Breast cancer (screening) in older individuals: the oncologist’s viewpoint for the geriatrician

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Past chairman of the EORTC elderly task force
President-elect of SIOG (international society of geriatric oncology)

Based on SIOG recommendations: Lancet Oncol 2007 p1101 and 2012 e148
CONFLICT OF INTEREST DISCLOSURE

I have the following potential conflict(s) of interest to report
- Research grant (to institute): Roche
- Lecture fee (to institute): Roche, Amgen, Novartis, Celldex, Pfizer, PUMA
- Travel support: Roche, Pfizer, PUMA
INCIDENCE

Age specific incidence increases with age

Median age at diagnosis: 62y ± 30% occurs ≥70y of age

Percent of new breast cancer cases by Age group

SEER database 2009-2013 females
Types of breast cancer

3 important classes:
- **Hormone sensitive (HER2 negatief)**
- **HER2 positive**
- **Triple negative**

ER = estrogen receptor
PR = progesterone receptor

ER = estrogen receptor in 80% of breast cancers
Her2 in 20% of breast cancers
TUMOR BIOLOGY

≥ 70y compared to younger

Slightly more favourable (in general)

• IHC studies: biology slightly more favorable:
  – More ER +
  – Less HER2+
  – Lower grade

• Intrinsic subtype (PAM50)

IHC = immunohistochemistry

Mol Oncol 2014 de Kruijf
Oncologist 2014 Jenskins
LESS TREATMENT with increasing age

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

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

- Mastectomy
- BCS + XRT
- BCS alone
- No initial surgery

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>67-69</td>
<td>40%</td>
</tr>
<tr>
<td>70-74</td>
<td>50%</td>
</tr>
<tr>
<td>75-79</td>
<td>60%</td>
</tr>
<tr>
<td>80-84</td>
<td>70%</td>
</tr>
<tr>
<td>85-89</td>
<td>80%</td>
</tr>
<tr>
<td>90+</td>
<td>90%</td>
</tr>
</tbody>
</table>

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

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<td>50%</td>
</tr>
<tr>
<td>85+</td>
<td>40%</td>
</tr>
</tbody>
</table>

**BCS** = breast conserving surgery; **XRT** = radiotherapy

JCO 2010 Schonberg
**Prognosis**

**MORE breast cancer deaths ➔ UNDERTREATMENT!**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR of Death Due to Breast Cancer</th>
<th>Range</th>
<th>HR of Death Due to Other Causes</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>67-69</td>
<td>Reference</td>
<td>1.0</td>
<td>Reference</td>
<td>1.3</td>
</tr>
<tr>
<td>70-74</td>
<td>1.1</td>
<td>0.9-1.2</td>
<td>1.9</td>
<td>1.2-1.4</td>
</tr>
<tr>
<td>75-79</td>
<td>1.2</td>
<td>1.0-1.4</td>
<td>3.0</td>
<td>1.8-2.2</td>
</tr>
<tr>
<td>80-84</td>
<td>1.6</td>
<td>1.3-1.7</td>
<td>4.1</td>
<td>2.7-3.3</td>
</tr>
<tr>
<td>≥ 85</td>
<td>1.8</td>
<td>1.5-2.2</td>
<td>5.9</td>
<td>3.7-4.6</td>
</tr>
</tbody>
</table>

Substudy from TEAM trial (adjuvant exemestane)

- 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

Schonberg JCO 2010; Van de Water JAMA 2012
Prognosis

OVERTREATMENT if treated identically to younger pts!

- 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 surgery and adjuvant (chemo/radio)therapy is lower
Regional differences in treatment and outcome!

- Large population based study, early breast cancer ≥70y
- 6 European countries, n=214,673

Stage I, 70-79y

Treatments given
- Breast surgery
- Axillary surgery
- Radiotherapy
- Endocrine therapy
- Chemotherapy
- Missing

Radiotherapy 57%

Endocrine R/ 86%

Endocrine R/ 18%

Multivariate Relative Excess Risk of death adjusted for age, year of diagnosis, grade, morphology

Relative survival ±100%
(compared to non-breast cancer population)

Courtesy to Marloes Derks and EURECCA
Regional differences in treatment and outcome!

**UNDERTREATMENT**!

- Large population based study, early breast cancer ≥70y
- 6 European countries, n=214,673

**Stage III, 70-79y**

- **Chemotherapy**
  - Belgium: 53%
  - Ireland: 61%
  - The Netherlands: 65%
  - Poland: 63%
  - England: 53%

- **Chemotherapy**
  - Belgium: 17%
  - Ireland: 17%
  - The Netherlands: 20%
  - Poland: 19%
  - England: 17%

Multivariate **Relative Excess Risk of Death** adjusted for age, year of diagnosis, grade, morphology

**Relative survival** (compared to non-breast cancer population)
- Belgium 71%
- Netherlands 61%
- England 58%

Courtesy to Marloes Derks and EURECCA
Yearly decrease in breast cancer death rates for the US population from 1990 to 2007

Relative to 1990, the rate of breast cancer death in the general population decreased by 2.0 to 2.5%/yr for women age <75 years and 1.1%/yr for women age ≥75 years.
<table>
<thead>
<tr>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Better survival: regular screening can reduce the risk of dying from breast cancer</td>
<td>- False positive results</td>
</tr>
<tr>
<td></td>
<td>- Overdiagnosis and overtreatment</td>
</tr>
<tr>
<td></td>
<td>- Cost</td>
</tr>
<tr>
<td></td>
<td>- False reassurance</td>
</tr>
<tr>
<td></td>
<td>- Pain at examination</td>
</tr>
</tbody>
</table>

Breast cancer mortality declined 30% over last 20y:
- Due to *early detection*?  
- Due to *better treatment*?
Breast cancer screening programs

- Belgium:
  - screening mammography every 2y
  - between age 50 and 69 y

- Netherlands:
  - screening mammography every 2y
  - Between age 50 to 70y till 1998
  - Between age 50 to 75y since 1998

- Quality control!
Breast cancer **screening** in **general population**

- **1000** women 50y receive annual mammography during 10y
- **25** develop breast cancer
- **4** die from breast cancer WITH screening
- **5** die from breast cancer WITHOUT screening
- **1** (0,3 – 3) lifes saved: breast cancer deaths **20%**

- **400** false positive mammographies (echo needed)
- **80** receive biopsy
- **7** operations for in situ carcinoma

*Trials rarely included women >68y!*
Impact of screening on early versus late stage breast cancer in women ≥40y

Our analysis suggests that whatever the mortality benefit, breast-cancer screening involved a substantial harm of excess detection of additional early-stage cancers that was not matched by a reduction in late-stage cancers. This imbalance indicates a considerable amount of overdiagnosis.
Impact of screening on early versus late stage breast cancer in older women

Breast cancer incidence in women aged 70-75 years, the Netherlands.

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Early stage before screening</th>
<th>Early stage after screening</th>
<th>Advanced stage before screening</th>
<th>Advanced stage after screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td>59</td>
<td>52</td>
</tr>
<tr>
<td>2000</td>
<td>249</td>
<td>363</td>
<td>59</td>
<td>52</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
<td>59</td>
<td>52</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td>59</td>
<td>52</td>
</tr>
</tbody>
</table>

Nienke A de Glas et al. BMJ 2014;349
Conclusion breast cancer *screening* in older women

- Screening in older women leads to a large proportion of overdiagnosis

- Older patients are at risk of adverse events of breast cancer treatment

- Increased risk of competing mortality with increasing age ➔ even if breast cancer is diagnosed in an earlier stage this will possibly result in a very small survival benefit

- Tremendous health expenditure with few beneficial effects
Conclusion breast cancer screening in older women (2)

- Personalized screening based on
  - Remaining life expectancy
  - Breast cancer risk
  - Patients’ preferences: screening is a choice, not a public health imperative …

- Improve treatment strategies in older patients, rather than implementing mass screening programs in older women
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

Tumor biology

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

Today

Tumor (e.g. breast)
- proliferation
- ER
- HER2

- chemotherapy
- hormonal therapy
- targeted therapy

Host
- age
- ECOG
- (comorbidity)

Tomorrow

Tumor (e.g. breast)
- genetic alterations
- gene expression signat.
- epigenetic alterations
- protein/receptor: ILGF, AR, HER3, EGFR, mTOR, PTEN, RAS, ...

- individualized targeted therapy

Host
- functionality: ADL, IADL
- falls
- comorbidity: DM, aHT, ...
- comedication
- malnutrition
- cognition
- depression
- social support

- individualized geriatric interventions
Breast surgery or primary endocrine therapy alone?

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>F.U. (Mo)</th>
<th>Results Surg+Tamoxifen vs Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>381</td>
<td>151</td>
<td>Local relapse HR 0,25 (0,19 – 0,32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40% of control group received surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS HR 0,78 (0,63 – 0,96)</td>
</tr>
<tr>
<td>GRETA</td>
<td>474</td>
<td>80</td>
<td>Local relapse HR 0,38 (0,25 – 0,57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS HR 0,98 (0,77 – 1,25)</td>
</tr>
<tr>
<td>Nottingham2</td>
<td>147</td>
<td>60</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS HR 0,80 (0,28 – 2,32)</td>
</tr>
</tbody>
</table>

- Cochrane review: surgery + tamoxifen vs tamoxifen
  - HR for PFS: 0,65 (p 0,0001)
  - HR for OS: 0,86 (p 0,06)
Breast irradiation after Breast Conserving Surgery

<table>
<thead>
<tr>
<th></th>
<th>&lt;50y</th>
<th>≥70y</th>
</tr>
</thead>
<tbody>
<tr>
<td>5y local recurrence after BCS</td>
<td>33%</td>
<td>13%*</td>
</tr>
<tr>
<td>5y local recurrence risk reduction of RT</td>
<td>22%</td>
<td>11%*</td>
</tr>
</tbody>
</table>

*Less relapse with ageing, but still significant benefit from RT

BCS = breast conserving surgery; RT = radiotherapy

Lancet Oncol 2007 Wildiers, derived from EBCTCG (n=42000)
**Breast Radiotherapy after breast conserving surgery**

RT could should be omitted in this population (small tumors, N-, ER+)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Inclusion criteria</th>
<th>F.U. (y)</th>
<th>Local relapse</th>
<th>Overall survival (at 10y and 5y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9343</td>
<td>636</td>
<td>≥70y T ≤2 cm, N-, ER+</td>
<td>12,6</td>
<td>Local/regional recurrence</td>
<td>RT: 67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RT: 2%</td>
<td>13/166 died from BC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No RT: 10%</td>
<td>No RT: 66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/168 died from BC</td>
</tr>
<tr>
<td>PRIME II</td>
<td>1326</td>
<td>≥65y T ≤3 cm, N-, ER+</td>
<td>5</td>
<td>Ipsilateral BC recurrence</td>
<td>RT: 94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RT: 1%</td>
<td>4/40 died from BC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No RT: 4%</td>
<td>No RT: 94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/49 died from BC</td>
</tr>
</tbody>
</table>

*ER+ = estrogen receptor positive; RT = radiotherapy; ALND = axillary lymph node dissection; BC = breast cancer*
Adjuvant hormone and chemotherapy

- Antihormone therapy more beneficial than chemotherapy in older women

Fig 1: Age-related mortality reduction (%) with adjuvant tamoxifen and polychemotherapy

![Graph showing age-related mortality reduction with tamoxifen and chemotherapy]

- Numbers derived from EBCTG 2005 (n=42000),
- Numbers derived from Lancet Oncol 2007 Wildiers
## Pharmacokinetic parameters that might change with aging

<table>
<thead>
<tr>
<th>Parameter changes</th>
<th>Clinical consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption decreased</td>
<td>Oral chemotherapy (e.g. capecitabine) might be less effective in the elderly</td>
</tr>
<tr>
<td>Distribution volume decreased</td>
<td>Serum concentrations and toxicity of several chemotherapeutics might increase (e.g. taxanes)</td>
</tr>
<tr>
<td>Hepatic metabolism decreased</td>
<td>Not well known, may affect serum concentrations of chemotherapeutics eliminated by hepatic metabolism (e.g. taxanes, cyclophosphamide, anthracyclines)</td>
</tr>
<tr>
<td>Renal excretion decreased</td>
<td>Dosing should be adapted to recommendations in order to avoid excessive serum concentrations and toxicity from renally excreted chemotherapeutics (e.g. carboplatin, methotrexate)</td>
</tr>
</tbody>
</table>

17th SIOG Annual Conference, Warsaw - Poland

SAVE THE DATE - November 9-11, 2017

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