# Combining systemic treatment with radiation therapy: Quantifying the therapeutic gain.

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

# Disclosure slide

I have no conflicts of interest to declare

# outline

Introduction

Trends in outcome in stage IV, today compared to the past

A case report

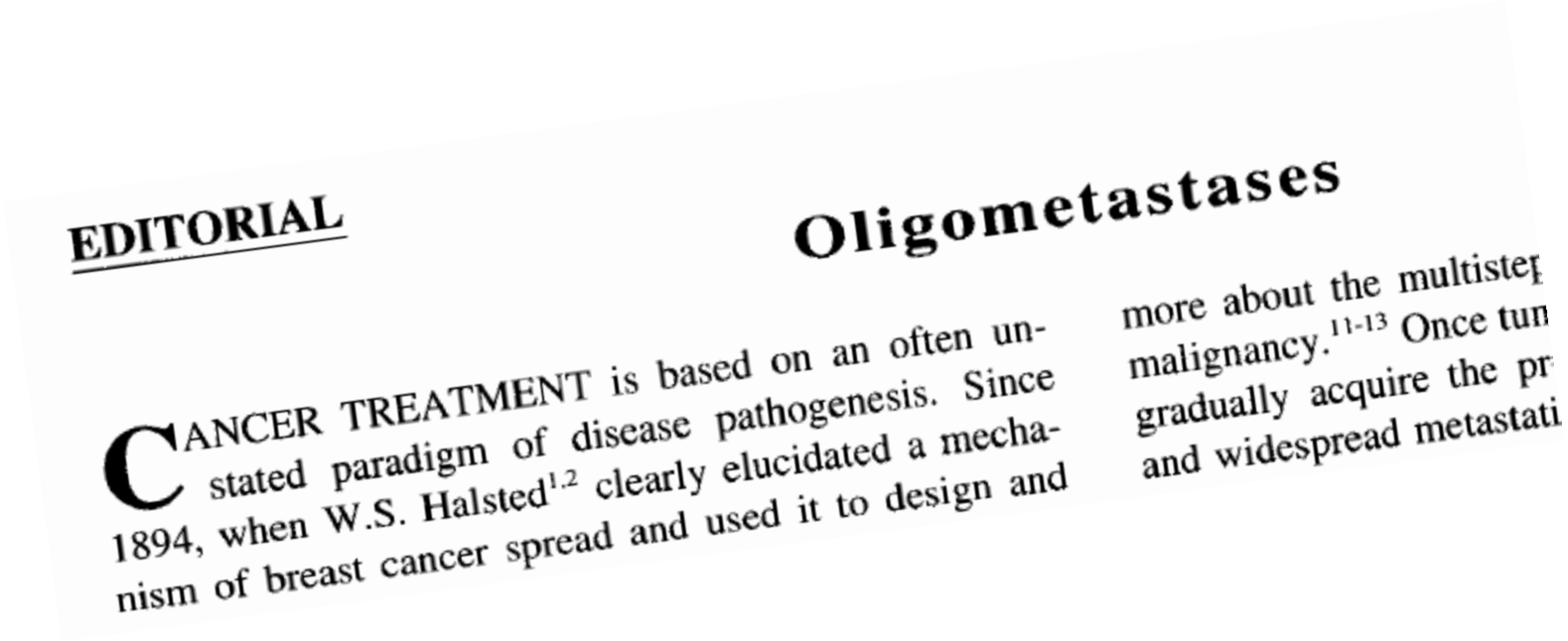
Link between better outcome and systemic therapy in prospective cohorts

RT in metastatic breast cancer, not only for palliation?

Concurrent radio-chemo approaches

Conclusions

# Introduction:



EDITORIAL

## Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and

more about the multistep malignancy.[11-13] Once tum gradually acquire the pr and widespread metastati

Samuel Hellman
Ralph R. Weichselbaum
*The University of Chicago*
*Chicago, IL*

*Journal of Clinical Oncology*, Vol 13, No 1 (January), 1995: pp 8-10

Review Article

Published online: February 11, 2014

Breast Care 2014;9:7–14
DOI: 10.1159/000358750

Breast Care

# Oligometastatic Breast Cancer: A Shift from Palliative to Potentially Curative

Simona Di Lascio[a,b]

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii11–vii19, 2012
doi:10.1093/annonc/mds232

# Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1,2], N. Harbeck[3], L. Fallowfield[4], S. Kyriakides[5] & E. Senkus[6], on behalf of the ESMO Guidelines Working Group*

Tumour Review

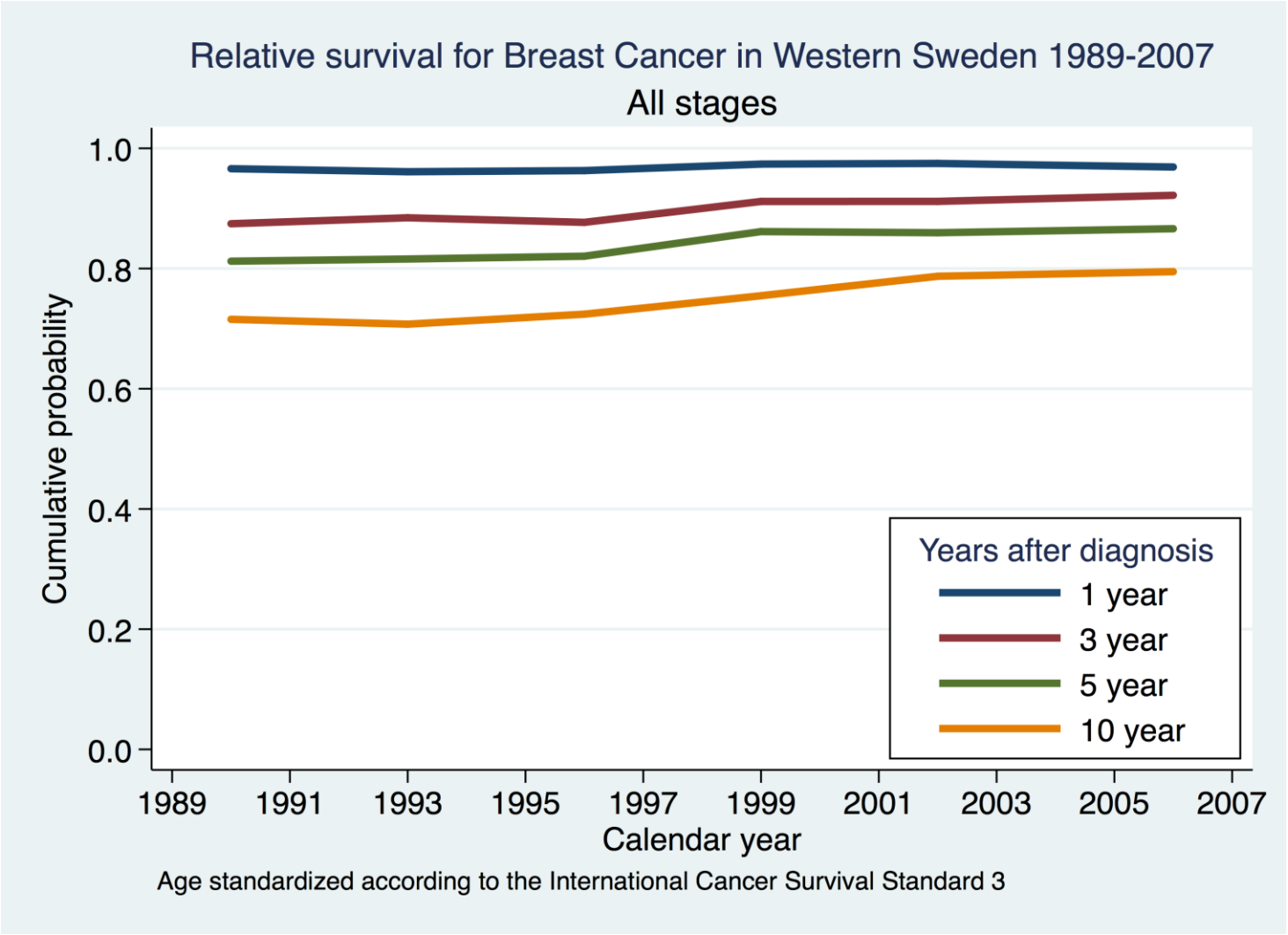
# Time for more optimism in metastatic breast cancer?

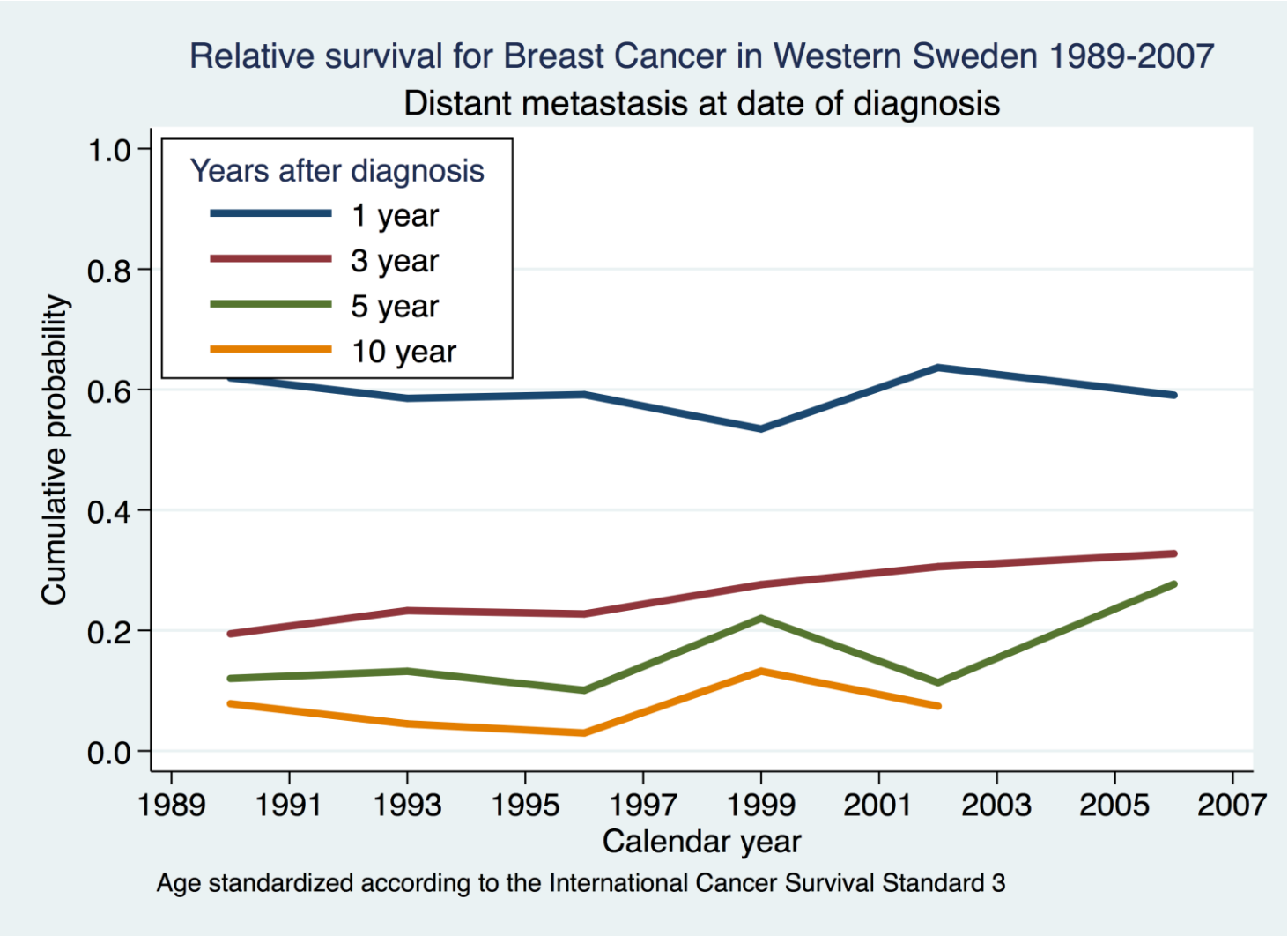
Elżbieta Senkus[a,*], Fatima Cardoso[b,1], Olivia Pagani[c,2]

1989-2007, <90 years

# Stage distribution Western Sweden

| year | Lok | Reg | Met | Missing | Total |
|---|---|---|---|---|---|
| 1990 | 1,696 | 938 | 92 | 214 | 2,940 |
| | 57.69 | 31.90 | **3.13** | 7.28 | 100.00 |
| 1993 | 1,613 | 867 | 89 | 123 | 2,692 |
| | 59.92 | 32.21 | **3.31** | 4.57 | 100.00 |
| 1996 | 1,696 | 812 | 84 | 269 | 2,861 |
| | 59.28 | 28.38 | **2.94** | 9.40 | 100.00 |
| 1999 | 1,839 | 872 | 68 | 306 | 3,085 |
| | 59.61 | 28.27 | **2.20** | 9.92 | 100.00 |
| 2002 | 1,999 | 1,011 | 76 | 264 | 3,350 |
| | 59.67 | 30.18 | **2.27** | 7.88 | 100.00 |
| 2006 | 2,864 | 1,411 | 114 | 240 | 4,629 |
| | 61.87 | 30.48 | **2.46** | 5.18 | 100.00 |
| Total | 11,707 | 5,911 | 523 | 1,416 | 19,557 |
| | 59.86 | 30.22 | **2.67** | 7.24 | 100.00 |


Relative survival for Breast Cancer in Western Sweden 1989-2007
All stages
Cumulative probability
1.0
0.8
0.6
0.4
0.2
0.0
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
Calendar year
Years after diagnosis
1 year
3 year
5 year
10 year
Age standardized according to the International Cancer Survival Standard 3


Relative survival for Breast Cancer in Western Sweden 1989-2007
Distant metastasis at date of diagnosis
Years after diagnosis
1 year
3 year
5 year
10 year
Cumulative probability
1.0
0.8
0.6
0.4
0.2
0.0
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
Calendar year
Age standardized according to the International Cancer Survival Standard 3

# Case report

- Late 90s, 30 year old women with right sided breast cancer, 26 mm, operated with mastectomy+ axillary clearance, 0/16 nodes, ER and PgR negative.
- AC X 4
- Profylactic mastectomy contralateral side and bilateral reconstruction 2 years after initial diagnosis.
- During reconstr. 2 subpectoral nodes on the initial treated side were removed and positve
- CMF X 6, followed by locoregional RT
- One year later solitary lungmet., cytologically verified

# Case report (cont´)

- RT  lungmet 3,7 Gy to 29,6 Gy
- Primary tumour was reviewed and were HER2 positive. Started trastuzumab/paclitaxel.
- One months later, visual disturbances, brain-MRI showed a 5 mm occipital brain met. Further screening at that time showed 2 liver mets.  (liver biopsy showed HER2-pos bc).
- Stereotactic RT for the brain met and  RF-ablation of the two liver mets.
- Continued trastuzumab/paclitaxel without further evidence of extracranial disease. The liver mets were gradually shrinking. After 1 year finished paclitaxel but continued on trastuzumab monotherapy.

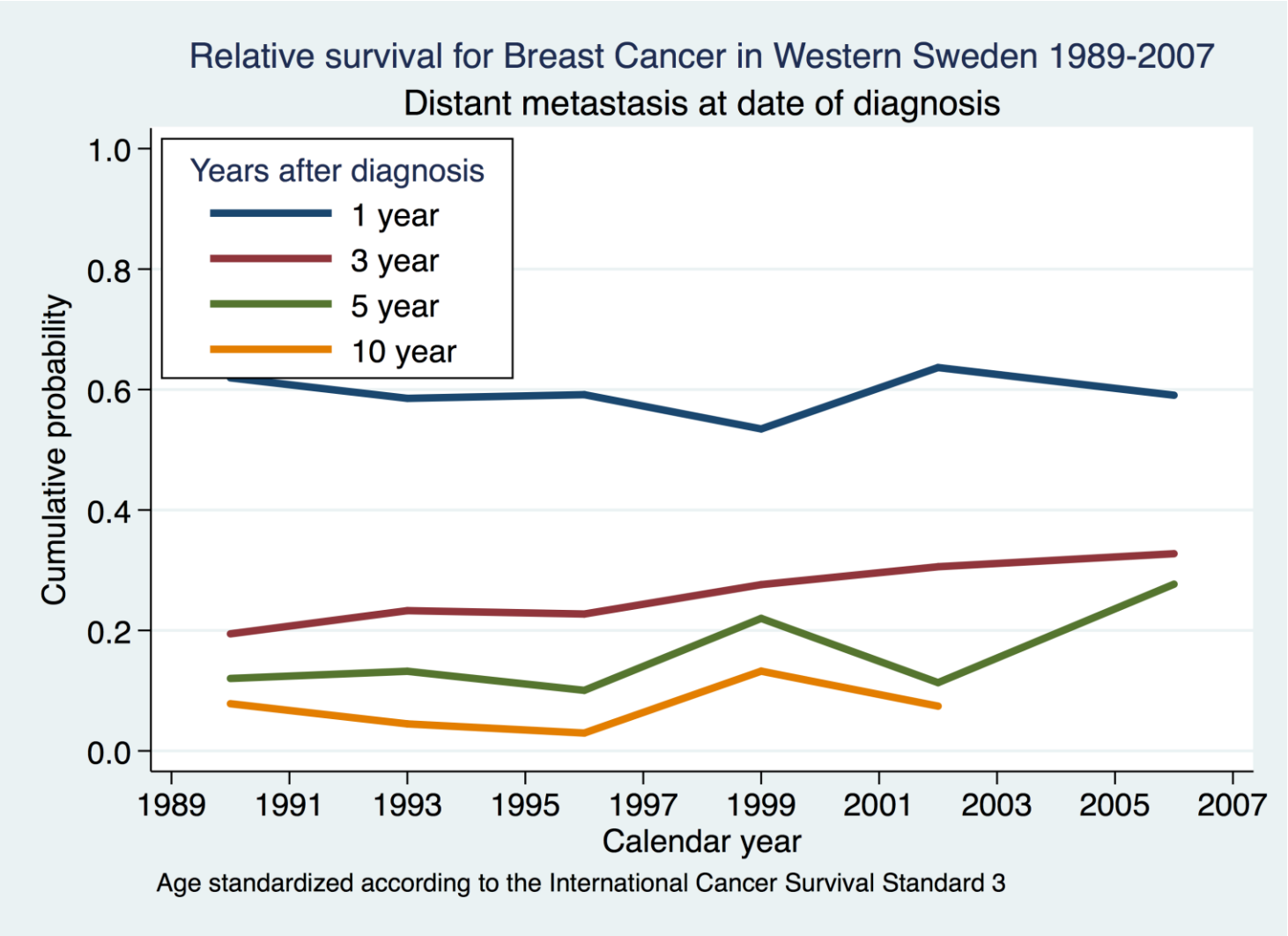
# Case report (cont´).

- Half a year later new  brain-CT showed two new small metastses.
- Offered total brain irradiation(TBI) but insisted on furher stereotactic RT for the two new lesions without TBI
- Three months later capecitabine were added to trastuzumab
- Levermets. continued to diminish but were still present.
- Stereotactic RT to the liver mets 6 months later.
- After that no evidence of active disease.

# Case report (cont´).

- More than 10 years of follow-up still no evidence of active disease but have some sequele after the three stereotactic RT against brain mets.

- No formal conclusions at all can be drawn from case reports but some long-term survivors with stage IV breast cancer exists also in prospective cohorts.


Relative survival for Breast Cancer in Western Sweden 1989-2007
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2007
Calendar year
Age standardized according to the International Cancer Survival Standard 3

# Stage, treatment and outcomes for patients with breast cancer in British Columbia in 2002: a population-based cohort study

N=2,927 incident cases 2002

Stage IV, n=123, 4%

10 year breast cancer specific survival 4%

**Davidson-A, Canadian medical association journal 2013**

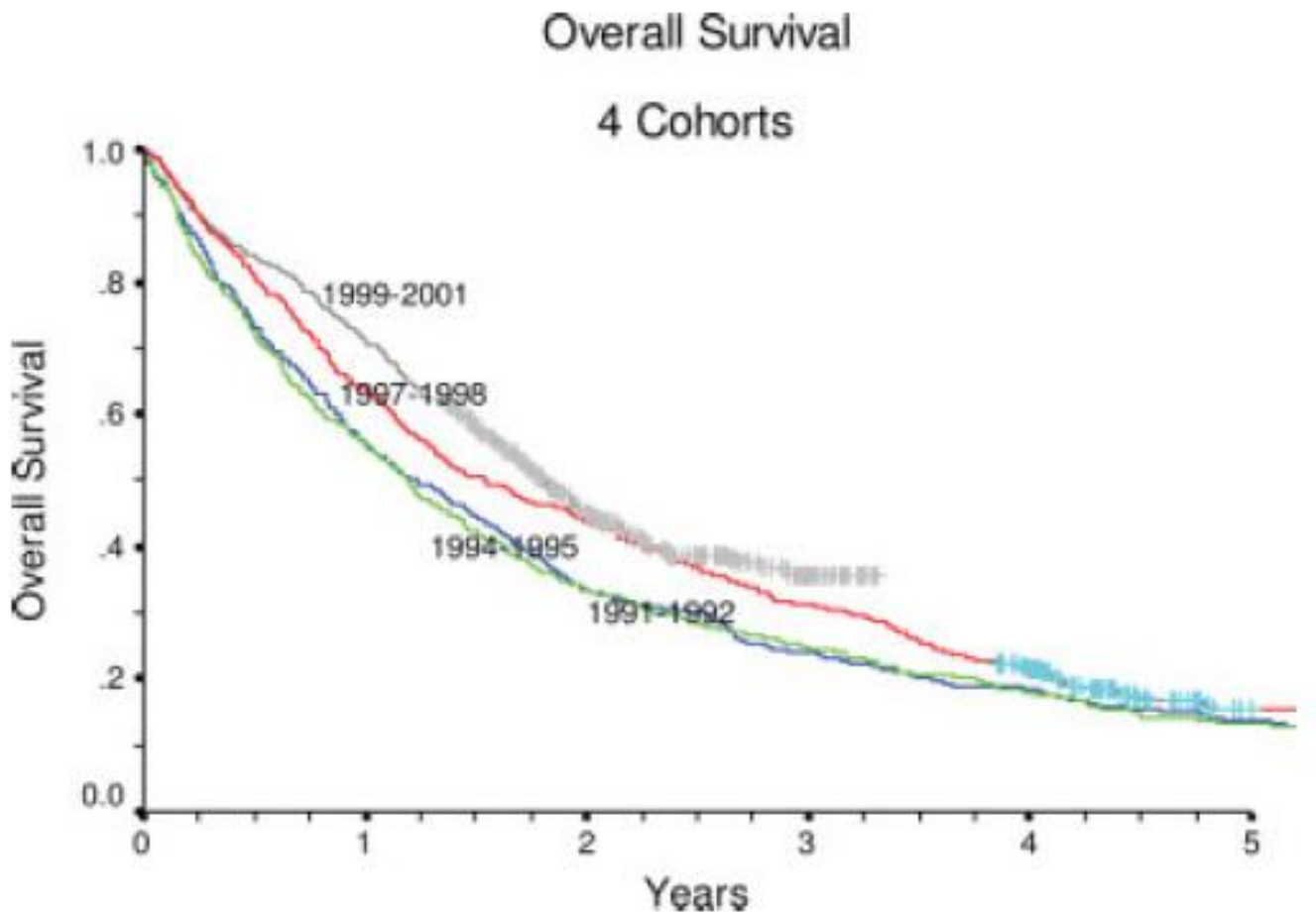
# Link between better outcome and systemic therapy

TABLE 2
Chemotherapies and Hormone Therapies Prescribed for the Treatment of Metastatic Breast Cancer for the 4 Time Cohorts

| Therapy | Cohort 1: 1991–1992 (n = 423) | Cohort 2: 1994–1995 (n = 561) | Cohort 3: 1997–1998 (n = 641) | Cohort 4: 1999–2001 (n = 525) |
|---|---|---|---|---|
| No. of treatments | | | | |
| Mean | 2.1 | 2.5 | 2.8 | 2.2 |
| Range | 0–9 | 0–10 | 0–10 | 0–7 |
| Median | 1 | 2 | 2 | 2 |
| Chemotherapy, % | | | | |
| None | 25 | 11 | 10 | 10 |
| Anthracyclines | 36 | 35 | 38 | 29 |
| Paclitaxel | 13 | 32 | 24 | 20 |
| Docetaxel | 1 | 2 | 18 | 20 |
| Vinorelbine | 4 | 16 | 26 | 17 |
| Trastuzumab | 0.7 | 0.1 | 5 | 13 |
| Capecitabine | 0.7 | 3 | 15 | 17 |
| Hormone therapy, % | | | | |
| Tamoxifen | 50 | 46 | 48 | 36 |
| Megestrol acetate | 42 | 45 | 30 | 10 |
| Aminoglutethimide | 18 | 18 | 4 | 0 |
| Nonsteroidal AI | 6 | 16 | 44 | 48 |
| Steroidal AI | 1 | 3 | 7 | 9 |

Chia et al Cancer 2007;110:973-979

# Link between better outcome and systemic therapy




Chia et al Cancer 2007;110:973-979

# Link between better outcome and systemic therapy

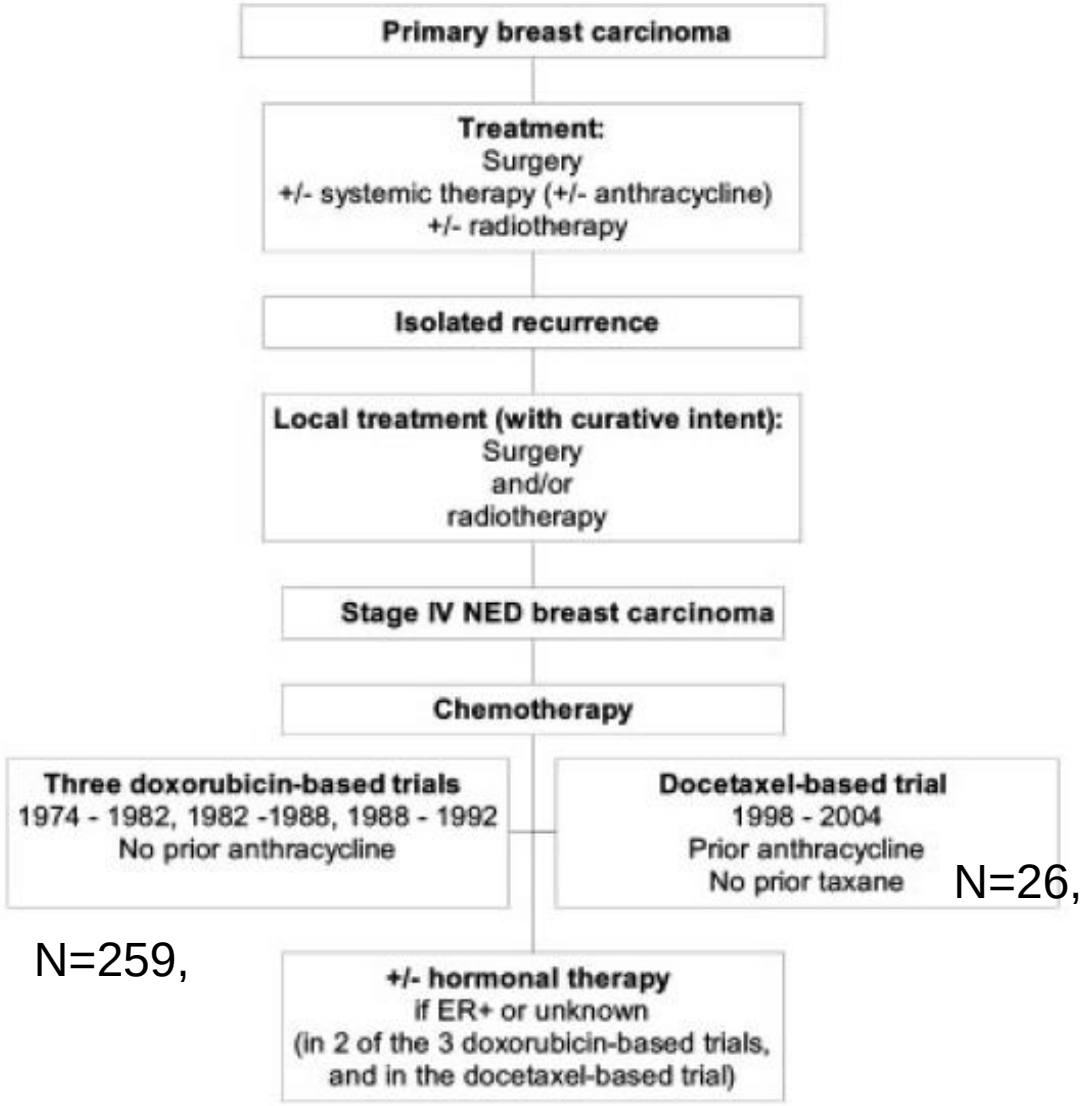
TABLE 3
Cox Regression Analysis for Survival in Metastatic Breast Cancer*

| Variable | HR | *P* | 95% CI |
|---|---|---|---|
| Grade | | | |
| 1/2 | 1 | | |
| 3 | 1.46 | <.001 | 1.30–1.64 |
| Unknown | 1.00 | .95 | 0.87–1.14 |
| ER status | | | |
| Positive | 1 | | |
| Negative | 1.83 | <.001 | 1.64–2.05 |
| Unknown | 1.32 | <.001 | 1.16–1.51 |
| Age, y* | | | |
| ≥65 | 1 | | |
| <35 | 1.07 | .61 | 0.82–1.40 |
| 35–44 | 0.88 | .075 | 0.76–1.01 |
| 45–54 | 0.79 | <.001 | 0.70–0.90 |
| 55–64 | 0.86 | .025 | 0.76–0.98 |
| Cohort | | | |
| 1 | 1 | | |
| 2 | 0.97 | .65 | 0.85–1.11 |
| 3 | 0.84 | .011 | 0.74–0.96 |
| 4 | 0.72 | <.001 | 0.61–0.84 |



Chia et al Cancer 2007;110:973-979

# Link between better outcome and systemic therapy




**MD Anderson,**

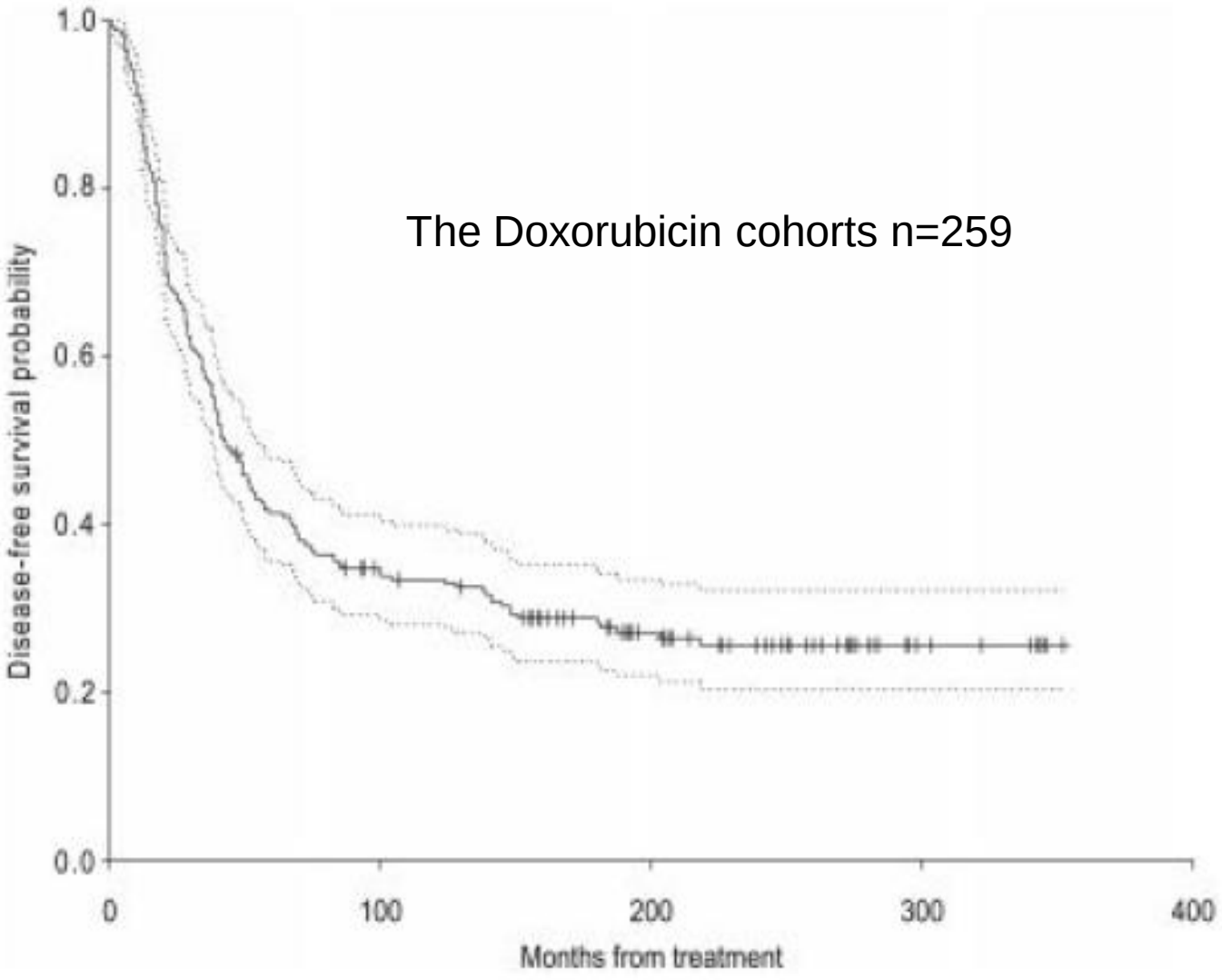
**4 prospective cohorts of stage IV breast cancer-NED**

Hanrahan-EO et al,

Cancer 2005; 104:1158-71

*Cancer* 2005;104:1158–71.

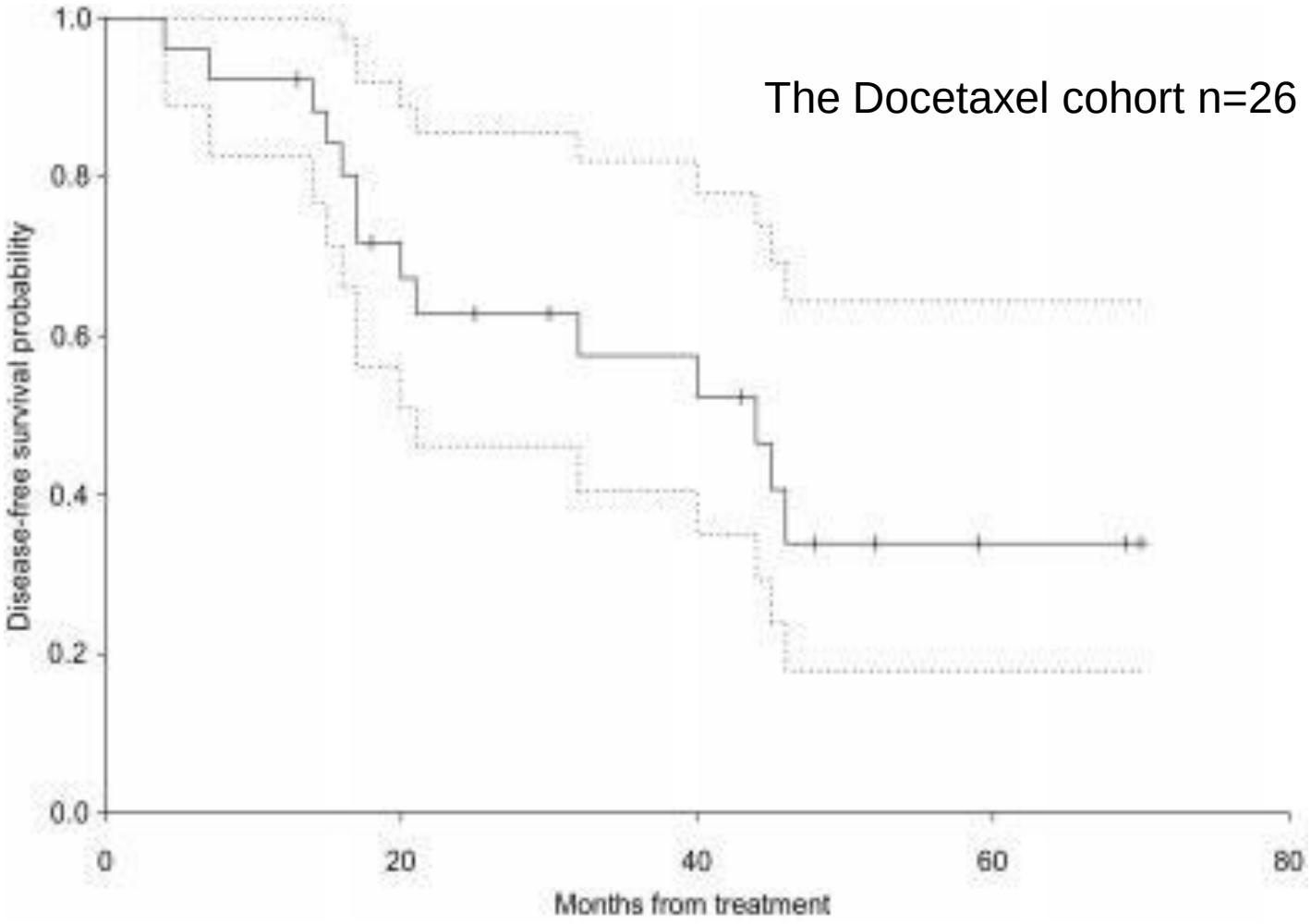
# Link between better outcome and systemic therapy




The Doxorubicin cohorts n=259

Hanrahan-EO et al, Cancer 2005; 104:1158-71

# Link between better outcome and systemic therapy

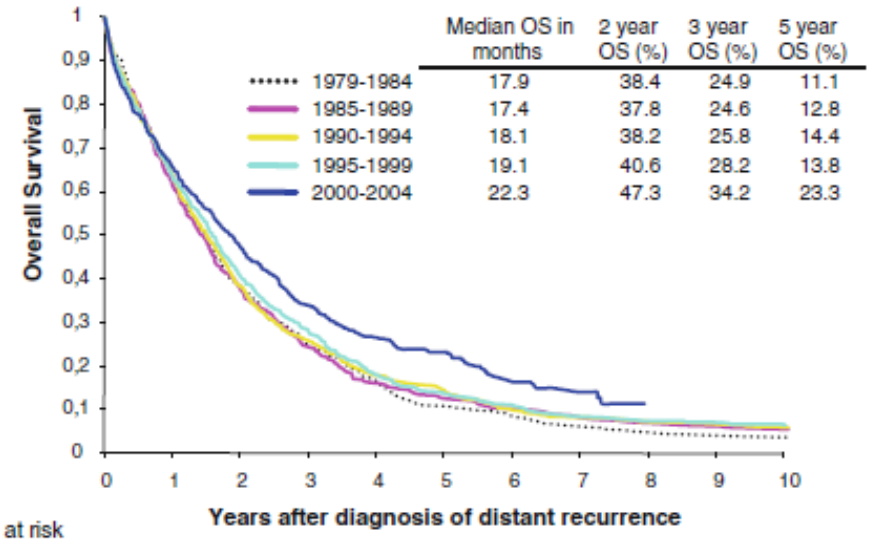





Hanrahan-EO et al, Cancer 2005; 104:1158-71

# Stockholm cohorts of metastatic breast cancer

B

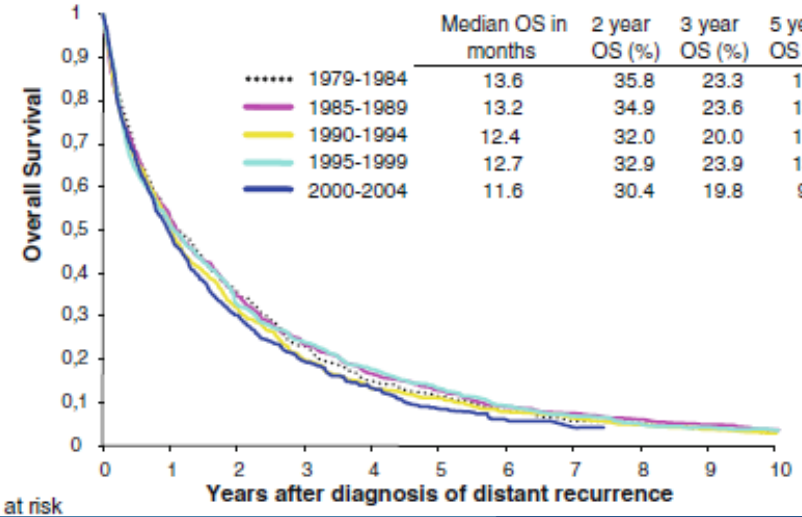



| | Median OS in months | 2 year OS (%) | 3 year OS (%) | 5 year OS (%) |
|---|---|---|---|---|
| 1979-1984 | 17.9 | 38.4 | 24.9 | 11.1 |
| 1985-1989 | 17.4 | 37.8 | 24.6 | 12.8 |
| 1990-1994 | 18.1 | 38.2 | 25.8 | 14.4 |
| 1995-1999 | 19.1 | 40.6 | 28.2 | 13.8 |
| 2000-2004 | 22.3 | 47.3 | 34.2 | 23.3 |

<= 60 years of age

Improved Outcome 2000-2004

C




| | Median OS in months | 2 year OS (%) | 3 year OS (%) | 5 year OS (%) |
|---|---|---|---|---|
| 1979-1984 | 13.6 | 35.8 | 23.3 | 11.6 |
| 1985-1989 | 13.2 | 34.9 | 23.6 | 13.0 |
| 1990-1994 | 12.4 | 32.0 | 20.0 | 11.1 |
| 1995-1999 | 12.7 | 32.9 | 23.9 | 13.4 |
| 2000-2004 | 11.6 | 30.4 | 19.8 | 9.0 |

- 60 years of age
- No change



**Foukakis-T, Breast Cancer Res Treat 2011**

# RT highly effective to palliate bone pain

| | Pain response | Complete pain response |
|---|---|---|
| Singe fraction | 59% | 34% |
| Multifraction | 60% | 32% |

N=3435 in 52 randomised trials

Cochrane Database Syst Rev. 2004;(2):CD004721.
**Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials.**
Sze WM, Shelley M, Held I, Mason M.

# RT in metastatic breast cancer, not only for palliation?

VOLUME 27 · NUMBER 9 · MARCH 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Breast Cancer With Synchronous Metastases: Survival Impact of Exclusive Locoregional Radiotherapy

*Romuald Le Scodan, Denise Stevens, Etienne Brain, Jean Louis Floiras, Christine Cohen-Solal, Brigitte De La Lande, Michelle Tubiana-Hulin, Sameh Yacoub, Maya Gutierrez, David Ali, Miriam Gardner, Patricia Moisson, Sylviane Villette, Florence Lerebours, Jean Nicolas Munck, and Alain Labib*

# RT in metastatic breast cancer, not only for palliation?

1980-2004

Patients with synchronic metastasis, n=581,
3,2% of all breast cancer treated

320 received locoregional treatment
(249 Locoregional RT exclusively)
(41 Surgery + Locoregional RT )
(30 surgery alone)

261 No locoregional treatment



Le Scodan et al, JCO March 2009

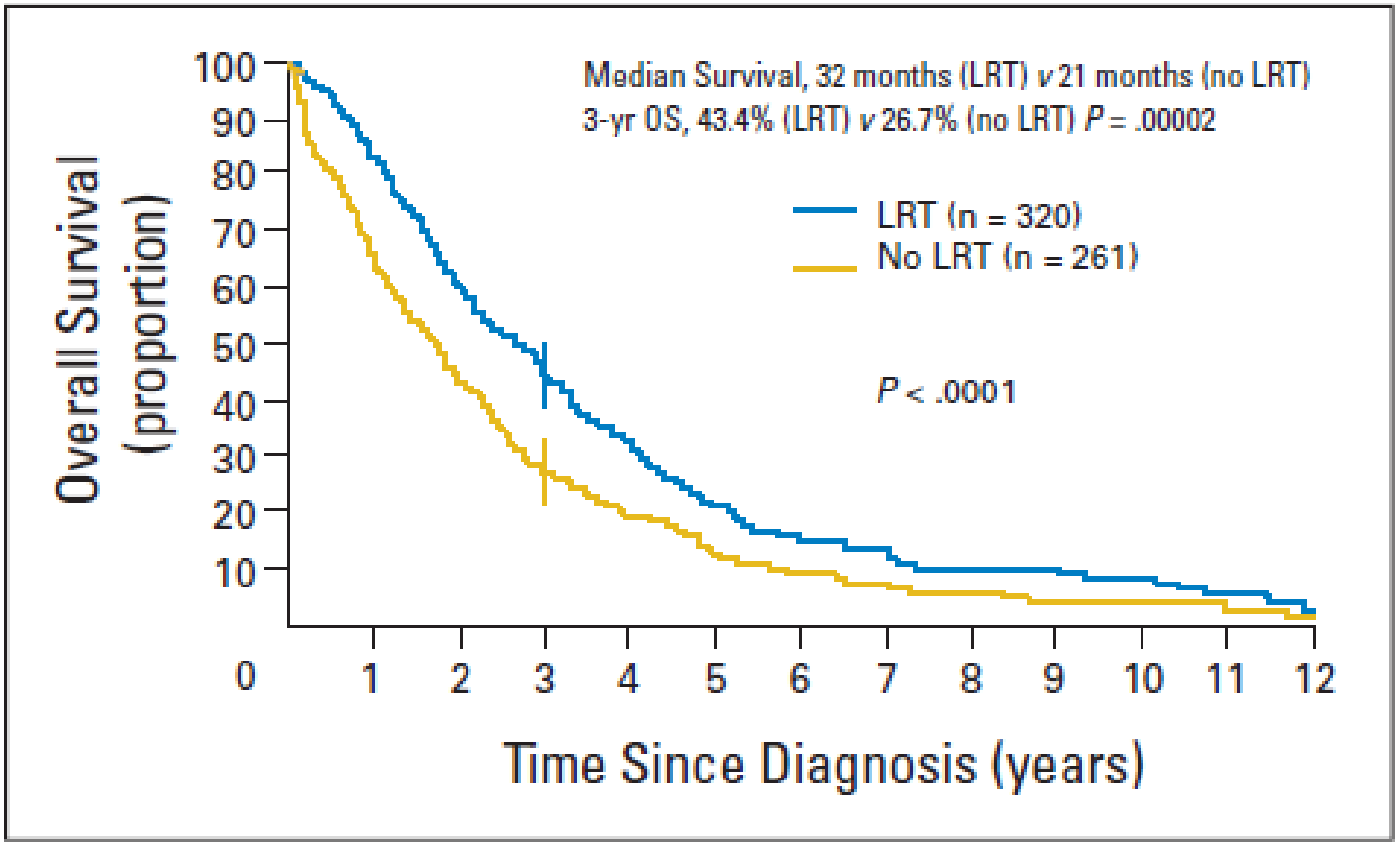



**Fig 1.** Survival curves according to locoregional treatment (LRT) in the entire population. OS, overall survival.

# Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study

Michael T. Milano, M.D., Ph.D.,* Alan W. Katz, M.D., M.P.H.,*
Hong Zhang, Ph.D., M.D.,* and Paul Okunieff, M.D.*,†

*Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY; and †Department of Radiation Oncology, University of Florida, Gainesville, FL

Received May 16, 2011, and in revised form Jul 3, 2011. Accepted for publication Aug 8, 2011

# Oligometastases Treated With Stereotactic Body Radiotherapy: Long-Term Follow-Up of Prospective Study

Michael T. Milano, M.D., Ph.D.,* Alan W. Katz, M.D., M.P.H.,*
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Received May 16, 2011, and in revised form Jul 3, 2011. Accepted for publication Aug 8, 2011

121 patients (39 with breast cancer)
with up to five clinically detectable metastases.

Prospectively followed.



Milano-MT et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 878e886, 2012

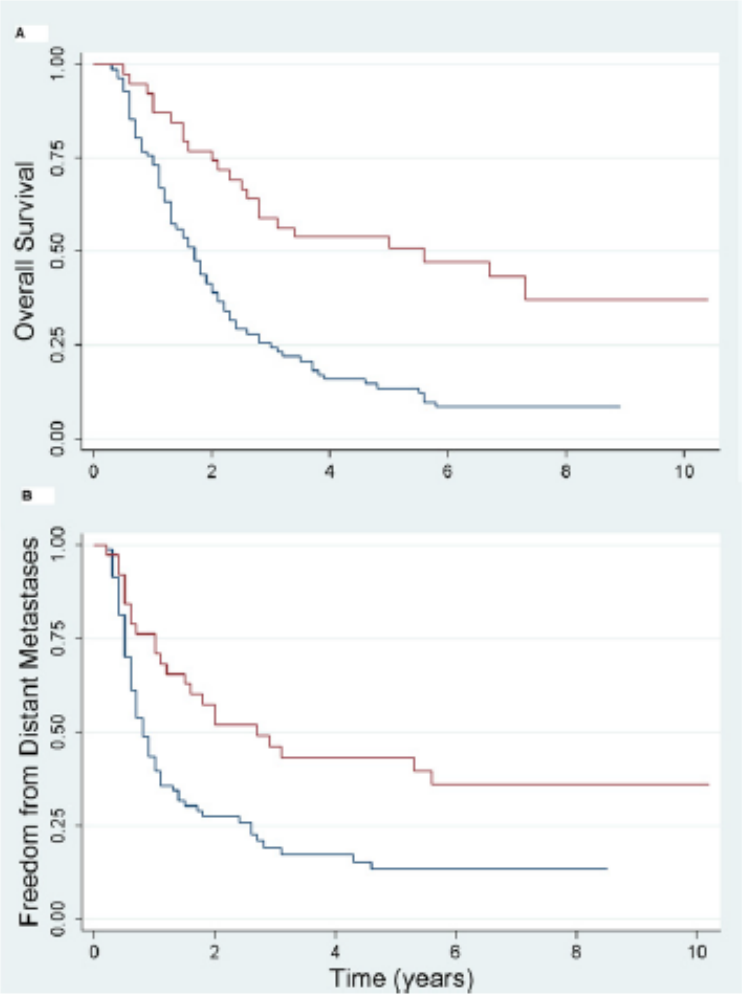



**Fig. 1.** Kaplan-Meier actuarial (A) overall survival and (B) freedom from distant progression for breast cancer (red line) and nonbreast cancer (blue line) patients. A color version of this figure is available at www.redjournals.com.

Breast cancer, red line

Non-breast cancer, blue line (colorectal, esophagus, H&N, lung)



Milano-MT et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 878e886, 2012

For the 11 breast cancer patients who before SBRT experienced progression of lesions after systemic therapy vs. the 16 patients who experienced stable or regressing disease, the 2-year OS rate was 55% vs. 81% ($p = .033$) and the 2-year FFDM rate was 23% vs. 60% ($p = .079$). For the 20 nonbreast cancer

**Stable or regressing disease on systemic treatment is important in patient selection for stereotactic radiotherapy**



Milano-MT et al. Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 878e886, 2012

Milano-MT et al.
Int J Radiation Oncol Biol Phys, Vol. 83
, 2012

| Variable | Breast cancer OS | Breast cancer FFDM |
|---|---|---|
| Sites involved with oligometastatic disease (UVA log rank) | | |
| Lung, *p* | 0.21 | 0.45 |
| Thoracic lymph nodes, *p* | 0.53 | 0.45 |
| Liver, *p* | 0.17 | 0.024* |
| MVA *p* | | 0.84 |
| Bone, *p* | 0.019† | 0.029† |
| MVA | | |
| *p* | 0.057 | 0.10 |
| HR | 0.24 | 0.34 |
| 95% CI | 0.05–1.04 | 0.09–1.23 |
| Oligometastatic lesions 1 vs. >1 | | |
| UVA (Cox), *p* | 0.004† | 0.010† |
| MVA | | |
| *p* | 0.055 | 0.12 |
| HR | 0.32 | 0.44 |
| 95% CI | 0.10–1.02 | 0.15–1.26 |
| Involved organs (1 vs. 2–3) | | |
| UVA (log rank), *p* | 0.032† | 0.016† |
| MVA | | 0.32 |
| *p* | 0.19 | |
| HR | 0.51 | |
| 95% CI | 0.18–1.41 | |
| Sum of GTV ($cm^3$) | | |
| UVA (Cox), *p* | 0.23 | 0.081 |
| UVA HR (95% CI) | | 0.72 |

# Concurrent radiochemo approcahes

Randomized trials in other cancers than breast cancer, e.g. locally advanced cervix[1], lung[2] and nasopharyngeal[3] cancers have shown local control rates as well overall survival advantages with concurrent radiochemo approaches .

[1] Lorvidhaya et al. [2]Takada et al. [3]Kwong et al.

Not much studied in breast cancer

3 randomized postoperative early breast cancer trials:

Rouesse (n=638, CNF+RT vs CEF-RT)
Toledano(n=706, CNF+RT vs CNF-RT)
Archangeli(n=206, CMF+RT vs CMF-RT)

Overall similar results for OS and DFS

# Neoadjuvant breast cancer trials with concurrent radiochemotherapy

| First Author | design | stage | n | Time | p-response | RT/CT |
|---|---|---|---|---|---|---|
| Semiglazov | Randomized (conc CT-RT vs RT) | IIb-IIIa | 271 | 1985-90 | 29.1% vs 19.4% | 60/40 Gy/ TMF |
| Shanta | Retrospect. | IIb-IIIb | 1,117 | 1990-99 | 45% | 40 Gy/ 3 CMF |
| Adams | Prospective | IIb-IIIc | 105 | 1997-2009 | 34% | 45Gy/ b. 14 Gy w. pacli 30mg/m$^2$ |
| Matuschek | Retrospect. | IIa-IIIc | 315 | 1991-98 | 29% | 50Gy/b 10Gy/ EC/ACx4 or CMF x 3 |
| Bollet | Prospective | IIa-IIIa | 60 | 2001-03 | 27% | 50/46 Gy/ 5FU vinorel. |

# Adams-S, Formenti-S et al.

Department of Radiation Oncology, New York University School of Medicine
New York, NY 10016, USA

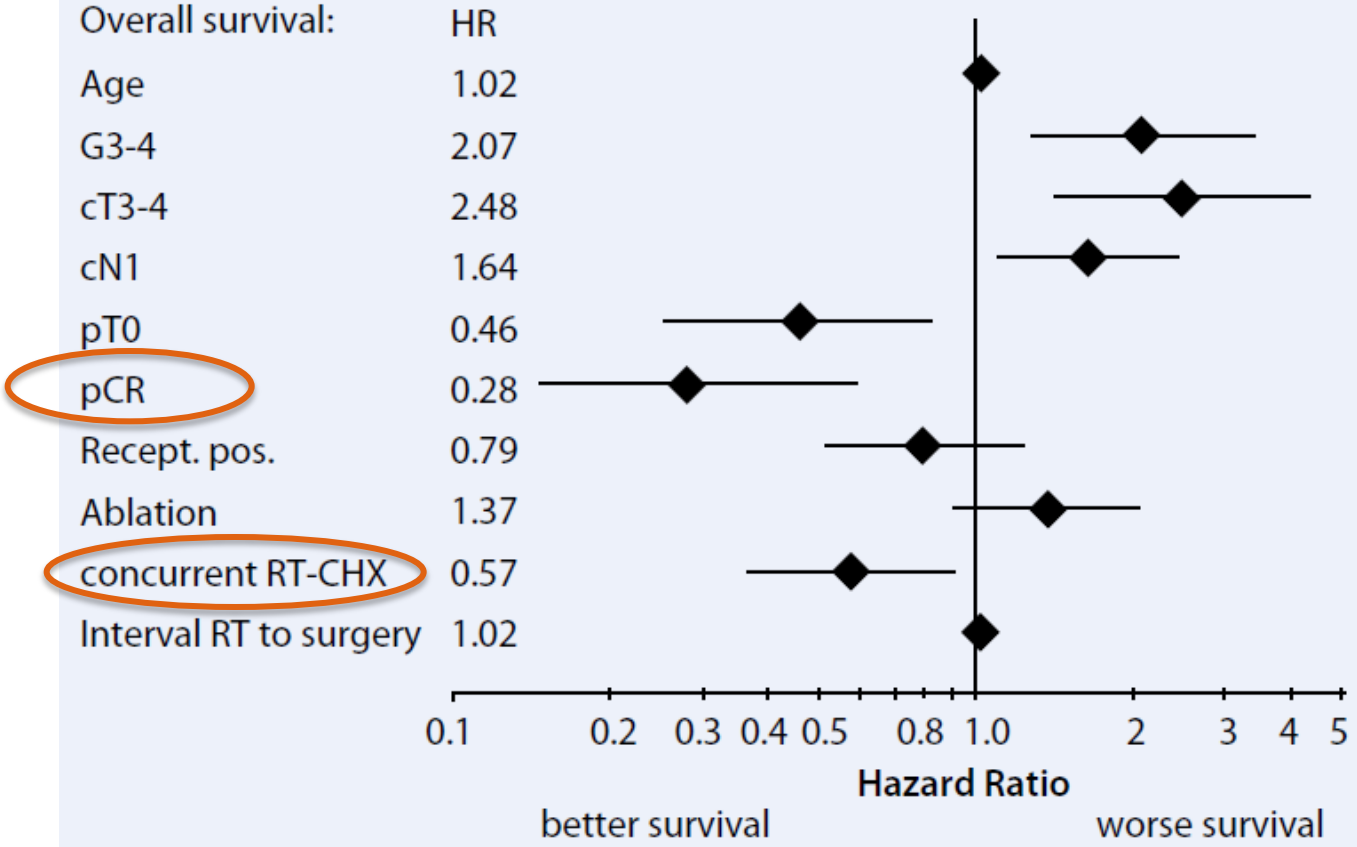
Pathologic response rate for breast cancer subtypes based on HR and Her2 status

| Subtype | Total | Proportion of patients who received trastuzumab | Proportion of patients with pathologic response (pCR + pPR) |
|---|---|---|---|
| Entire cohort ($n = 105$) | | | |
| HR positive | 57 | 5/57 (2 with pathologic response) | 10/57 (18%) |
| HR negative | 48 | 3/48 (3 with pathologic response) | 26/48 (54%) |
| Cohort with Her2 status available ($n = 85$) | | | |
| HR positive/Her2 negative | 34 | N/A | 6/34 (17.7%) |
| HR positive/Her2 positive | 13 | 5/13 (2 with pathologic response) | 3/13 (23.1%) |
| HR negative/Her2 positive | 14 | 3/14 (3 with pathologic response) | 7/14 (50.0%) |
| HR negative/Her2 negative (triple negative) | 24 | N/A | 13/24 (54.2%) |

*HR* hormone receptor, *Her2* human epidermal growth factor receptor, *pCR* pathologic complete response, *pPR* pathologic partial response

*Breast Cancer Res Treat.* 2010 December ; 124(3): 723–732.

## Overall survival after preoperative RT-CHX in breast cancer (n=315)
## Multivariate analysis




Matuschek et al. Strahlenther Onkol 2012 · 188:777–781

# However, there are reports of increased toxicity with the concurrent approach

informa
healthcare

*Acta Oncologica*, 2014; 53: 697–719

LETTERS TO THE EDITOR

## Radiation-induced lung injury after concurrent neoadjuvant chemoradiotherapy for locally advanced breast cancer

TIFFANY L. CHOW[1,2], ALEXANDER V. LOUIE[1], DAVID A. PALMA[1], DAVID P. D'SOUZA[1], FRANCISCO PERERA[1], GEORGE B. RODRIGUES[2,5], ANDREW WARNER[1], ANN F. CHAMBERS[3] & MURIEL BRACKSTONE[3,4]

[1]*Division of Radiation Oncology, London Regional Cancer Program, University of Western Ontario, London, Ontario, Canada,* [2]*University of Ottawa School of Medicine, Ottawa, Ontario, Canada,* [3]*Department of Oncology, London Regional Cancer Program, University of Western Ontario, London, Ontario, Canada,* [4]*Division of Biostatistics, University of Western Ontario, London, Ontario, Canada and* [5]*Department of Epidemiology and*

Prospective randomized trials are needed to establish the role of neoadjuvant concurrent chemoradiotherapy in locally advanced breast cancer

# Conclusions:

1. The outcome of stage IV breast cancer is better than in the past and among patients with oligometstatic disease there are some long term survivors.
2. Comparing population based cohorts of metastatic breast cancer over time indicates that newer systemic therapy are related to longer survival.
3. Stereotactic radiotherapy(or other local therapies) to lesions in oligometastatic breast cancer in case of stable or regressing disease on systemic therapy may prolong survival.
4. Locoregional therapy in metastatic brest cancer seems to prolong survival (no randomized evidence).
5. Concurrent neoadjuvant radiochemo approaches in LABC seem promising but no evidence exist and should only be used within trials
6. Oligometastatic breast cancer should be managed by an interdisiplinary team (medical/radiation/surgical/imaging oncologist, psychosocial support)

# Thank You!!