

> 40 % fjernmetastaser

~ 40 % 5 års overlevelse ved R0

TaTME(via anus) Local recurrences



At risk:

TaTME	152	96	55	22
NCCR	1188	775	375	47

2.4 - years estimates:

**TaTME cohort: 11.7
(Ci 6.7-20.1)**

**NCCR cohort : 2.4
(Ci 1.4-4.3)**

Kasus 2: Hvordan håndterer vi uønskede hendelser?

- Kort kasuistikk:
- Vår 2018. 2 pasienter med store, og omfattende tilbakefall ble henvist regionssykehuset i helse sørøst.
- Begge viste seg å være behandlet med samme, nye kirurgiske teknikk (taTME)
- Tilbakefallene var forbundet med alvorlig prognose



taTME: Recurrence after 5 months

BJS 2019; 106: 1120–1121

Leading article

Norwegian moratorium on transanal total mesorectal excision

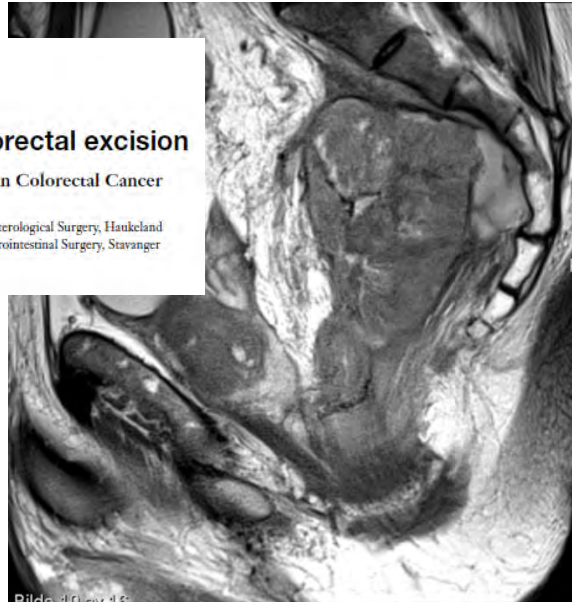
S. G. Larsen^{1,5}, F. Pfeffer^{2,3,5} and H. Korner^{2,4,5}, on behalf of the Norwegian Colorectal Cancer Group

¹Department of Gastroenterological Surgery, Oslo University Hospital, N-0424 Oslo, ²Department of Gastroenterological Surgery, Haukeland University Hospital, and ³Department of Clinical Medicine, University of Bergen, Bergen, ⁴Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, and ⁵Norwegian Colorectal Cancer Group, Norway (e-mail: stl@ous-hf.no)

Published online in Wiley Online Library (www.bis.co.uk). DOI: 10.1002/bis.11287

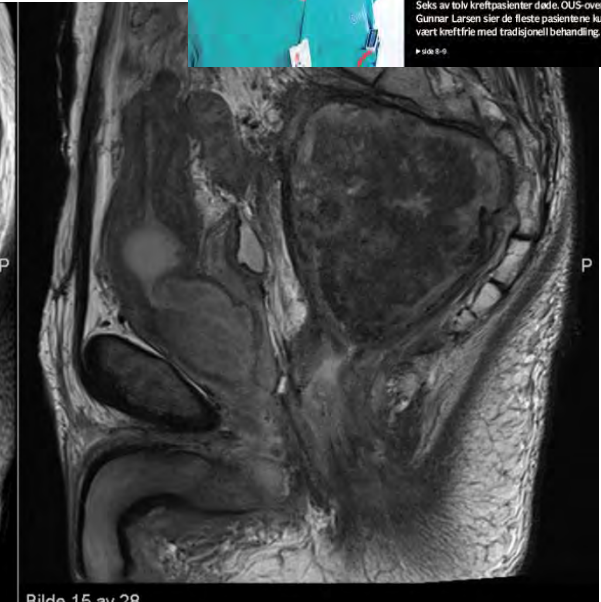


Primary



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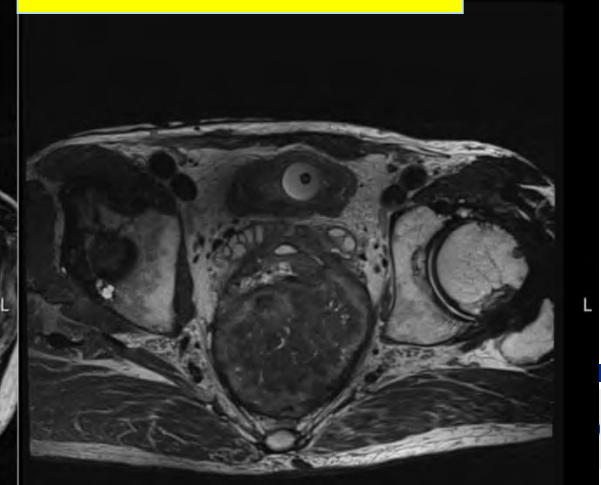
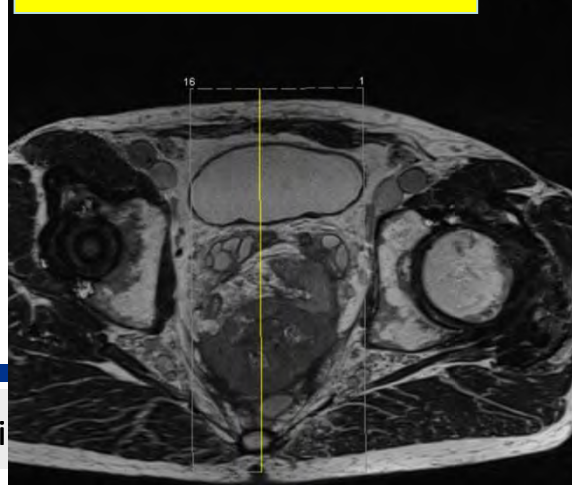


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24.05.2017, 10:52:41

F

Recurrence before R

Recurrence after RT



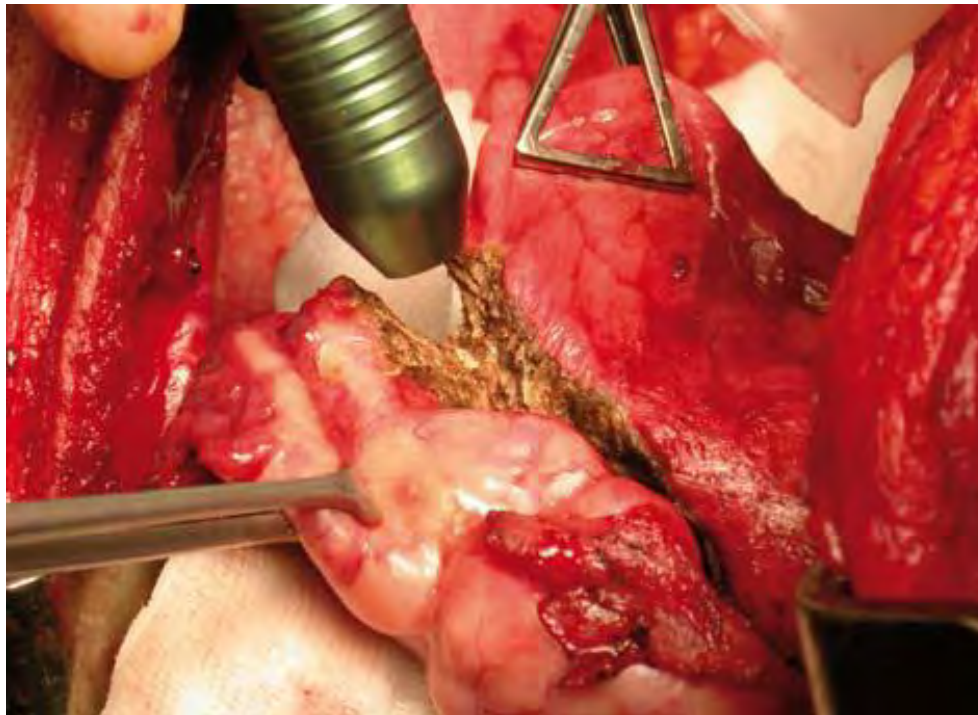
Granskning:
**Ny metode
ga flere
tilbakefall**

Ny operasjonsmetode firedoblet antallet tilbakefall. Seks av tolv kreftpasienter døde. OUS-overlege Stein Gunnar Larsen sier de fleste pasientene kunne ha vært kreftfrie med tradisjonell behandling.

» Side 5-6

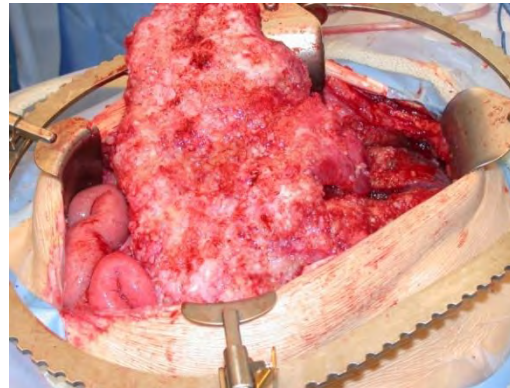
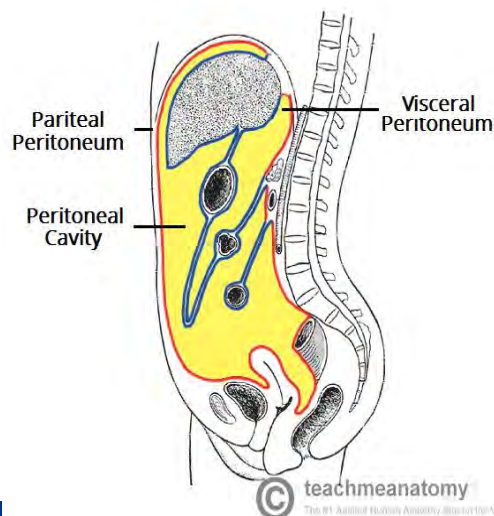
Lungemetastaser

- Ca. 5-10 % utvikler lungemetastaser.
- 50 % 5-års overlevelse
- Kilereseksjoner, segmentectomier, lobectomier
- Ofte bruk av laser for å spare lungevev, eller



Peritoneale metastaser fra colorectal cancer (PM-CRC)

- Hyppighet: 8.3 % synkron PM (Sjo et al, 2011), 4-12 % metakron PM (Sørbye 2013; Abdel-Rahman 2020)
- Ca 6-12 mnd median overlevelse ubehandlet (Sørbye 2013).
- Begrenset PM behandlet som får systemisk kjemoterapi: median overlevelse opp mot 24 mnd i studier.
- Pasienter som opereres med CRS og HIPEC: Økt lang-tids overlevelse og kurasjon, ca 40 % 5-års overlevelse.

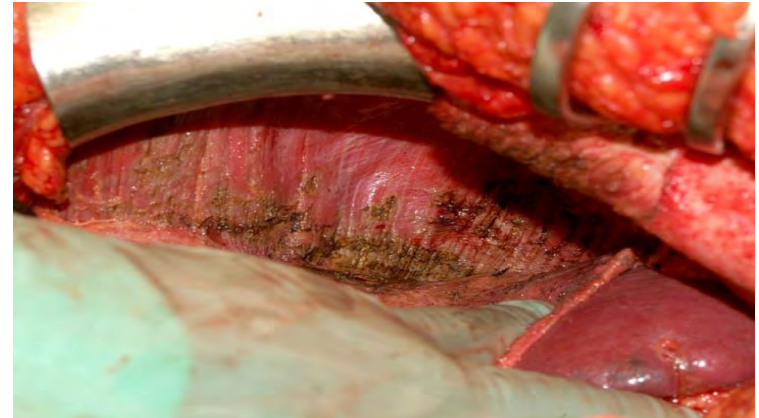
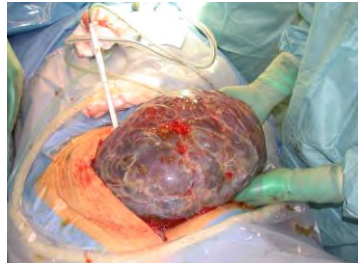
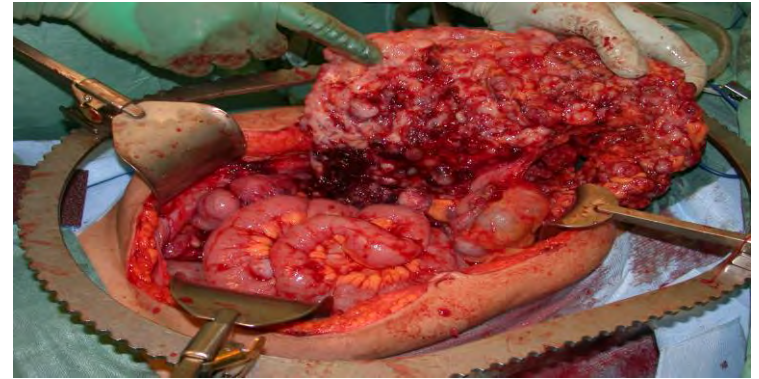


Maksimal cytoreduktiv kirurgi (CRS)

CRP-HIPEC kan gis hvis det er mulig å oppnå «komplett» reseksjon.

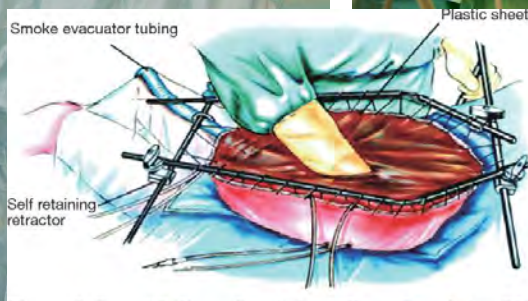
Omfatter ofte:

- Oment reseksjon
- Fjerning av affisert peritoneum
- Fjerning av affiserte organer i buken
- Fjerning av ovarier hos kvinner



Historie HIPEC

- EPIC 1994-2003
- Åpen skylling fra 2003-8 (bilder).
- Deretter lukket



Hyperterm intraperitoneal kjemoterapi (HIPEC)

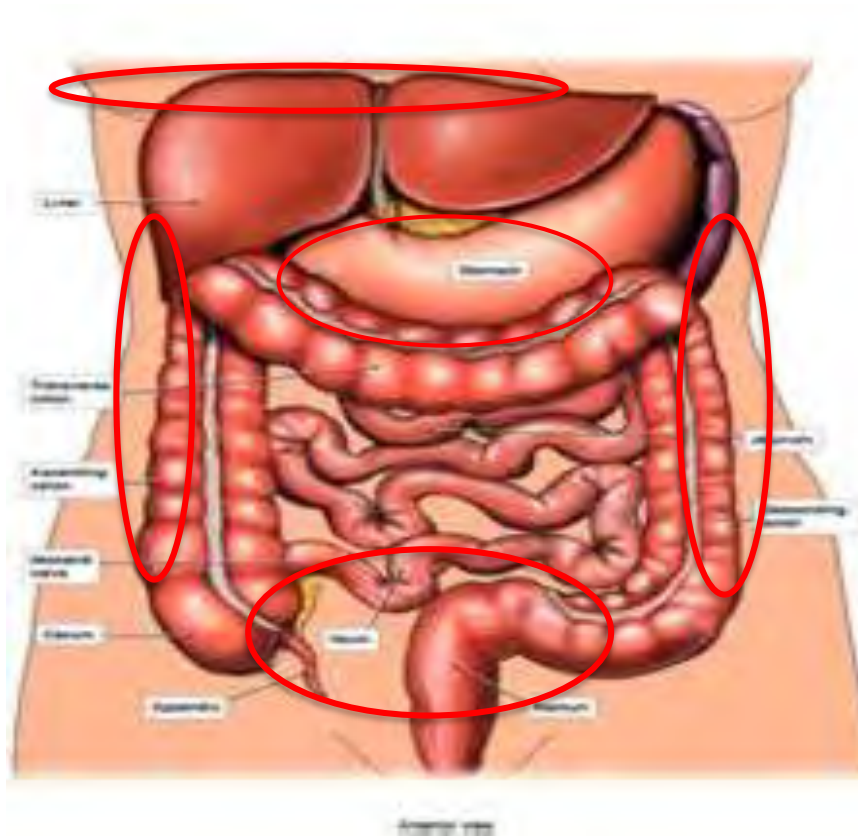
- Fjerner gjenværende mikroskopisk sykdom
- Eliminerer blodplater, granulocytter og monocytter
- Høy intraperitoneal konsentrasjon med lav systemisk toksisitet



Distribusjon i bukhulen

1:
Oppsugning
av væske

-oment
-over lever

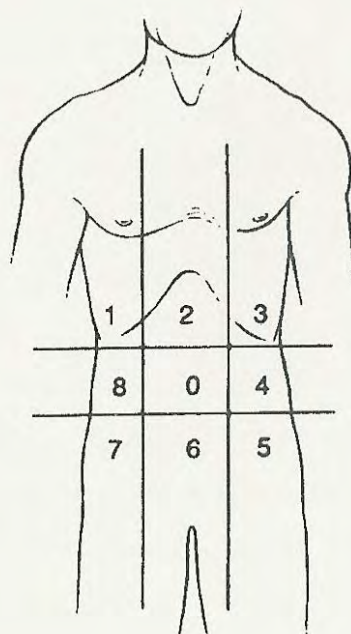


2:
Tyngdekraft

-parakolisk
-bekken

Sparer bevegelige organer lengst (tynntarm)

Peritoneal Cancer Index (PCI) (Esquivel J 1998)



Regions

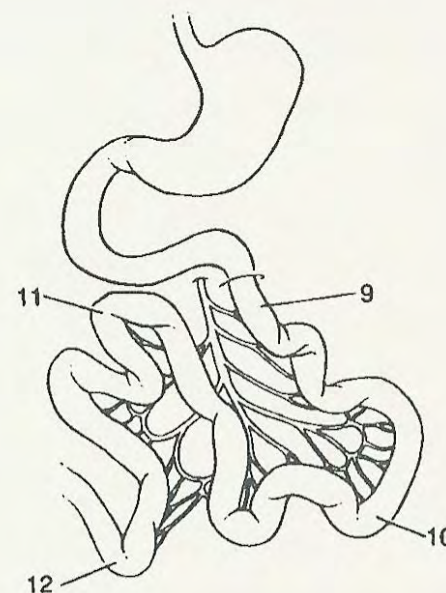
- 0 Central
- 1 Right Upper
- 2 Epigastrium
- 3 Left Upper
- 4 Left Flank
- 5 Left Lower
- 6 Pelvis
- 7 Right Lower
- 8 Right Flank
- 9 Upper Jejunum
- 10 Lower Jejunum
- 11 Upper Ileum
- 12 Lower Ileum

Lesion Size

Lesion Size Score

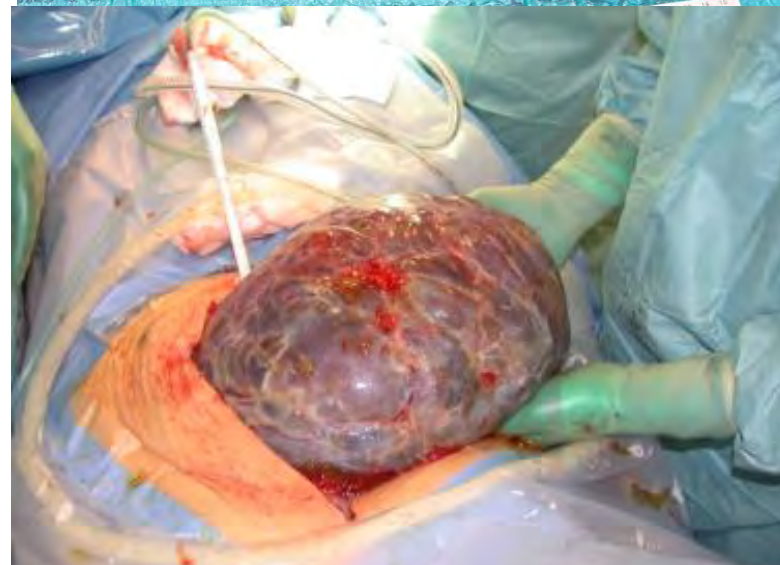
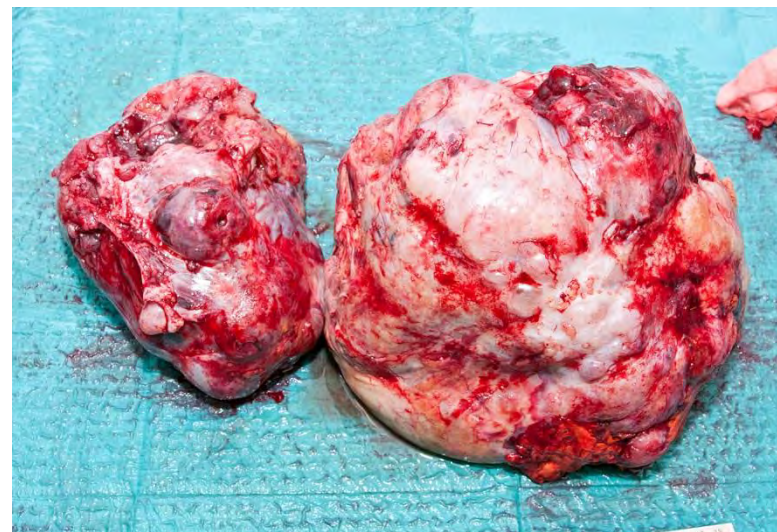
- LS 0 No tumor seen
- LS 1 Tumor up to 0.5 cm
- LS 2 Tumor up to 5.0 cm
- LS 3 Tumor > 5.0 cm or confluence

PCI



Ovariale metastaser

- 10 – 30 % av svulster i ovarier er metastaser (Evers et. al 2011)
- Ofte colorektalt utgangspunkt
- Halvparten har blitt misoppfattet som ovarial cancer
- Ofte økning i CEA med lav CA-125 (CA-125/CEA < 20-50).



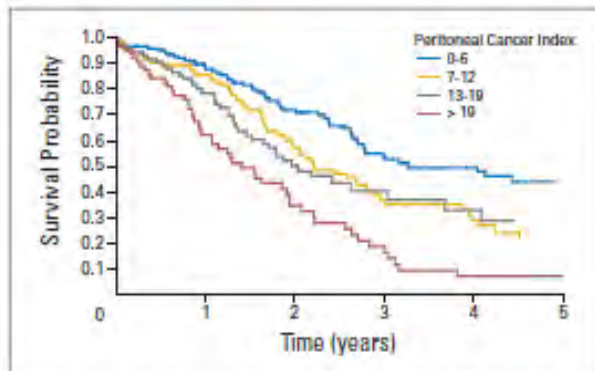


Fig 2. Prognostic impact of the extent of carcinomatosis (ie, peritoneal cancer index; $P < .001$) on overall survival.

Prognostiske faktorer indicators

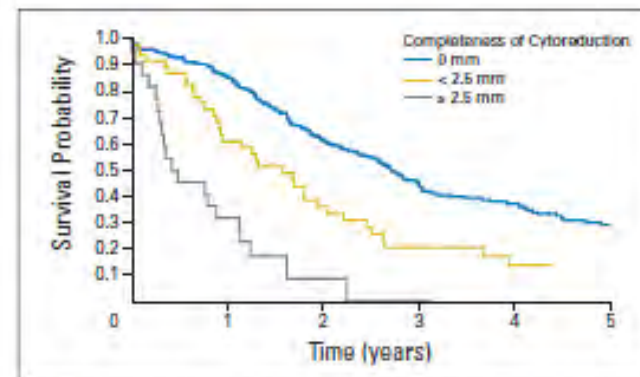
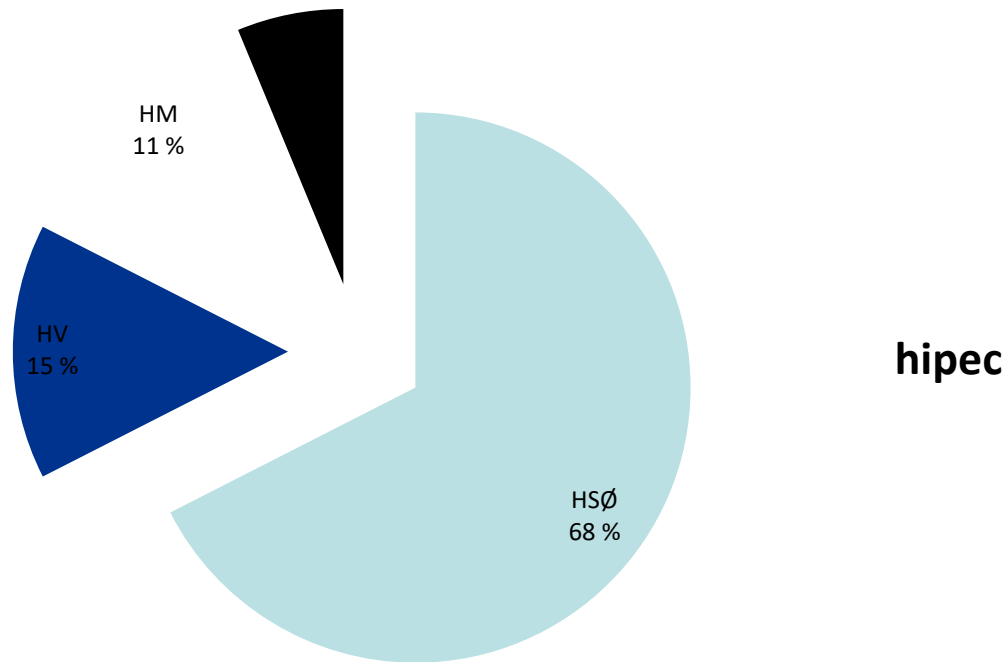


Fig 3. Prognostic impact of the completeness of the surgery ($P < .001$) on overall survival.

Indicator	Value	Med survival (months)	p
PCI	(<10; ≥10-<20; >20)		p<0.001 (Yan T 2008)
•Extent of cytoreduktion	CC-0	32.4	(Glehen 2004)
	CC-1/2/3	8.4	
•N-status at treatment	N0	38	p=0.003 (Chua TC 2009)
	N+	20	
•Histological grading:	high/moderate diff		p<0.001 (Yan T 2008)
	low diff		

Norwegian National Unit for HIPEC Volume 2017

New admissions 282; CRS-HIPEC 80; expl/pall. proc 43

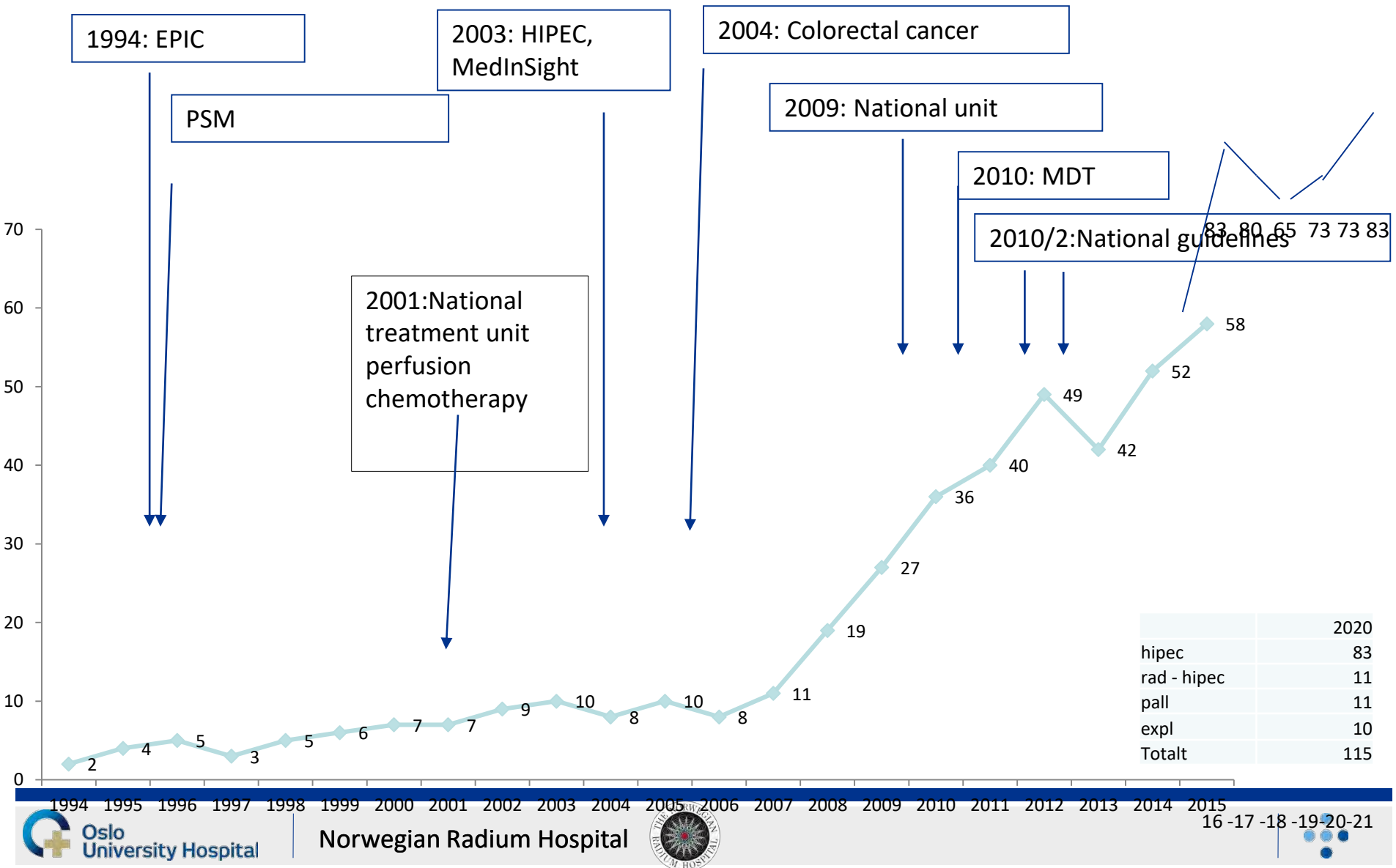


Population of Norway:

South-East Norway: 55.8%; West 20.9%; Mid 13.8%; North 9.5%

Utvikling ved Radiumhospitalet

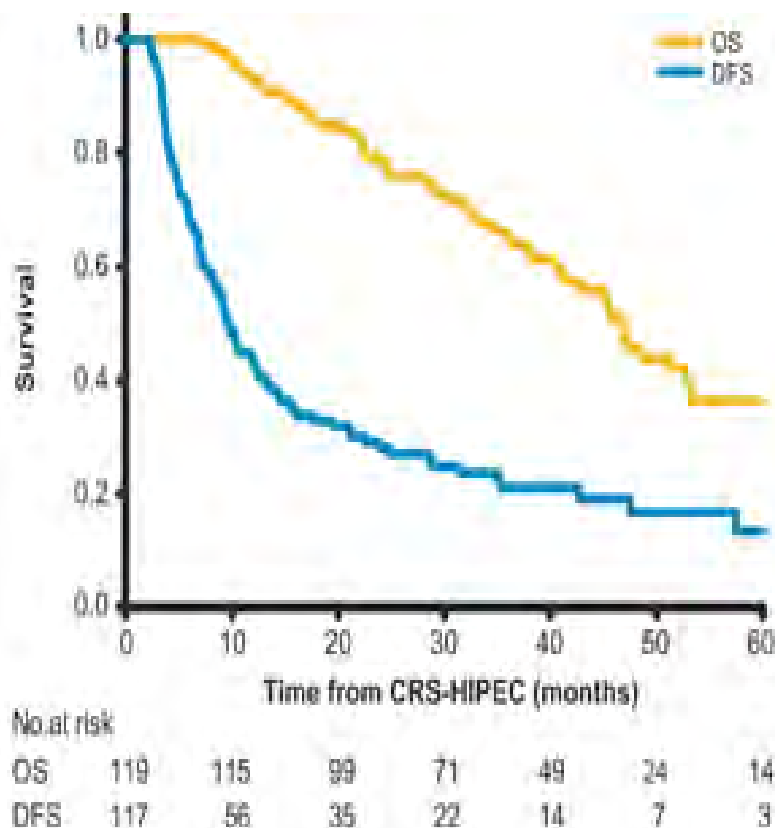
1994 - 2021



men.....

Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Peritoneal Metastasis in Norway: Prognostic Factors and Oncologic Outcome in a National Patient Cohort

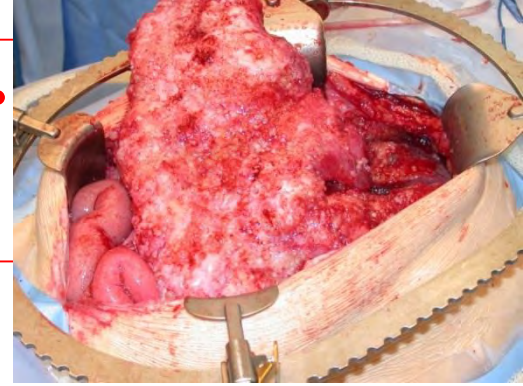
IDA S. FRØYSNES, MD,^{1,2} STEIN G. LARSEN, MD, PhD,³ MILAN SPASOJEVIC, MD, PhD,³
SVEIN DUELAND, MD, PhD,⁴ AND KJERSTI FLATMARK, MD, PhD^{3,1,2,4}



- 40 % 5-års OS etter CRS-HIPEC
- 11-12 mnd DFS etter CRS-HIPEC
- Halvparten som får rec eller met, får det i bukhulen

Recurrence/ Distant mets.

Oslo cohort 2004-15 (n=177)

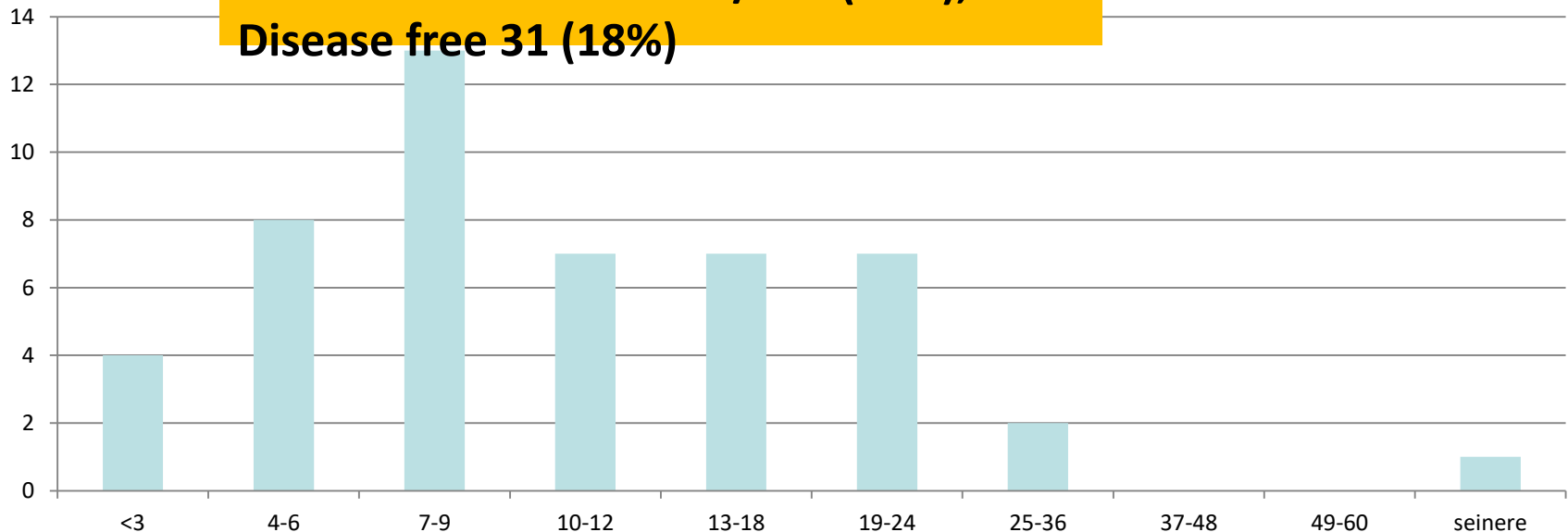


**Local recurrence (LR) alone in 48 of 177
HIPEC patients (27%)**

**Both LR and distant mets in 35/177 gets
(20%),**

Distant mets alone in 63/177 (36%),

Disease free 31 (18%)



Kan en finne tilleggsbehandlinger for å redusere lokale recidiv?

Lovende resultater vist:

- 1 RCT (Vervaaal 2008)
- 3 Case-control studier (Elias et al 2009; Franko 2010, Mahteme 2004)
- 1 meta analyse (Mirnezami 2014)
- En del cohort studier (for eksempel Frøysnes 2016)

- Men ikke i PRODIGE 7 (Quenet 2021)

Meta-analytical evaluation of survival outcomes in CRS-HIPEC in Colorectal PM (Mirnezami R 2014)

Cytoreductive surgery and HIPEC for colorectal peritoneal metastases

BRITISH JOURNAL OF CANCER

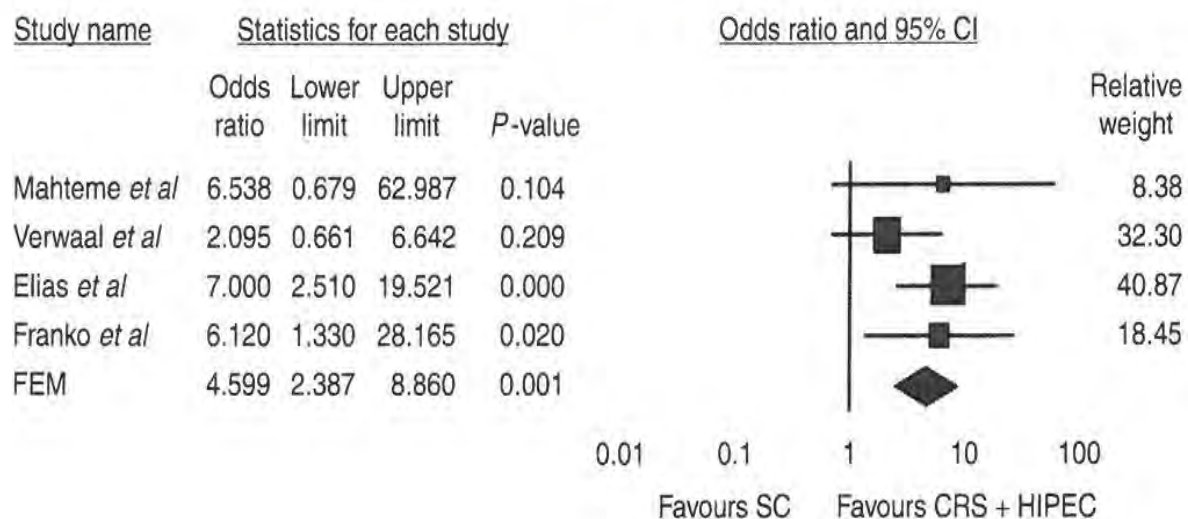


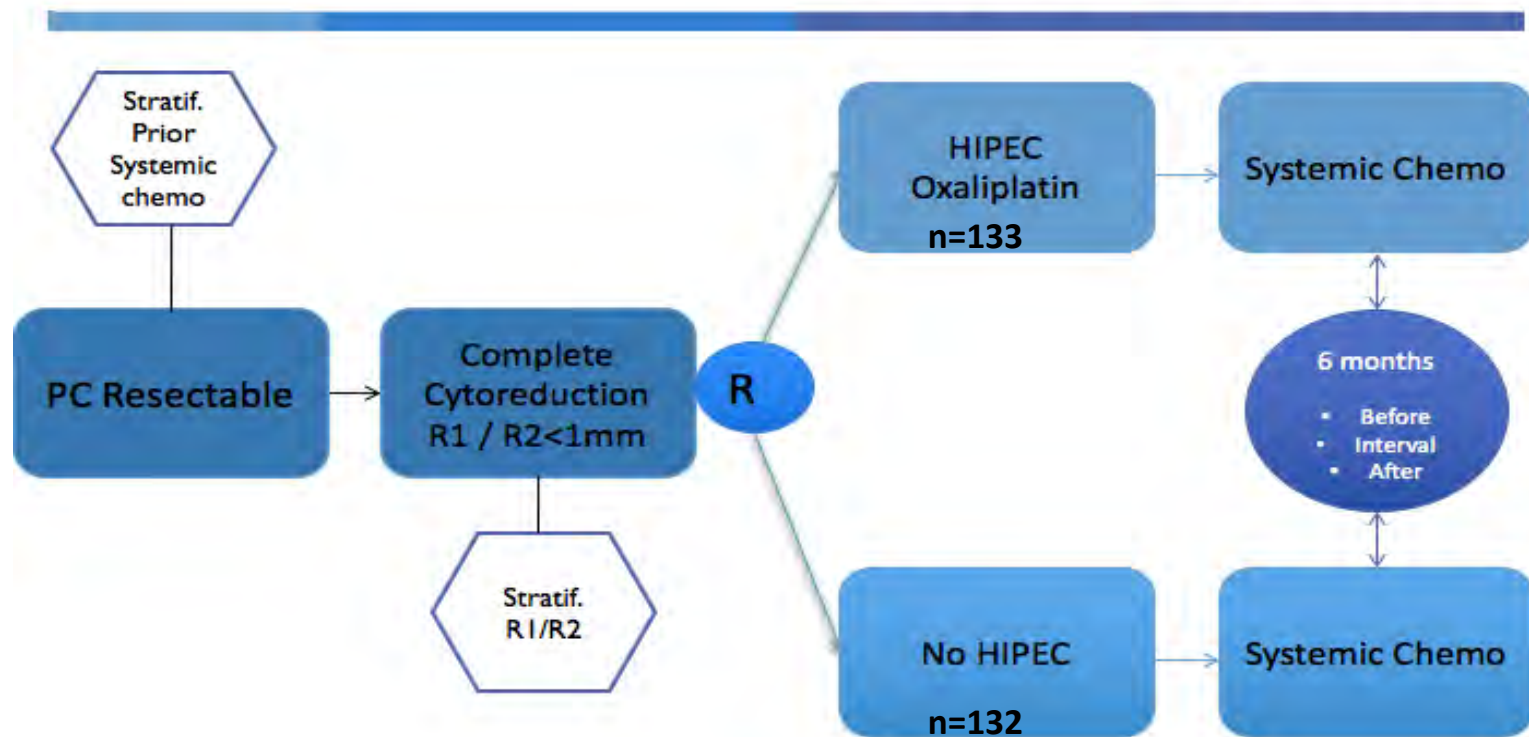
Figure 3. Summary of meta-analysis results for 5-year survival following CRS + HIPEC vs SC alone. The diamond represents the overall treatment effect, and squares are treatment effects for individual studies with 95% CI indicated by horizontal bars.

Clear and significant improval in survival at 2 and 5 years.

Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial

Lancet oncol 2021

PRODIGE7 TRIAL



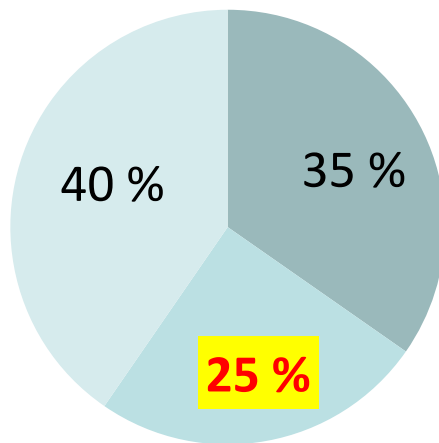
.....men

- Begge grupper 2% 30d mortalitet
- Lik morbiditet, ca 38% Accordion ≥ 3
- Svært mange kritiske kommentarer:
 - 15 pas. Med cross-over fra ikke non-HIPEC til HIPEC
 - Alle hadde fått 6 mnd systemisk oxaliplatin uten progresjon

Andel mut*BRAF* er høy i CRS-HIPEC gruppen

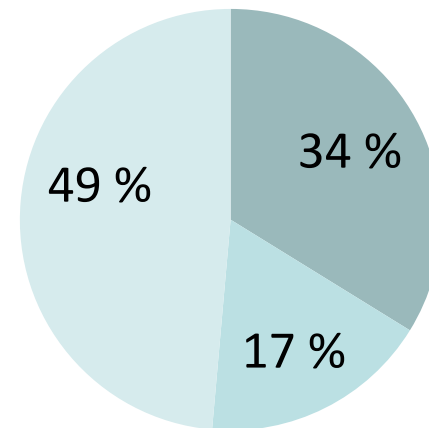
CRS-HIPEC

■ Ras mut ■ BRAFmut ■ dobbel wt



Palliative/explorative

■ Ras mut ■ BRAFmut ■ dobbel wt



ORIGINAL ARTICLE – COLORECTAL CANCER

Novel Treatment with Intraperitoneal MOC31PE Immunotoxin in Colorectal Peritoneal Metastasis: Results From the ImmunoPeCa Phase 1 Trial

Ida S. Frøysnes, MD^{1,2}, Yvonne Andersson, PhD¹, Stein G. Larsen, MD, PhD³, Ben Davidson, MD, PhD^{2,4}, Janne-Merete Torset Øien, MSc¹, Kari Hauge Olsen, BSc⁵, Karl-Erik Giercksky, MD, PhD^{2,3}, Lars Julsrud, MD⁶, Øystein Fodstad, MD, PhD^{1,2}, Svein Dueland, MD, PhD⁷, and Kjersti Flatmark, MD, PhD^{1,2,3}

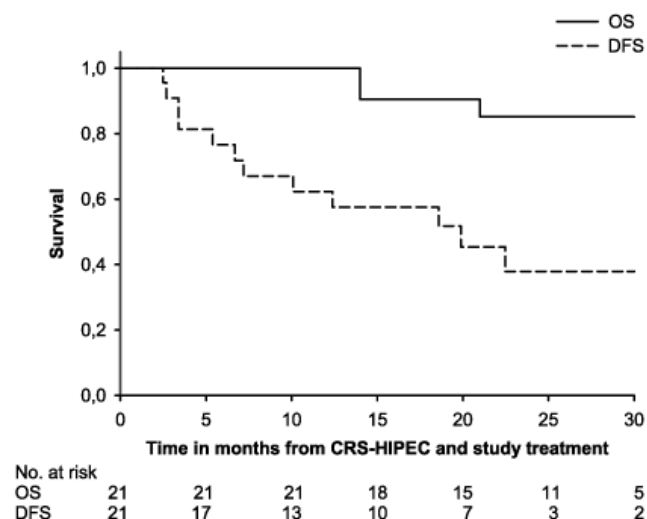


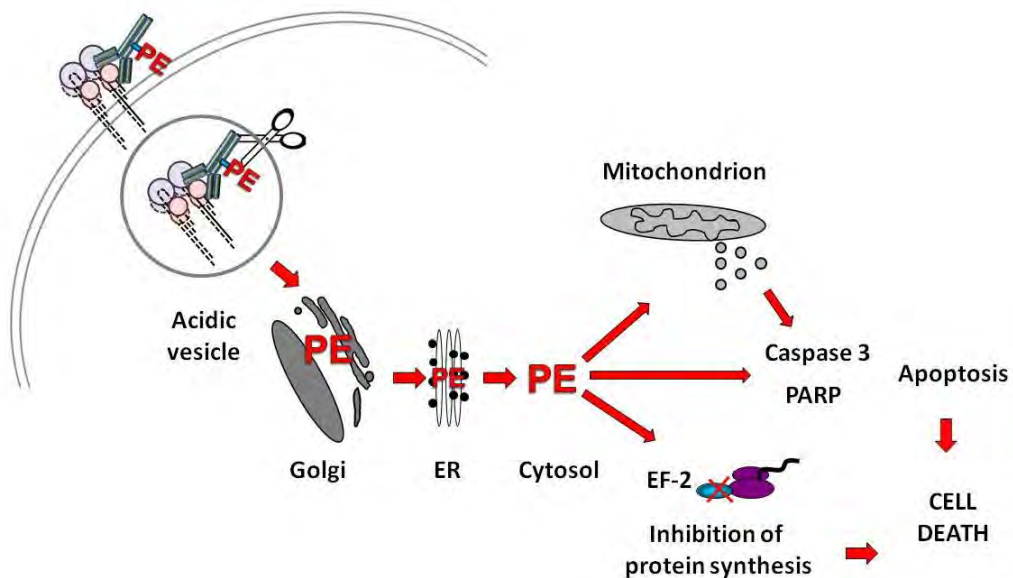
FIGURE 6
Survival curves from the ImmunoPeCa trial showing overall survival (OS) and disease-free survival (DFS). In this phase I/II trial patients with colorectal peritoneal metastasis were treated with CRS-HIPEC and intraperitoneal, perioperative MOC31PE immunotoxin.

Median DFS was 20 months (95% CI 7–34) (Median follow-up time 25 months (95% CI 17–30))

Estimated 3-year DFS 38%



Opportunity: Clinical intervention studies The ImmunoPeCa phase I-II trial

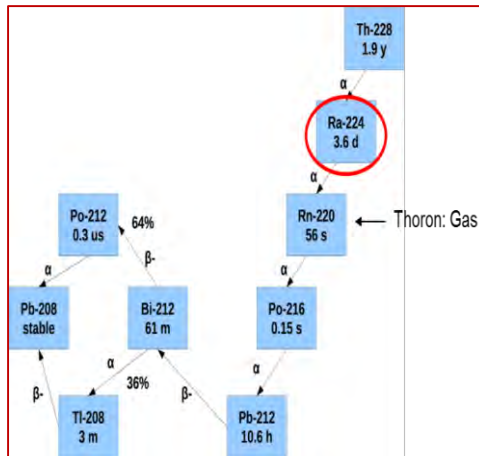


- MOC31PE immunotoxin
 - Developed at ICR
 - Researcher-initiated study
 - Clinical Trials Unit
 - Patients with peritoneal metastases from colorectal cancer

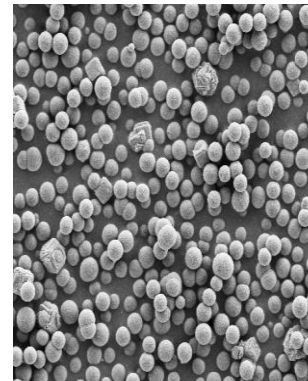
Radspherin®

α -emitting radionuclide Radium-224 (^{224}Ra)

- Adsorbed to a suspension of biodegradable calcium carbonate microparticles
- designed to give short-range radiation to the serosal peritoneal surface
- aiming to kill remaining free cancer cells and small tumor cell clusters



+



=



Thorium-228 half live 1.9 years, Radium-224 3.6 days

Behandling:

- Radspherin installeres 2 dager etter CRS-HIPEC, avbildes med SPECT-CT, og pas. kontrolleres i 12 mnd.
- Eksempel på whole body scintigrafi etter 7 MBq

