Very Late Relapse in Breast Cancer Survivors: a Report of 6 Cases

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Abstract

Background: Breast cancer is the most common cancer and the leading cause of cancer death among the women worldwide. The risk of local and distant recurrence is the highest during the first two years following the initial treatment. Very late relapse (after 12 years) is uncommon in breast cancer survivors.

Methods: Herein, we report the characteristics and outcomes of 6 such cases of breast cancer.

Results: The mean age of the patients was 40.1 years (range 30-57) and the mean disease free survival was 19.6 years.

Conclusion: Late relapse is not so common in breast cancer but can occur in any stage. Therefore, we suggest life-time follow up for every patient with breast cancer.

Keywords: Breast neoplasm; Recurrence; Survival

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Introduction

Breast cancer is the most common cancer among women and its incidence is increasing. However, its mortality decreases with better screening programs, public education, and medications [1]. Disease-free survival and overall survival depend on multiple factors, including the stage of the disease, hormone receptor status, age, and prescribed chemotherapy agents [2, 3]. Most relapses occur during the 2nd year after the treatment. Another peak is in the following 8 to 9.5 years. Then, the recurrence rate decreases. Of course, younger premenopausal women develop recurrence sooner [4] and recurrence after decades is not so common [5]. Here, we report 6 cases that remained disease-free for 13-32 years after the primary breast cancer. The goal of this report is to show that breast cancer survivors are at risk for relapse even after years. In addition, even high risk patients can have a long period of disease-free survival.

Report of Cases

In this report, we reviewed 6 cases with a mean age of 40.1 (30-57) years at diagnosis (Table 1).

Pathology reports were lost in 2 patients. In addition, 1 patient had Ductal Carcinoma In Situ (DCIS) and had received radiation. Besides, 2 patients had breast cancer with negative axillary lymph nodes and 1 case had 6 positive nodes. Except for 1 patient who had DCIS, others had received Cyclophosphamide, Methotrexate, and 5-Fluorouracil (CMF) (3-6 cycles).

Case 1

The patient was a 62-year-old lady who was operated for a right breast carcinoma 32 years ago (in 1979). At that time, right side Modified Radical Mastectomy (MRM) was done for her and then she received 6 cycles of combination chemotherapy (cyclophosphamide, methotrexate, and 5-Fluorouracil). Tamoxifen was also administered for 5 years. She had no regular follow up, but was well until February 2011 when she developed lymphadenopathy in the right supraclavicular fossa. Biopsy was taken and showed metastatic carcinoma. Immunohistochemical study on the biopsy samples showed positive estrogen and progesterone receptors. Moreover, physical examination and

mammography from the contralateral breast revealed no lesion and abdominal ultrasonography revealed liver metastases. Now, she is receiving chemotherapy with Adriamycin and cyclophosphamide.

Case 2

The patient was a 71-year-old lady who had breast cancer and underwent left side MRM and received 3 courses of combination chemotherapy by cyclophosphamide, methotrexate, and 5-flourouracil in 1986. Her primary pathology was lost. She also received tamoxifen for 5 years and was well until January 2012 when she developed severe pelvic pain. Whole body bone scan was performed for her and showed multiple bone metastases in the first and fifth lumbar spines, left humerus, and greater trochanter of the right femur. She received 20 Gray in 5 fractions for the involved areas of lumbar spines and femur. Now, she is receiving zoledronic acid and has no evidence of distance metastasis except in bones.

Case 3

The patient was a 70-year-old woman who was affected by left side breast cancer in October 1998 and left side MRM was done for her. Her primary disease was a 7 cm infiltrating ductal carcinoma. None of the 17 dissected lymph nodes were involved by tumor. She received 6 cycles of chemotherapy by CMF and then radiotherapy to the chest wall and the regional lymph nodes. She was under regular follow up when developed pelvic pain in March 2012. Her whole body bone scan showed multiple bone metastases at pelvic bones, multiple vertebrae, and skull. Nevertheless, the chest and abdominopelvic CT scan was normal. She received palliative radiotherapy to pelvis and is now receiving zoledronic acid.

Case 4

The patient was a 56-year-old woman who was operated (quadrantectomy and axillary lymph node dissection) due to the right side infiltrating ductal carcinoma in January 1991. She had a 2cm Infiltrating Ductal Carcinoma (IDC) and no lymph node involvement. Then, she received chemotherapy and radiotherapy and was under regular follow up. In November 2011, she developed some nodules on the skin of the right breast and biopsy showed the recurrence of the primary tumor. Other metastatic evaluations showed lung metastasis. She is now receiving chemotherapy.

Case 5

The patient was a 47-year-old woman who had right side DCIS in July 1997. The patient was operated (quadrantectomy without axillary nodal dissection) and afterward she only received radiotherapy to the breast. She did not have a regular follow up in spite of the history of breast cancer in her mother. Twelve years later in July 2009, she was operated (MRM) due to local recurrence. She had a 1.5 cm IDC and 6 positive axillary lymph nodes from the total of 9 nodes. Then, 8 cycles of chemotherapy (AC and Taxane) were performed for her and she received radiotherapy to the chest wall by superficial X- ray and the regional lymph nodes by Co^{60}. After that, letrozole was started for her Estrogen Receptor (ER), and Progestrone Receptor (PR) positive, and Human Epidermal growth factor Receptor 2 (HER2) negative (ER and PR positive, HER2 negative). One and a half years later in March 2010, she developed bone and lung metastasis and she is receiving chemotherapy now.

Case 6

The last patient was a 61-year-old woman who underwent left side MRM due to a 4 cm breast cancer in March 1993. She also had 6 positive lymph nodes among the 17 dissected nodes in axilla. She was treated with 6 cycles of CMF and then irradiation to the chest wall and the regional nodes. In November 2007, she developed abdominal pain and a mass was found in the epigastric area. In ultrasonography, multiple liver metastasis and ascites were detected, as well. Then, she received chemotherapy and developed dyspnea in March 2012. Chest CT scan showed pleural effusion and she died one month later.

Discussion

Breast cancer is the most common cancer in women worldwide [6]. Multiple factors, such as race and ethnicity, are effective in breast cancer survival. For instance, one study showed better survival in non-Hispanic whites compared to blacks and other groups. This difference is present in cases with the same stage, ER-PR status, and treatment [2, 7]. Tumor size and lymph node status are also directly related to the prognosis of breast cancer. In a study by Rosen et al., the mean recurrence time was 4.9 years in the cases with 1 involved lymph node and 3.9 years in those with 2 or more involved lymph nodes. Their study also revealed the importance of the menstruation status. In that study, the perimenopausal cases had higher mortality in comparison to pre and

Table 1. The patients' characteristic and outcomes

Patients	Age at diagnosis	Stage	Chemotherapy regimen	Site of recurrence	DFS (years)	Outcome
Case 1	30	NA	CMF × 6 cycles	Cervical lymph nodes	32	AWD
Case 2	46	NA	CMF × 6 cycles	Bone	25	AWD
Case 3	57	T3N0M	CMF × 6 cycles	Bone	14	AWD
Case 4	35	T1N0M0	CMF × 6 cycles	Chest wall and lung	20	AWD
Case 5	31	T0N0M0†	Not received	Chest wall	13	AWD
Case 6	42	T2N2M0	CMF × 6 cycles	Liver and peritoneum	14	DOD

DFS; disease free survival, AWD; alive with disease; DOD; dead of the disease, †; Ductal carcinoma in situ

post-menopausal women [8]. All the cases of the current study, except for 1, were in the pre-menopausal status.

Some authors suggested body weight as a negative prognostic factor which may influence the prognosis by interfering in the hormonal mechanism. Thus, after treatment completion, weight loss may improve the outcome [9].

Some studies have shown that younger age at presentation is accompanied by a higher risk of recurrence; however, no difference has been reported in some other studies [6, 10]. On the other hand, Chen et al. performed a retrospective study and found that younger age was accompanied by better local control [11]. In this study, the patients were not so old and the importance of age in late relapse should be studied in prospective studies.

The patients with negative tumoral tissue for ER, PR, and HER2 (or triple negative) comprise 15-20% of the breast cancer cases and are among the worst outcome groups. This feature is associated with other high risk factors, such as young age and high grade [6].

The time of recurrence has been studied widely and most of the recurrences have been shown to occur in the first decade [12]. The recurrence time and pattern has been reported to have a double peak shaped curve; the first peak occurring in the second year and the other one in the 6th to the 9th year post-treatment. In node negative and early stage tumors, however, the curves were more flat. In other words, the recurrence rates were more constant and relatively similar in both premenopausal and postmenopausal women. Moreover, recurrence happens earlier in hormone receptor negative individuals. Nevertheless, after 8 years of treatment, the recurrence rate in hormone receptor negative cases is less than the hormone positive ones. It should be mentioned that chemotherapy lowers the

recurrence rate and the second peak appears later [13].

Late failure (more than 5 years) is more prevalent in early stage breast cancer. In a study on patients by quadrantectomy, the rate of late recurrence was 53% for T1 lesions and 25% for T2 lesions. This might be due to the better long-term survival in earlier stages [14].

There are some reports of prolonged disease-free survival in breast cancer cases. These reports propose the importance of long life surveillance for breast cancer treated individuals. The first cases with prolonged DFS were reported in 1887 and recurrence occurred 25 and 19 years after mastectomy [15]. Surely, they had not used chemotherapy and radiotherapy. Therefore, genetic or molecular studies may be needed to enlighten the dark horizon to us.

DCIS by definition is a non-invasive disease; however, invasive components may be missed in tissue sampling or even in post-operative pathologic samples. These cases may have Lymph Node (LN) metastasis at presentation or may behave like an invasive disease [16, 17].

In general, HER2 receptor status and P53 mutation are widely checked in breast cancer cells, but their role in late relapse is not so clear [18]. In the recent years, some biomarkers are used to realize which patient is at risk for recurrence or metastasis. In this regard, cytokeratin-19 may be the best factor which can be used to find the tumor cells in bone marrow or blood. However, it is not accurate enough yet to be used as a test for decision making or as a prognostic index in breast cancer patients [19].

The current guidelines (NCCN 2012) recommend annual mammogram for long time [20]. The question is whether this time interval is enough, more, or less than what is required. The chemotherapy agent, surgery (especially lymph node dissection), hormone

therapy, and trastuzumab have also their own long-term side effects. Thus, more studies are needed in order to determine the effect of these factors on prolonged survival.

Another ethical point is whether a young woman with breast cancer should be told that she will have a short survival or not. Our first case that was 30 years old on arrival delivered and grew up 5 children after diagnosis of breast carcinoma. Furthermore, the need for stronger chemotherapy agents should be revised.

Conclusion

Late relapse is not so common in breast cancer but can occur in any stage. Therefore, we suggest life-time follow up for every patient with breast cancer including DCIS cases.

Acknowledgment

Conflict of Interest

None of the authors declare conflicts of interest.

Authors' Contribution

Shapour Omidvari involved in data collection, literature review and writing the manuscript. Seyed Hasan Hamedi involved in conception, design, literature review, writing the manuscript. Mohammad Mohammadianpanah contributed to design, data collection, analysis, and interpretation, literature review, writing and revising the manuscript. Hamid Nasrolahi involved in conception, writing the manuscript and literature review. Ahmad Mosalaei, Abdolrasool Talei and Niloofar Ahmadloo contributed in design, data collection, interpretation, writing and revising the manuscript. Mansour Ansari involved in data collection, literature review and writing the manuscript.

All authors read and approved the final manuscript.

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