University of Lund

NSGO

High risk stage I Endometrial Cancer To give or not to give adjuvant therapy and if – what therapy? Discussion

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Audience Question

What to do next?:

1. Nothing
2. Pelvic radiotherapy (EBRT)
3. Vaginal brachytherapy (VBT)
4. Pelvic+para-aortic radiotherapy
5. Chemotherapy (CT)
6. Sequential chemotherapy and radiotherapy
7. Concomitant chemo-radiotherapy
8. Vaginal brachytherapy and chemotherapy

Adjuvant therapy depending on LA or not

- My view is that LA can diagnose metastases by the lymphatic route but it is unlikely that it would by itself alter the course of disease which is mainly associated with distant metastases
- LA does not obviate the need for adjuvant therapy in presence of high risk factors. Compare with radiotherapy
- Proponents for LA hope that LN- patients would not need radiotherapy as part of adjuvant therapy. This is, however, not proven

What to do next?

Nothing

Pelvic radiotherapy (EBRT)

Vaginal brachytherapy (VBT)

Pelvic+para-aortic radiotherapy

Chemotherapy (CT)

Sequential chemotherapy and radiotherapy

Concomitant chemo-radiotherapy

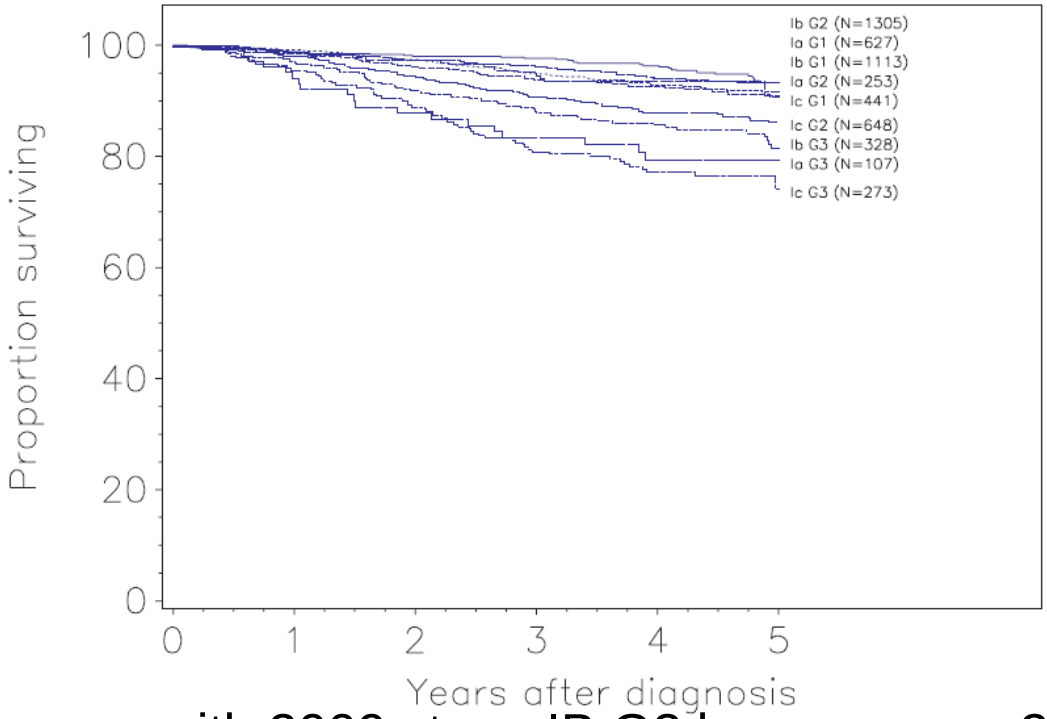
VBT and chemotherapy

Risk groups for EC in the 2009 FIGO staging system

- **Low risk**: Stage IA grade 1-2 and endometrioid type EC
- **Intermediate risk**: Stage IA grade 3 or IB grades 1-2 and endometrioid type EC
- **High intermediate risk**: Age of at least 60 years and/or LVSI and Stage IA grade 3 or IB grades 1-2 and endometrioid type EC
- **High risk**: IB grade 3 and endometrioid type EC or stage II-III or non-endometrioid types with infiltration

Adjuvant therapy?

Annual Report vol 27



The group of women with 2009 stage IB G3 have an over 25% risk to die within 5 years

Adjuvant therapy?

2009 Stage IB G3 PORTEC register

Overall survival 58%

Creutzberg et al. J Clin Oncol 2004

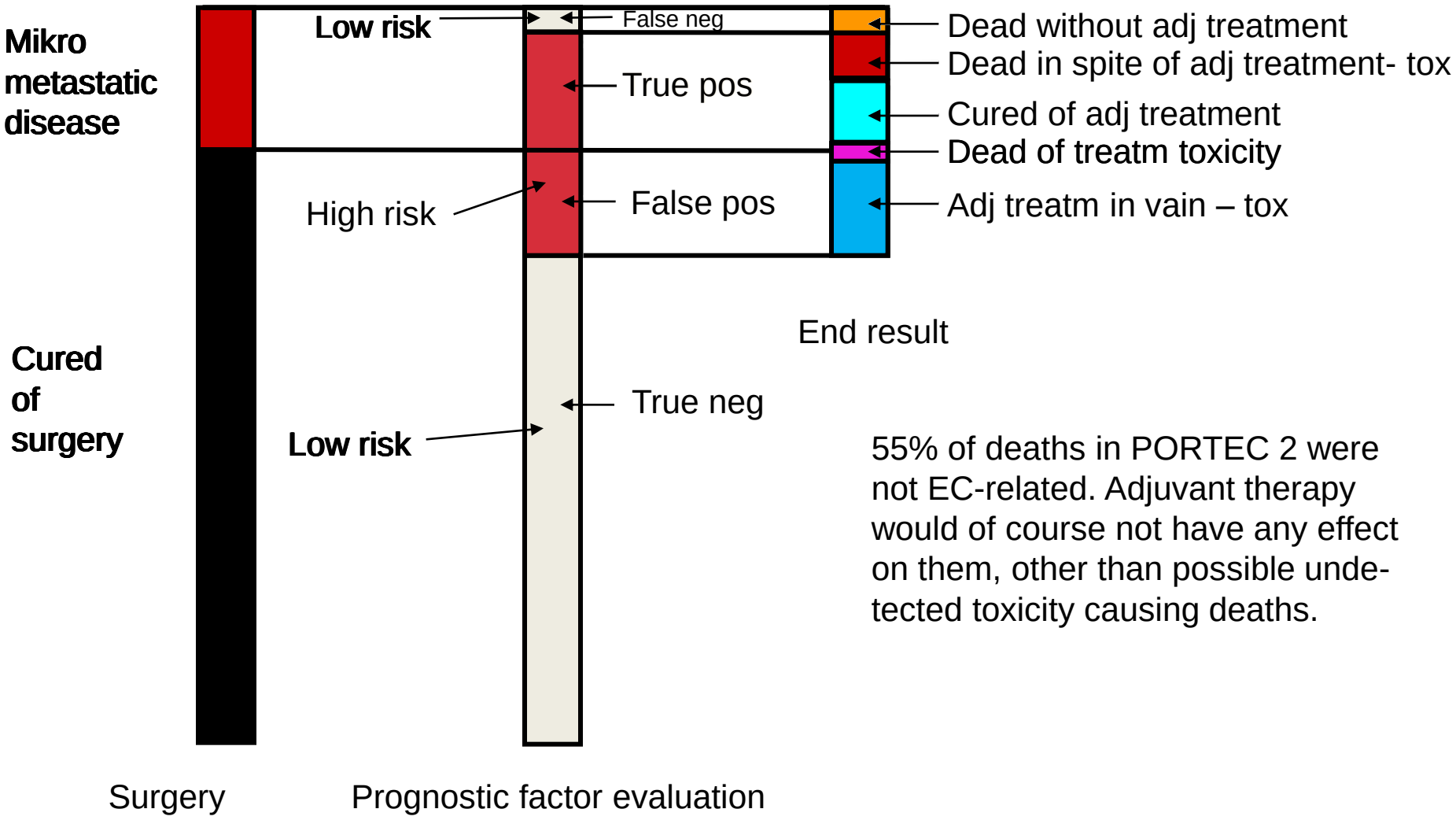
Swedish population statistics

The median survival time for Swedish women is 85.5 years

A Swedish 72 year women has a mean remaining life time of ~15 years

Her chance to survive 5 years is ~90%, and 10 years ~75%

Prognostic factor evaluation and treatment



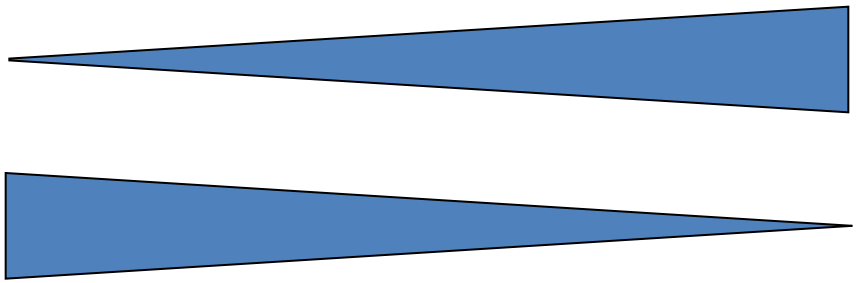
55% of deaths in PORTEC 2 were not EC-related. Adjuvant therapy would of course not have any effect on them, other than possible unde-tected toxicity causing deaths.

Interplay between treatment toxicity and efficacy

Adjuvant treatment:

Non-toxic

Effective



Adjuvant treatment:

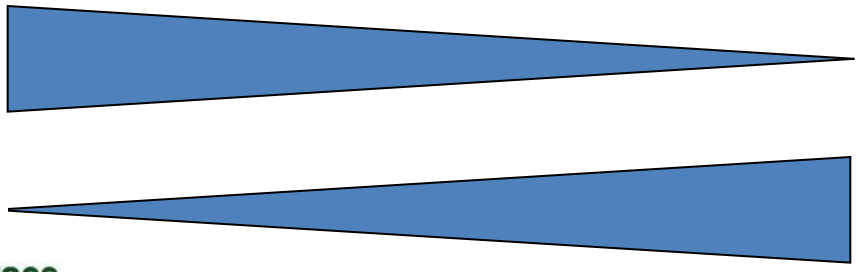
Toxic

Non-effective

Prognostic/predictive factors not needed

Great need of prognostic/predictive factors

Optimize sensitivity of progn fact



Optimize specificity of progn fact

Conclusions on doing nothing

- I would argue that adjuvant therapy is indicated in this case

but

- toxicity and efficacy of available adjuvant treatments are problematic

What to do next?

Nothing

Pelvic radiotherapy (EBRT)

Vaginal brachytherapy (VBT)

Pelvic+para-aortic radiotherapy

Chemotherapy (CT)

Sequential chemotherapy and radiotherapy

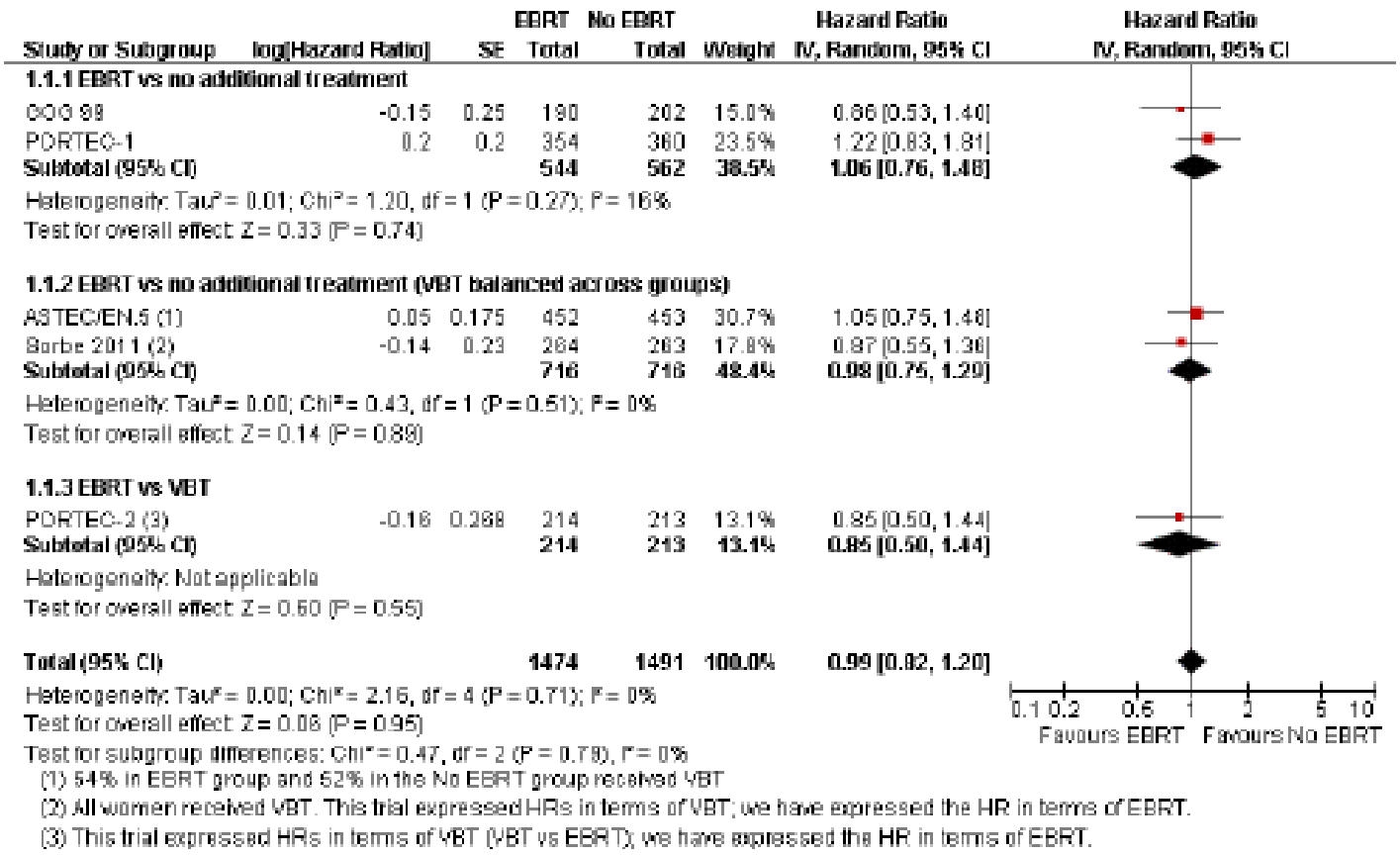
Concomitant chemo-radiotherapy

Vaginal brachytherapy and chemotherapy

External Beam Radiotherapy (EBRT)

Kong et al. Cochrane review Adjuvant radiotherapy for stage I endometrial cancer (update 2012)

Figure 2. Forest plot of comparison: 1 EBRT vs. No EBRT: All patients at 5 years, outcome: 1.1 Death from all causes (time-to-event data).



(1) 54% in EBRT group and 52% in the No EBRT group received VBT

(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.

(3) This trial expressed HRs in terms of VBT (VBT vs EBRT); we have expressed the HR in terms of EBRT.

But this is a patient with a high risk tumor

Kong et al. Cochrane review Adjuvant radiotherapy for stage I endometrial cancer (update 2012)

High risk tumors (as defined by investigators; OR stage IB AND G3)

- OS time to event no significant difference between XRT and no XRT
HR 0.91 (95% CI 0.60 to 1.39) (2 trials, n=334)
- OS dichotomous no significant difference between XRT and no XRT
RR 0.88 (95% CI 0.63 to 1.22) (3 trials, n=429)
- CCS No significant difference between XRT and no XRT
HR 0.84 (95% CI 0.51 to 1.40) (2 trials, n=334)

Insufficient evidence to draw conclusions in the high risk group. A benefit cannot be excluded in this group

Conclusions on pelvic EBRT

- I think routine EBRT should not be recommended in women with stage I endometrial carcinoma regardless of risk factors

but

- there is still controversy around the high risk group

But

While not affecting survival EBRT is very effective in reducing locoregional recurrence

- Time-to-event data

HR 0.36 (95% CI 0.25 to 0.52) (5 trials, n=2965)

- Dichotomous data

RR 0.33 (95% CI 0.23 to 0.47) (7 trials, n=3628)

Translates to a 67% reduction in the risk that the first relapse will be locoregional (95% CI 53% to 77%) with EBRT

What to do next?

Nothing

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Pelvic+para-aortic radiotherapy

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Sequential chemotherapy and radiotherapy

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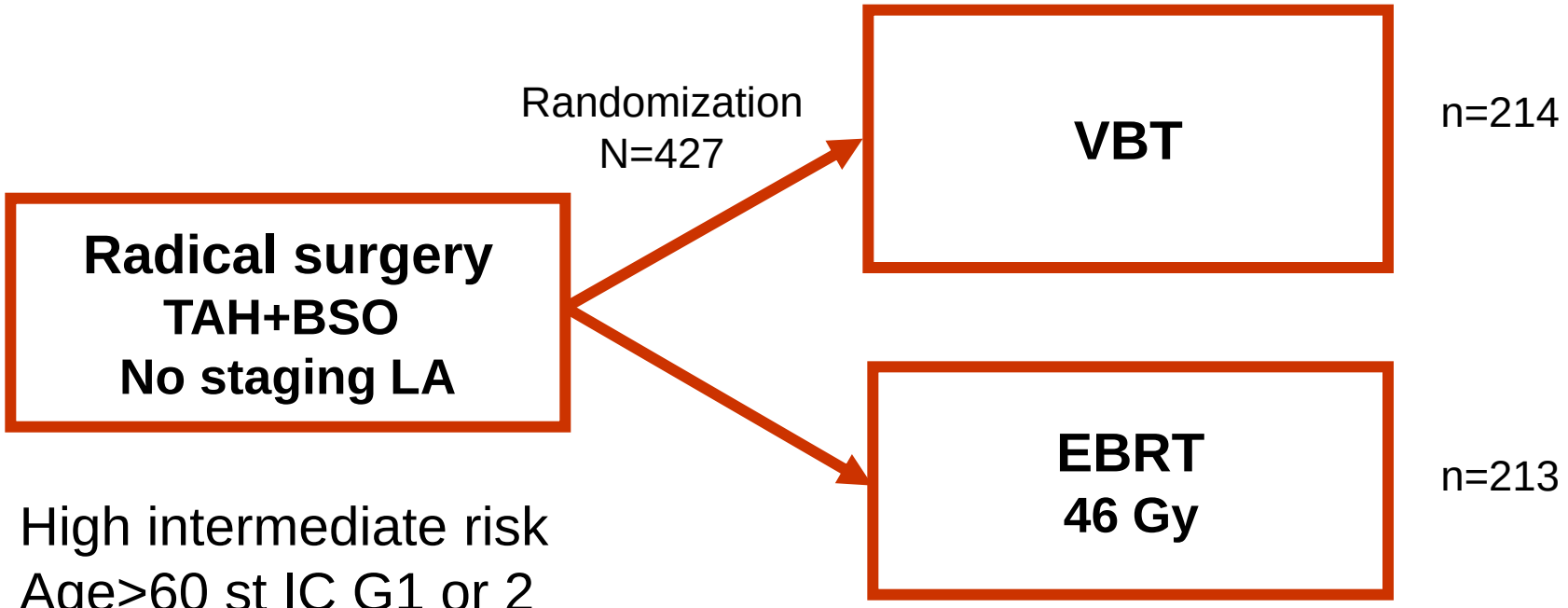
Vaginal brachytherapy and chemotherapy

PORTEC 2



High intermediate risk
Age>60 st IC G1 or 2
Age>60 St IB G3
St IIA

Primary end point vaginal recurrence rate, secondary locoregional recurrence, distant mets, OS, DFS, toxicity and QoL

Nout et al. Lancet 2010

Results PORTEC 2

End point	VBT (%)	EBRT (%)
Vaginal RR	1.8	1.6
Isol pelvic RR	1.5	0.5
Total pelvic RR	5.1	2.1
5-year OS	85	80
5-year DFS	83	78

- PORTEC 1: Observing100 patients for 5 years; 14 vaginal relapses 70% can be salvaged
- PORTEC 2: Observing 100 patients for 5 years; 2 vaginal relapses
- Treating 100 women with VBT would save 12 from vaginal relapses
- NNT to avoid 1 vaginal recurrence ~8, the ultimate outcome would be the same

Conclusions on VBT

- Excellent local control
- Fairly untoxic compared to EBRT
- The trial was performed on women with high-intermediate risk tumors
- The local effect may be the same on high risk tumors, but the risk for progression elsewhere is greater
- VBT has replaced EBRT /EBRT+VBT in many centers for the high-intermediate risk group (and maybe also the in high risk group)

What to do next?

Nothing

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Vaginal brachytherapy (VBT)

Pelvic+para-aortic radiotherapy

Chemotherapy (CT)

Sequential chemotherapy and radiotherapy

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Vaginal brachytherapy and chemotherapy

Para-aortic nodes

…When the pelvic nodes were dissected and were negative, the finding of aortic node metastasis was documented in only one case (1.5%). Conversely, when pelvic node metastasis was documented, the risk of aortic node metastasis was 60%.

Boronow RC Gynecol Oncol 66, 179 (1997)

Adequate para-aortic lymphadenectomy and pelvic and para-aortal EBRT

Table 5
Lymph node recurrences at 5 years according to type of therapy[a]

Type of therapy	Pelvic			Para-aortic		
	No. of patients ($n = 116$)[b]	PSW recurrences at 5 years, %	P value	No. of patients ($n = 41$)	Recurrences in PA at 5 years, %	P value
RT−, LND−	8	...[c]		9	56	
RT−, LND+	15	68[d]	0.003	13	34	0.09
RT+, LND+	72	10[e]	0.002	11	0	0.08
RT+, LND−	13	58[f]		8	69	

Mariani et al. Gynecol Oncol 101, 200 (2006)

Conclusions on

para-aortic irradiation without confirmed positive para-aortal nodes?

- When the risk for pelvic LN metastases is high the risk for para-aortic LN metastases is also high (although somewhat lower)
- Adjuvant pelvic and para-aortal EBRT seems to be a logical step but there is no randomized trial to support it
- Compelling results from small unrandomized studies with histologically confirmed para-aortic LN metastases
- Concerns about toxicity especially when combined with para-aortic lymphadenectomy

What to do next?

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Why systemic therapy?

176 progessions among 915 patients (19%)

Hematogenous	21%
Peritoneal	18%
Lymphatic	16%
Hematogenous+lymphatic	12.5%
Hematogenous+peritoneal	11%
Hematogenous+lymphatic+peritoneal	3%
Lymphatic+peritoneal	0.5%
Subtotal	82%
Isolated vaginal	18%
Total	100%

Radiotherapy (lymphatic + isol. vag.) 34% (6.5%)

Systemic therapy ± radiotherapy 66% (13%)

Mariani et al. Gynecol Oncol 2004

Chemotherapy

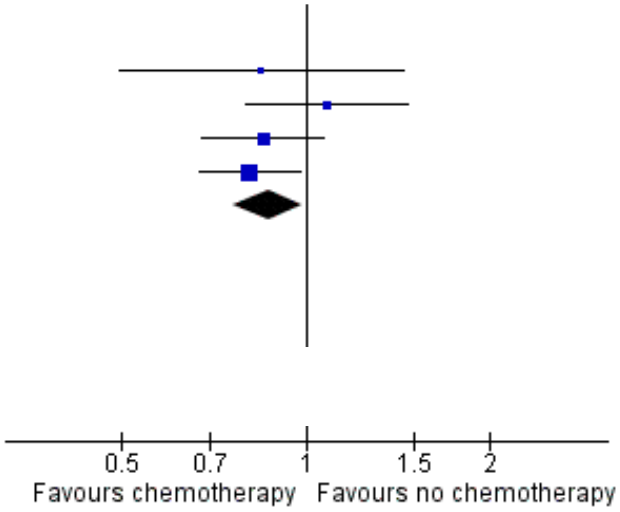
Johnson et al. Cochrane review Adjuvant chemotherapy for endometrial cancer after hysterectomy 2012

Figure 4. Indiscriminate forest plot for overall survival (risk of death 5 years after randomisation) from all trials of chemotherapy versus any other arm.

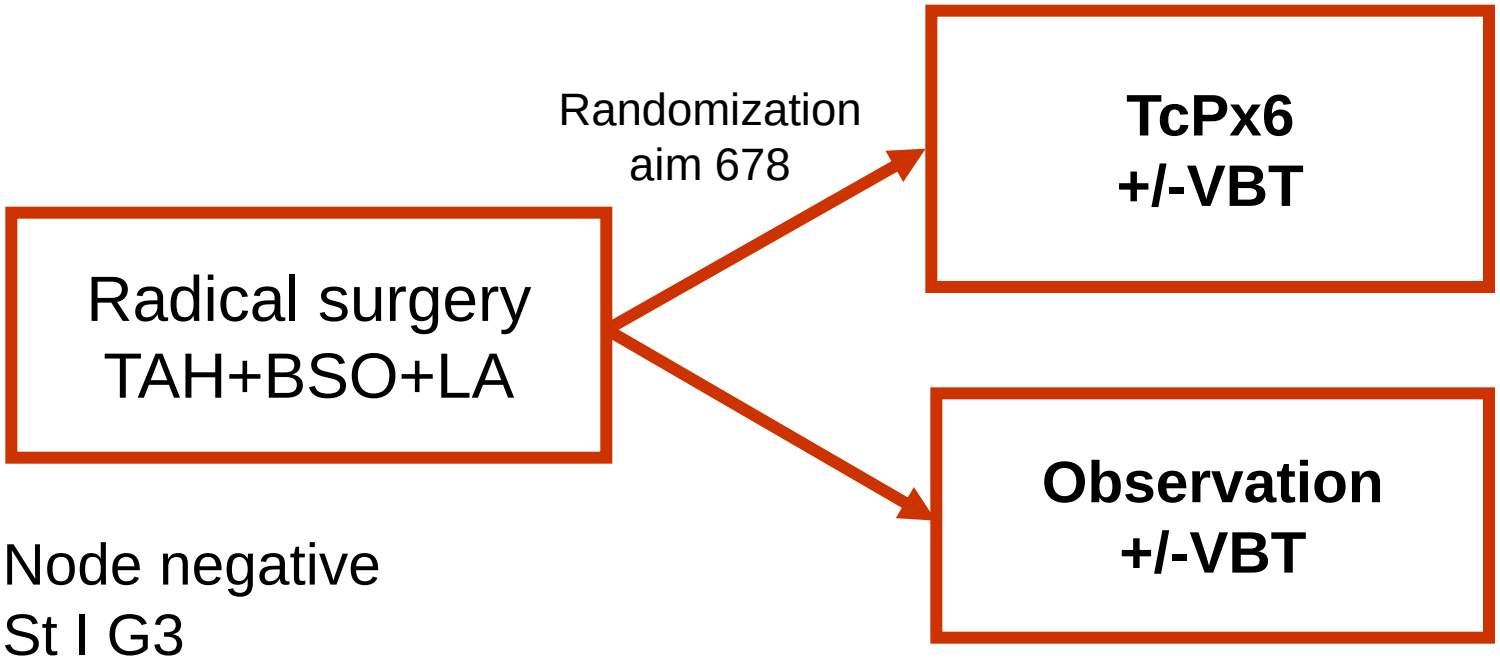
Study or Subgroup	Favours chemotherapy Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.2 Chemotherapy v radiotherapy						
J GOG 2033	22	192	26	192	4.6%	0.85 [0.50, 1.44]
GICOG	59	174	52	166	13.8%	1.08 [0.80, 1.47]
GOG 122	55	101	67	105	24.7%	0.85 [0.68, 1.07]
GOG 150	91	194	117	202	35.8%	0.81 [0.67, 0.98]
Subtotal (95% CI)		**661**		**665**	**78.8%**	**0.87 [0.76, 0.99]**
Total events	227		262			

Heterogeneity: Tau² = 0.00; Chi² = 2.54, df = 3 (P = 0.47); I² = 0%

Test for overall effect: Z = 2.16 (P = 0.03)



ENGOT-EN2-DCGC



Node negative
St I G3
St II
St I-II serous, CC, squamous, or undifferentiated

Primary end point; OS
Secondary: OS in edometrioid subgroup, CSS, PFS, toxicity, QoL isolated pelvic recurrence and distant metastases, and mixed relapses

Conclusions on chemotherapy vs EBRT

- Two studies (JGOG-2033 and GICOG) could not demonstrate superiority of chemotherapy over radiotherapy, both used CAP regimens
- Two studies GOG-122 (more advanced stages) and GOG-150 (carcinosarcoma, more advanced stages) showed superiority of chemotherapy over radiotherapy (whole abdominal EBRT)

What to do next?

Nothing

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Pelvic+para-aortic radiotherapy

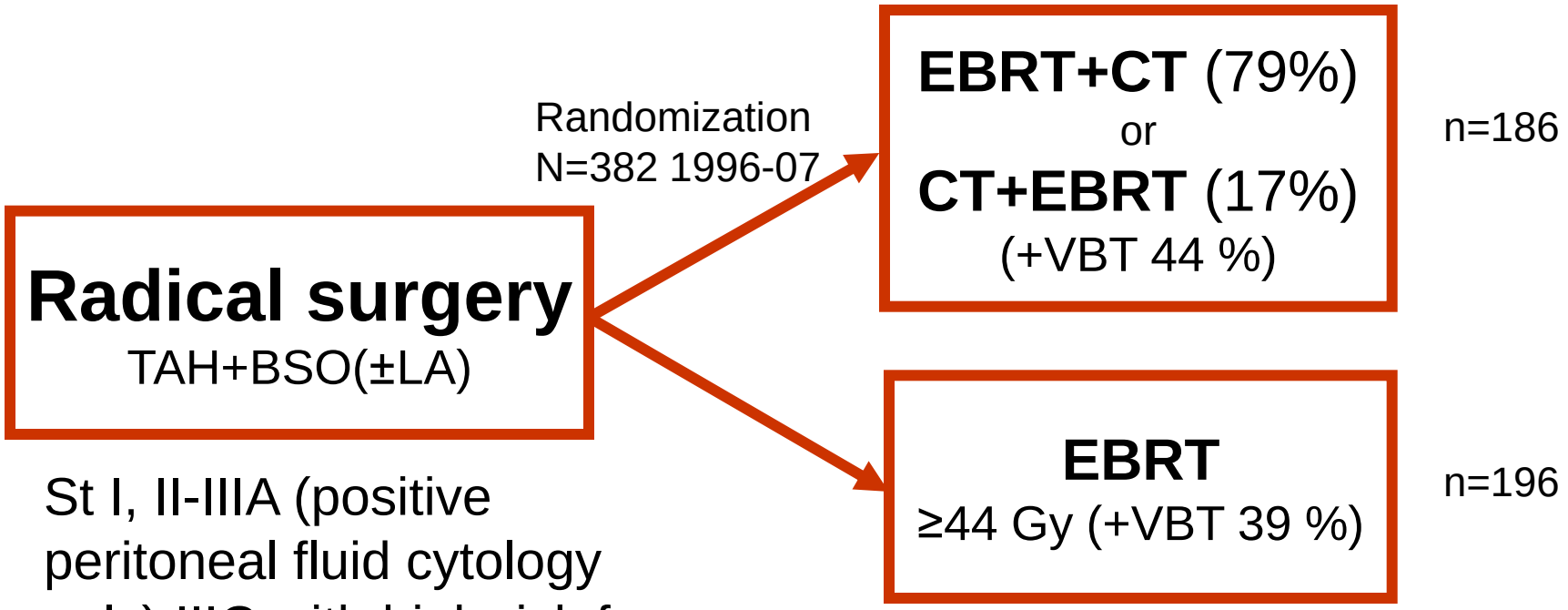
Chemotherapy (CT)

Sequential chemotherapy and radiotherapy

Concomitant chemo-radiotherapy

Vaginal brachytherapy and chemotherapy

NSGO-EC-9501/EORTC-55991

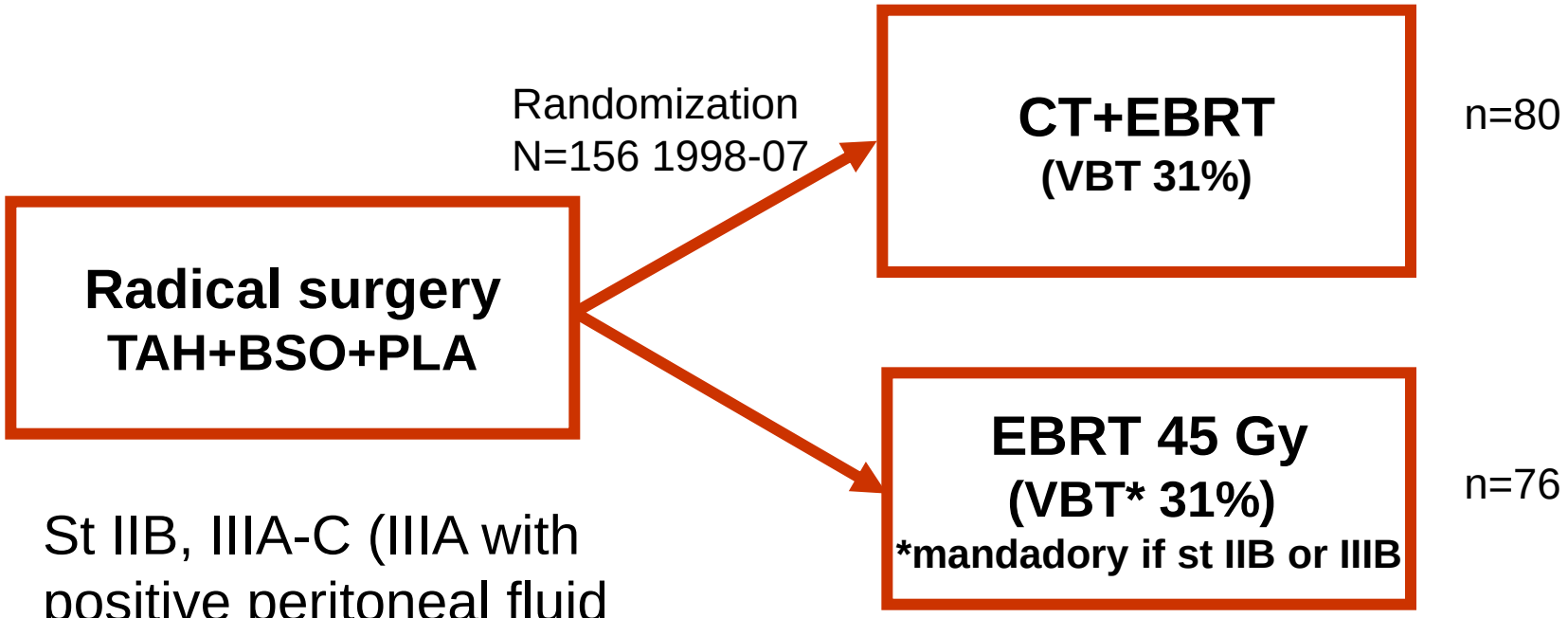


St I, II-IIIA (positive peritoneal fluid cytology only) IIIC with high risk for micrometastatic disease
Endometrioid, serous and clear cell carcinomas

CT: Doxo/epirubicin 50 and cisplatin 50 mg/m² q 4 weeks (87%). Later also TcP (10%), TAP, TEcP x4 q 3 weeks, 4 cycles (3%)
Primary end point PFS

Hogberg et al. Eur J Cancer 2010

MaNGO ILIADE3



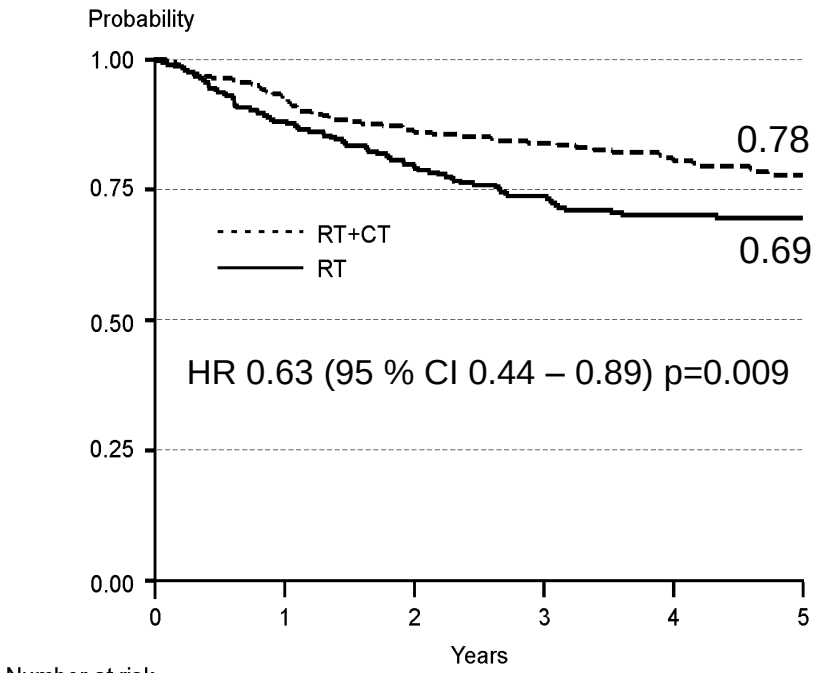
St IIB, IIIA-C (IIIA with positive peritoneal fluid cytology only not eligible)
Endometrioid carcinomas

CT: Doxorubicine 60 and cis-platin 50 mg/m²x3 q 3 weeks
Primary end point PFS, OS

Hogberg et al. Eur J Cancer 2010

Pooled data NSGO EC-9501/EORTC-55991/ILIADE3

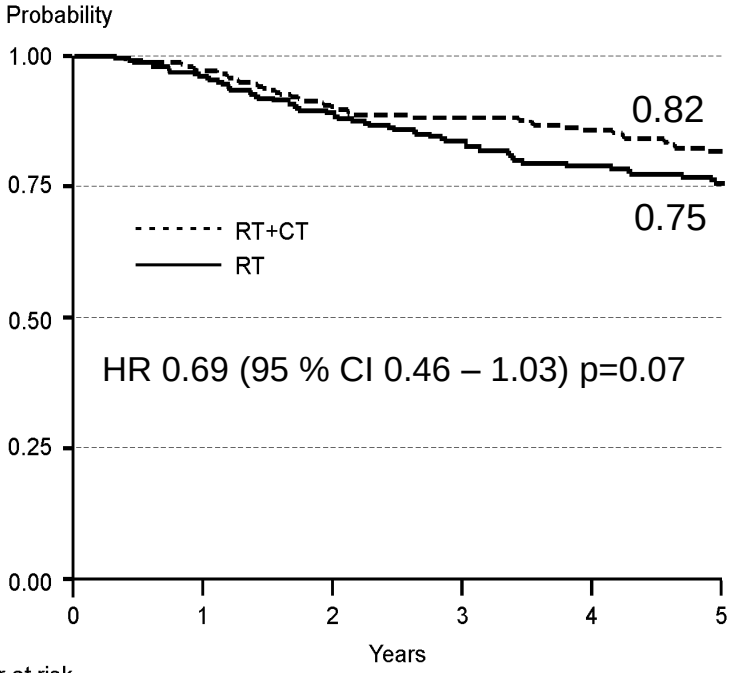
Progression-free survival



Number at risk

RT	267	231	198	165	138	104
RT+CT	267	242	214	195	159	113

Overall survival



Number at risk

RT	267	251	220	185	154	111
RT+CT	267	254	223	202	166	119

CSS HR 0.55 (CI 0.35-0.88) p=0.01; 0.78 ⇨ 0.87

Chemotherapy

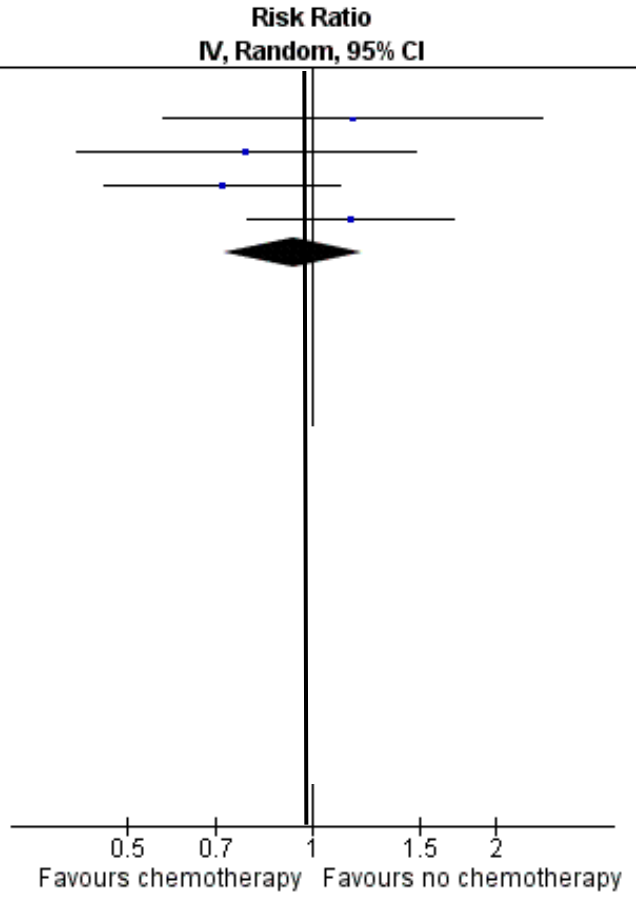
Johnson et al. Cochrane review Adjuvant chemotherapy for endometrial cancer after hysterectomy 2012

Figure 4. Indiscriminate forest plot for overall survival (risk of death 5 years after randomisation) from all trials of chemotherapy versus any other arm.

Study or Subgroup	Favours chemotherapy Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Chemotherpay versus no additional treatment (all receive EBRT+surgery)						
Kuoppala 2008	15	84	11	72	2.6%	1.17 [0.57, 2.38]
MaNGO	14	80	17	76	3.2%	0.78 [0.42, 1.47]
NSGO & EORTC	28	187	40	191	6.7%	0.71 [0.46, 1.11]
GOG 34	36	92	30	89	8.6%	1.16 [0.79, 1.71]
Subtotal (95% CI)		**443**		**428**	**21.2%**	**0.94 [0.72, 1.22]**
Total events	93		98			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.32$, df = 3 (P = 0.35); $I^2 = 10\%$

Test for overall effect: Z = 0.50 (P = 0.62)



Conclusions on

Sequential chemotherapy and radiotherapy

- Chemotherapy in combination with EBRT seems at present to be the most promising adjuvant treatment – but multimodal therapy results in increased toxicity
- What EBRT adds to chemotherapy is unknown

What to do next?

Nothing

Pelvic radiotherapy (EBRT)

Vaginal brachytherapy (VBT)

Pelvic+para-aortic radiotherapy

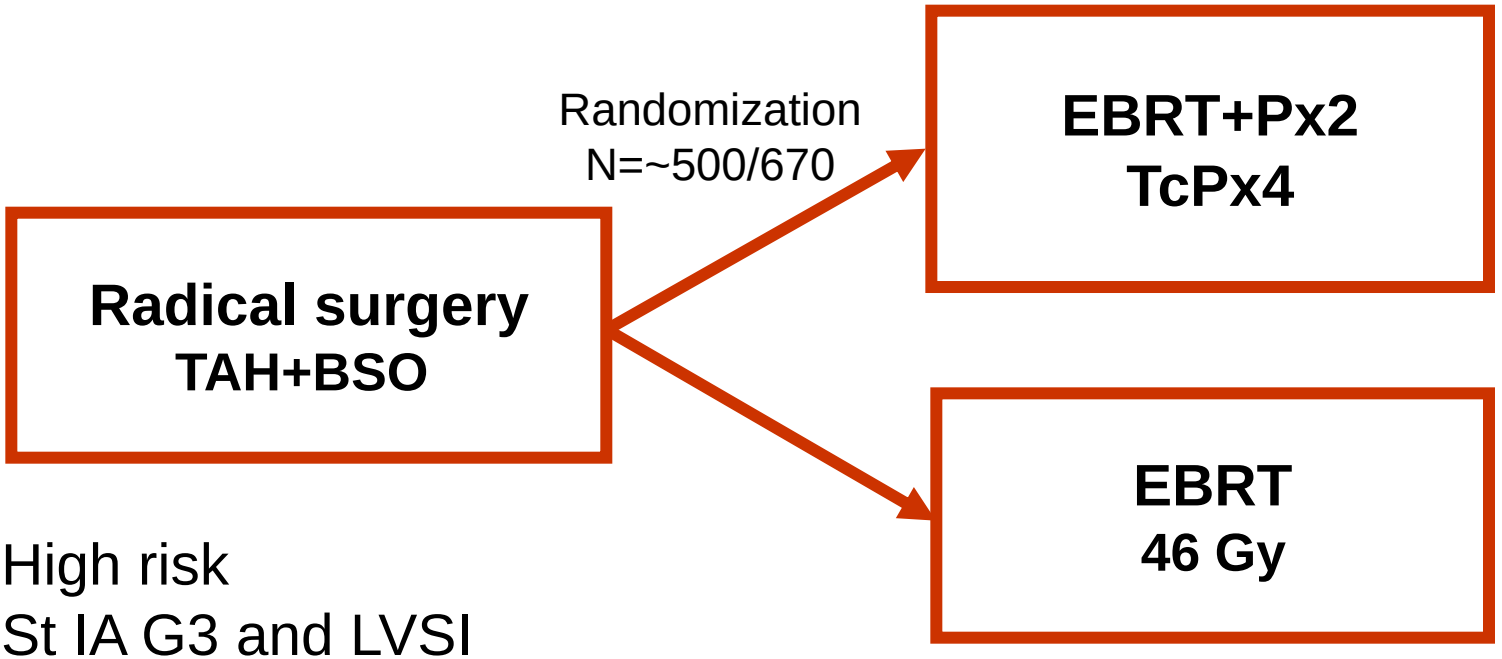
Chemotherapy (CT)

Sequential chemotherapy and radiotherapy

Concomitant chemo-radiotherapy

Vaginal brachytherapy and chemotherapy

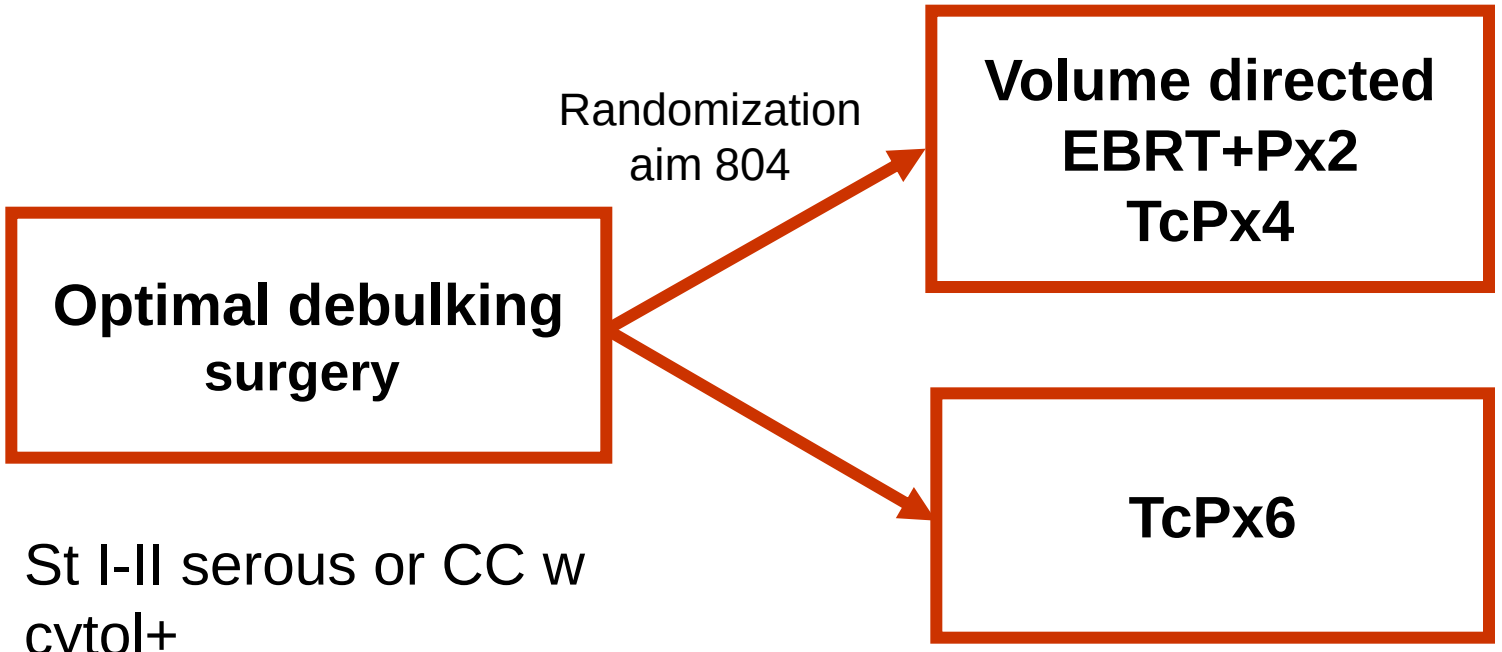
PORTEC 3 ongoing



High risk
St IA G3 and LVSI
St IB G3
St II, IIIA, IIIC
St IIIB if parametrial inv
Serous or CC with invasion

Primary end point; OS, FFS
Secondary: Vaginal and pelvic relapse, distant metastases, toxicity and QoL

GOG 258 ongoing



St I-II serous or CC w cytol+
St III-IVA

Primary end point; RFS
Secondary: OS, local recurrence and distant metastases, toxicity and QoL

Conclusions on
Concomitant chemoradiotherapy

- Trials ongoing
- Wait for results

What to do next?

Nothing

Pelvic radiotherapy (EBRT)

Vaginal brachytherapy (VBT)

Pelvic+para-aortic radiotherapy

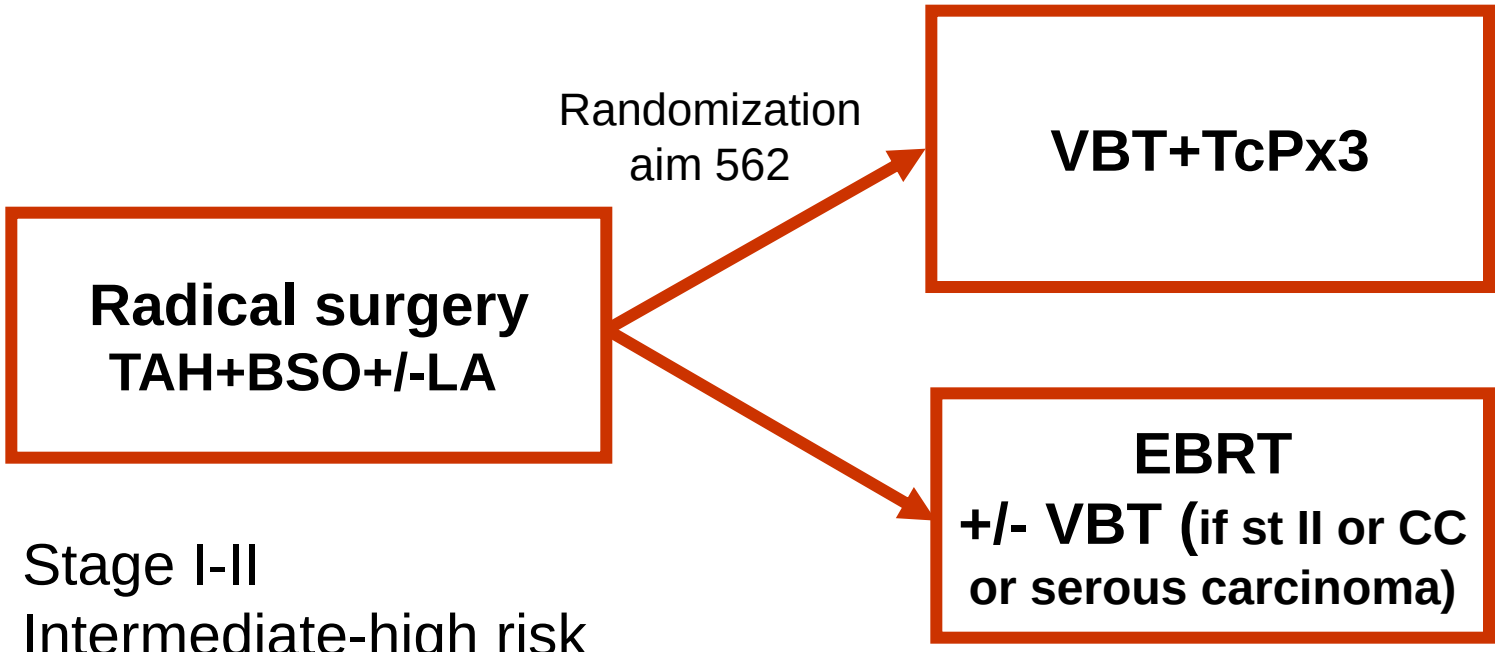
Chemotherapy (CT)

Concomitant chemo-radiotherapy

Sequential chemotherapy and radiotherapy

Vaginal brachytherapy and chemotherapy

GOG 249 ongoing



Stage I-II
Intermediate-high risk

Primary endpoint: RFS
Secondary endpoints: OS, vaginal recurrence, pelvic recurrence, distant recurrence, CSS, toxicity, and QoL

Audience Question

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Clinical case

- She is treated with pelvic radiotherapy and 18 months later returns for follow-up with complaints of persistent non-productive cough
- Chest x-ray reveals small bilateral pulmonary nodules (largest 1.8cm)
- Fine needle aspiration under CT guidance confirms endometrial adenocarcinoma
- CT scan of abdomen and pelvis shows no other evidence of recurrent disease

Audience Question
What would you recommend now?

1. Megestrol acetate (Megace)
2. Megestrol acetate alternating with tamoxifen
3. An aromatase inhibitor
4. Doxorubicin/epirubicin + cisplatin
5. Doxorubicin/epirubicin + cisplatin + paclitaxel
6. Carboplatin + paclitaxel

Discussion

- Thomas Hogberg

What would you recommend now?

Megestrol acetate (Megace)

Megestrol acetate alternating with tamoxifen

An aromatase inhibitor

Doxorubicin/epirubicin + cisplatin

Doxorubicin/epirubicin + cisplatin + paclitaxel

Carboplatin + paclitaxel

Endocrine treatment for advance or recurring EC

Table 1. Hormone studies by treatment type grouping

Hormone	Studies	Number	References	RR mean	Range	PFS mean	Range
Progestogens	8	1303	48, 49, 52–57	23	11–56	7.5	6–7
SERMs	7	319	26, 51, 58–61	29.8	10–53	4.9	1.9–7
Combinations	3	136	19, 23, 62, 63	25	5–33	4.6	1.8–5.8
Aromatase inhibitor	2	55	24, 64	10	NS	8.8	NS
GNRH analogs	5	143	18, 57, 65–67	28.8	7–58	NS	NS
Other	1	25	68	0	NS	NS	NS

NS, not stated; GNRH, gonadotrophin-releasing hormone; RR, response rate.

Decruze and Green Int J Gynecol Cancer 2007

- RR 11-56% PFS 2.5-14 months for progestogens in previously untreated patients with G1 or G2 tumors
- Higher response rates in progesterone receptor-positive case
- Heterogeneity between studies - meta-analysis was not possible
- G3 or G4 toxicity less than 5%
- Receptor-negative status should not be an absolute contra-indication
- Aromatase inhibitors an open question
- Low dose progesterone is better than high-dose (HR PFS 1.35, OS 1.31)*
- Sequential tamoxifen progesterone may be beneficial (phase II-data)**

Decruze and Green Int J Gynecol Cancer 2007
Kokka et al. Cochrane rev. The Cochrane library 2010

* Thigpen 1999
**Fiorica 2004, Whitney 2004

Audience Question

1. I always try to get receptor status before decision on endocrine therapy
    - I only use metastatic tissue if available
    - If I don´t get metastatic tissue I use tissue from the primary tumor
2. I don´t care about receptor status before decision on endocrine therapy, I chose salvage therapy individually mainly depending on the performance status of the patient

What would you recommend now?

Megestrol acetate (Megace)

Megestrol acetate alternating with tamoxifen

An aromatase inhibitor

Doxorubicin/epirubicin + cisplatin

Doxorubicin/epirubicin + cisplatin + paclitaxel

Carboplatin + paclitaxel

What chemotherapy?

Endometrial cancer is a chemosensitive tumor. Single drug phase II studies have shown response rates exceeding 20 % for

- Anthracyclines [doxorubicin (A), epirubicine (E)]
- Platinum drugs [cisplatin (P), carboplatin (cP)]
- Taxanes [paclitaxel (T), docetaxel (dT)]

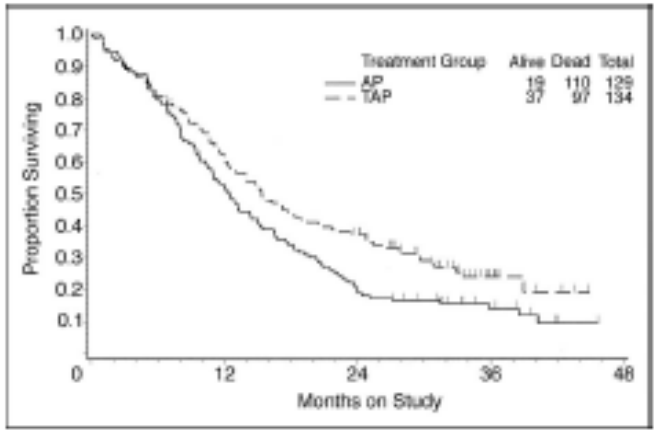
Standard for many years AP

Aapro et al. Ann Oncol 2003, Thigpen et al. J Clin Oncol 2004

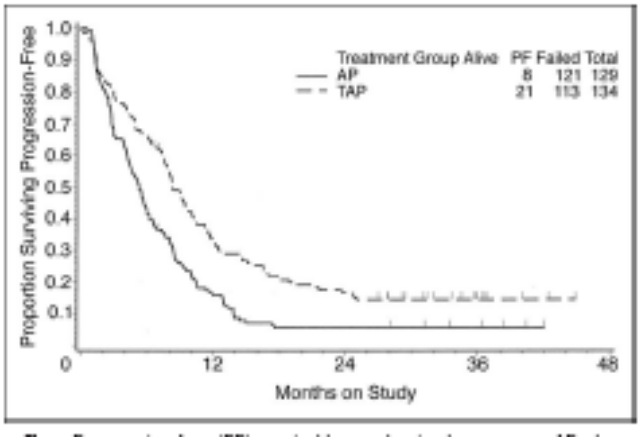
What chemotherapy?

GOG 177 - TAP versus AP. Fleming et al. J Clin Oncol 2004

OS

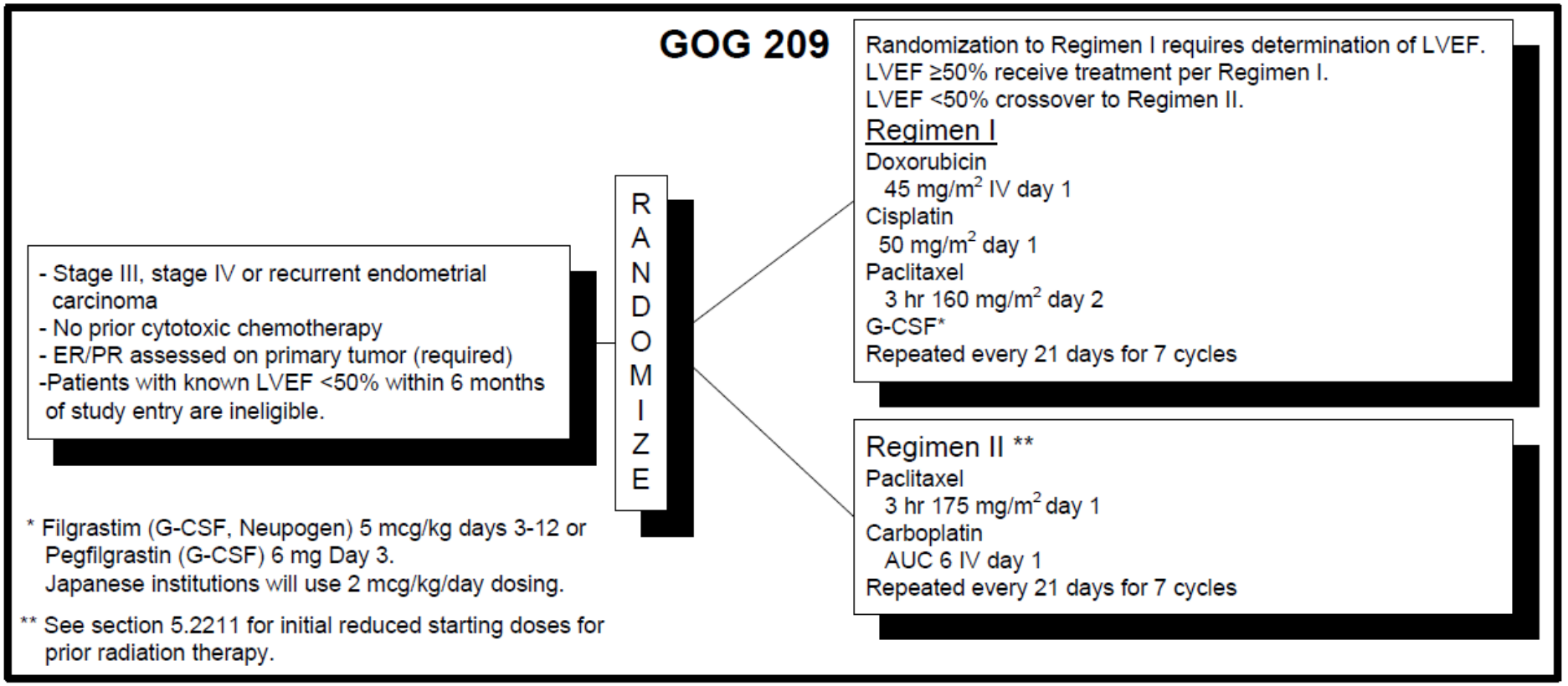


PFS



Paclitaxel 150, doxorubicin 60 and cisplatin 50 mg/m² (TAP) with filgrastim versus Doxorubicin 60 and cisplatin 50 mg/m² (AP)

OS and PFS better - but toxic



Slide from GOG – Miller et al. SGO 2012

GOG-209

Response		TAP		TC	
RECIST 1.0	**Total**	**n**	**%**	**n**	**%**
Complete	71	31	8.7	40	10.8
Partial	302	152	42.6	150	40.4
Stable	229	107	30.0	122	32.9
Increasing	47	17	4.8	30	8.1
Not evaluable	79	50	14.0	29	7.8

RR TAP 51.3% vs TC 51.2%

Slide from GOG – Miller et al. SGO 2012

GOG-209

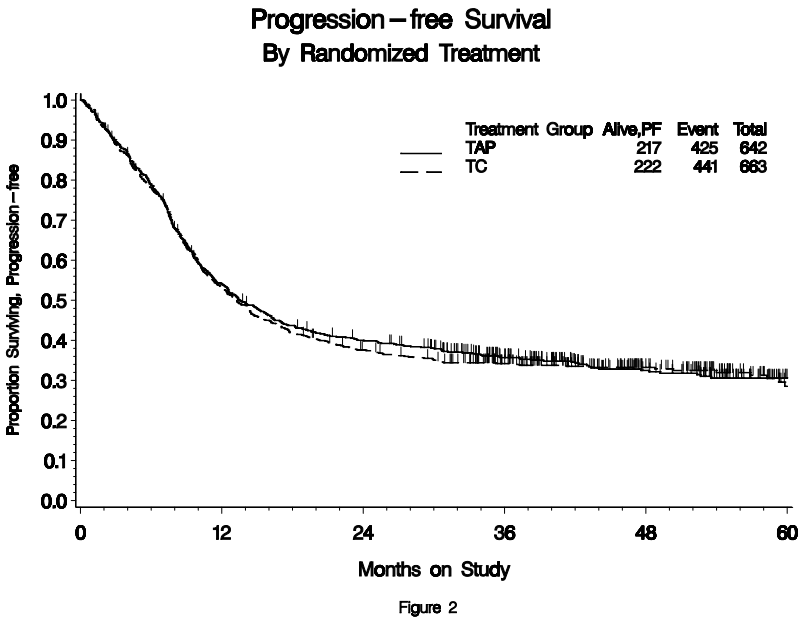


Figure 2

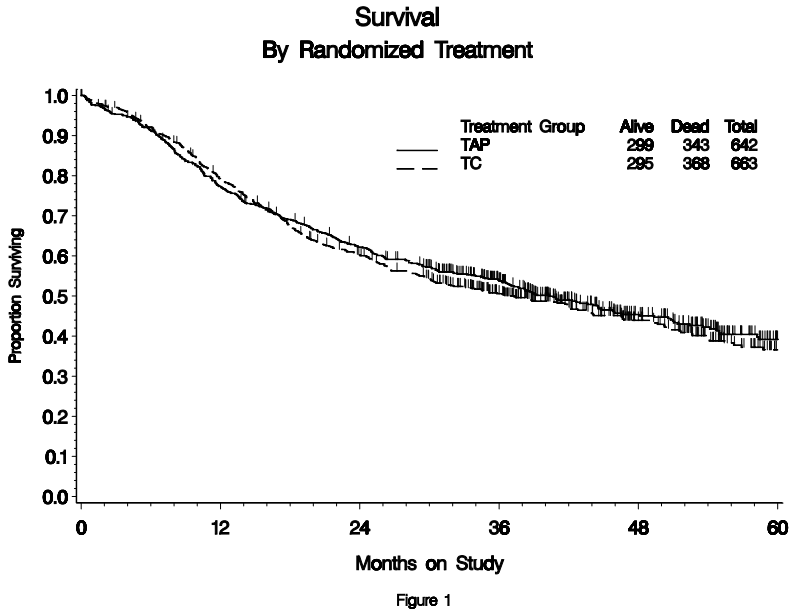


Figure 1

Median PFS (months) TAP 13.5 vs TC 13.3 HR=1.03

Median OS (months) TAP 40.3 vs TC 36.5 HR=1.05

Adjusted 90% upper confidence limit for the death hazard ratio (HR) of TC relative to TAP was 1.16 and excludes the inferiority region bounded at 1.2

Slide from GOG – Miller et al. SGO 2012

Adverse Effect	TAP		TC		
	Grade ≤ 2	Grade ≥ 3 (%)	Grade ≤ 2	Grade ≥ 3 (%)	p*
Neutropenia	300	327 (52.1)	133	522 (79.7)	<0.001
Thrombocytopenia	484	143 (22.8)	578	77 (11.8)	<0.001
Other Hematologic	435	192 (30.6)	516	139 (21.2)	<0.001
Fatigue	550	77 (12.3)	592	63 (9.6)	0.129
Nausea	571	56 (8.9)	618	37 (5.6)	0.024
Vomiting	583	44 (7.0)	632	23 (3.5)	0.006
Diarrhea	591	36 (5.7)	642	13 (2.0)	<0.001
Stomatitis	619	8 (1.3)	654	1 (0.2)	0.019
Other Gastrointestinal	581	46 (7.3)	623	32 (4.9)	0.079
Creatinine	615	12 (1.9)	651	4 (0.6)	0.044
Infection w/o neutropenia	606	21 (3.3)	643	12 (1.8)	0.111
Metabolic	541	86 (13.7)	604	51 (7.8)	<0.001
Myalgia	619	8 (1.3)	635	20 (3.0)	0.035
Arthralgia	621	6 (1.0)	637	18 (2.8)	0.022

*p-value from Fisher's Exact Test (two tail)

Slide from GOG – Miller et al. SGO 2012

Conclusion

- TC is not inferior to TAP in terms of PFS and OS based on interim analysis results
- Overall, the toxicity profile favors TC
- Thus, TC as prescribed in this study is an acceptable backbone for further trials in combination with "targeted" therapies

Slide from GOG – Miller et al. SGO 2012

Audience Question
What would you recommend now?

1. Megestrol acetate (Megace)
2. Megestrol acetate alternating with tamoxifen
3. An aromatase inhibitor
4. Doxorubicin/epirubicin + cisplatin
5. Doxorubicin/epirubicin + cisplatin + paclitaxel
6. Carboplatin + paclitaxel

2nd cancers after EBRT

Lonn et al Epidemiol Biomarkers Prev 2010

SEER 1973-2003 60,949 patients with EC surviving ≥1 year

IRR(incidence rate ratios) for 2nd cancers among irradiated patients vs those treated with surgery only

VBT	1.07 (95% CI 1.00-1.16)
EBRT	1.15 (95% CI 1.08-1.22)
EBRT+VBT	1.26 (95% CI 1.16-1.36)

11% of 2nd solid cancers ≥5 years after radiation could be attributed to RT

The risk for leukemia (excl CLL) and non-Hodgkin lymphoma were doubled

2nd cancers after EBRT

Kumar et al Gynecol Oncol 2009

SEER 1973-2004 90,502 patients with EC 52,182 got no RT and 5,563 developed 2nd cancers, 31,643 received RT and 4,203 developed 2nd cancers

RR for 2nd cancers among irradiated patients vs no irradiation

RR 1.25 (95% CI 1.20-1.29)
At ten years a 40% increased risk $p<0.001$

The increased risk of second cancers was most pronounced in the field of exposure and was affected by latency since exposure

Lindeman et al.:
Update of a 1980 Classic Trial

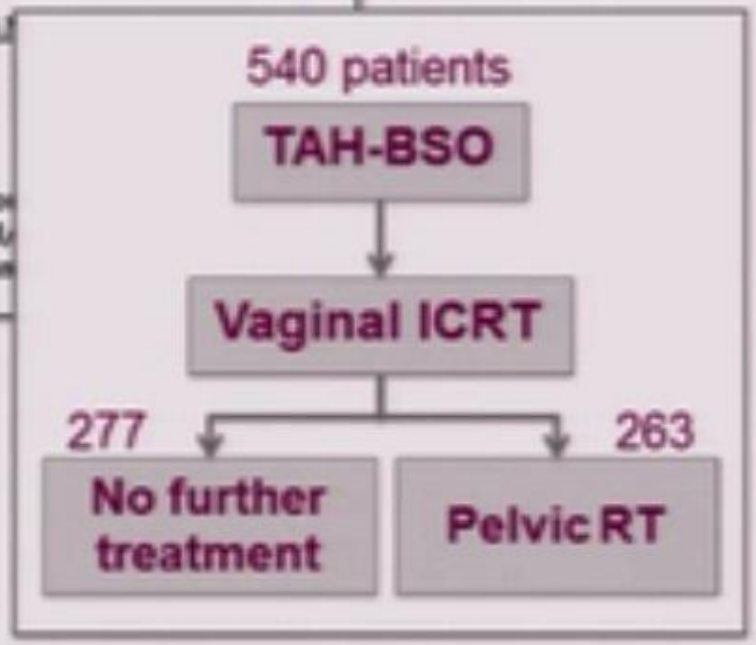
Postoperative External Irradiation and Prognostic Parameters in Stage I Endometrial Carcinoma

CLINICAL AND HISTOPATHOLOGIC STUDY OF 540 PATIENTS

JAN AALDERS, MD, VERA ABELER, MD, PER KOLSTAD, MD, A
MATHIAS ONSRUD, MD

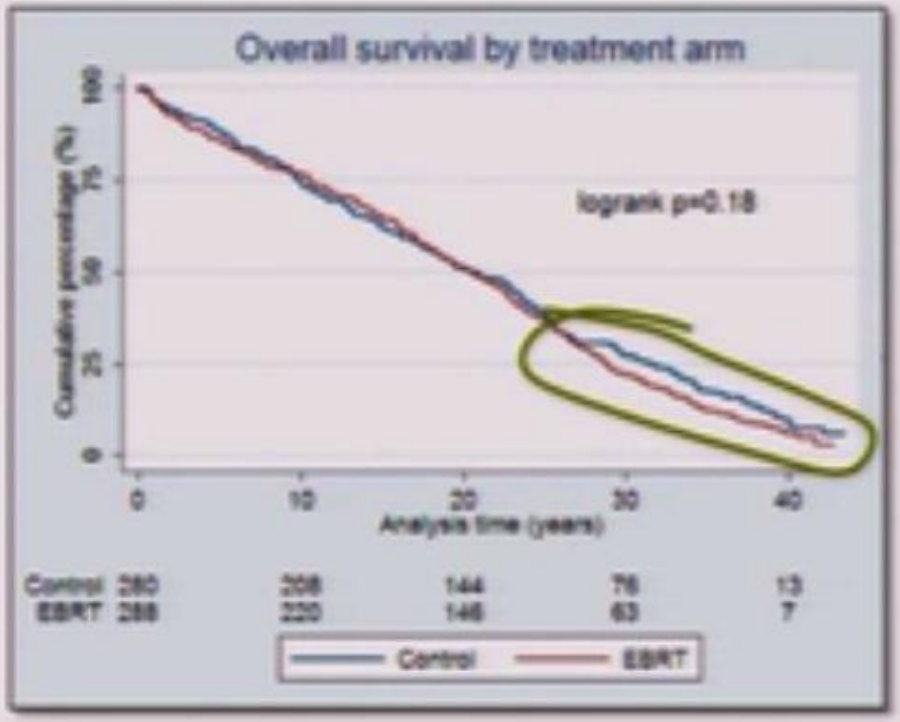
From 1968 to 1976, 540 patients with stage I adenocarcinoma of the corpus uteri entered a prospective clinical trial to evaluate the effect of postoperative external pelvic irradiation. After primary surgery all patients received intra-

recommendations vary fro
combined with removal and
vic lymph nodes[1-3] to radium
hysterectomy.[4-6]

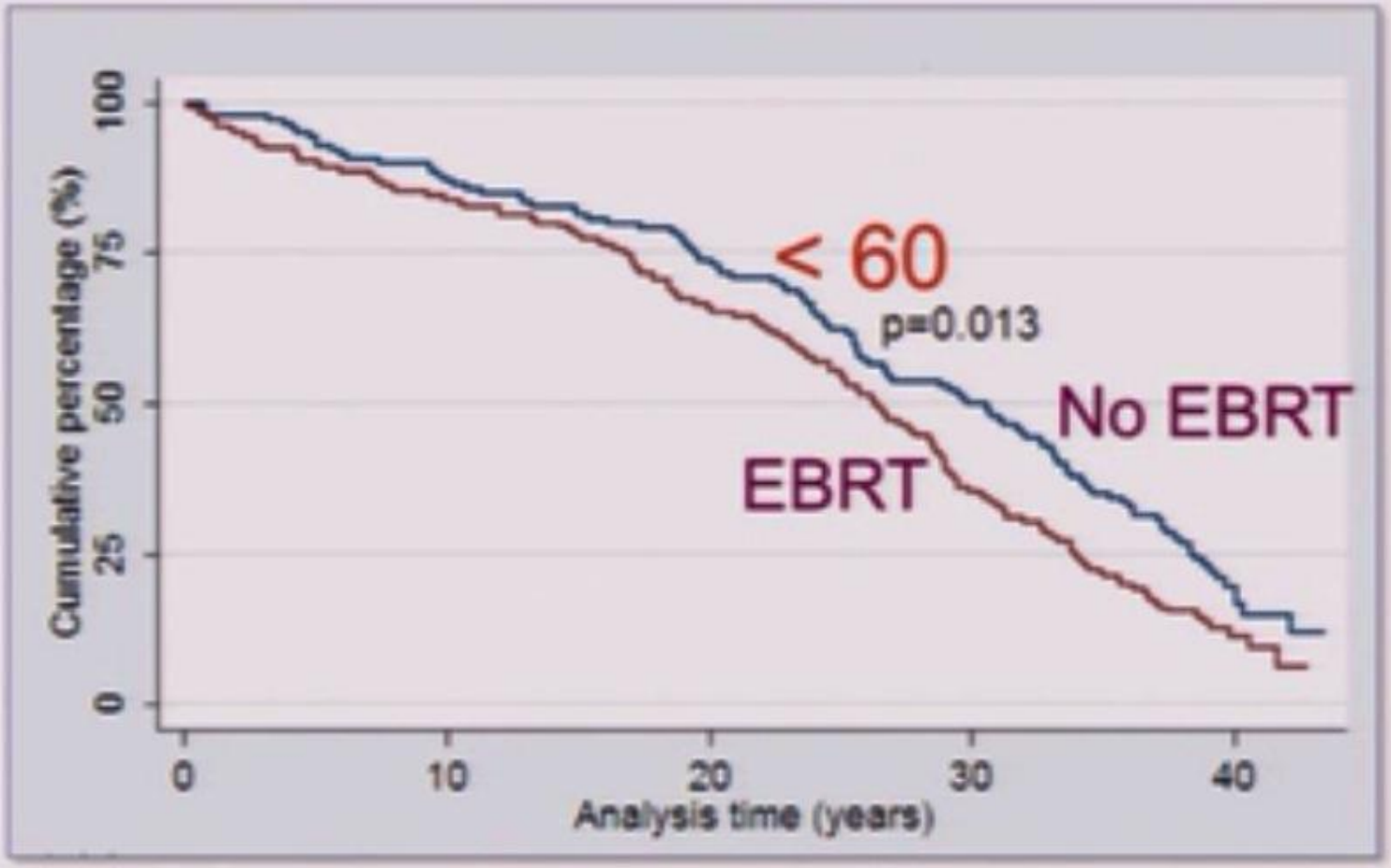


Lindeman et al.: Update of a 1980 Classic Trial

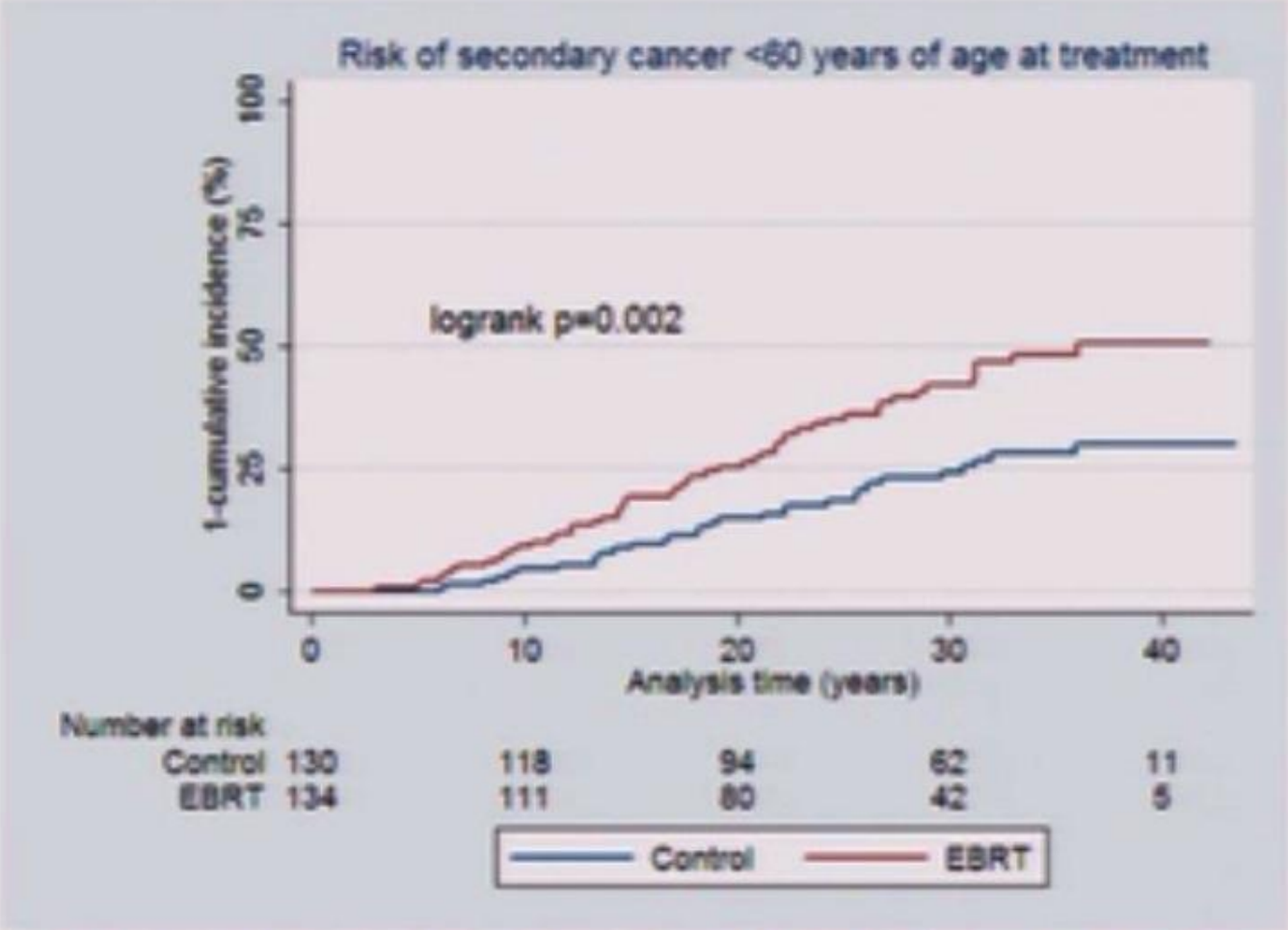
- 568 pts
  - Treated 1968-1974
  - Median age 60 years
- Extraordinary F/U
  - Median 20.5 years
  - Nearly complete
- Conclusions
  - No overall benefit
  - Harm > benefit for young patients—2nd cancers



Poorer outcome for young patients



Risk of secondary cancer <60 years – per protocol



Univariate Cox regression HR: 1.99 (95% CI: 1.27-3.10)