THE ROLE OF ^{18}F-FDG PET/CT IN COMPARISON WITH COMPUTED TOMOGRAPHY IN THE RESTAGING OF BREAST CANCER IN MALAYSIA

by

DR. LEE HWEE MENG, JOANNE

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DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine in Nuclear Medicine. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as a reference.

Sincerely,

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DR. LEE HWEE MENG, JOANNE
(P-IPM0022/19)
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ABBREVIATIONS

BCR	breast cancer recurrence
BI-RADS	Breast Imaging-Reporting and Data System
BGO	Bismuth germanate
CBE	Clinical breast examination
CECT	Contrast Enhanced Computed Tomography
CT	Computed tomography
ER	oestrogen receptor

^{18}F-FDG	18Fluorodeoxyglucose
GLUT	Glucose transporters
HER-2	human epidermal growth factor receptor 2
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
IR	incidence rates
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
LABC	locally advanced breast cancer
LSO	lutetium oxyorthosilicate
LYSO	lutetium yttrium oxyorthosilicate
MREC	Medical Research Ethics Committee
n	Frequency
NST	No special type
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography
PI	Primary Investigator
PR	progesterone receptor
PY	person-years
SD	Standard deviation
TCB	Trucut biopsy
WHO	World Health Organization

ABSTRAK

Tajuk: Mengenalpasti peranan di antara ^{18}F -FDG PET/CT dan Computed Tomography (CT) dalam mengenalpasti tahap kanser payudara di Malaysia.

Pendahuluan: Kanser payudara merupakan kanser yang paling banyak dihidap oleh rakyat Malaysia dan di negara-negara antarabangsa. Untuk tahap awal kanser payudara, tidak banyak ujian lanjutan yang diperlukan. Namun, untuk kanser tahap III dan IV, lebih banyak ujian lanjutan perlu dibuat untuk mengenalpasti tahap kanser payudara disebabkan ia berkait terus dengan jangka hayat pesakit-pesakit berkenaan. Apabila disyaki kanser payudara berulang ataupun kanser semakin merebak; ataupun selepas menghabiskan rawatan, ujian pengimejan ataupun "skan" biasanya perlu dilakukan untuk mengenalpasti perkara-perkara di atas. Biasanya, Computed Tomography (CT) akan menjadi pilihan utama, manakalanya skan ^{18}F-FDG PET/CT tidak selalu diamalkan. Keputusan skan yang diperolehi daripada pengimejan akan mempengaruhi pelan perancangan perawatan pesakit.

Objektif: Matlamat kajian ini adalah untuk menilai dari segi kelebihan ^{18}F-FDG PET/CT sebagai pengimejan tambahan berbanding dengan CT sahaja dalam mengenalpasti tahap kanser payudara termasuk tempat-tempat yang kanser telah merebak.

Kaedah: Pesakit yang dikenalpasti sebagai penghidap penyakit kanser payudara daripada umur 18 sehingga 90, yang membuat ujian pengimejan "Computed Tomography" (CT) di hospital-hospital utama dan juga dihantar untul membuat ujian lanjutan "^{18}F-FDG PET/CT" daripada tahun 2017 sehingga tahun 2021 di Hospital Pulau Pinang telah dimasukkan ke dalam kajian ini. Carta untuk mengumpul data (Performa) telah dicipta untuk merekodkan data daripada carta rawatan pesakit. Perebakan ketumbuhan dan tempat yang merebak dikenalpasti di CT dan ^{18}F-FDG PET/CT dicatit di performa tersebut dan keputusannya diklasifikasikan sebagai tiada unsur merebak, kemungkinkan telah merebak dan telah merebak mengikuti turutan "organ". Data klinikal seterusnya dianalisis menggunakan IBM SPSS versi 26.0.

Keputusan: Seramai 111 orang pesakit dengan kanser payudara telah dikenalpasti dan data dikumpul dengan purata umur 51.95 tahun. Hampir kesemuanya terdiri daripada wanita (99.1%)

dan kebanyakannya berbangsa Melayu(52.3%). Sebanyak 84.7% daripada pesakit kanser payudara terdiri daripada kumpulan pathologi “Invasive carcinoma of no special type (NST). Pesakit kanser payudara di tahap 2 merupakan kumpulan yang tertinggi untuk rujukan membuat pengimejan ^{18}F-FDG PET/CT iaitu pada 43.2%, diikuti tahap 3 (36.9%), tahap 1 (13.5%) dan kumpulan terendah terdiri daripada tahap 4 (6.3%). Daripada 111 pesakit, ^{18}F-FDG PET/CT berjaya menukar status 62 pesakit daripada kemungkinan ataupun telah merebak menjadi tiada unsur merebak, manakala 1 pesakit di mana pengimejan CT memutuskan bahawa tiada unsur merebak namun ujian ^{18}F-FDG PET/CT telah memutuskan bahawa penyakit kanser payudara dalam pesakit ini telah merebak. Dalam 44 pesakit di mana ujian CT dapat mencari unsur pesakit telah merebak dan dalam 4 pesakit di mana ujian pengimejan CT tidak dapat mencari unsur bahawa kanser telah merebak, ^{18}F-FDG PET/CT didapati mencapai keputusan yang sama. Menggunakan ujian Mc Nemar, didapati bahawa ada perubahan yang ketara di antara klasifikasi pengesanan lesi dalam pesakit kanser payudara di antara pesakit di mana hanya ujian pengimejan CT dibuat kalau dibandingkan dengan pesakit yang juga melalui pengimejan ^{18}F-FDG PET/CT ($p< 0.050$). Melalui pengimejan ^{18}F-FDG PET/CT, 32.4% daripada mereka telah diklasifikasi sebagai tahap penyakit kanser payudara yang lagi tinggi manakala seramai 3.6% pesakit telah diturunkan tahap penyakit kanser payudara manakala 64% pesakit telah didapati dalam tahap sama penyakit kanser payudara seperti mana yang dikenalpasti menggunakan pengimejan CT.

Kesimpulan: Ujian pengimejan ^{18}F-FDG PET/CT merupakan ujian pengimejan yang bermanfaat berbanding dengan CT sahaja dalam kanser payudara, terutamanya dalam mengenalpasti tempat-tempat kanser yang telah merebak, sekaligus mengubah perancangan rawatan pesakit-pesakit kanser payudara ini.

ABSTRACT

Title: The role of ^{18}F-FDG PET/CT in comparison with computed tomography (CT) in the restaging of breast cancer in Malaysia.

Introduction: Breast cancer is the leading cancer among women detected in Malaysia and worldwide. While limited investigation is needed for patients with early-stage breast cancer, those afflicted with stages III and IV breast cancer are recommended to undergo more imaging for staging since this is directly vital for their survival. The reasons for further evaluation or restaging include suspicion of disease recurrence, appraisal of disease progression, or restaging following completion of treatment, all these which require further radiological confirmation. Computed tomography (CT) is commonly used as first line imaging for restaging, whereas fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) is not frequently utilised. The imaging results directly affect further patient management.

Objective: To determine the role of ^{18}F-FDG PET/CT as a routine procedure in restaging breast cancer, especially in the detection of distant metastases.

Methods: This research involved histopathology-confirmed breast cancer patients whose ages ranged from 18 years to 90, and who had undergone CT in their respective hospitals; they were then sent for restaging using ^{18}F-FDG PET/CT from 2017 to 2021 at Hospital Pulau Pinang. A data collection sheet (proforma) was devised to obtain information from the patients' case records. The number and the locations of lesions on both CT and ^{18}F-FDG PET/CT were recorded. The outcomes were categorised for each organ into no evidence of metastasis, suspicious of metastasis or definite metastasis. The clinical data obtained were evaluated using IBM SPSS version 26.0.0.

Results: One hundred and eleven breast cancer patients with a mean age of 51.95 years were enrolled. Most were female (99.1%), with Malays comprising a slight majority (52.3%). Invasive carcinoma of no special type (NST) was the largest pathology subtype at 84.7%. The largest group (43.2%) in this study was in stage II, followed by stage III (36.9%), stage I (13.5%), with the fewest in stage IV (6.3%). Sixty-two patients' classification changed from

detection of lesion(s) to no evidence of disease, and in one patient from no evidence of disease to detection of lesions. Detection status of CT and ^{18}F-FDG PET/CT remained the same in 44 patients for lesions detected, while 4 patients had no evidence of disease. A statistically significant change was found using the McNemar Test in the detection of lesions between conventional CT and ^{18}F-FDG PET/CT, as the p value was < 0.050. By the supplementation of ^{18}F-FDG PET/CT, 32.4% were upstaged, 3.6% of the patients were downstaged, while 64% of the patients remained in the same stage.

Conclusion: There is an added advantage of ^{18}F-FDG PET/CT in restaging breast cancer, especially in the detection of distant metastases. This would lead to appropriate changes in patient management.

1.0 INTRODUCTION

Breast cancer affects more than 1 million people in the world each year (Baghawi et al., 2019). It is the most prevalent cancer in females worldwide, and is the top female malignancy in Malaysia (Azizah et al., 2019). It ranks second in cancer death among Malaysian females at 11.9% after lung cancer (International Agency for Research on Cancer, 2020). In the period 2012 – 2016, breast cancer made up 19.0% of all new cancer cases detected. A 12-year figure from 1993 till 2004 showed that around 60-70% of females presented stages I and II, while the remaining 30-40% presented later stages of breast cancer, i.e., stages III and IV (Azizah et al., 2019).

According to national and international guidelines, limited investigation is recommended for the early stages of breast cancer (Baghawi et al., 2019; NCCN Guidelines for management of breast cancer, 2022). However, for stages III and IV, it is recommended that more diagnostic tests be carried out for complete staging. This consists of bone scan, computed tomography (CT), magnetic resonance imaging (MRI) and / or positron emission tomography - computerised tomography (^{18}F-FDG PET/CT) according to the patient's individual presentation (Baghawi et al., 2019).

Once accurately staged, the primary team will decide on a definitive treatment plan. Throughout the course of treatment, the disease may need to be restaged for various reasons. This includes suspected recurrence of disease due to the rise in tumour markers such as CA 15-3, a suspicion of progression of the disease due to patients' new signs or symptoms, or the need for restaging following treatment completion. Computed tomography is commonly used as first-line imaging for restaging, with ^{18}F-FDG PET/CT used only sporadically or when faced with equivocal disease (Baghawi et al., 2019).

In the International Atomic Energy Agency (IAEA) human series No 9 (VIENNA, 2010), ^{18}F-FDG PET/CT's role in the management of breast cancer patients is classified as potentially appropriate (IAEA, 2010). In the Malaysian clinical practical guidelines for breast cancer management, ^{18}F-FDG PET/CT is suggested only after the usual imaging modalities

show ambiguous or dubious results, whether in locally advanced or metastatic disease (Baghawi et al., 2019). Over the years, there have been multiple publications that detail the advantages of ^{18}F-FDG PET/CT over CT in the detection of distant metastasis and its subsequent impact on the patient's restaging process and further clinical treatment (Niikura et al., 2011; Dose et al., 2002; Koolen et al., 2012).

Hence, this study aims to explore the diagnostic performance of ^{18}F-FDG PET/CT compared to CT in the restaging of breast cancer in the local Malaysian setting, and to advocate, if appropriate, the usage of ^{18}F-FDG PET/CT as a primary imaging modality in the restaging of breast cancer.

2.0 LITERATURE REVIEW

2.1 Definition, Histopathology and Demographics

Breast cancer consists of a group of malignancies which occur in the mammary glands. The most common risk factors of breast cancer include female gender, ageing, and family history of breast cancer (especially in the presence of a first degree relative with established breast cancer), and gene mutations most commonly in the BRCA1 or BRCA2 genes (Feng et al., 2018).

Breast carcinomas arise from the epithelial component of the mammary glands, which include the lobules and terminal ducts. Breast cancer classification is via the histological examination findings of the tumour tissue, either from biopsy or surgical specimen (i.e mastectomy). Currently, a trucut biopsy (TCB) is commonly done for the evaluation of suspicious breast lesions as it provides a sufficient sample size to accurately confirm breast cancer with excellent sensitivity and specificity. The adequate tissue sample is also able to evaluate histological type and grading and include modern molecular markers for the purpose of patient prognostication and management (Kamal et al., 2020). In 2019, World Health Organization (WHO) updated their breast lesions classifications to broadly include epithelial tumours, invasive breast carcinoma, neuroendocrine neoplasms, papillary neoplasms and epithelial-myoepithelial tumours amongst others. Most breast cancer patients present with invasive breast carcinoma, with subtypes including infiltrating ductal carcinoma (IDC) and others categorised as no special type (NST) (Tan et al., 2020). Approximately 80% of breast cancers are invasive ductal carcinomas. This is followed by invasive lobular carcinoma, where the epithelial or ductal lining cells are affected (Allison, 2012). Both ductal and lobular carcinomas need to be accurately identified as they have separate treatment options and different overall prognosis.

Traditionally, physicians also utilise immunohistochemistry to identify the individual receptor status of breast cancer, whether positively stained for oestrogen receptor (ER),

progesterone receptor (PR) and HER 2. However, with the latest WHO 2019 classification, features from newer molecular subtypes namely Luminal A and B, HER2- enriched and basal, are commonly taken into consideration in order to decide on patient management and further treatment options.

	ER	PR	HER2	Ki-67	Histologic Grade	Multiparameter Molecular Test Results
Luminal A	+	≥20%	- (can be positive)	<14%	Generally 1 or 2	Favorable prognosis, ie, lower recurrence scores
Luminal B	+ (generally, lower relative to Luminal A)	<20%	- (can be positive)	≥14%	Generally 3	Unfavorable prognosis, ie, higher recurrence scores
HER2-enriched	-	-	+	Any	Generally 3	
Basal	-	-	-	Any	Generally 3	

Figure 2.1 Clinical and Immunohistochemical Surrogates for Molecular Subtypes of Breast Cancer.

Reprinted from Johnson K S, et al, Molecular Subtypes of Breast Cancer: A Review for Breast Radiologists, Journal of Breast Imaging, Volume 3, Issue 1, January/February 2021, (12–24).

Metastatic breast cancer is, essentially, stage IV or late-stage breast cancer which has spread to other areas or organs in the human body. Some patients are diagnosed with metastatic breast cancer only upon diagnosis and staging, while others develop metastases as time passes throughout the course of their breast cancer treatment. Around 30% of patients who have been initially diagnosed as early- stage breast cancer will eventually develop metastasis (Feng et al., 2018). This is because even after mastectomy when the primary growth has been removed, micro-metastases or microscopic tumour cells can still be present in the body and in time

spread; this is diagnosed subsequently as local or distant recurrence (Polyak, 2007). Common sites of metastasis are the lymph nodes, with other sites being the lungs, liver, bone, and brain.

Breast cancer is the most prevalent malignancy among women worldwide, also claiming the number one spot for female cancer in Malaysia. Of the detected cancer cases diagnosed from 2012 – 2016, 19.0% were breast cancer, showing an increase in comparison with previous data, where only 17.7% was detected in the period 2007 – 2011 (Azizah et al., 2019). The Age Standardised Incidence Rate (ASR) showed an increase from 31.1 per 100,000 population from 2007 – 2011 to 34.1 per 100,000 population from 2012 - 2016. Breast cancer incidence starts increasing by age 25 and peaks from 60 to 64 years old. In Malaysia, it is most prevalent among the Chinese (40.7 per 100,000) and the Indian population (38.1 per 100,000) with lesser incidence among the Malays (31.5 per 100.000). Cumulative lifetime risk has been documented at 1 / 27, with 1 / 22 for Chinese, 1 / 23 for Indians, and 1 / 30 for Malays (Baghawi et al., 2019).

In Malaysia, 52% of breast cancer were initially detected at the early stages (stage I and II), with more diagnosed at stage II compared with stage I (34.5%). An increasing number of patients were detected at later stages (stages III and IV) in this country as evidenced by an increase in percentage to 47.9% in 2012 – 2016 as opposed to 43.2% detection rate in 2007 - 2011 (Baghawi et al., 2019). The relative survival rate is determined by the stage of the disease, with earlier stages having better prognosis. According to the Malaysia Study on Cancer Survival (MySCan), the 5-year relative survival rate for patients with stage I breast cancer was 87.5%; it was reduced to 80.7% for stage II patients, 59.7% for stage III patients, and drastically down to only 23.3% for stage IV patients (National Cancer Registry, 2018).

The overall 5-year relative survival for Malaysian women was 66.8%, as published by MySCAN in 2018. It is lower in comparison to that of advanced countries such as Japan, the USA and Australia, which boast of a 5-year relative survival of more than 80%. This is because the survival of these patients is impacted by several main prognostic variables, one of the most important of which being the stage of disease at first diagnosis, followed by other variables such as the size of the tumour, and the final histopathology. In Malaysia, delayed presentation or later

stage diagnosis has been acknowledged as a key factor contributing to the patient's poorer prognosis and outcome (Abdullah et al., 2013).

2.2 Clinical Presentation

Patients have typical signs and symptoms such as a new swelling or lump on one side of the breast. This can be accompanied by breast discharge or skin changes such as thickening of the overlying skin above the lump, redness, or even nipple retraction (Parthasarathy et al., 2012). Some patients have swellings over their axillary region. Apart from that, many asymptomatic women are detected through regular screening via imaging such as ultrasonography of the breasts and mammography. In Malaysia, medical professionals recommend clinical breast examination (CBE) from age 35 onwards as breast cancer risk increases after this age (Baghawi et al., 2019). According to the Ministry of Health Malaysia (2019a), biennial mammography screening for the general public in low-risk females from 50 – 74 years is advised, while yearly mammography is recommended for females categorised as moderate risk (40-59 years old) (Baghawi et al., 2019). 'Intensive screening', i.e., with clinical breast examination (CBE), mammography, and MRI screening, is recommended for high-risk women with documented family history (defined as a first-degree family member, such as a mother or sister with breast cancer) and genetic carriers of BRCA 1 and 2 (Htay et al., 2021).

Patients with typical cancer symptoms generally seek consultation at their clinics, from which they will be referred to tertiary hospitals for further tests and treatment. At tertiary hospitals, a complete medical examination will be carried out, followed by further investigations for staging, including the use of various imaging modalities.

2.3 Diagnosis

A surgical team evaluates the referred patient; subsequently, a triple assessment is used to reach a diagnosis. This includes clinical examination, further imaging such as ultrasound and

mammography. This is followed by pathological confirmation via histopathology to confirm the diagnosis of breast cancer.

2.3.1 Ultrasonography (US)

Patients with breast lumps and under 45 years of age are recommended to proceed with breast ultrasonography, especially if the mammography or breast MRI reveals abnormalities. This is because the breasts of women under 45 have denser fibro glandular tissue, and ultrasonography is said to have a greater sensitivity. Devolli-Disha et al. (2009) found that ultrasonography was more sensitive than mammography in detecting abnormalities in women younger than 45 years, with a sensitivity of ultrasound of 72.6%, while the sensitivity of mammography was 52.1%. In another study (Lehman et al., 2012), in symptomatic younger women (30-39 years old), 95.7% of cancer cells were detected using ultrasound, versus only 60.9% using mammography. The negative predictive value was, however, high in both, with 99.9% for ultrasonography and 99.2% for mammography. Features of malignant breast lesions on ultrasound include hypoechoic lesions with ill-defined borders, visualisation of hypoechoic nodular lesions described as ‘taller than broader’, and those with spiculated margins, posterior acoustic shadowing or other features such as microcalcifications (Gokhale, 2009). In the Malaysian setting, patients above 40 years of age are usually assessed with mammography as a routine, with complementary ultrasound of the breast performed if the need arises.

2.3.2 Mammography (MMG)

Women, aged 45 and above, who have been diagnosed with breast lumps are often further assessed via mammography as the gold standard (Oeffinger et al., 2015). Breast imaging using mammography is often reported with the BI-RADS (Breast Imaging-Reporting and Data System) classification. Assessment of malignancy of the breast by mammography includes identifying major and minor (or known as secondary) signs. Lump(s), local compact infiltration, micro calcification, burr-like boundary of lump or infiltration area are major signs in

mammography while nipple retraction, thickened skin, comet tail sign, increased number of thickened blood vessels, and peritumoral oedema rings are minor signs in mammography. The identification of one major sign and two secondary signs would usually be confirmatory of breast cancer (Li et al., 2016).

In this matter, a risk assessment and quality control tool called BI-RADS, created by the American College of Radiology, employs a reporting system that is generally regarded and utilised for the reporting of the breast including in ultrasound, mammograms and breast MRI (Magny et al., 2022). Published in 2013, the 5th edition, is the latest version. It is classified into several categories for assessment, where BI-RADS 1 denotes negative findings while BI-RADS 5 indicates a more than 95% probability of malignancy. It is classified into one of the following seven categories for assessment:

BI-RADS	Interpretation
BI-RADS 0: incomplete	○ need additional imaging evaluation (additional mammographic views or ultrasound) and/or ○ for mammography, obtaining previous images not available at the time of reading
BI-RADS 1: negative	○ symmetrical and no masses, architectural distortion, or suspicious calcifications
BI-RADS 2: benign	○ 0% probability of malignancy
BI-RADS 3: probably benign	○ <2% probability of malignancy ○ short interval follow-up suggested
BI-RADS 4: suspicious for malignancy	○ 2-94% probability of malignancy ○ for mammography and ultrasound, these can be further divided: ▪ BI-RADS 4A: low suspicion for malignancy (2-9%) ▪ BI-RADS 4B: moderate suspicion for malignancy (10-49%) ○ BI-RADS 4C: high suspicion for malignancy (50-94%) ○ biopsy should be considered
BI-RADS 5: highly suggestive of malignancy	○ >95% probability of malignancy ○ appropriate action should be taken

BI-RADS 6: known biopsy-proven malignancy	

Figure 2.2: BI-RADS Classification in Mammography

Reprinted from Balleyguier C, Ayadi S, et al, BIRADS™ classification in mammography, European Journal of Radiology, Volume 61, Issue 2, 2007(192-194)

2.3.3 Breast MRI

Apart from ultrasound breast or mammography, magnetic resonance imaging (MRI) of the breast can also be utilised as an additional tool for breast screening to further assess a breast lesion. Breast MRI, primarily performed in patients with established breast cancer, is aimed at further measuring the extent to which cancer cells have spread, apart from looking for tumours in other areas of the primary breast or the opposite breast (Radhakrishna et al., 2018). Features of malignancy on breast MRI include irregular shape, non-circumscribed margins, hypervascularity and typical washout kinetics (Meissnitzer et al., 2017). For females with high risk of breast cancer, a combination of screening mammogram and MRI is suggested annually to increase the probability of early lesion detection. In this matter, BIRADS scoring is used universally where breast lesions which show suspicious features are classified as BIRADS 4 and 5, while BIRADS 3 describes breast lesions that are likely benign with a very low probability of malignancy at less than 2% (Balleyguier et al., 2007).

MRI screening is advised against in patients with atypical hyperplasia or lobular carcinoma in situ (Baghawi et al., 2019) as it is known to provide occasional false-positive results, especially in small volume tumours where the lesions detected are ≤5 mm. The features of malignancy are more difficult to distinguish from benign lesions because they share similar characteristics (Meissnitzer et al., 2017). This translates into unnecessary worry and additional tests for the patient.

Other patients who are contraindicated for MRI include those with severe claustrophobia, previous instrumentations such as intracranial ferromagnetic clips and iron

components such as iron splinters in the eyes and iron pigments used for make up, and those with implanted electronic devices ie pacemakers and cardioverter defibrillators. Other contraindications include those with impaired renal function and MRI is generally not recommended in pregnancy (Mann et al., 2015). Consequently, although breast MRI is beneficial for females with high risk of breast cancer, it is rarely suggested as a screening test for females with low or average risk (Radhakrishna et al., 2018).

2.3.3 Positron Emission Mammography (PEM)

Apart from ultrasound, mammography and MRI, another modality is also available in the advanced nations. Positron Emission Mammography or PEM is a combination of positron emission mammography, and theoretically is superior as it combines both PET and mammography. PEM is a breast specific modality which boasts better spatial resolution and showed higher sensitivity than PET/CT, with equal or better sensitivity than MRI. Along with ultrasound and MRI, PEM is also able to be used to guide and obtain breast biopsy and hence is purportedly able to be used for breast cancer diagnosis (Kalles et al., 2013).

2. 4 Staging

2.4.1 TNM Staging

The currently used TNM staging for breast cancer is based on the American Joint Committee on Cancer (AJCC) recommendations as detailed in the 8th edition of the AJCC Cancer Staging Manual (Hortobagyi, 2018). It incorporates the anatomical stage of size of the tumour (T), nodal involvement (N), distant metastasis (M), and the prognostic stage, taking into account tumour grade, hormone receptor, and oncogene expression, all of which are used to predict patient outcome and survival. This manual, effective since January 1, 2018, describes the anatomical extent of the disease and also outlines a new prognostic staging system based on prognostic biomarkers. It incorporates TNM status, tumour grade, oestrogen (ER) and

progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) statuses if available (Hortobagyi et al., 2018).

Patients with early-stage breast cancer include those with Ductal Carcinoma in situ (DCIS), stages I, IIA and IIB, where routine work up for metastasis is not advised (Baghawi et al., 2019). For those with locally advanced breast cancer (LABC) (stage III) and advanced metastatic breast cancer or stage IV disease, further diagnostic studies are recommended for complete staging. These include single or combined diagnostic modalities, for instance, bone scan, CT, MRI, and FDG–PET/CT.

2.4.1.1 T Staging

Tumour size (T) refers to the size of the primary growth. Besides its size, extension into nearby structures such as the chest wall and skin ulceration also affects the T staging (Figure 2.3).

Stage	Definition
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (Paget's)	Paget's disease of nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in underlying breast parenchyma. Carcinomas in breast parenchyma associated with Paget disease are categorized based on size and characteristics of parenchymal disease, although presence of Paget disease should still be noted
T1	Tumor ≤ 20 mm in greatest dimension
T1mi	Tumor ≤ 1 mm in greatest dimension
T1a	Tumor > 1 mm but ≤ 5 mm in greatest dimension (round any measurement 1.0–1.9 mm to 2 mm)
T1b	Tumor > 5 mm but ≤ 10 mm in greatest dimension
T1c	Tumor > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumor > 20 mm but ≤ 50 mm in greatest dimension
T3	Tumor > 50 mm in greatest dimension
T4	Tumor of any size with direct extension to chest wall and/or to skin (ulceration or macroscopic nodules); invasion of dermis alone does not qualify as T4
T4a	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of skin, which do not meet criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Figure 2.3: Definition of primary tumour (T) category (Based on The American Joint Committee on Cancer (AJCC) 8th edition)

Reprinted from Koh et al, Introduction of a New Staging System of Breast Cancer for Radiologists: An Emphasis on the Prognostic Stage, Korean J Radiol 2019;20(1):69-82, eISSN 2005-8330

Apart from tumour size and number of positive lymph nodes, the tumour grade is a significant prognostic predictor. It reveals tumour differentiation, where individuals who have poor differentiation or higher histologic grade tumours have poorer outcome compared to patients who have well-differentiated or low-grade tumours. A modified Scarff-Bloom-Richardson system (Figure 2.4) is used whereby tubules (glands), mitotic counts, and nuclear pleomorphism are measured and utilised to determine the tumour grade (Bansal et al., 2014).

Feature	Score
Tubule formation (%)	
Majority of tumour (>75)	1
Moderate degree (10-75)	2
Little or none (<10)	3
Nuclear pleomorphism	
Small, uniform cells	1
Moderate increase in size/variation	2
Marked variation	3
Mitotic count (per 10-40x fields)	
0-5 (histo) or 0-1 (cyto)	1
6-10 (histo) or 2-4 (cyto)	2
>11 (histo) or >5 (cyto)	3
Grade 1 (Well-differentiated) (sum)	3-5
Grade 2 (moderately-differentiated) (sum)	6-7
Grade 3 (poorly differentiated) (sum)	8-9

Figure 2.4: Scarff-Bloom-Richardson's Breast Cancer Grading System
Reprinted from Bansal C, Pujani M, Sharma KL, Srivastava A N, Singh U S. Grading systems in the cytological diagnosis of breast cancer: A review. J Can Res Ther 2014;10:839-45

2.4.1.2 N Staging

Regional lymph nodes involvement can occur in various locations. Common locations include ipsilateral axillary, internal mammary, and supraclavicular regions. For nodal or N category, two separate classifications are used: either clinical N (cN) or pathologic N (pN). Clinical N staging is decided via clinical examination, and subsequently established via core biopsy or fine-needle aspiration (Figure 2.5). Pathological N staging is achieved through histopathological confirmation obtained post operatively to assess the metastasis of regional

lymph nodes (Figure 2.6). Pathologic classification is determined by the involvement of regional lymph nodes and the quantity of axillary lymph node metastases (Koh et al., 2019).

Definition of Clinical Regional Lymph Node (N) Category

Stage	Definition
cNX	Regional lymph nodes cannot be assessed (for example, previously removed)
cN0	No regional lymph node metastases
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in absence of clinically evident axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in absence of clinically evident level I, II axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Figure 2.5: Definition of Clinical Regional Lymph Node (N) Category (Based on The American Joint Committee on Cancer (AJCC) 8th edition)

Reprinted from Koh et al., Introduction of a New Staging System of Breast Cancer for Radiologists: An Emphasis on the Prognostic Stage, Korean J Radiol 2019;20(1):69-82, eISSN 2005-8330