

Original Article

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Routine X-ray of the chest is not justified in staging of patients with primary breast cancer

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ABSTRACT

INTRODUCTION. Chest X-rays (CXRs) are performed routinely as part of staging of primary breast cancer patients in most breast units in Denmark. However, several international studies have found exceedingly low detection rates for occult pulmonary metastatic disease among breast cancer patients. Even so, no data have previously been published on Danish patients.

METHODS. A retrospective study was conducted of all breast cancer patients undergoing CXRs at the Department of Breast Surgery, Herlev Hospital, from April 2016 to December 2017. The primary outcome was detection of pulmonary metastases on CXRs at the time of the patient's breast cancer diagnosis. The follow-up period was 12 months.

RESULTS. A total of 1,014 patients were included in this study. Among these, 11 (1%) had a positive CXR and 1,003 (99%) had a negative CXR. Three (0.3%) patients were diagnosed with lung metastases but had false negative CXRs. The sensitivity was 0%, the specificity was 98.9%, the positive predictive value was 0% and the negative predictive value was 99.6%.

CONCLUSION. Routine preoperative CXR did not impact staging or lead to changes in the treatment of breast cancer patients. Therefore, routine CXR cannot be justified and should be omitted.

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TRIAL REGISTRATION. The study was approved by the local hospital legal department (Herlev and Gentofte Hospital) as quality assurance research (workzone number: 19000557).

According to The Danish Health Data Authority, breast cancer has the highest incidence rate among women compared with other types of cancer in Denmark with approximately 4,800 new cases annually [1]. It is estimated that approximately 6% of all breast cancer patients present with metastatic disease at their initial diagnosis [2]. Lung, bone and liver constitute the most common sites for metastases [3]. Staging of patients with breast cancer is essential for treatment decisions. As a result, in most breast units in Denmark, chest X-rays (CXRs) are performed routinely to detect pulmonary metastasis as part of the staging of primary breast cancer patients without pulmonary symptoms. However, several international studies have shown exceedingly low detection rates for occult pulmonary disease in early breast cancer [4, 5].

The European guidelines on breast cancer screening and diagnosis do not recommend routine CXRs in patients

with stage I and II breast cancer and advise to use only conventional staging modalities such as CXRs, abdominal ultrasound or bone scans in stage III breast cancer if fluorodeoxyglucose positron emission tomography/computed tomography FDG-PET/CT is not available [6]. No official Danish recommendations exist on this subject and no data are available on Danish patients.

Our primary aim was, therefore, to determine the value of routine pre-operative CXRs for detecting occult pulmonary metastasis in Danish patients without pulmonary symptoms with newly diagnosed breast cancer.

METHODS

A retrospective study of breast cancer patients undergoing CXRs was conducted at the Department of Breast Surgery, Herlev Hospital, from 11 April 2016 to 31 December 2017. This period was selected as it coincided with the implementation of a new medical software system (Epic Systems Corporation) at our unit.

The patients were referred to our unit from the national breast cancer screening programme due to symptoms of breast cancer or incidental findings on imaging requested for other reasons. All patients without clinical signs of pulmonary metastasis had a routine CXR performed at the time of their breast cancer diagnosis.

The inclusion criteria were newly diagnosed patients with breast cancer with no apparent clinical signs of metastatic disease at the time of diagnosis and with one-year follow-up data. Excluded from the study were patients with previous breast cancer, ductal carcinoma in situ, Paget's disease of the breast, ulcerative breast cancer or who were in current treatment and/or in a follow-up programme for other cancers (other than non-melanoma skin cancer).

Eligible study patients were extracted through referrals for CXRs from the Department of Breast Surgery to the Department of Radiology at Herlev Hospital. Data on demographics, histopathology (from the Danish Pathology Register) and imaging reports were retrieved from the electronic medical records.

The primary outcome was detection of pulmonary metastases on CXRs at the time of the breast cancer diagnosis. If the CXR taken at the time of diagnosis was suggestive of pulmonary metastasis, the multidisciplinary team decided which further imaging should be conducted; chest CT and/or PET/CT.

If the CXR suggested pulmonary metastasis and the patient subsequently received this diagnosis, the CXR was defined as a true positive. If no correlation was found, the CXR was defined as a false positive. If the CXR at the time of diagnosis was negative, but the patient developed pulmonary metastasis, all further imaging was reanalysed at the time of the study by an experienced diagnostic radiologist and retrospectively defined as a true or a false negative. Incidental findings were also registered. The diagnosis of pulmonary metastasis was based on histopathological (if available) and/or FDG-PET/CT or CT suggestive of pulmonary metastasis.

At our unit, all patients had a one-year follow-up visit at the Department of Breast Surgery. In addition, patients receiving adjuvant therapy had outpatient follow-up appointments at the Department of Oncology. No laboratory tests or imaging was routinely performed during the first year of follow-up. If a patient presented with clinical signs or symptoms of pulmonary metastasis, further imaging was requested. All medical and imaging reports from regional public hospitals were assessed for evidence of metastatic disease during the follow-up period.

Statistical analysis

The SAS Enterprise Guide 7.1 (64-bit) was used for all analyses. Point estimates for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The sensitivity was the proportion of patients with pulmonary metastases correctly identified by preoperative CXRs. This was calculated as: true positives/(true positives + false negatives). The specificity was the proportion of patients without lung

metastases correctly identified by the preoperative CXRs. This was calculated as: true negatives/(true negatives + false positives). The PPV, which indicated the likelihood that the patient had lung metastases if the CXR was positive, was calculated as: true positives/(true positives + false positives). The NPV, which indicated the likelihood that the patient did not have lung metastases if the CXR was negative, was calculated as: true negatives/(true negatives + false negatives). Results were given as percentages and exact 95% confidence intervals (CIs).

Ethics

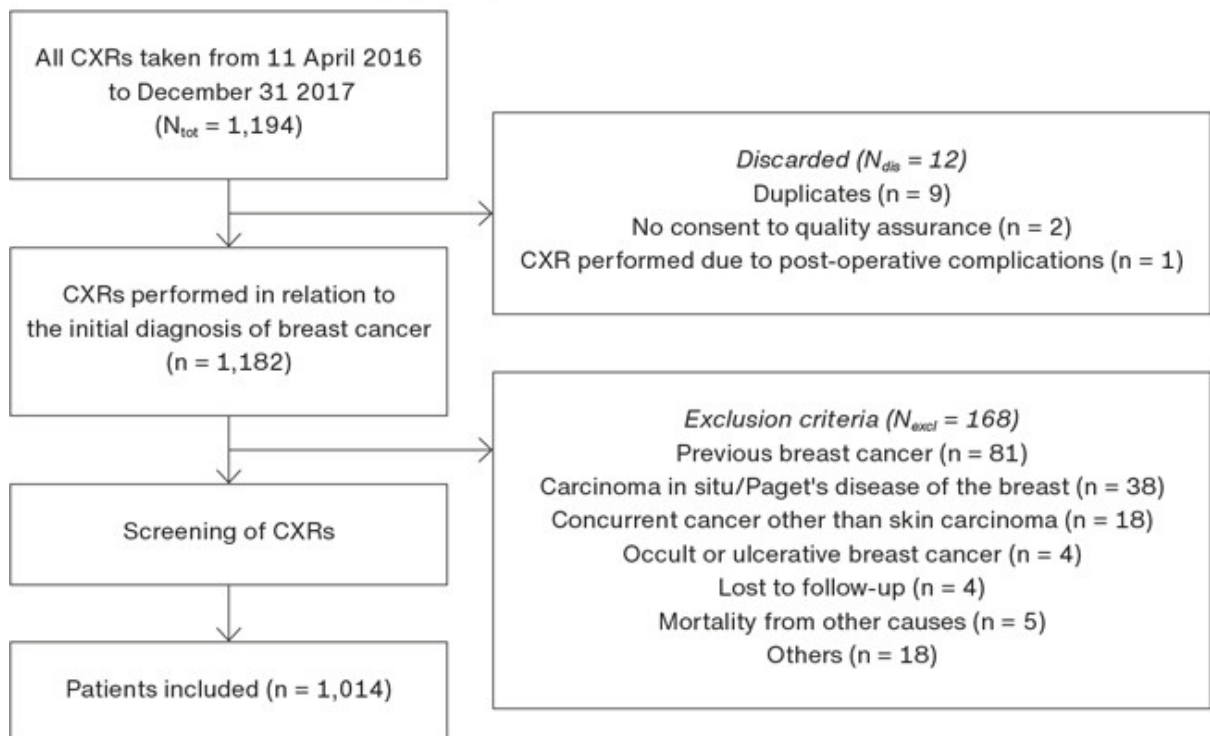
Access to relevant medical records without patient consent was granted if the patient had permitted participation in quality assurance research.

Trial registration: The study was approved by the local hospital legal department (Herlev and Gentofte Hospital) as quality assurance research (workzone number: 19000557) and no ethical approval was necessary.

RESULTS

A total of 1,194 CXRs were retrieved from 11 April 2016 to 31 December 2017. After screening for duplicates and exclusion criteria, 1,014 patients were included for the analysis (**Figure 1**). The median age of the patients was 64 years (range: 31-93 years). Approximately two-thirds of the patients were referred to our unit due to symptoms of breast cancer, whereas approximately one-third were included through the national screening programme. Only 2% were referred via other pathways such as incidental findings on imaging requested for other reasons. Patients and tumour characteristics are displayed in **Table 1**.

FIGURE 1 Flow chart of study participants.



CXR = chest X-ray.

TABLE 1 Population demographics, tumour characteristics and adjuvant therapy among 1,014 Danish patients with breast cancer. Median age (range) 64 (31-93) years.

| | n (%) | | n (%) |
|--|---------------------|---|--------------|
| <i>Demographics</i> | | <i>M stage^b:</i> | |
| Sex: female/male | 1,012 (99.8)/2(0.2) | M0 | 1,007 (99.3) |
| Referral: | | M1 | 7 (0.7) |
| National population screening programme | 354 (34.9) | <i>Histological grade of invasive cancer:</i> | |
| Symptoms | 636 (62.7) | Grade 1 | 341 (33.7) |
| Other ^a | 24 (2.4) | Grade 2 | 414 (40.9) |
| <i>Tumour characteristics and adjuvant therapy</i> | | Grade 3 | 185 (18.3) |
| Tumour type: | | Other | 73 (7.2) |
| Invasive ductal carcinoma | 809 (79.8) | N/A | 1 |
| Invasive lobular carcinoma | 131 (12.9) | <i>Oestrogen receptor status:</i> | |
| Other | 74 (7.3) | Positive | 904 (89.2) |
| Procedure: | | Negative | 110 (10.8) |
| Breast-conserving surgery | 739 (72.9) | <i>HER2 status:</i> | |
| Mastectomy | 269 (26.5) | Positive | 125 (12.3) |
| No surgery | 5 (0.5) | Negative | 888 (87.6) |
| Incidental finding after reconstructive surgery | 1 (0.1) | Borderline | 1 (0.1) |
| <i>T stage^b:</i> | | <i>Adjuvant radiotherapy:</i> | |
| T1 | 697 (68.7) | Intraoperatively | 148 (14.6) |
| T2 | 286 (28.2) | Post-operatively | 626 (61.7) |
| T3 | 26 (2.6) | None | 240 (23.7) |
| T4 | 4 (0.4) | <i>(Neo)adjuvant chemotherapy:</i> | |
| TX | 1 (0.1) | Yes | 359 (35.4) |
| <i>N stage^b:</i> | | None | 655 (64.6) |
| N0 | 683 (67.4) | <i>Adjuvant trastuzumab:</i> | |
| Micrometastasis | 64 (6.3) | Yes | 112 (11.0) |
| N1, 1-3 positive lymph nodes | 169 (16.7) | None | 902 (89.0) |
| N2, 4-9 positive lymph nodes | 57 (5.6) | <i>Adjuvant endocrine therapy:</i> | |
| N3, ≥ 10 positive lymph nodes | 33 (3.3) | Yes | 771 (76.0) |
| NX | 7 (0.7) | None | 243 (24.0) |
| N/A | 1 | | |

HER = human epidermal growth factor receptor; N/A = not applicable.

a) Referred due to other reasons such as incidental findings of breast cancer on imaging requested for other reasons.

b) TNM classification based on the Union for International Cancer Control.

Of the 1,014 patients, 12 (1.2%) had a positive CXR at the time of staging. These CXRs were reanalysed by an experienced diagnostic radiologist and the suspicion of pulmonary metastasis was maintained in 11 cases. Among these, nine patients had a chest CT performed, whereas the remaining two patients underwent an FDG-PET/CT. All imaging was without signs of lung metastasis. In addition, none of these cases developed signs of pulmonary metastasis within the first year, and the CXRs were therefore categorised as false positives (Table 2). In total, three patients developed pulmonary metastasis during the follow-up period. The CXRs at the time of staging were without signs of pulmonary metastasis despite all patients having evident signs of lung metastasis within 1-10 months post-operatively (mean: 5.3 months). These CXRs were, therefore, categorised as false negatives (Table 2). The sensitivity of routine CXR was thus found to be 0% (95% CI: 0-60), the specificity was 98.9 (95% CI: 98.1-99.5), the PPV was 0% (95% CI: 0-25) and the NPV was 99.6 (95% CI: 99.1-99.9) (Table 3).

TABLE 2 Frequencies of chest X-ray results and presence of pulmonary metastases among 1,014 Danish patients with breast cancer. The values are n (%).

| | Metastasis | No metastasis | Total |
|----------|----------------------|---------------------------|-------|
| Positive | 0 ^a | 11 (1.1) ^b | 11 |
| Negative | 3 (0.4) ^c | 1,000 (98.9) ^d | 1,003 |
| Total | 3 | 1,011 | 1,014 |

- a) True positive.
- b) False positive.
- c) False negative.
- d) True negative.

TABLE 3 Diagnostic accuracy of chest X-ray for pulmonary metastases among 1,014 Danish patients with early breast cancer.

| | % (95% CI) |
|---------------------------|------------------|
| Sensitivity | 0.0 (0.0-70.8) |
| Specificity | 98.9 (98.1-99.5) |
| Positive predictive value | 0.0 (0.0-28.5) |
| Negative predictive value | 99.6 (99.1-99.9) |

CI = confidence interval.

DISCUSSION

Staging of primary breast cancer is crucial in determining treatment strategies and prognosis. Routine CXRs are performed as screening for occult pulmonary metastasis in most breast units in Denmark. According to our data, however, only three (0.3%) of 1,014 patients developed pulmonary metastasis within the first year of follow-up, and none of these patients were diagnosed based on the CXR taken at the time of their breast cancer diagnosis, corresponding to a sensitivity of zero.

The patients with false positive CXRs underwent further imaging; either a chest CT or a PET/CT. Three of the 11 patients with false positive CXRs had primary lung cancer, two had pulmonary hamartomas, one had a thymoma, whereas no pathology was identified in the remainder. Considering the very low prevalence of incidental findings of other malignancies, routine CXR for this purpose is not justified. The CXRs did not lead to a change of management in any of our patients; but the false positive CXRs, however, may have resulted in unnecessary distress and anxiety in patients along with additional investigations, which not only entail unnecessary healthcare costs but may also delay treatment.

The results of our study are in line with those of several international studies [7-9]. In a study including 1,556 patients with breast cancer without pulmonary symptoms, Barrett et al. [7] found one true positive CXR (0.2%) and 20 (1.3%) false positive CXRs. Similarly, a German study by Rusch et al. [8] found that among 894 out of 896

patients (99.8%) undergoing staging for distant metastases by CXR, bone scintigraphy, liver sonography and/or CT/magnetic resonance imaging (MRI), only three (0.3%) had metastatic disease verified in the bone and/or lung. In line with this, a 2011 systematic review by Brennan & Houssami [9] found no evidence to support routine use of imaging for staging of early breast cancer (stage I and II), whereas they concluded that imaging may be warranted for stage III breast cancer, inflammatory cancer and cases with extensive lymph node involvement, which is in accordance with European guidelines [6]. The three patients in our study who did develop lung metastasis were stage I-III. As shown for other cancers, including melanoma, the role of CXRs for staging purposes is very limited [10-12].

Previous studies initiated by the Danish Breast Cancer Group have demonstrated that sequential CXRs as part of the post-operative follow-up in patients with stage I and II breast cancer are not warranted [13, 14]. Previously, annual CXRs were performed as part of the post-operative follow-up regime at Danish breast units. The cost/benefit-ratio, however, has been shown to be low in early breast cancer [13, 14]. Similarly, our study has shown that performing CXRs at the time of the breast cancer diagnosis in patients without pulmonary symptoms has no therapeutic consequence.

A recent Danish study by Vogensen et al. revealed that FDG-PET/CT has a substantial impact on staging and change of treatment in women with high-risk primary breast cancer [15]. Therefore, only primary breast cancer patients with a high risk of metastatic disease may benefit from FDG-PET/CT for staging and treatment planning. Still, this practice has yet to be implemented in national guidelines. Even in the high-risk patients in our study, of whom eight proved to have metastatic disease, CXRs were of no benefit as these patients were not diagnosed with pulmonary metastasis. Instead they presented with extra-pulmonary metastasis, which would have been captured by FDG-PET/CT.

To our knowledge, this is the first study of its kind with Danish patients. The major strengths of this study are the large sample size and the extensive data available from the patients' medical records, pathology database and imaging reports. Furthermore, all CXRs in which pulmonary metastasis was suspected were scrutinised and re-evaluated by an experienced diagnostic radiologist. Limitations include the inherent biases due to the retrospective nature of the study.

CONCLUSION

The CXRs did not impact staging or lead to any change in management. Therefore, the use of routine pre-operative CXR is not justified as a part of staging of primary breast cancer in patients without pulmonary symptoms. Based on these findings, the use of CXRs in staging of patients with breast cancer without pulmonary symptoms has been omitted at our unit.

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