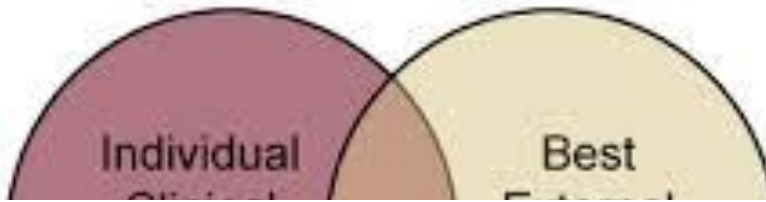




Evidence guided radiotherapy - focusing on brachytherapy

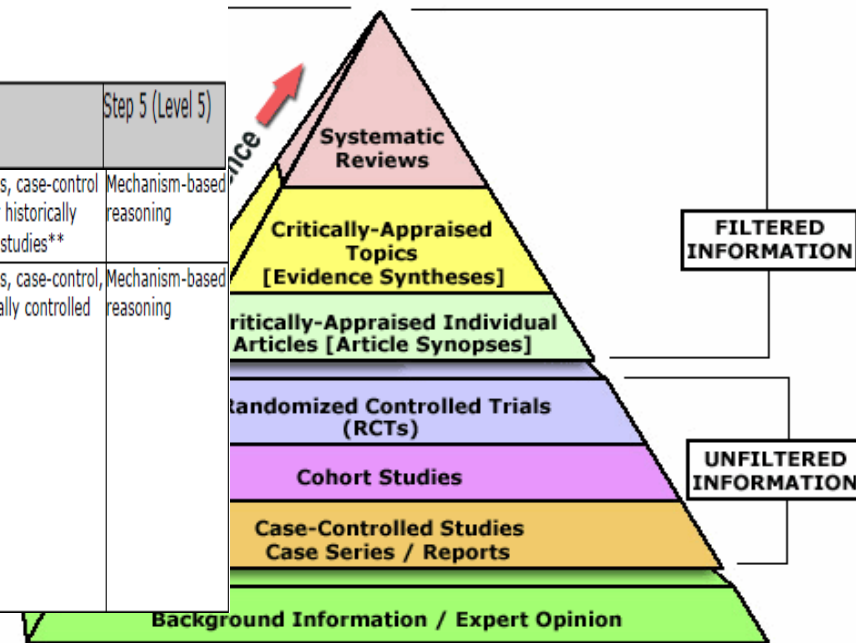
*Prof. Janusz Skowronek, MD, PhD,
Brachytherapy Department, Greater Poland Cancer Centre,
Electroradiology Department, University of Medical Sciences,
Poznań, Poland*

Issues: Evidence Based Medicine (EBM) Clinical Decision Making in Radiotherapy

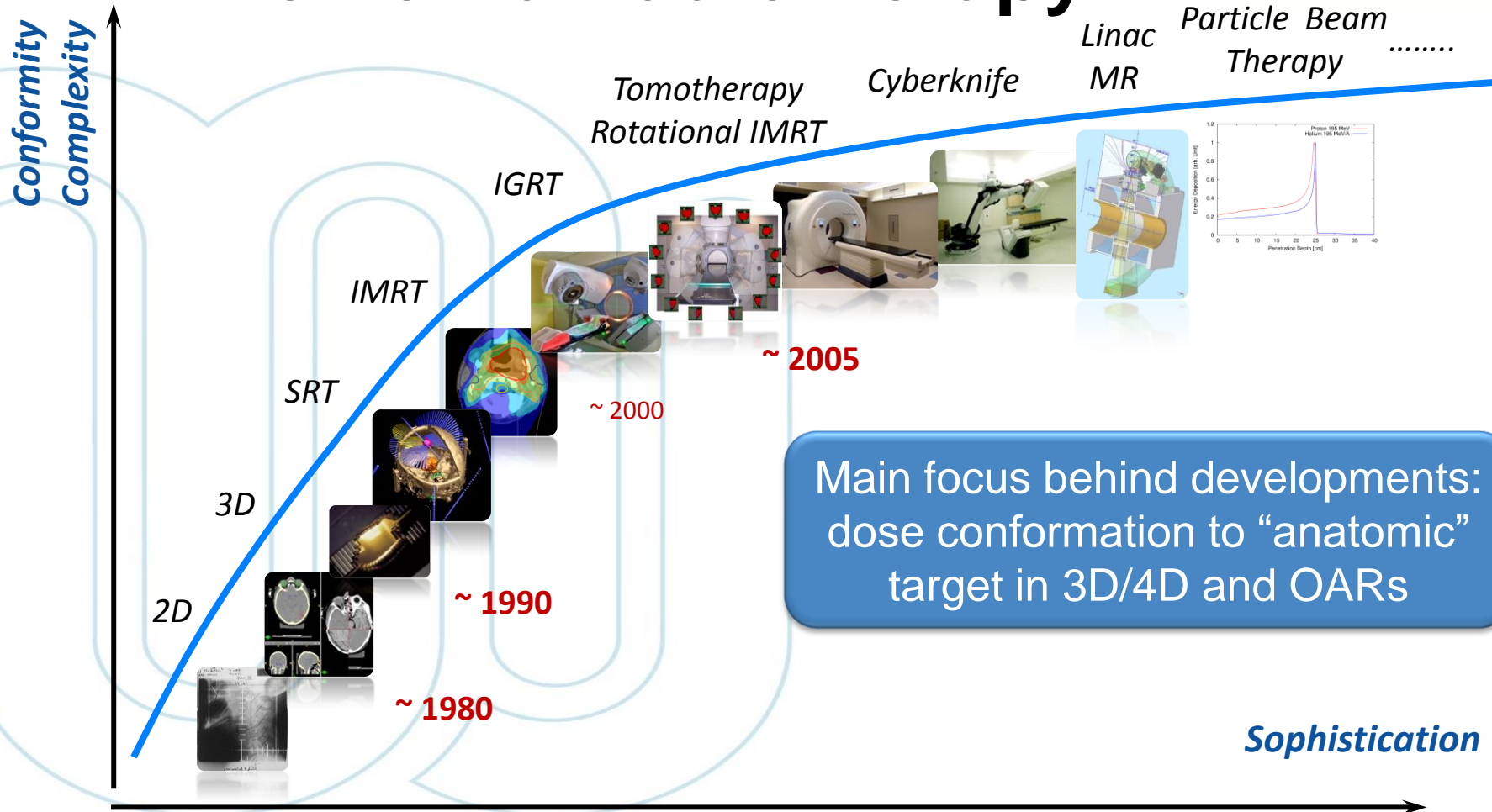


Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or <i>n</i> -of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, <i>n</i> -of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or <i>n</i> -of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			



technology evolution in external radiotherapy



Clinical Evidence (EBM)
often limited

Brachytherapy in Gynaecologic Cancer

Cervix: definitive

Endometrium: postoperative
(definitive in inoperable patients)

vaginal cancer

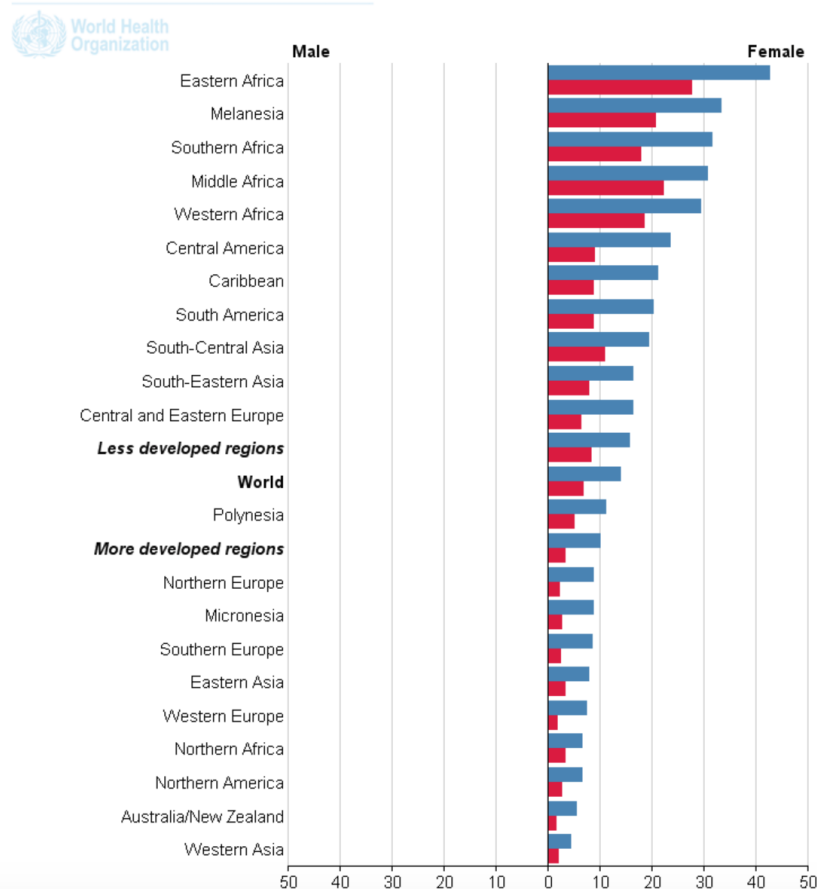
vaginal recurrence

vulvar cancer

Worldwide epidemiology of cervix cancer

- **Incidence and mortality — Globally, cervical cancer accounted for an estimated 528 000 new cases new cancer cases worldwide (85% from developing countries) and for 266,000 deaths in 2012 (rate of 52%)**

International Agency for Research on Cancer

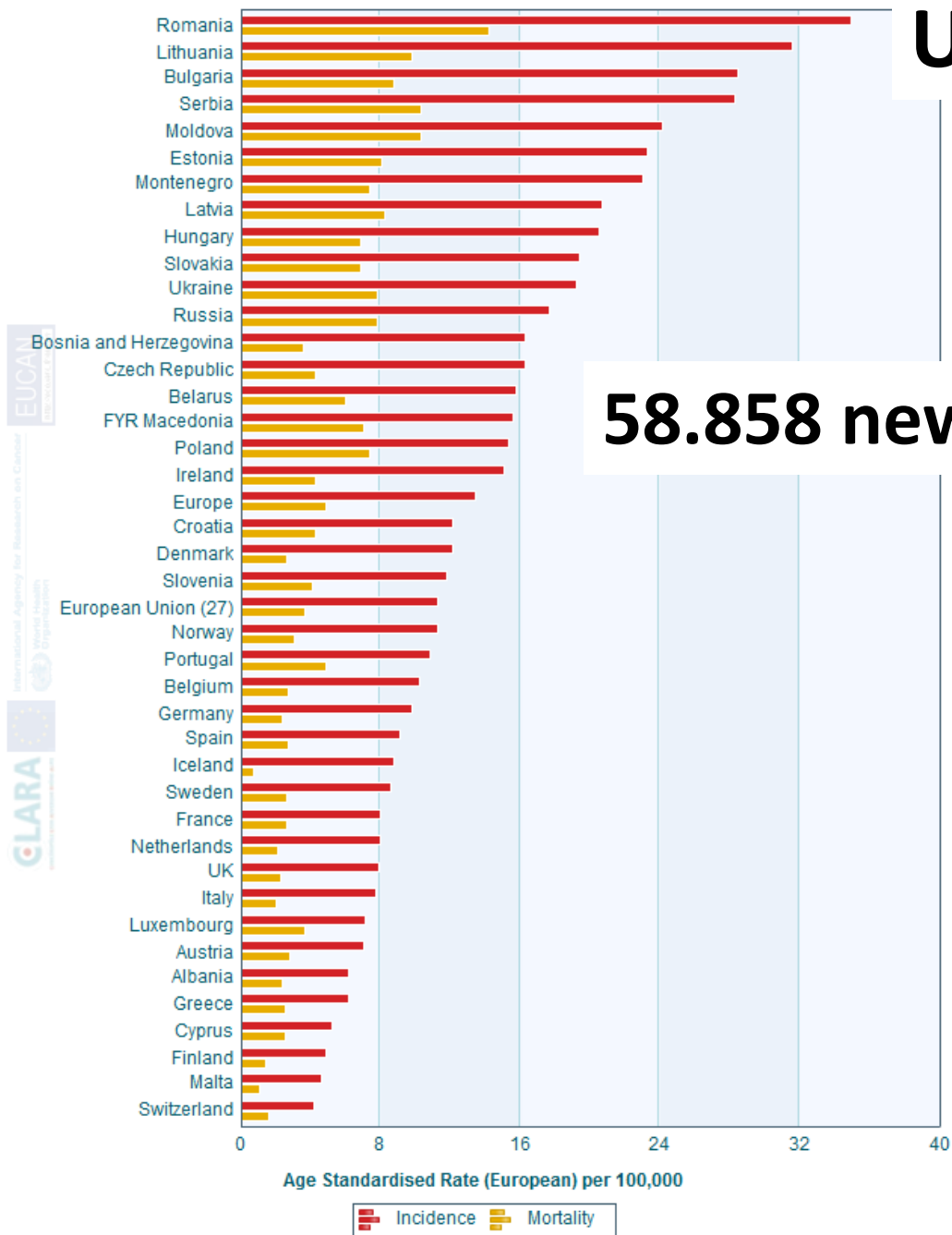


In developed countries in 2008, cervical cancer was the 10th most common type of cancer in women (9 per 100 000) and ranked below the top ten cause of cancer mortality (3,2 per 100 000)

In contrast, in developing country it was the second most common type of cancer (17.8 per 100 000) among women

On the African continent and Central America, cervical cancer is the number one cause of cancer-related mortality among women

Estimated incidence and mortality from cervical cancer, 2012

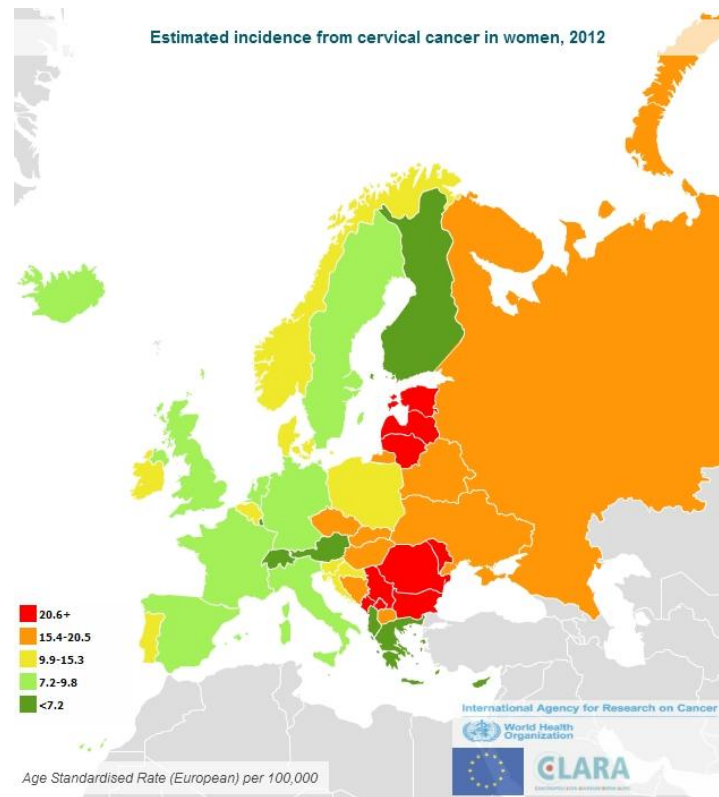


Uterine Cervix Cancer

Incidence and Mortality
2012

International Agency for
Research in Cancer (WHO)

58.858 new cases in Europe 2012



EUCAN
International Agency for Research on Cancer
CLARA
European Commission

International Agency for Research on Cancer
World Health Organization
CLARA

Brachytherapy: key component of treatment for locally advanced cervical cancer

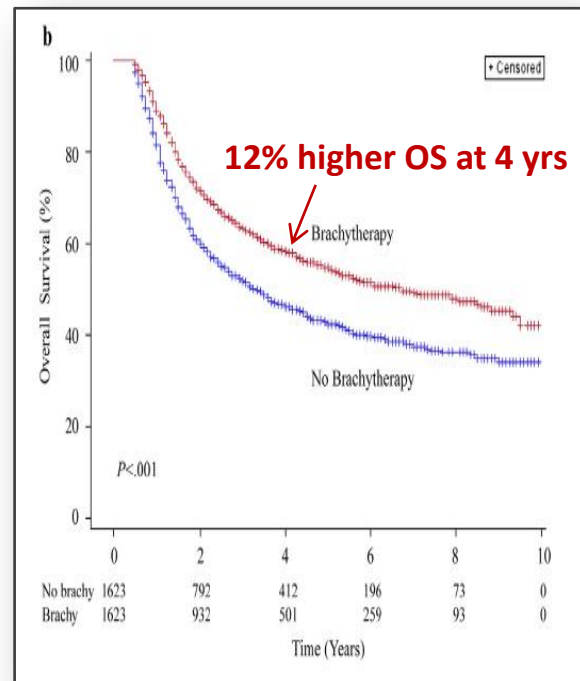
- **Guidelines** clearly indicate **that brachytherapy is standard of care in definitive treatment of locally advanced cervical cancer** (throughout all stages) with overall excellent outcome typically combined with EBRT and simultaneous chemotherapy in advanced stage (1B2 – IVA)¹⁻⁶.
- Brachytherapy allows the dose of radiation to the tumour to be escalated whilst minimizing the dose to the organs at risk.
- Patterns of care studies have clearly demonstrated brachytherapy use is associated with improved local control and survival.⁷



Brachytherapy is an essential part of treatment in locally advanced cervical cancer: HAN study 2013

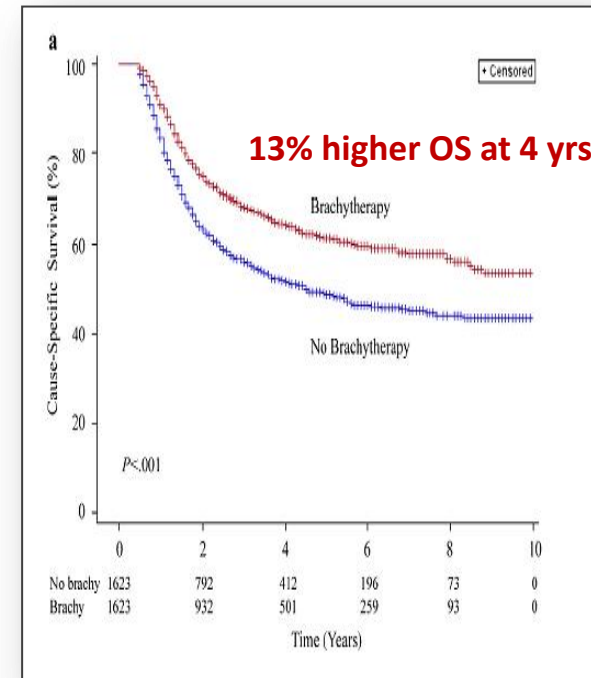
Higher 4 year Overall Survival

(58.2% vs 46.2%, $P < 0.001$)



Higher 4 year Cause-Specific Survival

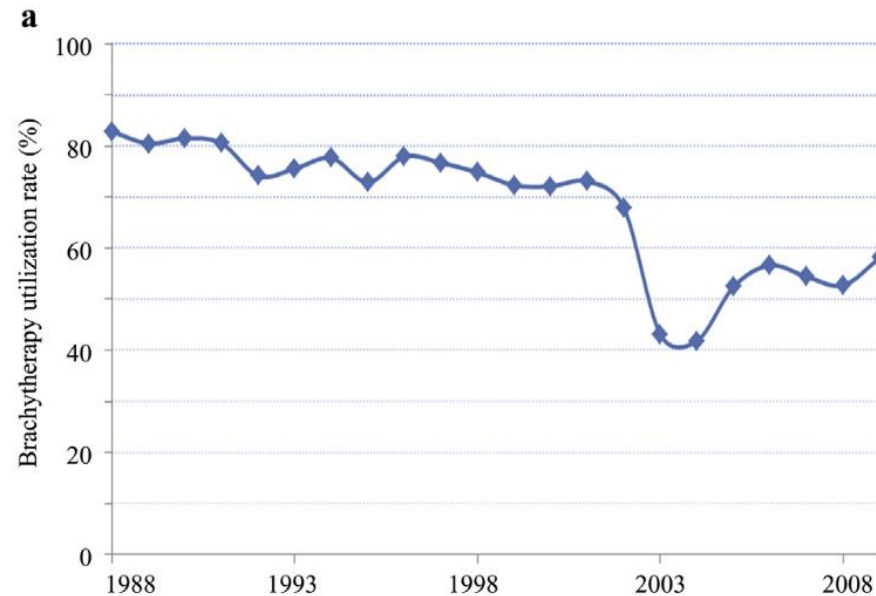
(64.3% vs 51.5%, $P < .001$)



More patients with cervical cancer survive when brachytherapy is used

Use of IMRT/SBRT as boost instead of brachytherapy in locally advanced cervix cancer has increased over the years

- 7359 women diagnosed between 1988 and 2009 with stage IB2-IVA cervical cancer, who were treated with EBRT



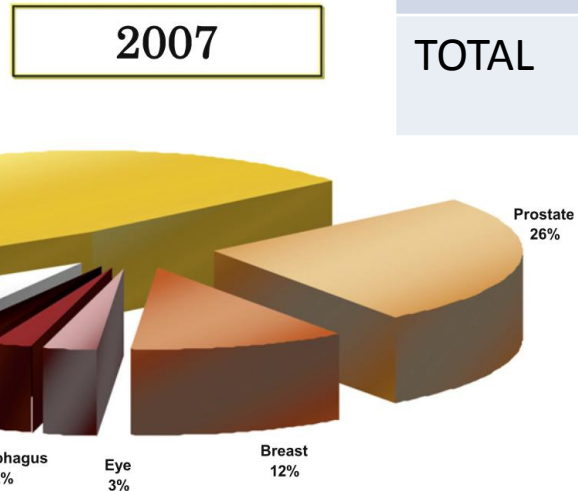
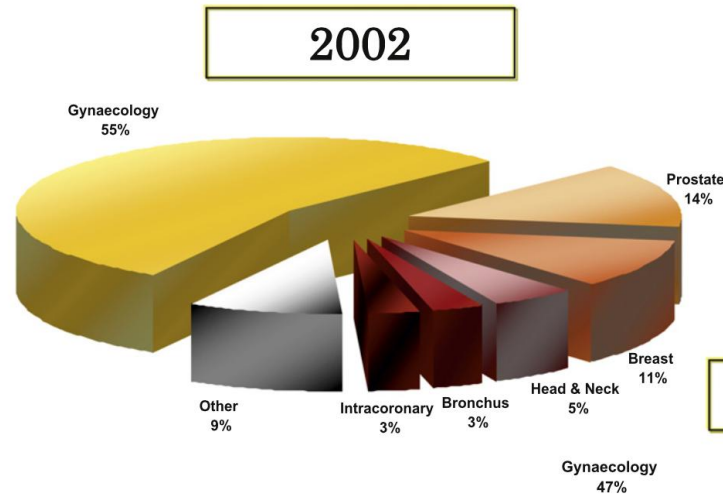
- Brachytherapy utilization rate decreased since 1988 (**83% in 1988 to 58% in 2009**)

Fig. 1. Brachytherapy use rate between 1988 and 2009 in 18 (a) and the original 9 (b) SEER registries.

Brachy in Gyn cancer in Europe

In 2007, most brachytherapy is used in gyn cancer:

Estimate of >20.000 pts cervix, >25.000 pts. corpus



	N of patients	Percent
Endometrium	14 197	31 %
Cervix	11 449	25 %
Vulva/vagina	1 374	3%
TOTAL	27 020	59% of all BT

Diagrams for Western Europe

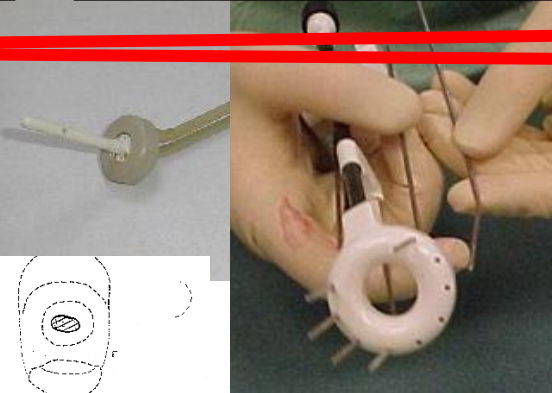
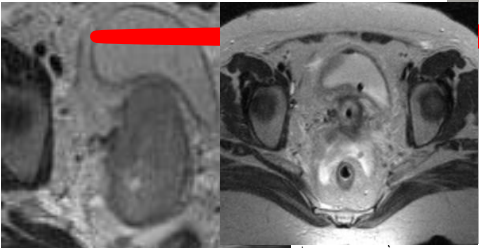
Related to incidence
35% of cervix pat
25% of corpus pat

*Increase of 55 pts/center to 59 pts/center from 2002 to 2007

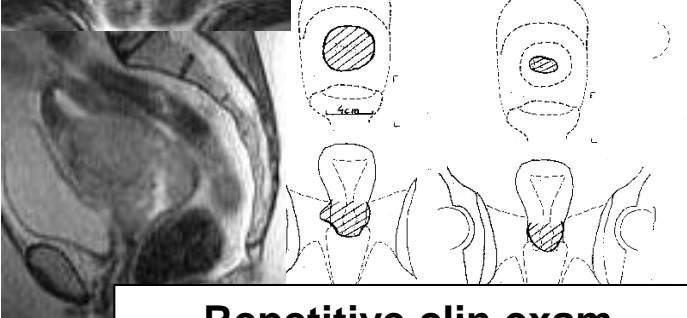
4D Image-guided adaptive Brachytherapy

Repetitive Imaging
diagnosis, EBRT/CbT

Individual application adaptation based on
response adapted target definition

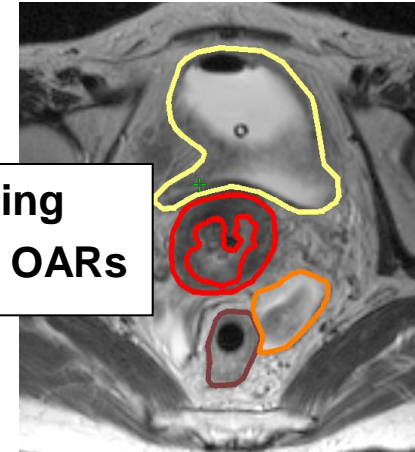


3D/4D imaging MRI

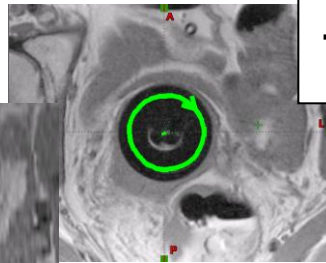


Repetitive clin exam
+3D/4D drawing

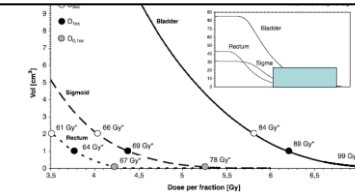
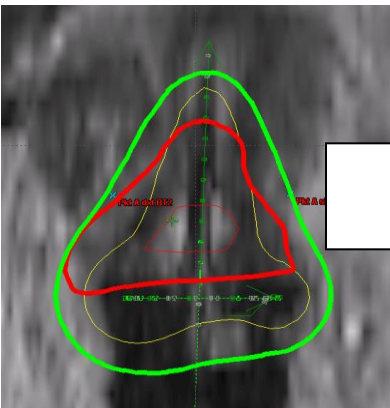
Contouring
Target and OARs



Applicator Reconstruction



Individualized 3D dose planning
dose volume constraints



Individualized dose
delivery

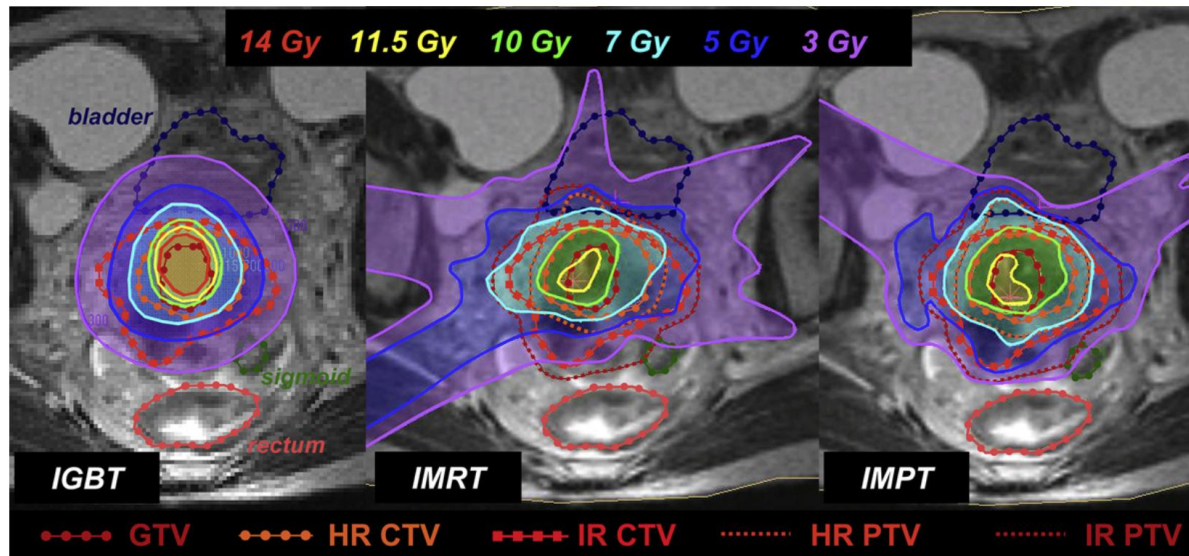


Image-guided adaptive brachytherapy (IGABT) vs IMRT vs IMPT in cervix cancer

9 patients with locally advanced cervix cancer

Target dose: HR-PTV and IR-PTV D90

is lower for IMRT and IMPT compared to IGABT

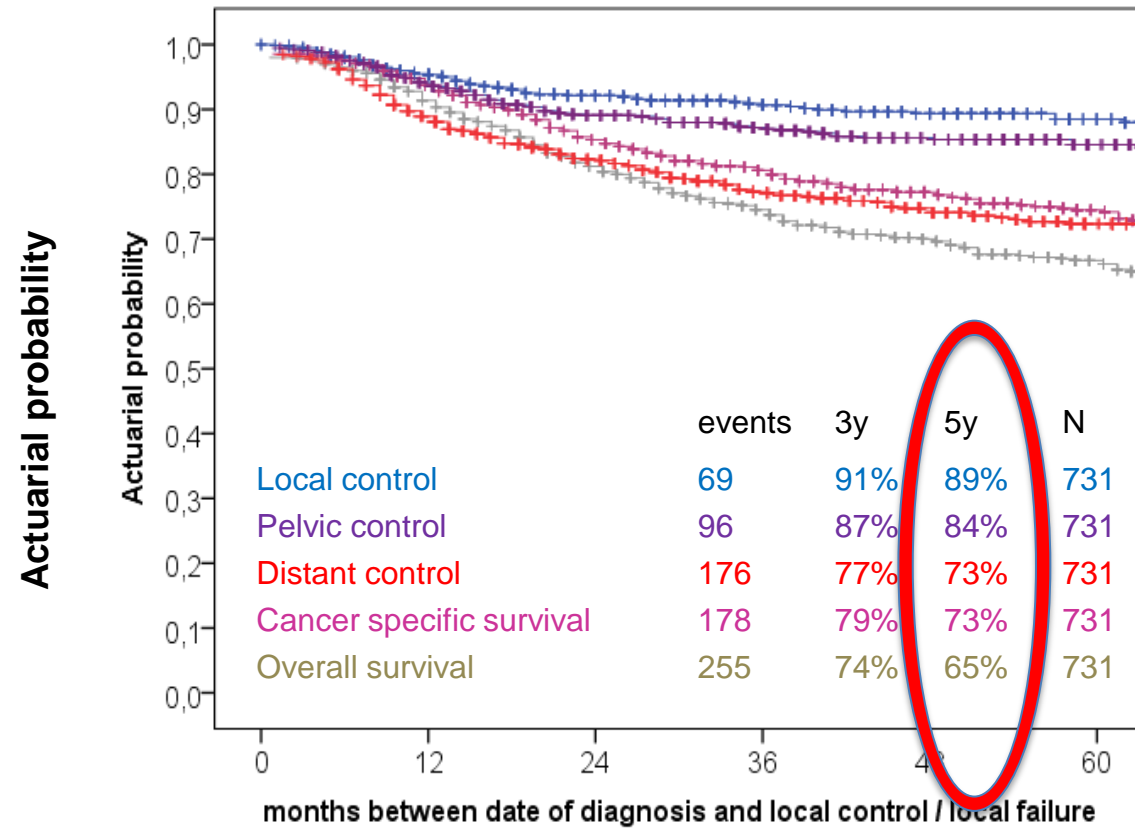


Volumes receiving
60 Gy is twice in
IMRT
compared to
IGABT

Fig. 1. Typical isodose distributions for image-guided brachytherapy (IGBT), intensity-modulated photon therapy (IMRT) and intensity-modulated proton beam therapy (IMPT).

* Georg D, Kirisits C, et al. IJROBP 2008

RetroEMBRACE outcome: Local, pelvic, distant control, CSS, OS (731 patients)



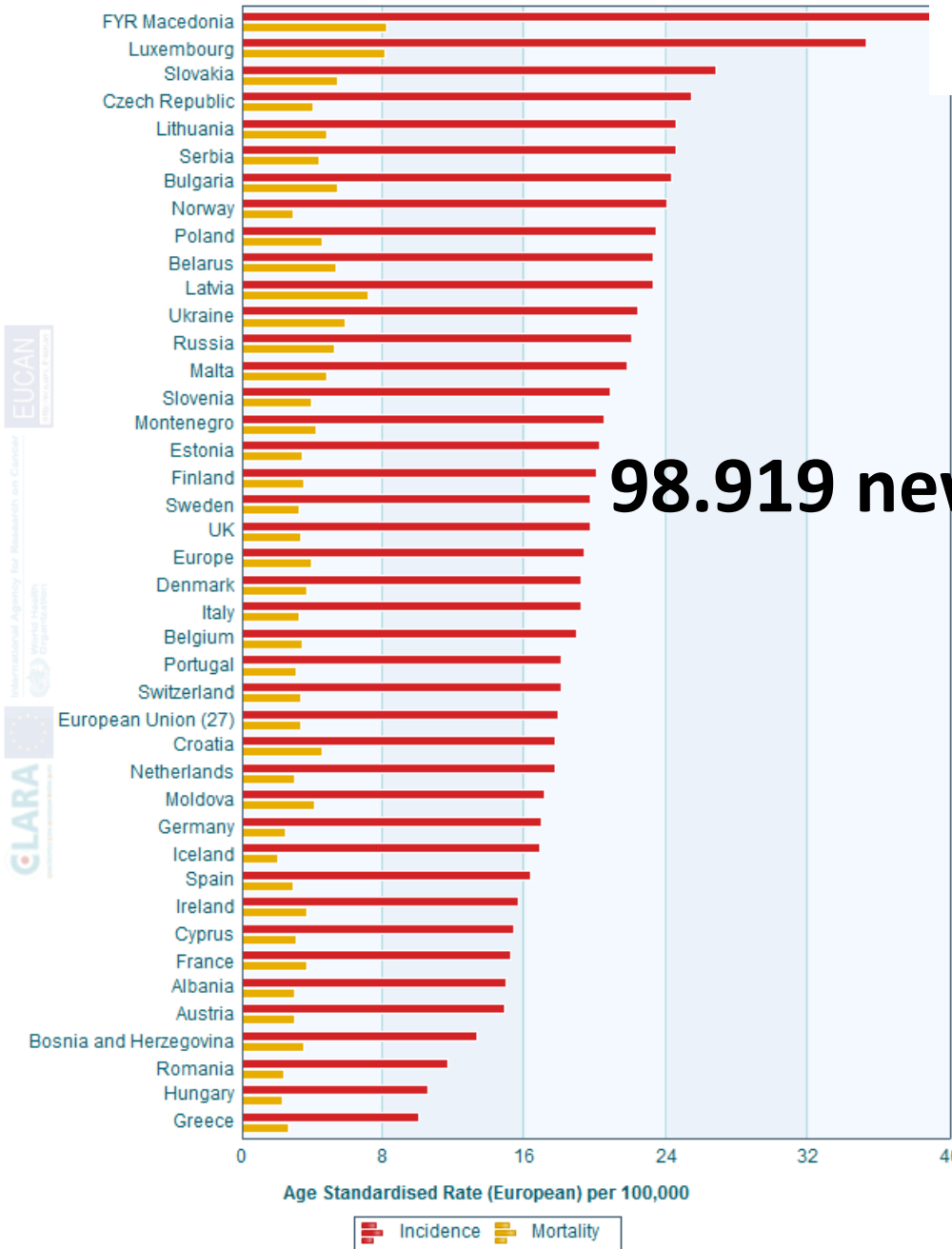
	Months					
LC	731	603	491	384	294	187
PC	731	603	491	384	294	187
DC	731	603	491	384	294	187
CSS	731	651	537	429	332	220
OS	731	651	537	429	332	220

Actuarial local control (LC), pelvic control (PC), distant control (DC), cancer specific survival (CSS) and overall survival (OS) in 731 patients, from retro-EMBRACE, Sturdza et al.

Conclusions: cervix cancer

- Brachytherapy is **ESSENTIAL** in achieving optimal outcomes in **any definitive radiotherapy cervix cancer treatment**.
- There is a minimum **10-15% decrease of LC and OS, if brachytherapy is omitted and replaced by EBRT (incl. ART)**.
- Expertise, adequate treatment quality and patient volume is crucial for achieving optimal results.
- **4D Image-guided brachytherapy allows an increase at least of 10% OS and LC compared to 2D BT**.
- **Underutilization of (advanced) BT leads to decrease in local control and survival.**

Estimated incidence and mortality from corpus uteri cancer, 2012



Uterine Corpus Cancer

Incidence and Mortality Europe
2012

International Agency for
Research in Cancer (WHO)

98.919 new cases in Europe 2012

Estimated incidence from corpus uteri cancer in women, 2012



23.5+
20.3-23.4
18.1-20.2
15.5-18
<15.5

Age Standardised Rate (European) per 100,000



Conclusions: endometrium cancer

- Brachytherapy leads to **similar local control as EBRT in high intermediate risk stage I endometrium cancer.**
- Brachytherapy is associated with **significantly less gastrointestinal morbidity** due to less irradiation of recto-sigmoid and bowel.
- **Underutilization of BT leads to increase in gastrointestinal morbidity** for a similar effect on disease control.

Brachytherapy in prostate cancer (LDR, HDR, PDR?)

definitive brachytherapy

boost combined with EBRT

salvage brachytherapy after local failure

Worldwide epidemiology

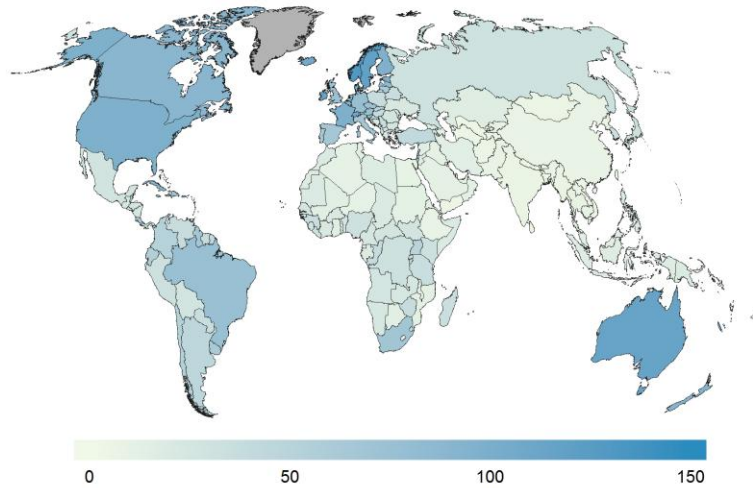
Prostate Cancer

prostate cancer

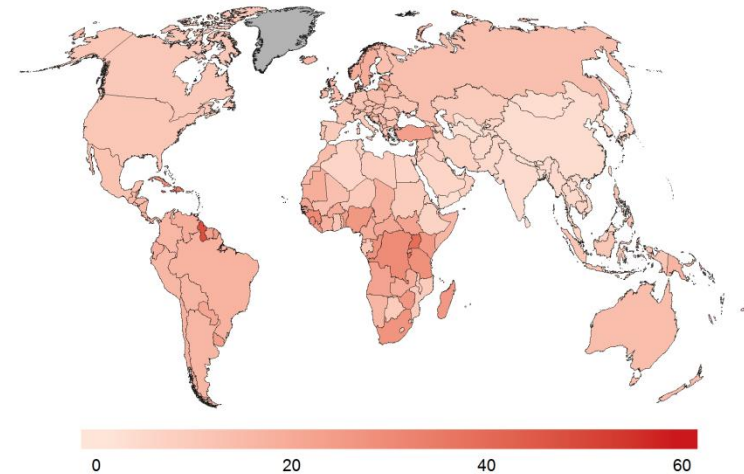
Estimated Incidence, Mortality and Prevalence Worldwide in 2012

Estimated numbers (thousands)	Cases	Deaths	5-year prev.
World	1095	307	3858
More developed regions	742	142	2871
Less developed regions	353	165	987
WHO Africa region (AFRO)	52	37	135
WHO Americas region (PAHO)	413	85	1539
WHO East Mediterranean region (EMRO)	19	12	47
WHO Europe region (EURO)	420	101	1513
WHO South-East Asia region (SEARO)	39	25	123
WHO Western Pacific region (WPRO)	153	46	499
IARC membership (24 countries)	791	157	2998
United States of America	233	30	980
China	47	23	104
India	19	12	64
European Union (EU-28)	345	72	1277

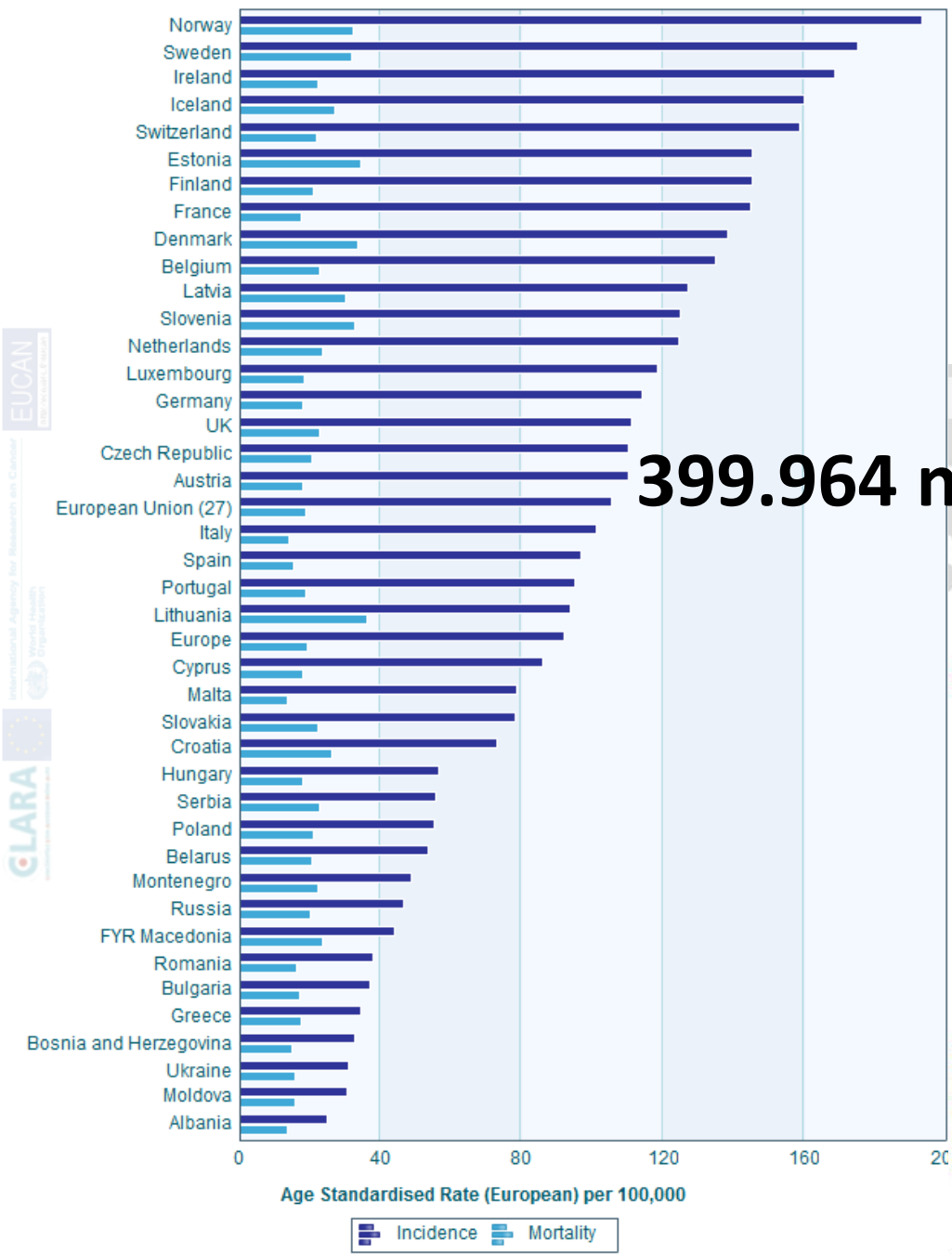
Estimated Prostate Cancer Incidence
Worldwide in 2012



Estimated Prostate Cancer Mortality
Worldwide in 2012



Estimated incidence and mortality from prostate cancer, 2012



399.964 new cases in Europe 2012

Prostate Cancer

Incidence and Mortality

Europe 2012

International Agency for Research in Cancer (WHO)

Estimated incidence from prostate cancer in men, 2012

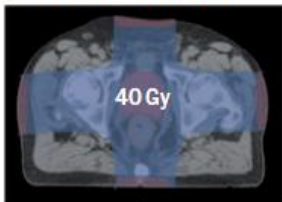


EUCAN

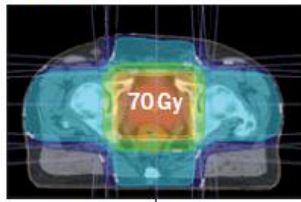
International Agency for Research on Cancer

CLARA

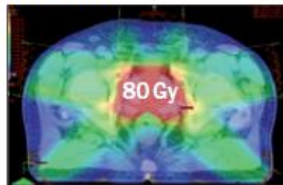
Schematic 200 kV RT



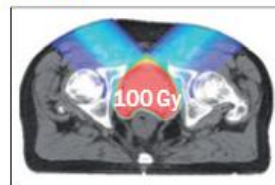
Linac 2D



Linac IMRT



Carbons



1935

1950

1960

1996

2000

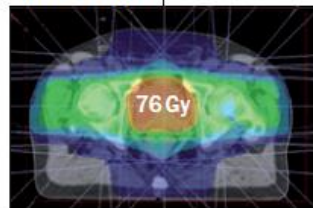
2005

2010

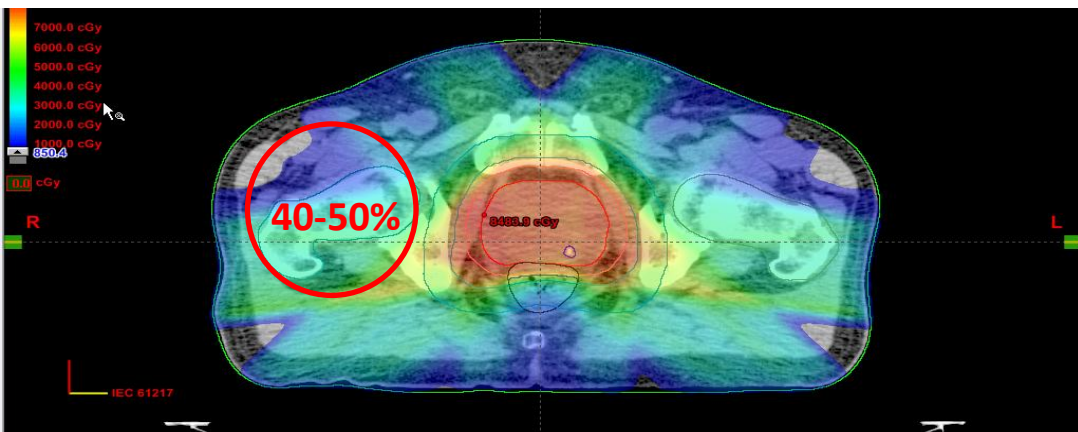
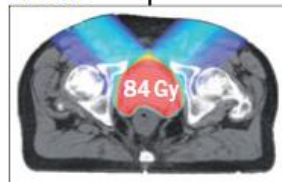
⁶⁰Co



Linac 3D-CRT

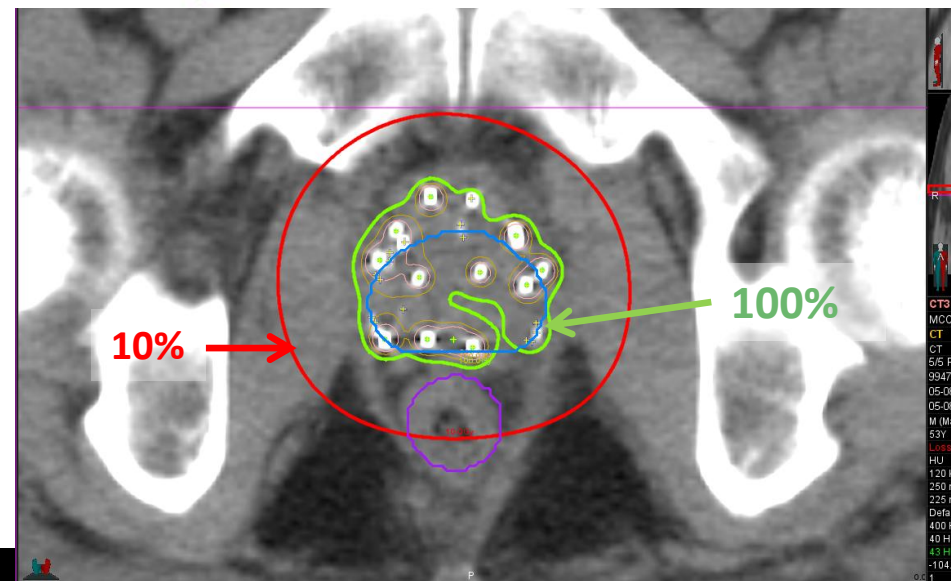
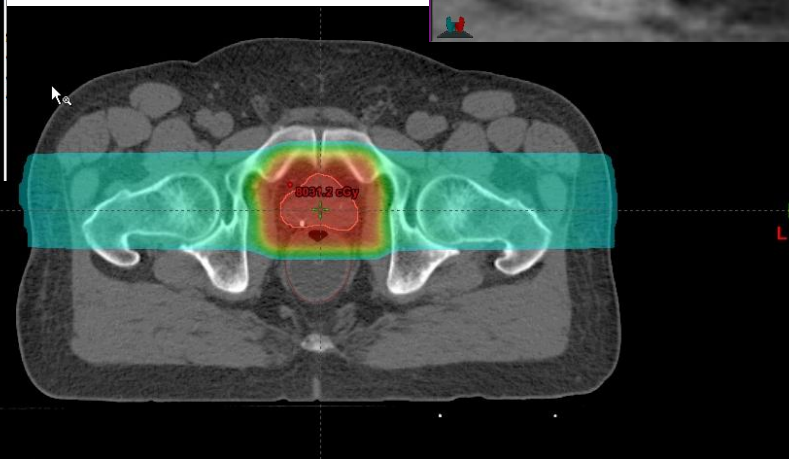


Protons



Target Volume IMRT

Target Volume Protons

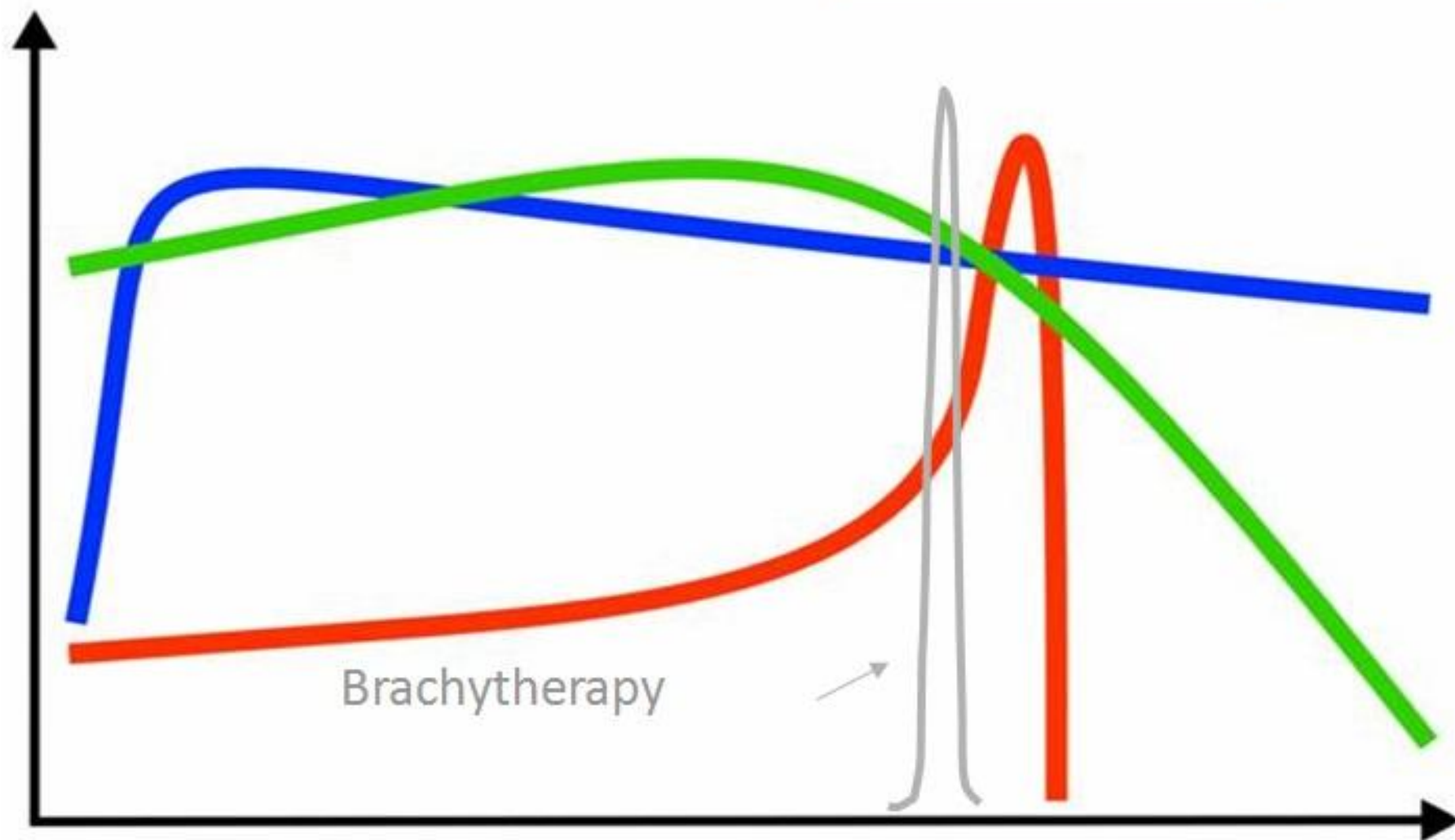


10% Isodose LDR Brachy

relative Dosis



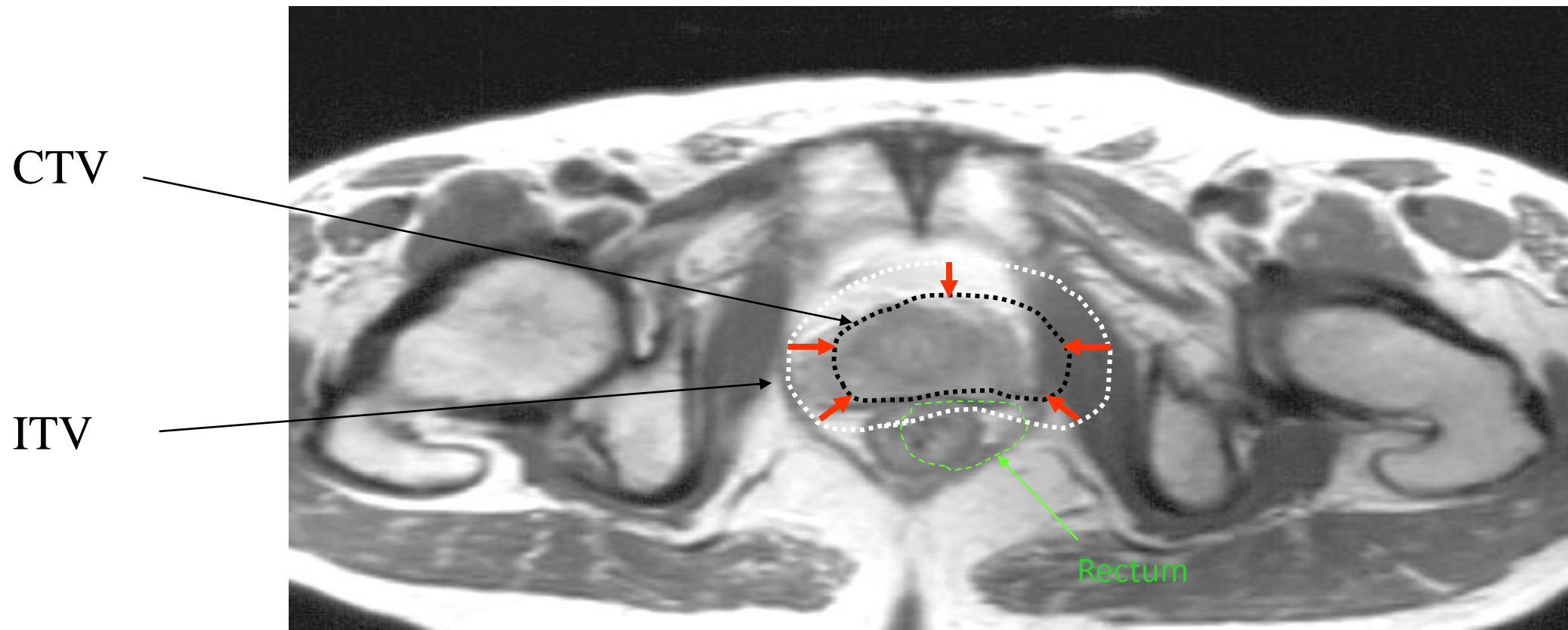
Protons
Gamma Beam
Electrons



**Potential of Brachytherapy:
Moving target is not a problem in BT
Moving target remains a problem in EBRT**

Interstitial Brachytherapy for Prostate: CTV = PTV

No margin necessary . Much smaller PTV



Conclusions

- 38,200+ prostate studies were published between 2000 and 2014.
- 1,292 of those studies featured treatment results.
- 179 of those met the criteria to be included in this review study.
- Some treatment methods are under-represented due to failure to meet criteria.

The role of brachytherapy should be considered for most men with localized prostate cancer

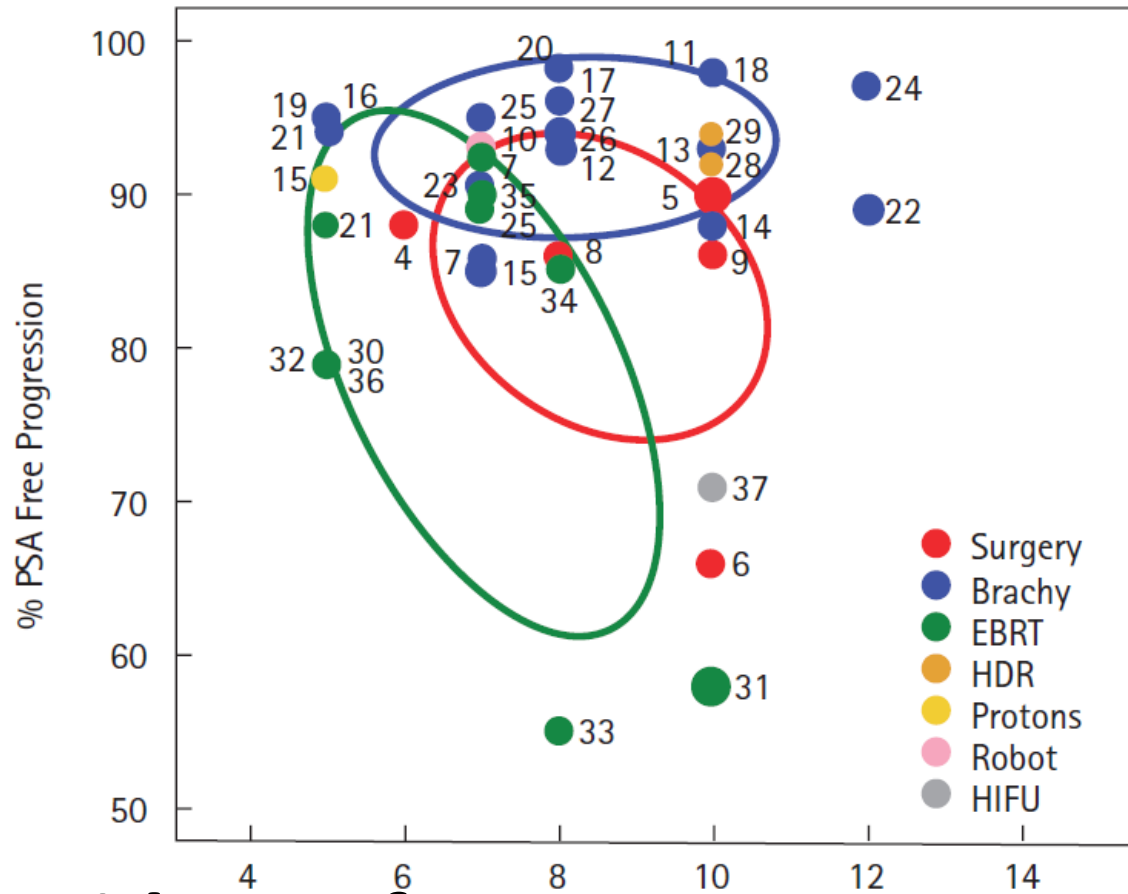
- Outcomes probably better than with other local treatments
- Consider adding EBRT and/or ADT for higher risk disease
 - Seeds or HDR brachytherapy?

Comparing Treatment Results of PROSTATE CANCER

Prostate Cancer Results Study Group - June 2015

Low-Risk Prostate-Cancer

Biochemical Free Survival



Seeds-BT 8859 Pat.

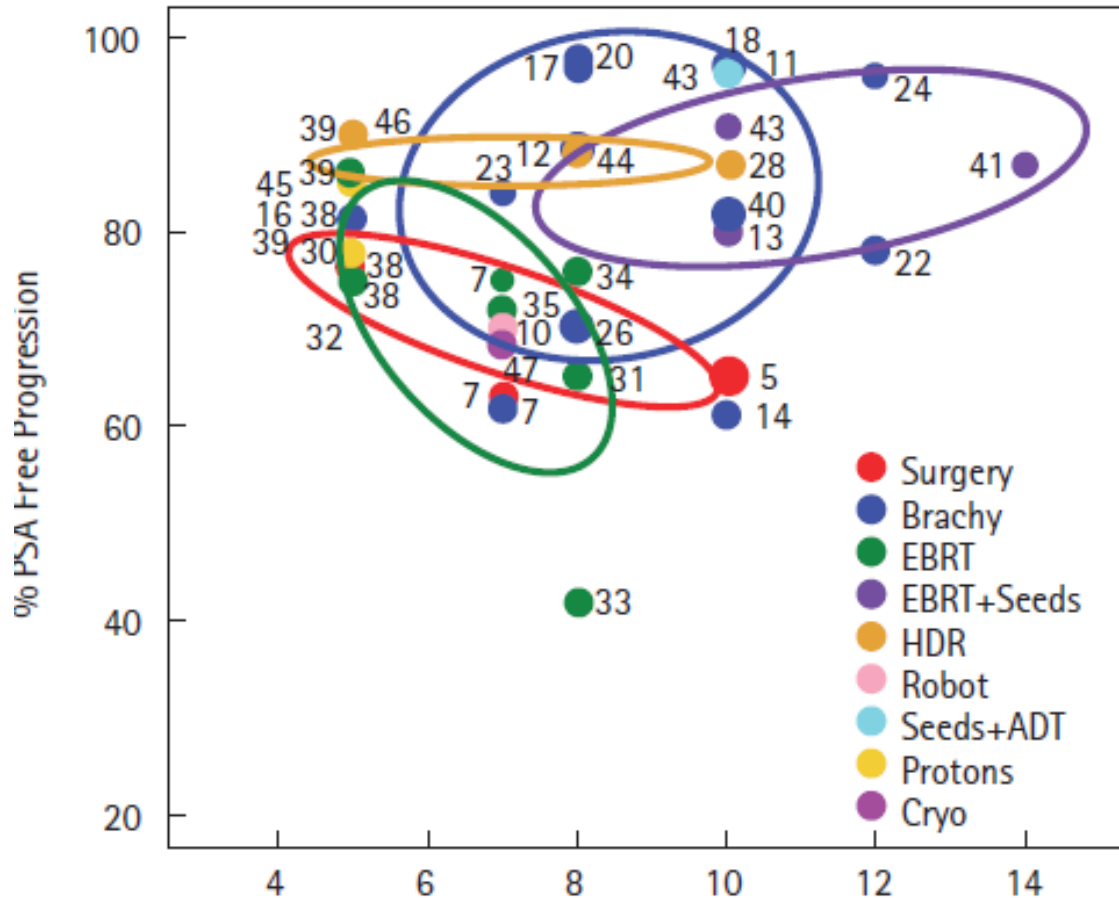
EBRT (≥ 72Gy) 5470 Pat.

RPE 7153 Pat.

Evidence for prostate cancer treatment (I)

Intermediate-Risk Prostate-Cancer

Biochemical Free Survival



EBRT+HDR 607 Pat

Seeds+EBRT 1554 Pat.

Seeds-BT 5667 Pat.

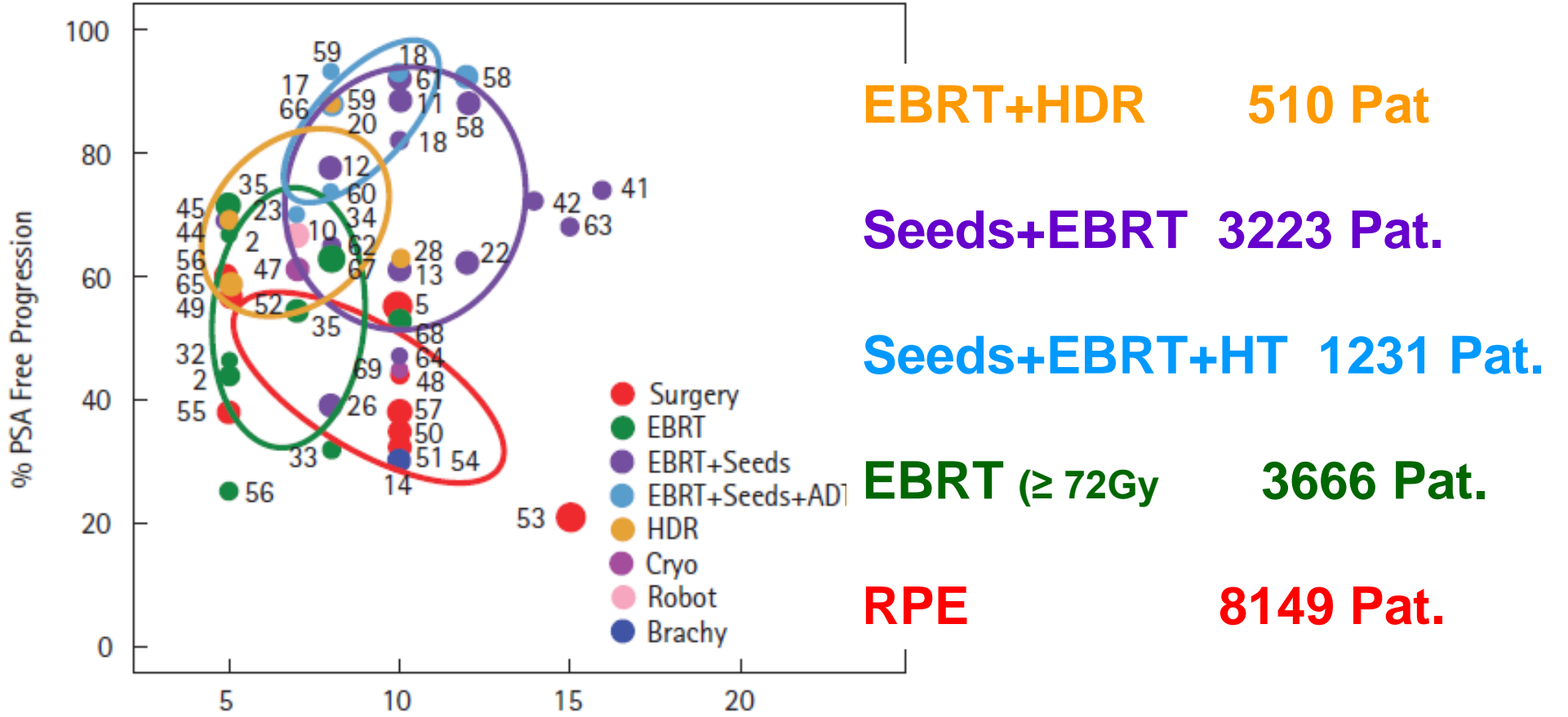
EBRT (≥ 72Gy) 2969 Pat.

RPE 4175 Pat.

Evidence for prostate cancer treatment (II)

High-Risk Prostate-Cancer

Biochemical Free Survival



Evidence for prostate cancer treatment (III)

Summary evidence prostate cancer

- **Low Risk**

*BT is as effective as EBRT or RPE (or AS >65 y)
different morbidity/PRO profiles*

- **Intermediate Risk**

BT+EBRT** (BT alone) at least as effective as
EBRT alone** or RPE
different morbidity/PRO profiles*

- **High Risk**

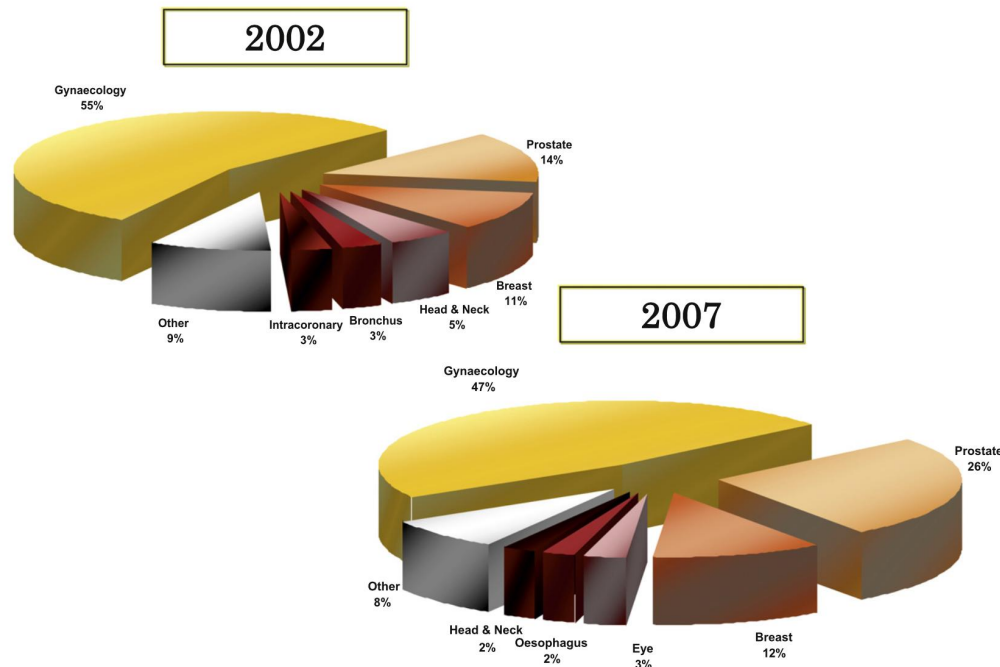
BT+EBRT** superior to RPE or EBRT alone***

*I-125 LDR or Ir 192 HDR BT

**Hormonal treatment, as indicated, is not considered here

Brachy in Prostate cancer in Europe

In 2007, total number of BT patients is >10.000 (estimate)
in 140 centres



	No of patients	Percent
Prostate (TOTAL)	7940 (estimate total >10.000)	100%
I-125 seeds	5890	74%
Ir-192 HDR	1782	22%
Ir-192 LDR	223	3%
Pa-103	45	1%

*Increase of 55 pts/center to 59 pts/center from 2002 to 2007

Guedea et al. 2010, R&O

National Cancer Data Base – US

Total number
≈ 230 000 pts

17 %	receiving Brachytherapy	2002	≈ 37 000 pts
8 %	receiving Brachytherapy	2010	≈ 18 000 pts
44 %	receiving prostatectomy	2000	≈ 97 000 pts
60 %	receiving prostatectomy (introduction of robotic surgery)	2010	≈ 132 000 pts

Increase of external beam radiotherapy (IMRT / VMAT / Protons)

Martin et al Cancer 2014

(1931: 80.000 BT pts. (no competitor))



Declining utilization of brachytherapy in the US: top 8 causes

1. \$\$\$\$\$
2. Increasing use of active surveillance
3. Lack of training/skill
4. Competing technologies: Robotic Prostatectomy
5. Lack of knowledge
6. Increasing sophistication of EBRT (IGRT, SBRT, Protons)
7. Bad Press
8. Excessive regulatory requirements


Primary Prostate Cancer Treatment (Radiotherapy)

AUSTRIA (2014) and EUROPE 2007/2012

1402 from total 5833 prostate patients receiving definitive Radiotherapy (24%)

**Europe
Total n
399 964**

 **1239** external beam radiotherapy (3D-CRT/VMAT/IMRT) 89 %

 **131** Brachytherapy (Seeds or HDR Mono) 9 %

**2.8% >10.000 BT
>2.5%**

 **32** EBRT + Brachytherapy 2 %

6/14 departments in Austria offering prostate brachytherapy

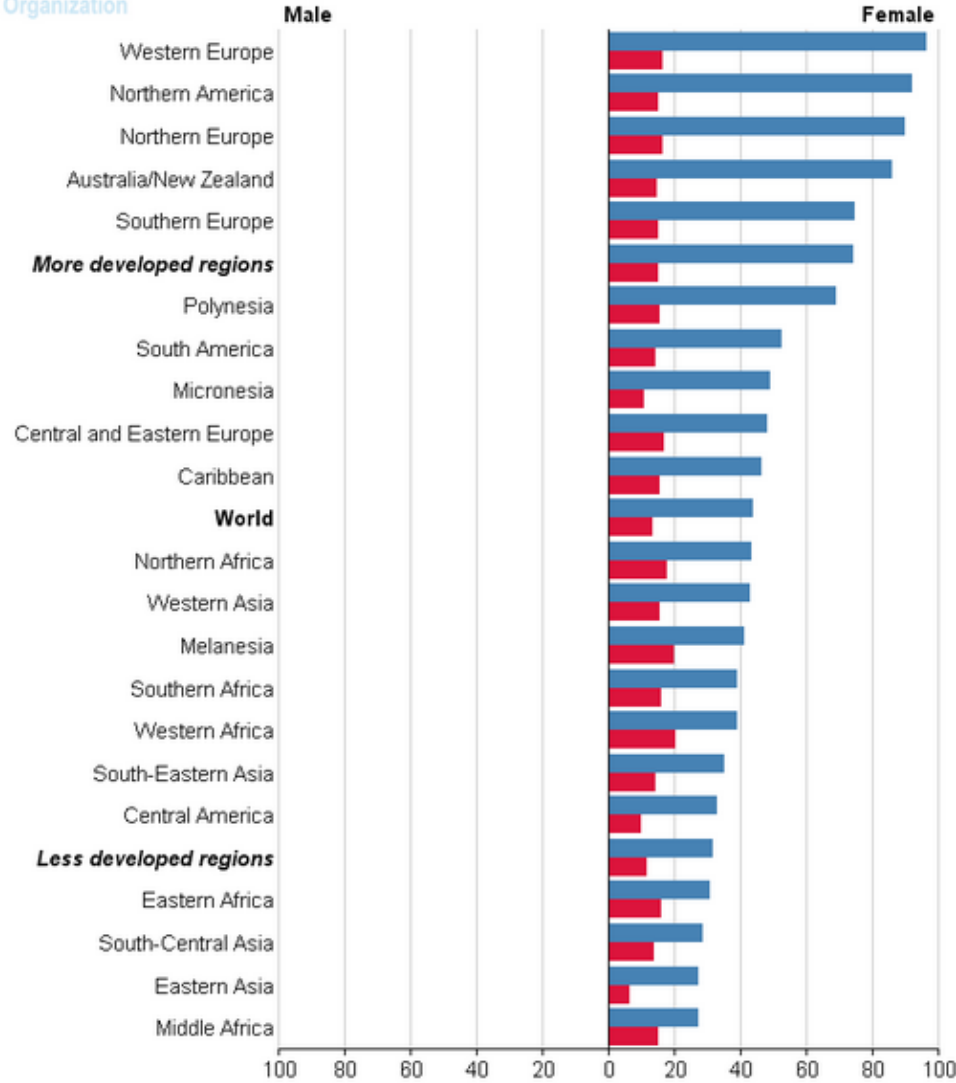
**>140/1121
Departm.**

Conclusions: prostate cancer

- Brachytherapy is an **alternative to EBRT alone or RPE in low risk prostate cancer patients.**
- Brachytherapy **combined with EBRT is at least as efficient as EBRT alone or RPE in intermediate risk patients with a favourable morbidity profile.**
- Brachytherapy **combined with EBRT in high risk patients is superior to EBRT alone or RPE in regard to oncological outcome.**
- **Underutilization of BT** may either have direct negative impact on oncological outcome (bNED or local control) or on morbidity and/or QoL, depending on the individual cancer risk and the morbidity risk of the patient.
- **Underutilization of BT** according to doctors' preferences **may not reflect patients' references** and therefore withhold an important therapeutic option from the patient.

Brachytherapy in Breast Cancer

**Boost combined EBRT (perioperative, after),
Accelerated partial breast irradiation,
Salvage breast conserving treatment.**



GLOBOCAN 2012 (IARC)

Estimated age-standardised rates (World) per 100,000

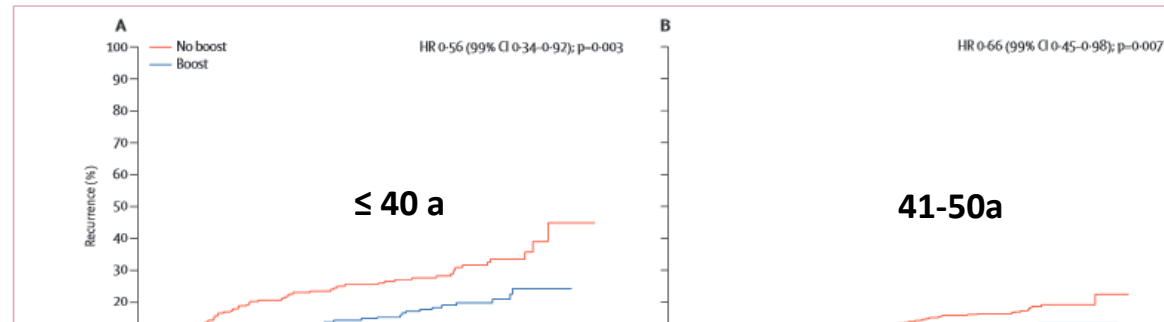
Breast Cancer

Worldwide in 2012

	Cases	Deaths	5-year prev.
	1671	522	6232
	788	198	3201
	883	324	3032
	100	49	318
	408	92	1618
	99	42	348
	494	143	1936
	240	110	735
	330	86	1276
	935	257	3591
	233	44	971
	187	48	697
	145	70	397
	362	92	1444

Current age	Risk of breast cancer in next 10 years	Or 1 in:
20	0.05%	1,985
30	0.44%	229
40	1.46%	68
50	2.73%	37
60	3.82%	26
70	4.14%	24
Lifetime	13.22%	8

Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial



**Significant effect on LC, no effect on DFS and OS,
 BUT reduction on rate of second mastectomy!
 Most benefit in women ≤ 40 yrs.**

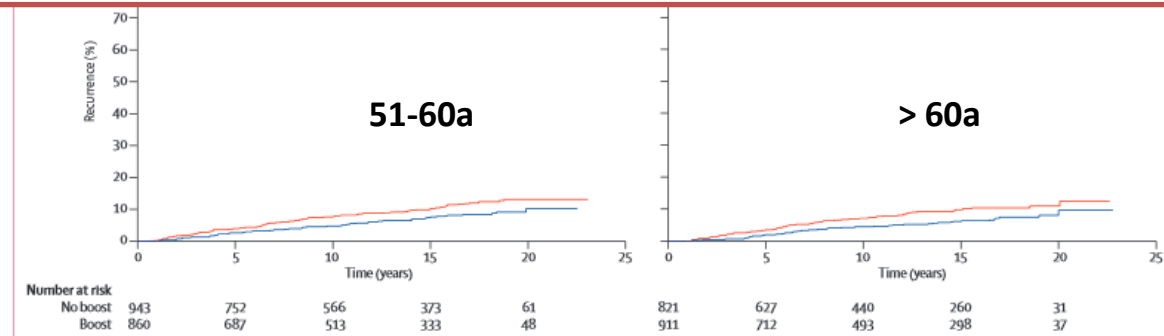


Figure 4: Cumulative incidence of ipsilateral breast tumour recurrence by age
 For patients aged ≤40 years, 71 patients in the no boost group versus 42 in the boost group had recurrence (A); for patients aged 41-50 years, 108 versus 74 had recurrence (B); for patients aged 51-60 years, 100 versus 64 had recurrence (C); and for patients aged >60 years, 75 versus 57 had recurrence (D). HR=hazard ratio.

Benefits of APBI with Brachytherapy for women with Early Breast Cancer

- Short convenient treatment offering benefit to many women including
 - More elderly women
 - Working women
 - Women with young children
 - Women who live far away from the hospital
- In the case of tumour recurrence BCT can be performed a 2nd time in the “salvage” setting with APBI brachytherapy
 - allows the breast to still be preserved and avoiding mastectomy

Use of breast brachytherapy in Europe

Radiotherapy and Oncology 97 (2010) 514–520



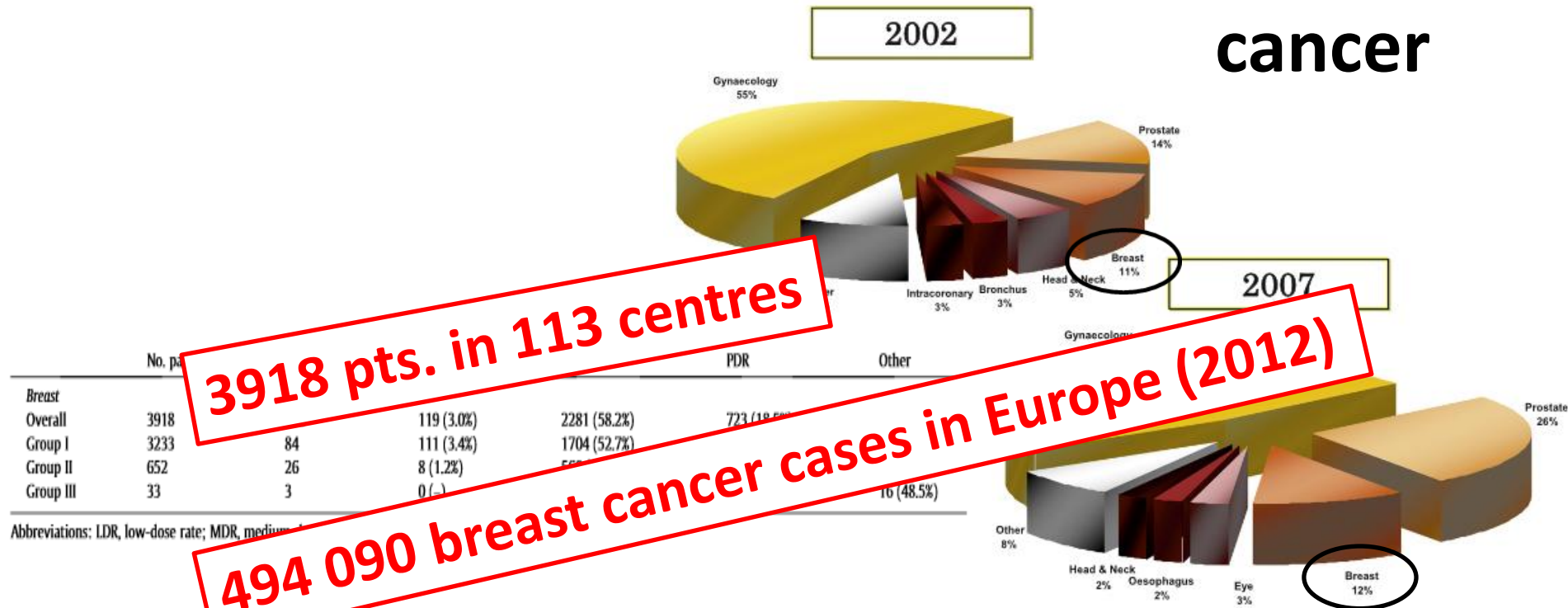
Brachytherapy

Patterns of care for brachytherapy in Europe: Updated results

Ferran Guedea^{a,*}, Jack Venselaar^b, Peter Hoskin^c, Taran Paulsen Hellebust^{d,e}, Didier Peiffert^f, Bradley Londres^a, Montse Ventura^a, Jean-Jacques Mazeron^g, Erik Van Limbergen^h, Richard Pötterⁱ, Gyorgy Kovacs^j

^a Department of Radiation Oncology, L'Hospitalet de Llobregat, Spain; ^b Department of Medical Physics and Engineering, Instituut Verbeeten, Tilburg, The Netherlands; ^c Mount Vernon Cancer Centre, Northwood, Middlesex, UK; ^d Norwegian Radiation Protection Authority, Østerns, Norway; ^e Department of Medical Physics, Oslo University Hospital, Norway; ^f Department of Radiation Oncology, Centre Alexis Vautrin, Vandœuvre-les-Nancy, France; ^g Centre des Tumeurs, Hôpital de la Pitié-Salpêtrière, Paris, France; ^h University Hospital Gasthuisberg KUL, Leuven, Belgium; ⁱ Allg. Krankenhaus der Stadt Wien, AKH, Wien, Austria; ^j University of Lübeck, Interdisciplinary Brachytherapy Unit, Lübeck, Germany

**BT
in 0.8%
of breast
cancer**



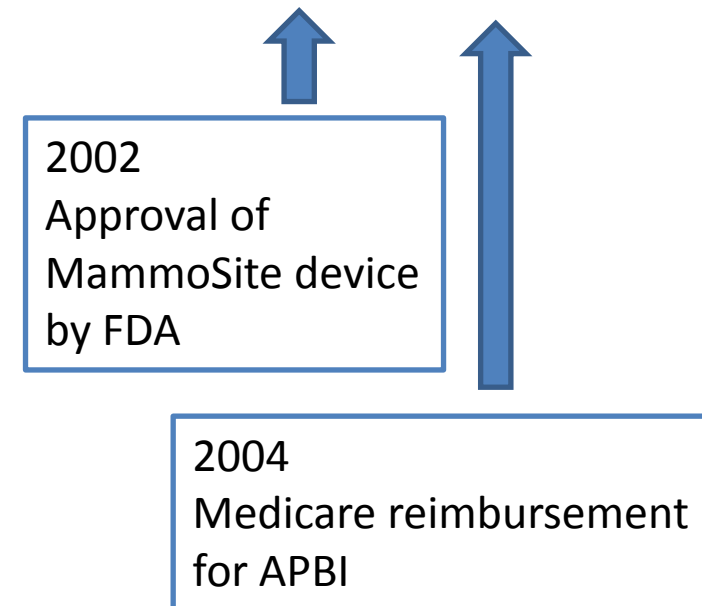
3918 pts. in 113 centres

494 090 breast cancer cases in Europe (2012)

Fig. 3. Most common treatment localizations, group I (2002 vs. 2007).

Utilization of APBI in USA

- Smith et al. 6882 pts. 1% (2001)→ 10% (2010)
- Abbot et al. (SEER-data) 125257pts 0,4% (2000)→ 6,8%(2007)



Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI)

- **GEC-ESTRO Multicentric Phase III APBI Trial**
 - 1233 patients included form 2004-2009
- **NSABP B-39/RTOG 0413**
 - 4214 patients included up 4/2013

Conclusions : breast cancer

- BT boost leads to **at least similar local control as EBRT boost in intermediate and high risk patients** with less irradiated breast tissue volume and **reduced dose to organs at risk** (lung, heart, skin)
- **BT alone (APBI) for low risk patients** leads to **similar oncological outcome, comparable cosmetic outcome and less acute morbidity compared to EBRT alone** (phase III trial 10/2015). Treatment time can be drastically reduced to 1-5 days for patients comfort.
- **Underutilization of BT will in future lead to overtreatment of patients** in particular of those who would as **low risk patients qualify for APBI**.
- Growing future role in **breast conserving treatment for salvage** (local recurrence) and **secondary breast cancer (5-10%)**

Miscellaneous Tumour Sites I

evidence (cohorts) and utilization (limited)

Head and neck: definitive BT for T1 lip, cheek, oral cavity, oropharynx, nasopharynx

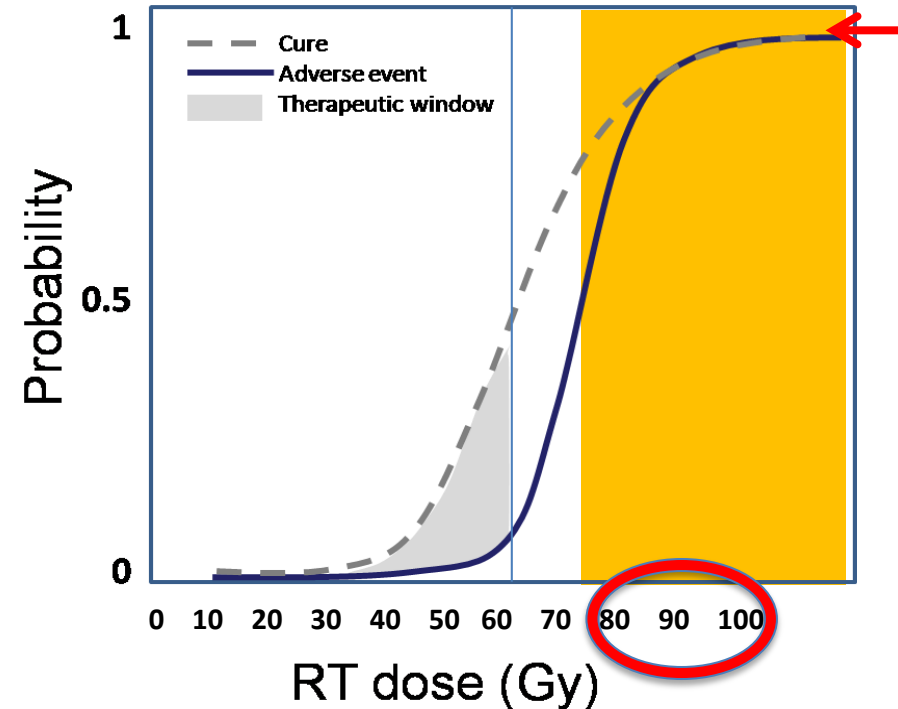
adjuvant BT associated with surgery

boost after EBRT chemoradiotherapy

Rectum: definitive BT for T1 (T2) (contact, interstitial) boost after EBRT chemoradiotherapy

Anus: boost after EBRT chemoradiotherapy

Bladder: definitive BT for T1 (robotic assistance)



Miscellaneous Tumour Sites II

evidence (cohorts) and utilization (limited)

Sarcoma: adjuvant BT associated with surgery
boost after neo-adjuvant chemo (paediat)

Eye: various applications incl. eye melanoma

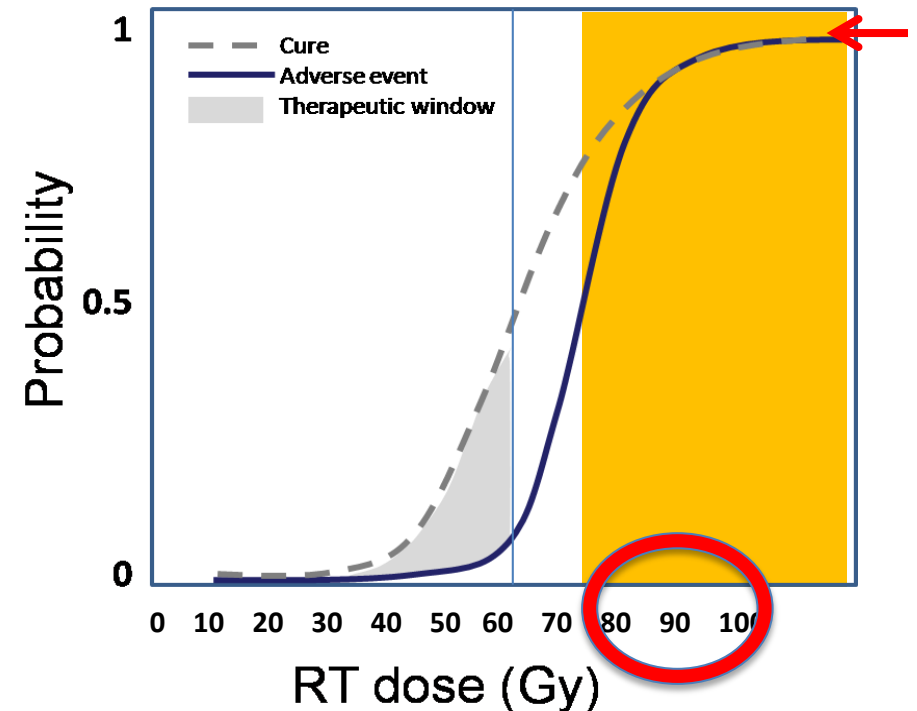
Skin: definitive BT of basalioma, PEC,

Oesophagus: definitive BT T1,
boost after EBRT, palliative

Bronchus: definitive BT for T1, pall.

Bile Duct: palliative

Penis, Urethra, pediatrics....



Utilization of Brachytherapy worldwide

Gynaecology (cervix + uterine corpus cancer)

remains „The“ Key Application

even more pronounced outside „Western World“

(Asia, South America, Africa)

Other sites are and may be also frequent: to different degrees

depending on regional traditions and developments

prostate/breast: North America, Europe (India), Japan

head and neck: India

Summary and Conclusions (I)

discrepancies

- **Growing level of evidence for Brachytherapy,**
at various cancer sites:
superiority: **cervix, postop. Endometrium, prostate**
noninferiority/comparable effects: **prostate, breast....**
- **Utilization of Brachytherapy overall stable/de-, increase/**
various scenarios in different regions
US: obvious trend except for breast („Mammosite“)
Europe: increase/decrease/stable (regional differences)

Summary and Conclusions II

Reasons for discrepancies between evidence and utilization of BT

- attitudes:** * increasing belief in the benefits of computer driven (non-manual) medicine „big“ and „clean“ advanced EBRT, „ART“.....,
- * brachytherapy seems not to represent modern „ART“
- „critical mass“** for BT often not reached
- organ specific applications, <10% of patient load
- education and training** for BT less available, complex,
- reimbursement** for BT often inferior to EBRT/surgery,

Summary and Conclusions III

to overcome discrepancies

between evidence and utilization of BT: seven to do's

- to provide more **high level clinical evidence**
- to explore **new indications** and **re-inforce tradional indications**
- **To rise awareness** for advantages of BT: „*The therapeutic window*“
- **To create critical mass scenarios** (>50 pts/year/organ site),
- To **increase** structures, opportunities, incentives for
BT education and training, (inclung hands-on),
- To make brachytherapy „**The Precise Interventional Oncology**“ -
get the *young generation* into the brachy-ART boat,
- To **increase income (reimbursement) for brachytherapy** to make BT
comparable to EBRT/surgery

Acknowledgements

In this presentation material were used:

- from an Elekta company, Elekta AB, Stockholm, Sweden,
- from prof. Richard Pötter presentation,
- from ABS Meeting in Orlando 2015.



Thank you