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Incorporating the 21-gene Recurrence Score (RS) Results in Breast Cancer Treatment Decisions in Real-life Clinical Practice: The Clalit Health Services (CHS) Experience (2006-2018)

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Clalit Health Services, Medicine Community Division
April, 2018

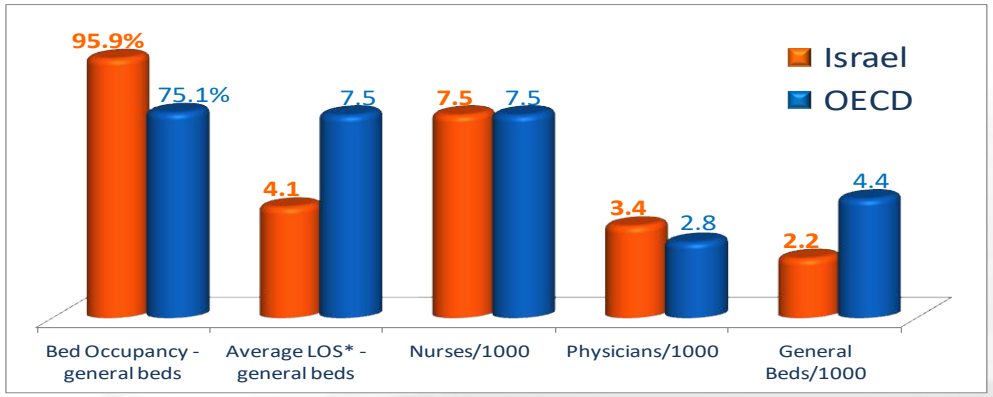
Background

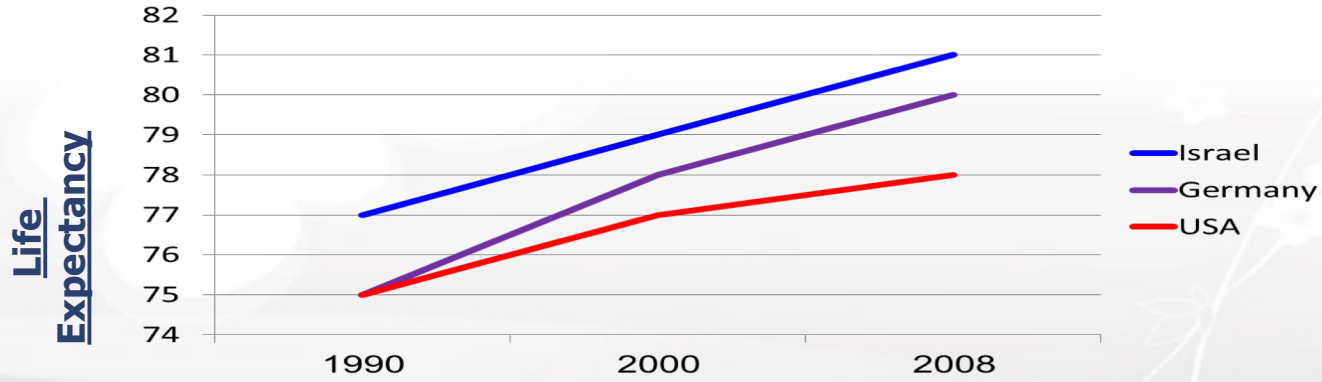
- CHS is the largest HMO in Israel, insuring 53% of the Israeli population (4.5 million individuals)*
- CHS approved reimbursement of the RS assay for N0 HR+ HER2-negative breast cancer (BC) patients in January 2006
  - CHS extended the approval to include N1mi/N1 patients in January 2008
- Since CHS approval of the assay, a total of about 900 N0 patients and N1mi/N1 patients yearly underwent RS testing through CHS

*As of 2018

Israel's Health System

- >8 million inhabitants (wide diversity of ethnicities)
- National obligatory Health Insurance to all (1995)
- Must be member in 1 of 4 health plans (insurer/provider)
- HP funding by capitation (age, sex and periphery)
- <1% move annually between health plans
  - 90% 'happy' or 'very happy' with their health plan





Clalit Health Services

since 1911 – sick fund – Bismarck system

- Largest HMO in Israel ("2nd Largest HMO in the world")
- 52 Market Share in Israel (>4.2 M members)
  - Overrepresentation of the sick, poor and elderly
- ~2000 community clinics including Child Health Centers, Women Health Centers and large Consultant Medicine Clinics, >3,000 pcp's, >2,000 nurses
- 14 hospitals – General, Children, Psychiatric, Rehabilitation & Geriatric
- Electronic information since 1980's – today a fully computerized system with a comprehensive EHR

Clalit health services

- >32,000 Employees
- 2013 budget – >6 B $
- 14 Hospitals
- 425 Pharmacies
- 60 Dentist Clinics
- 25 Laboratories
- 54 Medical Imaging Institutes – connected by PAX tech. to the EMR
- 17 Research Centers including Central community research

A unique health system

- Healthcare insurer and provider (>54% coverage)
- Primary, Secondary and Tertiary care - unified look
- Long term incentives (very low attrition rate)
- Emphasis on innovation and data

Data in Clalit

- **Centralized Data Warehouse**
  - Inpatient and outpatient detailed data
  - Single EMR Coverage in all community clinics
  - Smoking (willing to quit), BMI, BP measures…
  - Also - Labs, Pharmacies, imaging…
  - Detailed Socio-demographic data, Costs
- **Chronic Disease Registries (>180)**

Full life-span, ID-tagged, Geo-coded EMR-based data on > 4M people

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How we “entered” the field ?

February 13, 2006:

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A breakthrough and news for breast cancer patients:

‘Clalit Health Services’ will fund the most advanced test for breast cancer patients that will determine if they require chemotherapy.

The test, called 'Oncotype DX', allows identifying which patients will benefit from a chemotherapy treatment, and which patients can be spared this harsh treatment.

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Why ???

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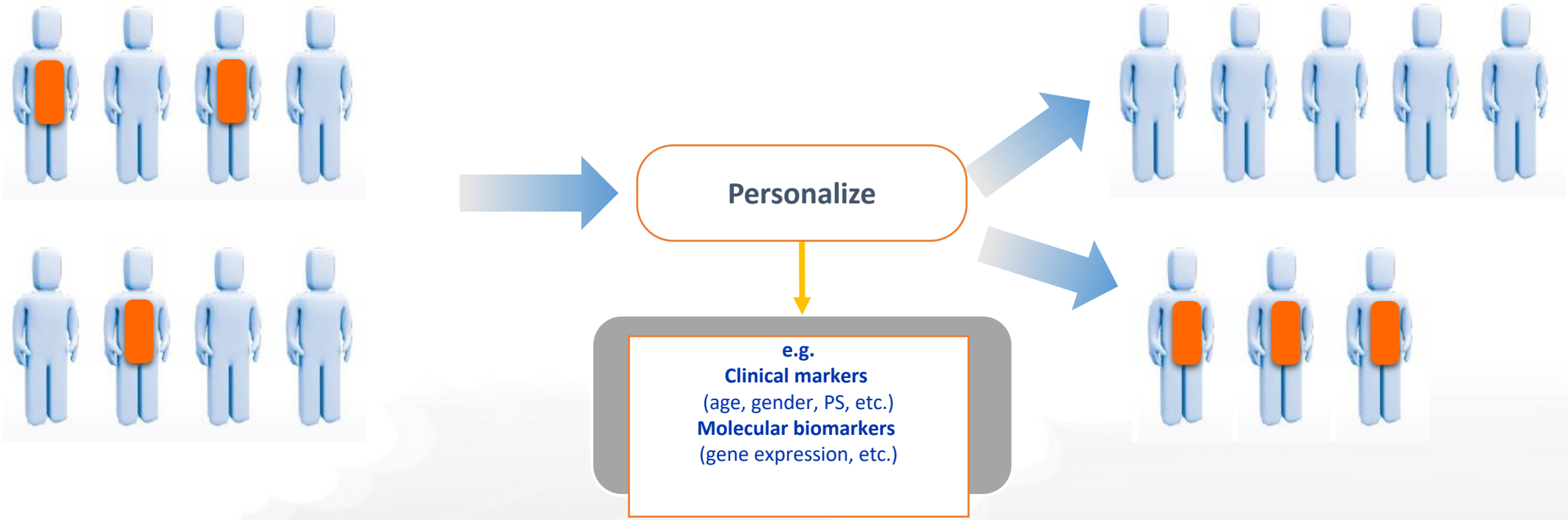
- In any medical insurance system **Competition** is the name of the game – and it should be on

  quality, service and innovation

- OncotypeDX-Breast presented the opportunity to tell breast cancer patients, with a sound level of certainty that after the surgery they are probably "healthy" !!!
- A wide psychological gap exists between the definition of a cancer patient, and a "cured" one. This impacts the health status of the whole family, it's life style, it's spirit.

The scope of Personalized medicine: selecting patients for specific therapy



Select patients that benefit the most

Avoid side effects for patients with little/no benefit

Cost effectiveness

The scope of Personalized medicine: selecting patients for specific therapy

- Personalized Medicine - Helps to achieve better results for patients
- Personalized Medicine - Can help to reduce adverse reactions
- Personalized Medicine - Improves allocation of healthcare resources and helps avoiding unnecessary costs

Current treatment decision making in breast cancer

- Current management of breast cancer includes surgery and one or several of the following treatments:
  - Chemotherapy
  - Hormone therapy
  - Radiotherapy
- Current treatment decisions are based on clinical and pathological criteria (e.g. age, tumour size, tumor grade, nodal status and receptors)
- These criteria do not allow a specific selection of patients that need chemotherapy

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The unmet need in treatment decisions following surgery

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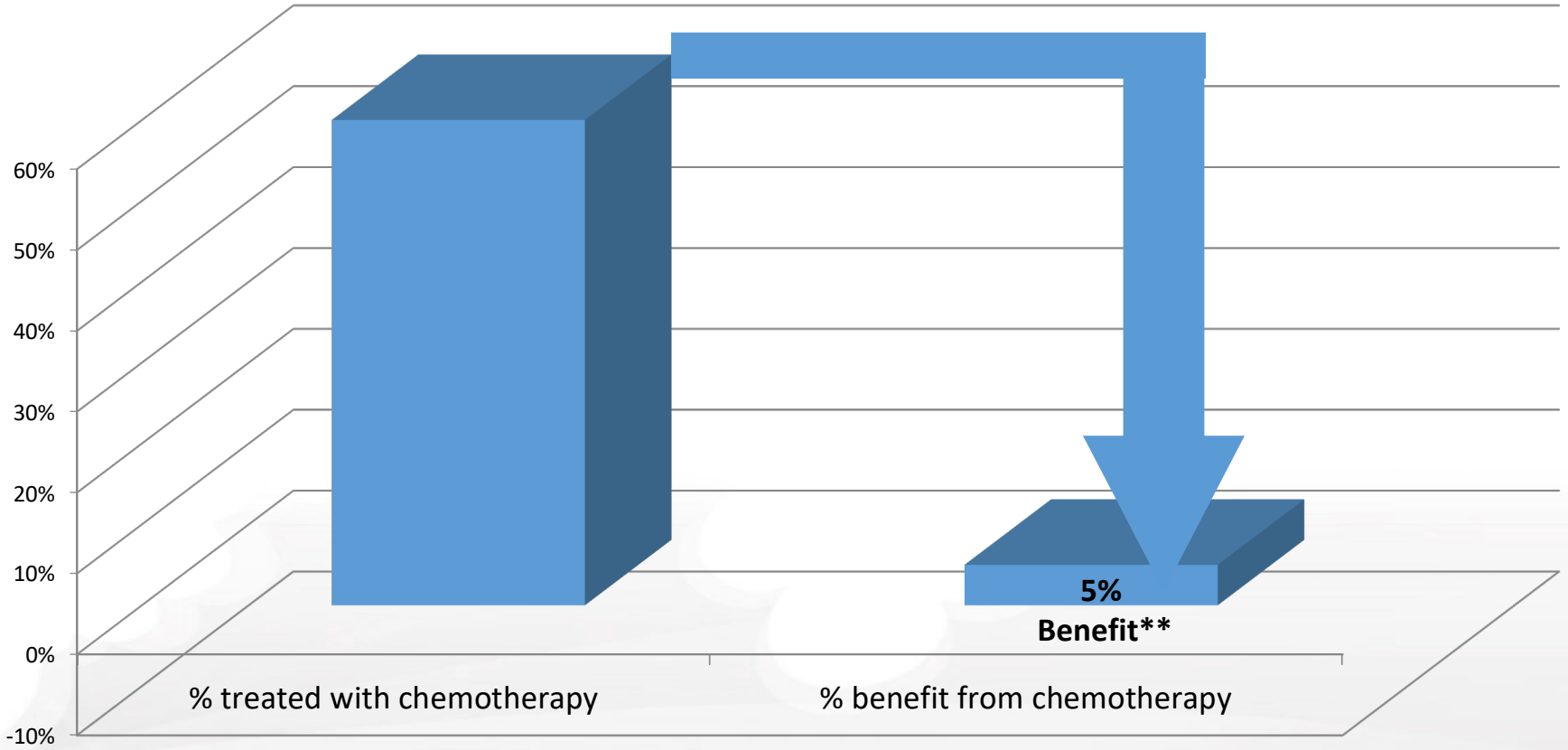
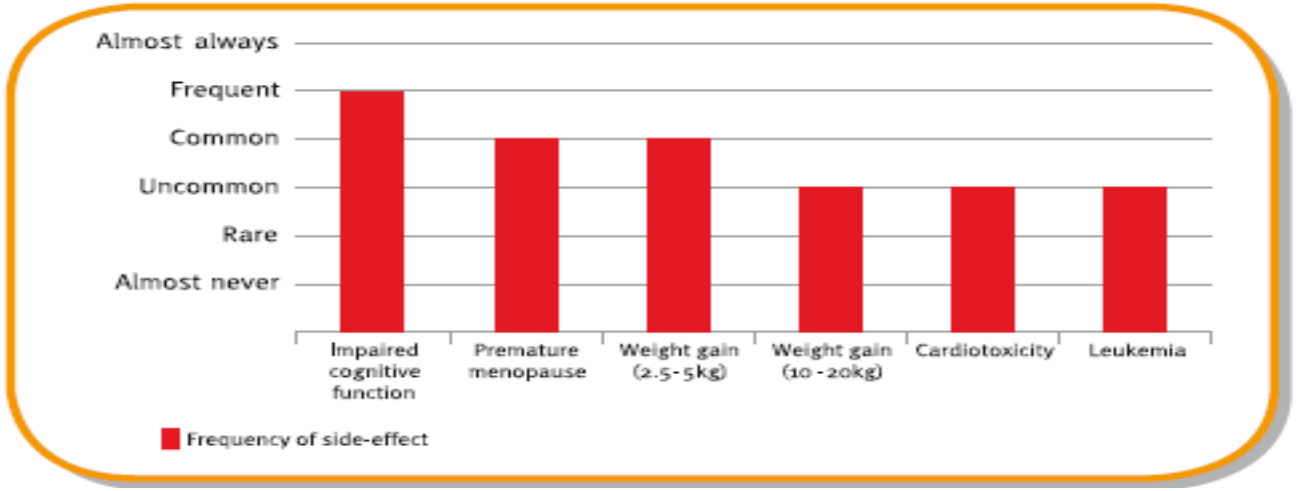
Current practice patterns lead to over-treatment with cytotoxic chemotherapy post-surgery

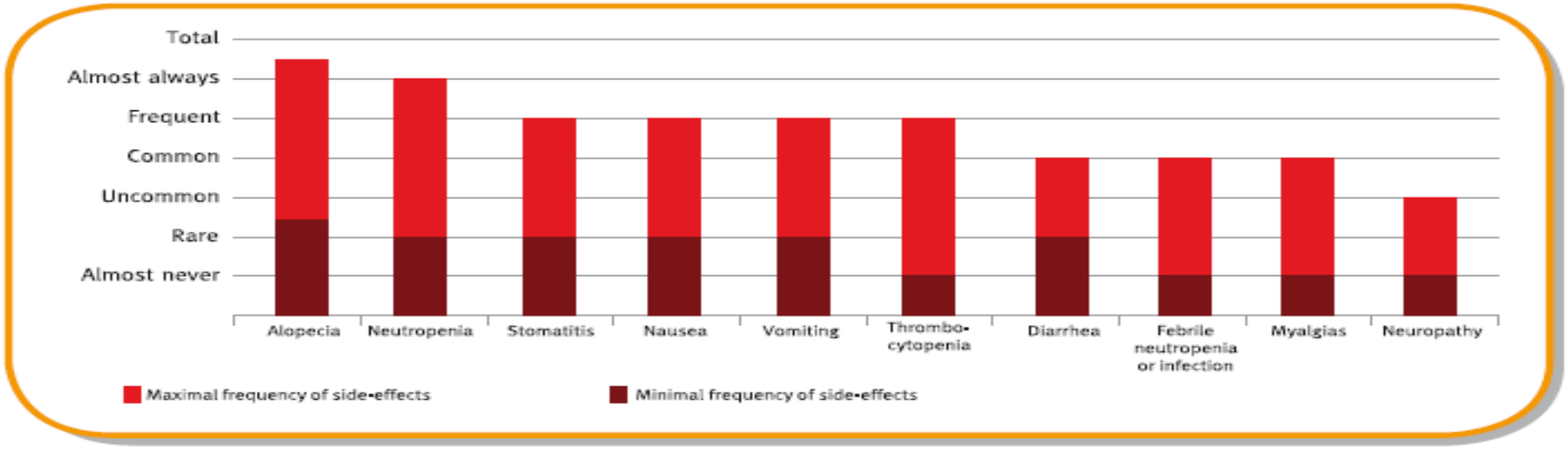


*Chereau E et al, Clin Breast Cancer 2011; **Paik et al, NEJM 2006.

Ineffective chemotherapy can be harmful

- Chemotherapy can be associated with long- and short-term side effects* leading to an **increased co-morbidity**





*Partridge A et al, 2001.

Chemotherapy represents a significant burden to the patients

Working life: More absence from work

More have to quit their job

Social life:

- Loss of income
- Social declassification

Family life:

- More time off work from family members to support patient
- Conscious and sub-conscious harm to children
- Private / sex life impact

Toxicity impact:

- Short- and long-term adverse events of chemotherapy regimens
- Patient well-being

- The burden to the patients and their families translates into additional out of pocket expenses:
  - A Mexican study* showed that the additional cost to the patient is around $1,000

*Gomez-Rico JA et al, 2008.

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And now back to our case –

The process

- Oncologists cooperation – Imperative !!!!
- Accepted guidelines/protocol
- Medical and economical survey and sharing of the DATA with the clinicians
- The decision was to introduce the new technology for Clalit's ensurees – accompanied by a common research with the company and the oncologists
- The oncologist ordering the test will declare his "intention to treat".

Economical and Clinical Applications

- The use of OncotypeDX Breast assay changed the treatment recommendation in 40% of the cases
  - 84% Shifted from hormonal therapy + chemo to hormonal therapy only.
  - 8% of high risk patients by RS shifted from hormonal therapy to hormonal + chemo – **Lives saved !!!**
- Shifting from combination Chemo + Hormonal therapy to Hormonal therapy only = side effect prevention and better health status.
- Preventing disease recurrence for some of the patients found to be high risk by the assay.

Cost-effectiveness ratio

The QALY is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death.

$$\frac{\textbf{Cost with Oncotype DX – Cost without Oncotype DX}}{\textbf{QALYs with Oncotype DX – QALYs without Oncotype DX}}$$

$$\frac{\$1{,}828}{0.170 \text{ QALYs}} = \$10{,}770 \text{ per QALY gained}$$

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Nice to mention

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- CHS approved reimbursement of the RS assay for N0 HR+ HER2-negative breast cancer (BC) patients in January 2006 – NCCN guidelines in 2007
  - CHS extended the approval to include N1mi/N1 patients in January 2008
- Since CHS approval of the assay, a total of about 900 N0 patients and N1mi/N1 patients yearly underwent RS testing through CHS

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CHS Initial Health Economics (HE) Analysis

- In 2010, CHS published a cost-effectiveness analysis based on decision impact data collected from the first 368 N0 BC patients who underwent RS testing through CHS. The clinical outcome data used for the model were from the published literature (NSABP B-14, B-20).

Volume 13 • Number 4 • 2010
VALUE IN HEALTH

Economic Implications of 21-Gene Breast Cancer Risk Assay from the Perspective of an Israeli-Managed Health-Care Organization

Shmuel H. Klang, PhD,[1] Ariel Hammerman, PhD,[1] Nicky Liebermann, MD,[1] Noa Efrat, MD,[2] Julie Doberne, BS,[3] John Hornberger, MD, MS[3,4]

Klang SH,et al. *Value Health*. 2010;13(4):381-7.

CHS Initial HE Analysis: Results

- 40% of patients had treatment recommendation changes after RS testing
- Of these 40%, 84% were changed from chemotherapy plus endocrine therapy to endocrine therapy alone
- The net QALY gained was 0.170 years per patient
- The cost per QALY gained was $10,770

HE, health economics, QALY, quality-adjusted life-years
Klang SH,et al. *Value Health*. 2010;13(4):381-7.

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The CHS Registry

- Collecting clinical outcome data from RS-tested BC patients was planned by CHS, in concert with the assay reimbursement approval
- The resulting prospective registry includes *all* patients who were RS-tested through CHS across Israel regardless of where the patients receive medical care (CHS-affiliated hospitals, government hospitals, private medical centers)

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Analyzing the CHS Registry: Goals

- Investigating the relationship between the RS results and adjuvant chemotherapy treatment decisions
- Investigating the relationship between the RS results and distant recurrence/breast cancer specific mortality (BCSM)
  - To the extent possible, assessing the benefit of adjuvant chemotherapy in RS-based risk categories
- Assessing the HE of RS testing (in progress)

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Published Reports Based on the CHS Registry: 5-year Data, N0 Patients

npj | Breast Cancer

www.nature.com/npjbcancer

ARTICLE OPEN

Clinical outcomes in patients with node-negative breast cancer treated based on the recurrence score results: evidence from a large prospectively designed registry

Salomon M. Stemmer[1,2], Mariana Steiner[3], Shulamith Rizel[1], Lior Soussan-Gutman[4], Noa Ben-Baruch[5], Avital Bareket-Samish[6], David B. Geffen[7], Bella Nisenbaum[8], Kevin Isaacs[9], Georgeta Fried[10], Ora Rosengarten[11], Beatrice Uziely[12], Christer Svedman[13], Debbie McCullough[13], Tara Maddala[13], Shmuel H. Klang[14,15], Jamal Zidan[16,17], Larisa Ryvo[18], Bella Kaufman[2,19], Ella Evron[2,20], Natalya Karminsky[21], Hadassah Goldberg[17,22], Steven Shak[13] and Nicky Liebermann[14]

Stemmer SM, et al. *NPJ Breast Cancer*. 2017;3:33.

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Published Reports Based on the CHS Registry: 5-year Data, N1mi/N1 Patients

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ARTICLE OPEN

Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry

Salomon M. Stemmer[1,2], Mariana Steiner[3], Shulamith Rizel[1], David B. Geffen[4], Bella Nisenbaum[5], Tamar Peretz[6], Lior Soussan-Gutman[7], Avital Bareket-Samish[8], Kevin Isaacs[9], Ora Rosengarten[10], Georgeta Fried[11], Debbie McCullough[12], Christer Svedman[12], Steven Shak[12], Nicky Liebermann[13] and Noa Ben-Baruch[14]

Stemmer SM, et al. *NPJ Breast Cancer*. 2017;3:32.

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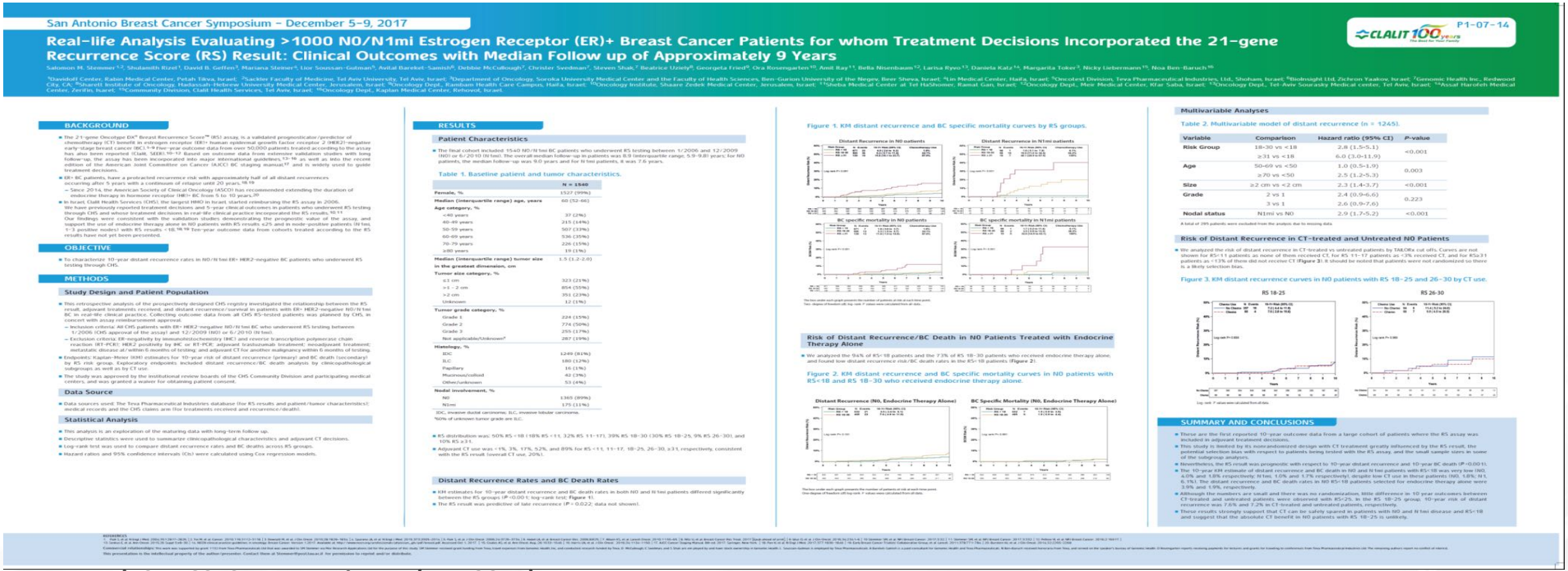
Published Reports Based on the CHS Registry: 10-year Data, N0/N1mi Patients



San Antonio Breast Cancer Symposium – December 5-9, 2017

Real-life Analysis Evaluating >1000 N0/N1mi Estrogen Receptor (ER)+ Breast Cancer Patients for whom Treatment Decisions Incorporated the 21-gene Recurrence Score (RS) Result: Clinical Outcomes with Median Follow up of Approximately 9 Years

CLALIT 100 years P1-07-14

Salomon M. Stemmer[1,2], Shulamith Rizel[1], David B. Geffen[3], Mariana Steiner[4], Uor Soussan-Gutman[5], Avital Bareket-Samish[6], Debbie McCullough[7], Christer Svedman[7], Steven Shak[7], Beatrice Uziely[8], Georgeta Fried[9], Ora Rosengarten[10], Amit Ray[11], Bella Nisenbaum[12], Larisa Ryvo[13], Daniela Katz[14], Margarita Toker[3], Nicky Liebermann[15], Noa Ben-Baruch[16]

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BACKGROUND

- The 21-gene Oncotype DX® Breast Recurrence Score™ (RS) assay, is a validated prognosticator/predictor of chemotherapy (CT) benefit in estrogen receptor (ER)+ human epidermal growth factor receptor 2 (HER2)-negative early-stage breast cancer (BC).[1-9] Five-year outcome data from over 50,000 patients treated according to the assay has also been reported (Clalit, SEER).[10-12] Based on outcome data from extensive validation studies with long follow-up, the assay has been incorporated into major international guidelines,[13-16] as well as into the recent edition of the American Joint Committee on Cancer (AJCC) BC staging manual,[17] and is widely used to guide treatment decisions.
- ER+ BC patients, have a protracted recurrence risk with approximately half of all distant recurrences occurring after 5 years with a continuum of relapse until 20 years.[18,19]
  - Since 2014, the American Society of Clinical Oncology (ASCO) has recommended extending the duration of endocrine therapy in hormone receptor (HR)+ BC from 5 to 10 years.[20]
- In Israel, Clalit Health Services (CHS), the largest HMO in Israel, started reimbursing the RS assay in 2006. We have previously reported treatment decisions and 5-year clinical outcomes in patients who underwent RS testing through CHS and whose treatment decisions in real-life clinical practice incorporated the RS results.[10,11] Our findings were consistent with the validation studies demonstrating the prognostic value of the assay, and support the use of endocrine therapy alone in N0 patients with RS results ≤25 and in node-positive patients (N 1mi, 1-3 positive nodes) with RS results <18.[18,19] Ten-year outcome data from cohorts treated according to the RS results have not yet been presented.

OBJECTIVE

- To characterize 10-year distant recurrence rates in N0/N1mi ER+ HER2-negative BC patients who underwent RS testing through CHS.

METHODS

Study Design and Patient Population

- This retrospective analysis of the prospectively designed CHS registry investigated the relationship between the RS result, adjuvant treatments received, and distant recurrence/survival in patients with ER+ HER2-negative N0/N1mi BC in real-life clinical practice. Collecting outcome data from all CHS RS-tested patients was planned by CHS, in concert with assay reimbursement approval.
  - Inclusion criteria: All CHS patients with ER+ HER2-negative N0/N1mi BC who underwent RS testing between 1/2006 (CHS approval of the assay) and 12/2009 (N0) or 6/2010 (N1mi).
  - Exclusion criteria: ER-negativity by immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR); HER2 positivity by IHC or RT-PCR; adjuvant trastuzumab treatment; neoadjuvant treatment; metastatic disease at/within 6 months of testing; and adjuvant CT for another malignancy within 6 months of testing.
- Endpoints: Kaplan-Meier (KM) estimates for 10-year risk of distant recurrence (primary) and BC death (secondary) by RS risk group. Exploratory endpoints included distant recurrence/BC death analysis by clinicopathological subgroups as well as by CT use.
- The study was approved by the institutional review boards of the CHS Community Division and participating medical centers, and was granted a waiver for obtaining patient consent.

Data Source

- Data sources used: The Teva Pharmaceutical Industries database (for RS results and patient/tumor characteristics); medical records and the CHS claims arm (for treatments received and recurrence/death).

Statistical Analysis

- This analysis is an exploration of the maturing data with long-term follow up.
- Descriptive statistics were used to summarize clinicopathological characteristics and adjuvant CT decisions.
- Log-rank test was used to compare distant recurrence rates and BC deaths across RS groups.
- Hazard ratios and 95% confidence intervals (CIs) were calculated using Cox regression models.

RESULTS

Patient Characteristics

- The final cohort included 1540 N0/N1mi BC patients who underwent RS testing between 1/2006 and 12/2009 (N0) or 6/2010 (N1mi). The overall median follow-up in patients was 8.9 (interquartile range, 5.9-9.8) years; for N0 patients, the median follow-up was 9.0 years and for N1mi patients, it was 7.6 years.

Table 1. Baseline patient and tumor characteristics.

	N = 1540
Female, %	1527 (99%)
Median (interquartile range) age, years	60 (52-66)
Age category, %	
<40 years	37 (2%)
40-49 years	215 (14%)
50-59 years	507 (33%)
60-69 years	536 (35%)
70-79 years	226 (15%)
≥80 years	19 (1%)
Median (interquartile range) tumor size in the greatest dimension, cm	1.5 (1.2-2.0)
Tumor size category, %	
≤1 cm	323 (21%)
>1 - 2 cm	854 (55%)
>2 cm	351 (23%)
Unknown	12 (1%)
Tumor grade category, %	
Grade 1	224 (15%)
Grade 2	774 (50%)
Grade 3	255 (17%)
Not applicable/Unknown*	287 (19%)
Histology, %	
IDC	1249 (81%)
ILC	180 (12%)
Papillary	16 (1%)
Mucinous/colloid	42 (3%)
Other/unknown	53 (4%)
Nodal involvement, %	
N0	1365 (89%)
N1mi	175 (11%)

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.
*60% of unknown tumor grade are ILC.

- RS distribution was: 50% RS <18 (18% RS <11, 32% RS 11-17), 39% RS 18-30 (30% RS 18-25, 9% RS 26-30), and 10% RS ≥31.
- Adjuvant CT use was <1%, 3%, 17%, 52%, and 89% for RS <11, 11-17, 18-25, 26-30, ≥31, respectively, consistent with the RS result (overall CT use, 20%).

Distant Recurrence Rates and BC Death Rates

- KM estimates for 10-year distant recurrence and BC death rates in both N0 and N1mi patients differed significantly between the RS groups (P <0.00 t; log-rank test; Figure 1).
- The RS result was predictive of late recurrence (P = 0.022; data not shown).

Figure 1. KM distant recurrence and BC specific mortality curves by RS groups.

Risk of Distant Recurrence/BC Death in N0 Patients Treated with Endocrine Therapy Alone

- We analyzed the 94% of RS<18 patients and the 73% of RS 18-30 patients who received endocrine therapy alone, and found low distant recurrence risk/BC death rates in the RS<18 patients (Figure 2).

Figure 2. KM distant recurrence and BC specific mortality curves in N0 patients with RS<18 and RS 18-30 who received endocrine therapy alone.

Multivariable Analyses

Table 2. Multivariable model of distant recurrence (n = 1245).

Variable	Comparison	Hazard ratio (95% CI)	*P*-value
Risk Group	18-30 vs <18	2.8 (1.5-5.1)	<0.001
	≥31 vs <18	6.0 (3.0-11.9)	
Age	50-69 vs <50	1.0 (0.5-1.9)	0.003
	≥70 vs <50	2.5 (1.2-5.3)	
Size	≥2 cm vs <2 cm	2.3 (1.4-3.7)	<0.001
Grade	2 vs 1	2.4 (0.9-6.6)	0.223
	3 vs 1	2.6 (0.9-7.6)	
Nodal status	N1mi vs N0	2.9 (1.7-5.2)	<0.001

A total of 295 patients were excluded from the analysis due to missing data.

Risk of Distant Recurrence in CT-treated and Untreated N0 Patients

- We analyzed the risk of distant recurrence in CT-treated vs untreated patients by TAILORx cut offs. Curves are not shown for RS<11 patients as none of them received CT, for RS 11-17 patients as <3% received CT, and for RS≥31 patients as <13% of them did not receive CT (Figure 3). It should be noted that patients were not randomized so there is a likely selection bias.

Figure 3. KM distant recurrence curves in N0 patients with RS 18-25 and 26-30 by CT use.

SUMMARY AND CONCLUSIONS

- These are the first reported 10-year outcome data from a large cohort of patients where the RS assay was included in adjuvant treatment decisions.
- This study is limited by its non-randomized design with CT treatment greatly influenced by the RS result, the potential selection bias with respect to patients being tested with the RS assay, and the small sample sizes in some of the subgroup analyses.
- Nevertheless, the RS result was prognostic with respect to 10-year distant recurrence and 10-year BC death (P <0.01).
- The 10-year KM estimate of distant recurrence and BC death in N0 and N1mi patients with RS<18 was very low (N0, 4.0% and 1.8% respectively; N1mi, 1.0% and 1.7% respectively); despite low CT use in these patients (N0, 1.8%; N1, 6.1%). The distant recurrence and BC death rates in N0 RS<18 patients selected for endocrine therapy alone were 3.9% and 1.9%, respectively.
- Although the numbers are small and there was no randomization, little difference in 10 year outcomes between CT-treated and untreated patients were observed with RS<25. In the RS 18-25 group, 10-year risk of distant recurrence was 7.6% and 7.2% in CT-treated and untreated patients, respectively.
- These results strongly support that CT can be safely spared in patients with N0 and N1mi disease and RS<18 and suggest that the absolute CT benefit in N0 patients with RS 18-25 is unlikely.

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Stemmer et al, SABCS, San Antonio, TX (Dec 2017).

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CHS Registry Analysis: 10-year Data

- **Objective:** To investigate 10-year distant recurrence and BCSM in N0/N1mi ER+ HER2-negative BC patients who underwent RS testing through CHS

Methods

- **Exploration of the maturing CHS data with long-term follow up**
- **Key inclusion criteria:**
  - CHS patients with N0/N1mi BC who underwent RS testing between 1/2006 (CHS approval of the assay) and 12/2009 (N0) or 6/2010 (N1mi)
  - ER+
- **Key exclusion criteria:**
  - Patients for whom the test is not indicated: Stage 4, ER-negative, HER2+ (by IHC or RT-PCR)
  - Neoadjuvant treatment
  - Recurrence within 6 months of testing

Methods (cont.)

- **Data source:**
  - RS, tumor characteristics: Teva
  - Treatments, recurrences: Medical records
  - Deaths: Interior Ministry registry/medical records
  - Additional/supporting information: CHS billing system

- **Statistical considerations:** Descriptive statistics, 10-year KM estimates for distant recurrence/BCSM, multivariable analysis

Baseline Patient/Tumor Characteristics

	N = 1540
Female	99%
Age, median (IQR), years	60 (52-66)
Age category	
<40 years	2%
40-49 years	14%
50-59 years	33%
60-69 years	35%
70-79 years	15%
≥80 years	1%
Nodal involvement	
N0	89%
N1mi	11%

	N = 1540
Tumor size, median (IQR), cm	1.5 (1.2, 2.0)
Tumor size category	
≤1 cm	21%
>1-2 cm	55%
>2 cm	23%
Unknown	1%
Tumor grade category	
Grade 1	15%
Grade 2	50%
Grade 3	17%
Not applicable/Unknown[a]	19%
Histology	
IDC	81%
ILC	12%
Mucinous/colloid	3%
Papillary	1%
Other/unknown	4%

[a] 60% of unknown tumor grade are ILC.

IDC, Invasive ductal carcinoma; ILC, invasive lobular carcinoma, IQR, interquartile range

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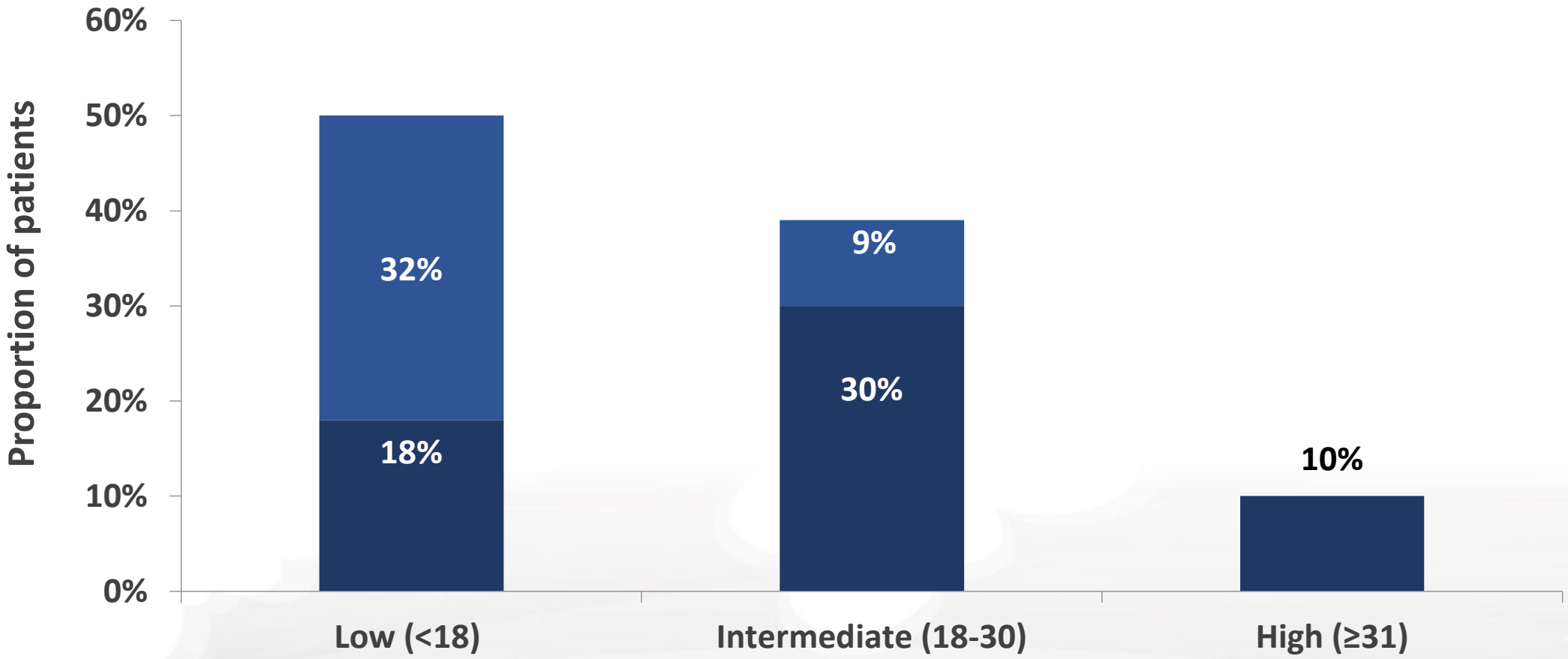
RS Distribution (N = 1540)



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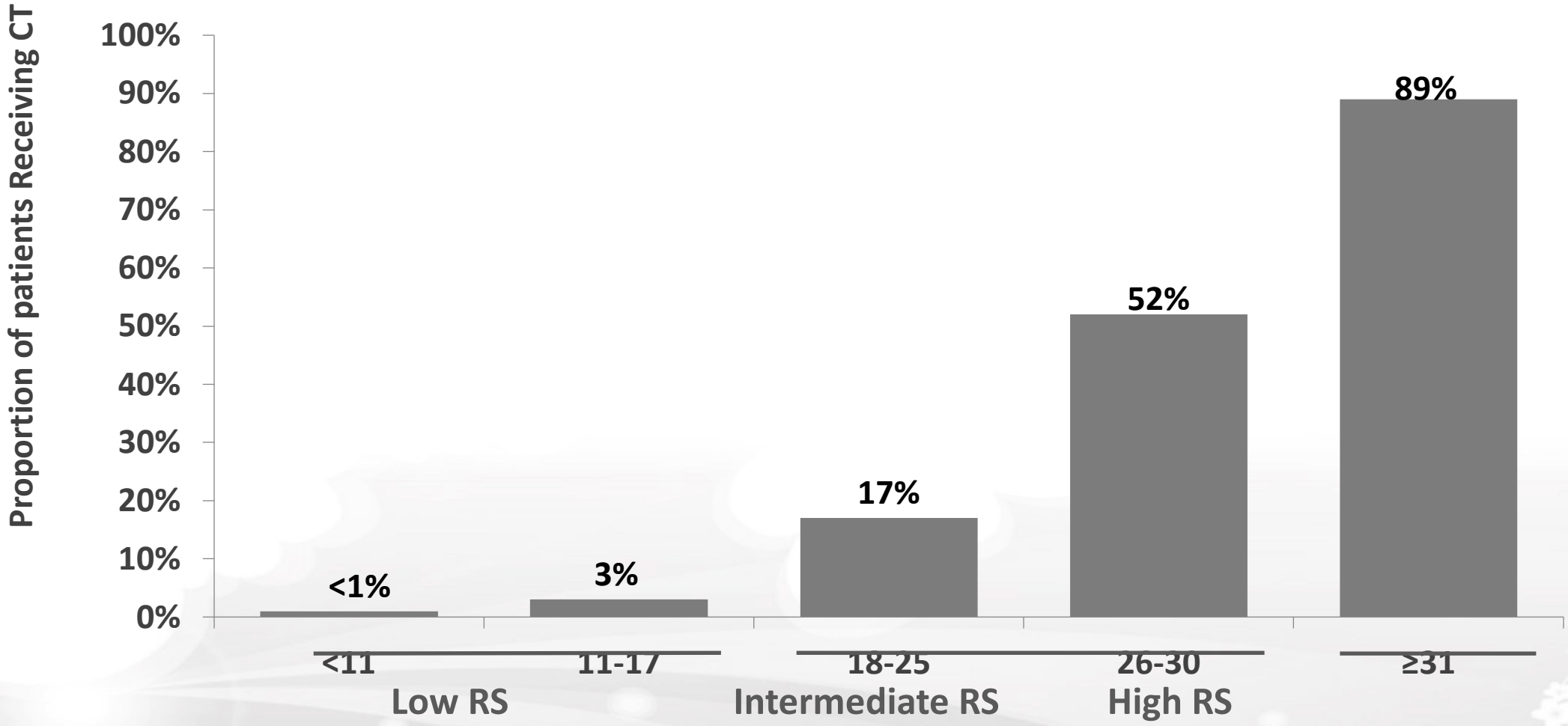
Adjuvant Chemotherapy (CT) Use (N = 1540)



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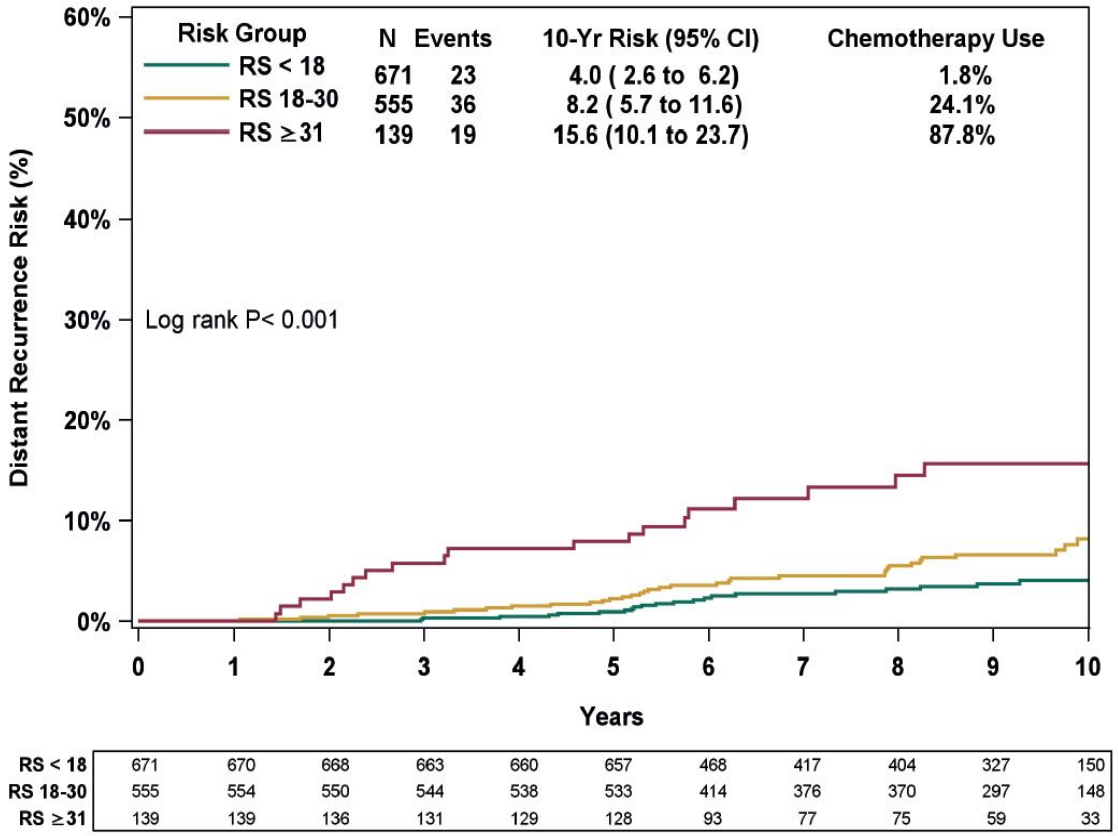
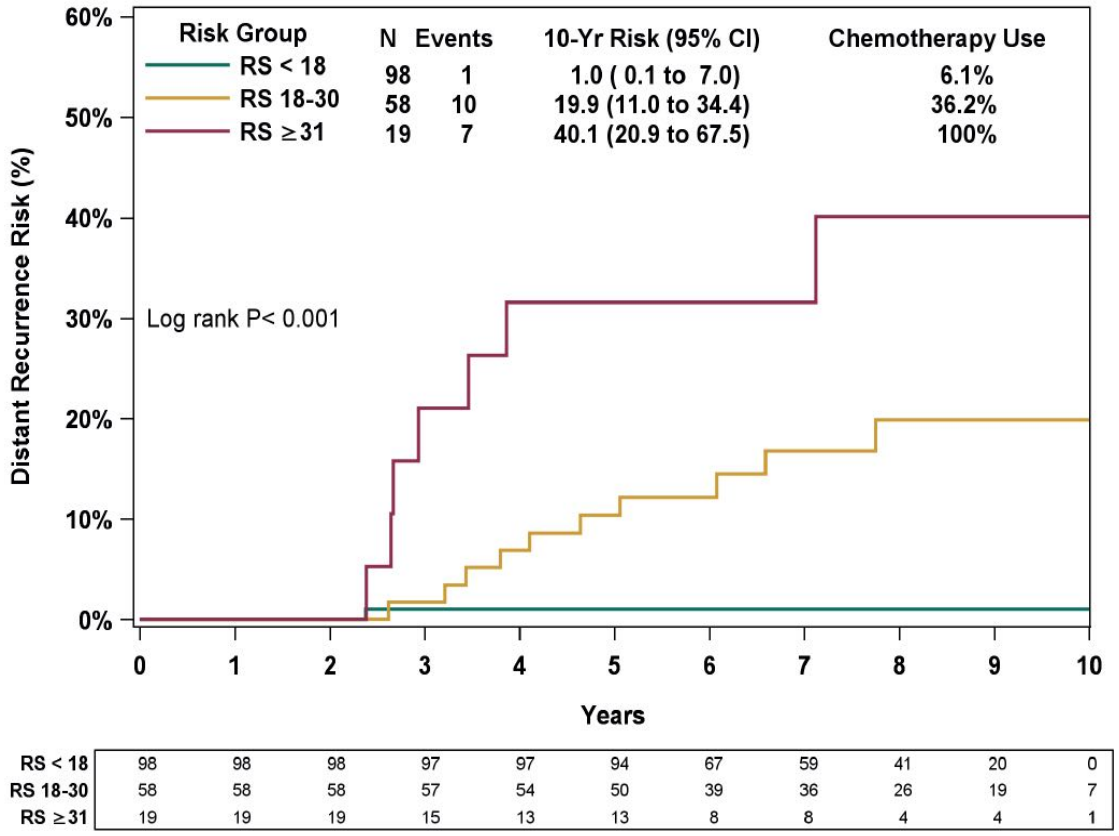
Distant Recurrence Risk by RS Group in N0 and N1mi Patients

N0 Patients (n = 1365)



RS < 18	671	670	668	663	660	657	468	417	404	327	150
RS 18-30	555	554	550	544	538	533	414	376	370	297	148
RS ≥31	139	139	136	131	129	128	93	77	75	59	33

N1mi Patients (n = 175)



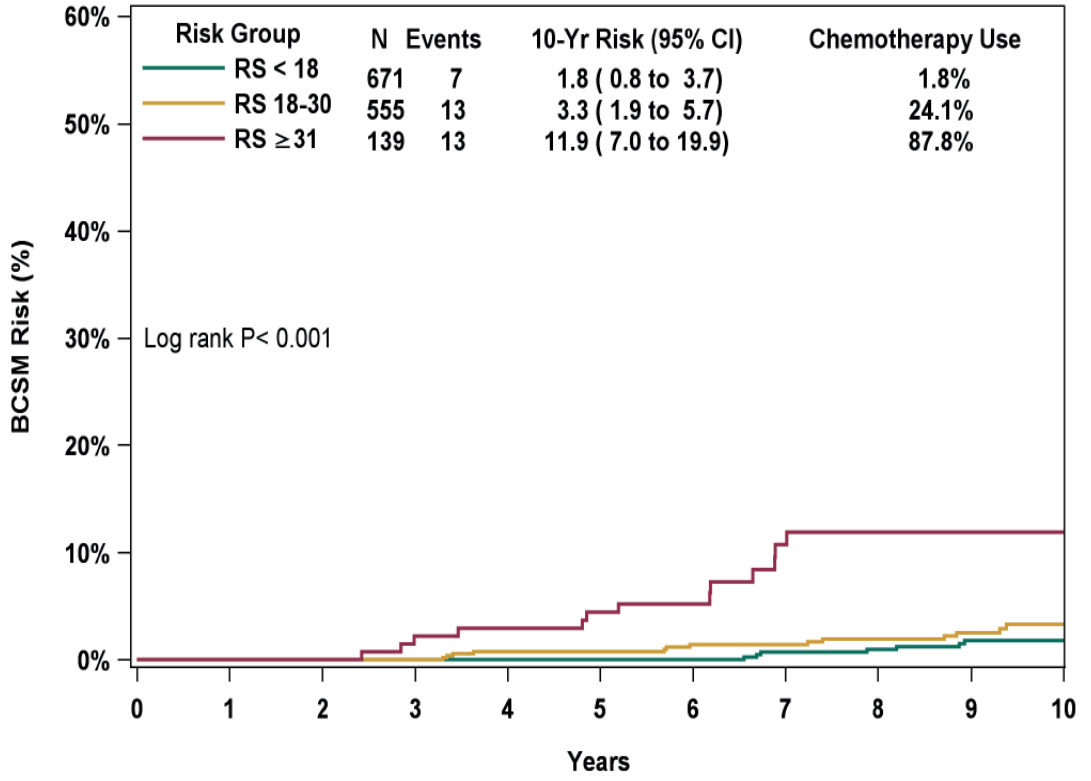
RS < 18	98	98	98	97	97	94	67	59	41	20	0
RS 18-30	58	58	58	57	54	50	39	36	26	19	7
RS ≥31	19	19	19	15	13	13	8	8	4	4	1

Median follow-up: 9.0/7.6 years for N0/N1mi patients.

Two-degree of freedom log-rank *P* values were calculated from all the data.

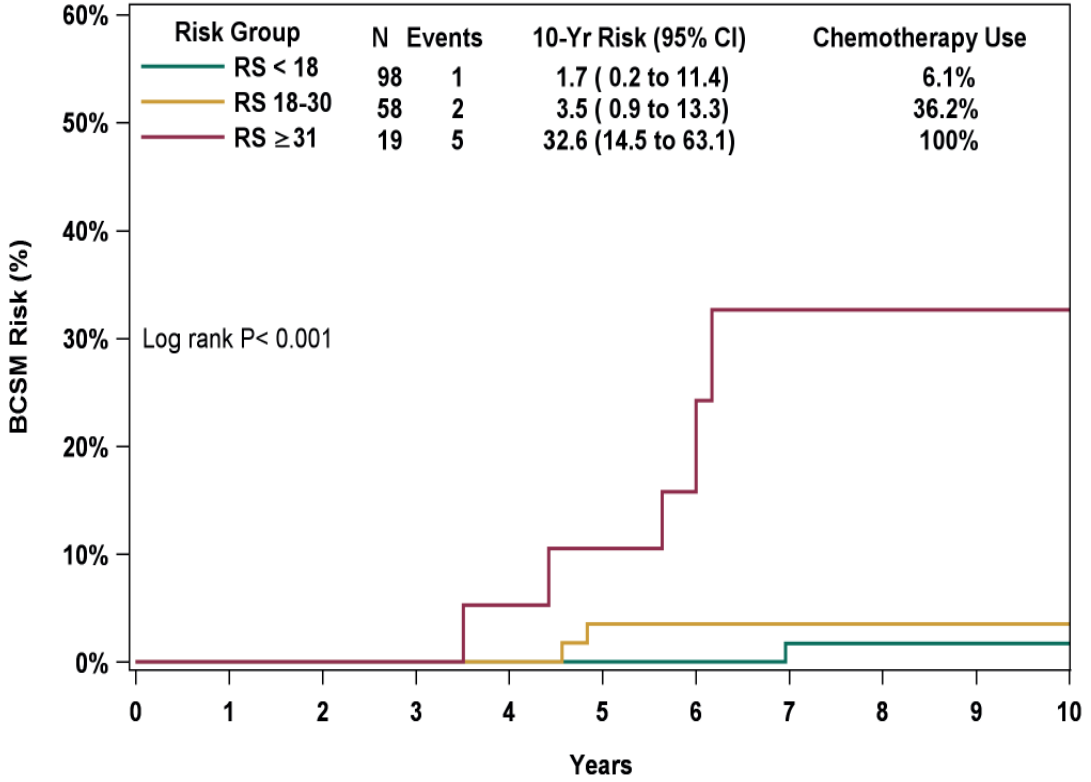
BCSM by RS Group in N0 and N1mi Patients

N0 Patients (n = 1365)



RS < 18	671	668	664	659	653	650	471	416	404	324	152
RS 18-30	555	554	553	546	539	537	418	383	376	299	145
RS ≥31	139	139	139	134	133	128	97	77	75	59	34

N1mi Patients (n = 175)



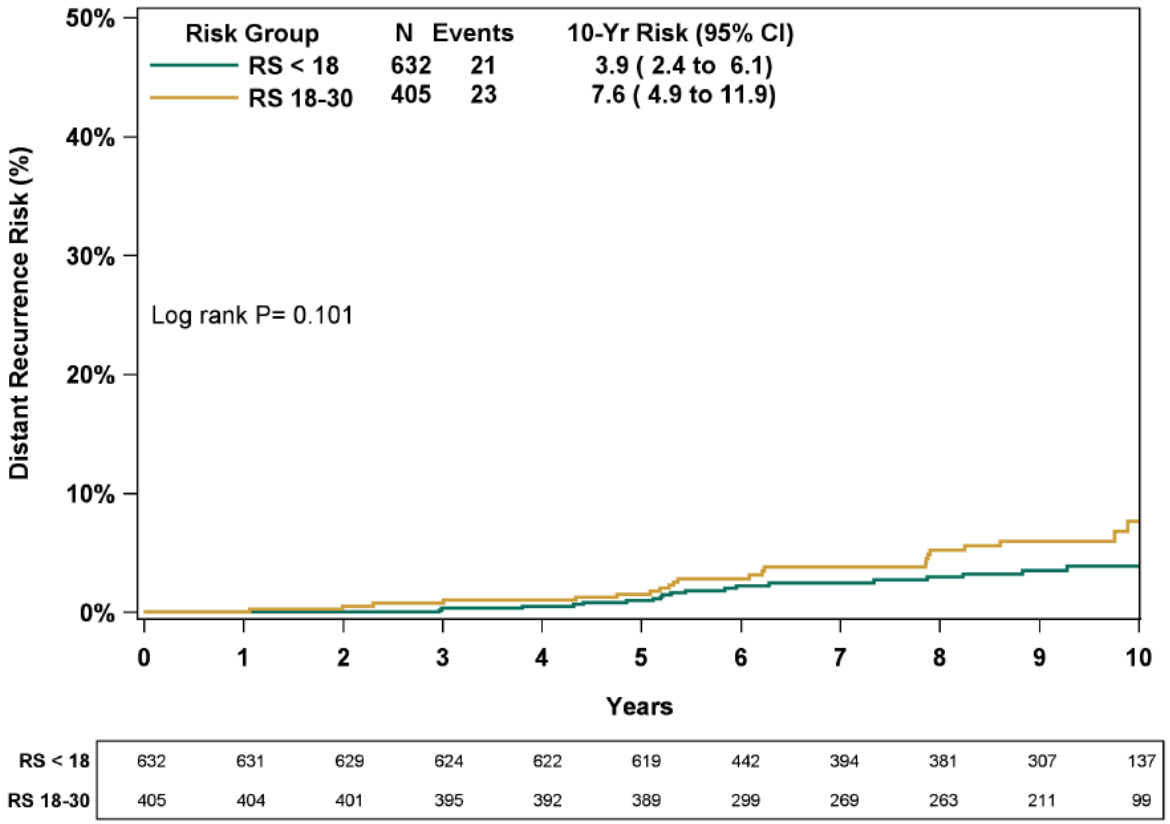
RS < 18	98	98	98	98	98	94	67	58	39	19	0
RS 18-30	58	58	58	58	58	54	43	39	29	21	8
RS ≥31	19	19	19	19	18	17	10	8	5	4	1

Median follow-up: 9.0/7.6 years for N0/N1mi patients.

Two-degree of freedom log-rank *P* values were calculated from all the data.

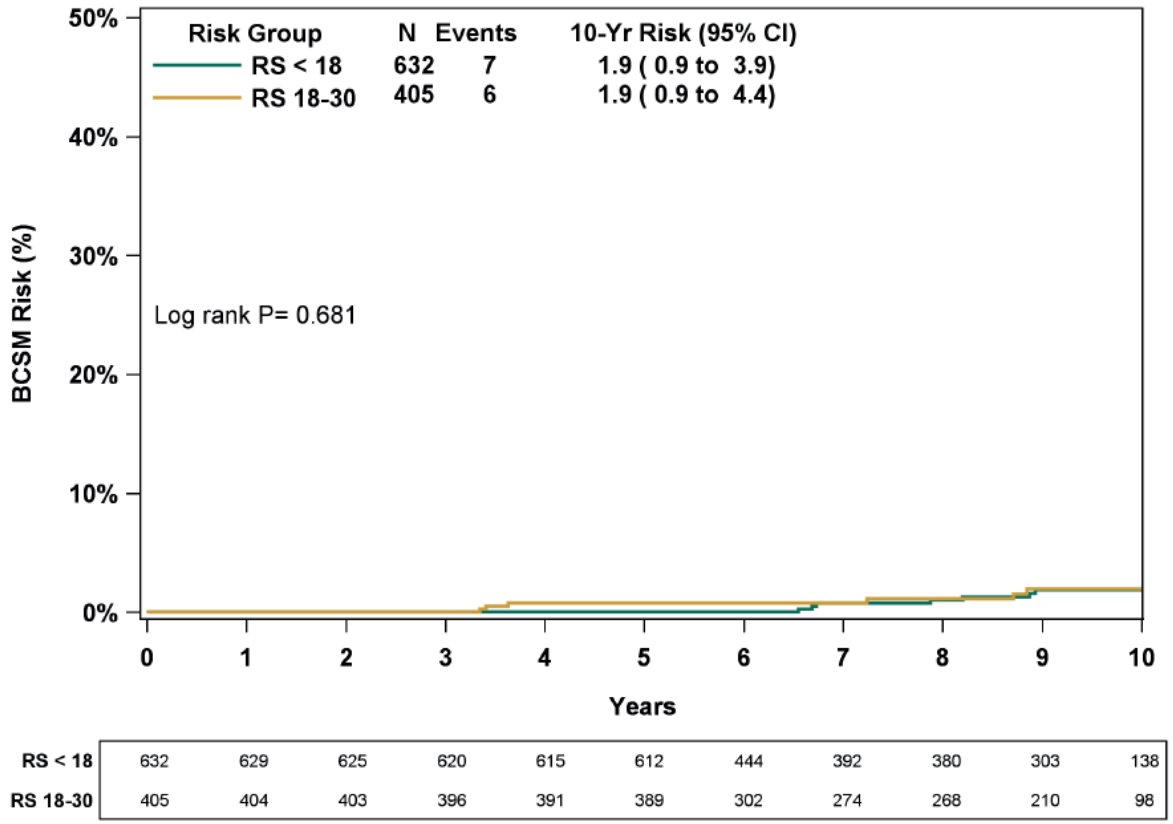
Risk of Distant Recurrence and BCSM in N0 Patients Treated with Endocrine Therapy Alone

Distant Recurrence (n = 1037)



RS < 18	632	631	629	624	622	619	442	394	381	307	137
RS 18-30	405	404	401	395	392	389	299	269	263	211	99

BC Specific Mortality (n = 1037)



RS < 18	632	629	625	620	615	612	444	392	380	303	138
RS 18-30	405	404	403	396	391	389	302	274	268	210	98

Median follow-up: 9.0/7.6 years for N0/N1mi patients.

One-degree of freedom log-rank *P* values were calculated from all the data.

Multivariable Analysis of Distant Recurrence (n = 1245)

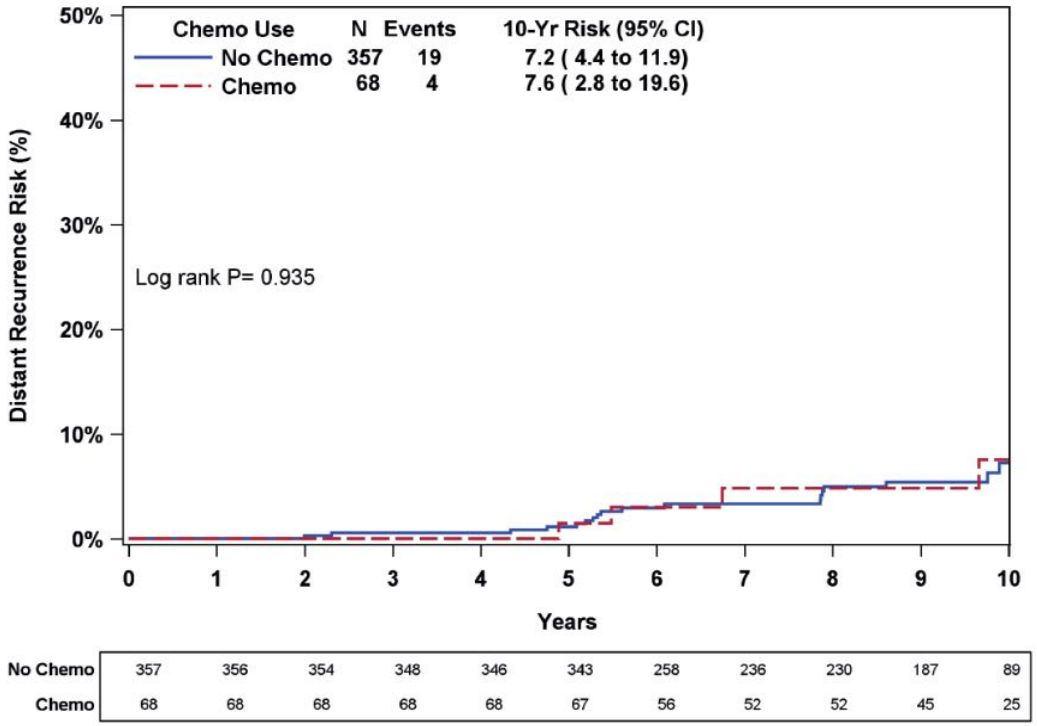
Variable	HR	95% CI	*P*-value
RS:			
18-30 vs <18	2.8	1.5-5.1	<0.001
≥31 vs <18	6.0	3.0-11.9	
Age:			
50-69 vs <50	1.0	0.5-1.9	0.003
≥70 vs <50	2.5	1.2-5.3	
Size: ≥2 cm vs <2 cm	2.3	1.4-3.7	<0.001
Grade:			
2 vs 1	2.4	0.9-6.6	0.223
3 vs 1	2.6	0.9-7.6	
Nodal status: N1mi vs N0	2.9	1.7-5.2	<0.001

A total of 295 patients were excluded from the analysis due to missing data.

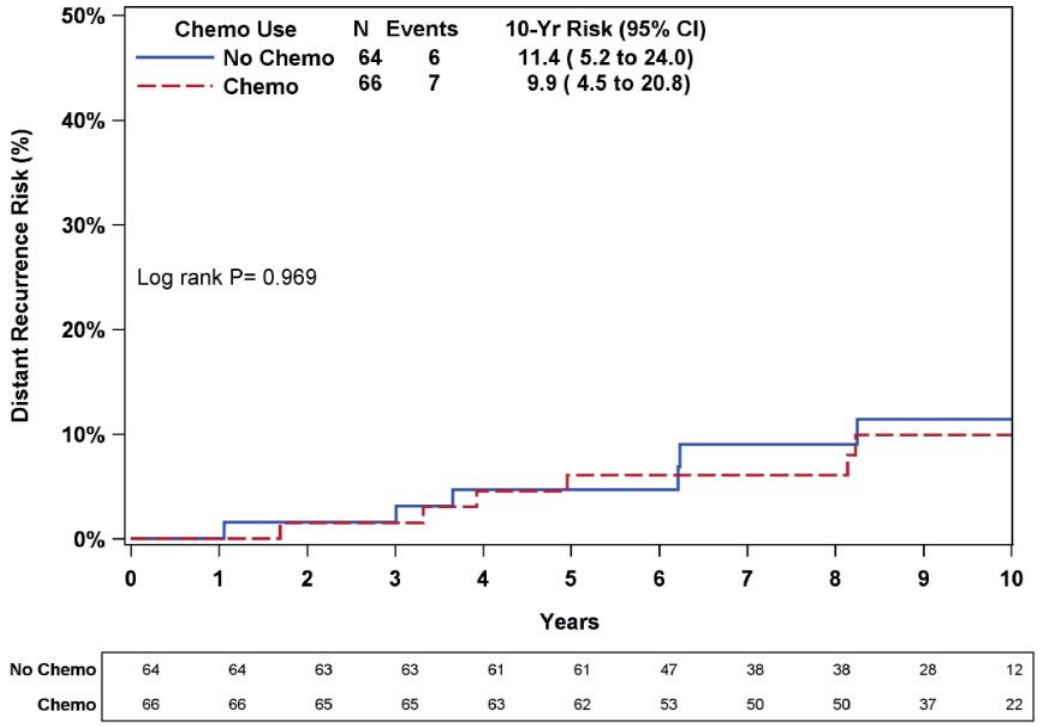
CI, confidence intervals; HR, hazard ratio.

Risk of Distant Recurrence in N0 Patients by CT Use (Int. RS)

RS 18-25 (n = 425)



RS 26-30 (n = 130)



***In RS<11 patients, none received CT; in RS 11-17 patients, <3% received CT; in RS≥31 patients <13% *did not* receive CT.**

Median follow-up: 9.0/7.6 years for N0/N1mi patients. Log-rank *P* values were calculated from all the data.

Strengths and Limitations

- **Strengths**
  - Real-life large registry analysis representing clinical practice and outcomes on a national level
    - No exclusion criteria with respect to age, gender, comorbidities, location, and socioeconomic status

- **Limitations**
  - Non-randomized
  - Some subgroups are small
  - Patients were not treated uniformly (e.g., chemotherapy regimens, endocrine therapy agents)
  - Potential for selection bias

Conclusions

- The first reported 10-year outcome data from a large cohort of patients where the RS was used in adjuvant treatment decisions
- The RS was prognostic for 10-year distant recurrence and 10-year BCSM ($P<0.001$)
- The 10-year KM estimates for distant recurrence and BCSM in RS<18 patients were very low, despite low CT use
  - **N0:** CT use, 1.8%; 10-year distant recurrence risk, 4.0%, 10-year BC death risk, 1.8%
  - **N1mi:** CT use, 6.1%; 10-year distant recurrence risk, 1.0%, 10-year BC death risk, 1.7%

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Conclusions (cont.)

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- N0 RS<18 patients treated with endocrine therapy alone had low risk of 10-year distant recurrence (3.9%) and BC death (1.9%)
- In N0 patients with RS 18-25, 10-year outcomes were similar in CT-treated and untreated patients
  - 7.6% in CT-treated vs 7.2% in CT-untreated patients

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Clinical Implications

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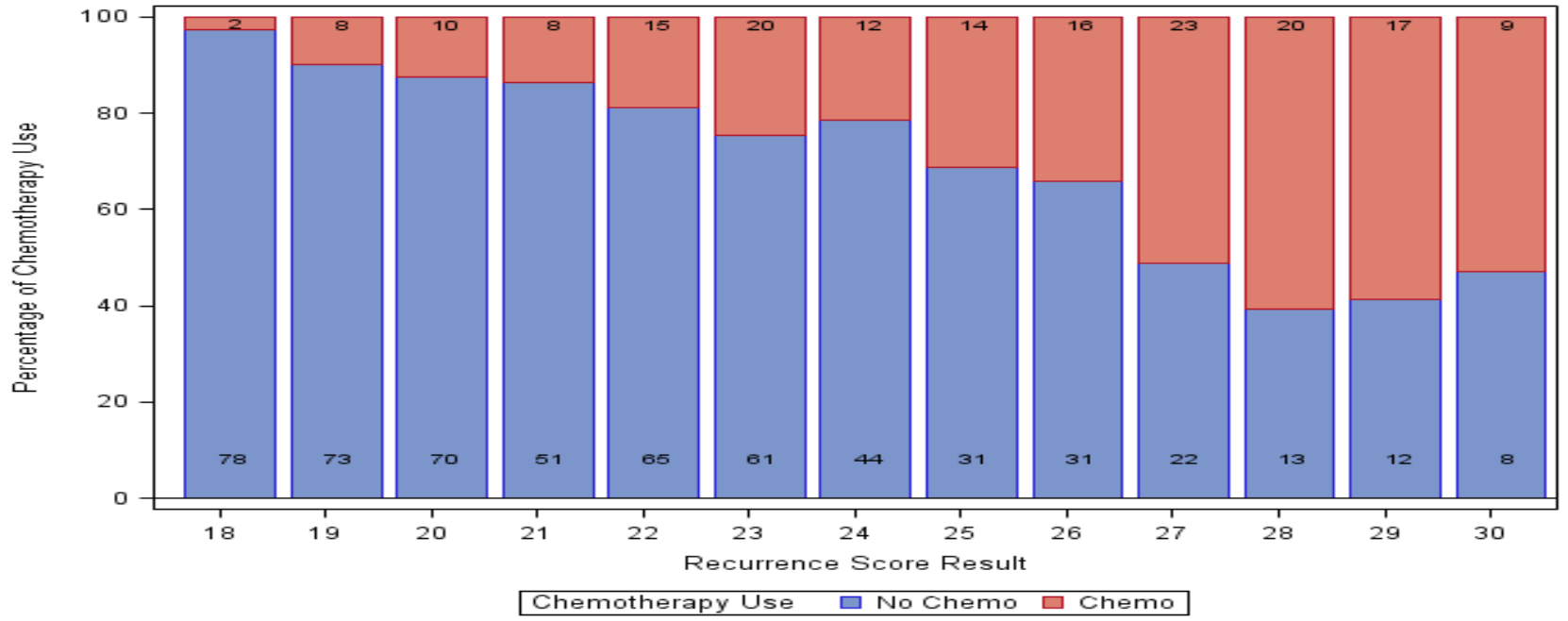
- In N0/N1mi patients with ER+ HER2-negative BC and RS<18, adjuvant CT can be spared as endocrine therapy alone confers very good long-term clinical outcomes
- The absolute CT benefit in N0 patients with RS 18-25 is unlikely

Use of the RS Assay in Israel: Insights

- Israeli oncologists were early adopters of the assay
- Use of RS testing increased over time as additional data became available (e.g., from 233 N0 patients in 2006 to 760 in 2010 and 949 in 2017)
- Currently, most eligible patients undergo RS testing (~95% of N0 patients and N1/N1mi patients)
- Most centers and many oncologists are involved in the CHS registry/analyses; furthermore, oncologists initiate various analyses of the data (e.g., by age, grade, etc)

Use of the RS Assay in Israel: Insights (cont.)

- BC treatment in Israel is based on the RS results
  - For patients with intermediate RS results, CT use increase with increasing RS*



*Stemmer SM, et al. *NPJ Breast Cancer*. 2017;3:33.

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Thank you