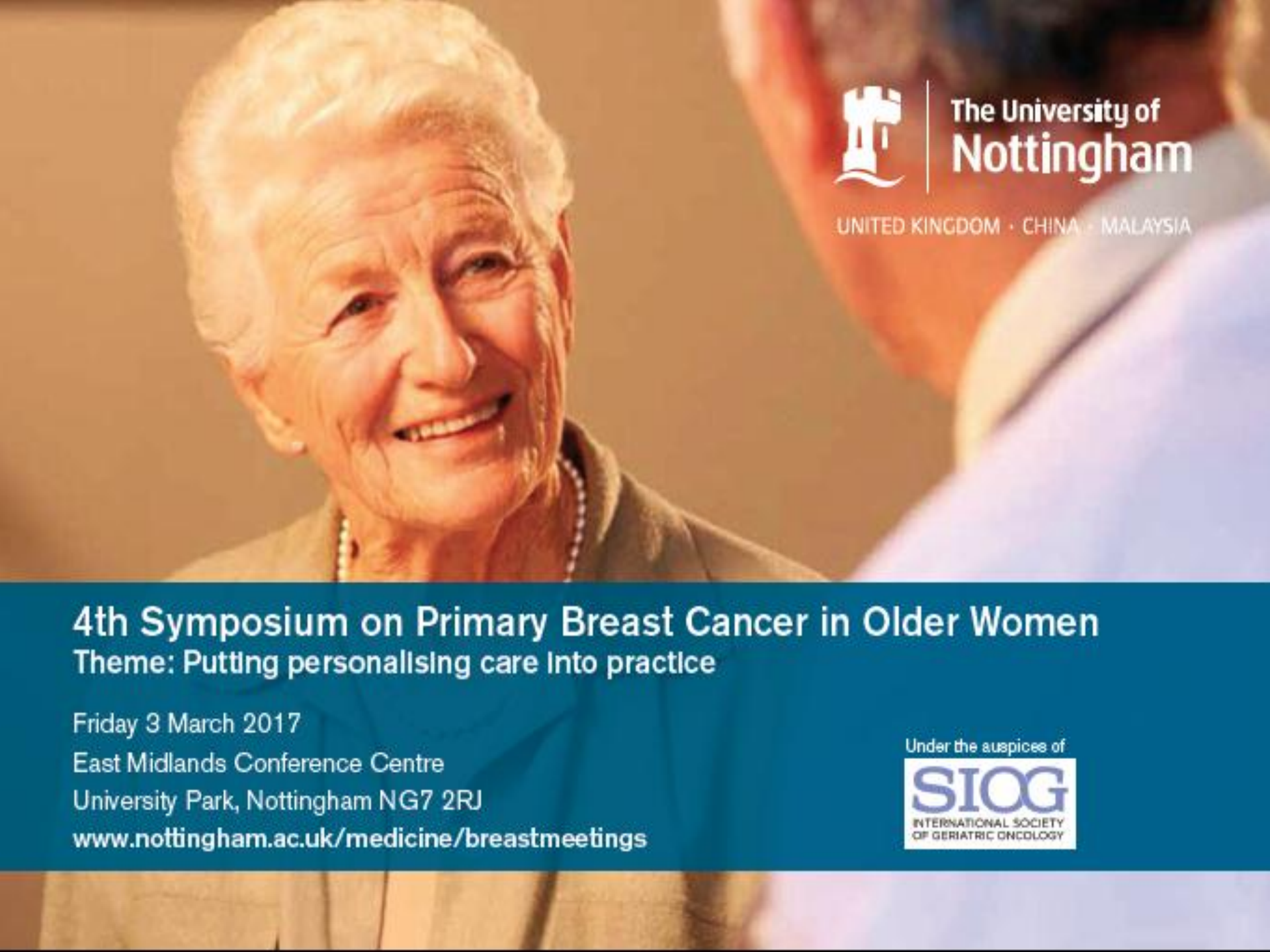


The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

4th Symposium on Primary Breast Cancer in Older Women

Theme: Putting personalising care into practice

Friday 3 March 2017

East Midlands Conference Centre

University Park, Nottingham NG7 2RJ

www.nottingham.ac.uk/medicine/breastmeetings

Under the auspices of

SIOG

INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

Local and systemic therapies:

Selecting for radiation therapy

Philip Poortmans, MD, PhD
03 March 2017

Past-President
President-Elect
Department of Radiation Oncology
Radboudumc


institutCurie

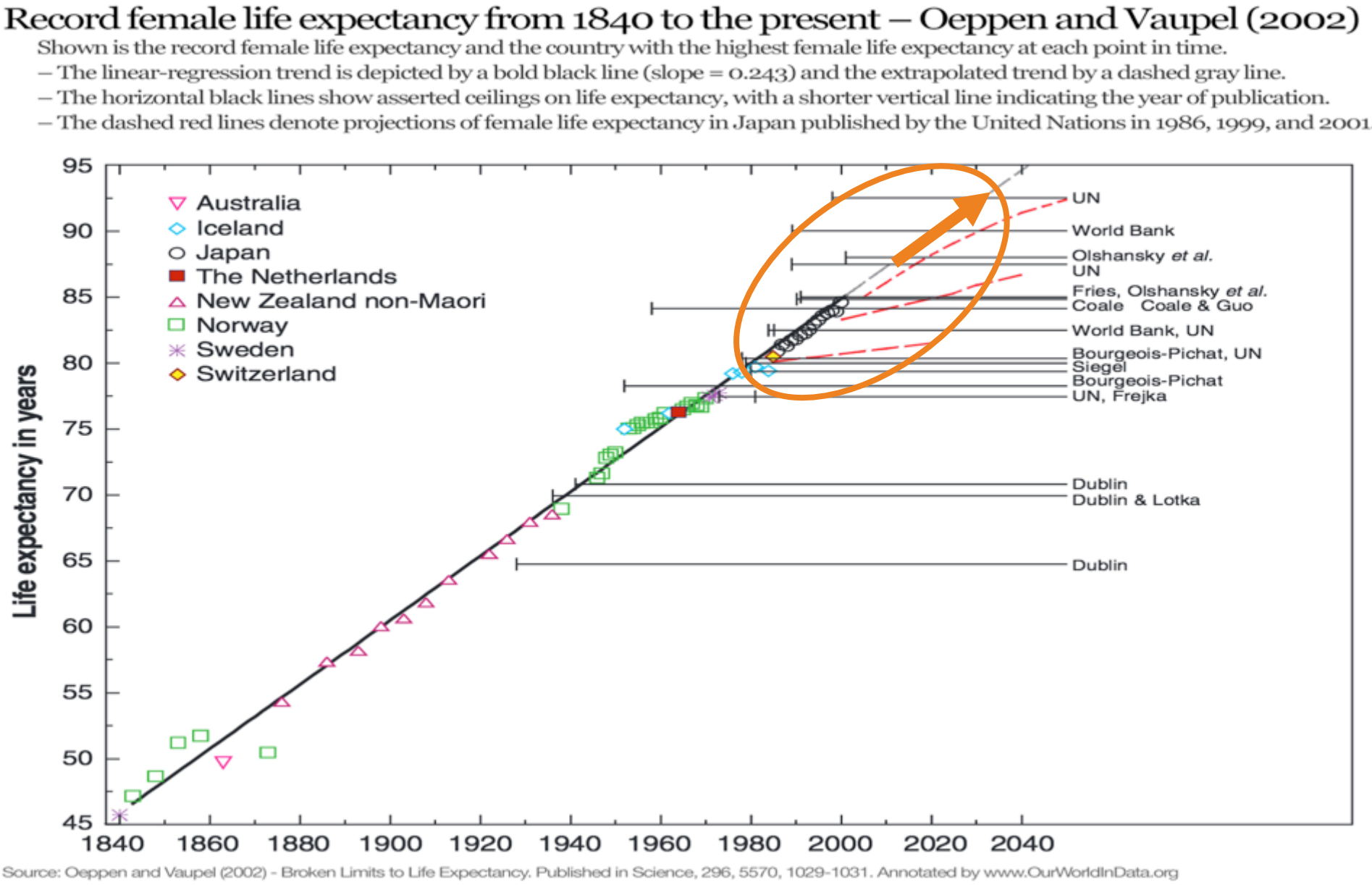
Conflict of interest:

I am a radiation oncologist

Selecting for radiation therapy

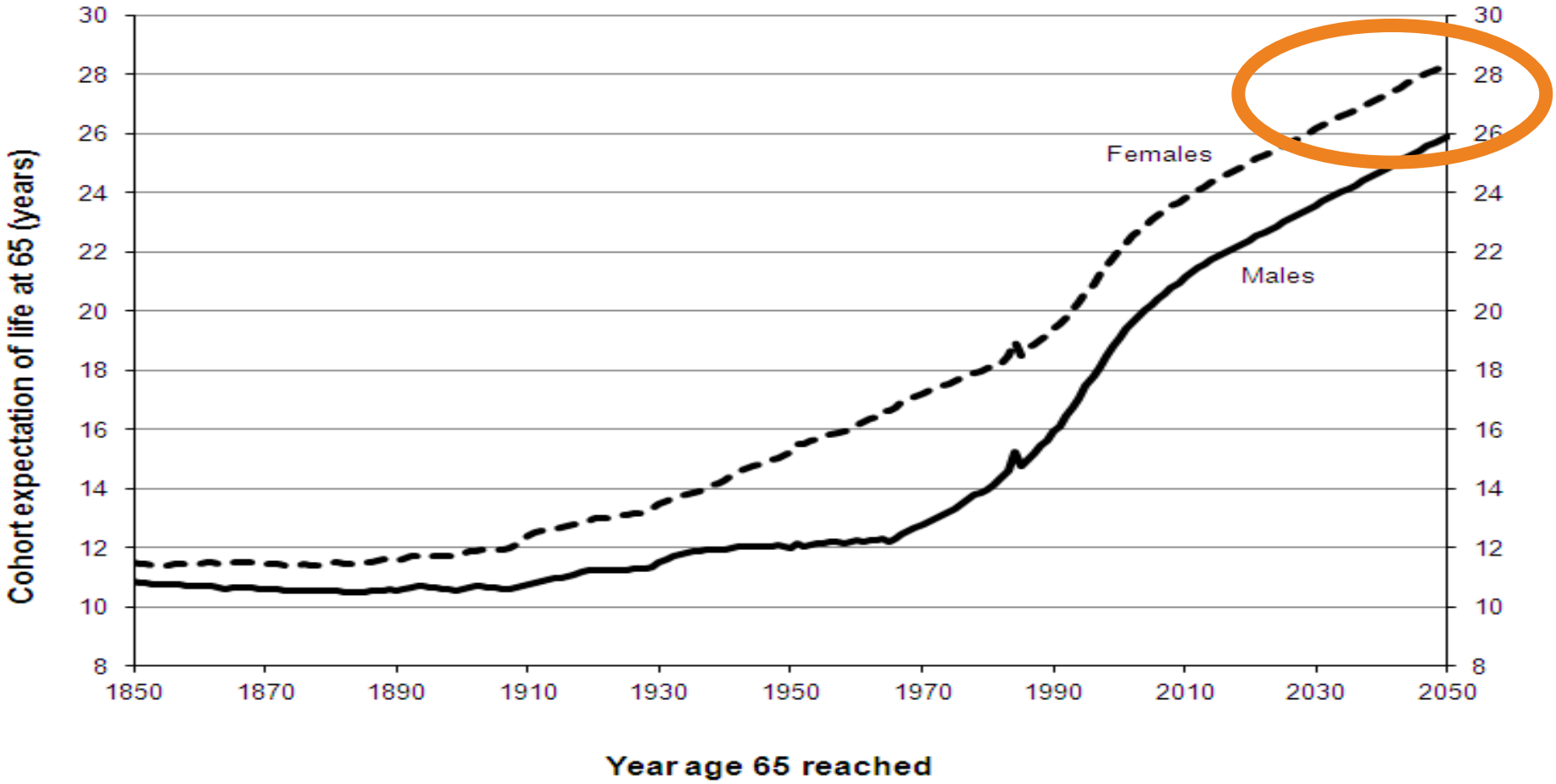
1. Introduction
2. The role of radiation therapy
3. A particular case
4. Discussion
5. Conclusions

Selecting for RT: *Introduction*



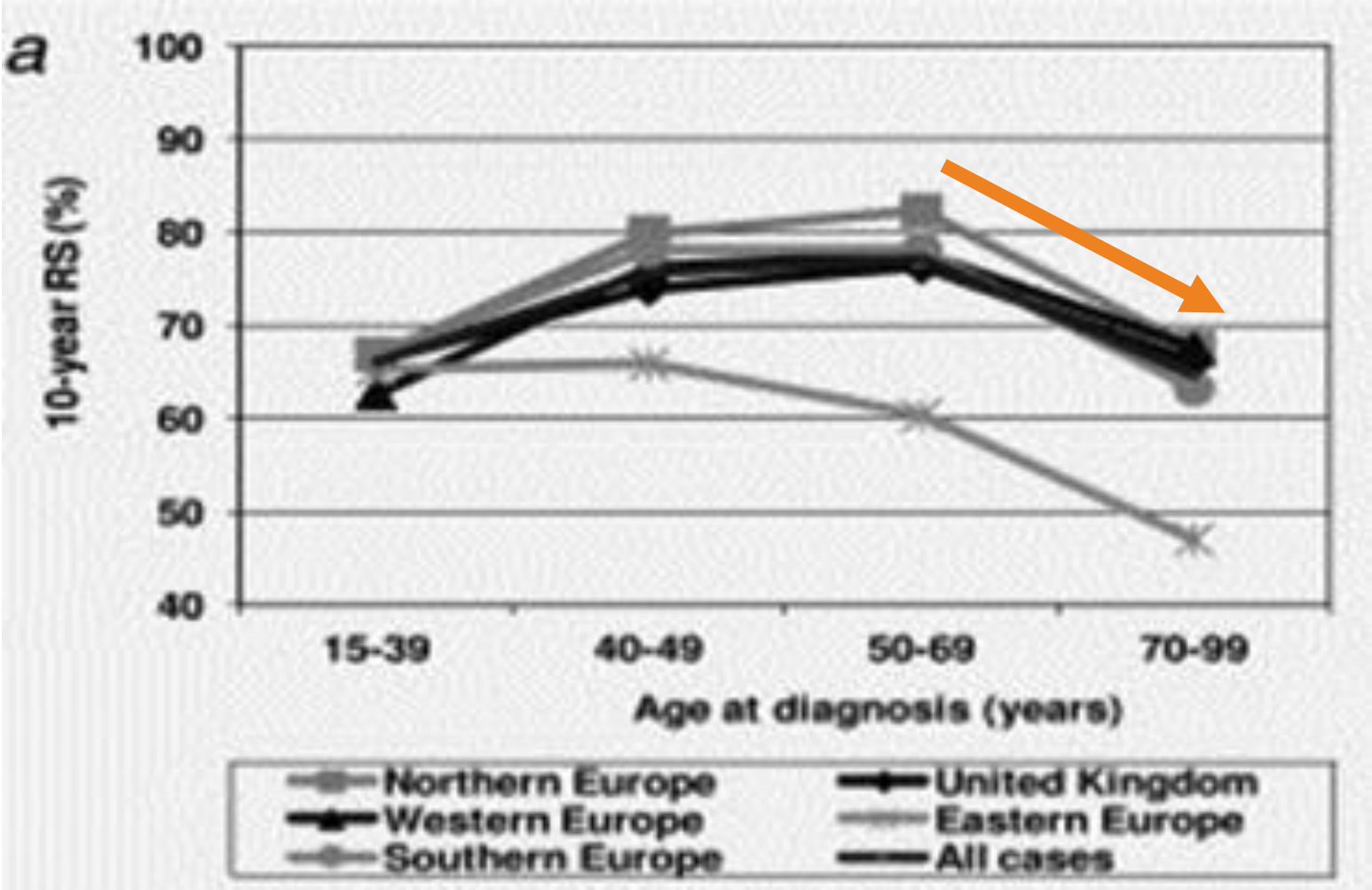
Selecting for RT: *Introduction*

Cohort expectation of life at age 65 according to historic and projected mortality rates, persons who reached age 65 1850–2050, England and Wales



Selecting for RT: *Introduction*

Predicted relative survival up to 10 years after diagnosis for European women with breast cancer in 2000-2002



Selecting for RT: *Introduction*

Evidence is what we need
To fully inform the patient

Selecting for radiation therapy

1. Introduction

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Selecting for RT: *The role of RT*

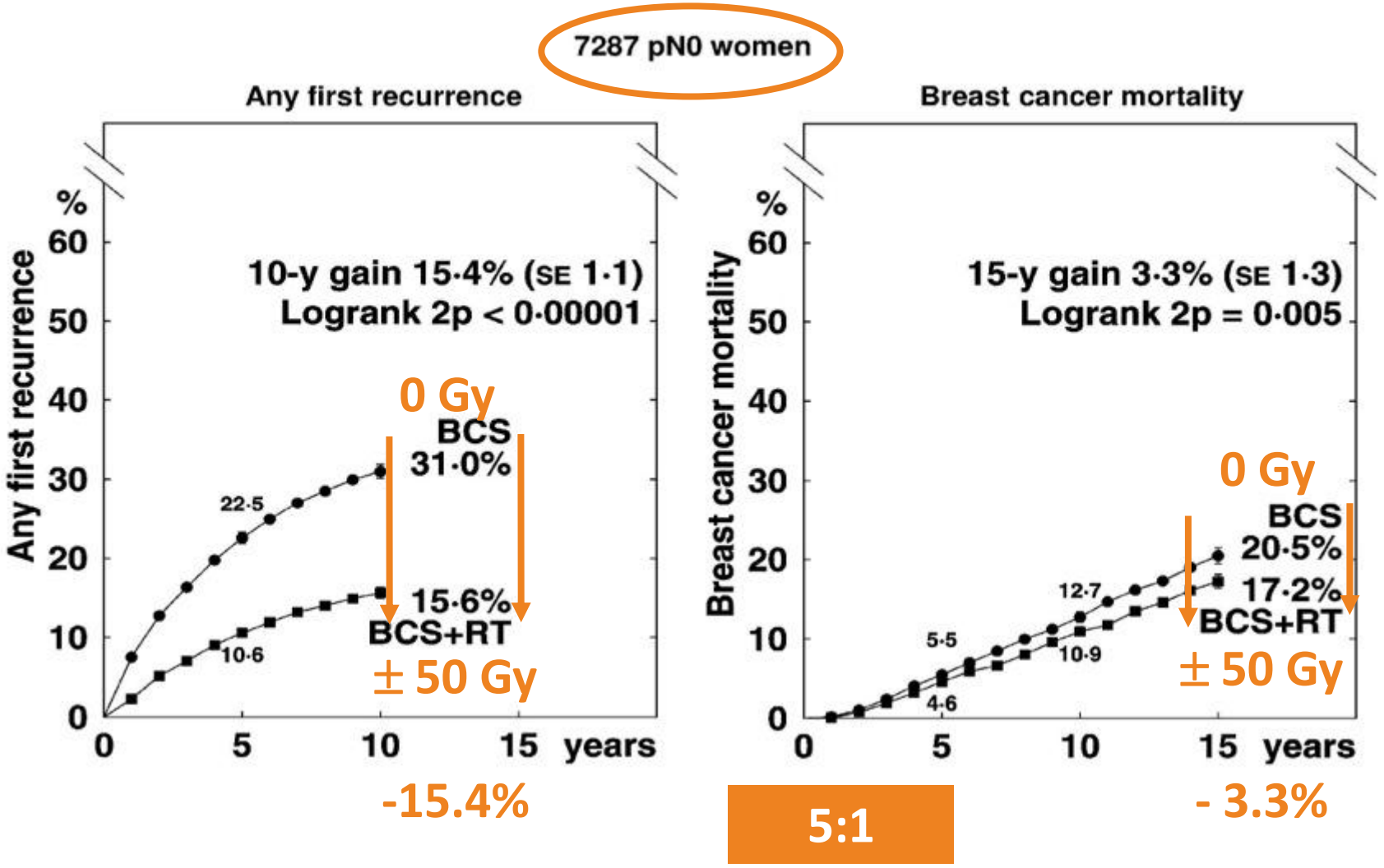
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 1707–16

Selecting for RT: *The role of RT*

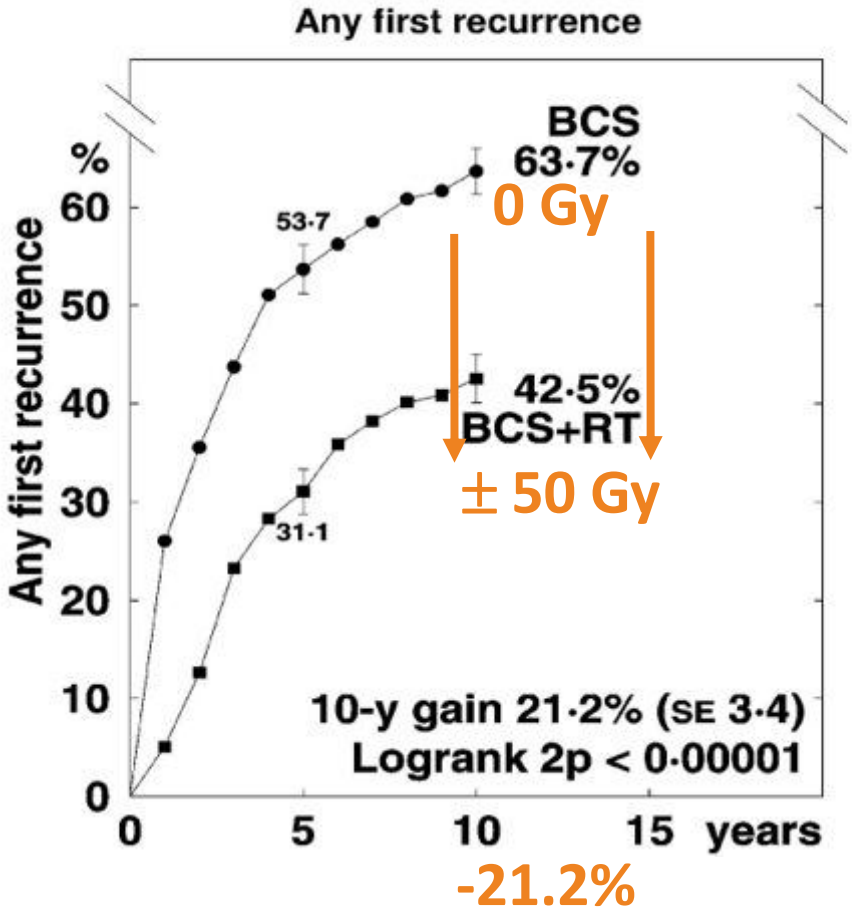
Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.

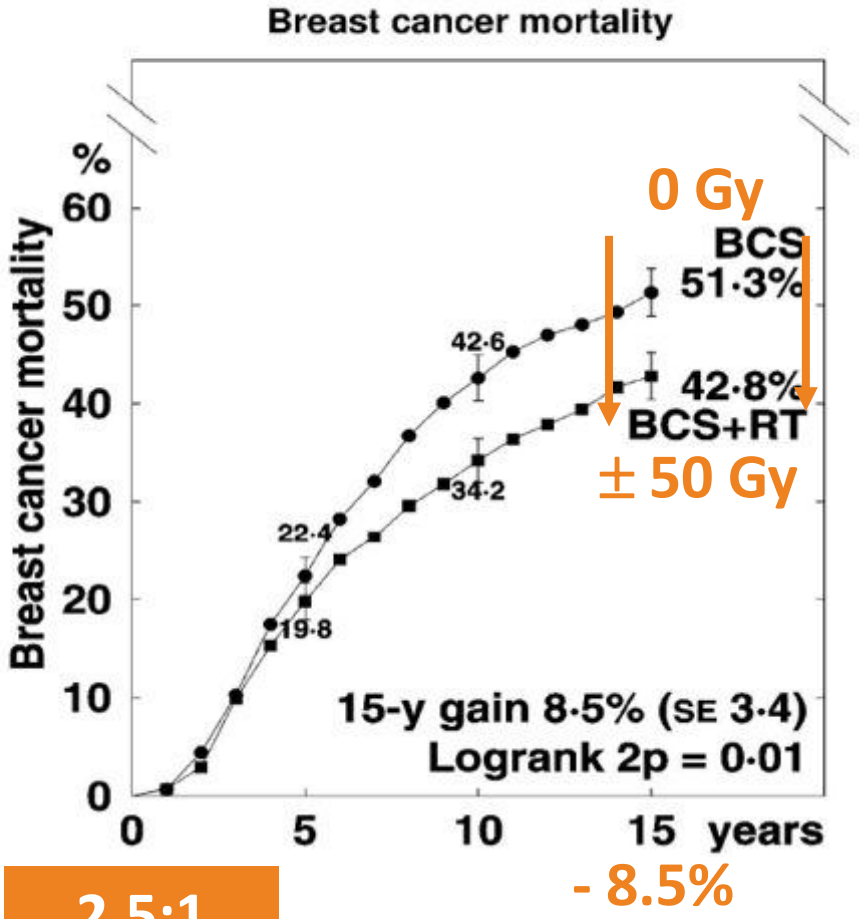


Selecting for RT: *The role of RT*

Effect of RT after BCS on recurrence and breast cancer mortality in pN+ women.

1050 pN+ women





2.5:1

Selecting for RT: *The role of RT*

RT after tumourectomy: not always required?

Overview of prospective clinical trials evaluating postoperative radiation therapy omission.

Author, Year	Patients	Study design	Local relapse	DFS	OS	Median FU
Fisher et al., 2002 [11]	1009	TAM vs. placebo + RT vs. TAM + RT	16.5% vs. 9.3% vs. 2.8% ($p = 0.008$; $p < 0.0001$; $p = 0.01$)	–	93% vs. 94% vs. 93% ($p = 0.93$)	87.5 months
Fyles et al., 2004 [7]	769	TAM vs. TAM + RT	7.7% vs. 0.6% at 5 years ($p < 0.001$)	84% vs. 91% at 5 years ($p = 0.004$)	92.8% vs. 93.2% ($p = 0.83$)	67.2 months
Pötter et al., 2007 [9]	869	TAM/AI vs. TAM/AI + RT	5.1% vs. 0.4% ($p = 0.0001$)	HR 3.48 ($p = 0.0021$)	94.5% vs. 97.9% ($p = 0.18$)	53.8 months
Hughes et al., 2013 [10]	636	TAM vs. TAM + RT	9% vs. 2% ($p < 0.001$)	–	66% vs. 67% at 10 years ($p = 0.64$)	151.2 months
Blamey et al., 2013 [12]	1135	- without or with TAM - without or with RT 2 × 2 factorial design	- 13% vs. 4% - 11% vs. 3% Both treatments 0% ($p < 0.001$)	–	96% at 10 years	167 months
Kunkler et al., 2013 [13]	1326	TAM/AI vs. TAM/AI + RT	4.1% vs. 1.3% ($p = 0.0002$)	–	93.9% vs. 93.9% ($p = 0.34$)	60 months

Abbreviations: DFS, disease-free survival; OS, overall survival; FU, follow up; TAM, tamoxifen; AI, aromatase inhibitors; RT, radiation therapy; HR, Hazard Ratio.

Selecting for RT: *The role of RT*

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Available at www.sciencedirect.com

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journal homepage: www.ejcancer.info

Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial ☆

R.W. Blamey [a,j], T. Bates [b,*,j], U. Chetty [c,j], S.W. Duffy [d,j], I.O. Ellis [a,j], D. George [e,j], E. Mallon [f,j], M.J. Mitchell [a,j], I. Monypenny [g,j], D.A.L. Morgan [a,j], R.D. Macmillan [a,j], J. Patnick [h,j], S.E. Pinder [i,j]

Selecting for RT: *The role of RT*

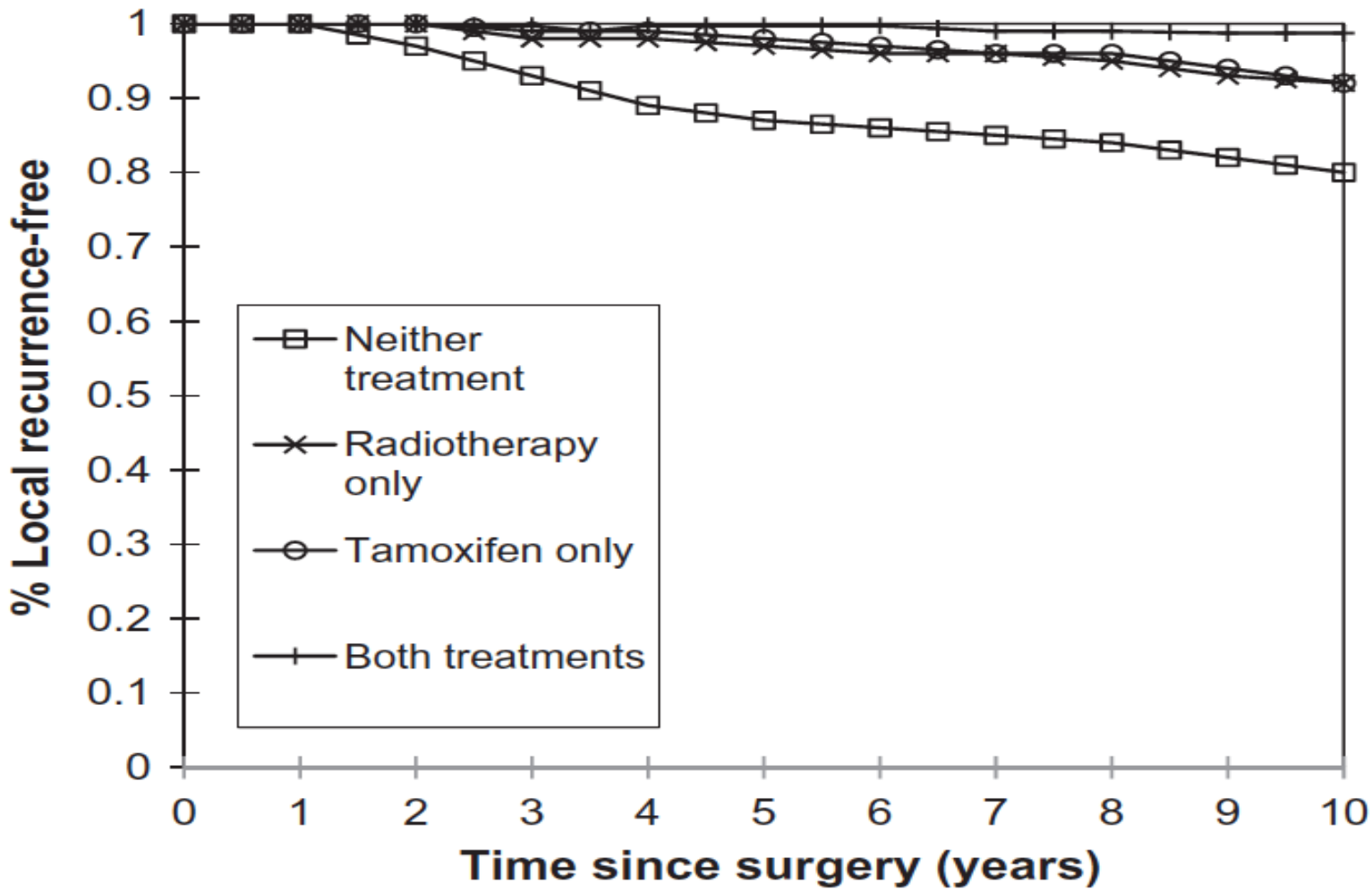

Fig. 2. Survival to first local recurrence by treatment actually received.

Selecting for RT: *The role of RT*

Even in these patients with tumours of excellent prognosis, ***LR after conservative surgery without adjuvant therapy was still very high****. This was reduced to a similar extent by either radiotherapy or tamoxifen but to a greater extent by the receipt of both treatments.*

Selecting for RT: *The role of RT*

…, LR after conservative surgery without adjuvant therapy was still very high…

Personal note:

Virtually none of those pts would get adjuvant systemic treatment according to the Dutch guidelines

Selecting for RT: *The role of RT*

RT after tumourectomy: not always required?

- 0.5% (1% still acceptable?) per year = limit for LRR
- Mind late relapses!
- Role of systemic treatment?

Selecting for radiation therapy

1. Introduction
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Selecting for RT: *A particular case*

- Born in 1918 ...
- Menarche 15; G0P0A0; familiar –
- Fashion specialist – kept a shop, smoked till 4 years before diagnosis
- Clinical history: breast reduction; hormonal replacement therapy until diagnosis (Ovestin = estriol)

- July 1996 (78 years old): she felt a large tumour laterally located in the right breast
- Biopsy: invasive ductal carcinoma

Selecting for RT: *A particular case*

- Modified radical mastectomy:
  - 4.0 cm invasive ductal carcinoma; tumour free margins
  - Axilla: 6/12 with capsular invasion up to apex
  - ER +; PR -
- Large hematoma post-surgery ➔ lymphatic drainage

Selecting for RT: *A particular case*

- Surgeon: ”Do we need to irradiate this nice old lady?"
- Rad.Onc: ”Let me see and talk with her to evaluate the general condition."
  - Excellent health for the age; .....
  - Back pain +++: < osteoporosis; M0
  - Local-regional complaints: lymphatic drainage
- Radiation therapy: chest wall + axilla levels 3-4; 50 Gy / 25 fractions
- Tamoxifen

Selecting for RT: *A particular case*

Follow-up

- June 1999 (after <3 years): stopped tamoxifen because of side effects
- September 2001 (after 5 years): NED; stopped regular FU ➔ / 5 years
- September 2006 (after 10 years): !!!!

- Identification obligation introduced in NL
- Age was not 88 but 98 !!!!
- NED; very active; travelling much.
- Drove car about 5 x / week: driving licence prolonged for 5 years.
- Some local & regional complaints ➔ continuation of lymphatic drainage

Selecting for RT: *A particular case*

Follow-up:

- 2008 (after 12 years): pleural effusion ➔ Arimidex; stopped because it was cardiac & M0
- 2008: very ill due to abdominal problem ➔ complete recovery
- 2010: fall in shower ➔ osteoporotic vertebral fractures
- 2011: died at the age of 103,5

Selecting for radiation therapy

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Medical Radiology | Diagnostic Imaging

Seymour H. Levitt
James A. Purdy
Carlos A. Perez
Philip Poortmans
Editors

Technical Basis of Radiation Therapy
Practical Clinical Applications
Fifth Edition

This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dosefractionation, and explains the various technological approaches to radiation therapy, such as intensity-modulated radiation therapy, tomotherapy, stereotactic radiotherapy, and high and low dose rate brachytherapy. Issues relating to quality assurance, technology assessment, and cost-benefit analysis are also reviewed. The second part of the book discusses in depth the practical clinical applications of the different radiation therapy techniques in a wide range of cancer sites. All of the chapters have been written by leaders in the field. This book will serve to instruct and acquaint teachers, students, and practitioners in the various fields of oncology with the basic technological factors and approaches in radiation therapy.

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Levitt · Purdy · Perez
Poortmans *Eds.*

Technical Basis of Radiation Therapy

5th Ed.

Medical Radiology
Diagnostic Imaging
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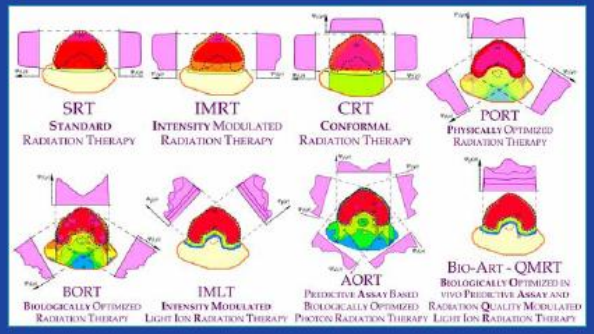
Editors

Technical Basis of Radiation Therapy

Practical Clinical Applications

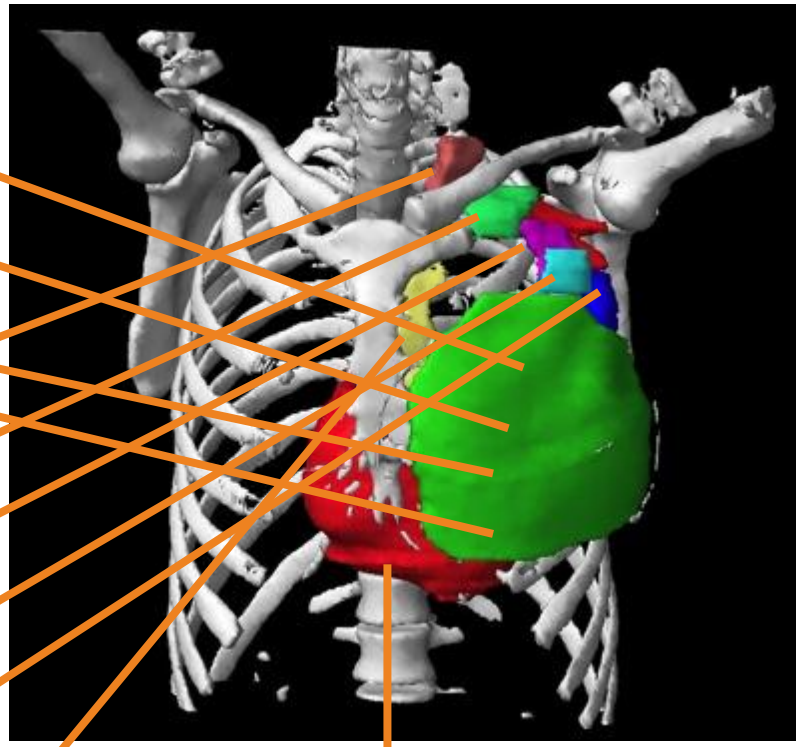
5th Edition



Springer

Selecting for RT: *Discussion*

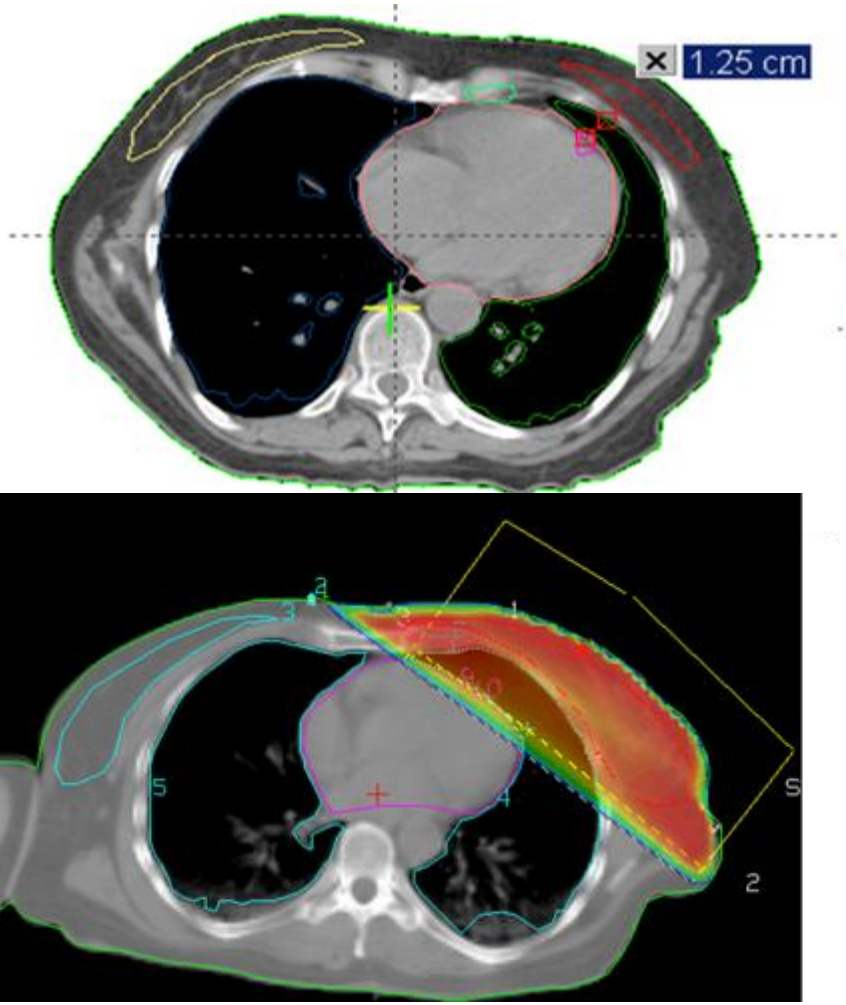
- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary



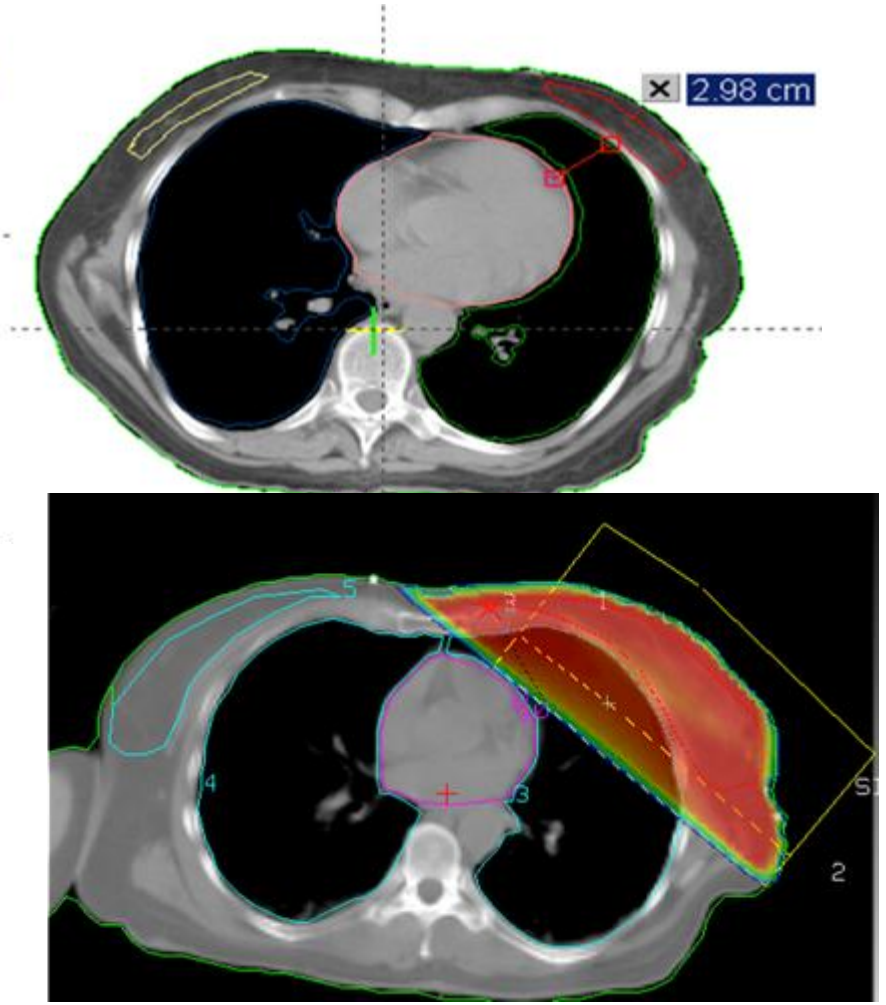
Heart

Selecting for RT: *Discussion*

Free respiration

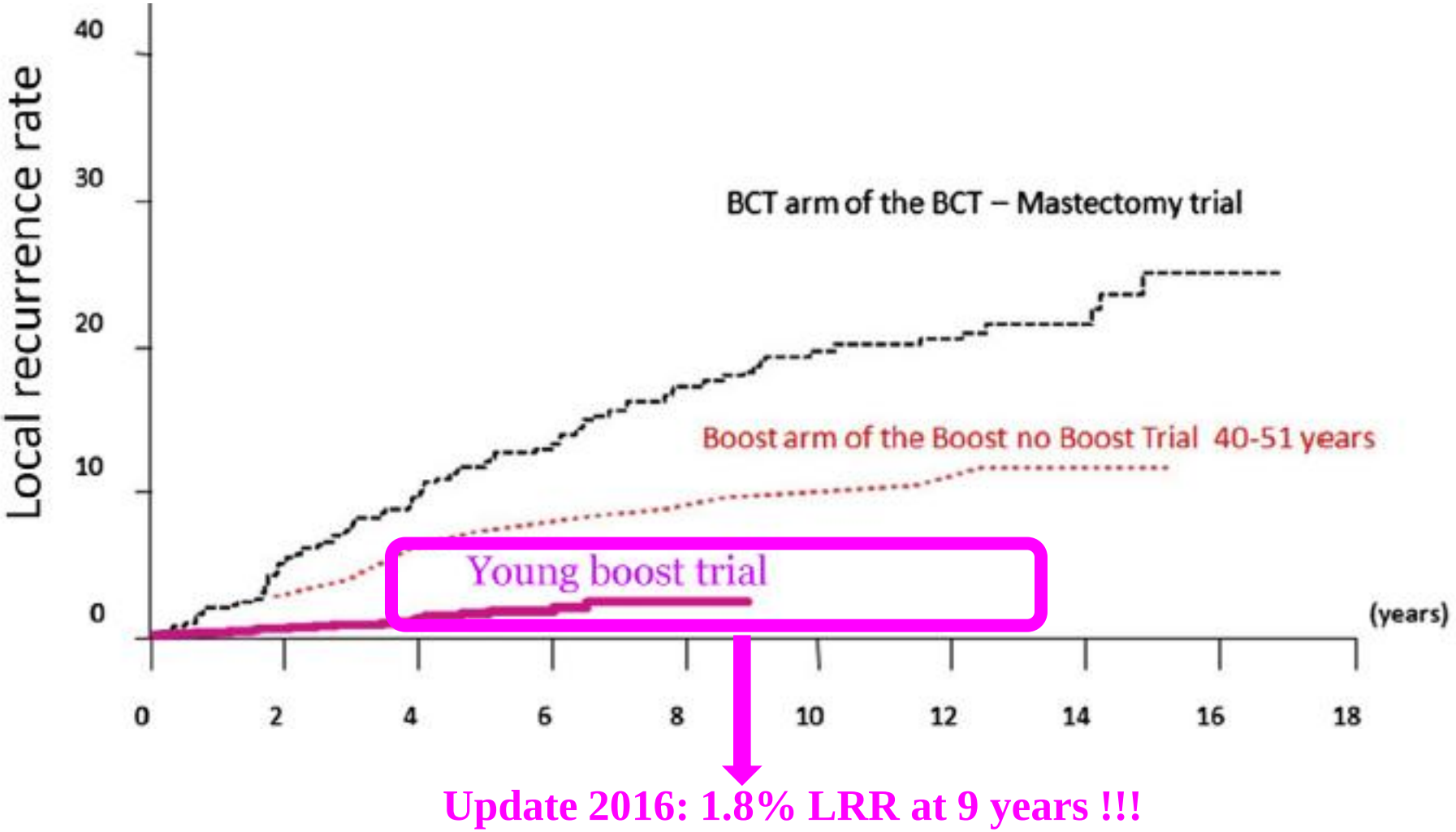


Breath hold



Selecting for RT: *Discussion*

We did improve BCT rates!

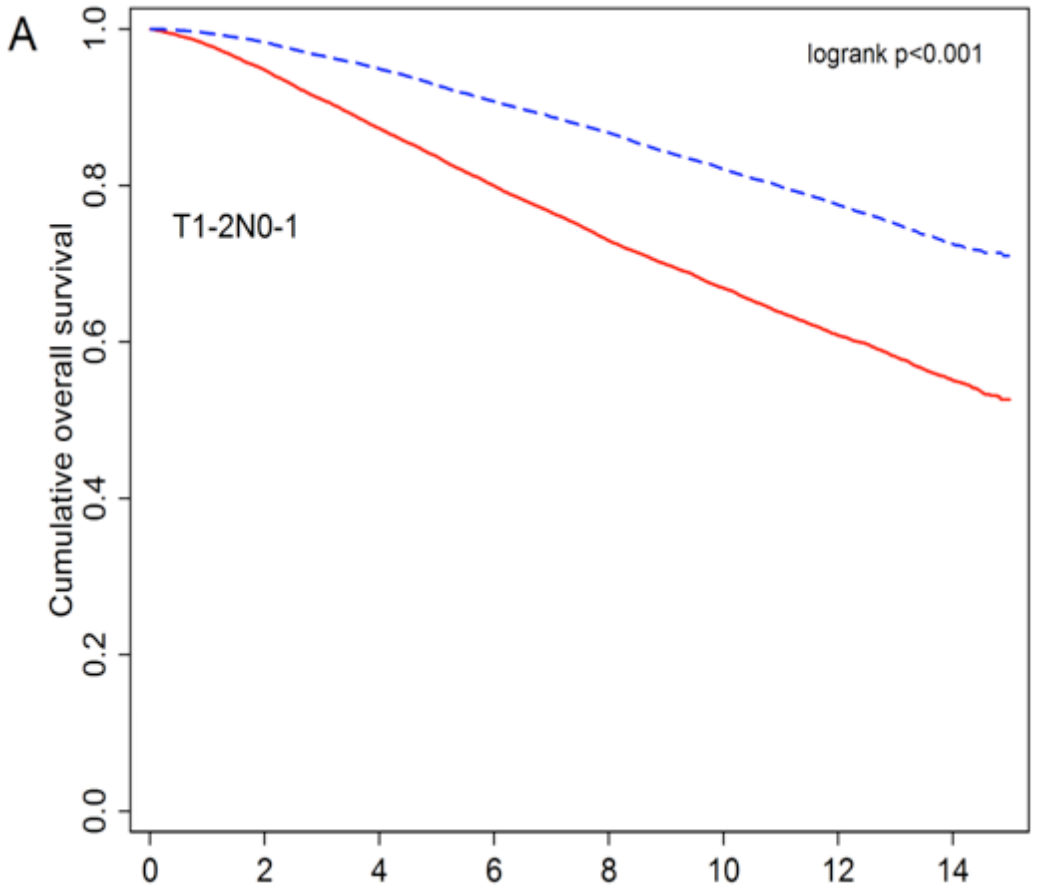


Selecting for RT: *The role of RT*

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients

- 58.4% BCT
- 41.6% MRM



Selecting for RT: *The role of RT*

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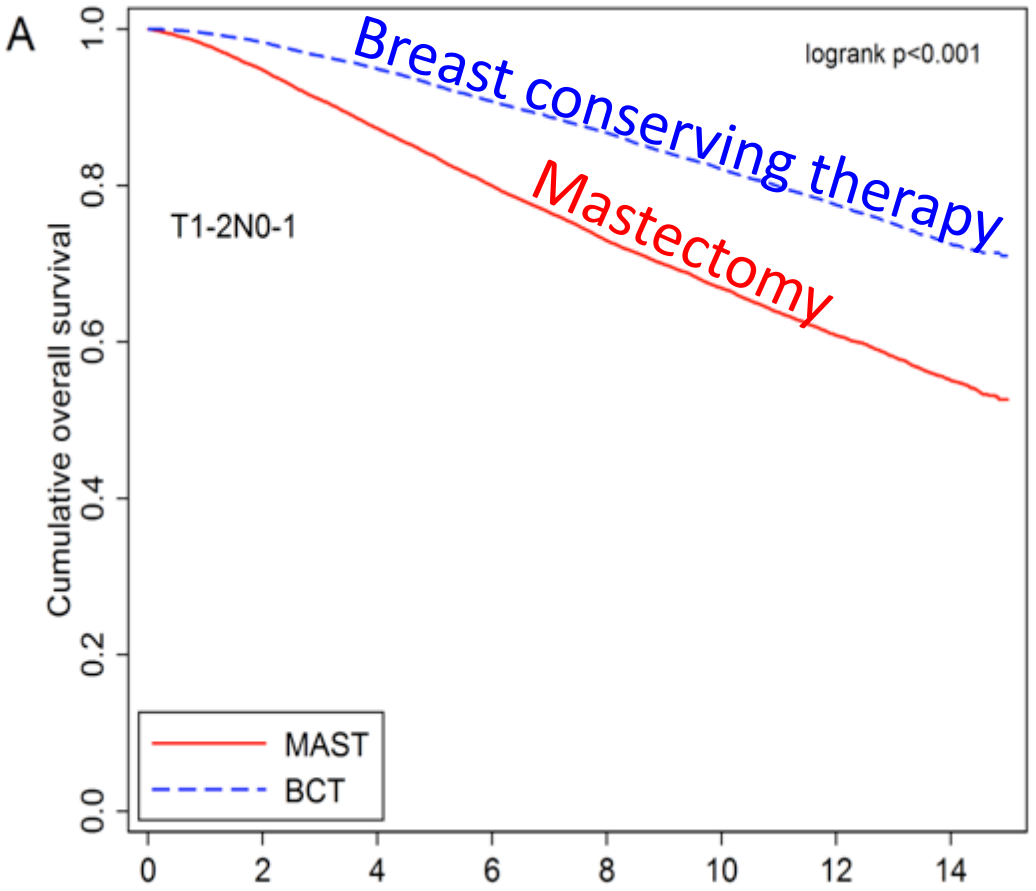

Selecting for RT: *Discussion*

Radiotherapy and Oncology 94 (2010) 264–273

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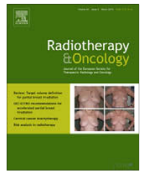
journal homepage: www.thegreenjournal.com



GEC-ESTRO Recommendations

Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009)

Csaba Polgár [a,*], Erik Van Limbergen [b], Richard Pötter [c], György Kovács [d], Alfredo Polo [e], Jaroslaw Lyczek [f], Guido Hildebrandt [g], Peter Niehoff [h], Jose Luis Guinot [i], Ferran Guedea [j], Bengt Johansson [k], Oliver J. Ott [l], Tibor Major [a], Vratislav Strnad [l], On behalf of the GEC-ESTRO breast cancer working group

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009

0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Benjamin D. Smith, M.D.,*† Douglas W. Arthur, M.D.,‡ Thomas A. Buchholz, M.D.,†
Bruce G. Haffty, M.D.,§ Carol A. Hahn, M.D.,‖ Patricia H. Hardenbergh, M.D.,¶
Thomas B. Julian, M.D.,# Lawrence B. Marks, M.D.,** Dorin A. Todor, Ph.D.,‡
Frank A. Vicini, M.D.,†† Timothy J. Whelan, M.D.,‡‡ Julia White, M.D.,§§ Jennifer Y. Wo, M.D.,‖‖
and Jay R. Harris, M.D.¶¶

Selecting for RT: *Discussion*

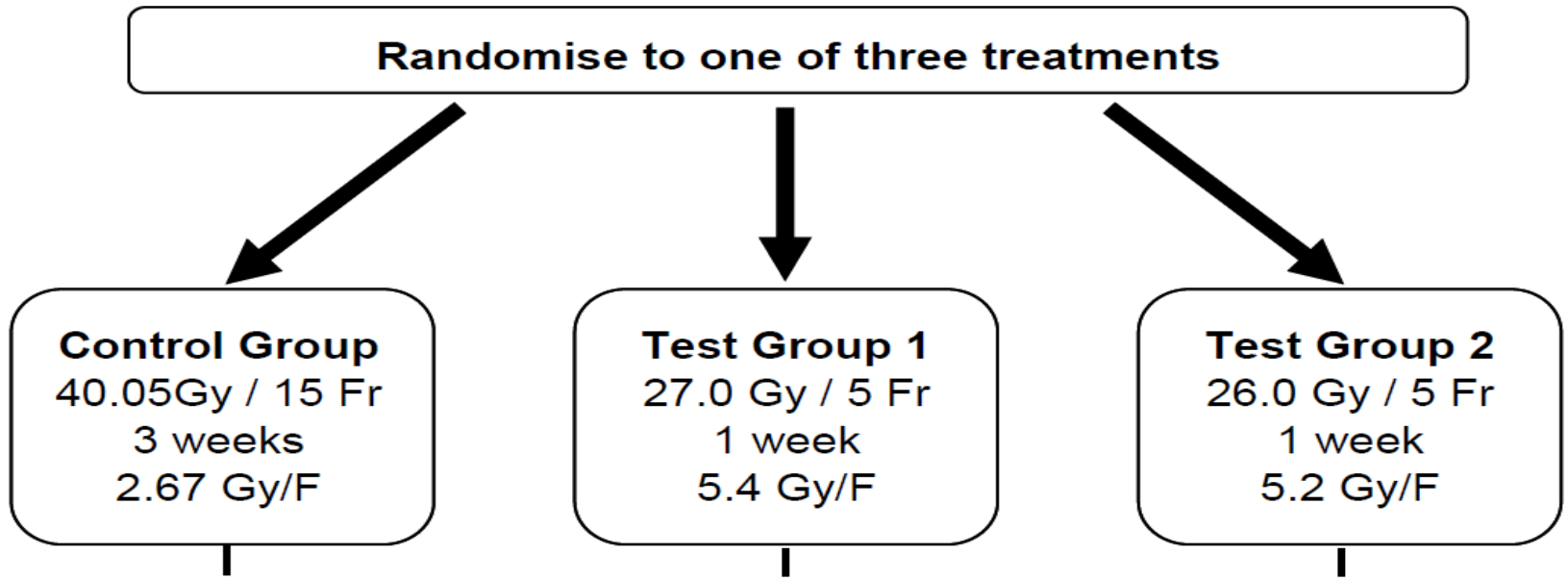
Prospective clinical trials evaluating (accelerated) partial breast irradiation.

Author, Year	Study design	Number of patients	Local relapse	DFS	OS	Median FU
Dodwell et al., 2005 [27]	Phase II WBI vs. APBI	174	4% vs. 12% (p = 0.05)	–	27% vs. 30% (p = 0.75)	96 months
Chen et al., 2010 [28]	Phase II 3D CRT APBI	94	1.1% at 4 years	95% at 4 years	97% at 4 years	50.4 months
Vicini et al., 2010 [29]	Phase II 3D CRT APBI	52	6% at 4 years	84% at 4 years	96% at 4 years	54 months
Lei et al., 2013 [30]	Phase II IMRT APBI	136	0.7% at 4 years	–	96.8% at 4 years	53.1 months
Veronesi et al., 2013 [32]	Phase III WBI vs. IORT	1305 (654 IORT vs. 651 EBRT)	0.4% vs. 4.4% at 5 years (p < 0.0001)	–	96.8% vs. 96.9% at 5 years (p = 0.59)	69.6 months
Vaidya et al., 2014 [31]	Phase III WBI vs. IORT	3451 (1730 EBRT vs. 1721 IORT)	1.3% vs. 3.3% at 5 years p = 0.042	–	96.1% vs. 94.7% at 5 years (p = 0.099)	29 months
Livi et al., 2015 [33]	Phase III WBI vs. IMRT APBI	520 (260 WBI vs. 260 APBI)	1.4% vs. 1.5% (p = 0.86)	–	96.6% vs. 99.4% at 5 years (p = 0.057)	60 months
Strnad et al., 2016 [34]	Phase III WBI vs. IBT	1184 (551 WBI vs. 633 APBI)	0.92% vs. 1.44% (p = 0.42)	94.45% vs. 95.03% at 5 years (p = 0.79)	95.55% vs. 97.27% at 5 years (p = 0.11)	79.2 months

Selecting for RT: *Discussion*

Treatment times are shortening!

FAST-Forward



*16 Gy or 10 Gy in 2 Gy fractions sequential electron or photon boost to the tumour bed is allowed in all 3 treatment arms (boost decision to be declared before randomisation for each individual patient)

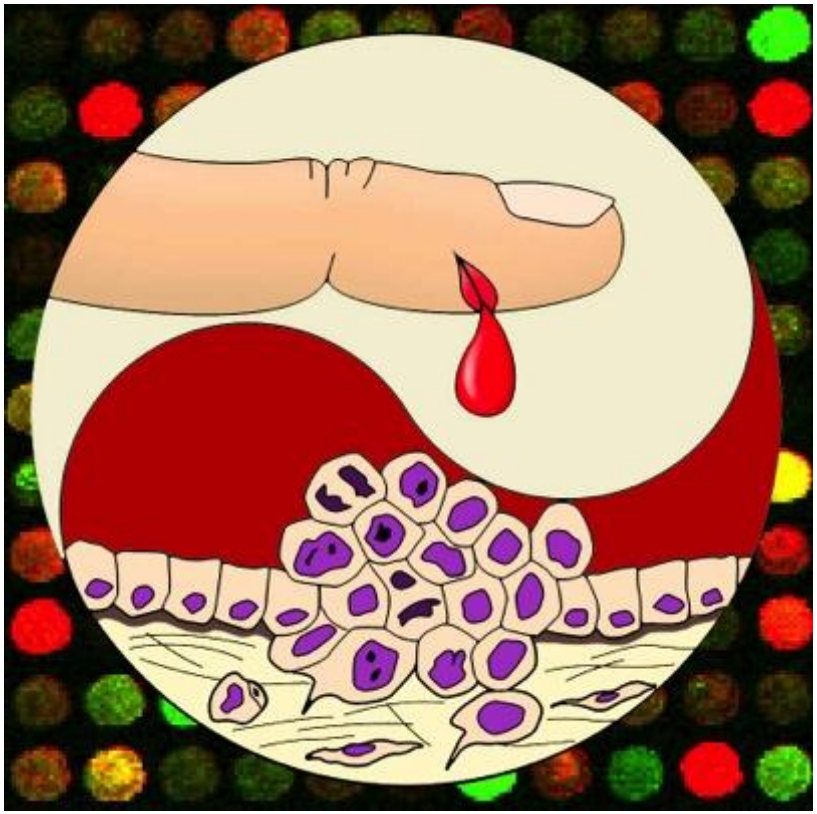
Selecting for RT: *Discussion*

Wound Response Signature

In vitro Wound Model – 516 genes

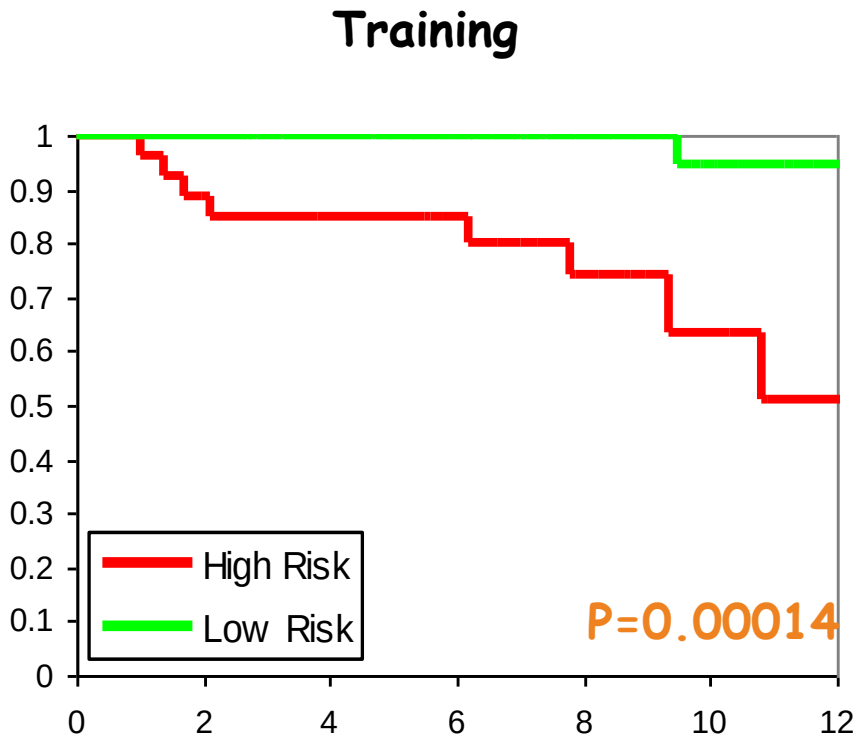
Prognostic Significance in

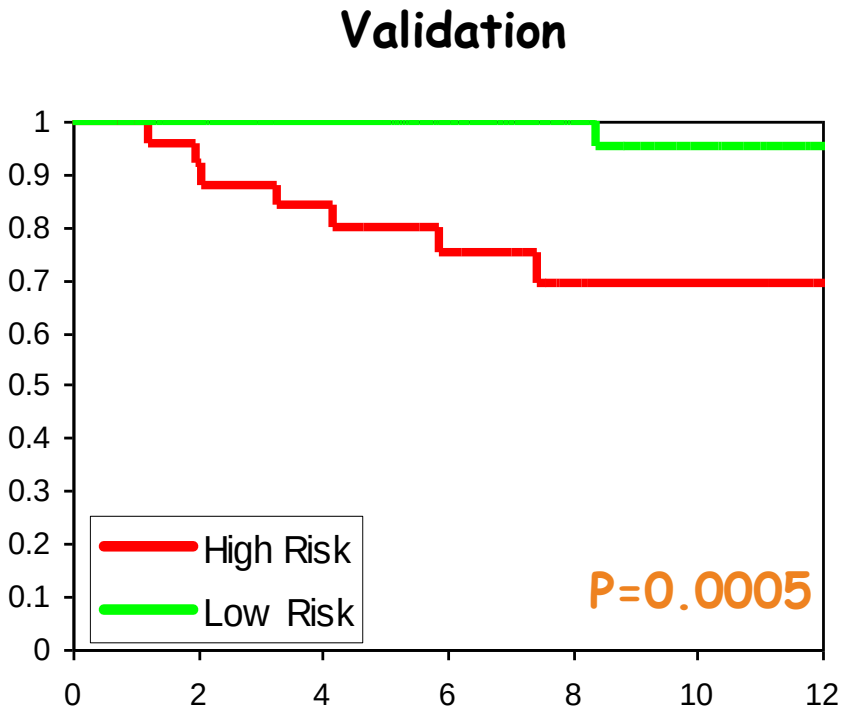
- Breast
- Lung
- Gastric cancer



Selecting for RT: *Discussion*

Predict of Local Recurrence in Early Breast Cancer





Selecting for RT: *Discussion*

Side effects

Radiation therapy:	21st C, only local RT:
- Inconvenience	- 7→5→3→1 weeks
- Skin	- Lowered
- Breast tissue	- No boost → low
- Pulmonary	- Unlikely
- Heart	- Unlikely
- Secondary tumours	- Seldom
- CL breast: more	- Less for older pts/proper techniques

Selecting for RT: *Discussion*

Endocrine therapy:

- Early side effects.
- Late side effects.
- Compliance.

Selecting for RT: *Discussion*

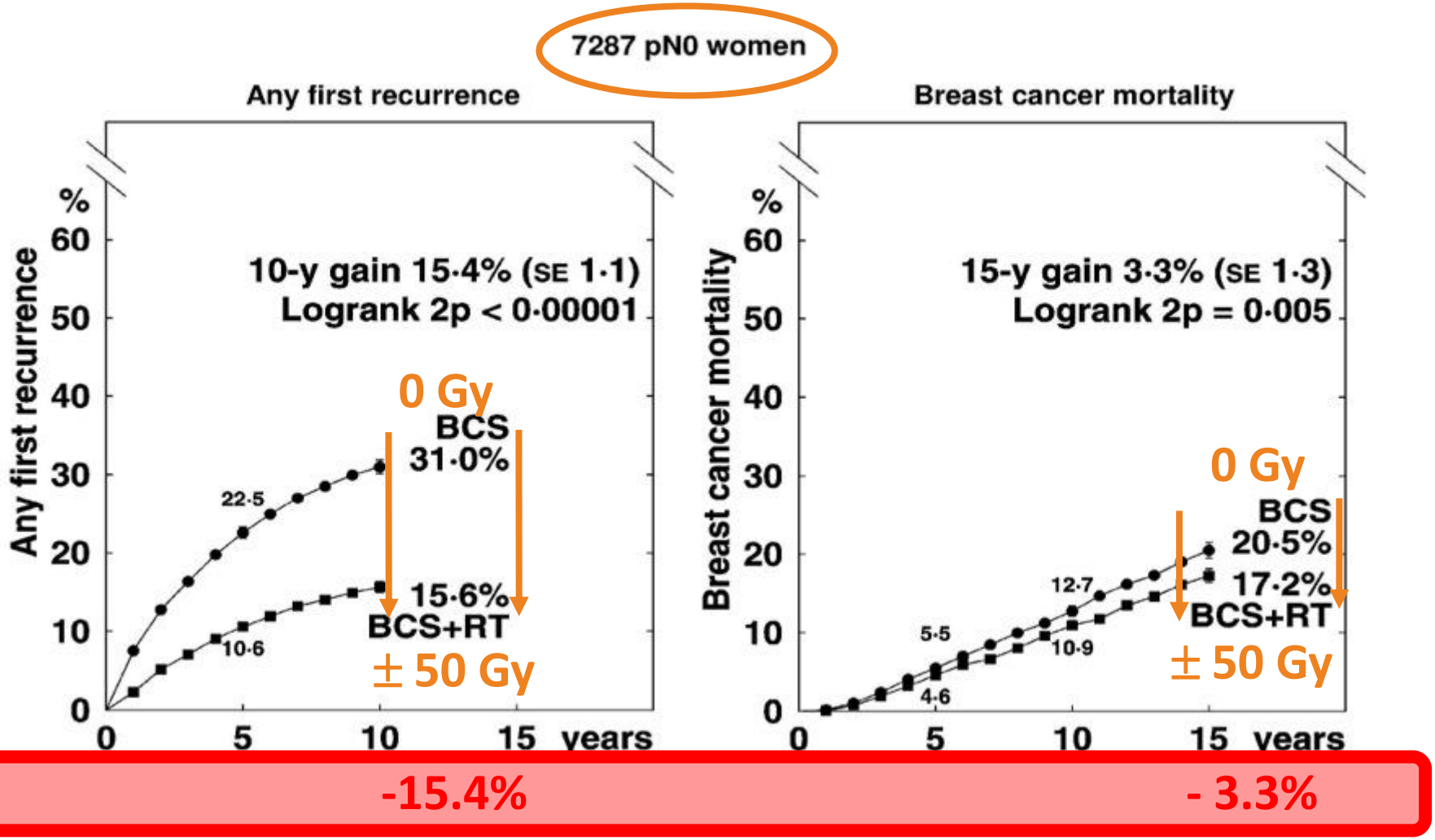
Stage (all 65y;N0;ER+;Her-)	Benefit HT DFS (%)	Benefit HT OS (%)
~~T1a-bG1-3~~	~~4.9-9.5~~	~~0.3-1.4~~
~~T1cG1~~	~~5.7-8.2~~	~~0.9~~
T1cG2	7.8-11.1	2.0
T1cG3	9.6-13.9	3.3
$T2_{<3cm}G1$	8.1-11.6	2.4
$T2_{<3cm}G2$	10.8-15.7	4.3
$T2_{<3cm}G3$	12.7-18.7	5.9

Selecting for RT: *Discussion*

Stage (all 65y;N0;ER+;Her-)	Benefit HT DFS (%)	Benefit HT OS (%)
~~T1a-bG1-3~~	~~4.9-9.5~~	~~0.3-1.4~~
~~T1cG1~~	~~5.7-8.2~~	~~0.9~~
T1cG2	7.8-11.1	2.0
T1cG3	9.6-13.9	3.3
T2<3cmG1	8.1-11.6	2.4
T2<3cmG2	10.8-15.7	4.3
T2<3cmG3	12.7-18.7	5.9

Selecting for RT: *Discussion*

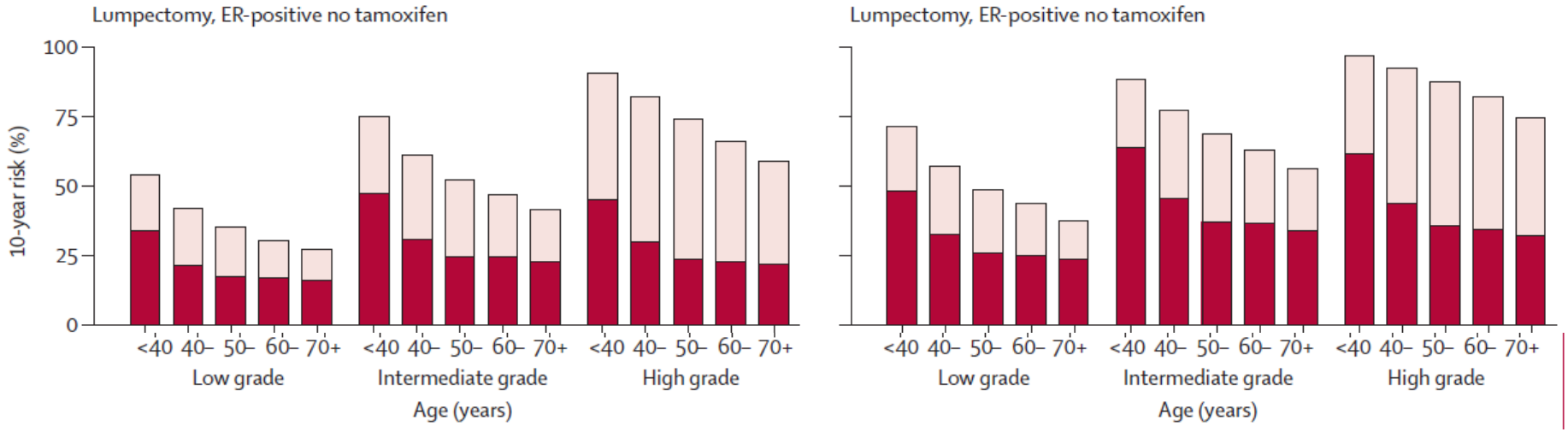
Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.



Selecting for RT: *Discussion*

Tumour size T1 (1–20 mm) | Tumour size T2 (21–50 mm)

Figure 4: Absolute 10-year risks (%) of any (locoregional or distant) first recurrence with and without radiotherapy (RT) following breast-conserving surgery (BCS) in pathologically node-negative women by patient and trial characteristics, as estimated by regression modelling of data for 7287 women



Selecting for RT: *Discussion*

Figure 4: Absolute 10-year risks (%) of any (locoregional or distant) first recurrence with and without radiotherapy (RT) following breast-conserving surgery (BCS) in pathologically node-negative women by patient and trial characteristics, as estimated by regression modelling of data for 7287 women

Selecting for RT: *Discussion*

Interaction systemic and locoregional treatments

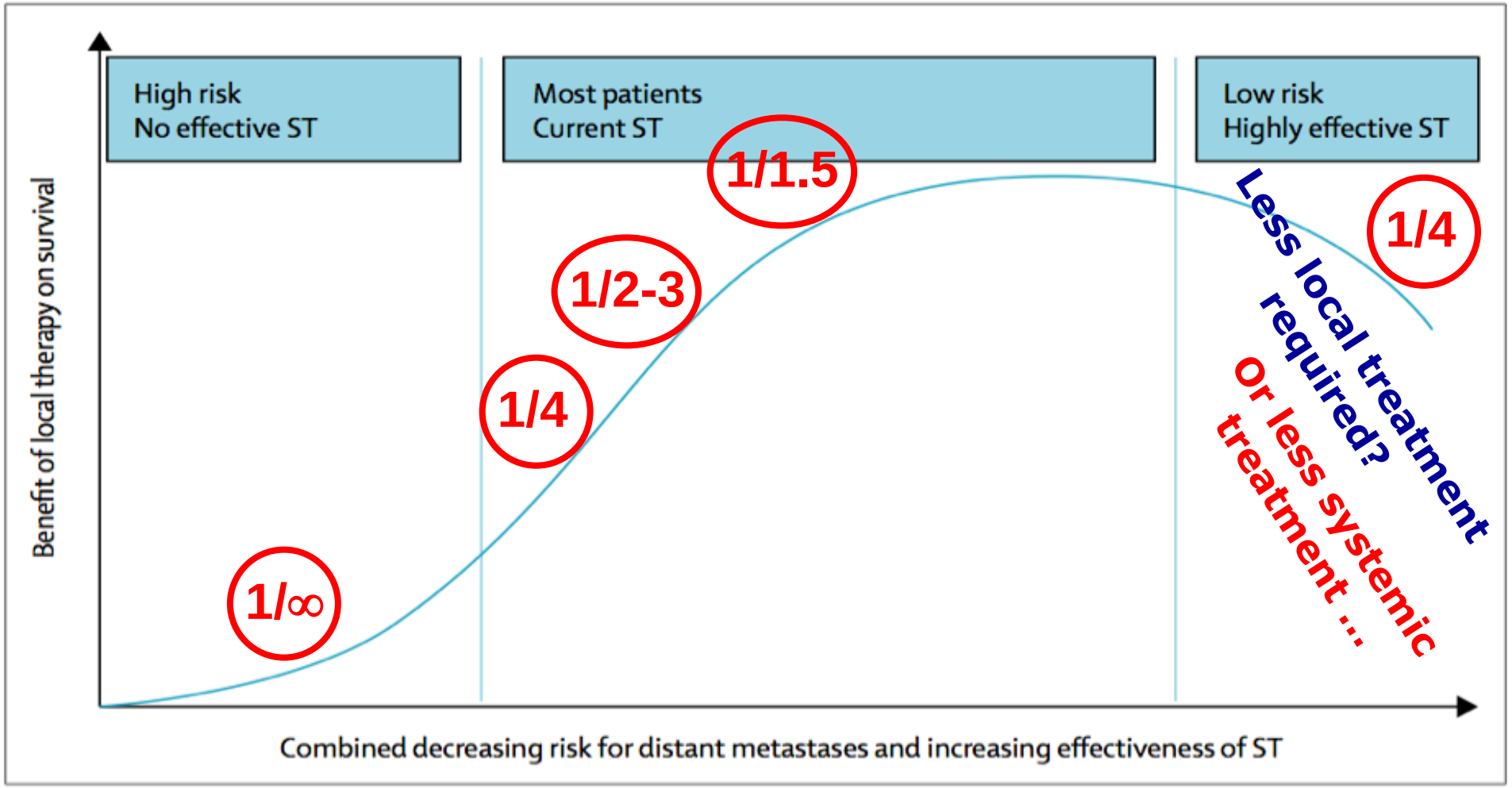
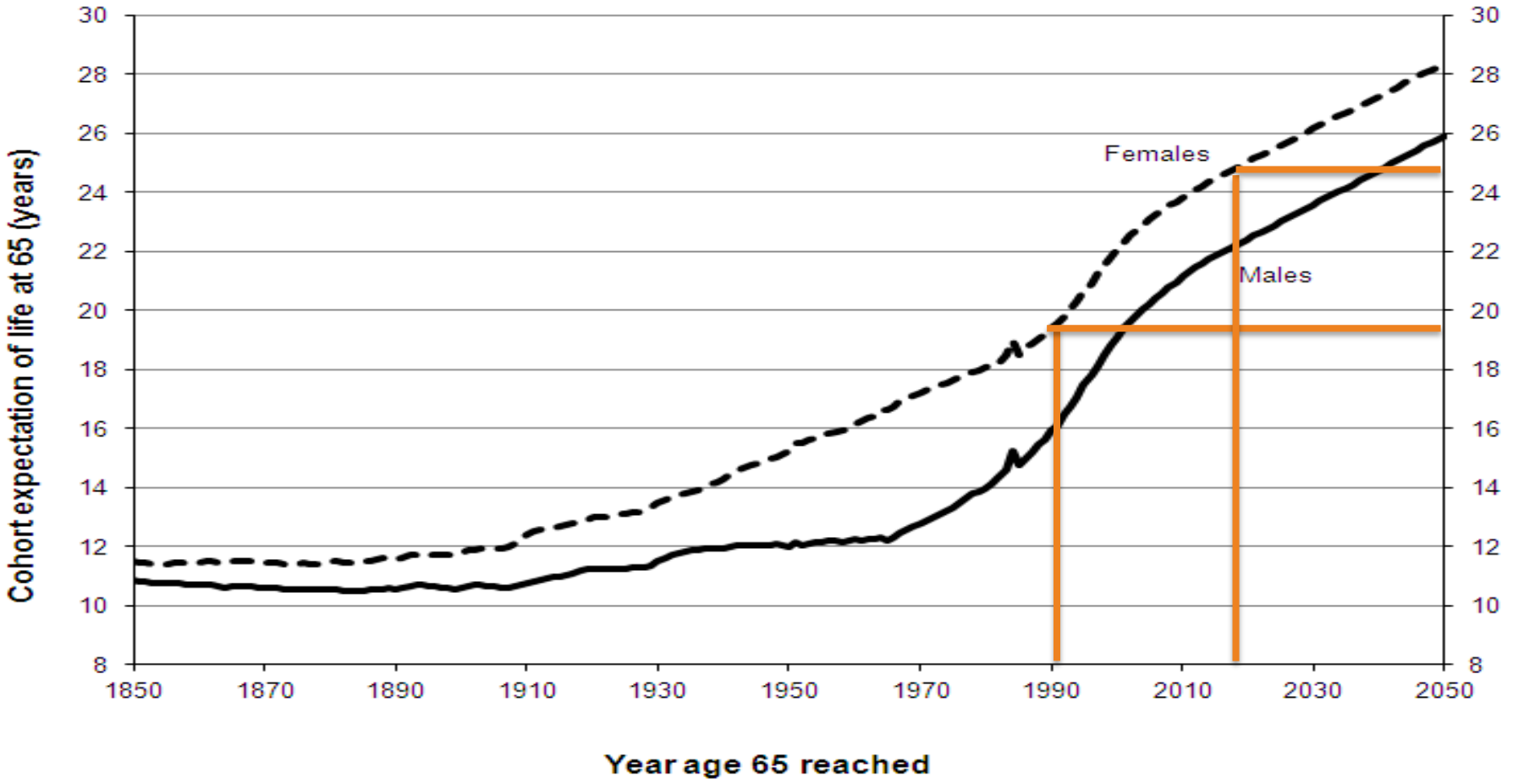


***Figure*: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour**

Selecting for RT: *Discussion*

Cohort expectation of life at age 65 according to historic and projected mortality rates, persons who reached age 65 1850–2050, England and Wales



Selecting for radiation therapy

1. Introduction
2. The role of radiation therapy
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Selecting for RT: *Conclusions*

1

Estimate life expectancy

Selecting for RT: *Conclusions*

2

Define tumour risk

Selecting for RT: *Conclusions*

3

Shared decision

making

Selecting for RT: *Conclusions*

Early stage, low risk

Short life expectancy: - Surgery alone

- Endocrine alone

- Nothing?

Long life expectancy: - Surgery + RT

Selecting for RT: *Conclusions*

Early stage, low risk

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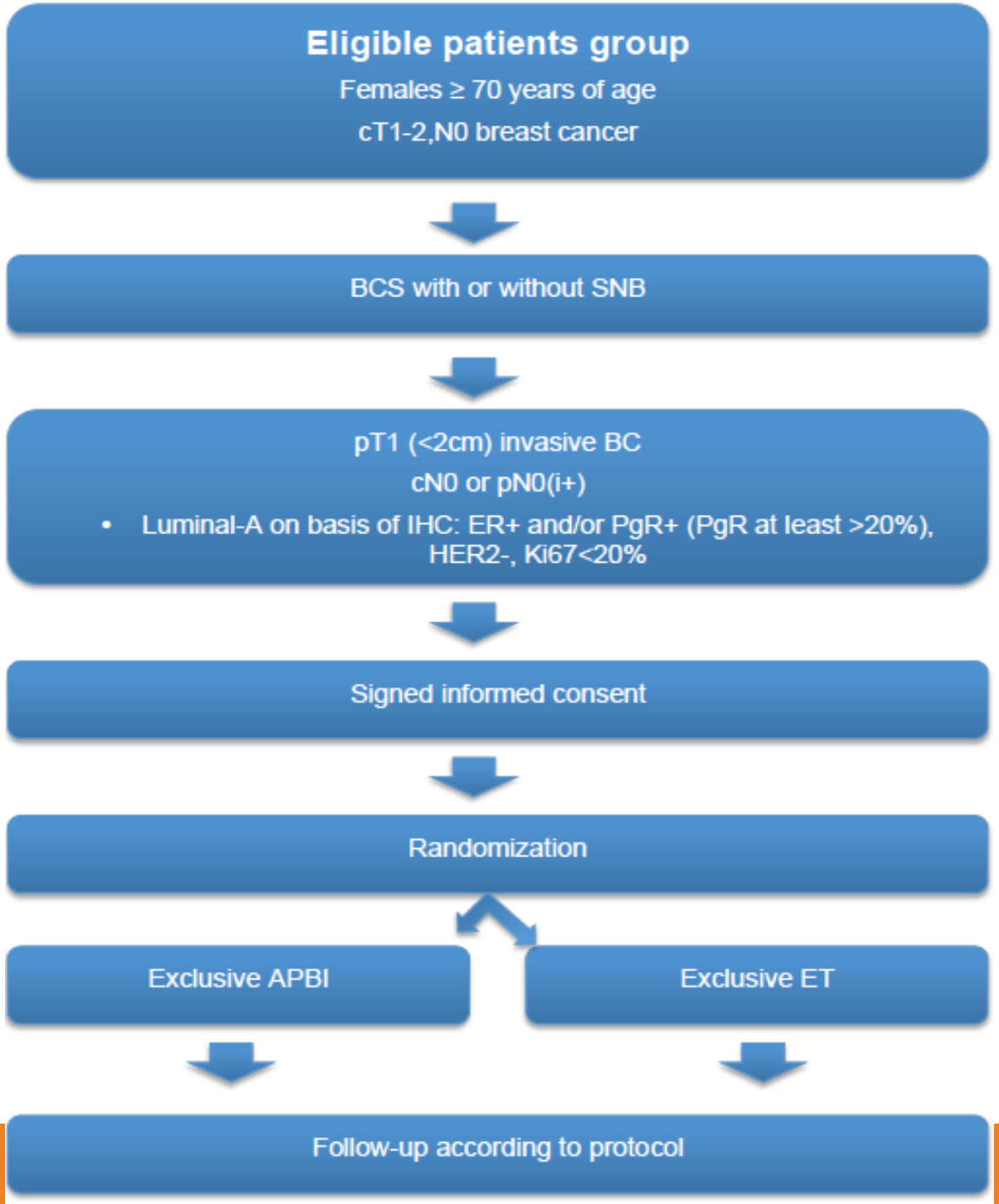
Study information	Outline form		
Title	Partial Breast Irradiation versus Endocrine Therapy for women age ≥70 years with Luminal-A early stage breast cancer: a randomized phase III trial comparing Quality of Life by Patient Reported Outcome Measures		
Short title (max 50 characters)	APBI or ET for elderly with early breast cancer		
Study Number	EORTC-1625 QoL-ROG-ETF-BCG	**Leading Group**	EORTC ROG

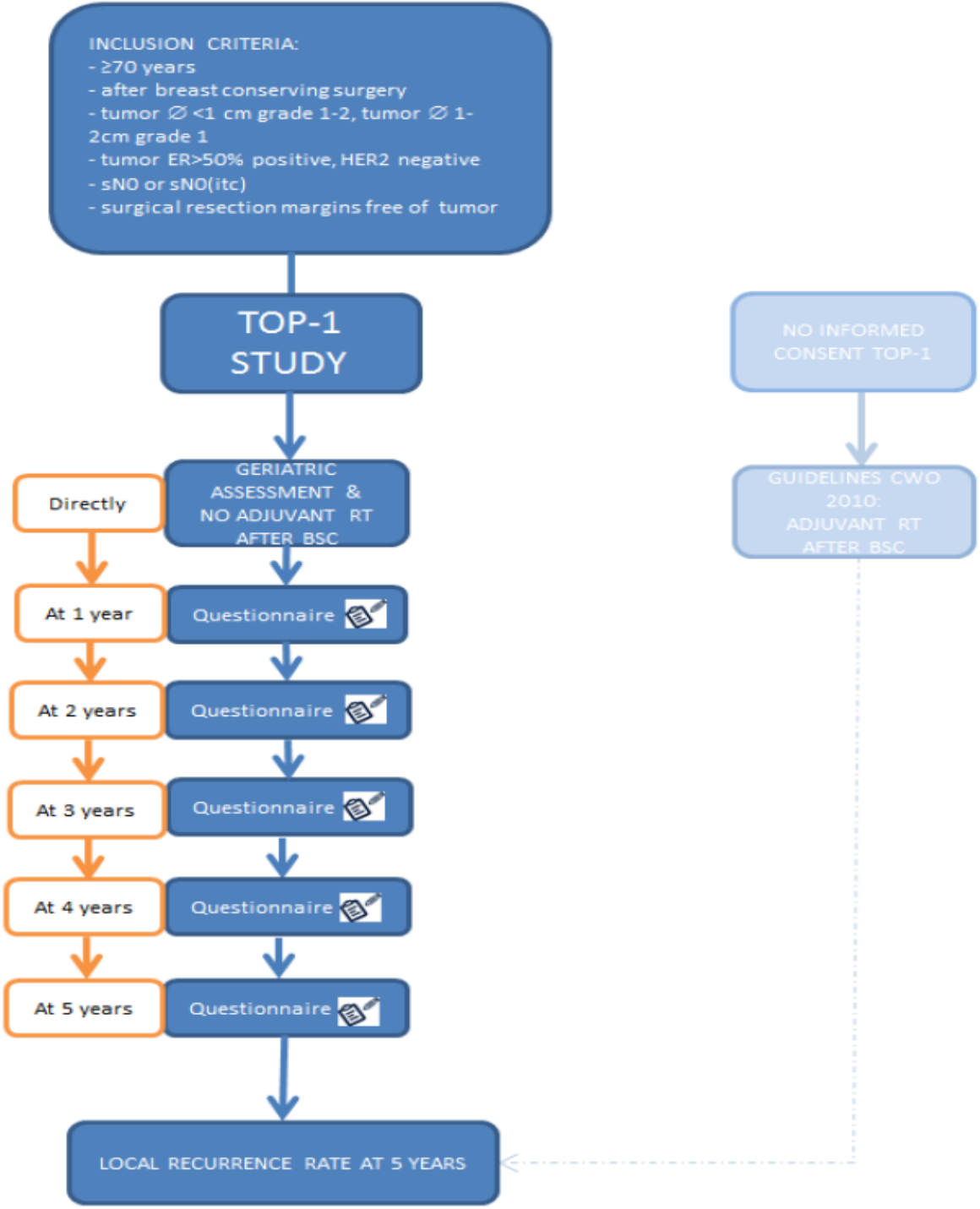

Eligible patients group
Females ≥ 70 years of age
cT1-2,N0 breast cancer
BCS with or without SNB
pT1 (<2cm) invasive BC
cN0 or pN0(i+)
• Luminal-A on basis of IHC: ER+ and/or PgR+ (PgR at least >20%), HER2-, Ki67<20%
Signed informed consent
Randomization
Exclusive APBI
Exclusive ET
Follow-up according to protocol

Selecting for RT: *Conclusions*

Early stage, low risk

***T**ailored treatment in **O**lder **P**atients*

TOP-1: Omission of radiotherapy in elderly patients with low risk breast cancer


INCLUSION CRITERIA:
- ≥70 years
- after breast conserving surgery
- tumor ∅ <1 cm grade 1-2, tumor ∅ 1-2cm grade 1
- tumor ER>50% positive, HER2 negative
- sNO or sNO(itc)
- surgical resection margins free of tumor
TOP-1 STUDY
NO INFORMED CONSENT TOP-1
GUIDELINES CWO 2010: ADJUVANT RT AFTER BSC
Directly
GERIATRIC ASSESSMENT & NO ADJUVANT RT AFTER BSC
At 1 year
Questionnaire
At 2 years
Questionnaire
At 3 years
Questionnaire
At 4 years
Questionnaire
At 5 years
Questionnaire
LOCAL RECURRENCE RATE AT 5 YEARS

Selecting for RT: *Conclusions*

Early stage, with risk factors

Short life expectancy:
- Surgery with
- Systemic T?
- RT?

Long life expectancy:
- Surgery with
- Systemic T
- RT

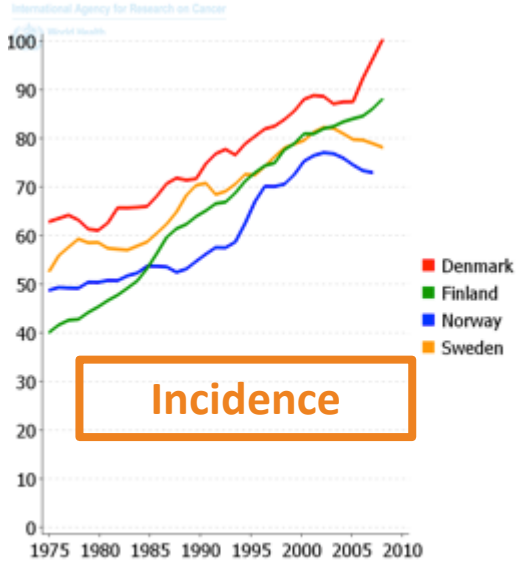
Selecting for RT: *Conclusions*

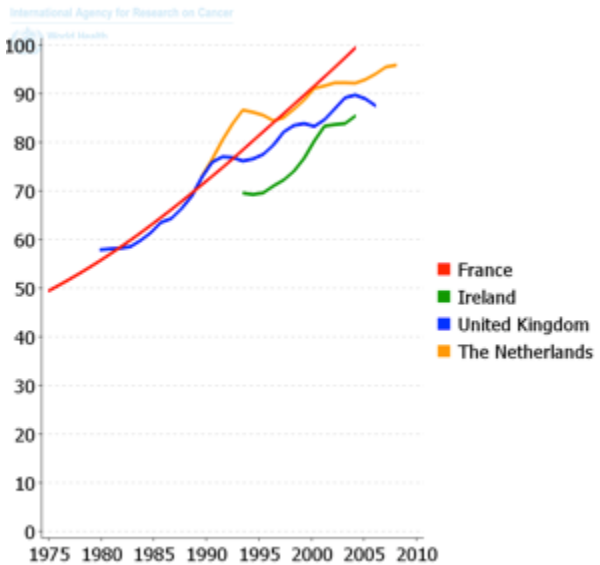
Advanced stage, with risk factors

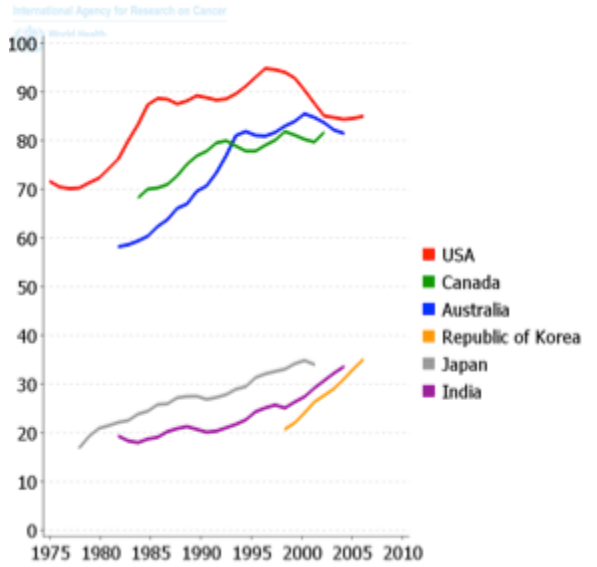
Short life expectancy:
- Surgery with
- Systemic T
- RT

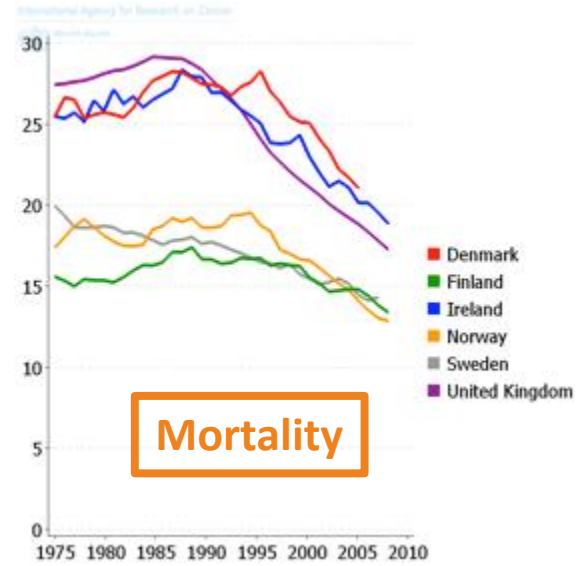
Long life expectancy:
- Surgery with
- Systemic T
- RT

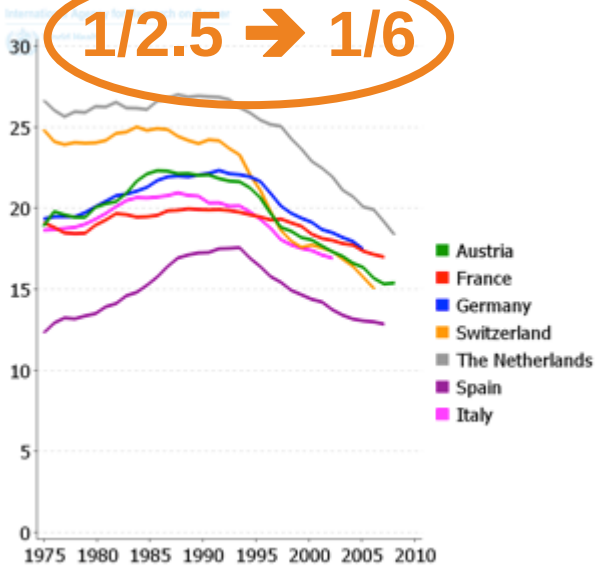
Selecting for RT: *Conclusions*

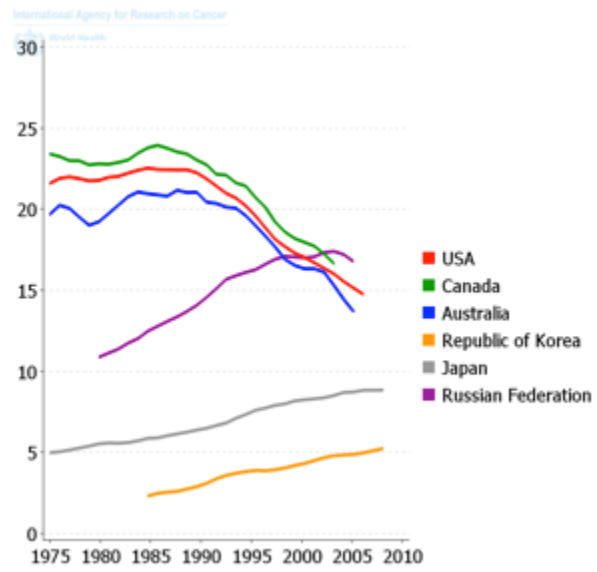












Source: Globocan, 2008. *Rates shown are age-standardised rate per 100,000 using the standard world population.*

Selecting for RT: *Conclusions*

We should mind not to kill our patients by kindness.

Birgitte Vrou Offersen, Aarhus, DK, 2013

Selecting for RT: *Conclusions*

Trust comes on foot and leaves on horseback!

Selecting for RT: *Acknowledgements*

- Harry Bartelink
- Laurence Collette
- Sarah Darby
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- Oliver Ott
- John Yarnold
- Icro Meattini
- Meritxell Arenas
- Lorenzo Livi
- And many others!