EVALUATION OF FATTY LIVER IN BREAST CANCER PATIENTS AND ITS METASTATIC POTENTIAL

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

CECT	Contrast-enhanced computed tomography
CT	Computed tomography
NECT	Non contrast enhanced computed tomography
HU value	Hounsfield unit
IV	Intravenous
LOCM	Low osmolality contrast media
PACS	Picture archiving and communication system
ROI	Region of interest
SD	Standard deviation
HPE	Histopathological examination
DICOM	Digital Imaging Communication in Medicine
HUSM	Hospital Universiti Sains Malaysia, Malaysia
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NAFL	Non-alcoholic fatty liver
NASH	Non-alcoholic steatohepatitis
MetS	Metabolic syndromes

ABSTRAK

Latar belakang: Penyakit hati berlemak yang bukan disebabkan alkohol (NAFLD) mempunyai kelaziman yang lebih tinggi di kalangan pesakit barah payudara berbanding populasi normal. NALFD adalah salah satu faktor risiko untuk karsinogenesis bagi organ selain hati. Kajian lebih lanjut menyatakan bahawa NALFD telah meningkatkan risiko perkembangan tumor primer, risiko perebakan jauh tumor dan risiko kanser berulang. Namun, tidak banyak kajian klinikal yang telah dibuat untuk mengetahui perkaitan antara hati berlemak dan risiko perebakan kanser. Jadi, kajian klinikal yang lebih lanjut perlu dibuat. Tujuan kajian ini adalah untuk mengetahui perkaitan di antara hati berlemak dengan metastatik jauh dan lokasi metastasis jauh. Perkaitan di antara hati berlemak dan dengan metastatik jauh dan lokasi metastasis jauh dilakukan dengan menggunakan analisis statistik Chi Square Test.

Kaedah: Kajian keratan rentas dilakukan di Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia terhadap pesakit kanser payudara wanita yang disahkan secara histopatologi dari Januari 2014 hingga Disember 2020. Penilaian hati berlemak dilakukan dengan menggunakan imej CT abdomen tanpa kontras (NECT) dengan berpandukan imej CT dengan kontras. Tiga kawasan yang terpilih (ROI) di dalam hati dan limpa diambil. Bacaan unit Hounsfield (HU) direkod. Nisbah hati ke splenik (nisbah L / S) dikira dengan membahagikan purata HU hati ke nisbah HU limpa. Nisbah L / S kurang dari 1.0 dianggap sebagai hati berlemak. Penilaian metastasis dilakukan. Perkaitan antara hati berlemak dengan metastasis jauh dan tempat metastatik jauh dinilai.

Keputusan: Sebanyak 332 subjek daripada 624 subjek yang disaring dalam kalangan pesakit kanser payudara yang terbukti secara histopatologi yang menjalani imbasan CT termasuk pemeriksaan dada, abdomen dan pelvis adalah peserta kajian ini. Purata umur adalah 53 tahun (SD±10.93) berumur antara 28 hingga 82 tahun. 45.5% (n=151) subjek mempunyai saiz tumor primer > 5 cm, dan 51.8% (n=172) mempunyai metastasis jauh pada awal diagnosis. Tempat metastasis jauh yang paling kerap adalah ke paru-paru dan pleura, diikuti tulang dan hati. Sebanyak 27.2% (n = 91) subjek kajian ini mempunyai hati berlemak. Kajian ini mendapati ada perkaitan di antara perlemakan hati dan metastasis jauh. Kajian ini juga mendapati ada perkaitan di antara perlemakan hati dan metastasis ke paru-paru dan selaput paru-paru. Akan tetapi, tiada perkaitan didapati antara perlemakan hati dengan metastasis jauh and tempat metastasis jauh bagi subjek yang mempunyai saiz kanser yang ≤ 5cm.

Kesimpulan: Sebanyak 27.2% pesakit kanser payudara mengalami perlemakan hati, di mana tiada perbezaan ketara dengan kajian- kajian yang dijalankan sebelum ini. Kajian kami mendapati ada perkaitan diantara perlemakan hati dengan metastasis jauh dan metastasis ke paru-paru dan pleura. Namun, tiada perkaitan yang jelas di antara perlemakan hati dan metastasis jauh serta tempat metastasis bagi saiz kanser primary ≤ 5cm.

Kata kunci: *Kanser payudara; Lemak hati; Steatosis hepatik; Penyakit hati berlemak bukan disebabkan alkohol; Metastasis*

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) has a higher prevalence among breast cancer patients compared to the normal population and is one of the risk factors for extrahepatic carcinogenesis. It has also increased the risk of primary tumour progression, risk of distant metastasis, and tumour recurrent. However, to date, not many clinical studies were done to evaluate fatty liver and metastatic risk. Thus, further clinical study is needed. This study aims to evaluate the association of fatty liver with distant metastasis and metastatic site.

Methods: A cross-sectional study was conducted in Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia on histopathological confirmed female breast carcinoma patients from January 2014 till December 2020. The evaluation of fatty liver done were made on a plain CT abdomen images with reference of contrasted images. Three regions of interest (ROI) were drawn on the liver and spleen and the Hounsfield unit (HU) was documented. Liver to splenic ratio (L/S ratio) was calculated by dividing the average liver HU to splenic ratio. L/S ratio of less than 1.0 was taken as fatty liver. Evaluation of distant metastasis was also done. The association of fatty liver with distant metastasis and metastatic site were evaluated.

Results: Out of 624 screened subjects, a total of 332 subjects with histopathologically proven breast carcinoma patients that underwent CT scan stage including thorax, abdomen, and pelvis scans were included as participants in this study. Mean age was 53 years (SD±10.93) ranging from 28 to 82 years old, 45.5% (n=151) had tumour size of > 5 cm, 51.8% (n=172) had metastasis at diagnosis. The

most common metastasis site was the lung, followed by bone and liver. The prevalence of fatty liver in the study population was 27.2% (n=91). This current study showed association of fatty liver with distant metastasis. Association of fatty liver with lung metastasis were also demonstrated. However, there was no association between fatty liver and distant metastasis or with the site of metastasis in tumour size of ≤ 5cm.

Conclusion: Prevalence of fatty liver in breast carcinoma patients in our study was 27.2%, which corresponds to most of other studies. Considering the existing studies investigating the relationship between fatty liver and breast cancer, our study results showed a similar finding of an association of fatty liver with distant metastasis. Association of fatty liver with distant metastatic site to lung and pleura were also demonstrated. However, no association between fatty liver and distant metastasis or metastatic sites in tumour size of ≤ 5cm.

Keywords: Breast cancer; Fatty liver; Hepatic steatosis; Nonalcoholic fatty liver disease; Metastasis

CHAPTER 1:

BACKGROUND

CHAPTER 1: BACKGROUND

1.1 Introduction/Problem Statement

Breast cancer is the most frequently diagnosed cancer in women worldwide with more than 2 million new cases expected to be diagnosed in 2018 (Lindsey Torre et al., 2018). Rising breast cancer incidence was also noted in the previously considered low-risk country including Asian countries. The second most leading cause of death worldwide is malignant neoplasm and the most common leading cause of death in women is breast carcinoma (Lindsey Torre et al., 2018). In Malaysia, the National Cancer Registry report showed that the most common cancer among Malaysian is breast cancer (17.7%) followed by colorectal (13.2%) and lungs (10.2%). The prevalence of distant metastatic breast cancer (stage IV) at diagnosis is 16.4% (Azizah, 2015).

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide. Worldwide, NAFLD has a reported prevalence of 6 to 35 percent (median 20 percent). The estimated prevalence of NALFD in Malaysia is < 10% (Younossi et al., 2018). Fatty liver has an association and increased risk of developing extrahepatic cancers (Sanna et al., 2016). Non-alcoholic liver disease is found to be a significantly higher in breast cancer patients compared to the normal population (Nseir et al., 2017, Chu, 2003). Previous studies show the prevalence of NALFD among breast cancer patients is approximately 26.2% - 63 % (Lee et al., 2019, Nseir et al., 2017, Ocak Duran et al., 2015). However, a study among breast cancer patients in Indonesia shows significantly higher prevalence of NALFD (93.3%)

among their breast cancer patients (Philip Waruna, 2014). No exclusion of post tamoxifen therapy patients in their study thus could be one the factor that NALFD prevalence is significantly higher compared to other studies. There is no published study regarding the prevalence of NALFD among breast cancer patients in Malaysia. Association of breast cancer and NALFD is observed in a previous study (Nseir et al., 2017). NALFD is associated with hyperinsulinemia, high level of inflammatory cytokines especially tumour necrosis factor-alpha (TNFα), decreased adinopectin levels, high level of leptin, and reduced adinopeptin:leptin ratio. Preclinical studies show these are the contributing factors of mammary tumorigenesis, tumour growth, and distant metastasis (Makoto Ishikawa, 2004, Grossmann and Cleary, 2012). Metastasis consists of a series of sequential steps, all of which must be successfully completed. These include cells intravasation from a primary tumour into the blood circulation, survival of the cells in the circulation, arrest in a new organ, extravasation into the surrounding tissue, initiation, and maintenance of growth, and vascularization of the metastatic tumour (Chambers et al., 2002). Breast cancer spread through hematogenous, most commonly metastasized to bone, lung, and liver. Metastatic breast carcinoma carries a poor prognosis and outcome. Furthermore, fatty liver is also associated with a significantly increased risk of breast cancer recurrence after curative surgery (Lee et al., 2019).

Given the current NALFD prevalence and its relationship with breast cancer carcinogenesis and its metastatic risk, it is important to evaluate the clinical correlation between NALFD and distant metastasis. A previous study in southern China involving Chinese patients had shown that fatty liver at the time of cancer diagnosis decrease liver metastasis in patients with breast cancer (Wu et al., 2017).

Thus, we design this study to evaluate fatty liver among breast cancer. The aim of this study is to establish the NALFD prevalence among breast cancer patients in Hospital Universiti Sains Malaysia, which represents a part of the Malaysian population, and evaluate the association of NALFD with distant metastasis. The findings from this study can help in the management decision of follow-up interval.

1.2 Objectives

1.2.1 General Objective

This study aims to look at the association between fatty liver and distant metastasis among breast cancer patients.

1.2.2 Specific Objectives

1) To look for prevalence of fatty liver among breast cancer patients.
2) To determine association of fatty liver with breast cancer distant metastasis (bone, lung, liver and others) with primary tumour size less than or equal to 5 cm.

1.3 Hypothesis

Distant metastasis is higher in fatty liver group compared to non - fatty liver group of breast cancer patients.

1.4 Research Question

Is distant metastasis being higher in breast cancer patients who had fatty liver?

CHAPTER 2:

LITERATURE REVIEW

CHAPTER 2: LITERATURE REVIEW

2.1 Non-alcoholic fatty liver disease and breast carcinoma.

Hepatic steatosis or fatty liver is characterized by the histologic finding of ⩾ 5% macrovesicular steatosis of the hepatocytes. Non-alcoholic fatty liver disease (NAFLD) is a clinical disease characterized by the presence of fat in the liver (hepatic steatosis) either on imaging or on liver histology after the exclusion of secondary causes of fat accumulation in the liver (e.g., significant alcohol consumption, certain medications, and other medical conditions). Significant alcohol consumption is considered when alcohol consumption is ⩾ 30 g/day for men and ⩾ 20 g/day for women. NAFLD is further categorised histologically into the non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (Ma et al., 2009). NAFL is defined as hepatic steatosis with no evidence of hepatocellular injury in the form of hepatocyte ballooning. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis (Puri and Sanyal, 2012).

Currently, non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide (Sanna et al., 2016). NALFD may be progressive resulting in cirrhosis that may be complicated by hepatocellular carcinoma and liver failure (Adams et al., 2005). Overall, about 5% of patients with NAFLD develop cirrhosis over an average of a seven-year period with 1.7% mortality from complications of liver cirrhosis. The high prevalence and chronic course of NAFLD subsequently caused a significant health burden for the general

community. In addition, subjects with a diagnosis of NAFLD have a higher mortality risk than the general population (Adams et al., 2005).

NAFLD is a complex multifactorial disease closely interrelated with obesity, and type 2 diabetes. NALFD, obesity and the type 2 diabetes have a significantly increased risk of several types of cancer. Other than the risk of hepatocellular carcinoma, NAFLD is an independent risk factor for cancers, particularly in the gastrointestinal tract (Sanna et al., 2016).

Treatment strategies for NAFLD have revolved around the identification and treatment of associated metabolic conditions such as diabetes and hyperlipidaemia; improving insulin resistance by weight loss, exercise, or pharmacotherapy and also using hepato-protective agents such as antioxidants. Weight loss can also be achieved by bariatric surgery consideration in a morbidly obese patient (Adams and Angulo, 2006).

Research in recent years has characterised important pathways that might link metabolism, inflammation, and cancer development. Mediators derived mainly from the adipose tissue such as adiponectin or leptin (called adipocytokines) could be critically involved in such processes and therefore might reflect linking obesity-related disorders with tumour development both intra- and extrahepatically (Fracanzani et al., 2011). Non-alcoholic liver disease is found to be significantly higher in breast cancer patients compared to the normal populations (Nseir et al., 2017, Chu et al., 2003). The prevalence of fatty liver in breast cancer patients is 45.2% compared to normal population, 16.4% (Nseir et al., 2017). Tamoxifen therapy is also associated with fatty liver among breast cancer patients (Pan et al., 2016, Yoo et al., 2020).

The proposed mechanism(s) for extrahepatic carcinogenesis of fatty liver is still not completely understood. Muhidin et al.(2012) proposed three major factors that may explain the linkage mechanism (Muhidin et al., 2012). The first mechanism is via high levels of inflammatory cytokines, especially tumour necrosis factor-alpha. These inflammatory cytokines promote insulin resistance, increase circulating triglycerides, influence growth, and increase apoptosis and tumour cell proliferation in many cancers including breast cancers (Shoelson et al., 2006). The second factor is high insulin level in the blood and high levels of leptin which induce the carcinogenesis effect (Tilg and Diehl, 2011). Elevated insulin levels lead to increased secretion of oestrogen by binding to the circulating sex hormone-binding globulin. The increased oestrogen-mediated downstream signalling favours breast carcinogenesis (Khan et al., 2013). The third factor is the decreased levels of adiponectin, which leads to marked insulin resistance and subsequent increased levels of insulin growth factor-1 (IGF-1). Insulin binds to IGF-1 receptors and plays an important role in cell proliferation, apoptosis, and increased production of vascular endothelial growth factor.

In the context of primary tumour progression, the presence of fatty liver may also promote primary tumour progression. In NALFD subjects, lower adiponectin serum levels compared to healthy controls were reported (Hui et al., 2004). Adiponectin demonstrates anti-carcinogenic effects in vitro as it is able to inhibit the growth of cancer cells through stimulating AMP-activated protein kinase activity (Wei et al., 2005). Most of the studies indicate that leptin can potentiate the growth of cancer cells (breast, oesophageal, gastric, pancreatic, colorectal, prostate, ovarian and lung carcinoma cell lines), whereas adiponectin seems to decrease cell proliferation.

In contrast to tumour development, the metastatic process to secondary organs follows a basic sequence – local invasion, intravasation, survival in circulation, extravasation, and growth at metastatic foci (Woodhouse et al., 1997). However, metastasis is considered an inefficient process because the only significantly low number of cells among the numerous cancer cells in the circulation can invade and form distant nodules (Chambers et al., 2002). There are many other factors affecting distant metastasis in breast cancer. Distant spread to certain organs is regulated by a number of factors including intrinsic breast cancer subtypes, metabolic changes, molecular alterations of the cancer cells, host immune responses, and tumour microenvironment. Luminal A subtype, infiltration of the tumour to the skin and chest wall, and nodal involvement are associated with the risk of distant metastasis (Anwar et al., 2020). Tumour size of > 5cm is one of the confounding factors that might affect the distant metastasis in view of tumour size > 5 cm was identified as an independent risk factor for distant metastasis of primary triple-negative breast cancer (Yao et al., 2019). Tumour size > 5cm also shows an increased risk of bone metastasis (Yazdani et al., 2019). Several studies have been done to assess the relationship between fatty liver and metastasis. According to a murine colonic liver metastases model, dietary fatty acids may decrease malignant metastatic tumour growth in the liver (Tamura et al., 1999, Gutt et al., 2007). Furthermore, fatty liver was also reported to play an important role in neovascularization inhibition in the metastatic liver lesion and decreased activity of pyrimidine nucleoside phosphorylase (Karube et al., 2000). These studies suggest that hepatic steatosis may be protective against the extravasation and growth of cancer cells in the liver. In contrast to distant metastasis to the liver, fatty liver may not protect the cancer cells to survive in the other parts of metastatic site. A clinical

study has shown that fatty liver at the time of cancer diagnosis increases risk of liver metastasis, however the sample size is too small with involvement of 107 subjects (Ocak Duran et al., 2015). Following that study, a cohort study was subsequently carried out. It shows that hepatic steatosis may serve as an independent factor to decrease liver metastasis in patients with breast cancer. The survival cumulative liver metastasis-free survival (MFS) rate was significantly higher in the hepatic steatosis group than in the non-hepatic steatosis (Wu et al., 2017). In the other hand, fatty liver can progress to liver malignancy and fibrosis. Furthermore, fatty liver is also associated with significant increased risk of cancer recurrence (Lee et al., 2019).

2.2 Evaluation of hepatic steatosis

Histologic examination is accurate in detection of hepatic fat content, but it is invasive and time consuming, and sampling errors can occur (Kodama et al., 2007). Other than histopathological examination, there are multiple imaging modalities which are non-invasive can be used for assessment of fatty liver including ultrasound, unenhanced computed tomography (CT), enhanced CT, Magnetic resonance imaging (MRI) as well as Magnetic resonance Spectroscopy (MRS) (Ma et al., 2009) .

Ultrasound is widely used, cheap and does not involved ionizing radiation, however accuracy is dependent on the operator, transducer, equipment and presence of hepatic and renal parenchymal disease. It is also unable to differentiate between fibrosis or iron overload and only useful for qualitative assessment but not quantitative. Qualitative assessment was found to have sensitivity of 60%–100%, specificity of 77%–95%, and accuracy of 96% (Ma et al., 2009).

Computed tomography (CT) is a better tool for fatty liver evaluation. Unenhanced CT is simple, readily available and widely used for qualitative and quantitative assessment. It has high sensitivity for steatosis of >30%. However the accuracy is dependent on scanning parameters (kVp, mAs), acute liver injury, other depositional diseases of liver (eg, iron, glycogen, amyloid accumulation (Ma et al., 2009). Contrasted CT is almost similar to unenhanced CT, however it is less accurate due to scanning parameters, iodinated contrast material dose, scanning delay after injection of contrast material (Ma et al., 2009).

Magnetic resonance (MR) imaging is one of the most sensitive modalities for detection and characterisation of fatty infiltration of the liver. It utilised chemical

shift, single shot fast spin ECHO and MR spectroscopy. Generally, it is more sensitive to detect lower percentage of steatosis, whereby chemical shift detect steatosis 10-15 % and single shot fast spin ECHO detect > 8 % steatosis. However, it is expensive, not readily available and more complex in term of analysis (Ma et al., 2009). It is not practical to be used for evaluation of fatty liver in breast cancer patient in view of it is not part of routine examination.

This study uses non enhanced CT to detect the fatty liver among breast using Hounsfield unit or CT number measurement. Unenhanced CT imaging is widely available, reproducible measurement, easy to analyse and no additional ionizing radiation is needed as patient had done CT for cancer staging.

Hounsfield scale, named after Sir Godfrey Hounsfield, is a quantitative scale for describing radiodensity. It is used in CT scans, where its value is also termed as CT number. The CT Hounsfield scale calibrated such that the Hounsfield unit value of water is 0 HU and that for air is -1000 at all tube energies used. Thus, represent 2 fixed points on the Hounsfield unit scale (Bushberg, 2002). Hounsfield number measurements allow a quick and simple method to characterized certain tissue types. Fat attenuation is lower than liver attenuation. As such, in the presence of fat deposition in the liver, the Hounsfield unit of liver will become lower.

Various methods are used for the hepatic steatosis diagnosis in unenhanced CT including attenuation of 40 HU, hepatic to splenic ratio <0.8 - < 1.0 and hepatic – splenic attenuation difference by -10 HU. In a study of CT fatty liver evaluation by Zeb *et al*, 2012, hepatic and splenic HU attenuation values were measured using regions of interest (ROI) greater than 100 mm^2 in area. There were two ROI placed in the right liver lobe anteroposteriorly, one ROI in the left liver lobe and one ROI in

the spleen. ROI with larger areas were used in their study. Whenever possible, they include a greater area of the liver and spleen while excluding regions of non-uniform parenchymal attenuation, including hepatic vessels. Liver to splenic (L/S) ratio was calculated by taking mean HU measurement of both right liver lobe ROIs and dividing it by the spleen HU measurement. L/S ratio <1.0 was taken as the cut off point for the diagnosis of presence of liver fat. As another parameter, liver attenuation <40 HU was used as a cut off of >30% liver fat content. Comparing two criteria to determine the presence of moderate to severe steatosis; L/S ratio <1.0 and <40HU, the study shows that the prevalence provided by L/S ratio <1.0 (17.2%) is higher than that provided by liver attenuation <40HU cut off (6.3%). This was concluded as may be because of the fact that L/S ratio <1.0 may include some of the mild steatosis cases in addition to identifying moderate to severe steatosis on CT images (Zeb et al., 2012).

Another study by Ma *et al,* 2009 have been described the proper technique of measuring the liver attenuation, thus more representative HU values can be obtained. The ROI should be made as large as possible (at least 1 cm^2). Furthermore, the inclusion of any large vessels or biliary structures should be avoided. The use of multiple ROIs in both liver lobes may help to reduce CT number variability due to the heterogeneous distribution of fat. Although the use of as many as 12 ROIs has been reported, one or two ROIs are usually sufficient (Ma et al., 2009).

2.3 Imaging of distant metastasis

Breast cancer staging performed using TNM staging by American Joint Committee on Cancer's Staging System for Breast Cancer guideline. Clinical anatomic staging assesses the extent of disease involving the primary tumour (Tis to T4), regional lymph node status (N0 to N3), and distant metastasis (M0 or M1) to yield an overall anatomic stage (0 to IV). The final anatomic stage then carries a prognosis from most favourable (stage 0) to least favourable (stage IV). Figure 1 shows the categories of clinical anatomic staging of the primary tumour (T categories) range from Tis to T4 and are identical to those of pathologic anatomic staging of the primary tumour, figure 2 shows clinical anatomic regional lymph node staging and figure 3 shows distant metastasis staging (Kalli et al., 2018). Figure 4 shows anatomic staging summary (Kalli et al., 2018).

Primary Tumour Anatomic Staging: Clinical and Pathologic T Category	
T Criteria	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis (Paget)	Paget disease not associated with invasive carcinoma or DCIS
Tis (DCIS)	Ductal carcinoma in situ
T1	Tumour size ≤ 20 mm T1mi Tumour size ≤ 1 mm T1a Tumour size > 1 mm but ≤ 5 mm T1b Tumour size > 5 mm but ≤ 10 mm T1c Tumour size > 10 mm but ≤ 20 mm T2 Tumour size > 20 mm but ≤ 50 mm T3 Tumour size > 50 mm
T4	Tumour with direct extension to the chest wall and/or the skin with macroscopic changes T4a Tumour with chest wall invasion T4b Tumour with macroscopic skin changes including ulceration and/or satellite skin nodules and/or oedema T4c Tumour with criteria of both T4a and T4b T4d Inflammatory carcinoma

Figure 1: Categories of clinical anatomic staging of the primary tumour (T categories) range from Tis to T4 and are identical to those of pathologic anatomic staging of the primary tumour.

Figure adapted from American Joint Committee on Cancer's Staging System for Breast Cancer guideline (Kalli et al., 2018).

Clinical Anatomic Regional Lymph Node Staging	
cN Category	cN Criteria
cNX	Regional nodes cannot be assessed (previously removed)
cN0	No regional nodal metastases
cN1	Metastases to movable ipsilateral level I and/or level II axillary nodes cN1mi Micrometastases
cN2	Metastases to fixed or matted ipsilateral level I and/or level II axillary nodes; or metastases to ipsilateral internal mammary nodes without axillary metastases cN2a Metastases to fixed or matted ipsilateral level I and/or level II axillary nodes cN2b Metastases to ipsilateral internal mammary nodes without axillary metastases
cN3	Metastases to ipsilateral level III axillary nodes with or without level I and/or level II axillary metastases; or metastases to ipsilateral internal mammary nodes with level I and/or level II axillary metastases; or metastases to ipsilateral supraclavicular nodes cN3a Metastases to ipsilateral level III axillary nodes with or without level I and/or level II axillary metastases cN3b Metastases to ipsilateral internal mammary nodes with level I and/or level II axillary metastases cN3c Metastases to ipsilateral supraclavicular nodes

Figure 2: Clinical anatomic regional lymph node staging.

Figure adapted from American Joint Committee on Cancer's Staging System for Breast Cancer guideline (Kalli et al., 2018).

Table 3: Distant Metastases: Anatomic Staging (Clinical and Pathologic)	
M Category	M Criteria
M0	No clinical or imaging evidence of distant metastases cM0(i+) No clinical or imaging evidence of distant metastases, but with tumor cells or deposits measuring ≤0.2 mm detected in circulating blood, bone marrow, or other nonregional nodal tissue in the absence of clinical signs and symptoms of metastases
cM1	Distant metastases on the basis of clinical or imaging findings
pM1	Histologically proven distant metastases in solid organs; or, if in nonregional nodes, metastases measuring >0.2 mm

Figure 3: Distant metastasis staging.

Figure adapted from American Joint Committee on Cancer's Staging System for Breast Cancer guideline (Kalli et al., 2018).

Anatomic Staging Summary	
Stage	TNM
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 IIIC	Any T, N3, M0
Stage IV	Any T, Any N, M1

Figure 4: Anatomic staging summary.

Figure adapted from American Joint Committee on Cancer's Staging System for Breast Cancer guideline (Kalli et al., 2018).

The distant metastasis is considered when there is evidence of metastasis to the distant organ; bone, lung, liver and other parts of the body. Lymph node involvement other than regional including cervical lymph nodes, contralateral internal mammary

lymph nodes, or contralateral axillary lymph nodes, are considered distant metastases (Kalli et al., 2018).

2.4 Imaging of skeletal metastasis

In term of radiology, skeletal metastases can be lytic or sclerotic lesions or a combination of both. Radionuclide imaging is often performed to evaluate for possible skeletal metastases because it is more sensitive than radiology for the detection of the lesion (Coleman, 1997).

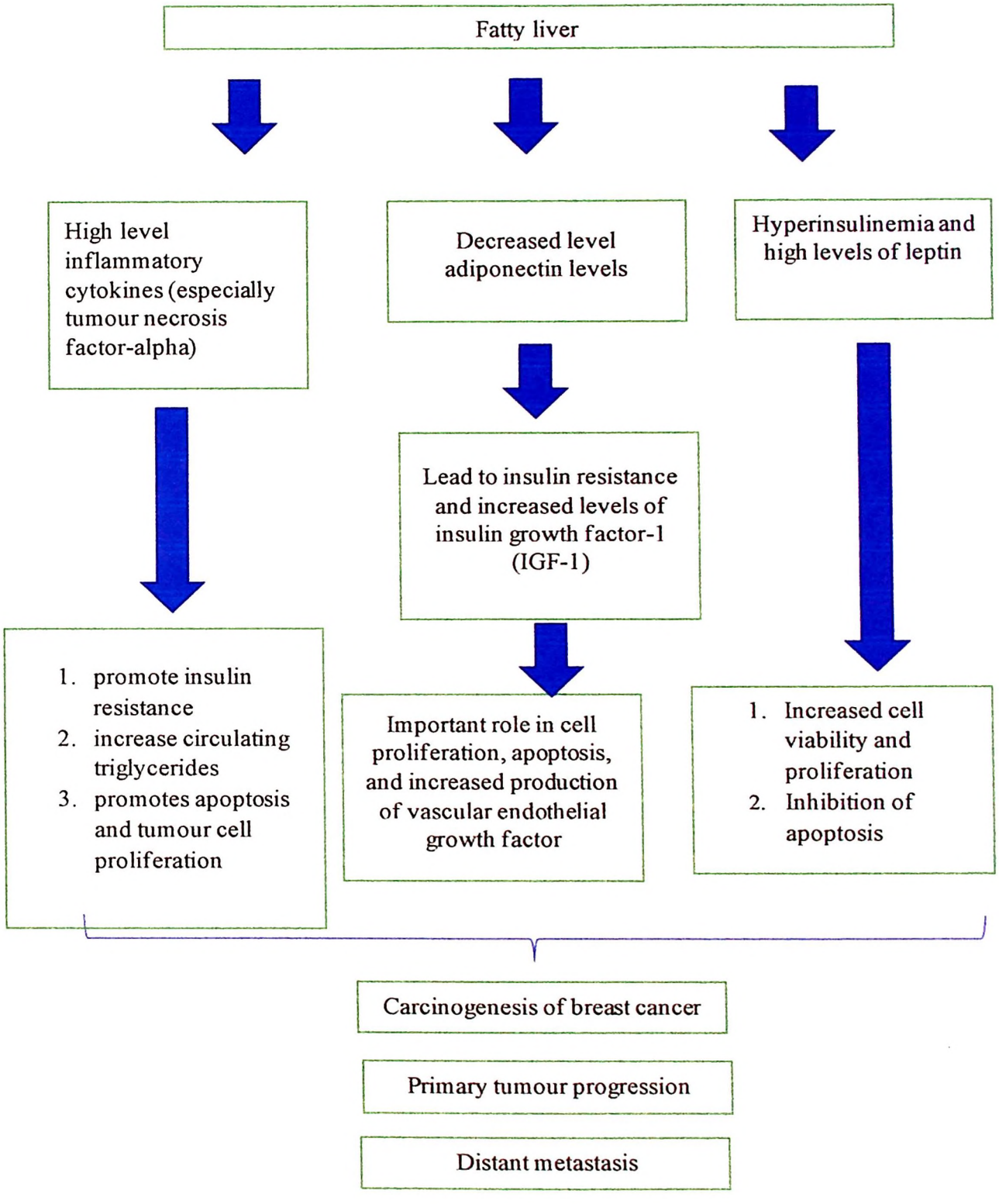
2.5 Imaging of thoracic metastasis

Multiple pulmonary nodules are common findings in lung metastasis as a result of breast cancer. They occur by means of hematogenous tumour spread. In general, metastatic lesions are spherical or ovoid, vary in size, are sharply marginated, and is located mostly in the periphery of the lung. The pattern of lung metastasis includes solitary pulmonary nodule, multiple pulmonary nodules, airspace pattern metastasis, lymphangitic metastasis or endobronchial metastasis. The pleura is a frequent target of metastatic breast cancer (Jung et al., 2004). Pleural effusion is the most common manifestation of pleural metastasis in patients with breast cancer. The effusion is more commonly unilateral and ipsilateral to the primary tumour. Pleural nodularity, irregular pleural thickening, and plaque are fewer common findings in pleural metastases. It is rarely occur without an accompanying pleural effusion (Connolly et al., 1999).

2.6 Imaging of liver metastasis

Most metastases are as low or isoattenuating masses on CT. Depending on lesion size, the margins tend to be irregular, and necrosis may be present, but margins are sharp and well defined. Central low attenuation may be the result of necrosis or cystic change. Calcification may be present with metastases from primary breast cancer. Most metastases are hypovascular and during the arterial phase show a complete ring of enhancement. Hypervascular metastases have diffuse enhancement. During the portal venous phase of imaging, a thickened ring enhances pro gressively but to a lesser extent than liver.

2.7 Conceptual framework



Distant metastasis in breast carcinoma patient.