AN OVERVIEW OF THE NOTTINGHAM RESEARCH PROGRAMME ON PRIMARY BREAST CANCER IN OLDER WOMEN

Ruth M Parks and Kowk-Leung Cheung

Nottingham Breast Cancer Research Centre, University of Nottingham, United kingdom

Correspondence:
Dr. Ruth M Parks
School of Medicine, University of Nottingham, Biodiscovery Institute
University Park, Nottingham, NG7 2RD
United Kingdom
Email: ruth.parks@nottingham.ac.uk

DOI:
10.38106/LMRJ.2021.3.3-01

Received: 20.09.2021
Accepted: 25. 09..2021
Published: 30. 09.2021

ABSTRACT

The incidence of breast cancer increases with age. Despite this, most research in this field is aimed at the younger patient. Preliminary studies have shown that older women with breast cancer have distinct biological features compared to their younger counterparts. In addition, the focus of treatment of older women may not simply be curative but may be a trade-off between risks of treatment and impact on independence and quality of life. The Nottingham research programme is a unique programme dedicated to primary breast cancer in older women. There are two arms of the research programme 1) determining the biological differences of breast cancer in this cohort 2) exploring the use of geriatric assessment to understand the complex needs and factors contributing to treatment decision making in this group of patients. The overall aim of the research programme is to optimise both the biological and geriatric assessment of older women with primary breast cancer, to provide personalised data at diagnosis, on likely survival and quality of life outcomes following breast cancer treatment. This article will outline why this research programme is important, what it has achieved so far and future aspirations.

Key Words: Primary breast cancer, older women, biology, biomarkers, geriatric assessment, personalised medicine

INTRODUCTION

Importance of Breast cancer in older women

Breast cancer is the most common cancer in women worldwide (1) and age is the biggest risk factor for development of breast cancer; risk increasing proportionally with age (2). In 2018, the number of new breast cancers diagnosed worldwide was approximately 2 million (3) with around 25% of cases in patients ≥70 years (4). Due to ageing of the world's population, it is expected that the number of older women living with breast cancer will double by 2040 to nearly 1 million cases in patients ≥70 worldwide per year (1, 5).

The ageing of the world's population is the result of the continued decline in fertility rates and increased life expectancy (6). This demographic change has resulted in increasing proportions of older persons. In 2019, approximately 9% of the global population were ≥65 years of age (7) and this is expected to double by 2050 (8). The crisis of our ageing population has been well documented (9, 10); the burden on health service resources in terms of financial and service provision will be unprecedented. Breast cancer in older women will have a significant impact on this.

Differences between breast cancer in older compared to younger women

Existing data suggests that the biology of breast cancer in older women is different compared to their younger counterparts (11) and this may impact treatment decision making, alongside conventional factors, patient preference and discussion with the multidisciplinary healthcare team. For example, ER-positivity of breast

cancer increases with increasing age (12), thereby making primary endocrine therapy (PET) a potential primary treatment option in older women. A number of other biomarkers have been identified outside of those routinely measured, which could potentially have predictive and prognostic significance in older women with primary breast cancer (13).
Furthermore, it is recognized that there are other factors which influence treatment decision making in older compared to younger women, such as impact of treatment on quality of life and preservation of independence (14, 15). Whilst younger women may consider curative intent the end goal of breast cancer treatment, older women may not be willing to tolerate the same level of invasive treatment if it means a reduction in their usual functioning, especially giving the slow growing nature of breast cancer in this age group.

Nottingham Breast Cancer Research Programme
The Nottingham team based in the United Kingdom has a dedicated research programme focused on primary operable breast cancer in older women. The centre describes a large consecutive series of older women with primary breast cancer, for whom long-term follow-up data is available (11, 16). There is also a younger cohort of primary breast cancer patients, available for comparative analysis (17). There are currently two arms of the research programme in older women, one focussing on profiling the unique biology of primary breast cancer in this series and the second arm, focussing on the application of geriatric assessment (GA).
Biology theme
The cohort consists of 1,758 women with early operable breast cancer aged ≥70 years. Long-term follow-up data (up to 37 years) and survival outcomes for the whole cohort has been collected and described (18) for all patients, where available. From the whole series, 813 patients underwent primary surgery. It has been possible to construct 575 tissue microarrays (TMAs) using the surgical excision (SE) samples and a panel of 25 biomarkers has been assessed in these SE TMAs (11). It has been possible to construct 693 TMAs from CNB samples from the overall cohort. A panel of 18 biomarkers has been measured in the CNB TMAs in patients who had ER-positive breast cancer (19).
Summary of significant findings to date
Cluster analysis in both the SE TMAs and CNB TMAs identified a novel biological cluster of disease, which is distinct from standard clusters seen in younger women (11, 19). The unique cluster, termed 'low ER luminal' had high expression of luminal cytokeratins, mucin (MUC)1 and HER3 compared to the other conventional clusters and had different BCSS compared to conventional clusters. Similar findings suggesting a differing biology (with differing clinical outcomes) according to age, have also been found in terms of histological type (20), as well as in HER2-positive (21) and TNBC (22) and in response to treatment (23). Both the work in the SE and CNB TMAs have identified potential biomarkers which may be of use in predicting response to therapy and overall survival in older women with primary breast cancer.
Geriatric assessment theme
A prospective pilot study implementing a cancer-specific GA in older patients with primary breast cancer is in progress and is currently being conducted in four centres internationally. Patient recruitment commenced in 2009 and invites women aged ≥70 years with early-stage operable primary breast cancer to participate. The aim is to examine the value of using a validated cancer-specific comprehensive geriatric assessment (CGA) (24) to assess older patients undergoing surgery versus non-operative treatment. The CGA is performed within 6-weeks and 6-months post-diagnosis, supplemented by using EORTC QLQ C-30 and BR23 as formal measures of QOL (25, 26).

Summary of significant findings to date
A pilot study performed in Nottingham specifically examined feasibility of implementation of GA in 47 older women (≥70 years) with early operable primary breast cancer (27). Decision of primary treatment followed consultation with the clinical team and was not guided by GA. GA determined that increasing age, greater

comorbidity, greater number of daily medications and slower timed up and go (a measure of physical function) were significantly related to non-surgical treatment. Quality of life remained stable at 6 months in all patients regardless of treatment. Average time to complete the GA was 32 minutes (range 15 – 65 minutes) and was conducted by a variety of trained research team members, who were not necessarily clinicians; this pilot study confirmed the feasibility of GA in a research setting.
The most recent findings of the study data from three UK centres, was presented at the International Society of Geriatric Oncology (SIOG) 2019 annual conference and reported results from 88 women who underwent surgery (28). Results were conflicting in that there was an improvement in some questions related to functional status and a decline in others, with no clear pattern and no relationship with intensity of surgery.

The study is currently ongoing and involves several centres across the UK and Hong Kong, with the aim of recruiting over 1000 patients.

Summary – future of the research programme

In the future we see the development of a tool to analyse an extensive panel of biomarkers for each individual older women with primary breast cancer, based on their core needle biopsy specimen. This would help to generate a predicted outcome for each potential treatment option they are considering.
Furthermore, development of a GA specific for primary breast cancer patients, which can be utilised alongside the above measures of biology either in the surgical clinic or before referral at the level of general practice in the community, will provide a detailed understanding of individual issues which must be considered in discussions between healthcare professionals and patient and their families. Clear guidance needs to be developed as to how to use information derived from GA further and how to standardise potential interventions.
Effective utilisation of the unique biology and geriatric needs of older women with primary breast cancer will result in optimal treatment and quality of life outcomes for these patients and will provide a truly personalised approach.

REFERENCES

1. World Health Organisation. International Agency for Research on Cancer. Available at: https://www.iarc.fr [Accessed: 24th June 2019]. 2019.
2. CRUK. Cancer Research UK. Breast cancer incidence (invasive) statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One [Accessed: 29th May 2020]. 2016.
3. American Institue for Cancer Research: World Cancer Reserach Fund. Breast cancer statistics. Available at: https://www.wcrf.org/dietandcancer/cancer-trends/breast-cancer-statistics [Accessed: 12th May 2021]. 2018.
4. American Institute for Cancer Research: World Cancer Research Fund. Breast cancer [online]. Available at: https://www.wcrf.org/dietandcancer/breast-cancer [Accessed: 12th May 2021]. 2018.
5. Macmillan Cancer Support publication: Breast cancer in older women. Key statistics. 2012.
6. (WHO) WHO. Population ageing. World Health Organization online. 2010.
7. UN. United Nations. World Population Prospects 2019 [online]. Available at: https://www.un.org/en/sections/issues-depth/population/index.html [Accessed: 19th May 2020]. 2019.
8. UN. United Nations, Department of Economics and Social Affairs, Population Division. World Population Prospects 2019: Data booklet (ST/ESA/SER.A/424). 2019.
9. United Nations. Economic and Social Affairs Publication: World Population Ageing. Highlights. 2017.
10. Office for National Statistics. How would you support our ageing population? Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/howwouldyousupportourageingpopulation/2019-06-24 [Accessed: 29th April 2020]. 2019.

11. Syed BM, Green AR, Paish EC, Soria D, Garibaldi J, Morgan L, et al. Biology of primary breast cancer in older women treated by surgery: with correlation with long-term clinical outcome and comparison with their younger counterparts. British Journal of Cancer. 2013;108(5):1042-51.
12. Cheung KL, Wong AWS, Parker H, Li VWY, Winterbottom L, Morgan DAL, et al. Pathological features of primary breast cancer in the elderly based on needle core biopsies—A large series from a single centre. Critical Reviews in Oncology/Hematology. 2008;67(3):263-7.
13. Parks RM, Alfarsi LH, Green AR, Cheung KL. Biology of primary breast cancer in older women beyond routine biomarkers. Breast Cancer. 2021;28(5):991-1001.
14. Howard P CK, Cox K. Decision making in older women with primary breast cancer: The trade-off of the risks and benefits of treatments. Future Oncol. 2019;15:02.
15. Penny Howard KC, Kwok-Leung Cheung. O2. Decision making in older women with primary breast cancer: The trade-off of the risks and benefits of treatment. Future Oncology. 2019;15(7s):14-5.
16. Syed BM, Al-Khyatt W, Johnston SJ, Wong DWM, Winterbottom L, Kennedy H, et al. Long-term clinical outcome of oestrogen receptor-positive operable primary breast cancer in older women: a large series from a single centre. British Journal of Cancer. 2011;104(9):1393-400.
17. Abd El-Rehim DM, Ball G, Pinder SE, Rakha E, Paish C, Robertson JFR, et al. High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. International Journal of Cancer. 2005;116(3):340-50.
18. Syed BM, Johnston SJ, Wong DWM, Green AR, Winterbottom L, Kennedy H, et al. Long-term (37 years) clinical outcome of older women with early operable primary breast cancer managed in a dedicated clinic. Annals of Oncology. 2012;23(6):1465-71.
19. Parks RM, Albanghali M, Syed BM, Green AR, Ellis IO, Cheung KL. Biology of Oestrogen-Receptor Positive Primary Breast Cancer in Older Women with Utilisation of Core Needle Biopsy Samples and Correlation with Clinical Outcome. Cancers (Basel). 2020;12(8).
20. Mathew J, Lee S, Syed BM, Morgan DAL, Ellis IO, Cheung KL. A study of ductal versus non-ductal invasive breast carcinomas in older women: long-term clinical outcome and comparison with their younger counterparts. Breast Cancer Research and Treatment. 2014;147(3):671-4.
21. Syed BM, Green AR, Ellis IO, Cheung KL. Human epidermal growth receptor-2 overexpressing early operable primary breast cancers in older (≥70 years) women: biology and clinical outcome in comparison with younger (<70 years) patients. Annals of Oncology. 2014;25(4):837-42.
22. Syed BM, Green AR, Nolan CC, Morgan DAL, Ellis IO, Cheung K-L. Biological Characteristics and Clinical Outcome of Triple Negative Primary Breast Cancer in Older Women – Comparison with Their Younger Counterparts. PLoS One. 2014;9(7):e100573.
23. Parks RM, Albanghali MA, Syed BM, Green AR, Ellis IO, Cheung KL. Patterns of biomarker expression in patients treated with primary endocrine therapy - a unique insight using core needle biopsy tissue microarray. Breast Cancer Res Treat. 2021;185(3):647-55.
24. Hurria A, Gupta S, Zauderer M, Zuckerman EL, Cohen HJ, Muss H, et al. Developing a cancer-specific geriatric assessment: a feasibility study. Cancer. 2005;104(9):1998-2005.
25. ZE Winters MA, G Rumpold, B Holzner, A Oberguggenburger, RA Vieira, S Hartnup et al. International phase 4 validation of the EORTC patientreported outcome measure (PROM) in breast reconstruction (BRR): Evaluating the psychometric properties and clinical effectiveness. 2016;25:66.
26. Z Winters MA, C Rutherford, B Holzner, G Rumpold, RA Da Costa Vieira, S Hartup et al. International validation of the european organisation for research and treatment of cancer QLQ-BRECON23 quality-of-life questionnaire for women undergoing breast reconstruction. 2018;44:867.
27. Parks RM, Hall L, Tang S-W, Howard P, Lakshmanan R, Winterbottom L, et al. The potential value of comprehensive geriatric assessment in evaluating older women with primary operable breast cancer undergoing surgery or non-operative treatment — A pilot study. Journal of Geriatric Oncology. 2015;6(1):46-51.
28. Parks R. Impact of breast cancer surgery on functional status and independence. Journal of Geriatric Oncology. 2019;10(6):S1.