Treatment of DCIS in the USA

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Background

Selection of Treatment for Patients with DCIS is Complex

- **Heterogeneity in biology/extent**
- **Difficulties assessing size and margins**
- **Protracted natural history (especially for low grade lesions) requires long follow up**
- **Inability to predict clinical outcome can lead to over- or under-treatment**

Margins Consensus Statement for DCIS Managed with Excision + RT

2 mm margin is enough

- Multidisciplinary panel
- Used meta-analyses of margin width and ipsilateral LR
- Included 20 studies, 7883 patients
- 2 mm margin minimized LR compared w/smaller margins
- Wider margins not significantly better than 2 mm

Morrow, J Clin Oncol 2016

Options:

1. Lumpectomy + standard whole breast RT
2. Role of Tamoxifen or Arimidex
3. Role of a boost
4. Lumpectomy with hypofractionation WBI
5. Lumpectomy and Partial Breast Irradiation
6. Lumpectomy alone
7. Oncotype
8. Observation without excision (trial)

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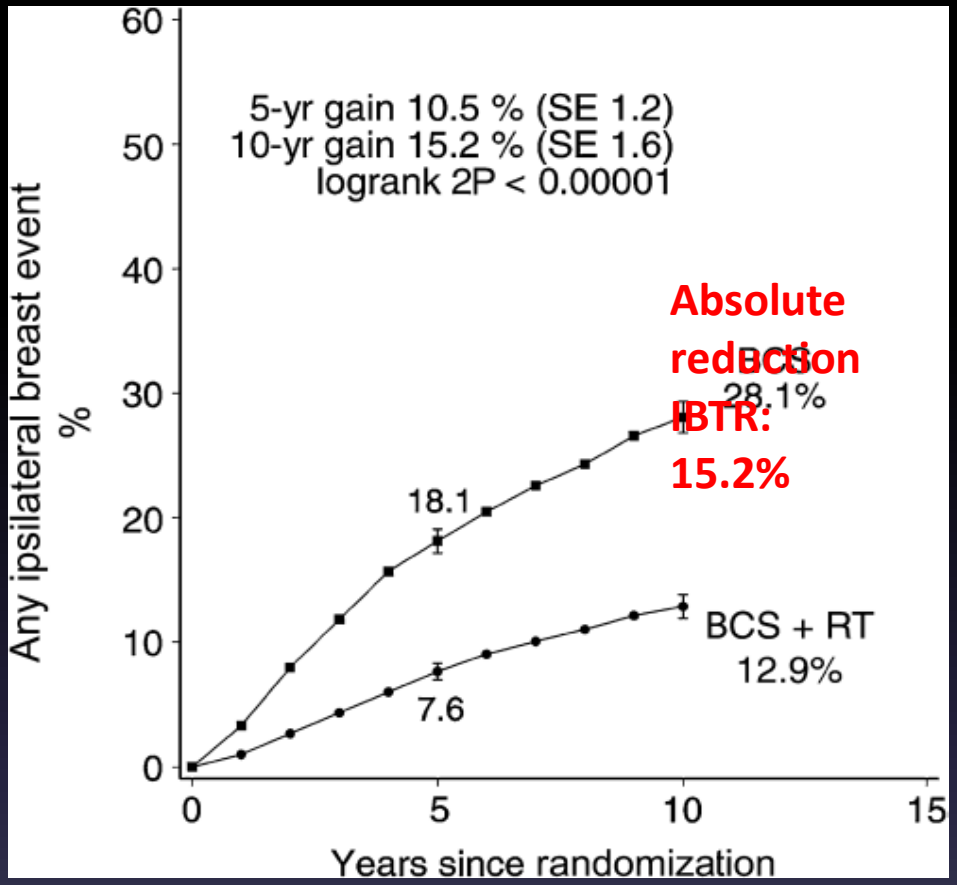
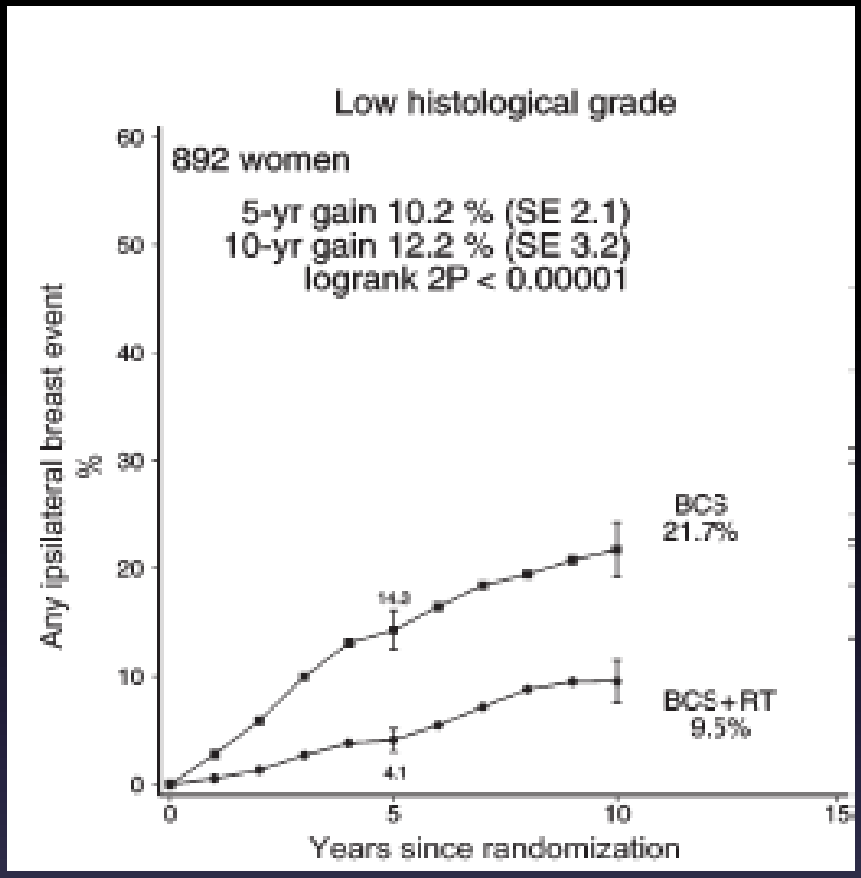
Randomized Trials of Excision +/- RT

	N	FU	E alone	E + RT
NSABP B-17	814	17 y	35%	20%
			invasive: 20%	11%
			DCIS: 15%	9%
EORTC	1010	15.8 y	30%	17%
			invasive: 15%	9%
			DCIS: 15%	8%
UK	1030	12.7 y	19%	7%
			invasive: 7%	4%
			DCIS: 12%	3%
Swedish	1067	8 y	27%	12%
			invasive: 12%	7%
			DCIS: 15%	5%

Wapnir, J Natl Cancer Inst 103:478-88, 2011, Donker, J Clin Oncol 31:4054-9, 2013
Cuzick, Lancet Oncol 12:21-9, 2011, Holmberg, J Clin Oncol 26:1247-52, 2008

EBCTCG Meta-Analysis





All 4 randomized trials of RT vs no RT

N = 3729

Regardless of age, extent of surgery, use of tamoxifen, margins, grade, size

Correa, JNCI Monogr 41:162-177, 2010

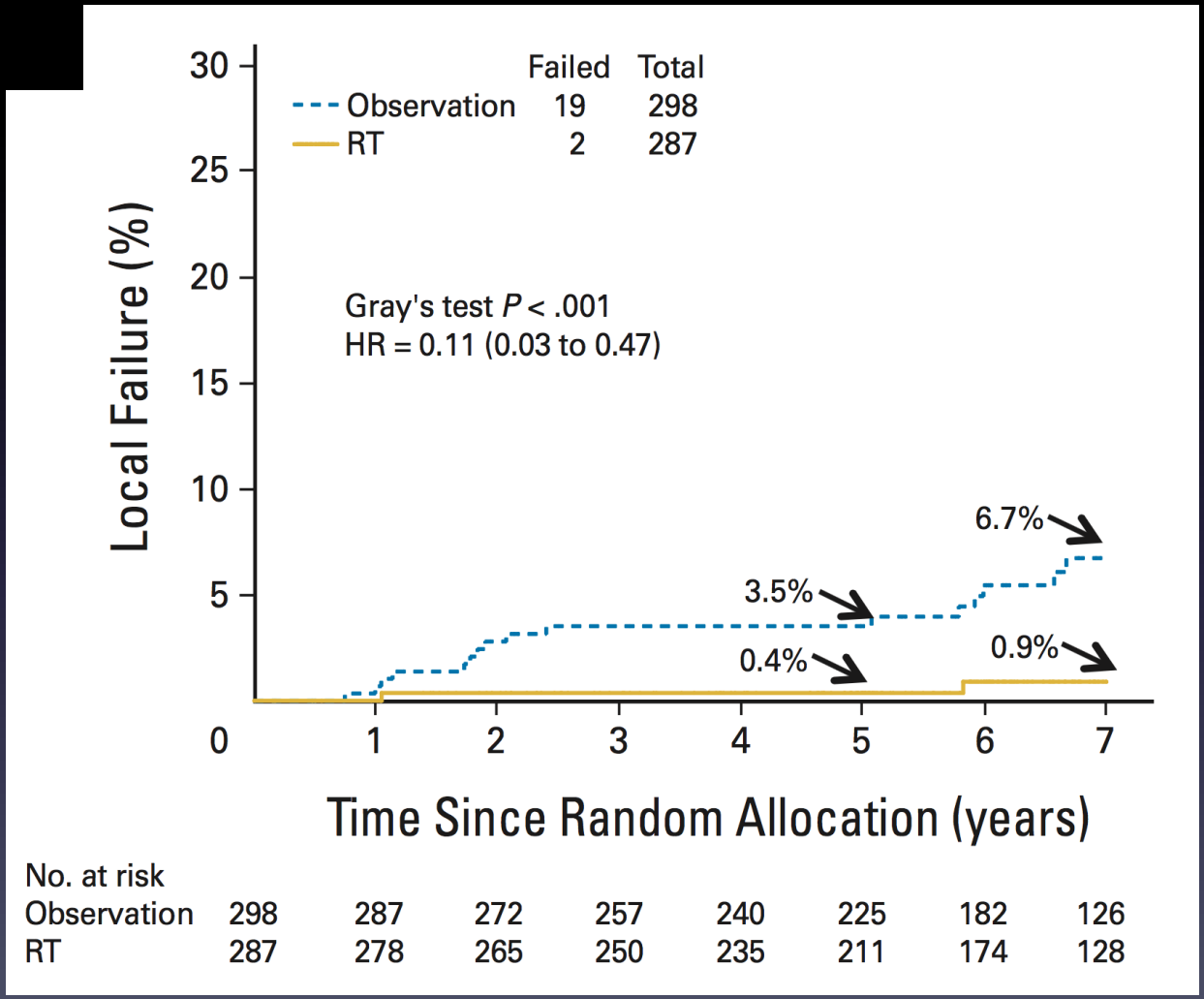
Higher Local Recurrence with RT in Earlier Trials (7-20%)

Excision + RT: Local Recurrence in Modern Retrospective Series

	N	Year	FU (mos)	LR
MDACC	977	1996-2007	62	2.4%
Harvard	246	2001-2007	58	0%
Norway	871	1993-2007	120	3.6%

Alvarado, Ann Surg Oncol 2012
Halasz, Int J Radiation Oncol Biol Phys 2012
Falk, Breast Cancer Res Treat 2011

RTOG 9804: RCT of lumpectomy vs lumpectomy/RT for low risk DCIS



N = 585, median FU 7 yrs
Tamoxifen in 62%

Eligibility Criteria:

- Grade 1, 2 DCIS
- <2.5 cm
- 3mm margins or greater

McCormick B et al, JCO 2015

Radiation Therapy for DCIS

- **Consistently reduces local recurrence**
- **Reduces LR by >60% (both DCIS and invasive LR)**
- **Reduces LR across all subsets**
- **No demonstrated survival benefit…**

USA

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Long-Term Results from NSABP B-24
(Median FU = 13.6 yrs)

	RT	RT + Tam	p-value
Ipsilateral Event	16.6%	13.2%	
Invasive	9.0%	6.6%	0.025
DCIS	7.6%	6.7%	NS
Contralateral Event	8.1%	4.9%	0.023

Reduction = 32% for ipsilateral and contralateral events
Nonsignificant reduction in ipsilateral DCIS events
Benefit only in ER+ DCIS

Wapnir, JNCI 2011

Adding Tamoxifen to Excision: UK/ANZ Trial

2,566 pts
12 y FU

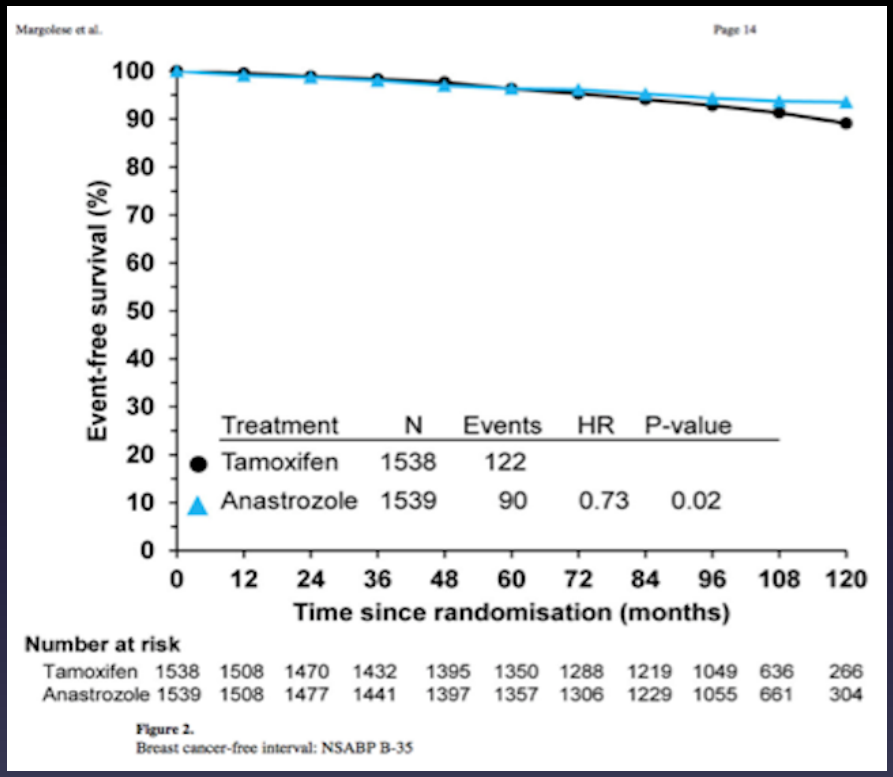
	No Tam	Tam	p-value
IBTR			
No RT	**17%**	**13%**	**0.04**
RT	**2.4%**	**2.6%**	**0.8**
CBC	**4%**	**2%**	**0.005**

Cuzick, Lancet Oncol 2011

Lancet 2016

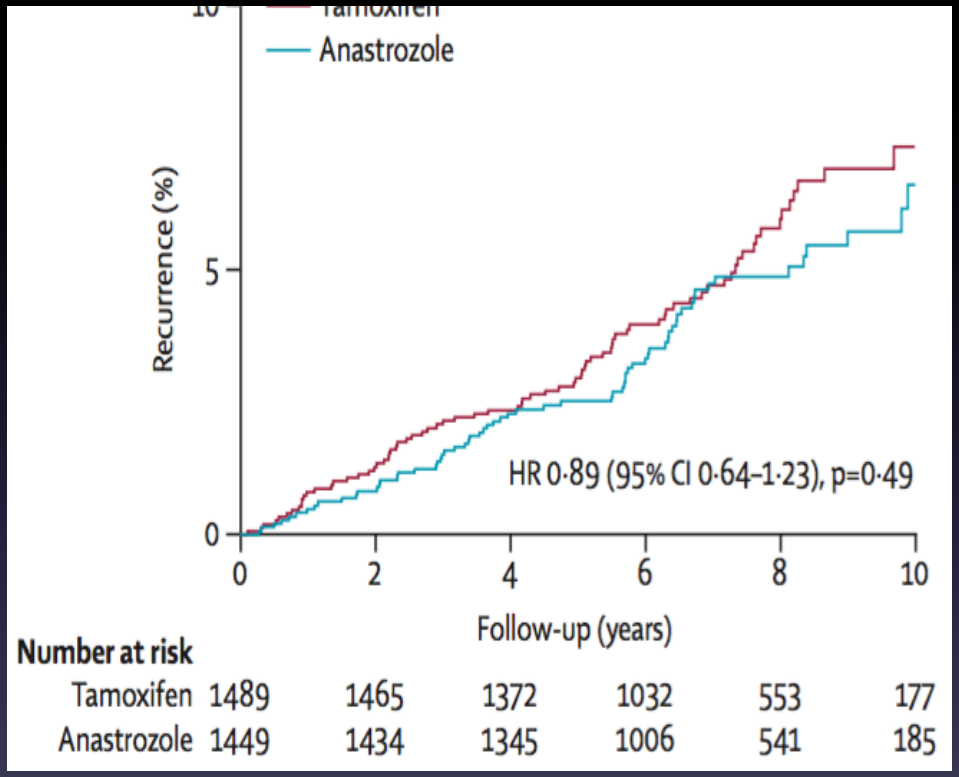
Tamoxifen vs Arimidex

NSABP B-35



- 3,104 post-menauposal pts
- FU 10 years
- Improvement mostly in pts <60 yo

IBIS II



- 2,980 post-menopausal patients
- FU median 7.5 years
- No difference (AI non-inferior)

Tamoxifen or Arimidex in DCIS

- **Modest benefit in ER+ DCIS**
  - **Reduces Contralateral Breast Cancer**
- **With RT, may further reduce LR**
- **Small benefit after excision alone**
- **No or little superiority in favor of AI**
- **Await data from NSABP B-43 (trastuzumab)**

USA

Options:

1. Lumpectomy + standard whole breast RT
2. Role of Tamoxifen
3. Role of a boost
4. Lumpectomy with hypofractionation WBI
5. Lumpectomy and PBI
6. Lumpectomy alone
7. Oncotype
8. Observation without excision (trial)

BOOST : Séries RETROSPECTIVES

	Annee Public	n	Age med	Follow-up (Year)	No bst/ boost	RL (%)	*p*
I. Curie (1)	2002	343			243 / 100*	13 / 6%	0,08
Rare Cancer NetWork (2)	2006	373	41	6	150 / 166	28 /14 %	0,02
NSABP B-24 (3)	2008	1569	53	14	877 / 692	14,3/ 13,8	0,69
Wai ES (4)	2011	957	56	9,3	-	6 / 9%	0,65
Mc Gill (5)	2012	220	58	3,8	121 / 79	4 / 0	Effet boost
Canada (6)	2013	1895	56	10	1344/ 561	12 / 13%	0,30

Conflicting results

Biases: High grade, close/positive margins, young patients

Courtesy David Azria

(1) Fourquet A: in DCIS book Silverstein 2002 - (2) Rare Cancer Network : Omlin A, Lancet Oncology 2006, 7 : 652-56 - (3) Julian TB, JCO 2008; 28 - (4) Wai ES , Cancer 2011, 117:54-62 - (5) Wong P; IJROBP 2012, Vol 82 e153 - (6) Rakovitch E - JROBP 2013 Jul 1, 86(3):491-7

Etude BONBIS: PHRC 2008

TUMORECTOMIE

- Age
- HT
- Centre
- Grade
- Circonstances
- Marges

RANDOMISATION

→ Whole breast RT

→ **Whole breast RT + 16Gy boost**

Courtesy David Azria

BOOST in DCIS

Role is not clear

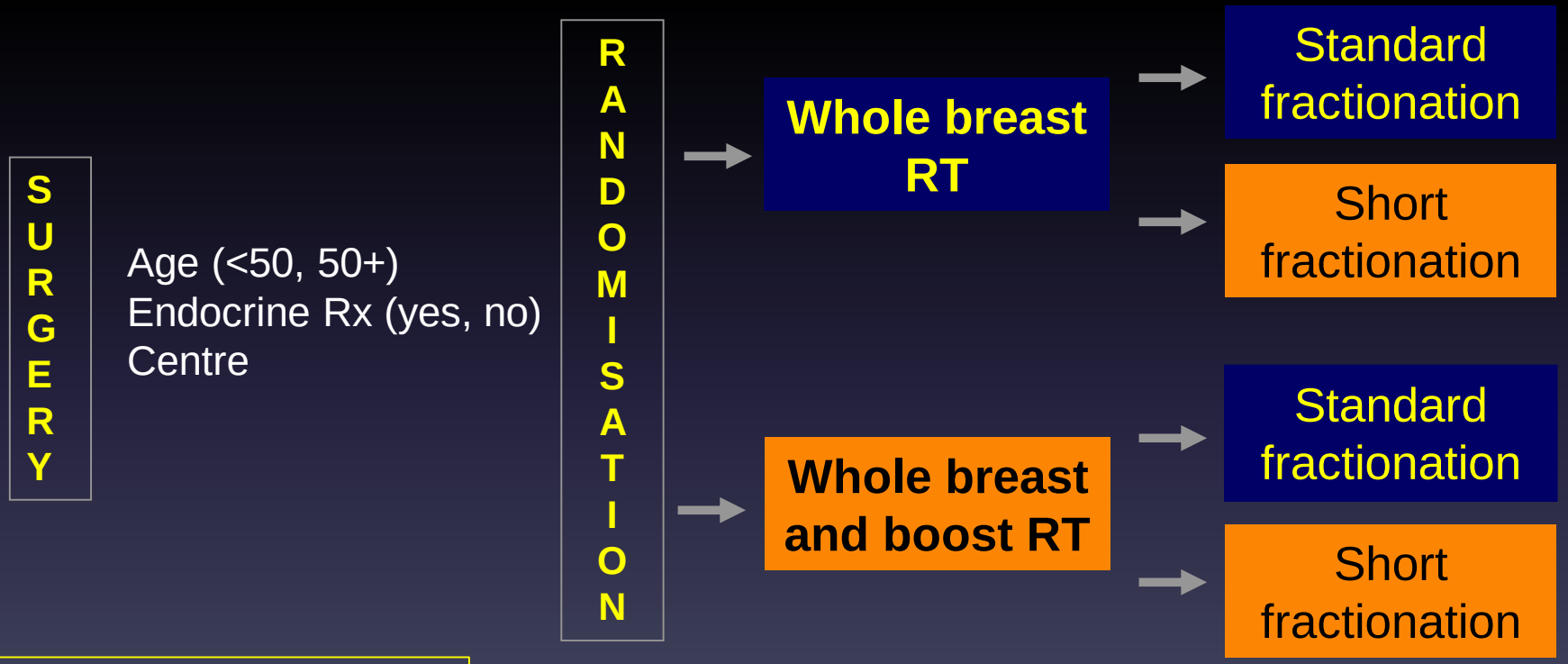
USA

Options:

1. Lumpectomy + standard whole breast RT
2. Role of Tamoxifen
3. Role of a boost
4. **Lumpectomy with WBI using hypofractionation**
5. Lumpectomy and PBI
6. Lumpectomy alone
7. Oncotype
8. Observation without excision (trial)

BIG 3-07 / **TROG** 07-01

Randomisation A



Courtesy David Azria

HYPOFRACTIONATION in DCIS

Role is not clear

USA

Options:

1. Lumpectomy + standard whole breast RT
2. Role of Tamoxifen
3. Role of a boost
4. Lumpectomy with hypofractionation WBI
5. **Lumpectomy and PBI (Partial Breast Irradiation)**
6. Lumpectomy alone
7. Oncotype
8. Observation without excision (trial)

PBI: Retrospective studies

Study	Pts#	DCIS grade	Technique	FU	LF (%)
Park et al	53	I, II, III	Mammosite	3.6 y	2%
Jeruss et al	194	I, II, III	Mammosite	4.5 y	3.1%
Goyal et al	41	I, II	Mammosite	5 y	0%
	29	III	Mammosite	5 y	5.3%
Stull et al	106	I, II, III, unknown	Mammosite	3 y	2.8%

- DCIS excluded from 11 of 13 ABPI studies with ≥ 4yrs F/U

NSABP B-39/RTOG 0413
Phase III APBI Trial

Eligible Patients with Lumpectomy

RANDOMIZED

Whole Breast Irradiation after Adjuvant Chemotherapy

50 Gy (2.0 Gy/fraction) or
50.4 Gy (1.8 Gy/fraction) to whole breast, followed by optional boost to ≥ 60 Gy

Partial Breast Irradiation prior to Adjuvant Chemotherapy

For a total of 10 treatments given on 5 days over 5 to 10 days:

34 Gy in 3.4 Gy fractions
Interstitial Brachytherapy or
Mammosite Balloon Catheter
or
38.5 Gy in 3.85 Gy fractions
3D Conformal External Beam

DCIS grade I, II, III
4,217 pts
2005-2013

ASTRO and GEC ESTRO guidelines

- Guidelines based on published trials released by ASTRO, ESTRO, etc.

ASTRO-suitable

Table 2. Patients "suitable" for APBI if all criteria are present

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm‡
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

GEC-ESTRO-low-risk

Characteristic	A/low-risk group – good c
Patient age	>50 years
Histology	IDC, mucinous, tubular, m colloid cc.
ILC	Not allowed
Associated LCIS	Allowed
DCIS	Not allowed
HG	Any
Tumour size	pT1–2 (⩽30 mm)
Surgical margins	Negative (⩾2 mm)
Multicentricity	Unicentric
Multifocality	Unifocal
EIC	Not allowed
LVI	Not allowed
ER, PR status	Any
Nodal status	pN0 (by SLNB or ALND[a])
Neoadjuvant chemotherapy	Not allowed

ASTRO –suitable 2016 Guidelines Update

Age: >50 years

Stage: Tis / T1

DCIS: <2.5 cm grade I-II, 3 mm margins

Smith et al., 2009 IJROBP

Polgar et al., 2010 Radiot Onc

Off-protocol guidelines

ASTRO-cautionary

Table 3. "Cautionary" group: Any of these criteria should invoke caution and concern when considering APBI

Factor	Criterion
Patient factors	
Age	50–59 y
Pathologic factors	
Tumor size	2.1–3.0 cm*
T stage	T0 or T2
Margins	Close (<2 mm)
LVSI	Limited/focal
ER status	Negative†
Multifocality	Clinically unifocal with total size 2.1–3.0 cm‡
Histology	Invasive lobular
Pure DCIS	≤3 cm
EIC	≤3 cm

GEC-ESTRO-int-risk

Characteristic	B/intermediate-risk group – possible candidates for APBI
Patient age	>40–50 years
Histology	IDC, ILC, mucinous, tubular, medullary, and colloid cc
ILC	Allowed
Associated LCIS	Allowed
DCIS	Allowed
HG	Any
Tumour size	pT1–2 (⩽30 mm)
Surgical margins	Negative, but close (<2 mm)
Multicentricity	Unicentric
Multifocality	Multifocal (limited within 2 cm of the index lesion)
EIC	Not allowed
LVI	Not allowed
ER, PR status	Any
Nodal status	pN1mi, pN1a (by ALND[a])
Neoadjuvant chemotherapy	Not allowed

ASTRO –cautionary 2016 Guidelines Update

Age: 40 – 49 years if all criteria of suitable

50 + if at least one path criteria

DCIS: <3 cm if criteria in suitable are not fully met

PBI in DCIS

Promising but not definitive data

USA

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Prospective Trials of Excision Alone for Low or Intermediate Grade DCIS

	N	Median age (range)	Median FU (yrs)	Median size (range)	Margins	Tam	LR @ 10 yrs
Wong (2014)	143	51 (35-81)	11	0.9 cm (0.1-2.5)	≥ 1 cm	No	15.6%
Hughes/Solin (2013)	273	60 (22-88)	8.8	0.6 cm (0.1-2.5)	≥ 0.3 cm (50% ≥ 1 cm)	31%	14.6%

RTOG 9804: RT vs. Observation

7-yr LR:

RT 0.9%
No RT 6.4% (p=0.0005)

Wong JS, J Clin Oncol 2006
Wong JS, Breast Cancer Res Treat 2014
Hughes LL, J Clin Oncol 2009
Solin LJ, J Natl Cancer Inst 2013

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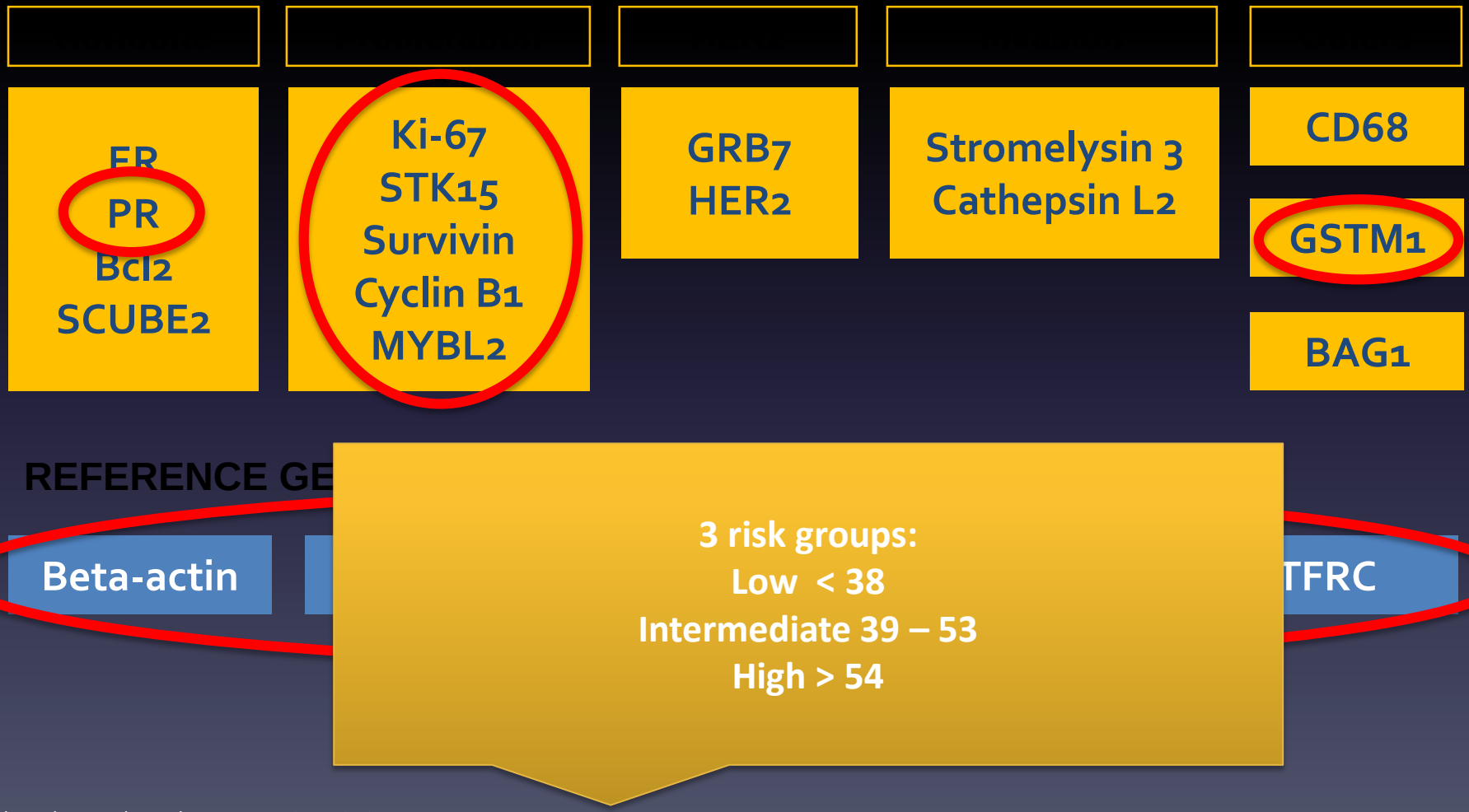
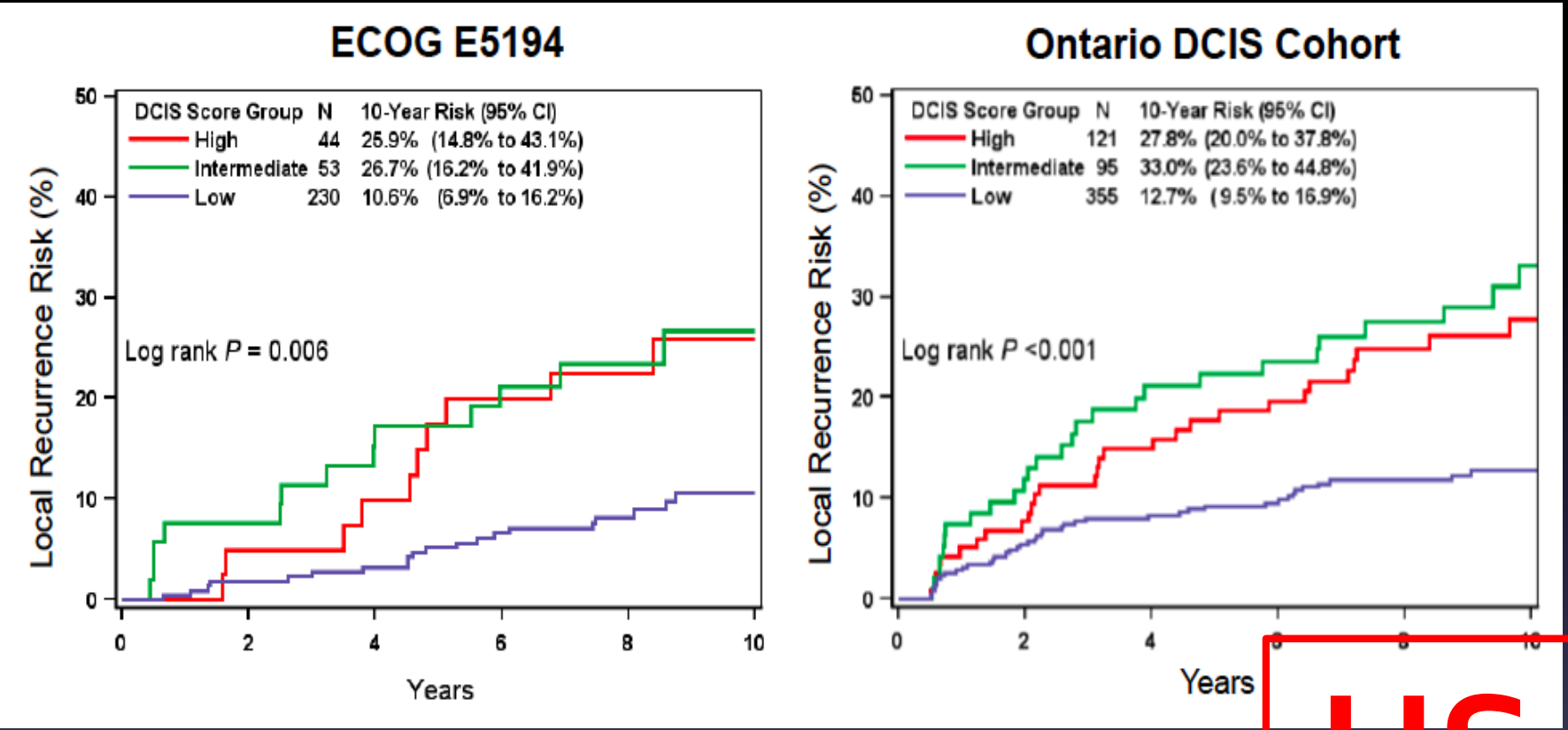
The 12-gene "DCIS Score" is a subset of the Recurrence Score



Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Comparison of 10-year Risk of Local Recurrence by DCIS Score Group: Ontario Cohort and E5194



USA

3 pre-specified risk groups defined, score associated with LR at 10 yrs

- "low risk" = 10.6% (invasive: 3.7%)
- "intermediate risk" = 26.7% (invasive: 12.3%)
- "high risk" = 25.9% (invasive: 19.2%)

Solin L, JNCI 2013
Rakovitch E, BCRT 2015

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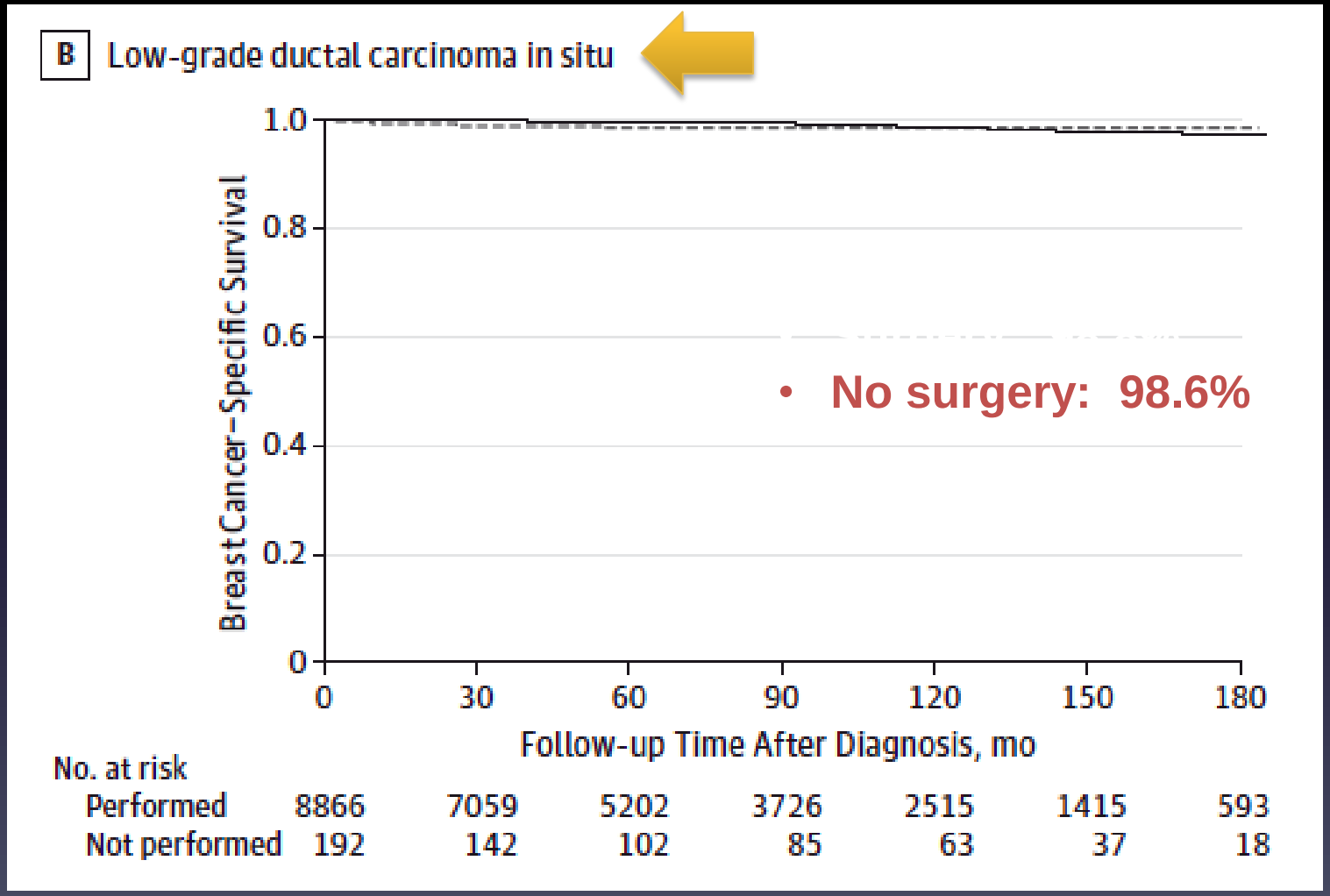
What happens if you don't "treat" DCIS? SEER 1988-2011



- **No surgery: 98.6%**

Sagara et al, JAMA Surgery 2015

Active Surveillance Trials for DCIS

- Trials have been initiated
- Newly diagnosed clinically “low risk” DCIS
- Primary outcome: ipsilateral invasive cancer-free survival
- Randomization: usual care (surgery and/or RT) vs. active surveillance
- Regular surveillance with imaging
- Intervene if evidence of progression to invasive cancer

LORIS -> UK
LORD -> EORTC
COMET-> USA

USA

NCCN guidelines 2017

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Ductal Carcinoma in Situ (DCIS)
NCCN Evidence Blocks™

NCCN Guidelines Index
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DIAGNOSIS	WORKUP	PRIMARY TREATMENT	
DCIS Stage 0 Tis, N0, M0 →	• History and physical exam • Diagnostic bilateral mammogram • Pathology review[a] • Determination of tumor estrogen receptor (ER) status • Genetic counseling if patient is high-risk for hereditary breast cancer[b] • Breast MRI[c,d] (optional)	Lumpectomy[e,f] without lymph node surgery[g] + whole breast radiation therapy[h,i,j,k,l] (category 1) or Total mastectomy with or without sentinel node biopsy[g,j] ± reconstruction[m] or Lumpectomy[e,f] without lymph node surgery[g] without radiation therapy[h,i,j,k,l] (category 2B)	→ See Postsurgical Treatment (DCIS-2)

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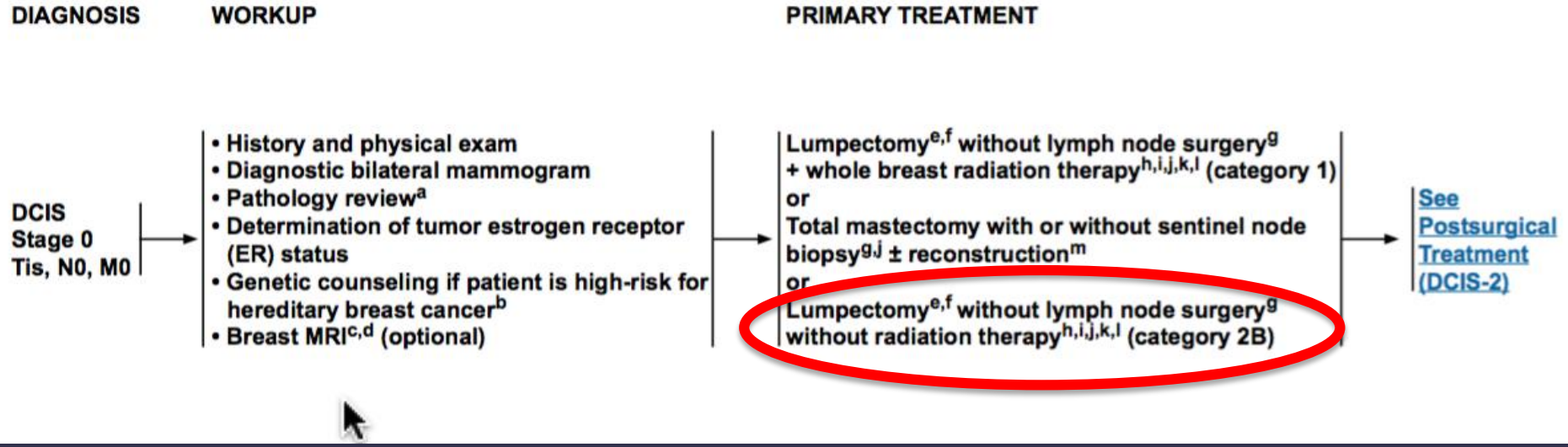

Merci pour

votre Attention

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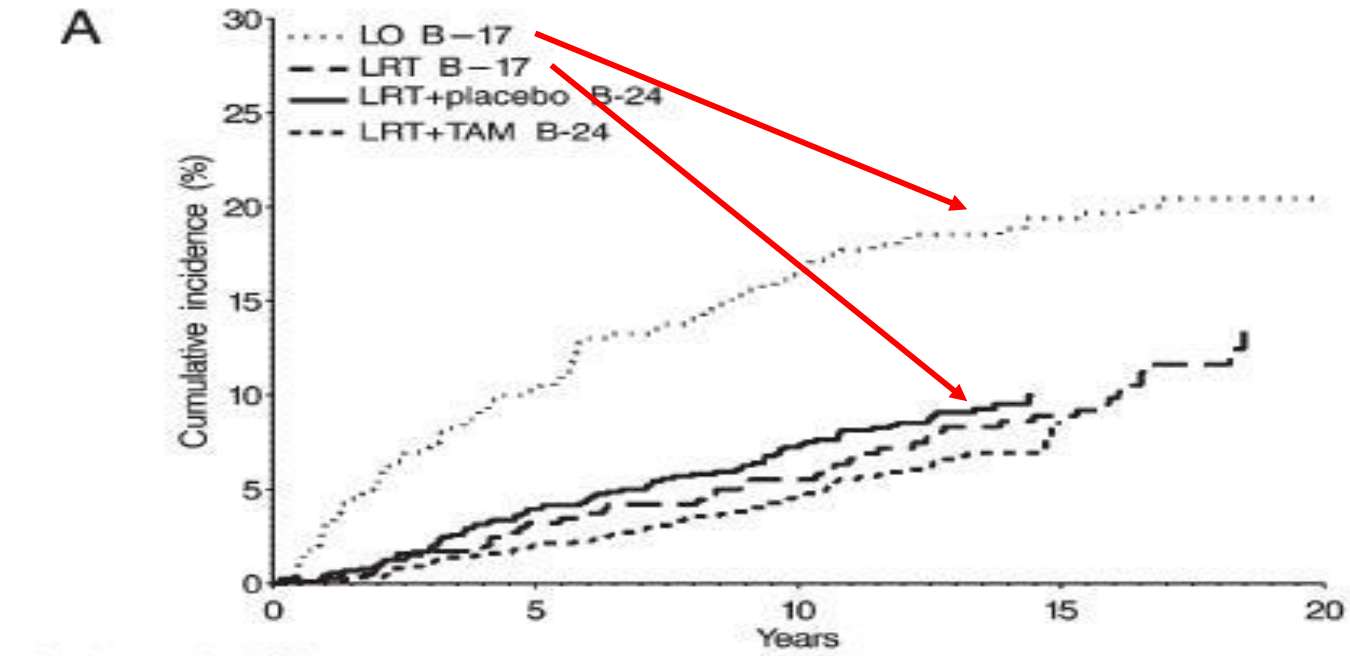
Active Surveillance Trials for DCIS (COMET)

- Age >40 at diagnosis; agree to randomization
- Pathologic confirmation of grade I/II DCIS without invasion by 2 local pathologists (microinvasion not allowed)
- ER ≥ 10%; HER2-negative (0, 1+, or 2+ if testing performed)

USA

Long-Term Outcomes for Invasive IBTR for NSABP B-17, B-24



LO B-17 No. of patients at risk	403	288	207	153	10
Cumulative Incidence, %	0	10.2	16.4	19.4	20.4
(95% CI)	0	(7.8 to 12.6)	(13.7 to 19.1)	(16.6 to 22.2)	(17.6 to 23.3)
LRT B-17 No. of patients at risk	410	335	256	186	13
Cumulative Incidence, %	0	3.2	5.5	8.9	13.5
(95% CI)	0	(1.4 to 5.0)	(3.4 to 7.6)	(6.5 to 11.3)	(10.6 to 16.4)
LRT+placebo B-24 No. of patients at risk	900	731	563	41	
Cumulative Incidence, %	0	3.9	7.3	10.0	
(95% CI)	0	(2.4 to 5.5)	(5.4 to 9.1)	(7.9 to 12.1)	
LRT+TAM B-24 No. of patients at risk	899	764	621	54	
Cumulative Incidence, %	0	2.0	4.6	8.5	
(95% CI)	0	(0.7 to 3.4)	(3.0 to 6.3)	(6.2 to 10.8)	

Wapnir, et al, JNCI 2011

NSABP B-24

(N=732, median FU = 14.5 yrs)

	RT	RT + Tamoxifen
IBTR		
ER+	17%	14%
ER-	17%	21%
CBC		
ER+	12%	6%
ER-	7%	4%

Allred, J Clin Oncol 2012

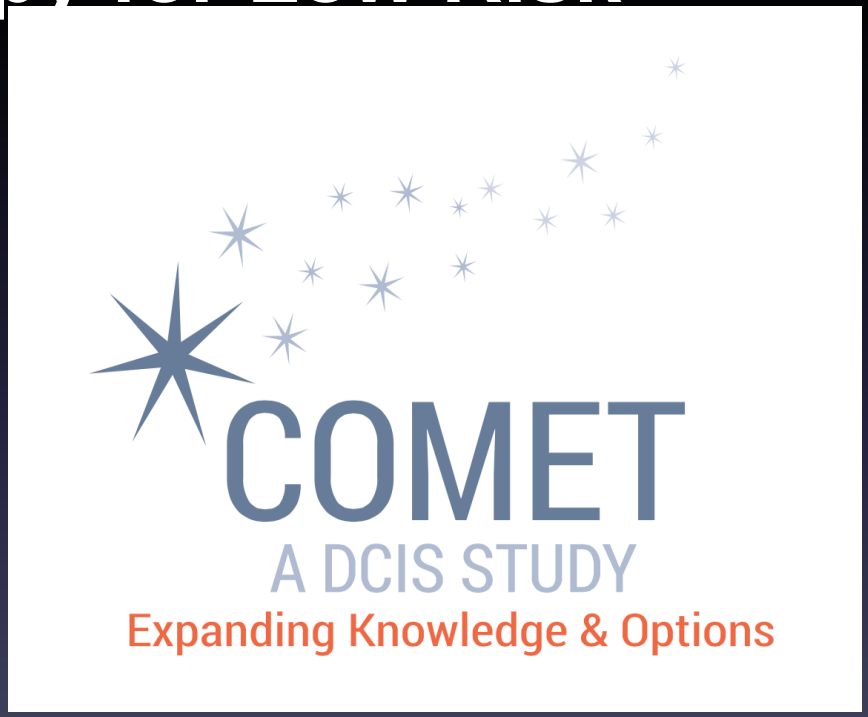
Conclusions

- Role of APBI in DCIS remains unclear
- Clinical & pathological features of DCIS suggest significant portion are widely spread
- Few studies to date suggest possible role for ABPI in small, localized DCIS
- No randomized trials to date
  - Few prospective studies
  - Small sample sizes
  - Await results of NSABP B-39

COMET Trial for low risk DCIS

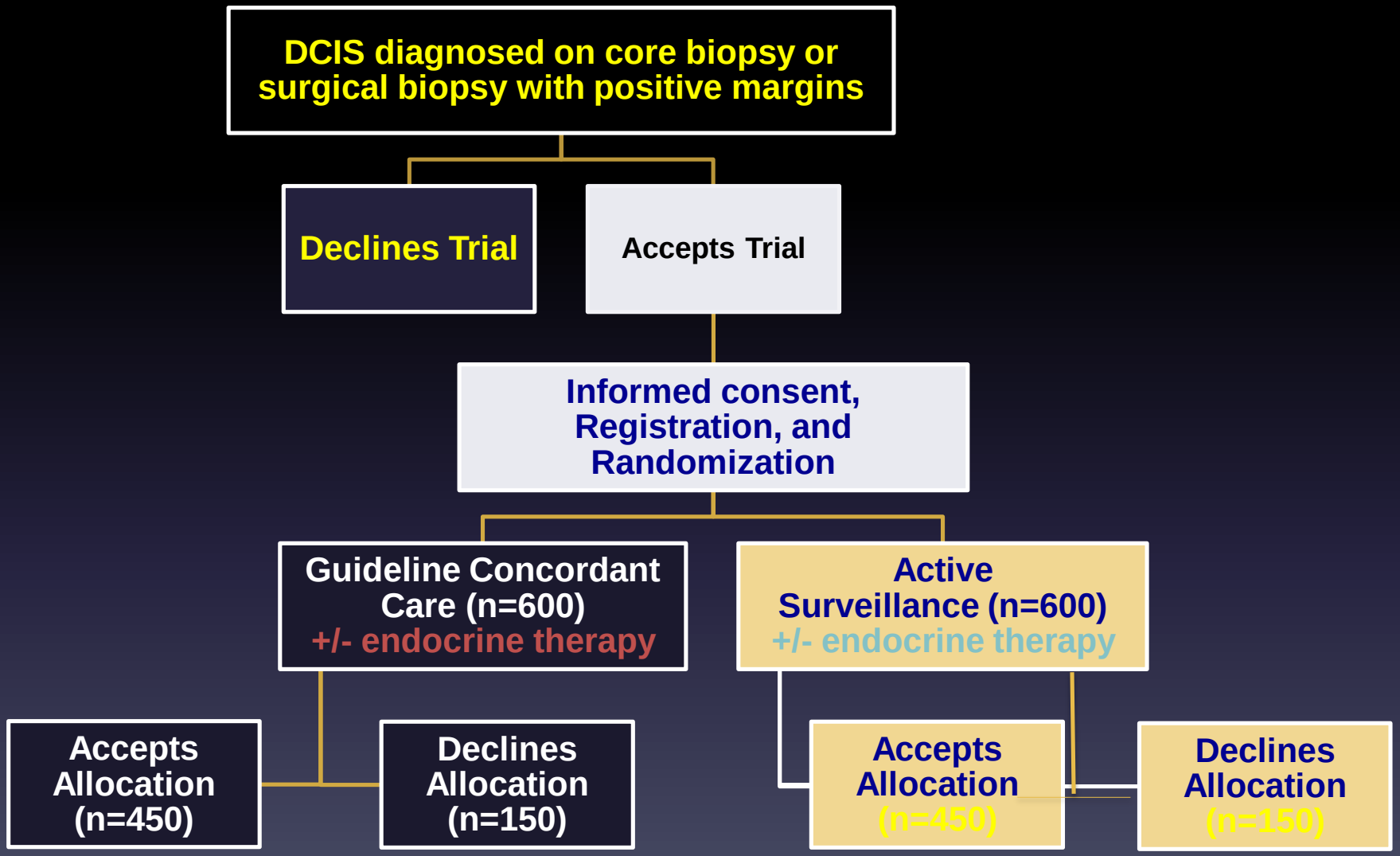
Comparison of Operative to Monitoring and Endocrine Therapy for Low Risk DCIS:
The COMET Trial

E. Shelley Hwang
Ann Partridge
Alastair Thompson
Advocate Lead: Liz Frank



Sponsors: PCORI and Alliance Foundation Trials (AFT)

Study Flow Diagram



Adding Tamoxifen to Excision: UK/ANZ Trial

- Randomized 2 x 2 trial of RT and tamoxifen
- Tamoxifen randomized: 1536
- RT randomized: 1030
- Median FU: 12.7 years
- Study design allowed for one or both randomizations
- Only randomized trial assessing role of tamoxifen after excision alone

Cuzick, Lancet Oncol 2011

Background

Selection of Treatment for Patients with DCIS is Complex

- **Heterogeneity in biology/extent**
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- **Inability to predict clinical outcome can lead to over- or under-treatment**

Margins Consensus Statement for DCIS Managed with Excision + RT

2 mm margin is enough

- Multidisciplinary panel
- Used meta-analyses of margin width and ipsilateral LR
- Included 20 studies, 7883 patients
- 2 mm margin minimized LR compared w/smaller margins
- Wider margins not significantly better than 2 mm

Morrow, J Clin Oncol 2016

EBCTCG Meta-Analysis

- All 4 randomized trials of RT vs no RT
- N = 3729
- RT reduced absolute 10-yr risk of ipsilateral breast events by 15.2%
- Regardless of age, extent of surgery, use of tamoxifen, margins, grade, size
- Greater proportional reduction in older patients
- No effect on survival
- No excess mortality from RT

Correa, JNCI Monogr 41:162-177, 2010

Oncotype DX Recurrence Score for DCIS

- 327 patients (ECOG E5194)
- Median FU 8.8 yrs
- Recurrence score calculated using optimized gene expression algorithm
- 3 prespecified risk groups defined, score associated with LR at 10 yrs
  - "low risk" = 10.6% (invasive: 3.7%)
  - "intermediate risk" = 26.7% (invasive: 12.3%)
  - "high risk" = 25.9% (invasive: 19.2%)

Solin, et al., JNCI 2013

Higher Local Recurrence in Earlier Trials

- Older mammographic techniques, lack of magnification views, post-excision mammograms
- Patient selection
- Less meticulous pathologic evaluation and surgical techniques
- Less attention to margins