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Original Research

Predictors of seroma formation and the associated impact on adjuvant chemotherapy initiation for women undergoing mastectomy for breast cancer at a national referral hospital in Dar es Salaam, Tanzania: A prospective, observational study

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Abstract

Background

This study aimed to determine the incidence and predictors of seroma among post mastectomy breast cancer women and its impact on adjuvant therapy timing.

Methods

We conducted a prospective observational study among women who received mastectomy plus axillary dissection for invasive breast cancer at Muhimbili National Hospital between April 2021 and May 2022. Patients' clinical demography, tumor characteristics, drainage features, and the development of seroma was documented. Use of adjuvant therapy was collected at a follow visit. Prediction of seroma development and impact of adjuvant therapy initiations was determined by chi -square test with significance set at p value of <5%.

Results

We recruited 106 patients of which seroma was present in 49% with age >50 years and drainage of >150cc in first 24hours being significant predictors (p-0.03 and 0.002 respectively). Long-term follow up was done to 86 (81%) of which 74 (87%) received adjuvant chemotherapy with delay being significant among those with seroma formation, p-value 0.018

Conclusions

Seroma formation is common among women post mastectomy with no modifiable factor. Delay in adjuvant therapy is significant in the setting of a seroma formation. More studies are needed to reduce seroma occurrence as well as mitigate its impact on adjuvant therapy initiation.

Introduction

Breast cancer (BC) is a significant public health concern in Tanzania, as it is globally.[1] In recent years, there has been a growing emphasis on improving breast cancer awareness, early detection, and treatment options in the country. Mastectomy, a surgical procedure to remove the breast, remains a common treatment for breast cancer patients in Tanzania given the prevalence of locally advanced disease at initial diagnosis.[2] While the primary goal of mastectomy is to eliminate cancerous cells and prevent the spread of the disease, it can result in various post-operative unwanted effects. Among these side effects, seroma formation is a no-

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table concern due to its potential to impact patient outcomes and healthcare resources utilization.[3]

Seroma is a collection of clear fluid that can accumulate in the space left behind after the removal of breast tissue during mastectomy.[4,5] This fluid buildup often occurs during the early postoperative period, causing localized swelling, pain, and discomfort for patients. Although seroma is generally non-life-threatening, it can lead to a range of physical and psychological issues, making it a matter of substantial importance in the Tanzanian healthcare setting.

Seroma following mastectomy in the Tanzanian and similar settings is thus a matter of importance that has the potential to negatively impact on the quality of life, resource allocation, psychological well-being, and the overall healthcare system. Recognizing the significance of seroma in this context is essential for improving breast cancer care and survivorship in the country. This study aimed to study the rate of seroma formation, its predisposing factors and consequences on timing of adjuvant therapy among post mastectomy women at Muhimbili National Hospital (MNH) in Tanzania.

Methods

Study design and setting

A prospective study of women with breast cancer who were treated by mastectomy and axillary lymph node dissection between April 2021 and May 2022 was carried out at MNH. The hospital is the largest tertiary level facility in Tanzania located in the commercial capital of Dar es Salaam and also serving as the apex of the referral system for the country. In conjunction with its sister hospital, Ocean Road Cancer Institute (ORCI), the hospital offers comprehensive cancer care to patients with cancer including those with breast cancer. Patients post mastectomy are followed up at the facility, MNH, until when they are deemed fit and ready for adjuvant therapies when they are sent over to ORCI. The study received ethical clearance from MUHAS IRB 06-2021-682 and approval from the MNH Research and Training Unit. A written informed consent was obtained from all participants.

Patient recruitment and variables

All female patients diagnosed histologically to have BC and were treated by Modified Radical Mastectomy (Mastectomy plus level II axillary dissection) for their cancer were recruited in the study. Age of the patients was calculated from the year of birth at the time of diagnosis. All patients had Body Mass Index estimated from weight(kg) and height(cm^2) collected at admission as $kgcm^{-2}$. Patients were assessed for presence of diabetes mellitus and hypertension as standard preoperative evaluation. Clinical stage of the disease was taken from that estimated by the treating physician while hemoglobin was taken from laboratory results used during surgery.

Regarding tumor characteristics, histological grades and molecular subtypes were collected. The histological grade was categorized from well differentiated (Grade I) to poorly differentiated (Grade II) depending on resemblance of normal breast cells. The number of lymph nodes harvested was not counted to determine completeness of axillary dissection. Molecular subtypes were grouped as Luminal A (Hormonal receptor positive and Her-2 negative), Luminal B (Hormonal receptor positive and Her-2 positive), Her-2 enriched (Hormonal receptor negative and Her-2 positive) and Triple negative when both hormonal and Her-2 are negative.

Surgical variables were collected from the operative notes as follows: type of drainage used (normal tube for open drainage vs. suction system), duration of surgery from skin cut to closure in minutes. Drainage amount was estimated on the first 24 hours post-surgery and recorded in milliliters. Time of drain removal was estimated in total days the patient stayed with the drain with removal when 24hour collection was <50mls. Seroma was considered to have developed when there was a clinically significant collection of fluid pulpable under the skin and requiring needle aspiration following drain removal. Finally arm exercise was recorded as any deliberate exercise of moving the shoulder on the side of the mastectomy after surgery. Initiation of adjuvant therapy was categorized as delayed if started at beyond 12 weeks of surgery as stipulated in Tanzania national Guideline for cancer care.

Operative technique

Mastectomy followed the normal procedure of ensuring the nipple areolar complex and breast tissues including pectoral fascia is removed along with overlying skin in excess of that needed to cover the wound. The level I axillary clearance was achieved by clearing all fibrofatty tissue in the axillar exposing the axillary vein superiorly, long thoracic nerve medially, thoracodorsal pedicle laterally and latissimus dorsi lateral and medial pectoral vein inferiorly.

All patients underwent mastectomy with level 2 axillary lymph node dissection using monopolar electrocautery. Level II axillary clearance was achieved by lifting the pectoralis major and clearing all fibrofatty tissue underneath it to the Halsted's fascia medially. The dissections were achieved with electrocautery and suture ligation only to visible bleeders not controlled by cautery. A single drain was placed under the skin flap: the use of a suction versus gravity drain was determined by availability within the hospital hence the possibility of a patient having either of the two. The wound was closed using interrupted skin sutures and dressed with a compression-type dressing. No restrictions were placed on the timing of arm physiotherapy. Patients were discharged home on the second postoperative day with a drain in place, after instructions that included

how to empty the drainage bottle/bag, and how to record the daily drainage volume.

Follow-up procedures

Postoperatively, patients had follow-up through our surgical clinic for volume drainage review and wound status. Those who missed scheduled appointments or received postoperative care at another facility were followed-up via mobile phone. The drain was maintained until a drainage volume <50 ml/24 hours was achieved or as decided by the attending surgeon. Seroma was clinically detected by palpation of the fluid under the skin flaps of the mastectomy and confirmed by needle aspiration after drain removal. Patients with seroma were followed with frequent needle aspirations in sterile conditions until when their seroma resolved. All patients were then re-contacted between September 9 to 12, 2022 to collect data on the adjuvant treatment received and its timing from surgery.

Data analysis

Data collected in a special research questionnaire was entered into SPSS version 27.0 where continuous variables were summarized as measures of central tendency with standard deviation or interquartile range, and categorical variables as proportions. The relationship between the clinical demography and perioperative factors to seroma formation was determined by comparing the proportions and significant association was considered when a p-value of <0.05 was recorded. Effect of seroma on initiation of adjuvant therapy was considered present when difference between the seroma group delaying adjuvant therapy was significantly more than those not having seroma by a p value of <5%. Results are summarized in three tables and 1 figure.

Results

Between April 2021 and May 2022, 106 female patients with a mean age of 51.9±12.7 years underwent a modified radical mastectomy for breast cancer. In **Fig. 1**, we display the molecular subtypes of breast cancer among women who underwent a mastectomy for BC. It can be seen that 19(18%) of the patients did not have information on the molecular subtype leaving only 87 patients with results: Luminal A subtype was the most predominant at 46% followed by Triple negative subtypes at 36% while luminal B and Her2 enriched were least common.

Table 1 depicts the clinical demography and their relationship to seroma formation among post mastectomy patients. Seroma was clinically detected in 52 (49.1%) of the patients. The mean BMI was 24.5±3.9 kg/m^2. Most of the patients, 72 (68%), were in stage III of their cancer with the rest in stage II. Only 45 (42.5%) received neoadjuvant chemotherapy with the remaining receiving upfront surgery. All patients were assigned an histological grade with majority in Grade II, 57(53.7%) while Grade I was the list. Forty-nine, 46.2%, had a comorbidity as either hypertension or diabetic at time of surgery and 65 (61.3%) had anemia diagnosed to be hemoglobin value of less than 12 g/dl at the time of surgery.

Additionally, looking at the associations of these variables to seroma formation, having a mastectomy at age over 50 years was statistically associated with 20% more seroma formation, p=0.03. Other non-significant factors with more seroma formation included: overweight, 8% more p=0.42; 7% more prevalent among patients with Stage III disease compared to those with stage II, p=0.5; 11% more among patient with comorbidity, p=0.3; 4% more among patients who received NAT, p=.79; tumor grade and molecular subtypes of the tumor, p-values of .14 and .47 respectively.

In **Table 2**, we display the perioperative parameters in relation to seroma formations among 106 post mastectomy patients. The average duration of surgery was 129 minutes with the majority of patients' surgery lasting <120 minutes, 55 (51.9%). Most of the patients, 93(87.7%) had less than 12 lymph nodes reported in the mastectomy specimen. Drains were randomly used with a slight majority of patients being on suction drainage system, 54 (50.1%). The mean postoperative drainage in the first 24 hours was 179cc with most patients draining at <150cc, 75 (70.8%). Drainage tube was kept on an average of 9 days with most patients retaining it for at least 7 days, 73 (68.9%). Most patients started arm exercise on the second day post-surgery at 73 (68.9%).

When looking at associations between these factors and seroma formation, only drainage of more than 150mls in the first 24 hours of a modified radical mastectomy demonstrated a significant association: most of the patients, 75, had a drain of more than 150 of which 59% vs. 26% of those with less drain had developed a seroma, p=.002. Of the cohort, only 13 patients had at least 12 lymph nodes reported from the submitted specimen and these had 3% less seroma development compared to those reported to have yielded less than 12 nodes, p=.83. Early shoulder exercise has 13.6% more incidence of seroma compared to late shoulder exercise but failed to reach significant levels, p=0.31.

In **Table 3**, we followed up 86 of the patients at one year equivalent to 81.1% for timing of adjuvant therapy. Adjuvant therapy was administered to 74 (86%) of the patients with 20.8% more patients who did not get adjuvant therapy being in the seroma group but this was not significant, p=0.183. While the majority of the patients received adjuvant therapy within the locally acceptable 12 weeks of mastectomy, significant delay was more notable in the seroma group, p=0.018.

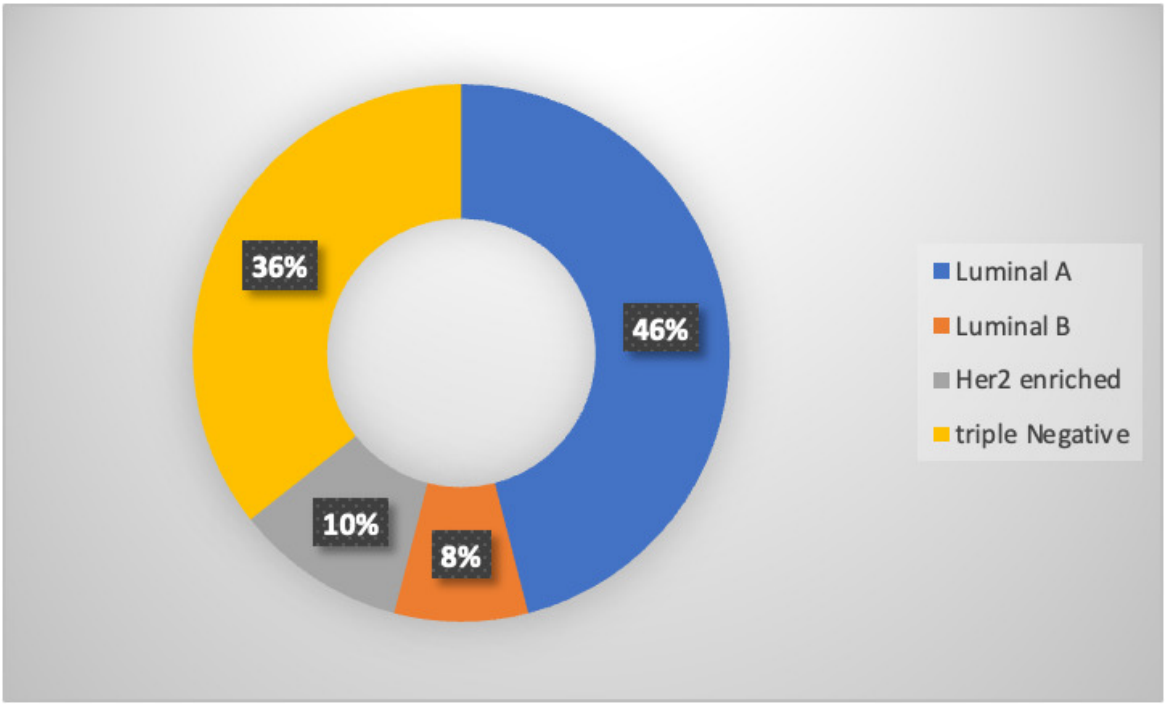

Figure 1. Molecular subtypes of Breast cancer seen at MNH in 2021/2022

Discussion

This is probably the first study shading light on seroma formation among women with breast cancer treated by modified radical mastectomy from Tanzania. Nearly half of the patient developed a clinically significant seroma, seroma requiring aspiration. This is on the higher side to that reported for mastectomy alone of up to 85%.[6,7] This study should be interpreted with caution since definition of seroma adopted might differ with contact and the need for aspiration, and the mastectomy including extensiveness of lymph node dissection which have long been implicated in seroma formation has not been standardized as was seen with number of lymph nodes harvested. Finally, it should be considered that all patients had their surgery by electrocautery, a well-established risk factor for seroma formation.

While theories behind the origin of seroma fluid have contradicted between being lymphatic or cellular in origin, it has been concluded recently that it is lymphatic with CD4 helper rich accumulation.[8] This calls for expanded search of the immunological origin of seroma by comparing patients who did and those who did not develop seroma. Possibility of an infection as a cause of seroma was ruled out in the above study.

Delayed shoulder exercise was shown to significantly reduce seroma rate and promotes wound healing while not affecting the shoulder function either.[9] Our study reported 13.6% more sermons cases among those starting shoulder exercise early. This practice of early physiotherapy as a way of improving shoulder function should be studied further in the local context with standardization of the exercise to inform local practice.

Role of electrocautery due to increased thermal trauma has long been associated with increased seroma rates[10] but benefits of reduced need for blood and shortened duration of surgery makes it indispensable. Alternatives such as ultrasonic and lesser dissection gadgets, while have produced some promising reductions in seroma rates, have exorbitant cost implications.[11,12] All patients were treated with electrocautery in this series and this can explain the high rates of seroma. Is it time to reconsider non usage of energy devices so that surgeons can locate blood vessels and ligate them appropriately and thus avoid cautery related tissue damage?

Seroma rates have been shown to be less with a Wide local excision plus axillary dissection, breast conserving surgery, than following a mastectomy.[13,14] This calls for ramping up efforts to detect breast cancer early and hence promote breast conserving surgery over a mastectomy in Tanzania. One hindrance to this approach would be the longer treatment times needed and the absence of a vast network of radiation therapy. For instance, in Tanzania, there are currently only two public centers (ocean road cancer institute in Dar es Salaam and Bugando Medical center in Mwanza) and three private centers (Agha Khan Hospital and Besta Diagnostics both in Dar es Salaam and Good Samaritan Cancer center in the outskirts of Morogoro).

In this era when seroma is now considered a side effect rather than a complication from surgery due to failure to adjust any surgical variable to meaningfully reproduce seroma reduction rates, surgeon and oncologists should relook at some of the possibilities to avoid the unintended consequences of seroma notably that of delayed or missed adjuvant therapies. Only age and drainage volume in excess

Table 1. Relationship between clinical demography and seroma formation among 106 women who underwent modified radical mastectomy for breast cancer at MNH in 2021/2022

Variables	Seroma N(%)	No Seroma N(%)	P - Value[s]
Age			
<50	21 (39)	33 (61)	0.033
≥50	31 (60)	21 (40)	
Body Mass Index			
Normal weight	20 (44)	25 (56)	0.415
Overweight	32 (52)	29 (48)	
Neoadjuvant therapy			
Yes	23 (51)	22 (49)	0.716
No	29 (48)	32 (52)	
Comorbidity			
HTN/DM	27 (55)	22 (45)	0.3
None	25 (44)	32 (56)	
Hemoglobin level (g/dl)			
<12	32 (49)	33 (51)	0.964
12 – 15	20 (49)	21 (51)	
Tumor stage			
II	15 (44)	19 (56)	0.485
III	37 (51)	35 (49)	
Tumor grade			
G-1	12 (71)	5 (29)	
G-2	25 (44)	32 (56)	0.147
G-3	15 (47)	17 (53)	
Receptor status			
Luminal A (HR+/HER2-)	20 (50)	20 (50.0)	
Luminal B (HR+/HER2+)	4 (57.0)	3 (43.0)	0.467
Her2+ enriched (HR-/HER2+)	4 (44.4)	5 (65.6)	
Triple Negative (HR-/HER2-)	18 (58.0)	13 (41.9)	

of 150cc in the first 24 hours were significantly related to seroma formation but both are not controllable. Some unreported cases starting chemotherapy adjuvant regardless of seroma formation while radiation therapy awaits seroma clearance could be tried in a large scale given the higher prevalence of seroma in this patients group. Aseptic regular aspirations while continuing chemotherapy should be explored. This will avoid delays in adjuvant therapy as was largely significant in our seroma group.

Further studies should look at female breast size and try to standardize surgical techniques including flap quality to better understand seroma risk factors in a multicenter large sample size study. Additionally, longer systematic follow up of patients to further understand the consequences of seroma in mastectomy patients is needed.

Conclusions

Seroma is a common side effect following mastectomy for breast cancer since it affects almost half of all the female patients. Only age above 50 years and 24hours drainage of at least 150cc significantly predicted seroma formation. Use of less expensive drains did not predispose to more seroma formation. While most of the patients started adjuvant chemotherapy within 12 weeks, delay was significant among those with seroma calling for further studies to address seroma related delays and understand long term consequences of seroma formation.

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Table 2. Relationship between perioperative characteristics and the development of seroma among of 106 women post modified radical mastectomy for for breast cancer at MNH in 2021/2022

Variables	Seroma N(%)	No seroma N(%)	P-value
Duration of surgery (mins)			
<120	30 (55)	25 (45)	0.240
≥120	22 (43)	29 (57)	
No. lymph node harvested			
<12	46 (49)	47 (51)	0.823
≥12	6 (46)	7 (54)	
Type of drain used			
Suction	25 (46)	29 (54)	0.562
Non-suction	27 (52)	25 (48)	
Drainage volume in 1st 24 hours (mls)			
<150	8 (26)	23 (74)	0.002
≥150	44 (59)	31 (41)	
Duration of drainage (days)			
<7	19 (58)	14 (42)	0.238
≥7	33 (45)	40 (55)	
Arm exercise day			
Day 1	46 (51.1)	44 (48.9)	0.31
Day ≥7	6 (37.5)	10 (62.5)	

Table 3. Impact of seroma on Adjuvant therapy among patients with Breast cancer post mastectomy at MNH, 2021/2022

Variables	Seroma N(%)	No seroma N(%)	P-Value
Adjuvant therapy (n=86)			
Yes	34 (45.9)	40 (54.1)	0.183
None	8 (66.7)	4 (33.3)	
Timing of adjuvant therapy (n=74)			
Delayed	11 (73.3)	4 (26.7)	0.018
Not delayed	23 (39.0)	36 (61.0)	

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