Okkült ve İnsitu Meme Kanseri'nde Cerrahi

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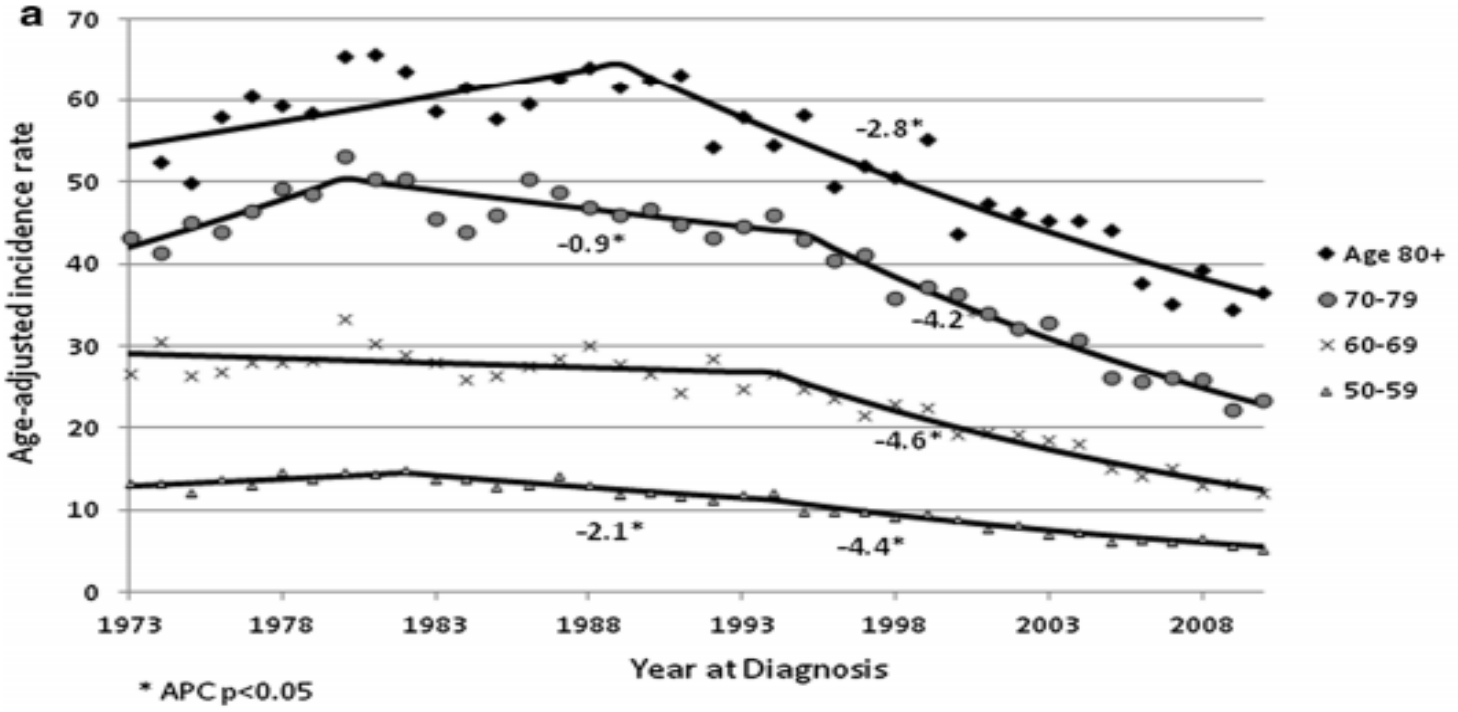
SBÜ Gülhane EAH Genel Cerrahi Kliniği

Okkült Meme Kanseri

- Memedeki primer odağın bilinmediği/bulunamadığı, aksiller bölgedeki lenf bezi metastazı ile tanı alan meme kanserleri
- % 0,3-1 tüm meme kanserleri içinde*



- * Toss A, Chin Clin Oncol. 2019,8. **Mnatsakanyan E, Cancer Causes Control. 2014.25.

- Primer meme kanserinin radyolojik ve patolojik değerlendirmesi ile ekarte edilmesi sonrası adlandırma,
- Mamografi ve USG ile saptanamayan lezyonların MRI ile değerlendirilmesi,*
- Aksiller lenf nodunun kalın iğne biyopsisi ile değerlendirilmesi, patoloğun değerlendirmesi için yetersiz ise biyopsi tekrarı, eksizyonel biyopsi, ..
- Artmış ER/PR meme kanseri tanısı için faydalı, HER2 çalışılmalı
- Evreleme yapılmalı? Metastaz taraması? Kemik, Akciğer, Abdomen

- *Olson JA, Ann Surg Oncol. 2000 Jul;7

- ***T0, N1, M0** 1) Mastektomi+ ALND+/- Postmastektomi RT
- 2) ALND + tüm meme RT+/- Aksilla Rt
- Sistemik kemoterapi, hormonoterapi, transtuzumab vb

- ***T0, N2, M0** Neoadjuvan kemoterapi+Mastektomi ile birlikte ALN+RT
- Hormonoterapi

- *https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Table 4

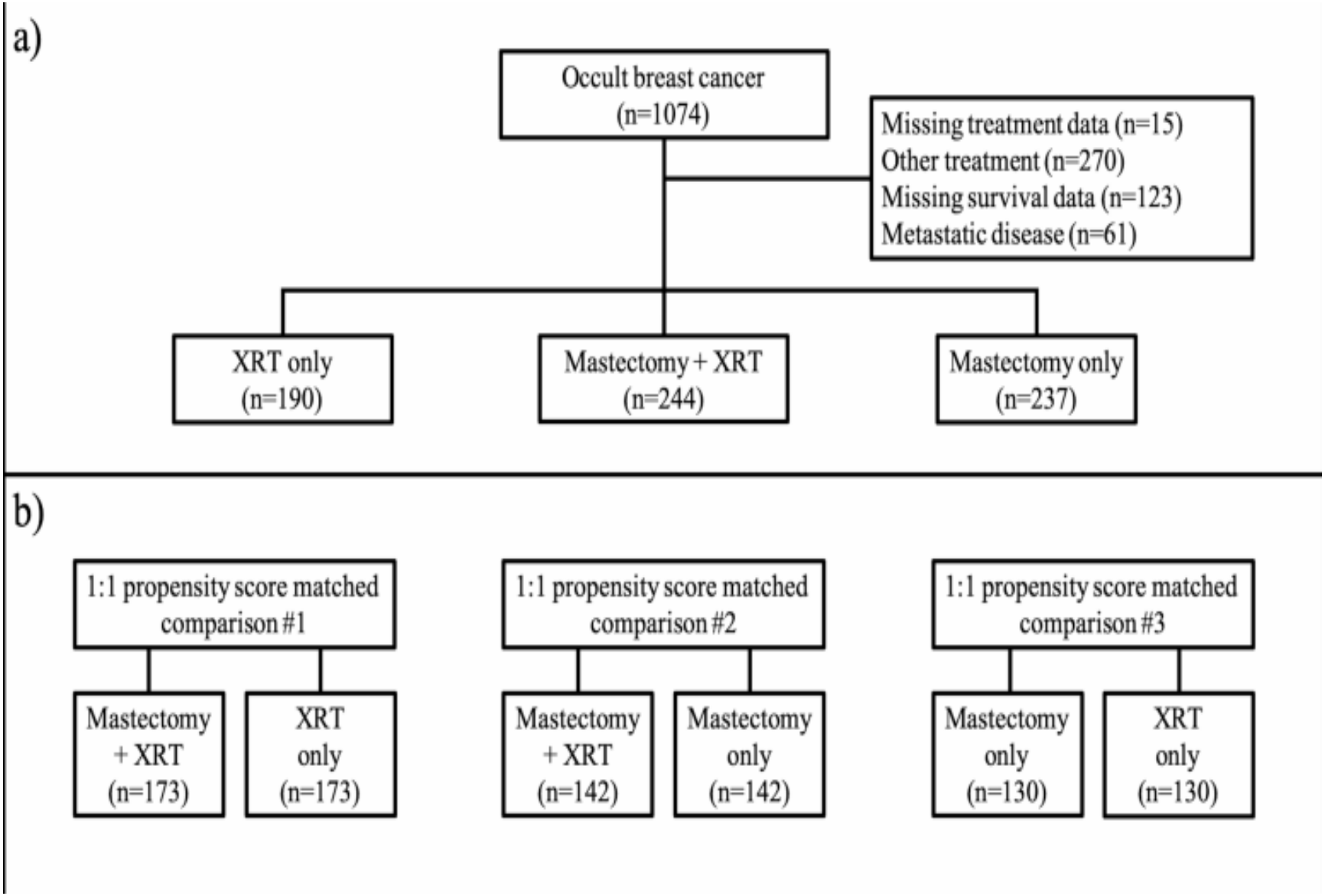
Prognostic factors for disease-free survival.

Characteristics		5-yr DFS (%)	10-yr DFS (%)	Univariate	Multivariate[a]	HR (95% CI)
Age	≤50 (n = 28)	89.1	77.8	0.58	–	–
	>50 (n = 38)	94.4	81.0			
Number of metastatic nodes	≤4 (n = 39)	97.3	84.1	0.19	–	–
	>4 (n = 27)	85.2	74.5			
Nodal location	ALN only (n = 54)	96.1	87.7	0.02	0.01	5.9 (1.4–25.5)
	ALN + SCN/IMN (n = 12)	75.0	60.0			
Surgery for breast	Not performed (n = 51)	91.7	82.1	0.92	–	–
	Performed (n = 15)	93.3	77.8			
Radiotherapy to breast	Not performed (n = 3)	100.0	0.0	0.02	–	–
	Performed (n = 63)	91.7	89.5			
HR + subtype	No or unknown (n = 38)	91.6	73.7	0.30	–	–
	Yes (n = 28)	90.6	92.9			
Taxane-based CTx	Not received (n = 14)	100.0	100.0	0.15	–	–
	Received (n = 52)	85.9	80.6			

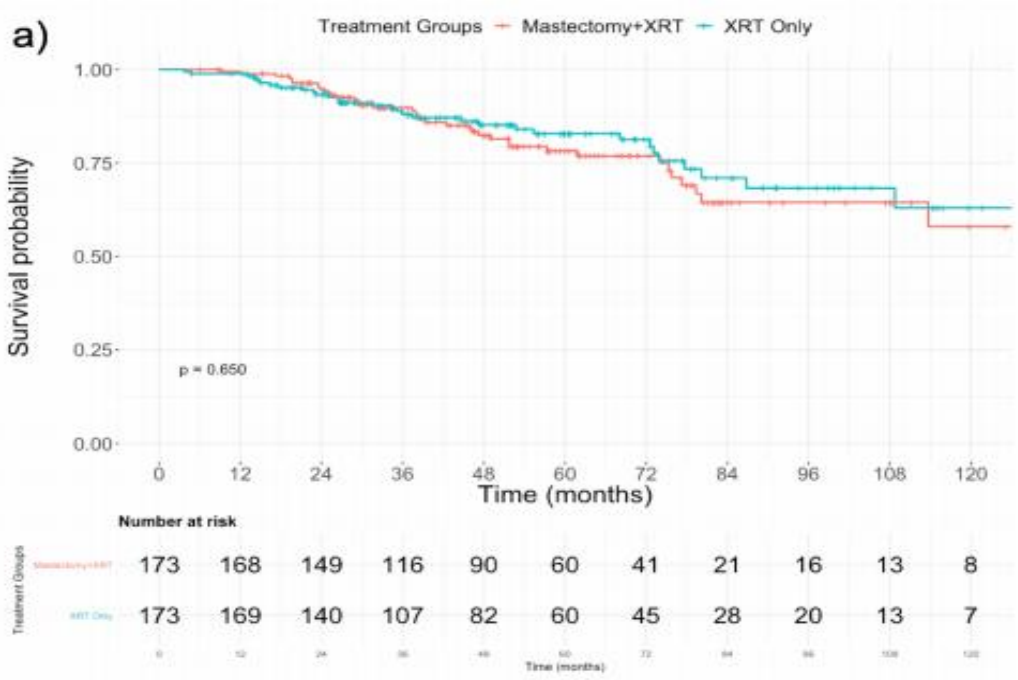
Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; LNs, lymph nodes; ALN, axillary lymph nodes; SCN, supraclavicular lymph nodes; IMN, internal mammary lymph nodes; HR+, hormone-receptor positive; CTx, chemotherapy.

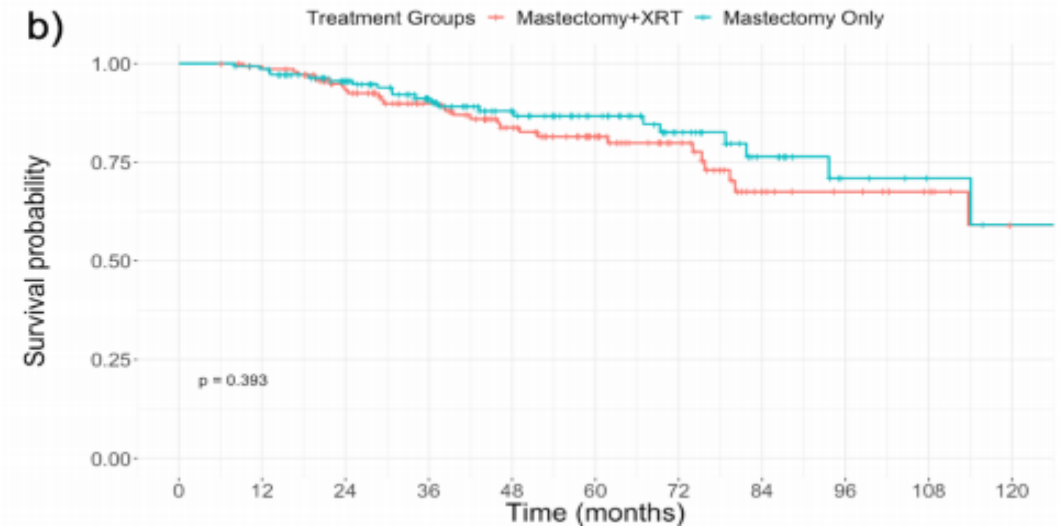
[a] Variables with significance at $p < 0.05$ on univariate analysis were retained for multivariate analysis.

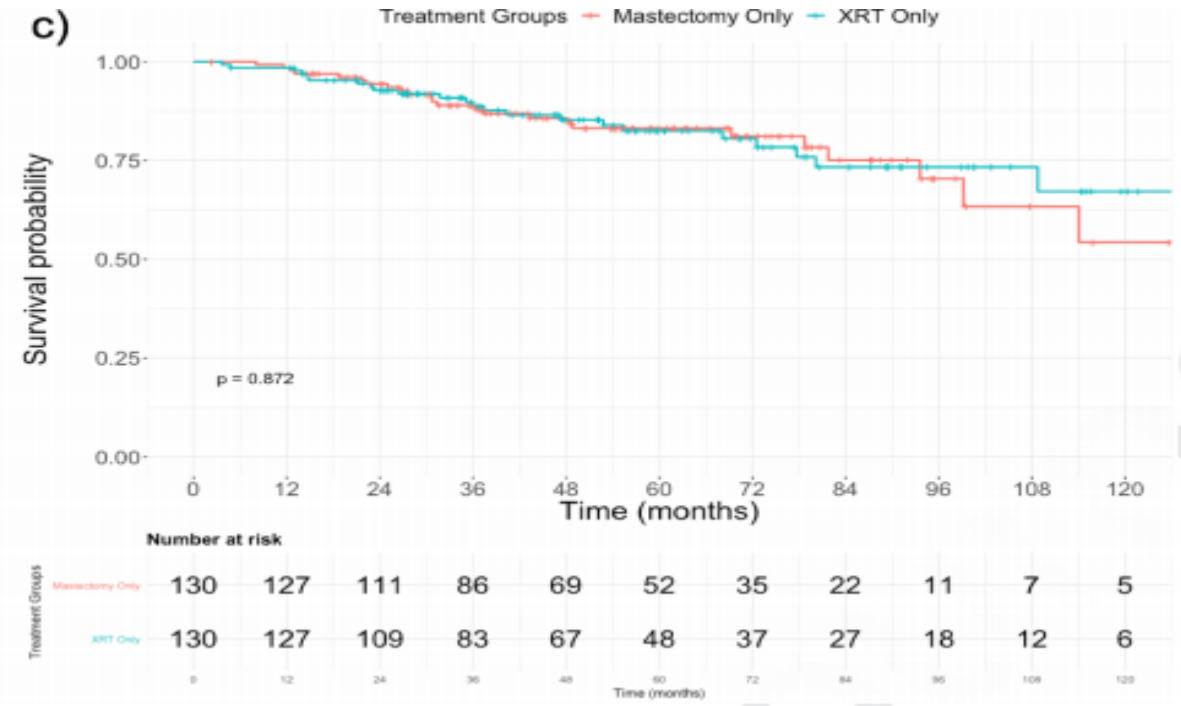
- * Kim H, The Breast, 2020, 49.



- * Tsai C, Am J Surg. 2019 Nov 11


a)
Treatment Groups
Mastectomy+XRT
XRT Only
1.00
0.75
0.50
0.25
0.00
Survival probability
p = 0.650
0
12
24
36
48
60
72
84
96
108
120
Time (months)
Number at risk
173 168 149 116 90 60 41 21 16 13 8
173 169 140 107 82 60 45 28 20 13 7

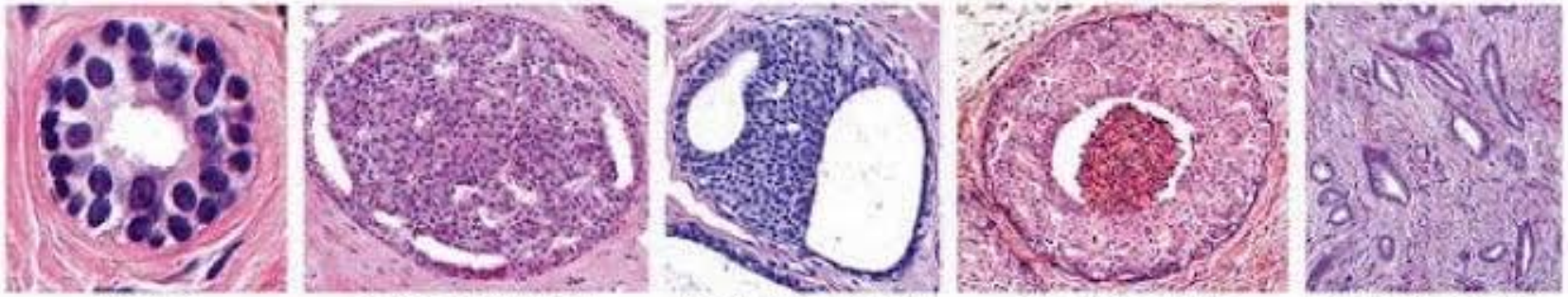

b)
Treatment Groups
Mastectomy+XRT
Mastectomy Only
1.00
0.75
0.50
0.25
0.00
Survival probability
p = 0.393
0
12
24
36
48
60
72
84
96
108
120
Time (months)



- Sağ kalım açısından fark yok,
- ALND sonrası RT yeterli olduğunu,

- Duktal Karsinoma in Situ (DKİS) memenin duktuslarından kaynaklanan ve bazal membranı aşmamış (invazyon yapmamış), morfolojik, genetik ve klinik davranış olarak **heterojen** bir grubu temsil eden prekürsör neoplastik hücre proliferasyonu

- DKİS: TisN0M0



Accumulation of genetic and epigenetic changes

Abnormal response to growth factors (e.g., estrogen receptor)

Abnormal oncogene expression (e.g., *HER2/neu*)

Tissue invasion (gain of function by malignant cells vs. loss of function of normal cells)

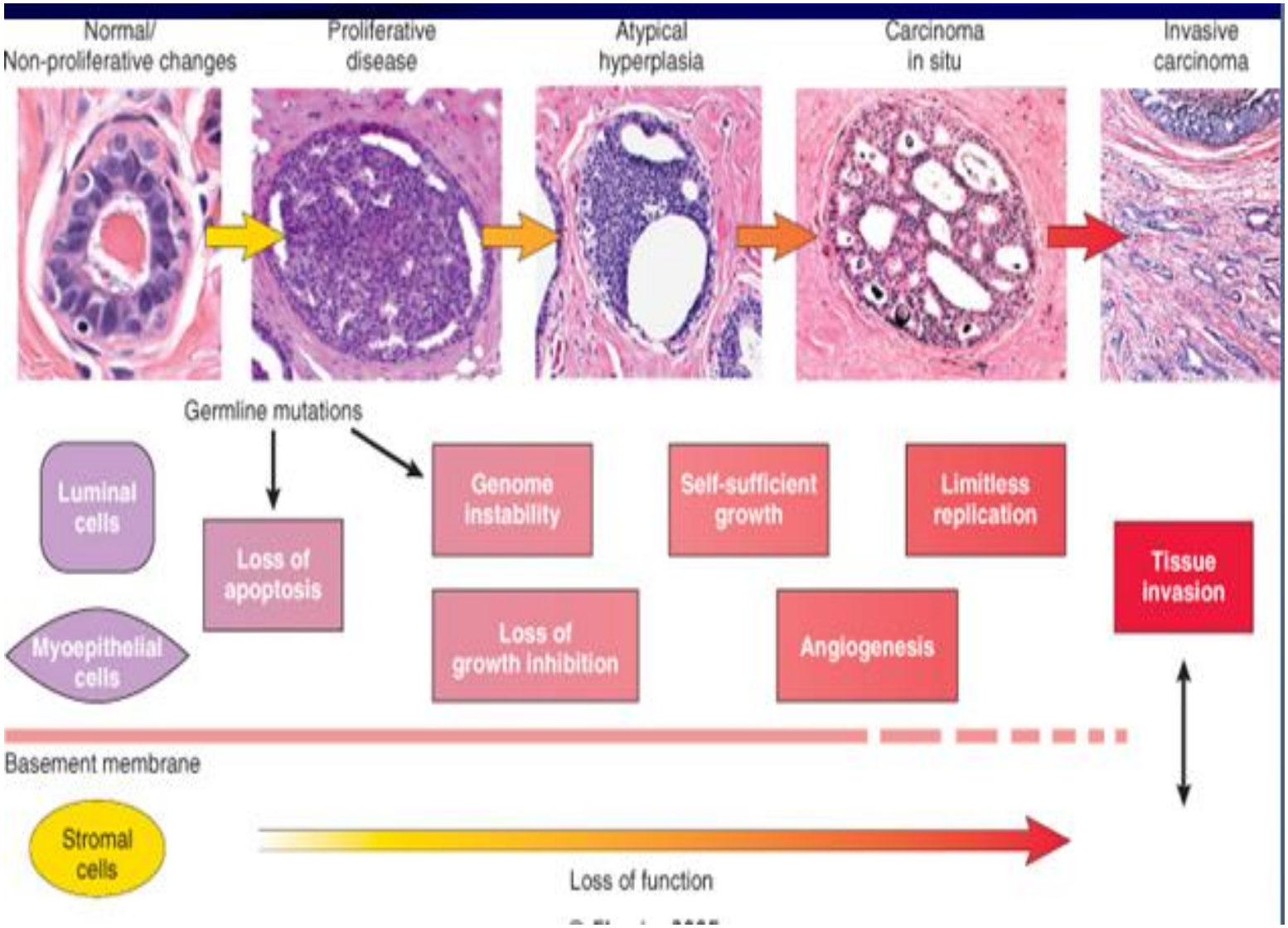
Loss of tumor-suppressor function (e.g., p53)

Stromal changes (e.g., angiogenesis)

Failure to respond to normal signals for apoptosis

Genetic instability (e.g., loss of heterozygosity)

Clinical phenotype of tumor determined


Normal/
Non-proliferative changes
Proliferative
disease
Atypical
hyperplasia
Carcinoma
in situ
Invasive
carcinoma
Germline mutations
Luminal
cells
Myoepithelial
cells
Loss of
apoptosis
Genome
instability
Loss of
growth inhibition
Self-sufficient
growth
Angiogenesis
Limitless
replication
Tissue
invasion
Basement membrane
Stromal
cells
Loss of function

- Metastatik olmadığı

Table 1. Prevalence of occult DCIS in autopsy studies

Study	Population/ Timeframe	Number	Median Age	Occult DCIS		Invasive Breast Cancer	
				#	%	#	%
Kramer, 1973[169]	Autopsy series before 1972	70	79	3	4.3	1	1.4
Nielsen, 1984[170]	Autopsy series 1976-1977	77	NR	11	14.3	1	1.3
Alpers, 1985[171]	Autopsy series before 1984	101	57	9	8.9	NR	
Bhathal, 1985[172]	Autopsy series before 1985	207	60	25	12.0	3	1.5
Bartow, 1987[173]	Autopsy series 1978-1983	490	39	1	<1	5	3.3
Nielsen, 1987[174]	Autopsy series 1983-1984	109	39	1	<1	5	1

- İnvaziv kansere progresyon olguların %13- 50'sinde gerçekleşir*

- Tedavi de amaç tedavi ile birlikte **invaziv kanser olarak nüksün önlenmesi,**

- Tedavi planlanmasında; Hangi DKİS lezyonunun progresyon göstereceğini saptamak zor

- Kümülatif meme kanseri mortalitesi, DKİS tanısı aldıktan 10 yıl sonra % 2.3 < 50 yaş, 1,4 > 50 yaş**

- * Page DL, Cancer, 1995.76.
- ** Elshof LE, Ann Surg. 2018, 267.

İnsidans

- Tarama mamografisinin kullanımı ile son 20 yıl içinde insidansta artış
- 1994 yılında 100.000'de 22.31 iken 2014 yılında 34,43 olarak raporlanmış, mamografi ile saptanan meme hastalıklarının %15-30'u DKİS*

- *Howlader N, SEER Cancer Statistics Review, National Cancer Institute.

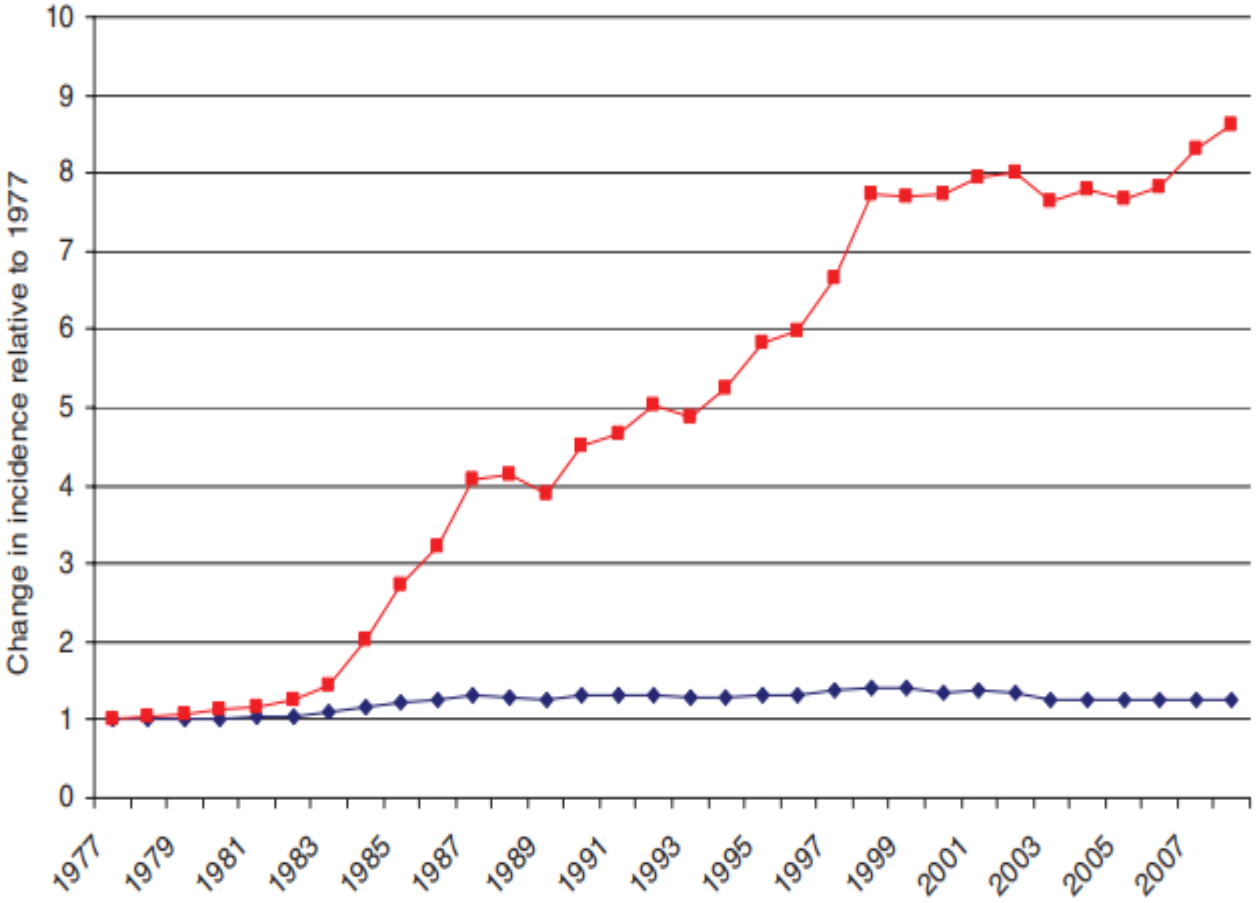
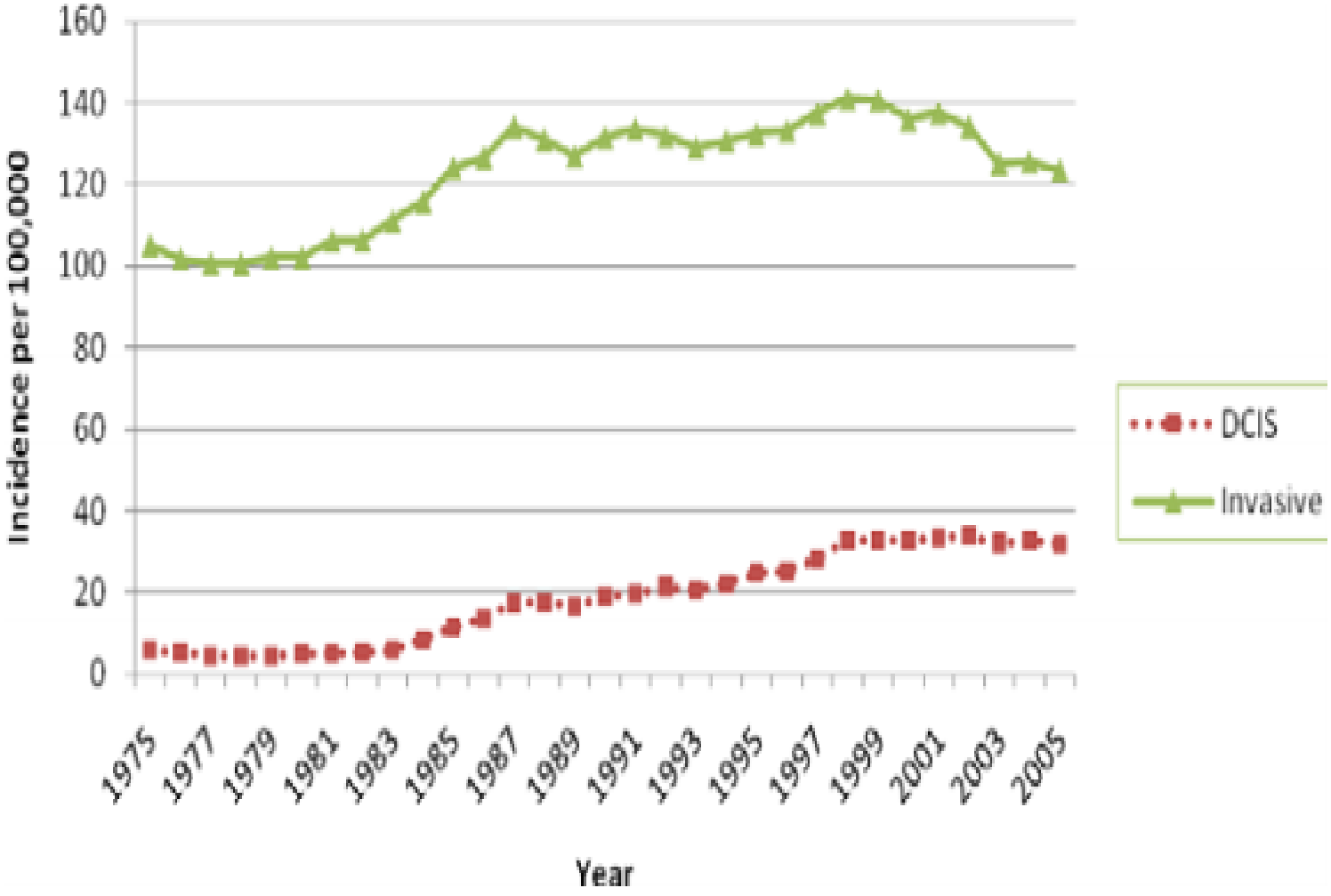


Figure 1. Change in age-adjusted incidence of invasive breast cancer (**blue diamonds**) and ductal carcinoma in situ (DCIS) relative to the number of diagnoses in 1977, revealing the marked increase in DCIS diagnoses over the past 30 years and the relative stability of invasive breast cancer diagnoses over the same period. Source: all registries of the National Cancer Institute Surveillance Epidemiology and End Results (SEER).

- Rinaa S. Punglia, J Natl Cancer Inst;2013;105.

Figure 1. Trends in the incidence of DCIS and invasive cancer (1975-2005)[4]



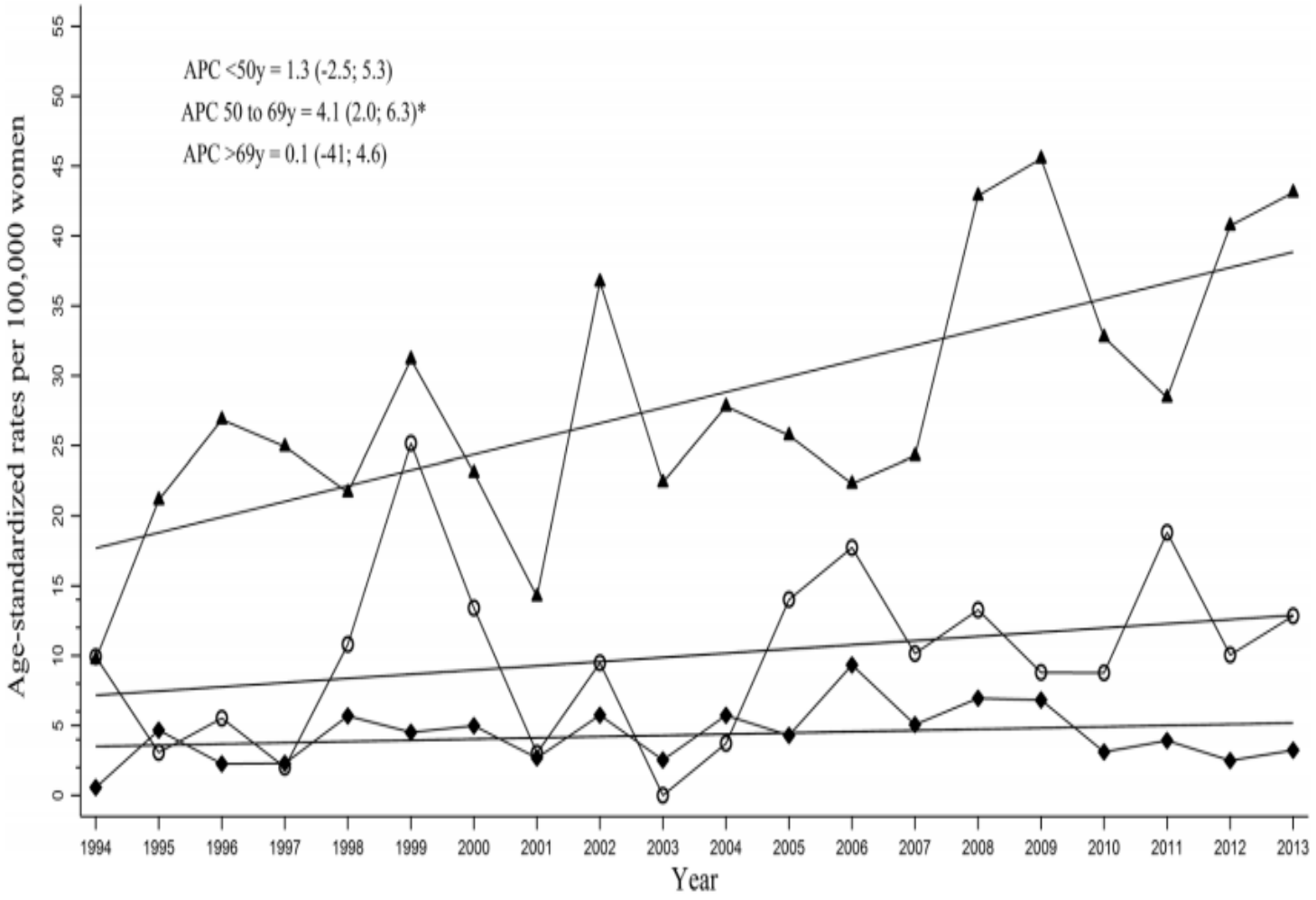
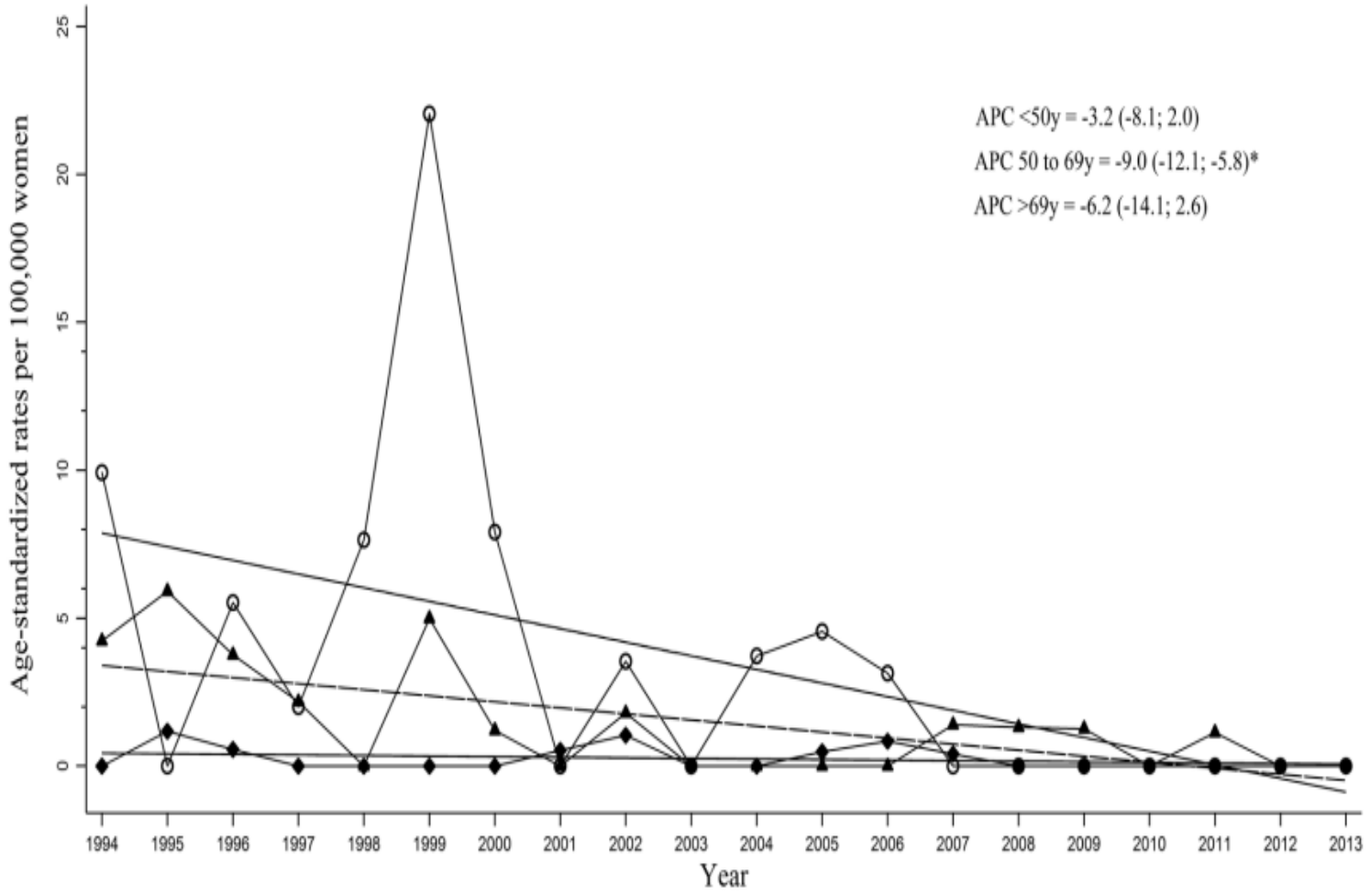


Fig. 1 Age-standardized annual incidence rates of DCIS among women aged < 50 (black diamond), 50–69 (black triangle) and > 69 years old (white circle). Dotted lines for linear trend. *Significant trend (p value < 0.05)



ig. 2 Age-standardized annual mortality rates of DCIS among women aged < 50 (black diamond), 50–69 (black triangle) and > 69 years old white circle). Dotted lines for linear trend. *Significant trend (p value < 0.05)

DKİS Radyolojisi, Histolojik Tanı

- DKİS tipik olarak mamografide atipik kalsifikasyonlar olarak tanı almaktadır.
- DKİS lezyonlarının %44'ünün hem mamografi hem de USG, %46'sının sadece mamografi, %8'inin sadece USG ile ama %2'sinin hem mamografi hem de sonografik değerlendirmeler ile tanı alamadığı*
- Nükleer grade veya komedo nekrozun vizüalize edilmesine etkisi yok
- *Scggins ME, Am J Roentgenol, 2015.204.

- Tanı koyma şekli tedavi/cerrahi planlanmasını etkiler,
- DKİS nadir olarak multifokal ve tek segmente sınırlı olarak vurgulanırken*
- DKİS %63 olgu da büyüme paterni boyunca bitişik olmayan büyüme paterni gösterebileceği,**
- Devamlı patern %90 yüksek grade,
- İyi diferansiye ve orta grade'li DKİS'de ise %30-45***

- *Holland R, Lancet 1990.335
- **Faverly DR, Semin Diagn Pathol, 1994.11
- ***Hong YK, The Am J Of Surg,2018

- Biyopsi, tanı ve tedavisinde tru-cut/kalın iğne, tel işaretli biyopsi, ROLL(Radioguded Occult Lesion Localisation), SNOLL (Sentinel Node and Occult Lesion Localisation)
- Spesmenin işaretlenmesi, tümör yatağının klips ile işaretlemesi
- Patoloji ile intraoperatif konsülte edilmesi,

Comparison of different techniques to detect occult lesions

Technique	Available	Negative Margin rate	Advantages	Disadvantages
Wire localisation	Yes, gold standard	70-88%[18,19,20,21.]	Readily available, simple, carried out in radiology	Wire displacement, transection, vasovagal attack, radiology expertise needed and theatre scheduling required
Carbon marking	Yes	81%[22]	Simple, cheap	Foreign body reaction, needle occlusion while administering
ROLL	Yes	75-94%[18,24]	Performed days before surgery	Radioactive-Nuclear medicine, cost, legislation etc
SNOLL	Yes	82 - 92%[12,23]	Detects both lesion and sentinel node	Radioactive-Nuclear medicine, cost, legislation etc

– Green M, Clinical Breast Cancer (2018),

www.oncotarget.com Oncotarget, 2019, Vol. 10, (No. 60), pp: 6494-6508

Research Paper

SNiPER: a novel hypermethylation biomarker panel for liquid biopsy based early breast cancer detection

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[6]Institute of Clinical Molecular Biology, University Medical Centre Schleswig-Holstein, Campus Kiel, Christian-Albrechts-University, Kiel, Germany

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[9]Current address: Bayer AG, Pharmaceuticals Division, Biomarker Research, Wuppertal, Germany

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***Keywords**: liquid biopsy; breast cancer; early detection; hypermethylation; discriminative CpG dinucleotides*

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- **SPAG6 ve ITIH5** 63% sensitivite/ DKİS 51% sensitivite, erken invaziv tümör (pT1, pN0) tespitinde 80% spesifite.
- 50% sensitivite DKİS tespitinde **NKX2-6 ve ITIH5**

Tedavi

- Meme Koruyucu Cerrahi/Onkoplastik cerrahi + Tüm meme RT
- ER(+)-- Hormonoterapi

Mastektomi

- 10 yılda %1-3'lük düşük lokal rekürrens riski*
- Multisentrisite,
- Meme parankiminde yaygın tutulum ile MKC için kabul edilemeyecek kozmetik sonuçlar
- Meme Başı Koruyucu Mastektomi selektif hastalar için risk artmadan ** kulanılabileceği, cilt koruyucu mastektomi ile ise (%5,6 ile %0) ***

- *Stuart KE, BMC Cancer. 2015, 10.
- **de Alcantara Filho P, Ann Surg Oncol. 2011, 18.
- ***Timbrell S, Ann Surg Oncol. 2017, 24.

Meme Koruyucu Cerrahi ve Radyoterapi

Table 1. Summary of the effect of radiotherapy on breast conservation for DCIS
NSABP B-17[16], EORTC[17], UK/ANZ[18], Swedish Breast Cancer Group[19] trials demonstrate the importance of reduction of ipsilateral breast cancer recurrence for patients who undergo breast conservation therapy.

			% Ipsilateral Breast Cancer Recurrence					
			Lumpectomy Alone		Lumpectomy + Radiotherapy		% Breast Cancer Specific Survival	
Trial	N	Median F/U (years)	All	Invasive	All	Invasive	Lumpectomy	Lumpectomy + RT
NASBP B-17	813	17.25	35%	20%	20%	11%	96.9%	95.3%
EORTC 10853	1010	10.5	26%	13%	15%	8%	96%	96%
UK/ANZ	1030	12.7	19%	9.1%	7.1%	3.3%	97.3%	98.5%
SweDCIS	1046	8.4	27%	12%	12%	7.2%	97.1%	96%



J Natl Cancer Inst Monogr. 2010;2010(41):162-77. doi: 10.1093/jncimonographs/lgq039.

Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, Wang Y, Clarke M, Davies C, Peto R, Bijker N, Solin L, Darby S.

Collaborators (610)

Abstract

Individual patient data were available for all four of the randomized trials that began before 1995, and that compared adjuvant radiotherapy vs no radiotherapy following breast-conserving surgery for ductal carcinoma in situ (DCIS). A total of 3729 women were eligible for analysis. Radiotherapy reduced the absolute 10-year risk of any ipsilateral breast event (ie, either recurrent DCIS or invasive cancer) by 15.2% (SE 1.6%, 12.9% vs 28.1% 2 P <.00001), and it was effective regardless of the age at diagnosis, extent of breast-conserving surgery, use of tamoxifen, method of DCIS detection, margin status, focality, grade, comedonecrosis, architecture, or tumor size. The proportional reduction in ipsilateral breast events was greater in older than in younger women (2P < .0004 for difference between proportional reductions; 10-year absolute risks: 18.5% vs 29.1% at ages <50 years, 10.8% vs 27.8% at ages ≥ 50 years) but did not differ significantly according to any other available factor. Even for women with negative margins and small low-grade tumors, the absolute reduction in the 10-year risk of ipsilateral breast events was 18.0% (SE 5.5, 12.1% vs 30.1%, 2P = .002). After 10 years of follow-up, there was, however, no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or all-cause mortality.

- Yaş, cerrahi genişlik, tamoxifen kullanımı, grade, komedonekroz, tümör boyutu, tanı yöntemi, cerrahi sınırdan bağımsız
- 10 yıllık takiplerde sağkalıma etkisi yok

Sentinel Lenf Nodu Biyopsisi

- SLNB (%5,3) 5 yıllık lenfödem riski ile ilişkili, RT alınca artmış risk*
- Tru-cut biyopsi ile patoloji spesmeni arasındaki farklar ve patolojik sonuçlar arasındaki farklar (underestimation/overestimation) 19·1 (17·1 to 21·3) and 9·3 (7·7 to 11·4) sırası ile**
- 470 yüksek riskli DKİS hastasında 43 (%9) hasta da pozitif SLN.***

- * Nguyen TT, Ann Surg Oncol. 2017, 24.
- ** Knuttel FM, Br J Surg. 2016, 103.
- *** Moore KH, Ann Surg Oncol. 2007 Oct;14

- Mastektomi,
- >5cm DKİS olguları,
- Multisentrik hastalık,
- İnvaziv kanser şüphesi taşıyan radyolojik olarak kitlesel lezyon veya palpable lezyonları olan DKİS olgularında SLNB,
- DKİS olgularında rutin aksiller örnekleme önerilmiyor ama yüksek riskli DKİS hastalarında, invaziv kanser riski taşıyan olgular veya mastektomi planlananlar*
- *Hong YK, Am J Surg. 2018 Nov;216

Cerrahi Sınır

- DKİS; invaziv rekürrenslerini yeterli cerrahi sınır lokal rekürrensi azaltmak için önemli,

Table 2. Optimum Margin Threshold for DCIS Resection (n = 2,514)

Negative Margin Width	No. of Patients	% of Patients With IBTR	Relapse *v* > 5 mm		
			OR	95% CI	*P*
No cells on ink	914	9.4	2.56	1.1 to 7.3	< .05
1-mm margin	1,239	10.4	2.89	1.3 to 8.1	< .05
2-mm margin	207	5.8	1.51	0.51 to 5.0	> .05
≥ 5-mm margin	154	3.9	1		

Abbreviations: DCIS, ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence; OR, odds ratio.

Table 2. Minimum Treatment Recommendations to Achieve a Local Recurrence Rate <20% at 12 years Using the USC/VNPI Scoring System

USC/VNPI	Treatment	12-year recur (%)
4, 5, or 6	Excision alone	<8
7, margins ≥3 mm	Excision alone	13
7, margins <3 mm	Radiation	19
8, margins ≥3 mm	Radiation	13
8, margins <3 mm	Mastectomy	0
9, margins ≥5 mm	Radiation	17
9, margins <5 mm	Mastectomy	0
10, 11, or 12	Mastectomy	8

- Lagios MD, Silverstein MJ.Breast J. 2015,21.

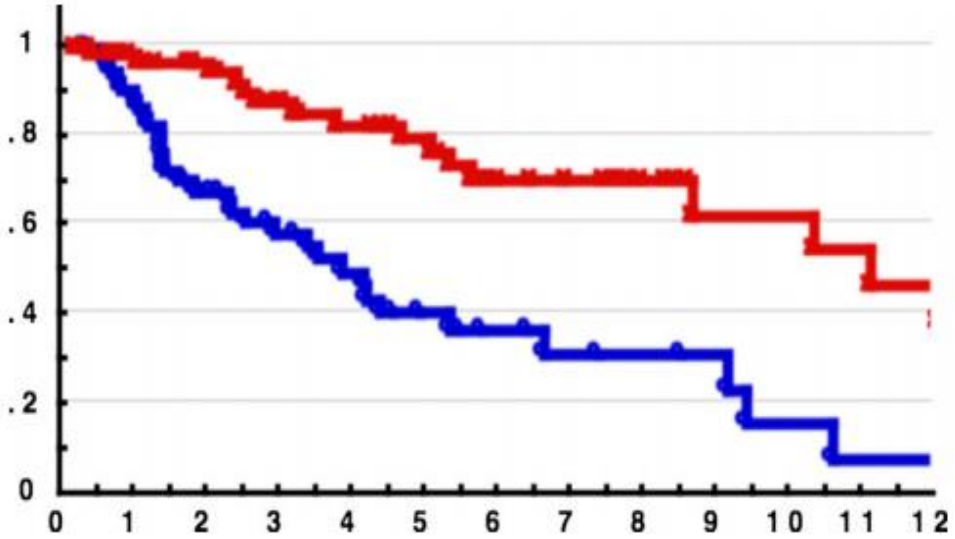

Figure 4. Local recurrence-free survival for 116 patients with USC/VNPI scores of 10, 11, or 12 analyzed by treatment: 56 excision plus radiation therapy (red, top line) versus 60 excision alone (blue, bottom line).

MARGIN STATUS RECOMMENDATIONS FOR DCIS AND INVASIVE BREAST CANCER

- Margins should be evaluated on all surgical specimens from breast-conserving surgery (BCS). Requirements for optimal margin evaluation include:
  - Orientation of the surgical specimens
  - Description of the gross and microscopic margin status
  - Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.
- For mammographically detected DCIS with microcalcifications, complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography could also be performed whenever uncertainty about adequacy of excision remains.
- The NCCN Panel accepts the definitions of negative margins after breast conservation therapy from the 2014 SSO/ASTRO Margins Guideline[1] for Stage I/II Invasive Cancers and the 2016 SSO/ASTRO/ASCO Guideline for DCIS.[2] For patients with stage I or II invasive cancers after BCS, a positive margin is defined as "ink on tumor" (any invasive cancer or DCIS cells on ink). These patients generally require further surgery—either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for BCS to achieve "no ink on tumor," this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity. There may be select patients with stage III invasive cancers who may be eligible for BCS. For these patients, the margins status would be accessed with similar definitions.

DCIS

- For patients with pure DCIS treated by BCS and whole breast radiation therapy (WBRT), a quantitative description of any tumor close to margin resection width of at least 2 mm is associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths, while the routine practice of obtaining margins greater than 2 mm to further improve outcomes is not supported by the evidence. When there is only minimal or focal DCIS involvement near the margin, clinical judgment can be applied to determine if re-excision might be avoided in individual cases.
- For patients with DCIS treated with excision alone (no WBRT), regardless of margin width, there is a substantially higher rate of IBTR than treatment with excision and WBRT, even in predefined, low-risk patients. Although the optimal margin width for treatment with excision alone is unknown, it should be at least 2 mm, with some evidence suggesting improved IBTR rates with margin widths wider than 2 mm.
- DCIS with microinvasion (DCIS-M), defined as an invasive focus ≤1 mm in size, should refer to the DCIS margin definition when considering the optimal margin width (>2 mm), given that the majority of DCIS-M is comprised of DCIS and systemic therapy utilization for this lesion more closely reflects the treatment pattern for DCIS than for invasive carcinoma.

- Cerrahi sınır pozitifliğini; «Tümör üzerinde mürekkep»
- Tümör üzerinde mürekkep olmaması
- Sadece eksizyon için yeterli CS bilinmiyor, artmış lokal rekürrens ile ilişkili
- >2 mm

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Invasive Breast Cancer

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Discussion

MARGIN STATUS RECOMMENDATIONS FOR BOTH DCIS AND INVASIVE BREAST CANCER

Invasive Breast Cancer

- For invasive breast cancers that have a component of DCIS, regardless of the extent of DCIS, the negative margin definition of "no ink on tumor" should be based on the invasive margin guideline. In this setting, "no ink on tumor" is recommended for either DCIS or invasive cancer cells, primarily because the natural history, treatment, and outcomes of these lesions are more similar to invasive cancer than DCIS. Clinical judgment should be applied in specific cases for which following discussion with the patient, re-excision may be prudent.
- These margin recommendations cannot be applied directly to patients undergoing APBI,[1] where data regarding local recurrence are more limited. Furthermore, individualized clinical judgment should be utilized on a case-by-case basis, using postoperative mammography to identify residual calcifications and clinical-pathologic factors such as quantitative extent of disease near margin, presence of extensive intraductal component (EIC), young age, or multiple close margins to assist in identifying patients who may have an increased risk of IBTR and therefore may be selected to benefit from re-excision.
- For patients with invasive breast cancer, after BCS if margin is microscopically focally positive, in the absence of an EIC,[3] the use of a higher radiation boost dose to the tumor bed should be considered. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical doses are 10–16 Gy at 2 Gy/fx.

- DKİS rekürrensleri invaziv kanser olarak ortaya çıktığı için CS negatifliği sağlanması önemli

- Tedavi hastalığın biyolojisini anladıkça yıllar içinde değişim göstermeye başladı.
- Bugün gelinen nokta da soru?
- Düşük riskli DKİS hastalarını nasıl tedavi edeceğiz?
- Tedavisiz takibi bir seçenek olarak hastalarımıza sunacak mıyız?
- Hangi DKİS hastası invaziv kansere progresyon gösterecek?
- Hangi DKİS hastaları riskli?

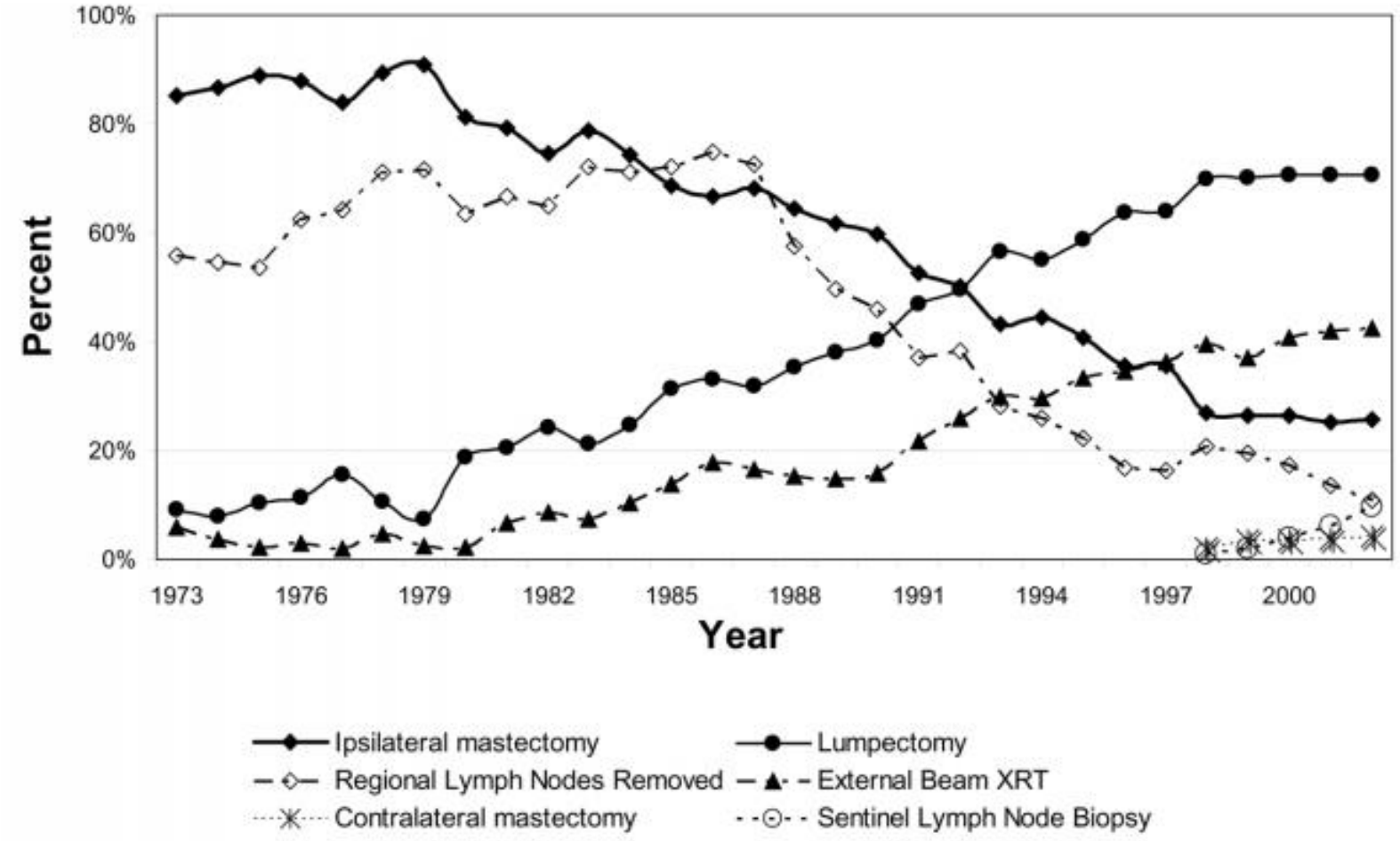
Risk Gruplaması

- Nomogramlar --- Van Nuys, MSKCC
- Oncotype Dx---Genetik analiz
- Klinik çalışma sonuçlarına göre

Feature	Score 1	Score 2	Score 3
Size (mm)	≤15	16–40	>40
Margins (mm)	≥10	1–9	<1
Grade and necrosis	Low or intermediate without necrosis	Low or intermediate with necrosis	High grade with/without necrosis
Age (years)	>60	40–60	<40
	Low score (4–6)	**Intermediate (7–9)**	**High (10–12)**
% patients	32.6%	56.7%	10.8%
Treatment recommendation	Wide-local excision (WLE)	WLE + radiotherapy (RT)	Mastectomy
10 year recurrence-free survival[a]	97%	73%	34%
10 year breast cancer-specific survival	100%	98%	98%

[a]*After WLE ± RT, mastectomy excluded (40).*

- M.J. Silverstein ,Am J of Surg, 2003,186.



- Treatment of DCIS, 1973 to 2002. Source: SEER (Surveillance, Epidemiology, and End Results).
- Kumar AS, 2005, Breast Cancer Res

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NCCN Guidelines Version 3.2019
Ductal Carcinoma in Situ (DCIS)

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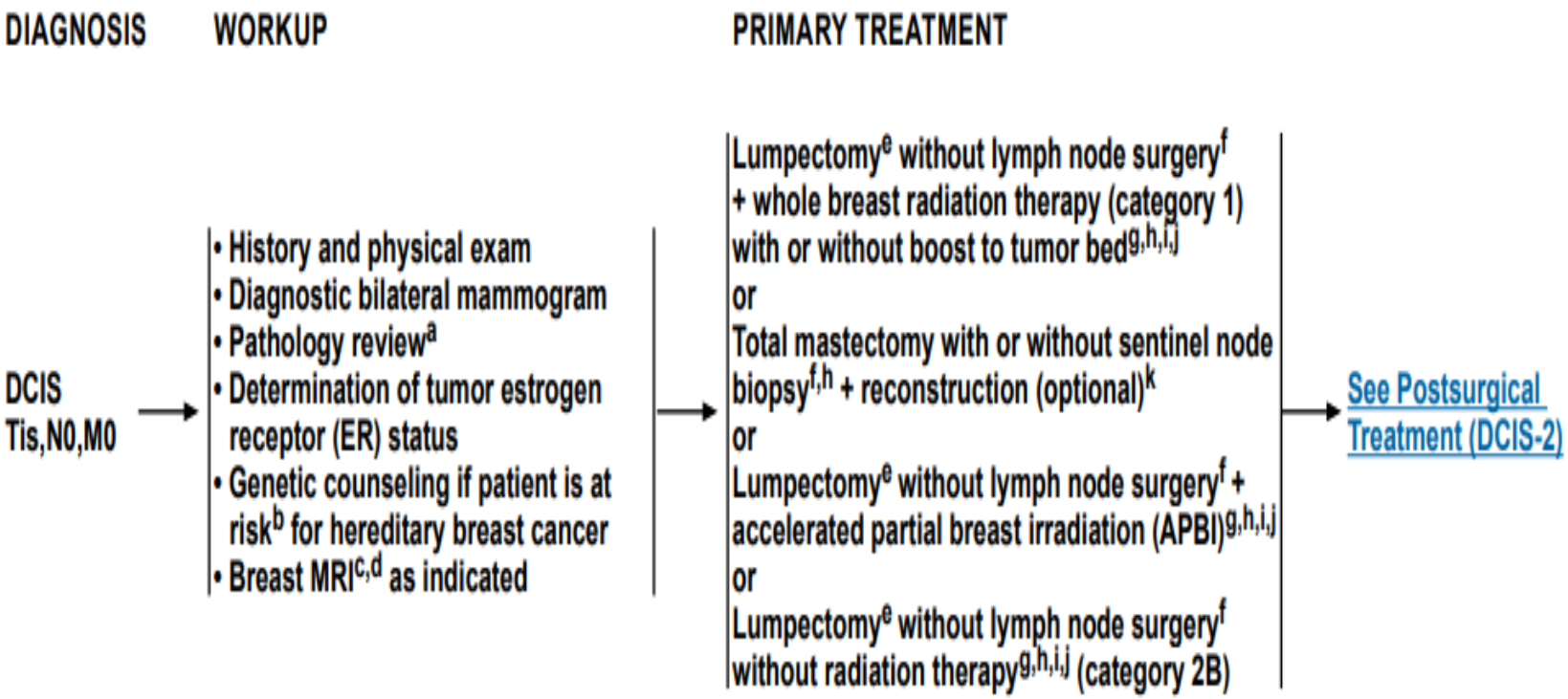

NCCN Guidelines Version 3.2019
Ductal Carcinoma in Situ (DCIS)

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DCIS POSTSURGICAL TREATMENT

Risk reduction therapy for ipsilateral breast following breast-conserving surgery:

- Consider endocrine therapy for 5 years for:
  - Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy[m] (category 1), especially for those with ER-positive DCIS.
  - The benefit of endocrine therapy for ER-negative DCIS is uncertain
  - Patients treated with excision alone[l]
- Endocrine therapy:
  - Tamoxifen[m] for premenopausal patients
  - Tamoxifen[m] or aromatase inhibitor for postmenopausal patients with some advantage for aromatase inhibitor therapy in patients <60 years or with concerns for thromboembolism

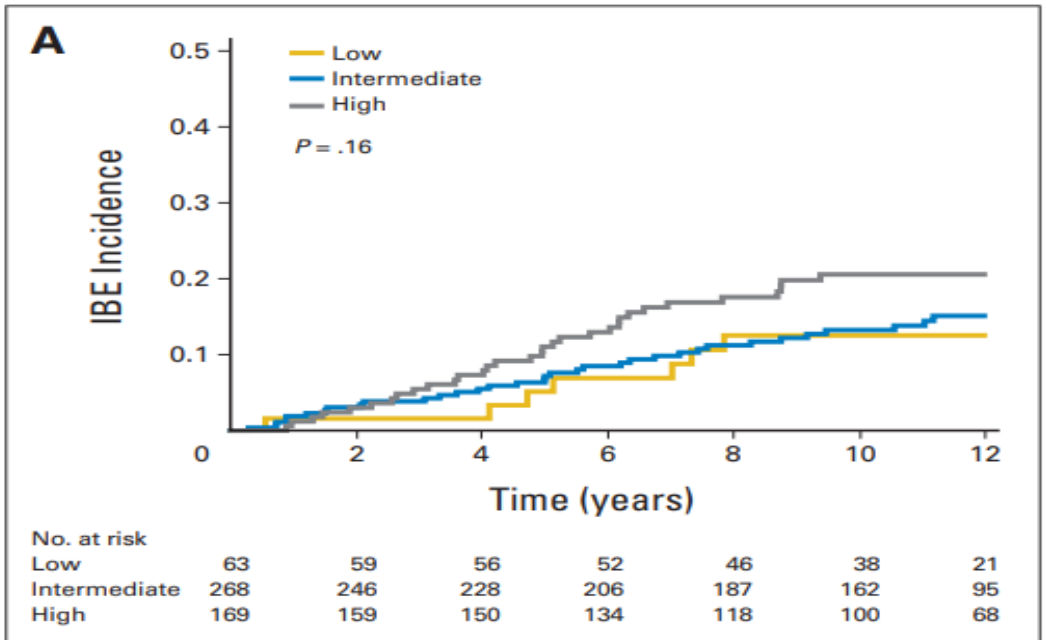
Risk reduction therapy for contralateral breast:

- Counseling regarding risk reduction

See NCCN Guidelines for Breast Cancer Risk Reduction

SURVEILLANCE/FOLLOW-UP

- Interval history and physical exam every 6–12 mo for 5 y, then annually
- Mammogram every 12 mo (first mammogram 6–12 mo, after breast conservation therapy, category 2B)
- If treated with endocrine therapy, monitor per NCCN Guidelines for Breast Cancer Risk Reduction



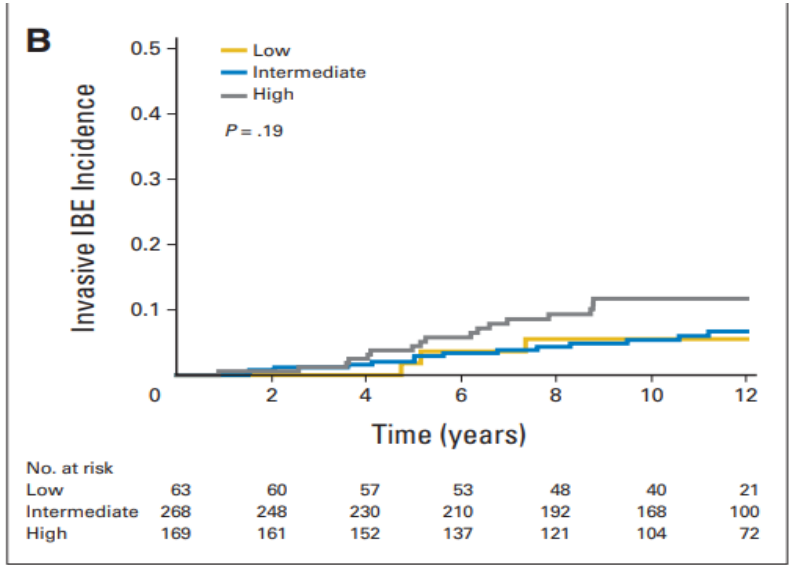


Fig A1. Ipsilateral breast events (IBEs) according to grade as scored using current College of American Pathology guidelines. Analyses exclude cases not evaluated. The numbers at risk are given beneath the *x*-axis. (A) Any IBE. (B) Subset of invasive IBE.

Review

Overdiagnosis and overtreatment of breast cancer

Rates of ductal carcinoma *in situ*: a US perspective

Anjali S Kumar, Vinona Bhatia and I Craig Henderson

University of California, 1600 Divisadero Street, San Francisco, CA 94115, USA

Corresponding author: I Craig Henderson, chenderson@keryx.com

Published: 11 November 2005 *Breast Cancer Research* 2005, **7**:271-275 (DOI 10.1186/bcr1346)

Ann Surg Oncol. 2018 Oct;25(10):2807-2812. doi: 10.1245/s10434-018-6618-z. Epub 2018 Jul 2.

The Changing Paradigms for Breast Cancer Surgery: Performing Fewer and Less-Invasive Operations.

Ollila DW[1], Hwang ES[2], Brenin DR[3], Kuerer HM[4], Yao K[5], Feldman S[6].

⊕ **Author information**

Abstract

Historically, through the conduct of prospective clinical trials, breast cancer surgeons have performed less radical breast and axillary surgeries with no survival decrement to our patients. Currently, other opportunities exist for the treating breast surgeon to do less. Possibilities include active surveillance for ductal carcinoma in situ, ablative therapy for small primary breast cancers, selective omission of a sentinel node biopsy, and selective elimination of breast surgery after neoadjuvant systemic therapy. Breast surgeons must be leaders in the development and testing of effective therapy with the least intervention possible.

PMID: 29968033 DOI: 10.1245/s10434-018-6618-z

Br J Cancer. 2019 Aug 13; 121(4): 285–292.
Published online 2019 Jul 9. doi: 10.1038/s41416-019-0478-6

PMCID: PMC6697179
EMSID: EMS83733
PMID: 31285590

Ductal carcinoma in situ: to treat or not to treat, that is the question

Maartje van Seijen,[#1] Esther H. Lips,[#1] Alastair M. Thompson,[2] Serena Nik-Zainal,[3] Andrew Futreal,[4] E. Shelley Hwang,[5] Ellen Verschuur,[6] Joanna Lane,[7] Jos Jonkers,[1,8] Daniel W. Rea,[9] Jelle Wesseling,[✉1,10,11] and on behalf of the PRECISION team

- Biyopsi sonuçları benign olarak raporlanan ve yıllar sonrasında rekonsülte edildiğinde DKİS gösterilen hastaların %39-53 oranında aynı taraf memesinde invaziv kanser gelişmiş*

- DKİS için yeterli tedavi sonrası aynı taraf memede 4 kata varan meme kanseri insidansı olması gerçek öncü lezyon*

- *Barrio AV, Advances in Surgery, 53, 2019.

	LORIS [14]	LORD [13]	COMET [15]
Age, y	≥46	≥45	≥40
Presentation	Screen-detected calcifications	Screen-detected calcifications	Screen-detected calcifications
DCIS grade	Non-high grade	Pure low grade	Non-high grade
Comedo necrosis	No	No	No
Hormone receptors	—	—	ER and/or PR ≥10%
Endocrine therapy	Allowed	Not allowed	Allowed
Primary endpoint	5-y ipsilateral invasive breast cancer-free survival	10-y ipsilateral invasive breast cancer-free survival	2-y ipsilateral invasive breast cancer-free survival

Abbreviations: COMET, Comparison of Operative to Monitoring and Endocrine Therapy; DCIS, ductal carcinoma in situ; ER, estrogen receptor; LORD, low-risk DCIS; LORIS, surgery versus active monitoring for low-risk DCIS; PR, progesterone receptor.

Data from Youngwirth LM, Boughey JC, Hwang ES. Surgery versus monitoring and endocrine therapy for low-risk DCIS: The COMET Trial. Bulletin of the American College of Surgeons 2017;102(1):62–63.

Cerrahi vs aktif izlem

- Cerrahi eksizyon uygulanan; LORIS çalışmasına uygun hastalarda %20 oranında tru-cut biyopsinde invaziv kansere rastlanmış*
- DKİS tedavisinde biyopsi ile kanıtlanmış tüm olgularda cerrahi eksizyon kesin önerilmektedir.**
- DKİS rekürrensinin invaziv olarak olması, sadece MKC sonrası %12 LR olması ve %6'sının invaziv olması
- Biopsi olarak kanıtlanmış tüm DKİS olgularına cerrahi eksizyon

- *Pilewskie M, Ann Surg Oncol 2016;23-11.
- **Barrio AV, Advances in Surgery, 53, 2019.
- ***Pilewskie M, Ann Surg Oncol 2016;23-13.

- DKİS nedeni ile tedavi edilen 108,196 hastanın (SEER) sonuçları değerlendirildiğinde uygulanan cerrahiden veya adjuvan tedaviden bağımsız olarak 20 yıllık meme kanserine bağlı ölüm riskini %3,3 olarak sunmuşlar. *
- DCIS, temel olarak, **“ölümcül olmayan”** bir hastalıktır.**

- *Narod SA, JAMA Oncol. 2015,1.
- **Barrio AV, Advances in Surgery, 53, 2019.

- Tedavi evrimi mastektomi---MKC+RT---- düşük riskli DKİS sadece MKC?
- Komplet eksizyon, cerrahi sınır negatifliği invaziv lokal rekürrensi minimize etmek için önemli,
- Lokal risk, klinik ve patolojik faktörlerden etkilenen bir değişken, risk analizi yapılmalı
- RT; lokal rekürrensi MKC sonrasında azaltıyor ama sağkalıma faydası yok, yan etkiler açısından da değerlendirilmeli
- Adjuvan endokrin tedavi lokal rekürrensi ve kontralateral kanser insidansını da azaltıyor ama yan etkileri ile değerlendirilmeli

Cancer Epidemiology, Biomarkers & Prevention

Review

Predictors of an Invasive Breast Cancer Recurrence after DCIS: A Systematic Review and Meta-analyses

Lindy L. Visser, Emma J. Groen, Flora E. van Leeuwen, Esther H. Lips, Marjanka K. Schmidt, and Jelle Wesseling

DOI: 10.1158/1055-9965.EPI-18-0976

Clin Breast Cancer. 2019 Feb;19(1):35-46. doi: 10.1016/j.clbc.2018.07.018. Epub 2018 Jul 29.

Including the Ductal Carcinoma-In-Situ (DCIS) Score in the Development of a Multivariable Prediction Model for Recurrence After Excision of DCIS.

Paszat L[1], Sutradhar R[2], Zhou L[3], Nofech-Mozes S[4], Rakovitch E[5].

Author information

1 University of Toronto, Toronto, Ontario, Canada; Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. Electronic address: lawrence.paszat@sunnybrook.ca.
2 University of Toronto, Toronto, Ontario, Canada; Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada.
3 Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada.
4 University of Toronto, Toronto, Ontario, Canada; Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.
5 University of Toronto, Toronto, Ontario, Canada; Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Acad Radiol. 2019 Nov 4. pii: S1076-6332(19)30481-7. doi: 10.1016/j.acra.2019.09.025. [Epub ahead of print]

Ductal Carcinoma In Situ (DCIS) at Breast MRI: Predictors of Upgrade to Invasive Carcinoma.

Lamb LR[1], Lehman CD[1], Oseni TO[2], Bahl M[3].

Author information

1 Massachusetts General Hospital, Department of Radiology, 55 Fruit Street, WAC 240, Boston, MA 02114.
2 Massachusetts General Hospital, Department of Surgery, Boston, Massachusetts.
3 Massachusetts General Hospital, Department of Radiology, 55 Fruit Street, WAC 240, Boston, MA 02114. Electronic address: mbahl1@mgh.harvard.edu.

Table 3. List of factors that were assessed in the HQ studies

Factor	Number of HQ studies: Assessed factor	Statistical significant finding
Age at DCIS diagnosis	6	4
Calcification	2	1
Calgranulin status	1	0
COX-2 status	2	1
Cyclin D1 status	1	0
DCIS architecture	6	2
Detection method	4	2
ER status	3	0
Focality	1	0
Grade, histologic	7	1
HER2 status	3	0
Ki67 status	2	0
Lesion size	7	0
Margin status	4	0
Menopausal status	2	2
Necrosis	4	0
p16 status	2	1
p21 status	1	0
p53 status	3	0
Periductal fibrosis	1	1
Periductal lymphocytes	1	0
PR status	3	0
Psoriasin status	1	0
Race and/or ethnicity	2	1
Subtypes, intrinsic	2	0
Year of DCIS diagnosis	1	0

- * Visser LL, et al. Cancer Epidemiol Biomarkers Prev; 28. 2019.

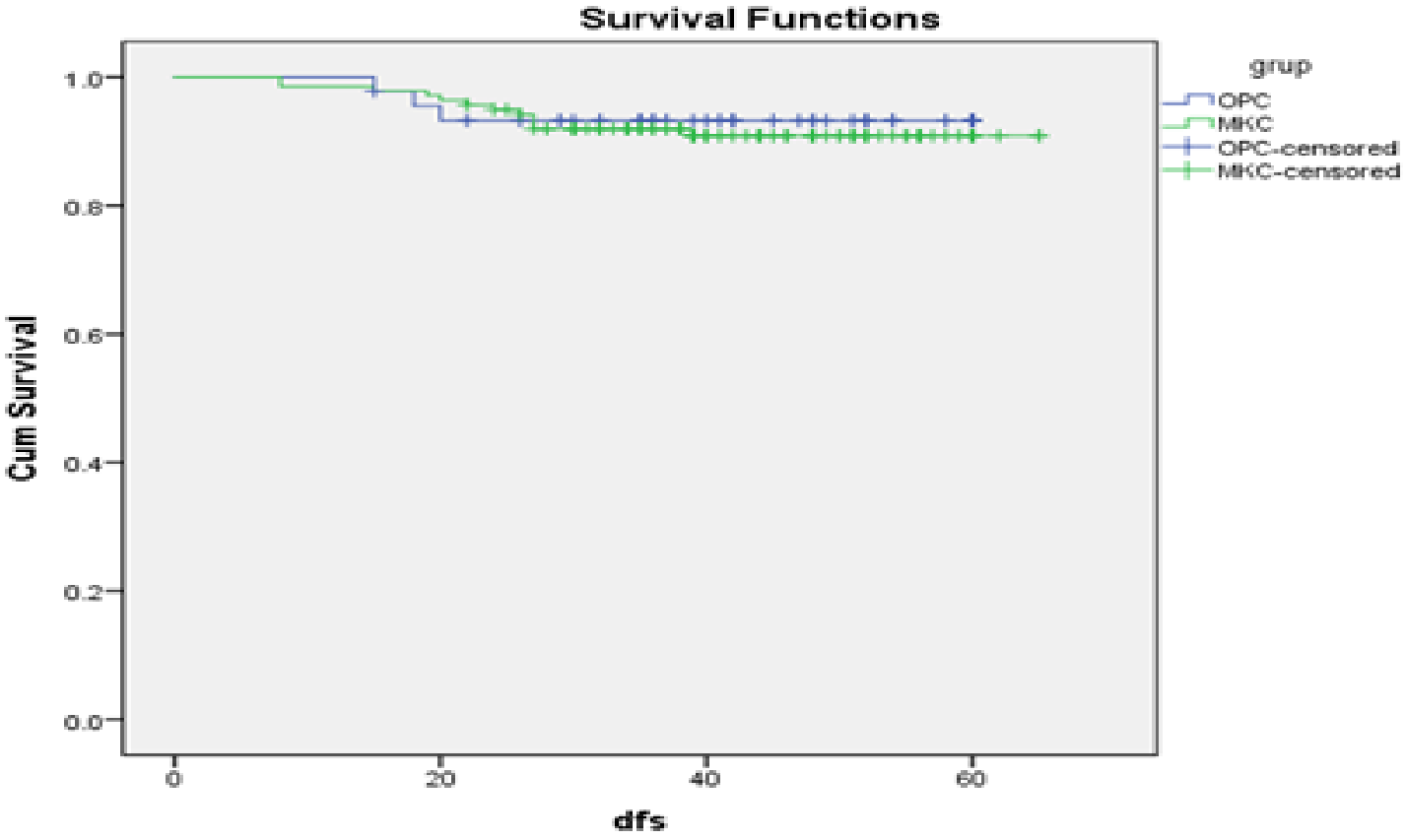
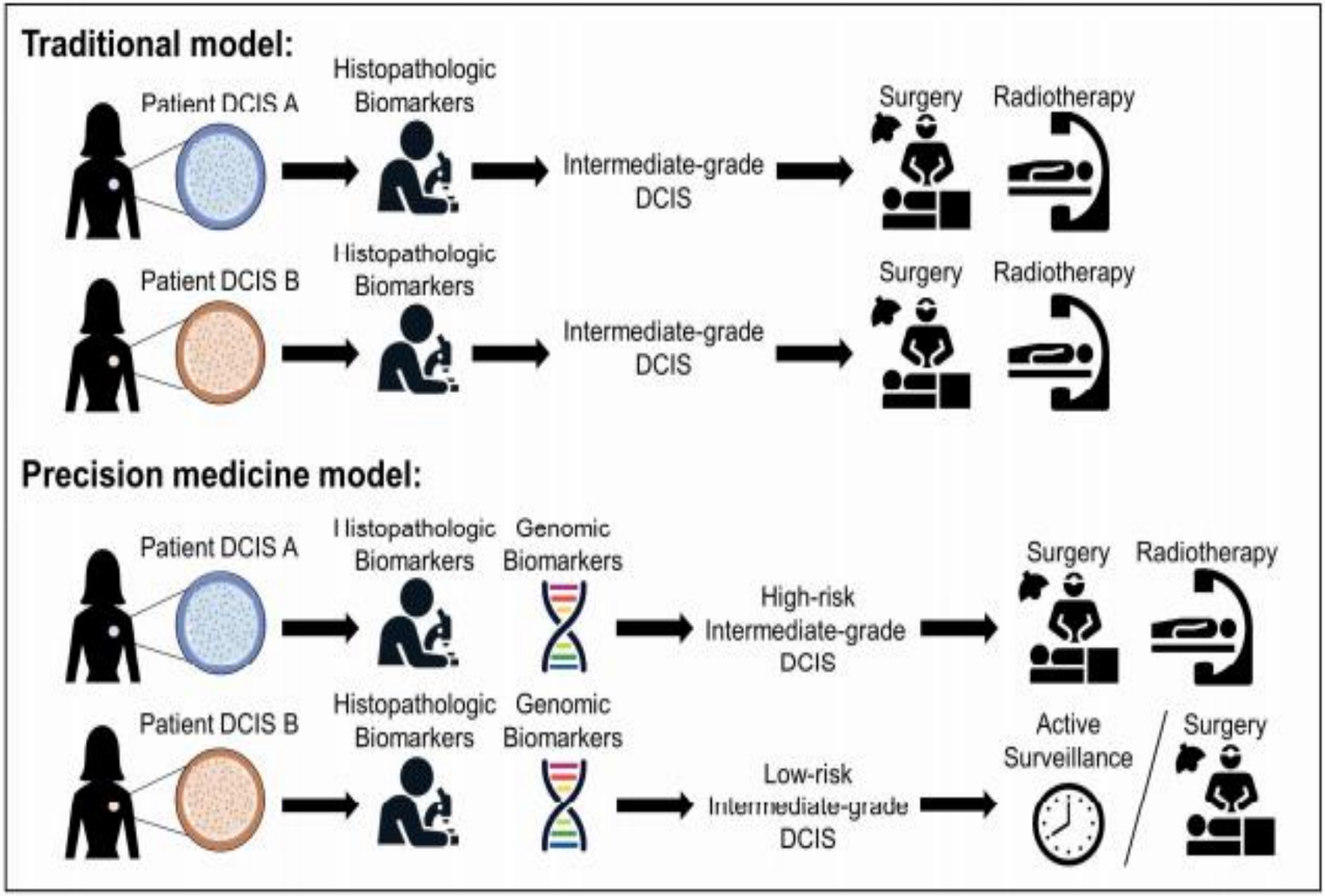


Figure-1. 5 years local recurrence free survival curves

- 189 hasta 42 ay ortalama takip süresi, lokal nüks % 6,3
- **(yayınlanmamış veri)**


Traditional model:
Patient DCIS A
Histopathologic Biomarkers
Intermediate-grade DCIS
Surgery
Radiotherapy
Patient DCIS B
Histopathologic Biomarkers
Intermediate-grade DCIS
Surgery
Radiotherapy
Precision medicine model:
Patient DCIS A
Histopathologic Biomarkers
Genomic Biomarkers
High-risk Intermediate-grade DCIS
Surgery
Radiotherapy
Patient DCIS B
Histopathologic Biomarkers
Genomic Biomarkers
Low-risk Intermediate-grade DCIS
Active Surveillance
Surgery

Front Immunol. 2019 Jun 19;10:1401. doi: 10.3389/fimmu.2019.01401. eCollection 2019.

Circulating Myeloid Derived Suppressor Cells (MDSC) That Accumulate in Premalignancy Share Phenotypic and Functional Characteristics With MDSC in Cancer.

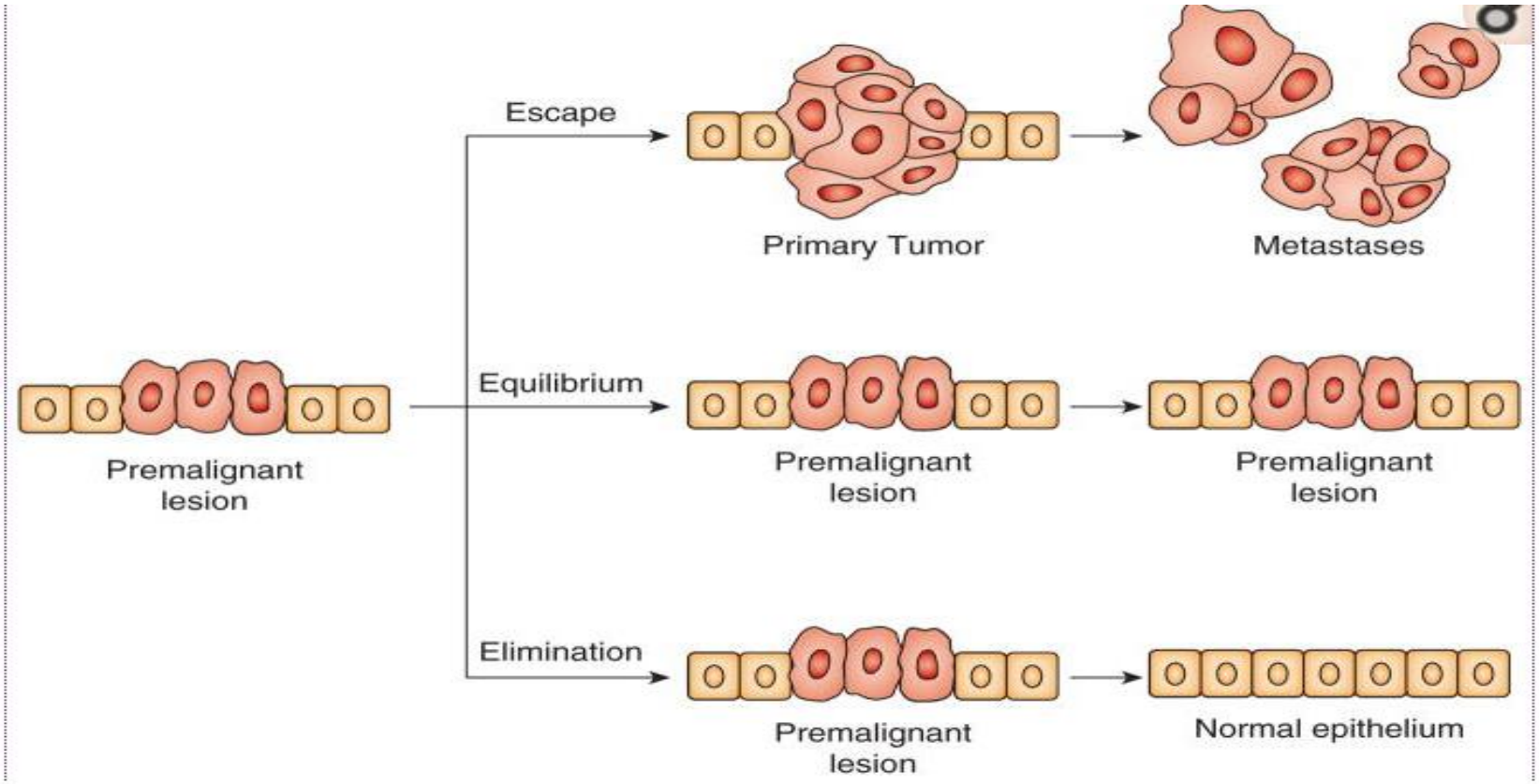
Ma P[1,2], Beatty PL[1], McKolanis J[1], Brand R[3], Schoen RE[3], Finn OJ[1].

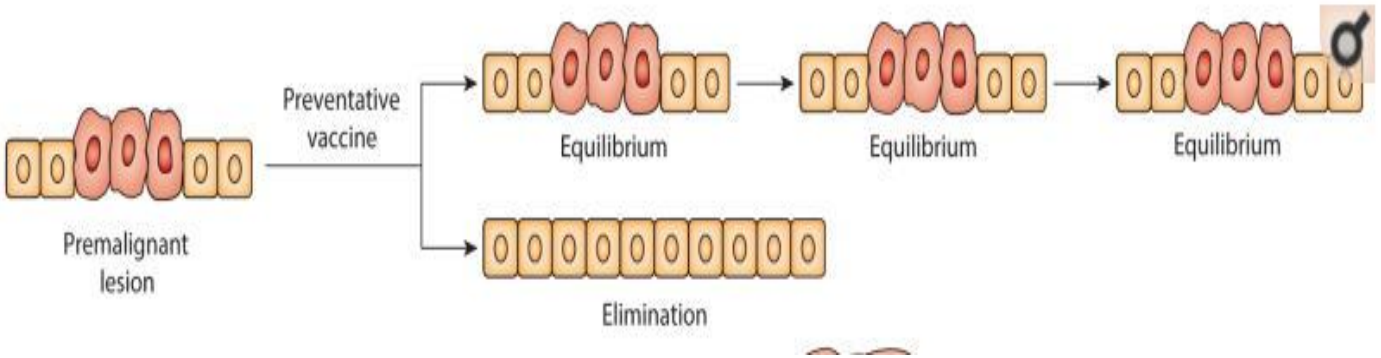
Author information

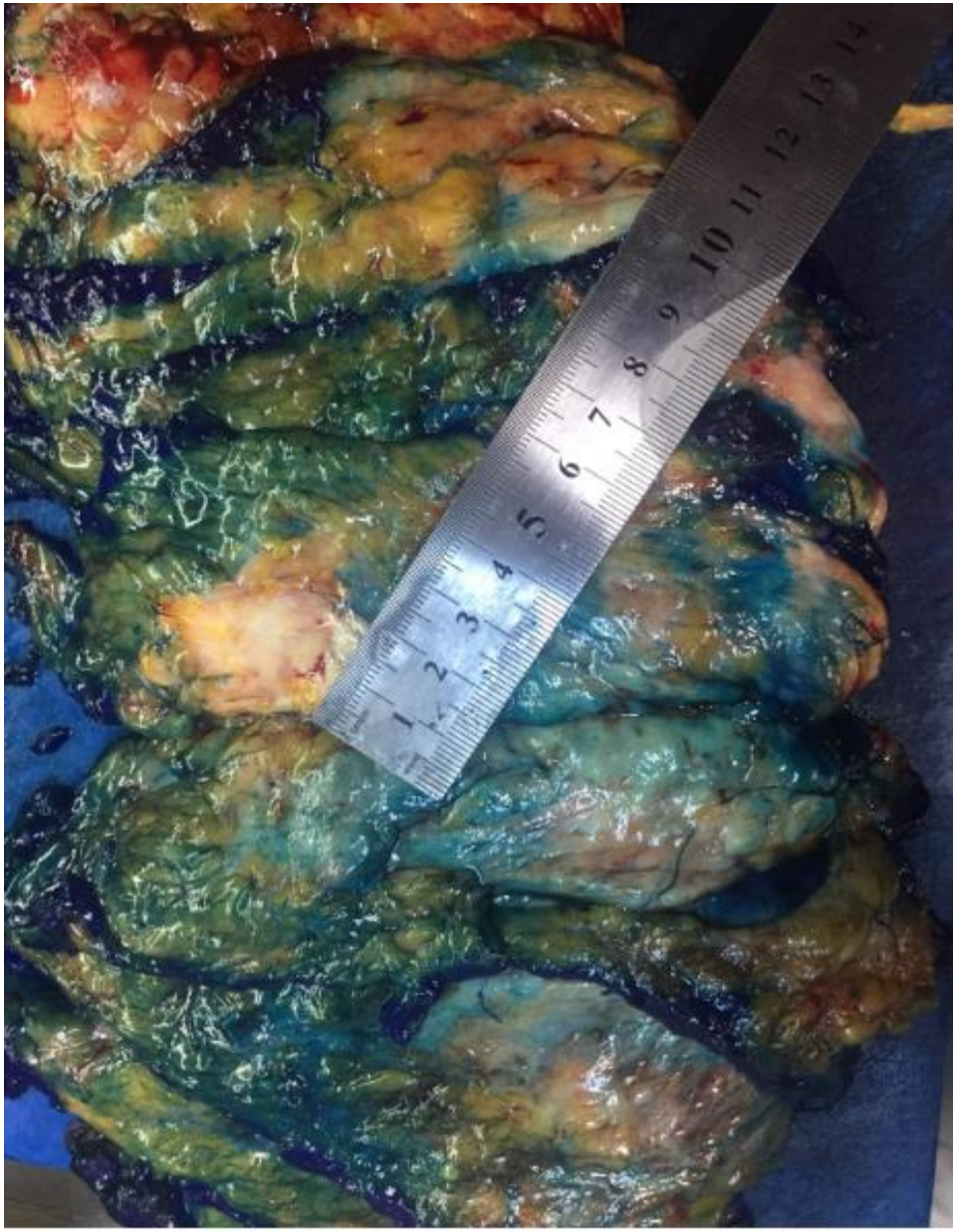
1 Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States.
2 Tsinghua MD Program, Tsinghua University School of Medicine, Beijing, China.
3 Division of Gastroenterology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States.

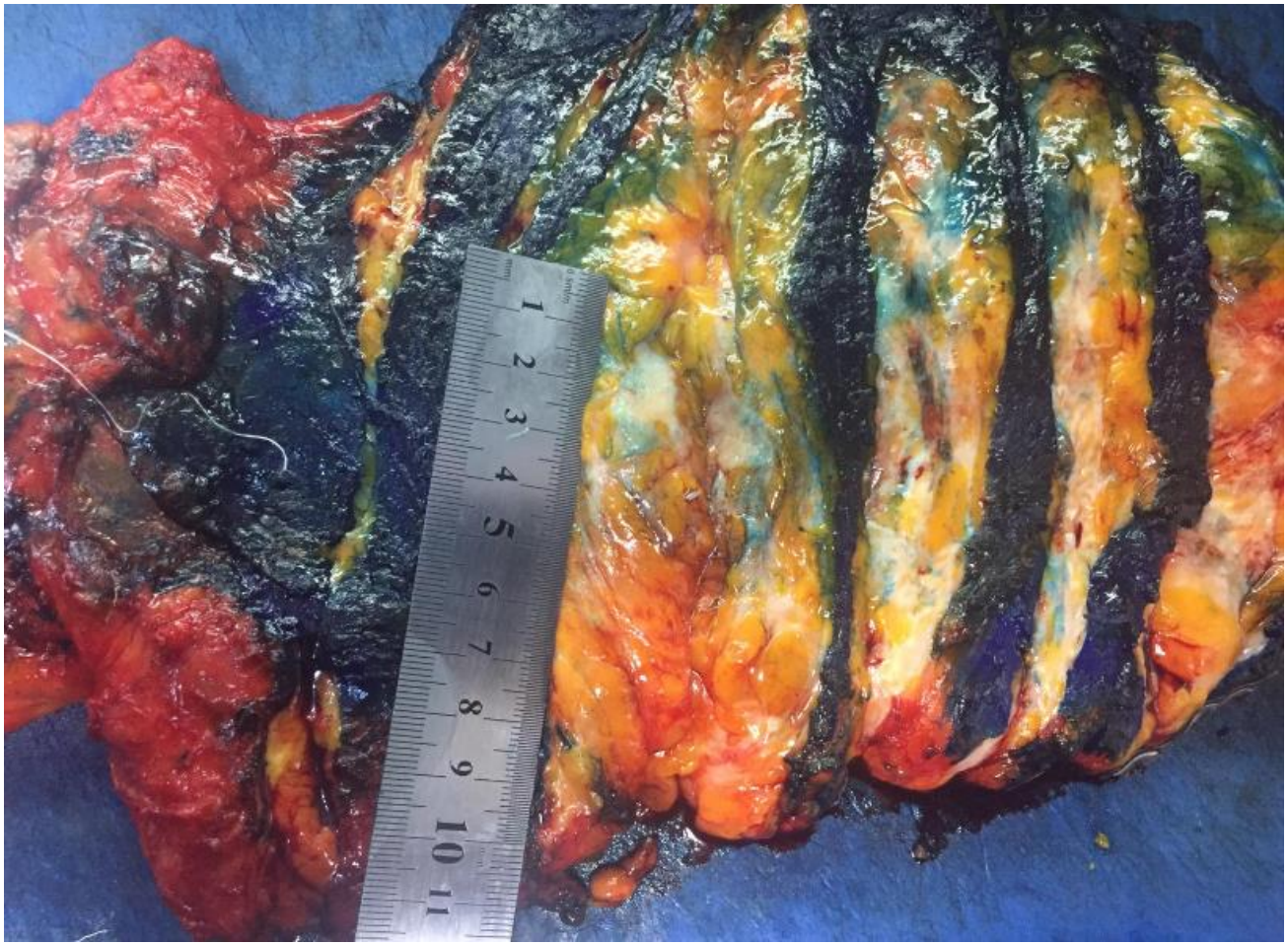
Abstract

Myeloid derived suppressor cells (MDSC) are a heterogeneous population of immature myeloid cells that accumulate in circulation of cancer patients and at tumor sites where they suppress anti-tumor immunity. We previously reported that in a colon cancer prevention trial of a MUC1 vaccine tested in individuals at increased risk for colon cancer, those who did not mount immune response to the vaccine had higher pre-vaccination levels of circulating MDSC compared to those who did. We also reported that individuals with pancreatic premalignancy, Intraductal Papillary Mucinous Neoplasm (IPMN), had increased circulating levels of MDSC that inversely correlated with spontaneous antibody responses against the pancreatic tumor associated antigen MUC1, abnormally expressed on IPMN. Accumulation of MDSC in cancer and their immunosuppressive role had been well established but their presence in premalignancy was unexpected. In this study we compared MDSC in premalignancy with those in cancer with the hypothesis that there might be differences in the composition of various MDSC subpopulations and their immunosuppressive functions due to different lengths of exposure to disease and/or different tissue microenvironments. In cohorts of patients with premalignant polyps, colon cancer, premalignant IPMN, and pancreatic cancer, we confirmed higher levels of MDSC in premalignancy compared to healthy controls, higher levels of MDSC in cancer compared to premalignancy, but no difference in their subpopulation composition or immunosuppressive capacity. We show that levels of MDSC in premalignancy correlate negatively *in vivo* with spontaneous MUC1-specific antibody responses and *in vitro* with polyclonal T cell proliferation and IFN-γ secretion.


Escape
Primary Tumor
Metastases
Premalignant lesion
Equilibrium
Premalignant lesion
Premalignant lesion
Elimination
Premalignant lesion
Normal epithelium


Preventative vaccine
Premalignant lesion
Equilibrium
Equilibrium
Equilibrium
Elimination





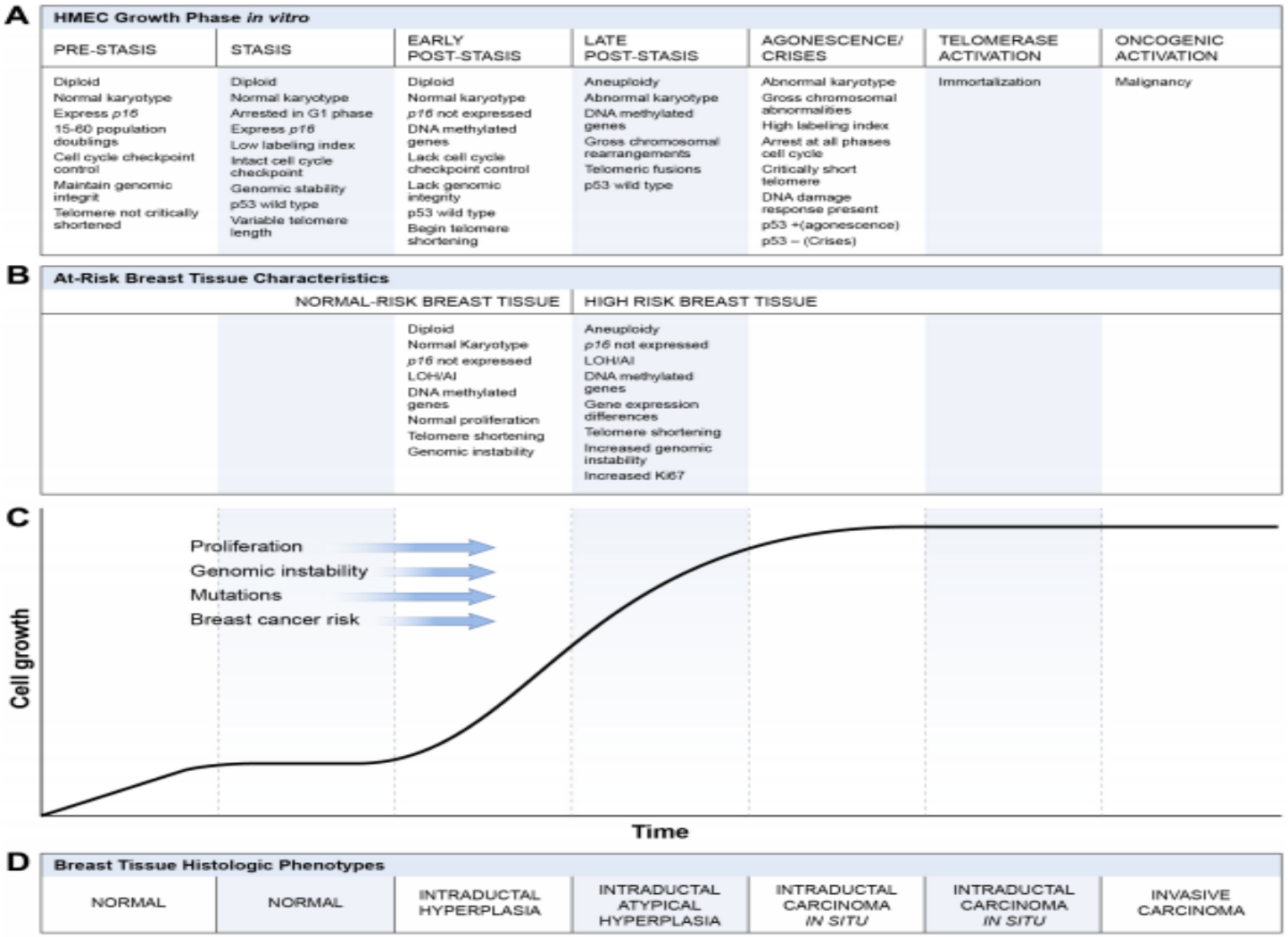


Figure 2. Characteristics of breast carcinogenesis in vitro and in at-risk breast tissues. (**A**) The molecular and cellular characteristics of disease-free HMECs observed in vitro are indicated for each life cycle growth phase.[20,22–24,126–128] (**B**) The genomic changes observed in normal breast tissue at normal risk and at high risk for breast cancer (as described in Part I and Part II, respectively, of this review) are indicated. The phases of the HMEC life cycle to which the genomic changes in normal risk and high-risk breast tissues correspond are shown. (**C**) The growth curve of HMEC in vitro is depicted (adapted from TIsty et al,[75,127] Romanov et al,[22] and Novak et al).[24] Progression through the carcinogenic pathway is accompanied by increased proliferation, genomic instability, mutations, and breast cancer risk. (**D**) The histologic phenotypes which have been proposed to correspond to the HMEC phases are indicated.[75]

Abbreviations: LOH, loss of heterozygosity; AI, allelic imbalance; P16, $p16^{INK4A}$.

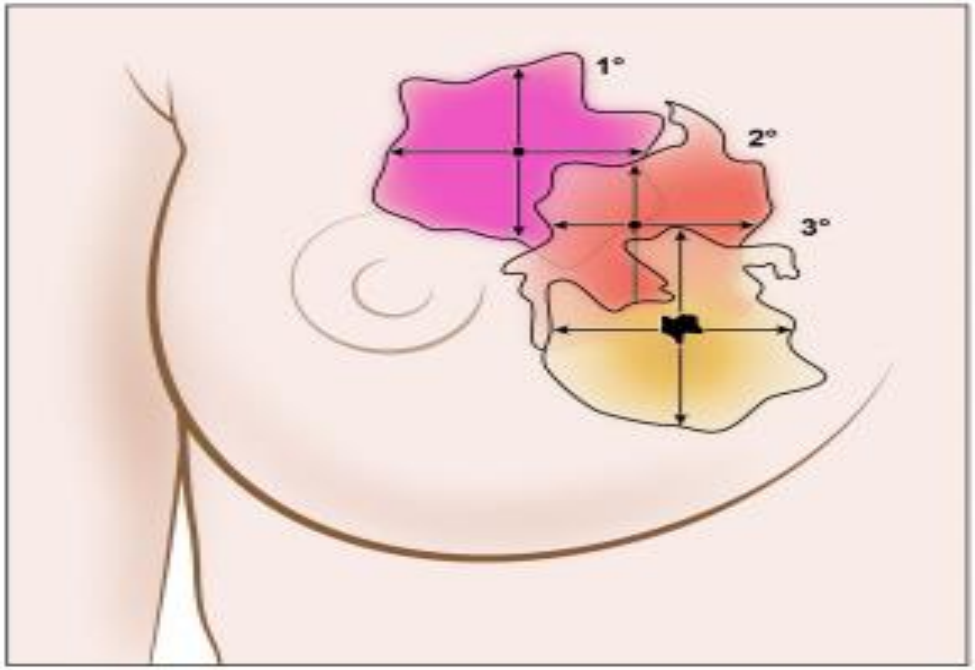
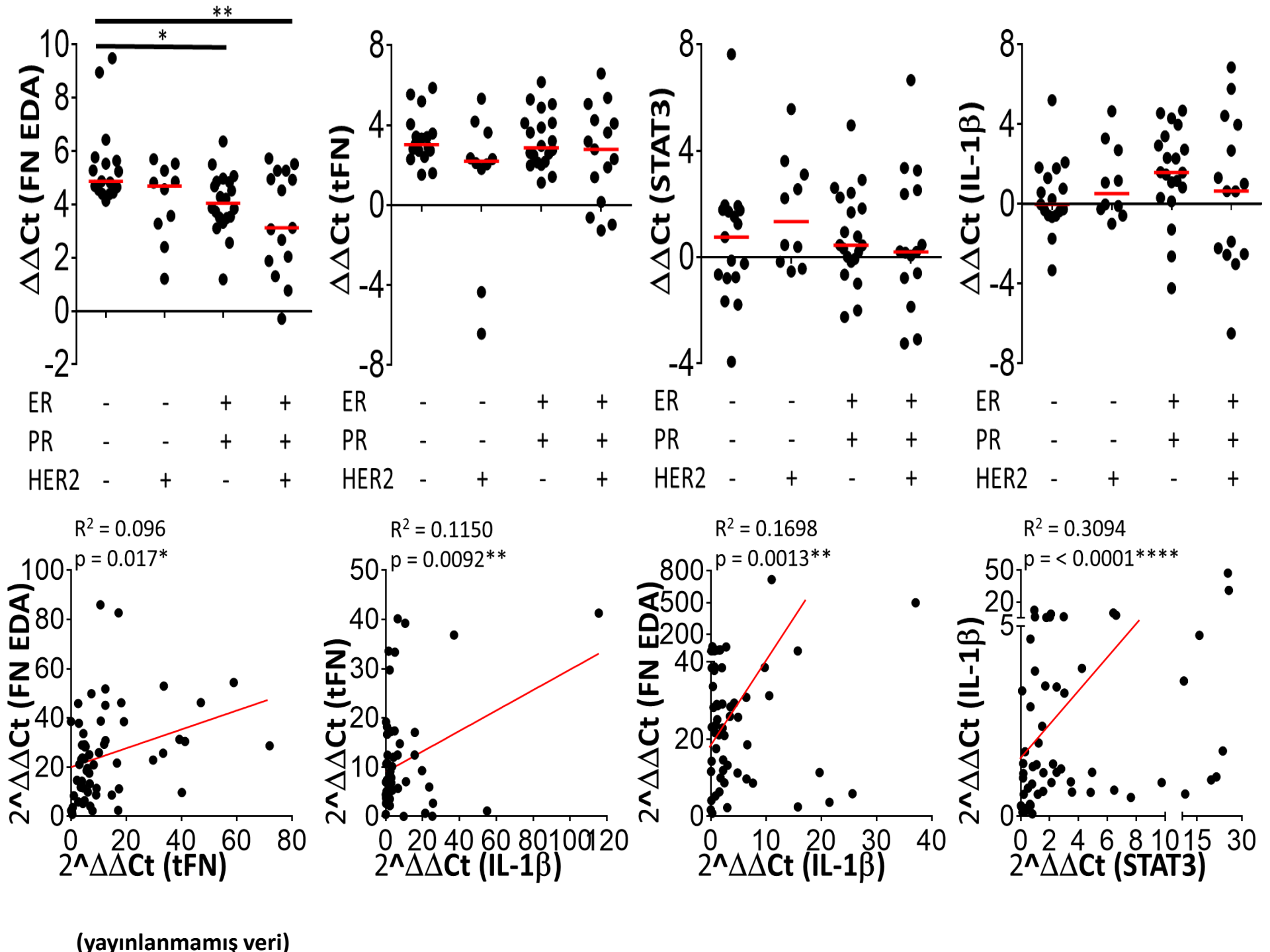


Figure 1. Development of cancerized fields within the breast. Acquisition of initial genomic changes results in clonal expansions of cells to form a field of altered cells with increased genomic instability (rose field, 1°). Acquisition of additional molecular changes in altered cells within this field leads to focal clonal expansion and the sequential development of additional cancerized fields (orange 2° and yellow 3°), with a continued increase in genomic instability and the ultimate transition to cancer in a tertiary field (3°). The presence of multiple cancerized fields with different patterns of genomic alterations may contribute to genomic heterogeneity within the breast. Clonal expansion is accompanied by displacement of surrounding normal breast tissue (often with irregular boundaries), which may contribute to varying frequencies of mutational changes with increasing distance from the center of a developing tumor. Figure 1 is after the concept of Rivenbark and Coleman.[12]



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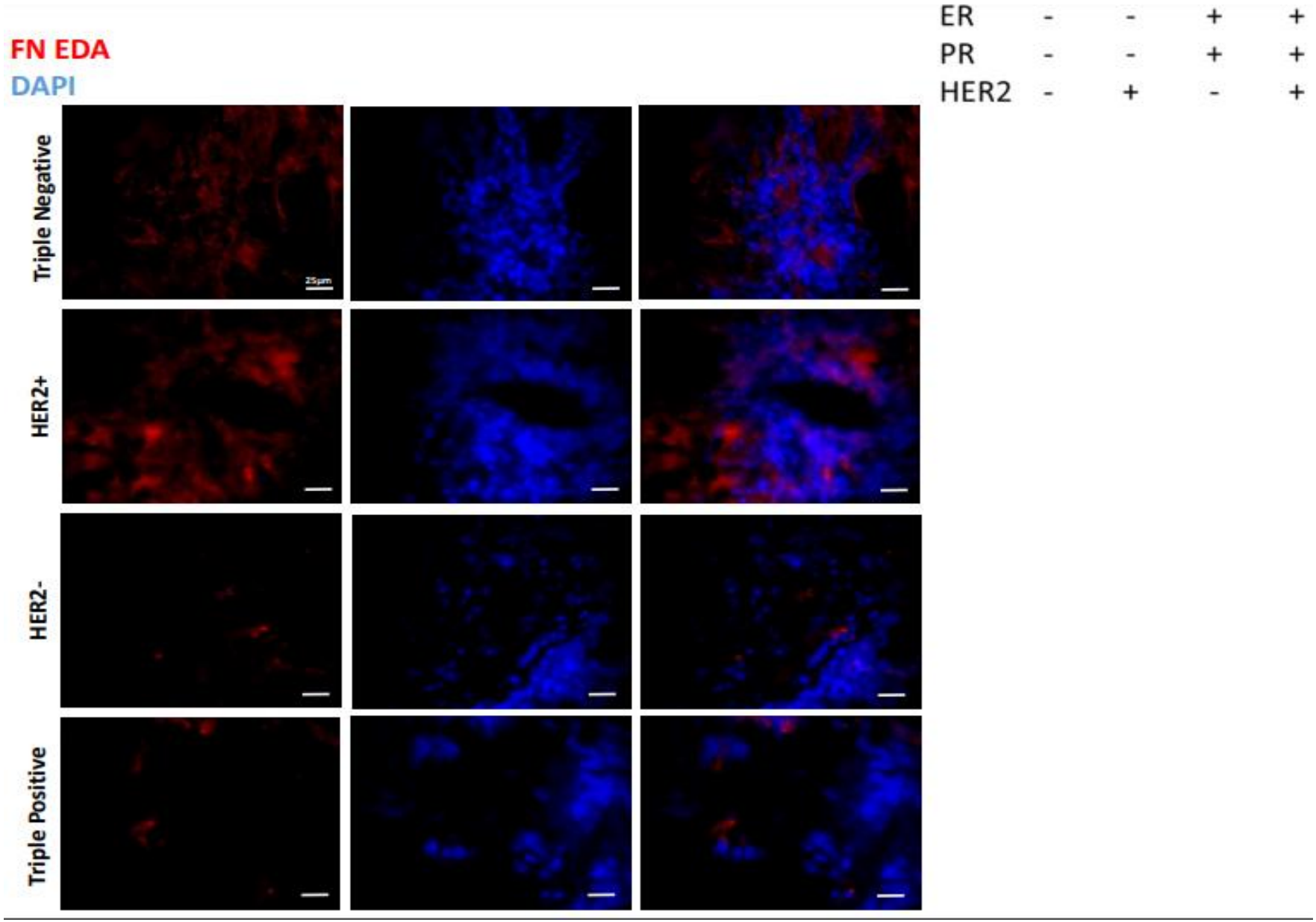

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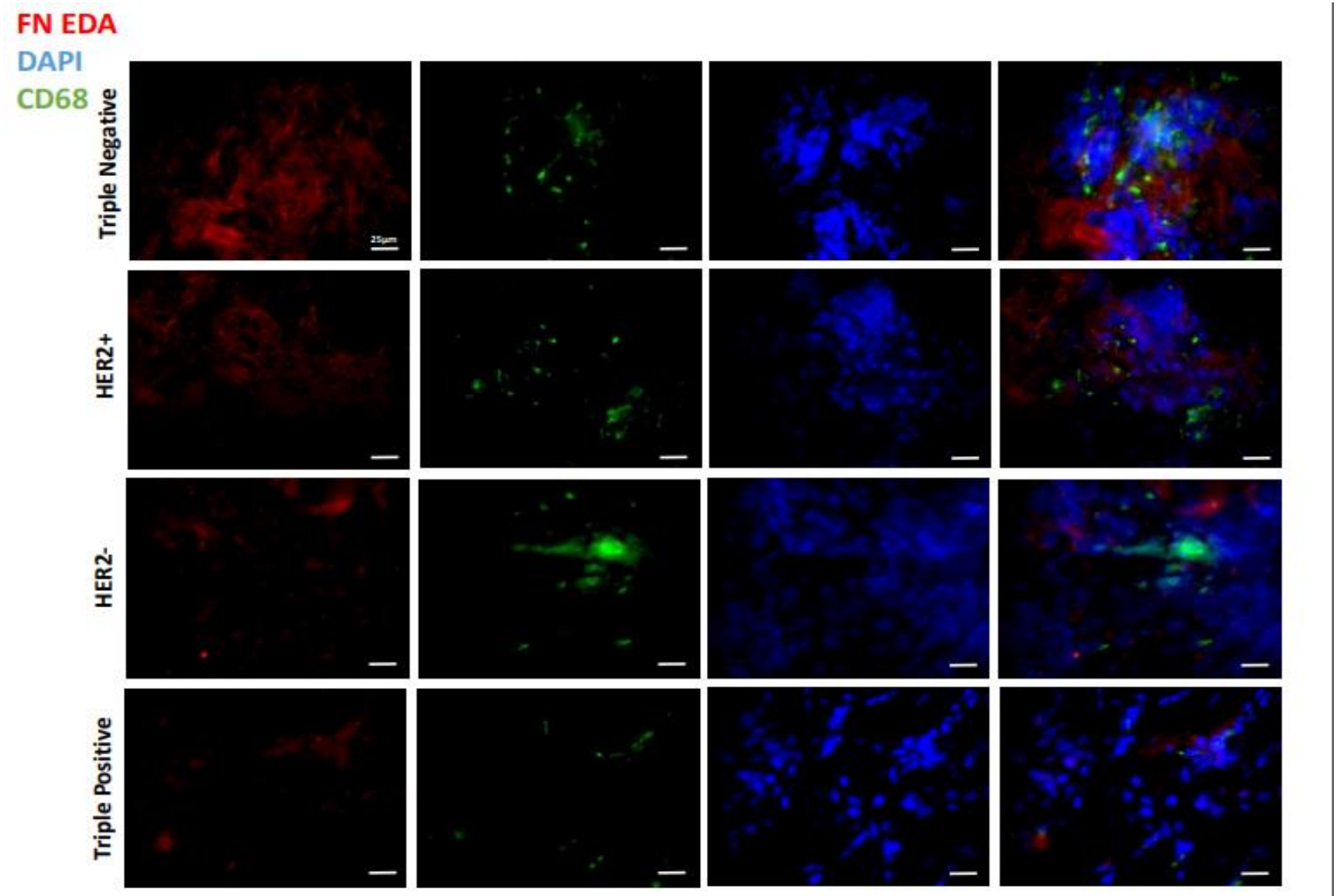
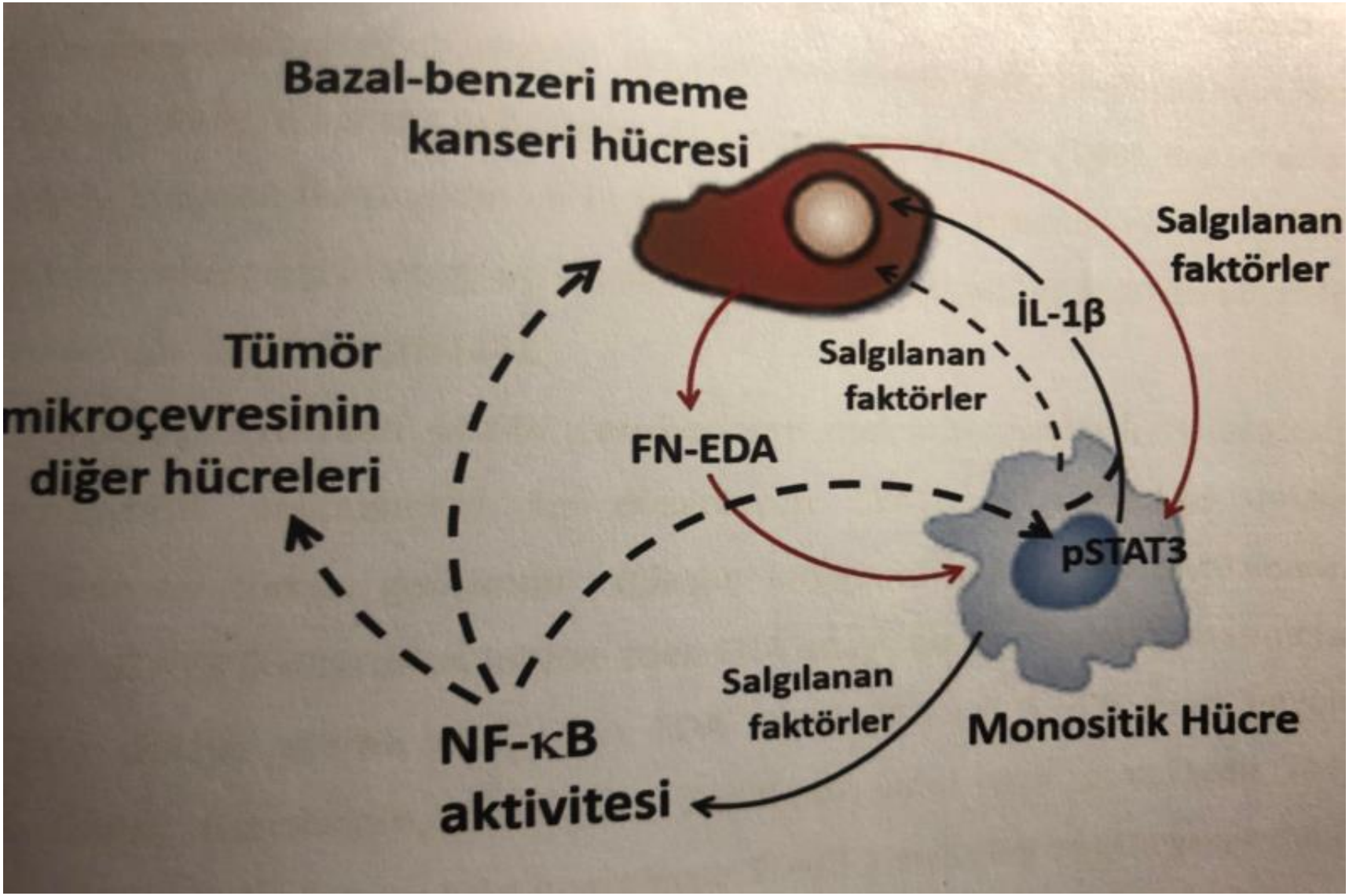


- **(yayınlanmamış veri)**

- DKİS, invaziv kansere progresyon gösterirken Fibronektin ve izoformlarının (EDA ve EDB) düzeyinin artması tümör hücrelerinin sağkalımı ve progresyonu ile ilişkilendirilmiş
- Meme kanseri mikroçevresinde fibronektin-integrin etkileşimi tümör hücrelerinin adezyonu, sağ kalımı, çoğalması
- Mikroçevrede miyeloid hücreler/monositler tarafından İL1Betanın tümör hücrelerinde FN EDA artırması
- STAT3 -IL1Beta- Fibronektin aracılı pozitif geri besleme mekanizması meme kanseri mikroçevresindeki inflamasyon


Bazal-benzeri meme kanseri hücresi
Salgılanan faktörler
İL-1β
Salgılanan faktörler
Tümör mikroçevresinin diğer hücreleri
FN-EDA
pSTAT3
Salgılanan faktörler
NF-κB aktivitesi
Monositik Hücre

- http://www.esendaglilab.com/

-
- Teşekkürler