Highlights of the San Antonio Breast Cancer Symposium 2020: part 1

John R Benson1,2, Dorin Dumitru*,3,4 & Ismail Jatoi5

1Cambridge Breast Unit, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ, UK
2School of Medicine, Anglia Ruskin University, Alan Cherry Dr, Chelmsford, CM1 1SQ, UK
3Breast Unit, Hull University Teaching Hospitals NHS Trust, Castle Road, Cottingham, HU16 5JQ, UK
4Hull York Medical School, Allam Medical Building, University of Hull, Hull, HU6 7RX, UK
5Division of Surgical Oncology, Dale H. Dorn Chair in Surgery, University of Texas Health Science Centre, San Antonio, TX 78229, USA

*Author for correspondence: drdumitrudorin@gmail.com

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The annual San Antonio Breast Cancer Symposium (SABCS) combines the principles of multidisciplinary management with the basic science underlying pathobiological processes in breast cancer. The 43rd meeting was a virtual event held 8–11 December 2020. The symposium reassuringly delivered the usual range of presentations covering basic, translational and clinical sciences. Important trials that are potentially practice changing are presented as late-breaking news and published concurrently or shortly thereafter. This is the first of a two-part report highlighting important presentations and focuses on topics relating to the COVID-19 pandemic, axillary surgery after neoadjuvant chemotherapy, omission of radiotherapy, mental well-being in younger breast cancer survivors, under-recognition of breast symptoms and pregnancy after breast cancer. Relevant background information is included where context appropriate.

Impact of COVID-19 pandemic on breast cancer management

A feature of this year’s symposium was inclusion of a special session devoted to how the COVID-19 pandemic has impacted breast cancer management both in the USA and around the globe. Deborah Doroshaw (Icahn School of Medicine at Mount Sinai, NY, USA) opened this session with a pertinent reference to ‘double jeopardy’ and how Black and Asian minority ethnic groups appear more susceptible to COVID-19 infection with a higher likelihood of death from the disease. She cited how almost three-quarters of COVID-19 patients in the state of Louisiana are Black despite constituting only 30% of the local population. Although there is evidence that ethnic groups are at increased risk for a range of comorbidities and many have lower socioeconomic status, there are conflicting data on the relationship between race and COVID-19 risk [1]. Doroshaw and colleagues examined disruption of cancer care in a combined retrospective (December 2019–March 2020) and prospective (March–June 2020) study. They looked at a variety of cancers, including breast and genitourinary malignancy with breakdown according to ethnicity. There was a reduction of consultations across all specialties of 46% with more than half of cancer patients (52%) having fewer in-person visits, and this was more pronounced for breast cancer patients. Of note, Black and Hispanic patients were less likely to demonstrate an increased number of telephone ‘visits,’ and Hispanic patients had more pandemic-related changes in routine cancer care. It was surmised that these disparities in impact of the COVID-19 pandemic among ethnic minorities were likely related to increased vulnerability as a group, being frontline workers in hospitals and living in multigenerational homes where social distancing is often impractical. There may also be some pervasive geopolitical factors including institutional racism. Further research is needed with development of supportive educational programs that are nonjudgmental and ensure that individuals are able to participate in telehealth and are receptive to these alternative modes of care. Annie Tang (Permanente Medical Group Breast Research Collaborative, CA, USA) reported how a large, integrated healthcare delivery system coped with managing breast cancer patients during COVID-19 with attention to stage at diagnosis and treatment plans. This double cohort study compared breast practice for the shelter-in-place period (March–May 2020) with a similar
period in 2019, with each group matched for age, race and comorbidities. Key changes attributable to COVID-19 were cessation of screening and outreach mammography and limitations on nonessential elective surgery that did not include cancer cases and resumed once rates of infection were stable. There was a 64% reduction in the number of newly diagnosed breast cancer cases between these time periods (700 vs 250) with an estimated 450 cases of undiagnosed breast cancer between March and May 2020. There were notable changes in characteristics of cancers diagnosed during the pandemic and included increased proportions of symptomatic cancers (37 vs 78%; p < 0.001) and T1c or larger tumors (64 vs 78%), a trend toward more node-positive tumors (18 vs 24%), increase in stage IV disease (2 vs 7%), a reduction in proportion of hormone-receptor-positive–HER2-negative tumors (76 vs 66%) and an increased proportion of triple negative breast cancer. Hence, patients presented during the pandemic with more advanced and biologically aggressive tumors, and it is important to consider the impact of delays in screening and treatment together with these stage shifts on morbidity and mortality. Surprisingly, the time to surgery and start of neoadjuvant chemotherapy (NACT) decreased with evidence of a higher proportion of patients receiving NACT in the COVID-19 cohort (15 vs 10%). Greater availability of operating capacity for cancer patients was consequent to widespread cancellation of noncancer elective surgical cases. Ko Un Park (The Ohio State University James Comprehensive Cancer Center) undertook a provider survey of neoadjuvant endocrine therapy (NET) use before and after the COVID-19 pandemic. Interestingly, almost half of respondents (46%) reported rarely prescribing NET before the pandemic and the majority (91%) were supportive of delaying breast cancer surgery in favor of NET due to restrictions imposed on operative capacity by COVID-19. Nonetheless, most planned to use NET for as short a period as possible and aimed to undertake primary surgery whenever circumstances permitted. It was noted that patients should not receive bridging endocrine therapy for more than 3–6 months, and measurement of Ki-67 levels after 3 months of treatment might help guide management (switch to surgery if Ki-67 levels remain high). There is generally a low risk of disease progression in a patient population with smaller, non-high-grade, node-negative tumors that are hormone receptor positive and HER2 negative.

Hence the COVID-19 pandemic has mandated changes in models of care delivery and clinical protocols with incorporation of virtual platforms for teledermatology. Vulnerable individuals are especially likely to have experienced disruptions in cancer care and suffer the emotional and cognitive consequences of enforced social isolation. Clearly there have been significant changes in the delivery of healthcare during the COVID-19 pandemic, but the effects of these changes on breast cancer mortality, if any, will not be apparent for several more years.

**Locoregional management of breast cancer**

Surgical techniques for management of early-stage breast cancer have become progressively less extensive both in terms of parenchymal and nodal resection of breast and axillary tissues [2]. More effective systemic therapies that target both the primary tumor and residual disease burden after neoadjuvant approaches have permitted deescalation of breast and axillary surgery. The surgical paradigm has shifted from maximum tolerated therapy toward minimum required therapy. However, in efforts to downstage breast tumors and nodal disease, it has become apparent that surgical challenges have inadvertently arisen due to poor correlation between assessment of radiological and pathological response to NACT. Histological evidence of metastasis within axillary nodes before starting NACT can be confirmed with percutaneous needle biopsy. Approximately one-third of biopsy-proven node-positive cases will have a complete pathological response (pCR) after NACT. Normalization of nodes on clinical and radiological examination after NACT justifies more limited axillary surgery initially with complete axillary lymph node dissection (ALND) representing overtreatment for many patients. However, it is imperative to ensure that this biopsy-proven positive node along with any other nodes potentially containing residual viable tumor or fibrosis are removed at the time of definitive surgery if formal ALND is abandoned as part of a deescalation strategy in the context of NACT. Axillary pCR after NACT is more likely in phenotype appropriate tumors such as TNBC and HER2-positive disease [3]. Treatment response within axillary nodes can be determined using different approaches that combine low false-negative rates (FNR) with a high negative predictive value (NPV). These include standard sentinel lymph node (SLN) biopsy with dual tracer agents and harvesting of at least three nodes [4], marking the axillary lymph node with radioactive iodine (MARI) [5] and targeted axillary dissection (TAD) [6]. The latter two methods aim to mark the biopsied node and retrieve this at the time of axillary surgery and thereby minimize the FNR. The FNR for MARI and TAD are 7 and 2–4% with a corresponding NPV of 83 and 92–97%, respectively (Table 1) [5,6]. Janine Simons (Maastricht University, the Netherlands) proposed a further method for managing the axilla in biopsy-proven node-positive disease that is successfully downstaged clinically and radiologically with NACT. The Radioactive Iodine Seed Localization in the Axilla with the Sentinel Node (RISAS) trial involves
Table 1. Identification rates and predictive value for different axillary staging techniques.

<table>
<thead>
<tr>
<th>Method</th>
<th>Identification rate</th>
<th>False-negative rate</th>
<th>Negative predictive value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB</td>
<td>89%</td>
<td>17%</td>
<td>57–86%</td>
<td>[13]</td>
</tr>
<tr>
<td>MARI</td>
<td>97%</td>
<td>7%</td>
<td>83.3%</td>
<td>[5]</td>
</tr>
<tr>
<td>TAD</td>
<td>100%</td>
<td>2-4%</td>
<td>92–97%</td>
<td>[6]</td>
</tr>
<tr>
<td>RISAS</td>
<td>98%</td>
<td>3.5%</td>
<td>93.6%</td>
<td></td>
</tr>
</tbody>
</table>

MARI: Marking the axilla with radioactive iodine seed; RISAS: Radioactive iodine seed localization in the axilla with the sentinel node; SLNB: Sentinel lymph node biopsy; TAD: Targeted axillary dissection.

Placement of a radioactive seed in a pathologically confirmed positive axillary node pre-NACT. Patients then undergo SLN biopsy after NACT with removal of the radioactive seed and completion ALND to calculate FNR. In this study of 227 patients, SLN was successfully identified in 98% of cases with an axillary pCR of 35.4%. The method was deemed noninferior to targeted ALND if four or fewer false-negative results were found among 144 ypN⁺ cases; there were five false-negative cases in this group of patients, representing an FNR of 3.47% and NPV of 93.6%. The investigators considered RISAS and targeted ALND to be the two most suitable methods for staging the axilla after NACT in node positive patients. Dual tracer localization is recommended, and there is no maximum number of nodes that can be clipped, but usually four or fewer suspicious nodes are discernable. The radioactive seed (iodine -125) is relatively inexpensive (Emil Rutgers, personal communication), but no formal cost–benefit analysis has been undertaken. Placement of the seed can be time-consuming, but this can be undertaken at the time of initial node biopsy rather than being scheduled immediately preoperatively (which may be impractical in a busy breast service) [7]. Limited data are currently available on regional recurrence rates following omission of formal ALND in node-positive patients with a subsequent negative SLN biopsy after NACT. However, these appear to be low, with one report of no recurrences at a median follow up of 60 months among 70 node-positive patients in this setting [8].

Ian Kunkler (University of Edinburgh, Scotland) presented updated results of the PRIME II trial evaluating omission of radiotherapy after breast-conserving surgery in women aged 65 years and over with early-stage breast cancer (n = 1326). In this Phase III trial, patients with node-negative and hormone-receptor-positive (ER and/or PR) tumors underwent wide local excision with a radial margin clearance of ≥1 mm, and all received endocrine therapy. Patients were randomized to either whole breast irradiation (WBI) (n=658) or no WBI (n = 668), and groups were well balanced with few cases of either grade III tumors or lymphovascular invasion. An initial analysis at 5 years showed a reduction in the primary endpoint of ipsilateral breast tumor recurrence (IBTR) from breast irradiation (4.1 vs 1.3%) [9]. There were no significant differences in secondary endpoints of overall survival, distant metastases or new breast cancers. The updated analysis with a median follow up of 7.3 years continued to show a significantly higher rate of IBTR for patients not receiving radiation treatment to the breast (hazard ratio [HR]: 0.12; 95% CI: 0.05–0.31). The reduction in IBTR from 9.8 to 0.9% (p = 0.0008) was also accompanied by a decrease in regional recurrence from 2.3 to 0.5% (p = 0.014) but none of the other aforementioned secondary endpoints. Subgroup analysis according to ER status revealed a higher rate of IBTR for tumors with low compared with high ER expression (18 vs 9%, respectively). No data were supplied on adherence to medication, but endocrine therapy should not be omitted for ER-poor patients not receiving breast irradiation. There was comment during discussion of this presentation that the emotional impact of local recurrence and need for further treatments should not be underestimated. Therefore, both the potential benefits and risks of withholding WBI should be discussed with older patients with early-stage breast cancer who undergo breast-conserving surgery, and patient preferences should be the basis for clinical decisions. These results may have relevance to older patients with competing risks of death and limited projected 5-year survival but should be applied cautiously in healthier women with right-sided tumors. Genetic testing may help further clarify in which patients WBI can be safely omitted.

Psychosocial issues in breast cancer patients

Approximately 20% of breast cancer occurs in women aged younger than 50 years, with younger patients being psychologically more vulnerable and prone to depressive symptoms relating to diagnosis of breast cancer and intensity of associated treatments [10]. Patricia Ganz (UCLA Jonsson Cancer Center, CA, USA) and colleagues presented results of the Pathways to Wellness Study that explored two interventional programs among young breast cancer survivors without evidence of metastatic disease. The programs aimed to improve mental health and quality of
life and consisted of either mindful awareness practices (MAPS) with trained instructors or survivor education (SE) with patients supplied with printed information and slides. In this Phase III multiinstitutional study a total of 247 patients were randomly assigned 1:1 to an interventional group (MAPS = 85; SE = 81) or control (n = 81). Of note, about three-quarters of patients in each group were white, and all patients had a documented history of depression or anxiety-related symptoms as assessed by the validated Center for Epidemiological Studies Depression Scale. Compliance rates were high, with 87% of patients completing the questionnaire immediately postintervention and 83% at 6 months. There was a significant reduction in depressive symptoms postintervention with MAPS, and this was sustained out to 6-month follow-up (p < 0.01). For the other intervention (SE), reduction in depressive symptoms was only evident out to 3 months (p < 0.01). Both interventions led to a significant decrease in anxiety levels immediately afterward, but this was not maintained with further follow-up. MAPS was also noted to improve symptoms of fatigue, sleep disturbance and hot flushes, and this was evident from questionnaires completed at 6 months.

Reshma Jagsi gave a provocative presentation that began with a consideration of broader issues relating to physician behavior, underrecognition of symptoms, nonverbal communication and quality of trial data based on physician reporting. She suggested that some of these problems had been exacerbated with the COVID-19 pandemic and practices such as wearing face masks and virtual clinics. There was some evidence of racial disparities in attitudes of doctors, with some believing there are innate differences in pain thresholds with Blacks less likely to experience severe pain. It was implied there may be an element of unconscious bias with less effort made by doctors to ascertain the true nature of complaints among some ethnic minority groups. Jagsi reported results of a large multicenter study involving almost 10,000 patients from the Michigan Quality Assurance Radiotherapy program who had completed radiotherapy after surgery. Comparisons were made between physician reporting and patient self-report outcomes from questionnaires administered during radiotherapy. There were 37,725 paired observations (physician vs patient) relating to four main symptoms—pain, pruritis, edema and fatigue—with strict definitions for underrecognition of each symptom. The study aimed to determine how frequently physicians underrecognized at least one of these four symptoms. Compared with their white counterparts, symptom underrecognition was found to be more frequent among Black patients (odds ratio [OR]: 1.92; 95% CI: 1.65–2.23) and those other than Black or Asian (OR: 1.82; 95% CI: 1.24–2.66). Furthermore, symptom underrecognition was observed more often in patients <50 years (OR: 1.35; 95% CI: 1.15–1.58) and those aged 50–59 years (OR: 1.21; 95% CI: 1.06–1.39) compared with older patients aged 60–69 years (35 vs 21%). More than half of women with a substantial number of symptoms had at least one of these underrecognized. Jagsi described these results as ‘concerning’ and emphasized the need for further research in this area. She concluded that doctors should be more discerning when dealing with racial minorities and be cognizant that some ethnic groups may deliberately fail to divulge the full extent of their symptoms due to a belief that these revelations may not be acted upon.

There is currently an opioid epidemic in the USA with an estimated 10% of cancer-related surgical patients becoming persistent users of opioids, representing an increase of almost 50% (from ~7%) in the past 2–3 years [11]. Moreover, one-quarter of patients develop signs of a formal psychiatric disorder while receiving cancer treatment. Jacob Cogan (New York Presbyterian/Columbia University, NY, USA) presented interesting data exploring usage of opioids among breast cancer patients undergoing mastectomy and immediate breast reconstruction (IBR). The recorded number of prescription fills for opioids were used as an indirect measure of consumption and examined in the 12 months before surgery as well as perioperative (31 days before and 90 days after surgery) and postoperative periods. The study aimed to identify factors that may be associated with new persistent use, including age, insurance status, geographic region and adjuvant therapies. Patients with a documented history of mental health issues and prior substance abuse were excluded. Patients were identified from a healthcare claims database (2008–2017) with two groups of eligible patients analyzed—opioid-naive patients (n = 25,720) and sedative/hypnotic-drug-naive (n = 27,651). Among this group of women undergoing mastectomy and IBR, 13% of opioid-naive patients and 6% of sedative/hypnotic-naive patients became new persistent users. Interestingly, for those patients exposed to opioids for the first time in the postoperative period, this figure rose to 17.5%. The retrospective nature of this study and reliance on prescription fills for opioids to gauge actual consumption is a major limitation. Moreover, there is no account taken of additional surgery for complications or cosmetic correction. Nonetheless, the study involved a large number of patients sourced from a national database and results were considered generalizable. There is an urgent need to encourage safe and effective use of medications that is restricted to the period of surgical pain and anxiety/insomnia. These results may have relevance to requests for ‘big surgery’ whereby breast cancer
patients without hereditary susceptibility demand bilateral mastectomy and reconstruction for smaller unilateral tumors that are otherwise amenable to less intrusive forms of breast conserving surgery.

**Pregnancy after breast cancer**

Eva Blondeaux presented an informative meta-analysis of pregnancy after a breast cancer diagnosis that focused on both reproductive and disease outcomes. Women are increasingly deferring childbirth until a later age, and this has led to an increase in pregnancy-associated breast cancer. Moreover, breast cancer is the most common malignancy among women of reproductive age, with almost one-third of new breast cancers diagnosed in women aged <40 years. There are inconsistent data on the prognostic impact of pregnancy after breast cancer has been diagnosed and treated and whether this can impact on fetal health. Comprehensive oncofertility counseling is not universally available, and breast cancer survivors with a favorable prognosis should not inappropriately be discouraged from conceiving at a future point in time. In reality, concerns about adverse impact on prognosis for hormone receptor-positive tumors and issues of fetal health have dissuaded many women from attempting conception after previous breast cancer treatment. This meta-analysis included a total of 114,573 women with breast cancer among whom 7505 (6.5%) became pregnant after completion of treatment. This represents a 60% lower chance of conceiving than for the general population (relative risk: 0.4; CI: 0.32–0.49). Nonetheless, this meta-analysis provided reassuring data on the feasibility and safety of pregnancy in breast cancer survivors who have no significantly increased risk of congenital abnormalities (OR: 1.63; 95% CI: 0.89–2.98) or obstetric complications including spontaneous abortion and hemorrhage. In particular, these investigators found no evidence of any detrimental impact on longer term breast cancer outcomes and indeed reported improved overall survival (HR: 0.56; 95% CI: 0.46–0.67) and disease-free survival (HR: 0.73; 95% CI: 0.56–0.94) that were independent of any 'healthy mother effect'. There was a suggestion that women with hormone-receptor-negative disease had better outcomes from pregnancy after breast cancer treatment. These findings accord with a previously published multicenter case-control study involving 333 patients who become pregnant after a breast cancer diagnosis. These were matched to 874 nonpregnant breast cancer treatment. This meta-analysis included a total of 114,573 women with breast cancer among whom 7505 (6.5%) became pregnant after completion of treatment. This represents a 60% lower chance of conceiving than for the general population (relative risk: 0.4; CI: 0.32–0.49). Nonetheless, this meta-analysis provided reassuring data on the feasibility and safety of pregnancy in breast cancer survivors who have no significantly increased risk of congenital abnormalities (OR: 1.63; 95% CI: 0.89–2.98) or obstetric complications including spontaneous abortion and hemorrhage. In particular, these investigators found no evidence of any detrimental impact on longer term breast cancer outcomes and indeed reported improved overall survival (HR: 0.56; 95% CI: 0.46–0.67) and disease-free survival (HR: 0.73; 95% CI: 0.56–0.94) that were independent of any 'healthy mother effect'. There was a suggestion that women with hormone-receptor-negative disease had better outcomes from pregnancy after breast cancer treatment. These findings accord with a previously published multicenter case-control study involving 333 patients who become pregnant after a breast cancer diagnosis. These were matched to 874 nonpregnant breast cancer survivors with adjustments for time bias. No differences were found for disease-free survival (HR: 0.94; 95% CI: 0.70–1.26; p = 0.68) and overall survival (HR: 0.84; 95% CI: 0.60–1.18; p = 0.32) between pregnant and nonpregnant women with ER-positive disease at a median follow-up of 7.2 months. However, an overall survival advantage was noted for pregnant women with ER negative breast cancer (HR: 0.57; 95% CI: 0.36–0.90; p = 0.01) [12].

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