Review

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Surgical Highlights from the 40th San Antonio Breast Cancer Symposium: 5-9 December 2017, San Antonio, Texas

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ABSTRACT

This year San Antonio Breast Cancer Symposium (SABCS) celebrated its 40th anniversary. As in the past years, this year's conference was held in Henry B. Gonzalez Convention Centre, San Antonio, Texas, on 5-9 December 2017. The conference highlighted many different topic on breast cancer including basic science, translational research, local therapies, systemic therapies, survivorship, early clinical trials, and surgical topics. Even though SABCS evolved towards basic science and systemic therapy based manner in recent years, there were some important topics about local therapies and surgical approach. In this conference report, presentations and keynote talks about surgical field and local therapies will be summarised.

Keywords: Axilla, breast neoplasm, San Antonio, sentinel lymph nodes, survival

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Introduction

San Antonio Breast Cancer Symposium (SABCS), which is the largest breast cancer meeting in the world, was held in Henry B. Gonzalez Convention Center, San Antonio, Texas, on 5-9 December 2017. This was the 40th anniversary of SABCS. More than 7000 clinicians and scientists from over 90 different countries attended the symposium. The symposium topics ranges from genetic and immunologic studies to surgical fields. As we consider most of the recent ongoing studies about breast cancer are oncological and immunological studies, majority of the presentations and keynote talks were highlighted these topics. Besides important sessions and keynote talks, there were many crucial posters presented in the poster sessions. In this conference report, we want to highlight surgical issues and the presentations that are related directly with surgical practice change. To ensure the integrity and clarity, instead of highlighting day by day, this conference report will be presented under the main subheadings as High-Risk Lesions, Genetics, Breast and Axilla, Screening and Diagnosis, and Other.

High-Risk Lesions

In the first day of the congress, Amy Degnim (Professor of Surgery, Mayo Clinic, United States) placed the focus on clinical management of women with increased breast cancer risk based on histologic lesions. High-risk breast lesions were defined as atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH), and lobular carcinoma in-situ (LCIS).

There are 2 main questions to be answered in the management of high-risk breast lesions:

1) Should we excise the lesion after core biopsy?

2) How high is long-term breast cancer risk?

According to American College of Radiology guideline, concordance between radiology and pathology needs to be assessed when high-risk lesions were detected. American Society of Breast Surgeons recommendations for excision are if there is a concern that target lesion was missed, if histology demonstrates atypia in presence of a palpable or imaging mass lesion, and if there is a discordant finding. Dr. Degnim summarized the management of high-risk lesions as below:

ADH: Published data shows 13-31% upgrade rates to cancer with an average rate of 15-25%. The **National Comprehensive Cancer Network** (NCCN) guideline recommends excision of ADH. Only a small group of patients with low risk (no concordant mass, small

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lesion size, complete or near complete removal with biopsy) may not require further excision.

FEA: It is usually associated with calcification (>90%) and ADH (27-53%) (1). Published data shows 0-17% upgrade rates to cancer, average of 7%. Most recent studies show lower upgrade rates with an average of 5%. Two-thirds of the lesions upgrade to ductal carcinoma in-situ (DCIS). Besides, FEA can upgrade to another high-risk lesion (ALH or LCIS) by 36%. Excision depends on clinical context. Patients with low risk criteria including having a small lesion (<1cm) and/or without accompanying mass, and if over 90% of the lesion is removed by core biopsy, may be considered for observation.

ALH/LCIS: Recent studies show <10% upgrade rates. Upgrade rates for lobular neoplasia is 3-4%, pure ALH is 0-19% and 7-28% for LCIS. Dr. Degnim briefly stated that these lesions should be excised in the presence of an accompanying mass or radiological-pathological-clinical discordance with high-risk lesion.

The second part of her presentation was about how to predict who is at high risk. There are four categories of lifetime breast cancer risk: Average (≤15%), moderate (16-25%), high (25-50%), and very high (>50%). Lifetime risk is highly dependent on patient age and life expectancy. Long-term absolute invasive cancer risk per year for FEA is 0.5%, ADH and ALH is 1-2%, and LCIS is 2%. Management and follow-up should be individualized depending on annual absolute breast cancer risk, volume of the disease, life expectancy, and competing morbidities. Taking side effects into account prevention therapy (tamoxifen, raloxifene, anastrozole, exemestane) is advised if the patient has >1% per year breast cancer risk or has ADH or LCIS. Risk reduction mastectomy can achieve 90-95% risk reduction and should be considered if other high-risk factors exists (genetics, very high-risk family history, etc.).

Genetics

Dr. Garber highlighted factors for reconsideration of genetics evaluation and testing in her oral presentation on management of increased breast cancer risk based on high and moderate penetrance gene. She discussed the recent update by Kuchenbaecker KB et al. (2) about cumulative risk of breast cancer and ovarian cancer among patients with *BRCA1* and *BRCA2* mutation carriers. The cumulative risk of breast cancer by age 80 years was 72% (95% CI, 65%-79%) for *BRCA1* carriers and 69% (95% CI, 61%-77%) for *BRCA2* carriers. While the cumulative risks for *BRCA1* and *BRCA2* carriers to age 80 years were similar, the cumulative risks to age 50 years were higher for *BRCA1* carriers (p=0.03). The cumulative risk of contralateral breast cancer for *BRCA1* carries 20 years after the first breast cancer diagnosis was 40% (95% CI, 35%-45%). For *BRCA2* carriers, the cumulative risk of contralateral breast cancer at 20 years after the first breast cancer diagnosis was 26% (95%CI, 20%-33%). The ovarian cancer cumulative risk to age 80 years was 44% (95%CI, 36%-53%) for *BRCA1* carriers and 17% (95% CI, 11%-25%) for *BRCA2* carriers. Modified NCCN management guidelines for *BRCA1/2* mutation carriers recommends annual (biannual depending on patient) screening starting at the age of 25.

As multigene tests are becoming more popular, Dr. Garber outlined elevated breast cancer risk for women with moderate penetrance mutations in selected genes such as PALP2, CHECK2, and TAM/NBN. PALB2 and TAM/NBN have cumulative lifetime risk of 44% and 30% respectively. Depending on the pathogenic mutation, CHEK2 has a risk of up to 31.8% for breast cancer. Physicians also must be aware of other associated cancers like pancreas cancer, colon cancer, etc. These patients should be started annual examination at age 40 while the age should be 30 for starting screening for patients with PALB2.

Breast and Axilla

Dr. Morrow mainly focused on challenges in the surgical management of locoregional recurrence. Due to the changes in the management of axilla and breast in recent years, Dr. Morrow raised new questions about loco-regional recurrence, how to manage axilla in the setting of axillary dissection was not initially done and secondly whether repeat lumpectomy without radiotherapy (RT) is appropriate.

There are three issues about axilla:

1) Management of nodal recurrence after sentinel node biopsy (SNB).

2) Management of the axilla and nodal re-staging after breast or chest wall recurrence.

3) Significance of contralateral axillary metastases after local recurrence (LR).

First step of managing LR is excluding distant metastasis, as almost 50% of the LR accompanied by distant metastases. Isolated axillary recurrence occurs in <0.6% after negative SNB and 1.1% after positive SNB without axillary lymph node dissection (ALND) with whole breast radiation. Study from the Dutch Cancer Registry about axillary recurrence after negative SNB between 2002 and 2004 showed the median time to recurrence was 30 months (3). Fourteen percent accompanied with distant metastasis. Five-year overall survival (OS) and disease-free survival (DFS) of patients is approximately 60% and 55%, respectively. ALND is suggested for surgical treatment of isolated axillary recurrences, and RT is indicated according to the findings of ALND and initial therapy. When there is an isolated supraclavicular recurrence without distant metastasis, data from Danish Breast Cancer Group Trials suggests that patients who receive both local and systemic therapy has statistically significantly survival improvement (4).

Subsequently, Dr. Morrow addressed two questions on reoperative SNB after LR. Is it feasible and accurate, and does it provide useful information to manage patients? Study from Memorial Sloan-Kettering group about reoperative SNB for patients that initially had breast conserving surgery (BCS) with negative SNB or ALND less than 10 nodes removed showed that sentinel nodes were identified in 55% (n=63) of 117 patients, and 16% (n=10) of them had nodal metastasis (5). Success of reoperative SNB significantly higher if patients initially had SNB rather than ALND and did not have RT. Success of reoperative SNB decreases as the initial number of removed sentinel nodes increases (80% for 0-2 nodes removed, 53% for 6-8 nodes removed). Location of the reoperated sentinel nodes in lymphoscintigraphy presented 70% in ipsilateral axilla only and 30% in non-axillary region (mainly internal mammary node followed by contralateral axilla). Reoperative SNB can be conducted after recurrences of mastectomy patients. Dual tracer application with injection of tracers to upper skin flap can detect sentinel nodes up to 65%. In the systematic review of 692 reoperative SNB patients by Maaskant-Braat A., 301 of them had SNB and 361 had ALND for axilla, and 574 of them had BCS±RT for the breast as the initial surgery (6). The author showed that, identification rates are higher in SNB patients as initial surgery and there is no difference between BCS and mastectomy patients. Aberrant drainage rates for

successfully mapped patients are 26% for prior SNB group and 74% for ALND group. Accuracy and outcomes of reoperative SNB is still scarce due to lack of enough data. Final suggestions about reoperation to axilla is using combined technique with radioactive colloid and blue dye for mapping, and making the injection to peritumoral region.

Identification of nodal metastasis in locally recurrent breast cancer is important because it maintains local control and gives us information about changing RT fields and changing systemic therapy. Contralateral axillary metastasis is defined as stage IV according to American Joint Committee on Cancer classification. Contralateral axillary metastasis constitutes 33% of cases after BCS with ALND. In a systemic review about contralateral lymph node recurrence, >50% of them occurred without ipsilateral breast tumour recurrence (7). Primary treatment was ALND in 71% of patients and almost half of the patients received chemotherapy. Five-year OS is 82.6% and DFS is 65.2% when contralateral axillary recurrence was treated with surgery and systemic therapy.

Dr. Morrow also discussed if lumpectomy alone is appropriate for local recurrence after BCS with RT. She stated that it is not a standard of care and additional local recurrences are high. In her surgical practice, she performs surgery, if patients meet the criteria for no RT after primary surgery (Age>70, cT1N0, ER+HER2- or low-intermediate grade DCIS≤1.5 cm), and if there is a long disease-free interval or tumour occurred to be a second primary.

On the 4th day of the conference, Tari King's speech was probably the most important and controversial recent topic of the breast surgery about individualizing management of the axillary nodes. She started her presentation highlighting to balance the risks and benefits of treatment options between SNB and ALND depending on disease burden, tumour biology, and treatment options like neoadjuvant chemotherapy (NAC). The goal should be minimizing local-regional management without compromising outcomes.

In clinically node positive patients, the choice could be either primary surgery with ALND or NAC followed by SNB for an opportunity to preserve the axilla. In clinically node negative setting, similarly, primary surgery with SNB or SNB after NAC surgical options. According to a meta-analysis, in the setting of clinically node negative patients undergoing NAC, identification rates and false-negative rates are the same for performing the SNB before or after NAC. However, performing the SNB after NAC decreases the needs for ALND (8). In patients with positive axilla after NAC, the standard of care is still performing ALND. In the group of cN0 patients who undergo primary surgery, ALND is still mandatory if the patient has 3 or more involved axillary lymph nodes, whereas patients with 1-2 positive sentinel lymph nodes have the option of axillary observation or axillary RT.

Dr. King then stated important prospective randomized trials about axillary manegament like ACOSOG Z0011, AMAROS, IBCSG 23-01, OTOASOR, and AATRM. In these trials, there is no difference in axillary recurrence rates between ALND and other options (observation or axillary RT). Furthermore, there is no difference in DFS or OS between ALND or observation in Z0011, IBCSG, and AATRM; or between ALND or nodal RT in AMAROS and OTOASAR. The results of POSNAC trial that includes T1-T2 patients with 1-2 sentinel node macrometastasis, who underwent lumpectomy or mastectomy, are awaited. These patients than randomized to systemic therapy alone in one arm and systemic therapy + axillary treatment even with ALND or axillary RT in the second arm. In mastectomy patients, ALND can be avoided if there is a micrometastatic disease and in macrometastatic patients with 1-2 positive lymph nodes with in favor of axillary RT when there is an indication for post-mastectomy RT.

Dr. King than presented Dana-Farber series of mastectomy patients eligible for AMAROS. In this series they looked for predictors of post-mastectomy RT population to spare these patients from routine inrtaoperative assesment of sentinel lymph nodes. They composed a multidiciplinary concensus for mastectomy patients eligible for AMAROS, and suggested not performing intraoperative assesment of sentinel lymph node in patients receiving post-mastectomy RT. Ten-year update results of the Z0011 by Giuliano and colleagues reported again no difference in OS, DFS or loco-regional recurrence between ALND arm and nodal RT group.

In the setting of clinically positive axillary nodes, NAC is a choice for the possiblity of axillary complete response. To evaluate axillary nodes after NAC, at least 3 or more snetinel node sampling with dual tracer is recommended to decrease the false negativitty rates. There are two important ongoing trials about management of the axilla after NAC for patients converted from cN1 to cN0. In the Alliance A11202 trial after NAC, patients with positive SNB were randomized to ALND without axillary RT or no further axillary surgery with axillary RT. In the NRG 9353 trial, patients with negative SNB after NAC were randomized to no regional nodal RT or regional nodal RT. Hormone receptor positive HER2 negative subset is less likely to have positive or high volume nodal disease, and less likely to present pathological complete response so that surgery first is suggested if Z0010 and AMAROS is eligible. For HER2 positive or triple negative group, as they present with reasonable pathologic complete response, principally NAC is considered. In CALGB 9343 trial, patients ≥70 years-old, T1N0, ER+ undergoing BCS followed by tamoxifen treatment, 392 (62%) of these patients had no axillary staging or treatment (9). Ten year axillary failure rate of this subset of group was 1.5% with no differences in OS, DFS or disease specific survival.

Local therapy of limited disease in advanced breast cancer was presented by Dr. Seema Khan from Northwestern University, United States, on educational session about Challenges in Advanced/Metastatic Breast Cancer. She started her talk stating recent clinical data suggest that patients with oligometastasis are potentially curable. So, the question is should we consider surgical resection, RT or other ablative therapies?

Lung metastasis resection series from Institute of Oncology in Milan demonstrated better OS (46% 5-year survival, p<0.0001) and disease-free interval (46.6 months mean DFI) with R0 resection (10). But this was not a pure breast cancer population. Resection for hepatic metastasis from primary breast cancer meta-analysis showed better survival. It also emphasized factors associated with poor survival as disease-free interval less than 4 years, hormone receptor negativity, poor response to chemotherapy, and positive resection margins. There is still no strong data and prospective randomized trials about local therapy for metastatic sites but there is a concensus about those most likely to benefit from ablative therapy. Those are patients with long disease-free interval, metastasis of primary breast cancers, and small number of metastatic lesions (1-3), small sizes of metastasis, and complete ablation of lesions (R0 resection or other means of complete ablation with different interventions like stereotactic body radiotherapy).

Another promising approach for oligometastasis is stereotactic body radiotherapy (SBRT) or hypofractionated image-guided radiotherapy. Milano and colleagues reported a prospective analysis of SBRT for 121 patients with oligometastasis and 39 of them was primarly breast metastasis (11). The most common metastatic sites for breast primary were bone and liver. Overall survival and DFS was better in breast primary group when compared to non-breast group. At a median follow-up of 4.5 years, they achieved 87% local control and 46% 6-years OS.

The approach for primary site of the stage IV breast cancer is also controversial. A meta-analysis that was published in 2012 demonstrated resection of the intact tumor is associated with longer survival but the data of the studies were biased (12). There are two randomised trials in this topic. One is from Turkey and the other one is from India. In the Turkish MF 07-01 trial, unpublished updated data in ASCO 2016 showed significant benefit in 5-year OS and loco-regional progression for local treatment arm (13). In the Indian study, patients were randomized after systemic therapy to loco-regional treatment and no loco-regional treatment (14). They found no survival benefit between two groups but they showed better local control in treated group.

Dr. Galimberti presented ten-year results of the IBCSG 23-01 trial comparing axillary dissection vs. no axillary dissection in patients with cT1-T2cN0M0 breast cancer patients only with micrometastases in the sentinel lymph node. Concordant with the 5-year results, there was no significant difference in DFS, OS, cumulative incidence of breast cancer, and rate of ipsilateral axillary events.

Frank Vicini presented a meta-analysis about appropriate margins for breast conserving surgery in patients with early stage breast cancer. They analysed 38 studies with 55302 patients with a minimum follow-up of 50 months and median of 7.2 years. They utilized 3 different models of analysis. What was different in this study from previous meta-analyses was the second modelling of the analysis. They performed to assess the impact of margin width 'range' rather than a set margin width (≤0mm, 0-2mm, 2-5mm, >5mm). They demonstrated in multivariate analysis that wider margins further reduced local recurrence. In conclusion, Dr. Vicini advocated that data suggest having a margin width beyond 'no tumour on ink' may further reduce rates of local recurrences. He finished his presentation with raising a question as which patient with 'no tumour on ink' need more surgery. At this point a long discussion started because this was an out of guideline suggestion. Dr. Morrow from Memorial Sloan-Kettering criticized about method and possible bias in the meta-analysis. In reply, Dr. Vicini clearly stated that there was no bias in the study, but he finalized his recommendation as wider margins may be necessary for some patients.

Dr. Amit Goyal's keynote talk was about sentinel lymph node mapping. He discussed on three posters about fluorescence techniques, 4 posters about non-operative axillary staging, and 1 poster about intra-operative assessment of sentinel lymph node. He suggested dual agent use as a standard of care for sentinel node mapping with a detection rate of >98% and false negative rate of <10%. However, he also stated that this is practically not so feasible for institutions in non-developed and developing countries. In a systematic review published in 2014, indocyanine green was found better than blue dye and approximately similar with the radioisotope for sentinel node identification (15). A group from Japan and a group from Italy used different real-time methods for sentinel node detection. Japanese group used a medical imaging projection system that is used in liver surgery, and Italian group used laparoscopic camera with a near-infrared filter after injection of indocyanine green. Another new agent for sentinel node detection is 10% fluorescein sodium. It is cheaper than indocyanine green, and does not need expensive devices to track nodes (It only needs goggles with blue light filter). Disadvantage is it has a lower molecular weight than other agents meaning that it can be detected in more sentinel nodes than other agents, leading the surgeon dissect more lymph nodes.

Dr. Goyal started the second part of his talk, which headlined as non-operative axillary staging, by referring the poster of Swedish SCAN-B study. In this study of 3023 patients, they looked for the predictors of axillary nodal metastasis based on gene expression and clinicopathological characteristics. They concluded that clinicopathological factors (age, tumour size, tumour grade, vascular invasion, molecular subtype, etc.) and gene expression, even in combined analysis, are not accurate predictors of nodal metastasis. Another study from Beijing, China retrospectively analysed ultrasonographically node negative women with invasive breast cancer who underwent SNB. Of the 3115 patients, 798 (25.6%) had macrometastasis, and 2317 (74.4%) did not. Even though they found some factors like age and tumour size as significant factors, there was no significance in multivariate analyses. Dr. Goyal concluded his talk stating that two very similar prospective randomized studies are still ongoing about not performing axillary surgery for early stage breast cancer patients in the setting of negative axillary ultrasound. First study is SOUND study, which finished recruitment and is in the follow-up phase. Second trial is INSEMA study, and still accepting recruitments.

Screening and Diagnosis

Dr. Sarah Friedewald made a speech on advances in breast cancer screening and diagnosis. In developed and developing countries, there are recommendations and suggestions about effectiveness of screening programs (16). In the United States, there are different guidelines about starting age of screening suggesting age 40, 45, and age 50. But substantial number of them recommend age 40 to reduce the number of deaths caused by breast cancer. Recent studies demonstrates screening with digital breast tomosynthesis shows decresing recall rates (13%, 7.8%, and 5.9% for 1st, 2nd, and 3rd year screening respectively) when compared to screening with digital mammogrraphy. As there is still no guideline for mammography screening frequency after lumpectomy for breast cancer; due to increased rates of false positive breast biopsies, Dr. Friedewald suggested annualy screening rather than semi-annual screening in this setting. She then presented a population based study titled "Risk of breast cancer after a false positive screening mammogram in relation to mammographic abnormality" from British Columbia with a 11.8 years follow-up. The results showed that women with false positive test almost showed 2 fold incresed relative risk for breast cancer. This statement is important for the follow-up of these patients.

Other

On the 4th day of the conference in general session, Dr. Kuijer from Netherlands presented self-reported 1-year data about risk of arm morbidity after local therapy from the young women's breast cancer study, which is a multicentre prospective cohort conducted in United States. She reported that ALND, increased body-mass index (BMI), less comfortable financial status, and tumour size were associated with increased risk of self-reported arm swelling. Patients with higher BMI and patients treated with mastectomy and RT compared to BCS are more likely to experience decreased range of arm motion.

Dr. Chlebowski underlined the importance of weight loss in postmenopausal patients. They analyzed 61,335 women from the database of Women's Health Initiative Observational study. Dr. Chlebowski and colleagues remarked that overweight women with weight loss of ≥5% were at a lower risk of breast cancer.

Lecture of Dr. Joseph Lo on Prediction of occult invasive disease in ductal carcinoma in situ using deep learning features is probably the most interesting presentation of the 40th SABCS. It gave us a future perspective about what medicine will evolve and what the role of physicians will be. Deep learning is a machine learning algorithm model with many layers to collect and analyze limitless data. In other words, a computer educating itself to diagnose disease. Dr. Lo utilized deep learning features to predict occult invasive disease in DCIS in his study, and achieved reasonable results by this method. However, he concluded that more data input is needed to improve this method.

Conclusion

High-risk breast lesions should be excised if there is a concern that target lesion was not totally or near totally excised in biopsy, if histology demonstrates atypia in presence of a palpable or imaging mass lesion, and if there is a discordant finding.

As multigene tests are becoming more popular, elevated breast cancer risk were established for women with moderate penetrance mutations in selected genes (PALB2, TAM/NBN, CHEK2, etc.).

Success of reoperative SNB (by peritumoral injection) after BCS is significantly higher if patient initially had SNB rather than ALND and did not have RT. Reoperative SNB can also be conducted after recurrences of mastectomy patients by injecting tracers to upper skin flap. In both cases, dual tracer application is recommended. Aberrant lymphatic drainage (internal mammary, contralateral axilla) in 1/3 of the patients should be kept in mind.

Lumpectomy for local recurrence after BCS with RT is feasible if the patient meets the criteria for no RT after surgery.

Intraoperative assesment of sentinel lymph node can be ignored for patients that will probably receive post-mastectomy RT.

To evaluate axillary nodes after NAC, at least 3 or more sentinel node sampling with dual tracer is recommended. If positive axilla after NAC is detected, the standard of care is still performing ALND.

Hormone receptor positive HER2 negative subset is less likely to have positive or high volume nodal disease and less likely to present pathological complete response so that we should consider surgery first if Z0010 and AMAROS eligible.

Recent clinical data suggest that patients with oligometastasis are potentially curable. The concensus about patients most likely to benefit from ablative therapy are patients with long disease-free interval, metastasis of primary breast cancers, small number of metastatic lesions (1-3), small sizes of metastasis, and complete ablation of lesions (R0 resection or other means of complete ablation with different interventions like stereotactic body radiotherapy).

Annualy mammography screening rather than semi-annual screening is recommended after lumpectomy for breast cancer.

Risk of breast cancer after a false positive screening mammogram showed 2-fold increased relative risk.

ALND, increased body-mass index (BMI), less comfortable financial status, and tumour size were associated with increased risk of self-reported arm swelling.

Overweight women with weight loss of ≥5% were at a lower risk of breast cancer.

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