**Highlights of the San Antonio Breast Cancer Symposium 2019: the challenge of tumour heterogeneity**

[CONFERENCE REPORT]

PART 1

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Abstract

The 42nd annual San Antonio Breast Cancer Symposium (SABCS) was convened in San Antonio Texas on December 10 – 14, 2019. More than 7000 clinicians and scientists from around the world participated in the symposium that featured presentations and keynote talks pertaining to epidemiology and biology, screening/prevention, loco-regional treatment together with systemic therapies for early and late stage disease. This two-part report highlights a selection of important studies presented at this premier breast cancer event with the first part focusing on stromal-epithelial interactions, long term outcomes of hormone replacement therapy, androgen receptor targeting, high risk MRI screening and whether breast surgery can be safely omitted in exceptional responders after neoadjuvant chemotherapy.

Keywords

Breast conserving surgery, stromal-epithelial, hormone replacement, MRI, partial breast irradiation, San Antonio

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Introduction

The annual SABCS uniquely combines the principles of multidisciplinary management with the basic science underlying pathobiological processes in breast cancer. The 42nd meeting was held at the Henry B Gonzales Convention Centre in downtown San Antonio, Texas on 10 – 14th December, 2019. The symposium delivers a range of presentations covering basic, translational and clinical sciences. Important trials that are potentially practice changing are often presented at SABCS and published concurrently or shortly thereafter. This is the first of a two-part report highlighting important presentations and focuses on topics relating to a) stromal-epithelial interactions b) long term outcomes of hormone replacement therapy and c) surgical management following neoadjuvant chemotherapy (NACT). Relevant background information is included where context appropriate.

Epidemiology/biology of breast cancer

In the first plenary lecture of the symposium Ellen Pure [University of Pennsylvania, Philadelphia, PA, USA] discussed the role of stromal-epithelial interactions in breast cancer and in particular the importance of stromal cells and matrix remodelling in regulation of the tumour microenvironment. Understanding the dynamics of tissue organization within tumours and mechanisms underlying remodeling can provide insight into how tumours develop resistance to various therapeutic agents. Tumour carcinoma cells recruit additional cell types from the surrounding stroma to promote growth and allow a permissive or pro-tumorigenic niche for both the primary tumour and cognate metastases [1]. Furthermore, the primary tumour can induce changes in distal target tissues such as the lung and bone marrow to influence disease progression. This occurs mechanistically through release of growth factors and other agents that enter the bloodstream and travel to distant tissues. Immune cells and adipocytes may have a key role in this conversation between primary tumour and distant metastases. It is now recognised that high mammographic density is a risk factor for breast cancer [2,3] and is a manifestation of a desmoplastic reaction induced in stromal tissues by carcinoma cells. These stromal elements provide mechanical support for tumours and constitute up to 90% of tumour bulk. This response is orchestrated by cancer-associated fibroblasts (CAF) which can influence many aspects of tumour cell behaviour and malignant progression through provision of biochemical and biomechanical signaling [4]. In particular, these cells can have immunosuppressive effects as part of multifaceted tumour promoting activities. Through processes linked to factors such as aging, obesity and smoking, quiescent fibroblasts can be re-programmed and transformed to activated fibroblasts that portend a worse prognosis. Nonetheless, activated fibroblasts are a heterogeneous group of cells and can be either tumour restraining or promote growth and stimulate cancer development. Different subsets of fibroblasts can be identified using specific cell markers. It was emphasized how therapeutic strategies should aim to promote a fibroblast restraining phenotype that typically has positive expression for smooth muscle antigen. Fibroblast activating protein (FAP) is a cell surface protein that influences epithelial-mesenchymal transition and is expressed in embryonic but not normal adult resting fibroblasts [5]. It is marker of a CAF that categorizes a pro-tumorigenic subpopulation. Targeting cancer-associated fibroblasts is technically challenging due to the complexity and context dependency of fibroblast function within tumours [6,7]. Interestingly, high levels of fibroblast fat expression are associated with a poor prognosis and a high fat diet is a risk factor for and likely contributes to breast cancer development through FAP mechanistically. Furthermore, fat negative fibroblasts cannot support mammary matrix development whilst fat positive cells are tumour-enabled and expression of fat is an early carcinogenic event. Dr Pure speculated that fat could be a target for anti-cancer therapy and further research into other cell types such as pre-adipocytes and adipose associated stromal cells is warranted.

Adoptive cell therapy using an FAP construct is currently being explored (FAP-CAR T cells). FAP in conjunction with a subset of activated fibroblasts promote tumour growth and targeting of molecular pathways that are dependent on cancer-associated fibroblasts is a potentially promising approach for maintenance of fibroblasts in a quiescent state. Deletion of functional FAP delays tumour progression independent of immune status and there is likely a ‘stromagenic switch’ that might be regulated for therapeutic benefit. Activation of this switch through pathways involving TGF beta and platelet-derived growth factor will induce a pre/pro-metastasis milieu; in contrast to carcinoma cells, the stroma is more genetically stable and less likely to develop drug resistance. Furthermore, FAP approaches may act synergistically with other targeted therapies, including immune modulation with minimal toxicities.

Rowan Cheblowski [UCLA Medical Center, Los Angeles, CA, USA] presented further data on the long-term influence of oestrogen combined with progestin compared with oestrogen alone on the incidence of breast cancer. Two Women’s Health Initiative randomized trials have evaluated conjugated equine oestrogen (CEE) alone or combined with medroxyprogesterone acetate (MPA) in postmenopausal women aged 50 - 79 years with or without a uterus [8,9]. Both of these trials recruited during the period 1993 - 1998 from 40 centres across the United States. Those women with an intact uterus were randomised to either CEE (0.625mg/day) plus MPA (2.5mg/day) (n=8506) or placebo (n=8102) whilst hysterectomised women were randomly allocated to either CEE (0.625mg/day) alone (n=5310) or placebo (n=5429). Follow-up for these two trials was 5.6 years and 7.2 years respectively and the primary endpoint was time-specific invasive breast cancer incidence. Study medication was discontinued at the time of trial publication (2002 and 2004). The incidence of breast cancer was specifically examined during the post-intervention period. For those women in receipt of CEE alone, the cumulative follow-up period was 16.1 years. In comparison with placebo, there was a 27% reduction in likelihood of being diagnosed with breast cancer and a 44% decrease in mortality from the disease. By contrast, for those women in receipt of CEE plus MPA, the cumulative follow-up period was 18.3 years. In comparison with placebo, there was a 29% increase in chance of being diagnosed with breast cancer together with an increased mortality from the disease (although this was not statistically significant). These trial results are counter-intuitive and have revealed opposite effects of CEE alone and CEE plus MPA on mortality that are long-term and persist for many years, even decades, after cessation of therapy. Notably, oestrogen alone decreases but when combined with progestin increases breast cancer incidence through patho-physiological mechanisms that remain elusive. There are potential implications for chemoprevention and improvements in all-cause mortality.

There has been resurgent interest in the androgen receptor (AR) as a therapeutic target in breast cancer patients. Amongst oestrogen receptor (ER) positive patients, AR is a predictor of survival and various pre-clinical models are under development for clinical prediction of androgen sensitivity. Androgen inhibits proliferation of ER positive breast cancer cells and E2-mediated regulation of cell cycle genes. Elgene Lim [Garvan Institute of Medical Research, University of New South Wales, Sidney] discussed how strategies that enhance AR signaling by agonist effects will modify chromatin binding on the ER and demonstrably inhibit E2-driven growth of cell lines in vitro. Experiments with xenograft tumor models have shown more prominent *cell inhibition* with CDK 4/6 inhibitors in AR positive compared with AR negative tumors. The AR is the ‘first point of call’ and a promising prevalent target in hormone receptor positive disease.

Breast cancer screening

In 2007, the American Cancer Society (ACS) issued guidelines for breast screening with magnetic resonance imaging (MRI) as an adjunct to mammography. In particular, the ACS recommended MRI screening for patients with a BRCA-1 or BRCA-2 gene mutation, untested first-degree relatives of BRCA mutation carriers, women with a lifetime breast cancer risk of at least 20% (based on validated risk-assessment models) and women in receipt of prior mantle chest irradiation between the ages of 10 and 30 years. However, the benefit of MRI as an additional screening modality to mammography alone has never been assessed in a randomised setting [10]. Maria Tilanus-Linthorst [Erasmus Medical Centre, Rotterdam, Netherlands] presented results of a Dutch multicenter randomized controlled trial that recruited women with a cumulative lifetime risk for breast cancer of 20 – 50%. In this trial, women were randomised to yearly screening with mammography plus clinical breast examination (CBE) versus annual MRI together with biennial CBE plus mammography. Women with BRCA-1, BRCA-2 or p53 mutations were excluded from the study, as this group were already receiving MRI as an adjunct to mammography in the Netherlands. A total of 1355 women were randomised and at 7 years median follow up, there were 40 cancers (both invasive and non-invasive disease) detected in the MRI group compared with just 15 cancers in the control group (P<0.002). Moreover, cancers were smaller in the MRI group (9mm versus 17mm; p=0.01) with proportionately more node positive cases in the mammogram group (63% versus 17%). Although screening with mammography plus MRI clearly increases breast cancer detection rates when compared to screening mammography alone, the impact on rates of mortality are not known. Nonetheless, use of MRI can potentially lead to a reduction in use of adjuvant therapies with corresponding cost savings.

Surgical management of breast cancer

When primary systemic therapy has eliminated any residual disease it might be argued that surgical excision of the tumour bed is redundant and confined to confirmation of pCR. This prompts the question of whether any tumour residuum can be identified without surgery using methods with a high negative predictive value (NPV). This might involve sampling of the tumour bed in exceptional responders for whom there is no clinical nor radiological evidence of residual disease. Percutaneous tumour bed biopsies can be performed under ultrasound-guidance with greater accuracy and performance parameters are likely to be influenced by size of the needle (standard or large gauge) and number of passes (Figure 1). A principle impediment to elimination of surgery after primary systemic therapy is the intrinsic limitations of standard and functional breast imaging. No current modality of imaging can predict residual disease with sufficient accuracy based on a sensitivity of >90% and a false negative rate (FNR) of ≤10%. It is possible to integrate percutaneous needle biopsy of the breast tumour bed and axillary nodes in ways that complement imaging and more accurately predict residual disease. Pre-surgery biopsy of the tumour bed with combined fine-needle aspiration cytology and large volume, vacuum-assisted biopsy (VACB) under image–guidance can reliably identify breast pCR with an accuracy of 98%, FNR of 5% and NPV of 95% [11] (Figure 2). This in turn may offer the opportunity of selectively eliminating breast and axillary surgery following NACT. Previous attempts to determine pCR pre-operatively with non-image directed core biopsy and random sampling of the tumour bed were associated with high rates of local recurrence. Several ongoing and upcoming trials are evaluating the safety of eliminating breast (and axillary) surgery following chemotherapy in phenotype appropriate cases – namely TNBC and HER2 positive. These studies are likely to initially be confined to T1-2N0 tumours at presentation with demonstration of a complete or partial/near complete radiological response on imaging. Percutaneous biopsy of the tumour bed can be carried out with either large gauge (VACB) or standard core biopsy. Absence of any residual disease on imaging or tumour bed biopsy would permit omission of breast surgery and possibly breast irradiation (i.e. no loco-regional treatment) whilst any evidence of residual disease would be an indication for standard therapy with surgery and irradiation.

There are four key questions to consider in the context of response-adjusted surgical management [12]. Firstly, what are the *performance* characteristics of diagnostic tools used to predict pCR post-chemotherapy? Secondly, what is the least morbid method to confirm or exclude residual disease in the breast and axillary nodes? Thirdly, what are the consequences in terms of clinical outcomesif any minimal residual disease is missed and a ‘watch and wait’ policy is adopted? Finally, how should clinical trials be designed and conducted in order to provide robust evidence to support changes in clinical practice? There were several presentations at SABCS2019 that addressed these questions and results were sobering.

Marios Tsoulis [Royal Marsden Hospital, London] reported on a multi-institutional pooled analysis of patient level data for image-guided tumour bed biopsy post-NACT. A total of 166 patients were included with a mean tumour size pre-NACT of 33.5mm and 10mm after chemotherapy. All tumours without residual calcification or residual mass had marker clip insertion and the overall pCR rate was 51%. Tumour bed biopsy was undertaken in the majority of cases (86%) with VACB and ultrasound (78%) or stereotactic (14%) guidance. The mean needle gauge was 10 (range 7 – 14) and number of passes 6 (range 2 – 18). This study reported an overall FNR of 18.7% that was lowest for hormone receptor positive/HER2 negative (10%) and TNBC (11.6%) and highest for hormone receptor positive/HER2 positive tumours (33.3%). The NPV was 84.3 (95% CI 76.7 – 91.8). A ‘planned’ subgroup analysis that was confined to patients (n = 76) with invasive ductal carcinoma, a tumour residuum ≤2mm and retrieval of at least 6 cores found a FNR of 3.2% (95% CI 0 – 8.8) and NPV 97.4% (95% CI 84.6 – 99.6). However, this was a retrospective study that precludes any formal ‘planned’ analysis. Despite this promising pooled study, other data presented from three individual studies do not support breast conservation therapy after NACT without surgery.

The first of these negative studies was the RESPONDER trial presented by Joerg Heil [University Hospital, Heidelberg, Germany]. This trial evaluated 452 patients with a range of tumour types (TNBC (33%), HER2 positive (34%) and hormone receptor positive/HER2 negative (33%)) and partial or complete response to NACT. The final analysis was performed on 398 patients (54 exclusions). All patients underwent image-guided VACB with a broad range of larger gauge needle sizes (10G = 31%; 9G = 6%; 8G = 50% 7G = 13%) and a mean number of 7 passes. Patients proceeded to breast surgery after NACT if tumour cells were present in the biopsy material or there was a sampling error (10% cases had a non-representative biopsy pathologically). Patients without evidence of tumour cells on needle biopsy received breast irradiation only as definitive local treatment to the breast. The overall FNR was 17.8% (95% CI 12.8 – 23.7) and residual tumour was missed in 37 out of 208 women. About half of these cases were considered to have minimal residual tumour (54.1%) and low residual invasive tumour content of <10% was recorded in three-quarters of patients with residual disease after NACT. Subgroup analysis on those biopsy cases performed with the largest needle size (7G) revealed a FNR of 0%, albeit with wide confidence intervals (95% CI 0 – 18.5)! Furthermore, when there was no evidence of residual disease in the breast either on imaging or tumour bed biopsy, the FNR was only 6.2%. It was concluded that up to half of these false negative cases were attributable to ‘avoidable causes’ and optimization of technique could yield an acceptable overall FNR for prediction of residual tumour in the future.

The NRG – BR005 phase II trial was designed to assess the accuracy of tumour bed biopsies in predicting pCR in patients with a complete or near complete imaging response post-NACT. In particular, the trial asked whether addition of tumour bed biopsies to clinical examination and tri-modality imaging [MMG, US, MRI] can identify patients for whom formal BCS can be safely omitted. The trial enrolled 105 patients with operable invasive ductal carcinoma [T1 – 3; Stage 1/IIIA] treated with NACT after insertion of a marker clip at the start of chemotherapy. A total of 98 patients were eligible for analysis and there was an *a priori* stipulated NPV ≥90%. Results of this study were reported by Mark Basik [Segal Cancer Centre, Jewish General Hospital, Montreal, Canada] on behalf of NRG and are shown in Table 2. The overall sensitivity for detection of residual disease with VACB was 50% (95% CI 22.9 – 67.1) and NPV 77.5% (95% CI 76.7 – 91.8). Sensitivity was dependent on tumour type and highest for HER2 positive (60.0%) and lowest for TNBC (36.4%). Hence the addition of tumour bed biopsy to tri-modality imaging failed to achieve a NPV of at least 90% and managed to identify only 50% of patients with residual disease at the time of surgery. Similar concerns about non-surgical methods for detection of pCR after NACT were expressed by Marie-Jeanne Vrancken Peeters [Netherlands Cancer Institute, Amsterdam, Netherlands] who was chief investigator for the Dutch MICRA(Minimal Invasive Complete Response Assessment) trial. This evaluated a combination of MRI and tumour bed sampling with standard core needle biopsy for prediction of response to NACT. All 167 patients recruited into the trial underwent MRI prior to starting chemotherapy. The majority of patients (n = 135) had a complete radiological response (rCR) with the remainder a partial response (n = 32). There was poor correlation between rCR and pCR – only 80 patients with rCR were found to have a corresponding pCR (59%). Therefore post-treatment tumour bed biopsy (14-gauge needle) missed residual tumour in more than one-third of patients (37%) with a FNR of 45% for cases with rCR on MRI. Hence neither standard core biopsy nor MRI was found to be sufficiently accurate to predict residual disease and the trial was closed prematurely. There was general consensus on importance of recognizing residual disease in order to offer further systemic treatment such as capecitabine or immunotherapy. With limited radio-pathological correlation, there should be a cautious approach to abandoning comprehensive pathological assessment of the tumour bed after NACT (scattered foci of tumour may only be evident on immunohistochemistry).

Collective results of these studies indicate that currently it is inappropriate to abandon surgical excision of the tumour bed following NACT. The combined use of imaging and tumour bed biopsies cannot reliably identify partial responders and risks missing between one-third and half of cases with residual disease. Nonetheless, refinements in patient selection and methods for tumour bed biopsy may yet improve key performance parameters (NPV, FNR) to within acceptable values.

Partial breast irradiation

Icro Meattini [University of Florence, Italy] presented 10-year follow up results of the phase III randomized trial of accelerated partial breast (APBI) (30Gy to tumor bed in 5 daily fractions) or whole breast irradiation (WBI) (50Gy in 25 fractions) following breast conserving surgery (BCS) for early stage breast cancer patients (Figure 3). A total of 520 stage I and II breast cancer patients aged >40 years with tumours ≤25mm were recruited between 2005 and 2013 with a 1:1 allocation to either APBI (intensity modulated radiotherapy) or WBI. There were no significant differences between these groups at 10 years in terms of ipsilateral breast tumour recurrence (IBTR) and survival parameters (overall, breast cancer specific and distant metastasis-free) (Table 1). The rate of IBTR was higher for the APBI group (3.9%) than the WBI group (2.6%) with a hazard ratio of 1.57. However, confidence intervals were wide (0.56 – 4.41) and there was no statistically significant difference between the two groups (p=0.39). Furthermore, both cosmetic scores and acute/late toxicity effects favored the APBI arm of the study. Based on these results, it was recommended that APBI should be more widely available and offered to post-menopausal women with hormone receptor positive and node negative pT1 breast cancer. Indeed, APBI is now arguably a standard of care and an alternative radiation schedule to WBI in low risk early stage breast cancer patients.

References

1. Barcellos-Hoff MH, Medina D. New highlights on stroma-epithelial interactions in breast cancer. Breast Cancer Res 2005; 7(1): 33 - 36
2. Rice, M.S., Bertrand, K.A., VanderWeele, T.J. *et al.* Mammographic density and breast cancer risk: a mediation analysis. Breast Cancer Res 2016; 18**:**94 <https://doi.org/10.1186/s13058-016-0750-0>
3. Duffy SW, Morrish OWE, Allgood PC, et al. Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. Eur J Cancer 2018; 88: 48–56. doi:10.1016/j.ejca.2017.10.022
4. Sahai, E., Astsaturov, I., Cukierman, E. *et al.* A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer 2020; 20:174–186 <https://doi.org/10.1038/s41568-019-0238-1>
5. Park JE, Lenter MC, Zimmermann RN, et al. Fibroblast activation protein, a dual specificity serine protease expressed in reactive human tumor stromal fibroblasts. J Biol Chem 1999; 274: 36505 – 36512
6. Allyson Lieberman, Richard Barrett, Jaewon Kim, Kathy L et al. Deletion of calcineurin promotes a pro-tumorigenic fibroblast phenotype Cancer Res 2019;  DOI: 10.1158/0008-5472.CAN-19-0056
7. Santos AM, Jung J, Aziz N, et al. Targeting fibroblast activation protein inhibits tumor stromagenesis and growth in mice. J Clin Invest 2009; 119: 3613 - 3625
8. Manson JE, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349(6): 523–34.
9. Hsia J, et al. Conjugated equine estrogens and coronary heart disease: the Women’s Health Initiative. Arch Intern Med 2006; 166(3): 357–65.
10. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007; 57(2): 75 – 89 doi: 10.3322/canjclin.57.2.7
11. Keurer HM, Rauch GM, et al. A clinical feasibility trial for identification of exceptional responders in whom breast cancer surgery can be eliminated following neoadjuvant systemic therapy. Ann Surg 2018; 267(5): 946 – 956
12. Heil J, Keurer HM, Pfob A, et al. Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges. https://doi.org/10.1016/j.annonc.2019.10.012