Onkologisk behandling av ca recti

OnkoLis 2012

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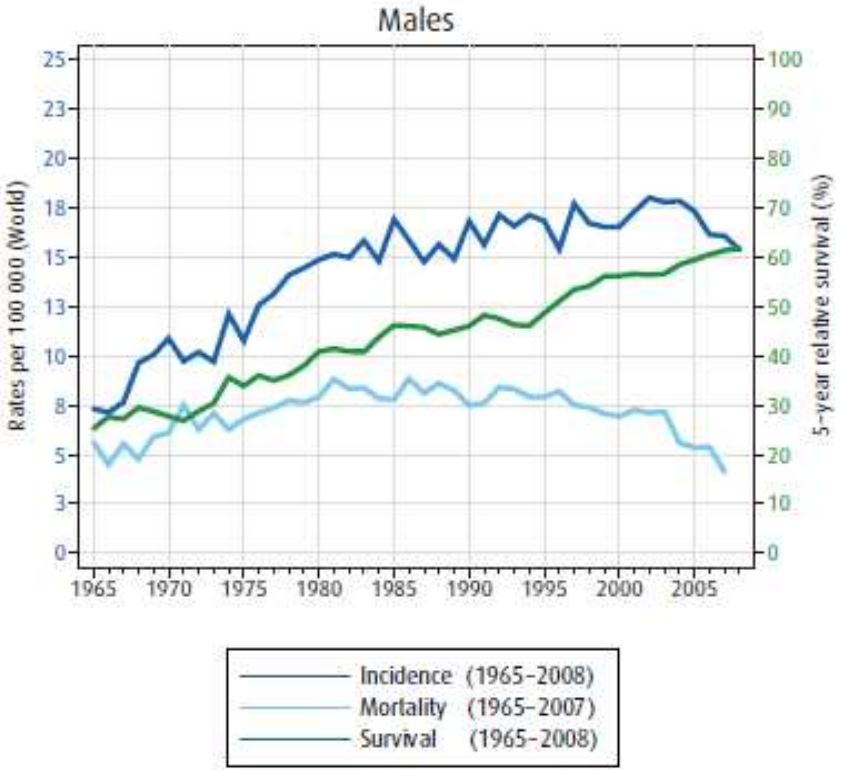
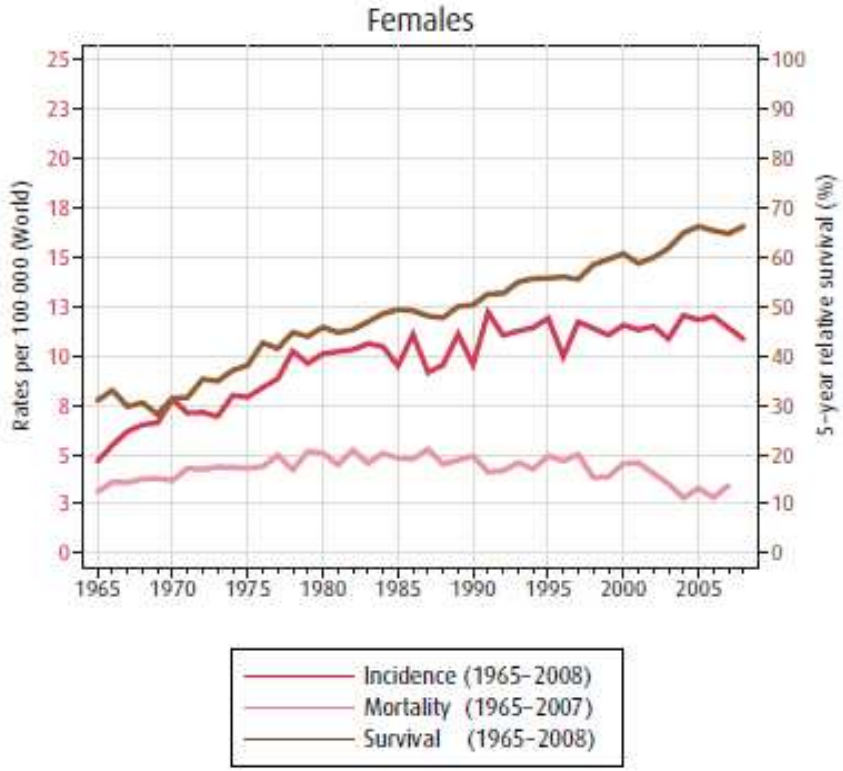
Kreftregisteret

- Cancer in Norway 2008





Bakgrunn

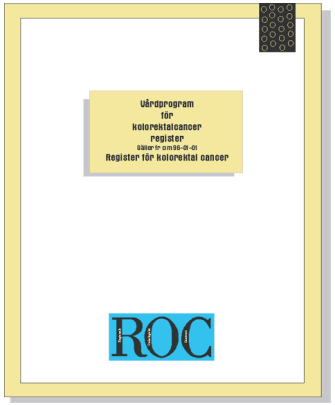
- ✓ Tidligere høy forekomst av lokale residiv
  - Stort problem, mye smerter

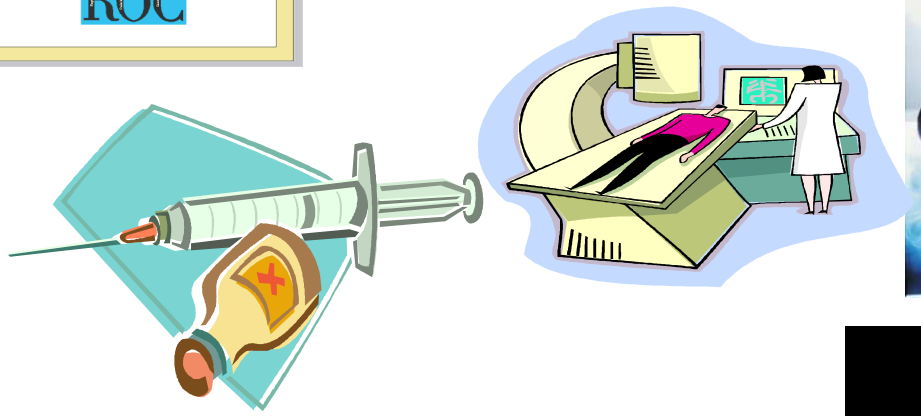
- ✓ Bedre operasjonsteknikk (TME)
- ✓ Bedre diagnostikk og staging (MR)
- ✓ Bedre patologisk vurdering
- ✓ Risikofaktorer for residiv identifisert preoperativt
- ✓ Økt bruk av strålebehandling

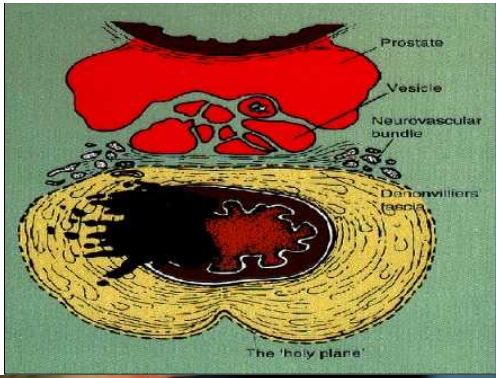
} MDT

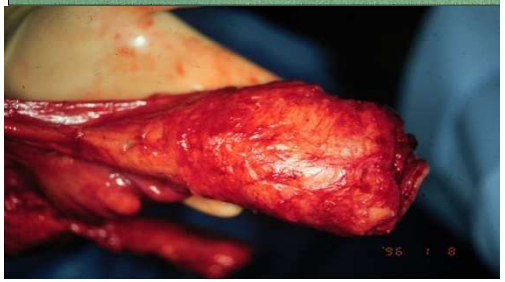
Ca recti

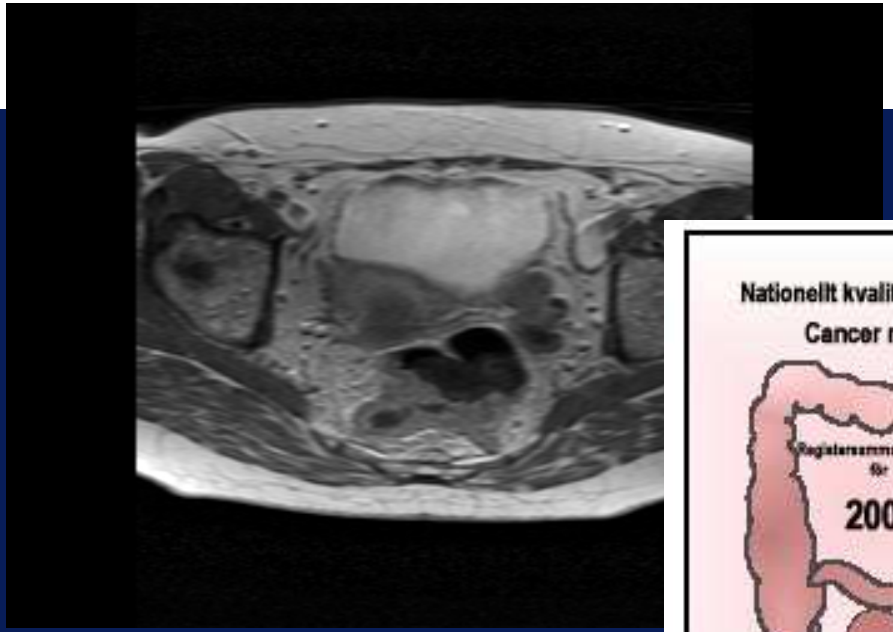
Et multidisiplinært samarbeid!

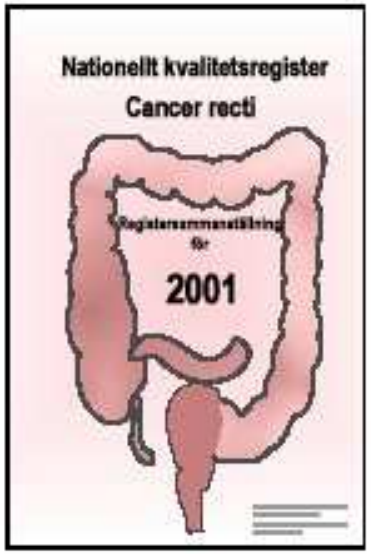






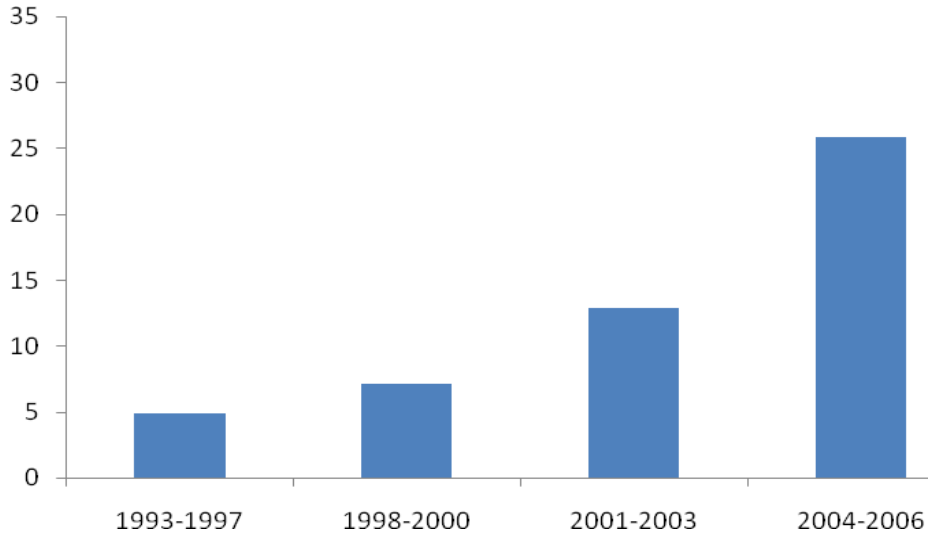






Utvikling 1993-2006

- Andel strålebehandlet økt fra ca 4,0 til 27,0%
  - Størst økning i preoperativ strålebehandling



Fra Colorectalcancer registeret 2010

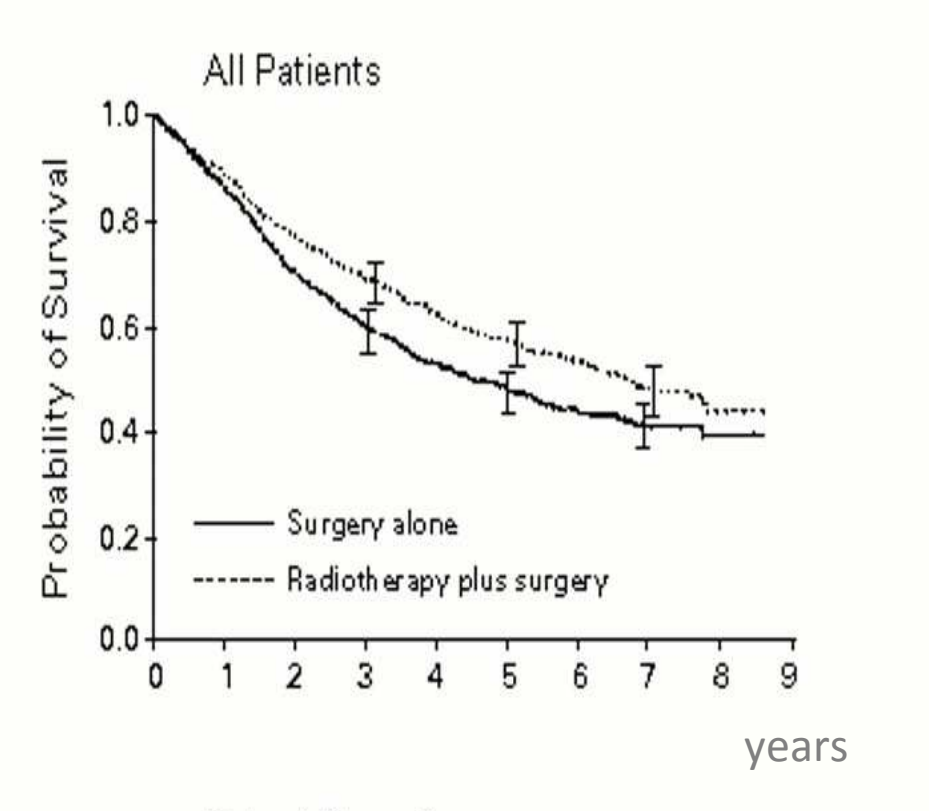
Hensikt

- ✓ Down-sizing / down-staging
- ✓ Bedre muligheten for radikal operasjon ved primært inoperabel tumor
- ✓ Redusere risiko for residiv i bekkenet
- ✓ Øke overlevelse ?

Litteratur - evidens

Increased survival with RT

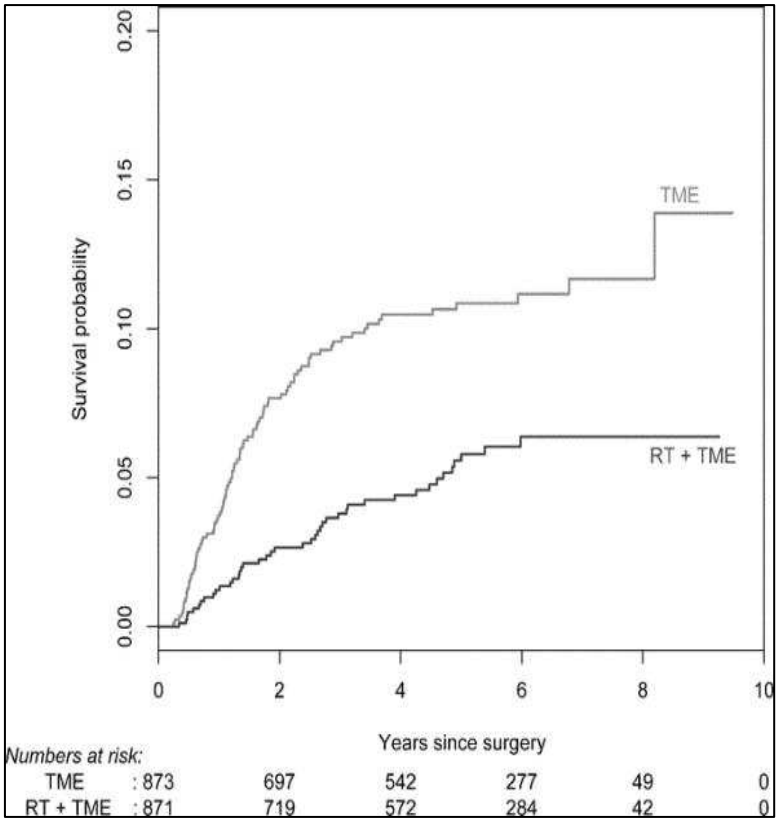
- 1186 patients with resectable rectal cancer (Stage I-III)
- Preoperative RT with 5Gy x 5 or surgery alone
- Significantly decreased local recurrence (11 vs 27%)
- Significantly increased survival:
  - 5 years (58 vs 48%)
  - 13 years (38 vs 30%)



Swedish Rectal Cancer Trial *NEJM* 1997
Folkesson *JCO* 2005

Preoperative RT superior to TME surgery alone

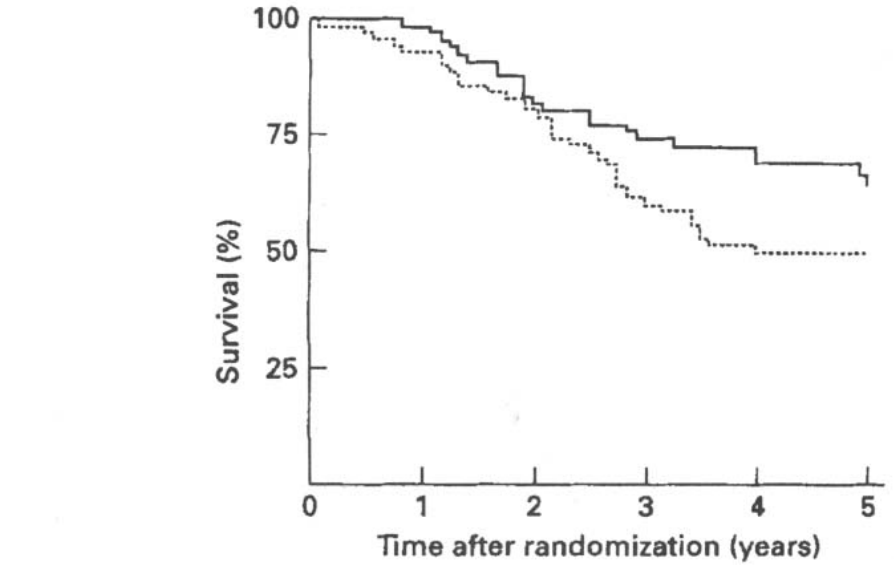
- 1861 patients with resectable rectal cancer
- Preoperative RT with 5 Gy x 5 or TME surgery alone
- Significant decrease in local recurrence after 5 years (5.6 vs 10.9%) – relative risk reduction of 49%
- No difference in survival



Peeters Annals of Surgery 2007

Postoperative CRT superior to surgery alone

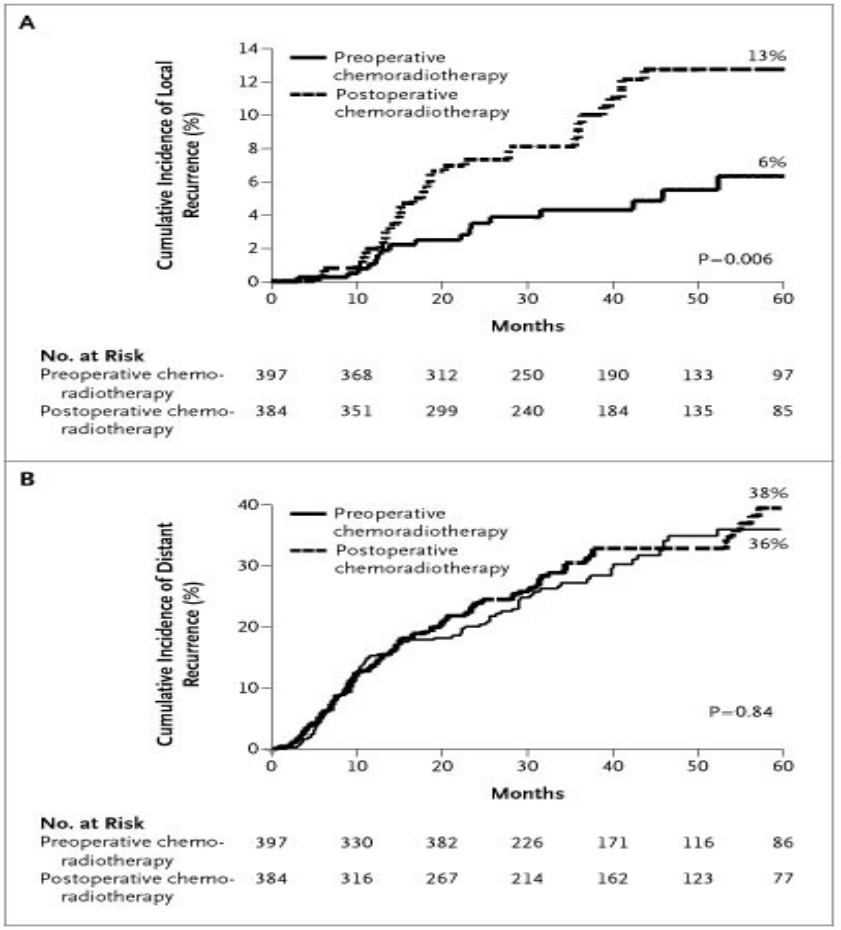
- 144 patients with Dukes B and C rectal cancer
- Postoperative CRT or surgery alone
- Significantly decreased local recurrence (12 vs 30%)
- Significantly better overall survival (64% vs 50%)



Tveit Br J Surg 1997

Preoperative CRT superior to postoperative CRT

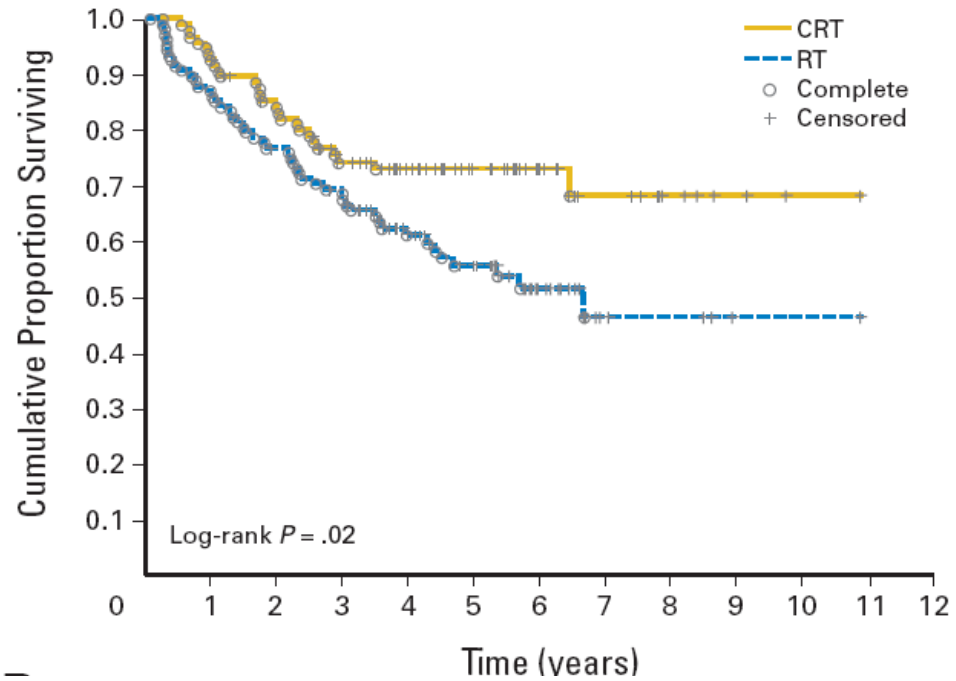
- 823 patients with locally advanced rectal cancer
- Pre- or postoperative CRT
  1,8 Gy x 28 + chemo
- Significantly decreased local recurrence (6% vs 13%) with preoperative RT
- No difference in survival
- Preoperative CRT associated with reduced late toxicity



Sauer *NEJM* 2004

Non-resectable cancers: Preoperative CRT superior to preoperative RT

- 207 patients - non-resectable or locally recurrent rectal cancer
- Preoperative CRT or RT
- Significantly improved local control with CRT (82% vs 67%)
- Signifiantly improved cancer specific survival (72% vs 55%) with CRT (figure)
- No benefit in overall survival



Brændengen JCO 2008

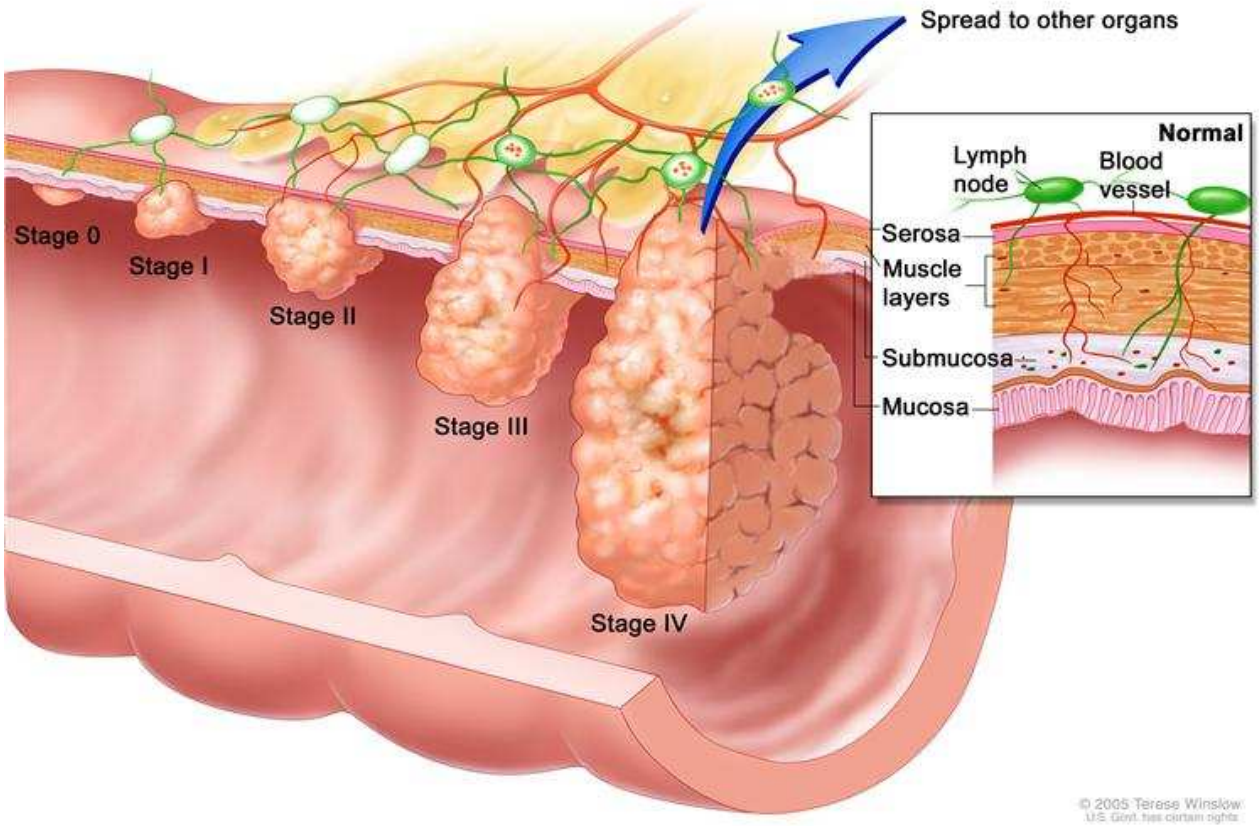
Preoperativ behandling av ca recti

Strålebehandling alene?

Kjemo-radioterapi?

Ca recti - staging

TNM very important - T3 (a-d), T4 (a-b) N+? M+?



Risiko grupper

Lav (good)	Middels (bad)	Høy (ugly)
T1-3a+b high	T3c+,T4b high	T4a*
T1-2 low	T3 low	crm+
N0+1	N-2	
crm-	crm- (>1 mm)	

*excl vagina

Indikasjon for strålebehandling

(Helsedirektoratets retningslinjer)

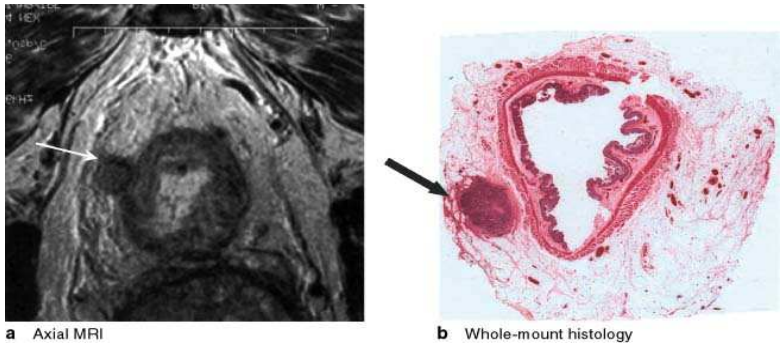
Diskuteres i multidisiplinært team

Preoperativ strålebehandling

- T4 svulst og/eller fiksert svulst
- Tumor eller malign lymfeknute ≤ 3 mm til MRF
- Residiv (ikke bestrålt)

Postoperativ strålebehandling

- T4 tumor påvist peroperativt
- Ikke fri reseksjonsrand
- CRM < 2 mm (histologi)
- Perforasjon av svulst eller tumornær tarm

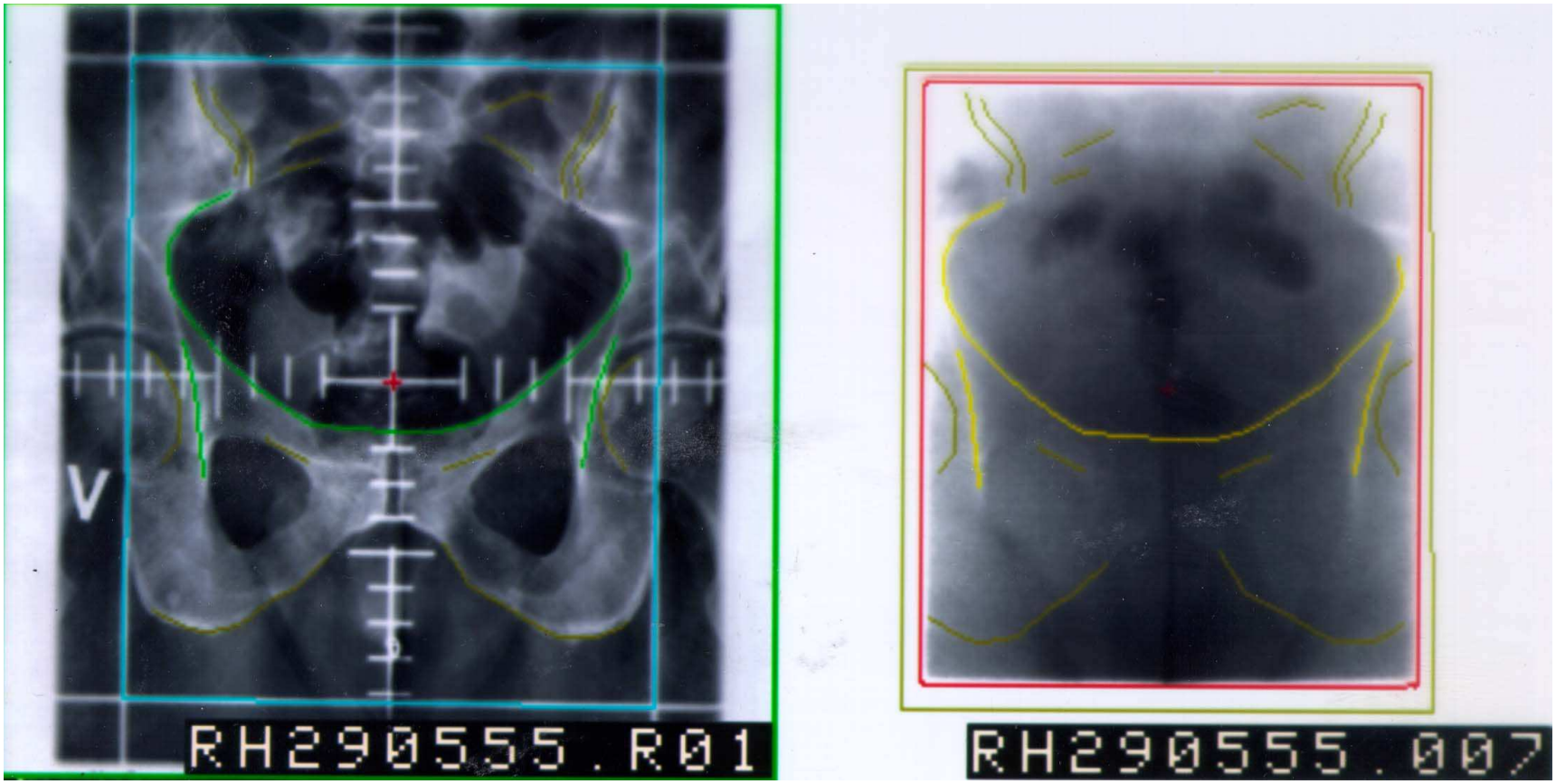


Involvert CRM på MR og på histologi.
Gina Brown Br J Surg 2003.

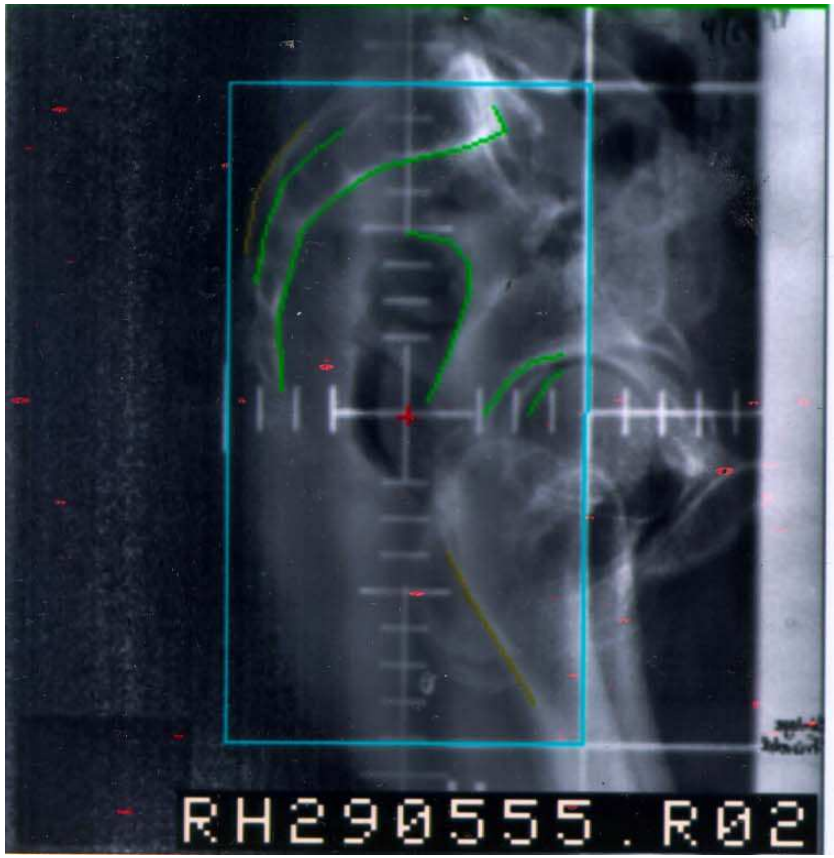
Planlegging av strålefelt

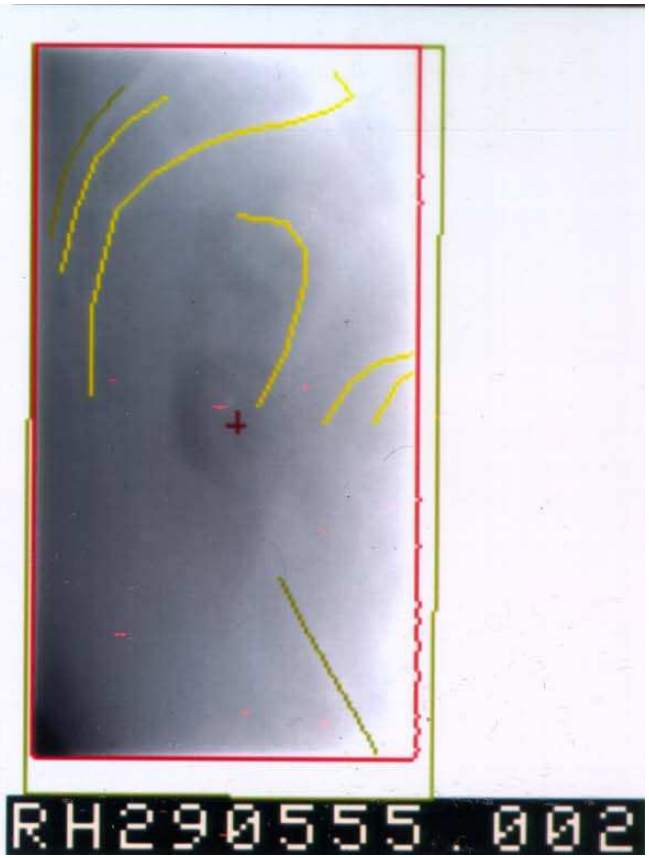
- ✓ CT tas for doseplanlegging
- ✓ Målvolum tegnes inn
  - tumor, patologiske lymfeknuter, og risiko-områder for residiv
- ✓ Marginer legges til
- ✓ Doseplan utarbeides
- ✓ Behandling gis med 3 (eller flere) felt
- ✓ Oftest i kombinasjon med kjemoterapi

Strålefelt – forfra/bakfra

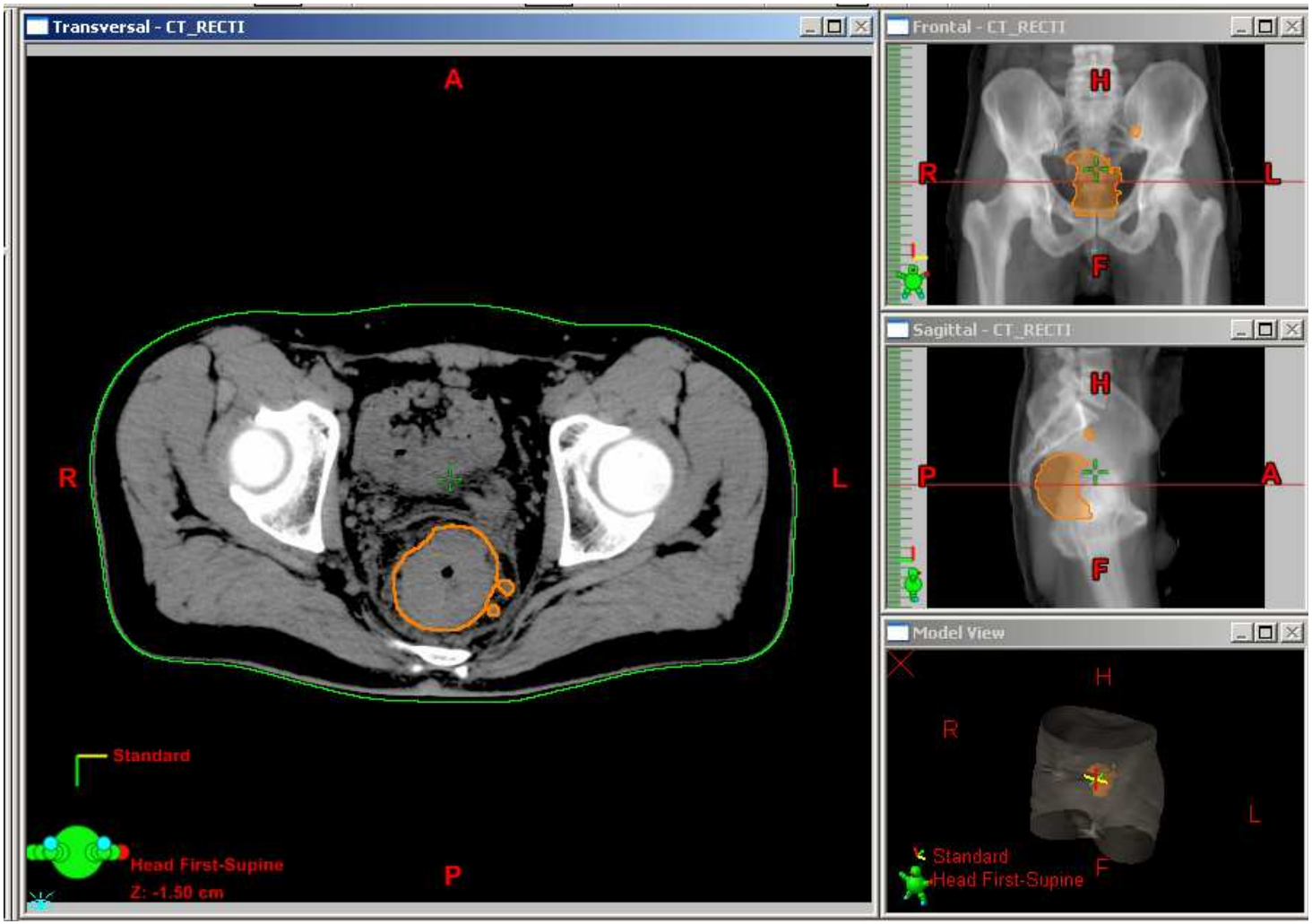


Strålefelt – fra siden

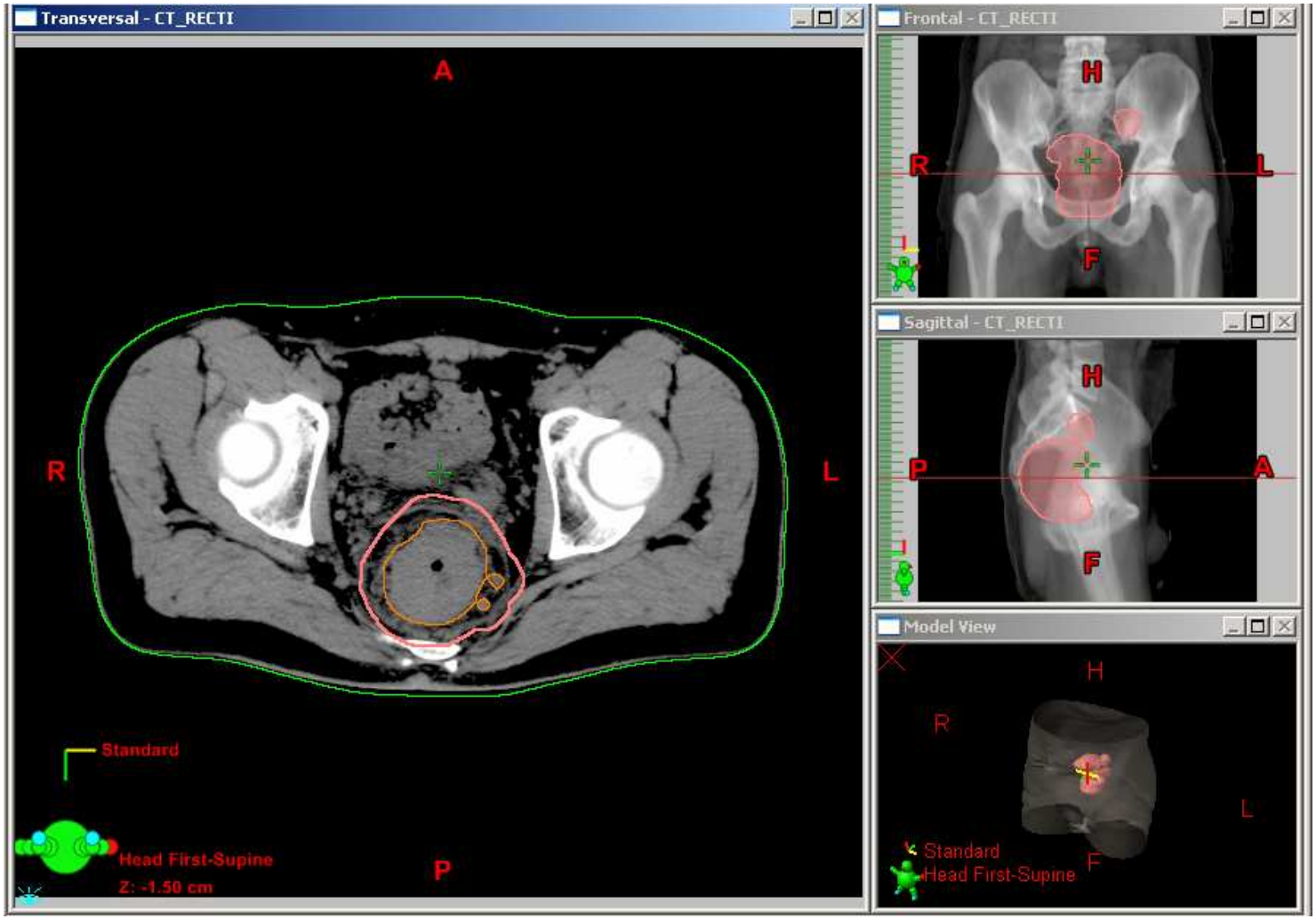




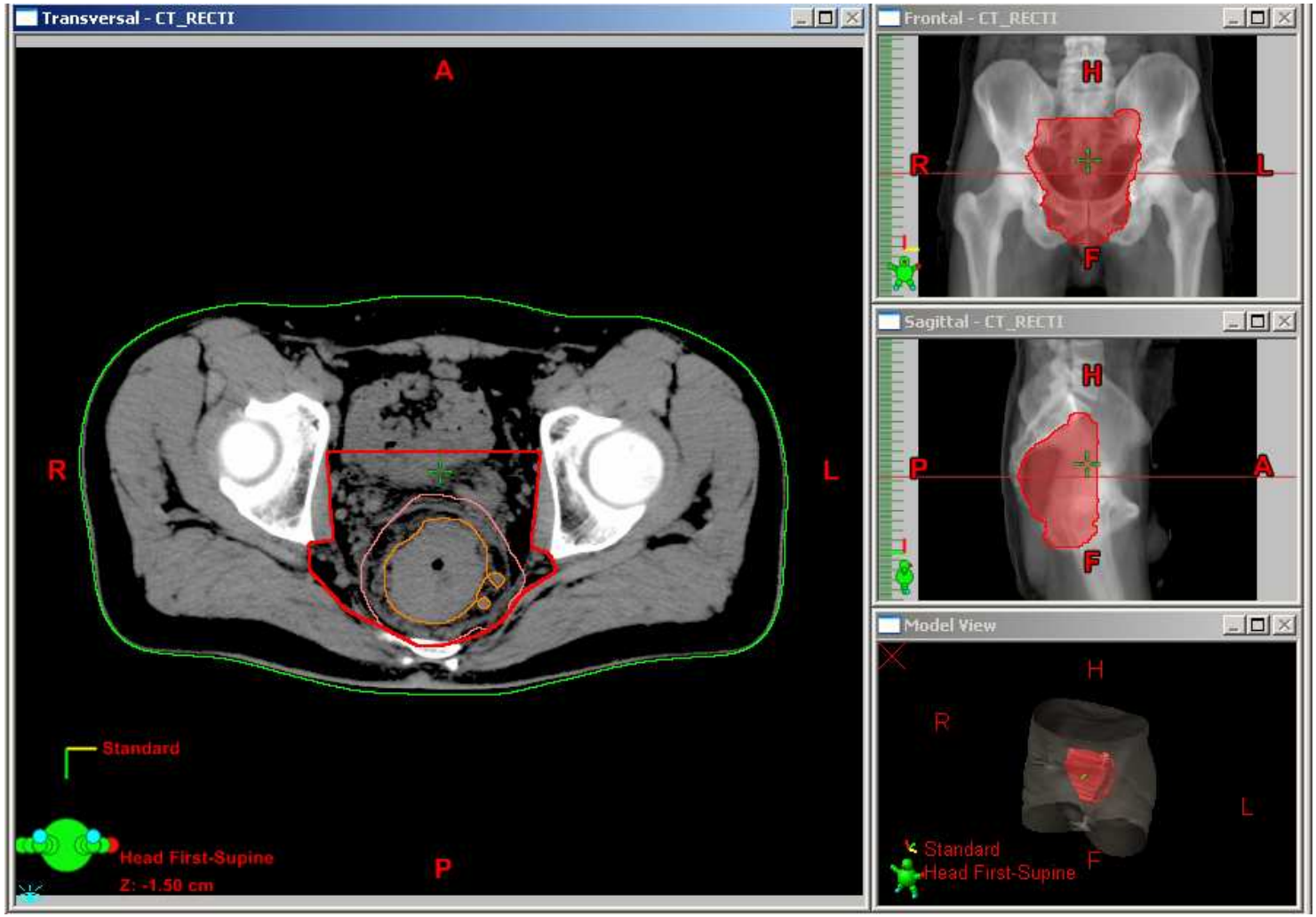
GTV – gross tumour volume – tegnes inn på CT



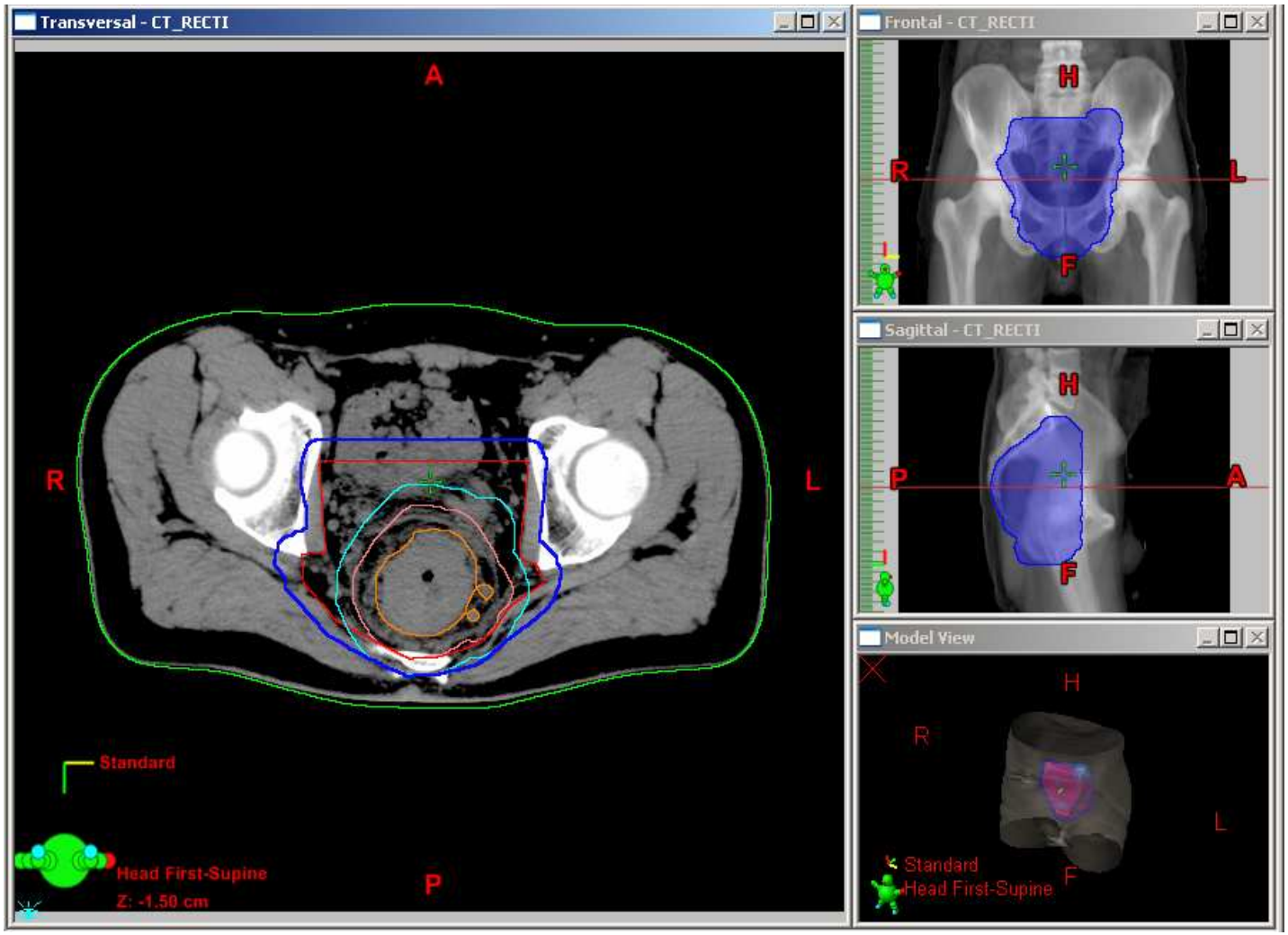
Marginer legges til



Risiko-områder for mikroskopisk spredning –clinical target volume (CTV) – tegnes inn

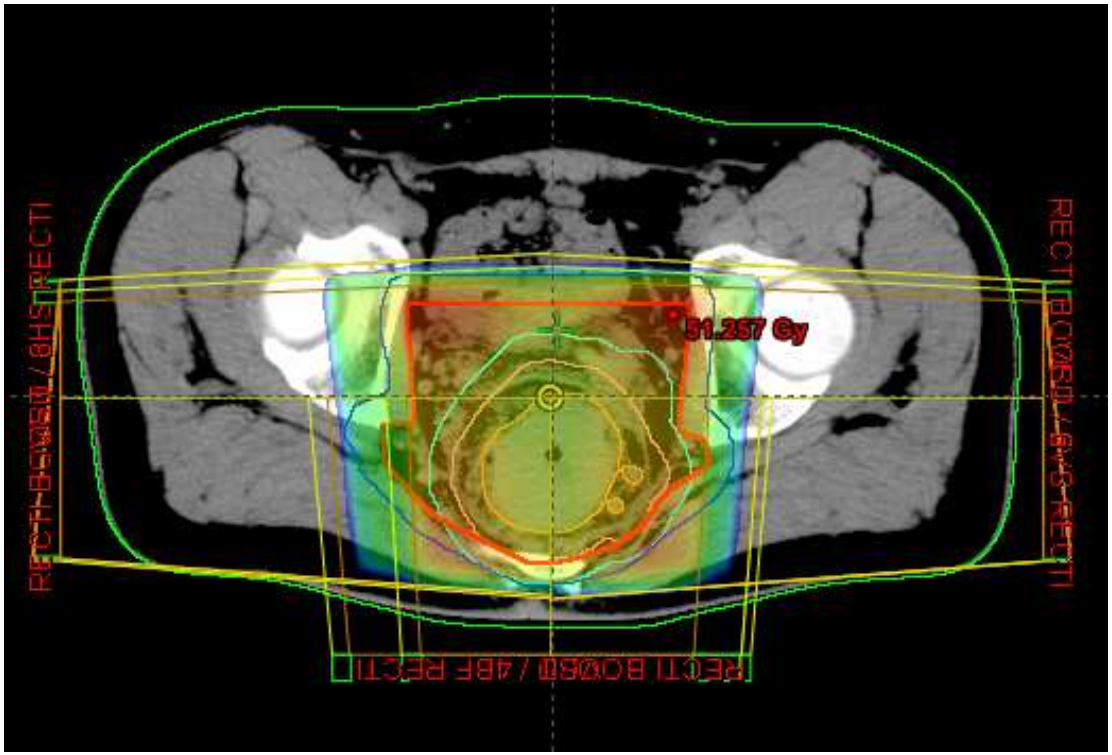


Marginer for indre bevegelse og innstillings-usikkerhet legges til

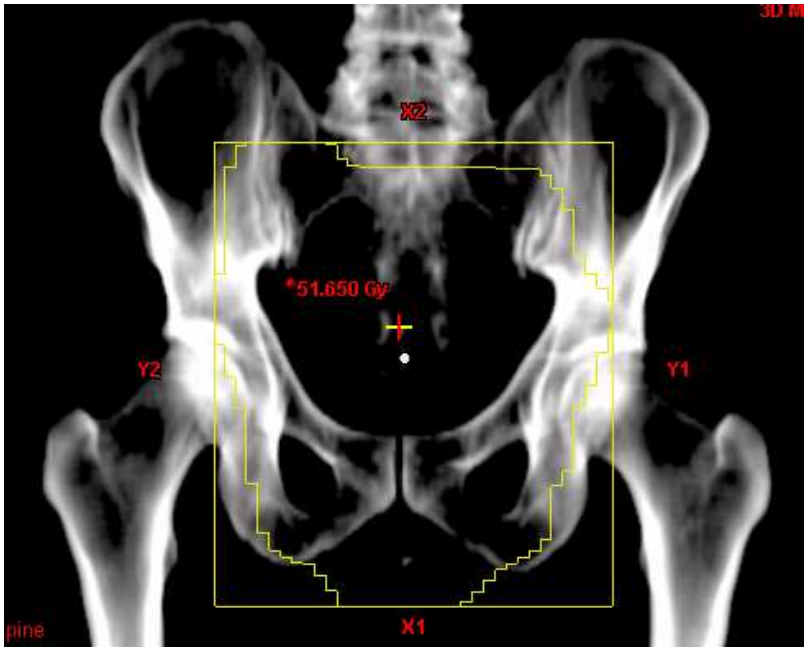


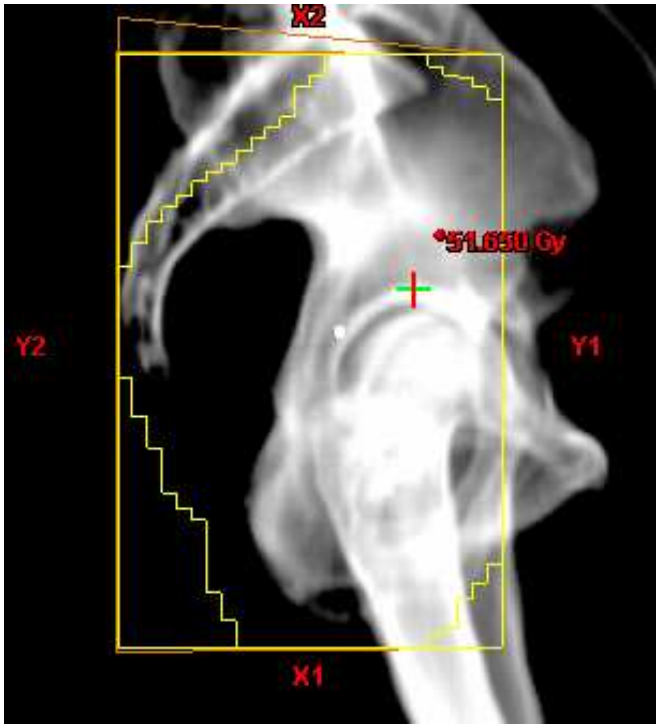
Utarbeide doseplan

- Som regel 3 felt (ett bakfra, ett fra hver side) – noen ganger flere
- Tilstrebe god dekning i målvolumet (tumor og risiko-organer)
- Unngå høye doser i normalvev og organer med risiko for stråleskade



Behandling, 3-felt teknikk



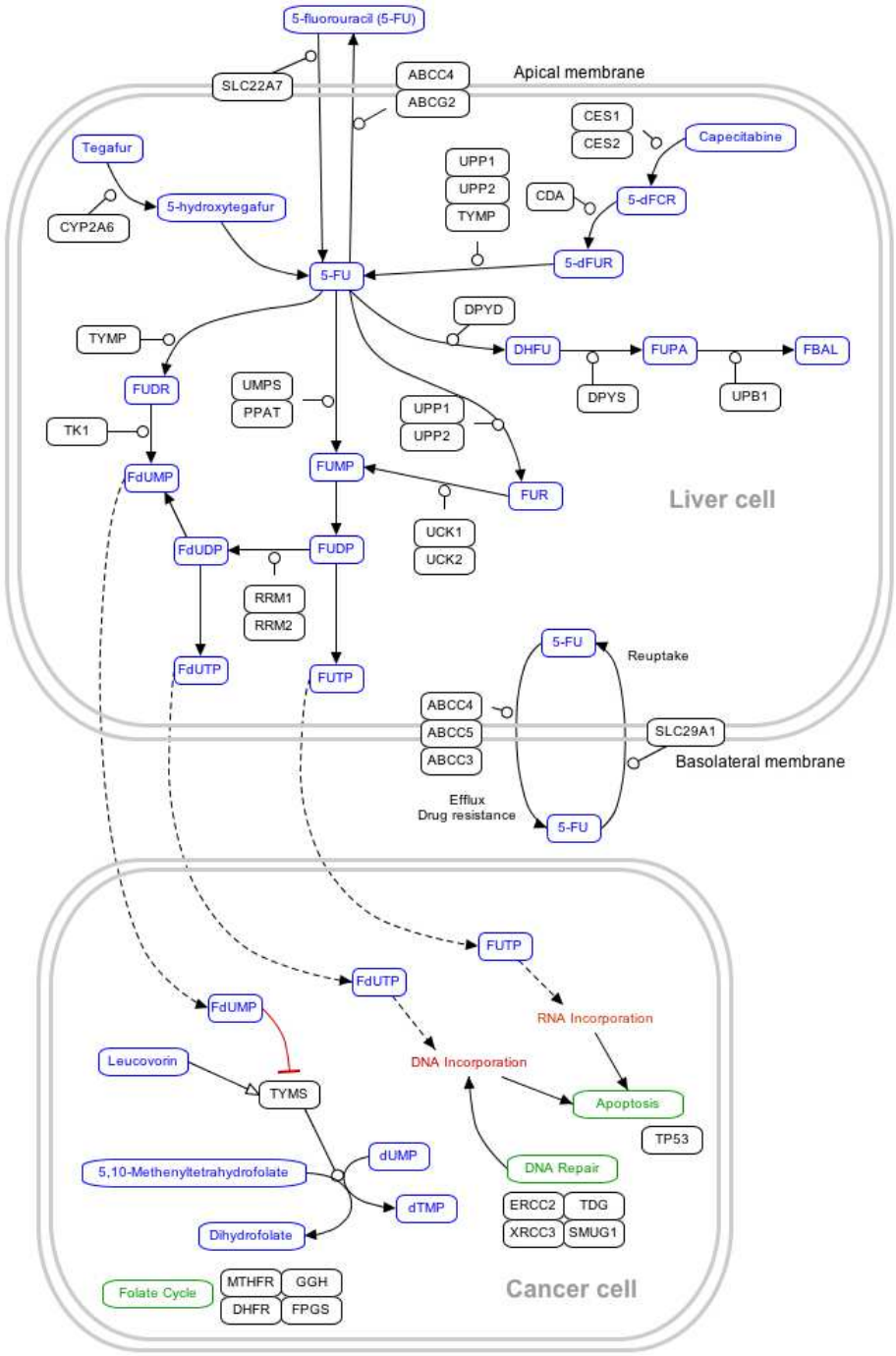


Gjennomføring av behandling

- ✓ 2 Gy x 25 (50 Gy)
  (1,8 Gy x 28, (50,4 Gy))
- ✓ Kombinert med kjemoterapi
  - FLv kur uke 1, 3 og 5 av behandlingen
  - Capecitabine (Xeloda®) tabletter mand-fred
- ✓ Kirurgi etter 6-10 uker

5 FU – Capecitabine

Komplisert metabolisme……



Ca recti – chemoradiotherapy (CRT)

- ✓ Infusional 5FU (Janjan , IJROBP 2000)
- ✓ Bolus 5 FU/leukovorin (Brændengen, JCO 2008)
- ✓ UFT/leukovorin (Pfeiffer, Acta Oncol 2008)
- ✓ Capecitabine (Liauw, Clin Colorectal Cancer 2008)
- ✓ Capecitabine/oxaliplatin - XELOX (Chau, JCO 2006)

- ✓ Irinotecan
- ✓ Cetuximab
- ✓ Bevacizumab
- ✓ Alimta (antifolat, reg i beh av mesotheliom)

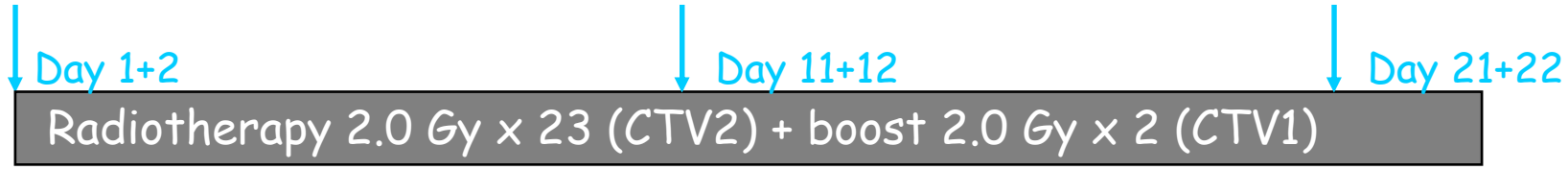
LARCS
Treatment schedule

Arm I RT

Radiotherapy 2.0 Gy x 23 (CTV2) + boost 2.0 Gy x 2 (CTV1)

Arm II CRT

Bolus 5 FU 400 mg/m^2 +
Leucovorin 100mg i.v.



Both arms: Surgery between 3-6 weeks (max 8 weeks) after last radiotherapy treatment

Arm II: Adjuvant chemotherapy for 16 weeks, start 4-6 weeks postoperatively ("Nordic schedule" 5 FU 500 mg/m^2 + leucovorin 100 mg i.v. day 1+2 every 2 weeks)
Also allowed for patients in arm I (RT)

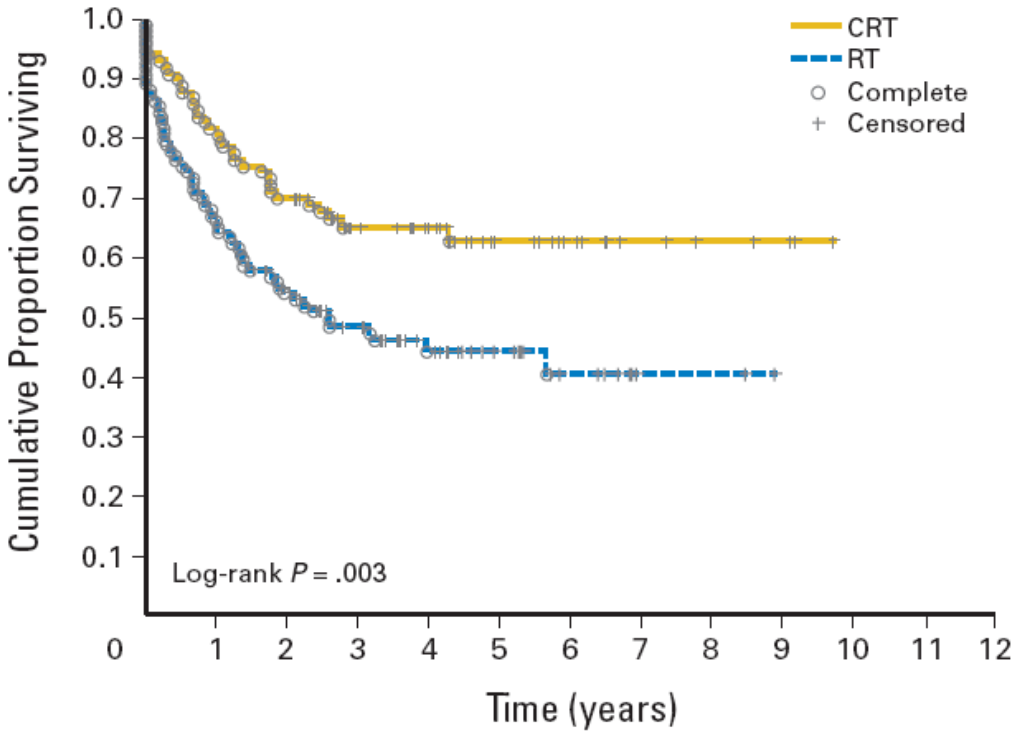
LARCS

- ✓ Preoperativ CRT gir bedre "downsizing/downstaging", økt resektabilitet og bedre lokal kontroll ved ikke-resektabel rektumcancer, sammenlignet med RT alene
- ✓ Etter median oppfølging på 5 år var det statistisk signifikant forskjell i TTF og CsS
- ✓ Det var ingen postoperativ mortalitet (30 dager)
- ✓ Det var mere grad 3-4 akutt toxicitet i CRT gruppen, men behandlingen ble generelt godt tolerert
- ✓ Ingen tydelig forskjell i sen toxicitet

LARCS

Time To Treatment failure (TTF)

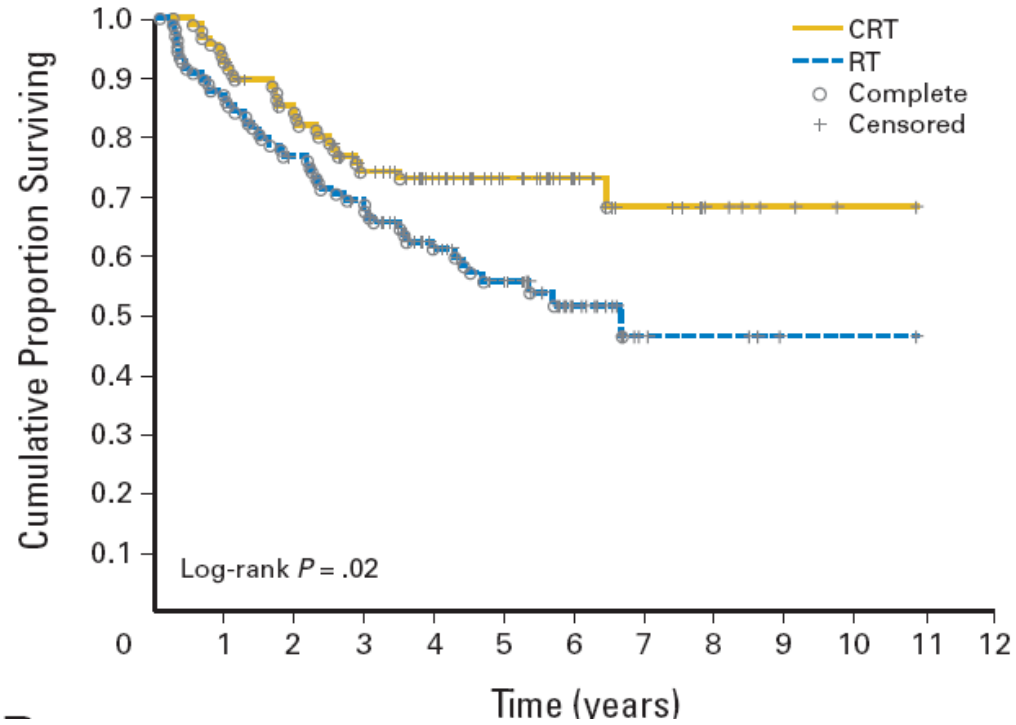
63% versus 44% (5 years)



LARCS

Cancer specific Survival (CsS)

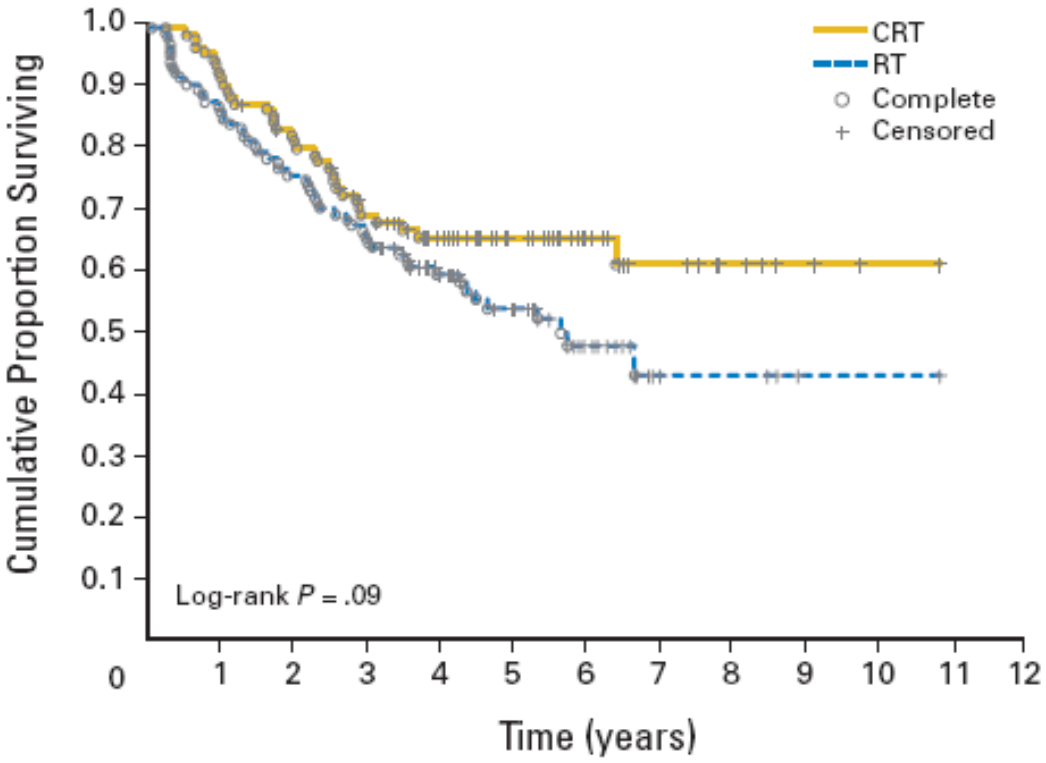
72% versus 55% (5 years)



LARCS

Overall survival (OS)

66% versus 53% (5 years)



Akutte bivirkninger under behandling

- ✓ Hudsårhet perianalt
  - Spesielt ved lave strålefelt
- ✓ Økt hyppighet avføring, diare
- ✓ Dysuri og hyppig vannlatning
- ✓ Menopause

- ✓ Ved stenoserende tumor, obs ødem ved oppstart strålebehandling, vurdere stomi, evt stent
- ✓ Stråle-enteritt, ødem i tynntarm, paralytisk ileus
- ✓ Ved kombinasjon med kjemoterapi, obs DPD-mangel (benmargssvikt, mucositt, enteritt)

Ca recti og strålebehandling – fokus på bivirkninger

PERGAMON

European Journal of Cancer 39 (2003) 587–594

European Journal of Cancer

www.ejconline.com

Quality of life during radiotherapy for rectal cancer

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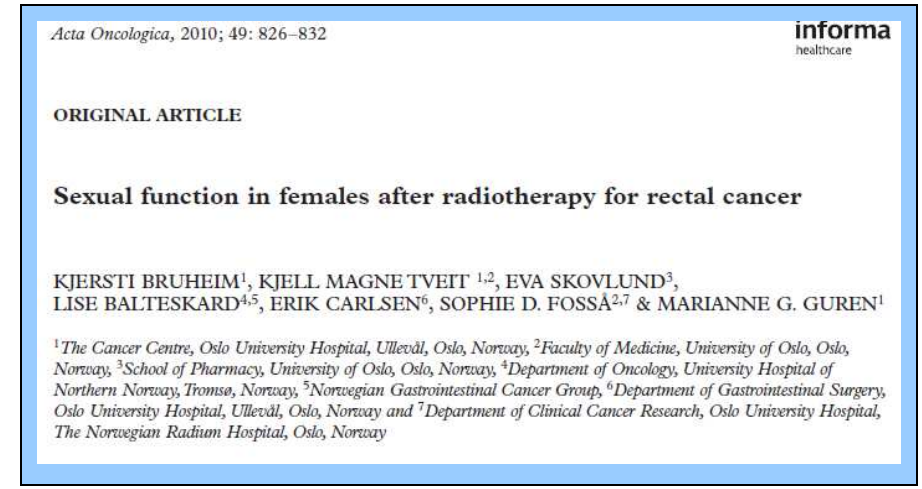

Acta Oncologica, 2010; 49: 826–832

informa healthcare

ORIGINAL ARTICLE

Sexual function in females after radiotherapy for rectal cancer

KJERSTI BRUHEIM[1], KJELL MAGNE TVEIT [1,2], EVA SKOVLUND[3], LISE BALTESKARD[4,5], ERIK CARLSEN[6], SOPHIE D. FOSSÅ[2,7] & MARIANNE G. GUREN[1]

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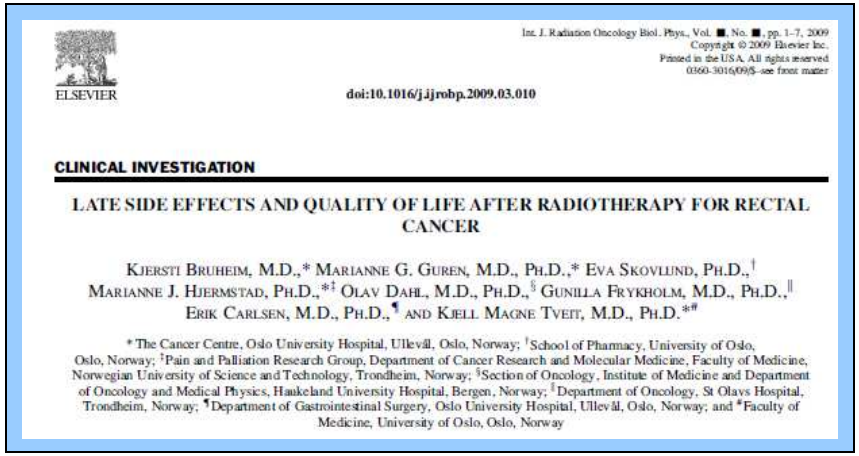

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CLINICAL INVESTIGATION

LATE SIDE EFFECTS AND QUALITY OF LIFE AFTER RADIOTHERAPY FOR RECTAL CANCER

KJERSTI BRUHEIM, M.D.,* MARIANNE G. GUREN, M.D., PH.D.,* EVA SKOVLUND, PH.D.,† MARIANNE J. HJERMSTAD, PH.D.,*‡ OLAV DAHL, M.D., PH.D.,§ GUNILLA FRYKHOLM, M.D., PH.D.,‖ ERIK CARLSEN, M.D., PH.D.,¶ AND KJELL MAGNE TVEIT, M.D., PH.D.*#

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doi:10.1016/j.ijrobp.2009.03.075

CLINICAL INVESTIGATION Rectum

SEXUAL FUNCTION IN MALES AFTER RADIOTHERAPY FOR RECTAL CANCER

KJERSTI BRUHEIM, M.D.,* MARIANNE G. GUREN, M.D., PH.D.,* ALV A. DAHL, M.D., PH.D.,†‡ EVA SKOVLUND, PH.D.,§ LISE BALTESKARD, M.D., PH.D.,¶ ERIK CARLSEN, M.D., PH.D.,‖ SOPHIE D. FOSSÅ, M.D., PH.D.,†‡ AND KJELL MAGNE TVEIT, M.D., PH.D.*‡

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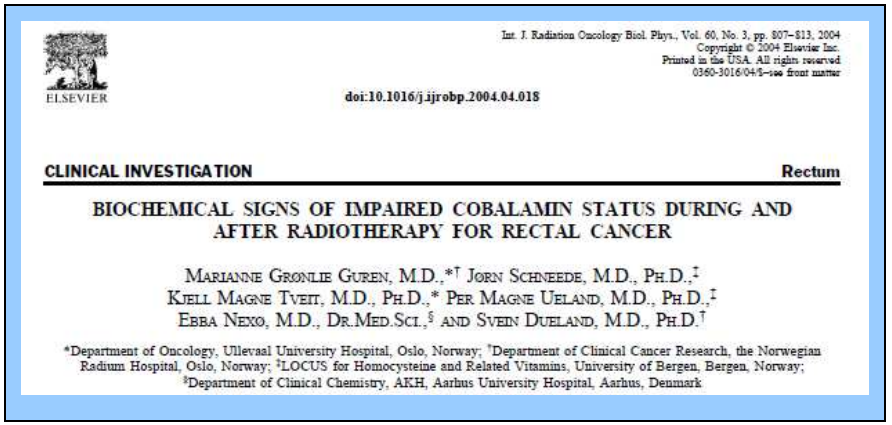

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0360-3016/04/$–see front matter

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doi:10.1016/j.ijrobp.2004.04.018

CLINICAL INVESTIGATION Rectum

BIOCHEMICAL SIGNS OF IMPAIRED COBALAMIN STATUS DURING AND AFTER RADIOTHERAPY FOR RECTAL CANCER

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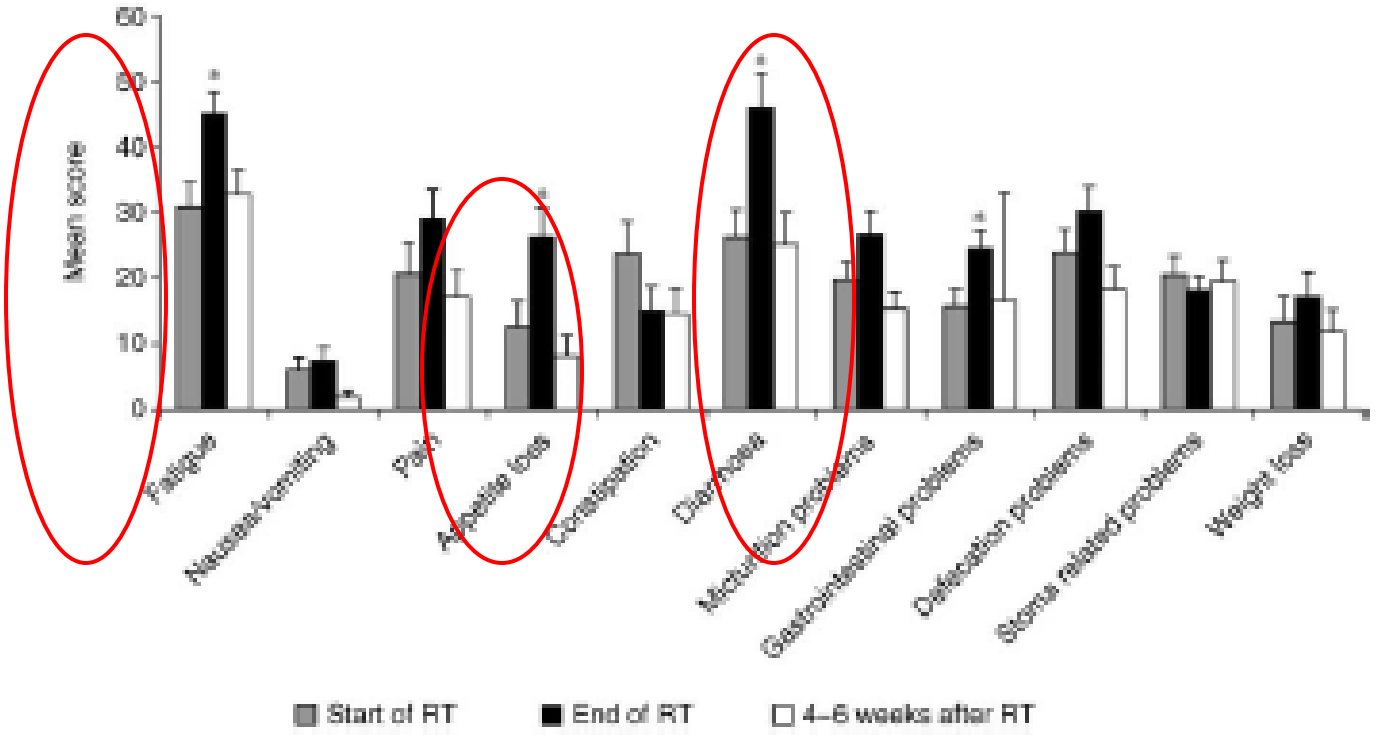
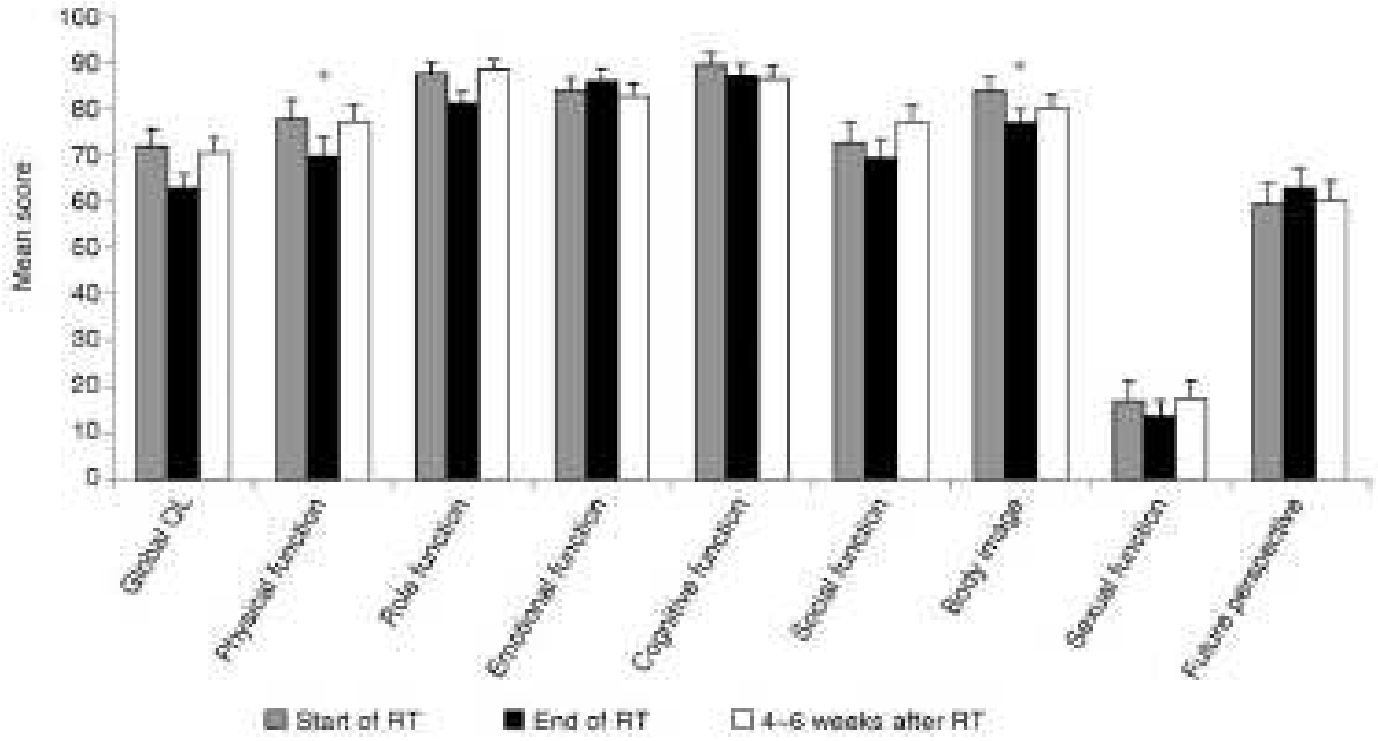
Økt "fatigue", dårligere appetitt, mer diare ved slutten av strålebehandling



Symptom score tilbake til utgangsverdi etter 4-6 uker

Guren MG, Eur J Cancer 2003

Ingen forskjell i funksjon score under strålebehandling



Guren MG, Eur J Cancer 2003

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CLINICAL INVESTIGATION

LATE PATIENT-REPORTED TOXICITY AFTER PREOPERATIVE RADIOTHERAPY OR CHEMORADIOTHERAPY IN NONRESECTABLE RECTAL CANCER: RESULTS FROM A RANDOMIZED PHASE III STUDY

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EJC

Health-related quality of life (HRQoL) after multimodal treatment for primarily non-resectable rectal cancer. Long-term results from a phase III study

Morten Brændengen [a,b,], Kjell M. Tveit [a,c], Marianne J. Hjermstad [a,d], Hemming Johansson [b], Åke Berglund [e], Yvonne Brandberg [b], Bengt Glimelius [b,e]*

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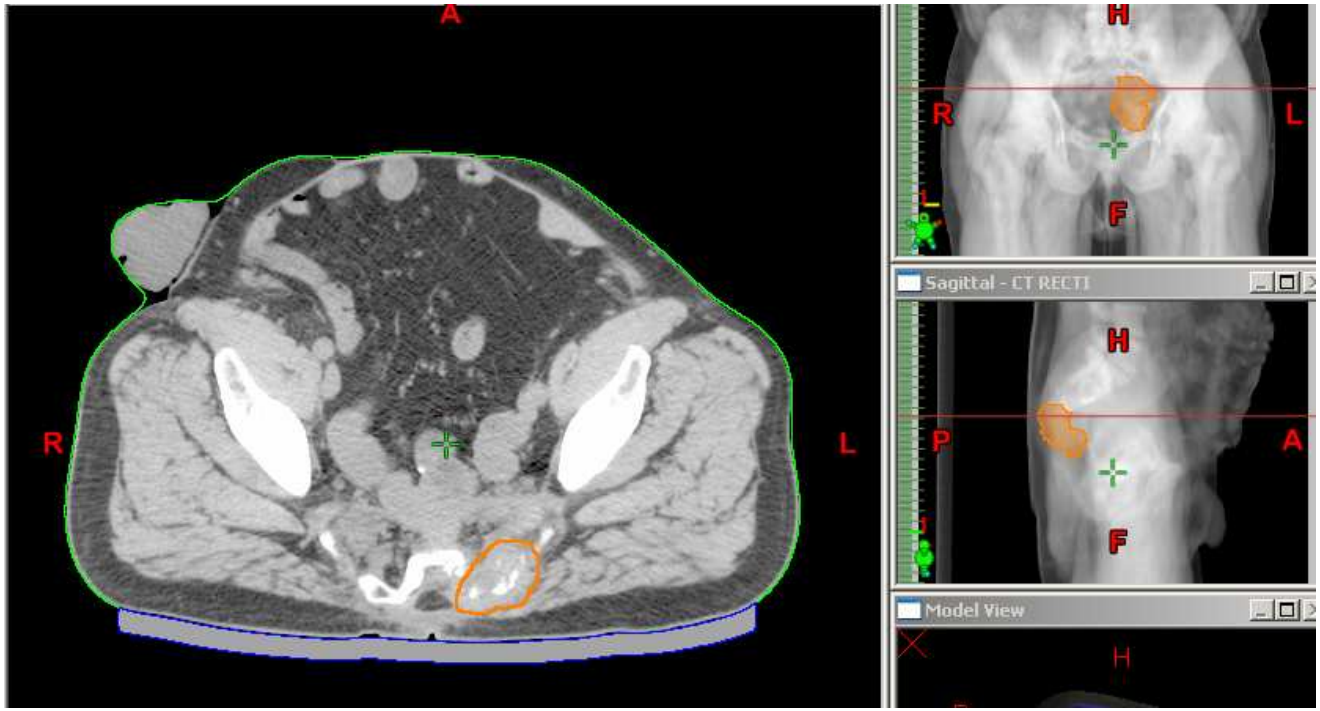
LARCS

Sen toxicitet - HRQoL

- ✓ Fecal inkontinens and erektil dysfunksjon er vanlig etter lang preoperativ (C)RT for LARC (ikke-resektabel T4).
- ✓ Våre data indikerer at sen-toxicitet fra tarm sees oftere i CRT gruppen, selv om det ikke er stat sign forskjellig.
- ✓ Tolkning av QLQ C-30 viste ingen stat sign forskjeller mellom RT og CRT gruppene.

Generelt , selv med redusert sosial funksjonsstatus og mere diare, rapporterte pasientene livskvalitet på lik linje med referansepopulasjonen fra normal befolkningen.

Rebestråling



- Rebestråling i tidligere bestrålt område
- Begrenset volum
- 40-45 Gy, 2 daglige fraksjoner, kjemoterapi (?)

Palliativ strålebehandling

- ✓ Symptomgivende inoperabel tumor, feks ved samtidig metastaser
- ✓ 3 Gy x 10-12, tumor med marginer, evt annen fraksjonering

- ✓ Pågående studie undersøker effekt på symptomlindring (PallRad)
  - Smerter, blødning, livskvalitet

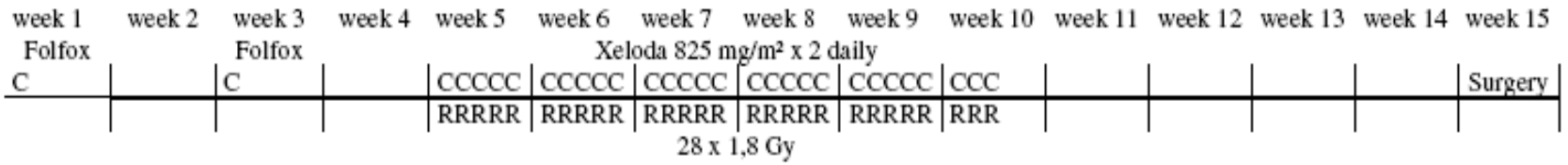
- ✓ Hjernemetastaser eller skjelettmetastaser

Veien videre

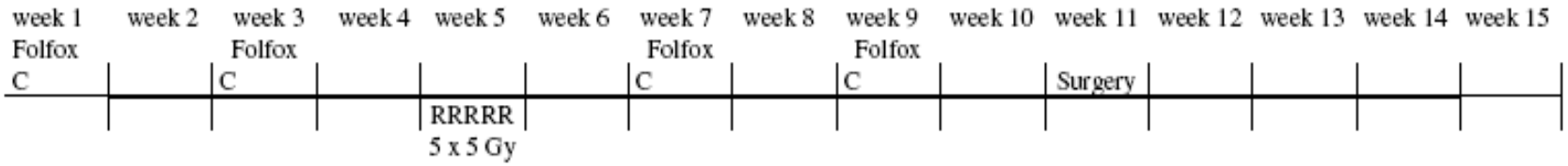
- ✓ Kombinasjonsbehandling med kjemoterapi?
- ✓ Tillegg av cetuximab/bevacizumab?
- ✓ Neoadjuvant kjemoterapi, og/eller postoperativt
- ✓ Bedre strålebehandlingsteknikker (IMRT)
- ✓ PET/CT
  - Inntegning av GTV og påvisning av fjernmetastaser
  - Image guiding (IGRT)

5 Gy x 5 ?
Økt dose-intensitet av kjemoterapi med SCRT enn med CRT (metastatisk sykdom)

RTCT



Chemotherapy + short course RT



C – chemotherapy, R - radiotherapy

Radu et al, Radiother Oncol 2008

RAPIDO studien

Rectal cancer **A**nd **P**re-operative **I**nduction therapy followed by **D**edicated **O**peration

Bakgrunn for studien

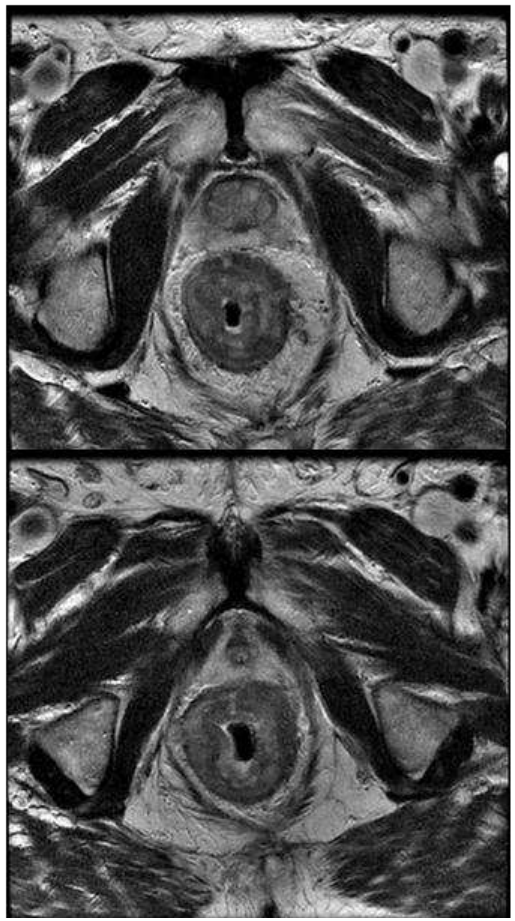
- Gode resultater mtp lokal kontroll med kjemoradioterapi og kirurgi
- Uendret høy risiko for metastaser
- Systemisk behandling med kjemoterapi før kirurgi – andre kreftformer
- Perioperativ kjemoterapi god effekt ved EORTC-EPOC (levermetastaser), MAGIC (ventrikkelcancer)
- Oxaliplatin og Xeloda (CapOx, Xelox) effektivt ved kolorektal kreft
- Ønsker rask lokal behandling av primærtumor
- Tidlig strålebehandling, 5 Gy x 5, tillate tid til tumorskrumping
- Erfaring med kjemoterapi og 5 Gy x 5 ved rektumcancer og synkrone metastaser (klinisk erfaring, M1 studien)

RAPIDO

Inklusjonskriterier:

MR av god kvalitet

- T4a
- T4b
- EMVI+
- N2 (>=4 pat glandler)
- CRM+ (<= 1 mm)
- LN+



RAPIDO

Standard arm

Preoperativ kjemoradioterapi (1.8 Gy x 28 med capecitabine)	(u1-6)
TME-kirurgi etter 6-8 uker	(u14-16)
Post-operativ capecitabine/oxaliplatin x 8	(u20-41)

VS.

Eksperimentell arm

Preoperativ radioterapi 5 Gy x 5	(u1)
capecitabine/oxaliplatin x 6	(u3-18)
TME-kirurgi	(u22-24)

Endepunkter, oppstart

- Primært endepunkt
  - Disease-free survival etter 3 år
- Sekundære endepunkt
  - Overall survival, CRM neg, pCR
  - QoL, lokalt residiv

- Pasienter n=885
- Multisenter studie
  - Sverige, Nederland, Norge, andre?
- Planlagt oppstart OUS ultimo oktober 2011

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CLINICAL INVESTIGATION

DELINEATION OF GROSS TUMOR VOLUME (GTV) FOR RADIATION TREATMENT PLANNING OF LOCALLY ADVANCED RECTAL CANCER USING INFORMATION FROM MRI OR FDG-PET/CT: A PROSPECTIVE STUDY

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