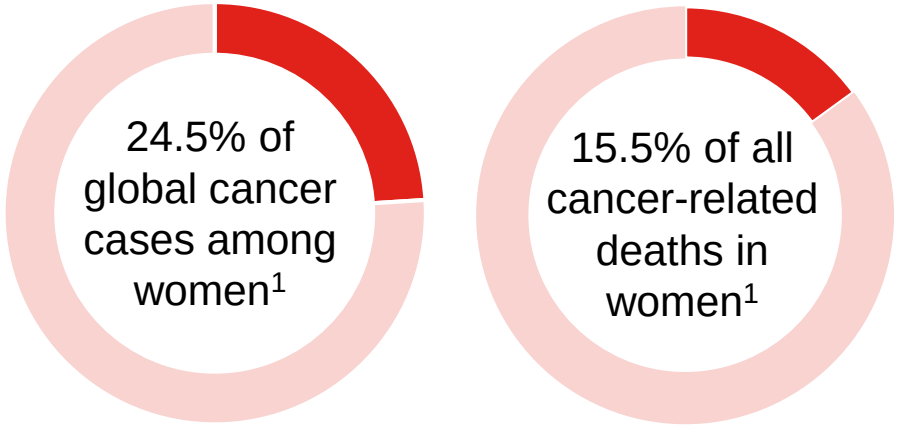
HR+/HER2- Early Breast Cancer Introduction

An Overview of Breast Cancer

Breast cancer is the most commonly diagnosed cancer and leading cause of cancer-related deaths among women worldwide[1]

Breast cancer accounts for:



1. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209-249.

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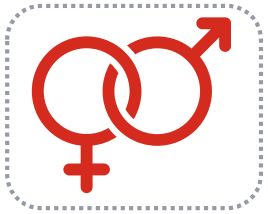
Factors Associated with Increased Incidence of Breast Cancer

Incidence of breast cancer is influenced by factors such as lifestyle, life expectancy, and breast cancer screening and awareness[1-3]

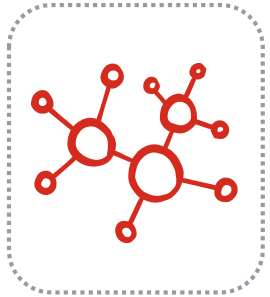


Gender
Women are at ~100-fold greater risk compared to men[4-6]

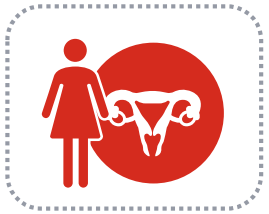
Genetics
Hereditary and genetic factors (e.g., family/personal history, *BRCA1* or *BRCA2* mutations) account for 5-10% of breast cancer cases[3]

Family history
About 15-20% of women with breast cancer have a family history[7]

Lifestyle
Obesity after menopause, alcohol consumption, lack of physical activity[8]



Hormones
Increased/abnormal estrogen and progesterone levels and postmenopausal hormone replacement therapy[9,10]



Reproductive History
Early menarche, late menopause, fewer number of children, giving birth at older age[1]

References available in speaker notes.

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Most Cases of Breast Cancer Are Diagnosed at an Early Stage

- Approximately 20-30% of patients with EBC may experience a recurrence and progress to incurable metastatic disease[1,2]

	Stage[3-5]	Definition
EBC* — Early-stage	0	Noninvasive; carcinoma *in situ*
	I	Tumor size <2 cm
	IIA IIB	Tumor size <5 cm without spreading or up to 2 cm with spread to <4 lymph nodes Tumor size >5 cm without spreading or 2-5 cm with spread to <4 lymph nodes
	IIIA	Any size tumor without spread to the chest wall/skin with spread to 4-9 nearby lymph nodes; Tumor >5 cm and spread to 1-3 nearby lymph nodes
EBC* — Locally advanced	IIIB IIIC	Disease spread to chest wall or skin of breast and <9 axillary lymph nodes Disease spread to ≥10 axillary lymph nodes or lymph nodes near the collarbone or breastbone
Metastatic	IV	Disease spread to distant organs

*Note that EBC is a term used in clinical trials and can include early stage and LABC.
EBC=Early Breast Cancer; LABC=Locally Advanced Breast Cancer.
References available in speaker notes.

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Incidence of EBC Based on Intrinsic Subtypes

HR+, HER2- is the most common subtype of EBC[1]

	HR+		HR-	
	HER2-	HER2+	HER2-	
	73%[1,a] HR+, HER2-	10%[1,a] HR+, HER2+	5%[1,a] HR-, HER2+	12%[1,a] HR-, HER2-
	Luminal A	**Luminal B**	**HER2-Enriched**	**Triple Negative/ Basal-Like**
Incidence among all breast cancers diagnosed worldwide[2,3]	42%-59%	6%-19%	7%-12%	15%-20%
Typical histologic grade[4]	1-2	2-3	2-3	3
Four-year survival rate[5]	93%	90%	83%	77%
Failed initial EBC treatment with 7 years median follow up[6,b]	8%	16%	28%	40%

Luminal A | Luminal B | HER2-Enriched | Triple Negative/ Basal-Like

Better prognosis
Less aggressive

Worse prognosis
More aggressive

[a]Incidence among US patients based on SEER 2014 data. [b]Local recurrence or distant metastases within a median of 7 years after initiating treatment for *de novo* EBC.
EBC=Early Breast Cancer; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; SEER=Surveillance, Epidemiology and End Results; US=United States.
References available in speaker notes.

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Identifying High Risk Patients (Risk of Recurrence)

Introduction to Risk of Breast Cancer Recurrence

Approximately 20% of patients with HR+, HER2- EBC experience relapse[1,2]

Factors that affect risk of recurrence in people with EBC[3-7]:

- Young age at diagnosis
- Tumor morphology (ductal versus lobular)
- Larger tumor size
- Higher tumor grade
- Symptomatic presentation
- Presence of lymphovascular invasion
- Axillary node involvement
- Negative ER or overexpressed tumour HER2 status
- Positive or close margins
- PR negativity
- High proliferation rate (eg, high Ki-67)
- Metaplastic carcinoma (vs. non-metaplastic)

EBC=Early Breast Cancer (Stages I-IIIC); HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor.

1. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2005;365(9472):1687-1717. 2. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2015;386(10001):1341-1352. 3. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11. 4. Dang CM, Giuliano AE. *Oncology*. 2011;25(10):895-6, 899. 5. Stuart-Harris R, et al. *Breast*. 2019;44:153-159. 6. Li LT, et al. JN. Mol Med Rep. 2015;11(3):1566-1572 7. Reddy TP, et al. *Breast Cancer Res*. 2020;22:121.

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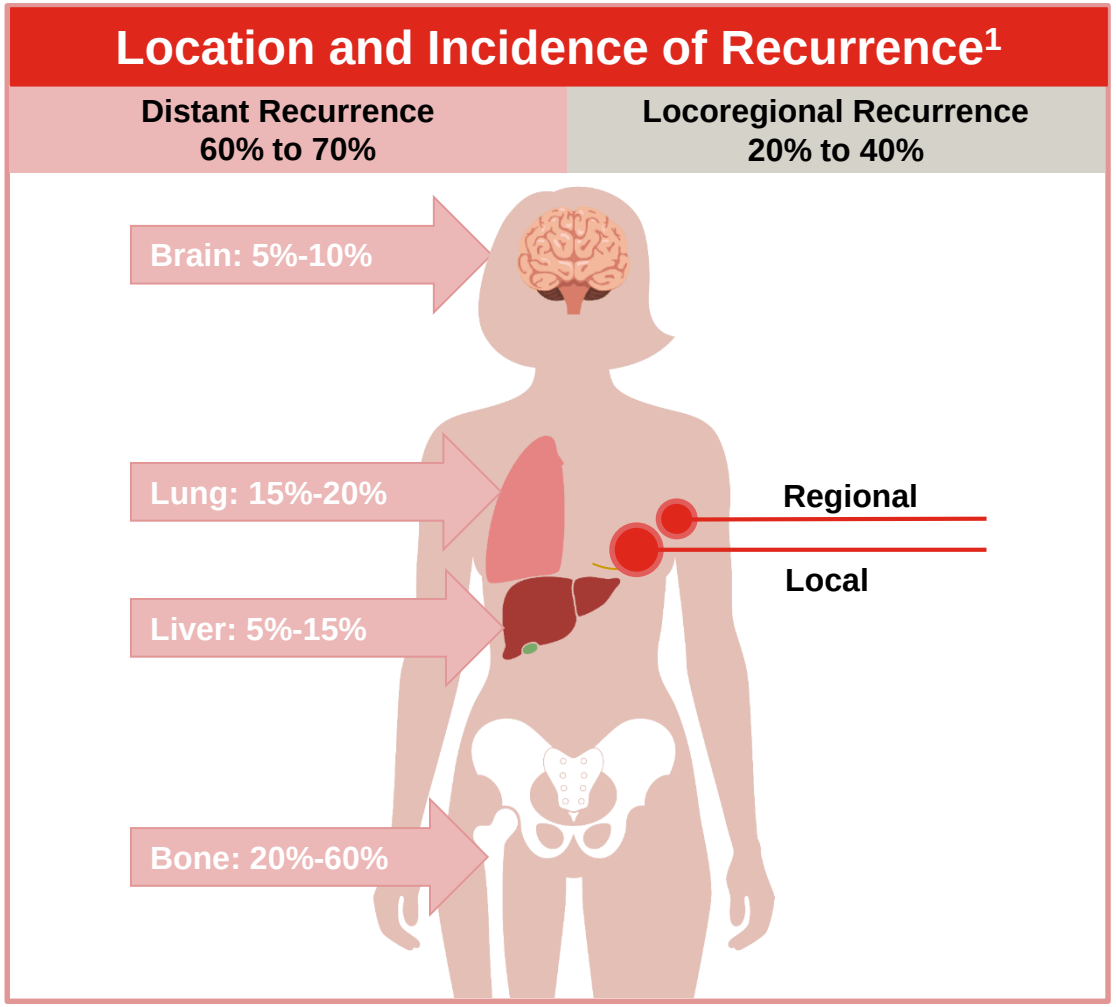
Types of Breast Cancer Recurrence

Location and Incidence of Recurrence[1]



- Three types of breast cancer recurrence[1]
  - Local: occurs in the breast where the cancer originally started or in the skin and underlying tissues of the chest wall
  - Regional: occurs in the lymph nodes near the affected breast
  - Distant: occurs in other parts of the body (common sites are bone, liver, lungs, and brain)
- Local and regional recurrences are treated with curative intent[1]
- Distant recurrences are treated with the intention of maintaining quality of life and relieving symptoms[1]
- Risk of recurrence can be used to guide treatment decisions[2]

1. Gerber B, et al. *Dtsch Arztebl Int*. 2010;107(6):85-91. 2. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11.

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Recurrence Rates by Breast Cancer Subtype

The frequencies of relapse at different sites vary depending on the intrinsic subtype of breast cancer

Subtype	Recurrence Localization				
	Bone	Lung	Liver	CNS	Pleura
Luminal B	36.6%	36.7%	11.1%	7.1%	41.7%
Luminal A	31.0%	6.7%	22.2%	7.1%	41.7%
Erbb2	19.7%	13.3%	33.3%	21.4%	0%
Basal	7.0%	40.0%	22.2%	57.1%	8.3%

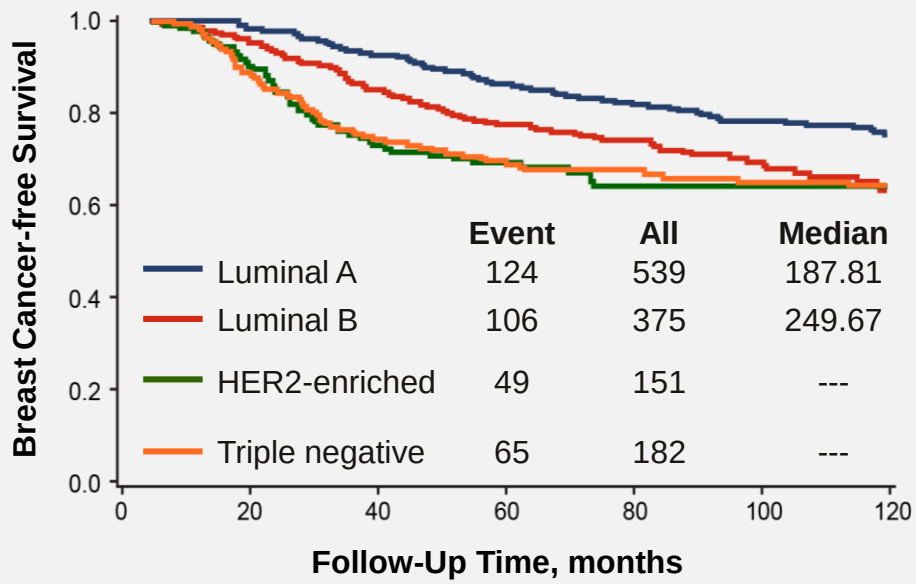
- Bone relapse was most frequent in the luminal subtypes but was found less than expected in the basal subtype
- The converse was true for patients with lung and brain relapses, with lung relapse being less frequent in the luminal A subtype
- Although rare, pleural relapse was found almost exclusively in both luminal subtypes

Smid M, et al. *Cancer Res*. 2008;68(9):3108-3114.

Recurrence Risk by Intrinsic Subtypes

- Different types of breast cancer have different recurrence patterns. HER2+ and triple negative cancers recur earlier than luminal cancers[1]
- Breast cancer subtypes differ significantly with respect to relapse-free survival, with luminal A tumors having the lowest risk of recurrence[2,3]
- This difference is generally less apparent over years[2]

Relapse-free Survival in EBC[2]



EBC=Early Breast Cancer (stages I-IIIC); HER2=Human Epidermal Growth Factor Receptor 2.

1. Stuart-Harris R, et al. *Breast*. 2019;44:153-159. 2. Ribelles N, et al. *Breast Cancer Research*. 2013;15(5):R98. 3. McGuire A, et al. *Ann Surg Oncol*. 2017;24(11):3124-3132.

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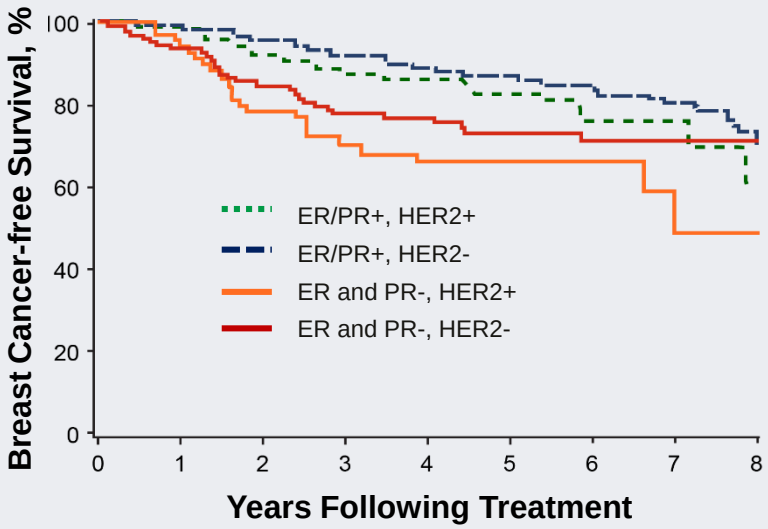
Recurrence Risk by Biomarker Expression

- Overall, patients with HR- breast cancer have a higher risk of recurrence and lower overall survival rates and relapse-free survival rates[1]

- HR- tumors tend to recur earlier and have a worse prognosis than HR+ ones, although the survival rates for both the tumors converge over time (after 5 years)[2]

Relapse-free Survival in EBC[1,a]



[a]Kaplan-Meier plot of relapse-free survival after treatment for primary stage I-III breast cancer adjusted for age, disease stage, histologic grade, chemotherapy, and lymph node status.
EBC=Early Breast Cancer (Stages I-IIIC); ER=Estrogen Receptor; HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; PR=Progesterone Receptor.

1. Ontilo AA, et al. *Clin Med Res*. 2009;7(1-2):4-13. 2. Bentzon N, et al. *Int J Cancer*. 2008;122(5):1089-1094.

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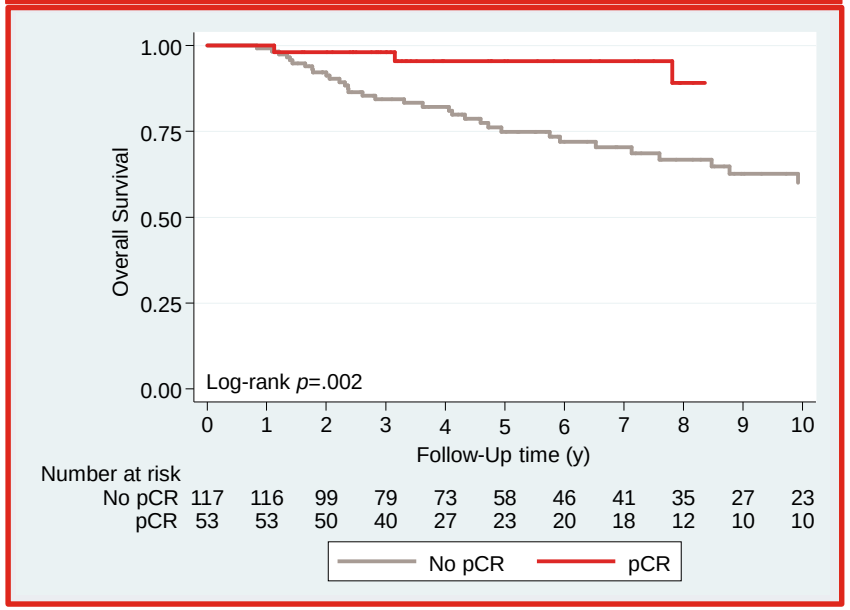
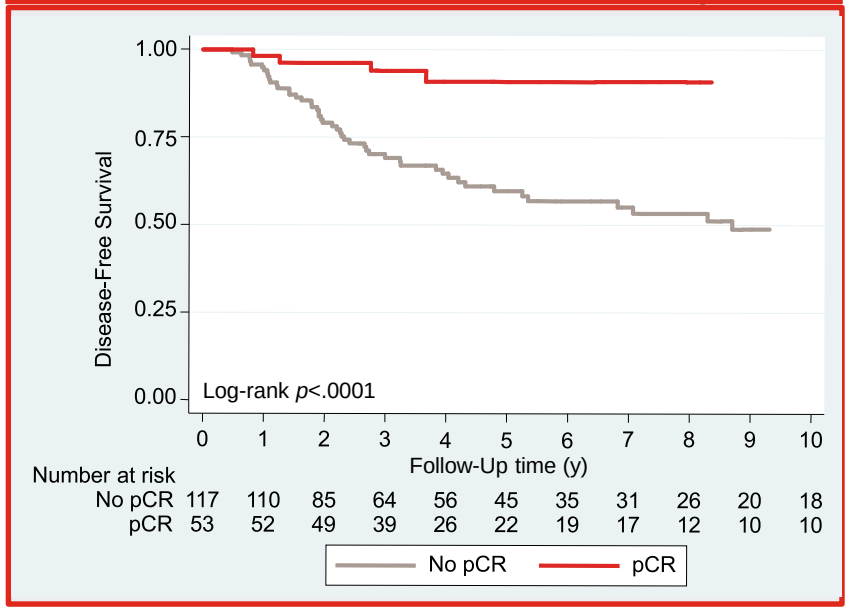
Prognostic Significance of Pathologic Complete Response After Neoadjuvant Chemotherapy

Pathologic complete response (pCR) after neoadjuvant therapy has been shown to be strongly associated with significantly improved DFS and OS in young women with breast cancer[1,2]

Overall Survival[1,a]



Disease-free Survival[1,a]



However, the correlation between pCR and long-term outcome of NAC is somewhat low for patients with HR+, HER2- disease, while being the strongest for TNBC[3,4]

[a]Among women aged ≤40 years.

DFS=Disease-free Survival; HER2= Human Epidermal Growth Factor Receptor 2; OS=Overall Survival; NAC=Neoadjuvant Chemotherapy; TNBC=Triple-negative Breast Cancer; y=Year.

1. Spring L, et al. *J Natl Compr Canc Netw*. 2017;15(10):1216-1223. 2. http://www.nccn.org (Accessed August 10, 2021). 3. von Minckwitz G, et al. *J Clin Oncol*. 2012;30(15):1796-1804. 4. Cortazar P, et al. *Lancet*. 2014;384(9938):164-172.

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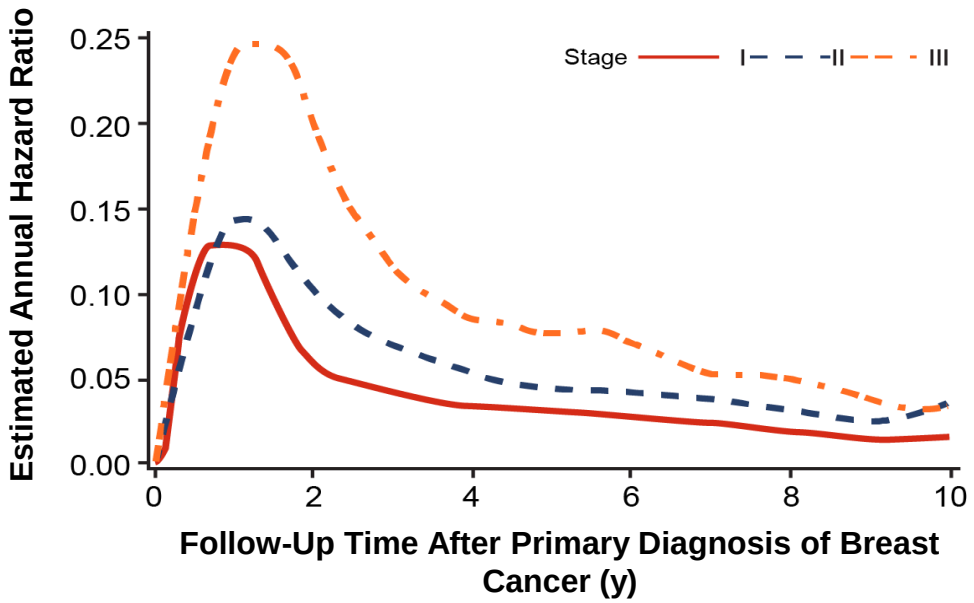
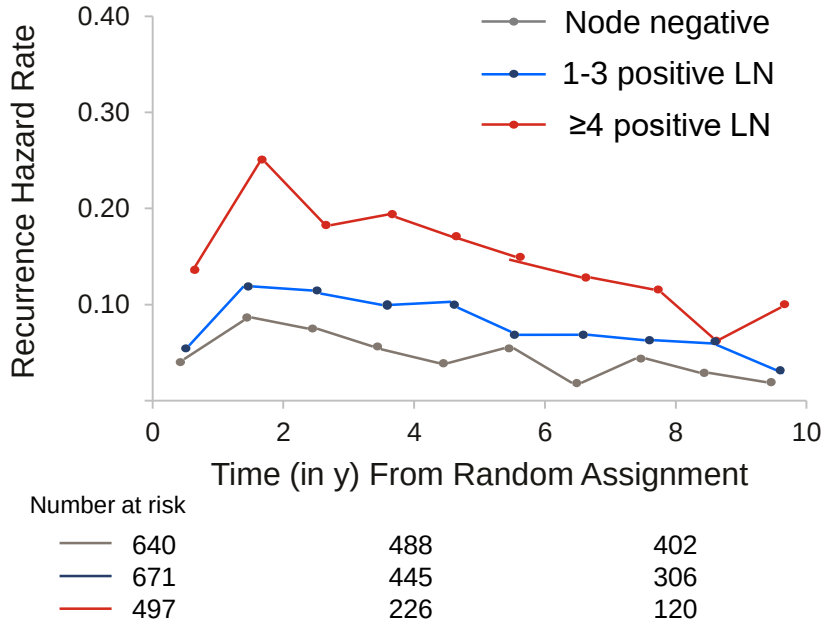
Early Recurrence Peak in the First Few Years on ET: Endocrine Resistance in ER+ breast cancer

Risk of Recurrence by Stage[1]



Risk of Recurrence by Nodal Status[2]



Early recurrence peak reflects endocrine resistance in ER+ breast cancer[1,2]

ER=Estrogen Receptor; ET=Endocrine Therapy; LN=Lymph Node; y=Years.

1. Cheng L, et al. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):800-809. 2. Colleoni M, et al. *J Clin Oncol*. 2016;34(9):927-935.

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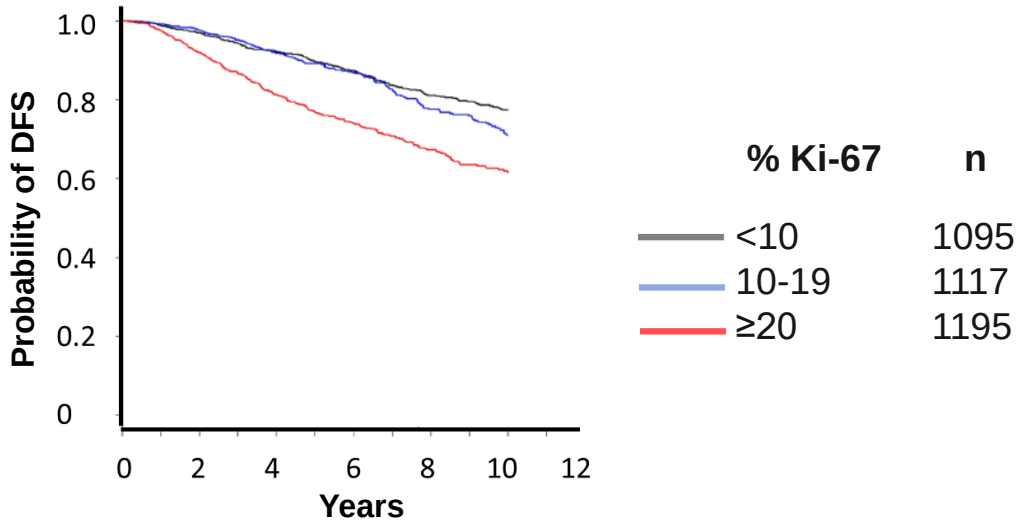
Ki-67 as a Prognostic Factor

Nuclear protein Ki-67 is expressed in proliferative cells and has been found to be a prognostic factor in EBC to identify patients at high risk of recurrence[1,2]

Ki-67 positivity correlates with worse survival (decreased rates of DFS) in patients with EBC[3]



The International Ki-67 in Breast Cancer Working Group has recognized Ki-67 as a prognostic marker in patients with ER+, HER2- breast cancer to identify those who do not need adjuvant chemotherapy[4]

DFS=Disease-free Survival; EBC=Early Breast Cancer (Stages I-IIIC); ER=Estrogen Receptor; HER2=Human Epidermal Growth Factor Receptor 2; n=Number of Patients.
References available in speaker notes.

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Mortality in Patients with HR+, HER2- EBC by Clinical and Pathological Factors (SEER data 2010-2016)

	5-year Mortality rate, % (95% CI) HR+, HER2-		
	Node positive n=50,321	N1mi: micrometastases n=10,096	Node negative n=1,54,161
Overall	18.15	10.31	10.54
Stage I	NA	7.29	8.35
Stage II	12.56	13.39	16.69
Stage III	26.41	19.10	44.46
1-3 Ips Ax lymph nodes positive	12.93	9.96	NA
≥4 Ips Ax lymph nodes positive	24.75	22.23	NA
BR grade 3	25.62	15.25	14.24
Tumor size <1 cm	10.39	6.14	6.70
Tumor size ≥1 to <2 cm	10.24	7.32	9.18
Tumor size ≥2 to <3 cm	15.10	11.76	13.66
Tumor size ≥3 to <4 cm	21.22	14.51	19.49
Tumor size ≥4 to <5 cm	26.41	16.14	22.07
Tumor size ≥5 cm	28.67	18.95	23.87

Consistent with literature[1], higher mortality rates (adjusted hazard ratio >1.4) in patients with HR+, HER2- EBC were associated with[2]:

- ≥4 positive lymph nodes
- BR grade 3
- Greater tumor size

Other factors associated with higher mortality rates were[2,3]:

- Male sex
- Aged ≥70 years
- American Indian/Alaska Native (non-Hispanic)
- Black (non-Hispanic)

Table adapted from: Brown J, et al. *SABCS*. 2019.

BR=Bloom-Richardson; EBC=Early Breast Cancer (Stages I-IIIC); HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; NA=Not Applicable; SEER=Surveillance, Epidemiology and End Results Data; US=United States.

1. Cianfrocca M, Goldstein LJ. *Oncologist*. 2004;9(6):606-616. 2. Brown J, et. al. *SABCS 2019*. Poster P5-08-18. 3. Daly B, Olopade OI. *JAMA*. 2015;313(2):141-142.

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Assessment of Recurrence Risk: Multigene Analyses

- Multigene assays can help identify patients with EBC who have a higher risk of recurrence. Multigene assays may also predict whether patients can benefit from adjuvant systemic therapy

- According to the NCCN guidelines, multigene assays complement TNM and biomarker information

Some of the commercially available gene-based assays:

- **Oncotype DX®**
- **MammaPrint®**
- **Prosigna® (PAM50)**
- **EndoPredict®**
- **Breast Cancer Index**

Oncotype DX is currently the only multigene (21 genes) assay that is both prognostic and predictive of benefit from chemotherapy and is preferred by the NCCN® Guidelines

Oncotype DX has been clinically validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence for patients with HR+, HER2- EBC with 0-3 positive lymph nodes

EBC=Early Breast Cancer (Stages I-IIIC); HER2=Human Epidermal Growth Factor Receptor 2; HR=Hormone Receptor; NCCN=National Comprehensive Cancer Network; TNM=Tumor, Node, Metastasis.

http://www.nccn.org/ (August 10, 2021).

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Summary

- **High recurrence rates** have been associated with some **disease characteristics** in patients with HR+, HER2- EBC which include high tumor grade, negative PR status, LVI, large tumor size, high Ki-67 levels and luminal B subtype
- **High Ki-67** is associated with **high risk of recurrence** and **worse survival**, thus has been recognised to be a prognostic marker to identify the patients with HR+, HER2- EBC who may benefit from further therapy
- **Higher mortality rates** have been observed in patients with HR+, HER2- EBC who have **≥4 positive lymph nodes, Grade 3 tumors,** and **greater tumor size**

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