DKIS: Radyoterapi

Dr. Melis Gültekin

Hacettepe Üniversitesi Tıp Fakültesi
Radyasyon Onkolojisi Anabilim Dalı

DKIS: TisN0M0

- Heterojen bir hastalık
- Sadece bx ile 10 yıl içinde %14-53 hastada invaziv kanser gelişir

- **Tedavide amaç: İnvaziv rekürrens riskini önlemek**

Donker, J Clin Oncol 2013
Wapnir, J Natl Cancer Inst 2011

Tedavi

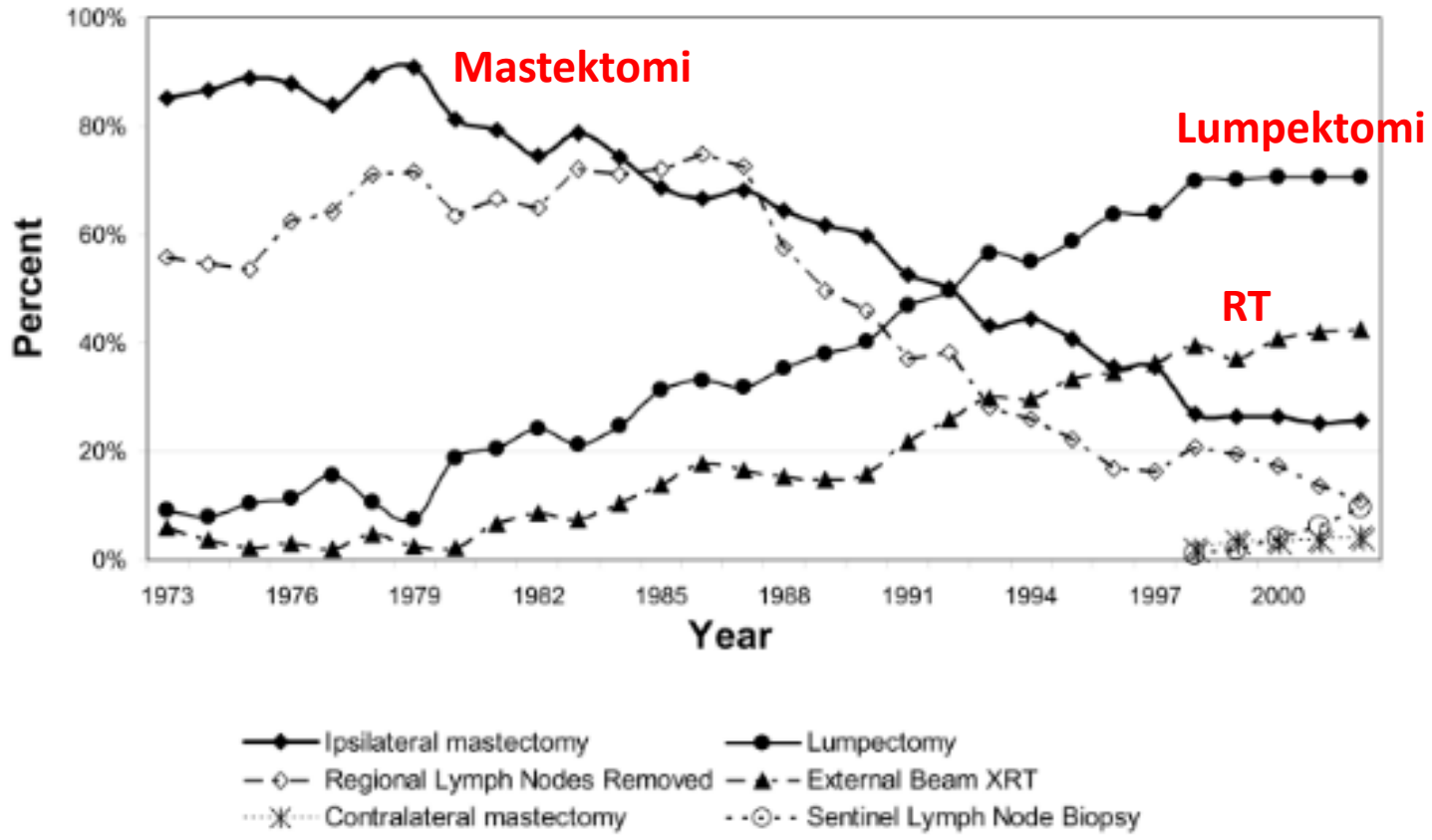
- Mastektomi
- MKC
- MKC + RT

} ± Hormonal tedavi

- Fazla tedavi/Eksik tedavi?

Tedavide neler değişti?

- **SEER 1973-2002**



Kumar AS, Breast Cancer Res 2005

Mastektomi Sonrası Kime RT?

Postmastektomi RT

- Mastektomi sonrası LR <%4
- Retrospektif seriler
  - cs ≤1mm
  - Yüksek grad

} LR ≥%10

RT

Carlson GW, J Am Coll Surg 2007
Rashtian A, IJROBP 2008
Chan LW, IJROBP, 2011
Childs SK, IJROBP, 2013

MKC Sonrası RT Gerekli mi?

MKC vs MKC+RT

- **4 faz III randomize çalışma**

	N	İzlem	MKC	MKC+RT
NSABP B-17	813	17 yıl	%35	%20
EORTC 10853	1010	15.8 yıl	%30	%17
UK/ANZ DCIS	1030	12.7 yıl	%19	%7
SweDCIS	1067	17.4 yıl	%32	%20

LR %50-60 ↓

Overview of the Randomized Trials of Radiotherapy in Ductal Carcinoma In Situ of the Breast

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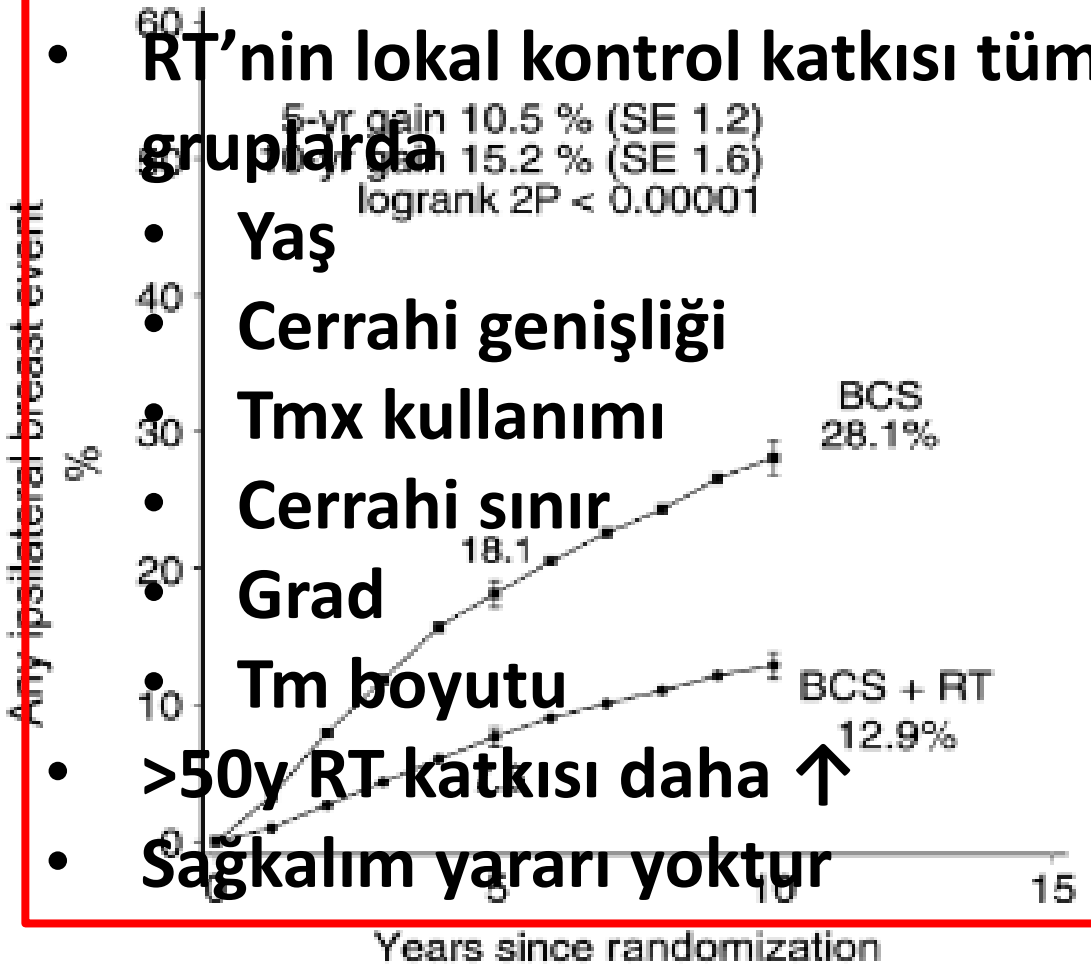
Correspondence to: EBCTCG Secretariat, Clinical Trial Service Unit (CTSU), Richard Doll Bldg, Old Road Campus, University of Oxford, Oxford OX3 7LF, United Kingdom (e-mail: bc.overview@ctsu.ox.ac.uk).

- **RT'nin lokal kontrol katkısı tüm alt gruplarda**
- **Yaş**
- **Cerrahi genişliği**
- **Tmx kullanımı**
- **Cerrahi sınır**
- **Grad**
- **Tm boyutu**
- **>50y RT katkısı daha ↑**
- **Sağkalım yararı yoktur**



EBCTCG, JNCI Monogr 2010

MKC Yapılan Bir Olguda Daima RT Gerekli mi?

Risk Gruplaması

- Nomogramlar
  - VNPI
  - MSKCC Nomogramı
- Genetik analiz
  - Oncotype DX
- Klinik çalışma sonuçları
  - ECOG-ACRIN E-5194
  - Harvard
  - RTOG 9804

VNPI

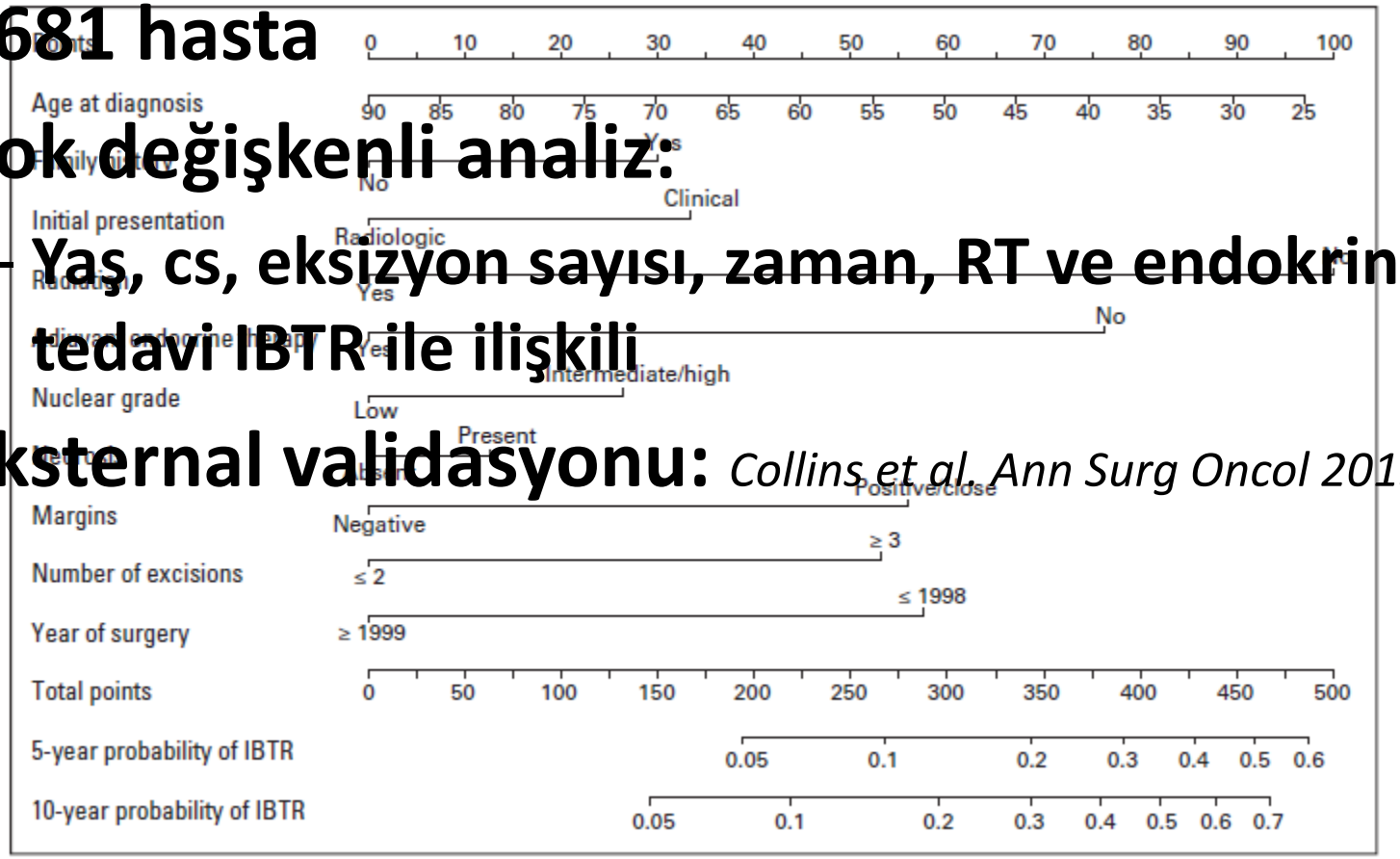
- **949 hasta, retrospektif analiz**
- **Grad, cs, tm boyutu, yaş (Skor: 4→12)**
- **Amaç: 12y LR <%20**

USC/VNPI	Treatment	12-yr recur, %
4, 5 or 6	Excision alone	≤6
7, margins ≥3 mm	Excision alone	16
7, margins <3 mm	Radiation	14
8, margins ≥3 mm	Radiation	15
8, margins <3 mm	Mastectomy	1
9, margins ≥5 mm	Radiation	19
9, margins <5 mm	Mastectomy	1
10, 11, or 12	Mastectomy	4

Silverstein, NEJM 1999
Silverstein, Am J Surg 2003
Silverstein, JNCI Monogr, 2010

MSKCC DKIS Nomogramı

- 1681 hasta
- Çok değişkenli analiz:
  - Yaş, cs, eksizyon sayısı, zaman, RT ve endokrin tedavi IBTR ile ilişkili
- Eksternal validasyonu: *Collins et al. Ann Surg Oncol 2015*



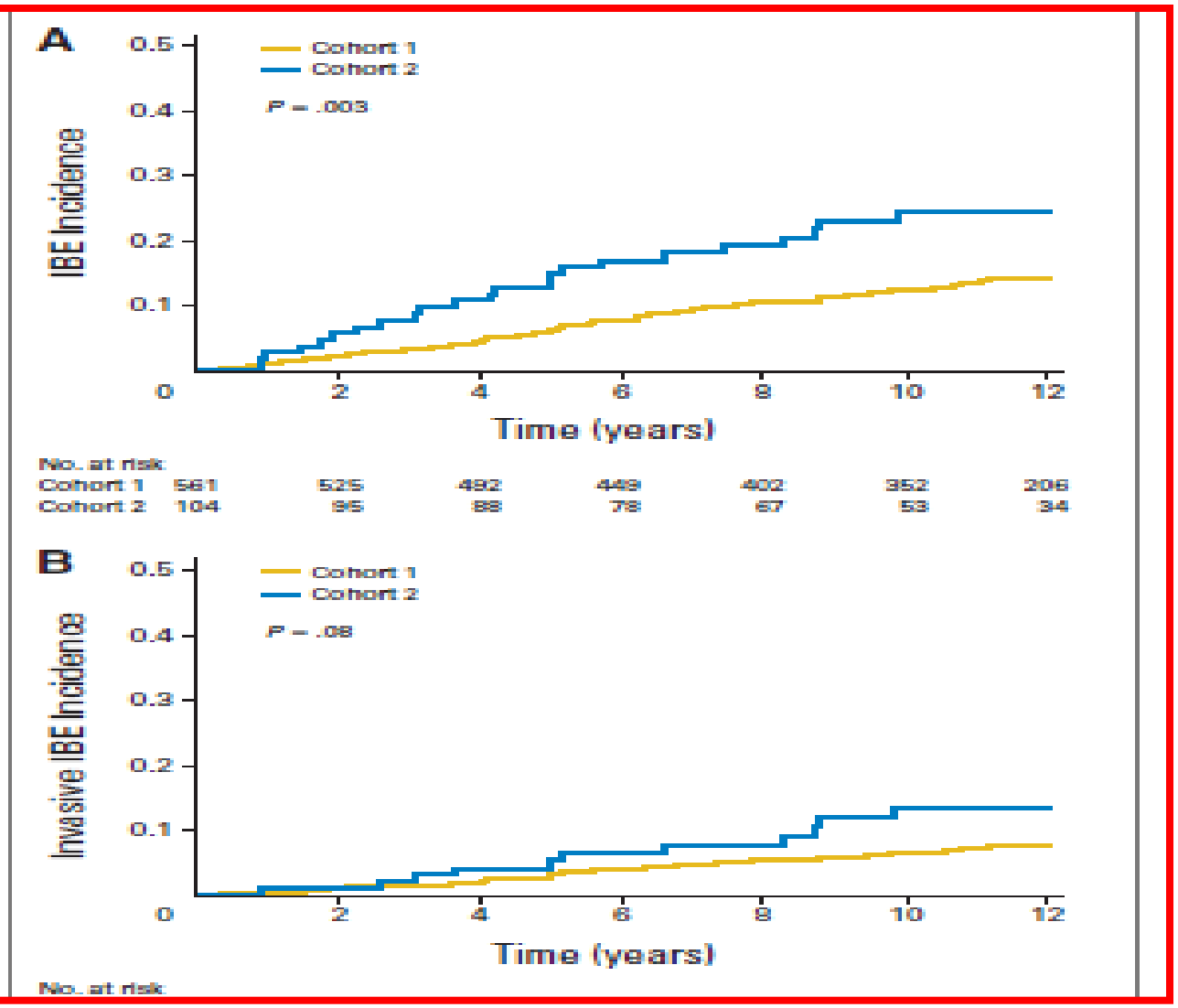
Rudloff U, J Clin Oncol 2010

ECOG-ACRIN E-5194

- Faz II, 665 düşük riskli hasta
- Düşük-orta grad, tm <2.5 cm (n= 561)
- Yüksek grad, tm <1 cm (n= 104)
- cs ≥3 mm
- Sadece MKC
- %30 hasta Tmx

Hughes LL, J Clin Oncol 2009
Solin LJ, SABCS 2012
Solin LJ, J Clin Oncol 2015

ECOG-ACRIN E-5194



10y	12y
12.5	14.4
24.6	24.6

Hughes LL, J Clin Oncol 2009
Solin LJ, SABCS 2012
Solin LJ, J Clin Oncol 2015

ECOG-ACRIN E-5194

- **500 hastada merkezi patoloji değerlendirmesi**

	12y IBE (%)	12y inv. nüks (%)
Düşük grad:	12.5	5.5
Orta dereceli:	15.1	6.7
Yüksek grad:	20.6	11.7

VNPI ve komedonekrozun prognostik önemi yok!!!!

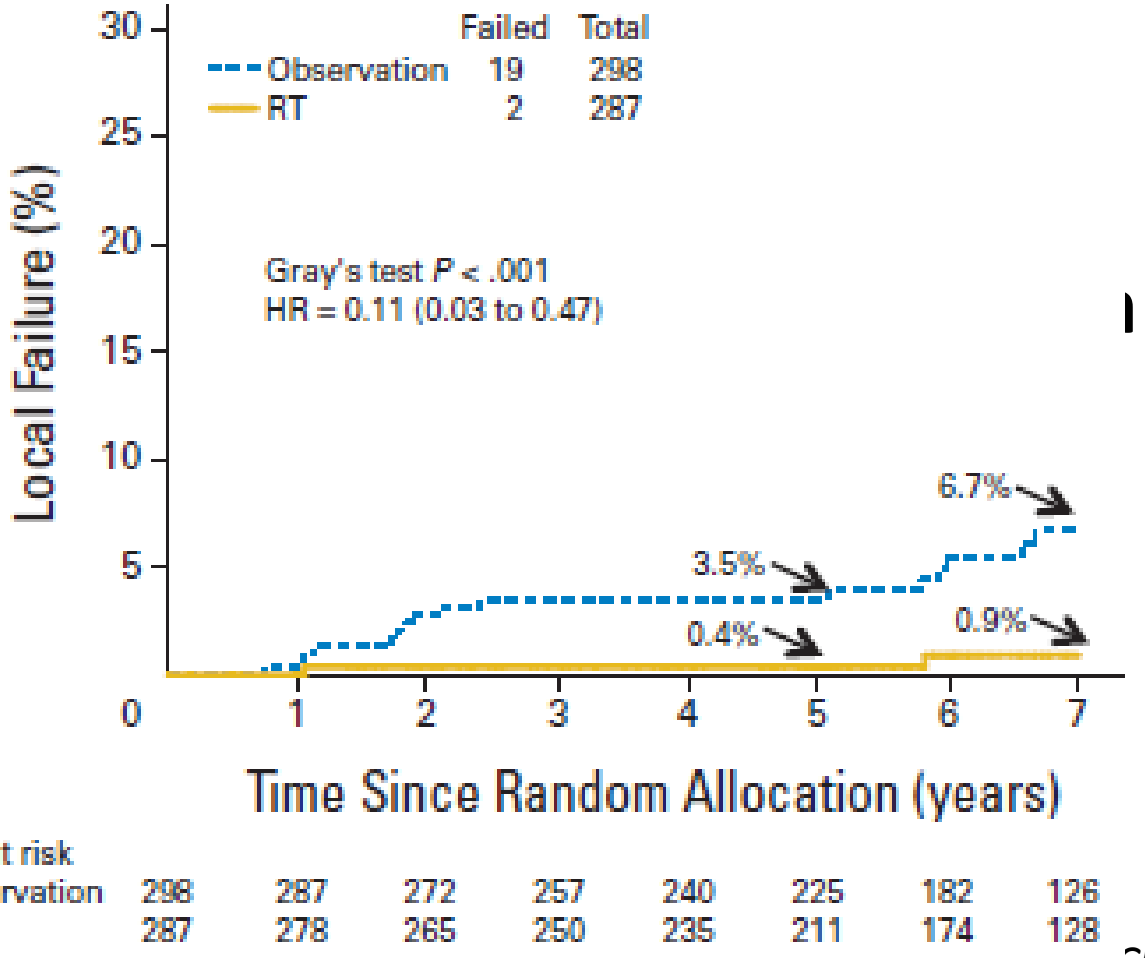
Harvard Serisi

- **Faz II, 158 hasta, tm ≤2.5 cm, Gr 1-2, cs ≥1 cm**
- **Sadece MKC**
- **Tmx yok**
- **Ortanca izlem: 11 yıl**
- **10y LR: %15.6**
  - **%68 DKIS**
  - **%32 invaziv**

Wong JS, Breast Cancer Res Treat 2014

RTOG 9804

- İyi r A
- Faz
- Düş
- Tmx
- İzle



Clin Oncol 2015

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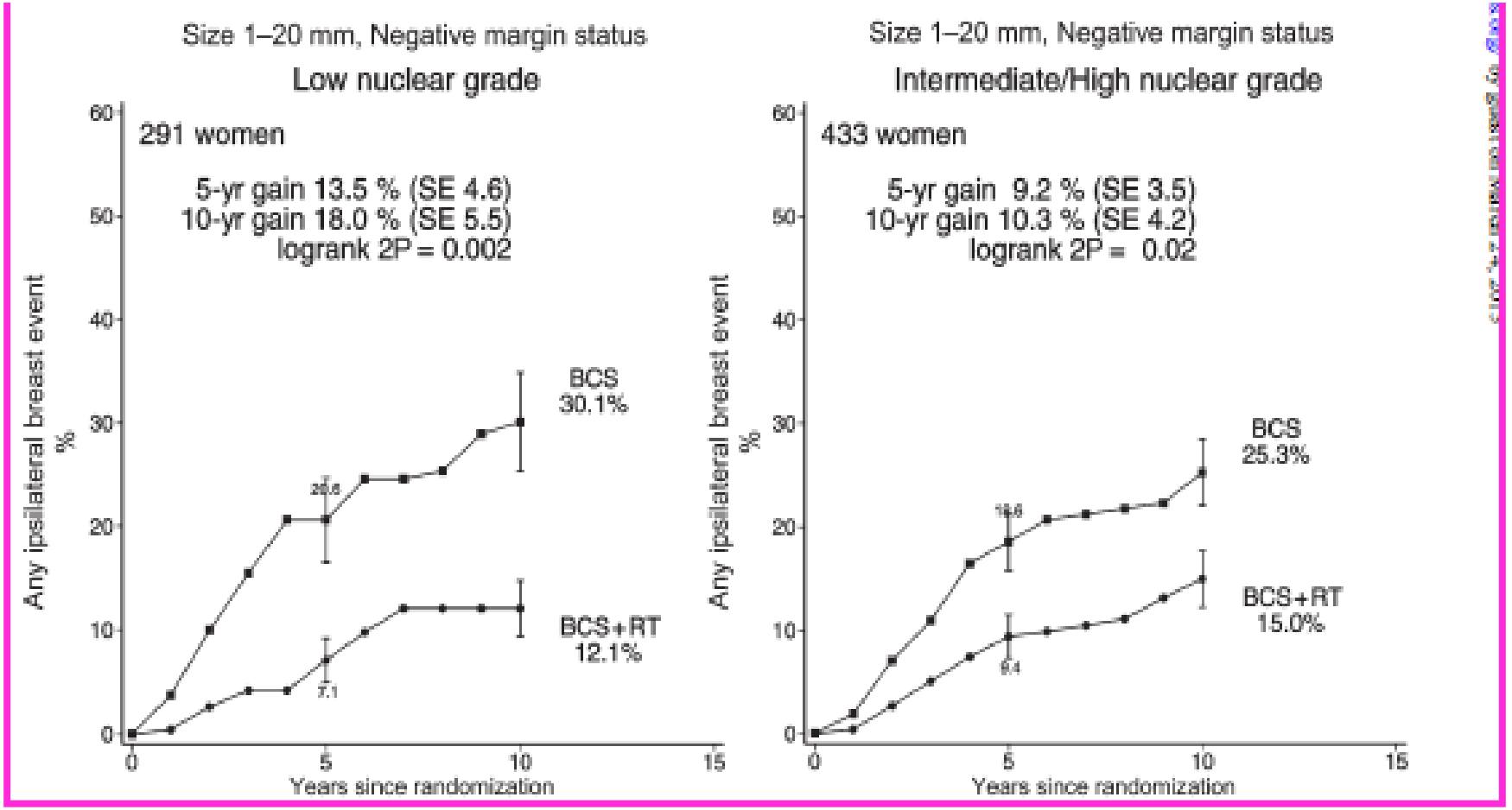
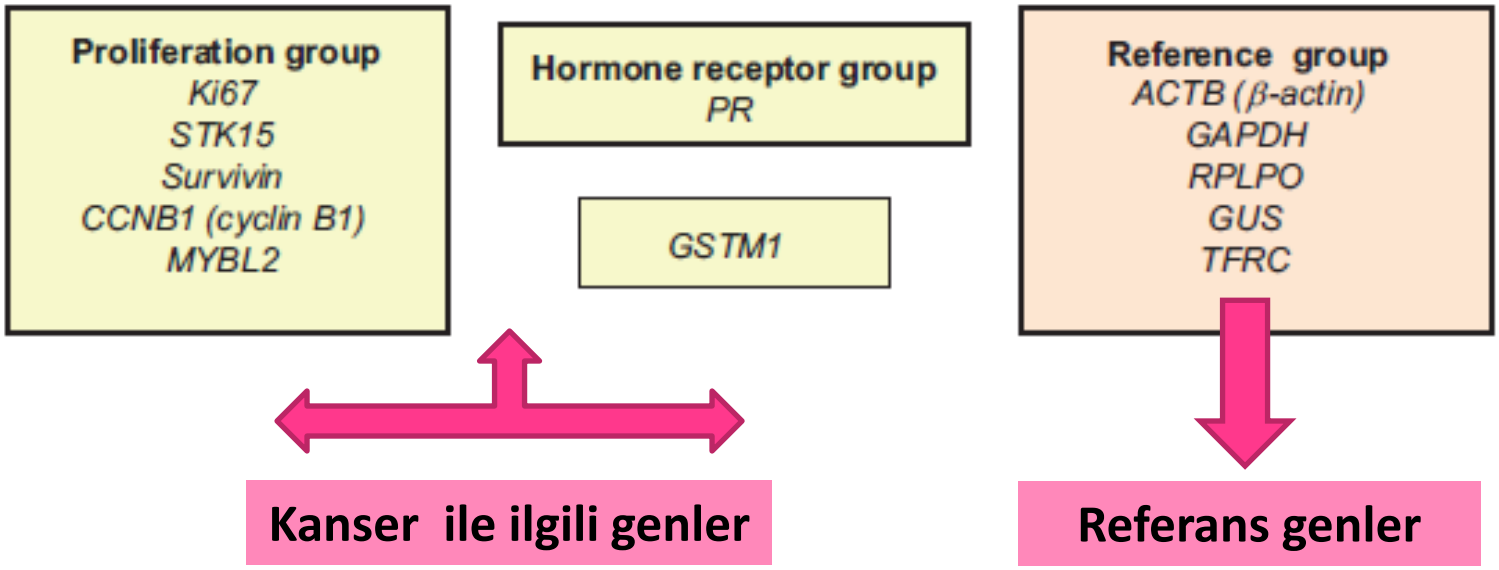


EBCTCG, JNCI Monogr 2010

Oncotype DX DCIS Score



$$\text{DCIS Score}_{\mu} = +0.31 \times \text{proliferation group score} - 0.08 \times PR - 0.09 \times GSTM1.$$

A Multigene Expression Assay to Predict Local Recurrence Risk for Ductal Carcinoma In Situ of the Breast

- **ECOG E5194**
- **327 hasta Oncotype DX RS**

		10y LR Riski	
DKIS risk skoru	**N**	**İpsilat nüks (DKIS+invaziv)**	**İnvaziv nüks**
Düşük (<39)	246	%10.6	%3.7
Orta (39-54)	45	%26.7	%12.3
Yüksek (≥55)	36	%25.9	%19.2
p değeri		0.02	0.01

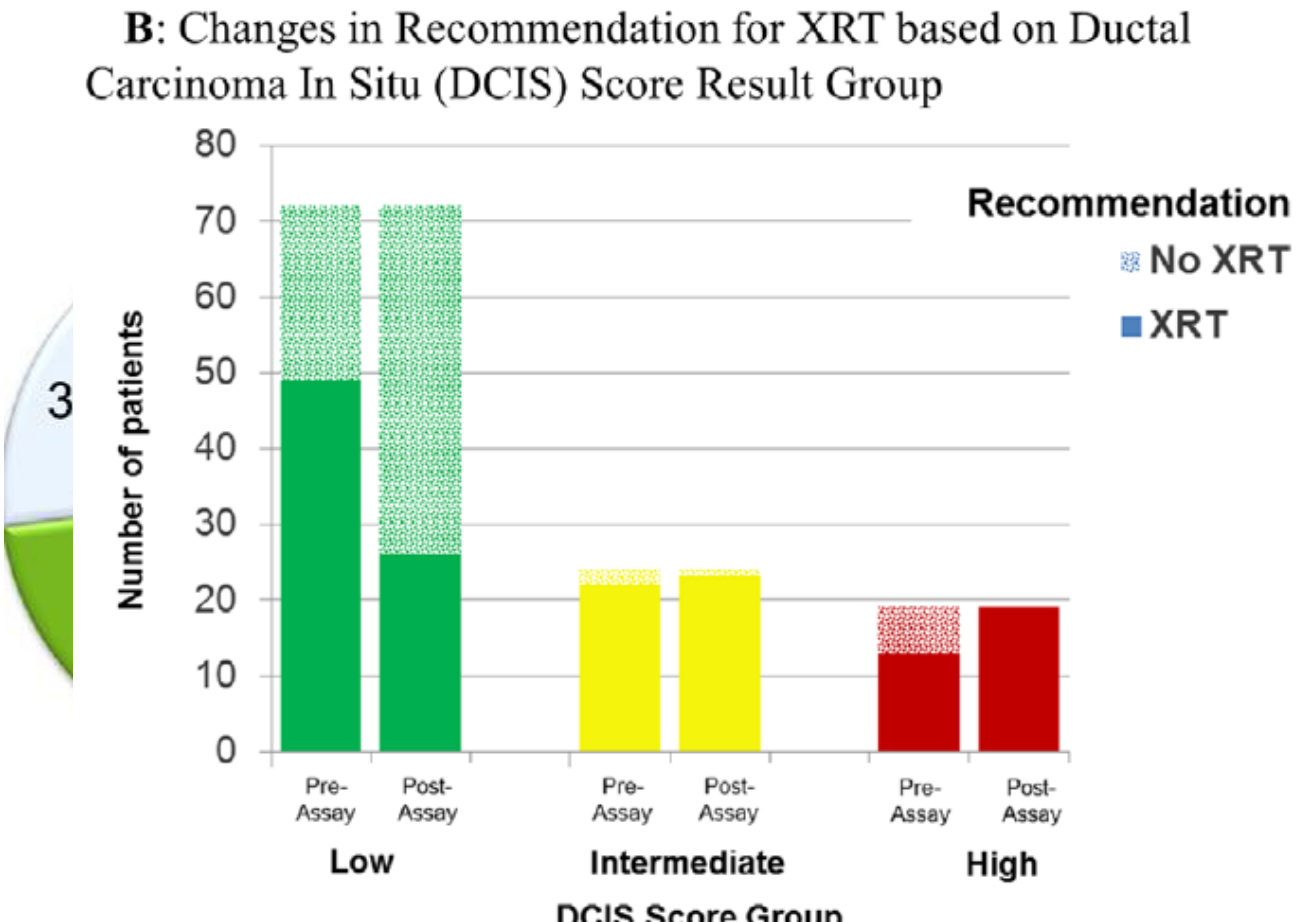
Solin J, J Natl Cancer Inst 2013

Journal of Surgical Oncology 2015;111:935–940

The Impact of Genomic Testing on the Recommendation for Radiation Therapy in Patients With Ductal Carcinoma In Situ: A Prospective Clinical Utility Assessment of the 12-Gene DCIS Score™ Result

MICHAEL ALVARADO, MD,[1] DENNIS L. CARTER, MD,[2] J. MICHAEL GUENTHER, MD,[3] JAMES HAGANS, MD,[4] RACHEL Y. LEI, BS, MA,[2] CHARLES E. LEONARD, MD,[5] JENNIFER MANDERS, MD,[6] AMY P. SING, MD,[7]* MICHAEL S. BRODER, MD,[8] DASHA CHEREPANOV, PhD,[8]* EUNICE CHANG, PhD,[8] MARIANNE EAGAN, MSc,[8] WENDY HSIAO, BS,[9] AND MICHAEL J. SCHULTZ, MD[10]

[1]University of California, San Francisco, California



Breast Cancer Res Treat (2015) 152:389–398
DOI 10.1007/s10549-015-3464-6

CLINICAL TRIAL

A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone

Eileen Rakovitch[1,2,3] · Sharon Nofech-Mozes[3,4] · Wedad Hanna[3,4] · Frederick L. Baehner[5,6] · Refik Saskin[2] · Steven M. Butler[5] · Alan Tuck[7] · Sandip Sengupta[8] · Leela Elavathil[9] · Prashant A. Jani[10,11] · Michel Bonin[12] · Martin C. Chang[3,13] · Susan J. Robertson[14] · Elzbieta Slodkowska[4] · Cindy Fong[2] · Joseph M. Anderson[5] · Farid Jamshidian[5] · Dave P. Miller[5] · Diana B. Cherbavaz[5] · Steven Shak[5] · Lawrence Paszat[1,2,3]

Received: 20 April 2015 / Accepted: 8 June 2015 / Published online: 29 June 2015

- **718 hasta, sadece MKC**
- **571 cs (-)**
- **İzlem: 9.6 yıl**
- **10 yıllık LR %19.2**

Characteristic	BCS alone ($N = 571$)
Age (median years)	61
Age category[a]	
<50 years	110 (19.3 %)
>50 years	459 (80.7 %)
Multifocality	
Absent/not reported	457 (80.0 %)
Present	114 (20.0 %)
Nuclear grade	
Low	55 (9.6 %)
Moderate	332 (58.1 %)
High	184 (32.2 %)
Comedo necrosis	
Absent	221 (38.7 %)
Present	350 (61.3 %)
Tumor size category	
Missing	281 (49.2 %)
>10 mm	140 (24.5 %)
≤10 mm	150 (26.3 %)
DCIS Score group	
Low	355 (62.2 %)
Intermediate	95 (16.6 %)
High	121 (21.2 %)
ER status	
Negative	30 (5.3 %)
Positive	541 (94.7 %)
HER2 Status	
Negative	420 (73.6 %)
Equivocal	51 (8.9 %)
Positive	100 (17.5 %)

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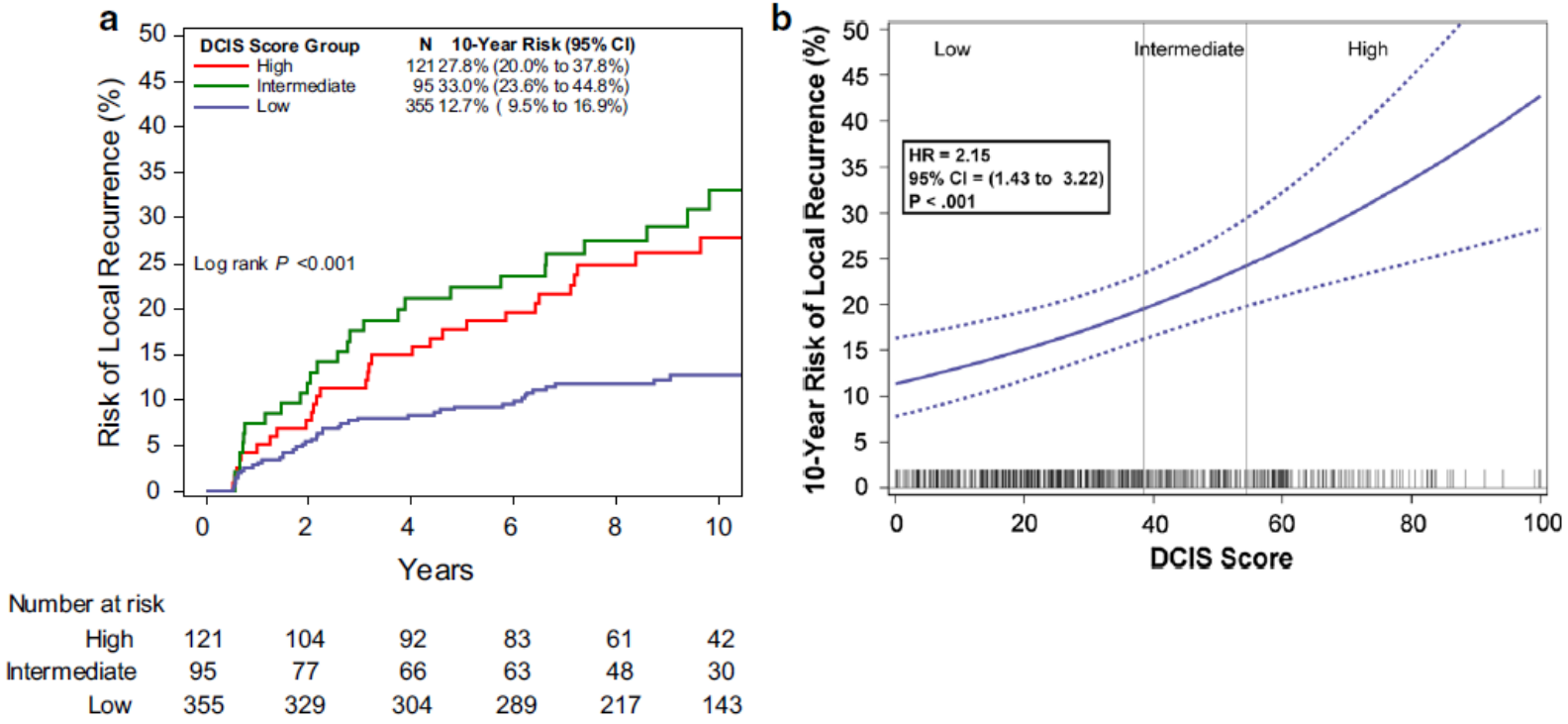
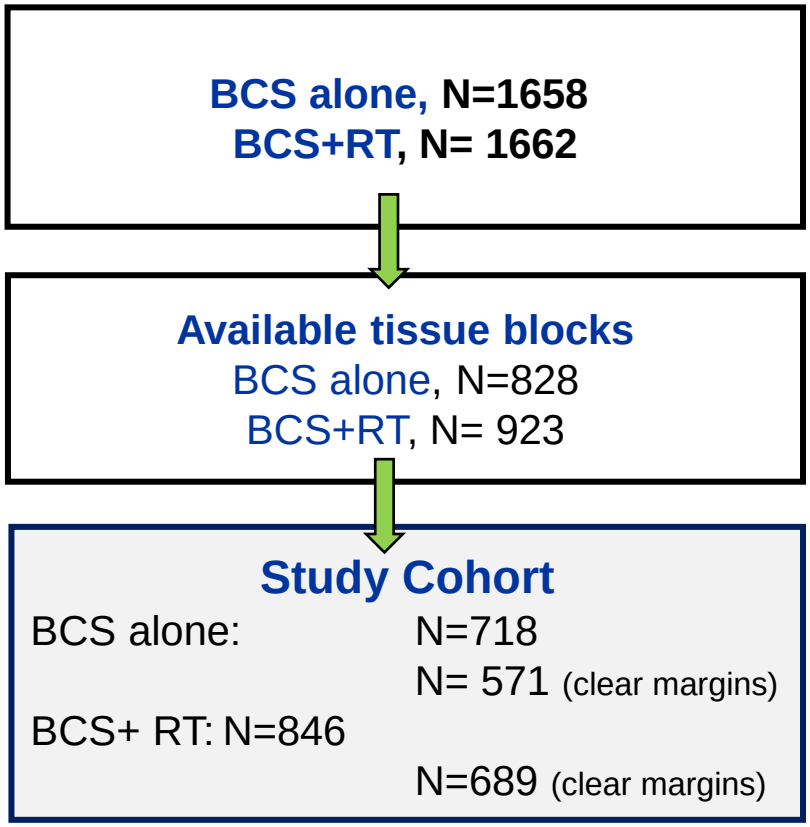


A Large Prospectively-Designed Study of the DCIS Score: Recurrence Risk After Local Excision For Ductal Carcinoma in Situ Patients With and Without Irradiation



Exclusions

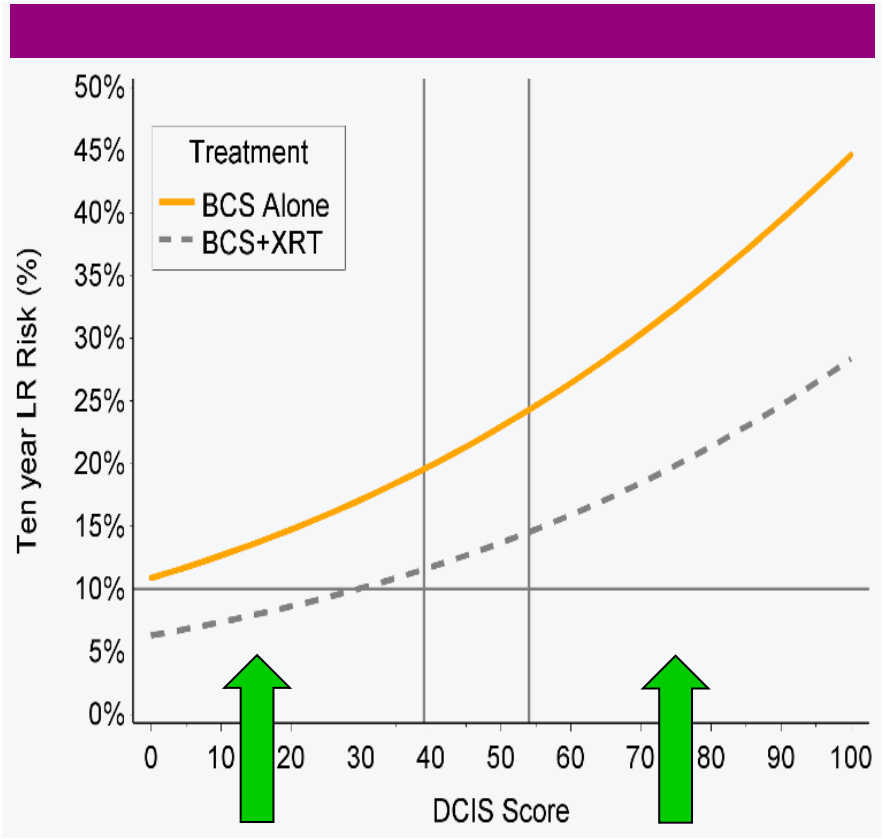
- No tumor (N=20)
- Invasive carcinoma (N=9)
- Insufficient RNA (n=108)
- Poor qPCR Sample Quality (N=49)

Rakovitch E, ASTRO 2015

A Large Prospectively-Designed Study of the DCIS Score: Recurrence Risk After Local Excision For Ductal Carcinoma in Situ Patients With and Without Irradiation

- **Ortanca izlem 9.6 yıl**
- **10 yıllık LR:**
  - **Yalnız MKC %19.2**
  - **MKC+RT %12.7**
- **DCIS skoru LR için prediktör**
  - Düşük riskli grupta daha faydalı
  - Yüksek riskli grupta; 50 yaş altı, >2.5 cm tm, multifokalite ve +/yakın cs da dikkate alınmalı

A Large Prospectively-Designed Study of the DCIS Score: Recurrence Risk After Local Excision For Ductal Carcinoma in Situ Patients With and Without Irradiation



- ✓ **Düşük riskte RT etkinliği az**
- ✓ **Yüksek riskte RT gerekli**

Tmx RT’nin Yerini Alabilir mi?

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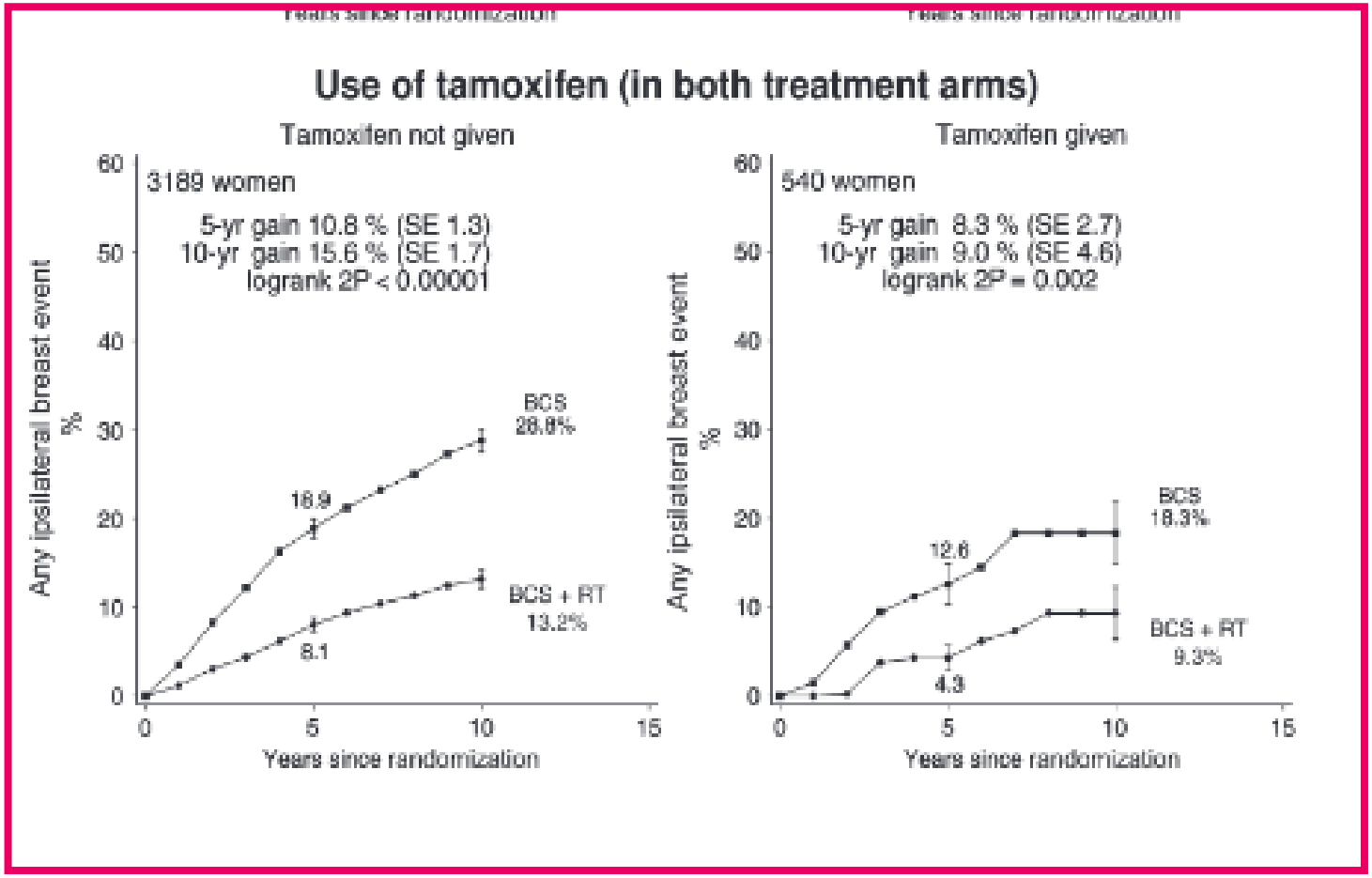

EBCTCG, JNCI Monogr 2010

UK/ANZ DCIS

- 1701 hasta, MKC, cs (-)

	İzlem vs.	Tmx vs.	RT vs.	RT+Tmx
5y olay	%22	%18	%8	%6
	Tüm meme olayı	İnsilat invaziv nüks	İnsilat DKIS nüks	Kontrlat meme olayı
RT	0.41	0.32	0.38	NSD
Tmx	0.71	0.95	0.70	0.44

Houghton J, Lancet 2003
Cuzick et al., Lancet Oncol 2011

RESEARCH ARTICLE Open Access

Long-term outcomes of ductal carcinoma in situ of the breast: a systematic review, meta-analysis and meta-regression analysis

Kirsty E. Stuart[1,2,3*], Nehmat Houssami[4], Richard Taylor[1,5], Andrew Hayen[5] and John Boyages[1,6]

	LR (%)
MKC	25.1
MKC+Tmx	24.7
MKC+RT	14.1
MKC+RT+Tmx	9.7

BMC Cancer 2015

Anastrozol vs Tmx

- NSABP B-35
- IBIS-2

- Postmenopozal
- ER pozitif DKIS
- Lumpektomi + RT
- Anastrozol 1 mg/gün vs Tmx 20 mg/gün
- 5 yıllık tedavi

Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial

Lancet, December 2015

Richard G Margolese, Patrick W Whitworth, Timothy F Wozniak, ... bacher, Keren Sturtz,

	Tamoxifen (n=1538)	Anastrozole (n=1539)	Hazard ratio (95% CI)	p value
All breast cancers				
Total	122	90	0·73 (0·56–0·96)	0·0234
Invasive	69	43	0·62 (0·42–0·90)	0·0123
Ductal carcinoma in situ	53	47	0·88 (0·59–1·30)	0·52
Ipsilateral recurrence				
Total	55	46	0·83 (0·56–1·22)	0·34
Invasive	22	17	0·76 (0·40–1·43)	0·39
Ductal carcinoma in situ	33	29	0·87 (0·53–1·43)	0·59
Contralateral breast cancer				
Total	60	39	0·64 (0·43–0·96)	0·0322
Invasive	40	21	0·52 (0·31–0·88)	0·0148
Ductal carcinoma in situ	20	18	0·90 (0·47–1·69)	0·73
Breast cancer at distant sites	7	4	0·57 (0·17–1·95)	0·37
Breast second primary cancer*	0	1	..	..

*Angiosarcoma in the ipsilateral breast.

Table 2: **Breast cancer first events**

Breast
<60 ye
≥60 ye
Diseas
<60 ye
≥60 ye
Table 3:

HR=hazard ratio.

Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial

Lancet, December 2015

*John F Forbes, Ivana Sestak, Anthony Howell, Bernardo Bonanni, Nigel Bundred, Christelle Levy, Gunter von Minckwitz, Wolfgang Eiermann, Patrick Neven, Michael Stierer, Chris Holcombe, Robert E Coleman, Louise Jones, Ian Ellis, Jack Cuzick, on behalf of the IBIS-II investigators**

	Tmx	Anastrozol
• 5y rekürrens:	%3	%2.5
• 10y rekürrens:	%7.3	%6.6

- **Anastrozol, Tmx'den üstün değildir (p=0.49)**

Hipofraksiyone RT’nin Rolü?

RT Şeması

- **Standart yaklaşım: 50 Gy/25 fr**

- **Erken evre invaziv Ca: Hipofraksiyone RT**
  - **Lokal kontrol, HS ve kozmetik sonuç benzer**

Whelan TJ, New Engl J Med, 2010

Haviland JS, START, Lancet Oncol 2013

Spooner D, J Clin Oncol 2012

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

- **13 çalışma**
- **CFRT vs HFRT**
  - **LR farkı yok**

Author, year	Country	No of patients	Median follow-up	Total dose/fraction (standard)	Total dose/fraction (hypofractionated)
Hathout L, 2013	Canada	440	4.4 yrs	–	42.5 Gy/16 fr
Julian TB, 2011	USA	1569	14.2 yrs	50 Gy/25 fr	–
Kim JH, 2014	Korea	728	82 mo	50.4*/28 fr	–
Lalani N, 2014	Canada	1609	9.2 yrs	50 Gy/25 fr	40–44 Gy/16 fr
Meattini I, 2013	Italy	389	7.7 yrs	50 Gy/25 fr	–
Omlin A, 2006	USA	373	72 mo	50* Gy/25 fr	–
Rakovitch E, 2013	Canada	1895	10 yrs	50 Gy/25 fr	40–44 Gy/16 fr
Tunon-de-Lara C, 2010	France	66	160 mo	50 Gy/25 fr	–
Vidali C, 2012	Italy	586	136 mo	50* Gy/25 fr	–
Wai ES, 2011	Canada	482	9.3 yrs	50 Gy/25 fr	44 Gy/16 fr
Williamson D, 2010	Canada	266	3.76 yrs	50 Gy/25 fr	42.4 Gy/16 fr or 40 Gy/16 fr
Wong P, 2012	Canada	220	46 mo	50 Gy/25 fr	45 Gy/20 fr or 42.5 Gy/16 fr
Yerushalmi R, 2006	Israel	75	81.5 mo	50 Gy/25 fr	–

Nilson C, Radiother Oncol 2015

Tm Yatağına Ek Doz Gerekli mi?

Tm Yatağına Ek Doz

- **Yayınlanmış prospektif randomize çalışma yok**
  - **Fransız BONBIS**
  - **TROG 07.01**

- **Retrospektif çalışmalar:**
  - **Genç yaş**
  - **Yüksek grad/komedonekroz**
  - **Yakın/+cs varlığında yararı olabilir**

Omlin A, Lancet Oncol 2006
Julian TB, J Clin Oncol 2008
Wong P, IJROBP 2012
Rakowitch E, IJROBP 2013

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journal homepage: www.thegreenjournal.com

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The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS: A meta-analysis of observational studies

Ek dozun katkısı yok

ANCAK .....

Cerrahi sınır pozitifliğinde rekürrens riskinde anlamlı azalma sağlar!

Risk %50 ↓

Nilson C, Radiother Oncol 2015

RT’ye bağlı yan etkilerden korkmalı mı?

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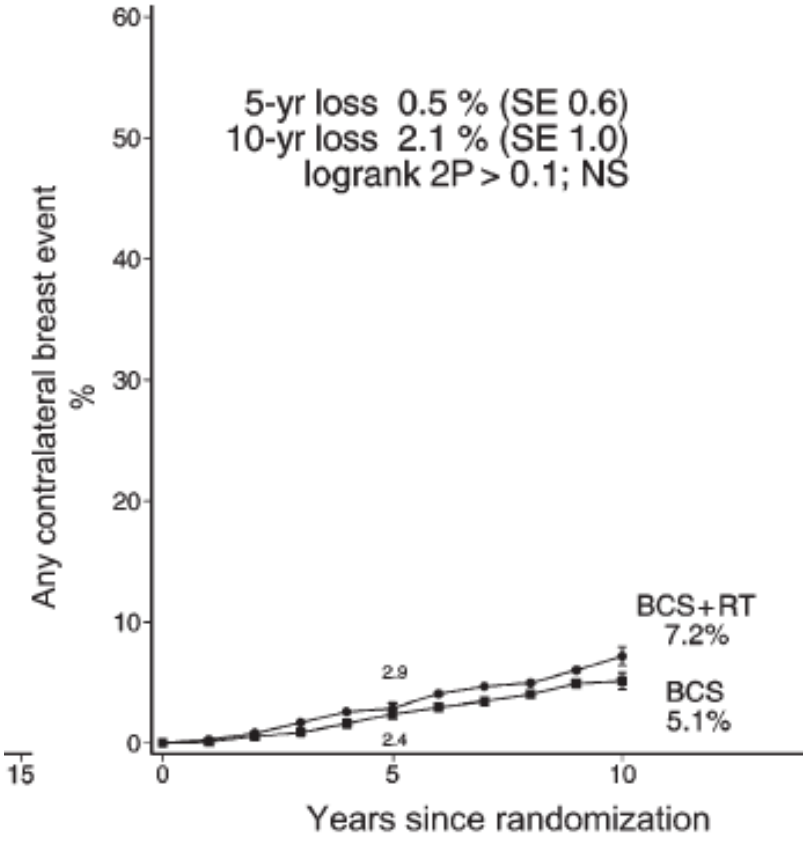
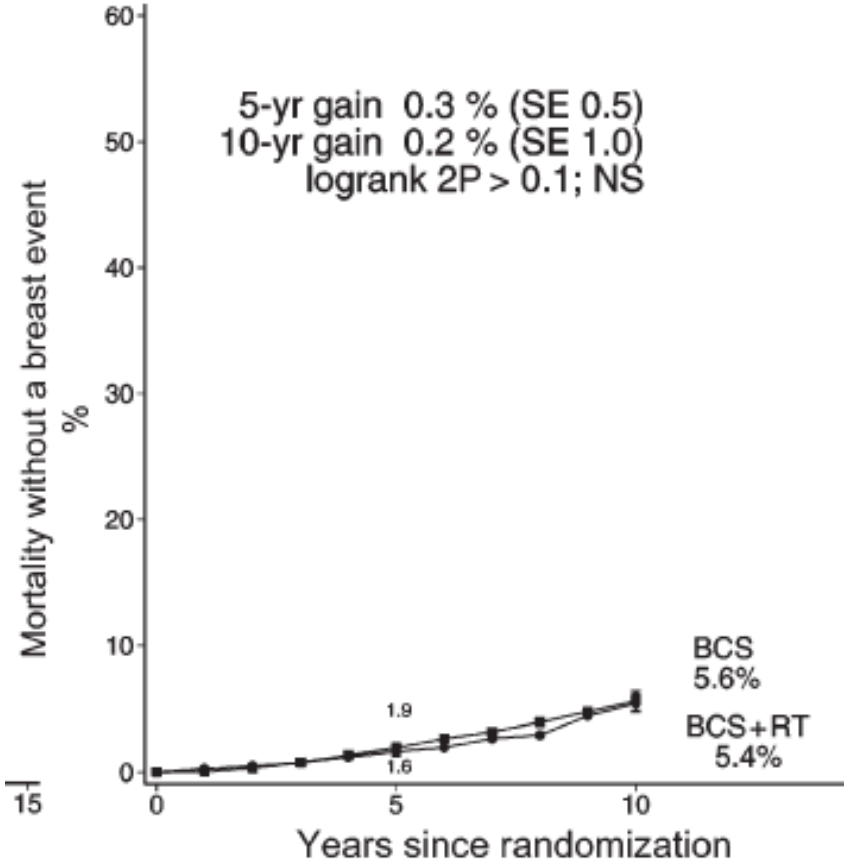


Karşı Meme Kanseri



Ölüm: Diğer

Cardiovascular Morbidity and Mortality After Treatment for Ductal Carcinoma In Situ of the Breast

Naomi B. Boekel, Michael Schaapveld, Jourik A. Gietema, Emiel J. T. Rutgers, Michel I. M. Versteegh, Otto Visser, Berthe M. P. Aleman, Flora E. van Leeuwen

Manuscript received January 2, 2014; revised April 21, 2014; accepted May 8, 2014.

Correspondence to: Flora E. van Leeuwen, PhD, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands (e-mail: f.v.leeuwen@nki.nl).

Background Recent concerns about potential overdiagnosis and overtreatment of ductal carcinoma in situ of the breast (DCIS) render evaluation of late effects of treatment, such as cardiovascular disease (CVD), of great importance. We studied cardiovascular morbidity and mortality in a large population-based cohort of DCIS patients.

Methods Data on all incident DCIS case patients in the Netherlands between 1989 and 2004 who were diagnosed before the age of 75 years were obtained (n = 10468). CVD data was acquired through linkage with population-based registries. Standardized mortality ratios were calculated by comparing mortality in our cohort with that in the Dutch

10 yıllık izlemde, RT:
Kardiyovasküler morbidite/mortalite riskini arttırmaz.

between treatment groups (left-sided vs right-sided radiotherapy: HR = 0.94; 95% CI = 0.68 to 1.29).

Conclusions After a median follow-up of 10 years, we did not find an increased risk for cardiovascular morbidity or mortality after radiotherapy for DCIS when comparing surgery and radiotherapy vs surgery only, nor when comparing radiotherapy for left-sided vs right-sided DCIS. Compared with the general population, DCIS patients have a decreased risk of cardiovascular death, independent of treatment.

JNCI J Natl Cancer Inst (2014) 106(8): dju156 doi:10.1093/jnci/dju156

Özetle...

- **Standart tedavi: MKC + Tüm meme RT**
- **MKC sonrası RT almayacak grubu belirlemede klinik ve patolojik faktörler yetersiz**
- **Oncotype DX: Düşük riskte sadece MKC olabilir ancak faz III çalışmalar ve uzun izlem gerekli**
- **Tmx RT'nin yerini alamaz**
- **ER+ → Adjuvan Tmx/Anastrozol**

- **Risk/yarar analizi ve hasta tercihine göre tedavi kararı verilmelidir**

TEŞEKKÜRLER!