Bridging the Age Gap in breast cancer: chemotherapy and quality of life

Alberto Costa / 2 March 2021

Interview with Lydia Wyld, Department of Oncology and Metabolism, University of Sheffield Medical School, UK.

Q. Surgery is in general more frightening in older people so the results of your study are very useful to guide physicians in clinical practice. Which is the key message of your paper?

A. The Age Gap study recruited nearly 3500 women over age 70 who were newly diagnosed with operable breast cancer. We wanted to collect very detailed data about their level of baseline fitness so we could understand treatment selection and age and health stratified outcomes. We had previously tried to recruit to randomised trials in this age group to look at both the surgery versus primary endocrine therapy (PET) question (ESTEEM Trial) or the use of adjuvant chemotherapy (ACTION Trial). Neither randomised trial was successful due to poor recruitment, which is often felt to be an issue in this age group. We therefore organised a prospective observational study, planning to adjust for bias by use of propensity score matching. The Age Gap study completed in 2018 and we have just reported on our findings. Of 2854 women with ER+ breast cancer 2354 (82%) had surgery and 500 (18%) had primary endocrine therapy. Women having PET were older and less fit than those having surgery. With median follow up of 52 months an unadjusted analysis of all cause mortality was lower in women having surgery (HR 0.27, 95% CI 0.23-0.33, P<0.001). Similarly for deaths due
to breast cancer, these were lower in the surgery group (HR: 0.41, CI: 0.29-0.58, P<0.001). However when we performed very specific propensity score matching for age, tumour characteristics and health status, whilst all cause mortality was still slightly better with surgery (denoting imperfect matching) (hazard ratio (HR)= 0.72, 95% CI: 0.53-0.98, P=0.04), breast cancer specific mortality was no longer significantly different (HR=0.74, 95% CI: 0.40-1.37, P=0.34).

We also looked in detail at chemotherapy outcomes in these women using the same methodology. Chemotherapy was given to 306/1100(27.8%) fit patients with high recurrence risk breast cancer. Unmatched comparison of chemotherapy versus no chemotherapy demonstrated reduced metastatic recurrence risk in high-risk patients (HR: 0.36, 95% CI 0.19-0.68) and in 541 propensity score matched patients (adjusted HR 0.43 [95% CI 0.20-0.92]) but no benefit to overall survival or breast cancer-specific survival in either group. Unplanned subgroup analysis found that chemotherapy improved overall and breast cancer specific survival in women with oestrogen receptor (ER)-negative cancer (OS: HR 0.20, 95% CI 0.08-0.49;BCSS: HR 0.12, 95% CI 0.03-0.44) (in press, British Journal Cancer).

In both of these analyses we also looked at the quality of life impacts of surgery or chemotherapy. In both analyses more aggressive treatment had negative impacts on quality of life but these changes were transient and largely resolved after 2 years of follow up (EJC in press for chemotherapy data and BJS for PET analysis).

We concluded that surgery should be advised for the majority of women over age 70 but in women over the age of 85-90, especially for those in poor health, consideration of PET may be appropriate. For the chemotherapy analysis we concluded that chemotherapy was associated with reduced risk of metastatic recurrence, but survival benefits were only seen in patients with ER-negative cancer. Quality-of-life impacts were significant but transient. This should be taken into account when discussing treatment options with older women.

**Q.** Not easy to enrol nearly 3,500 patients in a study. How long did it take and how many centres participate?

**A.** We were pleasantly surprised that our older women were very positive about taking part in this study. We started recruitment in 2013 and completed it in 2018 and recruited at 56 sites in the UK. The trial had been specially designed to be user friendly for older women. The study was observational with treatment as normal, but women were asked to complete quite a lot of questionnaires which took time to do. We allowed women to elect whether they wished to complete the quality of life questionnaires to keep the burden of participation as low as possible. We also permitted many of the follow up visits to be done by telephone and could post the questionnaires out. We also wanted to recruit women with dementia and designed the trial such that a proxy could consent on behalf of women who lacked capacity to consent for themselves. Overall the ratio of women screened to those recruited was about 50% which is very good. Retention rates were also excellent with very few women withdrawing. We did notice that we slightly over recruited the younger end of the over 70 age range and slightly under recruited at the older end but our oldest recruit was 102, so we are very pleased with what we achieved.

**Q.** Can you tell us more about the Age Gap online decision tool?

**A.** Part of the study was to develop an on-line decision support tool, which is now available online at https://agegap.shef.ac.uk/. The tool was carefully developed with input from older women to ensure it met their informational needs and was designed to meet their preferred options for data display and terminology. This tool permits age, cancer and fitness stratified outcome calculation for women who have been offered surgery or primary endocrine therapy or women who have had surgery and
are now facing a decision about whether to have chemotherapy or not. A screen shot from the tool is shown in figure 1.
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>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>3</td>
<td>15mm</td>
<td>No</td>
<td>Diabetes Mellitus (no complications)</td>
</tr>
</tbody>
</table>

Based on the details above, research suggests that the potential outcomes of surgery and Primary Endocrine Therapy (PET) are as described in the charts and diagrams below.

<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>87</td>
<td>3</td>
<td>15mm</td>
<td>No</td>
<td>Diabetes Mellitus (no complications)</td>
<td>ADL Stage 1</td>
</tr>
</tbody>
</table>

**Overall Survival At Two Years**

- Surgery
- PET

**Chance (%)**

- Survival
- Death due to other causes
- Death due to breast cancer

**Survival At Two Years**

57 out of 100 women are alive at 2 years with Surgery.

52 out of 100 women are alive at 2 years with PET.
The tool was embedded into the second half of the Age Gap project as a cluster randomised trial and we found that it modified treatment selection and improved patient knowledge (in press, BJS). We were surprised that use of the tool tended to make women more likely to choose a more conservative option, presumably when they saw that survival rates differed by only relatively small amounts.

The online tool was released for wider use about 12 months ago and has been accessed over 10 000 times in over 70 countries and we have had interest from groups in France and Canada to validate the tool for use in their own populations. We are currently developing the tool to add quality of life and adverse event data outputs alongside the survival outputs it already contains. The data from the Age Gap study will be used to develop age and health stratified outcome models for these metrics. We hope this will go live at the end of 2022.

Q. What were the key motivations for the study?

A. The main aim was to try and develop advisory thresholds for older women who might not benefit from aggressive primary treatment due to their age, frailty, comorbidity and disease biology, so we could minimise over and under treatment in this age group. Existing guidelines such as those by the International Society for Geriatric Oncology (SIOG) are rather imprecise. We therefore needed detailed health and fitness data at baseline so we could perform stratified analysis. We knew that there were some centres in the UK where very frail and unfit women were offered surgery which was unlikely to benefit them, and in other centres, relatively fit, older women were denied surgery and would undoubtedly develop progression within their expected lifetime. The Age Gap dataset has helped us to develop the online tool which can assist in this decision making process.

Another key aim was to explore these differences in rates of surgery versus primary endocrine therapy and differences in rates of chemotherapy across the UK which have long been a cause for concern. We analysed the data from the study and confirmed that rates do vary more than can be explained by case mix. We went on to study the reasons for this variation by conducting some qualitative research and a wider questionnaire study of UK breast professionals to explore the reasons for this variation. The questionnaire included a discrete choice instrument, which presents people with a set of clinical scenarios with 5 variables and looks at how these sway treatment choices. These studies clearly showed that clinicians have different thresholds for how they allocate women to treatments with age being a significant factor.

Q. The trial is exclusively a UK study. Do you expect its results to have an impact on other countries? Did you receive enquiries from other centres?

A. We only recruited in the UK as a key aim was to explore the differences in rates of surgery versus primary endocrine therapy and differences in rates of chemotherapy across the UK which have long been a cause for concern. We have had interest in the study from France, Canada, the Netherlands and the USA and are collaborating with the group from Leiden to compare our data with their own similar dataset (the CLIMB study) to see where practice and outcomes differ between the UK and the Netherlands. This analysis should be completed later in 2021.

Q. Was surgery mainly mastectomy or conservative procedures?

A. The surgical dispositions of women in the study have been published. Of 2854 surgical procedures 1138 (40%) had mastectomy compared to 1716 (60%) who had breast conservation. Increasing age, tumour size and nodal status were all significantly associated with receipt of mastectomy and this is likely to be linked to the lack of screening and reduced breast awareness in older women resulting in larger tumours with a higher risk of node positivity. Very few women had reconstruction in this over 70 age group with only 32/1138 (2.8%) having post mastectomy reconstruction in contrast to
published series in the UK in all ages where the rate is 20%. Outcomes were good, with no deaths directly attributable to surgery although the risk of adverse events was moderate. Excluding seromas (which we regard as inevitable after breast surgery) there were 761 complications after 551/2854 procedures. The vast majority were local complications and not classed as severe. Only 59/2854 procedures (2.1%) had systemic complications such as stroke, cardiorespiratory problems or DVT. Complications were more likely after major surgery (mastectomy or axillary clearance rather than BCS or SLNB). This suggests that for the majority of older women surgery is safe and well tolerated. However we also measured quality of life after surgery and found that it does have a negative impact on some domains of quality of life, in particular axillary clearance caused a 6 point reduction in the global health score of the EORTC QLQ C30 tool compared to SLNB and also greater arm symptoms. Similarly mastectomy had a greater negative impact than BCS. We found that in the early post operative period there was a decline of mean role function of 5.2 points for PET compared to 16 points for surgery. Pain scores increased by 1.8 for PET compared to 7.1 for S+ET and breast symptoms increased by 0.7 for PET compared to 12.7 for S+ET. The overall burden of illness increased by 4 in the PET group compared to 10.1 for S+ET. By 24 months many of these differences were largely back to baseline levels but with several domains treatment had a lasting negative impact out to 2 years. Changes were more notable when comparing major surgery (mastectomy or axillary clearance) with PET (Morgan et al, in press BJS).

We conclude therefore that surgery is generally safe and well tolerated but does have a largely transient negative impact on quality of life, and for the frailest older women may not be needed. Selection for treatment may be supported by use of the Age Gap decision tool.

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