Target volumes
needs learned for modern treatments

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Introduction

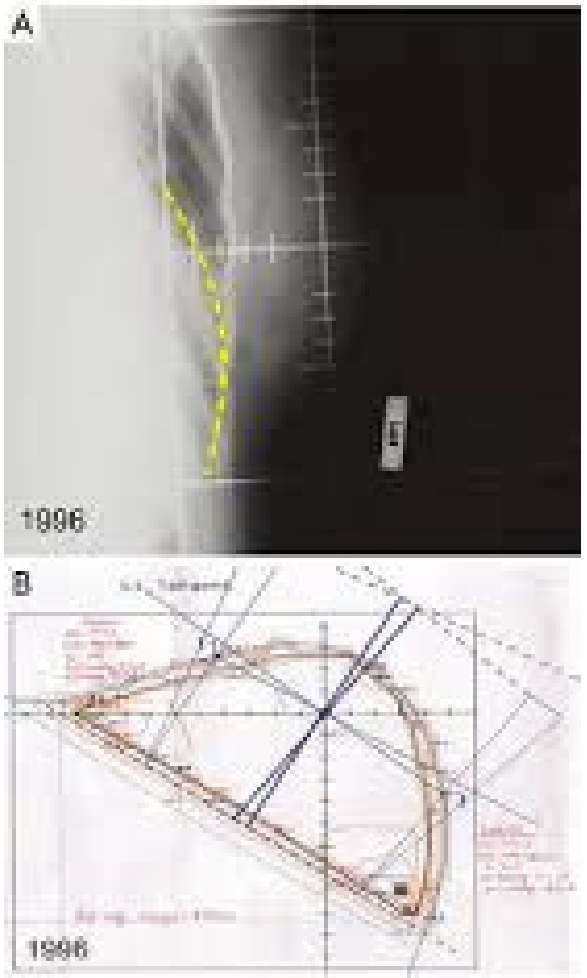
20th century:

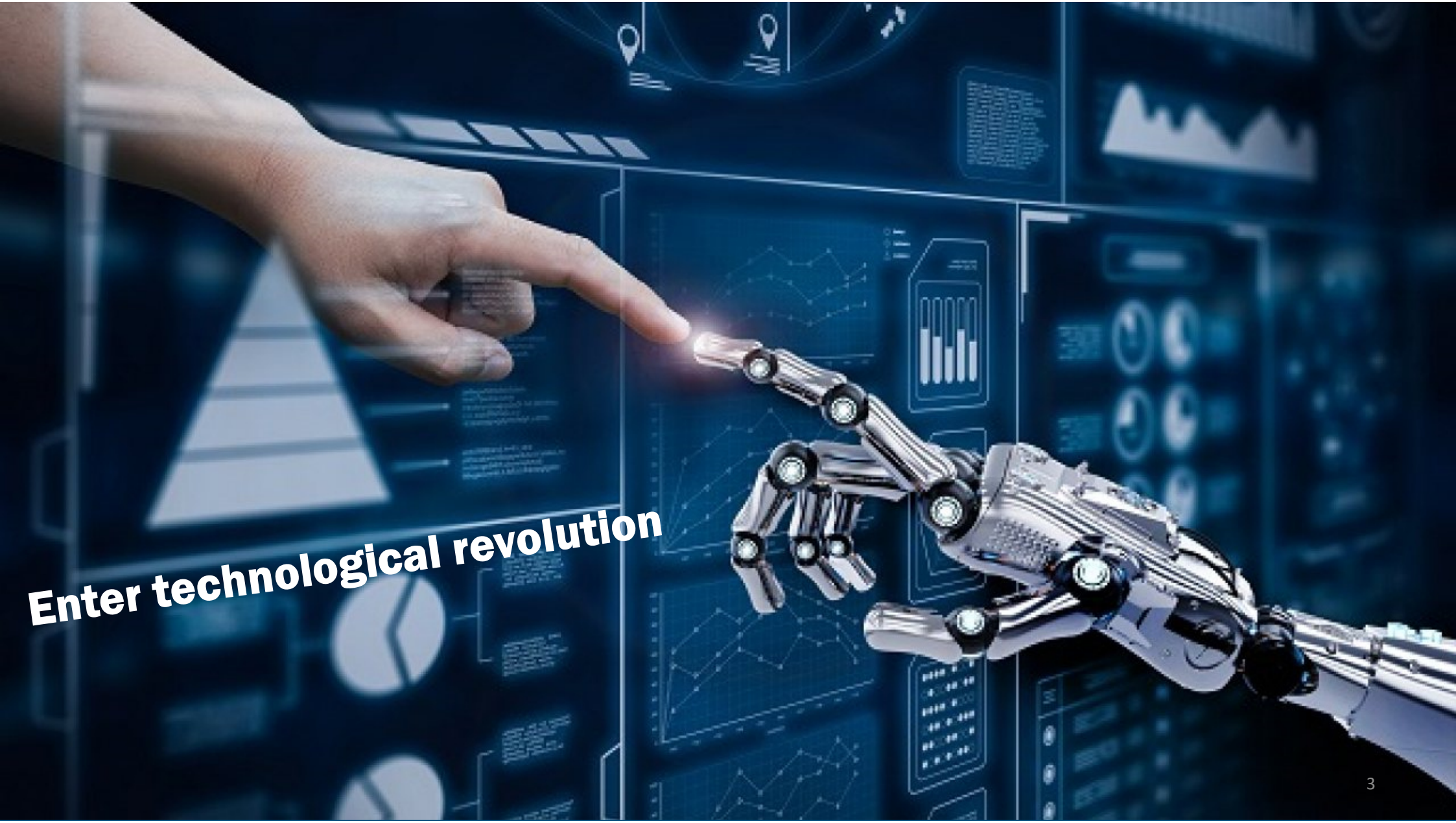
First breast RT studies > standard fields and dose/fractionation

- RT 2D, 3D… static IMRT
- 45-50 Gy +/- boost, fraction size 1.8 -2 Gy

One size-fits-all

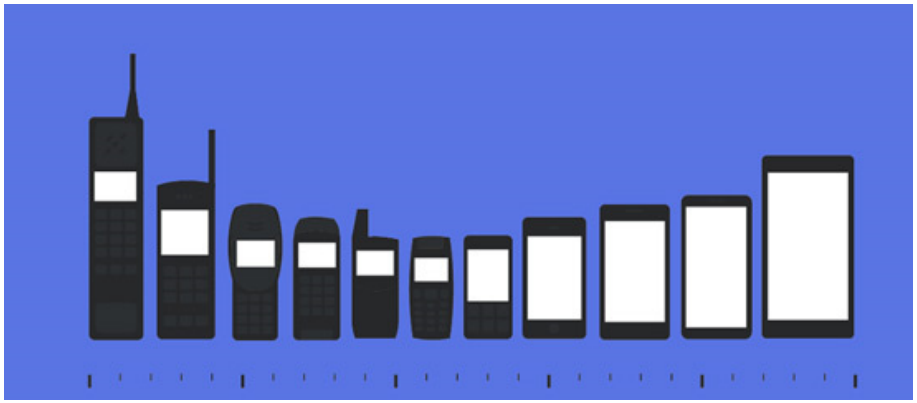
- Technology was limiting the possibilities




Enter technological revolution

Introduction

21st century:



- ***Technology +++***
  - CT simulation/planning
  - IMRT/VMAT
  - Improved dose homogeneity
  - Active respiration management strategies (DIBH)
- **Volume-based RT**
- Plus, innovations in:
  - Imaging
  - Surgical approaches (image guided surgery)
  - Pathological evaluation
  - Molecular biological understanding
- Increased use of (neo-)adjuvant systemic treatment

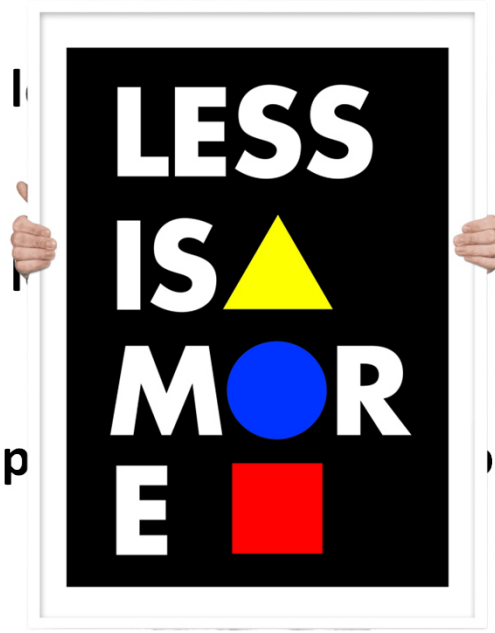
Introduction

21st century: it's all about.....

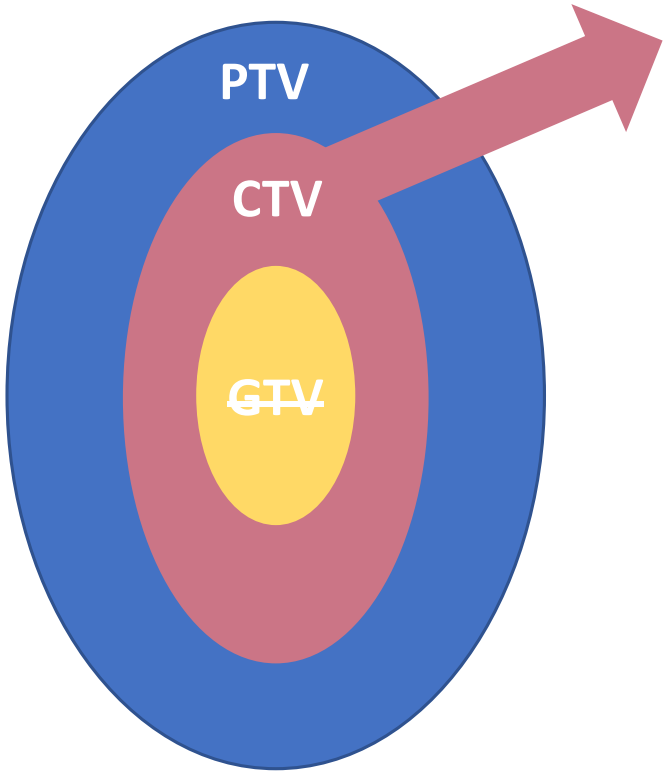
More survivors

- *late toxicity*
- *cosmetic outcome*
- *patient convenience*

- *Towards less (smaller) target volumes*
- Towards l
- Towards
- Risk-adap n



Target volumes in breast cancer RT

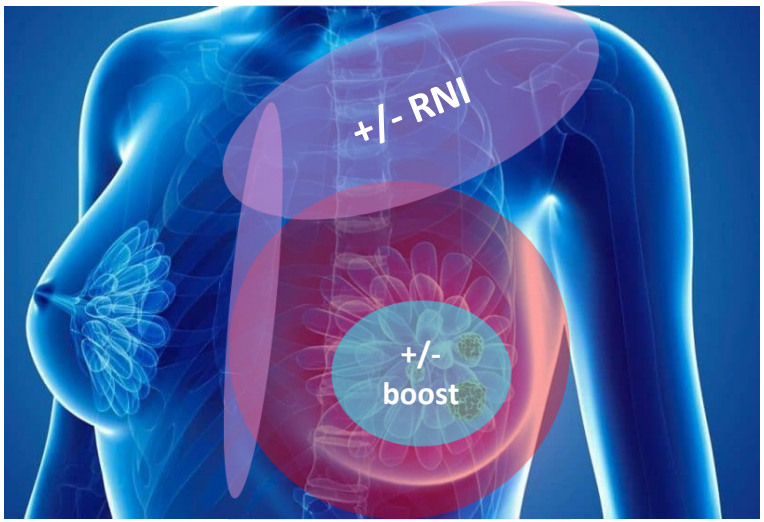


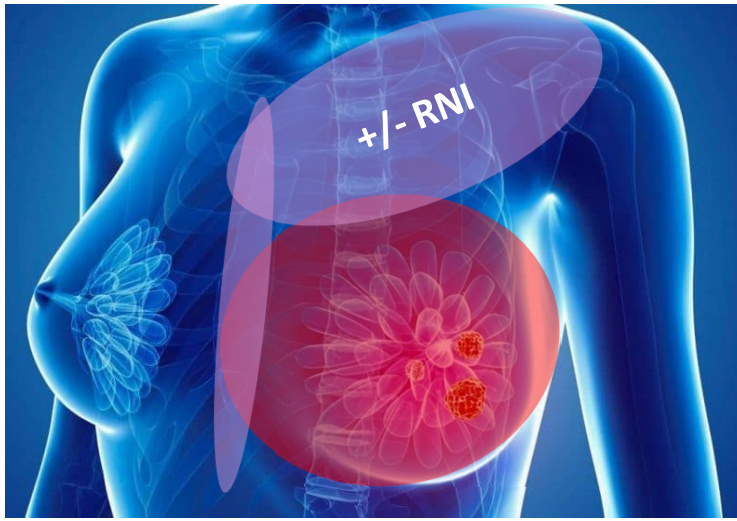
Whole breast radiation therapy (WBRT)

Post-mastectomy radiation therapy (PMRT)

+/- boost

+/- regional nodal irradiation (RNI)





Low risk

High risk

Intermediate risk

Sanders et al. 2007


LESS
IS
MORE


BUT HOW TO
LIGHTYEAR
DE-ESCALATE?

Target volumes in breast cancer RT

- **Pathology studies:**
  - Greatest tumor density in area surrounding the microscopic edge

- **Recurrence studies:**
  - 90% of local failures after BCT :
    - in **same** quadrant as original primary tumor
      - ➢ Area around tumour highest probability of in-breast recurrence

Partial breast irradiation sufficient in low risk patients?

- ➢ **Might maintain high rate of local tumor control?**
- ➢ **Might reduce side-effects?**

Sanders et al. 2007

Target volumes in breast cancer RT

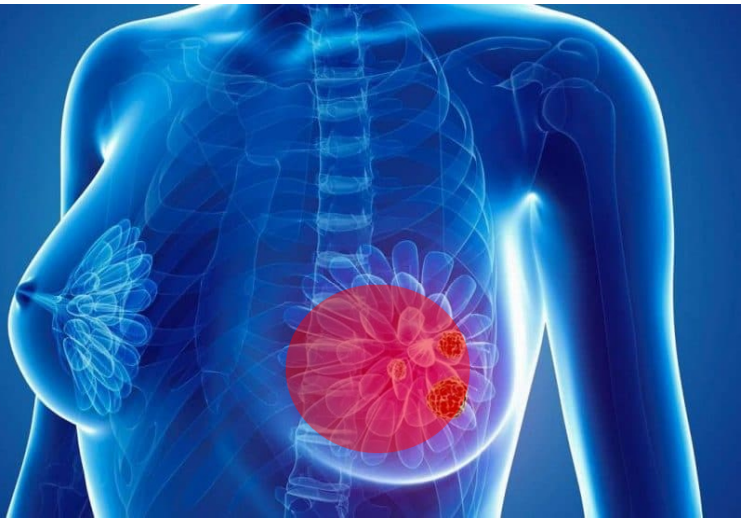
Whole breast radiation therapy (WBRT)

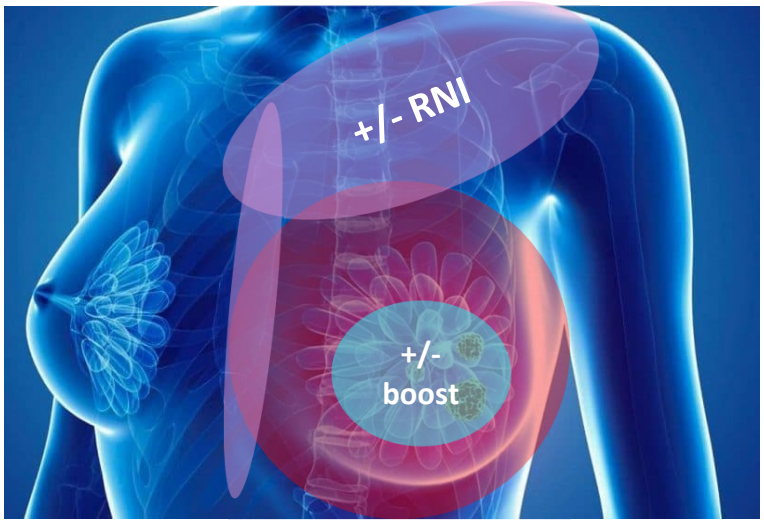
Post-mastectomy radiation therapy (PMRT)

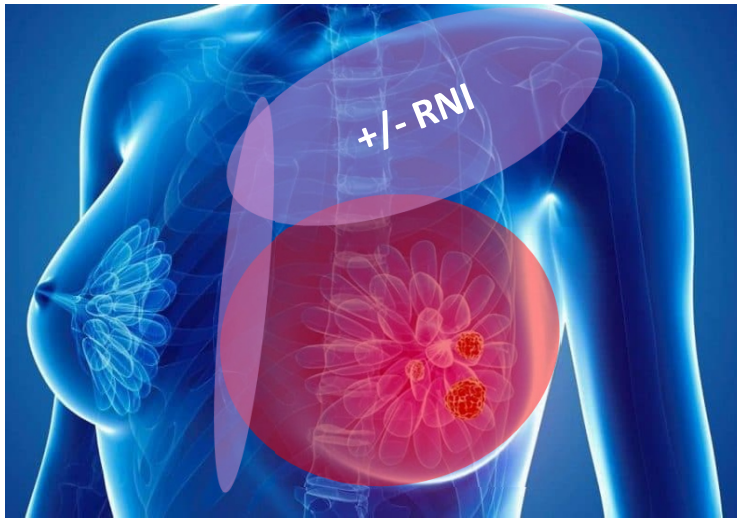
+/- boost

+/- regional nodal irradiation (RNI)

Partial breast irradation (PBI)?







Low risk?

High risk

Intermediate risk

Sanders et al. 2007

Partial breast irradiation

- **Available techniques include**

  A. **Intraoperative RT (IORT)**
  B. **Brachytherapy/Interventional Radiotherapy**
     - Multicathteter interstitial brachytherapy
     - Intracavitary balloon brachytherapy
  C. **External beam RT (EBRT)**

Partial breast irradiation

- **IORT = electrons or low-energy photons delivered during breast conserving surgery**

A. **TARGIT-A trial (2013) : use of a 50 kV device = very steep dose fall off! Remains controversial!**
B. **ELIOT (2022)**

IOeRT PBI remains a valid option in well-selected low-risk patients

disease and with *nodal involvement*

- Possible inferior IOeRT technique

Partial breast irradiation

RCT	FU (years)	LR (%)			
		WBI	PBI	Toxicity	Cosmesis
NIO	17	7.9	9.6	=	PBI>WBI
IMPORT LOW	6	0.5	1.1	Acute/Late toxicity better with PBI	=
GEC-ESTRO	10.4	1.6	3.5	Late skin reaction better with PBI	=
Florence	10.7	2.5	3.7	Acute/Late toxicity better with PBI	PBI>WBI
RAPID	8	2.8	3.0	Acute toxicity better with PBI *Late toxicity reduction with WBI*	*WBI>PBI*
NSABP-B39	10.2	3.9	4.6	=	=
BARCELONA	5	0	0	Acute skin reaction better with PBI	=

Partial breast irradiation

- **NSABP B-39/ RTOG 0413 trial vs. RAPID**

  - ➢ Equivalence RCT vs non-inferiority
  - ➢ Discrepant oncological outcome

    - HRs + associated CIs >> no material difference observed between the two studies.

    - ***If the investigators of both trials had used the design characteristics chosen by the other, it is probable that they would have drawn <u>the same conclusion</u>.***

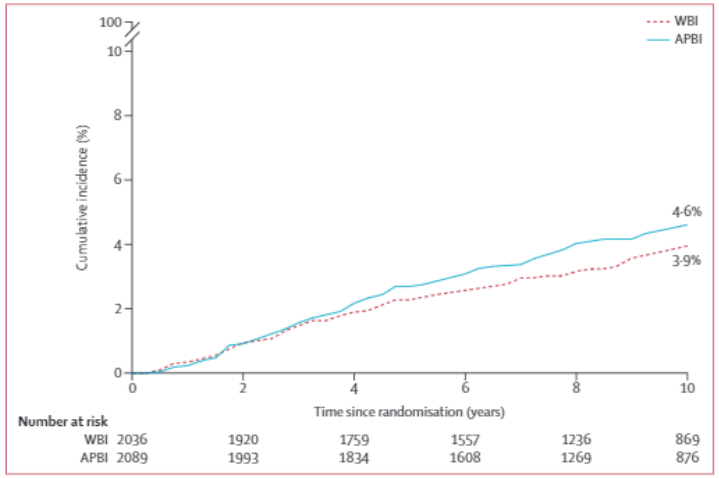


Figure 2: **Cumulative incidence of in-breast tumour recurrence**
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

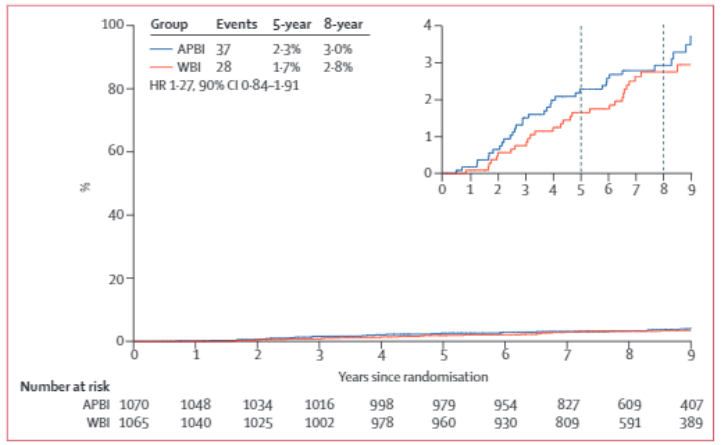


Figure 2: **Rates of IBTR over time**

Partial breast irradiation

RCT	FU (years)	LR (%)			
		WBI	PBI	Toxicity	Cosmesis
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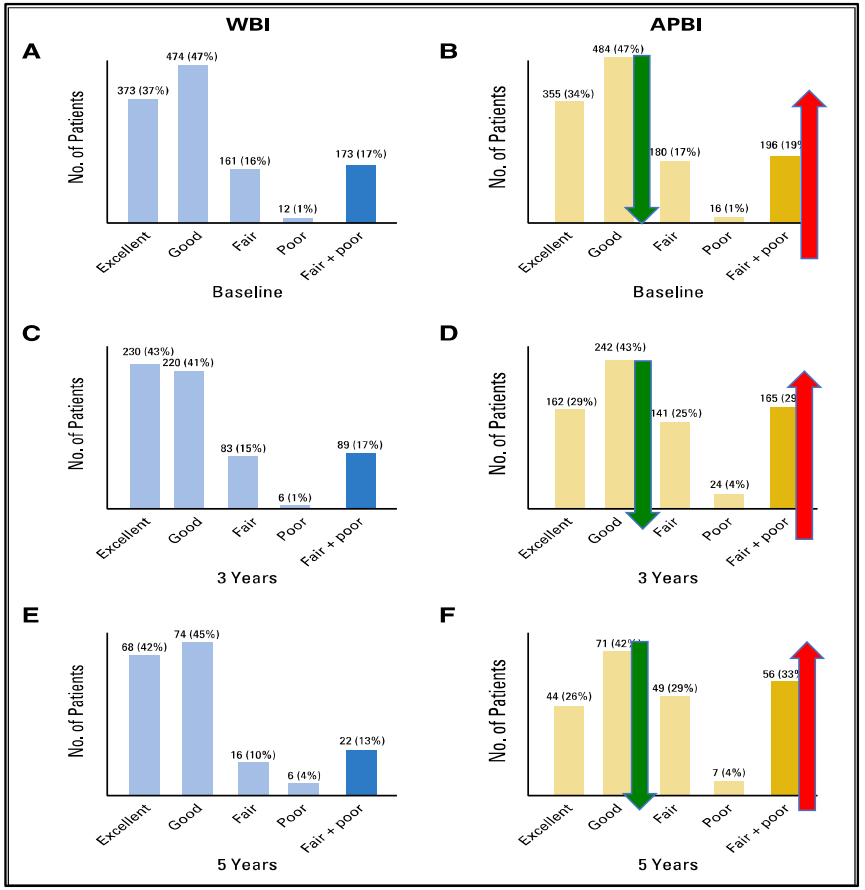
BARCELONA	5	0	0	Acute skin reaction better with PBI	=

Partial breast irradiation

- **RAPID trial (2019)**
  - Non-inferiority RCT
  - WBI (16 x 2,67 or 25 x 2 Gy)
  - APBI 10 x 3,8 Gy (twice daily)

  - 2135 patients: >40 year, unifocal < 3cm tumor, node negative
  - Primary endpoint: ipsilateral local recurrence
  - Secundary: cosmetic outcome, toxicity



➢ **Worse cosmetic outcome (29 vs 17% of patients) and late toxicity**

Partial breast irradiation

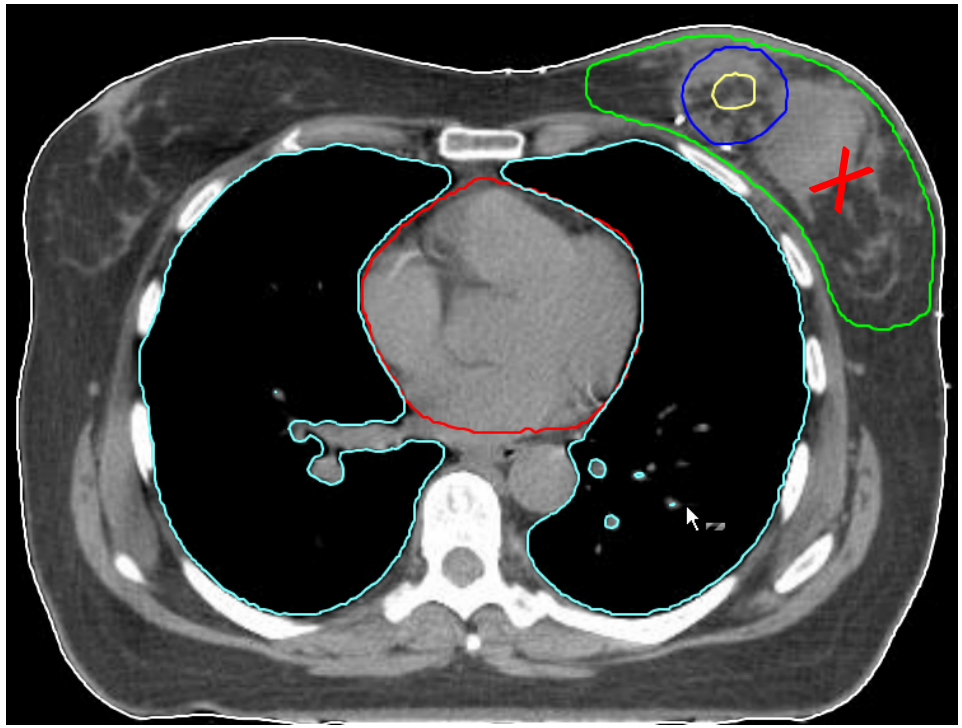
- **In well-selected patients similar local recurrence rates for (A)PBI compared to WBI**
  - But heterogeneity of suitable patients across the guidelines
  - *Consider offering PBI to postmenopausal patients with ER+, node negative, pT1 tumors*

- **(A)PBI similar and often better toxicity**
  - Depending on technique and schedule used
    - EBRT twice daily less favorable
    - EBRT 5 x 6 Gy superior

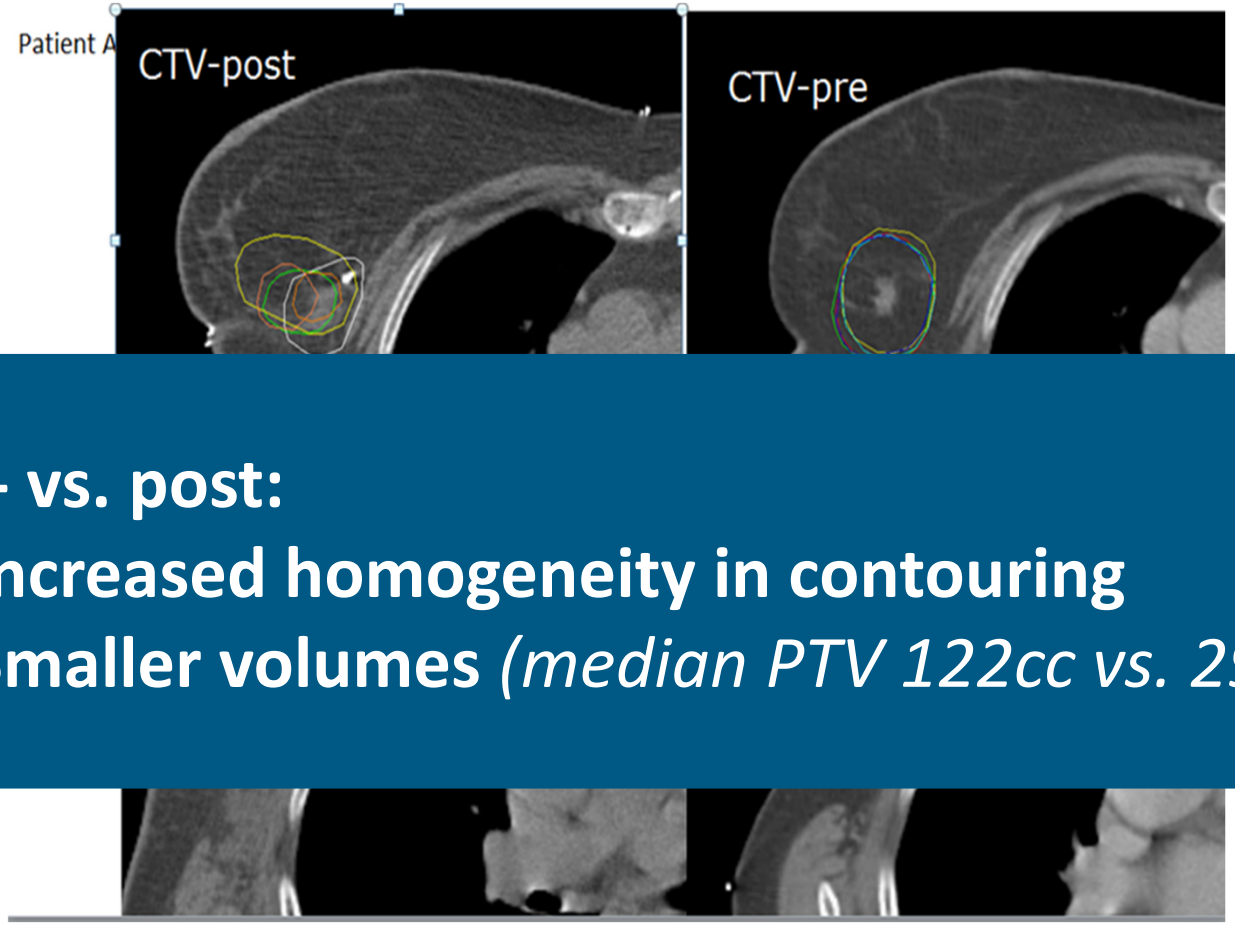
- **Differences in interpretation of oncological results is often the result of statistical analysis and design!**

Preoperative partial breast irradiation (PBI)

- **Post vs. preoperative RT**
  - ➢ May reduce risk of geographic miss
  - ➢ Facilitates contouring (i.e. oncoplastic surgery)?
  - ➢ Smaller volumes and hence better cosmetic outcome?



Preoperative partial breast irradiation (PBI)



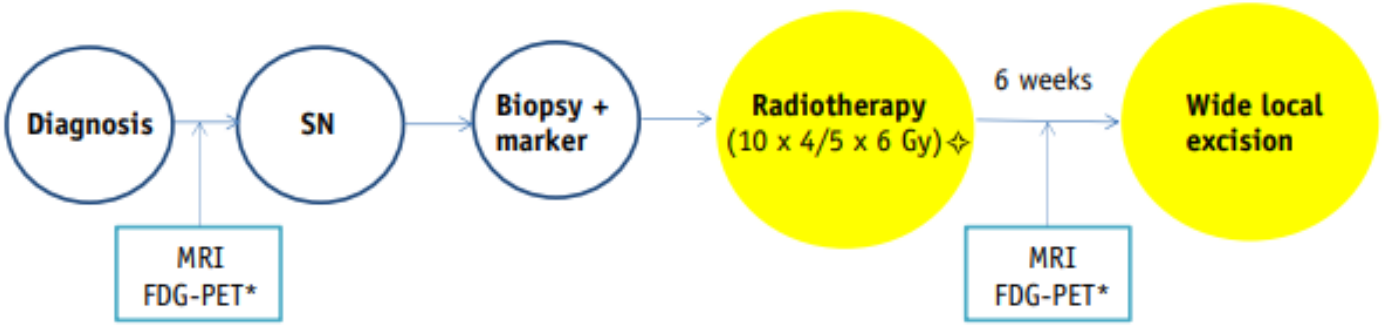
Pre- vs. post:

- **Increased homogeneity in contouring**
- **Smaller volumes** *(median PTV 122cc vs. 296cc)*

Van Der Leij F, Radiother Oncol 2014 + Hepel et al.

Preoperative partial breast irradiation (PBI)

- **PAPBI-1**
  - Multi-centric international phase II trial, n = 133
  - Feasibility of preoperative accelerated partial breast RT done by external beam radiotherapy
  - Endpoints: postop complications, fibrosis, cosmetic outcome, and local control.



Courtesy Scholten A. Elkhuizen P, Bartelink H. Data on file.

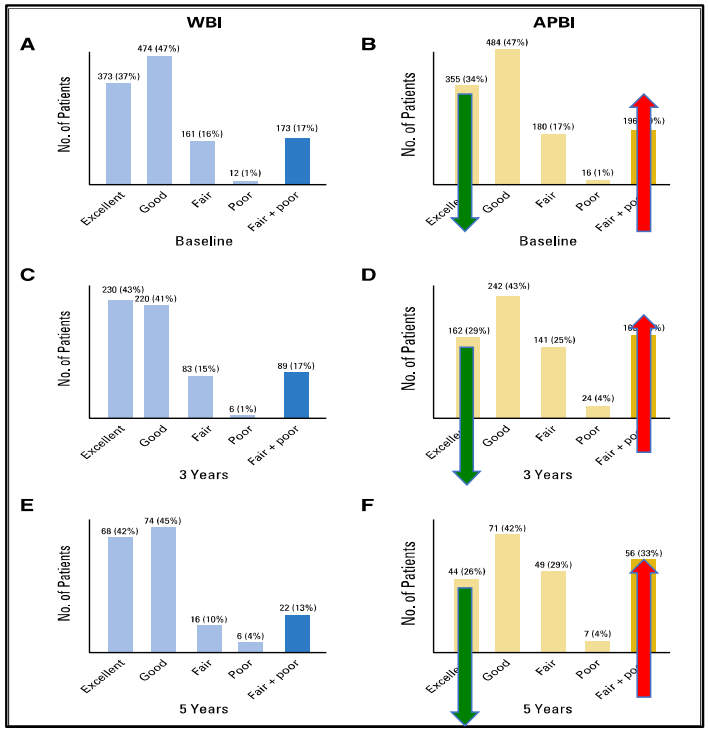
Preoperative partial breast irradiation (PBI)

Cosmetic outcome

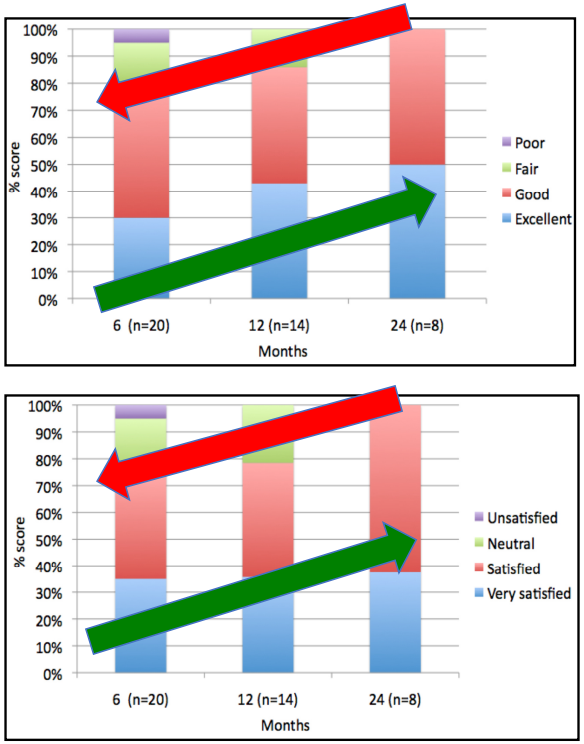
Bosma S, et al. IJROPB 2020.

Preoperative partial breast irradiation (PBI)

RAPID trial



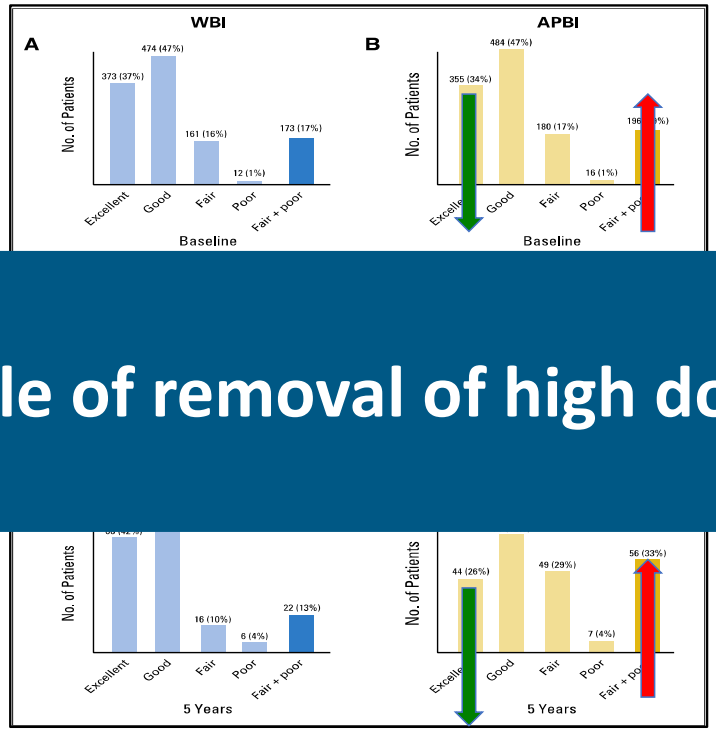
PAPBI trial



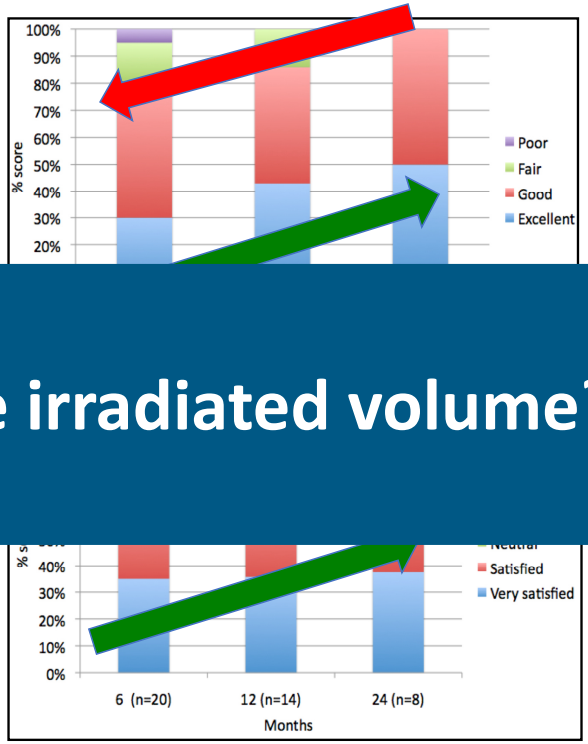
Olivotto IA, et al. J Clin Oncol. 2013;31:4038-45. *Van der Leij F, et al. Radiother Oncol 2015.*

Preoperative partial breast irradiation (PBI)

RAPID trial



PAPBI trial



Role of removal of high dose irradiated volume?

Olivotto IA, et al. J Clin Oncol. 2013;31:4038-45. *Van der Leij F, et al. Radiother Oncol 2015.*

Preoperative partial breast irradiation (PBI)

- 14% postoperative complications
- Low local recurrence rate of 3% at 5 years
- pCR 23% after 6 weeks

Low postoperative complication rate, good to excellent cosmetic outcome and a local recurrence rate of 3% at 5 years;

- Awaiting the results of the PAPBI-2 trial, the randomized successor of the PAPBI 1

Preoperative *stereotactic* PBI?

Study (year)	FU (months)	RT	Interval surgery	pCR	Efficacy	Toxicity
Bondiau (2013)	30	19.5–31.5Gy/3fr	4-8 weeks	36%	96% ORR, 92% BCS rate	None
SIGNAL (2019)	16	21Gy/1fr	1 week after RT	/	No relapses	=
ABLATIVE (2019)	36	20Gy/1fr	24-32 weeks	42%	2yDFS 97%	95% excellent/good outcome@2Y
Tiberi (2020)	10	20Gy/1fr	13 weeks	0%	/	/
ROCK (2022)	18	21Gy/1fr	2 weeks after RT	9%	No relapses	62% excellent/good outcome@1Y

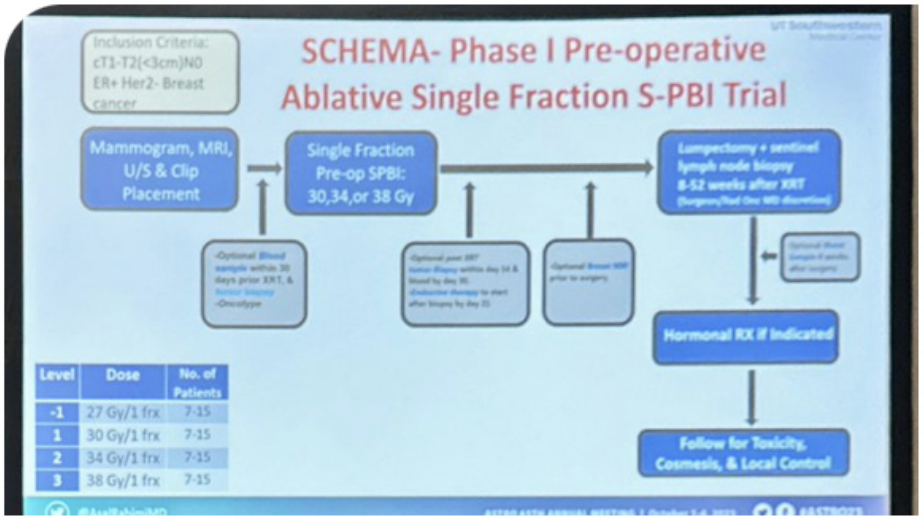
Preoperative *stereotactic* PBI?

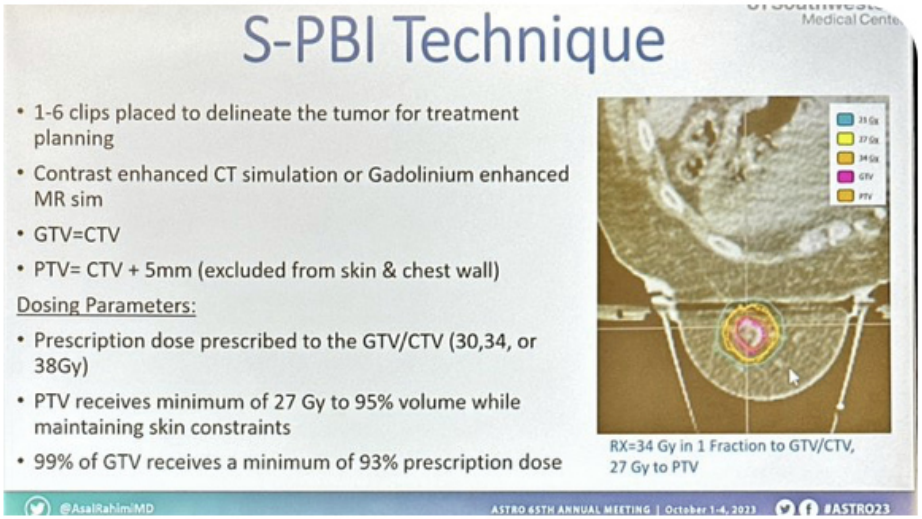
Trial ID, status	Title	Treatment
NCT05350722, recruiting	Single-dose preoperative partial breast irradiation in low-risk breast cancer patients (ABLATIVE-2)	Preoperative single-dose radiotherapy (20 Gy) and BCS after 12 months
NCT03917498, active/not recruiting	Single pre-operative radiation therapy - with delayed surgery for low risk breast cancer (SPORT-DS)	Preoperative single-dose radiotherapy and BCS after 3 months[a]
NCT02212860, active/not recruiting	Stereotactic image-guided neoadjuvant ablative radiation then lumpectomy (SIGNAL 2)	Preoperative PBI (21 Gy or 3× 10 Gy) and BCS after 14–20 days
NCT04679454, recruiting	Single fraction preoperative radiotherapy for early stage breast cancer (CRYSTAL)	Preoperative single dose radiotherapy (18 Gy, 21 Gy, 24 Gy) and BCS after 4–8 weeks
NCT03909282, recruiting	Phase 2 surgical excision vs neoadjuvant radiotherapy+delayed surgical excision of	Preoperative PBI (5× 6 Gy) and BCS after 3 months versus upfront surgery
NCT04040569, rec		4 Gy, 38 Gy) and BCS[b]
NCT02482376, acti		nd BCS[b]

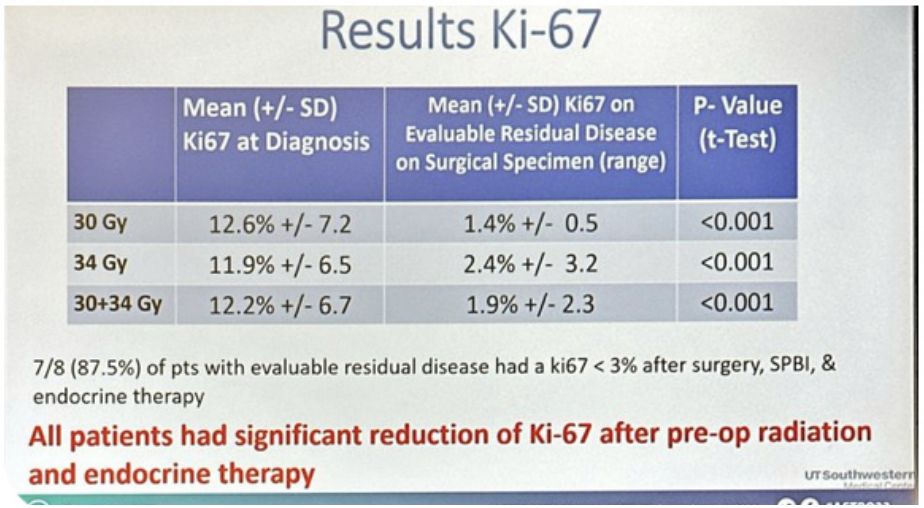
ABLATIVE-2, CRYSTAL, SPORT-DS, NORDIS, SIGNAL 2, etc

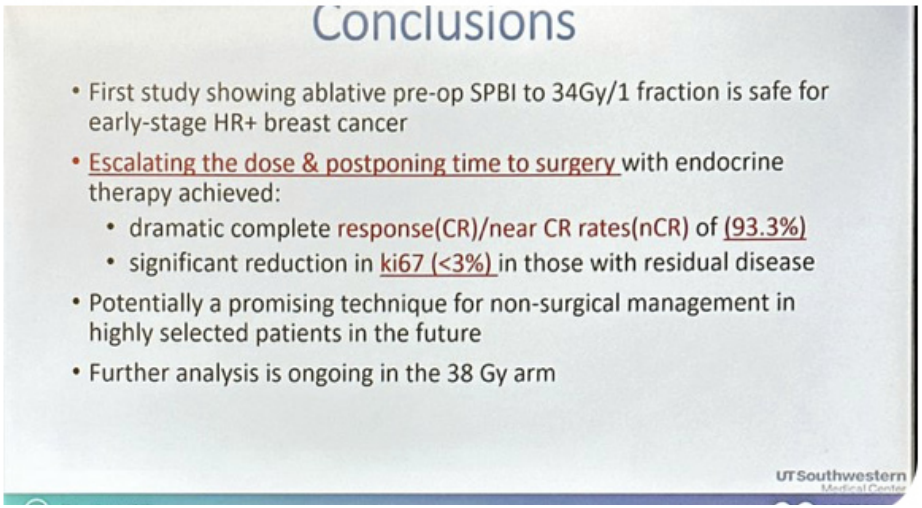
Many ongoing studies!

Preoperative *stereotactic* PBI?









Patient-tailored treatment?

- Preoperative RT allows for:
  - ➢ Direct evaluation of the RT effect on the tumour
  - ➢ Develop a genetic expression classification for radiosensitivity
  - ➢ Identify molecular biomarkers for tumour response
  - ➢ Identify the immunological modulation induced by RT

→ Shift to biologically-driven RT?

Target volumes in breast cancer RT

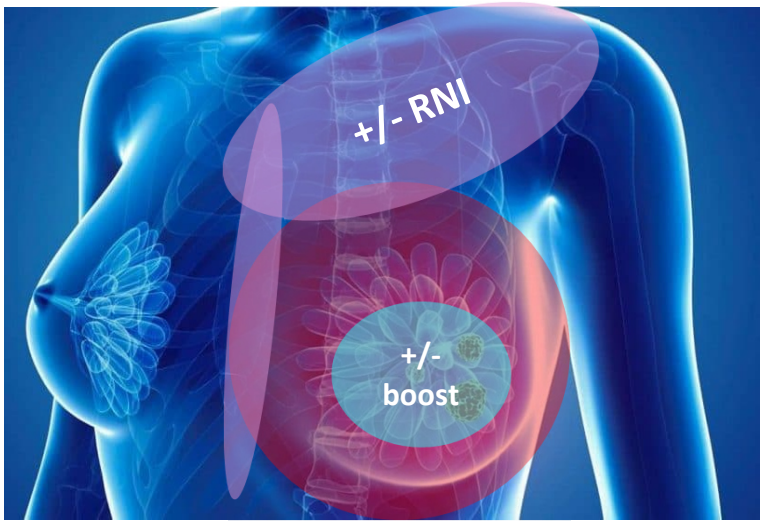
Partial breast irradiation (PBI)

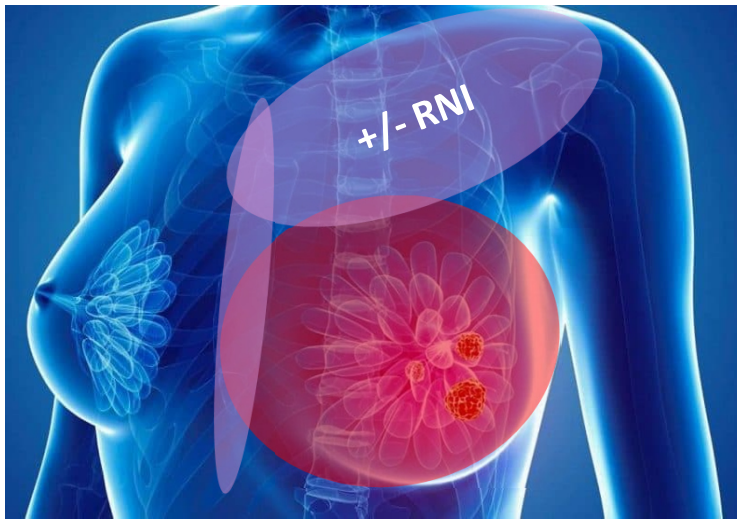
Whole breast radiation therapy (WBRT)

+/- boost

Post-mastectomy radiation therapy (PMRT)

+/- regional nodal irradiation (RNI)





Low risk

High risk

Intermediate risk

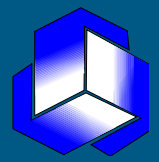
Sanders et al. 2007


EVEN MORE
LIGHTYEAR
DE-ESCALATION IDEAS?

Tumour bed boost

- The smallest a target volume can get is 0
  - Proper selection of patients for boost!

EORTC 22881/10882 “boost no-boost trial”



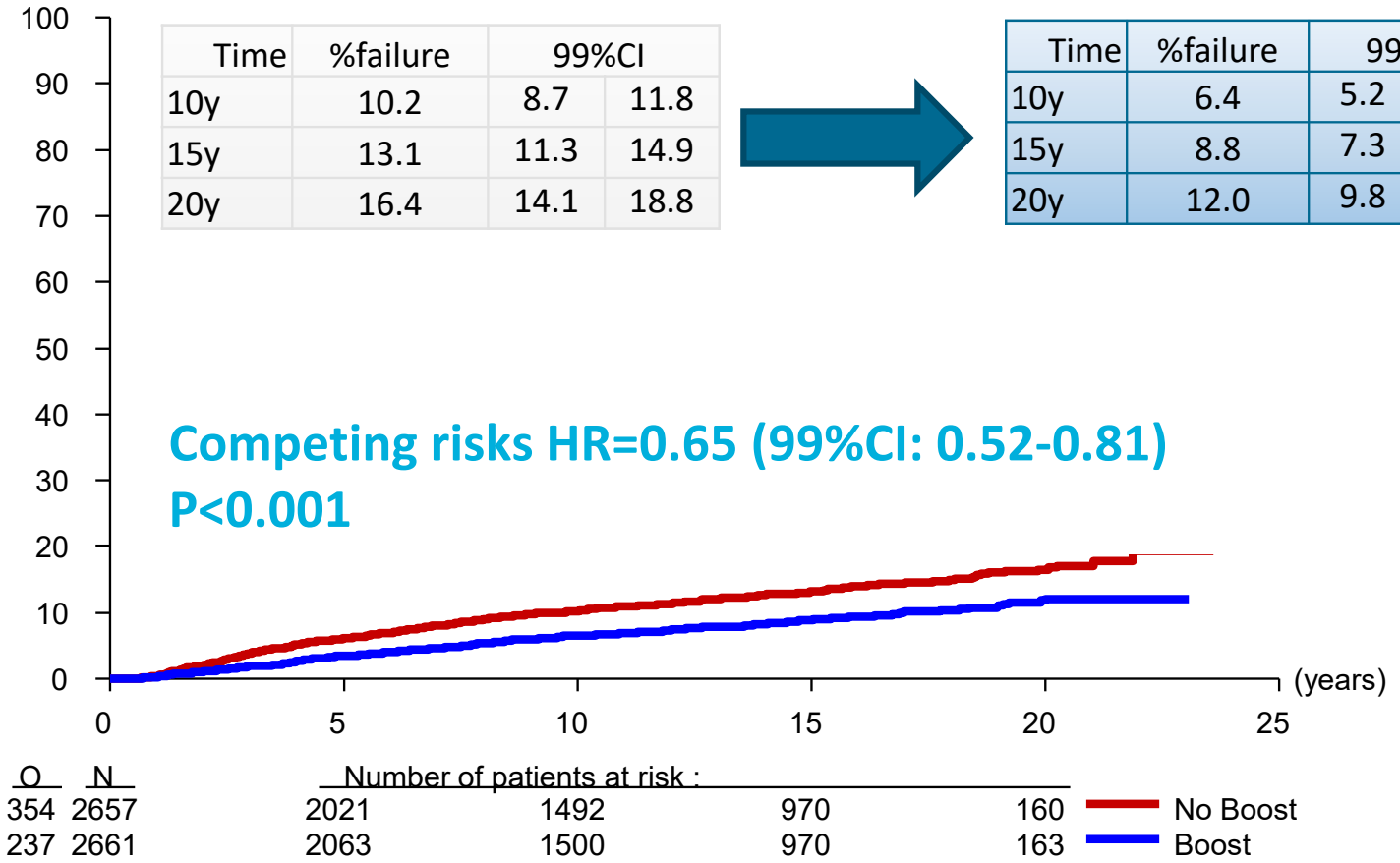
Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Tumour bed boost

Local recurrence

Time	%failure	99%CI	
10y	10.2	8.7	11.8
15y	13.1	11.3	14.9
20y	16.4	14.1	18.8

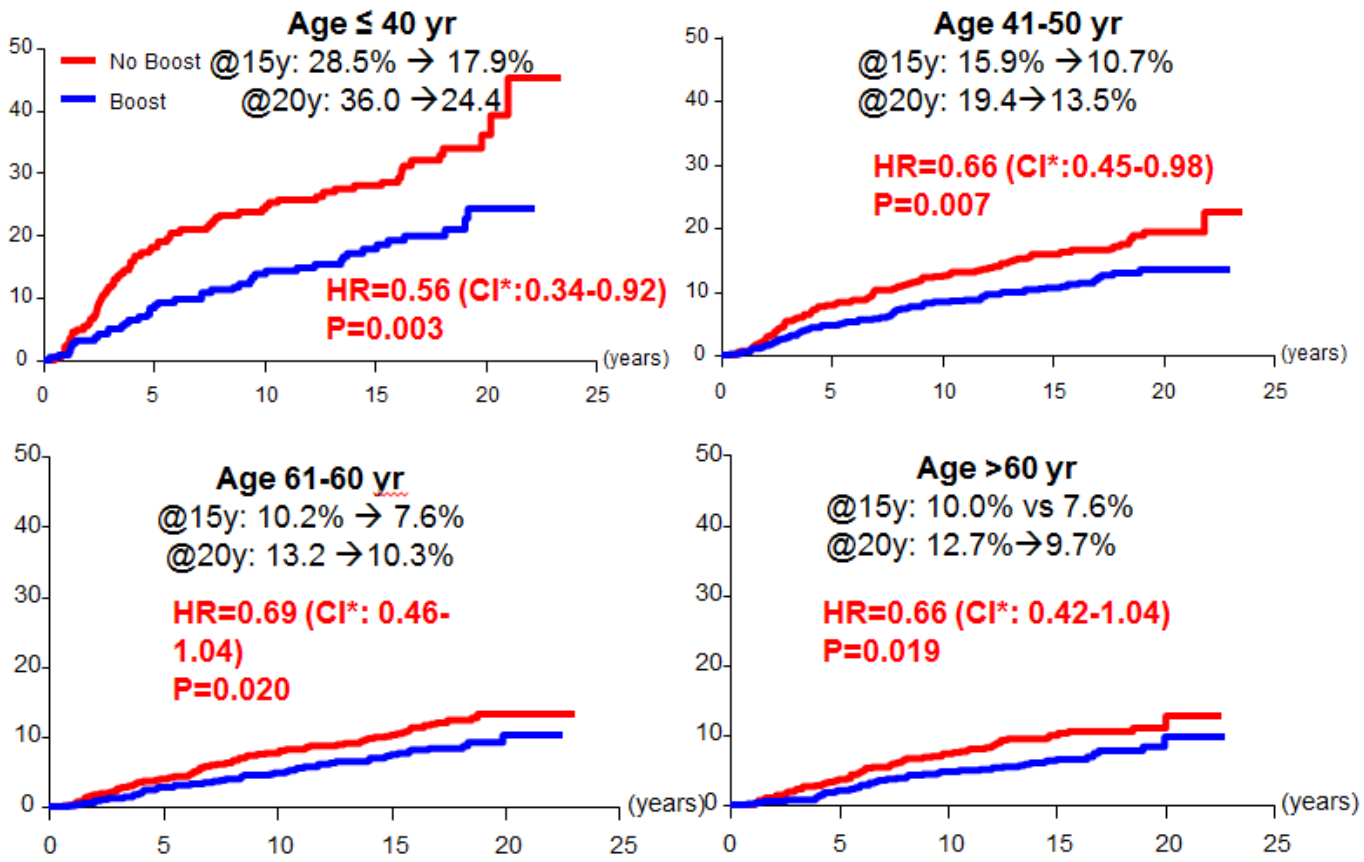
Time	%failure	99%CI	
10y	6.4	5.2	7.7
15y	8.8	7.3	10.4
20y	12.0	9.8	14.4



Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Tumour bed boost

Local recurrence as first event, by age



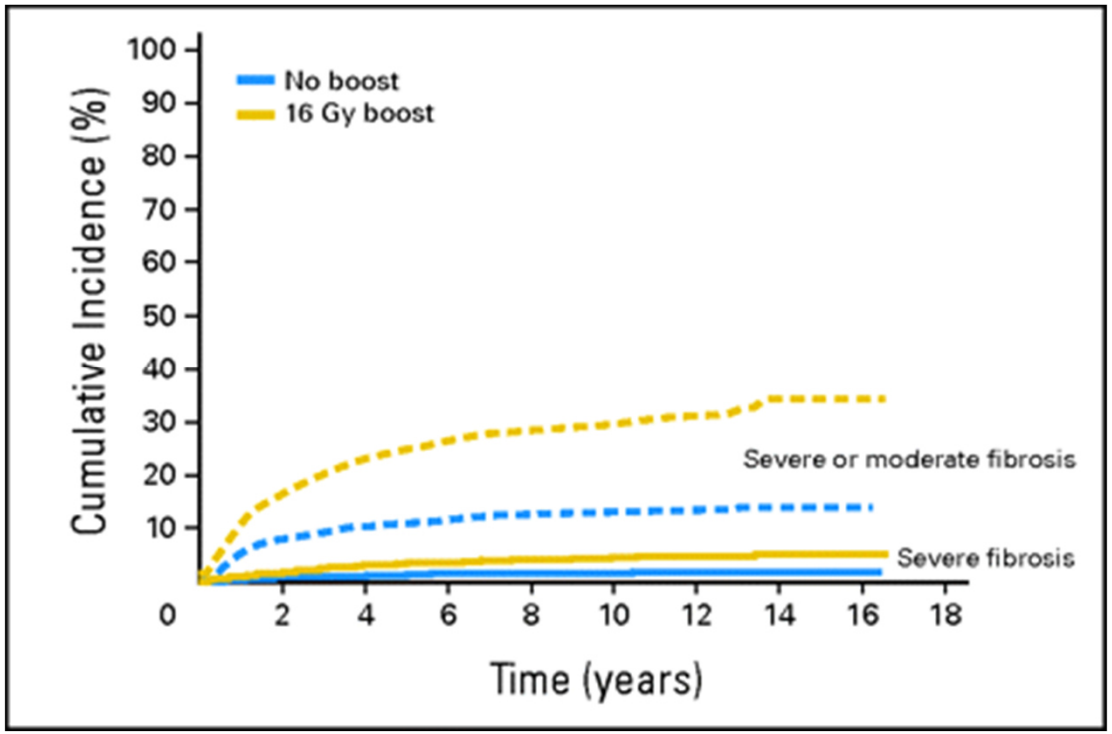
Other risk factors:

- LVI
- High grade
- TN
- Adjacent DCIS

Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Tumour bed boost

Boost dose increases fibrosis

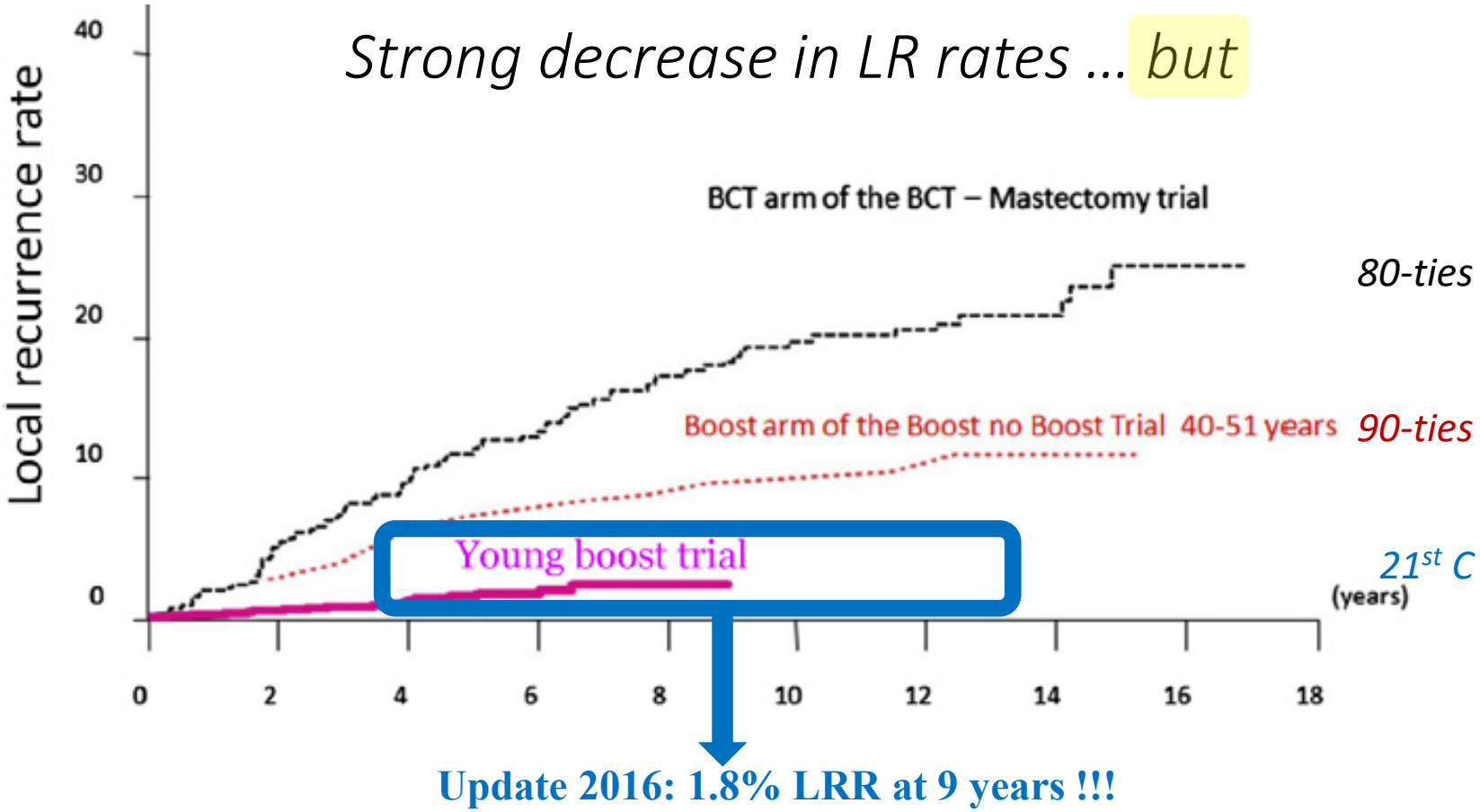


Moderate

Severe

Bartelink, Horiot, Poortmans et al. NEJM 2001, JCO 2007, Lancet Oncol 2015.

Tumour bed boost



Poortmans P, et al. Breast. 2017;31:295-302.

Recent results

… but … increasing complications after boost!

Radiotherapy and Oncology 128 (2018) 434–441

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

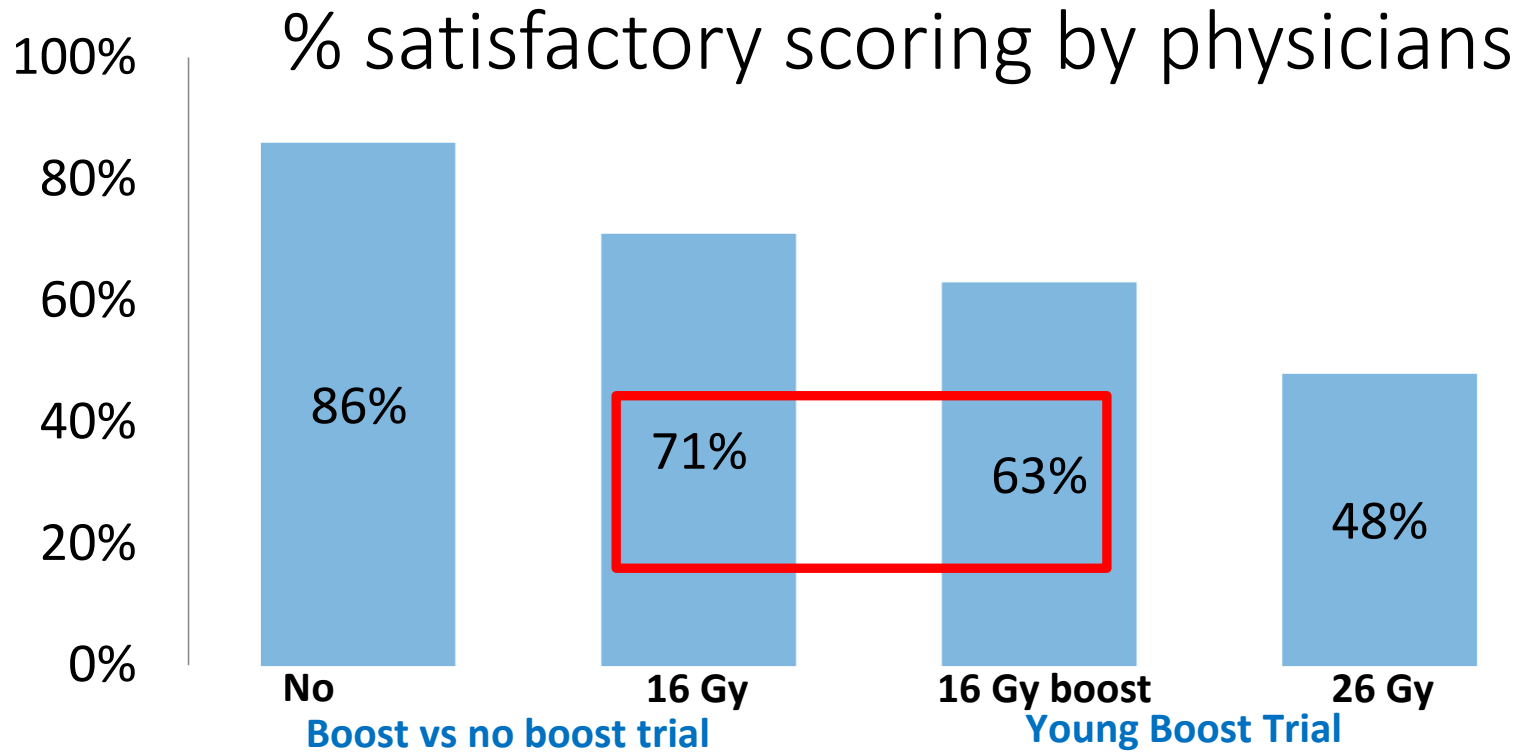
Phase III randomised trial

Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: Results of the Young boost trial

Patricia J.A.M. Brouwers [a,1,*], Erik van Werkhoven [b,1], Harry Bartelink [b], Alain Fourquet [c], Claire Lemanski [d], Judith van Loon [a], John H. Maduro [e], Nicola S. Russell [b], Luc J.E.E. Scheijmans [f], Dominic A.X. Schinagl [g], Antonia H. Westenberg [h], Philip Poortmans [c,2], Liesbeth J. Boersma [a,2], on behalf of the Young Boost Trial research group[3]

Tumour bed boost

Comparison with boost – no boost trial



Brouwers PJ, et al. Radiother Oncol. 2016;120:107-13 & 2018;128:434-41.

Tumour bed boost

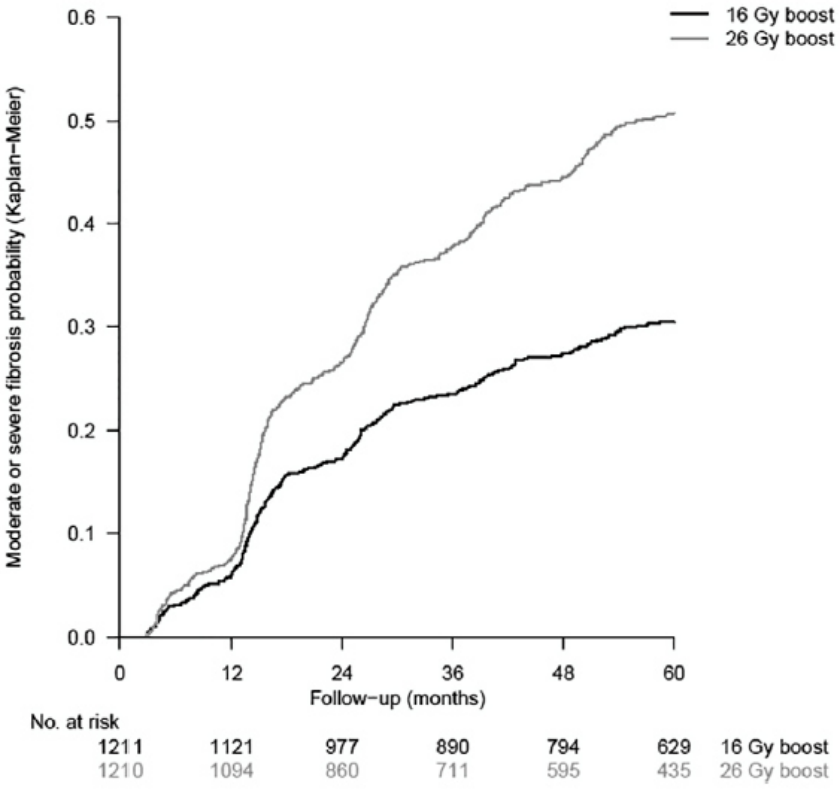


Fig. 2. Cumulative incidence of moderate or severe fibrosis in the boost area.

Risk factors for worse cosmesis:

- Use of a photon boost (vs. e-)
- High boost dose
- Cosmesis at baseline
- Adjuvant chemotherapy
- Boost volume

Brouwers PJ, et al. Radiother Oncol. 2016;120:107-13 & 2018;128:434-41.

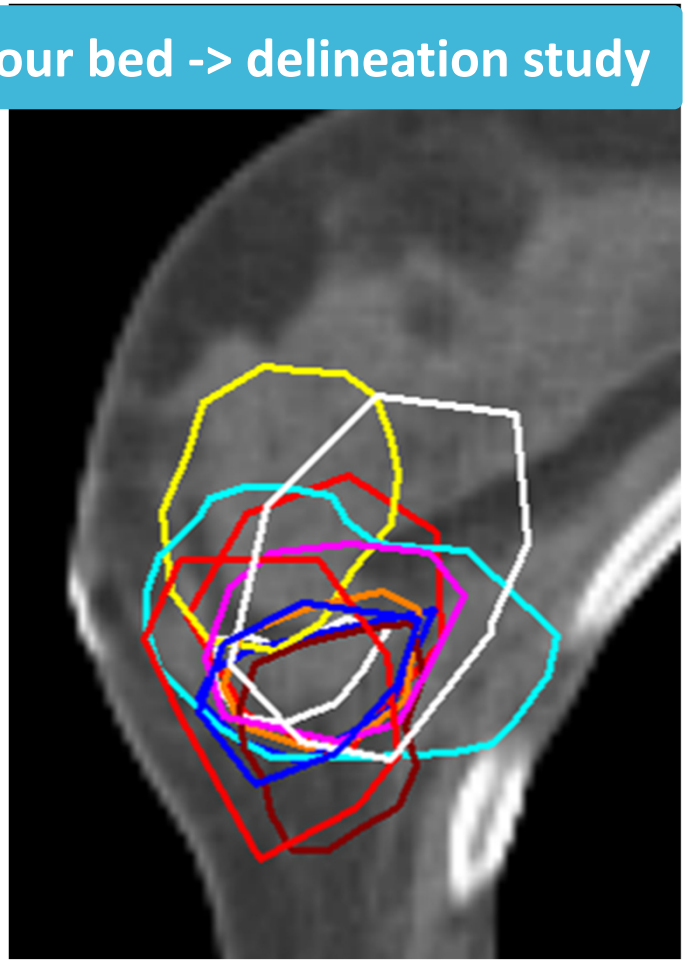
Tumour bed boost

Target volume delineation of primary tumour bed -> delineation study

- by dedicated RO's

- no clips

- no seroma



Van Mourik AM, et al. Radiother Oncol. 2010;94:286-91.

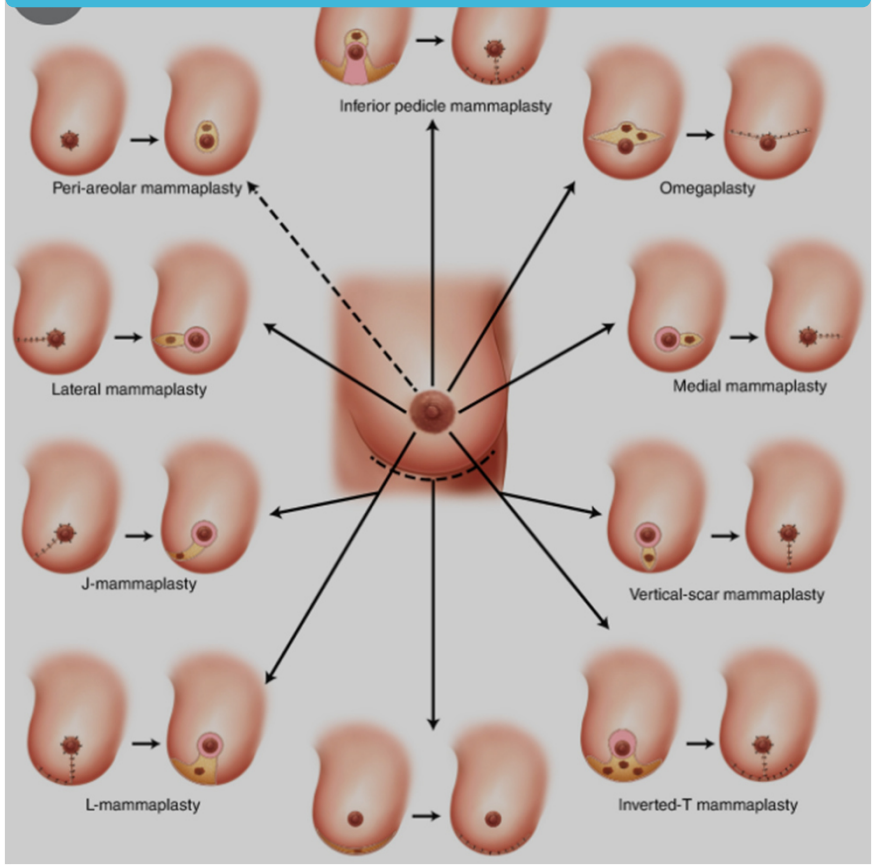
Tumour bed boost

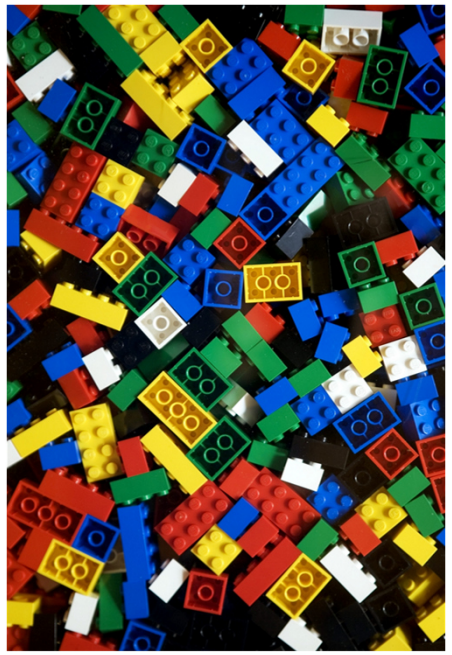
- Limited availability of reliable guidelines
- Difference in interpretation by observers

Reduction of this variation is essential in current de-escalation times

Target volume contouring

+ oncoplastic surgery

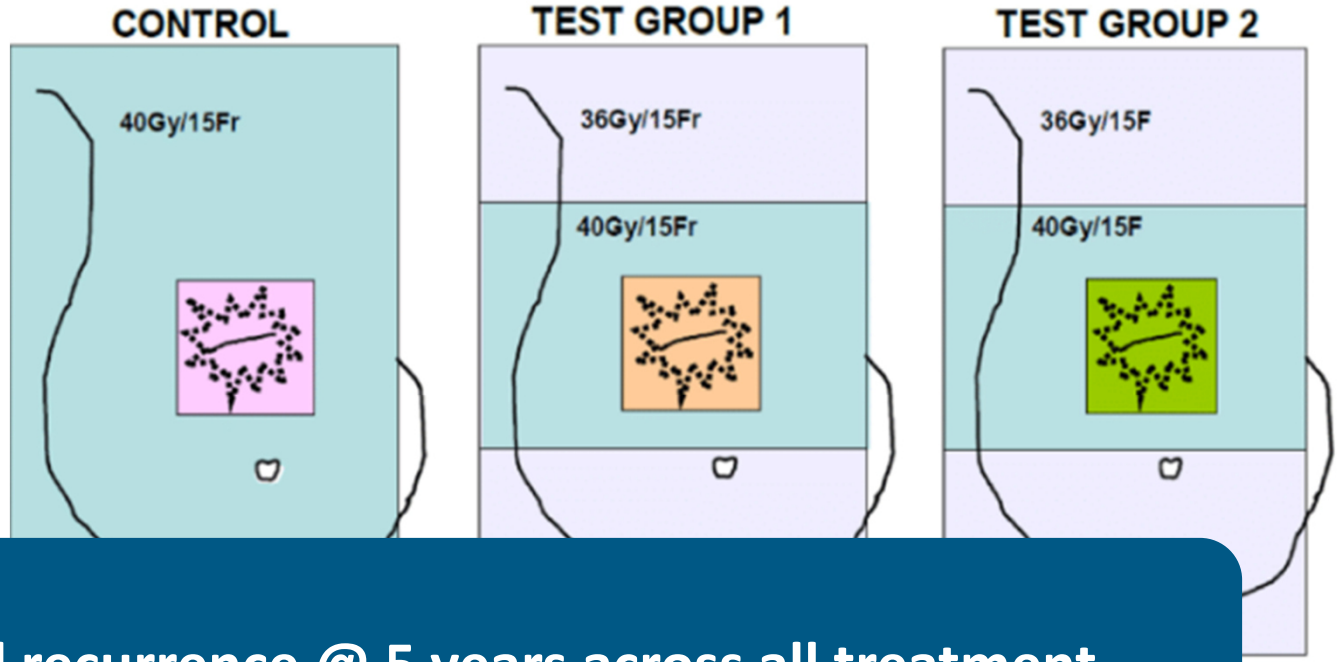




Tumour bed?

Tumour bed boost

- **IMPORT HIGH**
  - Non-inferiority RCT
  - Dose escalated SIB vs sequential boost
  - Early stage BC with *high local relapse risk*
  - Primary endpoint: IBTR
  - Secondary endpoints: late effects



- Lower than anticipated local recurrence @ 5 years across all treatment groups, with no significant differences between groups
- Increased risk of adverse events for the dose-escalated SIB group

Tumour bed boost

- Tumour bed boost has no impact on OS, but **decreases local recurrence relatively**
  - In c
  - No
- Tumou **outcome**

Boost only in well-selected patients, and not too large !!

→In the future maybe even further de-escalation of dose in the area around boost volume? *Different dose levels*? Cfr IMPORT-HIGH?

→ **If changing sequence from post- to pre-operative RT**

- **Smaller target volumes! Activation of immunomodulation????**

Target volumes in breast cancer RT

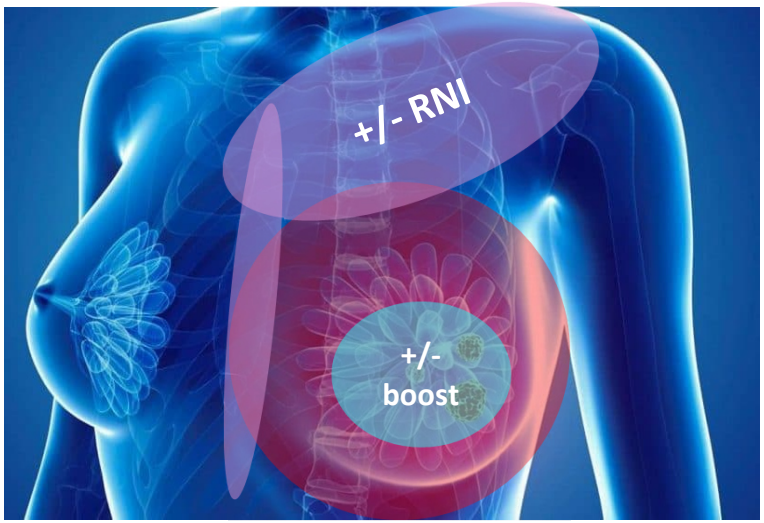
Partial breast irradiation (PBI)

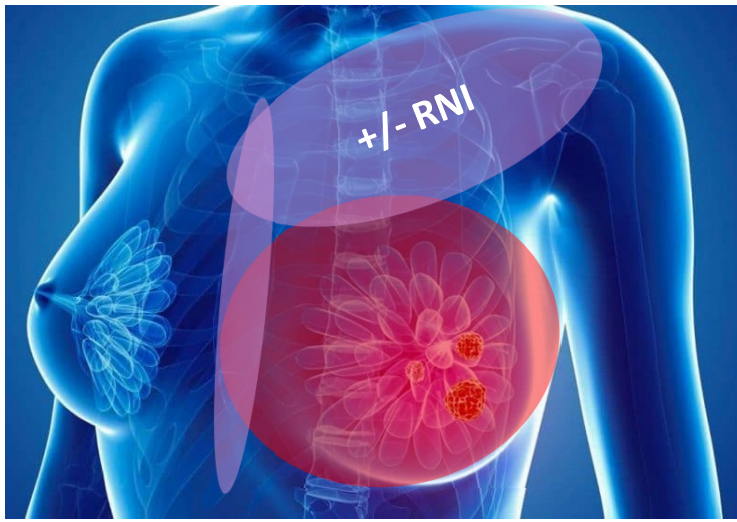
Whole breast radiation therapy (WBRT)

+/- boost

Post-mastectomy radiation therapy (PMRT)

+/- regional nodal irradiation (RNI)





Low risk

High risk

Intermediate risk

Sanders et al. 2007

Regional nodal irradiation (RNI)

- **The smallest a target volume can get is 0**

Based on Z0011 and AMAROS trials

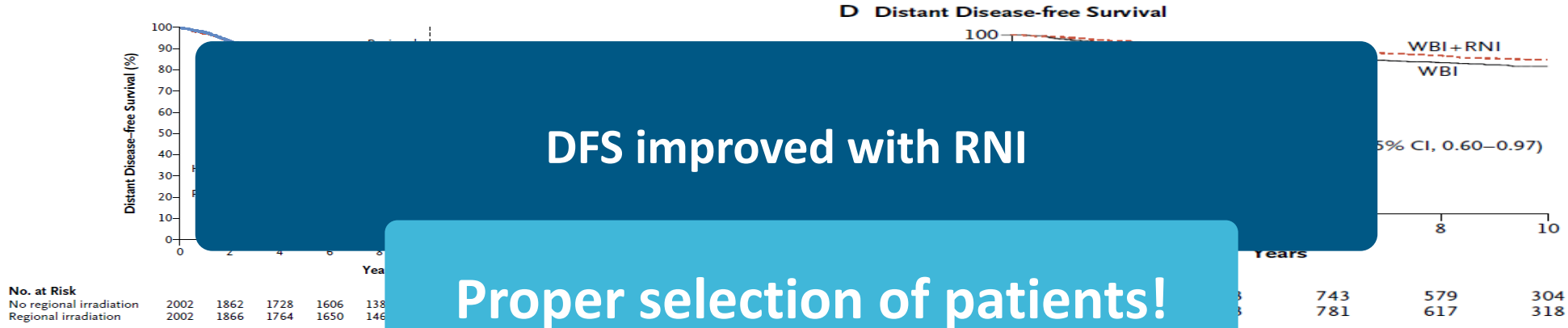
T1-2 cN0 disease with positive nodes on SLNB:

A. ALND is not recommended if patients will receive axillary RT and systemic therapy

B. Significantly less lymphedema after axillary RT

C. axillary RT can be considered standard

Regional nodal irradiation



DFS improved with RNI

Proper selection of patients!

Poortmans PM, et al. N Engl J ... ngl J Med 373:307-316, 2015

- **Late side effects at 10 y following regional RT:**
  - **Pulmonary and skin**
  - **Limited; most often ≤ grade 2; some transient**
  - **No increased lethal toxicity**

Thorsen LB, et al. J Clin Oncol 34:314-320, 2016

Target volumes in breast cancer RT

Treatment planning

- Planning CT
- Target and OAR delineation
- Treatment plan

Treatment delivery

- Setup verification
- Motion management strategy
- Adaptive procedures

A. Delineation/Planning uncertainties

B. Inter-fractional uncertainty

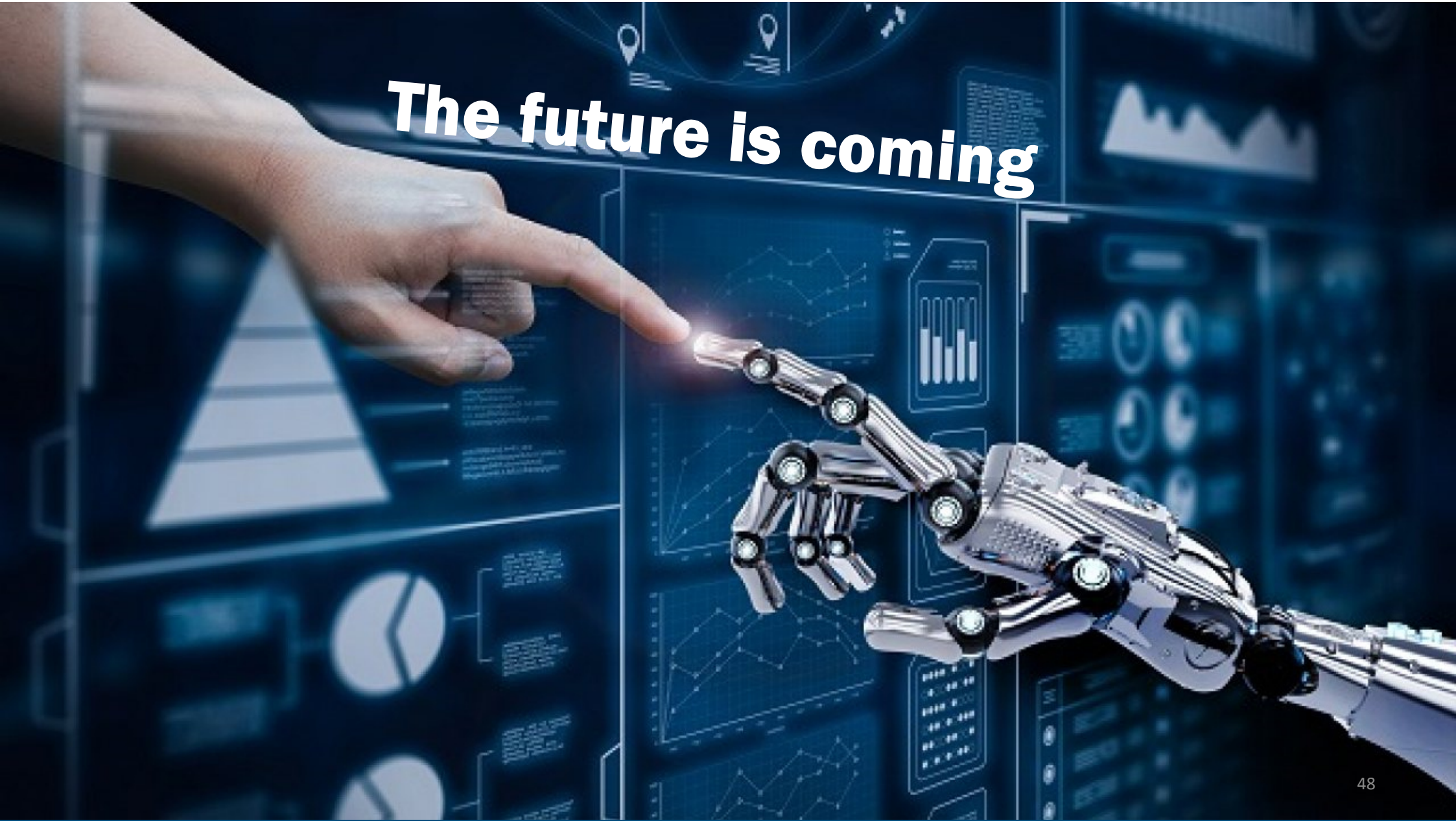
C. Intra-fractional uncertainty

PTV margin

Plannings target volume

- Delineation uncertainty ↓
  - with changing sequence from post- to preoperative
  - AI-based auto-segmentation
- Highly conformal planning techniques
- Daily adaptive RT (e.g. CBCT-oART, MR-oART...) + ultrahypofractionation

→ further reduce PTV margins


The future is coming

What do we need

- **Proper selection of patients for PBI**
  - ***Consider offering PBI to postmenopausal patients with ER+, node negative, pT1 tumors***
- **Being able to accurately predict pCR**
  - **Preoperative PBI could lead to the omission of completing surgery**
- **Boost only in well-selected patients, and not too large !!**
- **Proper selection of patients for RNI**

What do we need

- Proper selection of patients for PBI
  - *Consider offering PBI to postmenopausal patients with ER+, node negative, pT1 tumors*
- Being able to accurately predict pCR
  - Preoperative PBI could lead to the omission of completing surgery
- Boost only in well-selected patients, and not too large !!
- Proper selection of patients for RNI

What do we need

- Proper selection of patients for PBI
  - *Cons* *mors*
- Being ab
  - Preo patient care!
- Boost only in well-selected patien t too large !!
- Proper selection of patients for RNI

- ➢ Biomarkers
- ➢ Gene expression profiles
- ➢ Radiomics?

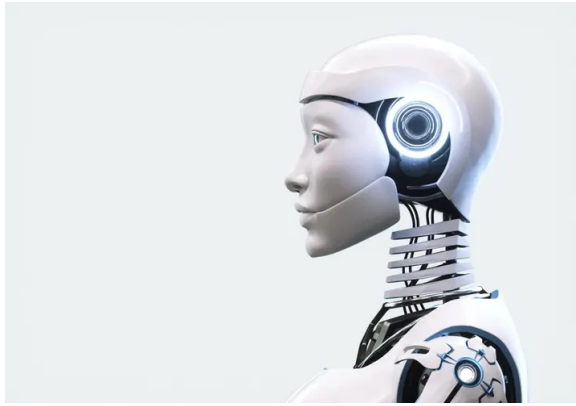
Individualisation

What do we need

- More research:
  - Shift to definitive RT
  - Different dose levels for different volumes at risk?
  - Shift to biologically-driven RT? Use RT only to activate immunomodulation??
- But does this research has to be done using the old methodology? AI-based?
- Innovations in the IGRT & AI-based segmentation field to help us further reduce PTV margins

Do we still need....

- Surgeons???
  - Shift to definitive RT for early stage disease?
- Radiation oncologists??
  - Shift to AI-based auto-segmentation?
- Elective irradiation???
  - All subtypes BC might receive immunotherapy in near future
  - Protect TILs, Tertiary Lymphoid Structures...
  - RT for immunomodulation



The Future


Medical oncology
Molecular biologist
Radiotherapy
Future RadOnc

Thank you!