Oncology
and Radiotherapy ©
16 (11) 2022: 029-033 • Research article

Axillary dissection may not be needed in early-stage breast cancer with clinically negative axilla- Cohort prospective study

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ABSTRACT

Background: Over many years breast cancer is managed by surgery to the primary tumor site and complete surgical axillary dissection. The last was done for proper axillary staging and may improve the loco-regional recurrence and overall survival. Axillary lymph node dissection is associated with many complications and morbidity, especially lymphedema. When the sentinel lymph node biopsy was introduced to the field of breast cancer management, it greatly decreased the need for axillary dissection and its sequela. In areas like our locality (Iraq-Basrah governorate), the sentinel lymph node biopsy procedure is not available. Avoiding axillary dissection in a breast cancer patient with clinically negative axilla is a challenging one for the patient who is afraid of avoiding such surgery and the relevant doctors who are not sure about its safety as the relevant studies about this issue are few. In this study, we will assess the management of early-stage breast cancer and clinically negative axilla with primary breast surgery and adjuvant treatment (chemotherapy and radiotherapy, and hormonal treatment according to the indications) only without axillary dissection and compare them with a similar group of patients with axillary dissection. This study aimed to answer the question: is the omission of the axillary lymph node dissection safe in early-stage breast cancer with clinically negative axilla?

Patients and methods: A single-center cohort study was conducted at Basra Oncology center. The study included 99 females aged ≥ 18 years with histologically confirmed invasive breast cancer stage I, II, and III, with clinically negative axillary lymphadenopathy (by clinical examination, ultrasound, CT scan ± PET scan). Out of those patients, 48 females had undergone surgery (mastectomy or BCS) without axillary surgery defined as (Cases) and the remaining females had primary breast surgery with axillary lymph node surgical assessment and were defined later as (controls). All the patients have undergone a surgical intervention to the negative margins (no tumor at ink), followed by adjuvant systemic therapy (including hormonal treatment for five years for hormone receptor-positive disease), and followed by whole breast opposing tangential field radiotherapy. Patients with distant metastasis were excluded from the study. All patients were followed up for 3 years for assessment of disease recurrence according to the recommended clinical practice of the European Society for Medical Oncology (ESMO) guidelines. Annual mammography was performed. The progression-free survival (the period from diagnosis of breast cancer until the loco-regional progression (axillary, internal mammary, supraclavicular or sub-clavicular LAP), distant metastasis, or death) between the two groups was the primary end-point of the study, in addition, to the other adverse events like lymphedema over 3 years. Statistical analysis was done using Statistical Package for the Social Sciences version 26 (SPSS Inc.).

Results: A total of ninety-nine patients were diagnosed with breast cancer. There were no significant differences regarding the mean age, the past medical history, the type of surgery, chemotherapy and radiotherapy regimens, loco-regional metastasis, distant metastasis, and lymphedema between both cases and controls. While the study showed significant differences between cases and controls in terms of the grade of carcinoma. Although, the study showed slightly higher rates of axillary and systemic recurrence (4.2%, and 0.0%) and metastasis to the ipsilateral shoulder (2.1%, 0.0%) among cases compared to controls respectively. Additionally, controls had a slightly higher rate of lymphedema compared to cases (11.8%. 8.3%) respectively.

Conclusions: the study showed no significant differences regarding the Loco regional metastasis, and distant metastasis between the two groups, lymphedema was low among those without axillary dissection, although loco-regional recurrences were higher in the group with axillary dissection.

Key words: axillary dissection, breast cancer, metastasis

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Word count: 3706 **Tables:** 03 **Figures:** 00 **References:** 26

Received: - 20-Oct-2022, Manuscript No. OAR-22-77838

Editor assigned:- 22-Oct-2022, PreQC No. OAR-22-77838 (PQ)

Reviewed:- 06-Nov-2022, QC No. OAR-22-77838 (Q)

Revised:- 09-Nov-2022, Manuscript No. OAR-22-77838 (R)

Published:- 12-Nov-2022, Invoice No. OAR-22-77838

INTRODUCTION

As one of the most common cancers, affecting 2.1 million women annually and accounting for approximately 15% of all cancer deaths, breast cancer is a major public health concern [1]. By 2020, developing nations are expected to have an increase of almost 1.7 million additional cases of breast cancer [2]. Lumpectomy and mastectomy are two surgical options for early breast cancer treatment, with or without axillary clearance or sentinel lymph node biopsy including radiation and chemotherapy following the operation [3].

The conventional treatment for axilla in invasive breast cancer has been axillary lymph node dissection. It offers effective local recurrence control and knowledge about the condition of the axillary lymph nodes, which is important for determining prognosis and directing subsequent therapies [4]. However, axillary lymph node dissection eventually resulted in functional aftereffects, mainly lymphedema and shoulder mobility restrictions [5]. In cases of clinically node-negative breast cancer, sentinel lymph node biopsy is recognized as an alternate technique for determining the status of the axillary lymph nodes [6].

Multiple clinical trials have shown that adjuvant lymph node dissection has no effect on survival and is not required to achieve local control of the disease for people with early breast carcinoma and limited nodal infiltration [7].

The evaluation of axillary lymph node metastases based on clinical, pathological, and molecular criteria is insufficient. Twenty-

five to thirty % with clinically detectable lymph nodes exhibit false findings on sentinel lymph node biopsy, and about 40% have positive results following negative ultrasonography [8,9]. However, Recent evidence suggests that the molecular profile of the original tumor is a more effective prognostic predictor of DFS and OS than lymph node status [10].

Even though sentinel lymph node biopsy helps to reduce the risk of morbidity and side effects in comparison to axillary lymph node dissection, it is nevertheless an invasive surgical technique that carries the risk of postoperative comorbidities. Some of these problems include lymphedema, seroma forming, sensory nerve damage, and range-of-motion constraints [11]. A noninvasive or minimally invasive option (like ultrasound, CT scan, PET scan) could be employed successfully for staging the axillary lymph nodes in the majority of patients who receive sentinel lymph node biopsy, eliminating the need for surgical intervention.

In some developing countries, like our locality (Iraq); the procedure of sentinel lymph node biopsy is not established yet, therefore, surgeons may over practice the axillary lymph node clearance procedure even for early stages of breast cancer.

To ought to weigh the reliability of axillary lymph node clearance in patients who underwent breast surgery for early stages of breast cancer, we did this prospective study; in which the patients either received adjuvant treatment alone (chemotherapy, radiotherapy, and hormonal treatment according to the indications) or adjuvant treatment plus axillary lymph node clearance.

MATERIALS AND METHODS

Study design and population

A single-center prospective cohort analytical study was conducted at Basra Oncology center from early 2018 to the end of 2022. The study included 99 females aged ≥18 years with histologically confirmed invasive breast cancer stage I, II, and III, with clinically negative axillary lymphadenopathy (by clinical examination, ultrasound, CT scan ± PET scan). A Sentinel lymph node biopsy was not done (unavailable). Out of those patients, 48 females had undergone surgery (mastectomy or BCS) without axillary surgery defined as (Cases) and the remaining females had primary breast surgery with axillary lymph node surgical assessment and were defined later as (controls). All the patients have undergone a surgical intervention to the negative margins (no tumor at ink), followed by adjuvant systemic therapy (including hormonal treatment for five years for hormone receptor-positive disease), and followed by whole breast opposing tangential field radiotherapy.

Exclusion criteria

We excluded patients with distant metastasis, and those who refused to be included in the study (the main cause was fear of locoregional recurrence).

Patients follow-up

All patients were kept under regular follow-up for 3 years for assessment of disease recurrence according to the recommended clinical practice. History and physical exams were performed every 3–4 months in the first 2 years, and every 6–8 months from 3 to 5 years thereafter European Society for Medical Oncology (ESMO) Guideline. Annual mammography was performed; another testing was directed by the patient's symptoms and the discretion of the treating physician. Regular pelvic ultrasound was performed twice yearly for a patient on adjuvant tamoxifen.

Primary end-point

The main comparative assessment was the progression-free survival between the two groups. Progression-free survival is defined as the period from diagnosis of breast cancer until the loco-regional progression (axillary, internal mammary, supraclavicular or subclavicular LAP), distant metastasis, or death. In addition, we assessed the other adverse events like lymphedema between the groups over 3 years.

Statistical analysis

Statistical calculations were done using Statistical Package for the Social Sciences version 26 (SPSS Inc.). In which categorical data were expressed as numbers and percentages, and the differences between the groups were analyzed using the Chi-square test (X2) and Fisher exact test. Continuous data expressed as mean ± SD and the differences between the groups were analyzed by the Independent sample T-test for normally distributed data. Shapiro-Wilk test was used to test the normality of the data, and outliers were detected using Boxplot methods. The confidence interval of 95% was applied as the dependent interval in statistics and

Tab. 1. Comparison between cases and controls regarding the demographical parameters.

Variables		Cases (No. 48)	Controls (No. 51)	P-value
Age (years) (mean± SD)		47.54 ± 12.048	47.96 ± 11.672	0.861
Past medical history	No	40 (83.3%)	37 (72.5%)	0.205
	Asthma	0 (0.0%)	1 (2.0%)	
	Diabetes mellitus	1 (2.1%)	1 (2.0%)	
	Diabetes mellitus and hypertension	3 (6.3%)	4 (7.8%)	
	Diabetes mellitus, hypertension, and ischemic heart disease	0 (0.0%)	1 (2.0%)	
	Hypertension	2 (4.2%)	6 (11.8%)	
	Hypothyroidism	1 (2.1%)	1 (2.0%)	
	Tuberculosis	1 (2.1%)	0 (0.0%)	
Grade	I	0 (0.0%)	1 (2.0%)	0.008
	II	34 (70.8%)	46 (90.2%)	
	III	14 (29.2%)	4 (7.8%)	
Type of surgery	Breast-conserving surgery	26 (54.17%)	28 (54.9%)	0.082
	Mastectomy	26 (45.83%)	23 (45.1%)	

Tab. 2. Comparison between cases and controls regarding the treatment regimen

Variables		Cases (No. 48)	Controls (No. 51)	P-value
Chemotherapy	No	1 (2.1%)	0 (0.0%)	0.554
	Refused	2 (4.2%)	0 (0.0%)	
	AC - T Neo Adjuvant	3 (6.3%)	0 (0.0%)	
	AC –T	28 (58.3%)	36 (70.6%)	
	AC * 6	5 (10.4%)	4 (7.8%)	
	AC *4	0 (0.0%)	1 (2.0%)	
	Default	1 (2.1%)	1 (2.0%)	
	FEC – T	2 (4.2%)	3 (5.9%)	
	TAC *6	1 (2.1%)	1 (2.0%)	
	TC * 4	5 (10.4%)	5 (9.8%)	
Radiotherapy	Yes	45 (93.8%)	42 (82.4%)	0.09
	No	1 (2.1%)	9 (17.6%)	
	Refused	2 (4.2%)	0 (0.0%)	

Tab. 3. Comparison between cases and controls regarding the loco-regional and distant metastasis.

Variables		Cases (No. 48)	Controls (No. 51)	P-value
Loco regional metastasis	Yes	5 (10.4%)	7 (13.7%)	0.614
	No	43 (89.6%)	44 (86.3%)	
	Axillary and systemic recurrence	2 (4.2%)	0 (0.0%)	0.28
	Ipsilateral shoulder	1 (2.1%)	0 (0.0%)	
	Local	0 (0.0%)	5 (9.8%)	
Distant metastasis	Yes	11 (22.9%)	10 (19.6%)	0.527
	No	37 (77%)	41 (80.4%)	
	Bone	2 (4.2%)	3 (5.88%)	0.956
	Lung	2 (4.2%)	6 (11.8%)	
	Brain	2 (4.2%)	1 (1.96%)	
	Liver	2 (4.2%)	1 (1.96%)	
	Local	1 (2.1%)	0 (0.0%)	
	Sternum	1 (2.1%)	0 (0.0%)	
Lymphedema	Yes	4 (8.3%)	6 (11.8%)	0.571
	No	44 (91.7%)	45 (88.2%)	

P-values <0.05 were accepted as statistically significant. (Table 1, 2 and 3)

RESULTS

The study included a total of ninety-nine patients diagnosed with breast cancer. There were no significant differences regarding the mean age, the past medical history, and the type of surgery between both cases (patients who had no history of axillary dissection) and controls (patients who underwent axillary dissection surgery). While, the study showed significant differences between cases and controls in terms of the grade of carcinoma (p=0.008), as most of the cases had a grade II cancer (70.8%) followed by grade III (29.2%), meanwhile, most of the controls were grade II (90.2%) followed by grade III and grade I (7.8%, 2.0%) respectively.

In terms of chemotherapy and radiotherapy regimens, there were no significant d ifferences be tween cases and controls (P value>0.05).

Regarding, loco-regional metastasis, distant metastasis, and lymphedema the results were statistically non-significant between cases and controls (P value>0.05). Although there were higher rates of axillary and systemic recurrence (4.2%, and 0.0%) and metastasis to the ipsilateral shoulder (2.1%, 0.0%) among cases compared to controls respectively. Lastly, controls had a slightly hig-her rate of lymphedema compared to cases (11.8%, 8.3%) respectively.

DISCUSSION

There is a rising trend toward omitting SLN biopsies in patients with a low risk of SLN involvement because of the lack of survival benefit from ALND [12], the low rate of SLN positivity, and the growing relevance of biology over anatomy in the decision-making strategy for adjuvant therapy [13, 14]. When axillary ultrasound results are negative for breast cancer, patients in the SOUND study and the INSEMA study are randomized to either SLN biopsy or no surgery in the axilla (INSEMA). The primary endpoint is long-term safety, while 1560 patients were included in the SOUND study and 5940 were included in the INSEMA study [15, 16]. Depending on the mentioned studies' results, as well as the practical unavailability of SLN in our locality, all patients in our study, were omitted from SLN.

When it concerns the long-term outcomes of patients with clinically negative nodes who underwent complete mastectomy for their breast cancer, the landmark NSABP-04 research found that delaying axillary dissection did not affect survival. Overt axillary metastases were found to emerge in the follow-up of non-dissected women at a significantly lower rate than anticipated [17].

Similar evidence suggests that internal mammary node dissection during mastectomy does not increase survival [18].

In the present study, no significant difference was observed between the two studied groups regarding the axillary or ipsilateral shoulder recurrence (P=0.28). The absence of significant difference regarding loco-regional recurrence may be explained by the added benefit of radiotherapy which has been given to all patients with breast-conserving surgery and some patients with mastectomy. In a study comparing two methods, ALND and regional radiation (RT), Spruit et al., [19] compared the two. There were no significant differences between the treatment groups other than age. It was shown that the average age of patients in the RT group was much higher than that of the ALND group. The average time people were tracked was 7.2 years. Both the RT and ALND groups had similarly low and equivalent regional relapse rates after 5 years (1.1% in the RT group and 1.5% in the ALND group). Similarly, comparable were the 5-year overall survival rates (92% vs. 90%). Zhang et al., did a systematic review of 12 reports and 4 clinical trials, comparing axillary radiotherapy as an alternative treatment option for adjuvant axillary management of breast cancer and they conclude that as opposed to axillary surgery, axillary radiation therapy has the potential to have the same "curative" impact while causing fewer complications, however, if axillary dissection is skipped, crucial information regarding axillary staging is eliminated [20].

In our study, distant metastasis during the follow-up period was comparable between the two groups and didn't exceed 23% of the included patients in each group. The results of individual investigations on the effects of mastectomy have been published in several different outlets. Overall, these studies do not find that avoiding ALND or substituting RT for it reduces disease-free survival or the recurrence rate [21,22]. As a result, axillary treatment has changed to favor less invasive surgery [23].

Regarding lymphedema, there is no significant difference between the groups, however, patients with ALND had slightly higher rates of lymphedema than the other group, although it was not statically significant, 11.8% of patients with ALND had lymphedema in comparison to 8.3% for the other group. It is well known that ALND may disrupt the lymphatic vessels' anatomy and cause lymphedema [24]. However, axillary management has shifted as a result of the findings of the Z1071 study and other prospective clinical trials; and routine ALND is being utilized less frequently in this situation. The degree of lymphedema may depend on the type of post-operative lymphatics in the axilla, according to Tsangaris and Abe's hypothesis [25,26], re-establishing the original conduit to the ipsilateral axilla may offer less resistance than collateral paths leading to distant lymph nodes, thus this seems like a reasonable idea.

CONCLUSIONS

No significant differences were seen in the Loco regional metastasis, and distant metastasis between the two groups, lymphedema was low among those without axillary dissection, although loco regional recurrences were higher in the group with axillary dissection.

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