

Retningslinier for visitation, diagnostik, behandling og kontrol af cancer corporis uteri

Version 2: 7.4.2009

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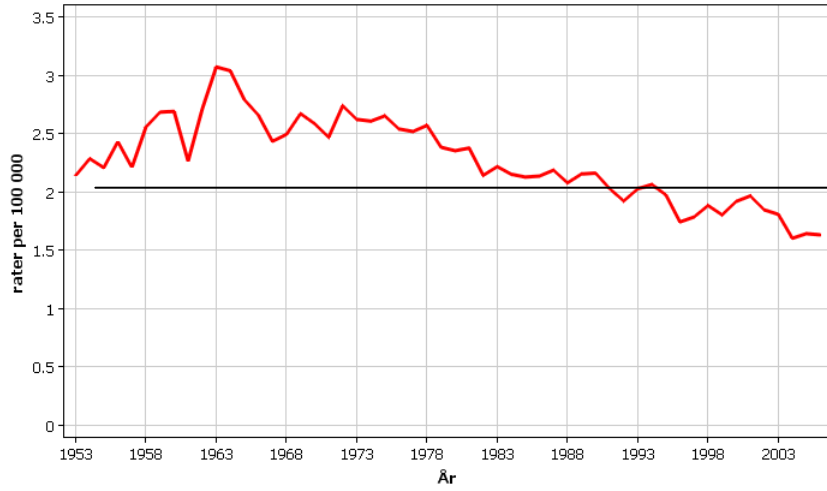
Hindsgavl Guidelines møde 2009

Lian Ulrich

Retningslinier for visitation, diagnostik, behandling og kontrol af cancer corporis uteri

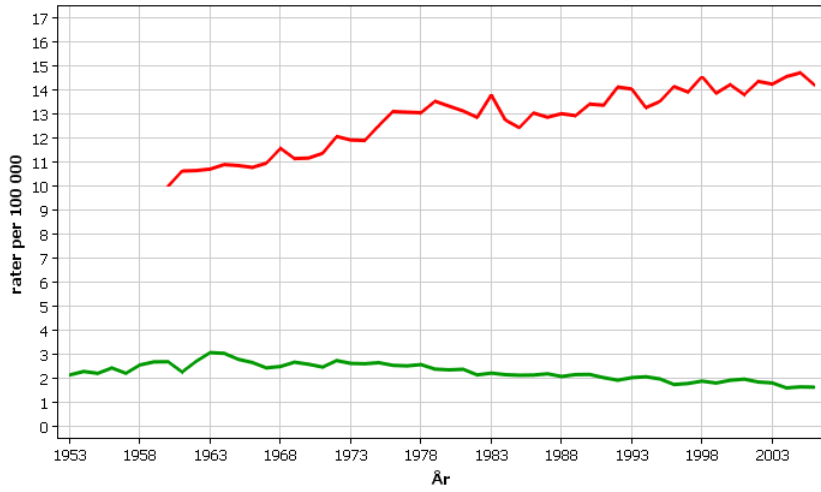
- Baggrund
- Hvad er nyt og hvad er kontroversielt?
- Lymfeknudefjernelse
- Kemo- eller stråleterapi
- Centralisering

Norden
Livmoder
Dødelighed: ASR (W) alder (0-85+)



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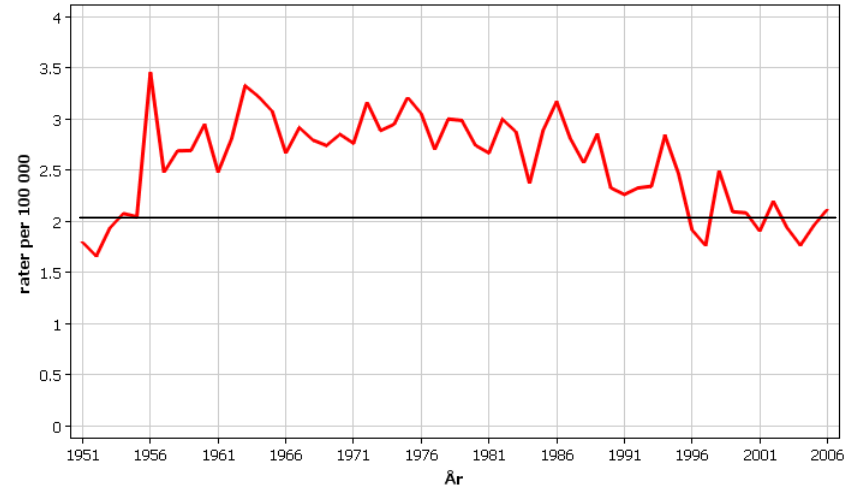
Norden
Livmoder
ASR (W) alder (0-85+)



■ Incidents- ■ Dødelighed-

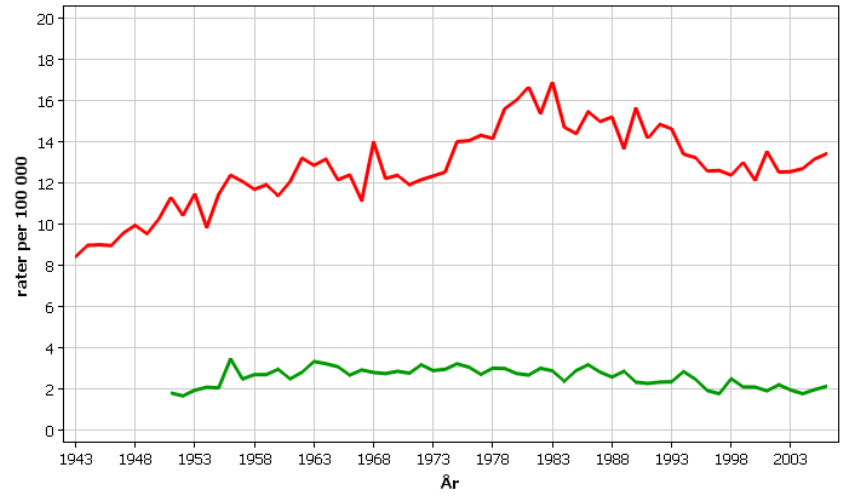
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Danmark
Livmoder
Dødelighed: ASR (W) alder (0-85+)



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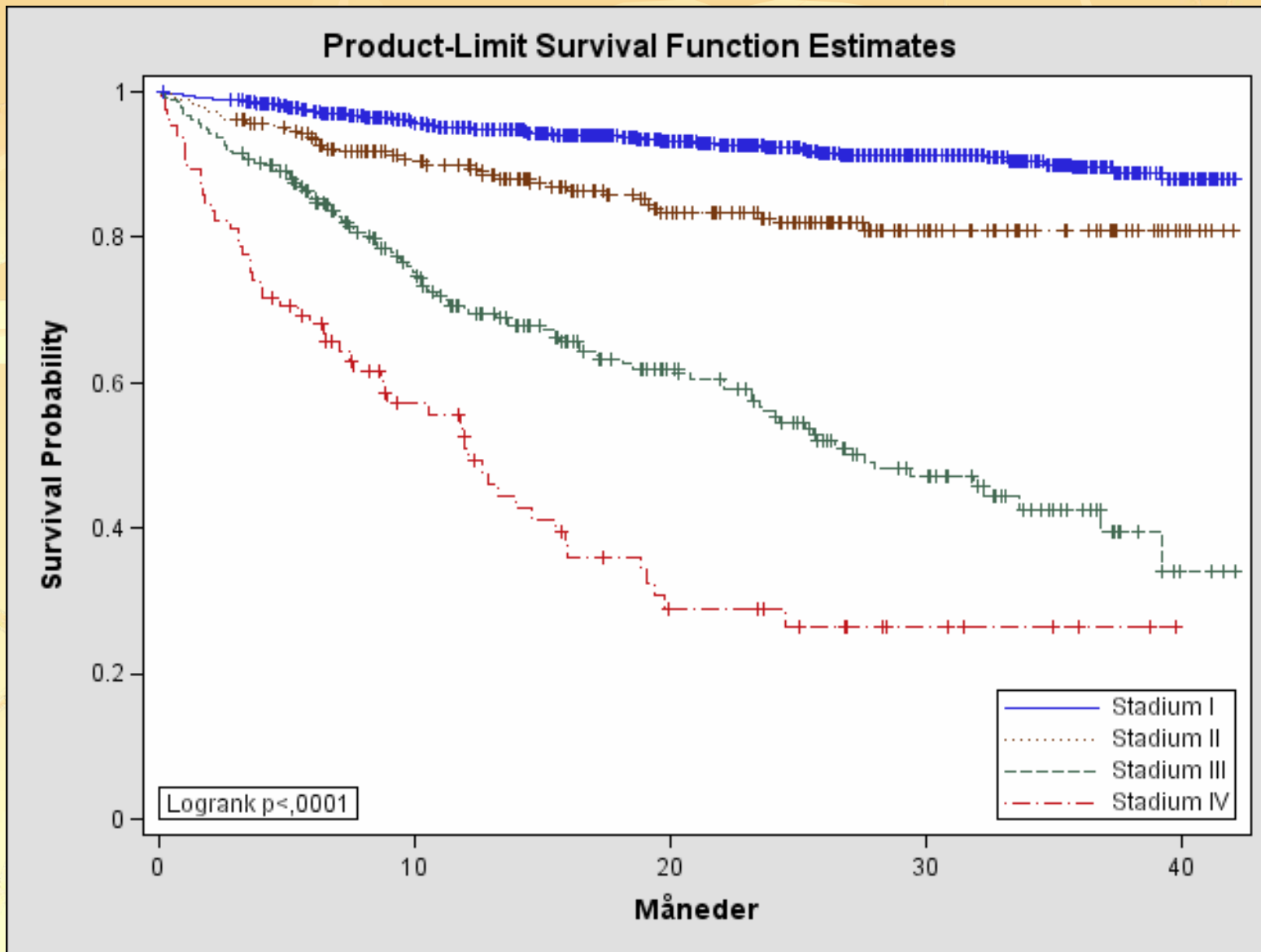
Danmark
Livmoder
ASR (W) alder (0-85+)



■ Incidents- ■ Dødelighed-

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Figur 6.4.a Corpuscancer stratificeret på stadie



Figur 6.4.b Corpuscancer st. I stratificeret på risikogruppe

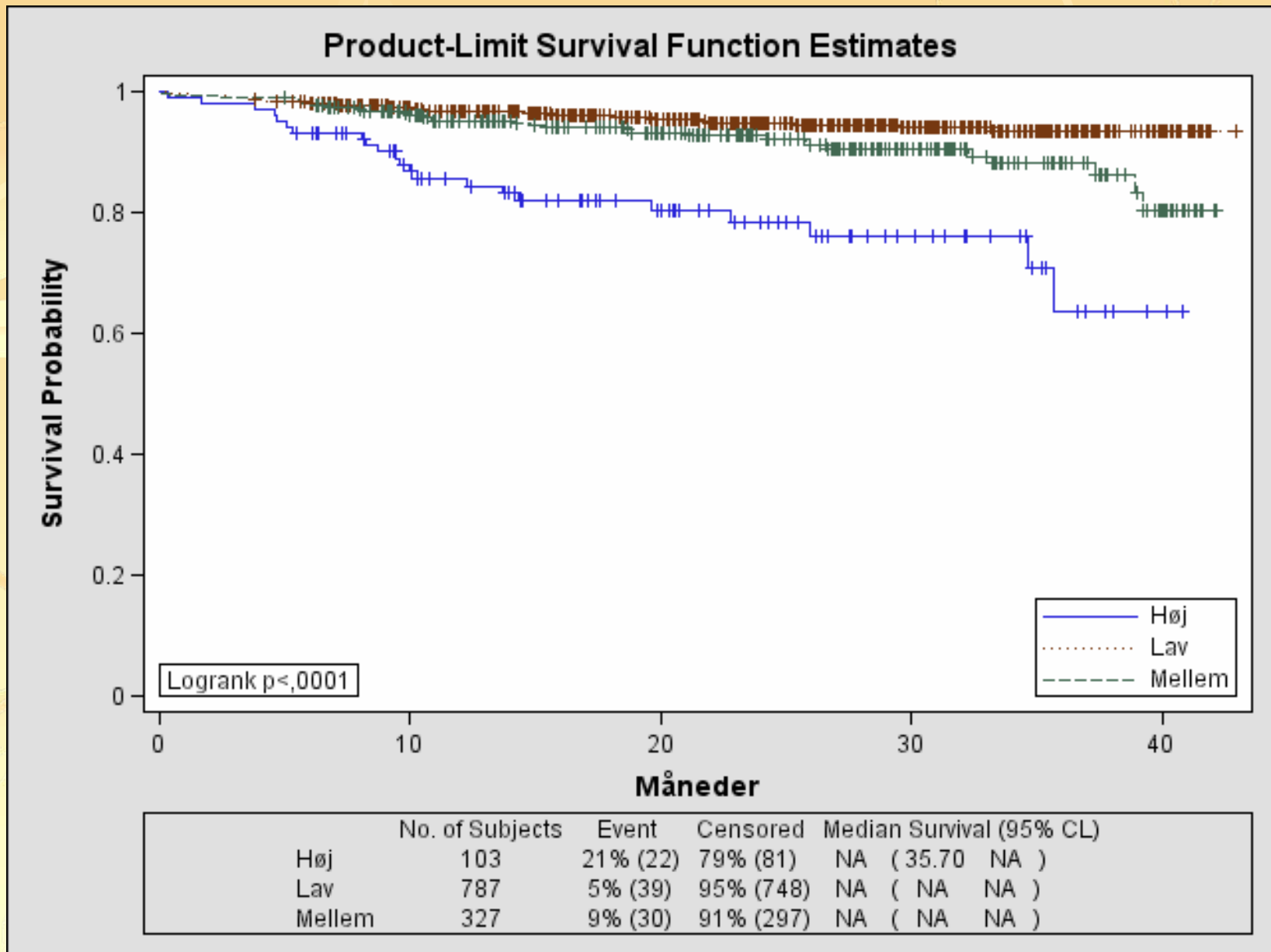
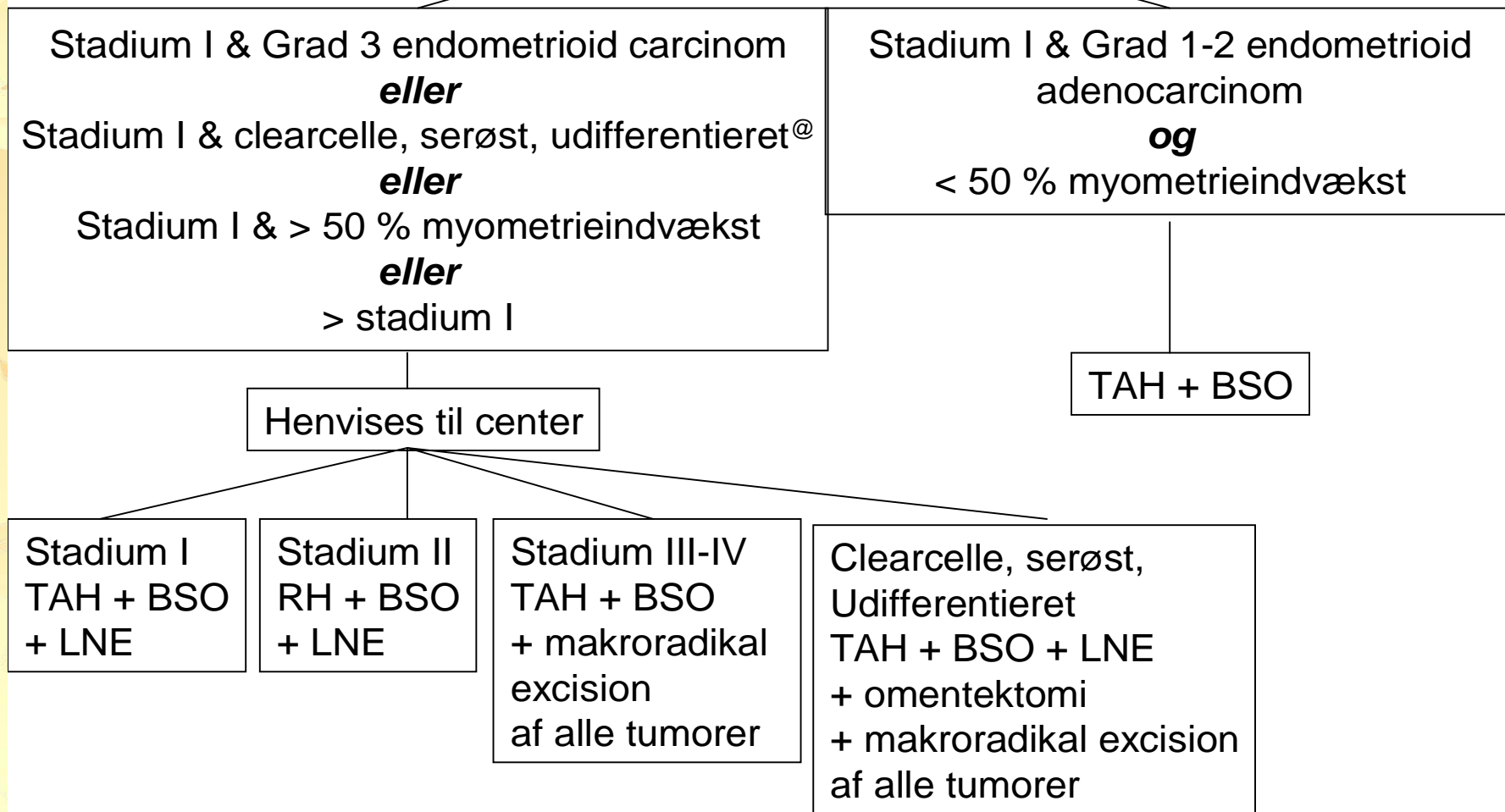


Diagram 1

Gamle guidelines

Endometriecancer



Endometriecancer Henvises til Gyn-Onk Center

Nye guidelines

Stadium I & Grad 3 endometrioidt carcinom
eller
Stadium I & clearcelle, serøst, udifferentieret
eller
Stadium I & > 50 % myometrieindvækst
eller
> stadium I

Stadium I & Grad 1-2 endometrioidt
adenocarcinom
og
< 50 % myometrieindvækst

TAH + BSO

Stadium I
TAH¹ + BSO¹
+ LNE¹

Stadium II
RH¹ + BSO
+ LNE

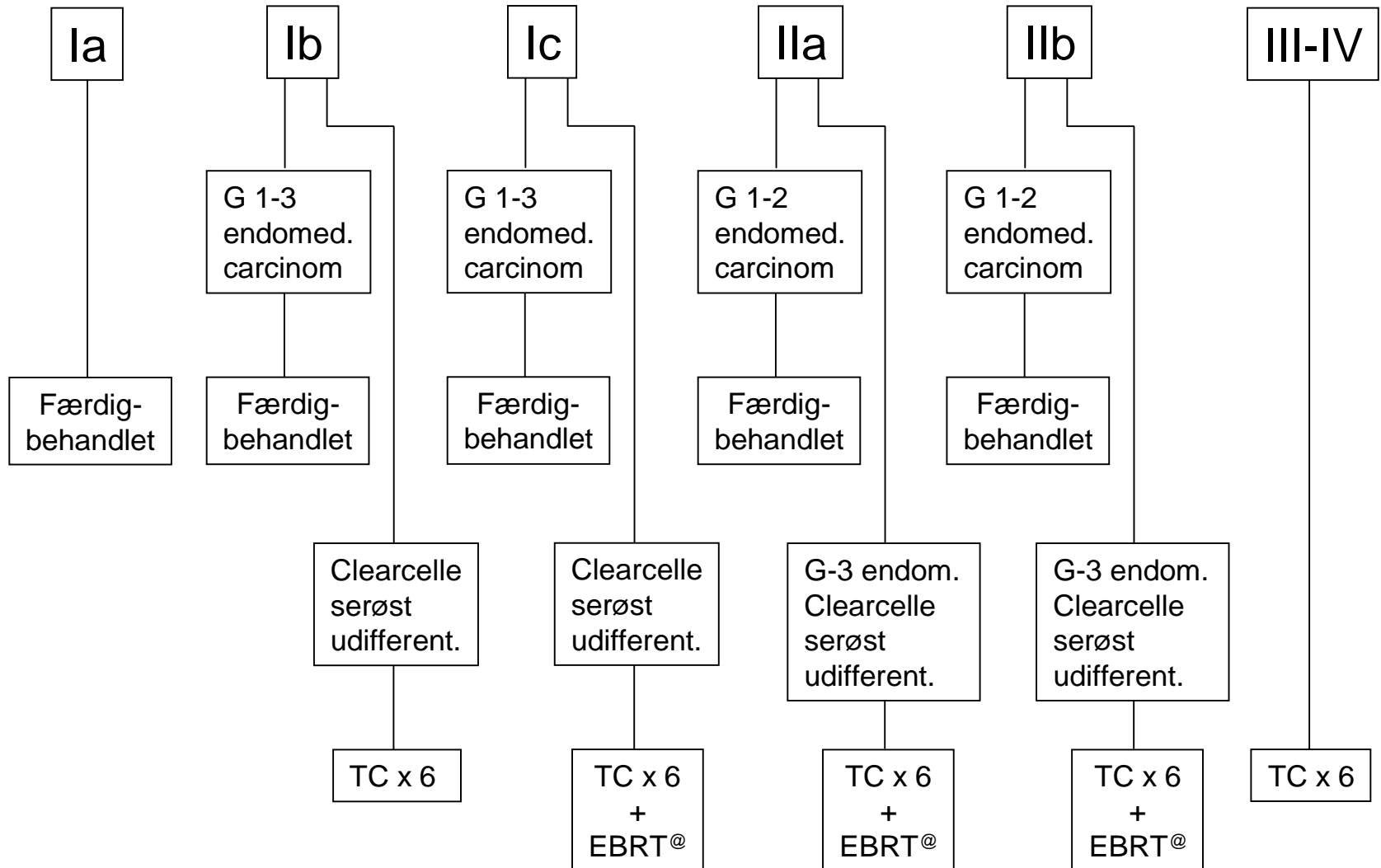
Stadium III-IV
TAH + BSO
+ optimal
debulking

Clearcelle, serøst,
Udifferentieret
TAH + BSO (+LNE for stadium 1a)
+ omentektomi
+ optimal debulking

Diagram 1

1. TAH: Total abdominal hysterectomi. BSO: Bilateral salpingoophorektomi. LNE: Lymfeknudejernelse. RH: Radikal hysterectomi

Kirurgisk stadium efter den anbefalede kirurgi



Postoperativ adjuverende behandling samt non-kirurgisk behandling af st. III-IV

Nye guidelines Kirurgisk stadium efter den anbefalede kirurgi

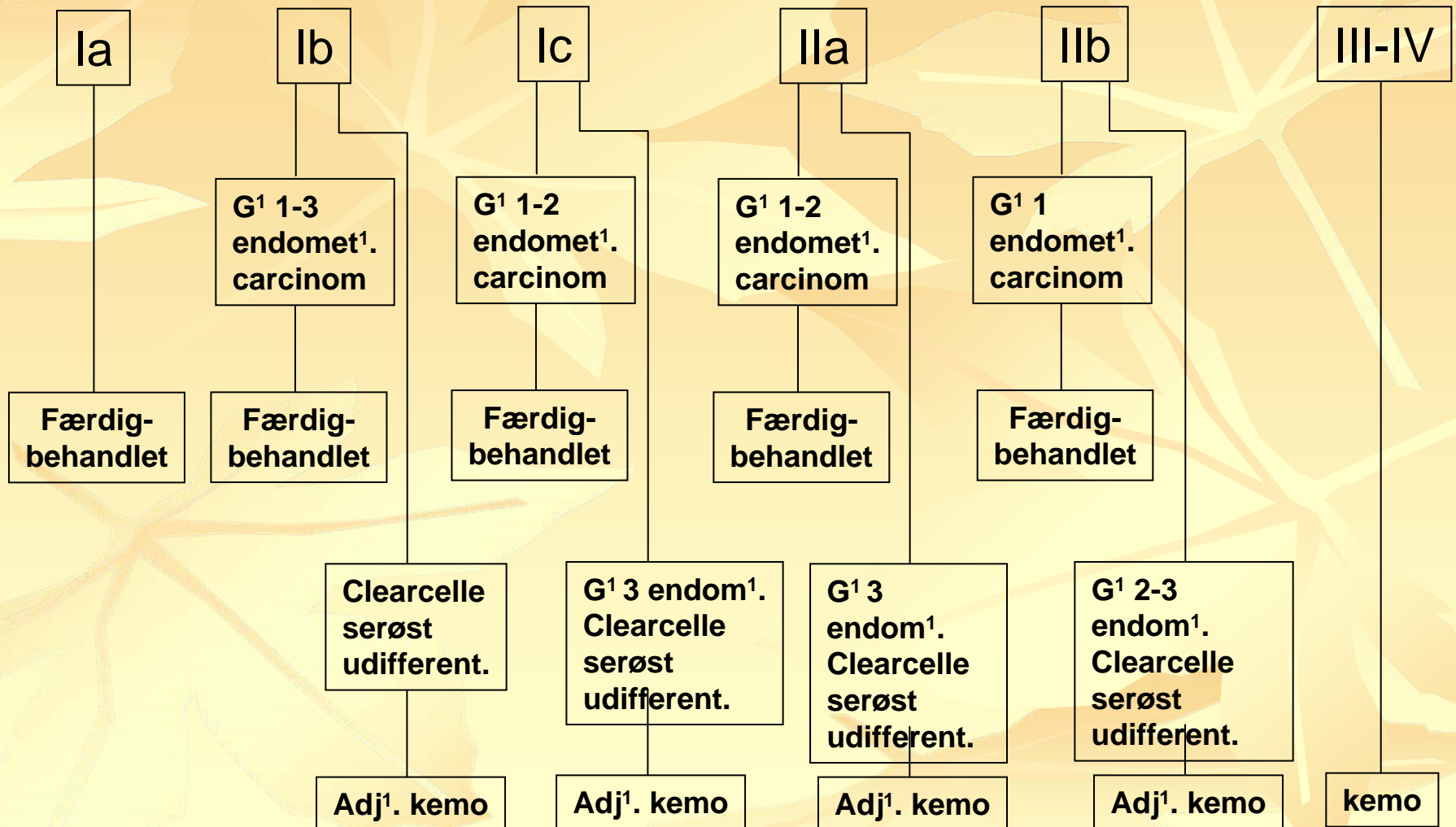


Diagram 2

Stadium	Risiko profil	Postoperativ behandling
Ia	Grad 1-3, endometrioidt carcinom Clearcelle, serøst & udifferentieret carcinom	Ingen efter behandling
Ia	Clearcelle, serøst & udifferentieret carcinom LNE ikke foretaget / ikke optimal LNE	Individuel vurdering: Reop. eller kemoterapi
Ib	Grad 1-2, endometrioidt carcinom	Ingen efter behandling
Ib	Grad 3, endometrioidt carcinom LNE ikke foretaget / ikke optimal LNE	Reoperation vedr. LNE Ingen efter behandling
Ic	Grad 1-2, endometrioidt carcinom LNE ikke foretaget / ikke optimal LNE	Reoperation vedr. LNE Ingen efter behandling
Ic	Grad 1-2, endometrioidt carcinom LNE foretaget: node-negativ	Ingen efter behandling
Ic	Grad 3, endometrioidt carcinom	Adj. kemoterapi
Ib-c, II	Clearcelle, serøst & udifferentieret carcinom Uanset procentmæssig andel	Adj. kemoterapi

Stadium	Risiko profil	Postoperativ behandling
---------	---------------	-------------------------

Ila Grad 1-2, endometrioidt carcinom
RH samt LNE foretaget: node-negativ
Ingen efter behandling

Iib Grad 1 endometrioidt carcinom
RH samt LNE foretaget: node-negativ
Ingen efter behandling

Ila Grad 1-2, endometrioidt carcinom
RH og/eller LNE ikke foretaget / ikke optimal LNE
Individuel vurdering

Iib Grad 1 endometrioidt carcinom
RH og/eller LNE ikke foretaget / ikke optimal LNE
Individuel vurdering

Iib Grad 2 endometrioidt carcinom
Adj. kemoterapi

Ila-Iib Grad 3, endometrioidt carcinom
Adj. kemoterapi

III-IV Radikalt opereret
postop. kemoterapi

III-IV Ikke radikalt opereret / ikke opereret
kemoterapi

@: EBRT giver ingen overlevelses gevinst men bedre lokal kontrol. EBRT har betragtlige bivirkninger. Patienter der ikke kan tåle både adjuvant kemoterapi og strålebehandling, bør tilbydes kemoterapi.

Pelvine lymfeknudemetastaser (%) GOG33

Invasions dybde	G1 Pelvis	G1 Aorta	G2 Pelvis	G2 Aorta	G3 Pelvis	G3 Aorta
N	180		288		153	
Ingen	0 (0%)	0 (0%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)
1/3 N=281	3 (3%)	1 (1%)	7 (5%)	5 (4%)	5 (9%)	2 (4%)
2/3 N=115	0 (0%)	1 (5%)	6 (9%)	0 (0%)	1 (4%)	0 (0%)
Over 2/3 (N=139)	2 (11%)	1 (6%)	11 (19%)	15 (23%)	22 (34%)	15 (23%)

Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987; 60: 2035-41

Incidens af pelvine lymfeknudemetastaser

Invasions dybde	Grad 1 (%)	Grad 2 (%)	Grad 3 (%)	Total (%)
Ingen	0/49 (0%)	2/45 (4%)	0/16 (0%)	2/110 (2%)
<50%	0/26 (0%)	10/96 (10%)	3/42 (7%)	13/164 (8%)
>50%	0/5 (0%)	7/41 (17%)	8/29 (28%)	15/75 (20%)
Total	0/80 (0%)	19/182 (10%)	11/87 (13%)	30/349 (9%)

Chi DS, Barakat RR, Palayekar MJ, Levine DA, Sonoda Y, Alektiar K, Brown CL, Abu-Rustum NR. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. Int J Gynecol Cancer 2008;18:269–273.

Surgical staging

Table 1

Guidelines for surgical management of endometrial cancer at Mayo Clinic, Rochester, Minnesota (2004–2006)

Hysterectomy

Bilateral salpingo-oophorectomy

Peritoneal cytology

Bilateral pelvic and para-aortic lymphadenectomy

Para-aortic dissection up to renal vessels

Excision of gonadal vessels at insertions (optional)

Omit lymphadenectomy if no disease beyond corpus and

(1) Endometrioid (grade 1 or 2), MI \leq 50%, and PTD \leq 2 cm; or

(2) Endometrioid and no MI (independent of grade and PTD)

Omentectomy, staging biopsies, or cytoreduction for nonendometrioid or advanced disease

Abbreviations: MI, myometrial invasion; PTD, primary tumor diameter.

Andrea Mariani et al: Prospective assesment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. *Gynecologic Oncology* 109 (2008) 11–18

Surgical staging

Prævalens af lymfatisk spredning – ptt med lymfeknude fjernelse

	Total	Node positive	Prevalence %
Endometrioid	209	34	16
Non endometrioid	72	29	40

Andrea Mariani et al: Prospective assesment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. Gynecologic Oncology 109 (2008) 11–18

Surgical staging

Patients with positive lymphnodes

	Endometrioid (n=32)	Non- endometrioid (n=25)	Total (n=57)
Kun pelvine	12 (37%)	7 (28%)	19 (33%)
Pelvine + paraortiske	14 (44%)	15 (60%)	29 (51%)
Kun paraortale	6 (19%)	3 (12%)	9 (16%)

Andrea Mariani et al: Prospective assesment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. Gynecologic Oncology 109 (2008) 11-18

Det italienske studie +/- LNE

pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250).

	+LNE	-LNE	P
Median antal LN removed	30 (22-42)	0 (0-0)	<0.001
Postoperative complications	81 ptt.	34 ptt.	<0.001
Ptt. w. lymphnode metast.	13,3%	3,2%	<0.001
5 Year disease free / overall survival	81% / 81,7%	85,9% / 90%	N.S

Median follow-up of **49 months**: 78 events incl. 53 deaths.

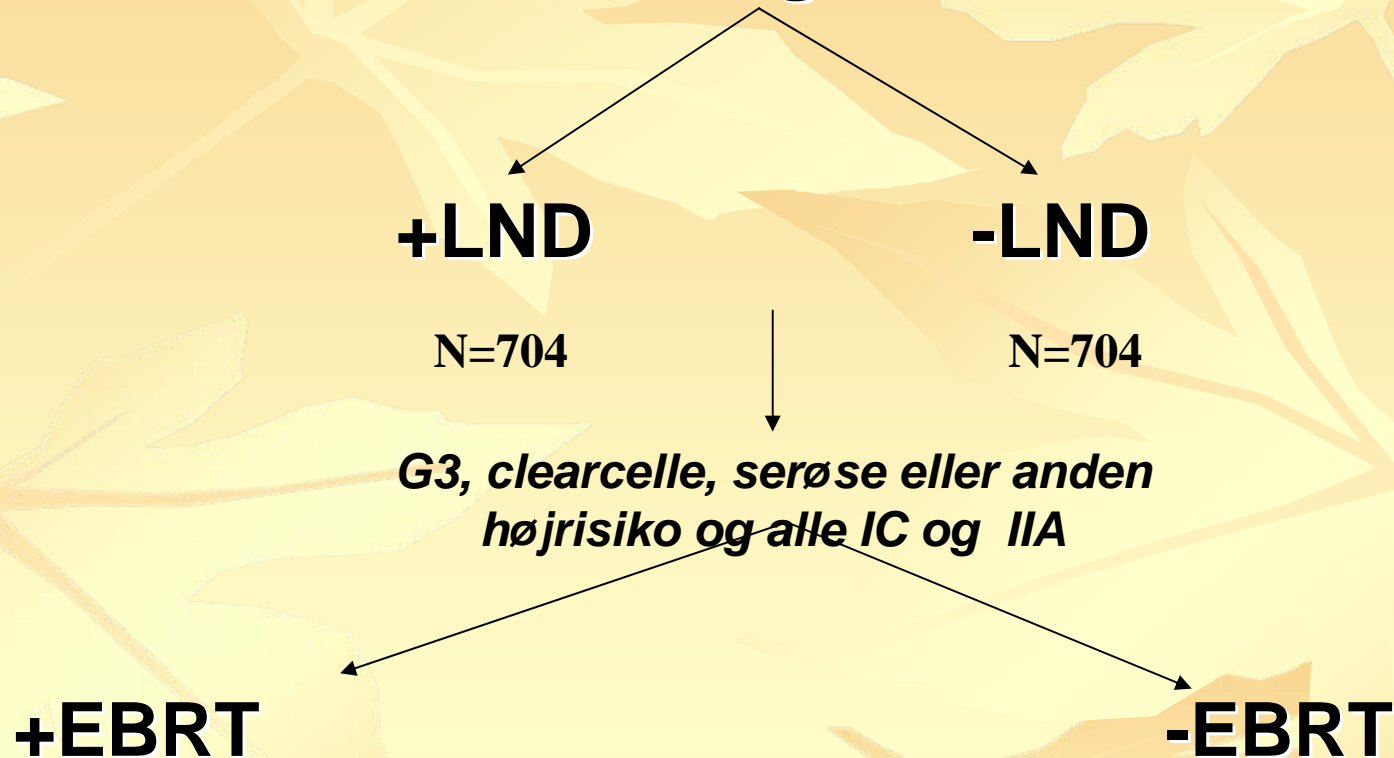
Unadjusted HR for first event = 1.10, 95% CI = 0.70 to 1.71, $P = .68$

Unadjusted HR for death = 1.20, 95% CI = 0.70 to 2.07, $P = .50$).

Panici PB, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst* 2008; **100**:1707–16.

ASTECC

Endometriecancer begrænset til uterus



The writing committee on behalf of the ASTEC study group. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373: 125-36.

ASTECC kirurgiske del +/-LND

No LND

LND

5Y DFS

79 %

73 %

5Y OS

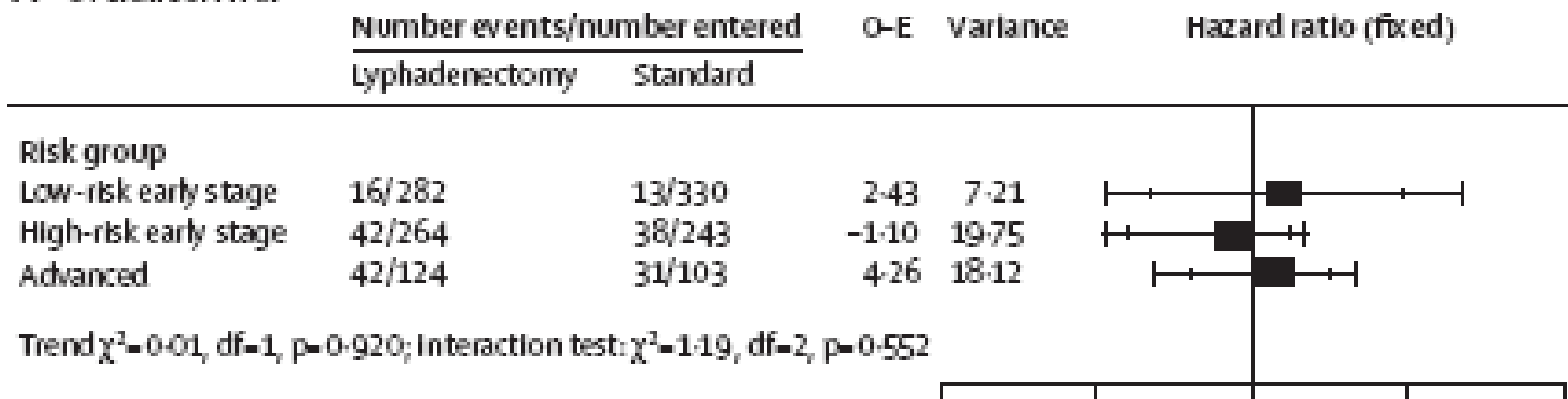
81 %

80 %

Median follow-up 37 mths (IQR 24-58)

The writing committee on behalf of the ASTEC study group. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373: 125-36.

A Overall survival



B Recurrence-free survival

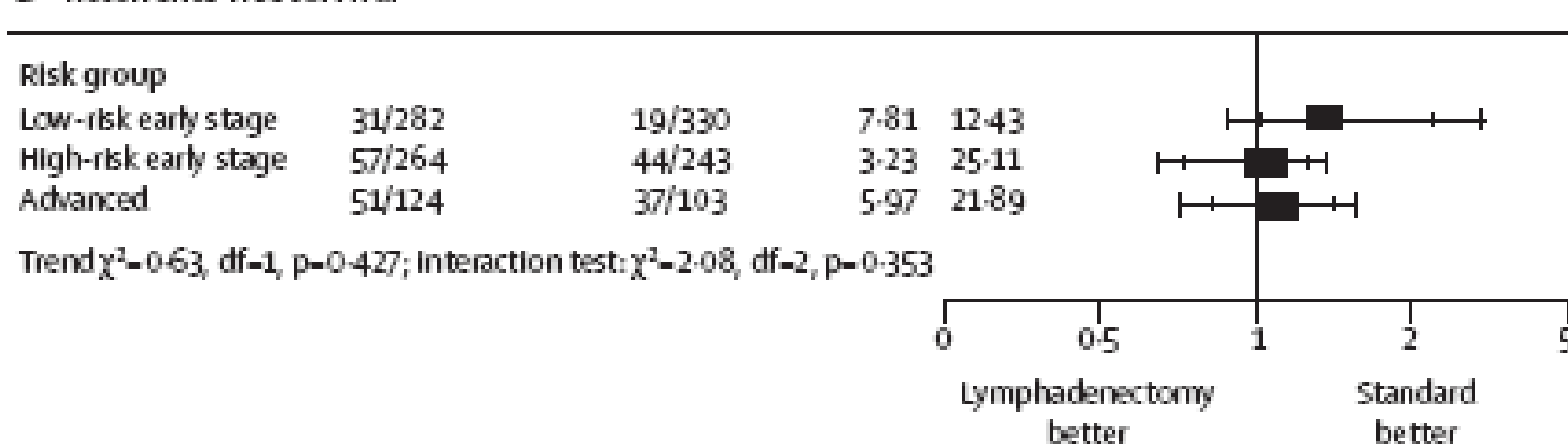
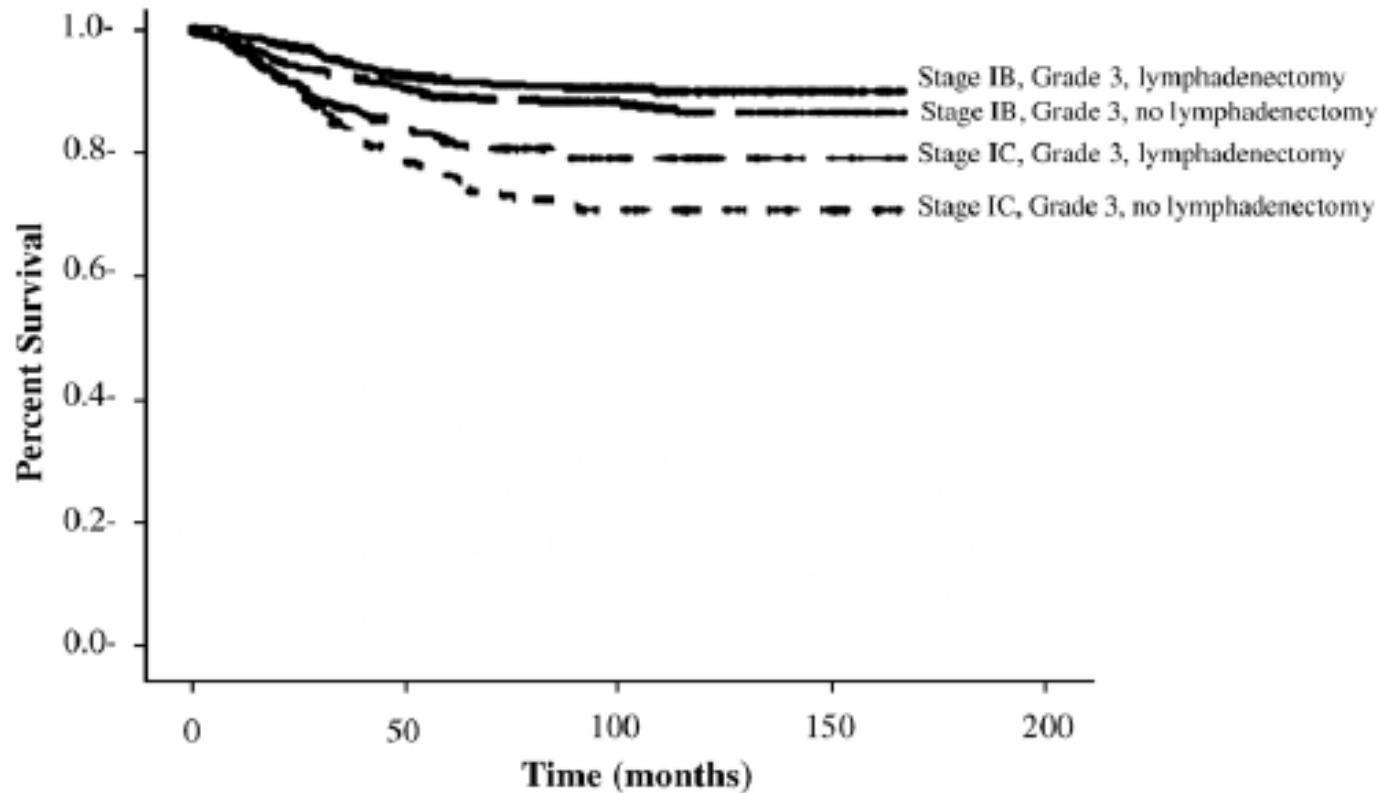


Figure 5: Effect of lymphadenectomy on overall survival (A) and recurrence-free survival (B) in women in different risk groups of recurrence

O-E=observed minus expected. Outer bars show 99% CI, inner bars show 95% CI.

Five year Disease specific survival +/- LND

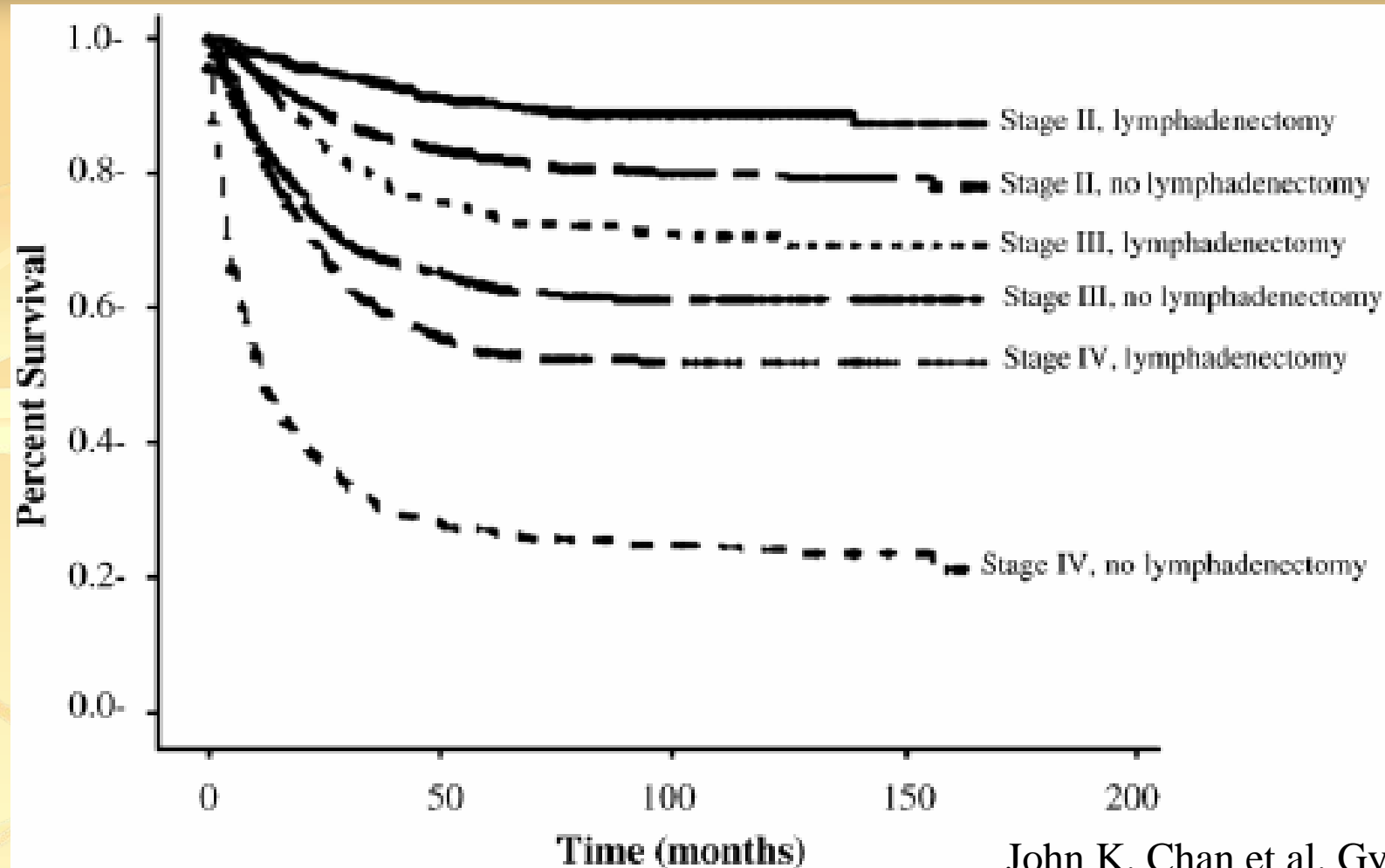


5-year disease-specific survival:

	Lymphadenectomy	No Lymphadenectomy	p-value
Stage IB grade3	91.7% (n=1,070)	89.1% (n=852)	p=0.048
Stage IC grade3	81.7% (n=483)	76.3% (n=401)	p=0.058

Fig. 1. Kaplan–Meier disease-specific survival of stage I grade 3 endometrioid uterine cancer patients based on lymphadenectomy.

John K. Chan et al. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. *Gynecologic Oncology* 106 (2007) 282–288



John K. Chan et al. Gynecologic
Oncology 106 (2007) 282–288

5-year disease-specific survival:

	Lymphadenectomy	No Lymphadenectomy	p-value
Stage II	90.4% (n=1,211)	82.2% (n=1,833)	p<0.001
Stage III	73.8% (n=1,223)	63.1% (n=954)	p<0.001
Stage IV	53.3% (n=890)	26.9% (n=1,496)	p<0.001

Strålebehandling

- Kvinder som ikke fik foretaget lymfeknuderesektion fik signifikant hyppigere efterfølgende strålebehandling 32,8% vs 16,4% $p < 0,001$
- Strålebehandling gav ikke øget overlevelse

Konklusion lymfeknude fjernelse

- Lymfeknude fjernelse anbefales IKKE til lavrisikogruppen
- Lymfeknude fjernelse udføres mhp korrekt stadieinddeling i mellem og højrisko grupperne.
- Lymfeknude fjernelse i sig selv øger formodentlig ikke overlevelsen

Lymfeknudefjernelse 2005-7 og 8 i stadium I

Risiko gruppe	ja	nej	uoplyst	ja	nej	uoplyst
Lav	62	694	32	28	255	4
	7,9%	88%	4,1%	9,8%	88,9%	1,4%
Mellem	59	259	9	43	60	3
	18%	79,2%	2,8%	40,6%	56,6%	2,8%
Høj	38	57	8	29	18	1
	36,9%	55,3%	7,8%	60,4%	37,5%	2,1%
Uoplyst	10	41	6	4	8	1
	17,5%	72%	10,5%	30,8%	61,5%	7,7%

NB 2008 tal er ikke valideret

Ref. DGCD årsrapport 2006-7 og 2008 statusrapport

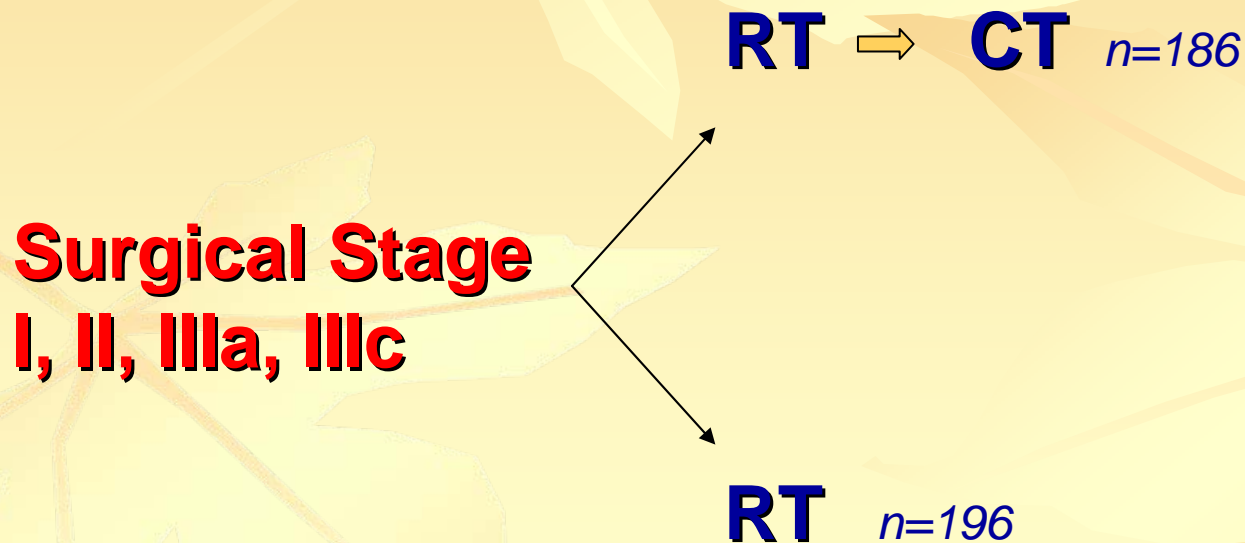
Lymfeknudefjernelse 2005-7 og 8 i stadium I

Risiko gruppe	ja	nej	uoplyst
Lav	62	694	32
	7,9%	88%	4,1%
Mellem	59	259	9
	18%	79,2%	2,8%
Høj	38	57	8
	36,9%	55,3%	7,8%
Uoplyst	10	41	6
	17,5%	72%	10,5%

De tilsvarende tal fra 2008 blev vist – men er ikke validerede og lægges derfor ikke på hjemmesiden.

I 2008 blev der fjernet lymfeknuder hos ca 10% i lavrisikogruppen, ca 40% i mellemrisikogruppen og ca 60% i højriskogruppen

Post-op adj kemo NSGO 9501 Design



Progression free survival

NSGO studiet

- 190 ptt. randomiseret til strålebehandling (RT)
- 177 ptt. til strålebehandling plus kemoterapi (CT)
- Inklusion over 11 år. Median follow-up 3,5 år
- HR for PFS : 0,58 (CI 0,34-0,99, p=0,046) til fordel for RT + CT
- Absolut forskel i 5 års PFS : 7% fra 75 % (95 % CI 67 % - 82 %) til 82 % (95 % CI 73 % - 88 %).

Kemoterapi: FIGO stadium III-IV GOG 122 (JCO 2006)

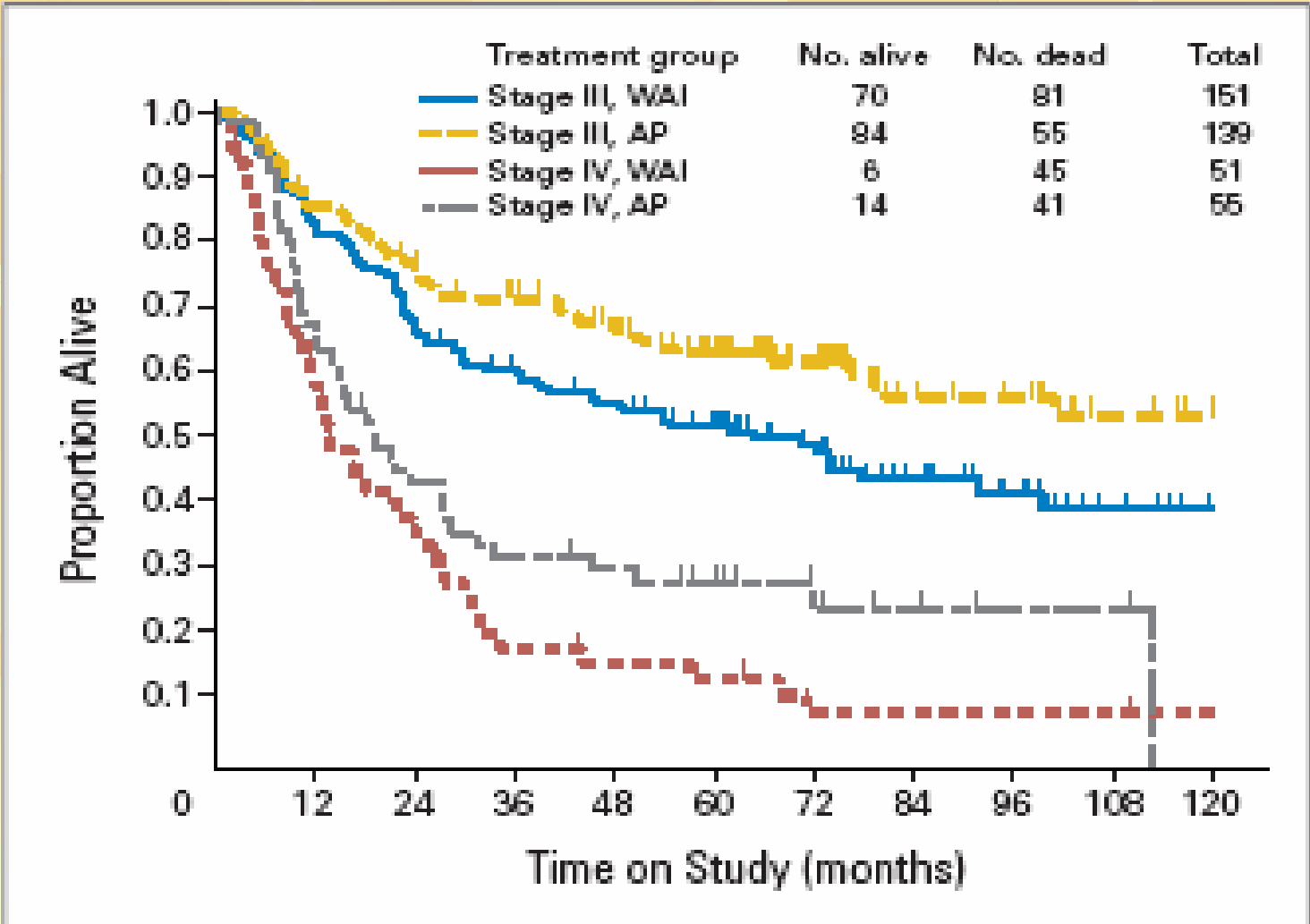


Fig 2. Overall survival by treatment and stage on the Gynecologic Oncology Group 122 trial. WAI, whole-abdominal irradiation; AP, doxorubicin and cisplatin. Reprinted with permission.⁵¹

Oslo studiet

FIGO Stage I
(n=540)

**Hysterectomy
+ vaginal BT**

No adjuvant treatment

EBRT



Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet. Gynecol.* 1980; 56: 419-27.

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Oslo Studiet

	Gruppe A	Gruppe B (EBRT)
Recidiv i vagina / pelvis % (P < 0.01)	6.9	1.9
Fjern metastaser %	5.4	9.9
5-års overlevelse %	91	89
9-års overlevelse %	90	87

Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet. Gynecol. 1980; 56: 419-27. og Retningslinier for visitation, diagnostik, behandling og kontrol af cancer corporis uteri Version 2: 7.4.2009

Portec studiet

FIGO Stage I
Medium risk patients
(*n*=715)

No adjuvant treatment
(*n*=354)

Hysterectomy

EBRT
(*n*=361)

C.L. Creutzberg, W.L.J. van Putten, P.C.M. Koper, et al. PORTEC Study Group and M. van Lent, Surgery and postoperative radiotherapy versus surgery alone for patients with stage-I endometrial carcinoma: multicentre randomised trial. *Lancet*; 355 (2000): 1404–1411.

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Portec studiet

5 års data

RT

no RT

**Locoregionalt
recidiv**

4 %

14 %

p < 0.001

**Overall
survival**

81 %

85 %

p = 0.31

C.L. Creutzberg, W.L.J. van Putten, P.C.M. Koper, et al. PORTEC Study Group and M. van Lent, Surgery and postoperative radiotherapy versus surgery alone for patients with stage-I endometrial carcinoma: multicentre randomised trial. Lancet; 355 (2000): 1404–1411.

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GOG-99

**Surgical
Stages G3, IB,
IC, II
(n=390)**

**No adjuvant treatment
(n=200)**

**Hysterectomy
+LND**

**EBRT
(n=190)**

Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group Study. *Gynecologic Oncology* 2004;92(3):744–51.

Retningslinier for visitation, diagnostik, behandling og kontrol af cancer corporis uteri
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GOG-99

	RT	ikke RT	
Locoreg. recidiv	1.6%	8.5%	P<0.001
3 års overlevelse	96%	89%	P=0.09

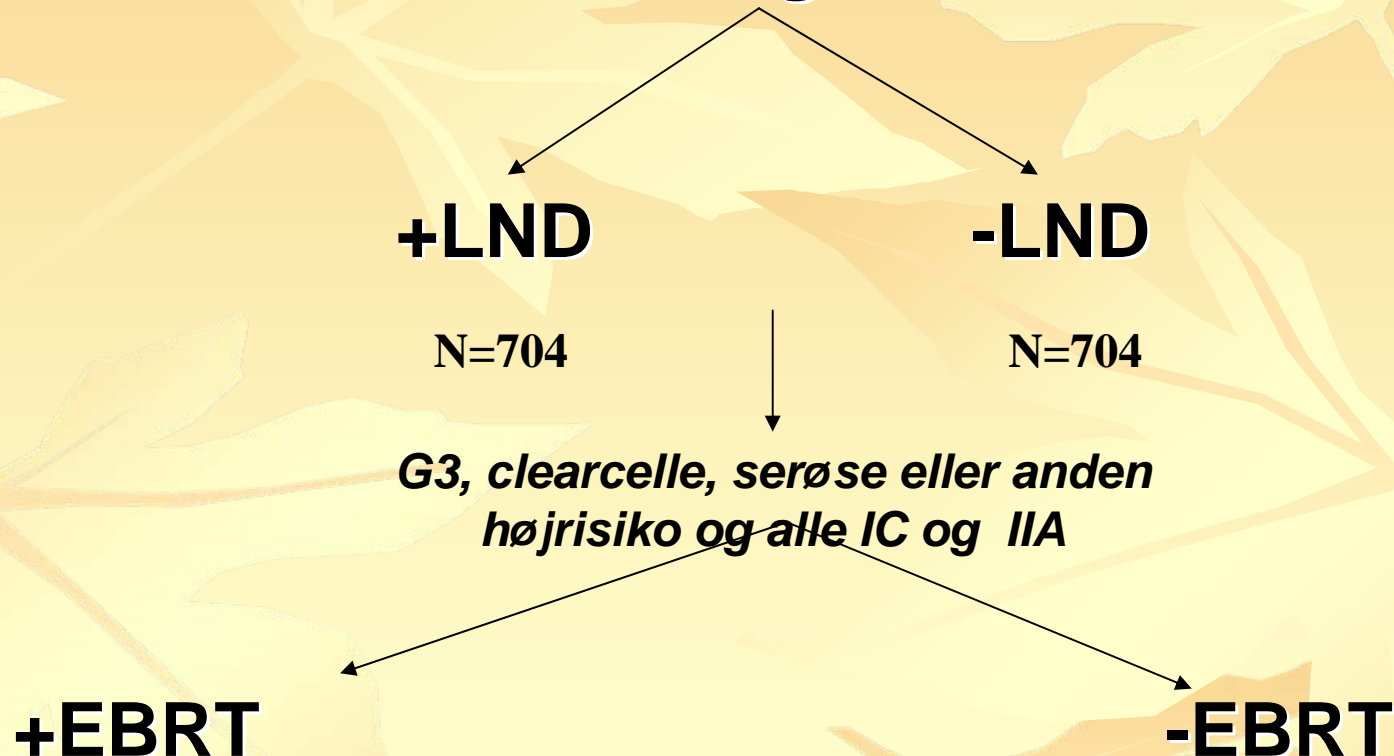
Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group Study. *Gynecologic Oncology* 2004;92(3):744–51.

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ASTECC

Endometriecancer begrænset til uterus



Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis The ASTEC/EN.5 writing committee on behalf of the ASTEC/EN.5 Study Group*
Lancet 2009; 373: 137–46

ASTECC

	RT	no RT	
5Y-kumulativ Locoreg. relapse	3,2%	6,1%	P=0.02
5Y-Overall survival	83,5%	83,9%	P=0.77
5Y disease spec. Recurrence free survival	85,3%	84,7%	P=0,68

Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis The ASTEC/EN.5 writing committee on behalf of the ASTEC/EN.5 Study Group* *Lancet* 2009; 373: 137–46

Konklusion onkologisk behandling

- Strålebehandling nedsætter risikoen for lokalrecidiv men øger ikke overlevelsen
- Gavnlig effekt af strålebehandling ved avanceret cancer er uafklaret – guideline vil blive tilrettet, så strålebehandling fortsat er mulig men ikke kræves
- Postoperativ kemoterapi anbefales til højrisikopatienter

Nye studier

- **The role of adjuvant chemotherapy in surgical stage I-II serous or clear cell endometrial carcinoma: a randomized phase III trial**
- Frederic Amant, MD PhD Leuven Belgien
- **A phase III Trial of postoperative chemotherapy or no further treatment for patients with stage I-II medium or high risk endometrioid adenocarcinoma of the uterus. ENTOG studie**
- Mansoor Raza Mirza, RH
- **PhD projekt på RH om præoperativ stadieinddeling**
- Sofie Leisby

Centralisering

- Staging foregår i dag peroperativt, hvorfor ptt. bør opereres på centre, som behersker radikal lymfeglandel exairese både pelvint og paraortalt
- Den bedste metode til præoperativ stadieinddeling er fortsat ikke identificeret
- Pågående forskning i bedre præoperative metoder til stadieinddeling
- Bedre muligheder for fremtidig forskning
- Yderligere centralisering af specielle grupper

DGCD april 2008

Histology	% of n=1818	% of total pre-OP diagnosis	
		Hyperplasia	Cancer
Atypical hyperplasia	6%	94%	5%
Endometrioid adenocarcinoma	74%	17%	82%
Serous adenocarcinoma	3%	2%	89%
Clearcell carcinoma	2%	-	97%
Carcinosarcoma	4%	3%	92%
Sarcoma	4%	3%	84%
Other	7%		

Information is missing on pre-operative diagnosis for some of the ptt.

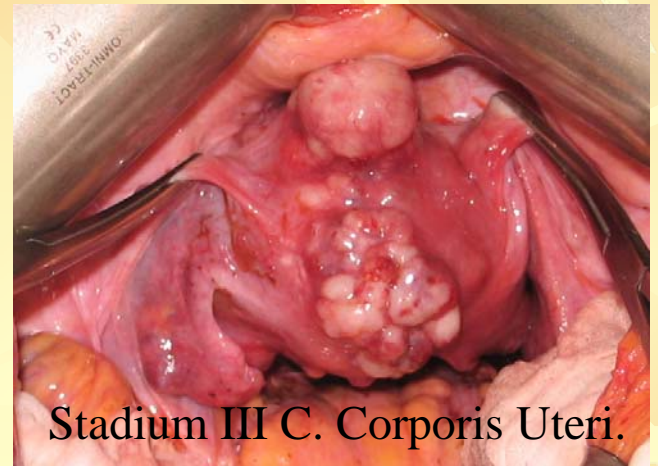
Konservativ behandling af endometriecancer er i visse tilfælde mulig – men aldrig ufarlig

Derfor er informed consent meget vigtig

Adenocarcinom	Varighed	Regression	Recidiv	Gravid
Kim 1997	3 mdr	4/7	2/4	0/7
Kim's review 1997	Op til 1år	9/14	1/9	2/14
Randall 1997	3-18 mdr	9/12	1/9	3/12
Kaku 2001	2-14 mdr	9/12	2/9	2/12
Atypisk hyperplasi				
Randall 1997	3-18 mdr	16/17	2/16	2/17
Kaku 2001	1-23 mdr	15/18	2/15	5/18

SLUT

■ Diskussion



Stadium III C. Corporis Uteri.