Updates on clinical trials in radiation therapy for gynecologic malignancies

Shira Felder

RADONC-GYNONC

Prince Margeret Hospital, University of Toronto

Zvi Symon, MD

RADONC, SHEBA

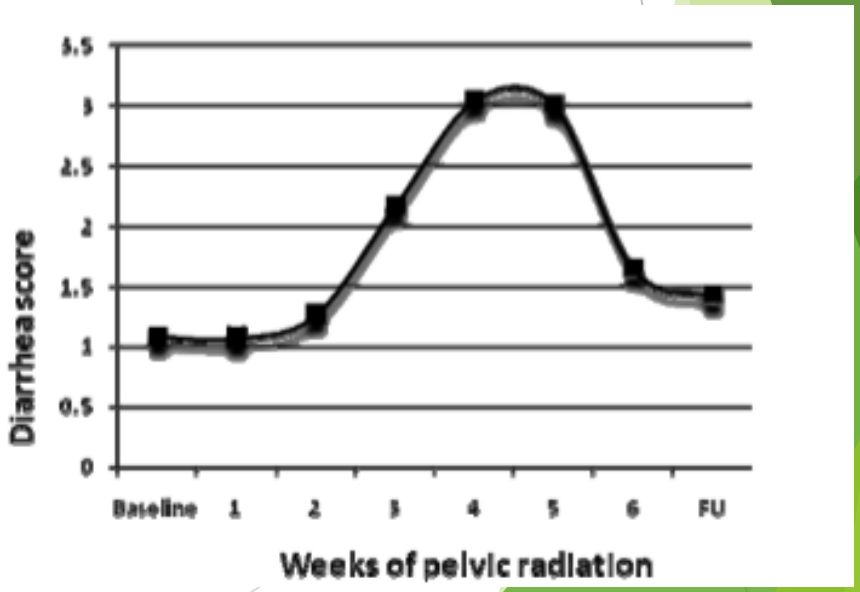
Adjuvant pelvic radiation therapy for Endometrial and Cervical cancer-

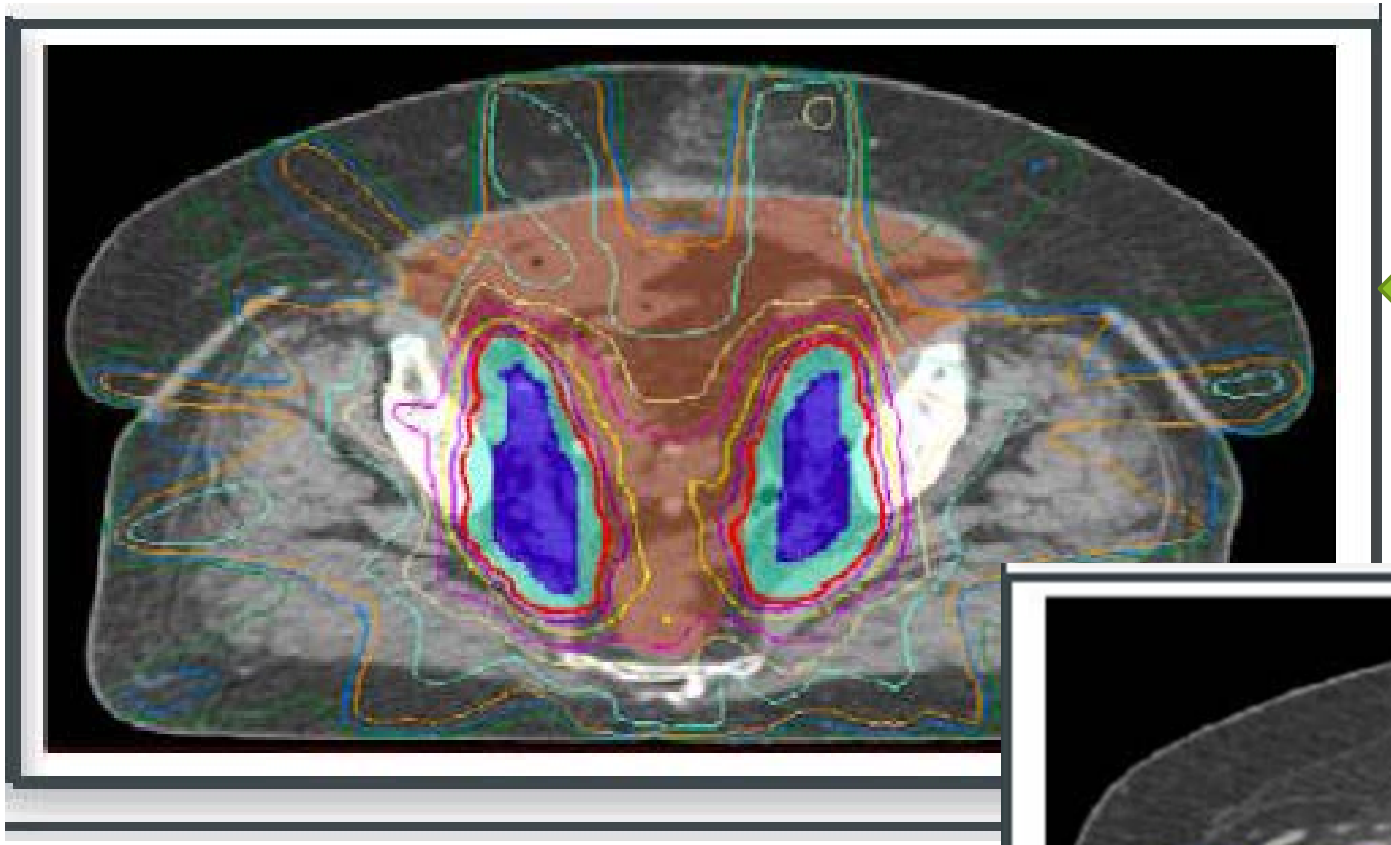
3D versus IMRT

RTOG 12-03 (TIME-C)

- A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

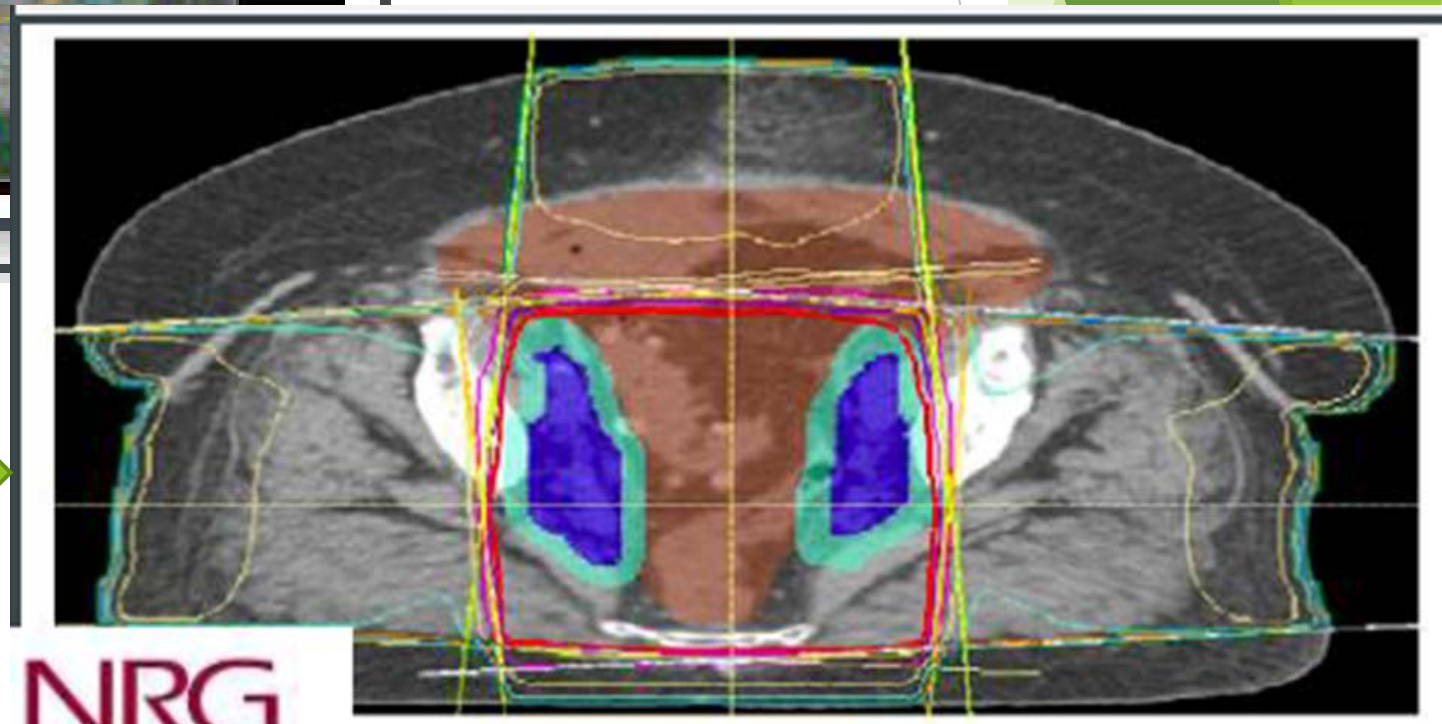
- **Primary Objective**
  - To determine if IMRT reduces acute gastrointestinal toxicity in the 5th week (after 23-25 fractions) of pelvic radiation as measured with EPIC (expanded prostate cancer index composite).





IMRT

4 FIELD BOX



NRG ONCOLOGY™

Plenary session, ASTRO 2016

SCHEMA

STRATIFY		RANDOMIZE	
	XRT Dose 1. 45 Gy 2. 50.4 Gy **Chemotherapy** 1. No Chemotherapy 2. 5 cycles of weekly cisplatin at 40mg/m2 **Disease Site** 1. Endometrial 2. Cervix		**Arm 1** IMRT pelvic radiation treatment
			Arm 2 4-field pelvic radiation treatment

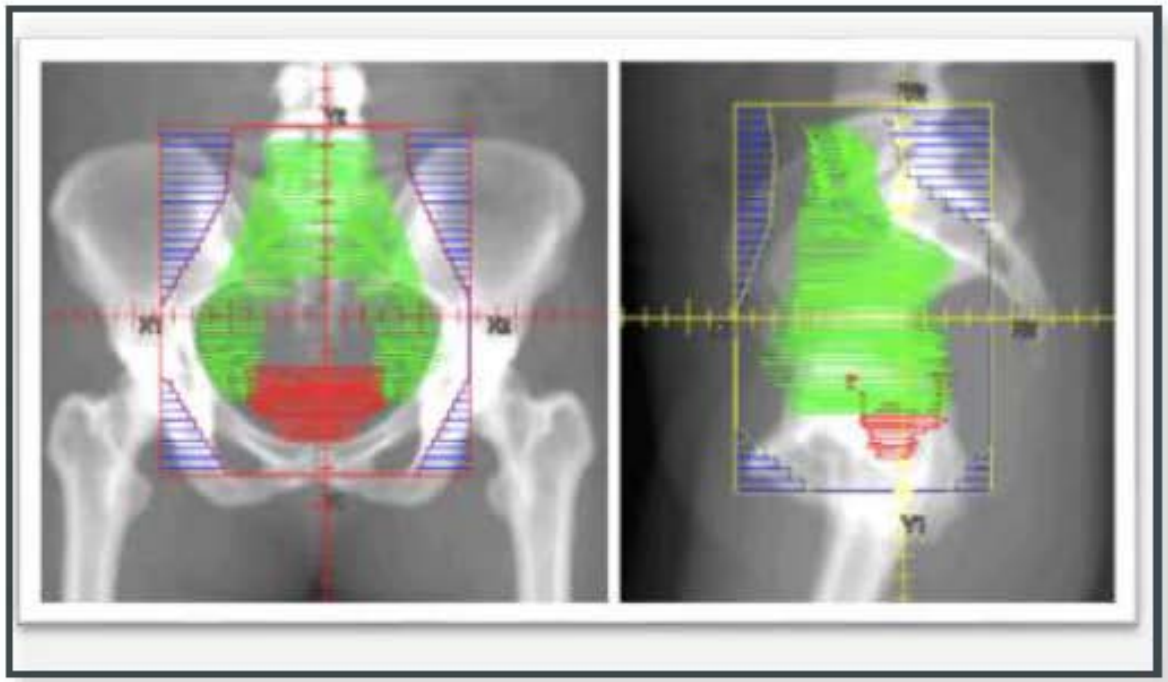
* Addition of HDR vaginal brachytherapy (2 fractions of 6GY prescribed at the surface) -at the discretion of the treating physician

Treatment planning

IMRT planning

- Nodal CTV
  - -RTOG atlas
- Vaginal
  - -ITV w bladder full and empty
- 7mm PTV expansion
- OARs: Bone marrow, bowel, bladder, rectum

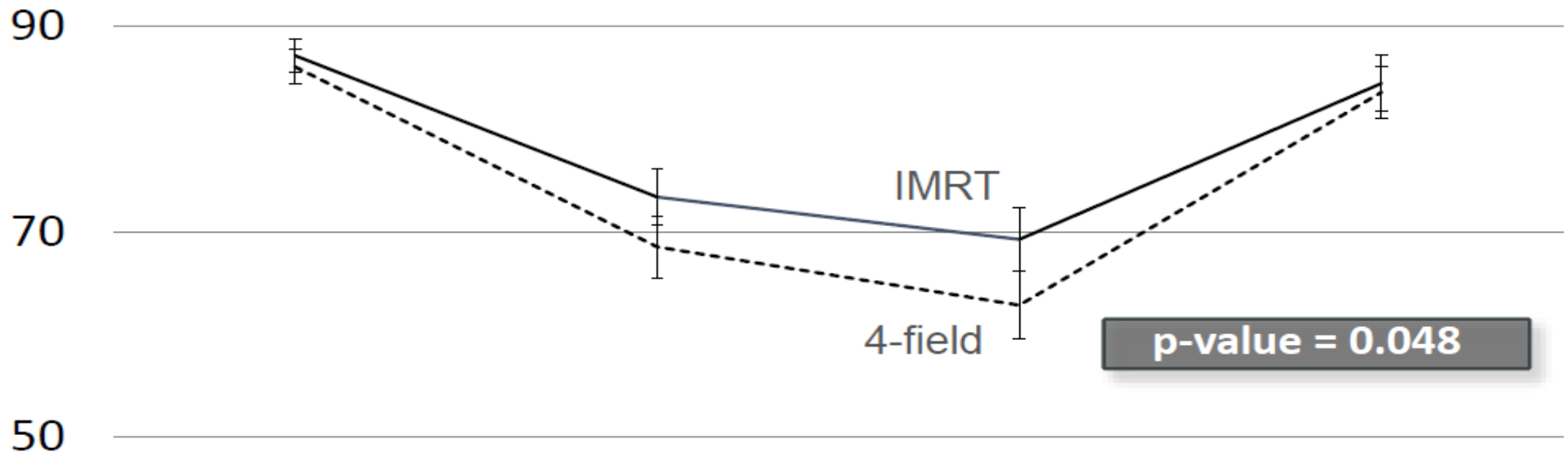
Standard RT



Rapid review of contours and plans required on the first case on each arm for a site.

RESULTS

EPIC Bowel Score



	Baseline	Week 3 of RT	Week 5 of RT	4-6 weeks post-RT
IMRT	128	113	111	102
4 Field	148	132	130	125

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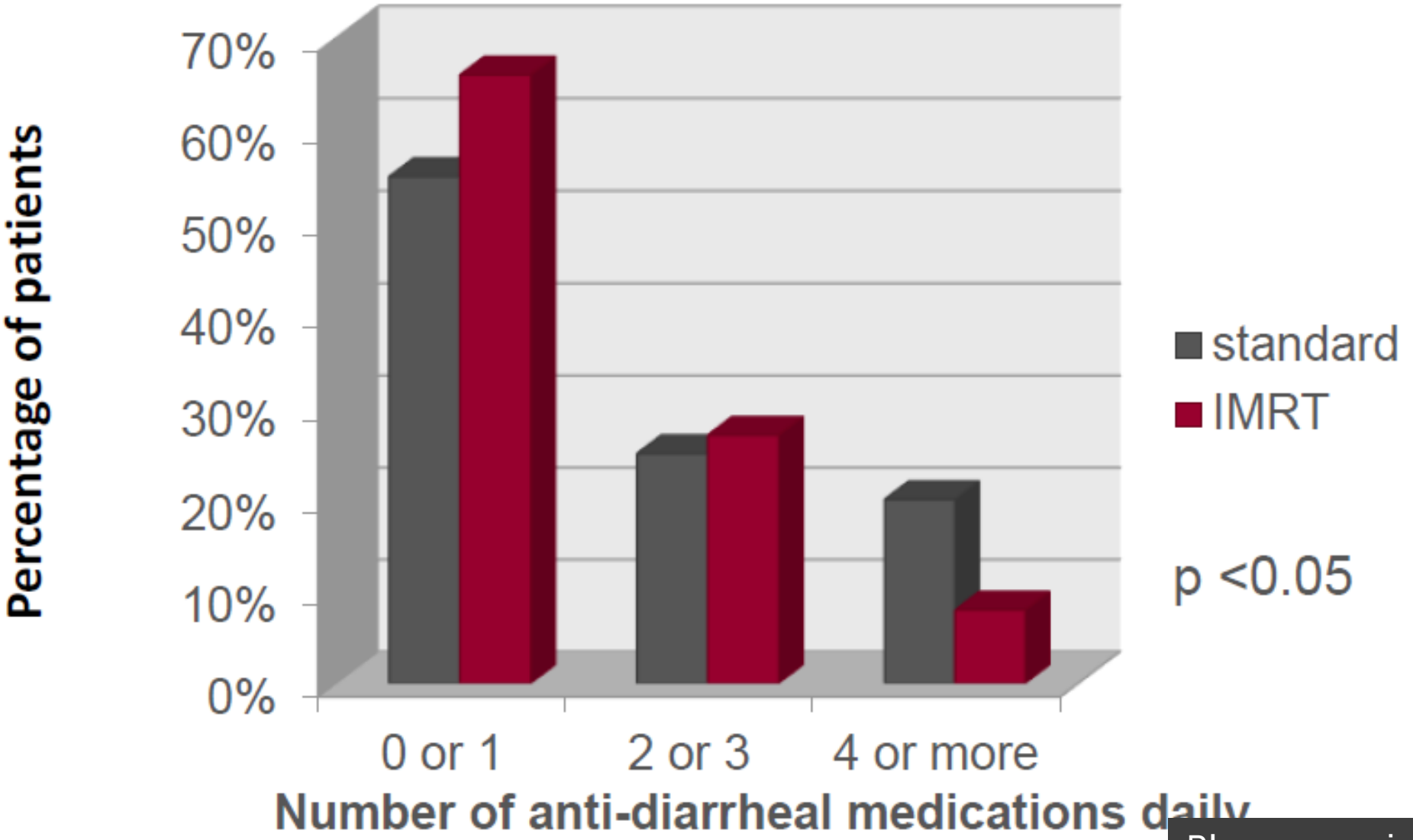
Use of Anti-Diarrheal Medications



Plenary session, ASTRO 2016

Conclusions

Pelvic IMRT reduces acute patient reported GI and GU toxicity compared to standard pelvic RT.

Pelvic IMRT reduces need for anti-diarrheal medications as compared to standard pelvic RT.

Pelvic IMRT improves quality of life with regard to physical functioning and other treatment effects during treatment .

Longer term follow up will be needed to determine if these differences in acute toxicity result in lower rates of late toxicity.

MRI-Guided Brachytherapy

EMBRACE (an international study on MRI-guided BRachytherapy in locally Advanced CErvical cancer)

- Prospective, observational, multi-center trial (24 centers located in Europe, Asia, and North America)
- Enrollment between 2008-2015, >1200 pts accrued
- MRI at diagnosis and at time of (first) BT with applicator in place required
- Contouring and reporting of dose as per the GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiation Oncology) recommendations *

* Haie-Meder, Christine, et al. *Radiotherapy and Oncology* 74.3 (2005): 235-245.
* Pötter, Richard, et al. *Radiotherapy and Oncology* 78.1 (2006): 67-77.
* Dimopoulos, Johannes CA, et al. *Radiotherapy and Oncology* 103.1 (2012): 113-122.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Image guided brachytherapy in cervical cancer

Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study ☆

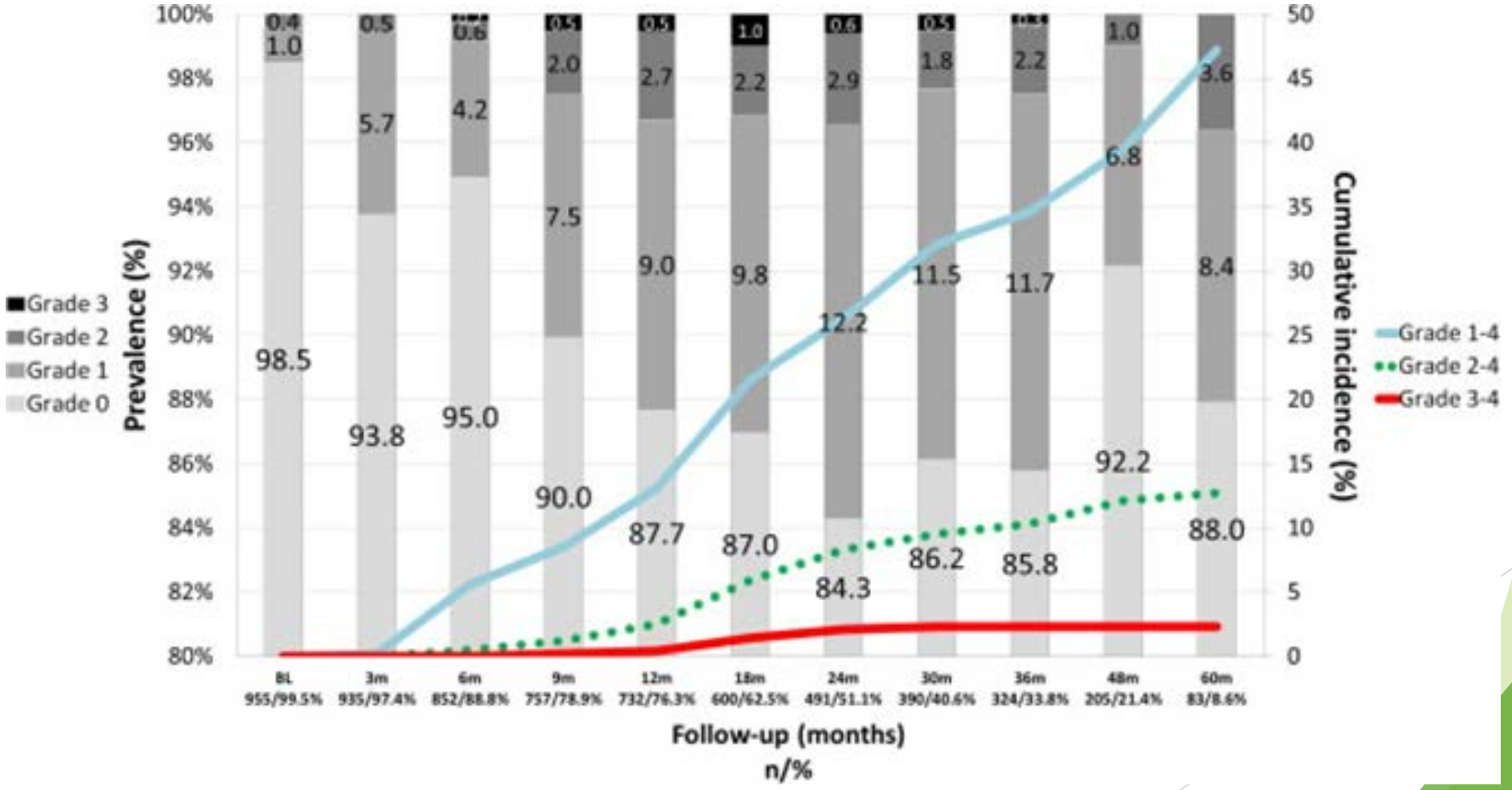
Renaud Mazeron [a,*], Lars U. Fokdal [b], Kathrin Kirchheiner [c], Petra Georg [c], Noha Jastaniyah [c], Barbara Šegedin [d], Umesh Mahantshetty [e], Peter Hoskin [f], Ina Jürgenliemk-Schulz [g], Christian Kirisits [c], Jacob C. Lindegaard [b], Wolfgang Dörr [c], Christine Haie-Meder [a], Kari Tanderup [b], Richard Pötter [c], on behalf of the EMBRACE collaborative group[1]

[a] *Department of Radiotherapy, Gustave Roussy, University of Paris-Saclay, Villejuif, France;* [b] *Department of Oncology, Aarhus University Hospital, Denmark;* [c] *Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna/General Hospital of Vienna, Austria;* [d] *Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia;* [e] *Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India;* [f] *Department of Radiotherapy, Mount Vernon Cancer Centre, United Kingdom; and* [g] *Department of Radiotherapy, University Medical Center Utrecht, The Netherlands*

METHODS AND RESULTS

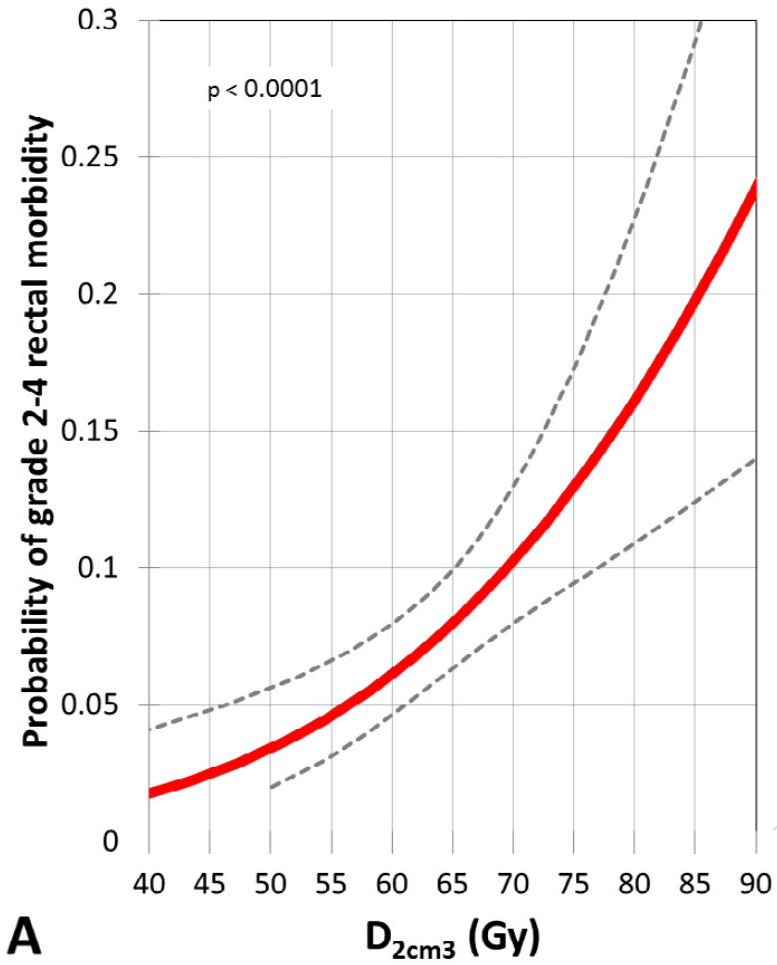
- 960 patients included
- Median follow-up of 25.4 months
- Rectal bleeding, stenosis, proctitis, rectovag fistula and overall rectal morbidity scored according to the CTC-AE 3.0
- Increase dose to D2cc of the rectum was associated with worse rectal toxicity:
  - increase severity of rectal bleeding, proctitis, fistula and overall rectal morbidity (grade 1–4) ($p < 0.001$)
  - No impact on rectal stenosis

Incidence and prevalence of rectal morbidity



The probability of grade 2–4 rectal morbidity according to dose

- D_{2cm}^{3} <55 Gy- 3.5%
- D_{2cm}^{3} 55–60 Gy - 6.5%
- D_{2cm}^{3} 60–65 Gy - 8.6%
- D_{2cm}^{3} 65-70 Gy - 15.1%
- D_{2cm}^{3} 70-75 Gy -18.0%
- D_{2cm}^{3} >75 Gy - 26.0%



Radiotherapy and Oncology 118 (2016) 160–166

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Brachytherapy

Dose–effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study

Kathrin Kirchheiner [a,*], Remi A. Nout [b], Jacob C. Lindegaard [c], Christine Haie-Meder [d], Umesh Mahantshetty [e], Barbara Segedin [f], Ina M. Jürgenliemk-Schulz [g], Peter J. Hoskin [h], Bhavana Rai [i], Wolfgang Dörr [a,j], Christian Kirisits [a], Søren M. Bentzen [k], Richard Pötter [a,j], Kari Tanderup [c], the EMBRACE Collaborative Group [1]

[a] Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna/General Hospital of Vienna, Austria; [b] Department of Radiation Oncology, Leiden University Medical Center, The Netherlands; [c] Department of Oncology, Aarhus University Hospital, Denmark; [d] Department of Radiotherapy, Gustave-Roussy, Villejuif, France; [e] Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India; [f] Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia; [g] Department of Radiation Oncology, University Medical Centre, Utrecht, The Netherlands; [h] Cancer Centre, Mount Vernon Hospital, London, UK; [i] Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [j] Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria; and [k] Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, USA

METHODS AND RESULTS

- 630 patients included
- Median follow-up of 24 months
- 2-year actuarial estimate for vaginal stenosis ≥ grade 2 (shortening and/or narrowing interfering with function) was 21%
- Risk factors for vaginal stenosis:
  - Recto-vaginal reference point dose
  - External-beam radiotherapy (EBRT) dose >45 Gy/25 fractions tumor
  - Vaginal extension of tumor

Recto-vaginal reference point

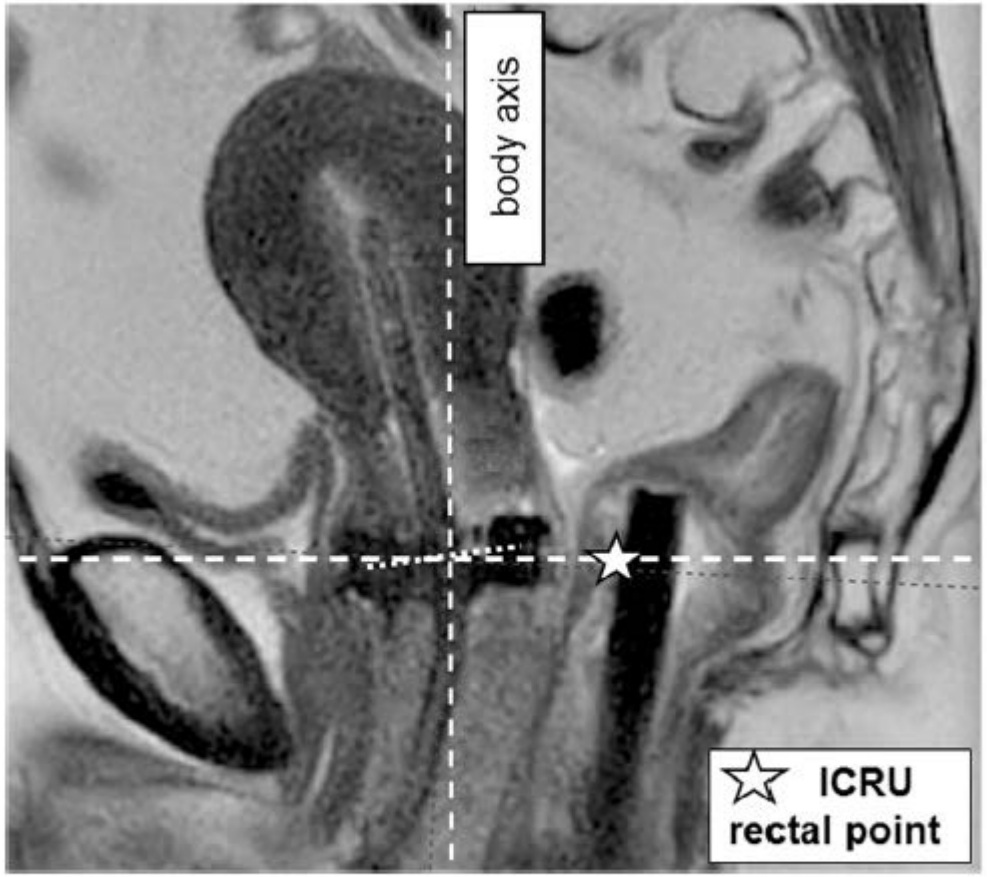
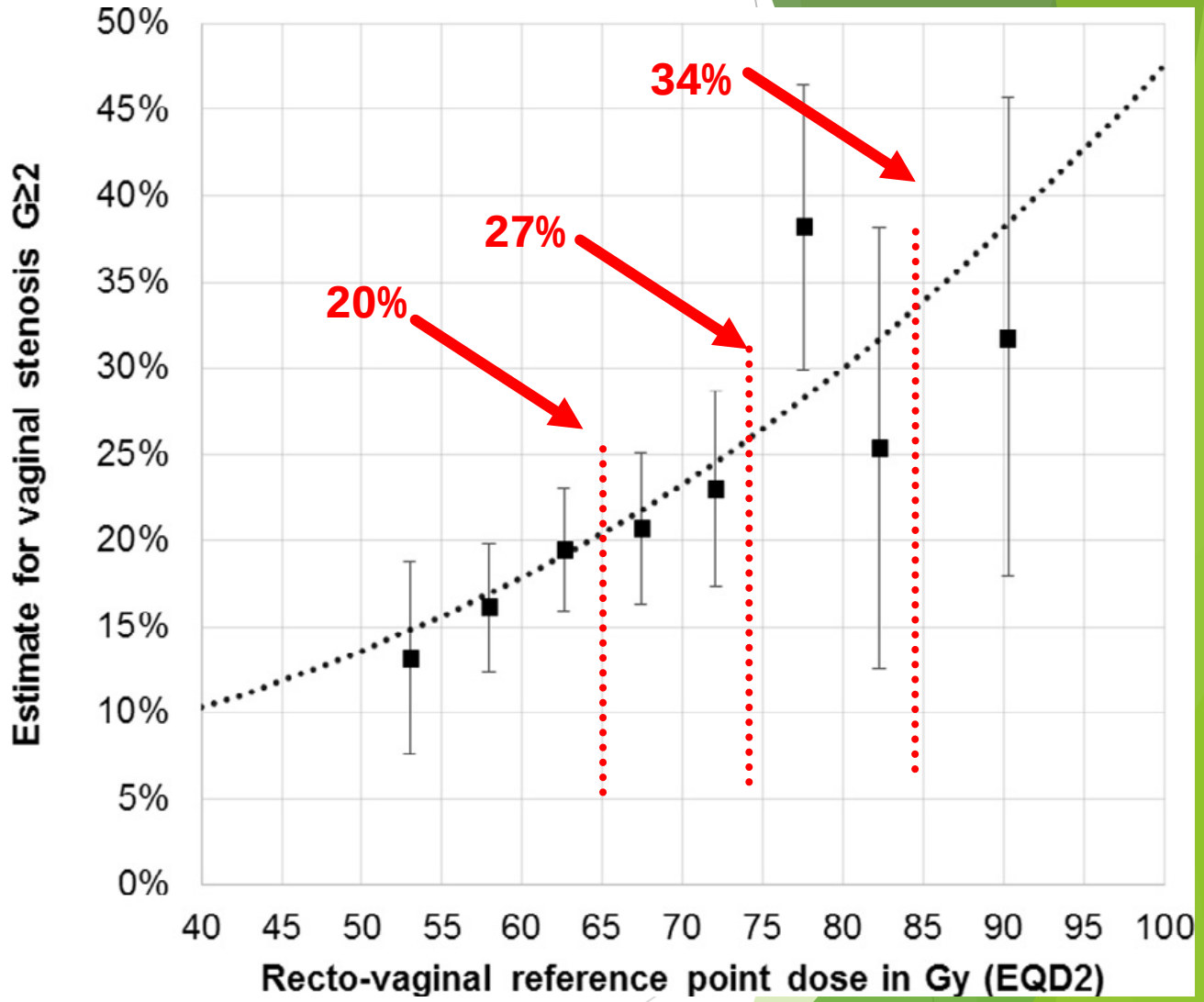


Fig. 1. ICRU rectal point depicted on sagittal T2 MRI, positioned at the intersection level between tandem and the source positions in the ring and 5 mm dorsal of the posterior vaginal wall on the axis perpendicular to the body axis.



Recommendation – Dose ≤65 Gy EQD2 (EBRT + brachytherapy dose) to the recto-vaginal reference point.

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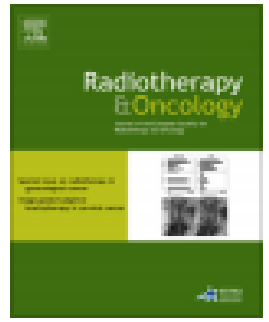


Image guided brachytherapy in cervical cancer

Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

Alina Sturdza [a], Richard Pötter [a,*], Lars Ulrik Fokdal [b], Christine Haie-Meder [c], Li Tee Tan [d], Renaud Mazeron [c], Primoz Petric [e], Barbara Šegedin [e], Ina Maria Jurgenliemk-Schulz [f], Christel Nomden [f], Charles Gillham [g], Orla McArdle [g], Erik Van Limbergen [h], Hilde Janssen [h], Peter Hoskin [i], Gerry Lowe [i], Ekkasit Tharavichitkul [j], Elena Villafranca [k], Umesh Mahantshetty [l], Petra Georg [a], Kathrin Kirchheiner [a], Christian Kirisits [a], Kari Tanderup [b], Jacob Christian Lindegaard [b]

[a] *Medical University of Vienna, Comprehensive Cancer Center, Department of Radiation Oncology, Austria;* [b] *Aarhus University Hospital, Department of Oncology, Denmark;* [c] *Gustave Roussy Cancer Campus Grand Paris, Department of Radiation Oncology, Villejuif, France;* [d] *Cambridge University Addenbrooke's Hospital, Department of Radiotherapy, United Kingdom;* [e] *Institute of Oncology Ljubljana, Division of Radiotherapy, Slovenia;* [f] *University Medical Center Utrecht, Department of Radiotherapy, The Netherlands;* [g] *St Luke's Hospital, Dublin, Ireland;* [h] *Department of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium;* [i] *Mount Vernon Hospital, Department of Radiotherapy, London, United Kingdom;* [j] *Faculty of Medicine, Chiang Mai University, Thailand; and* [k] *University of Navarra, Department of Oncology, Pamplona, Spain;* [l] *Tata Memorial Hospital, Mumbai, India*

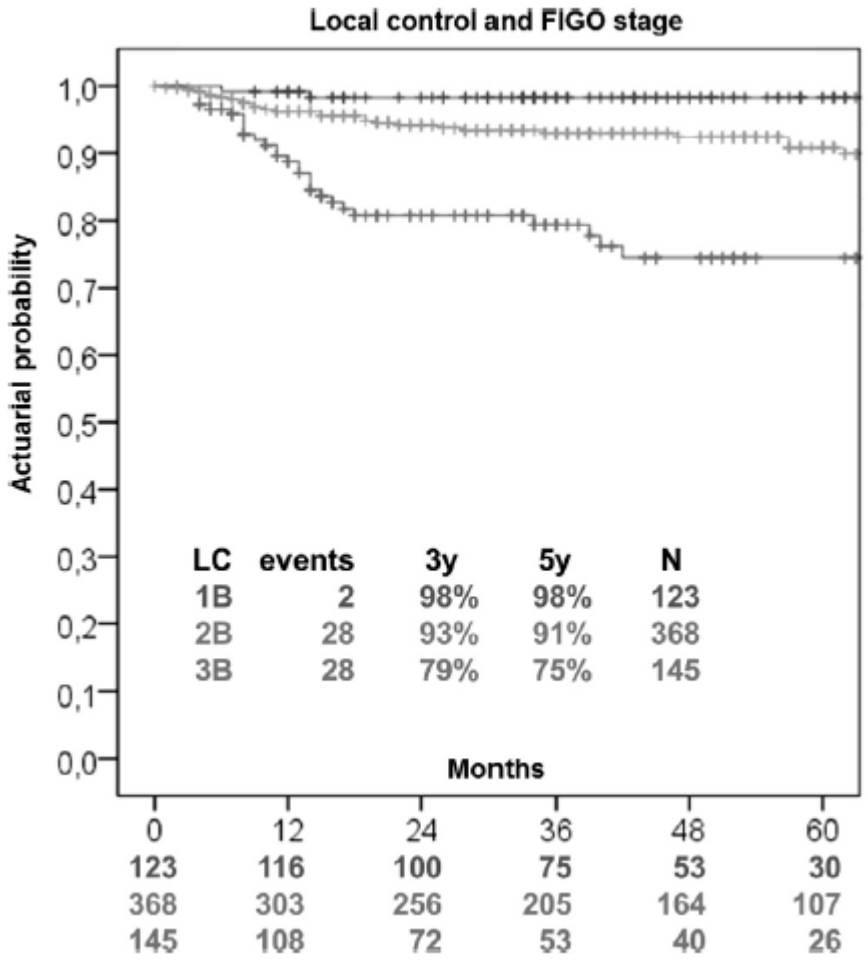
METHODS

- RetroEmbrace is a Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer. Reporting has to be done according to GEC ESTRO recommendations

- 731 patients from 12 centers
- Median follow up was 43 months

- Mean D90 HRCTV was 87 ± 15 Gy (EQD2)

Good local control with MRI guided brachytherapy



- Local Control at 3/5 years:
  - IB - 98%/98%
  - IIB - 93%/91%
  - IIIB -79%/75%
- Cancer specific survival at 3/5 years:
  - IB - 93%/90%
  - IIB - 83%/77%
  - IIIB - 65%/53%
- 5-year G3–G5 morbidity
  - Bladder-5%
  - Gastrointestinal tract-7%
  - Vagina -5%

So how can we increase the dose and at the same time reduce toxicity ? (In other words- How do we improve the “therapeutic ratio”) ?

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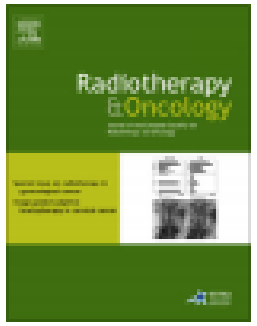


Image guided brachytherapy in cervical cancer

Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: Analysis from the retroEMBRACE study

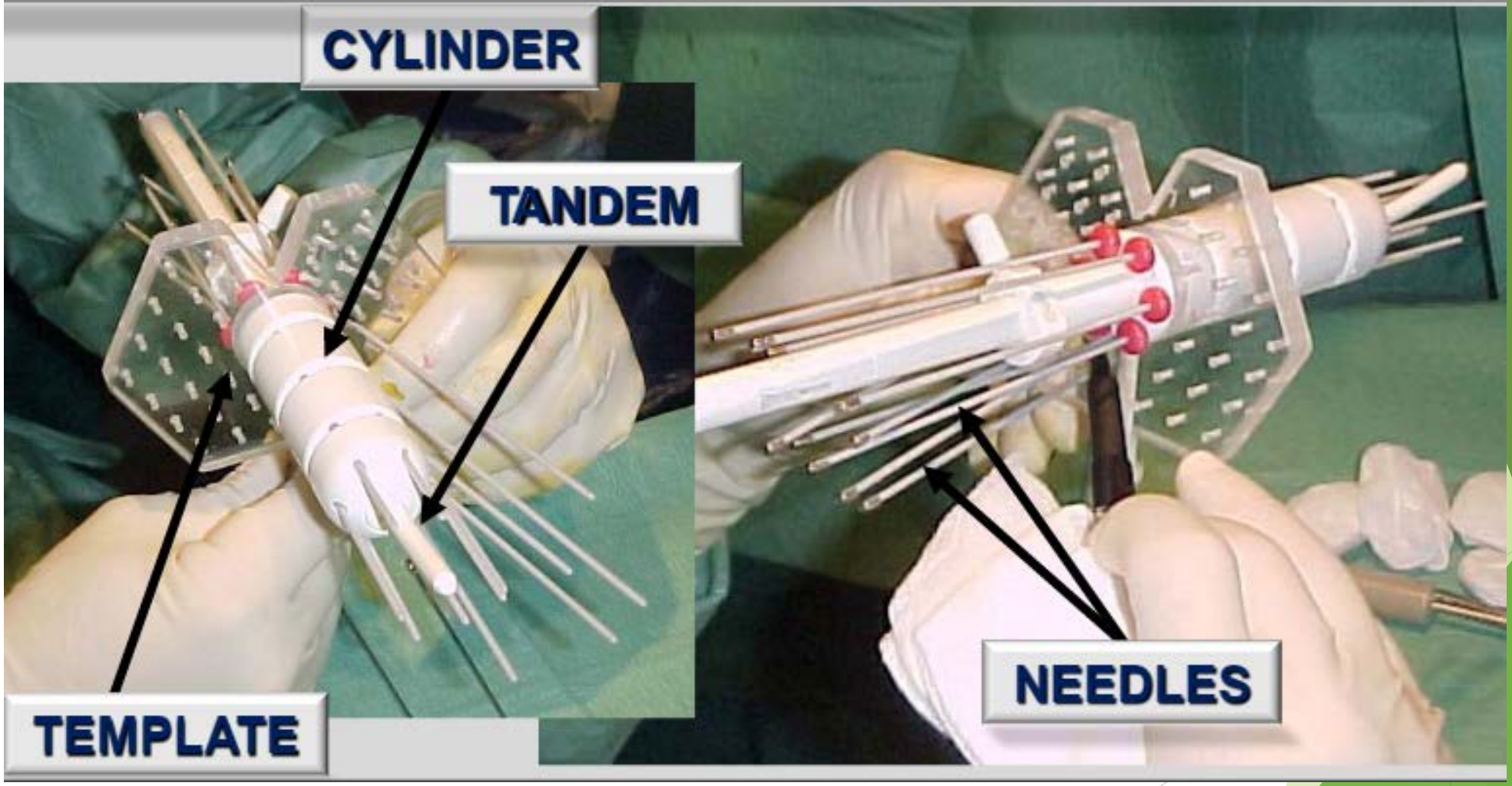
Lars Fokdal [a,*], Alina Sturdza [b], Renaud Mazeron [c], Christine Haie-Meder [c], Li Tee Tan [d], Charles Gillham [e], Barbara Šegedin [f], Ina Jürgenliemk-Schultz [g], Christian Kirisits [b], Peter Hoskin [h], Richard Pötter [b], Jacob C. Lindegaard [a], Kari Tanderup [a]

[a] Department of Oncology, Aarhus University Hospital, Denmark; [b] Department of Radiation Oncology, Medical University of Vienna, Austria; [c] Radiation Oncology Department, Gustave Roussy Cancer Campus Grand Paris, France; [d] Departments of Oncology, Radiology and Gynae-oncology, Addenbrooke's Hospital, Cambridge University Hospitals National Health Service Trust, United Kingdom; [e] Department of Radiation Oncology, St Luke's Hospital, Dublin, Ireland; [f] Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia; [g] Department of Radiation Oncology, University Medical Centre, Utrecht, The Netherlands; and [h] Cancer Centre, Mount Vernon Hospital, London, United Kingdom

METHODS

- 610 patients with LACC from the retroEMBRACE study (Web-based database with a retrospective multicentre collection of data on 3D RT plus IGABT in cervical cancer)
- 310 patients in the IC (INTRACAVITARY ALONE) group vs. 300 patients in the IC/IS (INTRACAVITARY +INTERSTITIAL) group
- The IC/IS group was defined from the time point, when a center performed IC/IS brachytherapy in more than 20% of cases

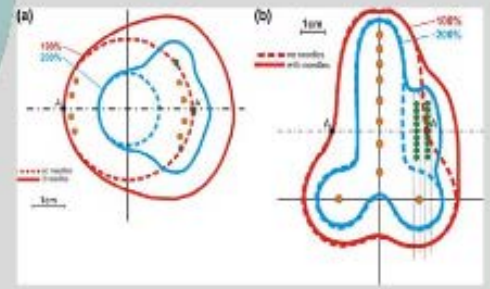
MRI-compatible cylinder + tandem + template



@ Umesh Mahantshetty, ESTRO – CARO TEACHING COURSE ON IMAGE-GUIDED RADIOTHERAPY & CHEMOTHERAPY IN CERVICAL CANCER – WITH A SPECIAL FOCUS ON ADAPTIVE BRACHYTHERAPY TORONTO: 4-6 APRIL 2016

The Vienna Applicator

Intercavitary / interstitial
Tandem-Ring Applicator

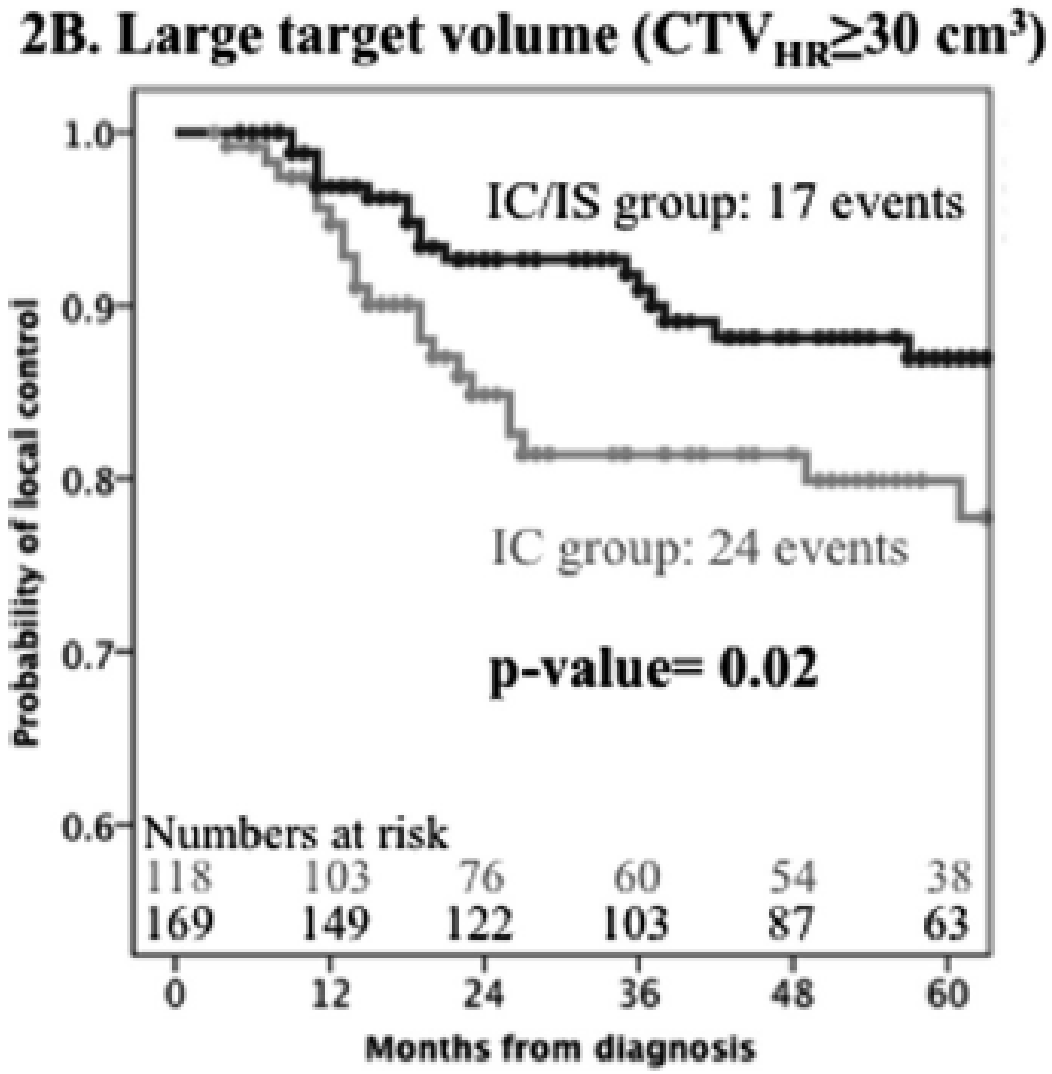


Modified Applicator: drilled holes into ring to insert needles parallel to the Tandem

Kirisits et al. IJROBP 2006 (technical note)

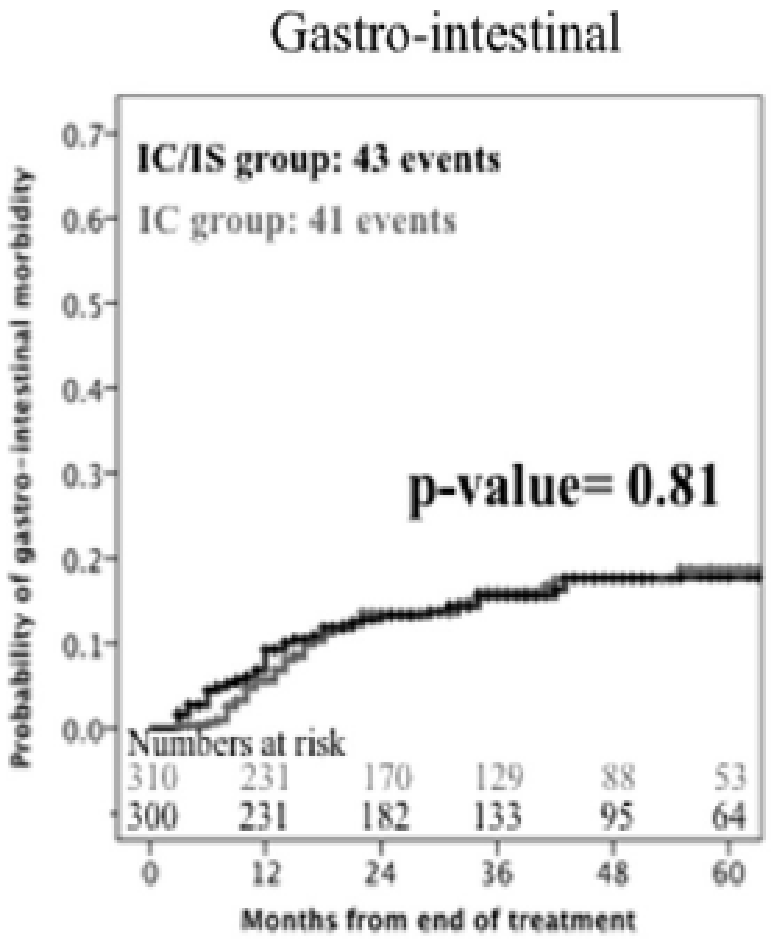
Dimopoulos et al. IJROBP 2006 (clinical results)

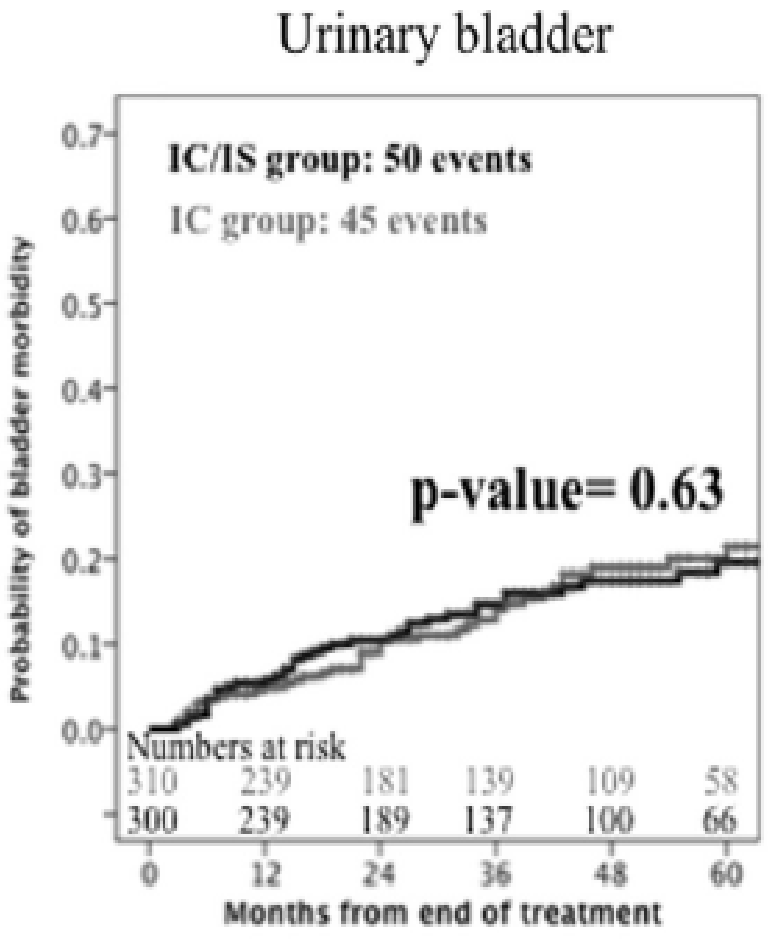
Local control for large tumors

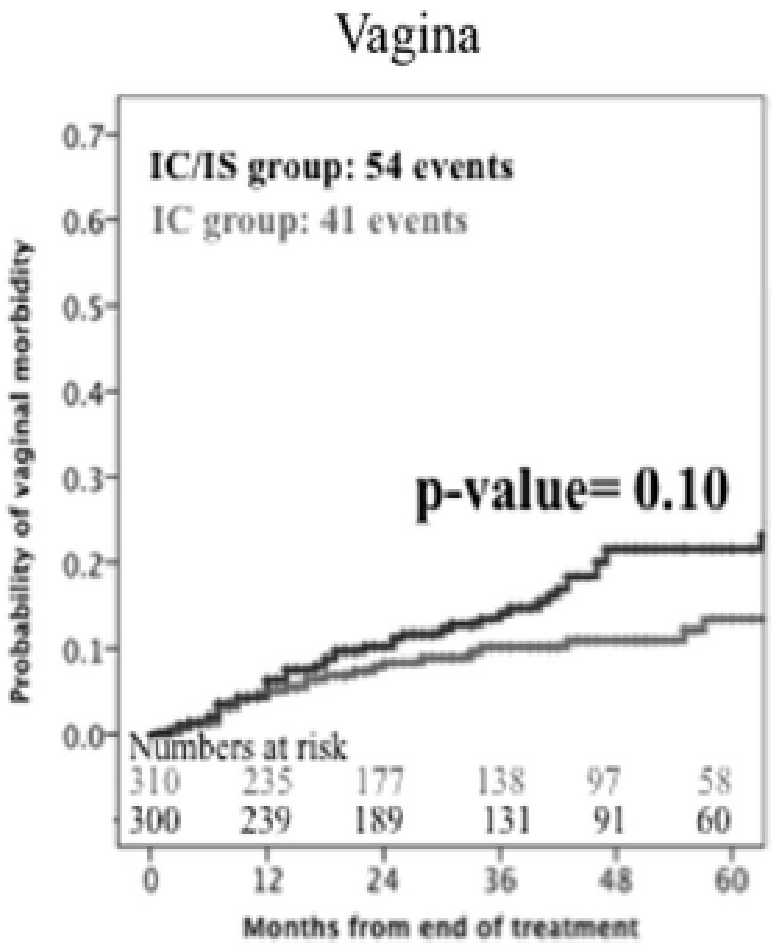


Grade 2-5 late toxicity

Grade 2-5







EMBRACE II

- Prospective interventional and observational study
- >25 centers, anticipating 1000 patients in 4 years
- Sub-studies on:
  - Adaptive EBRT
  - Vaginal morbidity
  - Functional imaging
  - Translational research

EMBRACE II-PROTOCOL

Target	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV_{res} $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-
OAR	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm^3} $EQD2_3$	Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*	< 75 Gy*

** Planning aims (soft constraints) and limits for prescribed dose (hard constraints) for treatment planning in Embrace II. The EQD2 include 45 Gy/25 fractions delivered by EBRT.

INTERMEDIATE RISK ENDOMETRIAL CANCER – adjuvant treatment

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Nomograms for Prediction of Outcome With or Without Adjuvant Radiation Therapy for Patients With Endometrial Cancer: A Pooled Analysis of PORTEC-1 and PORTEC-2 Trials

Carien L. Creutzberg, MD, PhD,* Ruud G.P.M. van Stiphout, MSc, PhD,† Remi A. Nout, MD, PhD,* Ludy C.H.W. Lutgens, MD, PhD,† Ina M. Jürgenliemk-Schulz, MD, PhD,‡ Jan J. Jobsen, MD, PhD,§ Vincent T.H.B.M. Smit, MD, PhD,‖ and Philippe Lambin, MD, PhD†

*Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; †Department of Radiation Oncology, MAASTRO, GROW, University Medical Centre Maastricht, Maastricht, The Netherlands; ‡Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; §Department of Radiotherapy, Medisch Spectrum Twente, Enschede, The Netherlands; and ‖Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

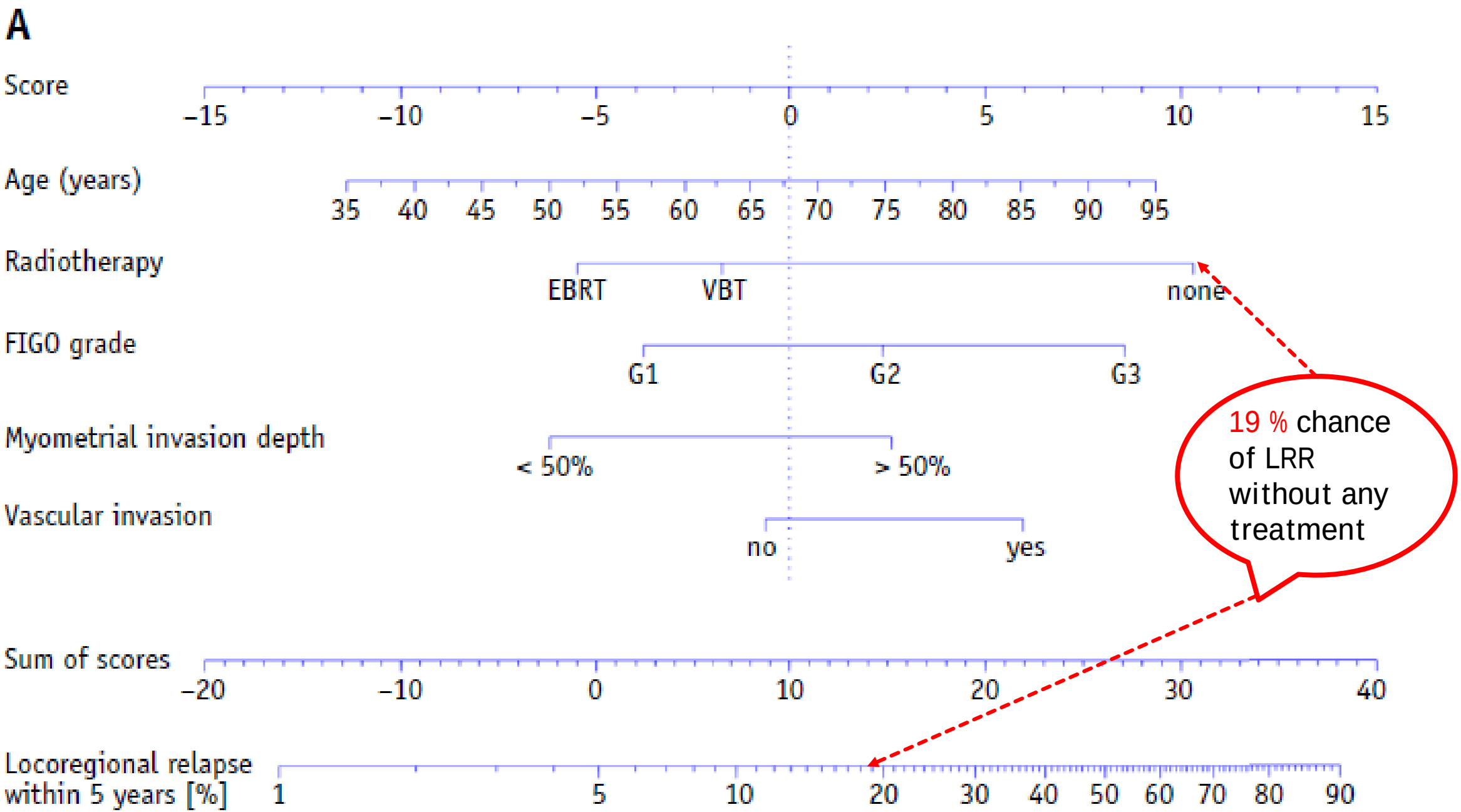
THE PORTEC TRIALS

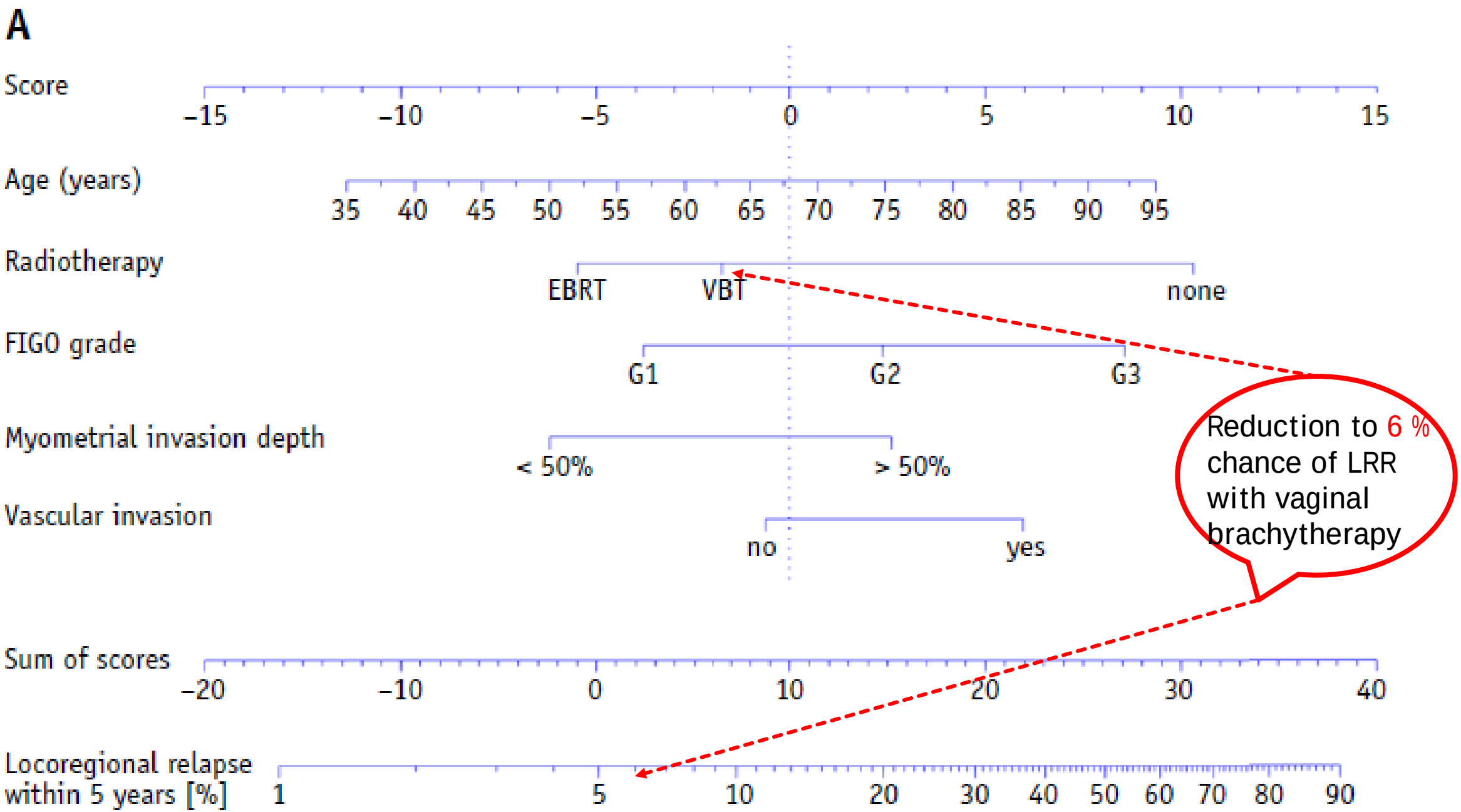
- PORTEC 1 Trial- Showed a decrease in 15 years locoregional recurrence from 25% to 5% with adjuvant pelvic radiation versus no adjuvant treatment in high – Intermediate risk endometrial cancer patients.
- PORTEC 2 Trial – Compared adjuvant pelvic radiation to vaginal brachytherapy in high –Intermediate risk endometrial cancer patients. Relapse-free survival, distant metastasis and overall survival were similar between the two groups.

EXAMPLE

65 yo lady with IB (> 50% myometrial invasion) grade 2 endometrioid adenocarcinoma with no LVSI

What is her risk for local recurrence with no adjuvant treatment, vaginal brachytherapy or EBRT ?


A
Score
−15
−10
−5
0
5
10
15
Age (years)
35
40
45
50
55
60
65
70
75
80
85
90
95
Radiotherapy
EBRT
VBT
none
FIGO grade
G1
G2
G3
Myometrial invasion depth
< 50%
> 50%
Vascular invasion
no
yes
19 % chance of LRR without any treatment
Sum of scores
−20
−10
0
10
20
30
40
Locoregional relapse within 5 years [%]
1
5
10
20
30
40
50
60
70
80
90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Score
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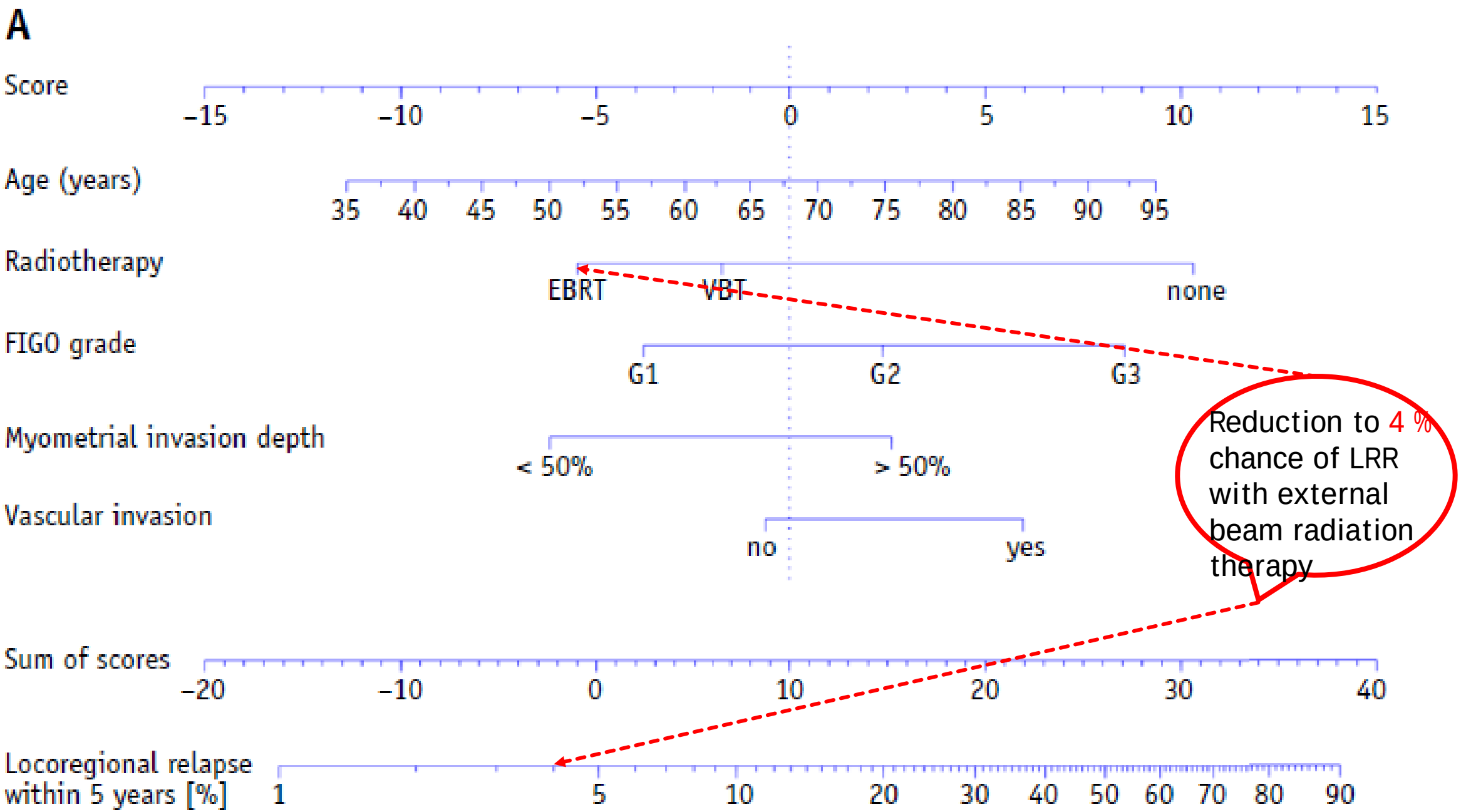
−5
0
5
10
15
Age (years)
35
40
45
50
55
60
65
70
75
80
85
90
95
Radiotherapy
EBRT
VBT
none
FIGO grade
G1
G2
G3
Myometrial invasion depth
< 50%
> 50%
Vascular invasion
no
yes
Reduction to 6 % chance of LRR with vaginal brachytherapy
Sum of scores
−20
−10
0
10
20
30
40
Locoregional relapse within 5 years [%]
1
5
10
20
30
40
50
60
70
80
90


A
Score
−15
−10
−5
0
5
10
15
Age (years)
35
40
45
50
55
60
65
70
75
80
85
90
95
Radiotherapy
EBRT
VBT
none
FIGO grade
G1
G2
G3
Myometrial invasion depth
< 50%
> 50%
Vascular invasion
no
yes
Reduction to 4 % chance of LRR with external beam radiation therapy
Sum of scores
−20
−10
0
10
20
30
40
Locoregional relapse within 5 years [%]
1
5
10
20
30
40
50
60
70
80
90

VULVAR CANCER

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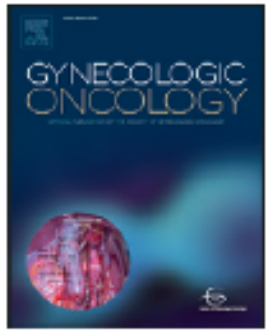


Prognostic importance of human papillomavirus (HPV) and p16 positivity in squamous cell carcinoma of the vulva treated with radiotherapy

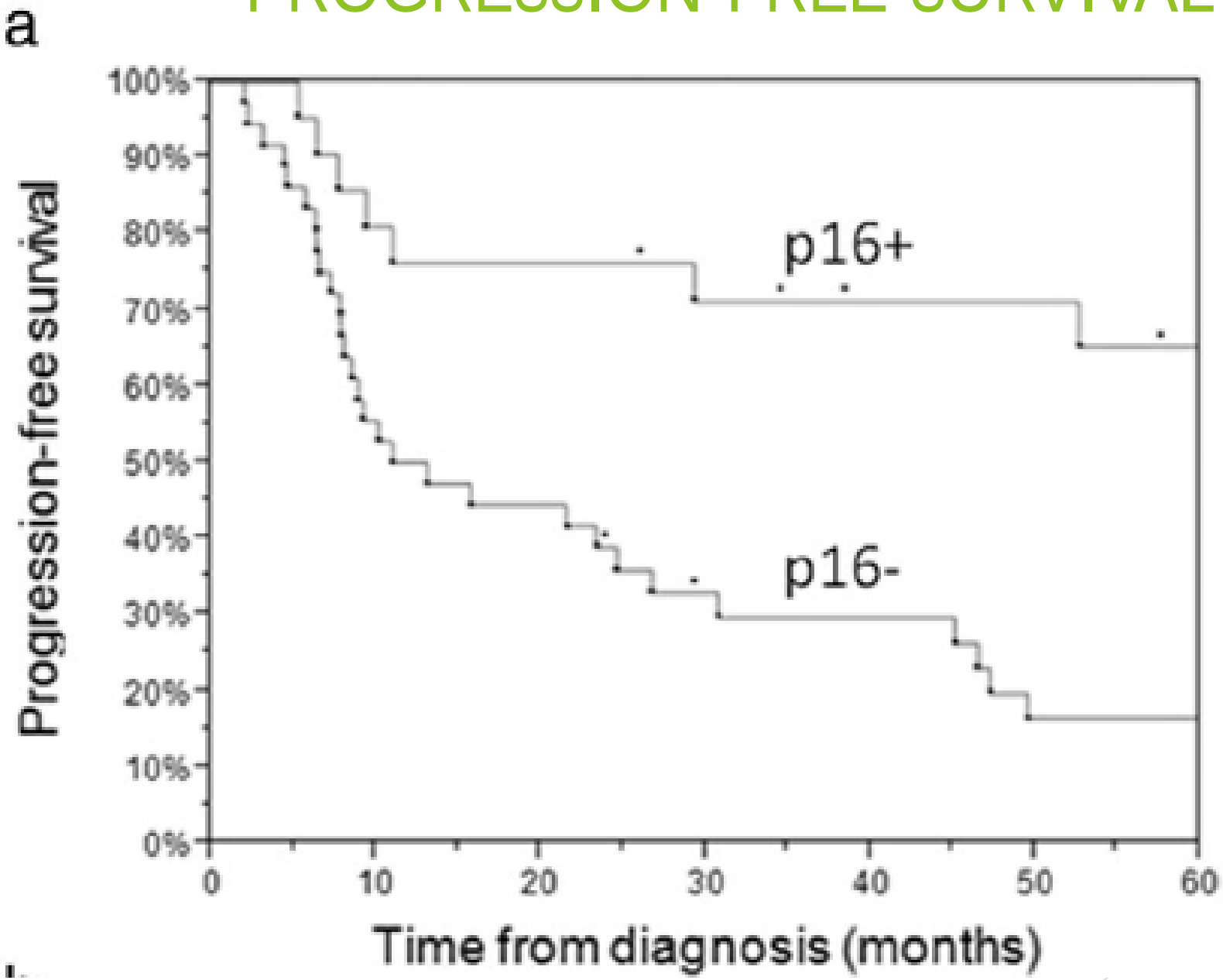
Larissa J. Lee [a,f,*], Brooke Howitt [b,f], Paul Catalano [d,f], Cynthia Tanaka [a], Rita Murphy [a], Nicole Cimbak [a], Rebecca DeMaria [a], Paula Bu [a], Christopher Crum [b,f], Neil Horowitz [c,f], Ursula Matulonis [e,f], Akila N. Viswanathan [a,f]

June 3rd, 2016

BACKGROUND

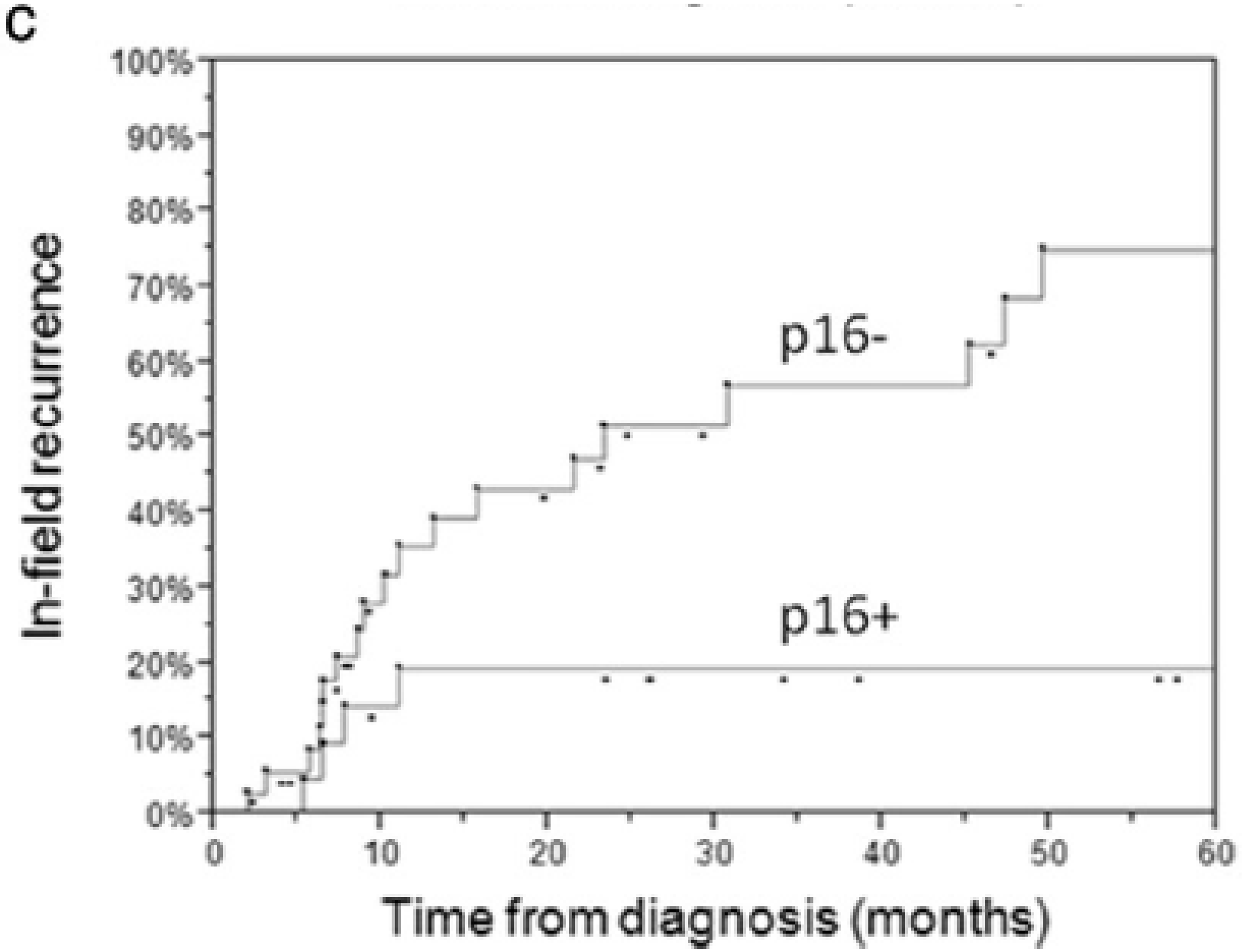
- 40% of vulvar SCCs are related to HPV infection
  - esp. young women, smokers
- ~60% of vulvar SCCs related to chronic inflammatory dermatosis or autoimmune condition, most commonly lichen sclerosus
- HPV is a known predictive marker for patients with oropharyngeal and anal cancers treated with radiotherapy

PROGRESSION FREE SURVIVAL



5y PFS
65% vs.16%
P =0.02

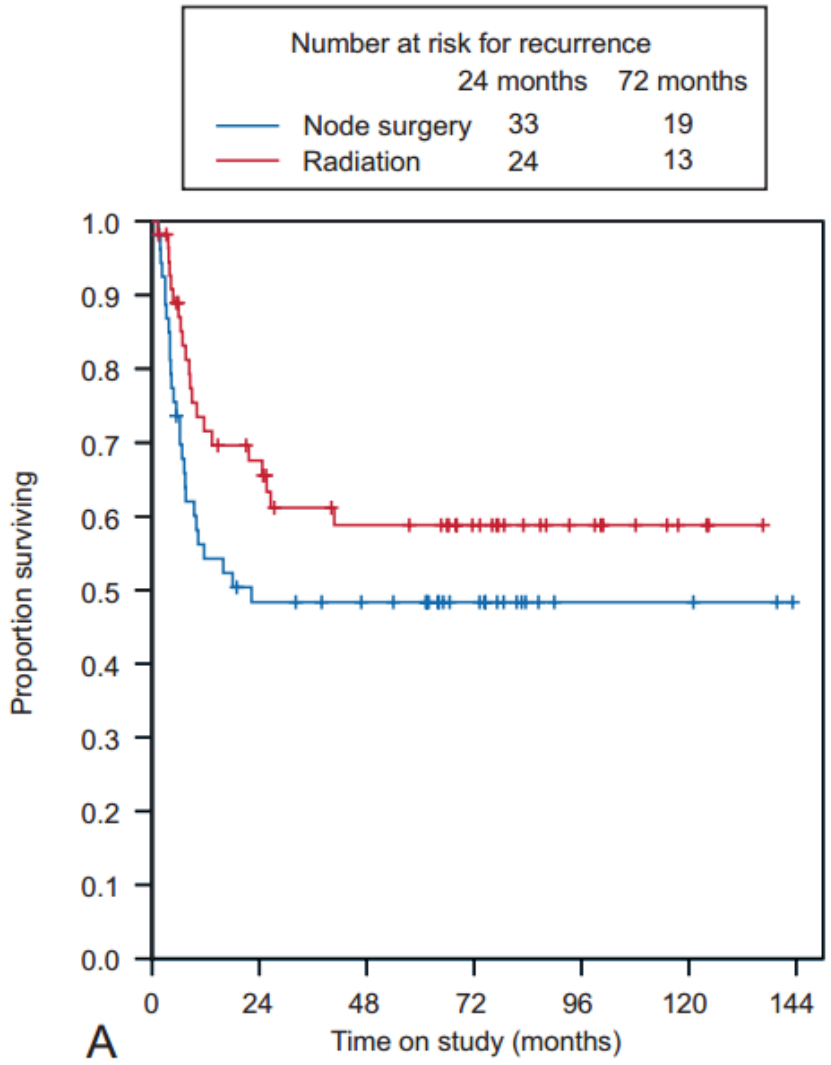
IN FIELD RECURRENCE

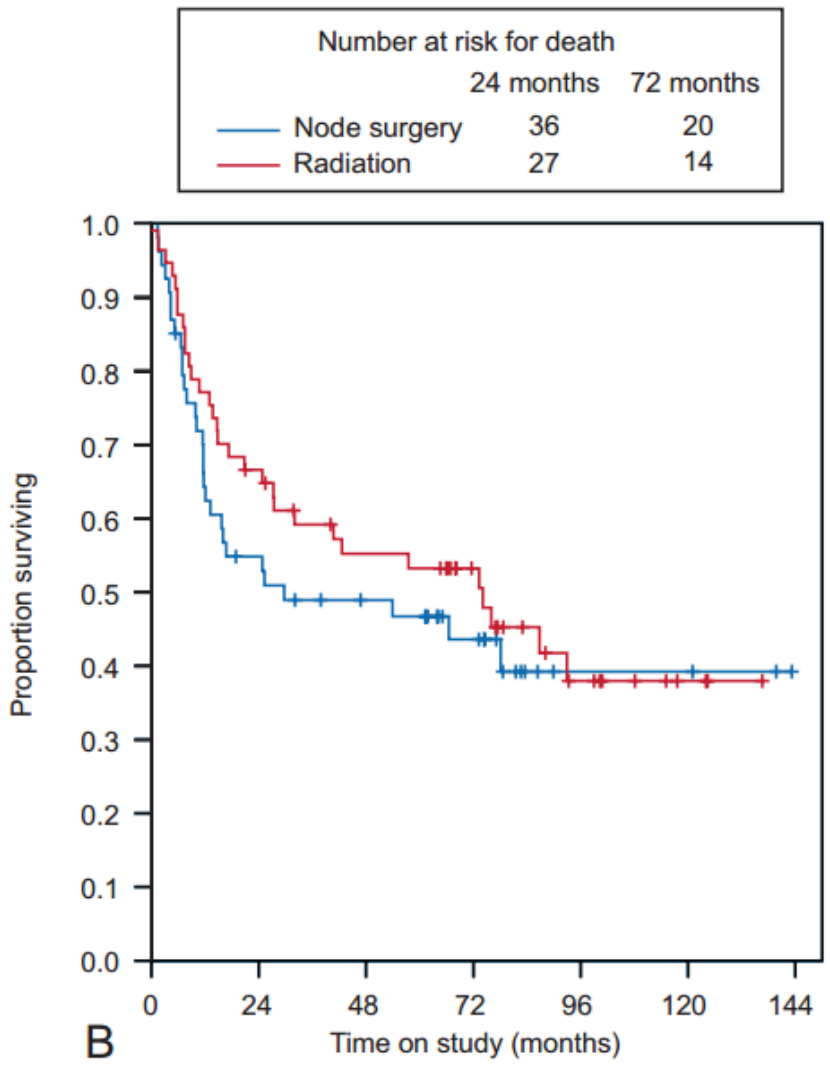


5y in field relapse
75% vs. 19%
P <0.01

GOG 37 (Kunos, ObstetGyn, 2009)

- 114 SCC Vulva Radical Vulvectomy + BL LN Dissection with positive nodes
- Arm 1) Ipsilateral pelvic LN dissection
- Arm 2) Bilateral inguinal/pelvic RT. RT AP/PA 45-50 Gy (midplane) to bilateral pelvic nodes and bilateral groins. Superior border L5/S1. No radiation to primary.
- Outcome favoring RT over Sx : CSS 71% vs. 49%


Number at risk for recurrence
24 months
72 months
Node surgery 33 19
Radiation 24 13
Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
Time on study (months)
A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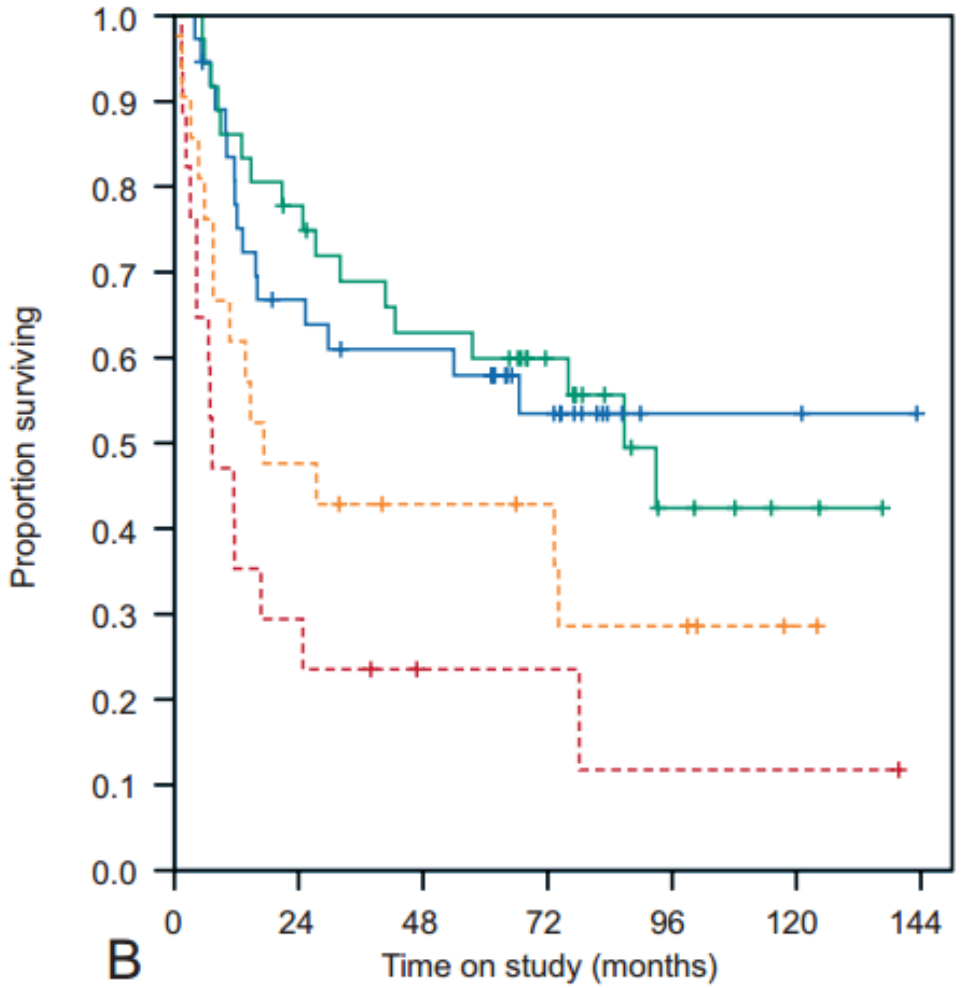
Time on study (months)
B

Number at risk for death	24 months	72 months
Node surgery, less than 20% node positive	23	12
Node surgery, more than 20% node positive	5	2
Radiation, less than 20% node positive	27	14
Radiation, more than 20% node positive	10	6



ONGOING TRIALS

PORTEC 3

High risk endometrial cancer ((FIGO 1988):

- IB G3 + LVSI
- IC-II G3
- IIIa/IIIc
- clear cell/serous histology

Pelvic RT +concomitant cisplatin followed by 4 cycles of carbo/taxol

Pelvic RT

GOG 258

ENDOMETRIAL CANCER
Stage III-IVA

Clear cell/ serous /undifferentiated histology

- 6 cycles of carbo/taxol
- Pelvic RT +concomitant cisplatin followed by 4 cycles of carbo/taxol

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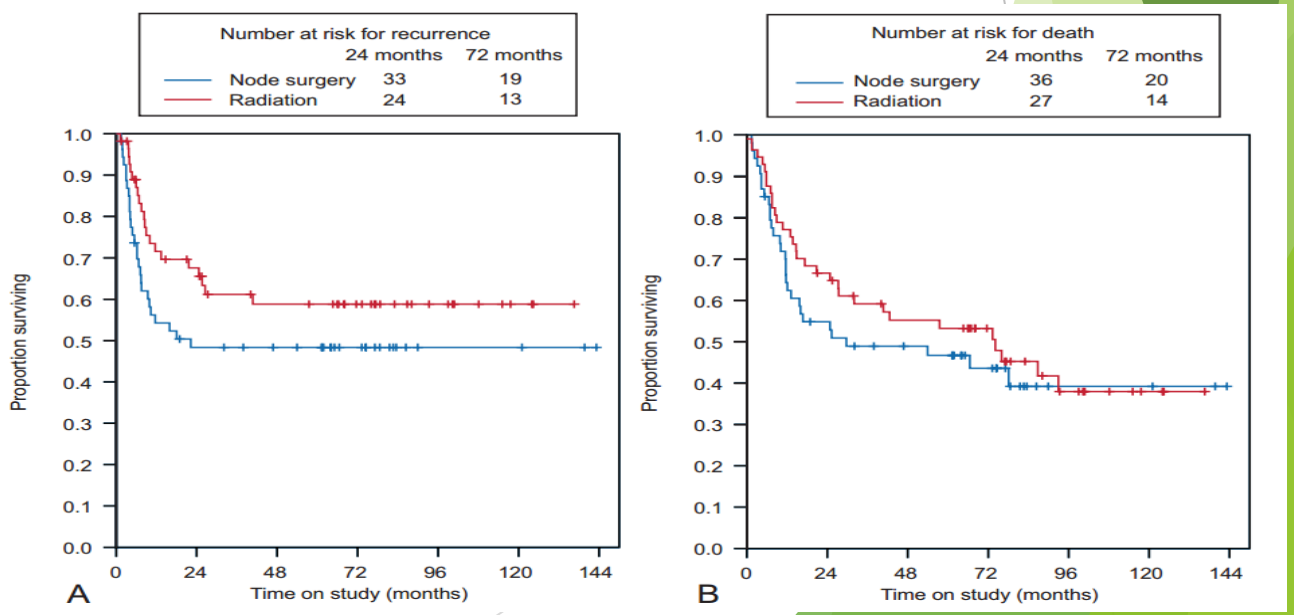

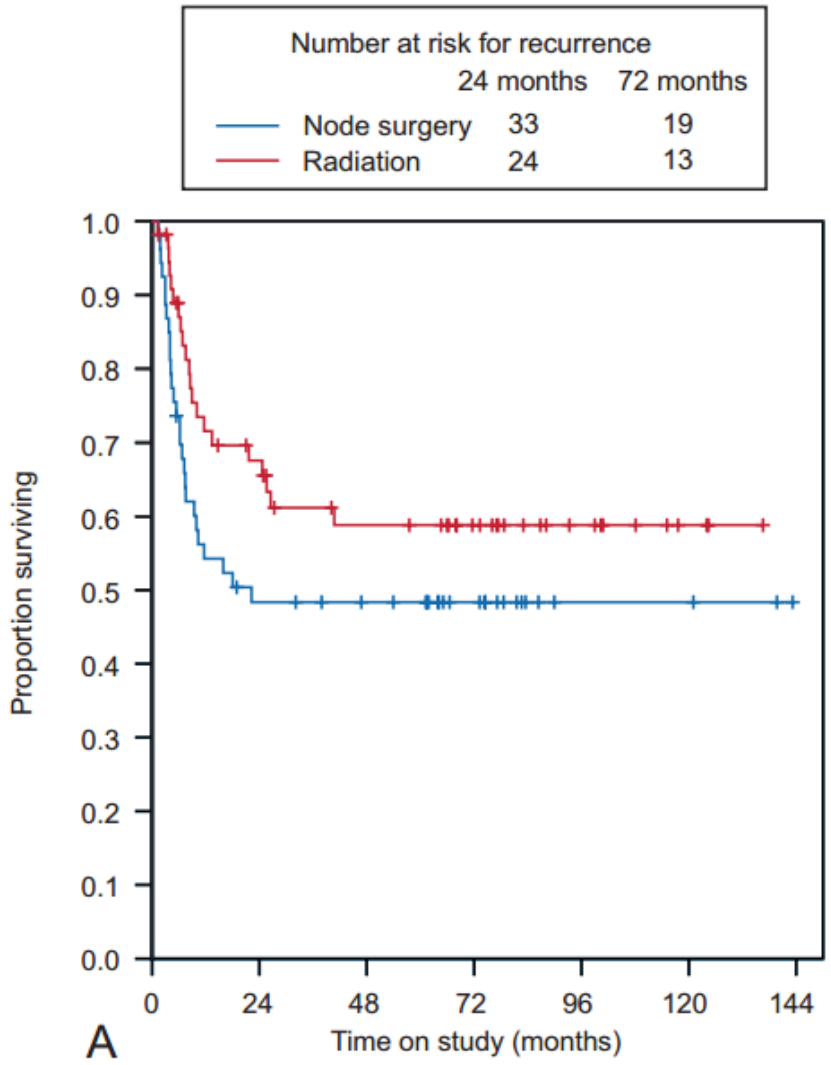
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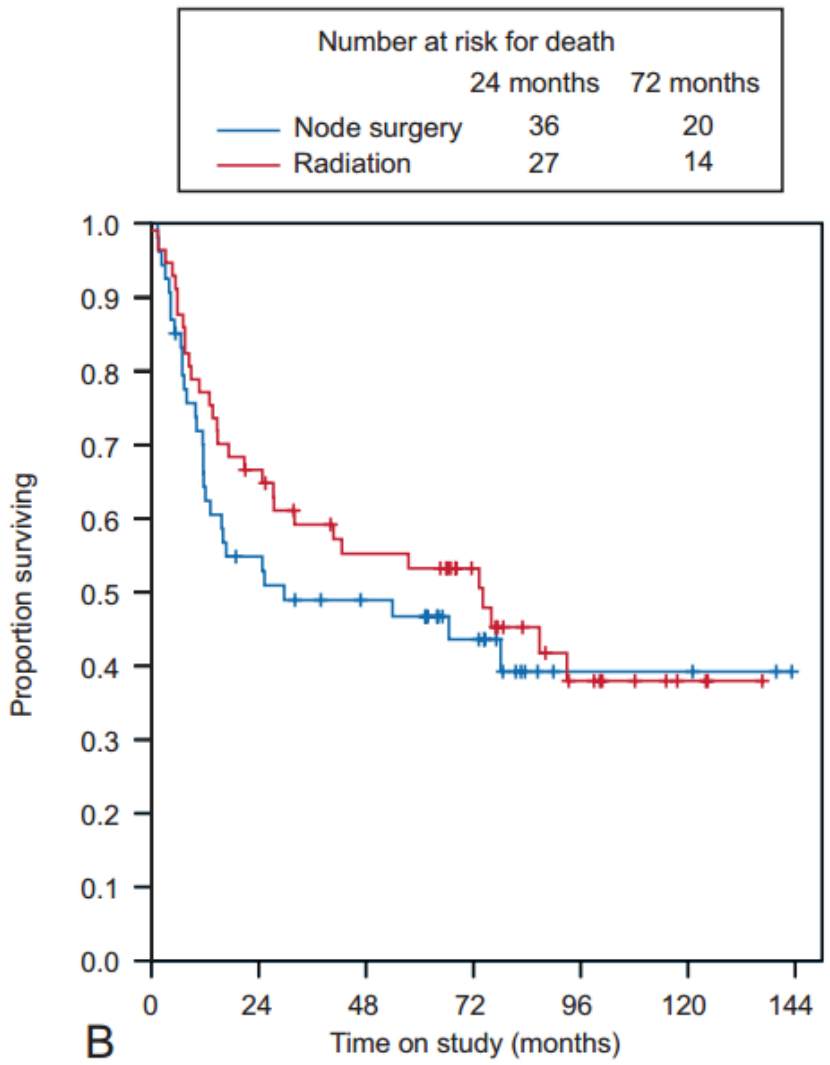
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