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REVIEW ARTICLE

Recent Advances in Breast Cancer Diagnosis Entering an Era of Precision Medicine

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ABSTRACT

This article will cover some of the most recent advances in the diagnosis of the world's most common cancer in women, namely, breast cancer as we enter the era of precision medicine. The authors will discuss the differences between East and West pertaining to the incidence and mortality rates, the types of breast cancer and the revised staging criteria of breast cancer according to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition. In addition, the advances of newer imaging modalities are presented and compared with traditional ultrasonography and mammography.

INTRODUCTION

Worldwide, breast cancer remains the most common cancer in women. According to WHO (2015) 1,700,000 new cases were diagnosed each year and 520,000 died from the disease[1]. In the USA alone (2017), 252,710 cases were added and 40,610 died from the disease. This translates into something like 1 in every 8 women in the USA will be diagnosed with breast cancer each year[2]. In Malaysia, the Ministry of Health's National Cancer Registry reported the Age Adjusted Incidence Rate to be 47.3/100,000. Simply put, 1 in every 20 women in Malaysia will be diagnosed with breast cancer each year. This rate is highest in Malaysians of Chinese descent followed by Indians and Malays. The mortality rate is exactly reversed among the three ethnic

groups leaving a lot of fertile ground for epidemiologists to sort through[3].

Is there a difference between breast cancers seen in the West compared to those seen in Southeast Asia? While the disease shares many common features, there are obvious differences. The peak incidence is 40 – 50 years in the East and 60 – 70 years in the West. The incidence is increasing in the West but the mortality is decreasing. However, in the East, both incidence and mortality are increasing. Most of the cancers seen in the West are at earlier stages compared to later stages in the East.

In 2018, the Age of Precision Medicine is upon us. The first and most common example of this modality of treatment was started in 2005 when Trastuzumab was used in treating HER positive breast cancer [4, 5]. Precision Medicine is the prescription of a specific therapy based on that individual's molecular characteristics. Recent breakthroughs in pharmacogenetics and pharmacogenomics have allowed us to predict which treatment(s) will be safe and effective and which are not. This model is changing the way we think and manage diseases and will only expand as our understanding and technology advances[6, 7, 8].

Traditionally, chemotherapy works by killing cells that are replicating rapidly. Precision medicine works differently by slowing and/or stopping the growth and even metastasis of cancer at the cellular level by interfering with cellular signalling and/or metabolic pathways. This method of treatment will improve outcome as well as decrease side effects[9].

While precision medicine is making great strikes in the treatments of melanoma, lung and genitourinary malignancies, its impact on breast cancer is still limited to clinical trials involving metastatic Triple Negative Breast and HER positive breast cancers. That too will change in the not too distant future.

The observations of a causal relationship between BRCA 1 & 2 mutations and increased risks for breast and ovarian cancers have increased the demand for genetic testing[10]. However, the conventional methodology is costly as well as time consuming. A new next-generation sequencing (NGS) technique is now available that supersedes conventional approach. This method is more accurate, less time consuming and more affordable[11, 12].

TYPES OF BREAST CANCERS

Traditionally, breast cancer is histologically classified as ductal or lobular assuming that the tumours arise from ductal and lobular epithelium respectively. However, it is now believed that both categories of tumours actually arise from cells in the terminal duct lobular unit (Figure 1A). The terms ductal carcinoma and lobular carcinoma now describe their histomorphologic likeness to normal ducts and lobular spaces respectively (Figure 1C). In combination, these two accounted for over 90% of breast cancers. The remainder is a mixture of other types like papillary, medullary and metaplastic.

A more informative and recent classification is molecular sub-typing of breast cancer. Studies are being done on how molecular subtypes of breast cancer may be useful in planning treatment and developing new therapies. Molecular and genetic information from tumour cells are used to determine the complicated profile of each subtype.

Most studies divide breast cancer into 4 major molecular subtypes (Figure 1B):

- Luminal A
- Luminal B
- Triple negative/basal-like
- HER2 type (human epidermal growth factor receptor 2 type)

Luminal A and Luminal B tumour cells look like those of breast cancer cells that start in the inner (luminal) cells lining the mammary ducts. However, there are differences between the two molecular subtypes.

Luminal A tumours tend to be estrogen receptor-positive (ER-positive), HER2 receptor-negative (HER2-negative) and Tumour grade 1 or 2. About 30 – 70 per cent of breast cancers are luminal A_tumours. Of the 4 subtypes, luminal A tumours tend to have the best prognosis and to a moderate extent high survival rates and fairly low recurrence rates[13].

Luminal B tumours tend to be ER-positive. They may be HER2-negative or HER2-positive. About 10 – 20 per cent of breast cancers are luminal B tumours. Women with luminal B subtype breast cancer tend to have fairly high survival rates, but not as high as those with luminal A tumours[13].

Triple negative breast cancers are oestrogen receptor-negative (ER-negative), Progesterone receptor-negative (PR-negative) and HER2-negative. Out of several subsets of triple negative breast cancer one variety is known as basal-like. Basal-like tumours have cells that look similar to those of the outer (basal) cells surrounding the mammary ducts which contract for milk ejection (Figure 1B). About 15 – 20 per cent of breast cancers are triple negative/basal-like. Triple negative/basal-like tumours behave aggressively and have a poorer prognosis compared to the ER-positive subtypes (luminal A and luminal B tumours) [13].

The molecular subtype HER2 type tumours are HER2-positive but a few percentages are HER2-negative (Figure 1D). HER2 type tumours tend to be ER-negative, PR-negative, Lymph node-positive and poorer tumour grade. About 5 – 15 per cent of breast cancers are HER2 type. HER2 type breast cancers that are HER2-positive can be treated with anti-HER2 drugs such as trastuzumab (Herceptin)[13].

Breast cancer pathogenesis and histologic vs molecular subtypes

Adapted from The McMaster Pathophysiologylogy Review (MPR)[14]

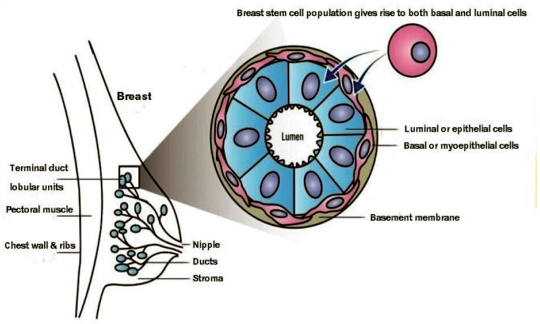

Figure 1A Cross section view of mammary duct in terminal duct lobular unit. All breast cancer lesions arise from the terminal duct lobular unit.

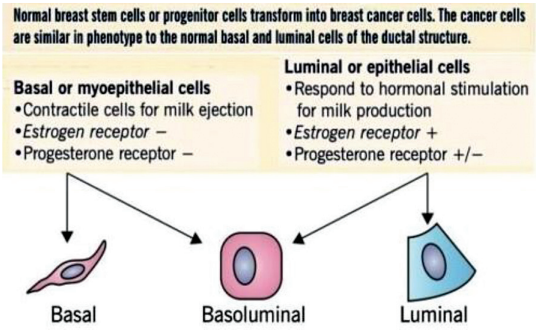

Figure 1B Cancer cell phenotype

Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+

Figure 1C Histological subtypes

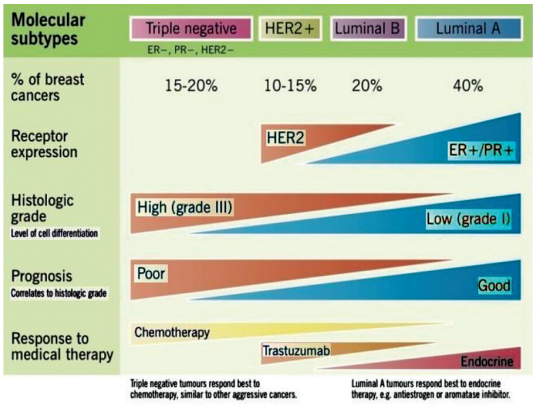

Figure 1D Molecular subtypes

IMPORTANT CHANGES MADE IN 8TH EDITION OF AJCC CANCER STAGING MANUAL[15]

Table 1 Shows the incorporation of TNM staging into the AJCC prognostic stage groups

ANATOMIC STAGE/ PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

T1* and N1** changes are discussed below.

Starting in 2018, the American Joint Committee on Cancer (AJCC) Staging Manual 8th edition requires inclusion of prognostic factors such as ER, PR, HER2 in breast cancer staging. In addition, whenever appropriate genomic tests like Oncotype-Dx, Mamma Print, Endopredict, PAM 50 Prosigna, and Breast cancer index are also to be included[15, 16]. Inclusion of multigene panels have resulted in changes in T1* category downstaging some tumours regardless of T size, and placing them in the same prognostic category as T1a-T1b N0 M0. These tumours will be staged using the AJCC prognostic stage group table as Stage I[16] (Table 1).

Isolated tumour cells clusters (ITC) in regional lymph nodes can be identified by haematoxylin and eosin (H&E) or immunohistochemistry (IHC). ITC that are 0.2 mm or less is classified as pN0(i+). The pN1 category includes pN1mi micrometastases which is defined as node deposits of tumour cells 0.2 – 2 mm. pN1a is defined as 1 – 3 nodes with at least 1 node with a deposit greater than 2 mm. pN2a is defined as 4 – 9 positive nodes and pN3a is 10 or more positive nodes. pN1b is defined as a positive internal mammary sentinel node with a deposit greater than 0.2 mm in the absence of axillary node metastases. pN1c is a combination of pN1a and pN1b[16].

Previously, any nodal involvement was considered N I or Stage II. Lobular carcinoma in situ is removed from the staging system because it is not a malignancy but a risk factor. It is no longer considered Tis. With these changes, it is anticipated that in the coming years, more Stage I breast cancers will be seen and less of Stage II and III.

With implementation of these changes, breast cancer treatment has entered the era of precision medicine where treatment is tailored for each patient based on genomic profiling of her breast cancer and its response to biopharmacologic manipulation.

CURRENT AND FUTURE STATUS OF BREAST IMAGING

Current modalities of breast imaging include Mammography, Breast Ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Thermography, Positron Emission Tomography (PET-CT, PET/MRI) and Breast Elastography, a new sonographic imaging technique. While mammography remains the Gold Standard, there are limitations associated with its use. One main issue is the lack of sensitivity in young women with dense breasts. However, the introduction of 3D Mammography (Tomosynthesis) is changing this old paradigm that young woman undergoes ultrasound but not mammographic imaging. Below are averages of sensitivity and specificity of the various modalities (Table 2).

Table 2 Shows the averages of sensitivity and specificity of the various modalities of imaging

Imaging modality	Sensitivity	Specificity
Mammography	~72%	~47%
MRI	~93%	~61%
Ultrasound	~61%	~87%
PET	~77-100%	~69-80%
CT	~71%	~83%
Thermography	~39%	~82%
3D (Tomosynthesis)	~100%	~75%

With 3D Mammography, the breast is placed between two compression plates (Figure 2). A robotic arm will move the scanner in an arc over the breast and over 60 multiple images are then taken. The procedure takes 10 – 20 minutes. The dose is slightly higher than standard 2D digital mammography. The software is similar to that used in CT and 3D reconstructed images are then ready for the radiologist to read. This method eliminates tissue overlap, increases the number of invasive cancer detected and initiates the number of women being recalled for further testing. A new Software called C-View Hologic allows Tomosynthesis to acquire both 2D and 3D images at the same time, hence decreasing further exposure[17].

Figure 2 3D mammography[17]

Automated Breast Ultrasound (ABUS)

Figure 3 Automated breast ultrasound (ABUS)

Photo Courtesy of U-Systems[17]

The automated breast ultrasound uses a transducer that is placed over the breast lightly and in about 10 minutes, 3D images of the **entire** breast are acquired automatically compared to the traditional hand-held method which obtains 2D images and takes over 30 minutes (Figure 3). This device is operator-independent. When used in conjunction with mammography it increases sensitivity to 97%. According to a University of Chicago study when ABUS was combined with mammography, there was an absolute increase of 31% in detection rate of breast cancer in asymptomatic women with dense breasts and a normal mammogram[17].

Photoacoustic Microscopy (PAM) or Photoacoustic Tomography (PAT)

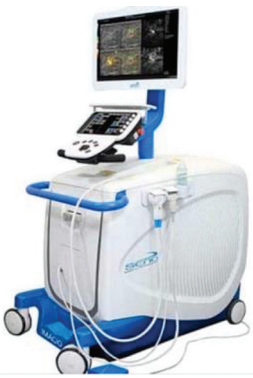

Figure 4 SENO Medical's Imagio Opto-Acoustic Breast Imaging System proves a strong predictor of malignancy[17]

This new hybrid technology combines light and sound to achieve a high optical as well as spatial resolution of the breast tissue structure as well as function (Figure 4, Figure 5). This modality can be used to follow progression and resolution of breast cancers following therapy. Potentially it can give the surgeon real intraoperative information as to the adequacy of his margins of resection[17].

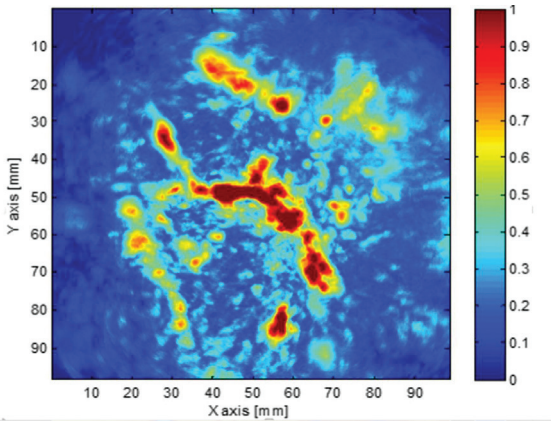

Figure 5 Photoacoustic Imaging of breast cancer Optical Imaging Laboratory, University of Michigan[17]

Molecular Breast Imaging (MBI)

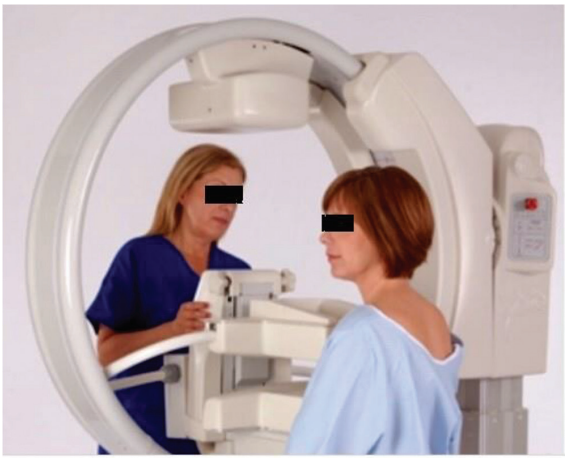

Figure 6 Molecular Breast Imaging (MBI)[17]

This new Nuclear Medicine technique employs injecting Technetium-99m Sestamibi intravenously about 5 minutes before scanning the breast under light compression between two plates (Figure 6). Overall sensitivity is 90% but only 82% if the tumour is <1.0 cm and much less if below 5.0 mm in size. MBI does detect 2 – 3 times more breast cancers in mammography dense breasts and in those women with an increased risk for cancer[17] (Figure 7).

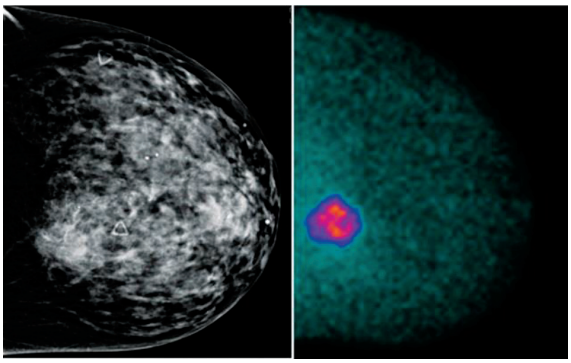

Figure 7 Using this new technology (MBI) a palpable mass that was difficult to see on mammography (left) is clearly visible on molecular breast imaging (right). (Images courtesy of Dr Beatriz Adrada)[17]

Breast Elastography

Elastography is an ultrasound imaging technique that evaluates the **stiffness** of a breast lesion. It is an attempt to differentiate between benign versus malignant breast lesions. The hope here is to reduce the number of unnecessary benign breast biopsies. Currently there are **two** techniques used:

A. Straw Elastography

It is a qualitative, fast, real time method but influenced by the size and characteristics of the lesions. This is also operator-dependent.

B. Shear Wave Elastography

It is a quantitative, more accurate method but is also limited in the assessment of a very **stiff** lesion. While this technique is used to complement traditional mammography and ultrasonography, its stand-alone sensitivity and specificity has yet to be determined[18].

CONCLUSION

This article discusses recent advances in the diagnosis of breast cancer, the differences between the incidences and mortality rates between the West and the East, the different types of breast cancers, the recent revision of the staging criteria of the American Joint Committee of Cancer Staging Manual (8th edition), and the new advances in the various medical imaging modalities. With these developments in diagnosis, it is hoped that treatment will be more targeted and personalized, thus improving health outcomes of women with breast cancer in the era of precision medicine.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

REFERENCES

1. World Health Organization(WHO). (Sep 2018). http://www.who.int/cancer/en
2. Cancer Statistics-National Cancer Institute. (n.d.). http://www.cancer.gov/aboutcancer/understanding/statistics
3. The Malaysian National Cancer Registry Report (MNCR) 2007 – 2011. (October 2016). http://www.nci.moh.gov.my
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. (2005). Trastuzumab after adjuvant chemotherapy in HER positive breast cancer. NEJM 353: 1659 – 1672.
5. Romond EH, Perez EA, Bryant J et al. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER positive breast cancer. NEJM 353: 1673 – 1684.
6. Hamburg MA, Collins FS. (2010). The path to personalized medicine. NEJM 363: 301 – 304.
7. Schork NJ. (2015). Personalized medicine: Time for one person trial. Nature 520: 609 – 611.
8. Hewitt RE. (2011) Biobanking: The frontier of personalized medicine. Current Opinion in Oncology (23) Issue 1: 112 – 119.
9. The Case for Personalized Medicine. (May 2009). http://www.personalizedmedicinecoalition.org
10. National Cancer Institute. (2018). BRCA Mutations: Cancer risk and genetic testing fact sheet. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet
11. D'Argenio V, Esposito MV, Telese A et al. (2015). The molecular analysis of BRCA 1 and BRCA 2: Next generation sequencing supersedes conventional approach. Clin Chim Acta 446: 221 – 225.
12. Elsevier Health Sciences. (2013). New diagnostic test for detecting BRCA1 and BRCA2 mutations. Science Daily. https://www.sciencedaily.com/releases/2013/10/131007162517.htm
13. Susan G Komen. (2017). Molecular subtypes of Breast Cancer. http://www.komen.org/BreastCancer/SubtypesofBreastCancer.html
14. Wong E, Chaudhry S, Rossi M. (2012 – 2018). Breast Cancer. McMaster Pathophysiology Review (MPR).
15. Amin MB, Edge S, Greene F et al. (2017). AJCC Cancer Staging System 8th Edition. Springer.com
16. Giuliano AE, Connolly JL, Edge SB et al. (2018). Breast Cancer - Major Changes in the American Joint Committee on Cancer Eighth Edition Cancer Staging Manual. Ca Cancer J Clin 67: 290 – 303.
17. Imaging Technology News (ITN). (2014). Emerging breast imaging technologies. https://www.itnonline.com/article/emerging-breast-imaging-technologies
18. Goddi A, Bonardi M, Alessi S. (2012). Breast elastography: A literature review. Journal of Ultrasound 16 (3): 192 – 198.