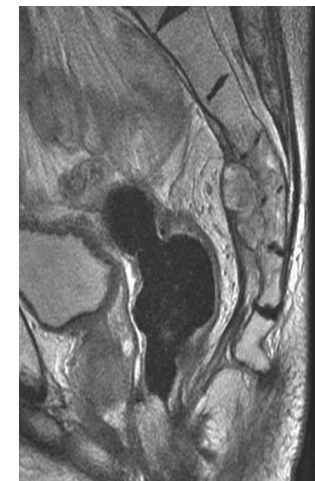
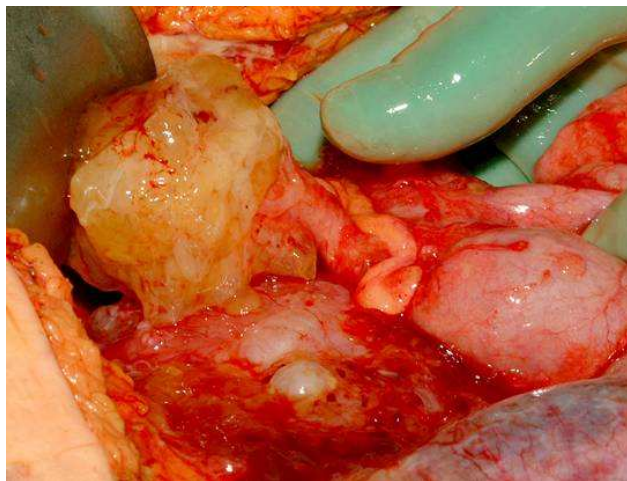
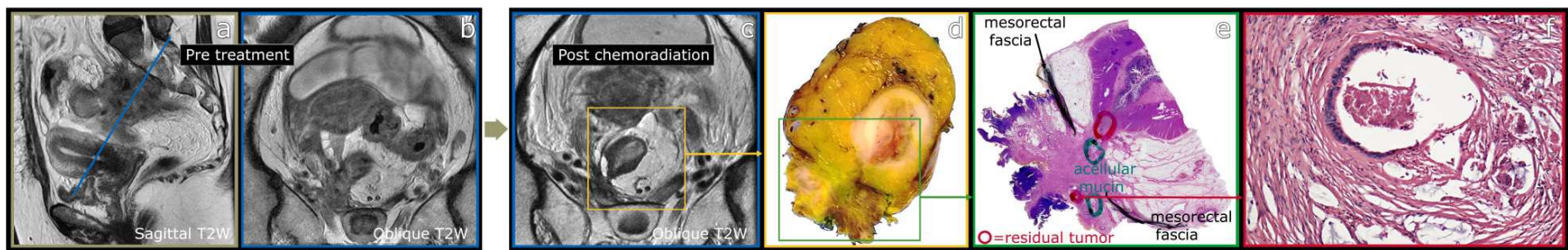


Kirurgi ved kolorektal cancer

Stein Gunnar Larsen
Seksjonsoverlege Radiumhospitalet, OUS



Colon cancer

- 2500 årlig
- 95 % kan reseceres, 5-års overlevelse 60 %
- Lokalisasjon: Hø.side 30 %, transversum/flexurer 20 %, descendens 5 %, sigmoid 45 %
- Reseksjon av tumor og lymfatisk spredningsvei

Colon cancer: Kirurgi

Høyresidig hemicolectomi

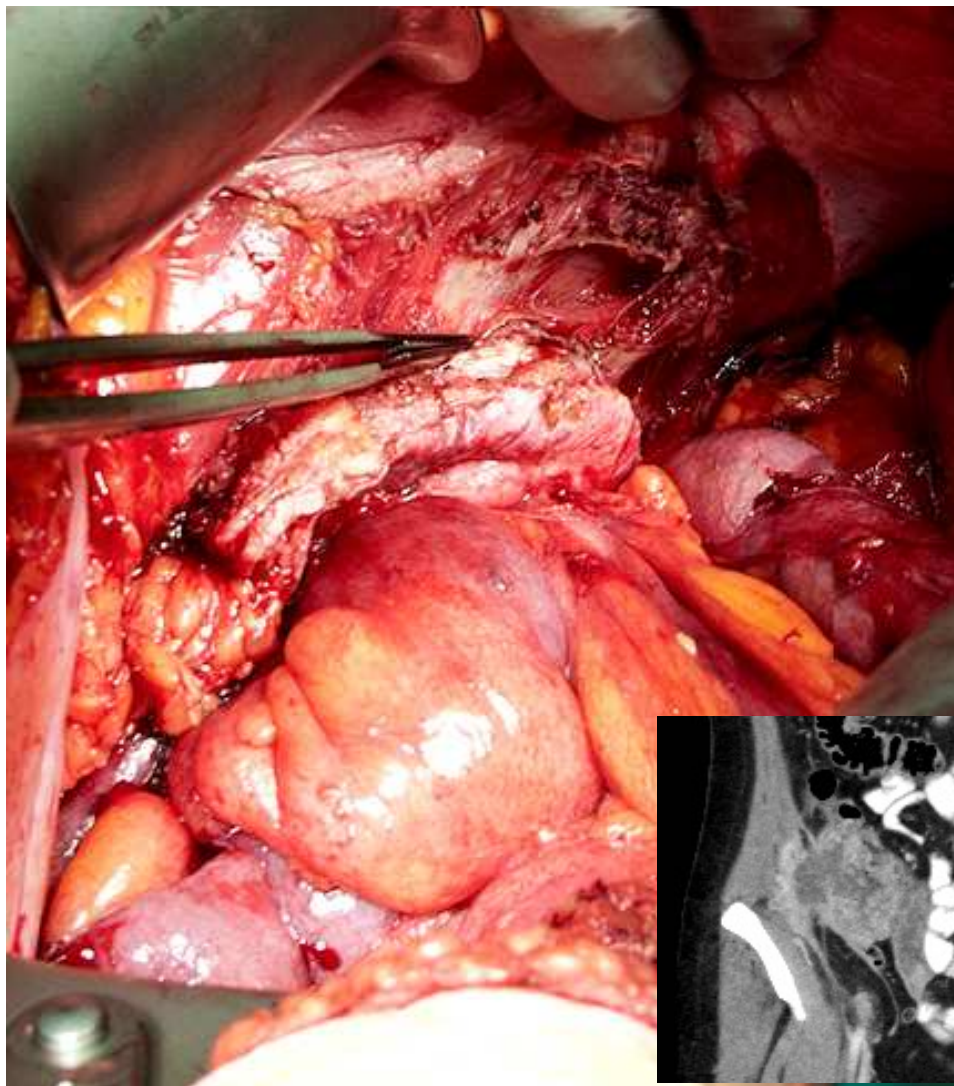
Venstresidig hemicolectomi

Sigmoideumreseksjon

Lokal eksisjon/ transanal endoskopisk
microkirurgi (TEM)

Hartmanns operasjon på sigmoideum

Innvekst bukvegg



Utvidete
reseksjoner
nødvendig hos
ca 10 %

Mål: R0 reseksjon

Prof. Hohenberger, Erlangen:

"If an R0 resection is possible, the cancer-specific survival is independent of whether there really has been tumour invasion into the adjacent structures".

Utfordring i colon cancer

Prof. Hohenberger, Erlangen:

"How to transfer optimal results of some surgeons to a broader basis, which means true implementation of the existing guidelines".

Levermetastaser

Synkrone 20 %

Metakrone 25-35 %

- Leverreseksjon, åpen eller laparoskopisk,
- Preoperativ portveneembolisering
- Leveroperasjon i to seanser, ofte i kombinasjon med portveneembolisering
- Radiofrekvensablasjon
- Komplekse kirurgiske prosedyrer (*ex citu*, TX)

5-års overlevelse 35-40 %

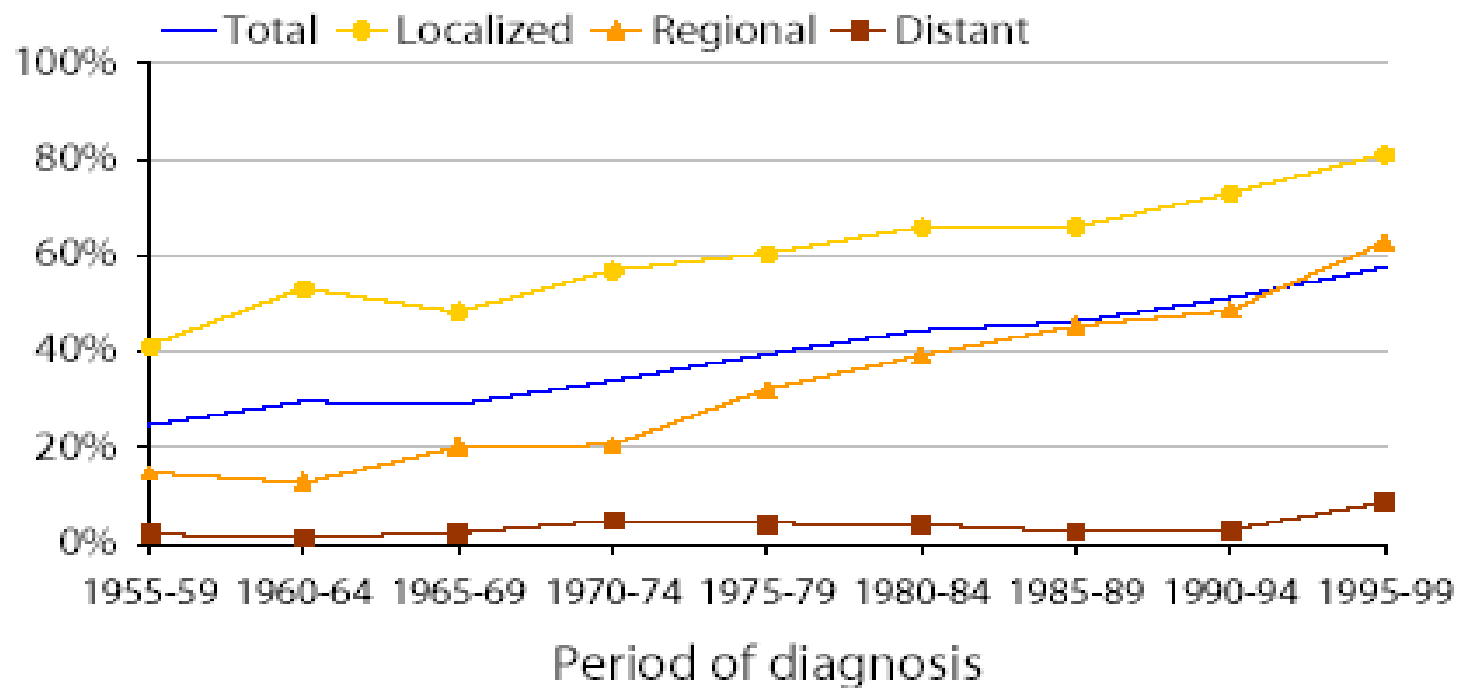
Lungemetastaser

- 10 % utvikler lungemet.
- Prognose best dersom tid til met > 3 år, kun 1 met, kun 1 lunge affisert, CEA <5, ikke andre organmetastaser
- 5-års overlevelse ca 40 - 50 %

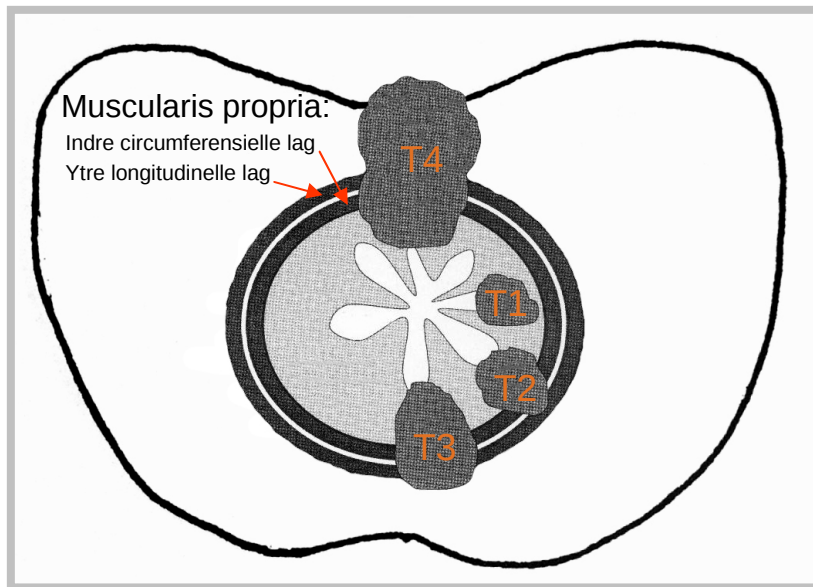
Rectum cancer

- 1100 årlig

Fig. 3.5.7 5-year relative survival in percent by period and stage - 1955-1999, males



TNM Staging



TNM

T1	Submucosa
T2	Muscularis propria
T3	Gjennom muscularis propria
T4	Innvekst til andre organ/stukturer
N1	1-3 regionale lymfeknuter
N2	4 eller flere lymfeknuter
M1	Fjernmetastaser

DUKE STADIUM

I	T1-T2, N0, M0
II	T3-T4, N0, M0
III	N1-N2, M0
IV	M1

Rectum cancer behandling i Norge før 1993

- 28% lokale recidiv i Norge i 1986-88.
- Heald 5% og Enker rapporterte på samme tid ca. 7 %

Rectum cancer etter 1993

Det Norske Rectumcancerprosjektet fra høsten 2003.

Innføring av **TME**(total mesorectal excisjon)

Utviklet av R J Heald, Basingstoke, publ. 1988.

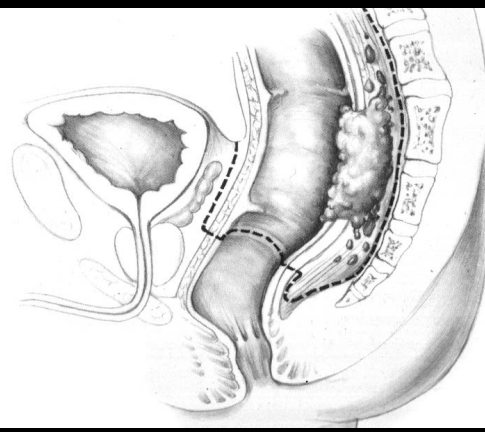
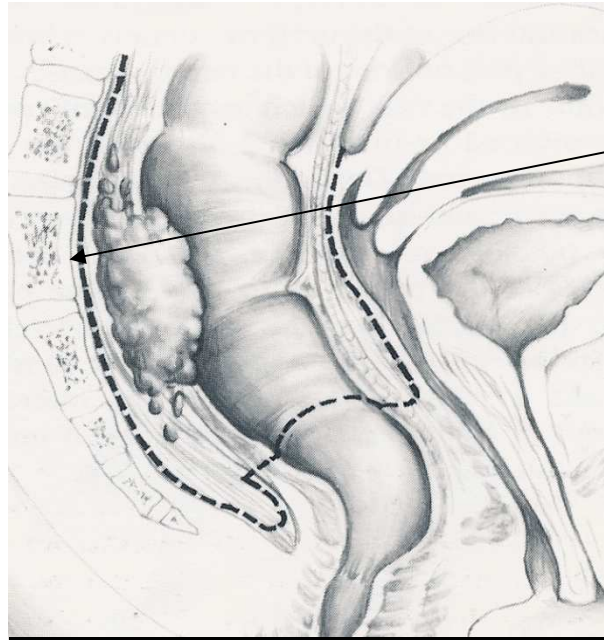
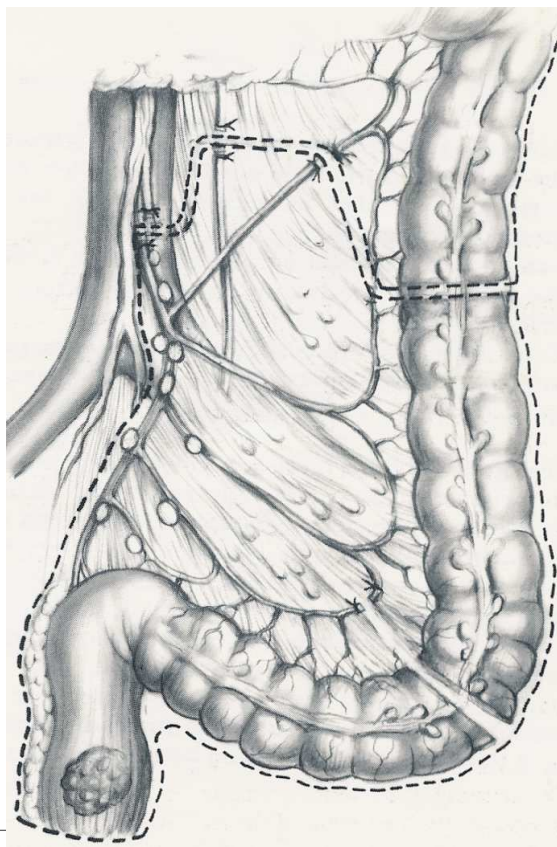
Kirurgi i "nye" anatomiske plan.

Teknikken er innført i Norge og Sverige fra 1993.
Seinere i andre land.

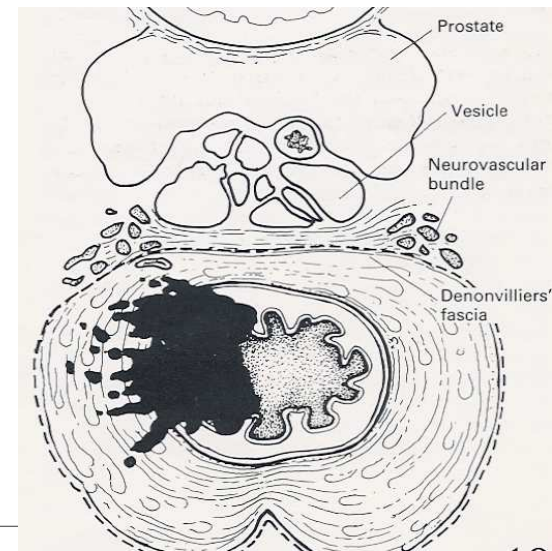
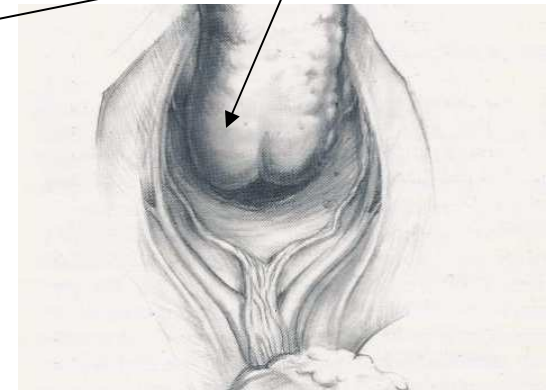
Økt volum (fra 54 sykehus i 1993 til 40 i 1999).

Spesialisering (knyttet til gastrokirurgene - elektivt)

TME (total mesorectal excision)



"Holy plane"



TME reseksjonspreparat

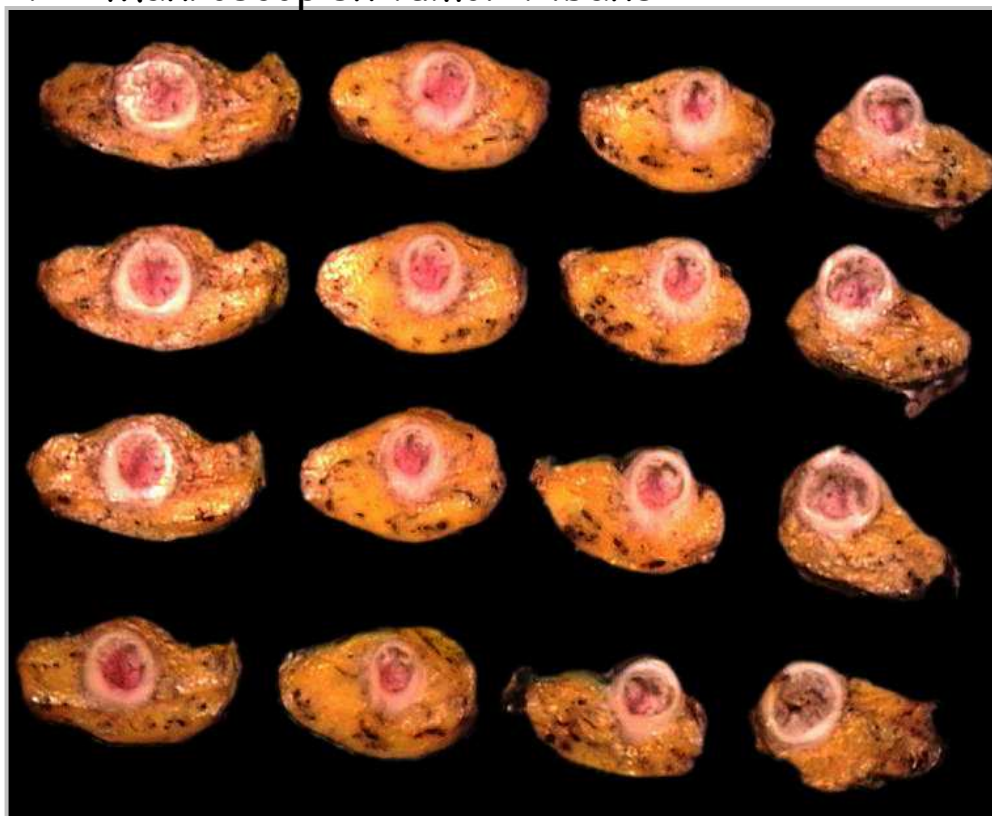
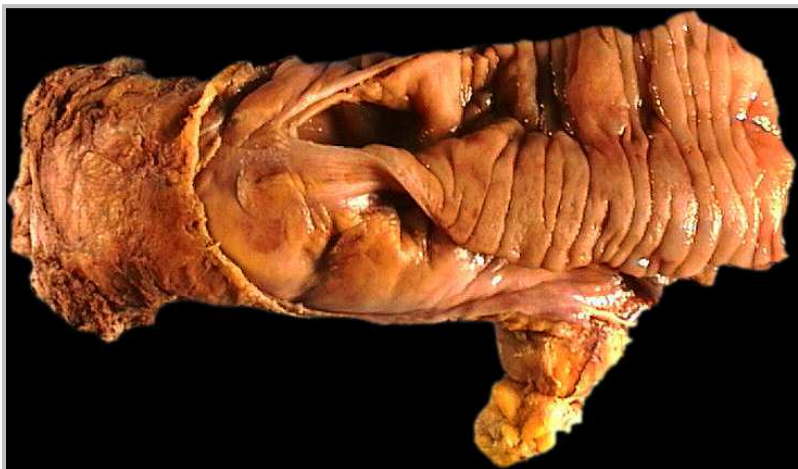
Prof Phil Quirke, 1986

Sirkulære reseksjonsmargin viktig (CRM)

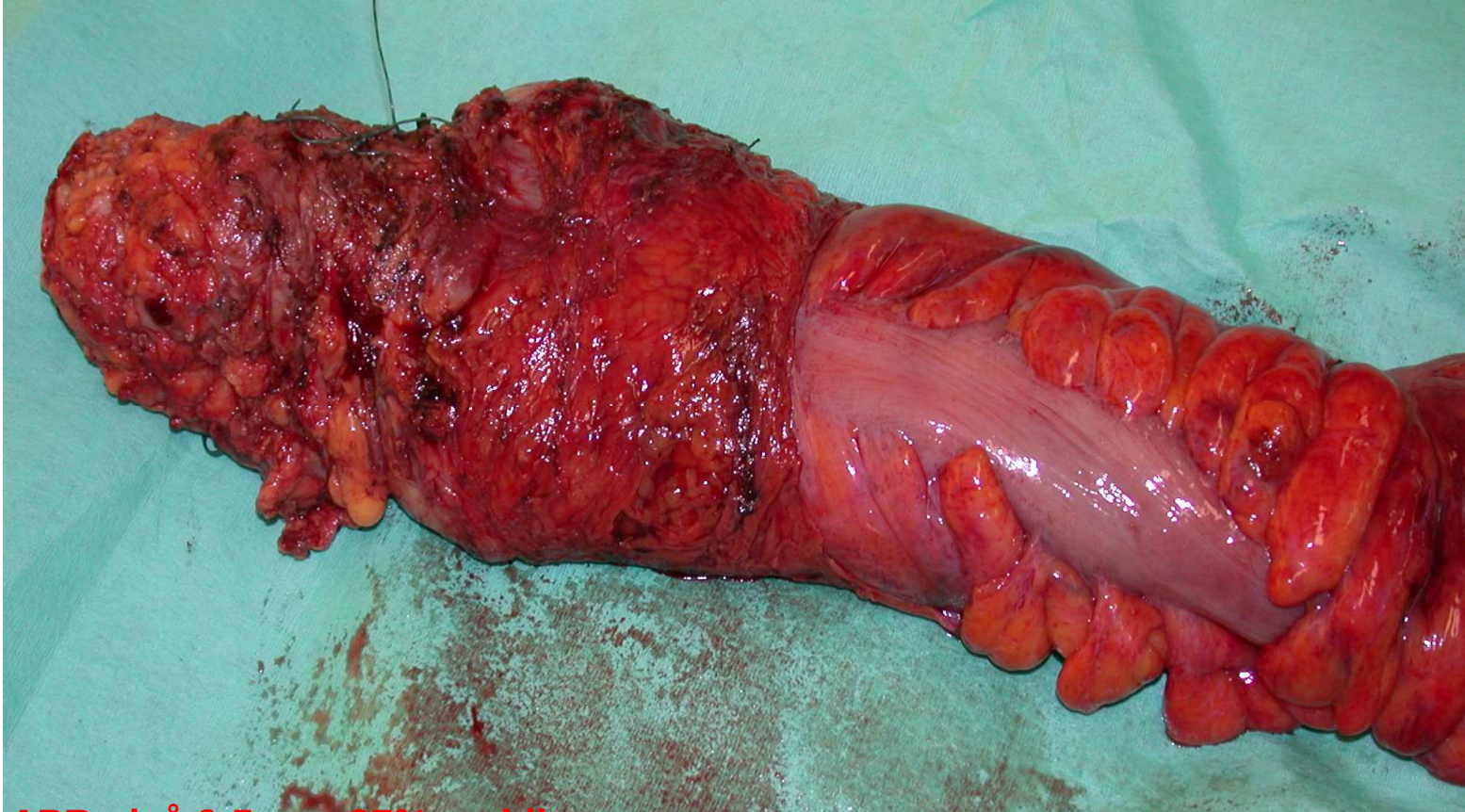
R0 >1 mm margin lateralt (fri margin)

R1 $\leq$ 1 mm (mikroskopisk tumor tilbake)

R2: Makroskopisk tumor tilbake



Rectum cancer kirurgi. Amputasjoner



Heald: APR nivå 0-5 cm: 27% recidiv.

Extended APR: Holm et al. BJS 2007;94:232-238. 7% recidiv



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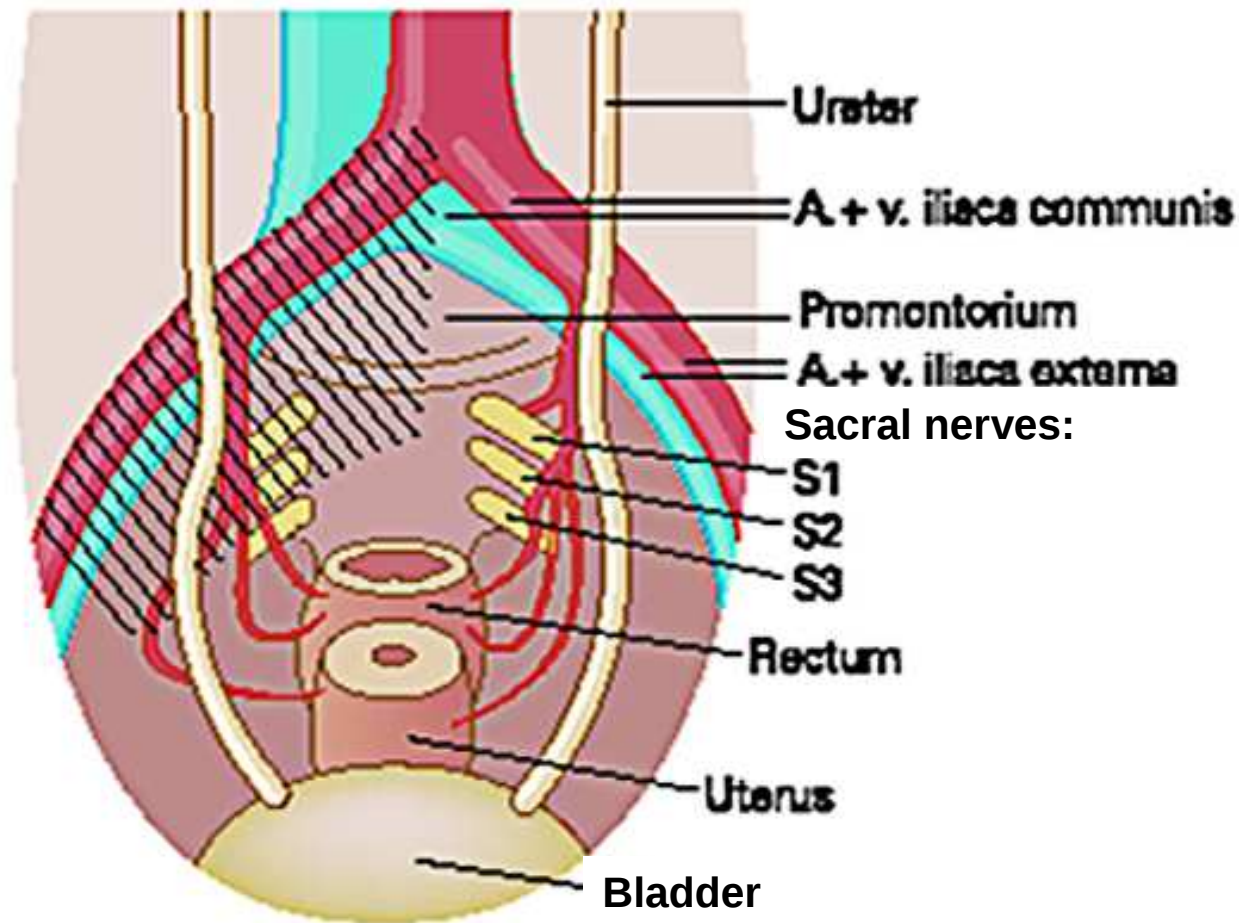


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Anatomy of the pelvis - areas of failure



Pelvic autonomic nerves.

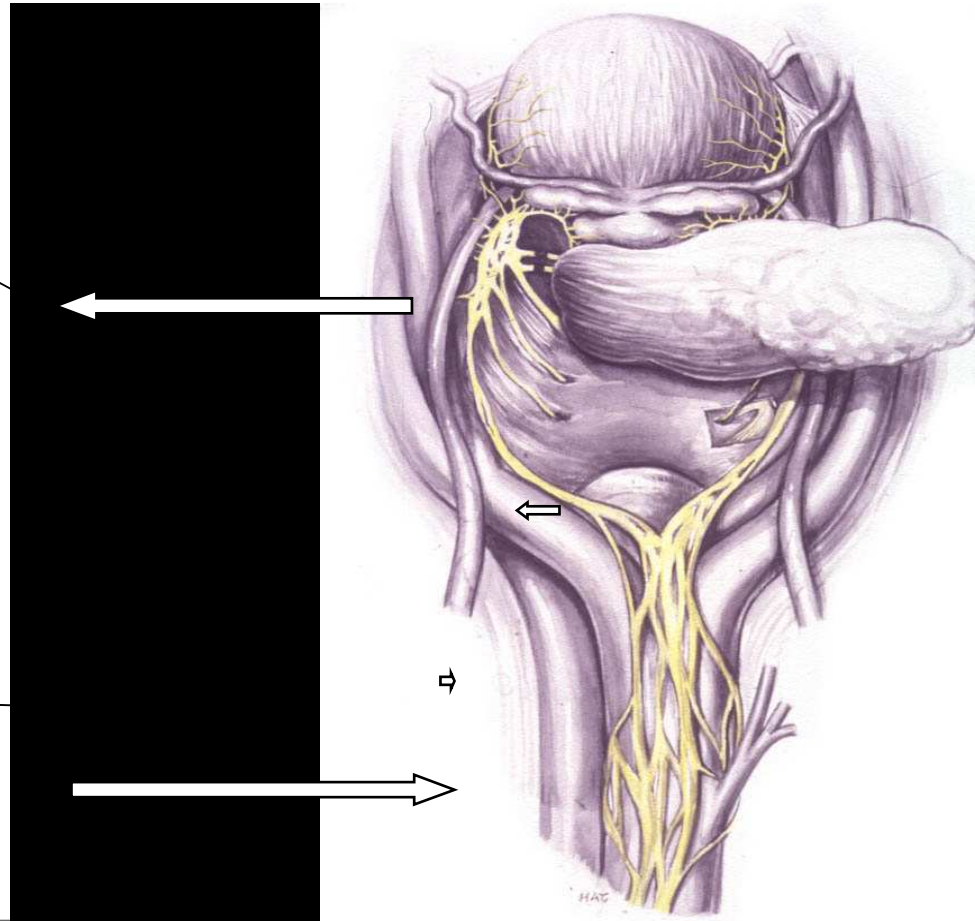
Areas of caution

Parasympatheticus:

ereksjonssvikt, tørr skjede, blæreforstyrrelser, sphincterforstyrrelser.

Sympathicus:

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

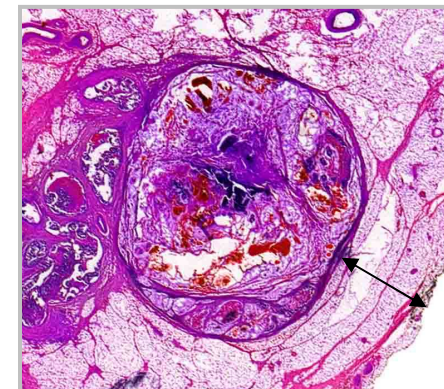
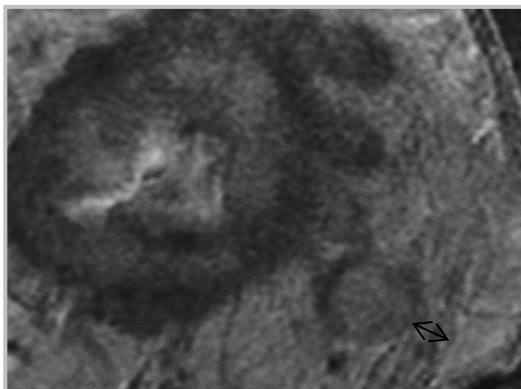


Introduction to locally advanced rectal cancer (LARC)

10%-20% have a primary non-resectable tumour (extensive growth and/ or fixation) (Pahlman 1985)

1/3 of rectal cancer patients have potentially threatened margins (Circular Resection Margins < 3 mm)

Preoperative magnetic resonance imaging (MRI) is considered the best investigative tool for examination of LARC and for predicting the CRM status (MERCURY study group 2006 and 2007; Beets-Tan 2005)

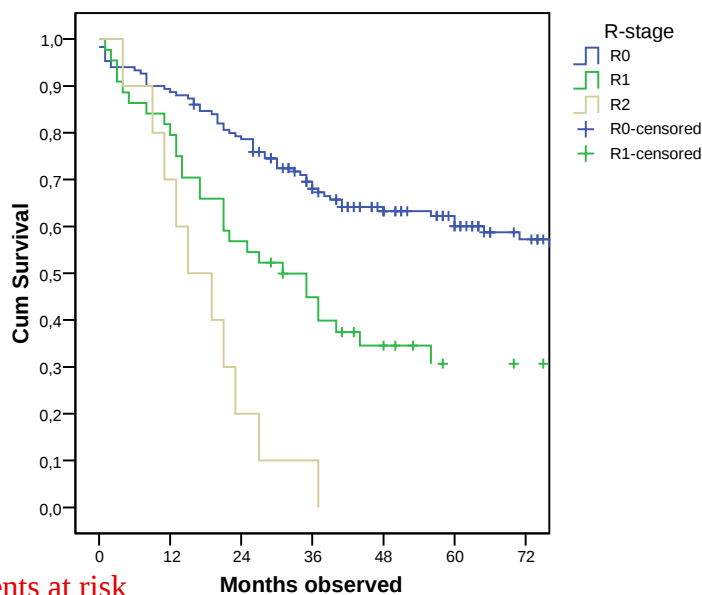


CRM

Prognostic factors after preoperative irradiation and surgery for locally advanced rectal cancer



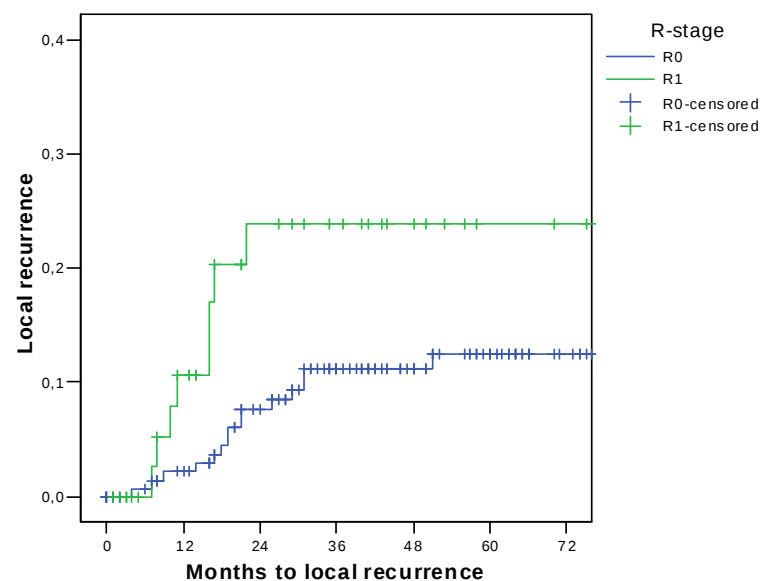
204 M0 LARC included 1991-2003



Patients at risk

74% R0

R0	150	134	118	93	71	57
R1	44	36	25	18	12	7
R2	10	7	2	1	0	0



Patients at risk

R0	150	132	113	90	69	54
R1	44	32	21	17	12	7



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Rectum cancer kirurgi.

Komplikasjoner

Anastomoselekkasje.

Endring i kontinens for luft/ avføring.

Endring i tømningsfølelse, frekvens og volum (verre etter strålebeh.).

Impotens (amputasjon 50%, TME 15%).

Sympaticus: Retrograd ejakulasjon, tørr skjede dysparauni.

Parasympaticus: ereksjonssvikt, tørr skjede.

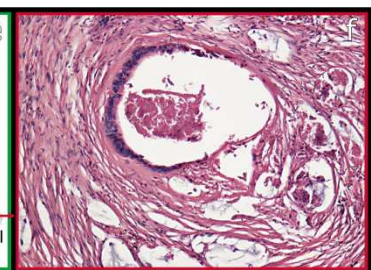
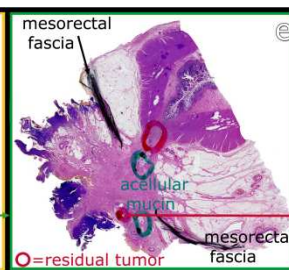
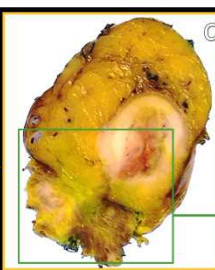
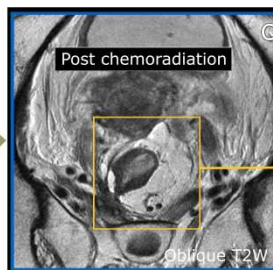
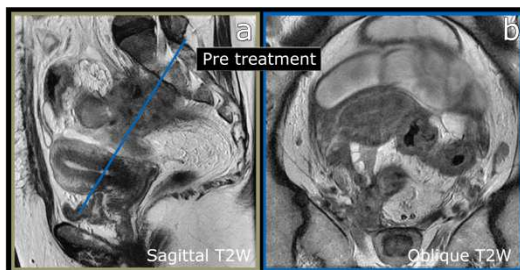
Blæreforstyrrelser.

Sphincterforstyrrelser.

Multimodality treatment

- Sufficient annual caseload (Wibe 2005), learning curve (Moran 2008)
- Education (Wibe 2002; Martling 2000/5; Kapitejn 2002; West 2008)
- Teamwork / multidisciplinary teams (MDT) (Burton 2006; Moran 2008)
- Discussion and interpretation of preoperative treatment strategy reduces positive CRM" (Burton 2006)

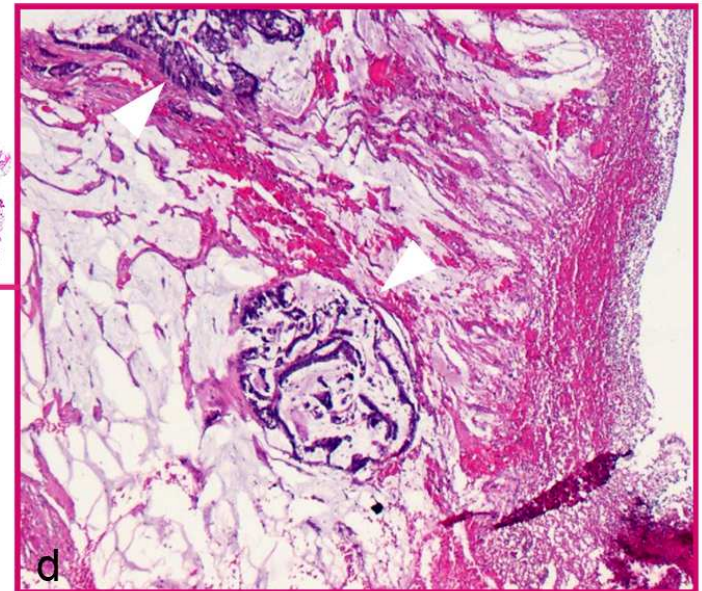
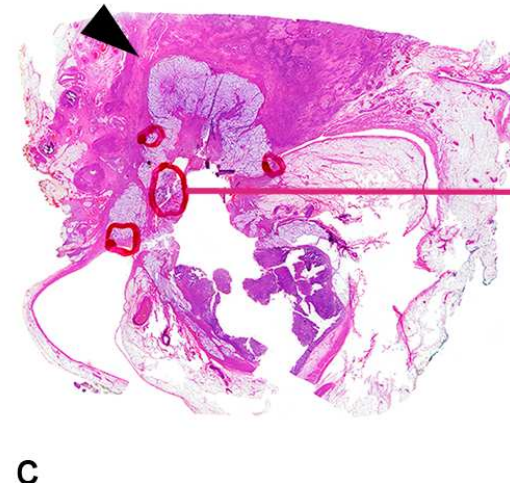
Preoperative staging	Targeted preoperative strategies	Precise surgery	Good anaesthetic care	Accurate histopath. assessment (Quirke 1986; Nagtegaal 2008)	Evaluation of adjuvant therapy
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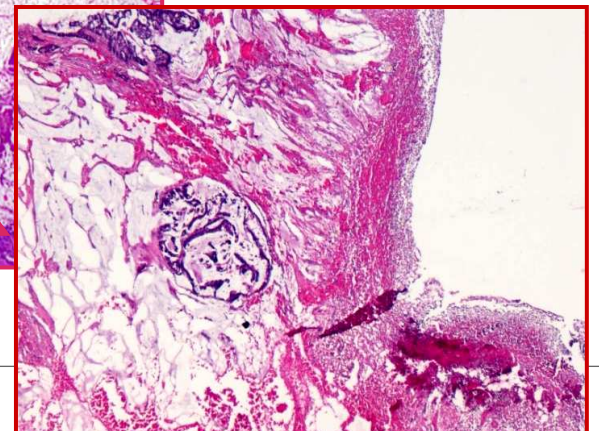
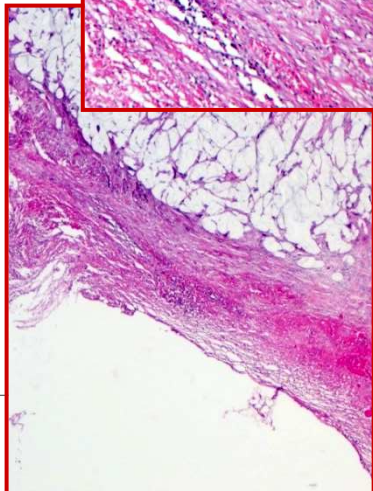
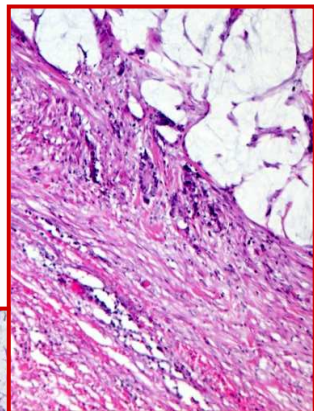
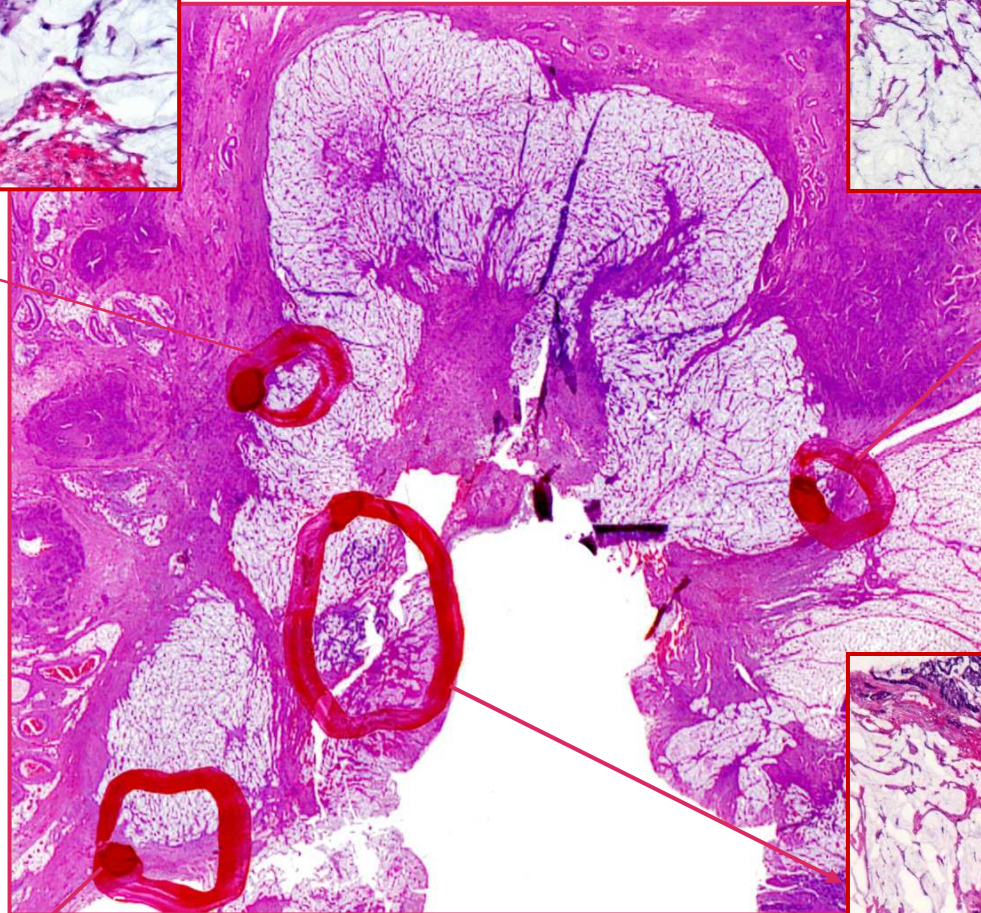
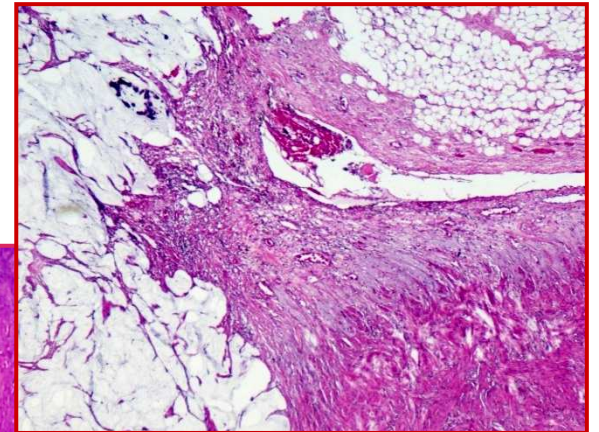
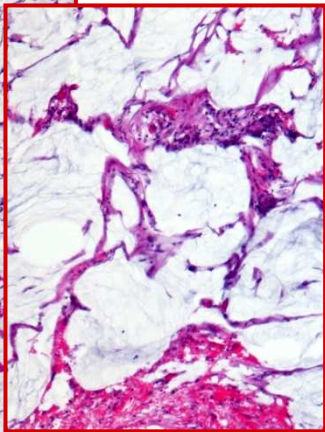
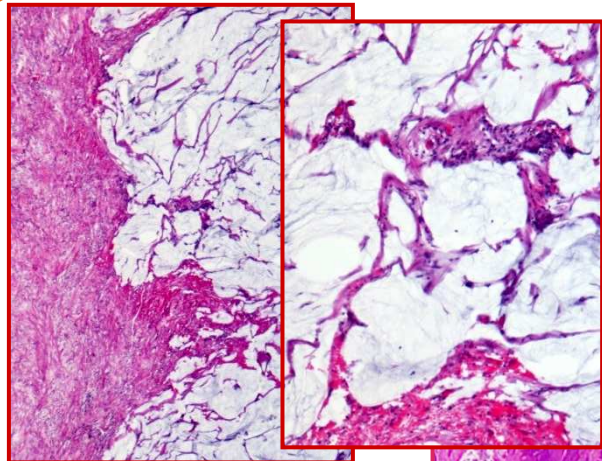


Tumour infiltration in adjacent organs

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).





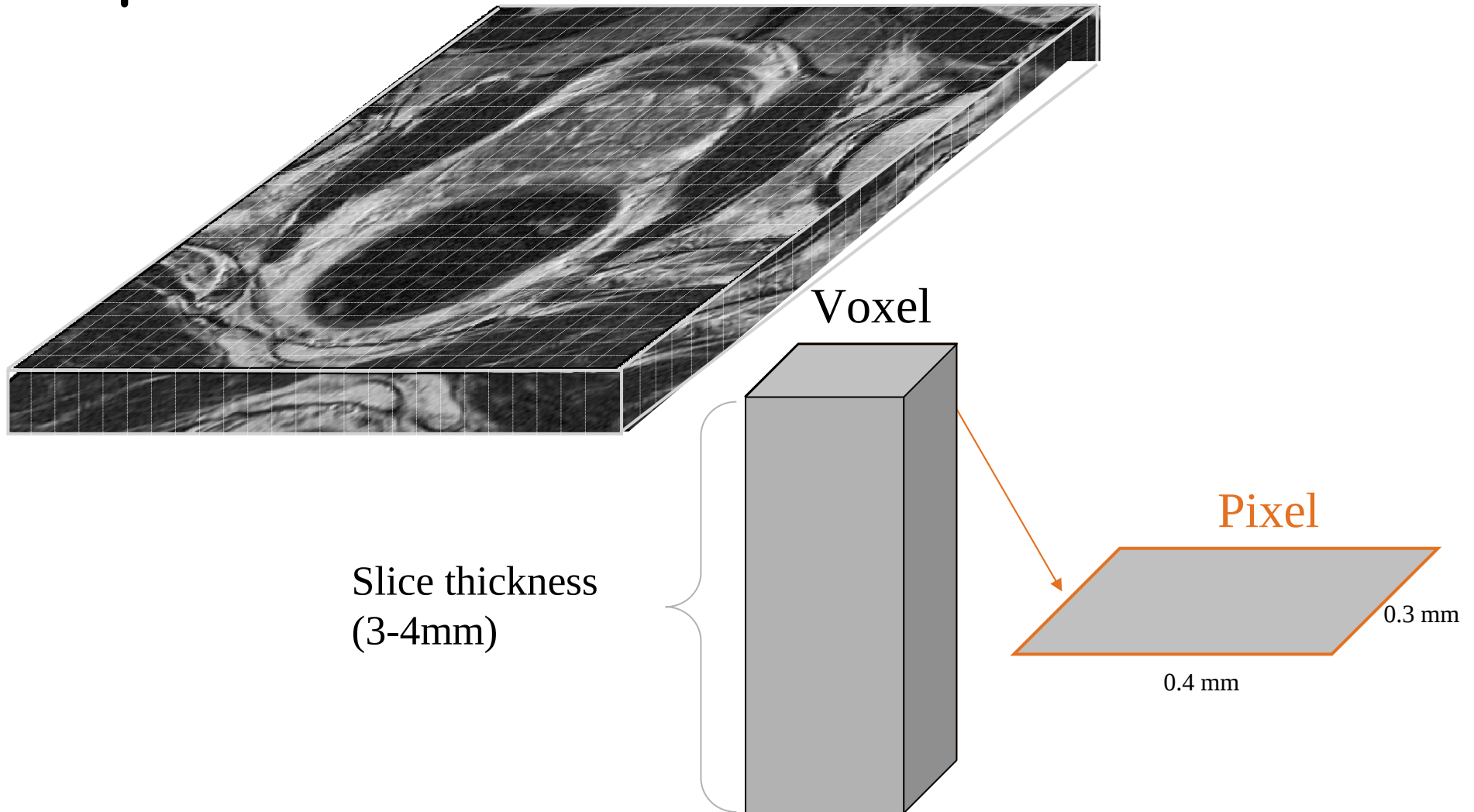
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MRI picture is dividid into voxels/ pixels



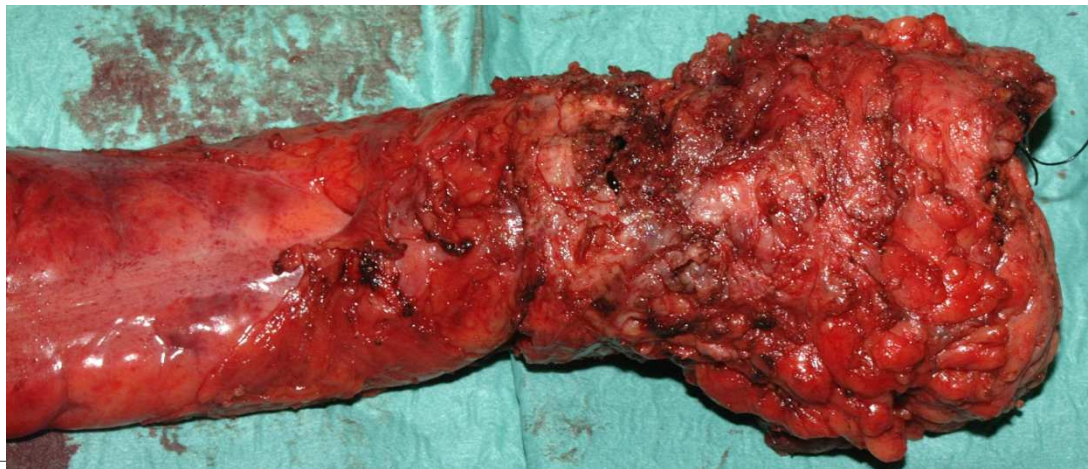
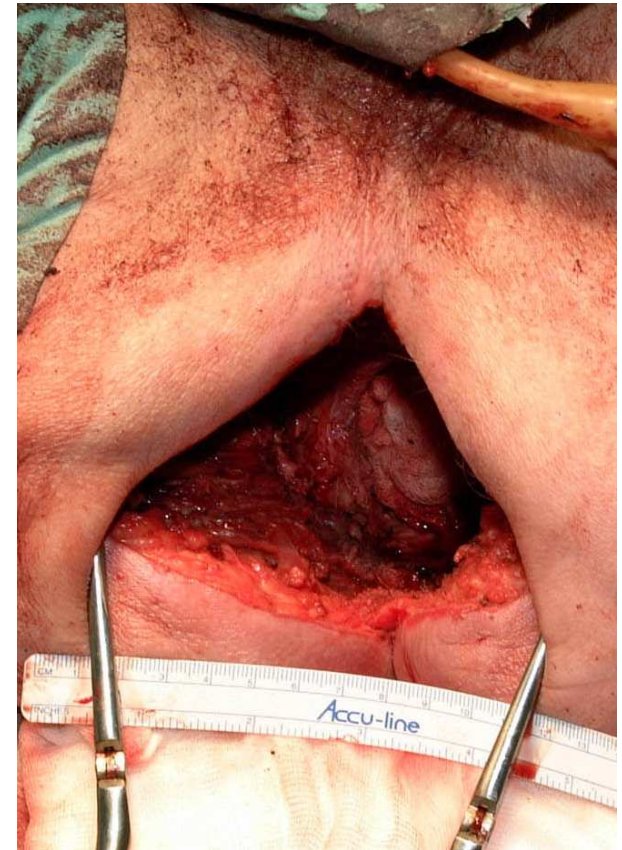
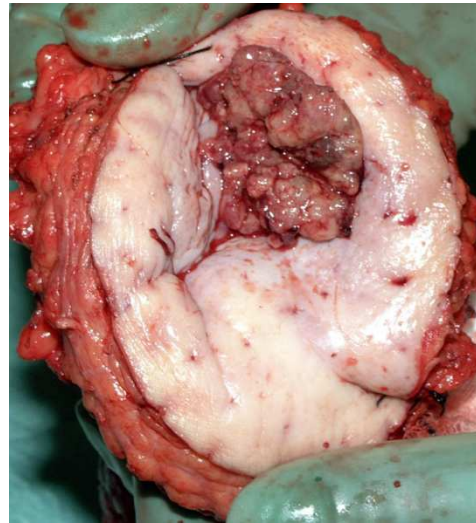
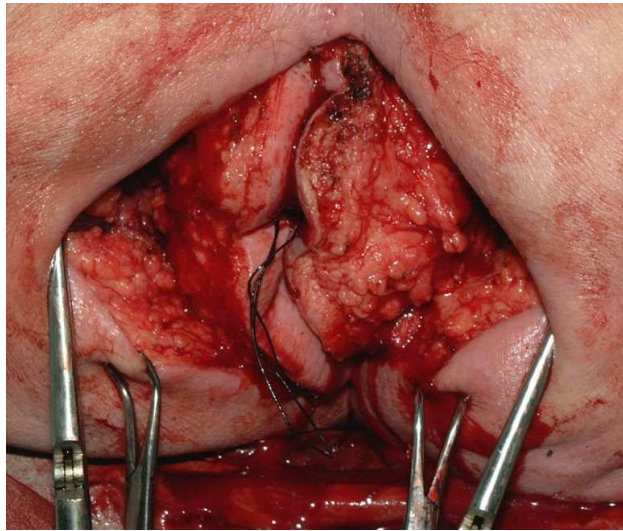
Message MRI

Many T4 tumours before and after neo-adjuvant treatment will still be histopathological T4 after treatment

MRI cannot detect islets of viable tumour within fibrosis or mucin deposits, but can detect mucin and fibrosis with high accuracy

Fibrosis left *in situ* may contain viable cells which may lead to late recurrences (6-28% later than 5 years postoperatively) (Guillem 2005; Moore 2005; Coco 2006)

Lokalavansert rectumcancer



Hva nå?



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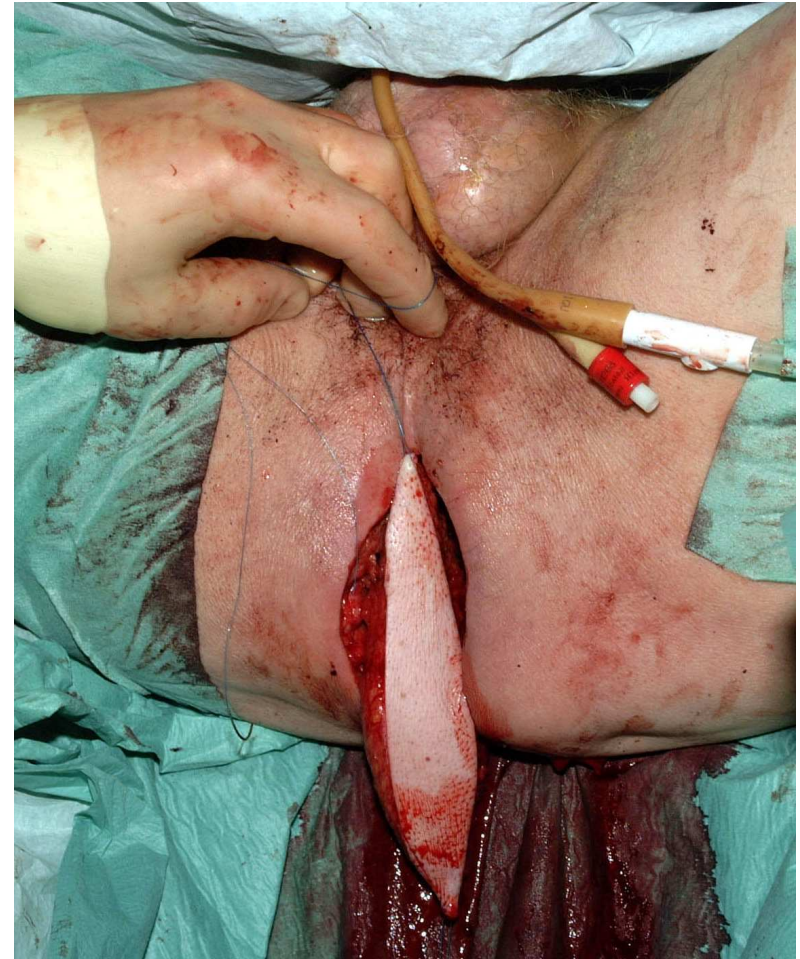
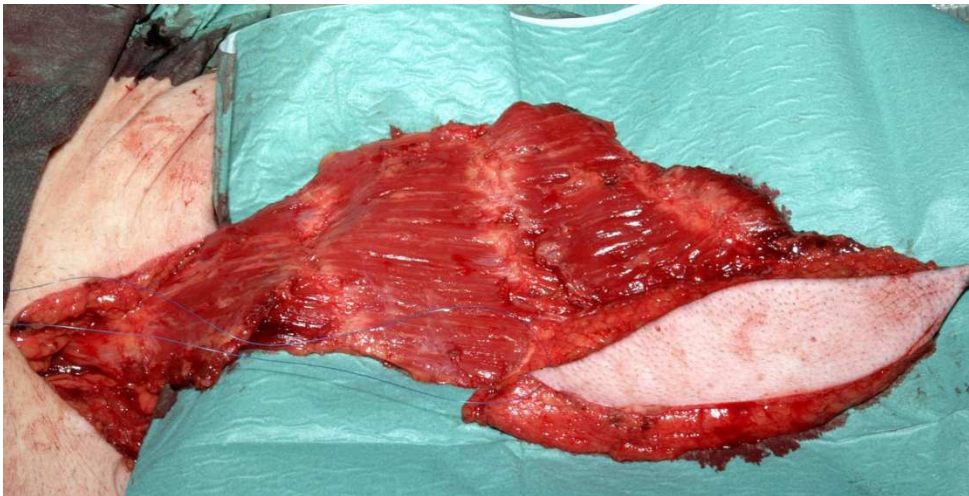
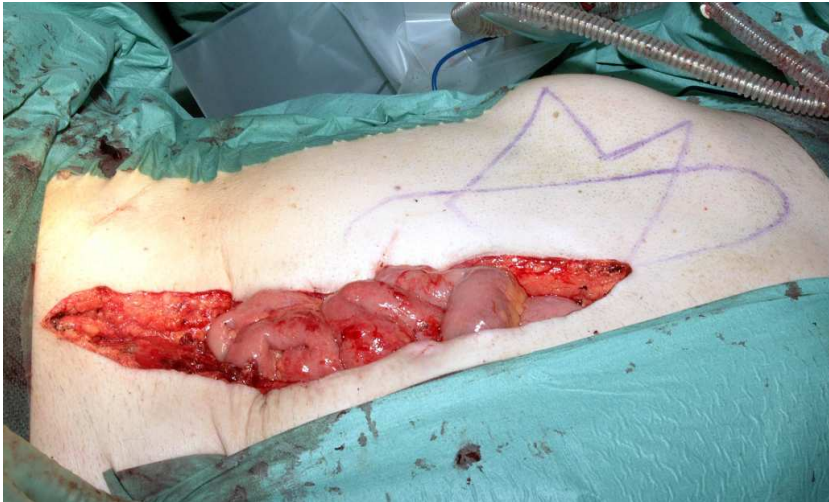


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VRAM - Flap



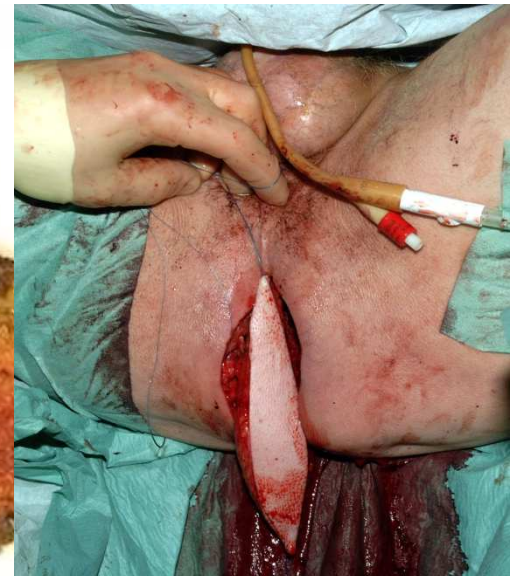
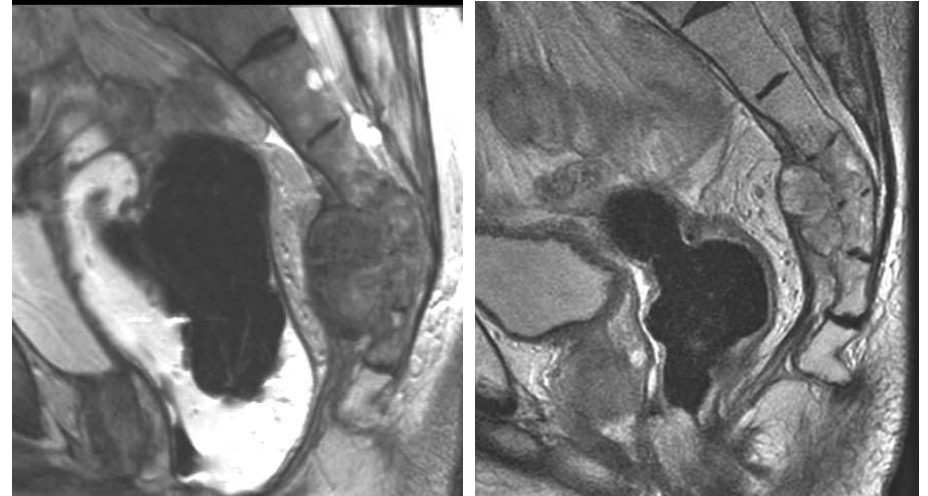
En-bloc/ multiorgan resections

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



Introduction to locally recurrent rectal cancer (LRRC)

Local recurrence has declined after the introduction of TME (Heald 1986; Wibe 2002), but local recurrence still poses an important clinical problem (Wiig 2007)

Before the TME-era, 25-50% of recurrent cases had cancer limited to the pelvis at time of death (Gundersson 1974; Welch 1978)

Recurrence may cause reduced quality of life with pelvic pain, bleeding, stenosis and fistulas to vagina, bowel or bladder (Welch 1978)

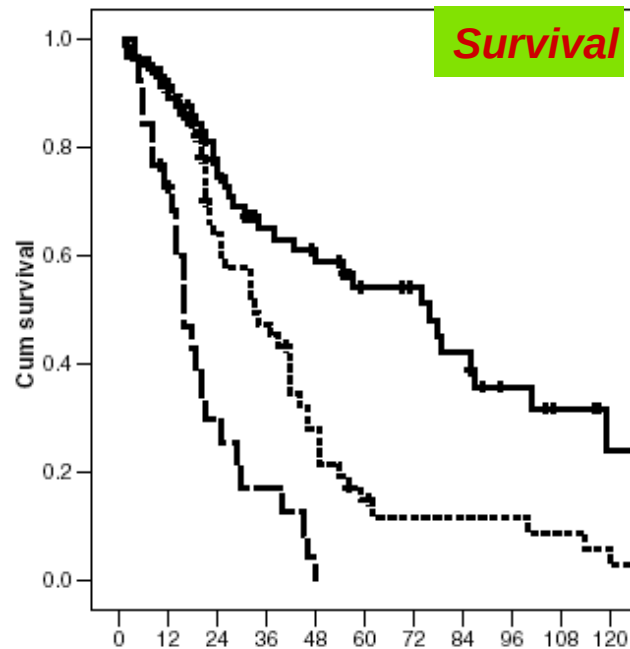
The 5 large single centre series in LRRC

Name	n	Observation time in months	Frequency R	Survival R	Mortality/ morbidity
Salo 1999 MSKCC	131 M0	-	R0: 54% R1: 10% R2: 36%	Total: 28 mnt R0: 35% R1: 23% R2: 0	-
Hahnloser 2003 Mayo	304 M0 respectable 166 pall. op. included 90 exp. excluded	-	R0: 45% R1: 9% R2: 46%	Total: 25%- 31 mnt R0: 37% R1/2: 16%	0.3/ 26
Bedrosian 2006 MD Andersson	85 M0	All: 43	R0: 76% R1: 24% R2: excluded	Total: 36%- R0: 35% R1: 15%	
Paper IV Wiig 2008 DNR	150 M0	All: 23	R0: 44% R1: 38% R2: 17%	Total: 27%- ? mnt R0: 52% R1: 14% R2: 0	0.7/ 46
Dresen 2008 Catharina, Eindhoven	147	Survivors: 34	R0: 57% R1: 23% R2: 20%	Total: 31% 28 mnt R0: 48%	4.8/ 59

Preoperative irradiation and surgery for local recurrence of rectal and rectorosigmoid cancer. Prognostic factors with regard to survival and further local recurrence.

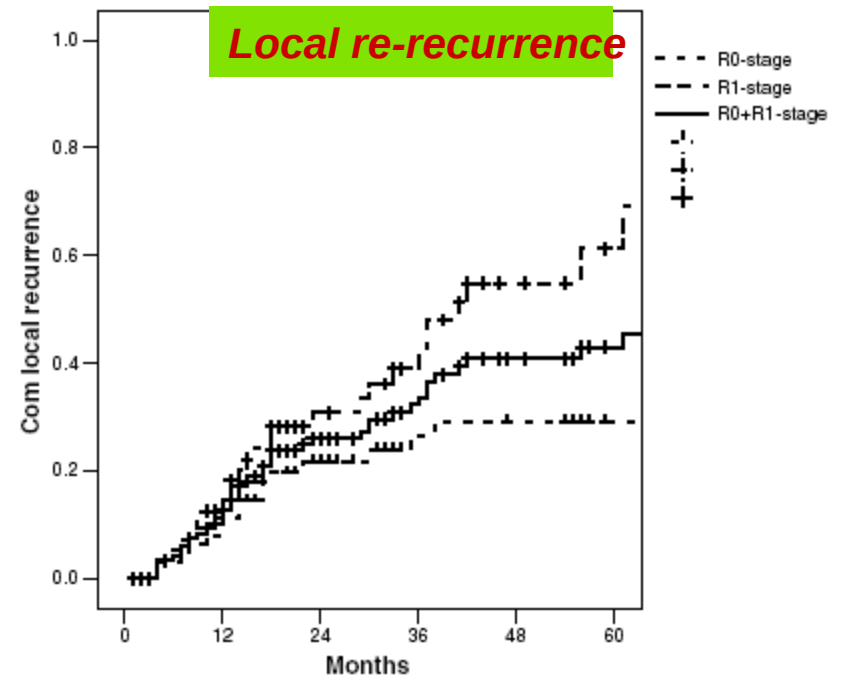


150 M0 recurrent rectal cancers, DNR 1990-2004



Patients at risk	R0	66	59	44	32	27	21	18	14	9	6	3
	R1	58	52	31	23	13	6	4	4	4	3	1
	R2	25	16	6	3	0						

44% R0



Patients at risk:	R0	66	56	38	28	25	19
	R1	58	45	27	19	10	5
	Total	122	101	65	47	35	24



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Preoperative irradiation and surgery for local recurrence of rectal and rectosigmoid cancer. Prognostic factors with regard to survival and further local recurrence

J. N. Wiig*, S.G. Larsen*, S. Dueland† and K.-E. Giercksky*

*Department of Operative treatment and †Department of oncology, The Norwegian Radium Hospital, Oslo, Norway

Received 1 April 2006; accepted 11 November 2006



**150 M0
recurrent rectal cancers,
DNR 1990-2004**

Pelvic wall	70
Sacrum	5
Cystoprostatectomy	21
Prostatectomy	1
Bladder resection	3
Vesicula seminalis	42
Hysterectomy	17
Vaginal resection	23

Complications in LARC/ LRRC

LARC

30-days mortality rate was 2.5%

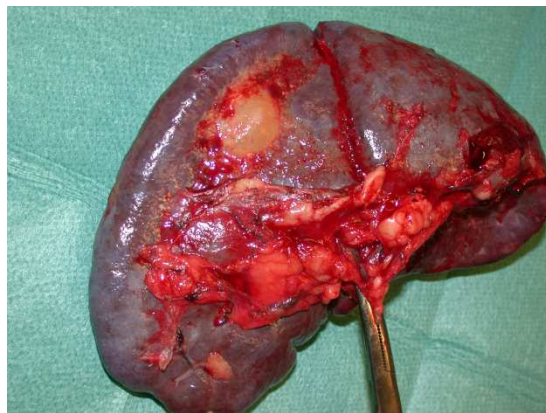
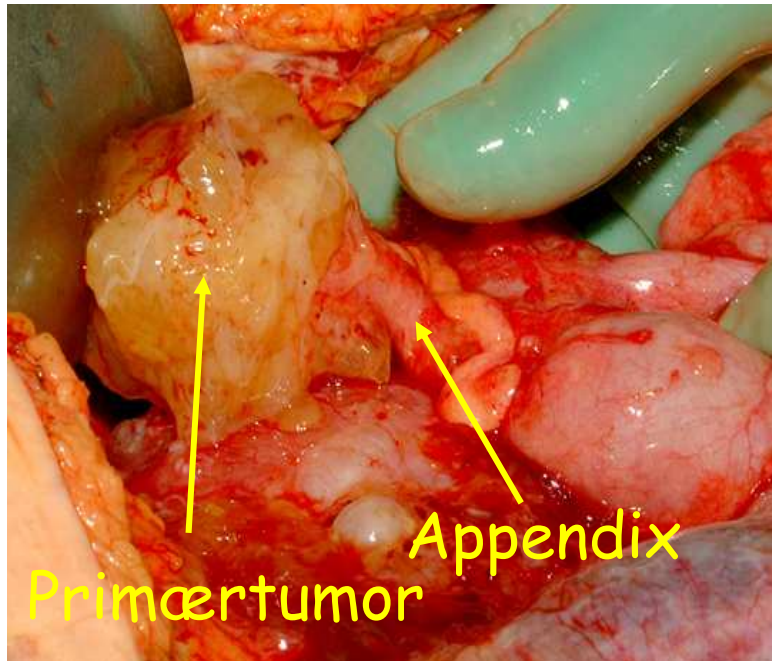
Non-lethal complications occurred in 41% of the patients (bowel leakage 6%, urinary leakage 6%). Reoperations in 20%

LRRC

30-days mortality rate was 0.7%

Non-lethal complications occurred in 46% of the patients (bowel leakage 6%, urinary leakage 8%). Reoperations in 27%

Pseudomyxoma peritonei

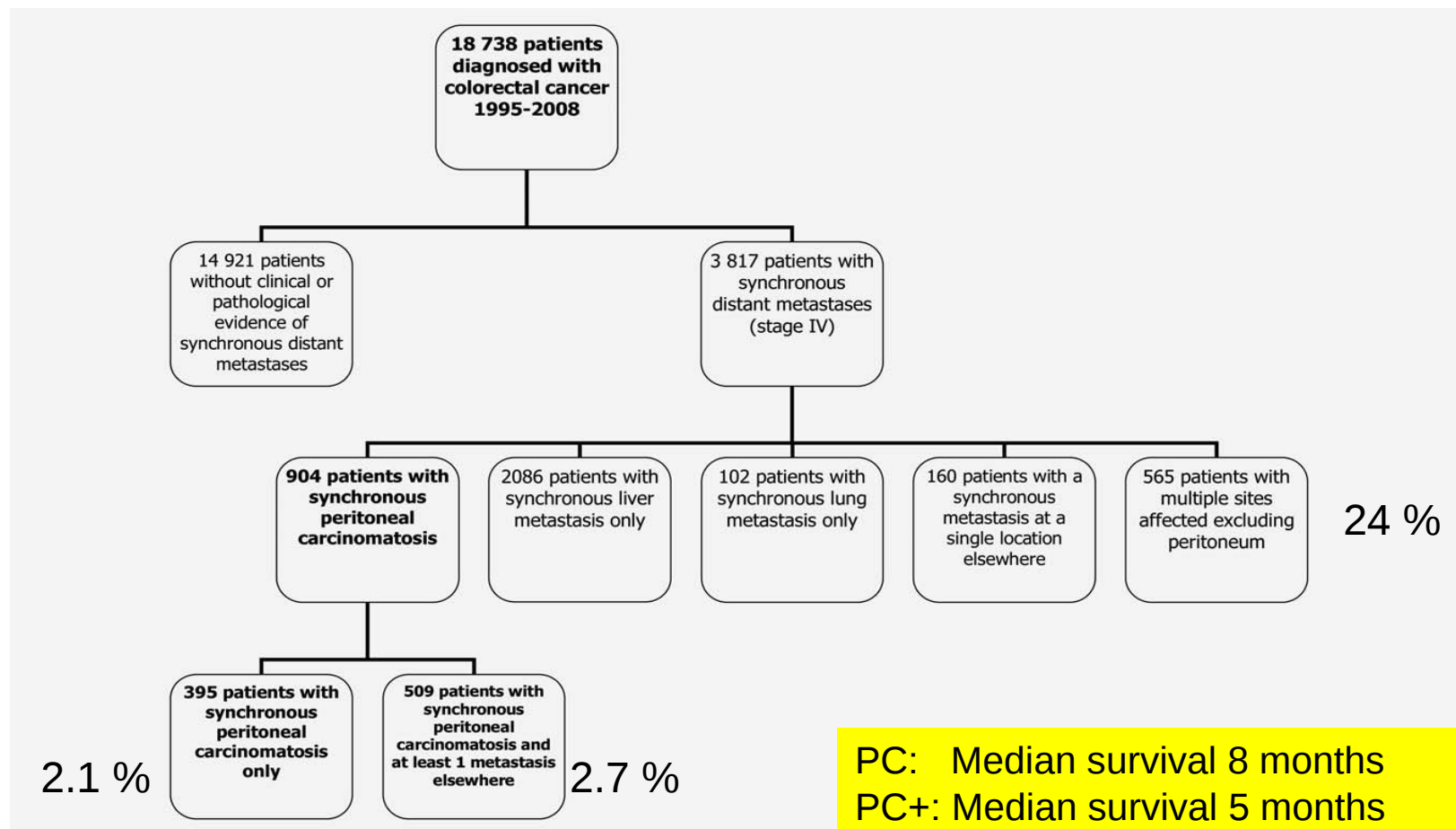


Introduction to carcinomatosis

- Peritoneal carcinomatosis has been considered a terminal disease with short median survival time; 5 -13 months (Jayne DG 2002; Koppe MJ 2006)
- Cytoreductive surgery (CRS) and systemic chemotherapy have limited success
- CRS-HIPEC (hyperterm intraperitoneal chemotherapy) offers a new treatment option for low/moderate volume disease in the peritoneal cavity

Synchronous peritoneal carcinomatosis

Eindhoven Cancer Registry (Lemmens V 2010)

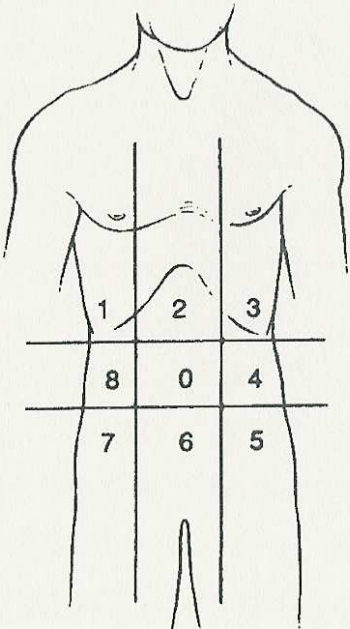
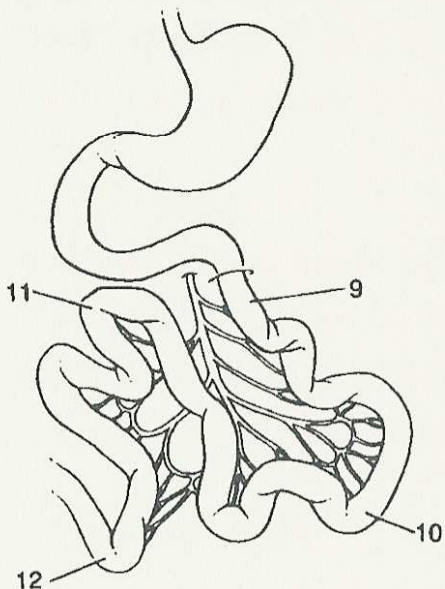


•Synchronous: 7-10 % (Sjo OH 2011); metachronous 4-19 % (Koppe MJ 2006)

Odds ratio for carcinomatosis (Lemmens V2011)

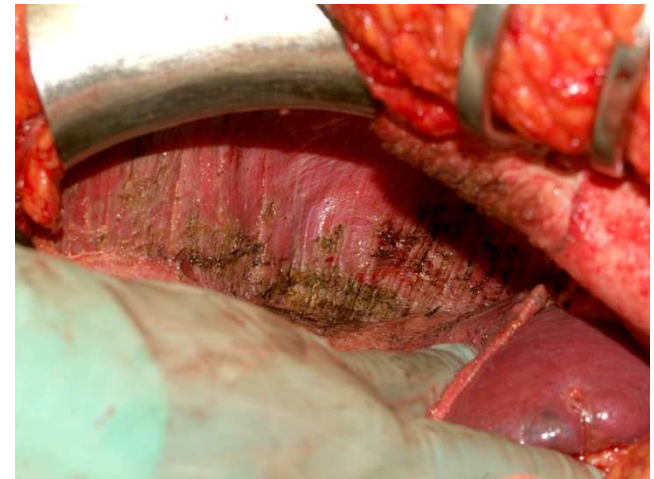
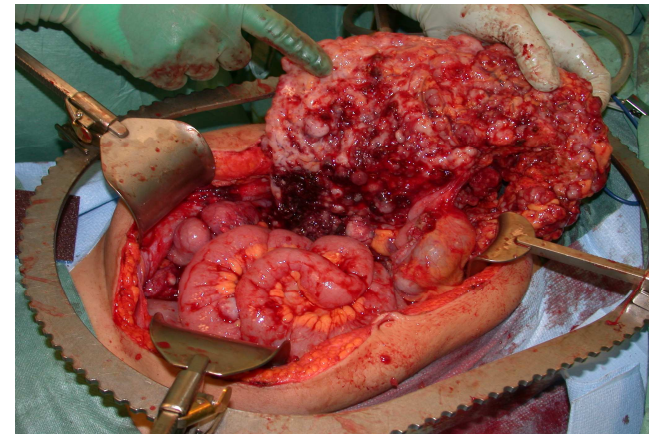
Factor	Odds ratio
Age < 60 years	1.4
Diagnosis last ½ of 1995-2008	1.3
Right-sided tumour	1.8
T4 vs. T3	4.7
N+ disease	5,9
Poor/ undiff. tumour vs. well/ mod.	2.1
Mucinous adenocarc	2,0

Peritoneal Cancer Index (PCI) (Esquivel J 1998)

	<u>Regions</u>	<u>Lesion Size</u>	<u>Lesion Size Score</u>
	0 Central	_____	LS 0 No tumor seen
	1 Right Upper	_____	LS 1 Tumor up to 0.5 cm
	2 Epigastrium	_____	LS 2 Tumor up to 5.0 cm
	3 Left Upper	_____	LS 3 Tumor > 5.0 cm or confluence
	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	_____	
PCI			

Teknikk ved max. cytoreduktiv kirurgi (CRS)

- Komplett adheranseløsning (PCI, kjemo tilgang)
- Omentectomi og reseksjon av affisert peritoneum (diafragmakupler, bakre bukvegg, flanker, bekken)
- Reseksjon av nødvendige organer (milt, colon, galleblære, ventrikkel)
- Multivisceral reseksjon (MVR) er 2 eller flere organer utover oment/ peritoneum
- Særlig områder med reabsorpsjon av peritonealvæske. Tynntarm er ofte spart lenge.



Literature

- 2 metaanalyses (Cao C 2009; Yan T 2007)
- 1 Cochrane Protocol 2010
- 1 completed randomized controlled trial (RCT) (Vervaaal VJ 2003)
- 3 attempted RCT or retrospective comparative (Elias D 2004/2009; Mahteme H 2004)
- 4 multicentre studies (Elias D 2010; Glehen O 2004, Gomez PA 2006; Cavaliere F 2010)
- >50 observational, single-institutional studies

RCT:

CRS-HIPEC + systhemic chemo vs. systhemic chemo/ palliativ kirurgi (Vervaal VC 2008)

- Performed 1998 – 2001
- Study group: Mitomycin C (35 mg/ m²) and systemic treatment
- Standard treatment: 26 weeks 5-FU 400 mg /m², leucovorin 80 mg/m². (Irinotecan if former 5-FU)
- Median disease-specific survival: 22.2 months vs. 12.6 months
- 5-year survival: 20 % vs 10 % (tumour < 2.5 mm after CRS: 45 %)

Studies on peritoneal carcinomatosis

Type	Author	Publ	Paper	n	Period	Surv contr 5 year (%)	Surv study 5 year (%)	M. surv contr (mnt)	M. surv study (mnt)	Mo rt (%)
RCT	Vervaaal	2003 /8	JCO/ An SuO	51/54	98-01	10	20	12.6	22.4	
MCS	Elias	2010	JCO	523	90-07	-	27	-	30	3
SC	Mahteme	2004	BJC	18/18	91-99	5	28	14	32	
SC	Elias	2009	JCO	48/48	98-03	13	51	23.9	63	

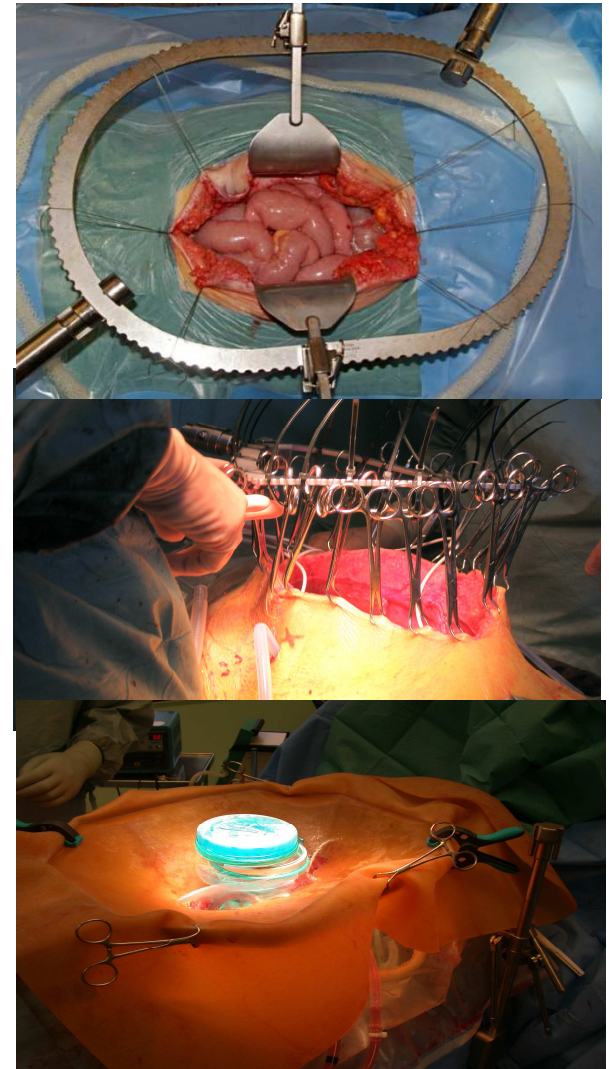
SC:

CRS-HIPEC vs systemic chemo (Elias D JCO 2009)

- Performed 1998 - 2003
- Study group: Oxaliplatin 460 mg/m² 5-FU IP/ 5-FU 400 mg /m², leucovorin 20 mg/m² IV perop, + systemic treatment (n=48).
- Standard group: comparable patients, systemic chemotherapy with or without surgery (n=48)
- Systemic chemotherapy lines: 101 vs 110
- Median survival: 62.7 months vs 23.9 months
- 5-years survival: 51 % vs 13 %

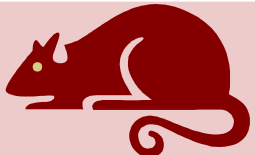
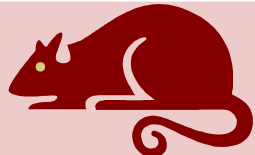
Intraperitoneal chemotherapy (IPEC)

- Uniform distribution in the peritoneal cavity
- Destruction of residual microscopic disease (Katz M 2003; Sugarbaker P 2006)
- High IP concentration with low systemic toxicity
- Good elimination of platelets, granulocytes and monocytes (reduced tumor growth)



Intraperitoneal chemotherapy after CRS

(Klaver Y 2010)

	CRS	CRS-HIPEC (MMC 15 mg/m ²)	CRS-HIPEC (MMC 35 mg/m ²)
			
Median surv (days):	43	75	97
Survived 120 days:	1/20	3/20	7/20
Mean PCI:	24	23	17

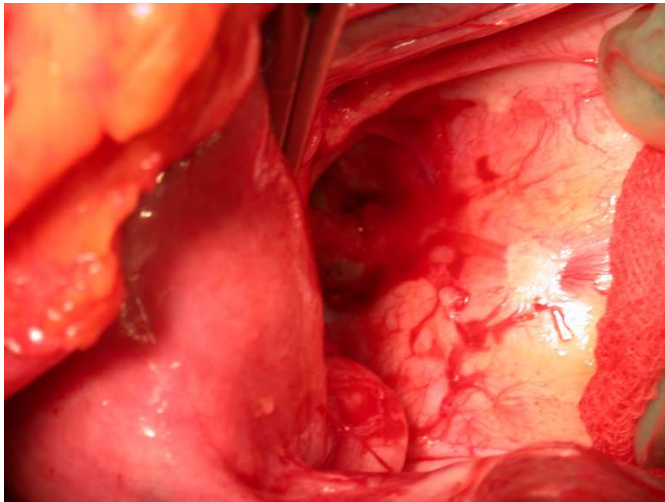
Advantage of hypertermia*?

- Believed to enhance the antitumour effect in several cytotoxic agents (higher drug conc. due to increased blood flow and oxygen content within tumour)
- No RCT performed comparing normo-/hyperterm intraperitoneal perfusion in CR cancer
- 1 randomized trial has reported survival benefit of hyperthermia in gastric cancer (n=139). 5-year surv 61 %, 43 %, 42 %. OR 3. (Yonemura Y 2001)
- Heat enhances the peritoneal tissue conc of oxaliplatin (Piché N 2011)
- An experimental study in rats failed to show increased value of hyperthermia with MMC after CRS-HIPEC (Klaver Y 2011)

*: increas of temperature in tumouraffected bodyregion to 39 – 43 C by external energy source

Selection of patients

- Acceptable performance status (ECOG Grade 0-1)
- Low rate of co-morbidity
- < 75 years of age?
- Proactive in low volume disease ($PCI \leq 20$)



- The treatment center should be contacted at time of diagnosis.

<u>Regions</u>	<u>Lesion Size</u>	<u>Lesion Size Score</u>
0 Central	_____	LS 0 No tumor seen
1 Right Upper	_____	LS 1 Tumor up to 0.5 cm
2 Epigastrium	_____	LS 2 Tumor up to 5.0 cm
3 Left Upper	_____	LS 3 Tumor > 5.0 cm
4 Left Flank	_____	or confluence
5 Left Lower	_____	
6 Pelvis	_____	
7 Right Lower	_____	
8 Right Flank	_____	
9 Upper Jejunum	_____	
10 Lower Jejunum	_____	
11 Upper Ileum	_____	
12 Lower Ileum	_____	

PCI



Variables in HIPEC

	Most common	Dose	Variasjon
Time (min)	90		30 - 120
Drugs (mg/m ²)	Mitomycin Oxaliplatin	35 (max 2m ²) 460	10 - 40
Temperature (°C)	41 – 43		40 - 43
Flow (l/min)	2 - 4		0.5 - 4.0
MMC can be given alone, with Doxorubicine ip/5FU iv, Oxaliplatine or Cisplatinum			

Volume carrier solution

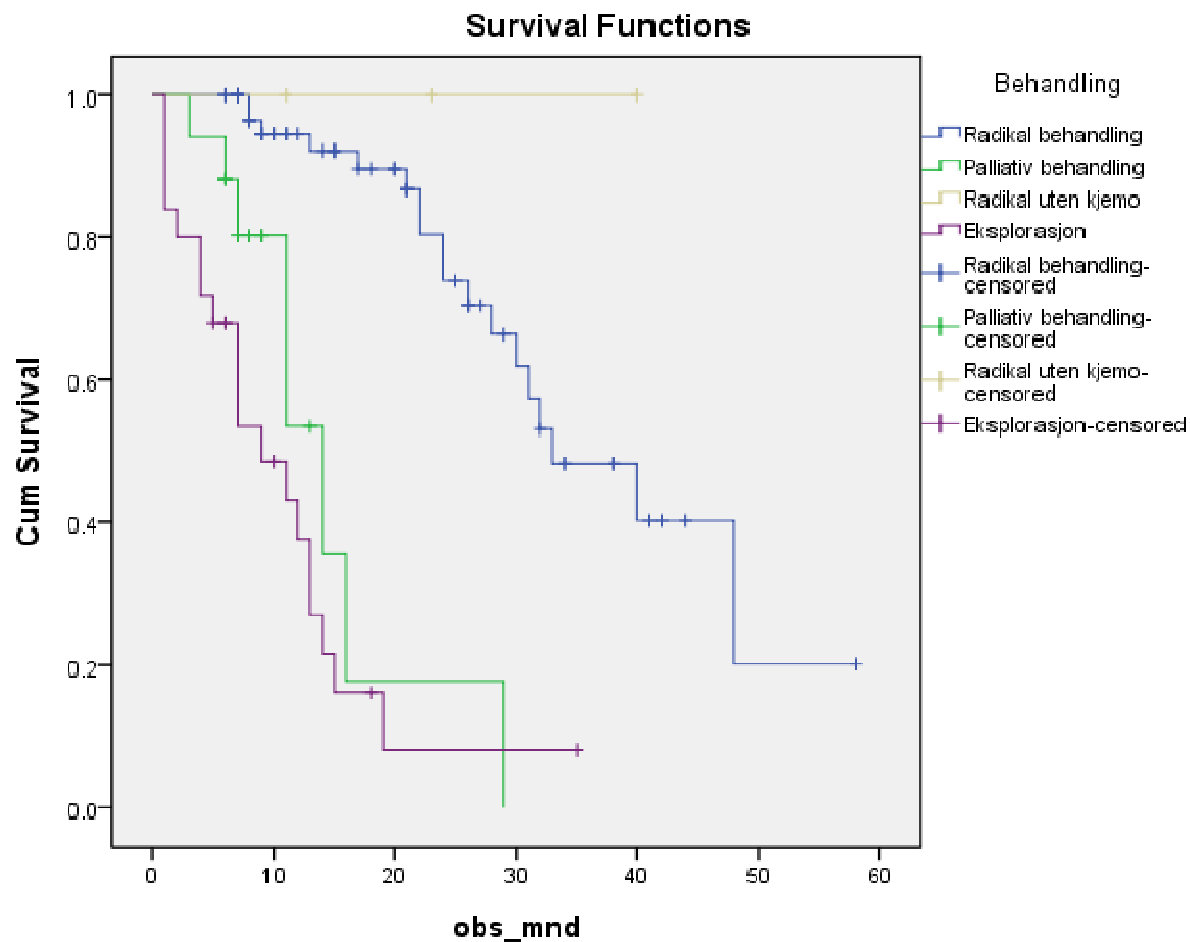
Mitomycin C

- Noncell-cycle specific, binds with DNA and inhibits DNA synthesis
- Stays in peritoneal cavity (334 D)
- Rapidly cleared from systemic circulation
- Favourable pharmacokinetics used i.p.
- Cytotoxic effect can be increased by hyperthermia



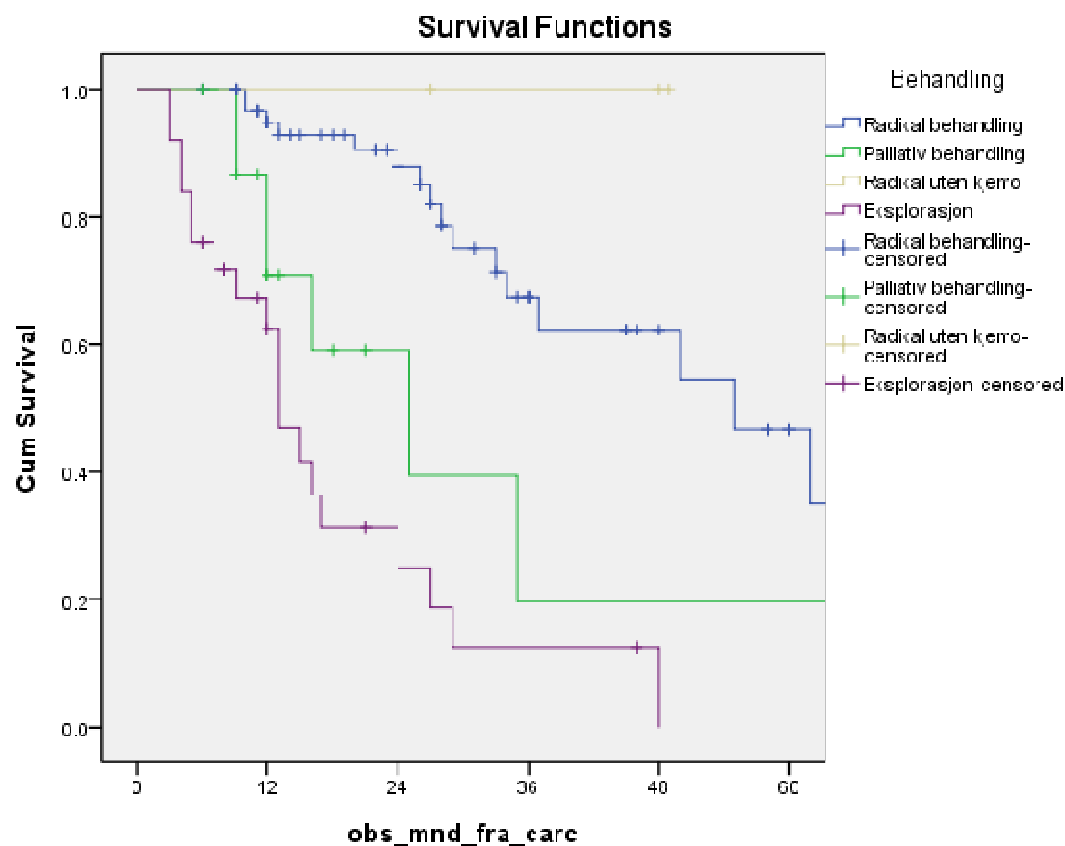
CRS-HIPEC ved colorectal carcinomatose

(n=104)



CRS-HIPEC ved colorectal carcinomatose

(n=104)



88 behandlet siste 4 år

62 (60 %) CRS-HIPEC

17 (16 %) palliativ kirurgi

25 (24 %) explorativ lap.

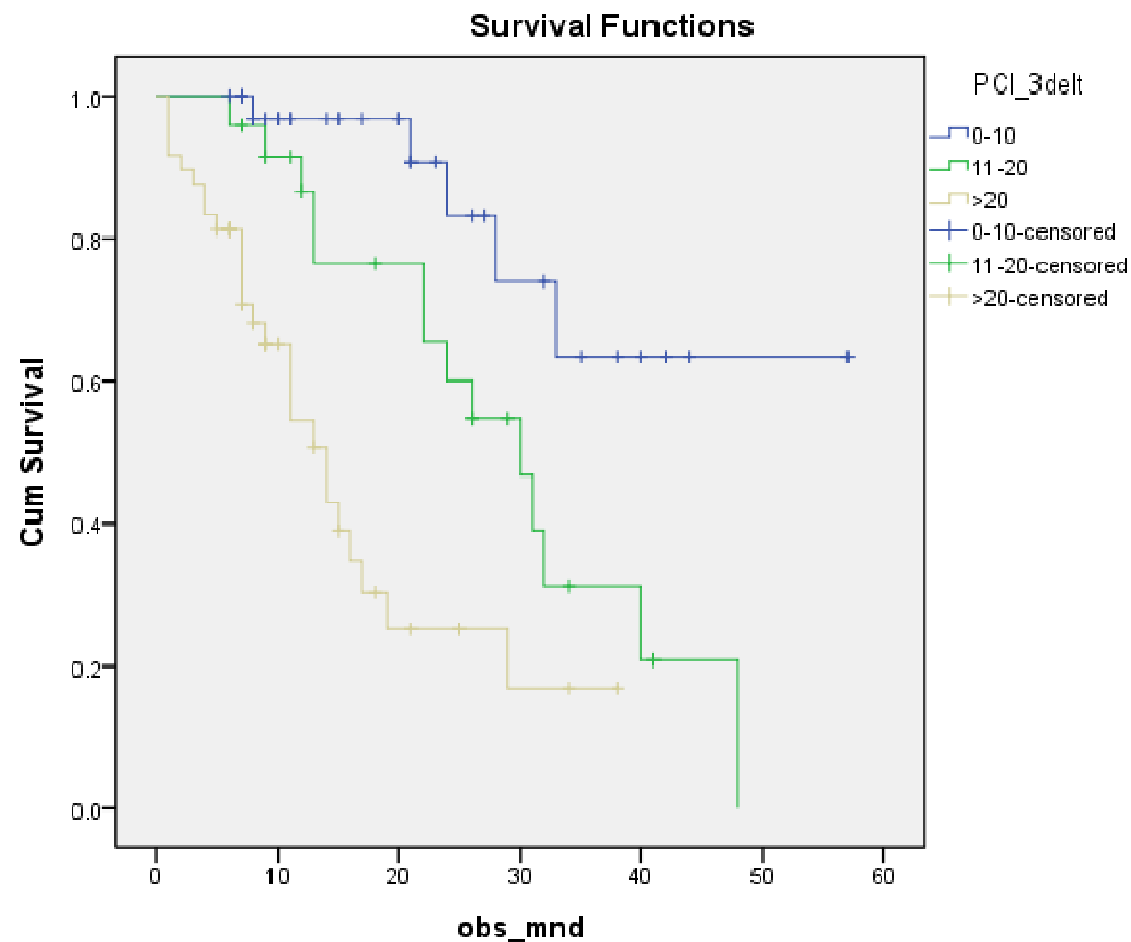
Median surv:

55 mnd (47 %)

25 mnd (20 %)

13 mnd (0 %)

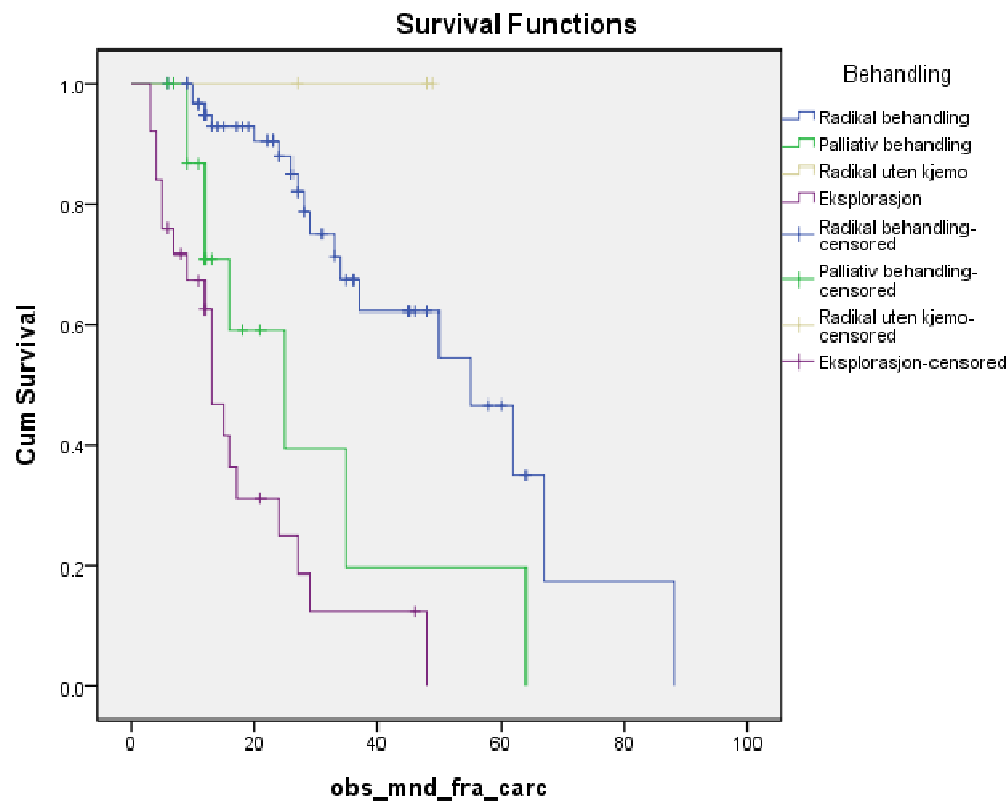
Peritoneal cancer index (n=104)



Gitt systemisk kjemoterapi

Kjemoterapi	n (%)
Adjuvant kjemoterapi	21 (34 %)
1. linje kjemoterapi (+ evt. adjuvant)	24 (39 %)
Minst 2 kjemoterapi linjer	4 (6 %)
Ingen kjemoterapi	13 (21 %)

CRS-HIPEC (n=62)



43 kvinner, 19 menn

Operasjonstid 7,5 t (4 – 14,5)

Mitomycin C 65 mg (51-70)

Perusjon 90 min (60-95)

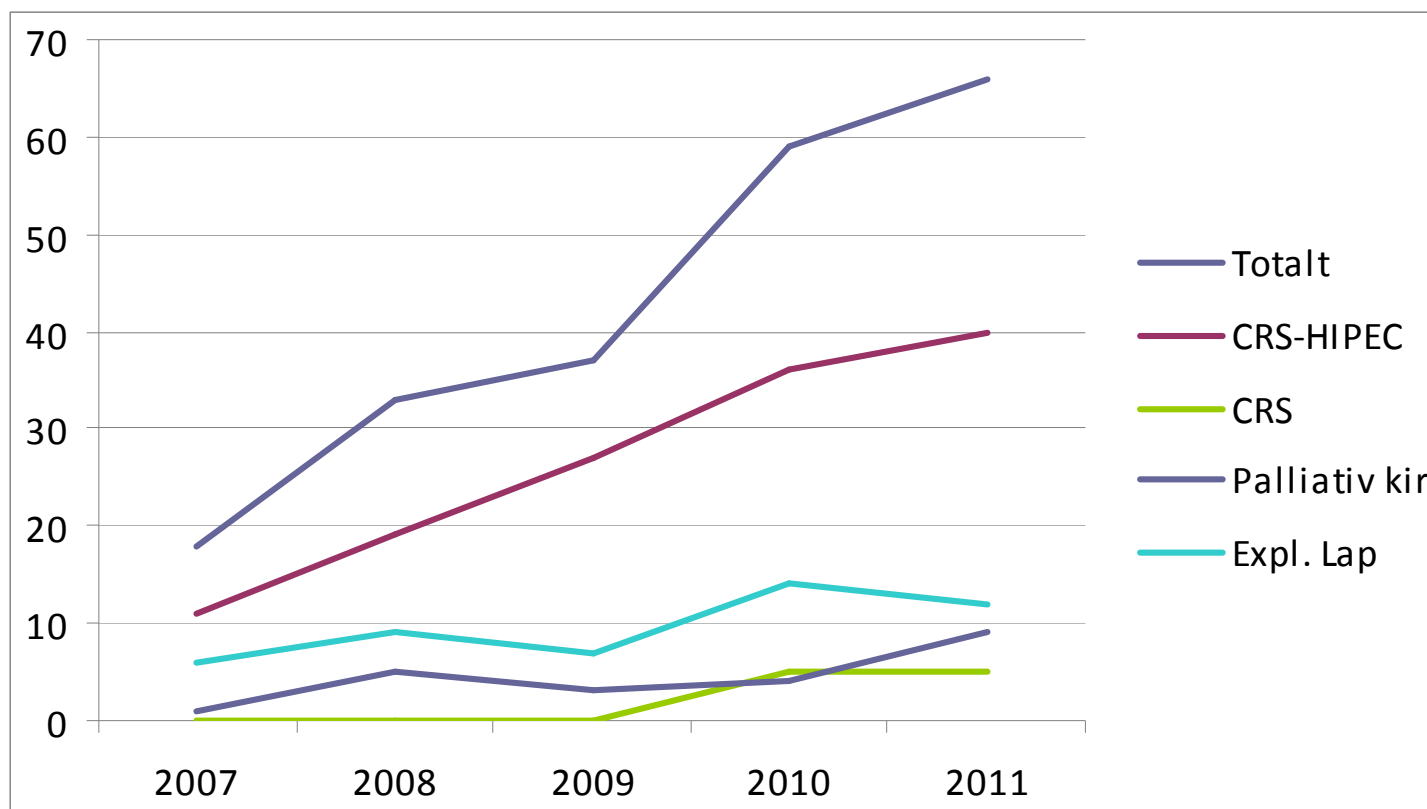
Temp 41,1 °C (39,5-41,7)

Liggetid 10 dager (6-57)

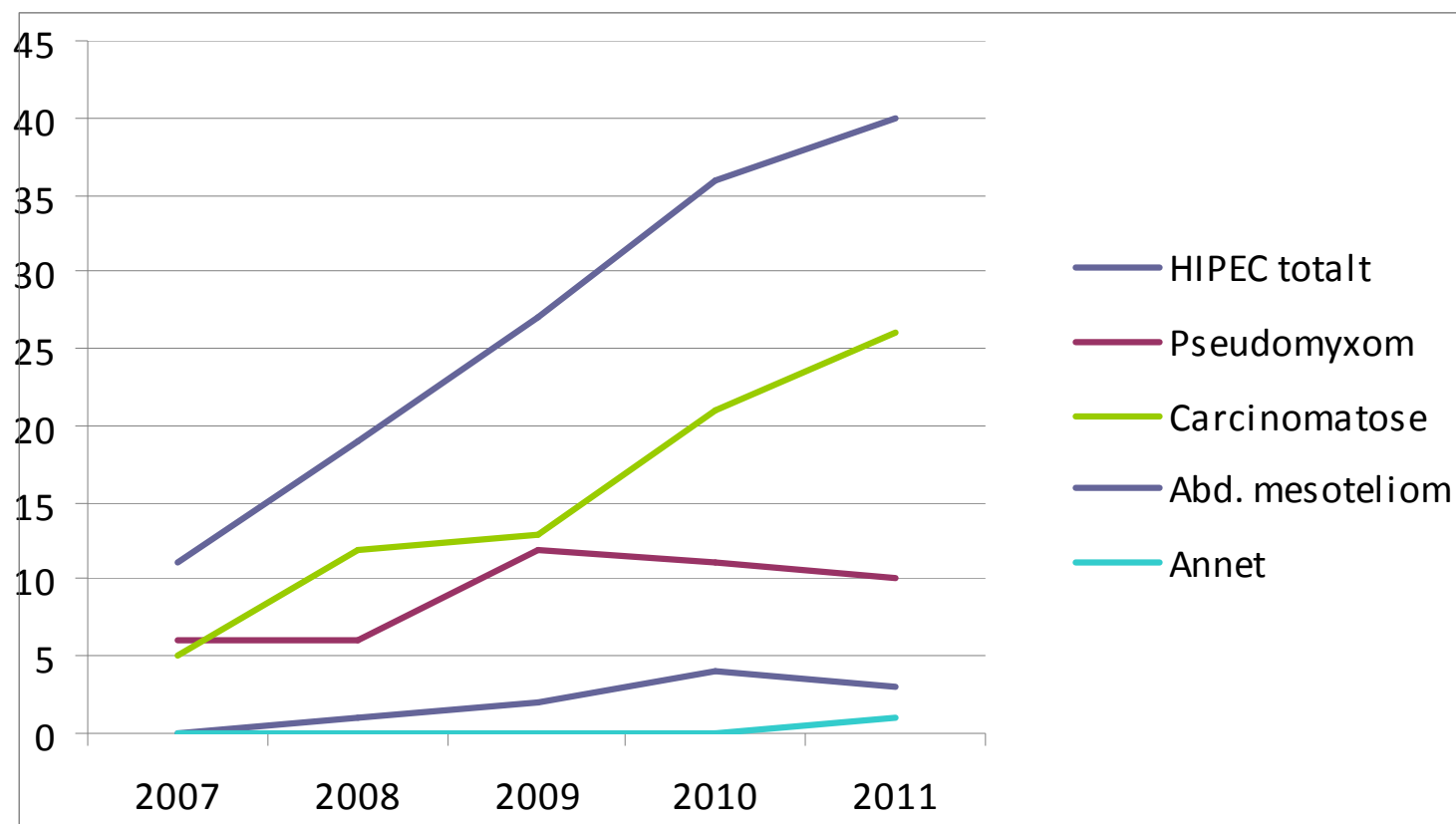
Mortalitet 6 mnd: 0

Nasjonale behandlingstjeneste med CRS-HIPEC

Pasientvolum 2007 - 2011



Nasjonale behandlingstjeneste med CRS-HIPEC



Nasjonale behandlingstjeneste med CRS-HIPEC

Fordeling på helseregioner

