Bridging the Age Gap
Treatment Variation and Outcomes in Older Women with Breast Cancer

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NABCOP Audit 2018; Treatment Omission Related to Age
Rate of surgery with/without case mix adjustment by NHS Trust in 2 UK regions

Adjustment for age, deprivation quintile, method of presentation, grade, stage, nodal status and co-morbidity
Decision Making for Older Women

61% favour PET, 26 equal and 12% surgery

Some scenarios gave an equal 3 way split in decision

Precision Guess Work!
Cochrane Review of Surgery plus Adjuvant Tamoxifen versus Tamoxifen Only

### 2.1 Survival - overall

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Surgery Events</th>
<th>Total</th>
<th>PET Events</th>
<th>Total</th>
<th>O-E</th>
<th>Variance</th>
<th>Weight</th>
<th>Peto Odds Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
<th>Peto Odds Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>158</td>
<td>225</td>
<td>187</td>
<td>230</td>
<td>-21.71</td>
<td>85.27</td>
<td>55.4%</td>
<td>0.78 [0.63, 0.96]</td>
<td></td>
</tr>
<tr>
<td>GRETA</td>
<td>130</td>
<td>239</td>
<td>144</td>
<td>235</td>
<td>-1.29</td>
<td>65.19</td>
<td>42.4%</td>
<td>0.98 [0.77, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Nottingham 2</td>
<td>8</td>
<td>53</td>
<td>14</td>
<td>94</td>
<td>-0.75</td>
<td>3.4</td>
<td>2.2%</td>
<td>0.80 [0.28, 2.32]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>517</strong></td>
<td><strong>559</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.86 [0.73, 1.00]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 297, 345

Heterogeneity: Chi² = 2.05, df = 2 (P = 0.36); I² = 3%

Test for overall effect: Z = 1.91 (P = 0.06)

### 2.2 Local disease control

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Surgery Events</th>
<th>Total</th>
<th>PET Events</th>
<th>Total</th>
<th>O-E</th>
<th>Variance</th>
<th>Weight</th>
<th>Peto Odds Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
<th>Peto Odds Ratio Exp[(O-E)/V], Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>36</td>
<td>225</td>
<td>115</td>
<td>230</td>
<td>-73.63</td>
<td>52.83</td>
<td>69.6%</td>
<td>0.25 [0.19, 0.32]</td>
<td></td>
</tr>
<tr>
<td>GRETA</td>
<td>27</td>
<td>239</td>
<td>95</td>
<td>235</td>
<td>-22.37</td>
<td>23.09</td>
<td>30.4%</td>
<td>0.38 [0.25, 0.57]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>464</strong></td>
<td><strong>465</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.28 [0.23, 0.35]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 63, 210

Heterogeneity: Chi² = 2.90, df = 1 (P = 0.09); I² = 66%

Test for overall effect: Z = 11.02 (P < 0.00001)

Hind, Wyld and Reed 2007
The flip side........US practice is surgery for all

- Recent US study of ~6000 nursing home residents in the USA with breast cancer undergoing surgery (Tang et al, JAMA Surgery, 2018)

  - The 30-day mortality rates were 8% after lumpectomy, 4% after mastectomy, and 2% after ALND....compared to 0.1% in the UK for all ages (and 0% out of ~3000 women over 70 in Age Gap)

  - The 1-year mortality rates were 41% after lumpectomy, 30% after mastectomy, and 29% after ALND.

  - Among 1-year survivors, the functional decline rate was 56% to 60%. The mean MDS-ADL score increased (signifying greater dependency) by 3 points for lumpectomy, 4 points for mastectomy, and 5 points for ALND.
The Patients Voice: Surgical Fears

- Fear of losing independence: 3 strongly disagree, 10 disagree, 9 neutral, 5 agree, 5 strongly agree
- Worried unable to carry on as normal: 2 strongly disagree, 6 disagree, 8 neutral, 10 agree, 1 strongly agree
- Worried about losing their breast: 7 strongly disagree, 5 disagree, 6 neutral, 6 agree, 6 strongly agree
- Worried about hospitalisation: 7 strongly disagree, 6 disagree, 5 neutral, 6 agree, 5 strongly agree
Views on Primary Endocrine Therapy

- Worried about needing an op in future: 2 strongly disagree, 4 disagree, 6 neutral, 7 agree, 8 strongly agree
- Reassured life carries on as normal: 2 strongly disagree, 6 disagree, 7 neutral, 1 agree
- Already take tablets: 15 strongly disagree, 13 disagree, 12 neutral, 7 agree, 6 strongly agree
- Reassured by HCPs: 13 strongly disagree, 12 disagree, 4 neutral, 4 agree, 1 strongly agree
- Reassured that surgery still in reserve: 1 strongly disagree, 2 disagree, 2 neutral, 4 agree, 1 strongly agree
Priorities of Older Women Faced with Cancer

- I value my independence
- I have a good relationship with my friends and family
- I would rather stay strong and independent than be dependent on my loved ones
- I have strong support from my family and friends
- I have a positive outlook on life
- My ability to take part in my hobbies and activities is important to me
- The life I have lived so far has been fulfilling
- I have a reasonable quality of life
- I am financially secure
- I am happy with my social life
- Living longer to me is important
- My family and friends are my priority. I want to be around as long as possible, despite being in worse health
- I feel I am in good health
- I was worried treatment would interfere with my ability to carry on with my normal activities
- I am not afraid of death
- I have a lot of physical problems
The Key Question

- When is Primary Endocrine Therapy Appropriate?

- Is there an age/fitness/tumour biology composite score that will guide best practice?
The Age Gap Cohort Study

Recruited 3460 women over age 70 across 56 sites.

Recruitment complete and analysis underway
## Cohort Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>77</td>
<td>70-102</td>
</tr>
<tr>
<td>75-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85-90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Charlson Co-morbidity score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Range 3-17</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Activities of Daily Living</strong></td>
<td>1</td>
<td>1-20</td>
</tr>
<tr>
<td>1-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cognition Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal to severely impaired</td>
</tr>
<tr>
<td>Mild impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe impairment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surgery versus Primary Endocrine Therapy

ADL scores between surgery (orange) and PET (blue)

Age between surgery (orange) and PET (blue)

Charlson co-morbidity score between surgery (orange) and PET (blue)
Survival Outcomes: Surgery versus PET

- Mortality rate at 3.5 year median survival is 27% for women treated with PET versus 11% for surgery.

- The percentage of deaths due to BC is 19% for PET group versus 48% for surgery.

- Propensity score matching will be used to identify a matched cohort and compare mortality which will also help identify a fitness threshold for PET.
Cohort consented 3460

Eligible 3375

85 excluded due to metastatic disease, withdrawal of consent or other factors

Primary endocrine therapy: 505
Other non-surgical treatments: 54 (either no treatment or palliative RT)

Surgery patients 2816

Surgery per patient 2793
Surgery per breast 2851
2735 unilateral, 58 bilateral

Mastectomy 316
BCS 132
+ Axillary Clearance

Mastectomy & reconstruction 7
Oncoplastic BCS 11

Mastectomy 35
BCS 53
+ No axillary surgery

Mastectomy & reconstruction 0
Oncoplastic BCS 2

Mastectomy 707
BCS 1506
+ SLNB

Mastectomy & reconstruction 23
Oncoplastic BCS 59

Excluded due to inadequate surgical data 23

Treatment Allocations
Demographics

Age

P<0.01

Frailty Activities of Daily Living

P<0.01

Charlson Co Morbidity Score

P<0.01
## Late or Systemic Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Mastectomy only</th>
<th>Reconstruction</th>
<th>Wide local excision</th>
<th>Therapeutic mammoplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=947</td>
<td>n=34</td>
<td>n=1458</td>
<td>n=43</td>
</tr>
<tr>
<td>Wound Pain</td>
<td>26 (2.7%)</td>
<td>2 (5.9%)</td>
<td>24 (1.6%)</td>
<td>2 (4.7%)</td>
</tr>
<tr>
<td>Functional difficulty</td>
<td>25 (2.6%)</td>
<td>1 (2.9%)</td>
<td>14 (1%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>26 (2.7%)</td>
<td>0</td>
<td>15 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>4 (0.4%)</td>
<td>0</td>
<td>4 (0.3%)</td>
<td>1 (2.3%)</td>
</tr>
</tbody>
</table>

### Systemic complications

<table>
<thead>
<tr>
<th></th>
<th>Mastectomy only</th>
<th>Reconstruction</th>
<th>Wide local excision</th>
<th>Therapeutic mammoplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>18 (1.9%)</td>
<td>0</td>
<td>10 (0.7%)</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>2 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (0.4%)</td>
<td>0</td>
<td>5 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>DVT</td>
<td>3 (0.3%)</td>
<td>0</td>
<td>1 (0.07%)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.2%)</td>
<td>0</td>
<td>2 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>1 (0.07%)</td>
<td>0</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1 (0.1%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Mortality According to Dementia Category

Dementia moderate and severe: 60/146 patients died at 3.5 year FU (rate 41%). 73% of deaths due to non breast cancer causes, 22% due to breast cancer.

No, or mild dementia: 421/3310 died at median 3.5 year FU, (rate 13%). 41% of deaths due to breast cancer, 55% due to non breast cancer.
Impact of Dementia on Treatment Choice

64% of women with severe dementia had surgery

- Normal
- Mild
- Moderate
- Severe

Surgery
Primary endocrine therapy
Quality of Life Impact of Surgery or PET

• Age Gap has collected QoL data at baseline, 1.5, 6, 12, 18 and 24 months

• EORTC validated tools for generic (C30), breast cancer specific (BR23) and elderly specific (ELD14) at all time points

• Data therefore adjusted for baseline variance and propensity score matched to adjust for fitness variation
Propensity Matching

- Surgical and PET patients assigned propensity score
- 1:1 matching
  - Age
  - Co-morbidities
  - Frailty (Activities of Daily Living Score (ADL))
  - Pre-operative tumour size, grade and nodal status
  - Oestrogen receptor +ve

• 169 patients matched

Matched cohort
- Surgery – too fit for PET
- PET – too frail for surgery
Comparative Analysis – Global QoL

Surgery - 11 points drop from baseline Vs 24 months (p<0.0001)

PET - 4 points drop from baseline Vs 24 months (p = 0.2)
EORTC-QLQ-C30 - Pain

PET – stable scores

Surgery – 14 points increase BS Vs 24 months (p < 0.0001)

EORTC-QLQ-C30 - Fatigue

PET – 8 points increase BS Vs 24 months (p = 0.7)

Surgery – 15 point increase BS Vs 24 months (p < 0.0001)
Baseline 6 weeks 6 months 12 months 18 months 24 months

**EORTC-QLQ-BR23 – Breast Symptoms**
- Surgery

**EORTC-QLQ-BR23 – Arm Symptoms**
- Surgery – 8 point increase BS vs 24 months (p = 0.0028)
Mortality in the Matched Cohort at 2 Years

PET → 11
- Breast Cancer – 1
- Other – 5
- Unknown - 5

Surgery → 10
- Breast Cancer – 5
- Other - 5
Conclusions

• In older frailer women, PET may have minimal detrimental effect on survival.

• In fit older women surgery enhances survival and is well tolerated in women selected for it

• This may be at the expense of Quality of Life in women of borderline fitness

• For this borderline group, a decision support tool was developed and trialled as part of the project
Age Gap Cluster Randomised Trial

- 50% of existing cohort sites trained in use of the tools and given access
- 50% usual care

- Outcome: Quality of life, treatment allocation and measures of decision regret.

- Study just closed. Recruited 1330 of 1328 cases. Analysis ongoing
2 booklets and 2 brief decision aids (frequently asked questions) developed using rigorous methodology.
Primary Endocrine Therapy:

Outcomes by age and fitness cohort

Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival


BJS 2018
**Age Gap Decision Tool: Surgery vs PET**

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumour grade</th>
<th>Tumour size</th>
<th>Disease node positive?</th>
<th>Comorbidities</th>
<th>Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>2</td>
<td>15mm</td>
<td>No</td>
<td>None</td>
<td>ADL Stage 0</td>
</tr>
</tbody>
</table>

**Overall Survival At Two Years**

- **Surgery**: 84 out of 100 women are alive at 2 years with Surgery.
- **PET**: 81 out of 100 women are alive at 2 years with PET.
Conclusions

• The Age Gap study has shown that recruiting older women to trials can be very successful

• Should give us evidence based guidelines on who to offer PET or surgery to and who to offer chemotherapy to.

• Data will be used to validate/calibrate the online tool which will be made open access on the internet
Acknowledgements

The Team

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Dierdre Revell – North Trent Cancer Network
Tracy Green- North Trent Cancer Network

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• ALL of the older women who took part in this study
• Local principle investigators and research nurses at all 56 Age Gap Recruiting sites