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CLINICAL STUDY

The significance of pulmonary nodule in breast cancer patients

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Abstract: *Background:* Pulmonary nodule in patients with breast cancer is a difficult problem and constitutes a therapeutic challenge. This study questioned the significance of solitary pulmonary nodule in breast cancer patients and compared the survival with patients who had normal thorax tomography.
Methods: There were 58 breast cancer patients included in the study. From these, 28 patients had normal preoperative tomography (group 1), and 30 patients had pulmonary nodule less than 1 cm on thorax tomography (group 2). Chi-square and Fisher tests were used for comparisons and Kaplan-Meier test for survival.
Results: Stage, tumour size, treatment, histology, lymph node involvement, adjuvant therapy, were similar in both groups. We did not find a significant difference in disease-free and overall survival rates, between two groups.
Conclusions: For the nodules that show benign properties at tomography, there is no need to do further investigation and no need to change treatment plan in breast cancer patients *(Tab. 2, Fig. 2, Ref. 12)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: breast neoplasms, solitary pulmonary nodule, staging, survival.

Lung metastases can be found in 5–10 % of breast cancer patients at presentation (1). This finding totally alters the treatment plan of patients. On the other hand, solitary pulmonary nodule, which is found incidentally during the work-up of breast cancer patients, constitutes a difficult problem. Determination of such a nodule can cause confusion in staging. Should we accept them as malignant and perform further investigation? In fact, most of these nodules have a benign cause, but metastases, bronchogenic carcinoma and other malignant processes are important causes as well and must be excluded in differential diagnosis (2). Determination of the aetiology of such a nodule is important to perform the appropriate therapy. The purpose of this study was to determine significance of these nodules in new diagnosed breast cancer patients and to compare the survival of these patients with the patients who had no pulmonary nodules.

Patients and methods

Breast cancer patients, operated on from January 1992 to December 2006 at the Ankara Numune Research and Training Hospital, fourth department of surgery, were evaluated. The data were obtained from our prospectively collected database. Information regarding physical findings, history of smoking, diagnostic studies, histology, local and systemic recurrences and survival of patients were analysed.

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All patients underwent a chest x-ray in the preoperative period. Fifty-eight patients who had solitary pulmonary nodule on the chest x-ray were included in this study. Further evaluation was performed in these 58 patients. For this purpose, thorax tomography was done. Preoperative computed tomography (CT) was reported by radiologists, from one unite. Patients were examined in the two groups according to the preoperative CT findings. In the first group the patients had normal tomography findings and in the second group, the patients had a solitary pulmonary nodule on CT. Nodules were less than 1 cm in diameter and smooth in margin. No further evaluation was done for the second group.

In both groups a modified radical mastectomy operation was performed. Patients were staged according to the TNM system of the American Joint Committee on Cancer (AJCC) (3). Histological type was the infiltrative ductal carcinoma in all patients.

In an univariate analyses, age, family history, body-mass index, smoking, menopausal status, tumour size, lymph node involvement, neoadjuvant and adjuvant chemotherapy, radiotherapy, and systemic metastases were all compared. A disease-specific survival was defined as the period between the diagnoses of primary cancer until death from breast cancer.

The disease-specific survival and disease free survival were estimated by the Kaplan-Meier analysis and comparisons were done by the log-rank test. $p<0.05$ was accepted as significant. The Chi-square and Fisher exact tests were used to determine the statistical significance of associations between the two groups.

Results

There were 58 patients included in the study who fulfilled the criteria mentioned above. The mean age of the patients was

Tab. 1. Properties of the patients according to groups.

	Group I	Group II	p
Mean age	47.3	50.8	0.21
Smoking	3(10.7%)	5(16.7%)	0.51
Mean body mass index	25.9	27.5	0.20
Premenapausal status	15(55.6)	14(46.7%)	0.50
Family history	6(22.6%)	3(10.0%)	0.20
Mean number dissected ln	19.9	19.3	0.78
Presence of metastatic ln	15(53.6%)	23(76.7%)	0.06
Mean number of metastatic ln	3.5	5.2	0.30
Metastatic ln ratio	0.19	0.29	0.22
Local recurrence	2(7.1%)	-	0.22
Systemic recurrence	8(28.6%)	6(20.0%)	0.44
Recurrence	9(32.1%)	6(20.0%)	0.29
Mean follow-up time(mo)	29.6	32.2	0.64
Recurrence time(mo)	27.2	29.9	0.64
Mortality	6(21.4%)	5(16.6%)	0.74
Disease free survival rate	61.8%	61.1%	0.37
Neoadjuvant chemotherapy	1(4.2%)	4(14.8%)	0.35
Chemotherapy	27(90.0%)	27(96.4%)	0.33
Radiotherapy	9(32%)	11(36%)	0.71
Pulmonary metastases	3(10.7%)	2(6.7%)	0.58
Second primary in lung	1(3.6%)	0	0.48

ln = lymph node, Mo: month

Tab. 2. Staging of the patients according to AJCC staging system.

Stage	Group I n (%)	Group II n (%)
I	5 (17)	3 (10)
IIA	10 (35)	9 (30)
IIB	7 (25)	6 (20)
IIIA	4 (17)	5 (17)
IIIB	1 (3)	5 (17)
IIIC	1 (3)	2 (6)
	28	30

AJCC = American Joint Committee on Cancer.

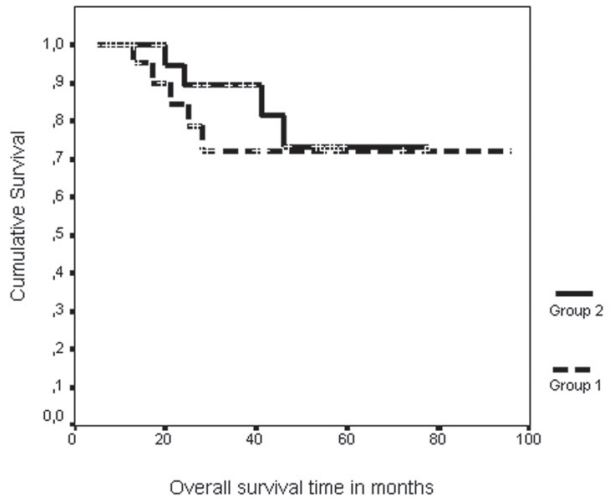

Fig. 1. Kaplan-Meier curve of a disease specific survival by the presence of pulmonary nodules.

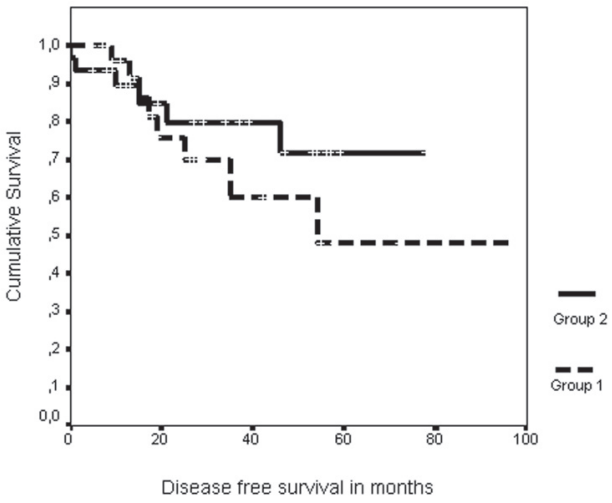

Fig. 2. Kaplan-Meier curve of a disease-free survival by the presence of pulmonary nodules.

49 years ranging between 32–73. There were 28 patients who had normal tomography findings (48.2 %) (Group I) and 30 patients who had a pulmonary nodule (51.7 %) (Group II). Nodules were less than 1 cm in diameter and smooth in margin and some of them were calcified.

There was no statistical difference between the two groups regarding the clinico-pathological findings and adjuvant chemoradiotherapy, local or systemic recurrence, mean follow-up time, disease free survival, mortality rate (Tab. 1). Dispersion of the TNM stages between the groups is presented in the Table 2. The survival analysis has shown that the mean disease specific survival time was 75 months for all patients; there was no statistical difference between the two groups according to the mean disease specific survival time ($p>0.05$) (Fig. 1).

The mean disease free survival was 61.1 months in the first group and 61.8 months in the second group ($p>0.05$) (Fig. 2). Systemic and local recurrences did not differ significantly between the two groups ($p>0.05$). Sixty percent of the patients with systemic recurrences had a normal preoperative thorax tomography while 40 % had nodules preoperatively. Mortality rates were also similar for both groups ($p>0.05$).

Three pulmonary metastases and a pulmonary Schwannoma were seen in the first group during the follow-up period. Three pulmonary metastases were found at 10th, 18th, 96th months. There were six mortalities in the first group and three of them due to brain metastases and three due to lung metastases.

A progress in the nodule diameter or new nodule formation was observed in two patients in the second group. Two pulmonary metastases were found at 10th and 14th months. There were four patients who had normal findings in later computed tomography scans. Previous infections might be the reason for the nodules that were seen in former CT scans. There were five mortalities (16.6 %) in this group and only one of them was related to pulmo-

nary metastases, which occurred in the 41st month. Three mortalities were due to brain metastases in the 20th, 24th, and 46th months. One of the mortalities was not a disease specific mortality.

Discussion

Solitary pulmonary nodules are seen in about 1–2 % per 1000 chest radiographs (4), most being detected on routine chest radiographs in asymptomatic individuals. In these cases, 60 % of nodules are benign. Granuloma constitutes the major portion of these lesions (54 %). Bronchogenic carcinoma (35 %), bronchial adenomas (2 %) and metastatic lesions (3.5 %) are amongst the other causes. Currently by the help of CT scan, it is easy to determine small nodules. It can also show a presence of calcification, fat and vascular connection (2). Small size and smooth, well-defined margins, <8 mm and calcified nodules are suggestive of benign lesions. Lobulated contour as well as an irregular or speculated margin with a distortion of adjacent vessels is typically associated with malignancy (5). The situation is more difficult in patients with the history of extrathoracic malignancy. In presence of an extrathoracic malignancy, determination of such a nodule especially in the preoperative period causes confusion. Solitary nodule on computed tomography might have different diagnostic implications. Nature of these nodules affects the treatment and follow-up of patients with a known primary extrathoracic neoplasm. The extrapulmonary neoplasm and the lung nodule can be either synchronous or metachronous (i.e., the extrapulmonary neoplasm occurring before the lung nodule) (6). Although a solitary pulmonary nodule (<8 mm) is common in patients with the extrathoracic malignancy, differentiation of malignant deposits from benign nodules remains a problem in the surgeon's mind (7).

Peuchot and Libshitz reviewed pulmonary nodules seen on tomography in 74 patients with previously treated extrathoracic malignancies. From these identified nodules, 78 % were metastatic (8). It was believed that the extrathoracic malignancies were more likely to have a primary lung cancer than metastases. To the best of our knowledge, there was no large series of breast cancer studying the faith of pulmonary nodule in English literature.

Adkins et al (9) reviewed 500 patients with metastatic disease of the lung and mediastinum. In those patients who were treated for carcinoma of the breast, the majority of the thoracic lesions proved to be unrelated to the initial primary malignancy, so the study supports the idea that a solitary nodule in the lung more commonly represents a second primary malignancy. On the other hand, Lee (10) reported on 665 patients with breast cancer during a 14 year period. The most common second primary malignancy in this study involved the opposite breast. Lung metastases were found in 9 % of the patients and less than 1 % of the patients had developed lung cancer. Similarly Holdener et al reported 4.2 % incidence of the second primary malignancy in patients with breast cancer reviewed retrospectively, and 3.7 % in a smaller group followed prospectively (11). In our study, 1.6 % of breast cancer patients were found to have the second primary malignancy in lung.

In the study by Quint et al, 30 benign nodules had been found on computed tomography amongst the 149 patients (20.1 %) with extrapulmonary neoplasm (6). Undoubtedly, more benign lesions are being detected in the current era, probably because of the ability to identify small nodules with computed tomography. The study by Cahan et al may have been biased toward malignant lesions, because it included only those patients who underwent thoracotomy (12). Quint has included also some patients with the clinical follow-up (6).

Based on their results, the authors questioned the value of computed tomography in identifying the nature of nodules. Most of the studies studied extrathoracic malignancies but few of them evaluated breast carcinoma patients separately. Furthermore, pulmonary nodules have been determined after the treatment of original tumour (9, 10) and discussion has concentrated around metastases or primary lung cancer. Only breast cancer patients were included in this study. We thought that significance of these nodules were higher at the time of breast cancer diagnosis. Because the treatment plan of the patients depend on the preoperative stage of the patients. If the nodule is malignant, this means that patient has metastatic disease and surgery is not going to be curative. Patient who had benign nodule could have a chance of cure depending on the stage of the disease. So the treatment strategies will be planned according to this decision. Number and percentage of benign lesions were higher in this study. Pulmonary nodule incidence was found to be 24.1 % on computed tomography and 96 % of them were thought to be benign according to CT finding. In our study, the follow-up was made by the radiological criteria of the lesion on computed tomography. For the follow-up of the lesion, we accept the criteria mostly used in literature. Small size and smooth, well-defined margins, <8 mm and calcified nodules are suggestive of benign lesions (5). Biopsy was performed only when the criteria of the lesion showed malignancy as irregular or speculated margin with distortion of adjacent vessels. Upon the suspicion of malignancy, two patients underwent the computed tomography-guided fine needle aspiration biopsy, and the results were malignant. One patient had a metastatic lesion of breast carcinoma and the other one had the second primary malignancy in the lung which was Schwannoma. These two patients had normal CT preoperatively.

All patients were followed-up postoperatively. The overall survival and disease free survival of these patients did not differ significantly between the two groups (disease-free survival was 61.1 months versus 61.8 months, $p>0.05$). In the group I, only one patient died due to lung metastases of breast cancer. We believe that the length of follow-up was enough to conclude that some of these nodules might not be in fact the primary malignancies. So we can ignore these nodules if the tomographic findings suggest a benign lesion.

There was a nearly significant difference with the $p=0.06$ in the lymph node positivity between the groups. From this point, the group II should have worse prognosis. But survivals of the patients were not different between the groups. We thought that the nodules detected on chest CT were not significant.

In literature, the extrathoracic malignancies were evaluated together and they concentrated on nodules detected postoperatively. In this study, we intended to evaluate the meaning of these

nodules in preoperative breast cancer patients. This study has shown that solitary pulmonary nodules detected on computed tomography were not related to breast cancer metastases. We ignored the nodules if we considered them as benign according to the computed tomography criteria and we treated these patients as patients with normal computed tomography findings. We did not routinely perform percutaneous or open biopsy of these pulmonary nodules. The adjuvant therapies were guided according to histopathologic findings of the mastectomy specimens.

We believe that for the pulmonary nodules detected in the preoperative period that show benign properties on CT, there is no need to further investigation to change the treatment plan because of the nodules. Further evaluation gives rise to unnecessary cost and more stress on patients. Criteria for a nodule to accept as benign will need to be developed based on the initial tomographic appearance of the nodule and the clinical status of the patient.

Conclusion

Appearance of the nodule on the chest tomography can guide the surgeons for further evaluation and treatment plan the breast cancer patients.

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