Breast Cancer in the Elderly 
Systemic Adjuvant Therapy 
& Genomic Tools

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Saint-Cloud, France
Cancer survival in Europe 1999–2007 by country and age: results of EUROCare–5—a population-based study


Summary

Background: Cancer survival is a key measure of the effectiveness of health-care systems. EUROCare—the largest prospective study of population-based cancer survival in Europe—has shown persistent differences between countries for cancer survival, although in general, cancer survival is improving. Major changes in cancer diagnosis, treatment, and rehabilitation occurred in the early 2000s. EUROCare–5 assessed their effect on cancer survival in 29 European countries.

Methods: In this retrospective observational study, we analysed data from 307 cancer registries for more than 30 million patients with cancer diagnosed up to 2007 and followed up to 2008. Uniform quality control procedures were applied to all datasets. For patients diagnosed 2000–07, we calculated 5-year relative survival for 14 cancers weighted by age and country. We also calculated country-specific and age-specific survival for ten common cancers, together with survival differences between time periods (for 1999–2001, 2002–04, and 2005–07).

Findings: 5-year relative survival generally increased steadily over time for all European regions. The largest increases were observed for prostate cancer (51–66% to 66–85% for men; 54–70% to 68–89% for women) and for non-Hodgkin lymphoma (69–75% to 77–82% for 53–54 years; 57–63% to 59–69% for 55–64 years). Survival in eastern Europe was generally low and below the European mean, particularly for cancers with good or intermediate prognosis. Survival was highest for northern, central, and southern Europe. Survival in the UK and Ireland was intermediate for rectal cancer, breast cancer, prostate cancer, skin melanoma, and non-Hodgkin lymphoma; but low for kidney, stomach, ovarian, colon, and lung cancers. Survival for lung cancer in the UK and Ireland was much lower than for other regions for all periods, although results for lung cancer in some regions (central and eastern Europe) might be affected by overestimation. Survival overall decreased with age, although in different degrees depending on region and cancer type.

Interpretation: The major advances in cancer management that occurred up to 2007 seem to have resulted in improved survival in Europe. Likely explanations for differences in survival between countries include: differences in stage at diagnosis and accessibility to good care, different diagnostic intensity and screening approaches, and differences in cancer biology. Variations in socioeconomic, lifestyle, and general health between populations might also have a role. Further studies are needed to fully interpret these findings and how to remedy disparities.

Funding: Italian Ministry of Health, European Commission, Compagnia di San Paolo Foundation, Cariplo Foundation.
Current dilemma and extreme positions

1. Therapeutic **nihilism**
   - Elderly patients **do not receive** any treatment

2. The **intermediate** position?
   - Elderly patients **may** benefit from treatments

3. Blind therapeutic **enthusiasm**
   - Elderly patients **receive futile/non beneficial** treatments

→ Place and role of **geriatrician** and **oncologist**
BC biology according to age

Undertreatment

SEER database; 49616 women with stage I/II breast cancer ≥67y

**Initial treatment** for stage II breast cancer by age

Treated with **chemotherapy** if ER+ N+ stage I/II breast cancer

*BCS = breast conserving surgery; XRT = radiotherapy*

Schonberg JCO 2010
Breast cancer mortality

Other cause mortality

• Univariate HR 1.66
  (95% CI 1.34-2.06), p<0.001
• Multivariable HR 1.63
  (95% CI 1.23-2.16), p<0.001

Substudy from TEAM trial (adjuvant exemestane)

Schonberg JCO 2010, Van de Water JAMA 2012
Overtreatment

- A sizeable proportion of elderly with operable breast cancer die of NON-CANCER-related causes
  - N = 14048 new early breast cancer, ≥50y, FUP 4.7y

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total deaths</th>
<th>Deaths from breast cancer</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-69</td>
<td>1334</td>
<td>933</td>
<td>70</td>
</tr>
<tr>
<td>70-74</td>
<td>514</td>
<td>293</td>
<td>57</td>
</tr>
<tr>
<td>75-79</td>
<td>696</td>
<td>329</td>
<td>47</td>
</tr>
<tr>
<td>≥80</td>
<td>1681</td>
<td>663</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>4225</td>
<td>2218</td>
<td>53</td>
</tr>
</tbody>
</table>

- Absolute benefit of treatments is lower

Ali Br J Cancer 2011
Adjuvant chemo

DFS

All

≤50

51-64

≥65

OS

All

≤50

51-64

≥65

Results

- Benefit identical
- Toxicity careful!!

• Toxic deaths 1.5%

• CALGB (1975-1999)
• 4 randomized trials
• 6487 pts
  > 65 yo 542 (8%)
  > 70 yo 159 (2%)

Muss JAMA 2005
## Adjuvant chemotherapy and mortality

<table>
<thead>
<tr>
<th></th>
<th>Giordano*</th>
<th>Elkin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. total</td>
<td>No. w/CT</td>
</tr>
<tr>
<td>I-III, $∀$ ER , 65+</td>
<td>41,390</td>
<td>4,500</td>
</tr>
<tr>
<td>I-III, ER-, 66+</td>
<td>5,081</td>
<td>1,711</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ER</th>
<th>HR (95% IC)</th>
<th>HR (95% IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>$∀$</td>
<td>1.05 (0.85-1.31)</td>
<td>NA</td>
</tr>
<tr>
<td>pN+</td>
<td>$+$</td>
<td>1.05 (0.85-1.31)</td>
<td>NA</td>
</tr>
<tr>
<td>both</td>
<td>-</td>
<td>NA</td>
<td>0.85 (0.77-0.95)</td>
</tr>
<tr>
<td>pN+</td>
<td>-</td>
<td>0.72 (0.54-0.96)</td>
<td>0.76 (0.65-0.88)</td>
</tr>
<tr>
<td>pN+ &gt; 70 yo</td>
<td>-</td>
<td>0.74 (0.56-0.97)</td>
<td></td>
</tr>
</tbody>
</table>

*: BC specific mortality

Adjuvant chemo is useful FIRST in ER-, pN0 or pN+, even > 70 yo

Giordano & Elkin J Clin Oncol 2006
Standard decision tools

- Adjuvant! Online
- Predict

Tumor extent:
- T (tumor size)
- N (nodal status)

Tumor biology
- Luminal A
- Luminal B HER2 neg
- Triple negative
- Her2+

Therapy choice depends on ...

Patient preference

General health status:
- Geriatric assessment
  - Estimate life-expectancy
  - Predict treatment toxicity

not accurate in older patients
quite accurate for OS prediction

De Glas Lancet Oncol 2014 & Br J Cancer 2016
Early 2000s: 1st GEP (intrinsic classification)

- Quantification of mRNA or cDNA of genes involved in tumour proliferation
- To identify patients requiring chemo despite good standard prognostic factors
- To avoid chemo in others
- Better individual risk stratification

Prat Mol Oncol 2011
<table>
<thead>
<tr>
<th></th>
<th>MammaPrint</th>
<th>Oncotype DX</th>
<th>Breast Cancer Index</th>
<th>Mapquant DX</th>
<th>PAM 50 ROR</th>
<th>EndoPredict</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Provider</strong></td>
<td>Agendia</td>
<td>Genomic Health</td>
<td>Biotheranostics</td>
<td>Ipsogen</td>
<td>NanoString</td>
<td>Savidon</td>
</tr>
<tr>
<td><strong>Type of Assay</strong></td>
<td>70-gene assay</td>
<td>21-gene recurrence score</td>
<td>2-gene ratio (H/I) and molecular grade index</td>
<td>Genomic grade</td>
<td>50-gene assay</td>
<td>12-gene assay</td>
</tr>
<tr>
<td><strong>Type of Sample</strong></td>
<td>Fresh or frozen or FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td>Fresh or frozen or FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
</tr>
<tr>
<td><strong>Technique</strong></td>
<td>DNA microarray or qRT-PCR</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
<td>DNA microarray or qRT-PCR</td>
<td>qRT-PCR</td>
<td>qRT-PCR</td>
</tr>
<tr>
<td><strong>Clinical Application</strong></td>
<td>Prognosis of N0, &lt; 5 cm, stage I/II, age &lt; 61</td>
<td>Prediction of recurrence risk in ER+ and NO treated with TAM</td>
<td>Prognostic in ER+, prediction of response to TAM</td>
<td>Molecular grading for ER+, histologic grade II disease</td>
<td>Originally for intrinsic subtyping, recurrence prediction</td>
<td>Recurrence prediction for ER+ HER2-</td>
</tr>
<tr>
<td><strong>Results Presentation</strong></td>
<td>Dichotomous, good or poor prognosis</td>
<td>Continuous variable</td>
<td>Continuous variable</td>
<td>Dichotomous, GGI I or GGI III</td>
<td>Continuous variable</td>
<td>Dichotomous, low or high risk</td>
</tr>
<tr>
<td><strong>Level of Evidence</strong></td>
<td>I</td>
<td>I</td>
<td>III</td>
<td>III</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td><strong>FDA Approval</strong></td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

Abbreviations: ER+, estrogen receptor-positive; FDA, U.S. Food and Drug Administration; FFPE, formalin-fixed, paraffin-embedded; GGI, Genomic Grade Index; qRT-PCR, quantitative reverse transcription polymerase chain reaction; TAM, tamoxifen.
Risk of distant recurrence risk @ 5 years w/ no treatment

http://www.agendia.com/healthcare-professionals/breast-cancer/test-results/
• 6,600 pts < 70
  – FEB 2007-AUG 2011
  – 11,291 registered pts
  – 6,673 enrolled (59.1%)
OncotypeDX

Risk of distant recurrence
@ 10 years
w/ TAM 5 years

Risk of distant recurrence
@ 5 years
w/ TAM 5 years

Personal results
OUTCOME DISPARITIES BY AGE AND 21-GENE RECURRENCE SCORE RESULT IN HORMONE RECEPTOR-POSITIVE (HR+) BREAST CANCER

Shak S,¹ Miller DP,¹ Howlader N,² Gliner N,¹ Howe W,³ Schussler N,³ Cronin K,² Baehner FL,¹,⁴ Penberthy L,² Petkov VI²

1. Genomic Health, Inc., Redwood City, CA, USA
2. National Cancer Institute, Rockville, MD, USA
3. IMS, Inc., Calverton, MD, USA
4. University of California, San Francisco, San Francisco, CA, USA
Methods

- SEER demographics, tumor characteristics, reported CT use, and BCSM available through 2013
- Genomic Health provided RS electronically to SEER, per registry operations
- Analysis population: N0, HR+ (by SEER and RT-PCR), HER2-negative (by RT-PCR), diagnosed between January 2004 and December 2012
  - Excluded: N+, prior invasive tumors, or concurrent multiple tumors
- RS groups standard cutpoints (18, 31)
- Actuarial estimates of survival (cause-specific and overall) and BCSM computed through 5 years with 95% CI
- The log-rank test was used to compare the three RS groups
SEER Population - STROBE Diagram

- **Diagnosed with primary invasive breast cancer (2004-2012) N=430,519**
  - **HR-positive; non-metastatic n=312,364**
  - **Node-negative n=211,586**
  - **Tested with 21-gene assay n=53,947**
  - **Untested with 21-gene assay\(^a\) n=157,639**
  - **With Recurrence Score results\(^b\) n=49,681**

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\(^a\) Untested cohort without RS results includes patients with HER2+ breast cancer because HER2 status was not reported to SEER before 2010.

\(^b\) Tested cohort with RS results excludes patients with HER2+ breast cancer, based on 21-gene assay quantitative single-gene HER2 result. Median follow-up for younger (<70 years) and older (≥70 years) patients were 45 and 40 months, respectively.
## Patient Testing and Demographics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age &lt;70 years</th>
<th>Age ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested (N=43,693)</td>
<td>Not Tested (N=100,519)</td>
</tr>
<tr>
<td>Female</td>
<td>99 %</td>
<td>99 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Age &lt;70 years</th>
<th>Age ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>84 %</td>
<td>81 %</td>
</tr>
<tr>
<td>Black</td>
<td>8 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>8 %</td>
<td>10 %</td>
</tr>
<tr>
<td>Am. Indian/Alaska Native</td>
<td>&lt;1 %</td>
<td>&lt;1 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Socioeconomic status, quintile</th>
<th>Age &lt;70 years</th>
<th>Age ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest SES</td>
<td>11 %</td>
<td>13 %</td>
</tr>
<tr>
<td>Second lowest SES</td>
<td>15 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Middle SES</td>
<td>19 %</td>
<td>20 %</td>
</tr>
<tr>
<td>Second highest SES</td>
<td>23 %</td>
<td>23 %</td>
</tr>
<tr>
<td>Highest SES</td>
<td>32 %</td>
<td>28 %</td>
</tr>
</tbody>
</table>

- Almost 6,000 patients ≥70 years with RS results
- Testing occurred 3.2 times less frequently in patients ≥70 years compared to <70 years
- Testing rates were similar by race and socioeconomic status

a. About 0.7% were male.
Reported Chemotherapy (CT) Use

<table>
<thead>
<tr>
<th>Age &lt;70 years</th>
<th>Age ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested (N=43,693)</td>
<td>Tested (N=5,988)</td>
</tr>
<tr>
<td>CT use 'yes'</td>
<td>CT use 'yes'</td>
</tr>
<tr>
<td>23%</td>
<td>11%</td>
</tr>
<tr>
<td>CT use 'no/unknown'</td>
<td>CT use 'no/unknown'</td>
</tr>
<tr>
<td>77%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Age ≥70 years

<table>
<thead>
<tr>
<th>Age ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested (N=5,988)</td>
</tr>
<tr>
<td>CT use 'yes'</td>
</tr>
<tr>
<td>11%</td>
</tr>
<tr>
<td>CT use 'no/unknown'</td>
</tr>
<tr>
<td>89%</td>
</tr>
</tbody>
</table>

Not Tested (N=57,120)

- CT use was lower in patients ≥70 years, in both RS-tested and untested cohorts

a. Chemotherapy use is known to be under-reported to SEER
5-year BCSM by Age and RS Group

- RS predicts BCSM in both age groups (p<0.001)
- Low 5-y BCSM was observed with RS <18 in both age groups
- Higher 5-y BCSM was observed with RS 18-30 and RS ≥31 in older patients
As expected, RS group does not predict other-cause mortality (p=NS)
As expected, higher other-cause mortality was observed in older patients
## 5-year BCSM (95% CI) by Age in Tested and Untested Patients

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RS &lt; 18</th>
<th>RS 18-30</th>
<th>RS ≥31</th>
<th>Untested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>CT Use&lt;sup&gt;a&lt;/sup&gt; (% of N)</td>
<td>5-y BCSM (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>&lt;70 y</td>
<td>24050</td>
<td>7% (0.2%, 0.5%)</td>
<td>16304</td>
<td>37% (0.9%, 1.4%)</td>
</tr>
<tr>
<td>70-74 y</td>
<td>3424</td>
<td>2% (0.8%, 2.1%)</td>
<td>2042</td>
<td>14% (1.8%, 3.8%)</td>
</tr>
<tr>
<td>75-79 y</td>
<td>2116</td>
<td>2% (0.6%, 2.0%)</td>
<td>1245</td>
<td>17% (1.4%, 3.9%)</td>
</tr>
<tr>
<td>≥80 y</td>
<td>968</td>
<td>2% (0.9%, 4.0%)</td>
<td>590</td>
<td>11% (1.1%, 5.2%)</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>1% (0.2%, 4.5%)</td>
<td>207</td>
<td>6% (2.3%, 9.9%)</td>
</tr>
</tbody>
</table>

- Notably, 5-y BCSM is relatively high in untested patients at all ages; this deserves further study

<sup>a</sup> Chemotherapy use reported as ‘yes’ (vs. ‘no/unknown’).
5-year BCSM by Age and RS Group in Nottingham Prognostic Index (NPI) >3.4

<table>
<thead>
<tr>
<th></th>
<th>RS &lt;18</th>
<th></th>
<th>RS 18-30</th>
<th></th>
<th>RS ≥31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>CT Use(^a) (% of N)</td>
<td>5-y BCSM (95% CI)</td>
<td>N</td>
<td>CT Use(^a) (% of N)</td>
</tr>
<tr>
<td>&lt;70 y</td>
<td>4727</td>
<td>12%</td>
<td>0.7 (0.4, 1.2)</td>
<td>4959</td>
<td>48%</td>
</tr>
<tr>
<td>≥70 y</td>
<td>940</td>
<td>2%</td>
<td>1.4 (0.5, 3.6)</td>
<td>821</td>
<td>20%</td>
</tr>
</tbody>
</table>

- RS predicts BCSM in both age groups (p<0.001)
- Similar results were seen for NPI >3.2 and ≤3.4

\(^a\) Chemotherapy use reported as 'yes' (vs. 'no/unknown').
Adjuvant chemotherapy
ASTER 70s (EUDRACT N° 2011-004744-22, PHRC national 2011, NCT01564056)

Complete curative surgery

Arm A = HT
Arm B = CT + HT

HT 5 yr

Chemo tolerance
Standard Lab

MMSE, IADL, QLQ C30 & ELD15
LVEF
Socioeconomic

Polymedications
MMSE, IADL, QLQ C30 & ELD15
LVEF
Socioeconomic

1 blood + serum

Baseline

q3w

Chemo = 4 TC or 4 AC or 4 MC

ER+ (ongoing study)

Group I
High GG

Group II
Low GG

1,000

NO CHEMOTHERAPY IS RECOMMENDED - Follow-up

1,2,3 & 4 year

2,000

1,989

Randomization stratified on pT, G8 and controls

** Group I include both high and equivocal G8 cases
Comparing Breast Cancer Multiparameter Tests in the OPTIMA Prelim Trial: No Test Is More Equal Than the Others

- Prospective study on 313 patients
- Risk of relapse
  - OncotypeDx 82.1%
  - Prosigna 65.5%
  - Mammaprint 61.4%
- Only 39% agreement
- Prosigna+Blueprint → 40% discordant
- Risk estimates are close at the population level but individual differences

Bartlett JNCI 2016
Competing causes for mortality

Cumulative probability of death / time of diagnosis

Cumulative probability of death / attained age

Log/log plot of probability of comorbid death vs corresponding probability for cancer-specific death

Deaths attributed to the primary cancer (solid dots) and those attributed to comorbidity (open circles)

Kendal Cancer 2008
Two worlds confronting one another?

- **Young patient**
  - Social and family obligations
  - Quantity of life +++

- **Elderly patient**
  - QoL+++ Independence
  - Staying at home
  - Symptoms, diagnosis
  - Quality of survival, i.e. amount of life with good QoL

- **Oncology**
  - Therapies and innovation
  - Toxicity, response
    - RECIST
    - NCI CTC v4.0
    - Survival (DFS, PFS, DDFS, OS)
  - Fast-moving world
  - “Molecular portrait” of tumour & GEP

- **Geriatrics**
  - Symptoms
  - Diagnosis
  - Quality of survival, i.e. amount of life with good QoL
  - Cognition
  - Functional status
  - QoL
  - Nutrition, etc.

**Genomic defect**
- Targeted therapy

**CGA defect**
- Targeted geriatric intervention

versus or + CGA

Two worlds confronting one another?
FEC, AACR, FAC, ASCO, anti-PDL1, anti-PD1, CMF, SABCS, PD-1, PDL1, DXR, PK/PD, CEX, 5FU CDDP, Calvert AUC, ESMO, Chatelut AUC, CTC, TILs, population PK, EORTC, FOLFIRI, ctDNA, FOLFOX 7, CPA, DFS, CALGB, DDFS, OS, TTP, NCI, CYP P450, JCO, JNCI, HER2, PI3K, mTOR, Phase 0, ECCO, ib and ab, Unicancer, EORTC, SWOG, CALGB, etc.

Charlson, CIRSG, CGA, AD, MCI, MNA, GDS, MMS, ADL, IADL, GFI, CMR2, JAGS, EUGMS, G8, CARG, Oncodage, VES-13, TRFs, JGO, NIA, SoFOG, Walter’s score, Lee’s score, CRASH, etc.
FEC, FAC, SoFOG, ADL, IADL, CMF, SABCS, DXR, PK/PD, CEX, G8, EORTC, 5FU CDDP, MCI, Calvert and Chatelut AUC, CARG, GDS, population PK, AD, FOLFIRI, MMS, FOLFOX, CPA, CRASH, SWOG, DFS, OS, TTP, NCI, GERICO, TILs, CARG, anti-PDL1, anti-PD1, EORTC TFE, JCO, JNCI, Charlson, JGO, CIRSG, PD-1, PDL-1, ctDNA, EGS, EGA, MNA, GFI, Unicancer, Lee’s score, JAGS, etc.

To be practice changing, let us be practice sharing!