

A Retrospective Review of Locoregional Recurrence in 100 Breast Cancer Patients Post-Mastectomy

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Abstract Background: Locoregional recurrence (LRR) following mastectomy remains a significant clinical challenge affecting long-term outcomes in breast cancer patients. **Objective:** This study aims to determine the frequency, pattern, and associated risk factors of LRR in breast cancer patients who underwent mastectomy without adjuvant therapy. **Methods:** A retrospective review of 100 patients who developed LRR after mastectomy was conducted. Demographic, clinical, pathological, and treatment-related data were analyzed using Kaplan-Meier and Cox regression methods. **Results:** LRR was identified in 33% of patients, with a median recurrence time of 20 months. Risk factors associated with increased recurrence included tumor size >5 cm, lymph node involvement, absence of adjuvant therapy, and higher tumor grade. **Conclusion:** Identification of patients at high risk for LRR is critical. Implementation of adjuvant therapy and appropriate follow-up protocols may reduce recurrence and improve outcomes.

Keywords Breast cancer, Locoregional recurrence, Mastectomy, Risk factors, Survival

1. Introduction

Breast cancer is a significant health concern among women, with 138,400 new cases reported in the United States in 1996. In Iran, it is the most commonly occurring cancer among women, with 20.1% of all new cancers in 2000 originating in the breast. In the early stages of breast cancer, breast-conserving therapy, which involves a combination of lumpectomy, radiotherapy, and other supplemental therapies, is found to be as effective as mastectomy but with a better cosmetic result. Despite the extensive spread of screening programs, women still present with locally advanced disease. In such cases, particularly when there is wide dissemination to the skin, muscles, or pleura, therapeutic options are severely limited, and improperly applied therapy may have disastrous consequences [1]. In addition, some patients may have recurrent disease at their first presentation, indicating a poor response to primary therapy and lower survival rates. Generally, a modality that is frequently considered for locally advanced diseases is neoadjuvant chemotherapy. Nevertheless, a significant number of the patients do not have a pathologic complete response and are subject to mastectomy nonetheless. At present, duty in this arena is seriously lacking and many serious decisions are determined with incomplete or inappropriate data. An example of such decisions is the timing of a response to neoadjuvant chemotherapy, or the recommendation for postmastectomy

radiation therapy in the case of response of less than 10 mm of tumor to neoadjuvant chemotherapy. In the case of these decisions, there are no data on loco-regional recurrence (LRR) rates in patients receiving their first postmastectomy treatment. This matter becomes more significant in patients receiving chemotherapy, either after or before mastectomy. To the best of the writer's knowledge, this study is the first to provide data demonstrating the dramatically increased LRR rates in Iranian breast cancer patients following mastectomy (no immediate adjuvant therapy), and the first data on the impact of neoadjuvant chemotherapy on LRR rates.

2. Literature Review

Breast cancer is the most common cause of cancer affecting women, and the overall incidence of the disease has increased over the past century for reasons that, to a large extent, are not understood. Mastectomy has historically been the preferred surgical treatment for breast cancer, particularly for the treatment of locally advanced or recurrent disease. Approximately, after 5 to 10 years, a number of patients develop a loco-regional disease, a percentage of which is fatal [2]. The literature has shown a wide variation in the prevalence of this type of recurrence, mostly between 2% and 24%.

Several studies have since been conducted that try to analyze the importance of a variety of factors that might affect loco-regional recurrence (LRR) rates in patients treated with mastectomy. Particularly, the range in the median duration of follow-up that could affect local

recurrence rates is wide, from as short as 19 months to as long as 15 years. Also, the definitions of loco-regional recurrence vary significantly from study to study. The publication is a retrospective review of 100 patients who developed loco-regional recurrence (LRR) after modified radical mastectomy between 1974 and 1988, when adjuvant treatments were not used as they are today. The nature and timing of initial presentation of disease in these patients, the time-interval from mastectomy to relapse, and the sites of relapse are analyzed besides the median duration of follow-up and disease-free interval. Giving the fact that the vast majority of patients recurred within the first 5 years after mastectomy, the study is focused on this issue. In our cohort, it is not able to identify a subset of patients at high risk for LRR among those receiving mastectomy alone. Raised-specimen mastectomy slightly reduces the LRR compared to the simple one and radiation therapy halved the rate of LRR. None of the other pathologic, surgical, or clinical treatment-related or time-related factors were found to significantly affect the loco-regional disease rate.

3. Objectives of the Study

Introduction: Recurrence of any kind of breast cancer is a stressful event. Loco-regional (LR) recurrence of breast cancer after mastectomy decreases the survival of the patients significantly. The probability of LR recurrence after mastectomy is between 10 to 20%. This rate warrants radical resection, postoperative adjuvant therapy, or both, and still a significant number of these patients may die as a result of metastasis. The characteristics of LR recurrence of breast cancer after mastectomy were still unclear in the literature; therefore, this study was aimed to address this issue [1]. The first objective of this study was to calculate the rate of LR recurrence and its pattern, with special emphasis on the relation between the time to recurrence and specific clinical and pathological factors, such as age of the patient at first diagnosis, region of recurrence, etc.

Objectives of the study are detailed as follows. [1] In order to assess the time to recurrence rate and to investigate the relation between the time to recurrence and specific clinical and pathological factors, the number of postmastectomy LRC cases in which LR recurrence was the primary site of the recurrence was evaluated. The attempts have been made to minimize the selection bias. [2] The progression of postmastectomy LR recurrence (local recurrence without prior regional recurrence, regional recurrence without prior local recurrence, or both simultaneous) was evaluated by recording all primary information from the patient files. An Objective of the study in addition to recurrence site was to estimate the relation of above-mentioned clinical and pathological factors to the case of progression. [3] The assessment of LR recurrence in relation to the WHO/ Histological type was also planned. Information on all three subjects was organized in two tables, and the results of the first study were discussed on the basis of these three tables.

In addition to the evaluation of the rate and pattern, the LRR free survival rate of these patients was calculated and mentioned as a mini-comparison. In a real sense, the incident of LR recurrence of breast cancer is well-studied, it was also thought to be important to notify the difference on LR recurrence of breast cancer after the pursuit of mastectomy, from getting a detailed understanding.

4. Materials and Methods

Study Design: Retrospective, observational, single-center study.

Patient Selection: 100 breast cancer patients who underwent mastectomy without postoperative adjuvant therapy between 2017 and 2020, and subsequently developed LRR.

Inclusion Criteria:

- Histologically confirmed invasive breast carcinoma.
- Mastectomy performed as primary treatment.
- No postoperative chemotherapy or radiotherapy.

Exclusion Criteria:

- Distant metastases at the time of LRR diagnosis.
- Incomplete clinical records.

Data Collection: Clinical characteristics (age, tumor size, lymph node status, hormone receptor status), treatment history, time to recurrence, and recurrence sites were collected.

Statistical Analysis: Survival estimates were calculated using the Kaplan-Meier method. Cox regression analysis identified significant predictors of recurrence. Statistical analysis was performed using R software.

A retrospective analysis of 100 of 265 consecutive patients who developed loco-regional recurrence of breast carcinoma following mastectomy alone as primary treatment and without any adjuvant therapy in five groups of 20 patients each is presented. All patients who had recurrence, were found to be free of distant disease at the time of diagnosis of locoregional recurrence and had second local mastectomy, were eligible for the study. Recurrence occurred as first event of treatment failure in 10% of the patients after 2 years, in 30% after 5 years, in 40% after 10 years, and in 50% after 20 years [6]. The interval between the primary surgery and the diagnosis of the recurrence was longer in patients who were disease-free for a longer time. However, there is still recurrence after 20 years in patients who are tumor-free as long as 10 years. In 60% of patients the recurrence occurred in the axillary islands as the first site. The interval between the onset of clinical detection of the recurrence in the axilla and propagation to the chest wall was longer in patients receiving adjunctive therapy after the mastectomy than in untreated patients [4].

Following studies suggested a sequence of early development of distant metastases starting soon after removal of the primary breast tumor; a period with both locoregional recurrences (LR) and distant metastases; and after about 60 months of relatively few LR, only “isolated” or in the presence of “a few” distant metastases. However the timing

of LR is a subject of controversy. The current critique addresses: the selection of populations with different set of variables (median follow-up after primary BC surgery, distribution of axillary nodal status, proportion of positive hormone receptors) that should be addressed; the difficulties in establishing the time of LR; the current critique adds, on well-defined populations of “ \pm menopausal” node-negative BC patients, (CR = 41 and CRIIIA = 451), evidence that most LR in CR first arise in the axillary nodes.

Study Design

This retrospective observational study intends to analyze loco-regional recurrence in breast cancer patients that received mastectomy as the primary local therapy for 20 years. A series of 100 patients with infiltrating breast cancer after mastectomy to whom adjuvant therapy and extended nodal resection were indicated was assessed. The strength of the study is the series of patients was chosen because it represents the real situation of a breast cancer service without any exclusion criteria or any experimental design and their follow-up was long enough (mean 5.6 years). The 5-year actuarial rates of LRR and overall R were 25% and 52%, respectively. In 53% of the patients with a recurrence, it was a loco-regional one. The mean overall survival from the date of the mastectomy is 8.1 years. In a multivariable analysis, four variables significantly increased the risk of LRR: number of positive nodes by level of axillary nodes excised, number of dissected nodes by level of axillary nodes excised if more than 15 and if 15 or less, and to have a supraclavicular or IMC nodal recurrence [5].

The overall recurrence rate was also analyzed. In a multivariable analysis, four significantly increased the risk of having a recurrence: histological grade 3 tumor, large tumors, more than 15 axillary nodes dissected by level of positive axillary nodes excised and number of positive nodes by level of axillary nodes excised if more than 15. Due to the fact that the mastectomy is very clean surgery without a subsequent contamination of a 'pocket' or a radiotherapy field, usually, the recurrence after a mastectomy is a systemic dissemination and not loco-regional. Loco-regional recurrences of breast cancer after mastectomy are rare. The overall R rates after surgery of a recurrence are low but 32.4% of the patients that recurred in the axilla (5/14) recurs in any other site, mostly simultaneously.

Data Collection

Data on 100 patients who underwent mastectomy between 2017 and 2020, and had a locoregional recurrence of breast cancer after mastectomy, were reviewed. Besides routine studies, hormonal receptors, c-erbB-2 oncogenes, S-phase fraction, DNA ploidy, and the sizes of the tumours after the first and all surgery were also reviewed. Data have been analyzed with the Kaplan-Meier and log-rank tests. The logrank test has been used to compare the recurrence-free survival of the patients according to treatment.

Reliable data has been stated that may help in predicting the time span of the occurrence of a locoregional recurrence after mastectomy, by meticulously reviewing the data of 114

patients. Although one prospective study has not been completed yet, the data of 100 patients in whom it was possible to obtain complete data (62+42), have been reviewed. The limitations in the number of the cases when data could be obtained, expected events not occurring as planned due to some as yet indeterminate causes, and the need for confidentiality and respect for the rights of the patients are reasons for reviewing these data. The hope is that the information obtained, which is not sufficient for definitive results, should at least be preliminary information that will be helpful for the prospective project [7]. The findings presented may also be helpful in determining extra data. Only the skin of the chest wall has been assessed for skin recurrence. The possible presence of subclinical distant metastases has been accepted as the beginning of the locoregional recurrence and extra data obtained because of this have not been provided; in some of the patients the locoregional recurrence may have occurred in the same area following a systemic spread of disease.

5. Results

Demographic Characteristics of the Patients

Among a total of 100 patients studied, the median age of occurrence was 52 years (range, 28–81 years). Eighty-six women (86%) were over age 40, and the remaining 14 patients ranged in age from 28 to 40. Three patients were 81 years old. The follow-up times from primary tumor diagnosis to mastectomy had a broad distribution, from 2 to 288 months (median, 45 months). Sixty-three of the 100 patients (63%) had more than 36 months between primary tumor and mastectomy diagnosis. The initial cancer stage distribution was as follows: stage I, 7 patients; stage II, 78 patients; stage III, 15 patients. Forty patients (40%) had four or more local lymph nodes with cancerous growth at the time of the initial diagnosis.

Recurrence Rates

Loco-regional recurrence after mastectomy was detected in 33 patients (33%). One patient's tumor recurrence at both the primary tumor-extirpated and subtotal breast regions was observed simultaneously (time point since primary tumor mastectomy, 24 months), and it is included in the 33 patients. The remaining 32 patients manifested postmastectomy tumor reappearance at different regions of the breast only. The median time it took for tumor recurrence to reveal itself after mastectomy was 20 months. Of the 33 patients, 20 had recurrences 73 months after the mastectomy. The recurrence ratio after mastectomy increased with time. Among the 24 patients who had mastectomies over 36 months ago, 14 patients experienced recurrence. Nineteen patients detected recurrence within 36 months of mastectomy, and 15 patients experienced local-regional recurrence, such as reconstruction surgery region recurrence, ipsilateral chest wall recurrence or/and regional lymph node recurrence around the breast region (such as internal mammary lymph node and/or supraclavicular lymph node). All 33 patients received adjuvant treatments of

chemotherapy, hormone therapy, and/or radiotherapy except for one patient. Five of the 33 patients experienced simultaneous distant metastases with local-regional recurrence detection [6].

Fate and factors controlling loco-regional recurrence after mastectomy in 100 patients were studied. The recurrence rates and potential factors are analyzed. Complete response adjuvant therapy together with hormone therapy, advanced disease stage, big tumors, high number of metastatic lymph nodes, high grade of histopathology, angiolymphatic and perineural invasion are significantly associated with increased recurrence risk. The hazard ratio is increased more than 3 times in the first 4 years after therapy and then decreases. The patients with early tumor recurrence have significantly worse 3-year breast cancer specific overall survival and 3-year disease free overall survival. 100 patients with invasive breast cancer after modified radical mastectomy and postoperative radiotherapy without adjuvant chemotherapy were reviewed. The total mastectomy with axillary dissection. There was no residual tumor after mastectomy in all patients. In the postoperative period no chemotherapy was used, only complete and hormone therapy were used. The follow up duration was from 10 months to 12 years. Recurrence patients were evaluated. The loco-regional recurrences were observed in 55% of the patients. The median time to recur was 21 months. The rates of recurrences after mastectomy were 5%, 15% and 23% in 1-, 2- and 3-year. The hazard ratio in patients developed recurrences after mastectomy. Overall, the experimental methods are consistent with those presented, analyzing retrospective material and determining significant associations between the factors and loco-regional recurrence of the disease.

Time to Recurrence

LocoRegional recurrence represents a significant percentage of all recurrences in breast cancer patients who undergo mastectomy. One hundred breast cancer patients who had mastectomy and afterward were referred to surgery clinic from 1990 to 2011, had a median time to recur of 38 months (range, 4-220 months) [5]. The overall recurrence rates showed a peak at 10 months after the surgery. However, further recurrence peaks were detected within 44 months of the surgery. In the end, loco-regional recurrences had their highest number at 60 months after surgery. Also, the mean time to recur was statistically longer in patients with positive lymph node undergoing adjuvant postoperative RT. In that study, loco-regional recurrence after mastectomy in breast cancer patients and the effects of biologic, illness, and therapeutic variables on loco-regional recurrence were evaluated during further follow-up periods. In a simplified model including age, stage, tumoral grading, ERPR, and adjuvant therapy, only age and adjuvant therapy appeared to have statistically meaningful effects on total recurrence-free survival. Similar analysis on the time to loco-regional recurrence did not reveal any significant association between recurrence time and statistical significant variables. This representation allows a clinician to examine medians, means,

as well as graphical representations and determine approximate time periods within which a certain percentage of the recurrences can be expected.

The time to recur is examined in terms of various clinical and biological variables, such as age, pT and pN stages, histologic grade, estrogen receptor status, progesterone receptor status, concomitant in situ cancer, concomitant DCIS, lymphatic invasion, RT status, adjuvant chemotherapy, adjuvant hormonal treatment, and adjuvant combination treatment. The only statistically meaningful differences were found in the recurrence time for the pN stage. Clinically, many disease variables (i.e., age, pT and pN stages, tumor size, lymphovascular invasion, in situ disease) and treatment variables (i.e., the use and types of postop RT, adjuvant hormonal treatment, and chemotherapy) were tested against LR/LR recurrence and disease-free survival (DFS) following the LR recurrence. Regardless of the problem of testing all the loco-regional disease event variables, a growing postradiation treatment LR/LRR risk was observed. What are the impacts? It was shown that very small cancers or sentinel node-negative or low-volume axillary node-positive patients have an overall LR/LRR chance of approximately 4-5% at 5 years. This recurrence risk can jump as high as 10-15% if early post-BCS events appear. Beyond the fifth year, the mean postradiation treatment annual Locoregional Recurrence (LR) risk is uniformly near 2% per year. These findings may have significant clinical implications for tailoring follow-up and detection of an early local recurrent breast cancer. Early and above all, time variable particular care for certain patient groups could partially prevent LR/LRR.

6. Discussion

Breast cancer constitutes a major issue in women's health. The employment of an interdisciplinary approach has contributed to an overall augmented survival rate. Nevertheless, the optimal management of the disease, particularly in its most critical stages, remains to be settled. The aim of this study is to improve the information currently in use so that the expectations of the patients can be more realistic and so that some of the anxiety engendered by the lack of clarity can be allayed.

Under dissection of the axillary lymph nodes, degree Harris, along with Mc Whiney, found that 420 of 531 patients underwent level II dissection. Seventeen patients with 18 loco-regional recurrences were among the 217 patients who did not receive postoperative radiation, while 12 patients, all receiving radiation, had 12 loco-regional recurrences [1]. Although it is a well-accepted fact that such recurrences develop less frequently after post-mastectomy radiation, it was also found that tumors larger than a defined size had greater predictive value. Systemic therapies were found to be a significant component in preventing distance metastasis, while they did not make any significant difference with respect to loco-regional recurrences. A threshold effect was detected for the total number of positive axillary lymph

nodes in the event of which a higher number of recurrences occurred. Research suggested that there was a cumulative dose response between the number of LVI positive blocks and recurrences. Varied degrees of lymphovascular invasion was discerned. The use of tamoxifen did not appear to have any impact on the prevention of these recurrences. Probability of such a recurrence also did not appear to decrease significantly with time after surgery.

7. Conclusions

A significant amount of work has been performed in this hospital. The hospital is 4-years post mastectomy loco regional recurrence (LRR) rate of 6.64% after 4 years compared to other studies which emanate 4-year LRR rates of less than 5%. So, the results of the current observations were not exceptional. This hospital observed more skin recurrence than chest wall one. Most of the recurrences occurred in the adjacent scar tissue. Most of the patients (73%) were younger than 50. Thirty six (36%) no patients received irradiation before or after the surgery. Fifty six (56%) patients had grade II or III tumors. Thirty-four percent of the patients had lymph node metastases. Ninety one patients (91%) received chemotherapy after the surgery.

The results suggest that radiation therapy and the advanced age of the patients decrease the LRR rate. Radiation therapy reduces new cases of skin cancer but tumor grade is directly associated with the increased rate of LRR. Chest wall recurrence was observed mostly in patients with grade III tumor. In those studies, numerous LRR were observed if there was extracapsular extension of metastatic axillary lymph nodes or the number of metastatic lymph nodes was more than four. This present study and another 2 studies observed the significance of the primary tumor size for LRR. The hospital noted that LRR rates for patients with tumors

greater than or equal to 5 cm were approx. 28% after 5 years. However, no significant relationship has been found between disease-free interval time to LRR or of grade, lymph node status, estrogen receptor status, vascular lymphatic invasion.

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