Original Article

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Clinical Significance of Radiologically Detected Small Indeterminate Extra-Mammary Lesions in Breast Cancer Patients

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ABSTRACT

Objective: Patients with breast cancer who have indeterminate extra-mammary lesions, for example in lung, liver or bone, without other metastatic lesions pose a clinical dilemma regarding subsequent management. This study aimed to investigate the prevalence, characteristics and outcomes of such lesions detected on initial staging imaging, and address the clinical significance of these incidental findings.

Materials and Methods: Medical records of patients with newly diagnosed breast cancer who underwent computed tomography scans and bone scintigraphy between January 1, 2015 and June 30, 2021 were reviewed. Patients with indeterminate extra-mammary lesions on imaging were included. Patients with obvious metastatic disease were excluded. Lesion characteristics, breast cancer staging, duration of follow-up and natural history of disease progression were analysed.

Results: The study included 52 patients with indeterminate lesions on pre-operative imaging. The median follow-up duration was 14 (range: 6–41) months. The most common site of occurrence of indeterminate lesions was the lung (60.9%) followed by the liver (26.1%). Forty-six had lesions that remained stable (88.5%), while six (11.5%) had progression to metastatic disease. Out of these six, only two (3.8%) developed metastasis in the same site as the original indeterminate lesion, whereas the remaining four developed metastases in other sites.

Conclusion: Patients with breast malignancy found to have indeterminate extra-mammary lesions without obvious distant metastasis on initial staging scans are associated with a small risk of subsequently developing metastatic disease. Although most of these lesions remain quiescent, surveillance imaging is recommended because a small but significant proportion of patients with such lesions eventually harbour actual metastatic disease.

Keywords: Breast cancer; extra-mammary; indeterminate lesion; metastatic

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Key Points

- This is the first study to evaluate the incidence and progression of indeterminate lesions in breast cancer in an Asian population.
- Most common site of occurrence of an indeterminate lesion was in the lung (60.9%).
- A small but significant proportion of these indeterminate lesions will progress to metastatic disease (3.8%).
- Routine biopsy of such lesions is not recommended, but dedicated imaging can be considered if resources permit.
- Surveillance of such indeterminate lesions is recommended.

Introduction

Breast cancer has the highest prevalence and is the leading cause of cancer-related deaths amongst women globally. There has been a 3.1% annual increase in the incidence of breast cancer from 1980 to 2010, with more than 1.6 million cases diagnosed yearly worldwide (1). In Singapore, the five-year age-standardised relative survival has increased significantly from 50.4 % in 1973–1977 to 81.4% in 2014–2018 (2). The majority of patients with breast cancer are diagnosed at an early-stage (close to 75% based on the 2018 Singapore Cancer Registry) and only 11.2% of patient present with metastatic disease (2).

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With pre-operative staging using computed tomography (CT) becoming more routine, we have observed an increasing number of patients presenting with radiologically indeterminate lesions in extra-mammary locations, such as the lung, liver and bone, without definitive evidence of metastatic disease. Indeterminate lesions are often too small to be characterised definitively. The term "indeterminate" also has varying definitions for differing organs in different studies. For instance, an indeterminate pulmonary nodule is defined as a small, focal radiographic opacity located completely within the lung measuring up to 1.5–3 cm in diameter without other abnormalities (3, 4), whereas an indeterminate liver nodule has been defined as a low-attenuating hepatocellular opacity smaller than 1.5–2 cm and visible on at least one phase of the dynamic helical CT scanning (5, 6).

In the absence of other metastatic lesions, the incidence of such lesions is reported to be in the range of 4.2% to 59% (4, 7-10). The significance of these lesions is often unknown at the time of diagnosis. Benign lesions represent the most frequent findings; however, the incidence of malignant incidental lesions have been shown to be higher in patients with a personal history of breast cancer (11). Rates of occult metastatic disease in patients with newly diagnosed breast cancer have also been shown to be low, estimated at between 5%–7% (12, 13). Hence, it is unclear whether such patients should be managed as early breast cancer with curative intent, or labelled as metastatic disease. Given the paucity of clinical data to guide management, surveillance is often recommended.

This retrospective study aimed to investigate the prevalence, characteristics and outcomes of extra-mammary indeterminate lesions detected on initial staging imaging in patients with newly diagnosed breast cancer. It also aimed to address the clinical significance of these incidental findings by evaluating if there was a higher propensity of progression to distant metastasis.

Materials and Methods

Medical records of all patients with newly diagnosed breast cancer, regardless of initial stage of disease, who underwent initial staging scans at Khoo Teck Puat Hospital, a tertiary regional hospital in Singapore, were collected retrospectively from January 1, 2015 to June 30, 2021. Routine staging imaging comprised of CT chest, abdomen and pelvis scan and also a bone scintigraphy scan.

Indeterminate lesions were defined as lesions less than 15 mm in diameter in the absence of other metastatic lesions, which were detected on contrasted single-phase CT imaging or on bone scintigraphy scan. These are lesions which could not be concluded as definitely benign or malignant, based on radiological appearances, and warrant further imaging or interval surveillance. Patients noted to have indeterminate lesions in extra-mammary locations, including lungs, liver, bone or other organs on pre-operative imaging were included. If there were greater than one indeterminate lesion noted within the same patient, they were included and lesions were recorded separately. Lesions that were characterized definitively by the radiologist as metastasis (Stage IV disease), or benign lesions without the suggestion of further radiologic follow-up, were excluded. Patients that were lost to follow-up or declined further surveillance scans were similarly excluded. All subsequent imaging scans of patients with indeterminate lesions were reviewed to assess for progression. Lesions with an increase in size or manifestation of malignant radiologic features over time were considered as likely metastasis.

Details about patient demographics, tumour characteristics [tumor-node-metastasis (TNM) staging, hormone receptor and human epidermal growth factor receptor 2 (HER2) status, grade] were abstracted from the electronic medical records. Characteristics of the indeterminate lesions on pre-operative staging scans, including site, size, location and presence of calcification, were recorded. These same lesion characteristics were similarly recorded for subsequent scans performed. The surveillance intervals and time interval to progression of these lesions were also analysed.

The statistical analysis compared the clinicopathologic and demographic data between patients with stable lesions on radiologic follow-up and patients with malignant lesions. The Mann–Whitney U test was used to compare age in the two groups. Fisher's exact probability test was used to check the association between patients' tumour histologic grade, tumour stage, lymph node status and receptor status with risk of metastatic disease progression. Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Armonk, NY, USA) was used for the analysis, and the significance level was set at 0.05.

Institutional Review Board approval was granted for this retrospective study, and a waiver of informed consent was obtained (DSRB reference number: 2020/00181).

Results

A total of 736 patients with breast cancer who were treated in Khoo Teck Puat Hospital in Singapore from January 1, 2015 to June 30, 2021 had pre-operative staging CT and bone scan performed. Fifty-two (7.1%) patients were identified as having indeterminate lesions that could not be definitively characterised.

The patients with indeterminate nodules were characterised according to patient demographics (Table 1). All patients were female and the mean age was 59.6 years. Out of 52 patients, 47 (90.4%) had invasive ductal carcinoma, two (3.8%) had invasive lobular carcinoma, one (1.9%) had a malignant phyllodes tumour and two (3.8%) had squamous cell carcinoma. Three (5.7%) were Grade 1, 21 (40.4%) were Grade 2 and 28 (53.8%) were Grade 3 tumours. When stratified according to stage of disease, 18 (34.6%) had Stage I, 22 (42.3%) had

Table 1. Patient demographics

Age	
Mean ± SD	59.6±11.8
(minimum, maximum)	(37, 86)
Sex (n = 52)	
Male	0 (0%)
Female	52 (100%)
Ethnic group (n = 52)	
Chinese	37 (71.2%)
Malay	7 (13.5%)
Indian	4 (7.6%)
Others	4 (7.6%)
Smoker (n = 52)	
Yes	5 (9.6%)
No	47 (90.4%)

SD: standard deviation

Stage II and 12 (23.1%) had Stage III disease. Further breakdown of the histopathological data of the primary breast tumour is summarised in Table 2.

Review of the imaging for the indeterminate lesions was undertaken to assess the location and characteristics of these lesions. The most common locations for indeterminate lesions were the lungs (n = 28, 60.9%), bone (n = 14, 30.4%), liver (n = 12, 26.1%), and adrenal glands (n = 6, 13.0%). There was an isolated case of an indeterminate large (8 cm) retrosternal thyroid lesion which was largely cystic with small areas of hypodensity on CT. Subsequently this lesion was worked up with an ultrasound thyroid and found to be a benign cystic lesion. There was another isolated case of a right adnexal lesion which remained stable on subsequent imaging.

Characteristics of these indeterminate lesions were also analysed. Amongst the 28 patients with indeterminate lung nodules, all had either one or two nodules with an average nodule size of 4.6 mm (range: 2 mm – 13 mm). None of the nodules were calcified and 5 (18%) had centrally located nodules, whilst 23 (82%) had peripherally located nodules. Of the 14 patients with indeterminate bony lesions, four (29%) had lytic lesions whilst 10 (71%) had sclerotic lesions. Of the 12 patients with indeterminate liver lesions, five (42%) had solid-cystic lesions compared to seven (58%) who had solid lesions. The indeterminate adrenal lesions ranged in size from 13 mm to 35 mm (mean: 22 mm), with Hounsfield units on unenhanced CT images of -22 HU up to 27 HU (mean: 6.3 HU). These patients subsequently underwent CT adrenal scan which revealed lipid-rich lesions and hence low likelihood for malignancy.

Patients were followed up for a median duration of 14 (range: 6–41) months with all patients undergoing subsequent surveillance imaging to reassess the indeterminate lesions. Amongst the cohort, 46 (88.5%) patients were shown to have stable lesions that were likely benign. Progression to metastatic disease from the original indeterminate lesion was found in only two patients (3.8%), whilst four (7.7%) developed metastases at other sites, as shown in Figure 1. The progression of the lesions in these six patients was seen on subsequent imaging performed at a median of 18 (range: 4–50) months after the initial staging CT scan. Four of these six patients subsequently died of advanced malignancy, and the rest received palliative treatment for metastatic disease.

For patients who had stable indeterminate lesions on subsequent imaging, 28 (60.1%) of them received adjuvant chemotherapy and 31 (67.4%) received adjuvant radiotherapy. There were 31 (67.4%) patients who were on endocrine therapy and 17 (37%) patients who received trastuzumab (Table 3). With regard to the two patients

Table 2. Histopathological results of the primary breast malignancy

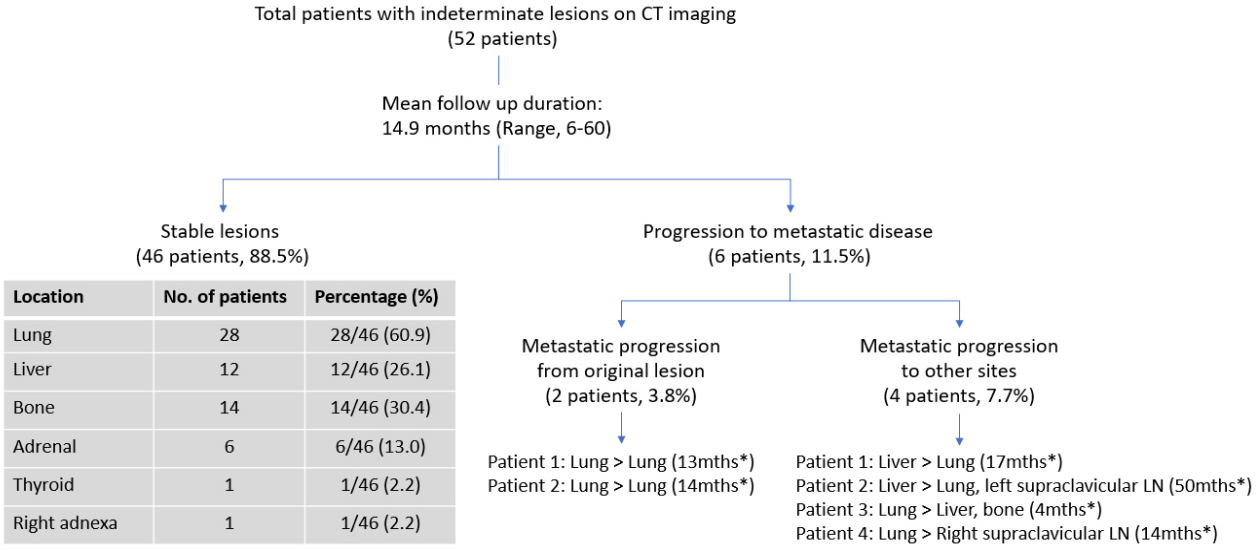
Histological grade (n = 52)	
Grade 1	3 (5.7%)
Grade 2	21 (40.4%)
Grade 3	28 (53.8%)
Number of lymph nodes involved (n = 52)	
0	36 (69.2%)
1–3	9 (17.3%)
≥4	7 (13.5%)
TMN staging (n = 52)	
T status	
T1	19 (36.5%)
T2	24 (46.1%)
T3	4 (7.7%)
T4	5 (9.6%)
N status	
N0	33 (63.5%)
N1	11 (21.2%)
N2	5 (9.6%)
N3	3 (5.7%)
Stage (n = 52)	
Stage I	18 (34.6%)
Stage II	22 (42.3%)
Stage III	12 (23.1%)
Histological subtype (n = 52)	
Invasive ductal carcinoma	47 (90.4%)
Invasive lobular carcinoma	2 (3.8%)
Squamous cell carcinoma	2 (3.8%)
Malignant phyllodes	1 (1.9%)
Receptor status (n = 52)	
Luminal A (ER+ PR+/- HER2-)	19 (36.5%)
Luminal B (ER+ PR+/- HER2+)	17 (32.7%)
HER2+ (ER- PR- HER2+)	5 (9.6%)
Triple negative (ER- PR- HER2-)	11 (21.2%)

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; n: number

Table 3. Treatment data of patients with indeterminate lesions, with or without clinical progression

	Stable indeterminate lesion (n = 46)	Progression from original lesion (n = 2)	Progression to other sites (n = 4)
Endocrine therapy	31 (67.4%)	1 (50%)	1 (25%)
Chemotherapy in neo-adjuvant setting	12 (26.1%)	2 (100%)	0
Chemotherapy in adjuvant setting	28 (60.1%)	1 (50%)	1 (25%)
Trastuzumab	17 (37.0%)	1 (50%)	1 (25%)
Radiotherapy in adjuvant setting	31 (67.4%)	1 (50%)	2 (50%)

n: number



Location	No. of patients	Percentage (%)
Lung	28	28/46 (60.9)
Liver	12	12/46 (26.1)
Bone	14	14/46 (30.4)
Adrenal	6	6/46 (13.0)
Thyroid	1	1/46 (2.2)
Right adnexa	1	1/46 (2.2)

Figure 1. Clinical progression of patients with indeterminate lesions on CT imaging

** indicates time interval to progression*

CT: computed tomography; LN: lymph node

found to have progression to metastatic disease from the original indeterminate lesion, both had indeterminate lesions in the lung. Both patients had two, non-calcified lung nodules each within the same side of the lung. The first patient was Stage IIIc (T4N3) on presentation, with biopsy showing Grade 3, triple negative malignant phyllodes. The size of her largest lung nodule measured 12 mm. The second patient was Stage II (T2N0) on presentation. She had Grade 2, triple positive invasive ductal carcinoma. Her largest lung nodule measured 13 mm. Both patients received neoadjuvant chemotherapy, with the second patient subsequently receiving adjuvant chemoradiotherapy in the adjuvant setting as well. The second patient also received trastuzumab and endocrine therapy.

No statistical significance was found in the demographic or clinicopathologic data between patients with stable lesions and those with malignant lesions on radiologic follow-up that could predict the natural history of these indeterminate extra-mammary lesions. However, this analysis may be limited by the small number of patients.

Discussion and Conclusion

Five-year survival rates for metastatic breast cancer have been reported to be 27%, as compared to 84% in locally advanced breast cancer (14), while 20%–30% of breast cancer patients can progress to metastases after diagnosis (13). It is known that breast cancer has metastatic heterogeneity, with a propensity towards bone (63%), liver (25%) and lung (23%) (15). Metastases to other organs, such as adrenals (16), thyroid (17) and adnexa (18) are considered rare. Different molecular subtypes have also been shown in certain studies to have different preferential sites of metastasis or relapse, such as a predominance of bone metastasis in luminal A and B subtypes, compared to non-luminal HER2 subtype which had a higher propensity for liver metastasis (9, 19).

Despite the latest National Comprehensive Cancer Network (NCCN) guidelines recommending that routine systemic staging in early breast cancer patients is not required because of the low likelihood of identification of metastatic disease (20), many centers still practice routine screening for breast cancer patients for evaluation of distant metastases. This commonly includes CT scans, positron emission tomography-CT (PET-CT) scans, and/or bone scintigraphy. Consequently, lesions of indeterminate nature are often noted. In our series, they were present in 7.1% of patients who got pre-operative staging scans, and these indeterminate lesions were mostly in the lung (60.9%), followed by bone (30.4%) and liver (26.1%). In a study performed by Brothers et al. (21), which was the only other study amongst the available literature that analyzed an array of indeterminate lesions in multiple organs, the lung was similarly the most common site. The incidences of indeterminate lesions recorded in their study were lung (50%), bone (26%) and liver (39%). Additionally, they reported close to 20% incidence of lymphadenopathy, adnexal and renal lesions which were not observed in our study. Other studies found a wide range of incidences of indeterminate nodules, varying from 4.2% to 59% (4, 7-10).

To our knowledge, this study is the first to evaluate the incidence and subsequent progression of indeterminate lesions in breast cancer on staging scans in an Asian population. The majority of the lesions (88.5%) in our series were stable on follow-up surveillance imaging with no progression of disease, at a median follow-up of 14 months. Only two patients (3.8%) with indeterminate lung lesions developed actual lung metastases on follow-up. These patients had Stage II and Stage IIIc disease respectively. Compared to the study by Brothers et al. (21) who reported progression in 29 out of 127 patients (22.8%) at a median follow-up of 4.9 years in patients with abnormal initial scan findings (20), ours was significantly lower. These differences are likely due to two main factors, the first being that their study population consisted of only Stage II and III breast cancer patients, whereas our study population had 34.6% Stage I patients, with the rest being Stage II and III. Secondly, the mean follow-up duration of our study was shorter, which could have resulted in fewer lesions having progressed to metastases.

Due to our small sample size and with only two patients progressing to metastatic lung disease, it was difficult to analyze them to determine if there were any significant factors associated with development of metastatic disease. Studies on indeterminate lesions found during staging for breast cancer have been focused mainly on pulmonary nodules. These studies have shown that significant risk factors associated with the development of lung metastases included large nodules ≥10 mm, multiple nodules, clinical Stage II-III and Grade 3 tumors (4, 21). This is similar to our two patients, who both had two unilateral non-calcified lung nodules each, of which the largest nodule measured >1 cm for both patients. Both patients also had a higher clinical stage of breast cancer. A study conducted by Lee at al. (4) concluded that sub-centimeter lung nodules with no other evidence of distant metastasis posed a low risk of progression and hence, should not preclude treatment with curative intent or entry into clinical trials. Thus, we suggest that an individualized risk-stratified approach, based on the probability of malignancy should be adopted for patients with indeterminate lung lesions. We have used serial CT imaging to monitor patients with indeterminate pulmonary nodules as an alternative to more invasive testing, such as biopsy. However, if progression of these indeterminate lesions is detected on surveillance, further diagnostic investigations, such as bronchoscopy or transthoracic needle aspiration/biopsy, can aid in excluding malignancy. Although the optimal frequency of follow-up imaging is unknown for these lung lesions in the setting of breast cancer, certain surveillance protocols can be extrapolated from indeterminate lung nodules in the setting of lung malignancy. According to the Fleischner Society Guidelines, the duration and frequency of surveillance of an indeterminate lung nodule is largely guided by the original size of the lesion and the individual risk factors for lung malignancy (22). Surveillance imaging at 3-monthly intervals during the first year after incidental nodule is discovered and then 6-monthly in the following year with high-resolution CT imaging has also been recommended (3).

Bone is another common site of distant metastases from breast cancer and is the first affected site in a substantial proportion of women (23, 24). Breast cancer guidelines and consensus recommendations indicate that various imaging studies may be used for staging or evaluation of bone metastasis in women with breast cancer (25, 26). Although the first choice is often a nuclear medicine bone scan (or bone scintigraphy), as this method shows only bone metabolism, another imaging study might be needed for an accurate diagnosis. This includes plain radiography, CT, magnetic resonance imaging (MRI), single-photon-emission CT (SPECT) and F-18-Deoxyglucose or Fluorodeoxyglucose (FDG) PET-CT (27). Bone scintigraphy relies on the radiotracer Tc99m methyl diphosphonate (MDP), which allows visualisation of uptake in regions of increased bone turnover and osteoblast activity and a resulting increase in blood perfusion (28). However, they are insensitive for tumours that are predominantly lytic. Additionally, bone metastases in avascular sites of disease can also result in false-negative scans due to the lack of increased perfusion that typically accompanies osteoblastic activity (29). Hence several studies have shown that FDG PET-CT or magnetic resonance imaging (MRI) should be recommended in high-risk patients for further evaluation of indeterminate bony findings due to their higher sensitivity (30, 31).

While incidental liver lesions are often found on cross sectional imaging, they pose a particular challenge for oncology patients when they are deemed indeterminate or too small to characterise. There are no established guidelines as of yet about how extensive or aggressive workup should be. In a study done by Khalil et al. (5), the presence of at least one indeterminate liver lesion was found in 29% of women with breast cancer who had cross sectional imaging performed. More than two-thirds (69%) of these women had follow-up imaging which showed the majority of the lesions were either unchanged (92%) or had disappeared (4%). Overall, in 92.7%–96.9% of women with indeterminate liver lesions, these lesions were eventually benign, after a median follow-up of 54 weeks. The same authors also evaluated the role of MRI in breast cancer patients with liver lesions on CT imaging (32). Out of 38 patients with indeterminate liver lesions on CT, only two eventually had metastatic liver disease on MRI liver. In the women who had indeterminate lesions even on MRI liver who received further workup (n = 8) such as biopsy or surveillance imaging, all had benign disease. The authors concluded that in these patients with indeterminate liver lesions, MRI of liver offered minimal further benefit in the majority of their patients, and they did not recommend immediate work-up with MRI or biopsy. In our opinion, one further utility of the MRI would be the confirmation of a benign diagnosis early in the diagnostic work-up. This would help to ease frequency of surveillance imaging as well as patient anxiety. Hence in a centre where resources permit, an MRI liver can be considered as the subsequent follow-up imaging after an initial CT finding of an indeterminate liver lesion.

This study has several limitations. Firstly, its clinical relevance is limited by its small sample size. Larger-scaled studies will be required to determine the applicability of these findings. Secondly, this is a retrospective cohort study and there was no standard follow-up protocol for patients with these small uncharacterized extra-mammary lesions. This is due to currently limited published data on the prevalence and nature of such indeterminate lesions. Therefore, this study hopes to contribute towards future efforts in creating a standardised protocol for follow-up of such indeterminate lesions.

In conclusion, indeterminate extra-mammary lesions detected on imaging for newly diagnosed breast cancer patients pose a pertinent diagnostic challenge. Routine biopsy is generally not indicated due to the indolent nature of the majority of these lesions. However, further dedicated imaging, such as MRI or PET scan, can be considered where resources are available. Continued surveillance imaging of such lesions is recommended as a small, albeit noteworthy, proportion of them eventually harbour actual metastatic disease. Clinicopathological characteristics of the patients can also be considered in the eventual surveillance strategy. We also suggest that these patients with primary breast cancer and indeterminate extra-mammary lesions should be offered treatment with curative intent.

Ethics Committee Approval: The protocol for this research project has been approved by our institutional research board, National Healthcare Group Domain Specific Review Board and it conforms to the provisions of the Declaration of Helsinki (DSRB Reference Number: 2020/00181).

Informed Consent: Informed consent was exempted in view of minimal potential risks to research subjects and that all attempts to preserve anonymity of the data by deidentification of the patients' data had been taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.Y.C., J.T.T.G., M.W.O., Design: M.W.O., Data Collection and/or Processing: R.Y.G., H.T.L., S.C., M.W.O., Analysis and/or Interpretation: R.Y.C., M.W.O., Literature Search: R.Y.C., R.Y.G., M.W.O., Writing: R.Y.C., R.Y.G., V.K.M.T., C.L.K.C., J.T.T.G., M.W.O.

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References

1. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International Variation in Female Breast Cancer Incidence and Mortality Rates. Cancer Epidemiol Biomarkers Prev 2015; 24: 1495-1506. (PMID: 26359465) [Crossref]
2. National Registry of Diseases Office. Singapore Cancer Registry Annual Report 2018. Available at: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/scr-annual-report-2018.pdf?sfvrsn=bcf56c25_0. (Accessed on July 1, 2021). [Crossref]
3. Ost D, Fein AM, Feinsilver SH. Clinical practice. The solitary pulmonary nodule. N Engl J Med 2003; 348: 2535-2542. (PMID: 12815140) [Crossref]
4. Lee B, Lim A, Lalvani A, Descamps MJ, Leonard R, Nallamala S, et al. The clinical significance of radiologically detected silent pulmonary nodules in early breast cancer. Ann Oncol 2008; 19: 2001-2006. (PMID: 18641008) [Crossref]
5. Khalil HI, Patterson SA, Panicek DM. Hepatic lesions deemed too small to characterize at CT: prevalence and importance in women with breast cancer. Radiology 2005; 235: 872-878. (PMID: 15833992) [Crossref]
6. Seo JW, Lim JH, Choi D, Jang HJ, Lee WJ, Lim HK. Indeterminate small, low-attenuating hepatocellular nodules on helical CT in patients with chronic liver disease: 2-year follow-up. Clin Imaging 2005; 29: 266-272. (PMID: 15967319) [Crossref]
7. Iodice D, Di Donato O, Liccardo I, Lamanna L, Segreto S, Salvatore M, et al. Prevalence of extramammary findings on breast MRI: a large retrospective single-centre study. Radiol Med 2013; 118: 1109-1118. (PMID: 23716293)
8. Alduk AM, Prutki M, Stern-Padovan R. Incidental extra-mammary findings in breast MRI. Clin Radiol 2015; 70: 523-527. (PMID: 25656660) [Crossref]
9. Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn JG, et al. Subtypes of breast cancer show preferential site of relapse. Cancer Res 2008; 68: 3108-3114. (PMID: 18451135) [Crossref]
10. Li F, Armato SG, Giger ML, MacMahon H. Clinical significance of noncalcified lung nodules in patients with breast cancer. Breast Cancer Res Treat 2016; 159: 265-271. (PMID: 27503305) [Crossref]
11. Moschetta M, Telegrafo M, Rella L, Stabile Ianora AA, Angelelli G. Let's go out of the breast: prevalence of extra-mammary findings and their characterization on breast MRI. Eur J Radiol 2014; 83: 930-934. (PMID: 24656879) [Crossref]
12. Lyratzopoulos G, Abel GA, Barbiere JM, Brown CH, Rous BA, Greenberg DC. Variation in advanced stage at diagnosis of lung and female breast cancer in an English region 2006-2009. Br J Cancer 2012; 106: 1068-1075. (PMID: 22382691) [Crossref]
13. Johnson RH, Chien FL, Bleyer A. Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. JAMA. 2013; 309: 800-805. JAMA. Erratum in: JAMA 2013; 309: 1229. (PMID: 23443443)[Crossref]
14. Ahmad A. Breast Cancer Metastasis and Drug Resistance. 2nd ed. Springer; 2019. [Crossref]
15. Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Semin Cancer Biol 2020; 60: 14-27. (PMID: 31421262) [Crossref]
16. Liu XJ, Shen P, Wang XF, Sun K, Sun FF. Solitary adrenal metastasis from invasive ductal breast cancer: an uncommon finding. World J Surg Oncol 2010; 8: 7. (PMID: 20105336) [Crossref]
17. Plonczak AM, DiMarco AN, Dina R, Gujral DM, Palazzo FF. Breast cancer metastases to the thyroid gland - an uncommon sentinel for diffuse metastatic disease: a case report and review of the literature. J Med Case Rep. 2017; 11: 269. Erratum in: J Med Case Rep. 2017; 11: 288. (PMID: 28934992) [Crossref]
18. Hann LE, Lui DM, Shi W, Bach AM, Selland DL, Castiel M. Adnexal masses in women with breast cancer: US findings with clinical and histopathologic correlation. Radiology 2000; 216: 242-247. (PMID: 10887255) [Crossref]
19. Gerratana L, Fanotto V, Bonotto M, Bolzonello S, Minisini AM, Fasola G, et al. Pattern of metastasis and outcome in patients with breast cancer. Clin Exp Metastasis 2015; 32: 125-133. (PMID: 25630269)[Crossref]
20. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Breast Cancer v8. 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. (Accessed on October 31, 2021). [Crossref]
21. Brothers JM, Kidwell KM, Brown RK, Henry NL. Incidental radiologic findings at breast cancer diagnosis and likelihood of disease recurrence. Breast Cancer Res Treat 2016; 155: 395-403. (PMID: 26797222) [Crossref]
22. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology 2017; 284: 228-243. (PMID: 28240562) [Crossref]
23. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. J Clin Oncol 2004; 22: 2942-2953. (PMID: 15254062) [Crossref]
24. Whitlock JP, Evans AJ, Jackson L, Chan SY, Robertson JF. Imaging of metastatic breast cancer: distribution and radiological assessment at presentation. Clin Oncol (R Coll Radiol) 2001; 13: 181-186. (PMID: 11527292) [Crossref]
25. National Institute for Health and Care Excellence. Advanced Breast Cancer: Diagnosis and Treatment Clinical Guideline, 2009. Available at: https://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-pdf-975683850181. (Accessed on July 5, 2021). [Crossref]
26. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, et al. Breast cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2009; 7: 122-192. (PMID: 19200416) [Crossref]
27. Houssami N, Costelloe CM. Imaging bone metastases in breast cancer: evidence on comparative test accuracy. Ann Oncol 2012; 23: 834-843. (PMID: 21896542) [Crossref]
28. Heindel W, Gübitz R, Vieth V, Weckesser M, Schober O, Schäfers M. The diagnostic imaging of bone metastases. Dtsch Arztebl Int 2014; 111: 741-747. (PMID: 25412631) [Crossref]
29. Costelloe CM, Rohren EM, Madewell JE, Hamaoka T, Theriault RL, Yu TK, et al. Imaging bone metastases in breast cancer: techniques and recommendations for diagnosis. Lancet Oncol 2009; 10: 606-614. (PMID: 19482249) [Crossref]
30. Abikhzer G, Srour S, Fried G, Drumea K, Kozlener E, Frenkel A, et al. Prospective comparison of whole-body bone SPECT and sodium 18F-fluoride PET in the detection of bone metastases from breast cancer. Nucl Med Commun 2016; 37: 1160-1168. (PMID: 27536906) [Crossref]
31. Ohta M, Tokuda Y, Suzuki Y, Kubota M, Makuuchi H, Tajima T, et al. Whole body PET for the evaluation of bony metastases in patients with breast cancer: comparison with 99Tcm-MDP bone scintigraphy. Nucl Med Commun 2001; 22: 875-879. (PMID: 11473206) [Crossref]
32. Patterson SA, Khalil HI, Panicek DM. MRI evaluation of small hepatic lesions in women with breast cancer. AJR Am J Roentgenol 2006; 187: 307-312. (PMID: 16861531) [Crossref]