Breast Cancer in Very Young Women

Asst. Prof Lazar Popovic, MD, PhD
Oncology Institute of Vojvodina
University of Novi Sad
“Young age by itself should not be the reason to prescribe more aggressive therapy than general recommendations.”
That's all Folks!
Breast Cancer in Young Women

- Epidemiology
- Biology and Genetics
- Screening
- Prognosis
- Treatment
- Fertility, Contraception and Premature Menopause
- Pregnancy after Breast Cancer
- QOL issues
- Survivorship
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Epidemiology

Hankey JNCI 1994
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Biology and Genetics

Figure 2 Proportion of breast cancer subtypes among California women by age group, 2005-2009. Hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2) negative (blue), HR+/HER2+ (red), HR-/HER2+ (green), and triple-negative (purple).
BC Subtypes by age (ICH)

<=40
- 38% Luminal A
- 29% Luminal B
- 13% Luminal-Her2
- 9% Her2
- 11% TNBC

>50
- 26% Luminal A
- 31% Luminal B
- 15% Luminal-Her2
- 8% Her2
- 20% TNBC

<35
- 47% Luminal A
- 19% Luminal B
- 17% Luminal-Her2
- 7% Her2
- 10% TNBC

35-50
- 25% Luminal A
- 52% Luminal B
- 11% Luminal-Her2
- 7% Her2
- 5% TNBC

LA: ER+ PR+/- HER2- Ki67<=14; LB ER+ PR+/- HER2- Ki67>14 L
Her2 ER+ PR+/- HER2+ Her2 ER- PR- HER2+ TNBC ER- PR- HER2-

Morrison Br J Cancer 2012
Cancello Ann Oncol 2012
BC Subtypes by age (GEP)

Azim et al, 2012 [9]
Subtypes defined by 3 gene classifier

Anders et al, 2011 [17]
Subtypes defined by PAM50
BC Subtypes (Niš/NS)

Age >=35, n=142

Cvetanovic 2015 (Unpublished Data)
BC Subtypes (Niš/NS)

Cvetanovic 2015 (Unpublished Data)

Age >=35, n=142
Delay of diagnosis and advanced stage

The Effect of Age on Delay in Diagnosis and Stage of Breast Cancer

Ann H. Partridge, a Melissa E. Hughes, a Rebecca A. Ottesen, b Yu-Ning Wong, c
Stephen B. Edge, d Richard L. Theriault, e Douglas W. Blayney, f Joyce C. Niland, h
Eric P. Winer, a Jane C. Weeks, a Rulla M. Tamimi a

<table>
<thead>
<tr>
<th>Mean</th>
<th>100.0</th>
<th>17.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>38.0 (0–4,070)</td>
<td>29.0 (0–7,280)</td>
</tr>
<tr>
<td>Delay in diagnosis &gt;60 days</td>
<td>861 (35.2)</td>
<td>4,886 (25.2)</td>
</tr>
<tr>
<td>Delay in diagnosis &gt;180 days</td>
<td>311 (12.7)</td>
<td>1,626 (8.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>1,804 (73.2)</td>
<td>15,802 (82.0)</td>
</tr>
</tbody>
</table>

| Stage at diagnosis |  |  | <.0001 |
|-------------------|-------|-------|
| I | 680 (27.8) | 8,852 (45.7) |
| II | 1,217 (49.8) | 7,477 (38.6) |
| III | 417 (17.1) | 2,303 (11.9) |
| IV | 131 (5.4) | 741 (3.8) |
Cancer Syndromes and BCY

- HOBC (Hereditary Breast and Ovarian Cancer) (BRCA 1/2)
- Li-Fraumeni (TP53)
- Cowden (PTEN)
- Hereditary Diffuse Gastric Cancer (CDH1)
- Peutz-Jeghers (STK11)
HBOC (Hereditary Breast and Ovarian Cancer)

- BRCA 1/2 mutations in 2-4%, >10% in BC <35 years
- BRCA 1 50-85% risk of BC (Young age!)
- 40-60% risk of second primary BC
- 35-45% risk of ovarian cancer
- Risk for prostate cancer, Hodgkin’s Lymphoma etc.
Why to test for BRCA 1/2 mutations?

• Guide decisions about systemic therapy (Platinum, PARP inhibitors)
• Guide decisions about screening and follow up approaches
• Guide decisions about (preventive) surgery (risk of contralateral BC)
• Define potential risk to family members
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Survival of BC by Age

Whole population ($n = 2,901$)

- $\leq 40$ ($n = 339$)
- 41–52 ($n = 968$)
- 53–64 ($n = 732$)
- $\geq 65$ ($n = 862$)

Log-rank: $P < 0.0001$
Log-rank test for $P_{\text{trend}} = 0.0003$

Azim Clin Cancer Res 2012
Survival of BC by Age

**B**

**Disease free survival**

All molecular subtypes

HR = 1.65 (1.30-2.10)  
Log-Rank P = 0.0001

**Overall survival**

35-50  
<35

HR = 1.78 (1.12-2.85)  
Log-Rank P = 0.0001

Cancaello Ann Oncol 2010; Anders JCO 2008
Does patients aged $\leq 30$ have worse outcome?

<=30: n=33 med=32 3y DFS 45.7%
31-35: n=96 med=NR 3y DFS 73.4%
p=0.004 HR=2.60 (CI 1.34-5.09)

<=30: n=34 med=NR 3y OS 70.7%
31-35: n=99 med=NR 3y OS 91.5%
p=0.037 HR=2.33 (CI 1.04-5.18)

Cvetanovic 2015 (Unpublished Data)
Survival of BC by Age and Subtype

B. Luminal A (n = 975)
- Log-rank: $P = 0.07$
- Log-rank test for $P_{\text{trend}} = 0.42$

C. Luminal B (n = 879)
- Log-rank: $P = 0.03$
- Log-rank test for $P_{\text{trend}} = 0.006$

D. HER2+ (n = 432)
- Log-rank: $P = 0.42$
- Log-rank test for $P_{\text{trend}} = 0.4$

E. ER-HER2- (n = 615)
- Log-rank: $P = 0.69$
- Log-rank test for $P_{\text{trend}} = 0.5$
OS all Stage IV pts using ≤ or ≥ 35 years of age

Small number < 35 but apparently similar outcomes than older pts with ABC

n | 3 year OS          | 5 year OS          |
---|--------------------|--------------------|
Age < 35 at diagnosis | 37 | 44.7 (28.2, 59.9) | 20.9 (9.4, 35.7) |
Age ≥ 35 at diagnosis | 1492 | 33.1 (30.7, 35.6) | 16.9 (14.9, 19.0) |

K. Gelmon, ABC 1
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Screening in very young population?

• Only for those with **HIGH RISK** (20-25% lifetime risk):
  - BRCA carriers, LI-Fraumeni, Cowden, Fanconi Anemia
  - 1st degree relative with BC not tested for BRCA mut
  - Previously Chest Irradiation (Hodgkin’s Lymphoma)
Mammography
Mammography

Sensitivity: 85-90%

Sensitivity: 50-65%

Sklair-Levy BCY2 2014
...but sometime too sensitive...

Sklair-Levy BCY2 2014
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Breast Cancer in Young Women

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• Biology and Genetics
• Prognosis
• Screening
• Treatment
  • Fertility, Contraception and Premature Menopause
  • Pregnancy after Breast Cancer
  • QOL issues
  • Survivorship
Analysis of local and regional recurrences in breast cancer after conservative surgery

E. Botteri¹, V. Bagnardi¹,², N. Rotmensz¹, O. Gentilini³, D. Disalvatore², B. Bazolli¹, A. Luini³ & U. Veronesi³,⁴

¹Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan; ²Department of Statistics, University of Milan-Bicocca, Milan; ³Division of Breast Surgery, European Institute of Oncology, Milan and ⁴Scientific Directorate, European Institute of Oncology, Milan, Italy

Table 2. Univariate analysis of prognostic factors for first events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Classification</th>
<th>Local recurrence</th>
<th>Regional recurrence</th>
<th>Distant metastasis or death</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>Events</td>
<td>Events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5 years cum inc)</td>
<td>(5 years cum inc)</td>
<td>(5 years cum inc)</td>
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<tr>
<td></td>
<td></td>
<td>P value</td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>33 (1.1)</td>
<td>35 (1.2)</td>
<td>222 (7.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;35</td>
<td>3 (2.5)</td>
<td>1 (0.8)</td>
<td>16 (10.5)</td>
</tr>
<tr>
<td></td>
<td>35–49</td>
<td>19 (1.7)</td>
<td>12 (1.2)</td>
<td>86 (8.3)</td>
</tr>
<tr>
<td></td>
<td>50–64</td>
<td>9 (0.7)</td>
<td>16 (1.1)</td>
<td>88 (6.8)</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>2 (0.5)</td>
<td>6 (1.6)</td>
<td>32 (7.6)</td>
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</tbody>
</table>

P value highlighted in red: 0.02
## Surgery

### Table 5. Treatments given to women with stage I breast cancer by age and tumour size.

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>Total No.</th>
<th>Mastectomy No. (%)</th>
<th>Chemotherapy No. (%)</th>
<th>Total no. with BCS</th>
<th>Radiotherapy if BCS No. (%)</th>
<th>Total no. with hormone positive tumour</th>
<th>Endocrine therapy if hormone positive tumour No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 mm</td>
<td>36</td>
<td>16 (44.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-34 years</td>
<td>36</td>
<td>16 (44.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39 years</td>
<td>78</td>
<td>22 (28.2)</td>
<td>9 (11.5)</td>
<td>56</td>
<td>49 (87.5)</td>
<td>48</td>
<td>24 (50.0)</td>
</tr>
<tr>
<td>40-49 years</td>
<td>623</td>
<td>115 (18.5)</td>
<td>26 (4.2)</td>
<td>503</td>
<td>473 (94.0)</td>
<td>365</td>
<td>161 (44.1)</td>
</tr>
<tr>
<td>50-69 years</td>
<td>2881</td>
<td>498 (17.3)</td>
<td>60 (2.1)</td>
<td>2363</td>
<td>2160 (91.4)</td>
<td>1744</td>
<td>951 (54.5)</td>
</tr>
<tr>
<td>11-20 mm</td>
<td>90</td>
<td>23 (25.8)</td>
<td>35 (38.9)</td>
<td>66</td>
<td>61 (92.4)</td>
<td>53</td>
<td>39 (73.6)</td>
</tr>
<tr>
<td>20-34 years</td>
<td>90</td>
<td>23 (25.8)</td>
<td>35 (38.9)</td>
<td>66</td>
<td>61 (92.4)</td>
<td>53</td>
<td>39 (73.6)</td>
</tr>
<tr>
<td>35-39 years</td>
<td>186</td>
<td>53 (28.7)</td>
<td>70 (37.6)</td>
<td>132</td>
<td>130 (98.5)</td>
<td>123</td>
<td>70 (56.9)</td>
</tr>
<tr>
<td>40-49 years</td>
<td>1212</td>
<td>277 (22.9)</td>
<td>212 (17.5)</td>
<td>926</td>
<td>879 (94.5)</td>
<td>859</td>
<td>538 (62.6)</td>
</tr>
<tr>
<td>50-69 years</td>
<td>4542</td>
<td>976 (21.5)</td>
<td>422 (9.3)</td>
<td>3542</td>
<td>3351 (94.6)</td>
<td>3296</td>
<td>2344 (71.1)</td>
</tr>
</tbody>
</table>

Proportions of women aged 20–69 years, diagnosed with primary breast cancer stage I between 1992 and 2005 (9656 women), receiving specific treatments, by tumour size and age at diagnosis.

<table>
<thead>
<tr>
<th>T stage</th>
<th>Number of patients</th>
<th>% Mastectomy</th>
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<tbody>
<tr>
<td>T1</td>
<td>41</td>
<td>31.7%</td>
</tr>
<tr>
<td>T2</td>
<td>73</td>
<td>63%</td>
</tr>
<tr>
<td>T3</td>
<td>10</td>
<td>80%</td>
</tr>
</tbody>
</table>
CLINICAL INVESTIGATION

EARLY-STAGE YOUNG BREAST CANCER PATIENTS: IMPACT OF LOCAL TREATMENT ON SURVIVAL

Enja J. Bantema-Joppe, M.D.,* Linda de Munck, M.Sc.,† Otto Visser, Ph.D.,‡ Pax H. B. Willemse, M.D., Ph.D.,§ Johannes A. Langendijk, M.D., Ph.D.,* Sabine Siesling, Ph.D.,†‖ and John H. Maduro, M.D., Ph.D.*

Fig. 1. Overall survival of patients after breast conserving therapy (BCT) or mastectomy (M) (unadjusted hazard ratio 1.37; 95% confidence interval, 1.09–1.72; p = 0.007).
Clinical Investigation: Breast Cancer

**Similar Survival With Breast Conservation Therapy or Mastectomy in the Management of Young Women With Early-Stage Breast Cancer**

Usama Mahmood, M.D.,* Christopher Morris, M.S.,* Geoffrey Neuner, M.D.,* Matthew Kosh, M.D.,§ Susan Kesmodel, M.D.,† Robert Buras, M.D.,‡ Saranya Chumsri, M.D.,‡ Ting Bao, M.D.,‡ Katherine Tkaczuk, M.D.,‡ and Steven Feigenberg, M.D.*

*Departments of *Radiation Oncology, †Surgery, and ‡Medicine, University of Maryland, Baltimore, Maryland; and §Department of Cellular and Radiation Oncology, University of Chicago, Chicago, Illinois

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**Fig. 1.** Matched pair analysis of OS (red, dashed line = mastectomy; blue, solid line = BCT; p = 0.99).
“Surgical treatment of young patients with EBC-while being tailored to the individual patient-should in general not differ from that of older patients.”
“Immediate breast reconstruction after mastectomy does not seem to affect survival as compared to mastectomy without reconstruction...”
Hormonal therapy

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer
HR 0.83
p=0.1
Neoadjuvant chemotherapy

“something for advanced stages”

Preferred standard in TNBC and Her2+ BC
pCR rates after neoadjuvant chemo

Loibl Cancer Res 2011
pCR rates after neoadjuvant chemo
pCR Rates (ypT0 ypN0)

Overall
OR 1.33 (0.96-1.85)
P = 0.107*
(level of significance < 0.2)

TNBC
OR 1.94 (1.24 – 3.04)
P = 0.005

von Minckwitz et al. Lancet Oncology, May 2014
### Prediction of Carboplatin Effect on pCR

<table>
<thead>
<tr>
<th>%</th>
<th>PM (N=146)</th>
<th>PMCb (N=149)</th>
<th>OR</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>No risk factor</td>
<td>34.5</td>
<td>46.0</td>
<td>1.61</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Δ 11.5</td>
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</tr>
<tr>
<td>Family history of BC/OC</td>
<td>30.8</td>
<td>57.5</td>
<td>3.04</td>
<td>0.02</td>
</tr>
<tr>
<td>without alteration</td>
<td>Δ 26.7</td>
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<tr>
<td>gBRCA/RAD alteration</td>
<td>43.5</td>
<td>66.7</td>
<td>2.60</td>
<td>0.13</td>
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<tr>
<td>with/without family history</td>
<td>Δ 23.2</td>
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**Prediction of Carboplatin Effect on pCR**

<table>
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<tr>
<th></th>
<th>PM</th>
<th>PMCb</th>
<th>OR</th>
<th>p</th>
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<td>%</td>
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<td>△ 11.5</td>
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</tr>
<tr>
<td></td>
<td>△ 26.7</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>43.5</td>
<td>66.7</td>
<td>2.60</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>△ 23.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

44% of all TNBC in women under 35 are BRCA mutated!
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Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study


A

Estrogen receptor–positive cohort (n = 686)

B

Estrogen receptor–negative cohort (n = 521)

**Relapse-Free Survival (%)**

A: Pregnant after breast cancer (n = 194) vs. Matched nonpregnant after breast cancer (n = 492)

HR, 0.91; 95% CI, 0.67 to 1.24; P = .55

B: Pregnant after breast cancer (n = 139) vs. Matched nonpregnant after breast cancer (n = 382)

HR, 0.75; 95% CI, 0.51 to 1.08; P = .12
Positive Trial

Screening/eligibility:
Patients with ER+ early breast cancer
≥ 18 and ≤42 years at enrollment
Completing 18-30 months of ET (SERMs alone, GnRH analogue + SERM or AIs)¹
Pregnancy desire

³ CT
² No more than 1 month prior enroll.

Stop ET

POSITIVE SCHEMA

Ovarian function evaluation
Uterine evaluation
Circulating tumor DNA (ctDNA)
Genomic evaluation of primary breast tumor

Psycho-oncology companion – psychological distress, fertility concerns, decisional conflict
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Prevention of Early Menopause Study (POEMS)-S0230

Phase III trial of LHRH analog during chemotherapy to reduce ovarian failure in early stage, hormone receptor-negative breast cancer: an international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance)

## POEMS Ovarian Failure

<table>
<thead>
<tr>
<th></th>
<th>Standard Chemotherapy</th>
<th>Chemotherapy + Goserelin</th>
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</thead>
<tbody>
<tr>
<td>Ovarian failure at 2 years</td>
<td>15/69 = 22%</td>
<td>5/66 = 8%</td>
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</tbody>
</table>

### Logistic Regression Results:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>One-sided</td>
<td>Two-sided</td>
<td></td>
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<tr>
<td>Univariate</td>
<td>0.30</td>
<td>0.10 – 0.87</td>
<td>p=.01</td>
<td>p=.03</td>
</tr>
<tr>
<td>Stratified*</td>
<td>0.30</td>
<td>0.09 – 0.97</td>
<td>p=.02</td>
<td>p=.04</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>0.36</td>
<td>0.11 – 1.14</td>
<td>p=.04</td>
<td>p=.08</td>
</tr>
</tbody>
</table>

*Accounting for age and regimen through stratification (“Stratified”) or covariate (“Multivariate”) adjustment, respectively*

---

**Courtesy of Halle Moore**
<table>
<thead>
<tr>
<th>Dr vs. Patient Perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tools</td>
</tr>
<tr>
<td>Heredity</td>
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<tr>
<td>Loco-regional treatment</td>
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<tr>
<td>Cancer biology</td>
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<tr>
<td>Systemic treatment</td>
</tr>
<tr>
<td>Fertility and pregnancy</td>
</tr>
<tr>
<td>Advanced disease</td>
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<tr>
<td>QOL</td>
</tr>
<tr>
<td>Survivorship</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Social support
Conclusion

- BC in very young women is often aggressive disease with poor prognosis
- Young age by itself should not be the reason to prescribe more aggressive therapy than general recommendations
- Pregnancy seems to be safe after BC
- Importance of social and MDs support
- We need new diagnostic tools and new therapies to have better outcomes
OS stage IV patients by Diagnosis Era age ≤ 35 or > 35 years of age

Outcome seems to have improved more for younger ABC pts than for older ones
... but too small numbers

<table>
<thead>
<tr>
<th>Group 1 vs. group 2</th>
<th>0.88</th>
<th>Group 1 vs. group 3</th>
<th>0.02</th>
<th>Group 1 vs. group 4</th>
<th>0.67</th>
<th>Group 2 vs. group 3</th>
<th>0.003</th>
<th>Group 2 vs. group 4</th>
<th>&lt;0.001</th>
<th>Group 3 vs. group 4</th>
<th>0.03</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>3 year overall survival &amp; 95% confidence intervals</th>
<th>5 year overall survival &amp; 95% confidence intervals</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989 – 1998, age &lt; 35 at dx (grp 1)</td>
<td>18</td>
<td>22.2 (6.9, 42.9)</td>
<td>16.7 (4.1, 36.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>1989 – 1998, age ≥ 35 at dx (grp 2)</td>
<td>604</td>
<td>31.0 (27.3, 34.7)</td>
<td>15.2 (12.5, 18.2)</td>
<td></td>
</tr>
<tr>
<td>1999 – 2008, age &lt; 35 at dx (grp 3)</td>
<td>19</td>
<td>77.2 (49.7, 90.8)</td>
<td>36.0 (12.1, 61.0)</td>
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<tr>
<td>1999 – 2008, age ≥ 35 at dx (grp 4)</td>
<td>888</td>
<td>37.3 (34.0, 40.7)</td>
<td>21.9 (18.8, 25.2)</td>
<td></td>
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</tbody>
</table>