Retrospective study of pattern of recurrence of breast cancer after surgery and adjuvant therapy

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Abstract:

Aim of the work:investigate pattern of breast cancer recurrence and the affecting factors on early and late recurrence and identify factors affecting site specific recurrence.

Patients and methods:A retrospective study of 141 patients presented to clinical oncology department ,sohag university hospital between January 2000 and December 2014 diagnosed with invasive breast cancer.All of them underwent surgery either modified radical mastectomy,simple mastectomy or breast conservative surgery then received adjuvant systemic therapyeitherchemotherapy,endocrine therapy or both.Adjuvant radiotherapy was given when indicated.This study was conducted by hand search in the files.

Results:90%(n=127) of our patients develop recurrence in first 5 year with 64.5%(n=91) of total number of patient in first 3 year. Patients still have risk of recurrence even after 10 years after primary treatment as 2 patients develop recurrence after 10 years. Among 141 patients with recurrence, 116 patients (82.2%) and 32 (22.6%) were involved with distant and loco regional recurrence, respectively.The most prevalent distant metastasis was seen in bone with liver , lung and brain metastasis in descending manner. Multiple organ metastasis was detected in 36% of patients.

In our study in early recurrence group 70% (n=89) had tumor size more than 2 cm ,88%(n=113) had positive axillary lymph node ,98%(n=125) had high tumor grade indicate that tumor size larger than 2 cm, axillary lymph node involvement ,high tumor grade tend to be important prognostic factors in early recurrence.

The present study has demonstrated that there is no significant tumor or patient characteristic associated with the site-specific risks of metastasis.

Conclusion: Most breast cancer recurrence occur during first 5 year with peakincidence in1and 2year.Tumor size larger than2cm, lymph node involvement and high tumor grade tend to be important prognostic factors in early recurrence before 5 year. The most common exclusive first site of metastasis was bone and the least common is the brain.The current clinical practice of screening for site specific metastatic disease based on concerning patient specific signs or symptoms is supported.

Introduction

characteristics. Both adjuvant chemotherapy and endocrine therapy, after initial surgery, have proven to be highly effective methods to reduce the risk of disease benefits of adjuvant therapy ,breast cancer patients remain at risk of recurrence even years after

Breast cancer is the most common cancer in women,and over 1.6 million cases are diagnosed annually(1) .

It is a highly heterogeneous disease with respect to clinical and molecular recurrence, preventing both local and distant metastasis and reducing mortality(2). Despite the proven

pathological data registered in patients'file,

Disease free survival(DFS) after primary treatment acquired from the files, recurrence site spotted in examinations and imaging, . Statistical data revealed the relation between these factors and breast cancer recurrence.

Receptors' status was determined via patients' pathological report following primary tumor biopsy. Her2 was determined by means of IHC test.

Disease free survival(DFS) was defined as the time interval between curative surgery and first recurrence irrespective of site. It was categorized in 2 groups of ≤5 years, and >5 years.

Overall survival was defined as time interval between first diagnosis till death or last time of follow up.

The patients were treated by surgery (modified radical mastectomy or breast conserving surgery), adjuvant chemotherapy , radiotherapy and hormone therapy according to receptor status.

141 patients experienced recurrence in the follow up period whose data were collected and analyzed. Recurrence sites were categorized as:

1. **Loco regional recurrence** including recurrence in breast skin and soft tissues if breast conservative surgery was done , chest wall, or in neck lymph nodes, and axillae.

2. **Distant recurrence** including Bone , Visceral recurrence (involvement of liver, lung, brain and others including any site at the body except mentioned above.

Data Analysis

The data acquired from the patients files was analyzed by STATA version 12.1. The effects of variables on early and late recurrence was evaluated and relation between variable and site specific recurrence. The data were significant with P <0.05.

intialtherapy, the maximum risk is in the first two years with a steep reduction to 5 years and then it gradually moves on to 12 years(3).

Distant metastasis is the most prevalent form of recurrence and the main cause of death in breast cancer patients. Prognostic factors estimated to cause recurrence and distant metastasis following the treatment of breast cancer, include molecular pathology of breast cancer, tumor grade, tumor size, involvement of lymph node, and hormone receptors' status of ER, PR, and HER2 (4).

Objectives

This study aims to investigate pattern of breast cancer recurrence and the affecting factors on early recurrence and late recurrence to identify a subcategory of patients with exposure to higher risk of recurrence,so that more invasive treatments could be prevented and replaced by more appropriate ones. Also,to identify factors affecting site specific recurrence.In this way, unnecessary diagnostic tests in care and follow up will be ruled out.

Methods

This retrospective study was conducted reviewing data acquired from 141 female patients suffering from breast cancer who developed recurrence after surgery and adjuvant therapy in sohag university hospital between January 2000 and December 2014 . **Exclusion criteria** were metastatic disease at the time of diagnosis , 40 patients were also excluded due to incomplete data.

This retrospective study was conducted by investigating medical files of patients. Factors investigated in this study include age, menopausal status,estrogen and progesterone receptor,human epidermal growth factor receptor 2 status,lymph node status, tumor size, tumor grade, with

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Results

After examination of all breast cancer patients' files in our hospital during the period from 2000 to 2014, we collected data for 141patients who experienced recurrences . The median age of patients was 49.7 years (range: 28 - 87 years). 53.9% of patients were postmenopausal .Tumors more than 2cm constitute 69.5%. Lymph node involvement was detected in 88.6% of patients.The most common pathology was IDC constituting 90% of cases with 81.5% were grade 2. 50%, 47.5% and 19.1% were ER, PR , HER2 positive respectively with 14% (n= 20)were triple negative.

After breast cancer diagnosis, surgical treatment was done on the patients, 12.8% patients underwent breast conserving surgery ,2.1% underwent simple mastectomy, 85.1 % underwent modified radical mastectomy.

Neo adjuvant chemotherapy was administered to 7% patients and 76.7% patients received adjuvant chemotherapy. Radiotherapy was administered to 74.5% patients and hormonal therapy was given to 39% patients .

Among 141 patients with recurrence, 116 patients (82.2%) and 32 (22.6%) were involved with distant and loco regional recurrence, respectively.The most prevalent distant metastasis was seen in bone (43% of patients) and liver,lung and brain metastasis were 7.1%,7.1% and 6.3% respectively,others including contralateral breast and axilla (n=11),malignant ascites(n=2)and malignant pleural effusion(n=7) with 1case show subcutaneous nodule at scalp. Multiple organ metastasis was detected in 36% of patients .Mean DFS was 2.5years (range: 0 -11 years). Disease free survival (DFS) was 90%(n=127) in first 5 year after treatment and 10%(n= 16)in 5-10 years.

We studied difference between factors affecting early and late recurrence and results were in early group ,70% (n=89) had tumor size more than 2 cm ,88%(n=113) had positive axillary lymph node ,98%(n=125) had high tumor grade ,none of these factors were statistically significant in comparsion between early and late recurrence table 3.

No patient or tumor characterstic proved to have statistically significant impact on site specific metastasis as shown in table 4.

Table 1: Patients And Tumor Characteristics

Character	Cases	
	No.	**Percent**
Age	32	22.7
Less than or equal to 40 y	109	77.3
>40 y		
Menses	60	42.6
Pre	76	53.9
Post	3	2.1
Peri	2	1.4
Male		
Tumor size	43	30.5
X	60	42.6
1	26	18.4
2	12	8.5
3		
Node staging	24	17
X	16	11.3
0	33	23.4
1	38	27
2	30	21.3
3		
Estrogen receptors	70	49.6
Negative	71	50.4
Positive		
Progesterone receptors	74	52.5
Negative	67	47.5
Positive		
HER-2		
Negative	36	25.5
Positive	27	19. 1
Unknown	77	54.6
equifocal	1	0.7
Tumor pathology	127	90.1
Invasive duct	11	7.8
Invasive lobular	1	0.7
Mucinous	2	1,4
Mixed		
Tumor grade	2	1.4
1	115	81.5
2	24	17
3		

Table 2: Pattern Of Breast Cancer Recurrence

Site	Frequency	Percent
Brain	9	6.4
Bone	61	43.3
Liver	10	7.1
Lung	10	7.1
Others	21	14
Multiple	51	36
Locoregional	32	22.6

Table 3 : Comparsion Of Factors Affecting Early And Late Recurrence

Factors	Disease free survival				P value
	5 year or less (early)		More than 5 years (late)		
	No.	%	No.	%	
Age group of the patient					0.341
≤ 40y	30	93.8	2	6.2	
> 40 y	97	89	12	11	
total	127	90.1	14	9.9	
Menopausal status					0.85
Pre	53	88.3	7	11.7	
Post	69	90.8	7	9.2	
Peri	3	100	0	0	
Male	2	100	0	0	
Total	127	90.1	14	9.9	
Tumor size		90.9			0.837
T x	30	80	3	9.1	
T1	8	91.7	2	20	
T2	55	88.5	5	8.3	
T3	23	91.7	3	11.5	
T4	11	90.1	1	8.3	
Total	127		14	9.9	
Node staging					0.786
Nx	22	91.7	2	8.3	
N0	14	87.5	2	12.5	
N1	28	84.8	5	15.2	
N2	35	92.1	3	7.9	
N3	28	93.3	2	6.7	
Node staging					
Negative	14	87.5	2	12.5	
Positive	113	90.4	12	9.6	
Grading of the tumor					0.813
Grade 1	2	100	0	0	
Grade 2	104	90.4	11	9.6	
Grade 3	21	87.5	3	12.5	
ER					0.401
Negative	64	91.4	6	8.6	
Positive	63	88.7	8	11.3	
PR					0.467
Negative	66	89.2	8	10.8	
Positive	61	91	6	9	
Total	127	90.1	14	9.9	

	No.	%	No.	%	P value
HER-2					0.107
Negative	35	97.2	1	2.8	
Positive	26	96.3	1	3.7	
Unknown	66	84.6	12	15.4	
Total	127	90.1	14	9.9	
Pathological feature					0.95
Invasive duct	114	89.8	13	10.2	
Invasive lobular	10	90.9	1	9.1	
Mucinous	1	100	0	0	
Mixed	2	100	0	0	
Total	127	90.1	14	9.9	
Surgical treatment	112				0.8
Modified radical mastectomy	2	93.3	8	6.7	
Simple mastectomy	13	66.7	1	33.3	
Conservative surgery	127	72.2	5	27.8	
Total		901	14	9.9	
Chemotherapy treatment	19 108 127				0.173
Not		62.6	4	17.4	
Yes		91.5	10	8.5	
Total		90.1	14	9.9	
Radiotherapy treatment	34				0.252
Not	93	94.4	2	5.6	
Yes	127	88.6	12	11.4	
Total		90.1	14	9.9	
Hormonal intake					0.773
Not	79	91.9	7	8.1	
Tamoxfen	37	88.1	5	11.9	
Femara	7	87.5	1	12.5	
Both	4	80	1	20	
Total	127	90.1	14	9.9	

Table 4: Factors affecting site specific metastasis

Variables	Distant metastasis										P value
	Lung		Liver		Bone		Brain		Multiple		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Age group											.77
≤40 y	2	7.7	3	11.5	17	65.4	2	7.7	2	7.7	
> 40 y	9	10.5	12	14.00	47	54.7	8	11.6	10	11.6	
Tumor size											.21
T x	3	14.3	2	5.9	12	57.1	2	9.5	2	9.5	
T 1	1	11.1	1	11.1	6	66.7	0	0.00	1	11.1	
T 2	3	5.9	7	13.7	33	64.7	2	3.9	6	11.8	
T 3	4	17.4	2	8.7	8	34.8	6	26.1	3	13	
T 4	0	0.00	3	37.5	5	62.5	0	0.00	0	0.00	
Node staging											.000
Negative	1	6.2	3	18.8	9	56.2	2	12.5	1	6.2	
Positive	10	10.4	12	12.5	55	57.3	8	8.3	11	11.5	
ER											0.13
Negative	7	12.7	10	18.2	33	60.0	3	5.5	2	3.6	
Positive	4	7	5	8.8	31	54.4	7	12.3	40	17.5	
PR											.29
Negative	7	12.5	9	16.1	31	55.4	4	7.1	5	8.9	
Positive	4	7.1	6	10.7	33	58.9	6	10.7	7	12.5	
HER-2											.38
Negative	2	6.5	4	12.9	18	58.1	4	12.9	3	9.7	
Positive	3	15.8	2	10.5	11	57.9	3	15.8	0	0.00	
unknown	6	9.7	9	14.5	35	56.5	3	4.8	9	14.5	

Discussion

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females(5). It is a highly heterogeneous disease with respect to clinical and molecular characteristics.

With advances in early detection and improvements in breast cancer treatment, markedly increasing long-term survivors who remain at risk of recurrence are raising issues for oncologists(6,7,8).

Almost 30% of patients with breast cancer who are free of disease after initial local and regional treatments present with disease recurrence during follow-up. The timing of breast cancer recurrence varies considerably, influenced by classic prognostic factors as well as adjuvant treatment strategies(8,9).

Breast cancer patients are at recurrence risk even years after receiving treatment which is the highest during the 2 - 3 years after detection of the primary tumor (10).

In Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up : the Results From the International Breast Cancer Study Group Trials I to V study :showed that annualized hazard of breast cancer recurrence was greatest for the first 5 years (10.4%), with a peak between years 1 and 2 after surgery (15.2%). The hazard decreased consistently during years 5 to 10 (4.5%) and then remained stable. It also demonstrated that the hazards of recurrence and death decreased consistently until year 10 but then remained stable after year 10 through year 25. ER positive patients maintains a significant risk of relapse even after more than 10 years of follow-up(11).

The results of study of Hazard of Recurrence among Women after Primary Breast Cancer Treatment with 10-Year Follow-up also show that

recurrence was most likely to occur in the first 5 years of follow-up, which supports the current guidelines for an intensive follow-up schedule in this time period(12).

This is consistent with our study in which 90% (n=127) of our patients developed recurrence in first 5 year with 64.5%(n=91) of total number of patient in first 3 year.Our study also confirmed that recurrence risk of breast cancer remain non neglibible even after 10 years after primary treatment as 2 patients develop recurrence after 10 years.

Distant metastasis is the most prevalent form of recurrence and the main cause of death in breast cancer patients. Prognostic factors estimated to cause recurrence and distant metastasis following the treatment of breast cancer, include molecular pathology of breast cancer, tumor grade, tumor size, involvement of lymph node, and hormone receptors' status of ER, PR, and HER2 (13).

In recent decades, studies have moved towards investigation of effective factors in early and late recurrence.In the large translational Arimidex, Tamioxiden Alone or in Combination (transATAC) trial, confirmed the role of nodal status but also found tumor size to be an independent prognostic factor for early and late distant recurrence, whereas grade was predictive only in the first 5 years after diagnosis(14).

In the study by Erick Sta et al. which focused on factors effective in less than 2-year recurrence, the major factors effective in early recurrence were tumor stage, and size and lymph node status. This study showed that her2 receptor overexpression was not the only determining factors(15).

In PattarapornWangchinda and SuthineeIthimakin study, which included 300 women with breast

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cancers recurrence, of whom 180 had recurrence within 5 years of diagnosis and 120 later than 5 years concluded that tumors larger than 2 cm, lymph node metastasis, and high nuclear grade were related to early recurrence. Estrogen receptor-positive, progesterone receptor-positive and HER-2 disease predicted late recurrence(16).

Won Jong Song,et al studies risk factors in recurrent patients within 2 years after operation and adjuvant chemotherapies as the early recurrence and those over 2 years as the late recurrence found that Histologic grade (p=0.005),nuclear grade (p<0.001), p53 (p=0.022), and Ki-67 (p<0.001)were significant factors that influenced the systemic recurrence between early and late recurrence. The stage is also an important prognostic factor as there was statistically significant difference (p=0.019) between early and late recurrence but in nodal status there was no statistically significant difference between them (p=0.365)in contrast to previous studies(17) .

In our study ,there was no statistically significant different factors that influenced recurrence between early recurrence and late recurrence as regard hormonal status,HER 2 status,tumor size ,nodal status and tumor grade (with tendency of the last 3 factors to be prognostic in early recurrence as70% (n=89) had tumor size more than 2 cm ,88%(n=113) had positive axillary lymph node ,98%(n=125) had high tumor grade early recurrence group).

In Time-dependent risk of developing distant metastasis in breast cancer patients according to treatment, age and tumour characteristics study, E Colzani ,et al concluded that metastasis to the skeleton (32.5%) and multiple sites of metastasis (28.3%)

were the most frequent presentations of distant metastasis within 10 years.

No particular combination pattern of multiple sites of first distant metastasis was found . The site distribution of first distant metastasis changed significantly over time for the following sites: skeleton, CNS and liver (18).

In their study of importance of Metastasis Site in Survival of Patients with Breast CancerBirsenYücel1 et al reported thatthe most common organ of distant metastasis was the bones, which was present in 111 (60%) patients. The other common distant organ metastases were respectively as follows: liver in 63 (34%) patients, lungs in 58 (31%) patients, and the brain in 49 (27%) patients. Single organ metastasis was seen in 75 (41%) patients, whereas 109 (59%) patients had multiple organ metastases.The results of the present study support the claim that patients with bone metastasis have the best survival rates, whereas the patients with brain metastasis have the shortest duration of survival(19).

Our study supports these findings. 82.2% of patients (116 patients)developeddistant organ metastasis and 22.6 %(32patients) developed loco regional recurrence. The most common type of distant metastasis is seen the bone metastasis (43. 3 % of total distant metastas).liver, lung and brain metastasis constitute 7. 1%,7. 1% and 6.3% respectively.No particular combination pattern of multiple organ metastasis.

Pattern of metastatic failure by specific anatomic site are not well described in the literature. In addition, methods to predict which patients will experience metastases at which sites remain limited. Predicting the incidence of metastases at specific sites could allow physicians to more accurately identify patients for specific screening and

prevention methods and to better tailor individualized clinical management.

Previous studies have not demonstrated associations between age, adjuvant therapy, tumor stage, grade, or lymphovascular invasion and site of relapse (20,21).

Abigail et al in a study of incidence and patterns of distant metastases for1754Patients With Early-Stage (stage I or II)Breast Cancer After Breast Conservation Treatmentconcluded that there is no site of metastasis with a large enough increased risk for any given patient or tumor characteristic to justify site-specific metastatic screening. Although there were multiple statistically significant increases in the risk of a specific metastatic site based on a patient or tumor characteristic; however, the hazard ratios generally contain large confedence interval. Therefore these data do not support the use of site-specific metastatic screening(22).

In contrast to previous studies , *Hagen Kennecke et al* demonstrated in metastatic behavior of breast cancer subtypes study that age greater than 50 years was associated with a reduced rate of brain metastasis possibly as a result of the significantly higher age in patients with luminal-subtype tumors. Large tumor size (T3/4) was associated with a significantly lower rate of brain and liver metastasis, a finding with no obvious explanation (23).

The present study has demonstrated that there is no significant tumor or patient characteristic associated with the site-specific risks of metastases. These data support current clinical practice of screening for site-specific metastatic disease based on concerning patient-specific signs or symptoms.

One limitation of this study is that the adjuvant therapy usedduring the era of this cohort is not necessarily representative of modern-era adjuvant chemotherapy, hormonal therapy, and biological therapy, such as anti-HER-2 therapy with trastuzumab. In addition, most of the tumors reported in the present study predate the era of routine HER-2 testing, and trastuzumab for HER-2+ breast cancer was introduced after the majority of patients in our cohort were treated, although trastuzumab has been shown to reduce recurrence risk.

With regard to identification of metastases, we identified eachmetastatic site by clinical examination or conventional imaging (radiography, bone scan,computed tomography, and magnetic resonance imaging). There could exist a misclassification bias in that metastases too small for detection by imaging were not detected and radiographic findings that were suggestive of tumor could in fact be benign, as biopsy confirmation was not required for classification in our study nor is it routinely used in clinical practice. This potential for misclassification bias, however, affects all patient subgroups.

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