NHOLUA

September 20, 2016
Lincoln, NE

Munich RE

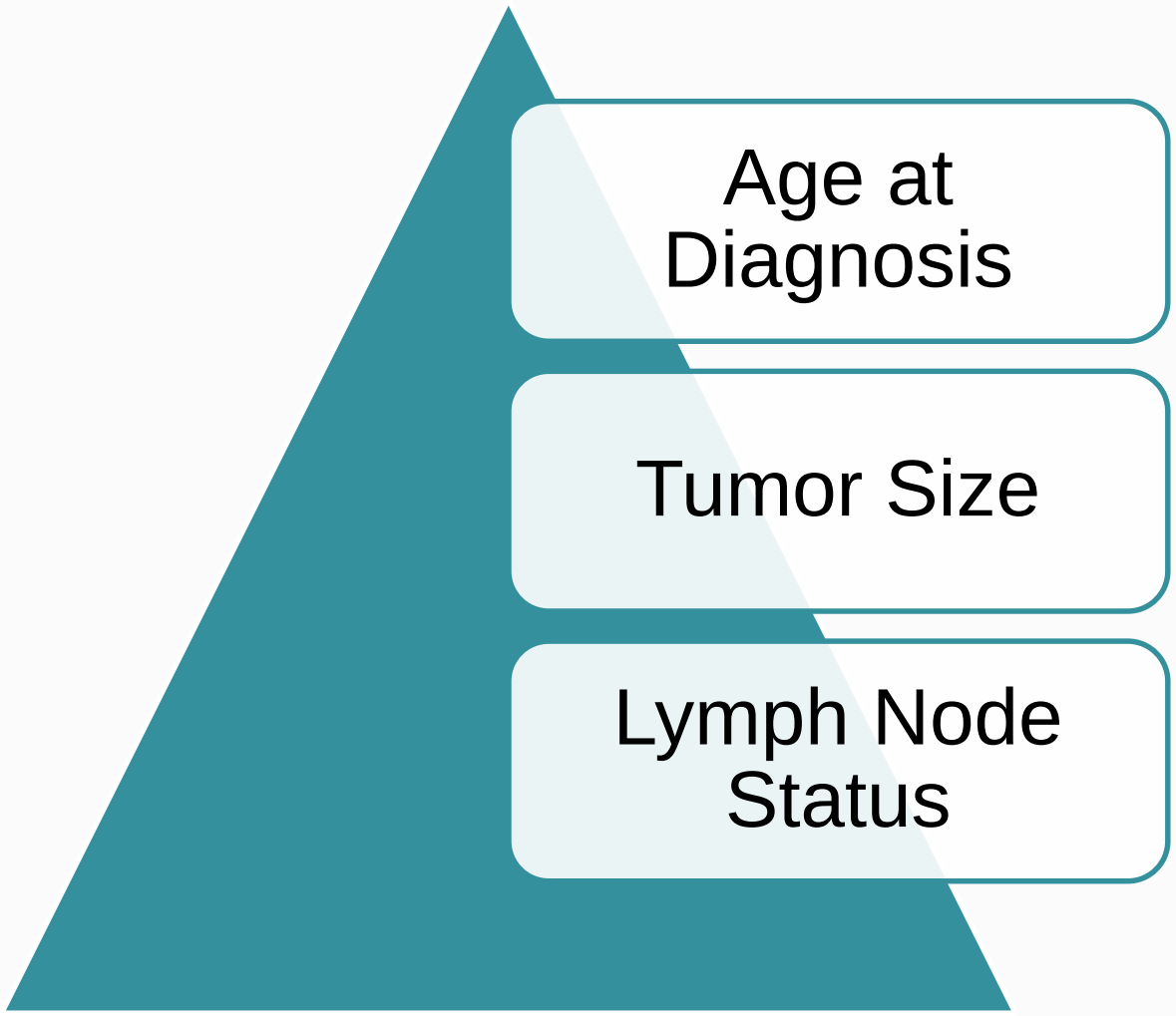
UNDERWRITING BREAST CANCER, A NEW APPROACH

Dr Robert Lund

Munich RE

Basics in Determination of Breast Cancer Prognosis

Munich RE



Breast Cancer “Stage” Not Presented in This Discussion Only T N M Characteristics

Munich RE

Breast Cancer Staging

Stage	Description
0	Tis, N0, M0
I	T1, N0, M0
II A	T0, N1, M0 or T1, N1, M0 or T2, N0, M0
II B	T2, N1, M0 or T3, N0, M0
III A	T0 - T2, N2, M0 or T3, N1- 2, M0
IIIB	T4, (any) N, M0 or (any) T, N3, M0
IV	(any) T, (any) N, M1

Early Stage (T1 T2 N0 M0) Breast Cancer

Munich RE

Survival curves are convex

- Debits fit better than temporary flat extra rating format
- Little advantage to postpone period

Age banding: recognize the menopause

Ages 70 & above, clinically negative axillary lymph nodes, Rx'd with lumpectomy & tamoxifen

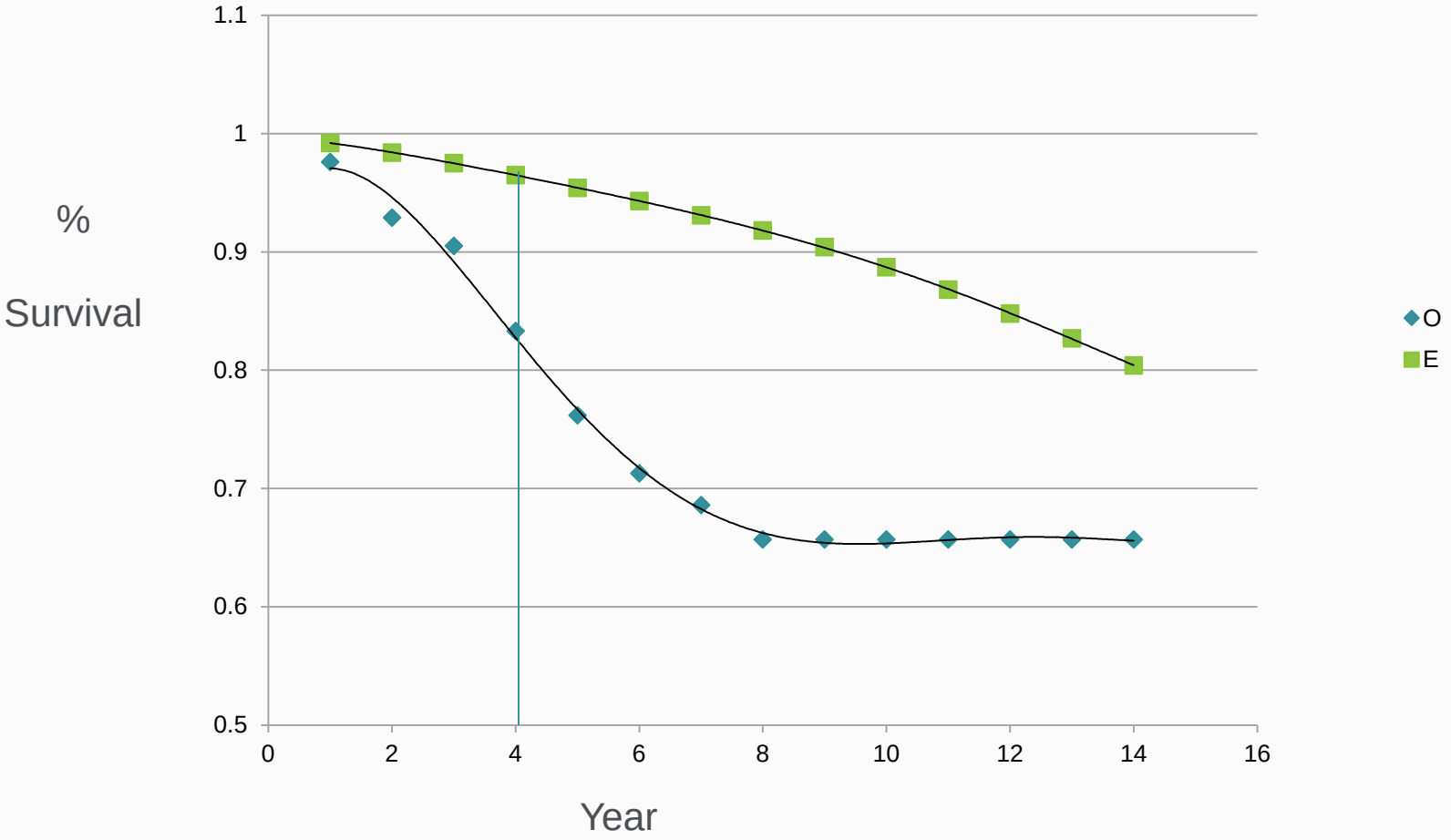
- No pathological axillary lymph node evaluation necessary unless adverse prognostic indicators present

Traditional Approach to Underwriting Cancer

T2 N1 M0, G2, ER Negative Breast Cancer, Ages 50 - 69

Munich RE

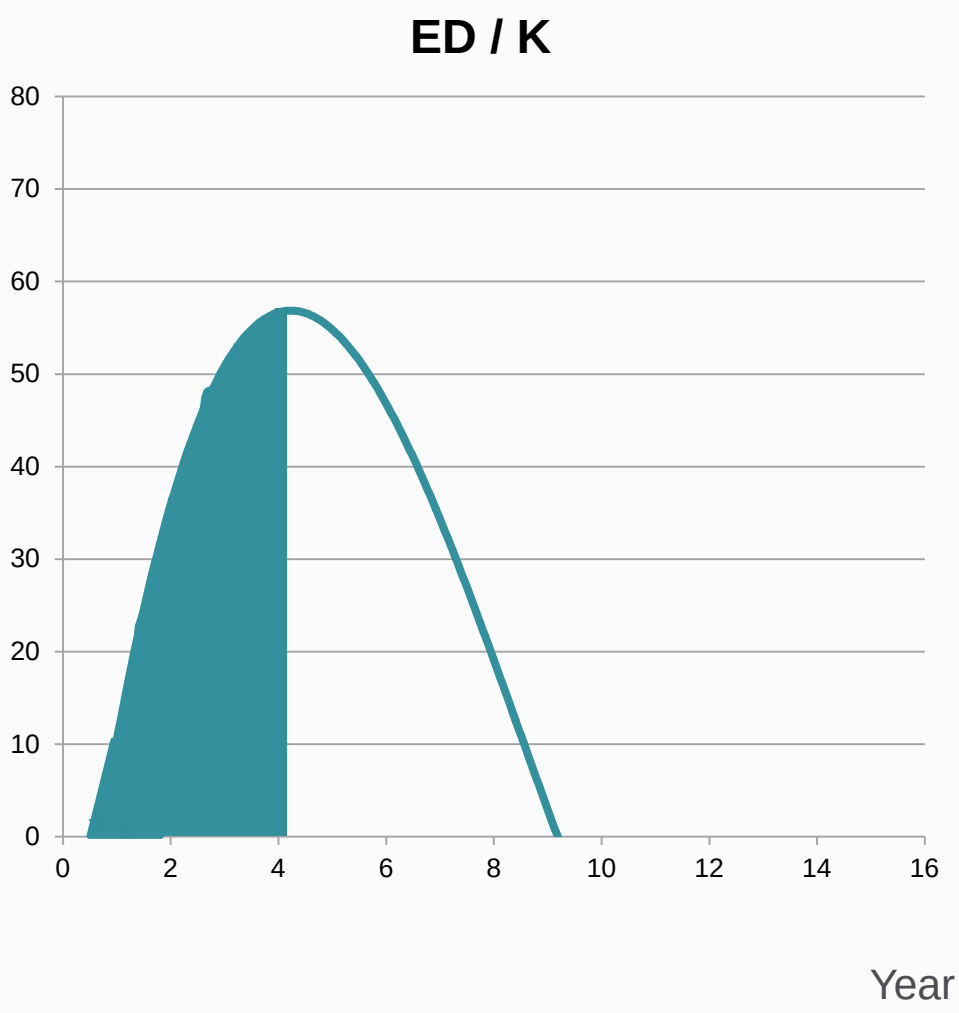
"Postpone" = cut off early, steep part of rapidly decreasing survival curve



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

T2 N1 M0, G2, ER Negative
Ages 50 - 69

Munich RE



+ 100 (Table 4)

Year	Total ED / K Remaining
5	159
6	116
7	61
8	23

Year	Flat Extra	ED/K Remaining
5	30 / m x 5 Y	159
6	25 / M x 4 Y	116
7	20 / M x 3 Y	61
8	12 / M x 2 Y	23

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Screening mammography has resulted in twice as many early stage breast cancers being detected yearly

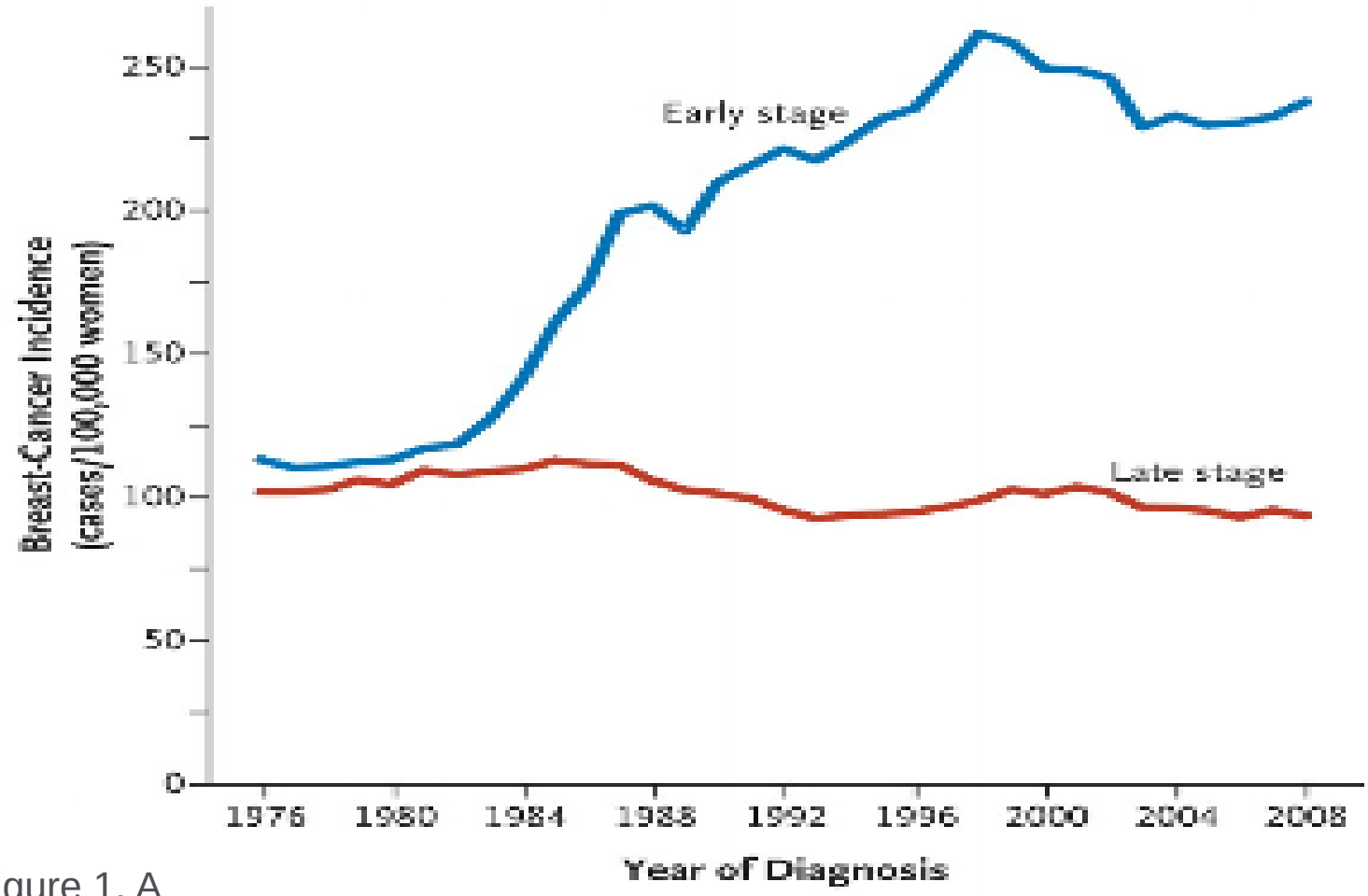


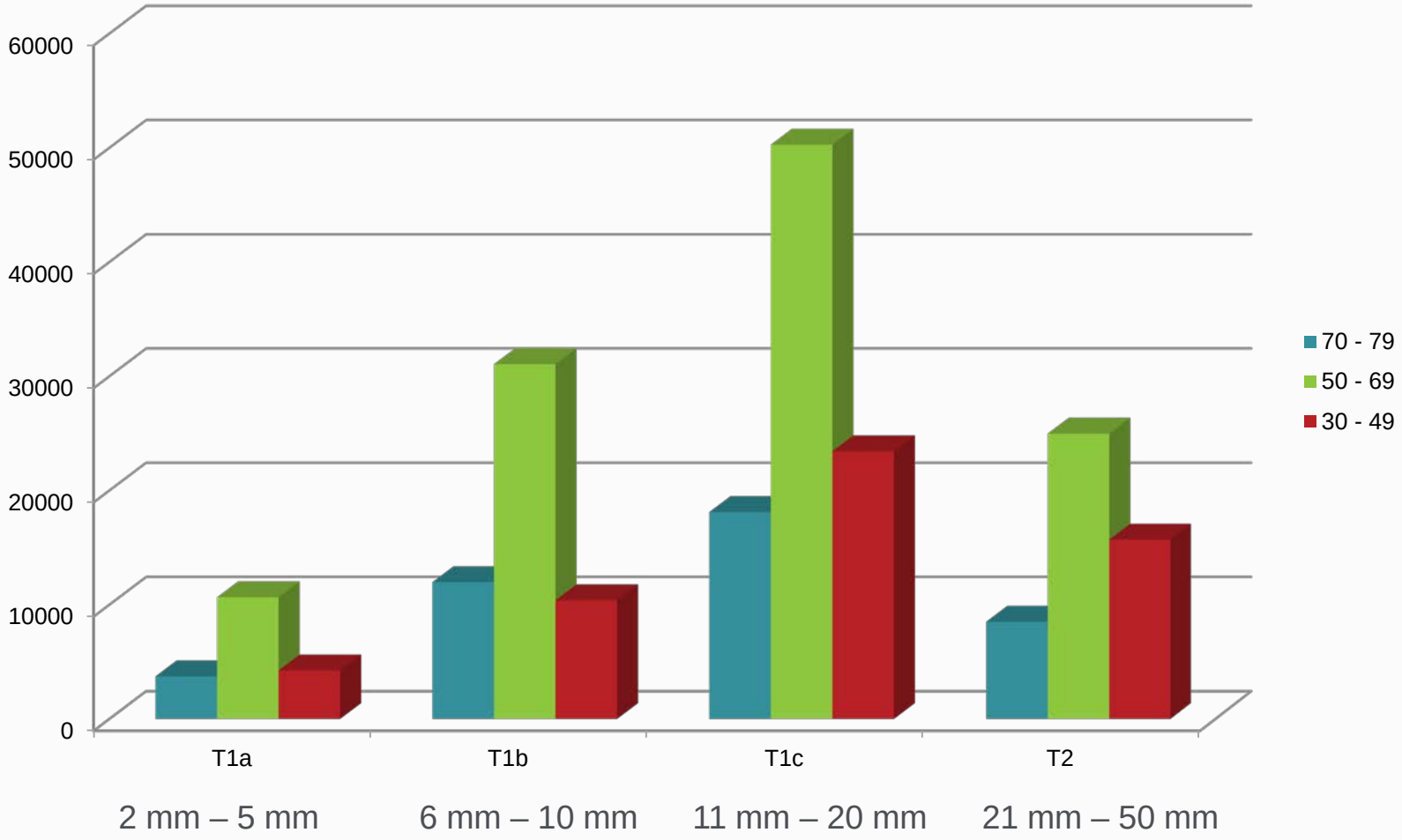
Figure 1. A

Women ≥ 40 years of age

Bleyer A and Welch HG, *NEJM* 2013;367(21):1998 – 2005.

Early Stage Breast Cancer

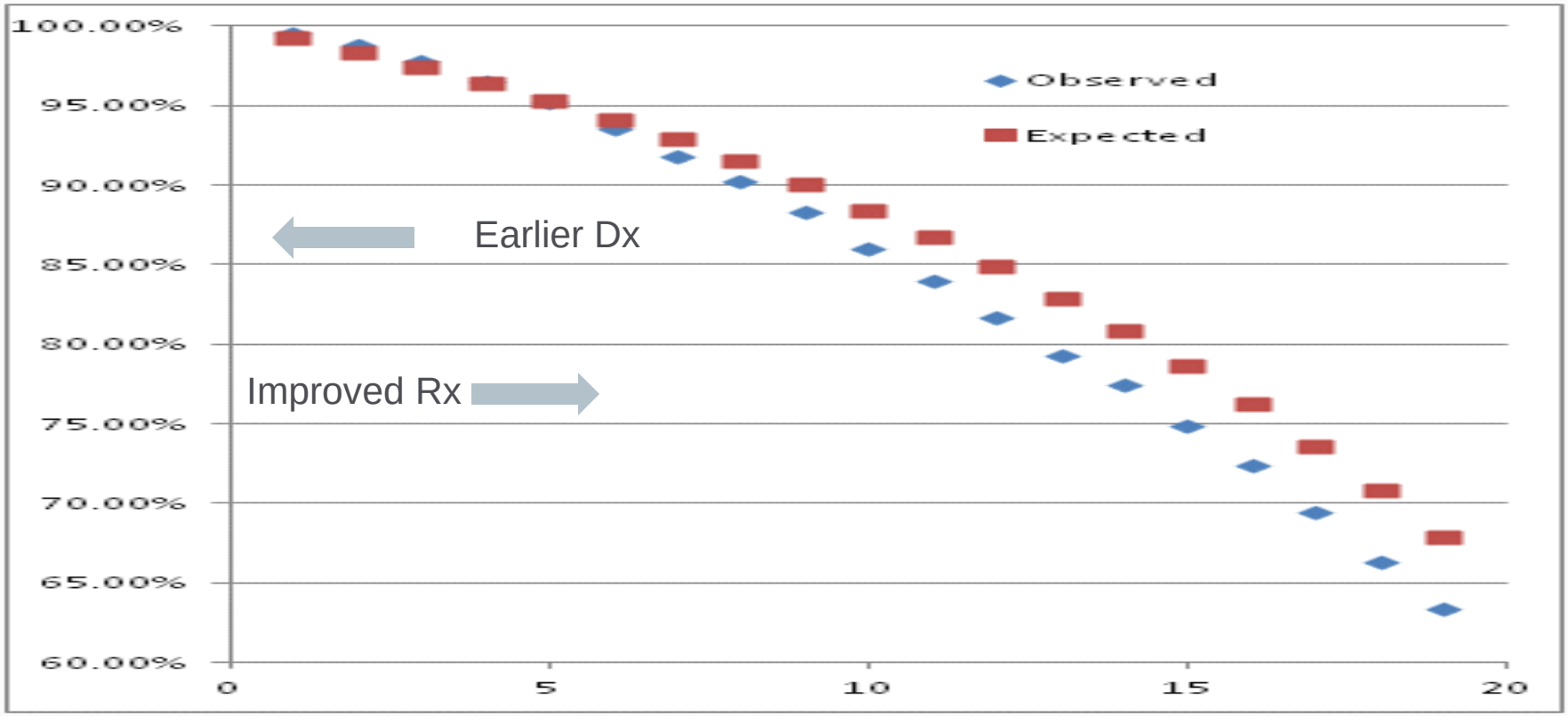
Distribution by T Stage and Age



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Breast Cancer T1c N0 M0, Grades 1 and 2
Ages 50 - 69

Survival curve is convex and similar to expected mortality
(Not initially steeply concave as in earlier example)



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

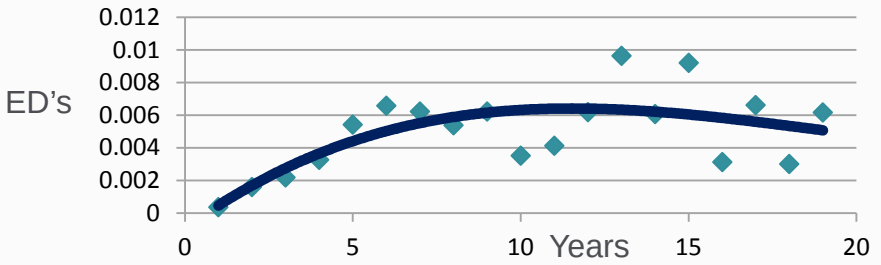
Temp Flat Extra Rating Paradigm Does Not Fit The Pattern of Excess Deaths in Early Stage Breast Cancer

Munich RE

Most of Excess Deaths Occur After Year 5 (and persist beyond year 19)

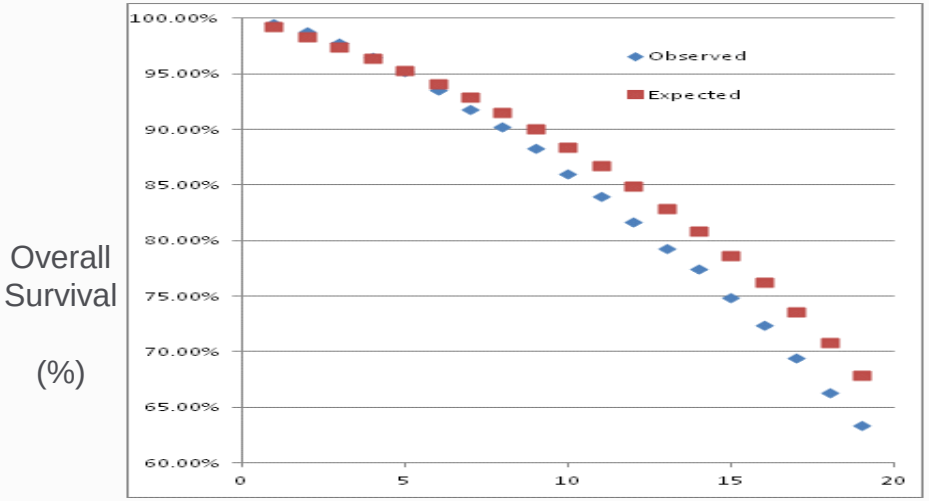
Duration (Years)	Temp. Flat Extra
0 – 1	PP
1 – 2	PP
2 – 3	15 x 5
3 – 4	12.5 x 4
4 – 5	10 x 3
5 – 6	7.5 x 2
6 – 7	5 x 1
7 – 8	0
8 – 9	0
9 - 10	0
10 yrs +	0

T1c (11 – 20mm) N0 M0, Grade 1 and 2 Ages 50 - 69



17 years of Excess Deaths
Average ED / Year = 0.004176

Total ED / K = 71,
Mortality Ratio = 115%



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Munich RE

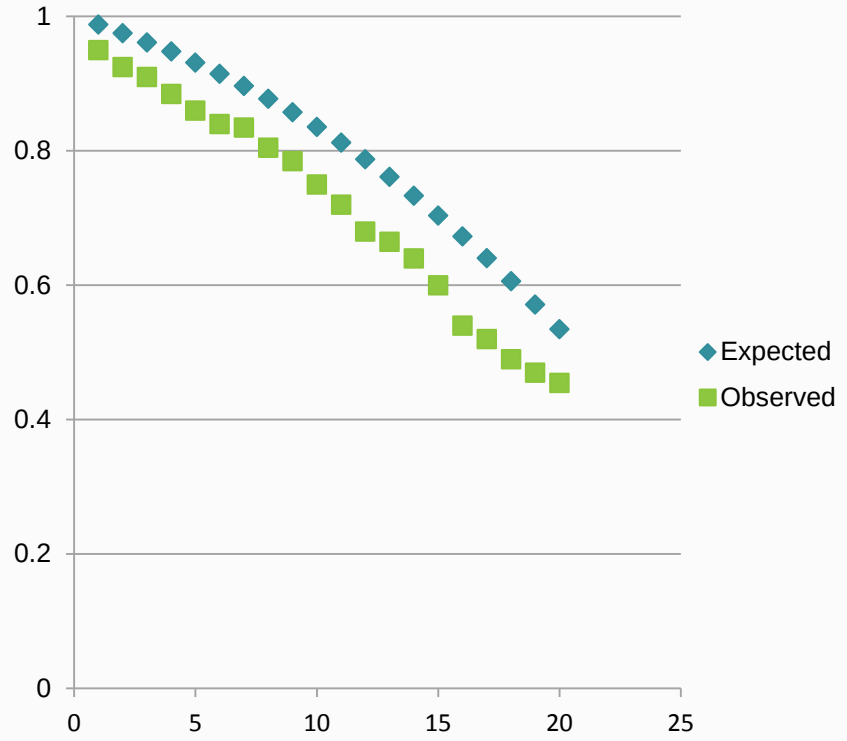
SURVIVAL PATTERNS OF EARLY BREAST CANCER RESEMBLE THOSE OF NON CANCER IMPAIRMENTS

FOR MOST NODE NEGATIVE DISEASE NO REAL ADVANTAGE POSTPONING FOR SEVERAL YEARS

Localized Breast Cancer Survival Curves Are Not Dissimilar from Non-Cancer Impairment Survival Curves

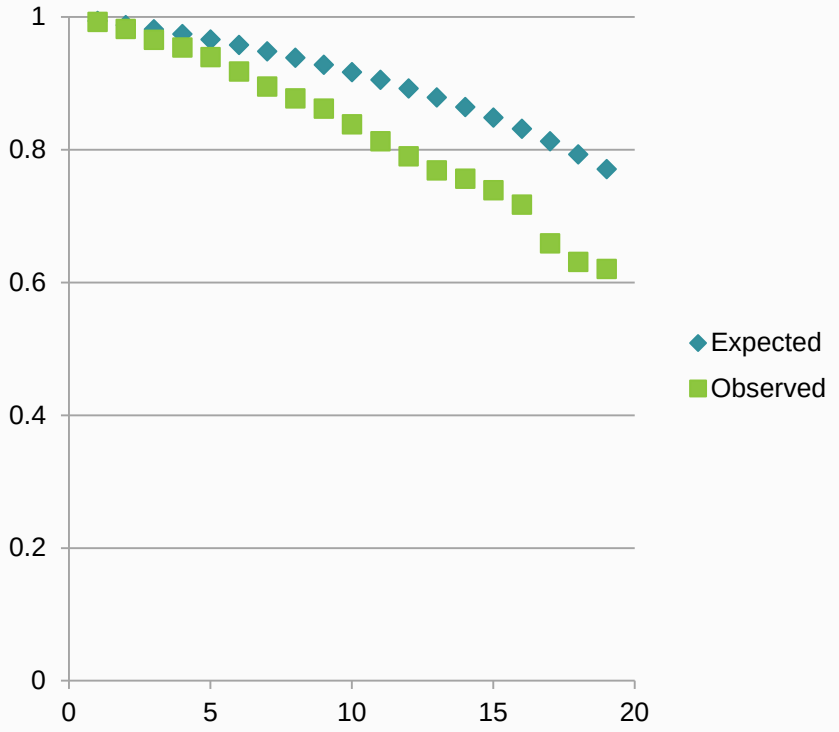
Munich RE

Surgical Repair of Non-Rheumatic Mitral Insufficiency: Median Age = 58 Years
Mort. Ratio = 131%



Braunberger E, et al, Circulation 2001;104:1 – 8.

Breast Cancer: T2 N0 M0, Gr1,2
55 – 59 Years
Mortality Ratio = 134 %

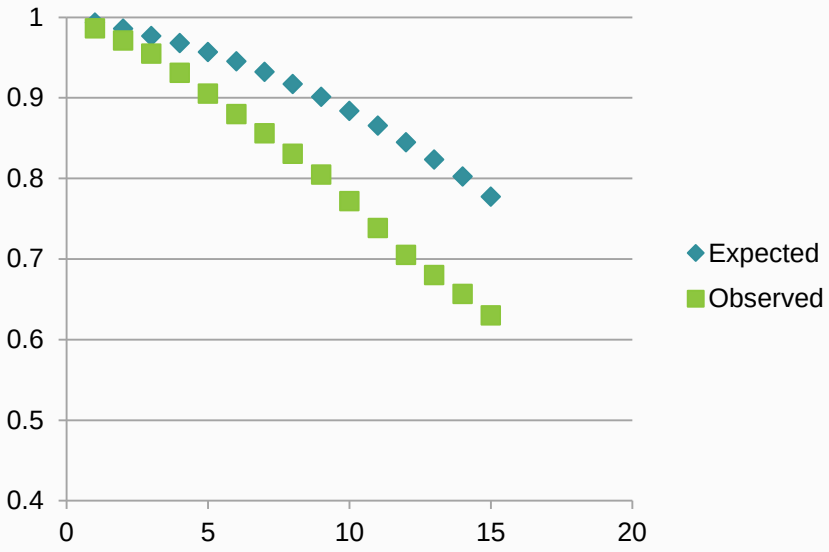


Surveillance Research Program, National Cancer Institute
SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

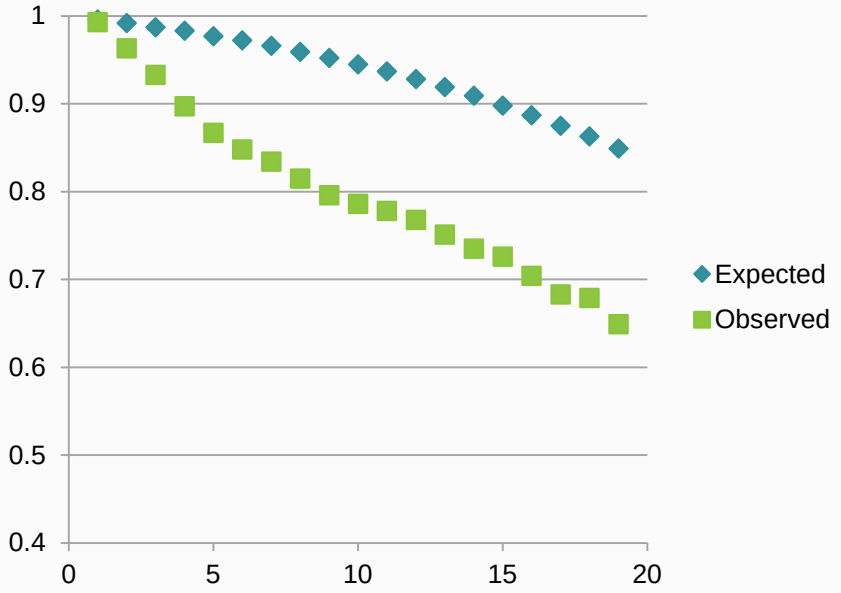
Not Until T2 N0 M0, Grade 3 Breast Cancer Does The Survival Curve Become Concave

Munich RE

Type 2 Diabetic Males
53 Years
Mortality Ratio = 194%



Breast Cancer: T2 N0 M0, Gr3
50 – 54 Years
Mortality Ratio = 168%
Total ED / K over first 19 years = 257



Hansen LJ, et al, *BMC Public Health* 2009;9:400

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Munich RE

EXTRA MORTALITY NEVER GOES AWAY

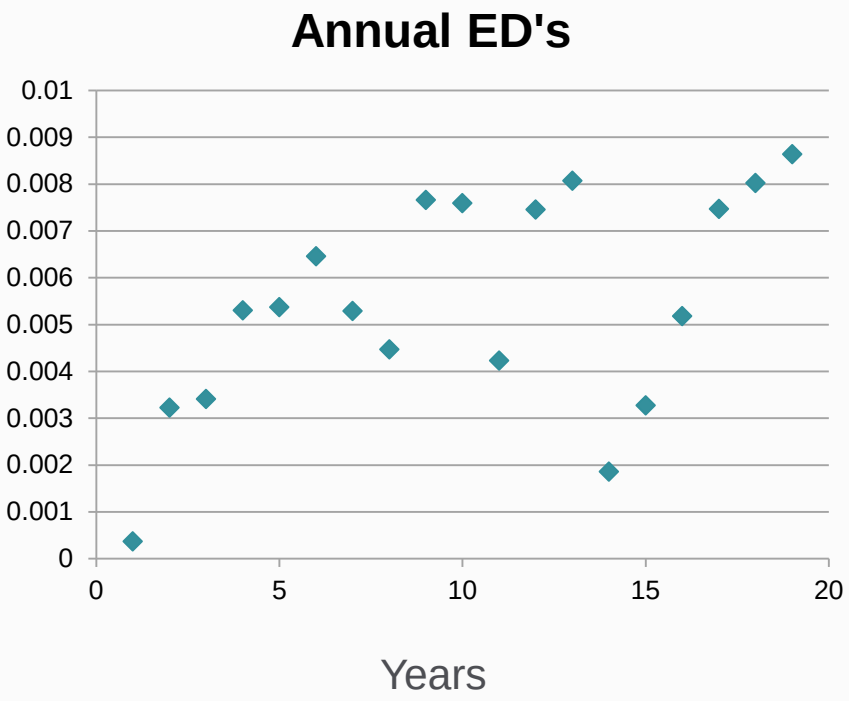
(BUT USUALLY IS MINIMAL)

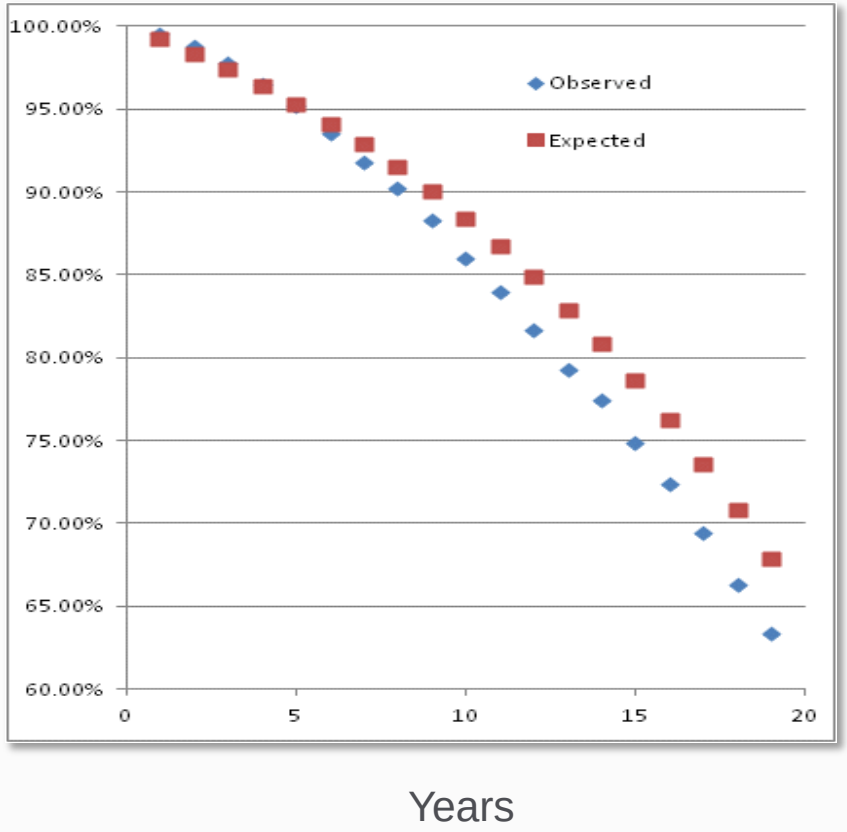
T1C N0 M0, Grade 1,2, Ages 50 – 69 Years
Mortality over first 19 years persists, although it is minimal

Munich RE

Total ED / K = 74 Over First 19 Years
Excess Deaths Persist for > 19 Years

Mortality Ratio = 115 %



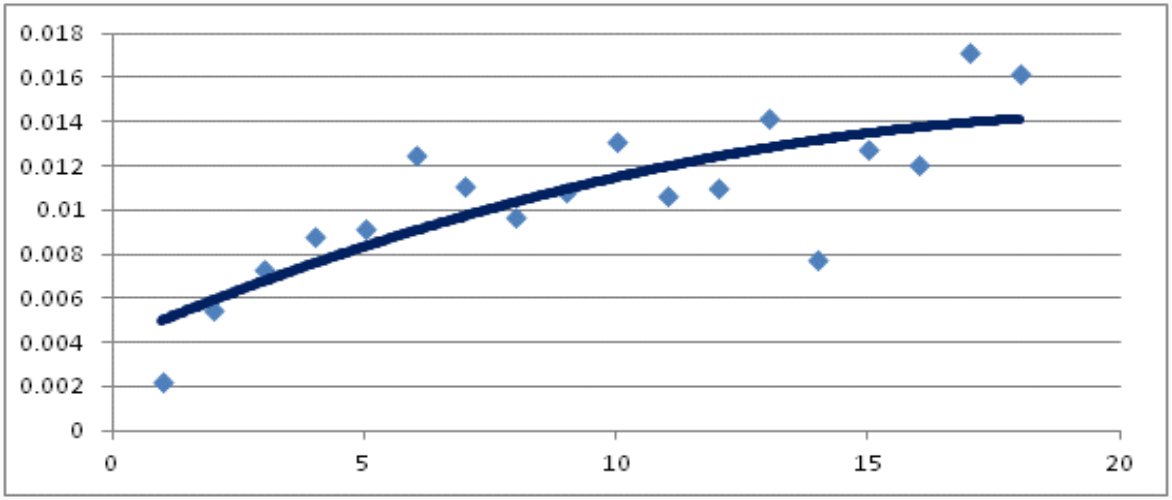


Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Temp Flat Extra Rating Paradigm Does Not Fit The Pattern of Excess Deaths

Munich RE

T2 (021 – 050 mm) N0 M0, Grade 1 and 2
Ages 50 - 69



Years

18 + years of Excess Deaths
Average ED / Year = 0.008528355

Total ED / K = 193,
Mortality Ratio = 131%

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Long-term adverse effects from therapy result in chronically increased mortality risk after treatment for breast cancer

Munich RE

- Radiation
  - Increase incidence of coronary artery disease
  - Myocardial damage from radiation
- Chemotherapy
  - Increased incidence of hematologic malignancies
  - Cardiomyopathy

Future Risk for **Early-Stage Hodgkin's Disease** Patients Treated with Both Chemotherapy and Radiotherapy

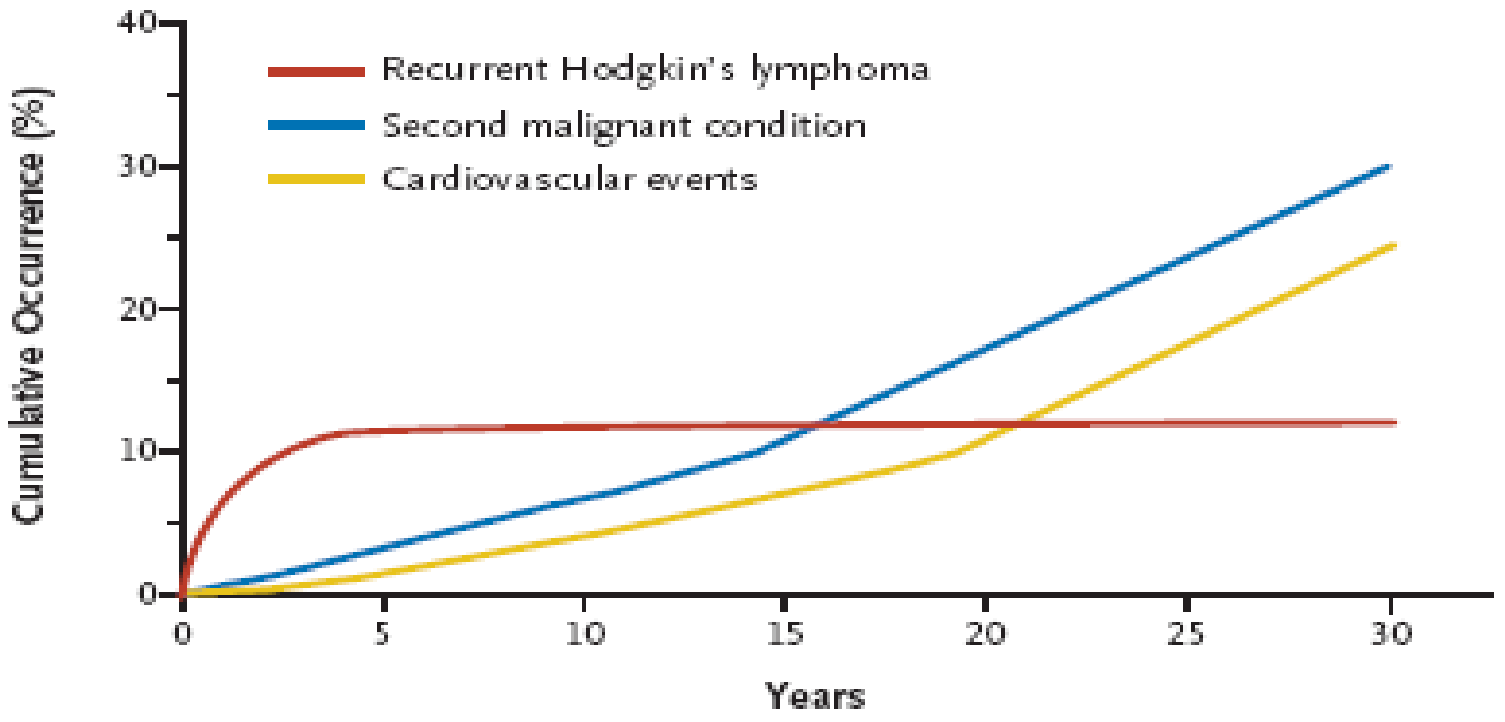


Figure 1. Approximate Cumulative Risk of Recurrent Hodgkin's Lymphoma, Second Malignant Conditions, and Cardiovascular Events among Patients Receiving Both Radiotherapy and Chemotherapy for Early-Stage Hodgkin's Lymphoma.

Armitage JO, *NEJM* 2010;363(7):653 – 62.

Munich RE

MENOPAUSAL EFFECT ON MORTALITY RISK OF BREAST CANCER

Menopause has great influence on Mortality of Breast Cancer (and on Tumor Grade Effect as well)

Munich RE

T N M Stage	Grade	Mortality Ratio (%)		
		Below 50 Years	50 – 69 Years	70 Years & Above
T1a, T1b N0 M0	1 & 2	**143**	96	94
	3	**209**	105	94
T1c N0 M0	1 & 2	**214**	115	104
	3	**299**	125	111

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

Munich RE

MORTALITY RISK PROGNOSTIC INDICATORS

HOW HELPFUL IN EARLY STAGE BREAST CANCER?

Prognostic Indicators

Munich RE

Positive prognostic indicators are those correlating with tumor grades I and II below

Tumor Grades	Grade I (well differentiated) or II (moderately differentiated)	Grade III (poorly differentiated)	Grade IV (undifferentiated, anaplastic)
Prognostic indicators correlating roughly with tumor grades			
Tumor Grade	Grades I & II	Grade III	Grade IV
Her-2 neu oncoprotein	0 to 1 +	2 +	3 +
S Phase	< 6.8 %	6.8 % to 10 %	> 10 %
DNA Ploidy	Diploid	Tetraploid	Anueploid
Mitotic Index	≤ 4.9	5 - 10	> 10

Tumors sized 0.2 to 3.0 centimeters in women aged 70 to 85 are either Grade I or Grade II about 75 % of the time

The Basics to Underwriting Breast Cancer
Age at Diagnosis, Tumor Size, Lymph Node Status

Munich RE

T1c N0 M0
Ages 50 – 69 Years

Size

1.1 – 2.0 cm
Mortality Ratio = 113 %
Number = 50271

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.1.5

Grade
Status Helpful ??

Munich RE

T1c N0 M0
Ages 50 – 69 Years

Size

1.1 – 2.0 cm
Mortality Ratio = 113 %
Number = 50271

Size, Grade

I
Mortality Ratio = 106 %
Number = 10488

II
Mortality Ratio = 113 %
Number = 20634

III
Mortality Ratio = 122 %
Number = 13380

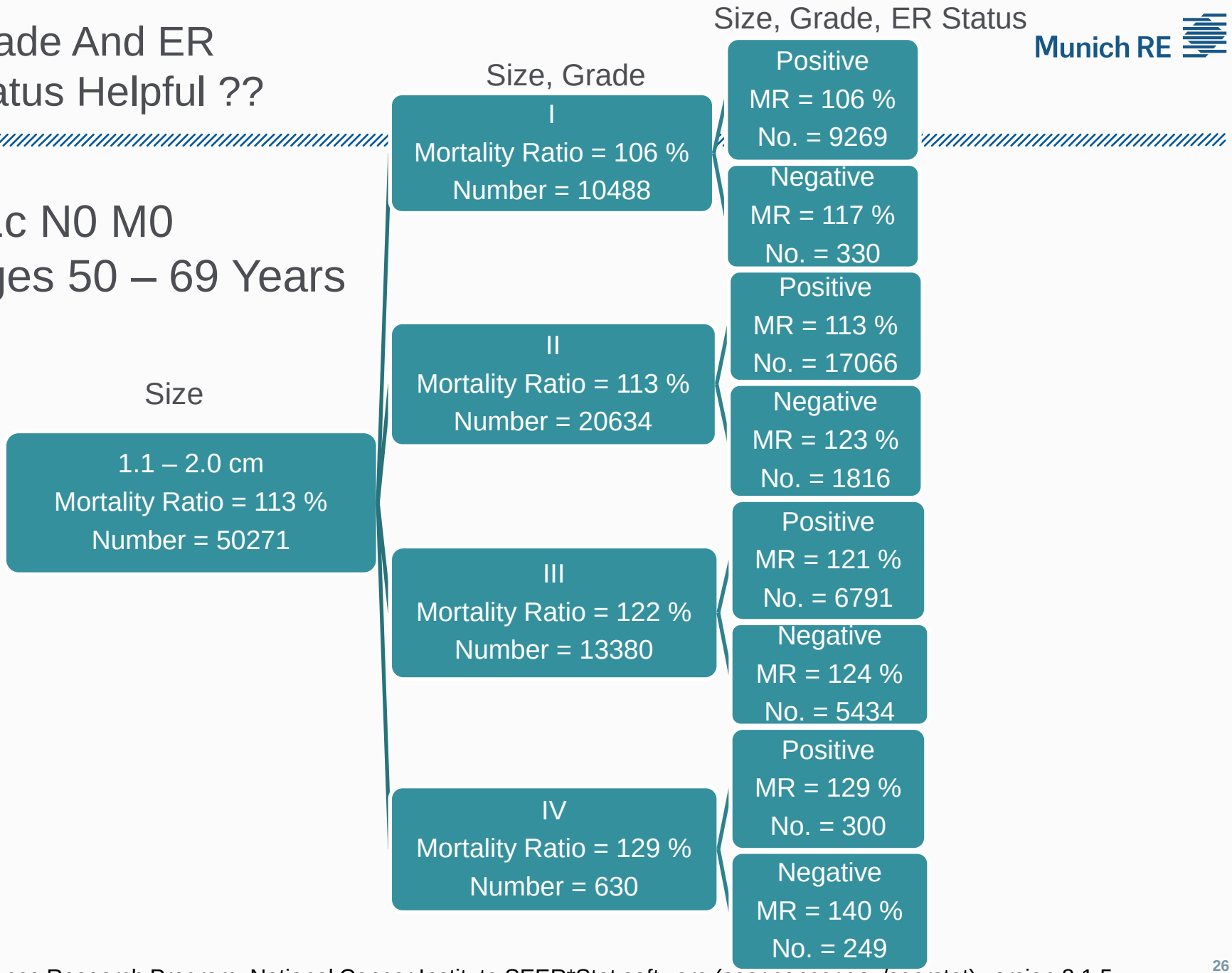
IV
Mortality Ratio = 129 %
Number = 630

Including Grade II T1c Breast Cancers Along With Grade I T1c Breast Cancer ~ Triples The Number Receiving The Best Offer With Little Change In Mortality Risk

Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.1.5

Grade And ER Status Helpful ??

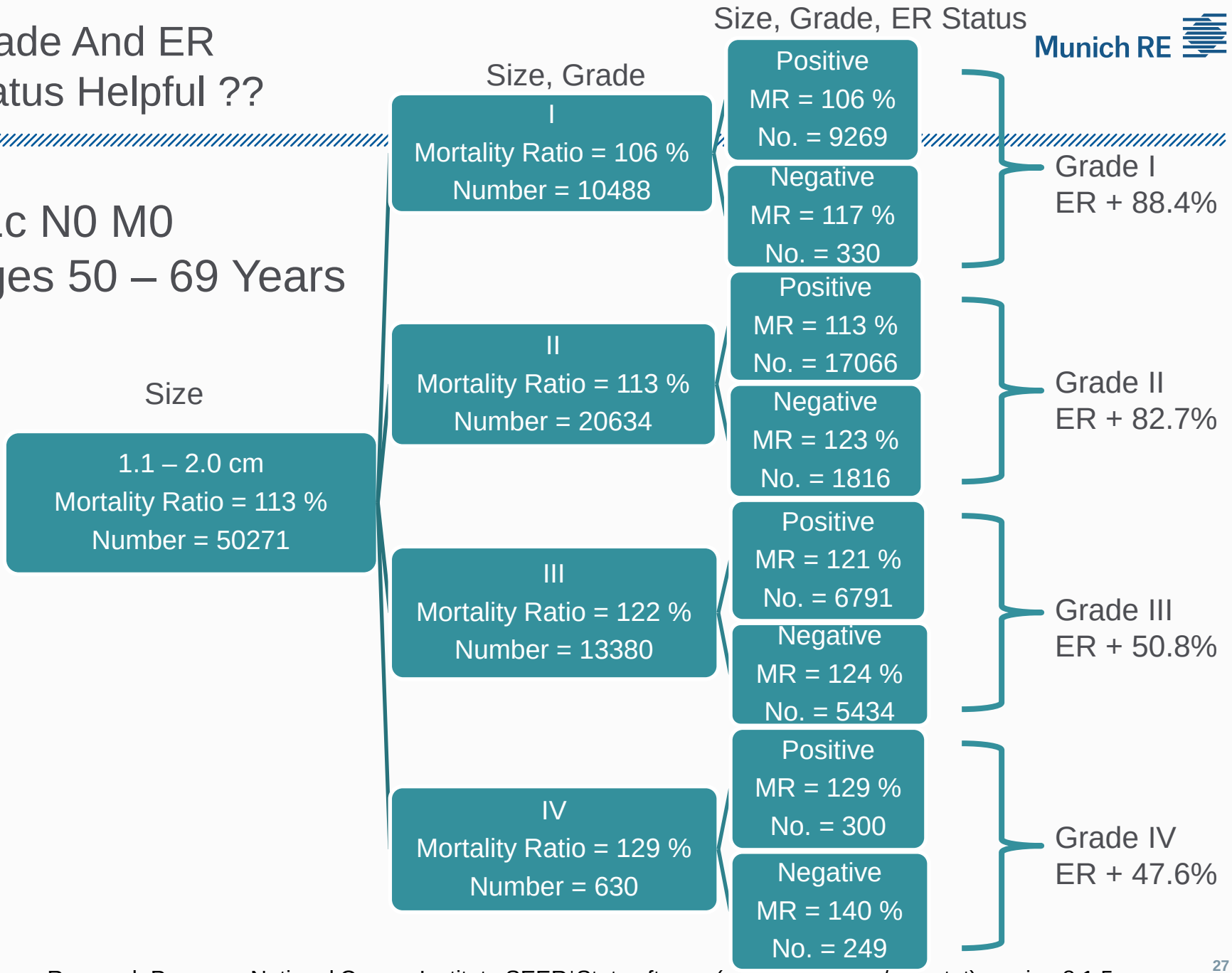
T1c N0 M0
Ages 50 – 69 Years



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.1.5

Grade And ER Status Helpful ??

T1c N0 M0
Ages 50 – 69 Years



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.1.5

BRCA 1 AND BRCA 2 – “THE BREAST CANCER GENES”

The Original Breast Cancer Gene Study: Autosomal Dominant with High Penetrance

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 3044–3048, May 1988
Genetics

Inheritance of human breast cancer: Evidence for autosomal dominant transmission in high-risk families

(breast neoplasms/epidemiology/gene mapping/medical genetics/pedigree analysis)

BETH NEWMAN, MELISSA A. AUSTIN, MING LEE, AND MARY-CLAIRE KING

School of Public Health, University of California, Berkeley, CA 94720

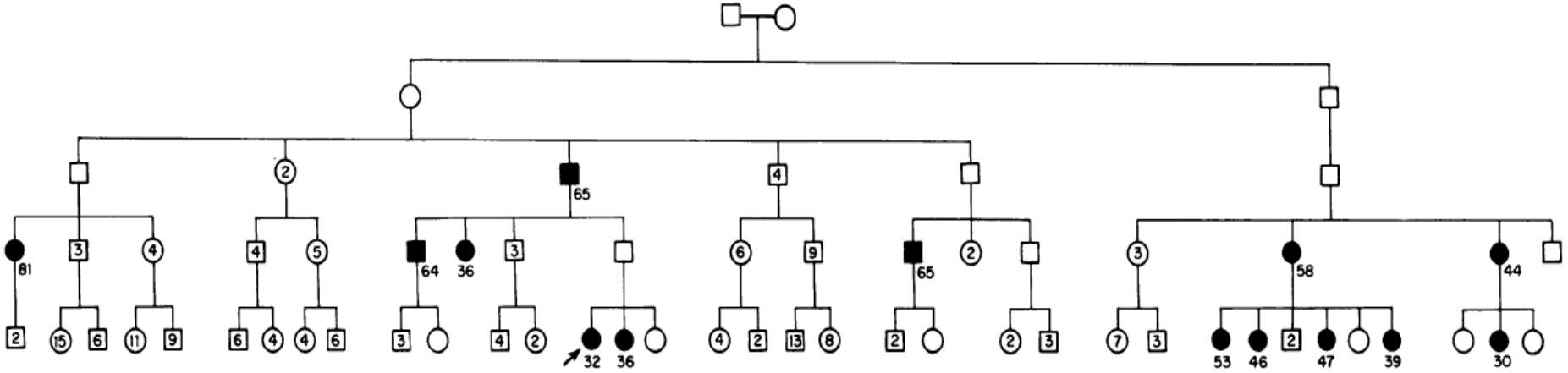


FIG. 1. An extended family at high risk of breast cancer. Affected women and men are represented by filled circles and squares, respectively, with the age at diagnosis of breast cancer indicated for each case. The maximum-likelihood autosomal dominant (or codominant) model for this family predicts lifetime risks of breast cancer of 86% for genetically susceptible women, 9% for genetically susceptible men, and 6% for women without genetic susceptibility.

Vast Majority of Breast Cancers Are Sporadic (e.g., No Inheritable Risk Factors)

Munich RE

About 9 % of All Women Will Get Breast Cancer

- Of these ~ 5 – 10 % hereditary

All Women with Breast Cancer

- 10 – 20 % have first degree relative also with breast cancer

Women with Breast Cancer And History of First Degree Relative with Breast Cancer

- Up to 20 % will have mutation in a major gene
  - Most often in breast cancer susceptibility genes 1 & 2 (*BRCA1* & *BRCA2*)

Characteristics Associated with BRCA Mutations

Munich RE

Several Generations with Breast Cancer

- Often premenopausal

Ovarian Cancer Also Associated with BRCA Mutations

- Other cancers: prostate, pancreatic and male breast cancer

Triple Negative Breast Cancer (TNBC)

- More than five-fold risk of being a BRCA1 carrier relative to women with Non-TNBC

Later age at first live birth may be protective against developing breast cancer in those with BRCA1

- A similar characteristic to those with triple negative breast cancer

No impact on age at first live birth regarding future risk for developing breast cancer in those with BRCA2

What Is The Long Term Risk of Cancer with BRCA ? (Up to Age 70)

Munich RE

BRCA1

- Breast cancer: 55 – 70 %
  - Mean age at diagnosis: 43 years
- Ovarian cancer: ~ 40 %

BRCA2

- Breast cancer: 45 – 70 %
  - Mean age at diagnosis: 47 years
- Ovarian cancer: 15 %

Life Time Risk for Cancer in Contralateral Breast

- More than 60 %

BRCA1 And BRCA2; No Personal History of Cancer Risk Reducing Surgery

Munich RE

Prophylactic Bilateral Mastectomy

- Often now “skin sparring” with immediate reconstruction
- Decreases risk of future breast cancer by as much as 90 %

Bilateral Salpingo-opherectomy (BSO)

- Between ages of 35 and 40 years once childbearing is complete
- Produces 72 % reduction in ovarian cancer, especially in BRCA1
- Reduces both ovarian and breast cancer risk (latter in premenopausal women)

Munich RE

TRIPLE NEGATIVE BREAST CANCER

SIGNIFICANT PROGNOSTIC RISK

Breast Cancers Depend upon Estrogen and/or Progesterone for Growth; Their Receptors Are Over Expressed

Munich RE

Triple negative breast cancer

- Negative for human epidermal growth factor receptor 2 (HER2)
- Negative for estrogen receptor and / or
- Negative for progesterone receptor

Targeted therapy not possible

Predilections of Triple Negative Breast Cancer

Relatively more frequent in African American women

Premenopausal
(relatively younger ages)

- More likely to have had several children
- Absence of breast feeding history

Higher BMI’s

Adverse Characteristics

Munich RE

Less frequently presents due to mammography finding

- Presents with more advanced stage
- 66% present with symptoms, usually breast mass

More likely of higher tumor grade

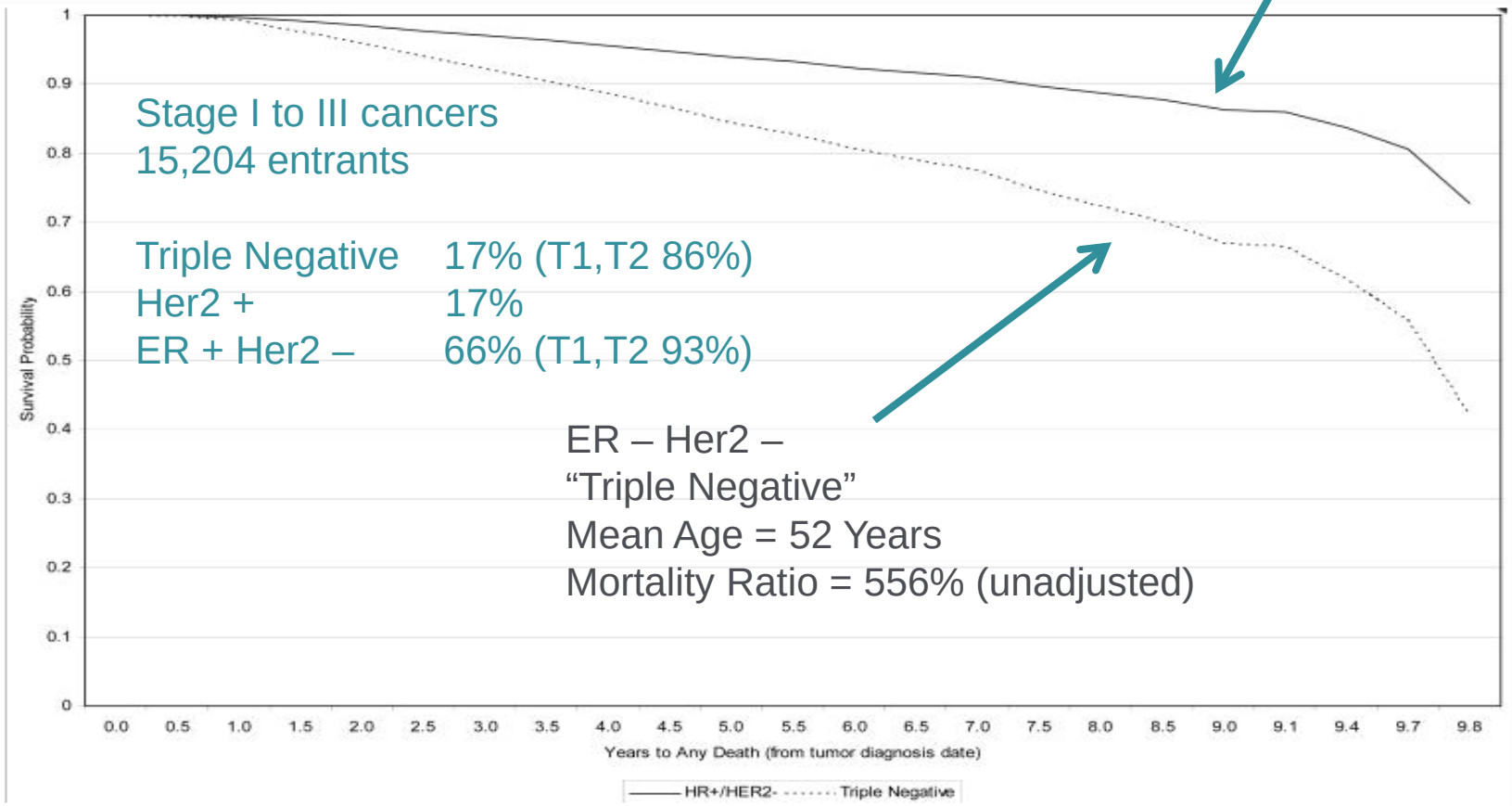
Greater likelihood of brain and lung metastatic disease

- Paradoxically, less likely to have axillary lymph node involvement
- Initially, or later, ~ 36% have CNS involvement

National Comprehensive Cancer Network Breast Outcomes Database: HER2 status determined since 1999

Munich RE

ER + Her2 –
Mean Age = 56 Years
Mortality Ratio = 136 %



Stage I to III cancers
15,204 entrants

Triple Negative	17% (T1,T2 86%)
Her2 +	17%
ER + Her2 –	66% (T1,T2 93%)

ER – Her2 –
"Triple Negative"
Mean Age = 52 Years
Mortality Ratio = 556% (unadjusted)

Lin NU, et al, *Cancer* 2012:5463 – 5472.

Risk of Death with Triple Negative Breast Cancer Most Pronounced, Relative to ER+Her2- Cancers, in First Two Years after Diagnosis

Endpoint	Unadjusted	Adjusted[c]
Any death		
Entire follow-up period	3.28 (2.93-3.66)	2.72 (2.39-3.10)
0-2 y	7.75 (6.17-9.74)	6.10 (4.81-7.74)
2-6 y	2.74 (1.67-4.51)	2.30 (1.39-3.82)
From 6 y to the end of follow-up	1.15 (0.46-2.88)	0.96 (0.38-2.42)

Lin NU, et al, *Cancer* 2012:5463 – 5472.

ABOVE 70 YEARS OF AGE: EARLY STAGE BREAST CANCER (≤ 3 CM LESIONS) IS EFFECTIVELY TREATED WITH LUMPECTOMY AND TAMOXIFEN ALONE IF….

Positive Prognostic Indicators Present and ….

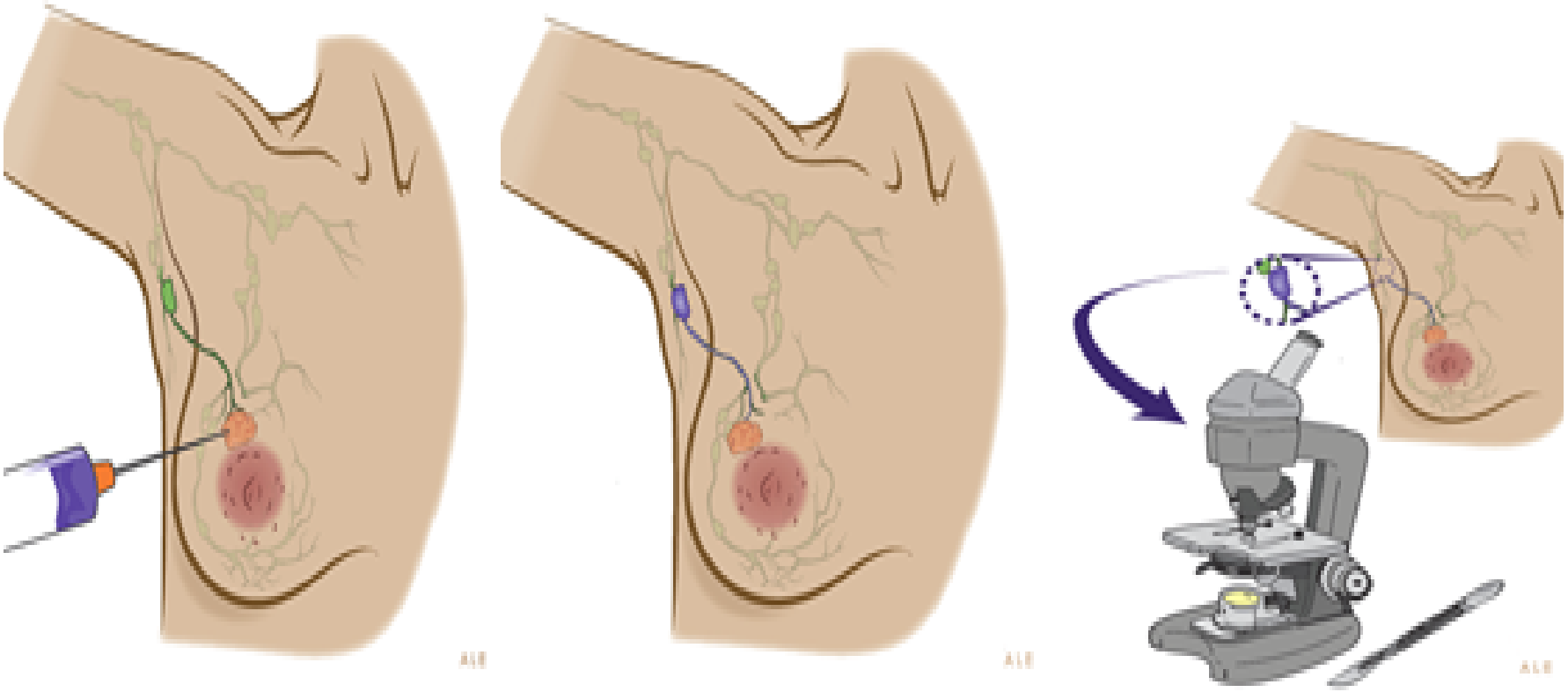
Munich RE

Positive prognostic indicators are those correlating with tumor grades I and II below

Tumor Grades	Grade I (well differentiated) or II (moderately differentiated)	Grade III (poorly differentiated)	Grade IV (undifferentiated, anaplastic)
Prognostic indicators correlating roughly with tumor grades			
Tumor Grade	Grades I & II	Grade III	Grade IV
Her-2 neu oncoprotein	0 to 1 +	2 +	3 +
S Phase	< 6.8 %	6.8 % to 10 %	> 10 %
DNA Ploidy	Diploid	Tetraploid	Anueploid
Mitotic Index	≤ 4.9	5 - 10	> 10

Tumors sized 0.2 to 3.0 centimeters in women aged 70 to 85 are either Grade I or Grade II about 75 % of the time

The Axillary Lymph Nodes Are Clinically Negative In Which Case…

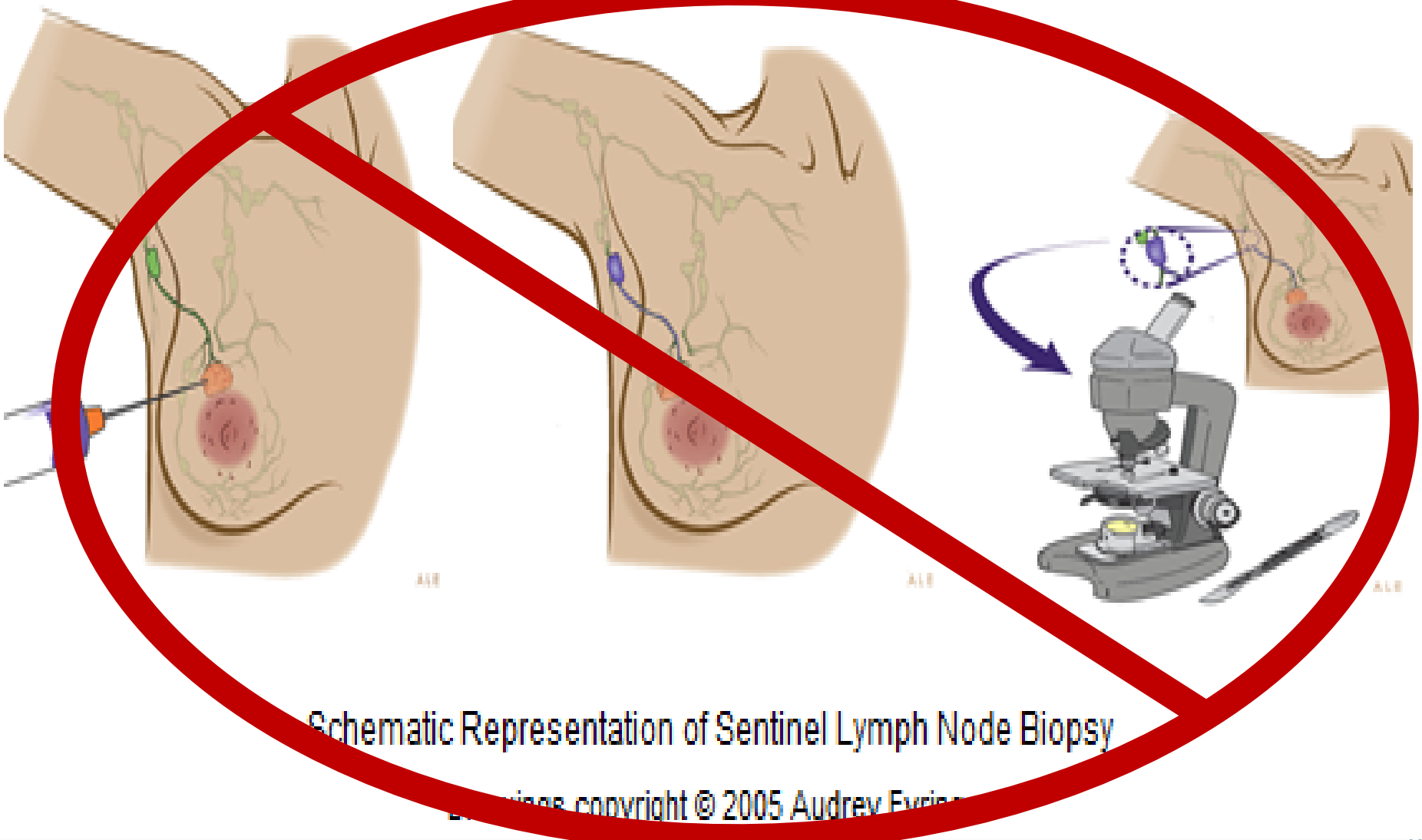


Sentinel Lymph Node Biopsy

Schematic Representation of Sentinel Lymph Node Biopsy

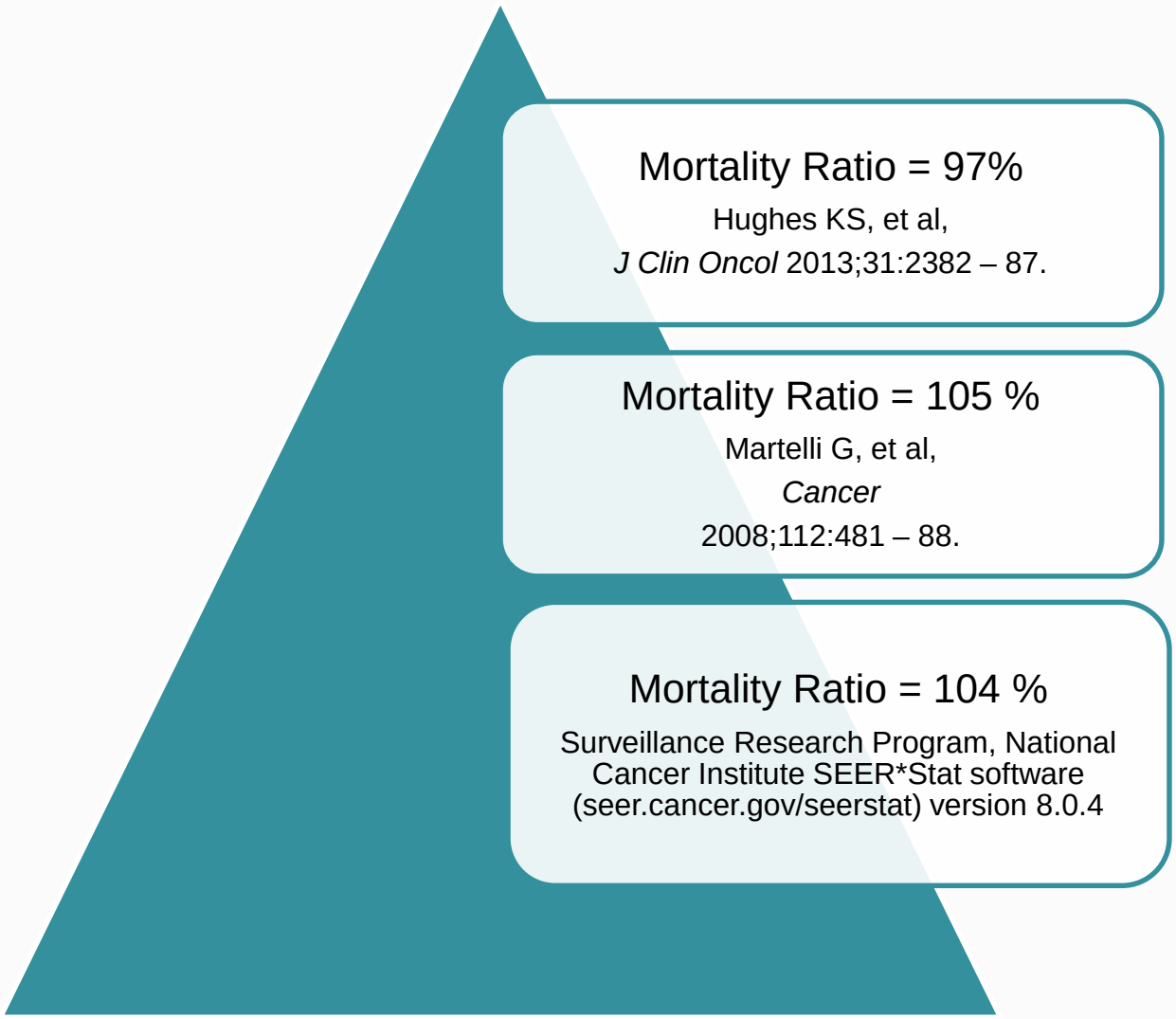
Surgical Removal of Lymph Node(s) for Pathological Examination Not Needed Above Age 70 with Low Grades

Munich RE



Minimal Increased Mortality Ages 70 & Above with Lumpectomy and Tamoxifen alone for ≤ 3cm tumors with Clinically Negative Lymph Nodes (no axillary lymph node dissection)

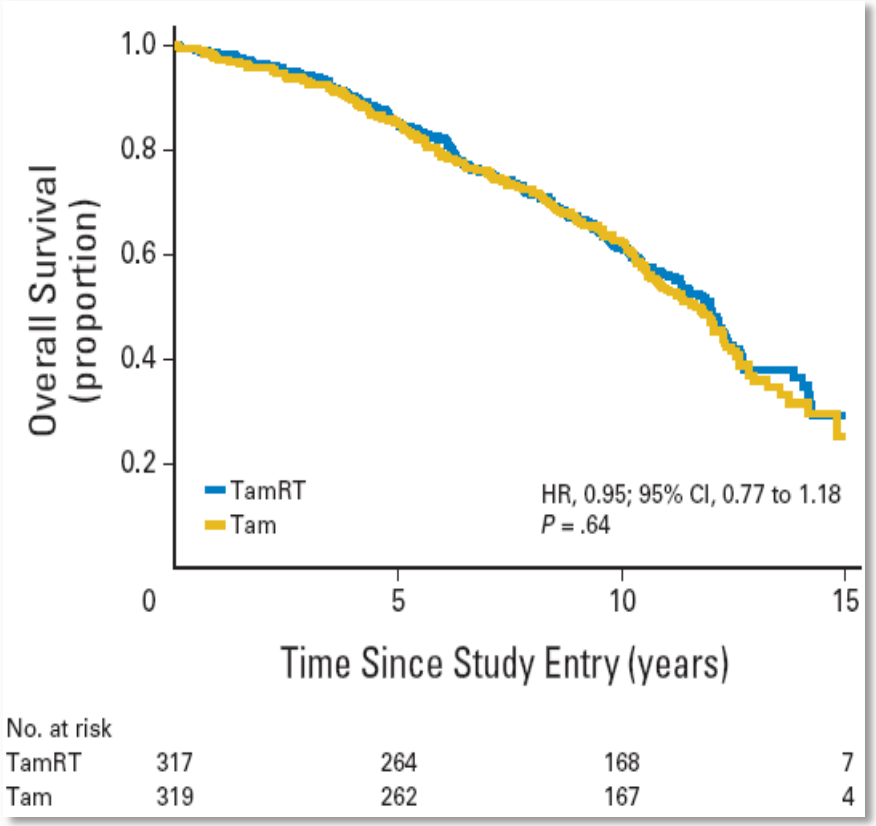
Munich RE



Women 70 Years or Older, T1 N0 M0, ER + Breast Cancer and Clinically Negative Axilla – No Increased Mortality

Munich RE

No survival benefit by adding RT to tamoxifen



Mortality Ratio = 97%

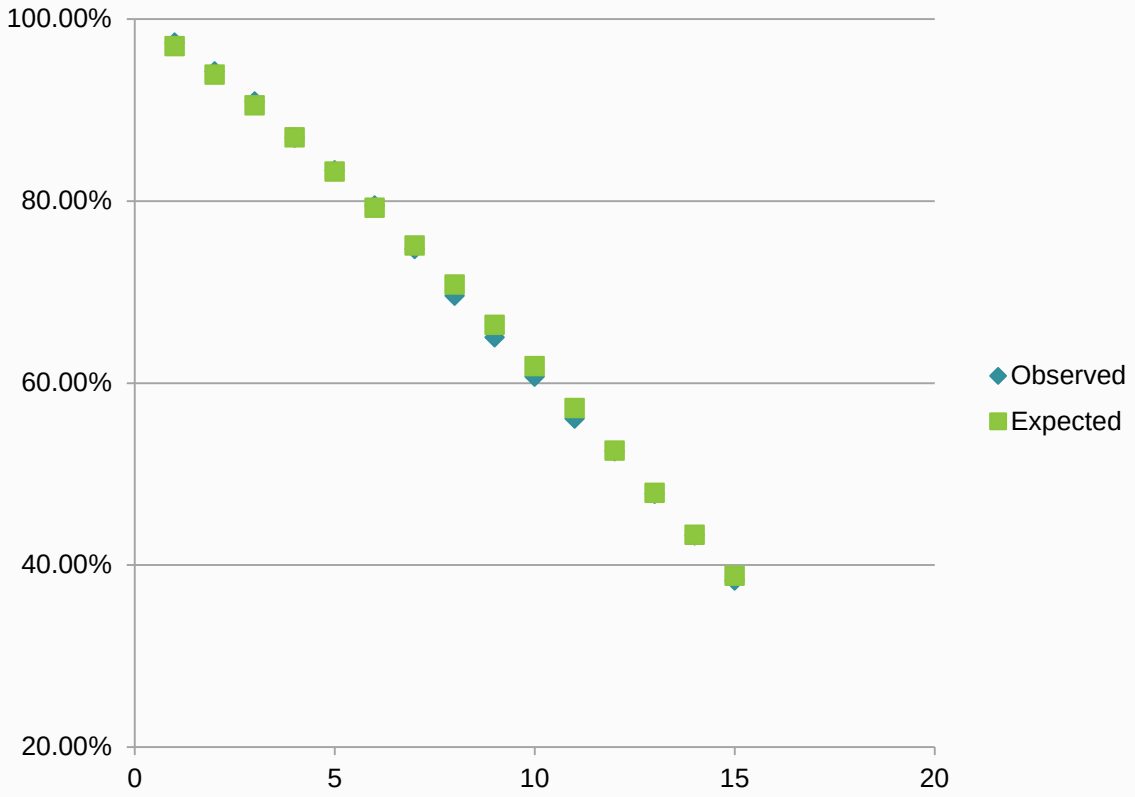
Only 1.5% later develop + axillary lymph nodes

Hughes KS, *J Clin Oncol* 2013;31:2382 – 2387.

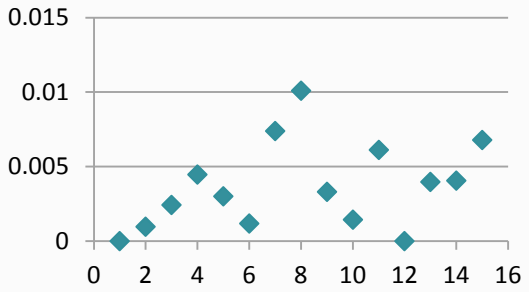
T1C LN Status Undefined, Grade Undefined, M0 Ages 70 and above

Munich RE

Mortality Ratio = 104 %



- Minimal excess late mortality for T1C breast cancer without consideration of axillary lymph node status in ages 70 & above



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

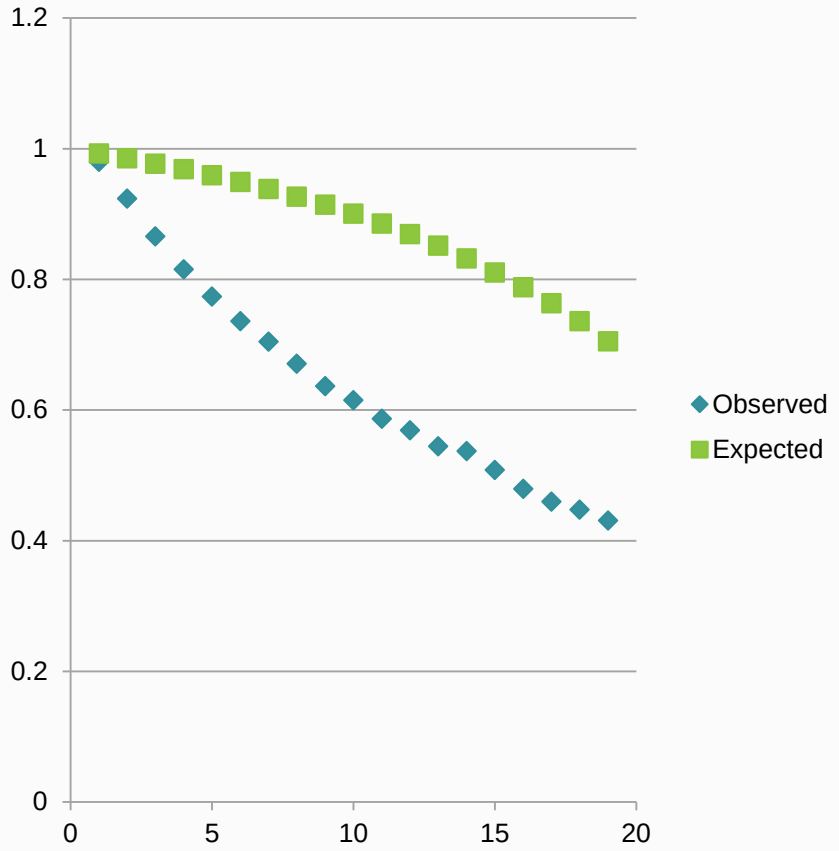
POSTPONE PERIOD IS PROTECTIVE FOR NODE POSITIVE DISEASE

UP TO 3 AXILLARY LYMPH NODES, NOT MATTED, FREELY MOVABLE, IPSILATERAL (SAME SIDE) AS BREAST CANCER

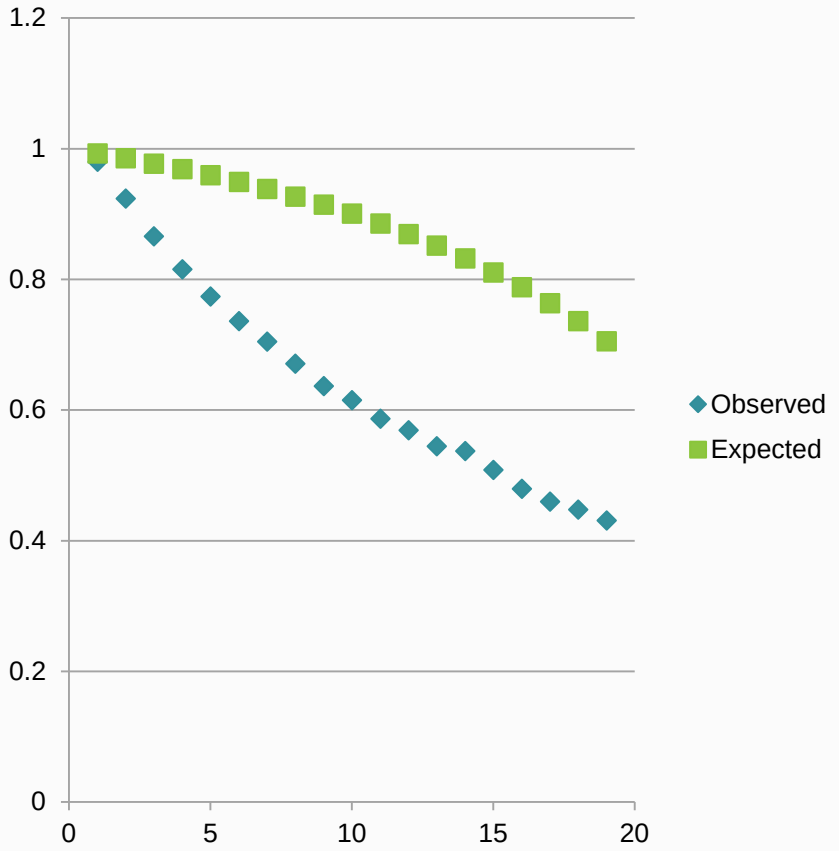
Node Positive Disease, Ages 50 – 69, Survival Curve Now Becoming Concave: Postpone Period Now Protective

Munich RE

T1c (1.1 – 2.0 cm) N1, Grade 1 & 2
Mortality Ratio = 169 %



T2 (2.1 – 5.0 cm) N1, Grade 1 & 2
Mortality Ratio = 190 %



Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.0.4

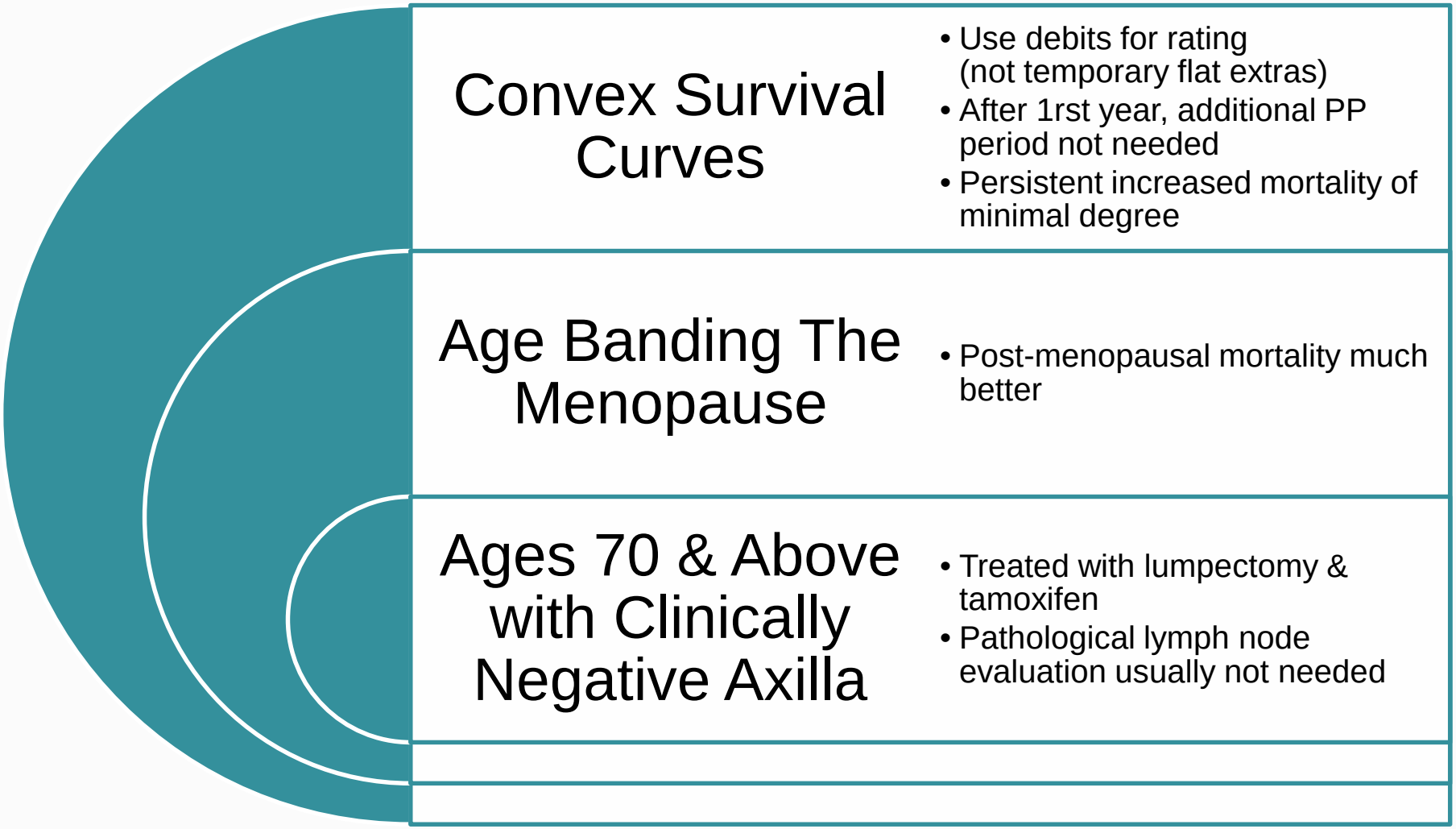
Munich RE

SUMMARY

Early Stage Breast Cancer

(T1 and T2 Disease, Negative Lymph Nodes, No Metastatic Disease)

Munich RE



Munich RE

THANK YOU FOR YOUR ATTENTION