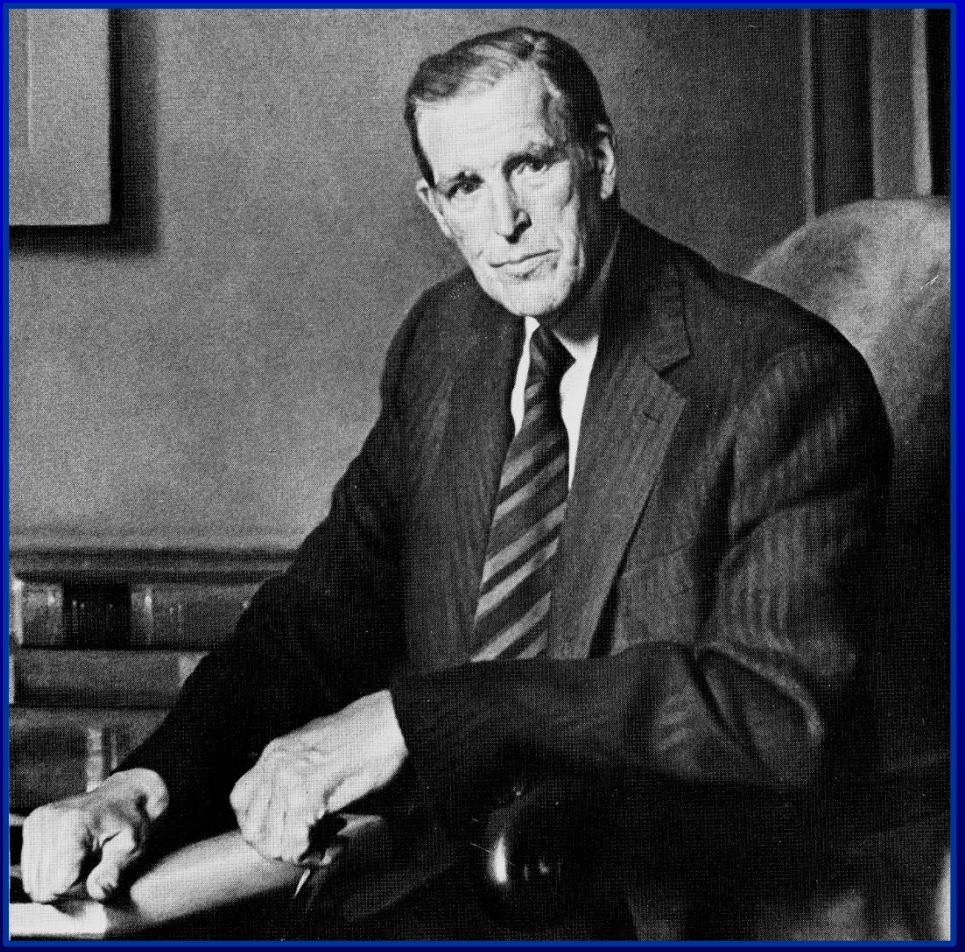
Main Line Health
Bryn Mawr Hospital

The Annual Rhoads Oration

Philadelphia Academy of Surgery

Monday
December 12, 2011



Dr. Jonathan E. Rhoads

Breast Cancer 2011

The Past, The Present and the Future!

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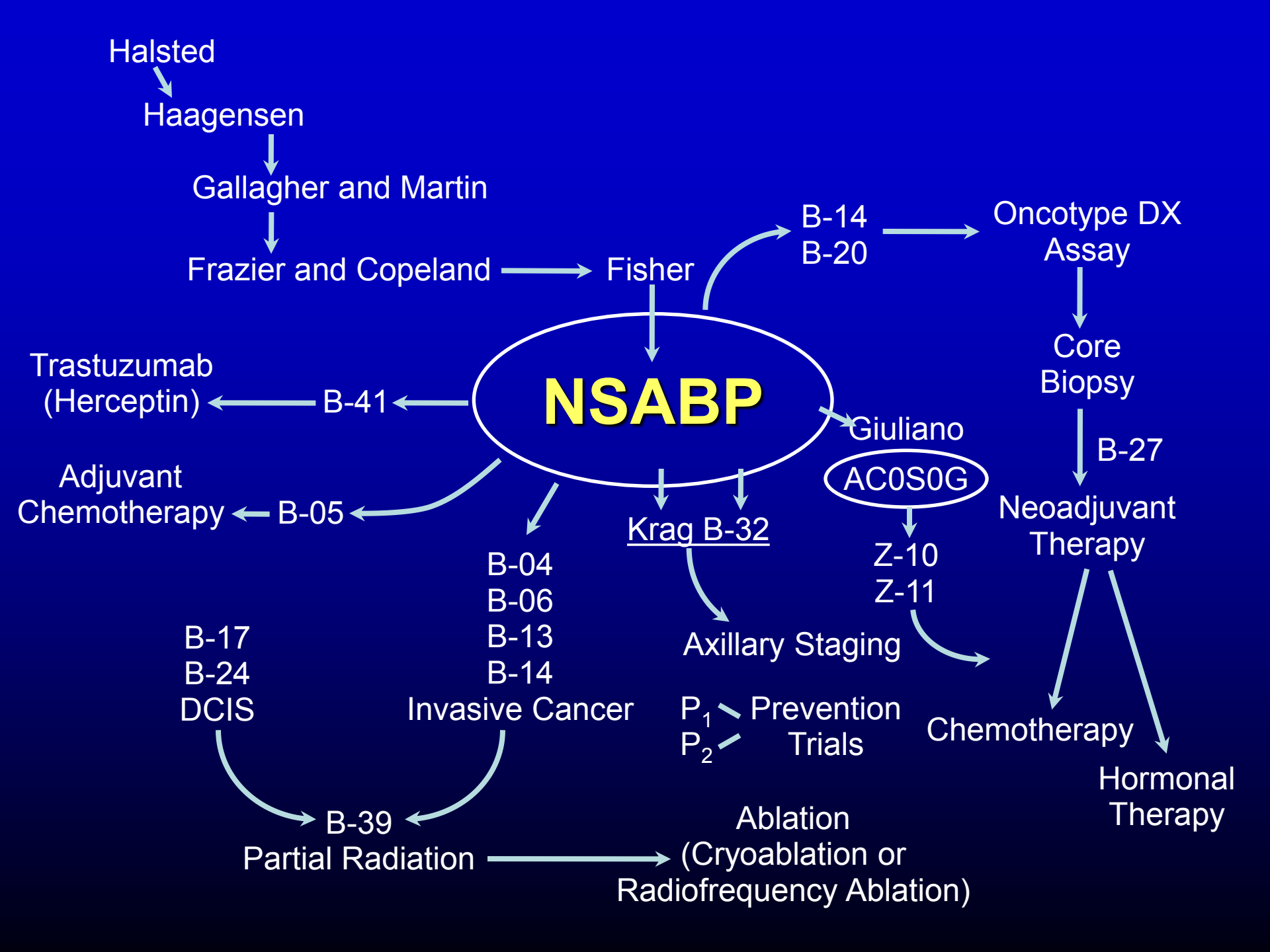
Bryn Mawr Hospital

Thomas G. Frazier, M.D., F.A.C.S.

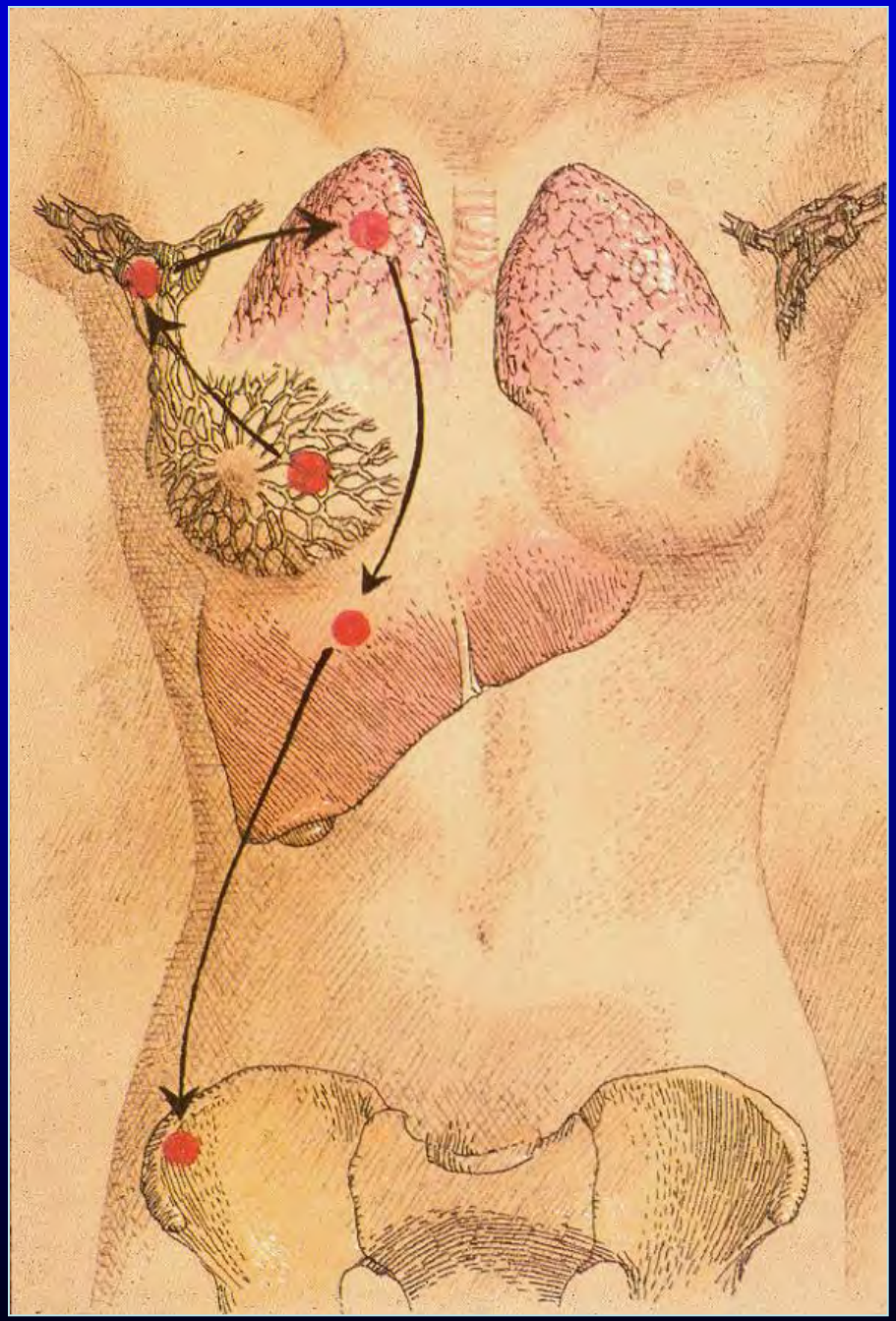
Medical Director,
Comprehensive Breast Center

Main Line Health
Bryn Mawr Hospital


Halsted
Haagensen
Gallagher and Martin
Frazier and Copeland
Fisher
B-14
B-20
Oncotype DX
Assay
Core
Biopsy
B-27
Neoadjuvant
Therapy
Trastuzumab
(Herceptin)
B-41
NSABP
Giuliano
AC0S0G
Z-10
Z-11
Adjuvant
Chemotherapy
B-05
Krag B-32
B-04
B-06
B-13
B-14
Invasive Cancer
Axillary Staging
B-17
B-24
DCIS
P1
P2
Prevention
Trials
Chemotherapy
Hormonal
Therapy
B-39
Partial Radiation
Ablation
(Cryoablation or
Radiofrequency Ablation)

1894

- Halsted – USA
- Willy Meyer – Great Britain
- Described classic radical mastectomy



1942

- Haagensen and Stout
- Columbia
- Criteria for radical mastectomy

Haagensen's Criteria

D istant spread

E dema > 1/3 breast

L ocal signs of disease 2/4

- ax node 2.5 cm
- fixation of ax node
- fixation to ch. wall
- edema breast 1/3

E dema of arm

S upraclavicular node

S atellite nodules

I nflammatory Ca

P arastermal (internal mammary) involvement

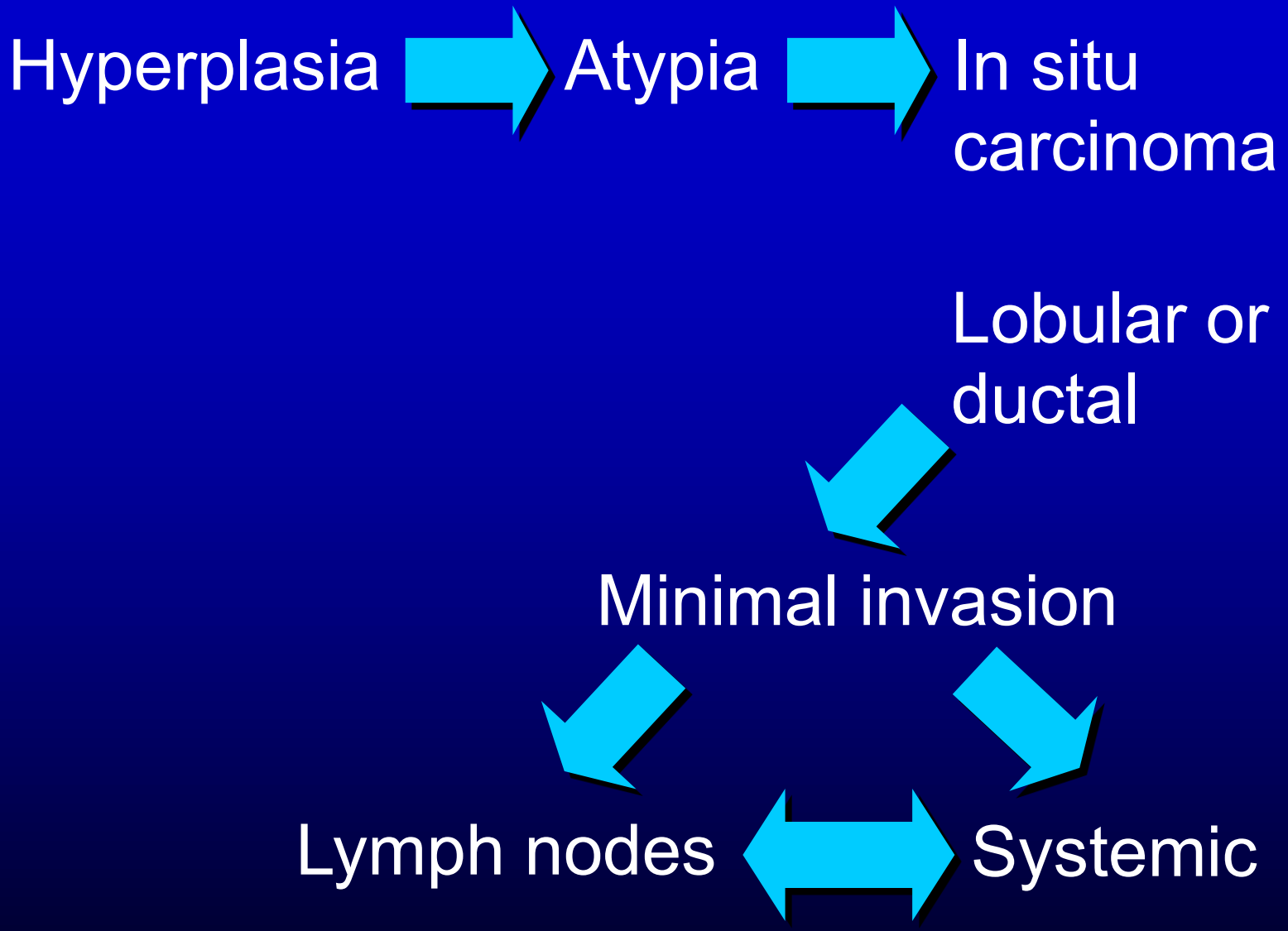
P regnancy - X

1970's

- Fisher: NSABP – Adjuvant therapy
- Bonadonna: Milan – C.M.F.

1970

- Gallager and Martin
- Pathophysiology of breast cancer


Hyperplasia
Atypia
In situ carcinoma
Lobular or ductal
Minimal invasion
Lymph nodes
Systemic

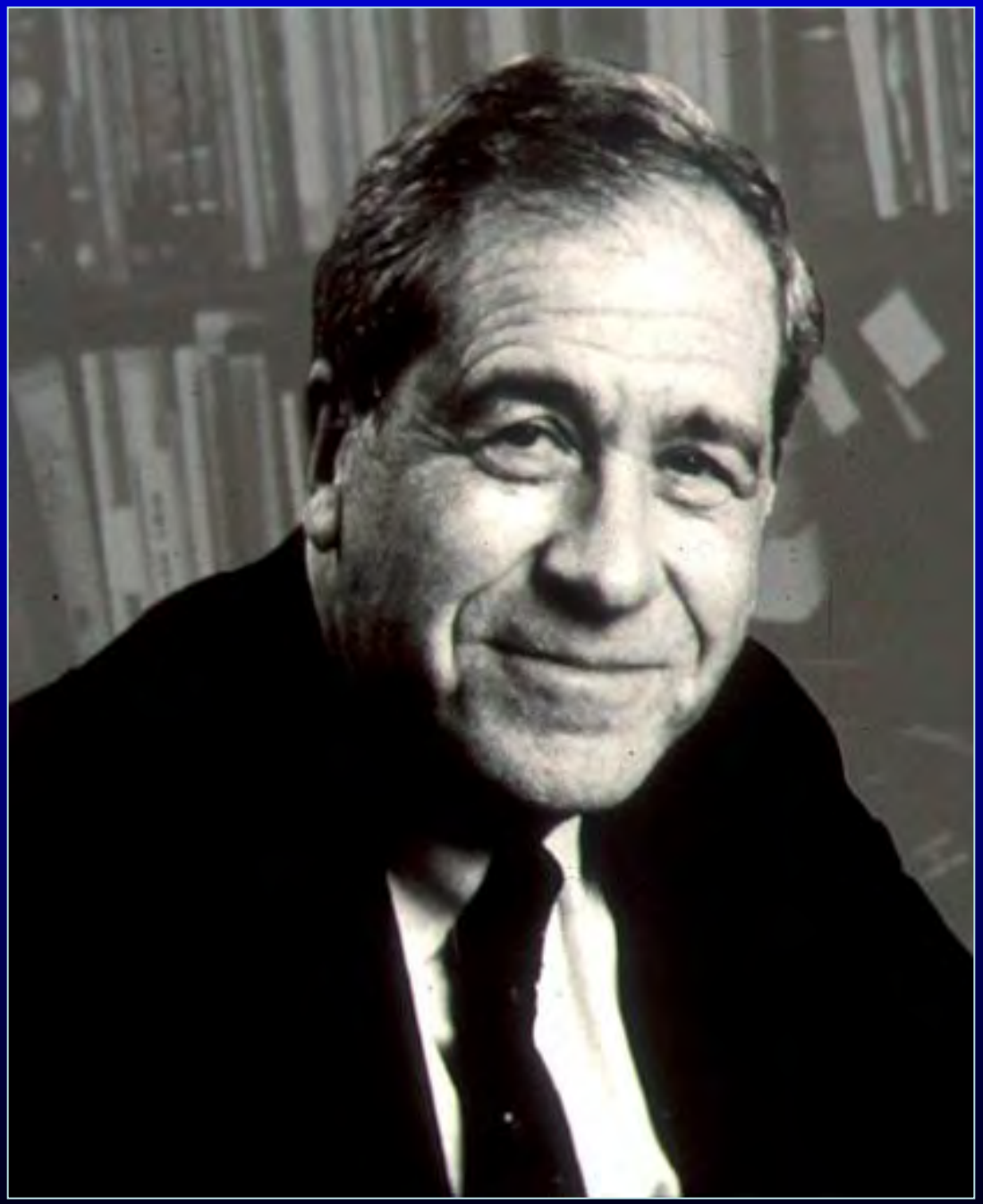
1977
Frazier, Copeland, Gallager, et al

- 176 patients
- 20 year survival
- Minimal breast cancer
- 96% (regardless of treatment)

Theory

- Local and regional therapy may have little impact on long term survival in carcinoma of the breast

Dr. Bob Ravdin



“In God We Trust, Everyone Else Needs Data!”

Bernard Fisher

NSABP Clinical Trials

1. Local and regional therapy
   - Invasive – B-04 & B-06
   - DCIS – B-17, B-24, B-35, B-43
2. Hormonal therapy
   - B-14, B-20, B-33, B-42
3. Prognostic and predictive markers Oncotype-Dx Assay
   - B-14, B-20
4. Adjuvant chemotherapy
   - B-13, B-19, B-23, B-36
   - Taxanes - B-28, B-30, B-38
5. Novel therapies
   - B-31, B-41, B-47
6. Neoadjuvant approaches
   - B-18, B-27, B-40, B-41

Protocol B-06

2200 patients enrolled

- 1/3 – Total mastectomy
- 1/3 – Segmental resection “Lumpectomy”
- 1/3 – “Lumpectomy” and XRT

All Patients Had Axillary Dissection

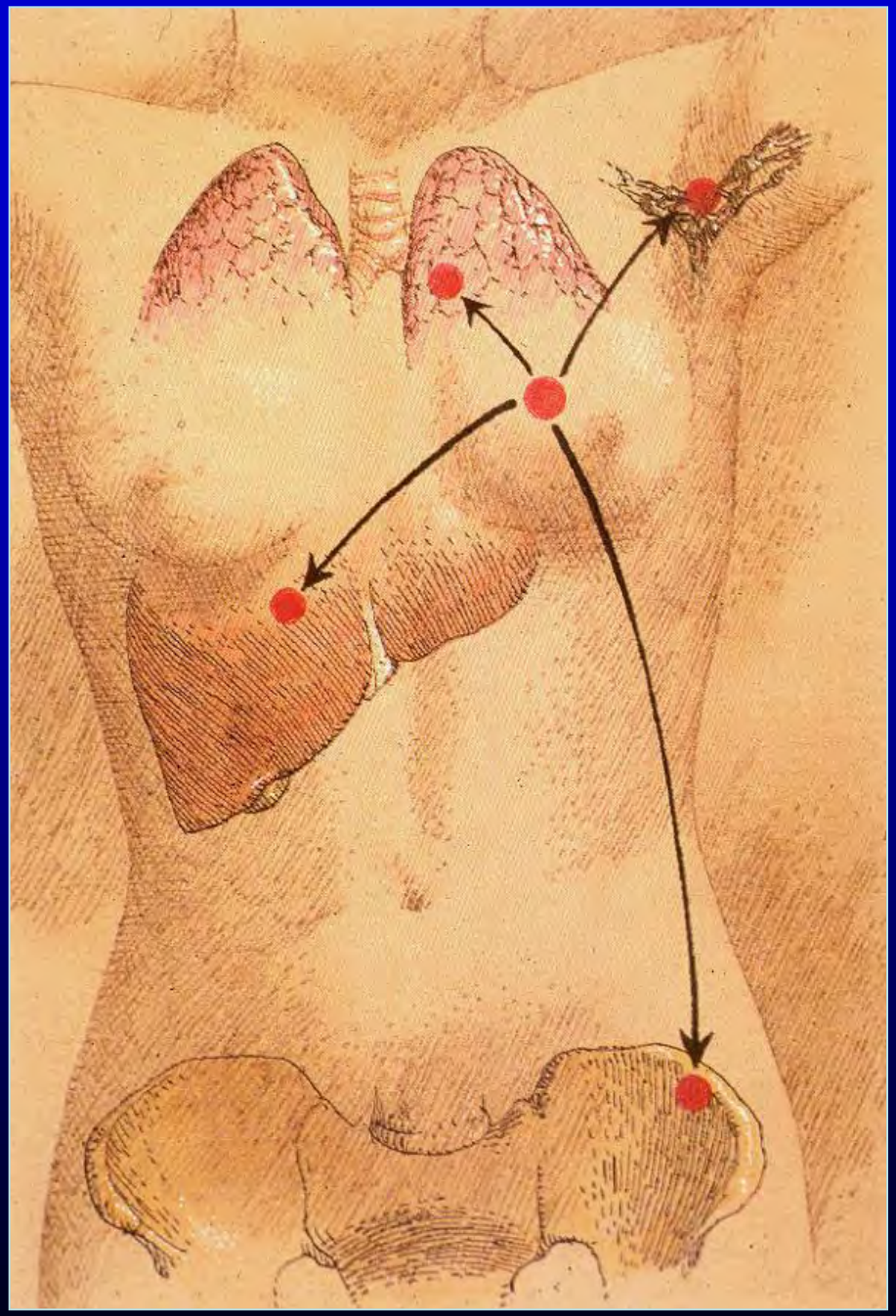
- Pos nodes - Chemotherapy
- Neg nodes - No chemotherapy

At 30 years
the survivals
are exactly the same
for all three options

Second Occurrence at 20 Years

Radiation: 12%

No Radiation: 42%



B-04 – Stage I and II Tumors

- 1/3 patients
  total mastectomy
  + axillary dissection
  40% positive nodes
- 1/3 patients
  total mastectomy
  + ax dissection + radiation
  40% positive nodes
- 1/3 patients
  total mastectomy only
  Only 20% developed
  axillary recurrence

Not Every Positive Axilla Becomes a Clinically Positive Cancer

B-05

- Patients with positive lymph nodes, but no evidence of spread by blood chemistry, chest x-ray, or bone scan
- ½ received L-pam
- ½ received placebo

Chemotherapy Works to Prevent Recurrence, Especially in Pre-Menopausal Patients with 1-3 Nodes Positive

Companion Studies
Stage I and II Tumors – Negative Nodes

- ER negative
  B-13: 2 years of chemotherapy or
  no other treatment

- ER positive
  B-14: 5 years of tamoxifen or
  5 years of placebo

Chemotherapy Works Best for ER Negative Tumors

Tamoxifen Works Best for ER Positive Tumors

B-17 DCIS

- ½ patients lumpectomy alone
- ½ patients lumpectomy + 6 weeks radiation whole breast

2nd Events	5 Years	10 Years
Natural History	22%	28%
Radiation	8%	12%

Radiation Reduces Second Occurrences in Patients Who Are Treated for DCIS

DCIS
B-24 – All Patients Had Lumpectomy + 6 Weeks Radiation

- ½ patients – 5 years tamoxifen
- ½ patients – 5 years placebo
- Recurrence: ↓ by additional 25% in affected breast

  ↓ by 50% in opposite breast

Tamoxifen Adds to Radiation to Decrease Second Occurrences in Patients with DCIS

Prevention Trials

P-1

All Patients Had a Risk of Breast Cancer > 1.7% in 5 Years as Predicted by Gail Model

- ½ patients - Tamoxifen x 5 years
- ½ patients - Placebo

Result

Tamoxifen ↓ risk of breast cancer by 50%

Tamoxifen Is an Active Medication to Prevent Breast Cancer in High-Risk Women

Caution: Side Effects of Tamoxifen

1) Increases uterine cancer in post menopausal women

   Approx 1/1000 → 2/1000

2) Increases blood clotting

   Approx 1/10,000 → 4/10,000

P-2

Post Menopausal Women Risk Greater Than 1.7% in Next 5 Years by Gail Model

- ½ patients – Tamoxifen
- ½ patients – Raloxifene (evista) x 5 years

<u>Result</u>

At 5 years – Prevention similar with ↓ in uterine cancer with evista

At 10 years – Prevention with tamoxifen (50%) superior to prevention with evista (35%)

Tamoxifen Is Superior to Evista in Preventing Breast Cancer and Can Be Used in Both Pre and Post Menopausal High Risk Women

Tamoxifen Does Carry a Higher Risk for Uterine Cancer and Blood Clots

B-20

ER Positive Patients – Node Negative

- ½ patients Had chemotherapy + tamoxifen
- ½ patients had tamoxifen alone

Result

Chemotherapy + tamoxifen had a survival benefit over tamoxifen only

This Raised the Question of Should Every Patient Who is ER Positive Be Treated with Both Chemotherapy and Hormonal Therapy

This Was the Beginning of "Targeted" or Individual Therapy

Oncotype – DX Assay

Breast Cancer Treatment Planning: History

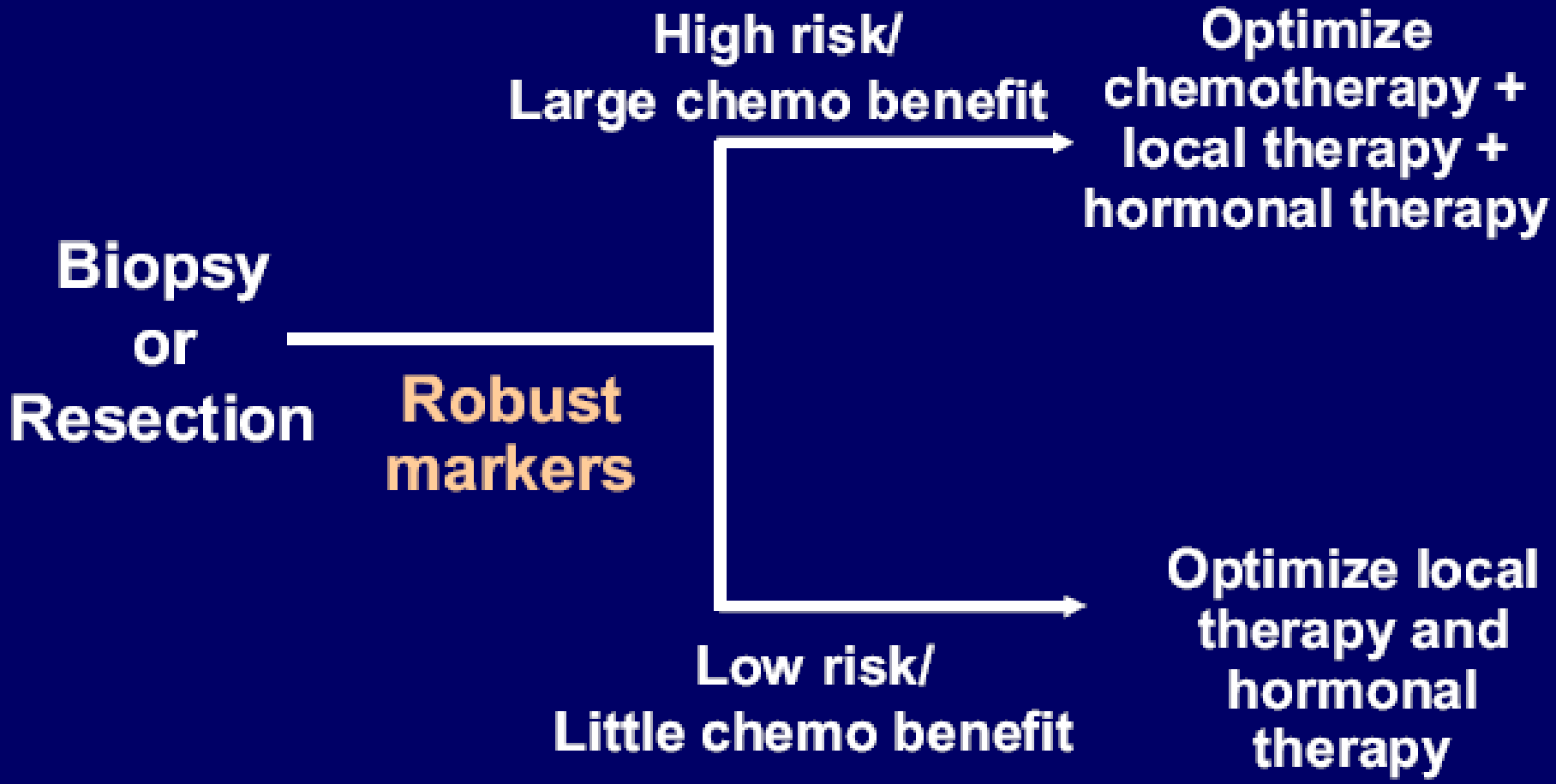
- Treatment planning for N–, ER+ disease is based on:
  - Traditional prognostic factors with limited predictive power (tumor size, patient age) or poor reproducibility (tumor grade)
  - IHC markers (eg, Ki-67) lacking standardization and validation
  - Limited insight into relative benefits of chemotherapy for different individuals

Bundred. *Cancer Treat Rev.* 2001;27:137-142.

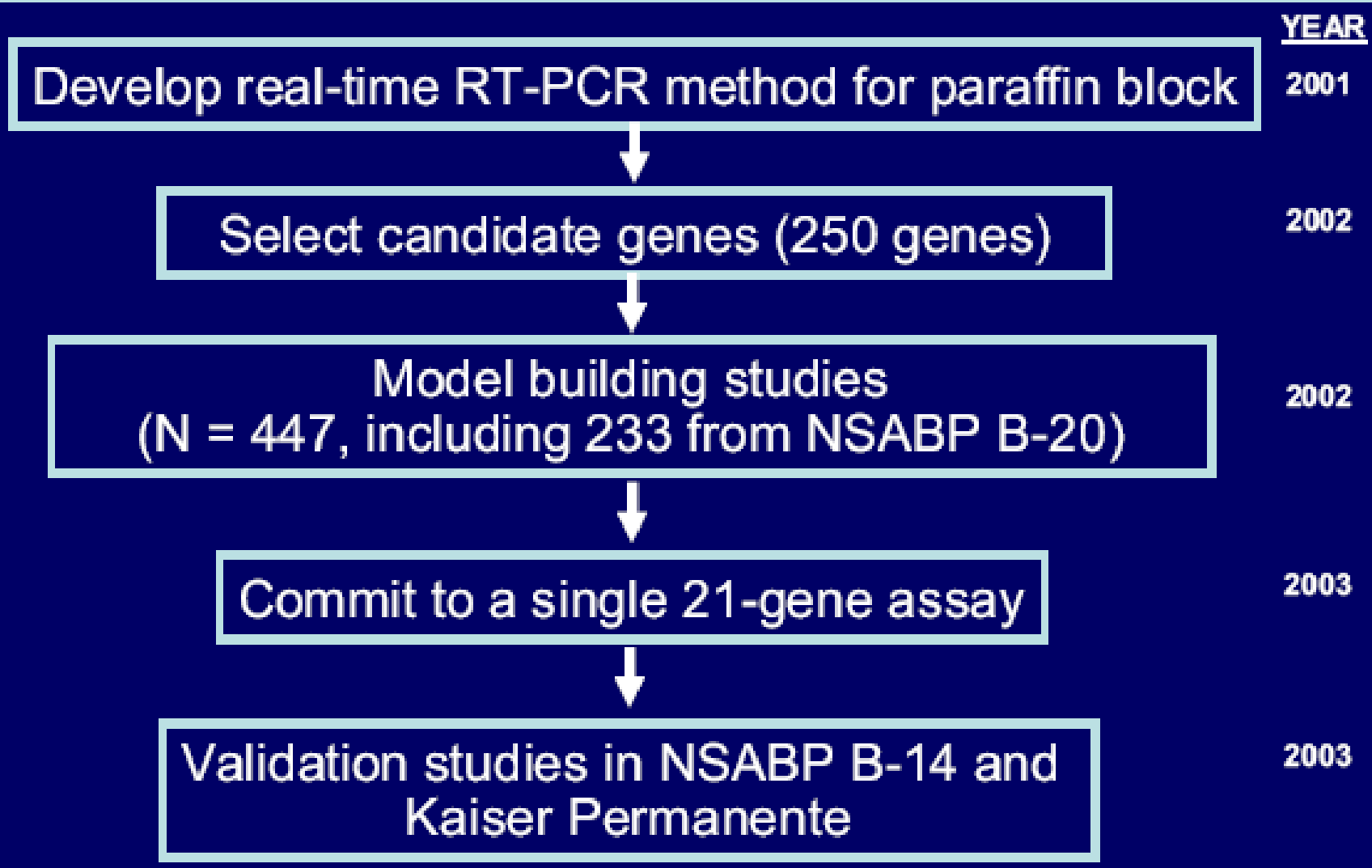
Breast Cancer Treatment Planning: Not Optimized

- Chemotherapy treatment for N–, ER+ disease
  - Many women are offered chemotherapy, knowing that few benefit
  - Prior to 2007, guidelines assumed all patients benefit equally
  - Some patients are under-treated, many others are over-treated

Oncotype DX®: Unmet Clinical Need for Better Markers



Development and Validation of a 21-Gene Assay for N–, ER+, Tam+ Patients



Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Oncotype DX® gene panel was developed from clinical trial evidence

- 250 cancer-related genes were selected
- Genes were analyzed for expression and relapse-free interval correlations across 3 independent studies of 447 breast cancer patients

Study site	N	Node status	ER status	Treatment
NSABP B-20, Pittsburgh, PA	233	N–	ER+	Tamoxifen (100%)
Rush University, Chicago, IL	78	≥ 10 positive nodes	ER+/–	Tamoxifen (54%) Chemotherapy (80%)
Providence St. Joseph's Hospital, Burbank, CA	136	N+/–	ER+/–	Tamoxifen (41%) Chemotherapy (39%)

From these studies, 21 genes were selected

Paik et al. SABCS 2003. Abstract #16.
Cobleigh et al. *Clin Cancer Res.* 2005;11(24 Pt 1):8623-8631.
Esteban et al. *Proc ASCO 2003.* Abstract #3416.

44

Oncotype DX® Recurrence Score® result:

calculated from 21 different genes

16 Cancer related genes

Estrogen	Proliferation	HER2	Invasion	Others
ER PR Bcl2 SCUBE2	Ki-67 STK15 Survivin Cyclin B1 MYBL2	GRB7 HER2	Stromelysin 3 Cathepsin L2	CD68 GSTM1 BAG1

5 Reference genes

Beta-actin	GAPDH	RPLPO	GUS	TFRC

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Oncotype DX® Recurrence Score® result calculation and risk categories

Recurrence Score =

+ 0.47 × HER2 Group Score
– 0.34 × Estrogen Group Score
+ 1.04 × Proliferation Group Score
+ 0.10 × Invasion Group Score
+ 0.05 × CD68
– 0.08 × GSTM1
– 0.07 × BAG1

Risk group	*Recurrence Score*
Low risk	< 18
Intermediate risk	18 - 30
High risk	≥ 31

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

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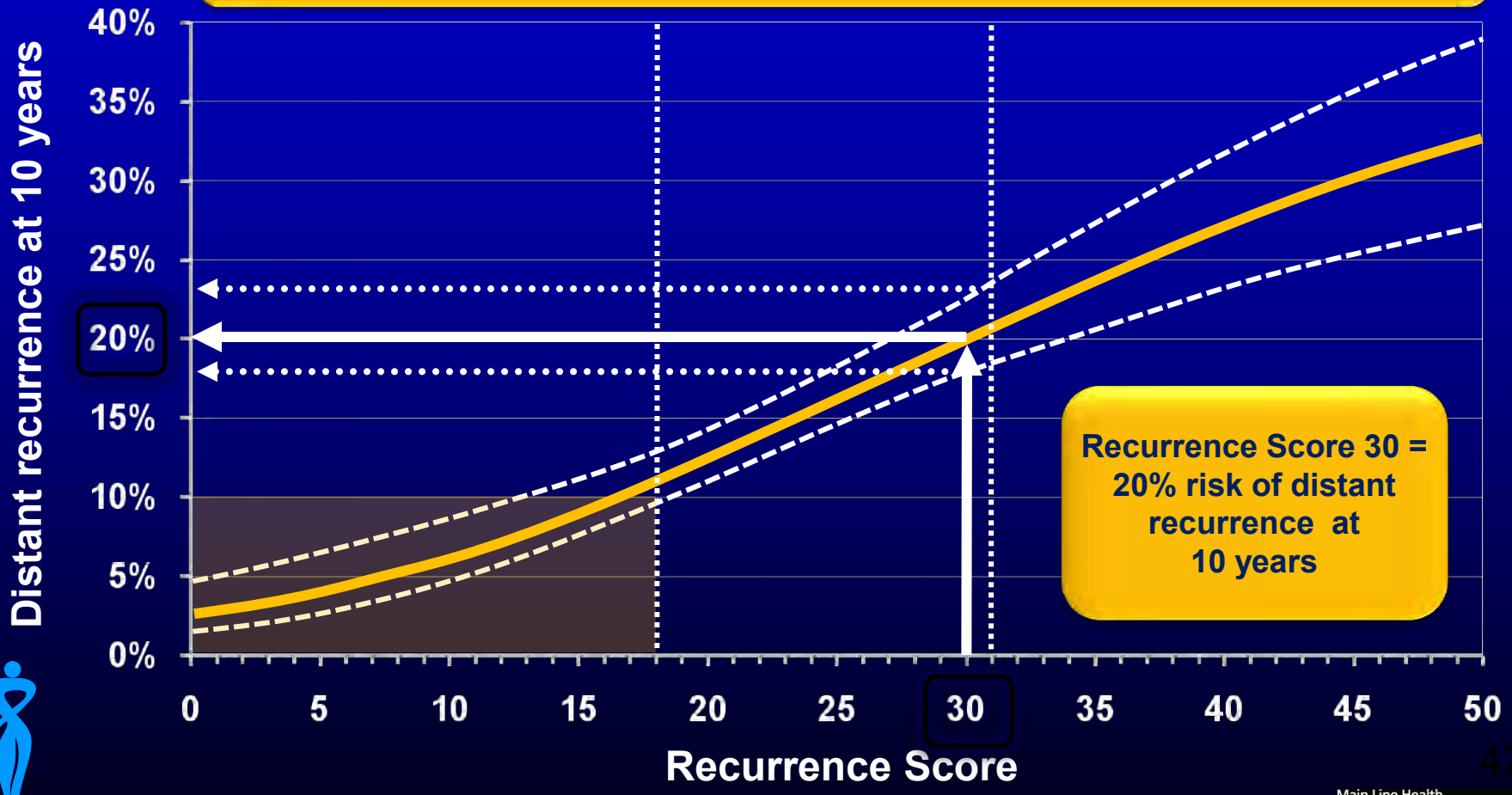
The Oncotype DX® Recurrence Score® result is a continuous predictor of recurrence risk

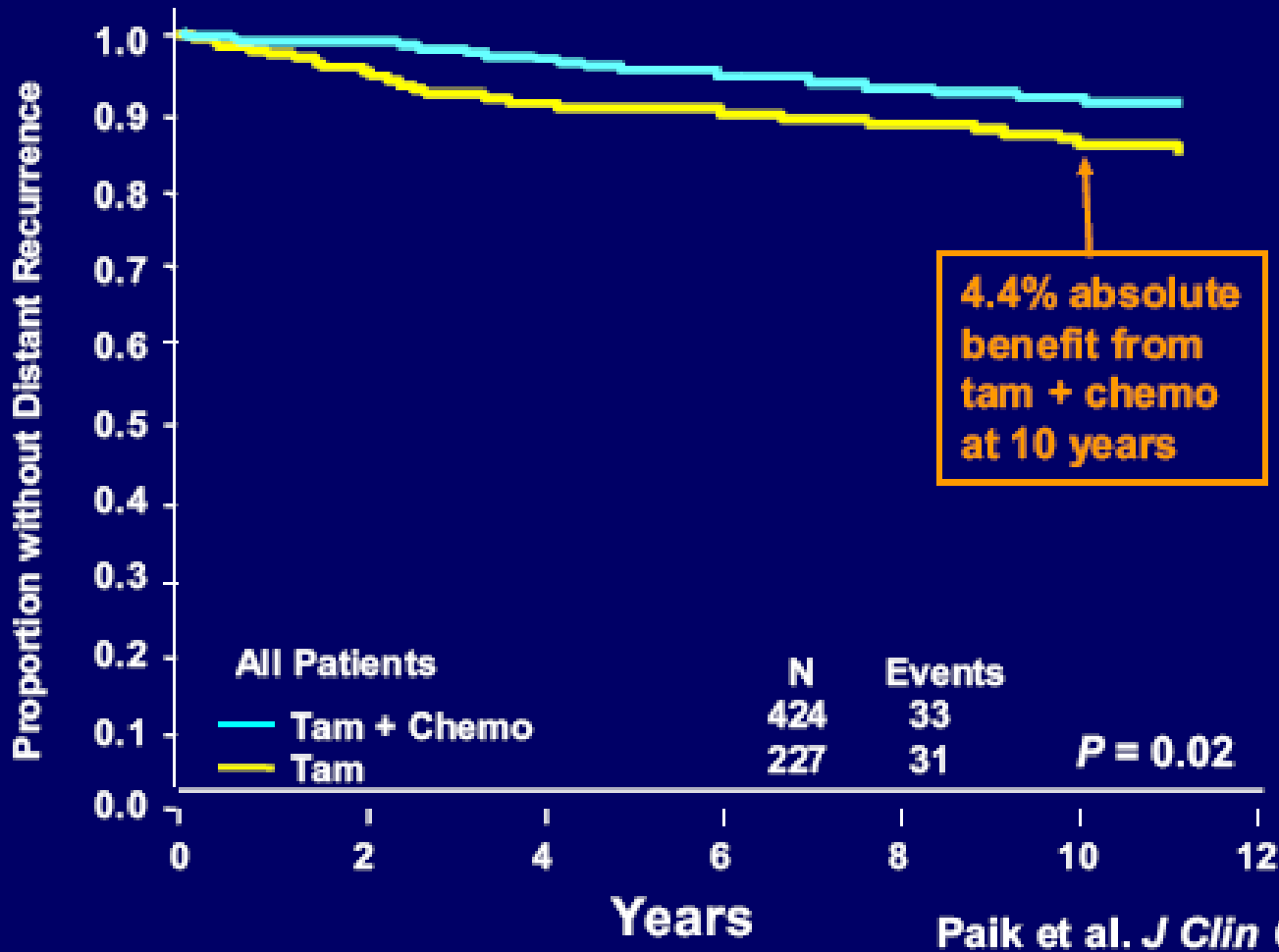
What is the 10-year probability of distant recurrence for a patient with a Recurrence Score of 30?



Dotted lines represent 95% CI

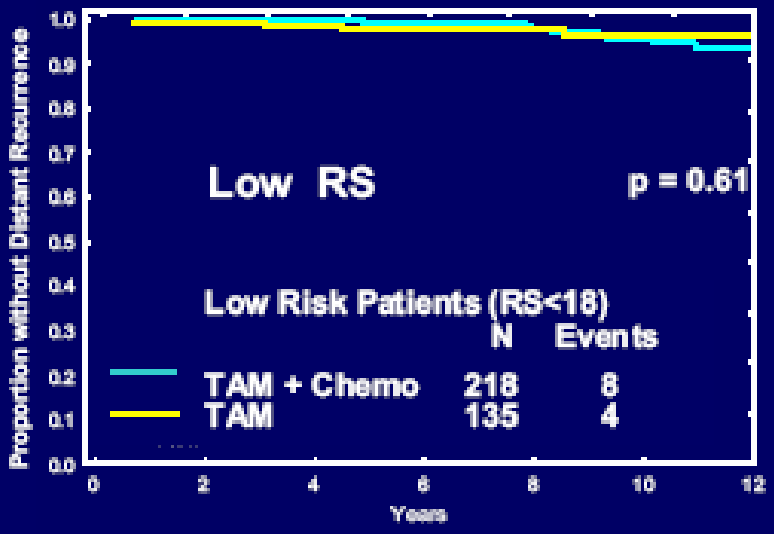
B-20 Results

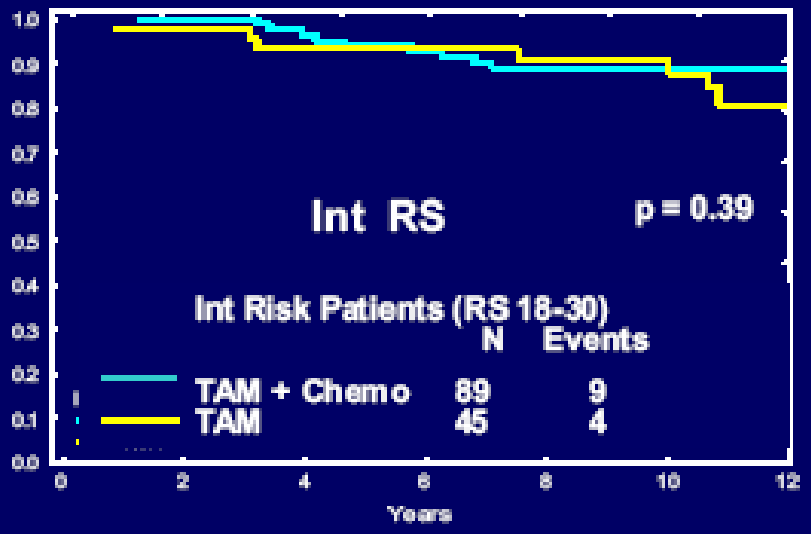
Tam vs Tam + Chemo – All 651 Patients

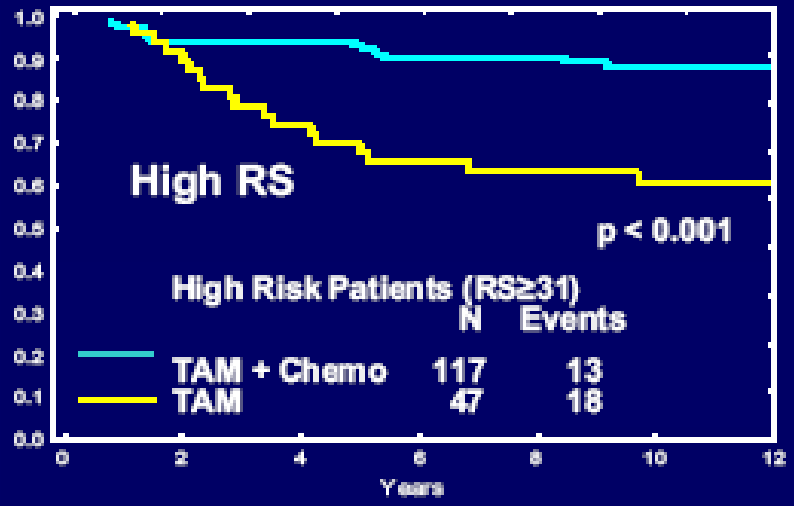


Paik et al. *J Clin Oncol.* 2006.

B-20 Results: Tam vs Tam + Chemo



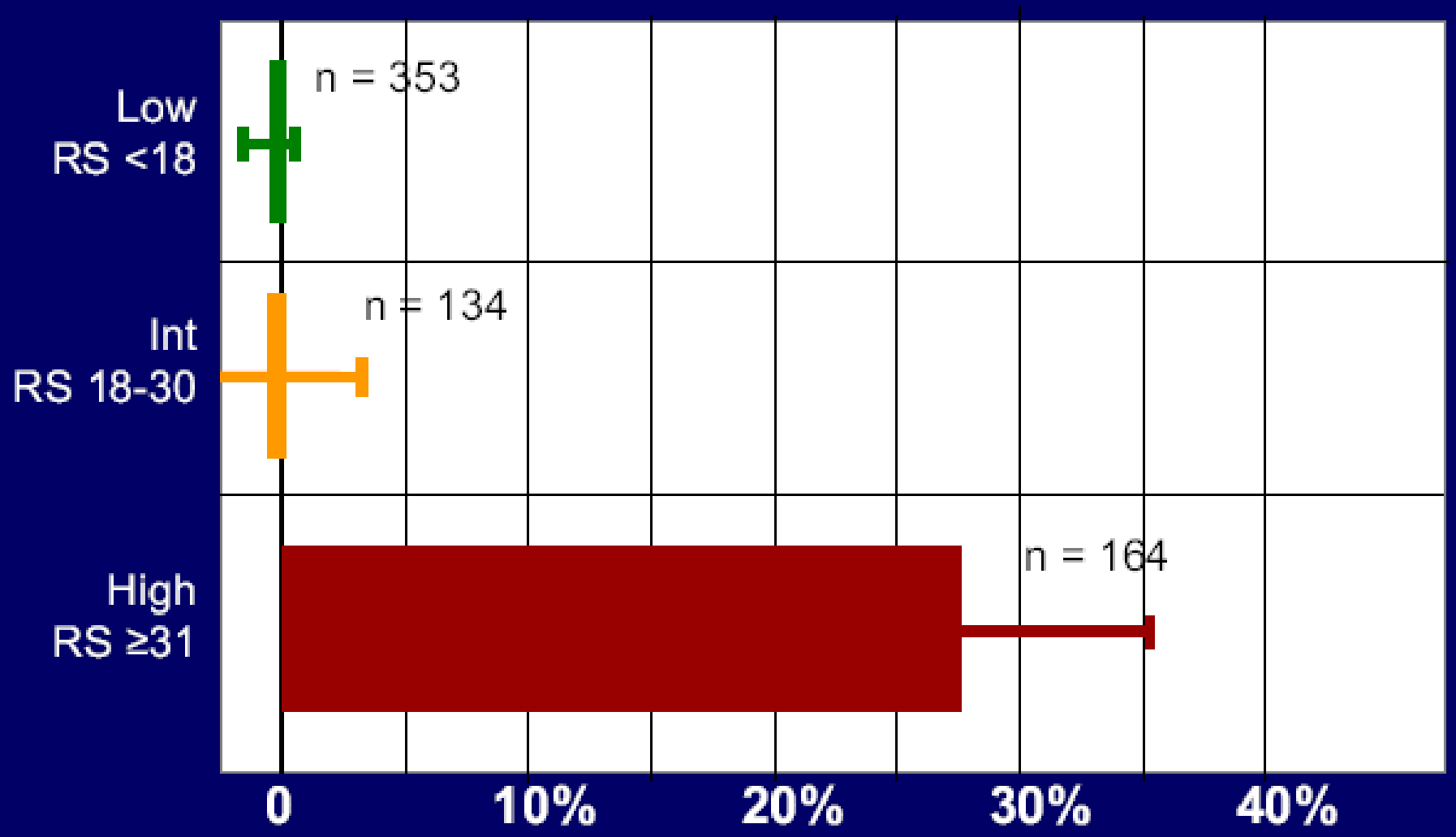




28% absolute benefit from tam + chemo

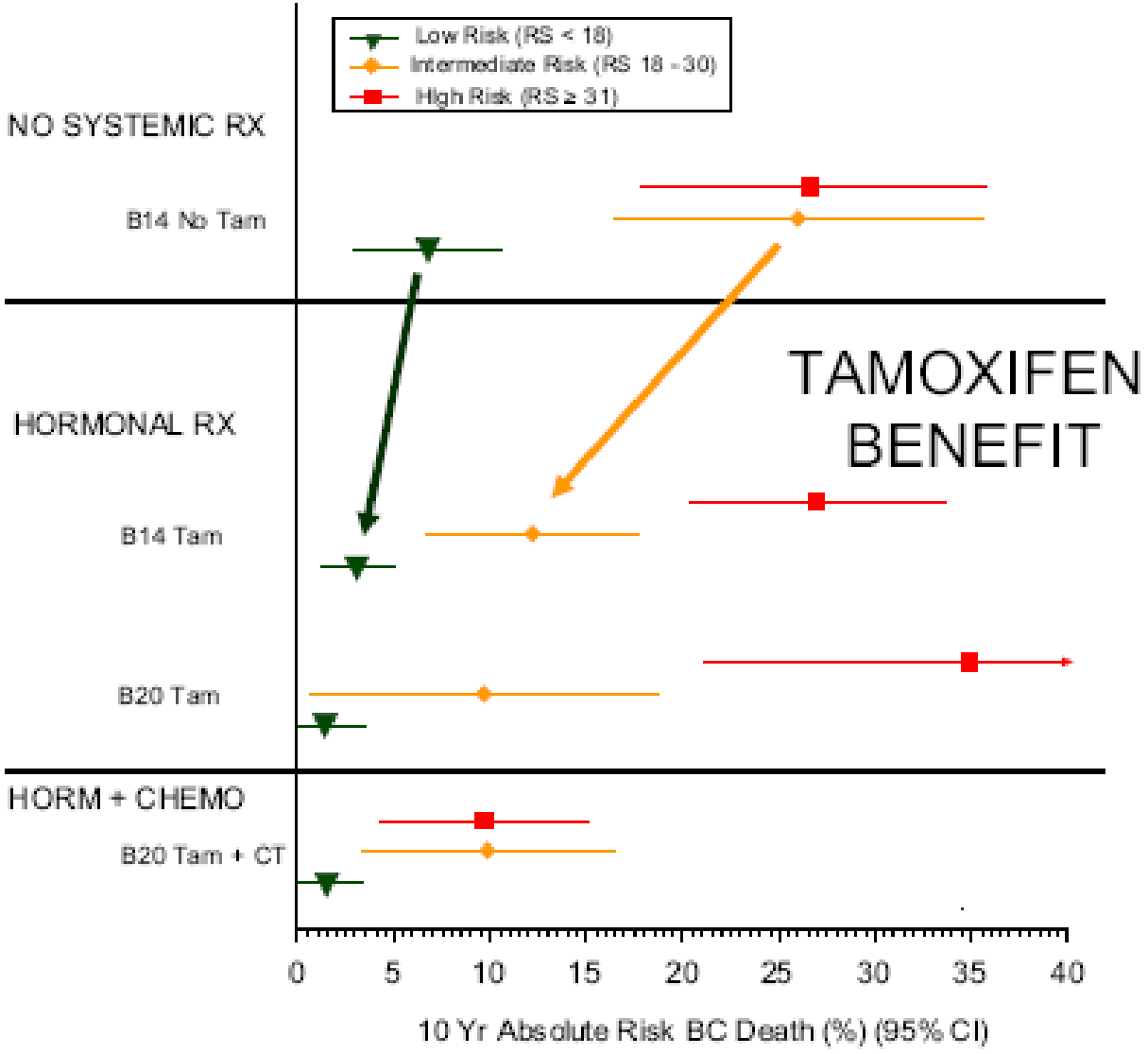
Paik et al. *J Clin Oncol.* 2006.

B-20 Results: Absolute % Increase in Proportion Distant Recurrence-Free at 10 Years

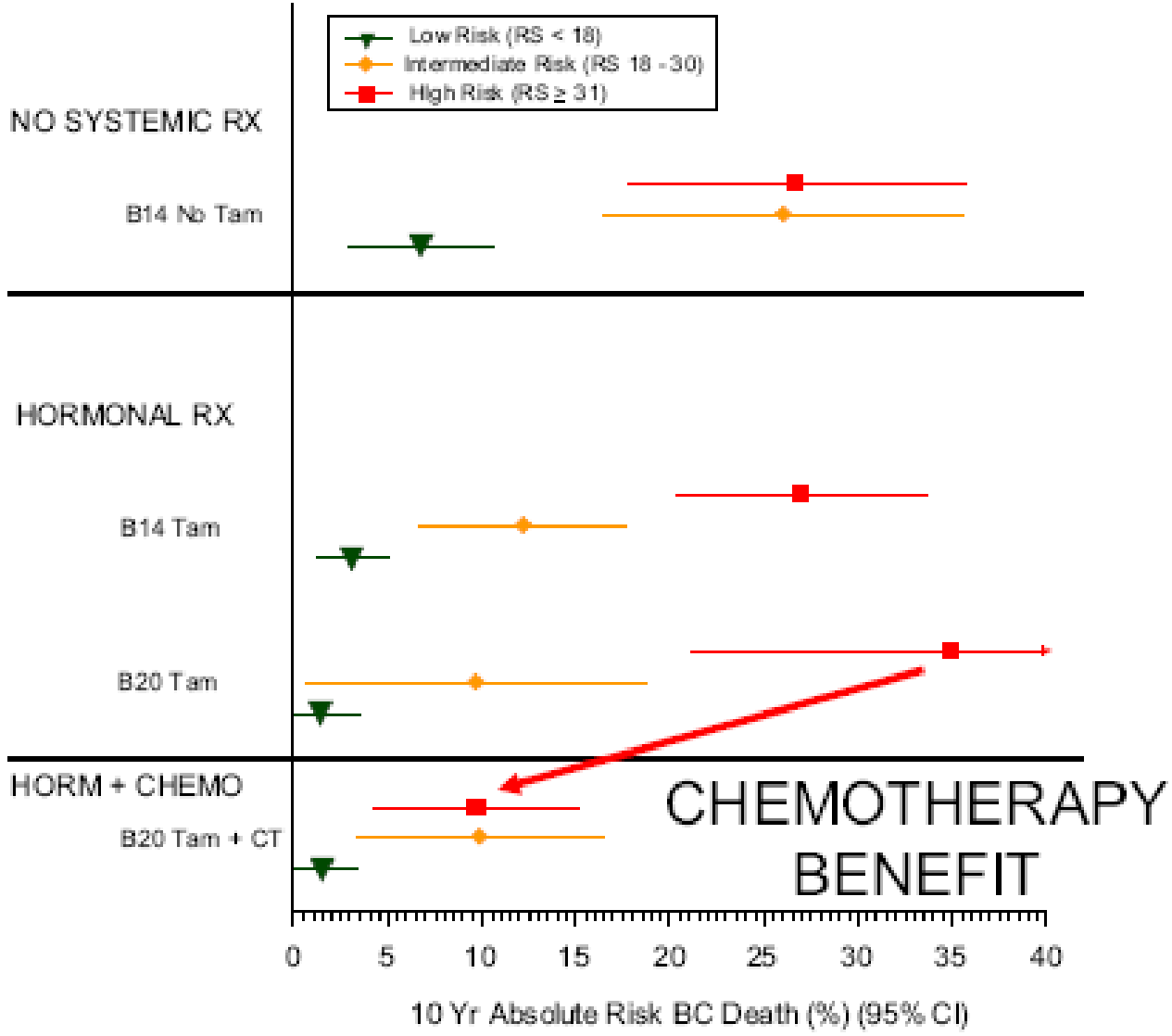


Paik et al. *J Clin Oncol.* 2006.

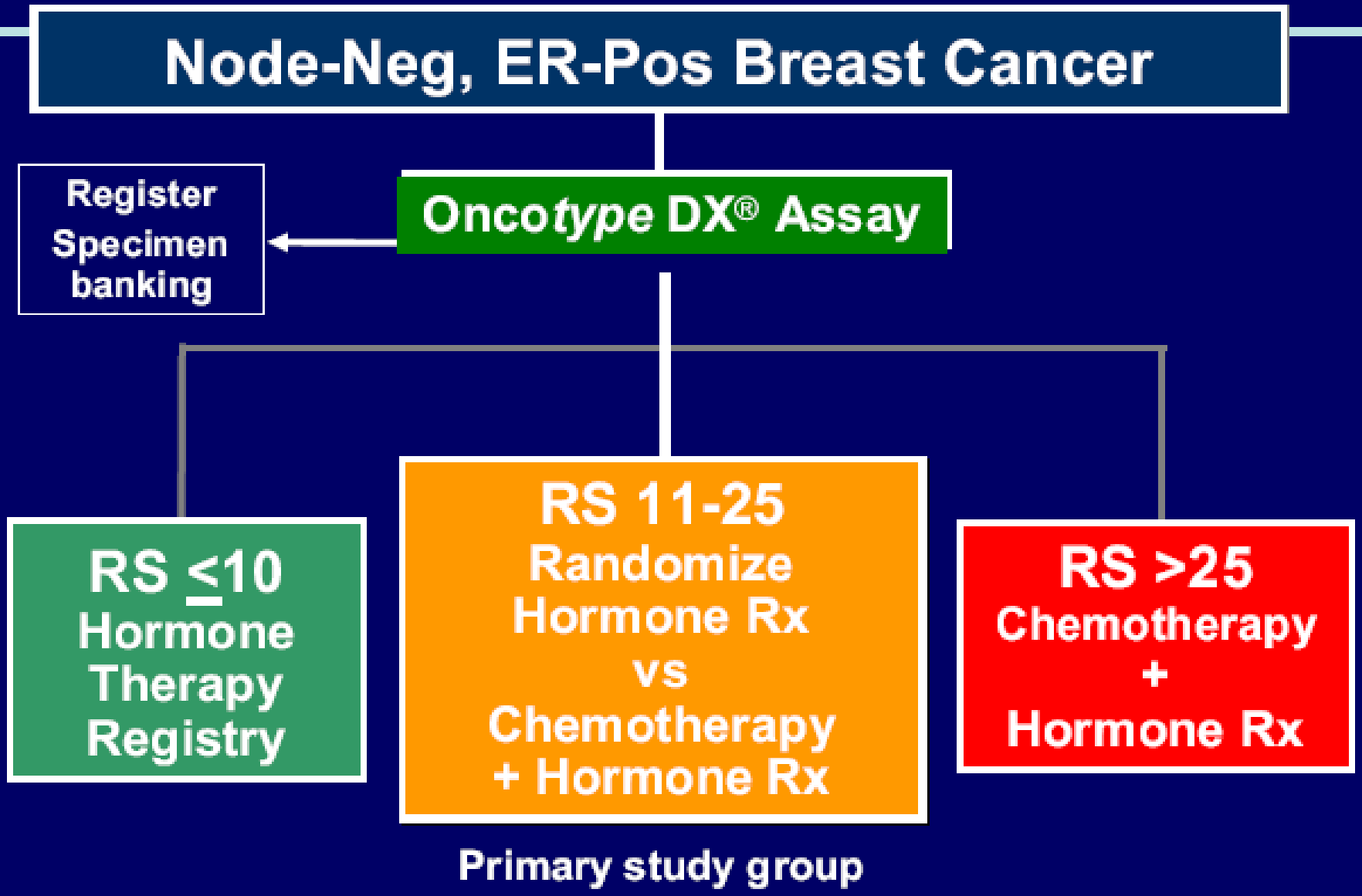
Largest Tamoxifen Benefit Observed in Low- and Intermediate-Risk Recurrence Score Groups



Largest Chemotherapy Benefit Observed in High-Risk Recurrence Score Group



Schema: TAILORx



A genomic approach should be the Gold Standard for adjuvant treatment recommendations.

Newer Approaches for Breast Cancer Treatment

1) Partial breast irradiation
2) Sentinel node mapping
   - B-32 results
   - Z011 results
3) Other areas of research

1991-1992
Morton – Lymphazurin Blue Dye
Melanoma

Morton - Concept of sentinel node mapping –

- Evaluation of first node(s) to drain from tumor
- If negative, no benefit to further dissection

Giuliano – Applied concept of "Blue Node" to axillary dissection for breast cancer

1923 - Braithwaite

Sentinel node in gastric carcinoma

1991-1992 - Morton

Blue node in melanoma

1993 - Krag

Radioisotopes for sentinel node detection

1993 - Krag

Used Technetium-99 for mapping, identifying sentinel node(s) with a hand-held gamma probe, rather than relying on visual identification alone

Question

Could less surgery be done (more precise surgery?) by limiting the axillary dissection to sentinel nodes only?

Two Major Trials – + One Companion Trial

NSABP – B-32- KRAG

- All Patients Had Mapping

  Sentinel Node Negative — ½ completion dissection
  ½ No further surgery

  Sentinel Node Positive — All had completion axillary dissection

ACOSOG – Z-010

- All Patients Had Sentinel Node Only

  If negative(-) – No further surgery

  If positive(+) – ACOSOG Z011
  ½ patients had completion axillary dissection
  ½ patients – No further surgery

B-32

232 Surgeons

4,000 Cases – Sentinel Nodes

Results

B-32

- No difference in recurrence if sentinel node is negative
- No benefit to completion axillary dissection

ACOSOG – Z-010

- No increase in axillary recurrence in sentinel node negative versus historical controls

***Z-011

- No increase in axillary recurrence in patients with 1-2 positive sentinel nodes versus completion dissection

There Is No Benefit to Completion Axillary Dissection in Patients with a Clinically Negative Axilla, Unless They Have 3 or More Sentinel Nodes Positive

B-06
B-14
B-17
B-24

- All studies showed that if patients did get a second occurrence in the breast – 90% were within the same quadrant!

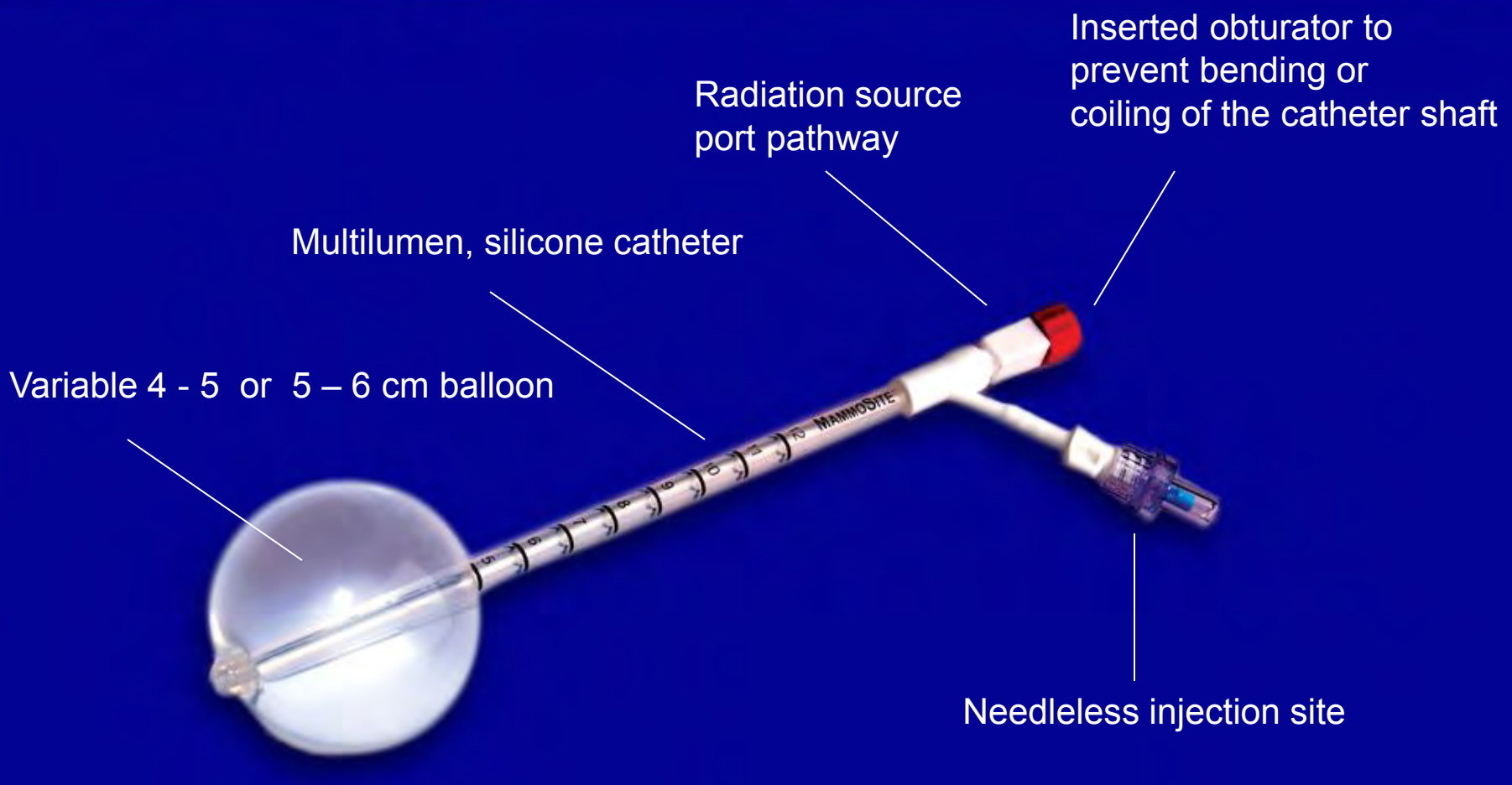
Question –

Is there a better way to give radiation??

Breast Brachytherapy Scientific Rationale

- The majority of local recurrences after breast conserving therapy occur at or near the tumor bed[1]
- Major effect of post-lumpectomy radiation therapy: Reduce risk of recurrence in tumor bed region
- Incidence of „elsewhere" failures appears to be unaffected by whole breast irradiation. $\leq$ 3.8% of patients fail elsewhere regardless of radiation[1]
- Whole breast radiation may not be needed in appropriately selected patients.

PROXIMA®
THERAPEUTICS, INC.



Balloon Configuration	Balloon Fill Volume
4 – 5 cm Sphere	35 – 70 cc
5 – 6 cm Sphere	70 – 125 cc

Protocol B-39 - Ongoing

- ½ patients receive standard whole breast irradiation 5 days/wk x 6 weeks
- ½ patients receive partial breast irradiation

Mammosite Balloon
or
3D Conformal Technique

Twice/day x 1 wk – 10 treatments

April 2004 – July 2010

238 patients with 243 breast cancers

Median F/U 3.2 years

April 2004 – July 2010

8 recurrences (ipsilateral breast) – 3.2%

Median 3.1 years

- 5 Regional recurrences (2.1%)
- 4 Distant recurrences (1.7%)
- 5 Significant infections requiring incision and drainage (2.1%)

Early Stage Breast Cancer Patients Treated with Accelerated Partial Breast Irradiation (APBI) Have a Low Rate of Recurrence and an Acceptable Complication Rate

Further "Targeted" Therapy

- Analysis of tumors for

  ER – Estrogen receptor

  PR – Progesterone receptor

  HER-2 – Growth protein seen in more aggressive tumors

B-31

All Patients with Positive Nodes – HER-2 Positive

- ½ patients – Chemotherapy alone
- ½ patients – Chemotherapy + Herceptin

Result

Addition of Herceptin decreased recurrence in node positive, HER-2 positive patients by 50%

Herceptin Is an Extremely Effective Drug in HER-2 Positive Node Positive Patients and Is Now the Standard of Care for this Group

Questions – Ongoing Studies

- Should node negative, HER-2 positive patients receive Herceptin?
- Should patients have Herceptin alone or only with chemotherapy?
- Should Herceptin be reserved for patients who recur after chemotherapy?
- What about the other 50% for whom Herceptin did not prevent spread of their cancer?

Future

Genomics - The tumor‟s genetic make-up

+

Genetics - Genetics – The patient‟s genetic make-up

Two Genes – BR CA1

BR CA2

Probably more -

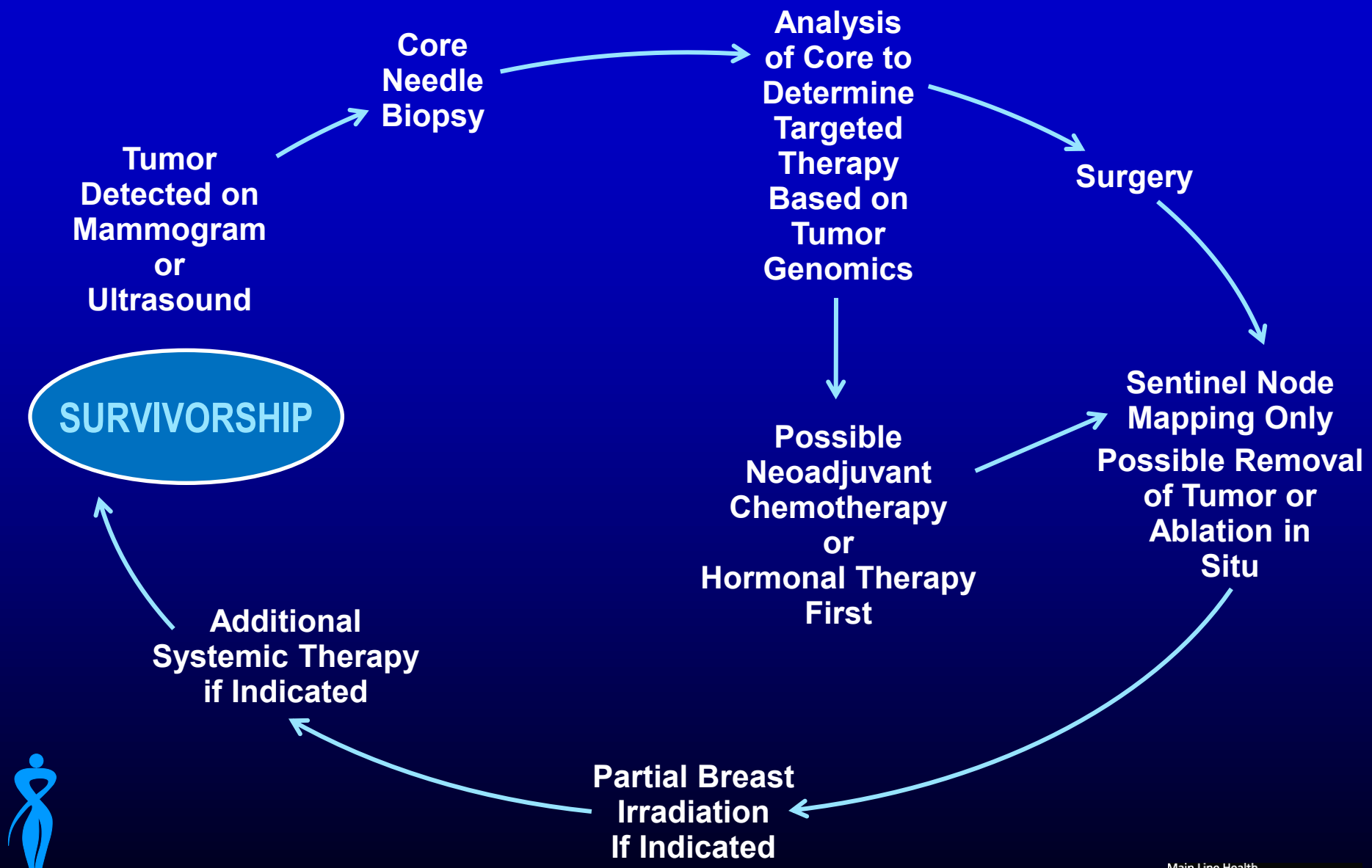
Of Interest

1. Prevention and early detection of lymphedema – L-Dex
2. Improved localization of small cancers – Iodine seed versus standard wire localization
3. Improved methods of detection.
   Breast Specific Gamma Imaging – BSGI
   Molecular Breast Imaging – MBI
   Improved Magnetic Resonance Imaging – IMRI
   Infrared Scanning
4. Methods of destroying a tumor in SITU
   - Radiofrequency ablation
   - Cryotherapy ablation

Of Interest (continued)

5. The role of Circulating Tumor Cells (CTCs) and Disseminated Tumor Cells (DTCs) in peripheral blood and bone marrow.

Potential for Future



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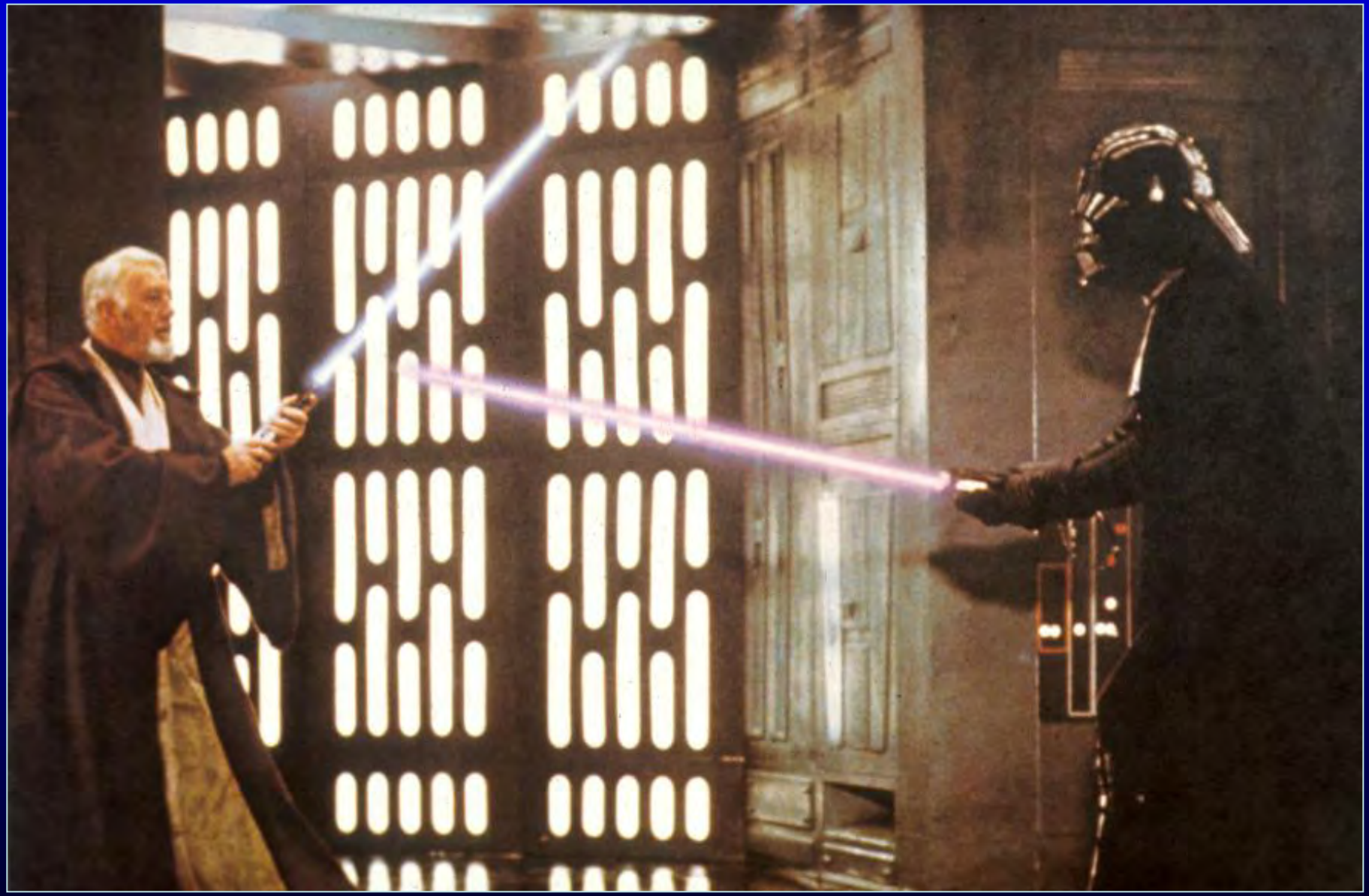

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