



第6回 GRACE Seminar

第一部：周術期ルミナールタイプ薬物療法：治療選択

Oncotype DX

がん研究会有明病院

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本日の議題

- Oncotype DXのエビデンス
- Oncotype DXの保険適応の対象
- 当院でのOncotype DXの適応
- 適応について悩む症例の検討



Oncotype DXのエビデンス



Oncotype DX[®]の21遺伝子と再発スコア (RS)

21種の遺伝子

増殖	ER	浸潤	HER2	他	reference
Ki-67 STK15 Survivin Cyclin B1 MYBL2	ER PGR BcL2 SCUBE2	Stromelysin3 Cathepsin L2	GRB7 HER2	GSTM1 CD68 BAG1	Beta-actin GAPDH RPLPO GUS TFRC

再発スコア (Recurrence Score : RS)

リスク分類	RS	リスクグループ毎の比率 (%) (n=668)
低リスク	< 18	51
中間リスク	18 ≤ RS < 31	22
高リスク	31 ≤	27

TAILORx Study Design: Treatment Assignment & Randomization

Accrued Between April 2006 – October 2010

Key Eligibility Criteria

- Node-negative
- ER-pos. HER2-neg
- T1c-T2 (high-risk T1b)

Statistical Design

- Non-inferiority - IDFS
- HR 1.332 (90 vs. 87% 5-yr DFS)
- Type I 10%, type II 5%
- Full info– 835 IDFS events

Preregister – Oncotype DX RS (N=11,232)

Register (N=10,273)

HG/NG II-III, Ly+

ARM A: Low RS 0-10

(N=1619 evaluable)

ASSIGN

Endocrine Therapy (ET)

Mid-Range RS 11-25

(N=6711 evaluable)

RANDOMIZE

Stratification Factors:

Menopausal Status, Planned Chemotherapy,
Planned Radiation, and RS 11-15, 16-20, 21-25

ARM D: High RS 26-100

(N=1389 evaluable)

ASSIGN

ET + Chemo

ARM B: Experimental Arm

(N=3399)

ET Alone

ARM C: Standard Arm

(N=3312)

ET + Chemo

Sparano et al. NEJM 2018
(PMID: 31157962)



Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano and Others | N Engl J Med 2018; 379:111-121

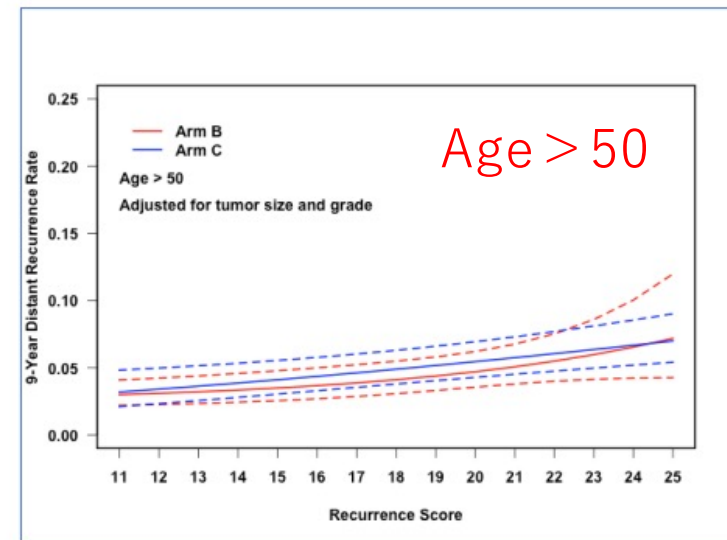
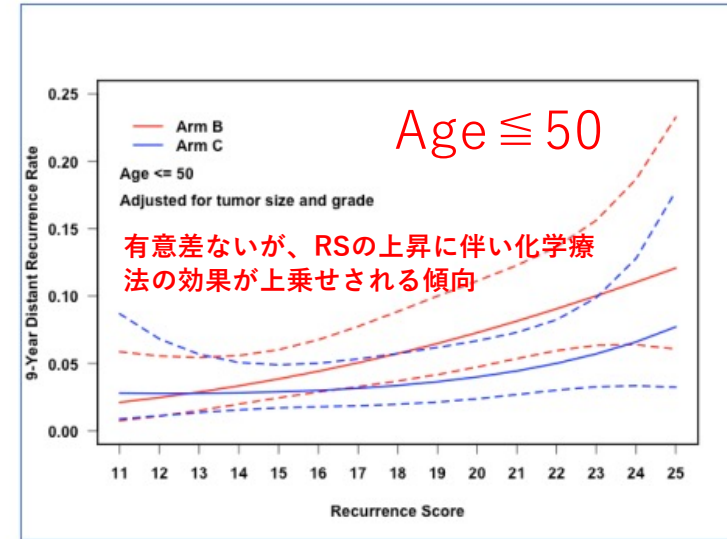
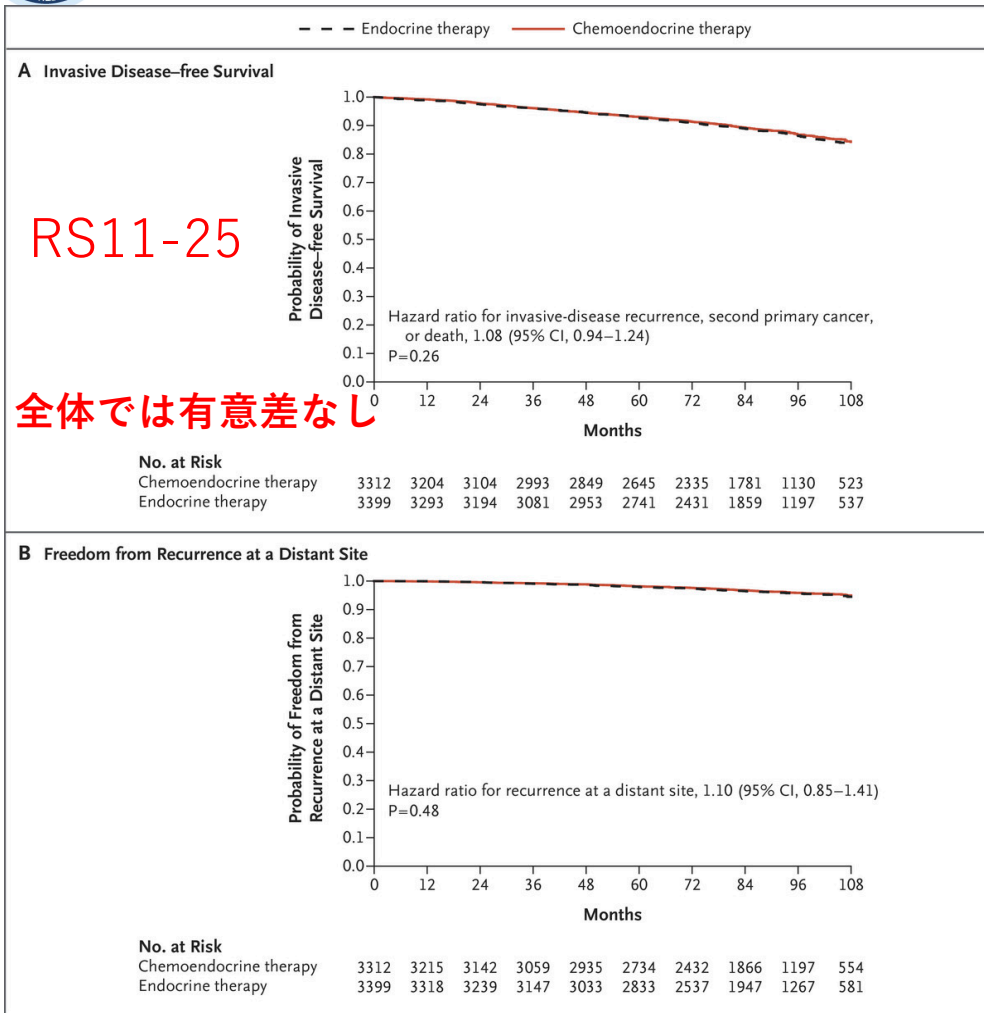


Figure S8. Continuous RS 11-25 and distant recurrence by age (≤ 50 vs. > 50 years). 9-



Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer

J.A. Sparano and Others | N Engl J Med 2019; 380:2395-2405

Table 2. Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy in Women Younger than 50 Years of Age, Stratified According to Recurrence Score and Clinical Risk (Intention-to-Treat Population).*

Variable	Clinical Risk	No. of Patients	Estimated Probability of Recurrence, Second Primary Cancer, or Death <i>percent</i>	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI) [†]	Estimated Probability of Distant Recurrence <i>percent</i>	Estimated Absolute Chemotherapy Benefit <i>percentage points</i>	Hazard Ratio for Distant Recurrence (95% CI) [†]
Recurrence score of 16–20							
No chemotherapy	Low	328	19.6±3.1	1.89 (1.18–3.04)	4.6±1.5	–0.2±2.1	1.00 (0.44–2.28)
Chemotherapy	Low	343	9.5±1.8		4.8±1.5		
No chemotherapy	High	107	19.0±4.5	1.68 (0.76–3.72)	11.9±3.9	6.5±4.9	2.26 (0.70–7.34)
Chemotherapy	High	108	16.3±5.8		5.5±3.0		
Recurrence score of 21–25							
No chemotherapy	Low	158	19.7±4.5	1.38 (0.74–2.57)	11.4±3.9	6.4±4.9	3.16 (1.01–9.94)
Chemotherapy	Low	161	15.8±4.0		5.0±3.0		
No chemotherapy	High	75	26.4±5.4	2.63 (1.14–6.05)	18.8±5.0	8.7±6.2	1.86 (0.73–4.74)
Chemotherapy	High	82	11.4±3.8		10.1±3.7		

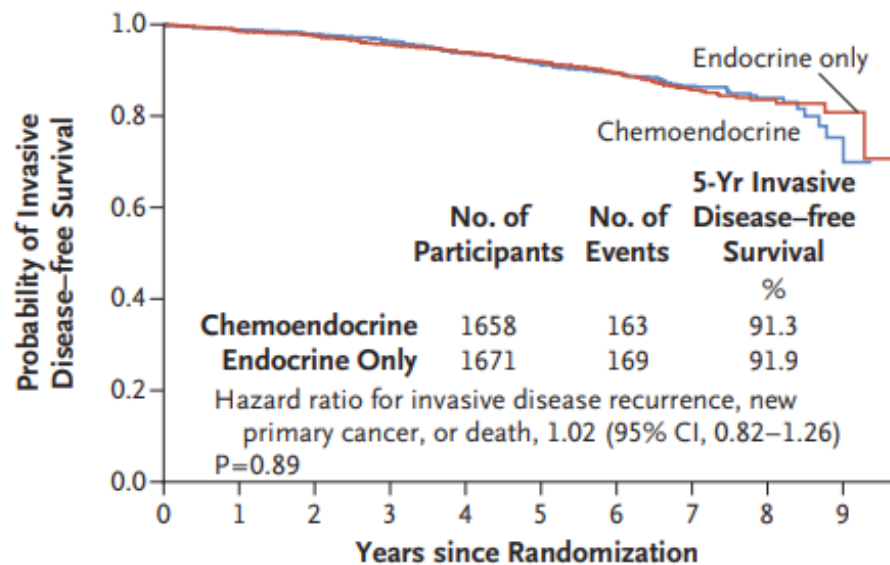


21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

RxPONDER試験

K. Kalinsky and Others | N Engl J Med 2021; 385:2336-2347 **T1-3**

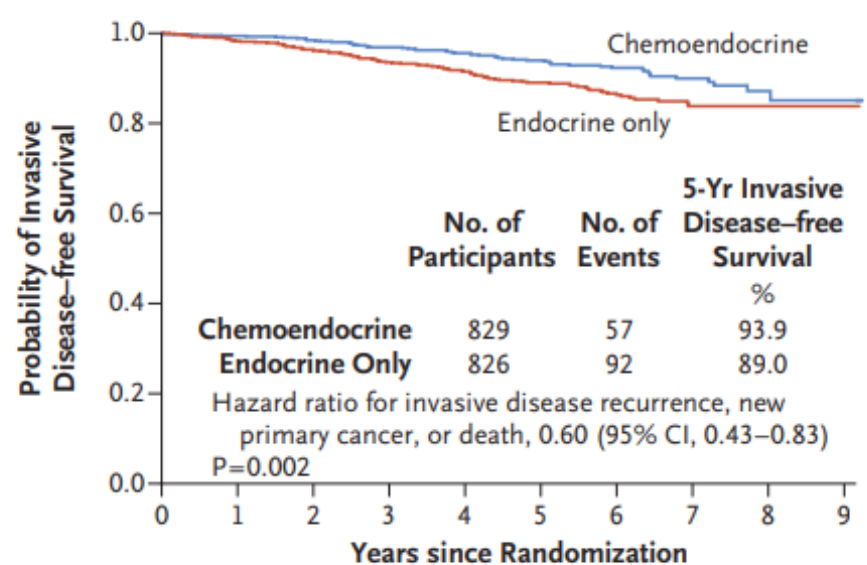
B Invasive Disease-free Survival, Postmenopausal Participants



No. at Risk

	0	1	2	3	4	5	6	7	8	9
Chemoendo- crine group	1658	1515	1413	1298	1145	993	659	358	129	14
Endocrine- only group	1671	1568	1474	1343	1196	1030	679	364	137	21

C Invasive Disease-free Survival, Premenopausal Participants



No. at Risk

	0	1	2	3	4	5	6	7	8	9
Chemoendo- crine group	829	764	710	642	546	484	312	153	46	5
Endocrine- only group	826	760	703	622	542	463	290	138	44	2

Trial Assigning Individualized Options for Treatment (TAILORx): An Update Including 12-Year Event Rates

12-Year DRFI Rates in Age ≤ 50 Years & RS 16-25				
	Estimated Absolute Chemo Benefit <u>Not Stratified</u> by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit <u>Stratified</u> by Clinical Risk
RS 16-20 (N=886)	$\Delta +0.4\%$ (\pm SE 2.1%)	Low	671 (76%)	$\Delta -0.5\%$ (\pm SE 2.2%)
		High	215 (24%)	$\Delta +3.1\%$ (\pm SE 5.4%)
RS 21-25 (N=476)	$\Delta +7.8\%$ (\pm SE 3.4%)	Low	319 (67%)	$\Delta +5.9\%$ (\pm SE 3.4%)
		High	157 (33%)	$\Delta +11.7\%$ (\pm SE 7.2%)



OncotypeDX[®]による化学療法上乗せ効果の解釈

リンパ節転移	年齢、閉経、臨床リスク	RS 0-15	RS 16-20	RS 21-25	RS 26-100
陰性	≥ 50歳	内分泌療法			化学療法併用
	< 50歳	臨床リスク低	内分泌療法		化学療法併用
				-0.2% → -0.5%	6.4% → 5.9%
	臨床リスク高	内分泌療法	化学療法併用		
6.5% → 3.1%			8.7% → 11.7%		
1-3個陽性	閉経後	内分泌療法			化学療法併用
1個以上陽性	閉経前	化学療法併用			
		3.9% (RS0-13)	5.8% (RS14-25)		

高臨床リスク：組織学的Grade1かつ腫瘍径3cm以上
 組織学的Grade2かつ腫瘍径2cm以上
 組織学的Grade3かつ腫瘍径1cm以上

低臨床リスク：上記以外

Sparano JA, Gray RJ, Makower DF, et al. N Engl J Med 379:111-121, 2018
 Joseph AS, Robert JG, Peter MR, et al. N Engl J Med 380:2395-2405, 2019
 Kevin K, William EB, Julie RG, et al. N Engl J Med 385:2336-2347, 2021
 Sparano JA, Gray RJ, Makower DF, et al. SABCS 2022

NRG-BR009: Phase III adjuvant trial evaluating the addition of adjuvant chemotherapy to Ovarian Function Suppression plus Endocrine Therapy in premenopausal patients with pN0-1, ER-positive/HER2-negative breast cancer and an onco[®]type recurrence score ≤ 25 (OFSET)

NRG-BR009 SCHEMA

- Premenopausal; resected ER-positive/HER2-negative BC
- pN0 with RS 21-25 or 16-20 and high clinical risk^{***}
 - pN1 with RS 0-25

STRATIFICATION

- Nodal/RS Status (pN0 RS 16-25 vs pN1 RS 0-15 and pN1 RS 16-25)
- Intent to receive CDK4/6 inhibitor (yes; no)
- Age (18-39; 40 and older)

RANDOMIZATION^{*}**

Arm 1

Ovarian function suppression
+
Aromatase inhibitor
x 5 years

Arm 2

Adjuvant chemotherapy
+
Ovarian function suppression
+
Aromatase inhibitor
x 5 years

化学療法の効果か、
化学療法閉経による
効果かは、本試験の
結果が待たれる



Oncotype DXの保険適応の対象



保険対象（2023年9月～）

- 早期浸潤性乳癌患者
- ホルモン受容体陽性かつHER2陰性
- リンパ節転移陰性、微小転移又はリンパ節転移1～3個

年齢、閉経状態、腫瘍径などによる制限なし



当院でのOncotype DXの適応



当院でのRSと化学療法の推奨

リンパ節転移	方針
陰性	50歳より上: RS25以下でケモ省略 50歳以下かつClinical risk-Low: RS20以下でケモ省略 50歳以下かつClinical risk-High: RS15以下でケモ省略
陽性	閉経後: LN1-3個+、RS25以下でケモ省略 閉経前: LN+なら基本的に全例ケモを推奨 (Case by caseでOncotypeDX提出可、解釈もRSに応じて)

Clinical risk-High
Grade 1 & T >3cm
Grade 2 & T >2cm
Grade 3 & T >1cm



当院でのOncotypeDX 検査の適応

リンパ節転移	方針
陰性	50歳より上: RS25以下でケモ省略 50歳以下かつClinical risk-Low: RS20以下でケモ省略 50歳以下かつClinical risk-High: RS15以下でケモ省略
陽性	閉経後:LN1-3個+, RS25以下でケモ省略 閉経前:LN+なら基本的に全例ケモを推奨 (Case by caseで提出可、解釈もRSに応じて)

Clinical risk-High
Grade 1 & T >3cm
Grade 2 & T >2cm
Grade 3 & T >1cm

閉経後はN+3個以下

閉経前はNO

+Risk factorから総合的に判断

- A: 強く推奨
- B: 弱く推奨
- C: 行わないことを弱く推奨
- D: 行わないことを強く推奨

	Low	Intermediate	High
St.Gallen 2007 Risk category *改変	全てを満たす	1つ以上満たす	全てを満たす
	pT1 Grade1 35歳以上 Ly(-) (Ki67 low)	pT2以上 Grade2-3 35歳未満 Ly(+) (Ki67 Intermediate以上)	
pN0	B	A	C
pN1-3個	A	B	C
pN4個	D	D	D



適応について悩む症例の検討



適応について悩む症例の検討

- RSの点数によって化学療法のレジメンは変更する？
- 特殊型：ILCの適応は？
- T1bN0は？
- 閉経前N1miは？
- RS低いが脈管侵襲+の症例はどう考える？



RSの点数によって化学療法レジメンは変更する？



Clinical Outcomes in Early Breast Cancer With a High 21-Gene Recurrence Score of 26 to 100 Assigned to Adjuvant Chemotherapy Plus Endocrine Therapy A Secondary Analysis of the TAILORx Randomized Clinical Trial

Table 2. Kaplan-Meier Estimates of Clinical Outcomes at 5 Years for Patients With a Recurrence Score of 26 to 100 Assigned to Chemotherapy Stratified by Adjuvant Chemotherapy Regimen in the Intention-to-Treat Population^a

Variable	Mean (SE) [95% CI]						
	All Patients	Taxane and Cyclophosphamide	Anthracycline Without Taxane	Anthracycline and Taxane	CMF	Other	No Chemotherapy
No.	1389	589 42%	334	244 18%	52	81	89
Invasive disease-free survival	87.6 (1.0) [85.5-89.4]	88.1 (1.5) [84.8-90.8]	87.4 (2.0) [83-90.8]	88.6 (2.3) [83.2-92.3]	84 (5.6) [69.3-92.1]	91.3 (3.4) [81.5-96]	79.7 (4.9) [67.9-87.5]
Freedom from recurrence of breast cancer at a distant site	93.0 (0.8) [91.4-94.4]	92.7 (1.2) [90-94.7]	92.3 (1.6) [88.5-94.9]	95.1 (1.5) [91-97.3]	88.5 (4.8) [74.6-95.1]	95.5 (2.5) [86.8-98.5]	92.8 (3.1) [83.6-97]
Freedom from recurrence of breast cancer at a distant or local-regional site	91.0 (0.8) [89.1-92.5]	91.0 (1.3) [88-93.2]	90.1 (1.8) [86-93]	93.6 (1.7) [89.1-96.2]	88.7 (4.8) [74.9-95.1]	95.5 (2.5) [86.8-98.5]	84 (4.5) [72.8-90.8]
Overall survival	95.9 (0.6) [94.6-96.9]	95.8 (0.9) [93.5-97.2]	96.7 (1.0) [93.9-98.2]	97.2 (1.1) [93.3-98.7]	90.1 (4.7) [75.8-96.2]	97.2 (2.0) [89.2-99.3]	90.7 (3.7) [80.3-95.7]

Abbreviation: CMF, cyclophosphamide/methotrexate/5-fluorouracil.

^a Five-year Kaplan-Meier estimates (percent), standard error, and 95% confidence intervals shown.

JAMA Oncol. 2020;6(3):367-374

TCとA-Tで有意な差はみられておらず、現時点ではTCで十分な可能性



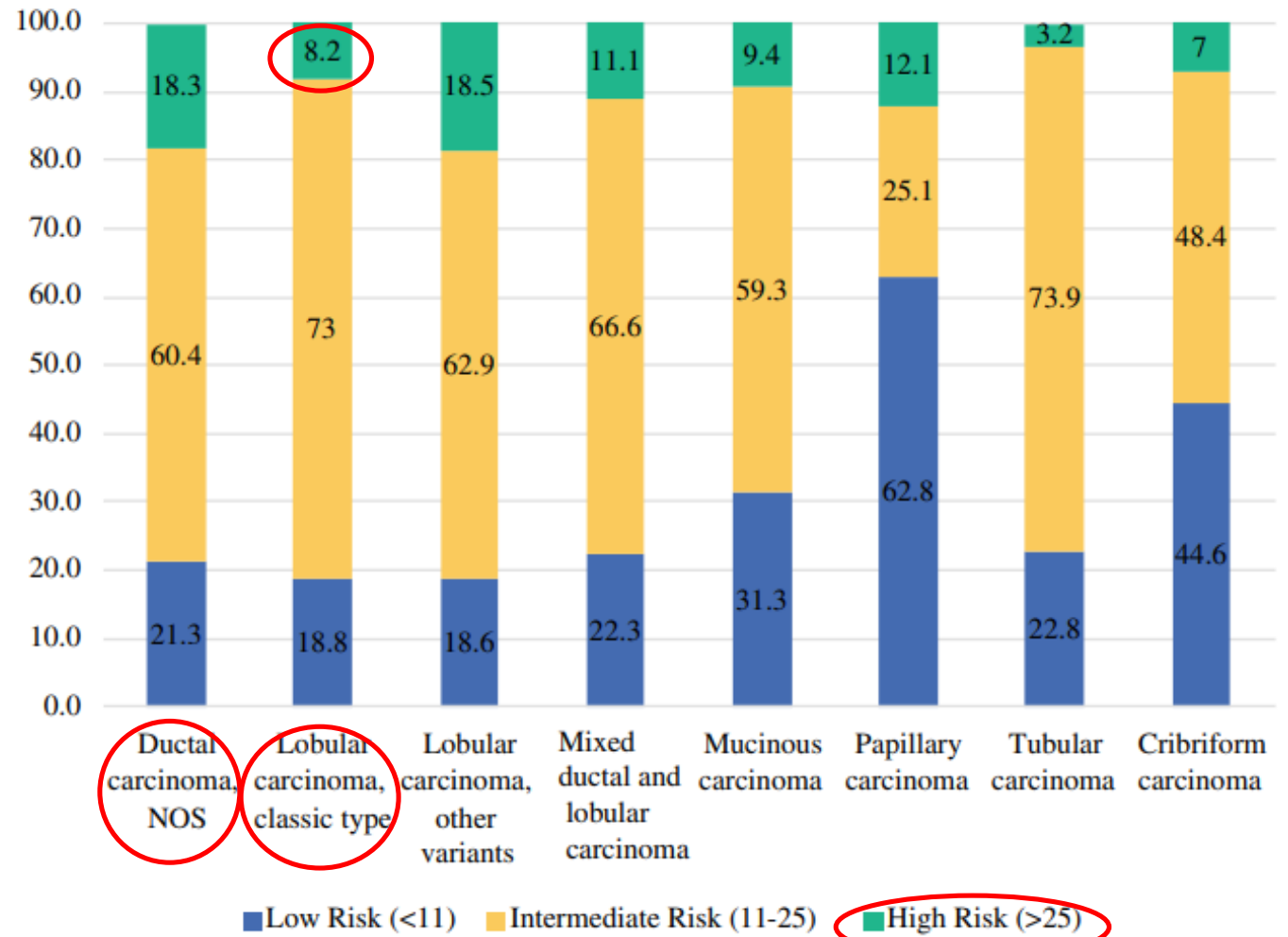
特殊型：浸潤性小葉癌（ILC）の適応は？



Breast Cancers of Special Histologic Subtypes Are Biologically Diverse

FIG. 2 Distribution of Recurrence Score result by tumor subtype using TAILORx cutoffs

	Total
Overall	610,350
<u>Ductal carcinoma, NOS</u>	<u>504,362</u>
<u>Lobular carcinoma, classic type</u>	<u>49,819</u>
<u>Lobular carcinoma, other variants</u>	<u>5069</u>
Invasive carcinoma, mixed	25,329
Mucinous carcinoma	16,116
Papillary carcinoma	4159
Tubular carcinoma	3599
Cribriform carcinoma	1897



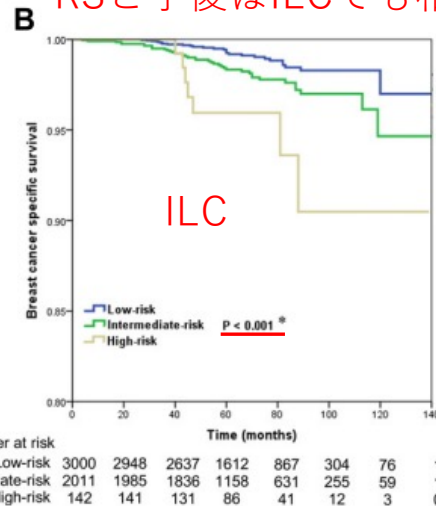
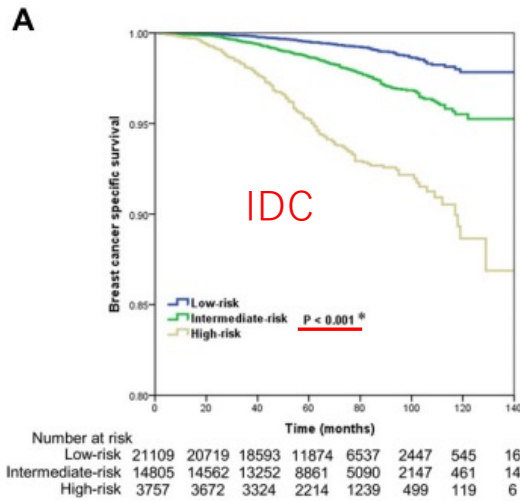
ILCではRS highが少ない



The Distribution and Outcomes of the 21-Gene Recurrence Score in T1-T2N0 Estrogen Receptor-Positive Breast Cancer With Different Histologic Subtypes

N=5153

RSと予後はILCでも相関あり

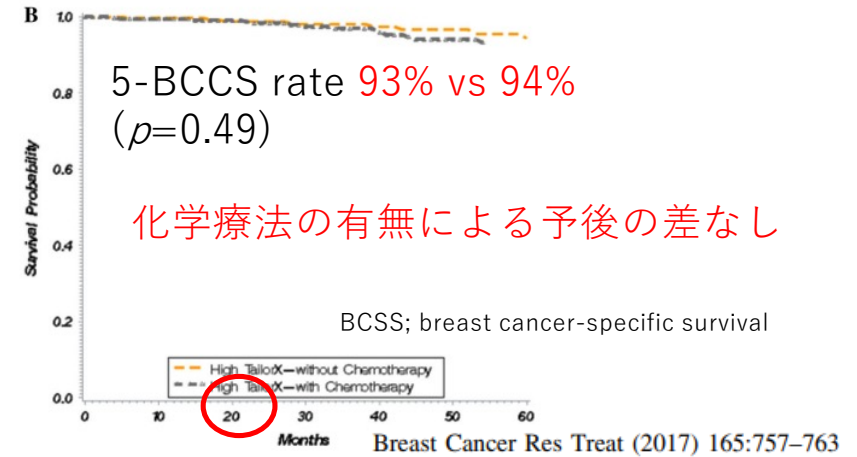


Front Genet. 2018 Dec 17:9:638.

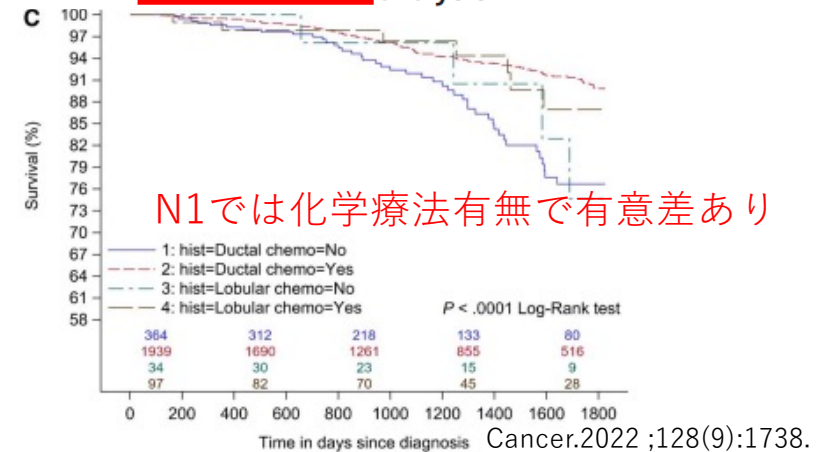
ILCでは、化学療法の上乗せ効果があるというデータと、ないというデータもあり、RSの解釈には注意が必要

Impact of the 21-gene recurrence score on outcome in patients with invasive lobular carcinoma of the breast

NCIのSEERのデータベース N=7316



Adjuvant chemotherapy in patients with invasive lobular carcinoma and use of the 21-gene recurrence score: A National Cancer Database analysis





T1bN0は？



TAILORxにおけるT1bの割合

Table S1. Characteristics of patients by assigned treatment in intention-to-treat population

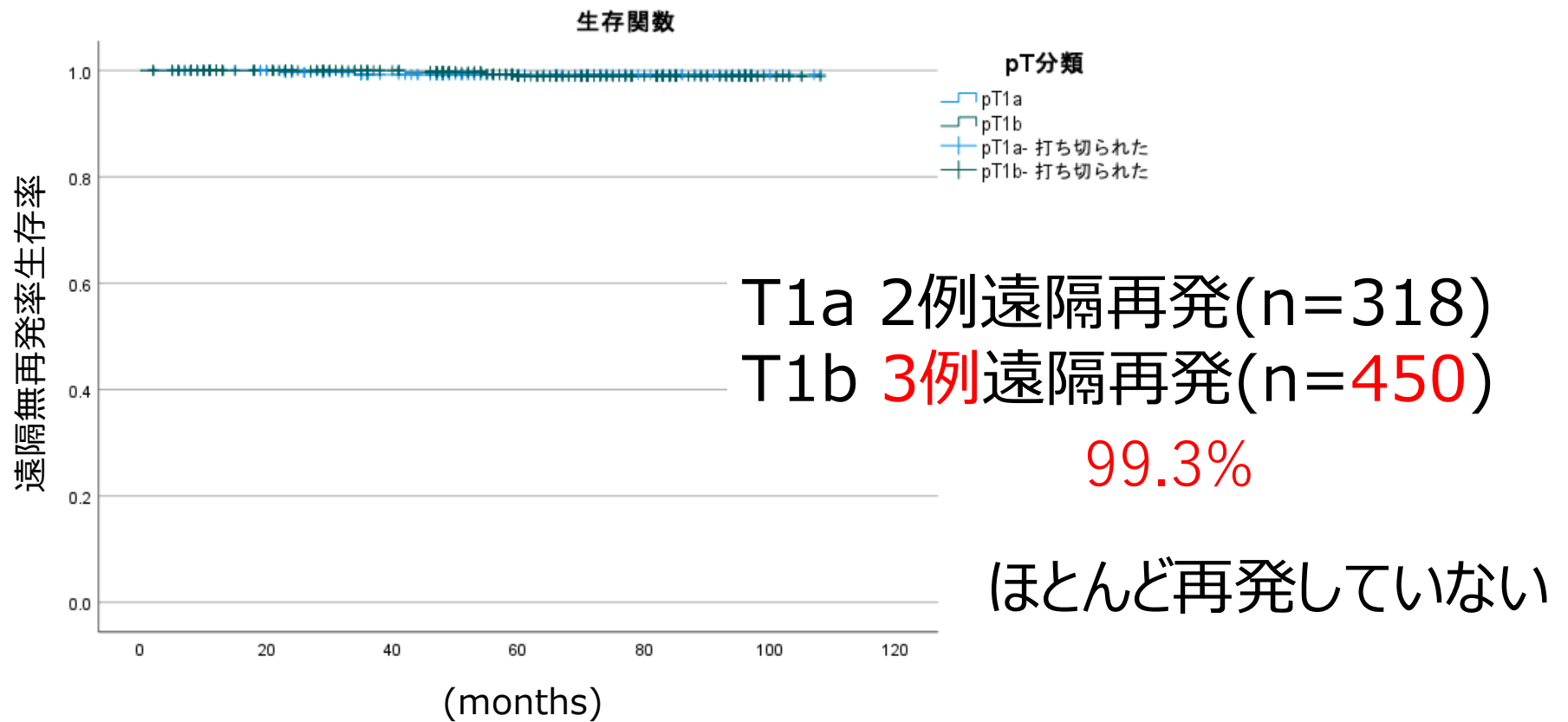
Study Arm	Recurrence Score 0-10		Recurrence Score 11 to 25		Recurrence Score 26 or Higher
	Arm A	Arm B	Arm C	Arm D	Arm D
Assigned Treatment	Endocrine Therapy	Endocrine Therapy	Chemoendocrine Therapy	Chemoendocrine Therapy	Chemoendocrine Therapy
Number	1619	3399	3312	1389	
Age (years)					
Median (range)	58 (25-75)	55 (23-75)	55 (25-75)	56 (23-75)	
<= 40	58 (4%)	154 (5%)	157 (5%)	79 (6%)	
41-50	371 (23%)	985 (29%)	920 (28%)	330 (24%)	
51- 60	563 (35%)	1235 (36%)	1206 (36%)	512 (37%)	
61-70	518 (32%)	868 (26%)	895 (27)	395 (28%)	
71-75	109 (7%)	157 (5%)	134 (4%)	73 (5%)	
Menopausal Status					
Pre	478 (30%)	1212 (36%)	1203 (36%)	407 (29%)	
Post	1141 (70%)	2187 (64%)	2109 (64%)	982 (71%)	
Tumor size (cm)					
Median (interquartile)	1.5 (1.2, 2.0)	1.5 (1.2, 2.0)	1.5 (1.2, 2.0)	1.7 (1.3, 2.3)	
Mean – cm (+/- SD)	1.74 (+/-0.76)	1.71 (+/-0.81)	1.71 (+/-0.77)	1.88 (+/-0.99)	
Distribution –no./total					
<= 1.0	202 (12%)	446 (13%)	423 (13%)	188 (14%)	
1.1 – 2.0	4048 (62%)	2450 (62%)	2402 (64%)	741 (52%)	
2.1 – 3.0	297 (18%)	640 (19%)	625 (19%)	348 (25%)	
3.1 – 4.0	83 (5%)	122 (4%)	119 (4%)	91 (7%)	
>= 4.1	19 (1%)	41 (1%)	40 (1%)	20 (1%)	
Unknown	0	0	2	1	
Histologic grade					
Low	530 (34%)	959 (29%)	934 (29%)	89 (7%)	
Intermediate	931 (59%)	1884 (57%)	1837 (57%)	590 (43%)	
High	111 (7%)	439 (13%)	445 (14%)	681 (50%)	
Unknown	47	117	96	29	
ER expression					
Negative	5 (0%)	6 (0%)	3 (0%)	40 (3%)	
Positive	1614 (100%)	3393 (100%)	3309 (100%)	1349 (97%)	
PgR expression					
Negative	28 (2%)	267 (8%)	251 (8%)	405 (30%)	
Positive	1555 (98%)	3072 (92%)	2989 (92%)	948 (70%)	
Unknown	36	60	72	36	
Clinical Risk					
Low	1227 (78%)	2440 (74%)	2359 (73%)	589 (43%)	
High	345 (22%)	842 (26%)	855 (27%)	770 (57%)	
Unknown	47	117	98	30	

	RS 0-10	RS 11-25	RS 26-100
T ≤ 1.0cm	202名	446 + 423名	188名
	16%	69%	15%

T1bは全体の13%しか入っていない



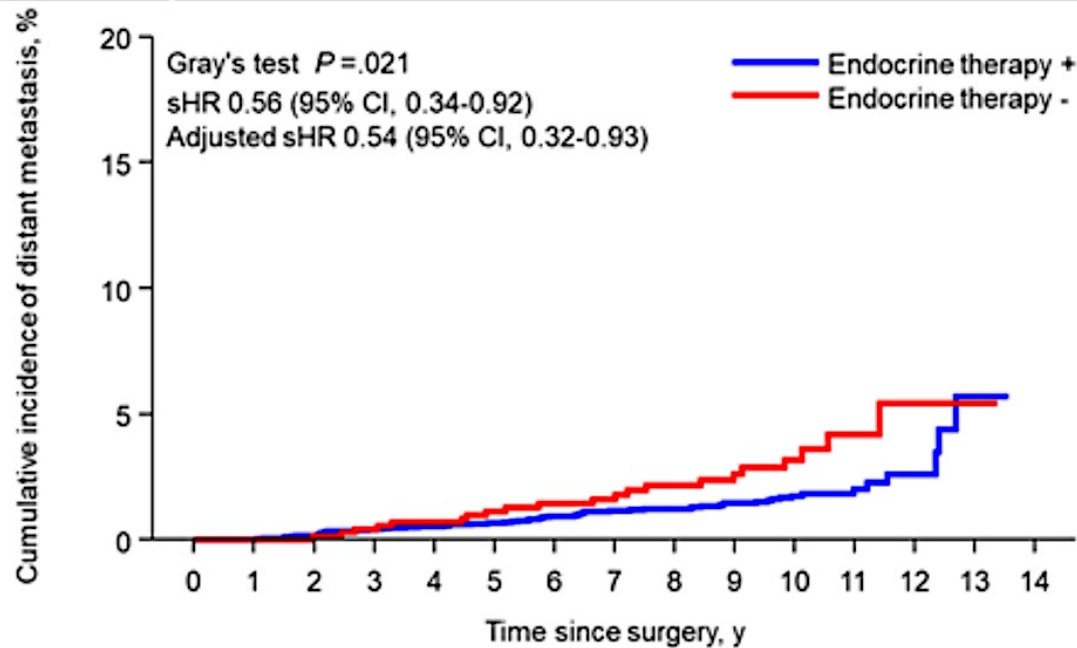
当院のT1a/bN0の予後(2010 - 2014)





日本の多施設でのT1a/bN0の予後

Figure 1. The 9-year Cumulative Incidence of Distant Metastasis



No. at risk

Endocrine therapy +	3991	3835	3695	3191	2715	1365	182	0
Endocrine therapy -	767	725	692	580	477	255	43	0

Multicenter (JCOG), retrospective study
n=4758

9-year **DDFS**

- **ET vs. non-ET: 96.2% vs. 82.9%**
(HR 0.51, $P < .001$)

9-year **DFS**

- **ET vs. non-ET: 93.6% vs. 83.5%**
(HR 0.39, $P < .001$)

**基本的には予後良好であり、
Oncotype DXの積極的な推奨はない**



閉経前N1miは？



Abstract GS2-07: Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) \leq 25 randomized to endocrine therapy (ET) +/- chemotherapy (CT): SWOG S1007 (RxPONDER) ✓

RxPONDER update

閉経前	n (%)	IDFS absolute benefit
pN1mi	206 (12.4%)	7.3% (HR = 0.44) *22 IDFS events
pN1	1403 (84.7%)	4.8% (HR = 0.64)

→N1miのIDFS イベント数がまだ22例と少なく immatureではあるが、現時点では、**原則化学療法推奨**



RS低いが脈管侵襲+の症例はどう考える？



Lymphovascular invasion in hormone-positive, human epidermal growth factor-negative, low-burden axillary disease in early breast cancer patients tested for oncotype DX recurrence score

N=107
単施設

Table 1. Lymphovascular invasion and its relation to oncotype DX RS and Ki-67 expression in invasive breast cancer

Pathological biomarkers	LVI		LVI-positive rate in the cohort (%)	χ^2	P
	Negative	Positive			
ODX-RS	73	34	31.7	11.1	0.29
High	12	3	2.8		
Low	61	31	29		
Ki-67 expression	73	34	31.7	0.43	0.51
High	35	14	13		
Low	38	20	19		

LVI – lymphovascular invasion, ODX-RS – oncotype DX recurrence score

Low ODX-RS < 25, High ODX-RS \geq 26

Low Ki-67 < 15, High Ki-67 \geq 15

Contemp Oncol (Pozn) 2022;26(2):139-143.

Oncotype DX-RSとは相関しないので、別のリスク因子として総合的にリスクを評価する必要あり



Take Home Message

- ▶ 対象は閉経後のN+3個以下、閉経前のN0症例（T3N0やT4N0/1の化学療法推奨例、化学療法拒否や不耐例、化学療法を予め希望例は除外）
- ▶ RSの点数に関わらず、化学療法のレジメンはTCで十分
- ▶ 特殊型のRSの解釈には注意が必要
- ▶ T1bN0は、予後良好のため原則不要
- ▶ 閉経前N1miは、現時点では化学療法推奨のため提出しない
- ▶ Ly+とRSのスコアは関連しないので、別の因子と考えた上でのリスク評価が望ましい



ご清聴ありがとうございました

