The Effect of Surveillance on the Outcome of Breast Cancer Patients

Kazem Anvari[1], Azar Fanipakdel[1], Yasmin Davoudi[2]

Abstract

Background: The beginning of metastasis poorly affects the prognosis of breast cancer patients. Lung is the most frequent site of visceral metastasis, and the rate of recurrence is 10-30%. We have tried to find out if the routine Chest X Ray (CXR) could play a role for early detection of lung metastasis, during the prognosis of these patients.

Methods: The files of the breast cancer patients between 1996 to 2006 (1739 patients) have reviewed. Clinical characteristics of patients with pulmonary metastasis have recorded. Patients, who lacked imaging files or lacked an appropriate follow-up, have excluded. Data have analyzed by SPSS 11.5. The survival analyses have performed by using the Kaplan-Meier method.

Results: Fifty-six patients, median age 46, have entered into this retrospective study. Median tumor size was 4cm; median number of Lymphadenopathy (LAP) was 4. The intermediate grade has detected in 74% of patients. All patients have received adjuvant treatment. Median time from cancer diagnosis to pulmonary metastasis was 22 months. Pulmonary metastasis has detected by control CXR in 77.4% and patients' symptoms in 22.6%. Forty eight patients have received chemotherapy in metastatic phase. In 28 patients (50%), other sites of metastasis (bone, liver, and brain) have discovered.

The most frequent pattern of lung recurrence was pulmonary nodule (44.6%), followed by pleural effusion (28.6%). Median survival was 27.5; median survival from pulmonary metastasis was 8 m.

Conclusion: Early detection of pulmonary metastasis by CXR did not affect patients' endpoints. None of the probable prognostic factors have shown a significant effect on patients' outcome. Despite systemic treatment, survival after metastasis is low.

Keywords: Breast cancer; Lung metastas; Surveillance

Please cite this article as: Anvari K, Fanipakdel A, Davoudi Y. The Effect of Surveillance on the Outcome of Breast Cancer Patients. Iran J Cancer Prev.2013; 6(1): 17-24.

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Received: 29 Apr. 2012
Accepted: 15 Oct. 2012
Iran J Cancer Prev 2013; 1:17-24

Introduction

Breast cancer is the most common cancer in women worldwide and the second most common cause of cancer-related mortality in the United-States [1].

Metastasis in these patients presents in various patterns and these patients respond to different kinds of antineoplastic drugs. Combination chemotherapy regimens make a better response and a longer survival, but unfortunately these patients would eventually submit to their disease [2-6]. Lung is the second most common site of metastases in all cancers but the most common site of visceral metastasis in the breast cancer. Pulmonary Metastasis (PM) is the first site of recurrence in 10 to 30 % of patients [7], and has a better response to chemotherapy than the other metastases, although isolated lung metastasis in not common [8].

It is not clear if early detection of distant metastasis could improve the outcome of patients. Distant metastases have usually discovered by patients' complaints such as dyspnea, bone pain, etc. Despite Intensive Surveillance (IS), screening laboratory or imaging studies might detect asymptomatic metastasis only in a small fraction of cases [9]. In 1994, two randomized trials have compared IS (by CXR, bone scan, sonography and

tumor markers) with routine follow up (physical examination and mammography, more assessments only if indicated). The authors concluded that IS resulted in modest gains in early detection of distant metastasis without any improvement in overall survival [10, 11]. Based on these findings, different organizations such as American Society of Clinical Oncology(ASCO), European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), do not recommend IS routinely, but they advise the clinicians to continue the routine follow up regularly and ask more assessments if only clinical evidences have indicated [12-14].

Despite the above accepted guidelines, some clinicians believe that early detection might improve the outcome of metastatic breast cancer, probably by early treatment with new chemotherapy medicines.

In this retrospective study, we have evaluated the breast cancers with lung recurrence, diagnostic way for lung metastasis (patient's symptoms or routine CXR), the interval between the diagnosis of breast cancer and metastatic occurrence, the response of lung metastasis to chemotherapy, the survival after metastasis, the overall survival, and finding out if early detection –then early treatment- in metastatic disease, could cause improvements in clinically important end points. We also have assessed the clinical, pathological and radiological findings in the patients.

Materials and Methods

This was a retrospective single institution study among a large population of Iranian patients with breast cancer who have referred to Omid Hospital, Mashad University of Medical Sciences, Mashad, Iran, between January1997 and December 2007, to find patients with pulmonary metastasis.

The clinicopathological parameters including age, sex, menstruation status, breast cancer diagnosis date, type of surgery, tumor size, lymphadenopathy, grade, immunohistochemistry results of Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 status, adjuvant treatment, date of pulmonary recurrence, the prescribed treatments at metastatic phase and the situation in the last visit of patients with pulmonary metastasis, have extracted from patients' medical records. We also have registered the way of lung metastasis detection (surveillance, or patient's symptoms).

CXR and CT scans of the lung have reviewed again by an academic radiologist and the findings about the pattern of metastasis and radiological response to treatment, have recorded.

Patients who did not have a suitable follow up and those, whose radiographic folders have missing, were excluded from the study.

Statistics

Descriptive analysis assessed patient and disease characteristics for diagnosis of breast cancer. Data have analyzed by SPSS 11.5. The survival endpoints have estimated by using the Kaplan-Meier method. The log-rank test has used for group comparisons. The study protocol has obeyed the guidelines of the 1996 Declaration of Helsinki.

Results

Within the period, 1739 breast cancer patients have been recorded; seventy eight with pulmonary metastasis. Twenty two patients without an appropriate follow-up and have required imaging files, so have excluded from the study. Fifty-six patients have qualified our study. The patients' age have ranged from 29 to 75 years with the 46 years old median. Patients have consisted of 26.8% postmenopausal and 73.6% premenopausal or primary-menopausal women.

The primary tumor size has extended from 1cm to 12 cm (median: 4 cm). Number of involved axillary lymph nodes have ranged from 0 to 12 (median: 4). Ninety one percent of patients had undergone mastectomy and only 9% had undergone breast saving surgery. The pathological grade was intermediate in 74%. Adjuvant chemotherapy has prescribed in all, adjuvant radiotherapy in 82% and adjuvant hormone therapy in 75% of patients.

The diagnosis of lung metastasis has been based on patients' symptoms in 22.6%, then on radiographic findings in 77.4% of patients. The major clinical-pathologic characteristics of patients have summarized in Table1.

The interval between the time of diagnosis and the occurrence of lung metastasis have ranged from 0 to 88 months (median disease free interval: 22 months) (Figure 1).

Forty eight patients have underwent chemotherapy, 67% had a partial response, 22.5% had stable disease and 10.5% had progression in lung lesions.

In 28 patients (50%), other metastases (bone, liver and brain, orderly) have also found.

The most common pattern of lung metastasis was pulmonary nodules (25 patients, 44.6%) (Figure 2), has followed by pleural effusion (16 patients, 28.6%). Nine patients (16.1%) had a combination of pulmonary nodules and pleural effusion. Only 6 patients (10.7%) have shown other patterns of

Table 1. Patients and tumors characteristics

Variable	Number	Frequency (%)
Menstruation status		
Premenopausal	29	52
Primary m.	12	21
Post m.	15	27
Surgery type		
Biopsy	4	7.1
Lumpectomy	1	1.8
Simple mastectomy	4	7.1
MRM	47	83.9
Grade		
Low	1	1.8
Intermediate	17	30.4
High	5	8.9
Missing	33	58.9
Other metastasis		
Bone	15	26.8
Liver	11	19.6
Brain	8	14.3
ER (In 32 patients)		
Negative to weak +	27	84.4
Mod to strong +	5	15.6
PR		
Negative to weak +	29	90.6
Mod to strong +	3	9.4
Her2 IHC (In 15)		
Negative to weak +	8	53.3
Mod to strong +	7	46.7
Lung metastasis DX (In 53)		
Routine CXR	41	77.4
Symptom	12	22.6
Lung metastasis response to chemotherapy (In 49)		
Partial Response		
Stable Disease	33	67.5
Progression	11	22.5
	5	10

metastases such as lymphangitis carcinomatosis, lymphadenopathy and/or consolidation.

Twelve patients had chest CT scan in which the most common finding was again a pulmonary nodule. Figure 3 and 4 show CXR of one patient with pulmonary nodules and another patient with pleural effusion, respectively.

Median survival time was 27.5 month (range: 4-156 month) (Figure 5). Survival duration (from the time of lung metastasis diagnosis), has ranged from 0 to 155 months (median: 8 months) (Figure 6).

Patient's condition in the last visit has estimated well in 5.4%, minor symptoms in 62.5% and near death in 30.4% of patients.

None of the clinicopathological factors such as age, tumor stage, lymph node involvement, immunohistochemical result type of surgery, lung metastatic pattern, distribution of metastasis in other parts of the body, type of the treatment, and the response to chemotherapeutic agents in metastatic phase had a statistically significant correlation with the presumed endpoints (DFI, overall survival, the survival of lung metastases diagnosis).

We have evaluated the impact of adjuvant chemotherapy regimen (CMF, n=12 vs Adriamycin and/or Taxan based regimens=53) on the patients' metastatic disease course, but it has not shown a significant difference (χ^2 =0.487, p= 0.485).

Due to the diverse heterogeneity in the CT regimens and the small number in each group, we couldn't make an analysis on it. Instead; regarding the old assumption that the response to CT could be a predictor of disease course in most metastatic conditions, we have analyzed the survival of metastatic disease according to its response to CT

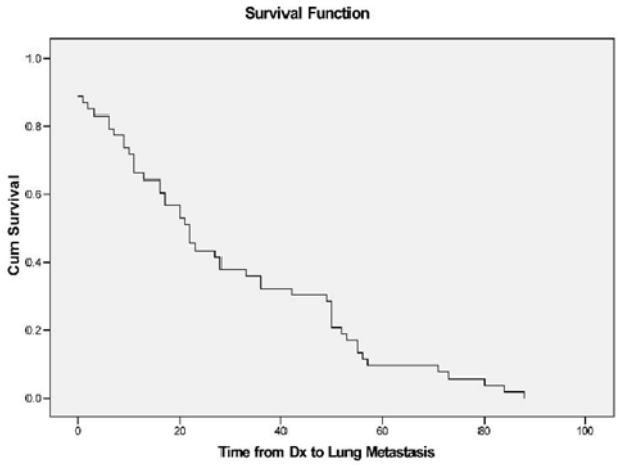

Figure 1. Survival curves for the interval between the time of diagnosis and the occurrence of lung metastasis

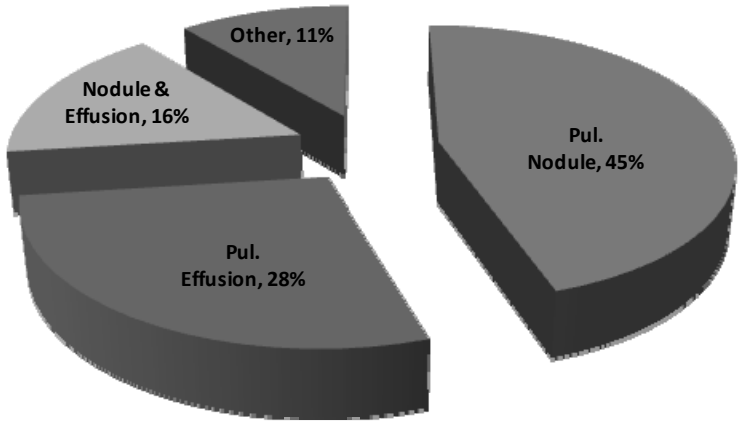

Figure 2. Distribution of radiologic patterns of pulmonary metastasis in BC patients

regimen, whatever it has been; however, we couldn't find a significant difference (partial response, n=32 vs. progressive or stable disease, n=16, χ^2 test, p=0.185).

The diagnosis of lung metastasis has based on CXR findings in 77.4% of cases, and in only 22.6% of cases, clinical symptoms have led to metastasis diagnosis. The outcome of the metastasis has diagnosed in this way, was not better than the symptomatic group. Median survival after metastasis was 7 months in comparison with 14 months in symptomatic (p= 0.348) (Figure 7).

We have classified the patients according to distribution of metastasis in other parts of the body into 3 groups: first, those with no other metastasis; second, those with lung and bone metastasis but no other visceral metastasis; then third, those with both lung and another visceral metastasis (liver and/or brain).

The survival of metastatic disease in the three group has not shown a significant difference (χ^2 =0.770, p= 0.681).

Discussion

Numerous studies have faced the higher incidence of PM among all MBCs and their poor outcome. Efforts have been made to improve the survival of these patients. In this study, we have tried to find whether regular CXR in the surveillance of BC patients and earlier detection of PMs contributes to improvement in the survival of these patients. The

Figure 3. Metastatic pulmonary nodule in a patient with BC

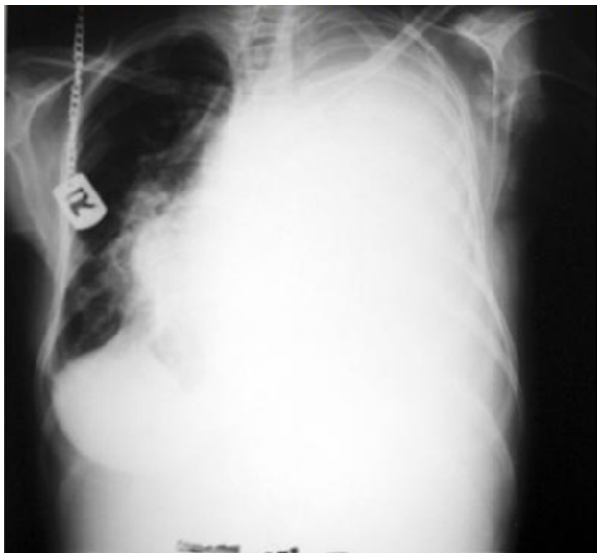

Figure 4. Metastatic pulmonary effusion in a BC patient

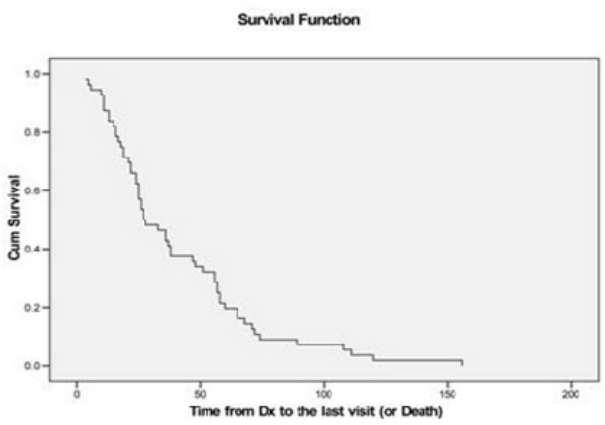

Figure 5. Survival curves for diagnosis

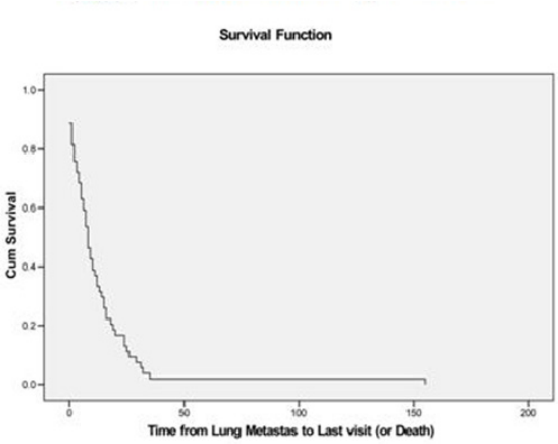

Figure 6. Survival curves for lung metastasis

diagnosis of lung metastasis has based on CXR findings in 77.4% of cases, and in only 22.6% of cases, clinical symptoms led to metastasis diagnosis. The median time from PM diagnosis to the last visit or death was 14 months, for patients who have presented with pulmonary symptoms, compared with patients who has shown asymptomatic PMs, and have detected within 7 months via CXR (χ^2 =0.882, p= 0.348), which implies that the outcome of the metastases which is diagnosed in this way is not better than the symptomatic group (Table 2) (Figure 7).

In a randomized multicenter controlled clinical trial involving 26 general hospitals in Italy, GIVIO investigators have studied 1320 women younger than 70 years with early unilateral primary breast cancer to evaluate the impact of intensive surveillance on patients' survival. Patients have randomly allocated to an IS, including physician visits, bone scan, liver sonography, CXR, and laboratory tests at predefined intervals (n=655), or to a control regimen (n=665), in which patients have seen by their physicians at the same frequency but tests have performed only when clinically indicated. Both groups had annual mammography. At a median follow-up of 71 months, there was no difference in overall survival of the intensive group with 132 deaths (20%) and the control group with 122 deaths

(18%). The time to detection of recurrence has not significant difference, either. The authors have concluded that routine use of IS after primary treatment for breast cancer should not be recommended as a routine policy [10].

Rosselli Del Turco et al has studied the effectiveness of early detection of pulmonary and bone metastasis in decreasing mortality of BC patients. He has randomized 1243 consecutive non metastatic BC patients to two alternative surveillance programs (clinical, with P/E and mammography every 6 months vs. intensive, with CXR and bone scan in addition).The primary endpoint was 5 years survival. The detection of isolated intrathoracic and bone metastases has increased in IS group compared with the clinical follow-up group (112 vs. 71 cases), but local/regional or other distant recurrences were similar in both groups. Because of earlier detection of recurrences in the intensive follow-up group, the 5-year relapse-free survival rate was significantly higher for the clinical follow-up group. There was no difference in 5-year overall mortality (18.6% vs. 19.5%) between the two groups. The authors have concluded that IS has no impact on prognosis and should be discouraged [11].

ASCO guideline emphasizes on physical

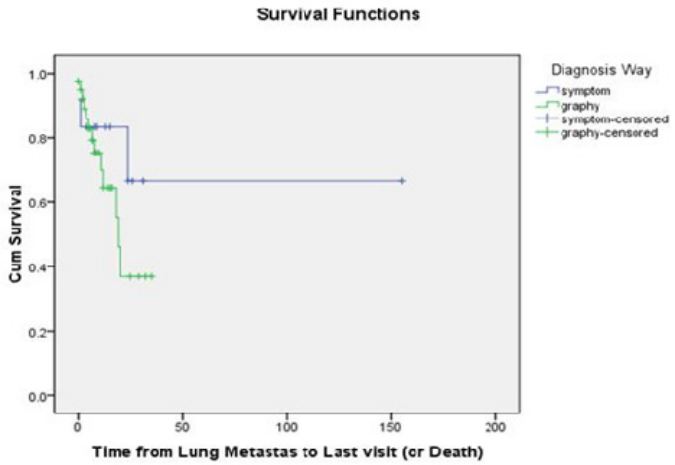

Figure 7. Survival curves of BC patients with PM according to diagnosis way

Table 2. Probable prognostic factors assessment on PFS in breast cancer patients with lung metastases

	Number	percent	PFS (Median)	P value
Isolated lung mets	25	47.5	5.5m	0.301
With other mets	28	52.5	10m	
Mets nodules only	25	50	8m	0.914
Pleural effusion with or without nodules	25	50	9m	
Asymptomatic mets (found via radiology)	40	77.4	7m	0.348
Symptomatic	12	22.6	14m	
Partial response to chemotherapy	32	67	9m	0.185
Persistent or progressive disease	16	33	7m	

mets: metastatic

examination and history and minimize the role of CXR and marker in asymptomatic patients [12].Whatever a follow-up program and its frequency is, it should include medical history, physical examination, and annual (in postmenopausal) or at least every 1-2 year mammography(for premenopausal group). It should aim at early detection of loco-regional recurrences or contralateral breast cancer, then psychological support to return the patient normal life, and then to work [13].

For the surveillance of non-metastatic breast cancer survivors, National Comprehensive Cancer Network (NCCN) recommends history taking and physical examination every 4-6 months for 5 years, and annually afterwards. Annual mammography and pelvic examination (in Tamoxifen users) and periodic bone densitometry (in aromatase inhibitor users), following an active lifestyle and gaining the ideal BMI is encouraged [14].

Routine CXR has been encouraged, especially in the series who has studied the role of surgery in isolated lung nodules. Murabito has shown that complete resection of coin lesions in the lung of breast cancer patients would significantly increase the survival in comparison with incomplete resection or no resection and this procedure would outshine the other prognostic factors in metastatic disease such as DFI, early stage of the disease, hormonal receptors and adjuvant chemotherapeutic regimens. For these reasons this researcher has considered routine CXR as a necessity [15]. None of our patients have underwent biopsy of the metastatic lesions, probably due to definite diagnosis and also because controversy between the role of metastasectomy in increasing the survival of breast cancers with lung metastasis. However, due to substantial discordance in receptor status between primary tumor and metastatic disease, that have demonstrated in some prospective studies which may alter management in about 20% of patients, some researchers advocate a tissue confirmation in all patients suspicious of metastatic recurrence [16].

In the past 40 years, systemic chemotherapy has improved the quality of life and survival of metastatic breast cancer patients. In spite of that, the outcome of these patients is still disappointing. In our study 48 patients (84%) had undergone chemotherapy for metastasis. Neither of them had a complete radiological response. Thirty two patients (67%) had a partial response (more than 50% decrease in the size or volume of the metastasis), and 16 patients (33%) had a persistent or progressive disease. However, there was not a significant difference in the median and overall survival after metastasis between these two groups (median survival 9m vs. 7m, χ^2 = 1.758, P=0.185) (Table 2).

In the systematic review of Y-TN LEE on seven autopsy series of breast cancer patients (overall 2000 patients), the most common sites of metastasis were lung (71%), bone (71%), lymph nodes (67%), liver (62%) and pleura (50%) [8]. Despite the general positive prospective about the prognosis of limited lung metastasis in breast cancer, there is still no systematic study with a sufficient number of patients to evaluate the response of these patients to modern chemotherapeutic regimens. Half of the patients in our study had metastasis limited to the lungs. This group had a median 5.5 months PFS compared within 10 months for patients with synchronous lung and other(s) organ(s) metastases, but the difference was not statistically significant (χ^2, p=0.301) (Table2).

There is a general presumption that CXR lack enough sensitivity for early detection of lung metastasis, CT could be a better substitute. B. Lee has evaluated the clinical importance of asymptomatic lung nodules in CTS of ESBC. In a multicentric study in London, 1578 new BCs have recorded between 2002 and 2008, 802 of them have underwent CTS for staging, 34 patients had suspicious lung nodule(s) without evidence of metastases in other parts of the body. In 18 months F/U, there was no change in the nodule(s) in 86% of patients with lesions less than 1cm. In contrast, all patients with larger nodule(s) have shown lesion progression (χ^2, p=0.004). He has concluded that suspicious nodules less than 1cm, without evidence of metastasis in other parts, are probably not metastatic and these patients should not be deprived from entering trials or treatment with curative intent [17].

MPE could be the first manifestation of recurrence after radical treatment BC [18]. Effusion indicates the spreading of the malignancy. In some cases, however, patients with MPE respond to anti-neoplastic treatment [19]. In our study 25 cases (44.6%) had only LNs without P/E and the same number of patients (25 out of 56) had MPE. They have not shown a significant difference in terms of median PFS (8 m vs. 9m, $\chi^2 = 0.012$, p =0.914) (Table2).

There are still some clinicians who keep on IS to assure the patients who want to trap metastasis sooner; however, experts claim that discussing the role of surveillance, false positive and false negative results of tests, and the slight, if any, impact of IS on

vital endpoints to the patients will convince them to follow the clinical surveillance programs [20].

In conclusion, serial CXR as the routine surveillance has not changed the endpoints of breast cancer patients with lung metastasis. Regarding the median survival time after metastasis (8months), we see that despite systemic treatment, the outcome of these patients is very disappointing. They might benefit from dose intensive regimens with newer agents bone marrow support especially after complete clinical response, which for sure needs further studies with more patients and a prospective design in the future.

Acknowledgment

We thank the radiology students Somaie Hesarnoei and Sakine Honarmand for extraction the information from the database and Saeideh Ahmadi Simab and Navid Nekoei Shahr for performing statistical analysis.

We also acknowledge Dr. Shahrzad Mohammadzadeh Lari and Dr. Haleh Rokni Yazdi for critical reading of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

Kazem Anvari designed the study and data interpretation and revised the manuscript. Azar Fani Pakdel contributed to the data gathering, data analysis and interpretation and wrote the manuscript. Yasmin Davoudi contributed to the radiology assessment, re- writing the manuscript, and English edition.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer Statistics.CA Cancer J Clin. 2008; 58:71-96.

2. Swenerton KD, Legha SS, Smith T, Hortobagyi GN, Gehan EA, Yap HY, et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. Cancer Res. 1979; 39: 1552-62.

3. Legha SS, Buzdar AU, Smith TL, Hortobagyi GN, Swenerton KD, Blumenschein GR, et al. Complete remissions in metastatic breast cancer treated with combination drug therapy. Ann Intern Med. 1979; 91: 847-52.

4. Ross MB, Buzdar AU, Smith TL. Improved survival of patients with metastatic breast cancer receiving combination chemotherapy. Cancer. 1985; 55: 341-6.

5. Henderson IC, Canellos GP. Cancer of the breast, the past decade. N Engl J Med. 1980; 302: 78-88.

6. Canellos GP, Pocock SJ, Taylor SG, Sears ME, Klaasen DJ, Band RP. Combination chemotherapy for metastatic breast carcinoma. Cancer. 1976; 38: 1882.

7. Pass HI. Treatment of metastatic cancer to the lung. In De Vita VT Jr, Hellman S, Rosemberg SA (eds): Cancer: Principles and Practice of Oncology, 4th edition. Philadelphia. PA: Lippincott 1993.

8. Y-TN Lee. Breast carcinoma: Pattern of metastasis at autopsy. J Surg Oncol. 1983; 23: 175-80.

9. Pandya KJ, McFadden ET, Kalish LA, Tormey DC, Taylor SG 4th, Falkson G. A retrospective study of earliest indicators of recurrence in patients on Eastern Cooperative Oncology Group adjuvant chemotherapy trials for breast cancer. A preliminary report. Cancer. 1985; 55(1):202.

10. GIVIO Investigators. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA. 1994; 271(20):1587.

11. Rosselli Del Turco M, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA. 1994; 271(20):1593.

12. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006; 24(31):5091.

13. Aebi S, Davidson T, Gruber G, Castiglione M. On behalf of the ESMO Guidelines Working Group, Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and Follow-up, Annals of Oncology 21 (Supplement 5): v9–v14; 2010.

14. NCCN Clinical Practice Guidelines In Oncology, Breast Cancer, version 2; 2011.

15. Murabito M, Salat A, Mueller MR. Complete resection of isolated lung metastases from breast cancer leads to a marked prolongation of survival. La resezione completa delle metastasi polmonari isolate in seguito a carcinoma mammario prolunga significativamente la sopravvivenza. 2000; 55(3):121-7.

16. Simmons C, Miller N, Geddie W, Gianfelice D, Oldfield M, Dranitsaris G, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Annals of Oncology, doi: 10.1093 /annonc /mdp028.

17. Lee B, Lim A, Lalvani A, Descamps MJL, Leonard R, Nallamala S, et al. The clinical significance of radiologically detected silent pulmonary nodules in early breast cancer. Annals of Oncology, Published online 17 July 2008.

18. Lynch TJ. Management of Malignant Pleural Effusions. Chest. 1993; 103(4): 385-89.

19. KACPRZAK G, KOŁODZIEJ J. The Efficacy Of Various Management Options For Malignant Pleural Effusions,Polski Przegląd Chirurgiczny .2007; 79(3): 196-208.

20. Loprinzi CL, Hayes D, Smith T. Doc, Shouldn't we be getting some tests? J Clin Oncol. 2003; 21(9 Suppl):108.