

Clinical and pathological factors predicting axillary nodal metastasis in breast cancer patients of central Sudan: A single institution experience

Mohamed Daffalla Awadalla Gismalla, Moawia Mohamed Ali Elhassan¹, Mohanned Omer Abass²

Department of Surgery, Faculty of Medicine, University of Gezira, ¹Department of Oncology, National Cancer Institute, University of Gezira, Wad Medani, ²Department of Surgery, Faculty of Medicine, Shendi University, Shendi, Sudan

Address for correspondence:

Dr. Mohamed Daffalla Awadalla Gismalla,
Department of Surgery, Faculty of Medicine,
University of Gezira, Wad Medani, Sudan.
E-mail: mohadaff22@gmail.com

ABSTRACT

Background: Data on factors predicting axillary lymph node (ALN) metastasis among Sudanese patients with breast cancer are rare. **Aim:** The aim of this study is to provide baseline information of the clinical and pathological factors predicting ALN metastasis in patients who underwent modified radical mastectomy or breast conserving surgery at Wad-Madani Teaching Hospital, Sudan. **Materials and Methods:** We performed a prospective study to examine the correlation between ALN status and clinicopathological characteristics of 81 patients with breast cancer. **Results:** The median age at diagnosis was 47 years (range, 25–85 years). The median number of lymph nodes (LNs) retrieved was 14 (range 2–31). ALNs containing metastases were found in 52 patients (64.2%); more than half of them ($n = 30$) had three or more positive LNs. Factors associated with lower chance of developing LN metastasis were age more than 60 years, postmenopausal status, smaller tumor size, and tumor that were positive for estrogen receptor and/or progesterone receptor. The number of ALNs retrieved was the only factor which showed statistically significant association with ALNs metastases. **Conclusions:** Our finding reveals a high incidence of ALN metastasis among patients with breast cancer in Sudan, which is likely due to various factors such as young age at diagnosis and large tumor size as a result of late diagnosis.

Key words: Breast cancer, lymph node, sub-Saharan Africa, Sudan

INTRODUCTION

Axillary lymph nodes (ALNs) status has long been considered the most powerful prognostic factor for patients with breast carcinoma.^[1-3] Patients with positive ALNs had approximately 40% less chance of surviving 5 years than those with negative ALNs.^[4] Previous studies identified a variety of clinical and pathological factors as independent predictors of ALNs involvement for patients with early-stage breast cancer. These include tumor size, lymphovascular invasion, tumor grade, and patient age.^[5-7] Moreover, the gene expression profile of invasive breast carcinoma has also been considered in the determination of prognosis for early-stage breast cancer patients.^[8,9]

In Sudan, like other countries with limited resource settings, most breast cancer patients presented with advanced stage disease, which negatively affects selecting of treatment modality and final management outcome.^[10,11] Financial incapacity, ignorance, and misinterpreting symptoms were the top three factors that may lead to late presentation.^[12]

ALNs dissection (ALND) has been the standard of care to estimate prognosis and to guide the choice of adjuvant treatment. Sentinel lymph node (SLN) biopsy has emerged as a most powerful tool to probe ALNs status and to spare completion of ALND in patients with uninvolved SLNs.^[13]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Gismalla MD, Elhassan MM, Abass MO. Clinical and pathological factors predicting axillary nodal metastasis in breast cancer patients of central Sudan: A single institution experience. Saudi J Health Sci 2019;8:146-50.

Access this article online

| | |
|---|---|
| Website: www.saudijhealthsci.org | Quick Response Code  |
| DOI: 10.4103/sjhs.sjhs_90_19 | |

This technique is unavailable in our settings. Therefore, the standard of care for Sudanese patients with breast cancer is modified radical mastectomy (MRM) or breast conserving surgery (BCS) with Level I and II ALND.^[14] The minimal number of lymph nodes (LNs) to be retrieved is 10 for adequate axillary clearances; however, below this level, it will be considered as LNs sampling.^[15]

There are limited studies among Sudanese patients with breast cancer that evaluated variables that predict involvement of ALNs with metastasis.^[16] Therefore, we conducted this study to estimate the likelihood of ALNs involvement for patients with early-stage breast cancer, based on a variety of clinical and pathological factors.

MATERIALS AND METHODS

Study design

We performed a prospective study of female patients that were diagnosed with breast cancer based on histologic confirmation and who were underwent MRM or BCS with ALND at Wad-Madani Teaching Hospital (WTH) and received adjuvant therapy in the Oncology department at the National Cancer Institute, University of Gezira (NCI-UG). The demographic, clinical, and histopathological data were extracted from patients' folders and histopathology reports.

Settings

All surgical operations were performed by general surgeons or senior registrars at WTH in Wad-Madani, the capital of Gezira state. This academic referral hospital serves the whole Gezira state and nearby states. Type of surgical intervention was selected based on tumor size, location, mammographic findings, and patient's preference. BCS was preferred when tumor <5 cm, more than 5 cm in big (giant) breast, not central mass (sub-areola), and not multicenter. Breast reconstruction was not available at time of the study; as a result of no trained plastic or breast oncoplastic surgeon.

Histopathologic studies are provided by the University of Gezira Medical Laboratory Center. All tissue specimens were fixed by keeping them in 10% formalin overnight and paraffin wax embedded; 4 µm sections were cut and stained with hematoxylin and eosin. After fixing, microscopic examination of the specimen was done and findings were recorded. Size was assessed accurately. LNs were retrieved, numbers were noted, and involved nodes were recorded. Grading of tumors was done according to Bloom–Richardson Grading System. Details of the immunohistochemistry for estrogen receptor (ER) and progesterone receptor (PR) were collected from histopathology records for each case.

The Oncology Department of the NCI-UG has a weekly multidisciplinary breast clinic for management decisions. The cancer treatment modalities available at the NCI-UG

include radiotherapy, chemotherapy, hormonal therapy, and palliative care.

Study population

Female patients with clinical negative ALNs and for whom staging investigations revealed no evidence of distant metastasis were included in the study. All male breast cancers were excluded. These patients underwent either BCS or MRM. ALNs staging was achieved through Level I and II ALND. Exclusion criteria included patients who received neoadjuvant chemotherapy.

Statistical analysis

Data were entered and analyzed using statistical Package for Social Sciences (Version 20.0 IBM SPSS Corp., Armonk, NY, USA) to find simple frequency and cross tabulation for patient and tumor characteristics related to nodal status. Median value was elicited for age, nodes retrieved, and node metastasis. Chi-square distribution was utilized to assess the statistical significance of the effect of age, tumor size, grade, and node retrieved. $P < 0.05$ was considered as statistically significant. These variables also stated with 95% confidence limits; odd ratio was obtained using logistic regression methods.

Ethical aspects

Ethical approval for this retrospective study was obtained from the ethical committee at the NCI UG.

RESULTS

The number of patients who were included in the study was 81. The median age at diagnosis was 47 years (range, 25–85 years). The majority of cases (95%) were invasive ductal carcinoma, while only 5% were invasive lobular carcinoma. Median tumor size was 4.00 cm (range, 1.5–13.5 cm). The majority of tumors (52%) are clinically staged as T2. The prevalence of estrogen and/or progesterone receptors in this study is shown in Figure 1 and it was found positive among 51 % of patients.

The distribution of our study population according to the number of LNs retrieved is presented in Figure 2. The median number of LNs retrieved was 14 (range, 2–31 LNs). We found 29 (35.8%) patients were diagnosed with negative axillary metastasis, while 52 (64.2%) patients were positive. Patient and tumor characteristics, based on the ALNs status, are presented in Table 1. For the cohort with ALNs metastasis, 30/52 (64.2%) patients had three or more positive LNs.

We found various clinical and pathological factors associated with an increased risk of ALNs metastasis as shown in Table 2. The number of ALNs retrieved was found to be the only factor associated with ALNs metastases ($P < 0.005$) as shown in Table 2. In addition, two trends were observed, although they did not reach the statistical significance: the first is that the majority of patients having Grade III (60.5%) had positive

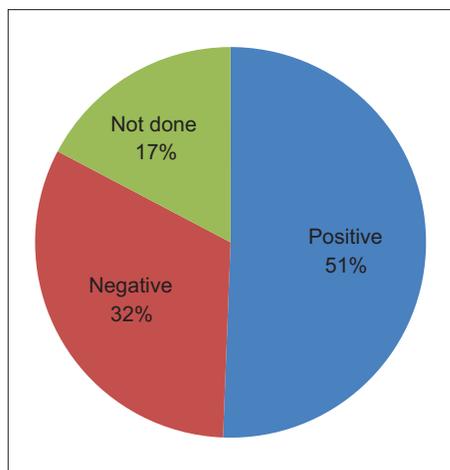


Figure 1: The prevalence of estrogen and/or progesterone receptors

ALNs metastasis and the second is that the patients having hormone receptor-negative tumors were more likely to have ALNs metastasis (68.3%).

DISCUSSION

Breast cancer is the most commonly diagnosed cancer among Sudanese women.^[17] Its incidence was found to be 25.1/100,000 in Khartoum state, Sudan.^[18] One in every 3 women admitted to NCIUG for treatment had breast cancer.^[19] Breast cancer in Sudanese women is characterized by younger age at onset and advanced stage at diagnosis.^[10-12,20] The low rate of BCS in this study may reflect the high rate of patients who presented with large tumor size.

In breast cancer management, ALND has an essential role in determining the pathological staging of the disease and is an integral part of the treatment of breast cancer.^[20] Although ALND has largely been replaced by SLN biopsy for patients with clinically node-negative breast cancer,^[21] this advanced technique is presently not available in Sudan. Therefore, nearly, all patients with invasive breast cancer undergo ALND.

In the present study, we evaluated the correlation between ALNs status and clinicopathological characteristics of 81 patients with breast cancer. We found ALNs metastasis in about two-thirds of our patients. Similar to a previous study conducted in Sudan,^[16] axillary metastases were not detected in about one-third of the examined patients. Correspondingly, for these cases, ALND could have been avoided if these patients were identified preoperatively.

In the current study, the median age was 47 years. It was reported that approximately two-third of the Sudanese women diagnosed with breast cancer were younger than 50 years of age.^[12] Breast cancer at a young age is generally associated with aggressive behavior, advanced stage at presentation, and poorer prognosis.^[22] We observed that approximately two-third of patients in the age groups

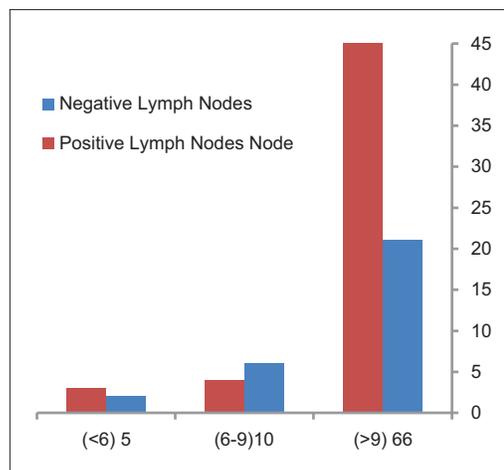


Figure 2: The distribution of our study population according to the number of axillary lymph nodes retrieved

Table 1: Patient and tumor characteristics, based on the axillary lymph node status

| Patients and tumor characteristics | Total number | ALNs status | |
|------------------------------------|--------------|-----------------|-----------------|
| | | Negative, n (%) | Positive, n (%) |
| Age group (years) | | | |
| <40 | 21 | 7 (33) | 14 (67) |
| 40-60 | 45 | 13 (29) | 32 (71) |
| >60 | 15 | 9 (60) | 6 (40) |
| Menopausal status | | | |
| Premenopausal | 46 | 13 (28) | 33 (72) |
| Postmenopausal | 35 | 16 (46) | 19 (54) |
| Clinical tumor size (cm) | | | |
| ≤2 | 3 | 1 (33) | 2 (67) |
| 2-5 | 46 | 22 (48) | 24 (52) |
| >5 | 32 | 6 (19) | 26 (81) |
| Type of surgery | | | |
| MRM | 37 | 13 (35) | 24 (65) |
| BCS | 44 | 16 (36) | 28 (64) |
| Level of surgeon | | | |
| Consultant | 49 | 19 (39) | 30 (61) |
| Registrar | 32 | 10 (31) | 22 (69) |

MRM: Modified radical mastectomy, BCS: Breast conserving surgery, LN: Lymph node, ALNs: Axillary LNs

<40 years and 40–60 years had metastatic ALNs, but this association between ages at breast cancer diagnosis and LNs metastases was statically not significant as reported earlier.^[23,24]

We observed that node positivity was not related to menopausal status, and premenopausal patients showed a nonsignificant trend toward a higher rate of LN metastases as also shown by Nouh *et al.*^[25] On other studies, tumor grade appeared to play an important role in ALNs metastasis.^[6,24,26,27] The present study did not find this correlation, which can be explained by the small number of our study population. Similar finding was reported by Viale *et al.* who reported

Table 2: The relationships between axillary lymph node metastasis and various clinicopathological factors

| Clinical and pathological factors | n | ALNs status | | OR | 95% CI | P |
|-----------------------------------|----|-------------|----------|-------|-------------|------|
| | | Positive | Negative | | | |
| Age (median age) (years) | | | | | | |
| ≤47 | 39 | 12 | 27 | 0.973 | 0.941-1.006 | 0.1 |
| >47 | 42 | 17 | 25 | | | |
| Tumor size (median size) (cm) | | | | | | |
| ≤4 | 41 | 13 | 28 | 0.867 | 0.694-1.082 | 0.4 |
| >4 | 50 | 26 | 24 | | | |
| Tumor grade | | | | | | |
| I | 4 | 0 | 4 | 1.199 | 0.472-3.044 | 0.20 |
| II | 34 | 12 | 22 | | | |
| III | 43 | 17 | 26 | | | |
| Hormonal status | | | | | | |
| Positive | 41 | 13 | 28 | - | - | 0.84 |
| Negative | 26 | 12 | 14 | | | |
| Not done | 14 | 4 | 10 | | | |
| Type of surgery | | | | | | |
| BCS | 37 | 13 | 24 | 1.055 | 0.424-2.628 | 0.20 |
| MRM | 44 | 16 | 28 | | | |
| Median number of LNs retrieved | | | | | | |
| ≤14 | 43 | 21 | 22 | 1.128 | 1.032-1.233 | 0.01 |
| >14 | 38 | 8 | 30 | | | |

MRM: Modified radical mastectomy, BCS: Breast conserving surgery, LNs: Lymph nodes, OR: Odds ratio, CI: Confidence interval, ALNs: Axillary LNs

that increasing tumor grade does not predict a higher risk for ALNs metastases in multivariate analysis.^[5]

The risk of ALNs metastasis increases as tumor size increases.^[28] Only three patients in this study were T1. We found ALNs metastasis in 81% and 52% of cases with tumor larger than 5 cm and 2–5 cm, respectively. Postacı *et al.* reported that T stage was significantly associated with nodal positivity.^[29] We observed no correlation between tumor sizes with axillary metastasis. Similar data have been published previously on the incidence of ALNs metastases according to tumor size.^[30]

The predictive role of hormone receptor status in previous investigations is controversial.^[6,7,24,30] In the present study patients with hormonal receptors negative tumors were more likely to have ALNs metastasis. This was in contrast to findings of Ashturkar *et al.* who reported that ER and PR-negative status was significantly associated with low risk of ALNs metastasis.^[30] Positive expression for ER and PR was significantly correlated with histological grade, mitotic score, and nuclear pleomorphism.^[31]

The removal of at least 10 axillary nodes represents the international gold standard for systematic axillary staging.^[32] In this study, the median number of ALNs retrieved during histopathology examination was 14. We found that the number of ALNs retrieved had a significant association with the number of positive LN metastasis. It is worth mentioning that complications of ALND are increased by the extent of

the dissection.^[33,34] Therefore, the potential benefit of ALND must be balanced against its well-known complications.^[35,36]

There are few limitations in the present study. First, the small sample only included patients from one tertiary hospital in Sudan. Thus, it is likely that findings seen in other regions of Sudan differ than reported in this study. Second, another weakness may be that different pathologists conducted the histopathological examination and the analysis for ER, PR. Furthermore, HER2 status and lymphovascular invasions were not included in our analysis, and ER/PR testing was not done for some cases.

CONCLUSIONS

We found a high incidence of ALNs metastasis among patients with breast cancer in Sudan, which is likely due to various factors such as young age at diagnosis and large tumor size at presentation. Factors associated with a lower chance of developing LN metastasis were age more than 60 years, postmenopausal status, smaller tumor size, and tumor that are positive for estrogen receptor and/or progesterone receptor. The number of ALNs retrieved was found is the only factor which demonstrates statistically significant association with ALNS metastases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Fisher B, Slack N, Karych D, Wolmark N. Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. *Surg Gynecol Obstet* 1975;140:528-34.
- Nemoto T, Vana J, Bedwani RN, Baker HW, McGregor FH, Murphy GP. Management and survival of female breast cancer: Results of a national survey by the American College Of Surgeons. *Cancer* 1980;45:2917-24.
- Rosen PP, Groshen S, Saigo PE, Kinne DW, Hellman S. Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma: A study of 644 patients with median follow-up of 18 years. *J Clin Oncol* 1989;7:1239-51.
- Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. *J Clin Oncol* 1989;7:355-66.
- Viale G, Zurrida S, Maiorano E, Mazzarol G, Pruneri G, Paganelli G, *et al.* Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. *Cancer* 2005;103:492-500.
- Barth A, Craig PH, Silverstein MJ. Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. *Cancer* 1997;79:1918-22.
- Van Calster B, Vanden Bempt I, Drijkoningen M, Pochet N, Cheng J, Van Huffel S, *et al.* Axillary lymph node status of operable breast cancers by combined steroid receptor and HER-2 status: Triple positive tumours are more likely lymph node positive. *Breast Cancer Res Treat* 2009;113:181-7.
- Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, *et al.* Breast cancer prognostic classification in the molecular era: The role of histological grade. *Breast Cancer Res* 2010;12:207.
- Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: Classification, prognostication, and prediction. *Lancet* 2011;378:1812-23.
- Elgaili EM, Abuidris DO, Rahman M, Michalek AM, Mohammed SI. Breast cancer burden in central Sudan. *Int J Womens Health* 2010;2:77-82.
- Mariani-Costantini R, Elhassan MM, Aceto GM, *et al.* Epidemiology, pathology, management and open challenges of breast cancer in central Sudan: A prototypical limited resource African setting. In: Pham PV, editor. *Breast Cancer: From Biology to Medicine*. London, UK: IntechOpen; 2017. p. 596-608.
- Salim OE, Mukhtar SI, Mohammed BI, Salih N, Hamad K. Breast cancer in Africa, are we dealing with a different disease. *Sudan Med J* 2014;11:1-24.
- Atalay C. New concepts in axillary management of breast cancer. *World J Clin Oncol* 2014;5:895-900.
- Elhaj A, Elshaikh AA. National guidelines for management of breast cancer: For enforcement or persuasion. *Sudan Med J* 2012;3:213-8.
- Somner JE, Dixon JM, Thomas JS. Node retrieval in axillary lymph node dissections: Recommendations for minimum numbers to be confident about node negative status. *J Clin Pathol* 2004;57:845-8.
- Abd-Alhadi H, Mohammed ME, Eltayeb MA. Correlation of four receptors expression and lymph node metastasis in Sudanese breast cancer patients. *Int J Curr Res* 2018;10:64420-4.
- Abdulrahman MA, Shaheen SM, N'Sanh MR, N'dri EA, Osman AA. The disparities of cancer incidence between sudanese men and women. *Int J Cancer Clin Res* 2018;5:101.
- Saeed IE, Weng HY, Mohamed KH, Mohammed SI. Cancer incidence in Khartoum, Sudan: First results from the cancer registry, 2009-2010. *Cancer Med* 2014;3:1075-84.
- Elhassan MM. Personal perspective: Access to treatment for gynaecological malignancies in Sudan. *South Afr J Gynecol Oncol* 2018;10:21-3.
- Awadelkarim KD, Arizzi C, Elamin EO, Hamad HM, De Blasio P, Mekki SO, *et al.* Pathological, clinical and prognostic characteristics of breast cancer in central Sudan versus Northern Italy: Implications for breast cancer in Africa. *Histopathology* 2008;52:445-56.
- Le VH, Brant KN, Blackhurst DW, Schammel CM, Schammel DP, Cornett WR, *et al.* The impact of the American College of Surgeons Oncology group (ACOSOG) Z0011 trial: An institutional review. *Breast* 2016;29:117-9.
- Swanson GM, Lin CS. Survival patterns among younger women with breast cancer: The effects of age, race, stage, and treatment. *J National Cancer Institute. Monographs* 1994;16:69-77.
- Wildiers H, Van Calster B, van de Poll-Franse LV, Hendrickx W, Røislien J, Smeets A, *et al.* Relationship between age and axillary lymph node involvement in women with breast cancer. *J Clin Oncol* 2009;27:2931-7.
- Chakraborty A, Bose CK, Basak J, Sen AN, Mishra R, Mukhopadhyay A. Determinants of lymph node status in women with breast cancer: A hospital based study from Eastern India. *Indian J Med Res* 2016;143:S45-S51.
- Nouh MA, Ismail H, El-Din NH, El-Bolkainy MN. Lymph node metastasis in breast carcinoma: Clinicopathological correlations in 3747 patients. *J Egypt Natl Canc Inst* 2004;16:50-6.
- Tsai HL, Lu CY, Hsieh JS, Wu DC, Jan CM, Chai CY, *et al.* The prognostic significance of total lymph node harvest in patients with T2-4N0M0 colorectal cancer. *J Gastrointest Surg* 2007;11:660-5.
- Yoshihara E, Smeets A, Laenen A, Reynders A, Soens J, Van Ongeval C, *et al.* Predictors of axillary lymph node metastases in early breast cancer and their applicability in clinical practice. *Breast* 2013;22:357-61.
- Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989;63:181-7.
- Postacı H, Zengel B, Yazarbaşı U, Uslu A, Eliyatkin N, Akpınar G, *et al.* Sentinel lymph node biopsy in breast cancer: Predictors of axillary and non-sentinel lymph node involvement. *Balkan Med J* 2013;30:415-21.
- Ashturkar AV, Pathak GS, Deshmukh SD, Pandave HT. Factors predicting the axillary lymph node metastasis in breast cancer: Is axillary node clearance indicated in every breast cancer patient? *Indian J Surg* 2011;73:3315.
- Thike AA, Chng MJ, Fook-Chong S, Tan PH. Immunohistochemical expression of hormone receptors in invasive breast carcinoma: Correlation of results of H-score with pathological parameters. *Pathology* 2001;33:21-5.
- Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish breast cancer cooperative group (DBCG). *Eur J Cancer* 1992;28A:1415-8.
- Larson D, Weinstein M, Goldberg I, Silver B, Recht A, Cady B, *et al.* Edema of the arm as a function of the extent of axillary surgery in patients with stage I-II carcinoma of the breast treated with primary radiotherapy. *Int J Radiat Oncol Biol Phys* 1986;12:1575-82.
- Burstein HJ, Winer EP. Primary care for survivors of breast cancer. *N Engl J Med* 2000;343:1086-94.
- Abass MO, Gismalla MD, Alsheikh AA, Elhassan MM. Axillary lymph node dissection for breast cancer: Efficacy and complication in developing countries. *J Glob Oncol* 2018;4:1-8.
- Roses DF, Brooks AD, Harris MN, Shapiro RL, Mitnick J. Complications of level I and II axillary dissection in the treatment of carcinoma of the breast. *Ann Surg* 1999;230:194-201.