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ORIGINAL ARTICLE

Screening for metastasis in primary breast cancer patients having four or more axillary lymph node involvement: is it really necessary?

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Summary

Purpose: *To evaluate the necessity and direct cost effectiveness of screening and staging procedures in breast cancer patients having ≥4 positive axillary lymph nodes and to identify further possible biopathological risk factors associated with increased risk of metastasis.*

Methods: *We reviewed the demographic and clinicopathological data from the medical records of 1897 newly diagnosed breast cancer patients. Patients having ≥4 positive axillary lymph nodes after primary surgery for breast cancer and who had staging examinations for metastasis were eligible. The impact of staging procedures (thoracoabdominal CT, bone scan etc.) for detecting metastasis, decision of adjuvant treatment and direct costs were analyzed in 329 patients with operable breast cancer.*

Results: *Thirty-five (10.6%) patients were found with metastasis at diagnosis. Seven (20.0%) among them had multiple metastases. Eighteen (51.4%) had lung, 17 (48.6%) bone, and 7 (20.0%) liver metastasis. Twenty-one (60.0%) patients needed further radiological investigation for metastasis confirmation. Treatment decision was changed in 27 (77.1%) patients. No statistically significant risk factor was identified among the metastatic patients by means of conventional demographic and biopathological parameters. The cost of screening was lower when compared to the cost of treatment without any screening procedure.*

Conclusion: *Since the conventional clinicopathological data seems not sufficient to define the risk of developing metastasis in breast cancer patients with ≥4 axillary lymph node involvement, all of them should undergo full staging examinations until new parameters based on genomic level are defined. Staging procedures need modification for high risk breast cancer patients.*

Key words: axillary lymph node involvement, biopathological parameters, breast cancer, costs, metastasis, staging

Introduction

Approximately 30-40% of patients who present with primary operable breast cancer subsequently develop metastases, indicating that this group might harbor occult metastatic disease when initially evaluated [1]. Although the estimation of possible risk for developing metastases in breast cancer patients by some tumor parameters seems questionable, axillary lymph node involvement seems to be the most important risk factor [2-5]. Initial staging has an important role in deciding for an adequate diagnostic and therapeutic programme. From the literature, it is well-known that patients having ≥4 positive axillary lymph nodes at the time of diagnosis are at greatest risk for developing either locoregional relapse or distant metastasis [6].

At Ege University Faculty of Medicine, routinely, and in a traditional way, preoperative radiological investigations [chest X-ray (CXR) and liver ultrasound (LUS)] are performed in patients newly diagnosed with breast cancer to provide information about distant metastases [7-10]. Since the clinical usage of bone scan (BS) is recommended for patients with stage III disease, this test is only limited for this subgroup of

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newly diagnosed patients [11]. However, the routine use of these tests is controversial, especially in the investigation of patient subgroups, such as those with small tumors (≤ 1 cm) and no axillary lymph node involvement.

Since January 2004, a local committee at our Faculty of Medicine, (medical/radiation oncologists, surgeons, radiologists) that is functional over 10 years for treatment decisions of newly diagnosed breast cancer patients, has decided to further examine patients with ≥4 positive axillary lymph nodes and no clinical evidence of distant metastases. The investigations included thoracoabdominal CT and BS. Since this subgroup of patients represents a higher risk group for having already distant metastases at diagnosis, the aim was to evaluate the prevalence of metastases and to prevent overtreatment of breast cancer patients with adjuvant chemotherapy, who are accepted as disease-free with conventional radiological (CXR, LUS) tests.

Because no official guidelines are present on this topic to date, the main purpose of this study was to evaluate the effectiveness of this staging procedure with CT and BS for this selected high risk subgroup of patients with primary breast cancer and to identify further possible biopathological risk factors, including hormonal receptor status, histological and nuclear grade, and cell proliferation activity or oncogenes or tumor suppressor genes such as c-erb B2 and p53, associated with metastasis at the time of diagnosis. Moreover, we searched whether these factors had any effect on changing treatment decision. And finally, taking into account the rising costs for routine extended staging workup in every newly diagnosed breast cancer, and also the possible important changes in treatment decision due to the presence of metastasis, direct costs of staging procedures and treatment were also assessed in this study.

Methods

We reviewed the medical records of 1897 cases with primary breast cancer referred to the Medical Oncology Department of Ege University Faculty of Medicine between January 2004 and December 2008. At the time of diagnosis, 357 (19%) patients were found to have ≥4 positive lymph nodes. Among these patients, 335 underwent full staging workup for metastasis with CT and BS and were eligible for analysis. Two male patients and 4 other cases lacking critical biopathological information were excluded, thus this retrospective analysis was done on 329 (17%) female patients.

All of the patients had histologically confirmed breast cancer. The analysis included pathological TNM stage, grading, pre-postmenopausal status, hormonal receptor status determined by immunocytochemistry, c-erb B2 status confirmed by fluorescein *in situ* hybridisation (FISH) method in cases with (++) on immunocytochemistry method, number of involved and dissected axillary lymph nodes, and percentage of cell proliferation with Ki67, and p53 status. Estrogen (ER) and progesterone receptors (PR) were accepted as positive with staining percentage ≥ 10%. Also, assessed were family history of breast cancer and history of parity. The primary treatment decision and alterations in decision in case of detection of metastasis were also recorded. Patients with a suspect lesion either on CT or BS were further evaluated with X-ray, MRI, PET/CT etc, according to the localization of the lesion.

Statistical analysis

Descriptive analysis of patients was done for risk factors, metastatic status, staging procedures and changes in treatment. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for MS- Windows operative system. The distribution of possible biopathological risk factors in metastatic and non-metastatic patients was compared univariately with chi-square test. Yates correction was used for 2×2 tables. Means between metastatic and non-metastatic patients were compared univariately using Student's t-test. Standard costs of diagnostic procedures were obtained from the scale of charges of the Turkish Ministry of Finance. Treatment costs were obtained from Rx Media Pharma® digital software program 2008 and calculated for a body surface area of 1.6 m^2. Costs were converted to Euro as of 31 December 2008 according to Central Bank of Turkey exchange rates.

Results

Features of patients and tumors

Mean patient age was 51.1±10.9 years (range 25-82) at diagnosis. Detailed demographic characteristics and family history of patients are shown in Table 1.

Mean tumor size was 3.4±1.9 cm (range 0.7-13). Mean number of dissected axillary lymph nodes was 20.4±8.0 (range 4-55). Median number of positive lymph nodes was 8 (range 4-54). Insufficient axillary dissection (<10 lymph nodes) was present in 4.6% (n=15) of patients, thus most of the patients had sufficient dissection for accurate disease staging. Conventional biopathological characteristics of the tumors are summarized in Table 2.

Table 1. Demographic, clinical and pathologic characteristics of breast cancer patients having ≥4 positive axillary lymph nodes at the time of diagnosis

Characteristics	*Patients, n*	*%*
Age at diagnosis (years)		
<35	20	6.1
35-49	134	40.7
≥50	175	53.2
Menopausal status		
Premenopausal	135	41.0
Postmenopausal	194	59.0
Parity		
No	37	11.2
Yes	292	88.8
Family history of breast cancer		
No	288	87.5
Yes	41	12.5

Table 2. Clinicopathological characteristics of breast tumors

Characteristics	*Patients, n*	*%*
Size* (cm)		
<2	84	25.6
2-4.9	186	56.7
≥5	58	17.7
Location*		
Upper outer quadrant	167	50.9
Retroareolary	68	20.7
Multifocal	43	13.1
Upper inner quadrant	21	6.4
Lower outer quadrant	15	4.6
Lower inner quadrant	14	4.3
Histology*		
Invasive ductal	216	65.9
Invasive ductal+lobular	55	16.8
Invasive lobular	30	9.1
Atypical medullary	14	4.2
Invasive micropapillary/papillary	6	1.8
Inflammatory	5	1.5
Other	2	0.6
Histologic grade*		
1	8	2.4
2	136	45.3
3	153	51.0
unclassified	3	1.0
Nuclear grade*		
1	42	14.3
2	211	71.8
3	38	12.9
unclassified	3	1.0
Lymphovascular invasion*		
No	147	45.0
Yes	180	55.0
Number of positive lymph nodes		
4-9	198	60.2
10+	131	39.8
Biopathological data**		
ER positive	202	62.0
PR positive	189	59.0
c-erb B2 positive	120	37.7
p53 positive	104	37.8
Ki67 positive	186	66.9
Triple negative (ER, PR and c-erbB2 negative tumors)	46	14.2

ER: estrogen receptor, PR: progesterone receptor, *Cases with missing data are excluded and percentages are calculated using the total number of cases with consistent data, **The total number of cases with markers detected varies

Screening for metastases

All patients underwent thoracoabdominal CT and BS for possible detection of metastasis. Of those patients, 304 (92.4%) had CT, 298 (90.6%) had BS, and 92 (28.0%) patients had further investigation because of suspicious lesions in either BS or CT. Among these patients, 62 (67.4%) had MRI of bone or visceral organs, 27 (29.3%) bone X-ray, 4 (4.3%) PET-CT and 3 (3.3%) CT of the suspected lesion.

Metastasis was detected in 35 (10.6%) patients. Seven (20.0%) among them had multiple metastases at the time of diagnosis. Eighteen (51.4%) had lung, 17 (48.6%) bone, and 7 (20.0%) liver metastasis. Of the 35 patients who had metastasis at the time of diagnosis, 14 (40.0%) had metastasis detected during primary investigation for metastasis, whereas 21 (60.0%) needed further investigations due to suspicious findings either on BS or CT.

No statistically significant risk factor(s) was identified among the metastatic group compared to non-metastatic group by means of conventional demographic and biopathological parameters (Tables 3 and 4). However, there was a trend for higher percentage of metastasis in patients under 35 years at the time of diagnosis, but without statistical significance (p=0.275).

Presence of metastasis was also compared among different types of tumor histology; no significant difference was found for invasive ductal vs. others, or invasive lobular vs. others, mixed vs. others or atypical medullary vs. others (p>0.05).

Treatment schedules

Treatment schedules planned initially for the whole study group were as follows: docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) (TAC) for 154 (46.8%) patients; dose-intense doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) followed by paclitaxel (175 mg/m^2 /AC-P) for 136 (41.3%); and cyclophosphamide (500 mg/m^2), epirubicin (100 mg/m^2), 5-fluorouracil (500 mg/m^2) (CEF_{100}) for 33 (10.0%). Due to comorbidities, 6 (1.8%) patients received other types of adjuvant treatment, like hormonotherapy or irradiation. Initial treatment plans for patients found to be metastatic were TAC for 17 (48.6%), dose-intense AC-P for 16 (45.7%) and CEF_{100} for 2 (5.7%),

Table 3. Univariate analysis of metastatic status according to conventional clinicopathological prognostic risk factors

Risk factor	*Metastasis*					
	No		*Yes*			
	n	*%*	*n*	*%*	X^2	*p-value*
Age at diagnosis (years)						
<35	17	85.0	3	15.0	2.510	0.275
35-49	124	92.5	10	7.5		
≥50	153	87.4	22	12.6		
Menopausal status						
Premenopausal	126	93.3	9	6.7	3.123	0.077
Postmenopausal	168	86.6	26	13.4		
Parity						
No	31	83.8	6	16.2	0.783	0.376
Yes	263	90.1	29	9.9		
Family history						
No	256	88.9	32	11.1	0.218	0.641
Yes	38	92.7	3	7.3		
Size of tumor						
T1	73	86.9	11	13.1	0.717	0.699
T2	168	90.3	18	9.7		
T3	52	89.7	6	10.3		
Histologic grade						
1	7	87.5	1	12.5	0.071	0.965
2	122	89.7	14	10.3		
3	138	90.2	15	9.8		
Lymphovascular invasion						
No	132	89.8	15	10.2	0.007	0.933
Yes	160	88.9	20	11.1		
Number of positive lymph nodes						
4-9	175	88.4	23	11.6	0.275	0.600
10+	119	90.8	12	9.2		
Receptors status						
ER^-	114	91.9	10	8.1	1.075	0.300
ER^+	177	87.6	25	12.4		
PR^-	129	94.2	8	5.8	5.064	0.240
PR^+	162	85.7	27	14.3		
ER and/or PR^-	82	94.3	5	5.7	2.413	0.120
ER and/or PR^+	209	87.4	30	12.6		
Biopathological status						
c-erb $B2^-$	129	85.4	22	14.6	1.195	0.274
c-erb $B2^+$	74	91.4	7	8.6		
Triple $negative^-$	246	88.5	32	11.5	0.568	0.451
Triple $negative^+$	43	93.5	3	6.5		
$p53^-$	152	88.9	19	11.1	0.036	0.850
$p53^+$	94	90.4	10	9.6		
$Ki67^-$	79	85.9	13	14.1	1.465	0.226
$Ki67^+$	170	91.4	16	8.6		

with a total direct cost of 264,927 €. Initial treatment regimens were changed for 27 (77.1%) out of 35 metastatic patients. The total direct cost of the unchanged treatment regimens for metastatic patients were 49,697 € for 3 TAC, 3 dose-intense AC-P and 2 CEF_{100} regimens. The difference of 215,230 € was more than sufficient for the total screening cost of 329 patients with 31,716 € and for the new treatment regimens which mostly consisted of either hormonotherapy or single-agent chemotherapy with bisphosphonates that could not be calculated due to the unknown number of cycles each patient had received. The details of costs are shown in Table 5.

Discussion

Although a large number of papers about staging of breast cancer may be found in the literature [4,12-14], most of them analyze the value of BS in early-stage breast cancer patients. However, in the literature, there is still limited data about the accuracy and value of staging of the subgroup of breast cancer patients having ≥4 positive axillary lymph nodes. Since this group represents the highest risk group for developing metastasis, there is a need to clarify whether to examine them more intensely compared to other newly diagnosed breast cancer patients.

Table 4. Comparison of means of some known clinicopathological risk factors between metastatic and non-metastatic breast cancer patients by univariate analysis

Variable	*Metastasis Mean (±SD) No*	*Yes*	*t-test*	*df*	*p-value*
Age at diagnosis (years)	50.7±10.8	53.9±10.9	–1.605	327	0.109
Size of tumor (cm)	3.4±1.9	3.4±2.1	–0.009	326	0.993
Number of positive lymph node	10.6±7.7	9.1±4.6	1.726	59.874	0.090
Percentage of involved lymph nodes	52.6±26.3	57.1±28.8	–0.955	327	0.340
ER positive	36.9±37.5	41.3±36.5	–0.655	324	0.513
PR positive	28.7±34.3	37.6±34.7	–1.456	324	0.146
c-erbB2 positive	37.9±39.5	25.7±36.5	1.735	325	0.084
Ki-67 positive	25.0±21.1	19.8±16.4	1.284	276	0.200
p53 % positive	25.3±34.6	26.2±37.3	–0.122	273	0.903

SD: standard deviation

Table 5. Direct costs of screening and treatment procedures in 329 breast cancer patients

If patients had not been screened for metastasis…			When patients are screened for metastasis…		
			Costs of screening	*Total number*	*Total cost (€)*
			Thoracoabdominal CT	303	18,561.80
			Bone scan	297	7,274.63
			X-ray	27	107.21
			MRI	62	2,305.09
			Bone CT	3	91.89
			PET/CT	4	3,375.21
			Total		31,715.84
Costs of planned treatment	*Total number*	*Total cost (€)*	*Costs of actual treatment*	*Total number*	*Total cost (€)*
TAC	17	142,920.50	TAC	3	25,221.26
Dose-intense AC-P	16	120,037.50	Dose-intense AC-P	3	22,507.03
CEF_{100}	2	1,968.87	CEF_{100}	2	1,968.87
Total	35	264,926.90	Total	8	49,697.17
Grand total		264,926.90			81,413.00

TAC: docetaxel, doxorubicin and cyclophosphamide, AC-P: doxorubicin, cyclophosphamide followed by paclitaxel, CEF_{100}: cyclophosphamide, epirubicin, 5- fluorouracil.
Direct costs of screening for metastasis in 329 patients and of planned and changed treatment schedules of 35 metastatic patients. The total direct cost of the unchanged treatment schedules for metastatic patients was 49,697€ for 3 TAC, 3 dose-intense AC-P and 2 CEF_{100} regimens. The difference of 215,230€ is more than enough for the total screening cost of 329 patients with 31,716 € and for the new treatment decisions

In this retrospective study, it has been shown that 35 (10.6%) of all patients analyzed were found to be metastatic at the time of diagnosis. Lung and bone were the most common sites for metastatic lesions. In a study by Ravaioli et al. it was recommended that patients with >3 positive lymph nodes and T4 tumors should be screened intensively for metastases since this group had 10.7% metastatic disease in contrast to 1.5% metastatic disease in the group with 1-3 axillary lymph node involved [15]. In another study by Gerber et al. it was shown that node-negative and patients with 1-3 involved lymph nodes had a similar risk for developing metastasis (1.9 vs. 1.8%). So, the authors also recommended staging tests for the high-risk patients to reduce the number of unnecessary examinations and costs [16]. Thus, the results of our study concerning the percentage of metastatic patients also support the evidence that this high risk subgroup of Turkish breast cancer patients should be screened intensely for detection of metastases, like other Western countries populations.

The primary treatment decision was changed in 27 (77.1%) out of 35 patients, showing that screening for metastases in this particular subgroup of patients has a significant impact on the clinician's daily practice for newly diagnosed breast cancer cases.

Many studies have shown that, apart from axillary lymph node involvement, there are some other parameters effecting the occurrence of distant metastases such as tumor size, age, menopausal status or the presence/ absence of hormonal receptors or some onco-

genes/ tumor suppressor genes (c-erbB2, p53 etc.) [3-5,16,17]. However, we couldn't identify any particular subgroup within the ≥4 axillary lymph node involved group of breast cancer patients when we analyzed their conventional demographic and biopathological parameters. Neither the demographic features of the patients, (age and menopausal status) nor the biopathological tumor parameters (tumor size, hormonal receptor status) were found to be associated with increased risk of presence of metastasis at the time of diagnosis. This may be a result of insufficient assessment of tumor biology with conventional clinicopathological parameters, especially in this homogeneous high risk patient population. It is possible that the risk factors associated with the occurrence of metastasis used in patients with 1-3 involved lymph nodes may not be adequate or enough to determine the risk of metastasis in patients with ≥4 involved lymph nodes, since the biology of tumor may differ in this subgroup of high risk patients. In our study group, it was interesting to see that the vast majority of patients were having either T1 or T2 tumors. So, new parameters based on gene expression profiles of tumors might be useful in this area, since this could help understand the heterogeneous biological nature of breast cancer on genomic level [18]. Such assays may have implications over how to modify care for the high risk group of patients, like the ones in our study.

It is also of interest to note that 21 (60%) out of 35 metastatic patients needed further investigations for suspicious lesions found either by CT or BS, indicating that even CT and BS may not be really sufficient for detecting metastasis in our group of patients. To our opinion this heralds a need for modification of staging procedures in breast cancer patients, especially in the subgroup having ≥4 axillary lymph node involvement.

We have also looked at the direct cost of modified staging procedures in this high risk group of patients, since this is also a very important issue for Turkey, a developing country. The total direct cost of the unchanged treatment schedules for metastatic patients was 49,697 € for 3 TAC, 3 dose-intense AC-P and 2 CEF_{100} regimens. The difference of 215,230 € is more than enough for the total screening cost of 329 high risk patients with 31,716 €. This staging approach is also important from the aspect of protecting the patient from overtreatment, not by only means of cost, but -more important than that- by improving the quality of life of the patient with metastatic disease.

Complete instrumental staging in all newly diagnosed breast cancer cases seems unnecessary and expensive. Among clinicians, there are two trends regarding the staging of new breast cancer cases. The first group may be called "interventionists", who prefer extensive staging. The second group may be called "abstentionists", who do not perform any staging procedures at the time of diagnosis. But these two contradictory approaches are not suitable for daily clinical practice and we believe that a more evidence-based approach should be carried out for accurate staging of newly diagnosed cases avoiding both over-treatment and over-diagnosis.

In conclusion, we recommend that full staging procedures should be performed in breast cancer patients having ≥4 axillary lymph node involvement, at least by CT and BS. Since the conventional clinicopathological data seems not sufficient to define subgroups in this high risk population, all of them should undergo screening until new parameters based on genomic level are defined and available. Based on our results we also recommend an urgent modification of staging procedures in high risk groups of breast cancer patients.

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