

Original Article

Natural progression and clinical significance of incidentally detected pulmonary nodules in radiotherapy planning CT scans of breast cancer patients: a retrospective cohort

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Abstract

Aim: Indeterminate pulmonary nodules incidentally detected during radiological imaging completed for radiotherapy planning always creates dilemma for the oncologist. The purpose of this study is to evaluate the clinical significance of pulmonary nodules incidentally detected in patients undergoing locoregional radiotherapy for breast cancer and present a retrospective analysis of the natural progression of such nodules.

Methods: A retrospective review of computed tomography scans of breast cancer patients who underwent radiotherapy over a period of 3 years to screen out patients with indeterminate lung nodules was undertaken. This was correlated with the patient and tumour characteristics and the status of the disease at last follow-up.

Results: Of the 132 patients reviewed 28 had indeterminate lung nodules. Of the 28 patients, four had progressive lung nodules on follow-up. Subgroup analyses did not show any significant correlation.

Discussion and conclusion: One fifth of patients may present with incidentally detected lung nodules. Multiple nodules, ER negative status and locally advanced breast cancer may point to a higher risk of these nodules progressing to metastatic cancer. There is no indication to stop locoregional therapy in the presence of indeterminate nodules, but close follow-up of high-risk group is recommended.

Keywords: breast cancer clinical dilemma; computed tomography; incidental findings; pulmonary nodules

INTRODUCTION

Breast cancer is the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all

cancers), and ranks second overall (10.9% of all cancers).¹ The Indian Council of Medical Research in a 2011 release has pointed out that the incidence of breast cancer in major cities of India has doubled compared with a decade ago.

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Of the newly diagnosed cases of breast cancer about 5% are metastatic, and 30% of those treated for the disease with radical intent have shown a systemic recurrence.² Once metastatic disease develops, the possibility of a cure is very limited or practically non-existent. In this heterogeneous group of patients with stage IV disease, the 5-year survival rate is 20%, and the median overall survival varies from 12 to 24 months.² Isolated metastases of the lung or pleural space were found in 15–23.9% of patients with metastatic breast cancer. These patients had a median survival of 18.9–22 months.³ With the advent of sophisticated imaging technology in radiotherapy planning and treatment, there is increased detection of incidental pulmonary nodules. The incidental detection of indeterminate lung nodules in the absence of other metastases on planning computed tomography (CT) scans of breast cancer patients poses a treatment dilemma. It makes it difficult for the physician to choose to either to further evaluate the lung nodule or to proceed with the locoregional treatment.

There are evidence-based recommendations for evaluating solid pulmonary nodules, in the context of early lung cancer. The Fleischner society pulmonary nodule recommendations are for the follow-up and management of pulmonary nodules <8 mm detected incidentally in patients >35 years on non-screening CT.⁴ These nodules are sub-classified as solid nodules that measure >8 mm in diameter, solid nodules that measure \leq 8 mm in diameter, and subsolid nodules.⁵ Lee et al.⁶ in 2008 reviewed more than 800 staging CT scans in early breast cancer and concluded that incidental nodules should not alter the definitive therapy for breast cancer. The scenario presented in this study is in locally advanced breast cancer, post surgery and systemic therapy when they present for adjuvant radiotherapy, an incidentally picked up nodule can still throw a clinical dilemma. The likelihood of these being metastatic and the adjuvant therapy being non-beneficial would make the clinician think twice about proceeding with radiotherapy. The high incidence of secondary infections following neutropenia episodes during chemotherapy and incidence of tuberculosis (TB) also makes it difficult to make a decision.

As there are no similar guidelines in the setting of advanced breast primary, the evaluation of nodules may follow the same principles as in the Fleischner's guidelines.⁴

Further, India has the highest burden of TB.⁷ The latest World Health Organisation statistics gives an estimated incidence of 2.1 million cases of TB in India, and TB prevalence for 2013 was reported as 2.6 million.⁷ Therefore, the nodules that are reported in the planning CT scan needs further evaluation in the Indian context. A solitary pulmonary nodule incidentally detected during planning CT scans in breast cancer poses a three-fold challenge, that is to distinguish them from metastatic breast nodule, primary lung cancer or from pulmonary TB. To address this issue, this study aims to find the incidence of indeterminate nodules in breast cancer patients and attempts to evaluate the clinical significance of these nodules.

METHODS AND MATERIALS

All breast cancer patients who received 3D conformal radiotherapy from January 2010 to May 2013 were included in this study. The group included a total of 132 patients with a median age of 50 years (range, 26–72 years). All patients had planning CT scan of the thorax for delineation of target volumes and the images were reviewed retrospectively for the presence or absence of indeterminate lung nodules. Nodules that did not conform to radiological classification of metastasis, solitary lesions <1.5 cm, unsuitable for biopsy or fine needle aspiration cytology and ground glass opacities were all classified as indeterminate nodules. Patients with indeterminate nodules were followed up till their last visit and incidence of pulmonary metastases were assessed with chest X-ray. The database provided the details regarding the number, location and size of the lung nodules, associated benign conditions, stage of the disease, histology, and the grade and hormonal status of the primary breast cancer. All patients had received systemic chemotherapy as per the standard norms. Any increase in pulmonary nodule size was evaluated with either positron emission tomography-computed tomography scan or biopsy of the lung nodules. The lung nodules

that had progressed were correlated with the patient and tumour characteristics.

Univariate analysis was done for each of the characteristics with exact Fischer's test. Results for the 28 indeterminate nodules are reported. The analyses were performed using SPSS software (Version 16). The patients gave written consent for use of their images for study and analysis and the institutional review board approved the study.

RESULTS

Among the 132 patients treated, 28 patients (21%) were found to have incidental indeterminate lung nodules in the planning CT scans. The median size of the nodules was 0.4 cm (range 0.2–1.5 cm). The 28 patients were categorized based on age, stage, hormonal status, type of surgery, number of nodules, size of the nodules and associated pulmonary conditions (like TB, COPD, asthma). Of the 28 patients, 25 (89%) were above 35 years and 19 patients (68%) had locally advanced disease. The hormonal status was positive in 16 patients (57%) and negative in 12 patients (43%). Twenty-five patients (89%) had undergone modified radical mastectomy. Thirteen patients (46%) had solitary lung nodule. Most lesions 71% ($n = 20$) were <5 mm. Three (11%) had associated pulmonary conditions. Table 1 shows the patient characteristics and the characteristics of lung nodule. The patients were followed up for a median period of 13 months (range, 6–36 months) (Table 1).

Among the 28 patients who were followed up, four patients (14%) progressed to lung metastases. Of these four patients only one was younger than 35 years.

- None of the patients who had early breast cancer developed lung metastases.
- Three out of the four (75%) of the lung metastases were seen in estrogen receptor (ER)/progesterone receptor (PR) negative subgroup.
- Among the ER positive subgroup, one out of 16 patients (6%) developed malignancy in the lung nodule.
- However, in ER negative group 3 (25%) out of 12 progressed. Of the four patients, three patients (75%) who progressed to lung metastases had multiple lung nodules.

Table 1. Patient characteristics and radiological characteristics

Characteristics	No. of patients	%
Patient characteristics		
Age		
≤35 years	3	11
>35 years	25	89
Stage		
Early (up to stage II B)	9	32
Locally advanced	19	68
Hormonal status		
Positive	16	57
Negative	12	43
Type of surgery		
Breast conservation surgery	3	11
Modified radical mastectomy	25	89
Radiological characteristics		
Number of nodules		
Solitary	13	46
Multiple	15	54
Size		
≤5 mm	20	71
>5 mm	8	29
Associated pulmonary conditions (TB, COPD, Asthma)		
Present	3	11
Absent	25	89

Abbreviations: TB, tuberculosis; COPD, chronic obstructive pulmonary disease.

- Only one patient (8%) in the group of solitary nodules developed lung metastases.
- Among the 20 patients who had lung nodules of size ≤5 mm, three patients (15%) progressed to lung metastases.
- Of the eight patients (13%) with nodule size >5 mm, one (13%) progressed to lung metastases.
- When the overall disease status was assessed in this group, of the 28 patients, seven patients (25%) had progressive disease (either lung metastases or extra pulmonary disease), 21 patients (75%) were disease free.
- None of the patients developed a locoregional relapse at last follow-up.

When correlated with the progression to lung nodules, neither the patient nor the radiological features were statistically significant in the univariate analysis (Figure 1). This was attributed to low occurrence of progression to lung metastases.

DISCUSSION

The study was a retrospective analysis of patients who were found to have indeterminate lung nodules, incidentally on their planning CT scan. There are no unique guidelines to evaluate these

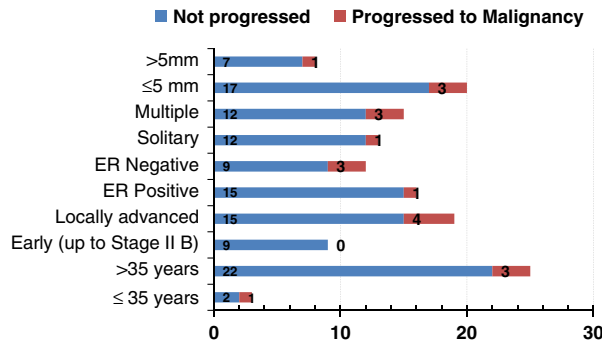


Figure 1. Correlation of progression of lung nodules to patient and radiological characteristics. The number of patients with indeterminate nodules under each subgroup who progressed locally or systemically following radiotherapy is shown in red.

nodules though the clinical queries remain unique to the situation. Whether to proceed with local therapy in the presence of possible lung metastases in this setting is always a practical dilemma for the oncologist. Also, the other differentials like infection or pulmonary TB contribute to the dilemma. This review evaluated the natural progression of such indeterminate nodules to generate a guideline for clinicians facing such a scenario.

In this study we found a fifth of the patients (28 out of 132 patients) to have indeterminate lung nodules. Of the 28 patients, four patients progressed to lung metastases (Figure 2). There was no statistically significant difference in the formation of lung metastases among the various groups compared. In the study done by Quint et al.,⁸ among patients with extrathoracic malignancies, 20% of the population was found to have incidental and indeterminate lung nodules on CT thorax. Daglar et al.⁹ found that 58 patients had solitary nodule on the chest X-ray and these patients when assessed with CT thorax, only 28 patients had shown pulmonary nodules. Similar analyses by Lee et al.⁶ in early untreated breast cancer found a much lower detection rate for indeterminate nodules. Thirty-four patients had pulmonary nodules out of 802 thoracic CT scans reviewed. Of the 34, 10 patients had nodules >1 cm.

Our study grouped these patients according to the tumour and patient characteristics and each of

the group was individually analysed for progression to pulmonary metastases. Daglar et al.⁹ who analysed the indeterminate pulmonary nodules in breast cancer patients that progressed to lung metastases used both chest X-ray and CT scan as imaging modalities. Hence a similar grouping based on tumour and patient's characteristics as in the analyses was not done.

Only four patients of the 28 patients progressed to lung metastases. It could not significantly correlate to the progression to any of the variables that were assessed. Daglar et al.⁹ also found only three patients with disease in lung and none of those patients in the study died due to lung metastases. Hence, they concluded that these nodules might not be primary malignancies and these can be ignored if CT scan findings are suggestive of benign lesions. Similar findings were seen in our retrospective analyses, which prompt us to ratify the recommendations by Daglar et al.⁹

Although the cohort is small, the study shows the high-risk features the clinician should be wary of namely; ER negativity, presence of multiple nodules, locally advanced breast cancer at presentation may show a trend towards higher risk of progression of nodules. These patients if screened out during the planning CT can be directed for systemic therapy or could continue a systemic approach along with the local therapy. It may be worthwhile to generate criteria for evaluation and further treatment of such lung nodules. Until we have a definite evidence to suggest a change in policy, patients should continue to have locoregional radiotherapy in the setting of indeterminate lung nodules. A closer follow-up and early institution of further systemic therapy in case of progression may be suggested.

CONCLUSION

Approximately one fifth of the breast cancer patients who had undergone CT thorax for locoregional radiotherapy planning were found to have indeterminate lung nodules. ER negativity, presence of multiple nodules, locally advanced breast cancer at presentation may be associated with high risk of progression of these

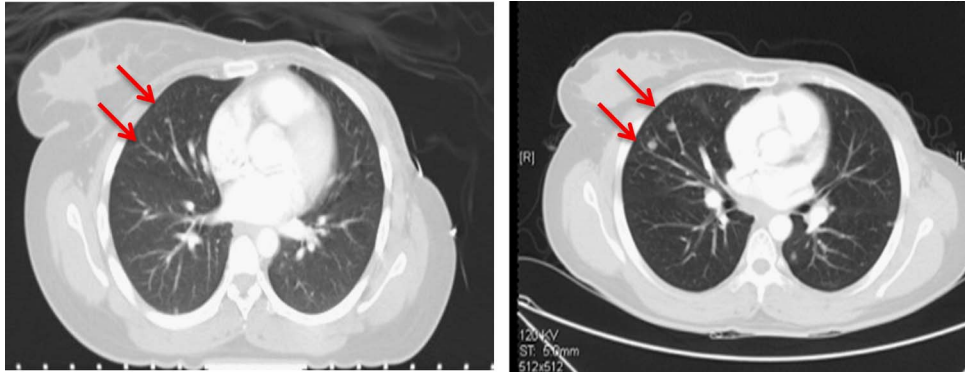


Figure 2. (a) Indeterminate nodules in the right lung on planning computed tomography (CT) scan. (b) Subsequent CT scan of the thorax showing progression of the same nodules to lung metastases.

nodules into lung metastases. Patients with these risk factors can be on close follow-up. Locoregional radiotherapy should not be delayed in patients in view of indeterminate lung nodules. Prospective studies with larger sample size are needed to validate our results.

Acknowledgements

None.

Conflicts of interest

None.

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