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AXILLARY LYMPH NODE DISSECTION FOR PATIENTS WITH INVASIVE BREAST CANCER AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL and CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

C Groenewald

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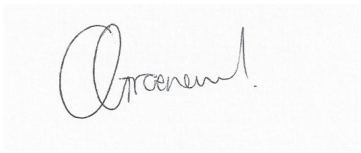


A Research Report submitted to the Faculty of Health Science, University of Witwatersrand, in fulfillment of the requirements for the degree of Masters in Surgery (Mmed in Surgery)

Johannesburg 2019

DECLARATION

I, Carolette Groenewald, declare that this Research Report is my own, unaided work. Any assistance that I received is stated in my acknowledgements. It is being submitted for the Degree of Mmed in Surgery at the University of the Witwatersrand, Johannesburg. This report is being submitted in the format for a submissible paper.
It has not been previously submitted for any degree or examination at this or any other University. This report does not utilise any previous or current work produced by another individual.
I certify that the protocol has been approved by the Human Ethics Committee (Medical) at the University of the Witwatersrand, Johannesburg (Appendix: Ethics Clearance Certificate number M150549)



3/7/2019

Carolette Groenewald Date

Dedicated to my husband, Renier Groenewald and the Penny family,
for your continuous love and support throughout this journey.

PRESENTATIONS ARISING FROM THIS STUDY

This publication's abstract was presented at the meeting of the Surgical Research Society of Southern Africa (SRS) in July 2017.

ABSTRACT

Background: The extent of axillary surgery correlates with its morbidity and sentinel lymph node biopsy (SLNB) has become the standard of care in clinically node-negative (cN0) breast cancer patients.

Objectives: This study aims to 1) evaluate the application of SLNB and axillary lymph node dissection (ALND) and determine the prevalence of pathological node negative (pN0) ALND's and 2) determine the factors associated with pN0 ALND outcome in two Johannesburg breast units.

Methods: We included female patients with primary breast cancer who underwent axillary surgery in the breast units at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) from March 2013 to March 2015. Univariate and multivariable logistic regression models were used to determine factors associated with pN0 ALND.

Results: Five hundred and five patients were included and 344 patients (68.1%) were staged clinically node-positive (cN1), 161 patients (31.9%) were assessed as cN0 and deemed eligible for SLNB. Sensitivity of clinical nodal staging was 85.9% with a positive predictive value (PPV) of 76.5%. The majority of patients (313, 61.9%) underwent primary surgery while 192 patients (38.1%) underwent surgery after Neoadjuvant chemotherapy (NACT). We performed 118 SLNBs and 387 ALNDs. There were 97 pN0 ALND's and of all the SLNB's and ALND's, a total of 199 were pN0 tumours.
Risk was not increased after NACT (OR 1.06, p=0.790). We identified a significant risk in patients with triple-negative and Human epidermal growth factor-2 (HER-2) enriched subtypes compared to hormone receptor-positive patients (OR 3.05, 95% CI: 1.6-5.7, p=0.001 and OR 2.25, 95% CI: 1.1-4.8, p=0.035).

Conclusions: The prevalence of pN0 ALND was 25.1%. Hormone receptor negative tumours were associated with a higher pN0 ALND outcome as compared to luminal cancers.

Preoperative nodal assessment needs to be optimised and include pathological confirmation. SLNB needs to be extended to patients after NACT despite resource-constraints.

ACKNOWLEDGMENTS

I thank my supervisors Ms. Sarah Nietz, head of CMJAH Breast Unit and Mr .Herbert Cubasch, head of CHBAH Breast Unit who allowed me to access the Breast Unit databases and patient records. They also provided insight and expertise that greatly assisted my research. You have cultivated a fondness and love for research in me.

I thank Tosin Ayeni for assistance with statistical analysis and the countless replies to my middle of the night questions regarding the statistics.

I would also like to show our gratitude to the Prof Aylwyn Mannell for sharing her pearls of wisdom with me during the course of this research

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NOMENCLATURE

ALND	- Axillary lymph node dissection
CHBAH	- Chris Hani Baragwanath Academic Hospital
CMJAH	- Charlotte Maxeke Johannesburg Academic Hospital
cN0	- Clinically node negative
cN1	- Clinically node positive
ER	- Estrogen receptor
FNA	- Fine needle aspiration
FNR	- False negative rate
HER2	- Human epidermal growth factor receptor 2
NACT	- Neoadjuvant chemotherapy
NCCN	- National Comprehensive Cancer Network
NPV	- Negative predictive value
OR	- Odds ratio
pN0	- Pathological node-negative
pN+	- Pathological node-positive
PPV	- Positive predictive value
PR	- Progesterone receptor
SLNB	- Sentinel lymph node biopsy
TNM	-Tumour, Node and Metastasis

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Cover Letter to the Editor of the SAJS

23.12.2018

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Prof J Krige, Prof S Thomson - Editor-in-Chief
South African Journal of Surgery
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Dear Professor Krige and Thomson

I am pleased to submit an original research article entitled “Axillary Lymph Node Surgery in Breast Cancer: Saving the Axilla” by Carolette Groenewald, Sarah Nietz, Prof Alwyn Mannell, Oluwatosin Ayeni and Herbert Cubasch for consideration for publication in the *South African Journal of Surgery*.

We show that 25% of patients that are undergoing axillary lymph node dissection in our practice have a pathologically node-negative dissection. Patients with hormone receptor-negative breast cancer were at a higher risk compared to patients with receptor-positive tumours. Neoadjuvant chemotherapy did not increase the risk. Omission of pre-operative cytology or core biopsy of suspicious nodes showed a trend towards increased the risk but this finding did not reach significance. Improvements in pre-operative clinical node assessment in conjunction with a broader application of SLNB require consideration in our resource-constrained environment to appropriately decrease the extent of axillary surgery in our patients.

My co-authors and I would be grateful if you would read the enclosed paper and consider for publication by *South African Journal of Surgery* as it is relevant to the South African context of surgery.

This manuscript has not been published and is not under consideration for publication

elsewhere. We have no conflicts of interest to disclose.

Thank you for your consideration.

Sincerely,

Dr. Carolette Groenewald
MBChB
Surgical Registrar, Department of General Surgery
Faculty of Health Sciences, University of the Witwatersrand

1. INTRODUCTION

The axillary lymph node status forms part of tumour staging and is an important prognostic factor for patients with invasive breast cancer. [1] [2] Methods to stage the axilla include physical examination, dedicated imaging and histopathological confirmation. Clinical evaluation of the axilla by palpation alone is relatively inaccurate and has a reported sensitivity of 35%. [3] Axillary lymph nodes may appear clinically and radiologically enlarged due to causes other than breast cancer. HIV infection is commonly associated with benign axillary lymphadenopathy and recent data from CHBAH showed that 19.7% of patients with breast cancer tested positive for HIV. [4] The term "clinically node-positive" has been redefined over the past years and in current practice it usually entails pre-operative confirmation of positive nodal involvement by cytology or core biopsy. In 2011 the results from a meta-analysis the median sensitivity of ultrasound in detecting positive lymph node involvement in patients with invasive breast cancer was found to be 61.4% and the specificity 82%, these values increased further to 79.4% and 100% with the addition of ultrasound-guided node biopsy. [5] In patients who appear cN1 due to palpable and/or sonographically suspicious lymph nodes, fine needle aspiration (FNA) or core needle biopsy of a suspicious lymph node can confirm nodal involvement and identify patients who may proceed directly to ALND rather than SLNB. In cases where the FNA is negative for nodal involvement the patient will undergo SLNB. [6] Unfortunately, we could not confirm positive lymph node involvement by FNA or core biopsy or both in our institutions, due to resource constraints. Patients who have palpable lymphadenopathy or sonographically suspicious nodes proceed directly to ALND.

A first world medical centre performed an observational study on pN0 breast cancer patients and found that 49% of patients ultimately underwent ALND either initially or after SLNB.[7] ALND carries morbidity and lymphoedema of the arm is the most frequent long-term complication. [8] ALND have up to a 40% life time risk of developing lymphoedema. [9] Since morbidities following ALND is directly related to the extent of surgery, SLNB has become the standard of care in patients who have no nodal involvement. ALND has no oncological benefit in node-negative patients and is thus difficult to justify. [10]

An aspect that has been recently evolving is the use of SLNB following NACT. The SLNB method has been adopted as an axilla-conserving option in the National Comprehensive Cancer Network (NCCN) guidelines for patients who were initially cN1, but who are down-staged following NACT to cN1 disease. [11] This was not adopted in our practice at the time of this study.

In view of the general trend towards axilla-preservation, we audited the use of SLNB and ALND in two breast units. Our study aimed to 1) evaluate the application of SLNB and ALND and determine the prevalence of pN0 ALND's, and 2) determine the factors associated with an increased likelihood of pN0 ALND's in two Johannesburg breast units.

2. METHODS

Study population

We performed a retrospective review at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) Breast Units. Female patients who presented with primary invasive breast cancer and who underwent axillary surgery from March 2013 to March 2015 were included. Patients were recruited via theatre and admission records at CMJAH and via the electronic database at CHBAH. Exclusion criteria were recurrent disease, the absence of invasive breast cancer, cases were breast cancer was not the primary presentation and incomplete data.

Data were extracted from histology records, patient records via the breast files at CMJAH and the database at CHBAH. Variables extracted included: site, age, Tumour, Node and Metastasis (TNM) staging at presentation, preoperative nodal staging as determined by physical examination and/or ultrasound, preoperative histological type of tumour, immunohistochemistry, preoperative histological confirmation of axillary metastasis where available, type of axillary surgery performed, timing of surgery and the final postoperative histopathology report.

Laboratory methods

Intrinsic subtypes were determined by immunohistochemistry according to the following criteria as part of the clinical standard at the time of data collection: Luminal A: Estrogen receptor (ER) and/or Progesterone receptor (PR) positive, Human epidermal growth factor 2 (HER-2) negative and Ki-67 <15; Luminal B: ER and/or PR positive, Ki 67≥ 15 or ER and/or PR positive with HER-2 positive; HER-2 enriched: HER-2 positive alone (ER and PR negative); Triple negative: ER negative, PR negative, HER-2 negative. [12] Patients were grouped according to pre-operative and post-operative node status.

Statistical analysis

Descriptive statistics was performed reporting percentages for categorical variables, means and medians for continuous variables. To determine factors associated with pathological node negative (pN0) ALND, we implemented univariate and multivariable logistic regression models. All variables that were

significant at $p<0.1$ in univariate analysis were evaluated in the multivariate analysis and non-significant factors were dropped with stepwise backward regression. A two-sided p-value of <0.05 was considered significant throughout. A goodness of fit test was carried out on the final model to determine how well the model fits into the set of variables. All available data were used for each univariate analysis. In the multivariable analysis, patients with missing data for included variables were dropped from the model. Analysis was carried out using Stata version 14 (StataCorp Limited, Texas, United States of America).

Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand prior to the commencement of this study (MP150549).

3. RESULTS

A total number of 624 patients underwent axillary surgery at CMJAH and CHBAH breast units from March 2013 to March 2015. We excluded 119 patients according to our predefined criteria and identified 505 eligible patients for our study (Figure 1). The main reasons for exclusion were recurrent disease and absence of invasive cancer.

The mean age (±SD) was 53.6 (13.4) years. The majority of patients presented with clinical stage II (49.3%) and III (37.4%) disease. Most of the patients (480, 95.1%) were diagnosed with ductal carcinoma, 22 patients (4.4%) had lobular carcinoma and one patient (0.2%) had a mixed type. Two patients (0.4%) had no information on histological subtype. .The majority of patients (313, 61.9%) underwent primary surgery and 192 (38.1%) patients had surgery following neoadjuvant chemotherapy (Table 1).

Table 1: Demographic and clinicopathological characteristics

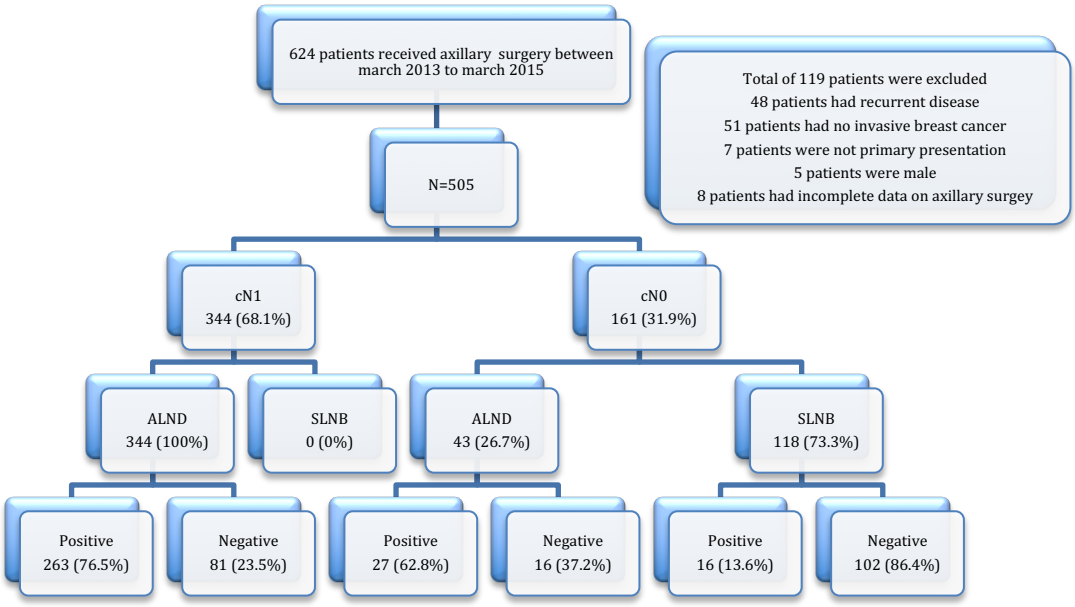
Factors		Total N=505 (%)
Age (mean± SD)		53.6 ±13.4
Age group		
	<40	71 (14.1%)
	40-49	139 (27.5%)
	50- 59	130 (25.7%)
	60-69	98 (19.4%)
	≥ 70	67 (13.3%)
Stage (%)		
	I	46 (9.1%)
	II	249 (49.3%)
	III	189 (37.4%)
	IV	21 (4.2%)
Staging groups		
	I & II	295 (58.4%)
	III & IV	210 (41.6%)
Histological subtype		
	Ductal	480 (95.0%)

	Lobular	22 (4.4%)
	Other	1 (0.2%)
	Missing	2 (0.4%)
Immunohistochemistry		
	Luminal A	87 (17.2%)
	Luminal B	303 (60%)
	HER-2 enriched	43 (8.5%)
	Triple negative	71 (14.1%)
	Missing	1 (0.2%)
Clinical nodal staging		
	cN0	161 (31.9%)
	cN+	344 (68.1%)
Pathological nodal staging		
	pN0	199
	pN+	306
Tumour size		
	Tx	3 (0.6%)
	T1	60 (11.9%)
	T2	253 (50.1%)
	T3	70 (13.9%)
	T4	119 (23.6)

Table 2: Comparison of clinical and pathological nodal staging

	cN1 (%)	cN0 (%)	Total (%)
pN1	263 (85.9)	43 (14.1)	306 (60.6)
pN0	81 (40.7)	118 (59.3)	199 (39.4)
Total	344 (68.1)	161b(31.9)	505

Figure 1: Flowchart of axillary surgery



On the basis of clinical examination and ultrasound 344 patients were staged cN1 (68.1%), 161 (31.9%) were assessed as clinically node negative (cN0) and were eligible for SLNB. A SLNB was performed in 118 out of these 161 cN0 patients (73.3%). A negative SLNB was found in 102 (86.4%) and a positive SLNB in 16 (13.6%) patients (Figure 1).

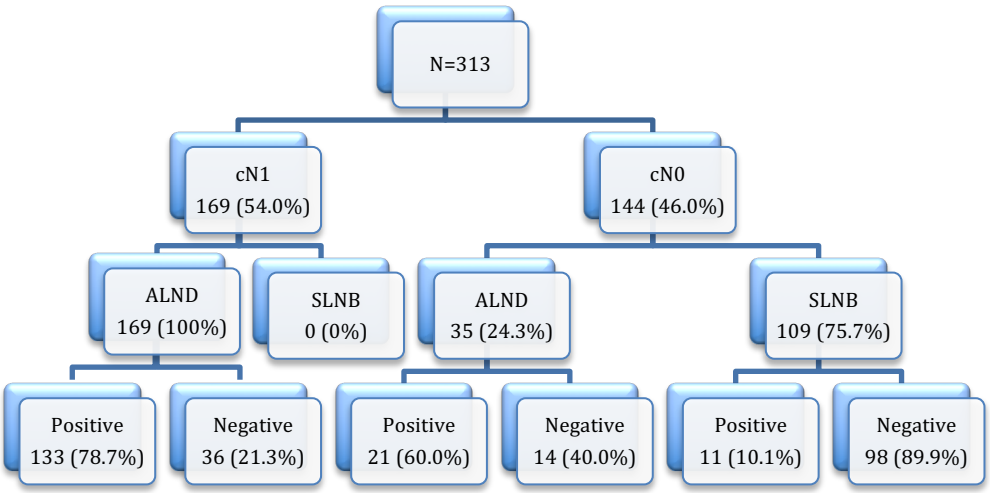
In the cN0 group, 43 patients (26.7%) underwent ALND, 27 (62.8%) had a positive ALND and 16 (37.2%) had a negative ALND. These patients underwent ALND for various reasons which include non-availability of tracer or gamma probe, “large” tumour size (> 4cm) and the surgeon’s clinical decision intra-operatively to proceed to an ALND.

In the cN1 group, 263 out of the 344 patients (76.4%) had a positive ALND and 81 (23.5%) a negative ALND.

Overall 306 patients were pN1 (60.6%) and 199 pN0 (39.4%). Overall 387 patients underwent ALND, with a total of 97 (25.1%) of patients having a pN0 ALND. Of the 97 patients, 81 (83.5%) patients were initially assessed as cN1. Of the 199 pN0 patients, 118 (59.3%) underwent SLNB correctly.

A total of 313 (62%) of 505 patients underwent primary surgery and 192 (38%) received NACT. After exclusion of patients who had NACT, 169 patients were staged as cN1 (54%) and 144 (46%) as cN0. (Figure 2) In the cN1 group undergoing primary surgery, 169 (100%) underwent ALND and 36 (21.3%) were found pN0. Overall 148 patients were pN0 and 98 (66.2%) underwent SLNB correctly.

Figure 2: Flowchart of women with invasive breast carcinoma who have primary surgery



The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of pre-op clinical assessment in predicting pathological status were 85.9%, 59.3%, 76.5% and 73.9%. In patients who had primary

surgery, the sensitivity, specificity, PPV and NPV were 80.6%, 73.9%, 78.7% and 76.1%. (Table 3)

Table 3: Validity of clinical staging and axillary surgery

	All patients N=505	Primary surgery alone (n=303)
Sensitivity	85.9 %	80.6%
Specificity	59.3%	73.9%
PPV	76.5%	78.7%
NPV	73.9%	76.1%

Of the 192 patients who received axillary surgery after NACT, 183 (95.3%) patients underwent ALND. A total number of 47 (25.7%) of these patients ultimately had a pN0 ALND. On univariate analysis, patients after NACT of whom only nine had a SLNB, were not statistically more likely to have a pN0 ALND compared to those patients who underwent primary surgery (OR 1.06, 95% CI: 0.7-1.7, p=0.790).

The factors associated with pN0 at p <0.1 on univariate analysis were: clinical nodal status and molecular subtype. These variables were further explored in the multivariate analysis controlling for the first treatment the patient had.

Only 40 (10.4%) out of all patients had a preoperative biopsy or FNA of the axilla. Patients without preoperative biopsy or FNA of the axilla were also not found more likely to have a pN0 ALND compared to patients who had pre-operative biopsy of the axilla, but numbers were small. (OR 1.71, 95% CI: 0.7-4.0, p=0.195). Triple–negative and HER-2 enriched patients were significantly more likely to have a pN0 ALND than those with luminal subtypes (OR 3.05, 95% CI: 1.6-5.7, p=0.001 and OR 2.25 , 95% CI: 1.1-4.8, p=0.035). cN0 was associated with an increased risk compared cN1 (OR 2.10, CI 95%: 1.0-4.3, p=0.039).

We get a Pearson's chi-squared goodness of fit value of 6.90 on 9 degree of freedom with a p-value of 0.6479, and thus no evidence of lack of fit.

Age, tumour size, histological type and pre-op biopsy of the axilla were not associated with pN0 ALND. (Table 4).

Table 4: Univariate and multivariate analysis of factors associated with a pN0 ALND

Characteristics		Univariate analysis OR (95%CI)	P value	Multivariate analysis OR (95%CI)	P value
Age		1.00 (0.99-1.02)	0.467		
Age group	<40	Reference	0.950		
	40-49	1.11 (0.5-2.4)			
	50-59	1.24 (0.6-2.7)			
	60-69	1.36 (0.6-3.0)			
	≥70	1.21 (0.5-3.0)			
T-stage	Tx	8.45 (0.7-97.5)	0.267		
	T1	1.63 (0.5-5.0)			
	T2	1.56 (0.9-2.7)			
	T3	1.61 (0.8-3.2)			
	T4	Reference			
Clinical nodal status	N0	1.92 (1.0-3.7)	**0.054**	2.10 (1.0-4.3)	**0.039**
	N1	Reference			
Clinical staging	I & II	1.40 (0.9-2.2)	0.151		
	IIII & IV	Reference			
Histological type	Ductal	Reference	0.908		
	Others	1.06 (0.4-3.0)			
Molecular subtype	Luminal A	1.02 (0.5-2.0)	**0.003**	1.07 (0.5-2.1)	0.849
	Luminal B	Reference		Reference	Reference
	HER2 enriched	2.05 (1.0-4.3)		2.25 (1.1-4.8)	**0.035**
	Triple negative	2.98 (1.6-5.5)		3.05 (1.6-5.7)	**0.001**
First Treatment	Surgery	Reference			
	Neoadjuvant chemotherapy	1.06 (0.7-1.7)	0.790	1.10 (0.6-1.7)	0.964
Pre-operative biopsy of the axilla	No	1.71 (0.7-4.0)	0.195		
	Yes	Reference			

multivariate model built with clinical nodal status, molecular subtype adjusting for first treatment.

3. DISCUSSION

Of the 505 patients included in our study, 386 (76.6%) underwent ALND and 119 (23.6%) underwent SLNB. A quarter of our patients (97, 25.1%) who underwent an ALND were ultimately node-negative on pathology. Node dissection has no oncological benefit in the node-negative patient and is associated with complications such as lymphoedema. Overtreatment of the axilla is regarded as obsolete in modern breast cancer surgery and European guidelines have set the benchmark standards on the proportion of invasive breast cancer patients with pN0 who did not undergo ALND at a minimum of 80% and the target at 90%. [13] These standards were not reached in our study cohort with only 66.2% of pN0 patients spared an ALND procedure in those that received primary surgery, and 59.3% of all pN0 patients spared overall.

The high sensitivity of preoperative assessments to determine clinical nodal status ultimately show that most of the true nodal positive axillae were operated on appropriately. Performing an ALND on cN0 patients for various reasons, as discussed below, can be justified as the majority of these cases (62.8%) were pN1 ALND's.

Various factors need to be considered.

Firstly, 81 of the 97 pN0 ALND patients were initially assessed as clinically node-positive (83.5%). Very few of our patients had pre-operative histopathological confirmation of nodal involvement and the clinical assessment in this cohort had a specificity of 59.3% and PPV of 76.5%. NACT may alter the nodal status but exclusion of patients who received NACT improved these values only to 73.9% and 78.7%. This highlights the limitations of our preoperative assessments. We were not able to demonstrate statistical association with a pN0 ALND outcome without preoperative attempted pathology confirmation but numbers were small and lacked statistical power. Negative predictive value of clinical assessment was equally limited at 73.9% and 76.1% after exclusion of patients who received NACT. Preoperative clinical assessment needs to be improved to allow for appropriate choice of surgical axillary approach. A future audit of axillary ultrasounds may assist to improve the accuracy of preoperative staging of the axilla in our practice.

Secondly, ALND was performed in 43 clinically node-negative patients for various reasons such as large tumour size, intraoperative impression of nodal involvement or non-availability of a gamma-probe or radio-colloid tracer. In more than a third of these above mentioned cases (68%); the intra-operative decision to perform an ALND was correct and in the seven patients where the decision was taken to proceed to an ALND intra-operatively, the axilla had nodal involvement in four patients (57%). Although 16 (37.2%) were pathologically node-negative these clinical decisions to proceed with ALND need to be viewed in the context of a resource-constrained environment. On the one hand, the majority (62.8%) were ultimately pN1 and a SLNB would have potentially required a second surgery to perform a completion ALND. On the other hand, SLNB should be offered in a well-resourced setting to patients with large breast cancers and the intraoperative impression of node involvement confirmed by intraoperative pathology before proceeding to ALND. Under our circumstances we need to find an appropriate balance to have both a cost effective and safe policy to manage the axilla in breast cancer.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Trials B-18 and B-27 demonstrated that NACT can downstage 30-40% of clinically node-positive patients with no residual disease found in the axilla at the time of surgery. [14] [15] The application of SLNB for initially node-positive patients after neoadjuvant chemotherapy has been evaluated in the ACOSOG Z1071 and SENTINA trials. [16] [17] A False negative rate (FNR) of under 10% can be achieved by using a dual-tracer technique and identifying at least three sentinel nodes. In a recent prospective study 68% of initially pathologically confirmed node-positive patients became candidates for SLNB after NACT and an ALND could be avoided in 48%.[18] Targeted axillary dissection, after placing clips into suspicious biopsy proven axillary nodes prior to chemotherapy has been shown to improve FNR of SLNB after NACT to 4.2%.[19] This opens up the possibility of avoiding ALND after NACT in a subset of our patients. During the study period, we did not yet apply this approach and the nine patients who underwent SLNB after NACT were initially cN0.

Complete pathologic response rates vary among intrinsic subtypes and are reportedly higher in hormone receptor negative tumours.[20] We demonstrated a significantly higher rate of pN0 ALND outcome in the triple-negative and HER-

2 enriched subtypes. This could indicate that our preoperative clinical staging is more accurate in the hormone receptor positive cancers as compared to HER-2 and triple-negative cancers, and this should be considered when revising preoperative clinical staging regimens.

47 of 183 patients in this study who received NACT and ALND had a pN0 axillary dissection (25.7%). It must be recognised that most patients did not have histological or cytological confirmation of axillary involvement before NACT, and therefore the pre-treatment assessment of the axilla was not in keeping with international standards. In addition, a pathologic complete response was found in only 11 cases out of the 192 patients who were operated following NACT; at 5.7% a rate considerably lower than what would be expected from the literature.

Clinical staging of this cohort is skewed towards lower stage compared to the stage at presentation of our general patient population. This is explained by the inclusion of patients who received axillary surgery in this study. Our units do not operate on stage 4 disease unless limited to bone metastases or visceral oligometastases responsive to NACT.

Limitations of this study include the fact that the HIV-status was not recorded in this study and it is likely to affect clinical assessment of lymph nodes. Benign lymphadenopathy is often clinically and sonographically misinterpreted as neoplastic spread. Other limitations of this study include the retrospective design, the often incomplete nature of clinical records and the relatively small number of patients.

3. CONCLUSION

More than a quarter (25.1%) of axillary node dissections were performed for pN0 disease in our study population. Pre-operative and intra-operative decision making for performing ALND's in cN0 patients is justified, particularly in patients with suspicious lymph nodes. Where few associated factors for pN0 ALND's were found in this study, triple-negative and HER-2 patients had a higher pN0 ALND's than hormone receptor -positive patients. Our pre-operative nodal

assessments should be revised to find an appropriate balance that is both cost effective and safe to manage the axilla in breast cancer.

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APPENDIX A – Approved research protocol

Axillary Lymph Node Dissection in Invasive Breast Cancer patients at CMJAH and CHBAH

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Protocol for MMed (Surg)

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List of abbreviations

ALND – Axillary Lymph Node Dissection
cN0 – Clinically node negative
cN1 – Clinically node positive
DCIS – Ductal carcinoma in situ
FNR – False negative rate
FNA – Fine needle aspiration
FPR – False positive rate
SLN – Sentinel Lymph Node
SLNB – Sentinel Lymph Node biopsy

Abstract

The assessment of axillary lymph nodes is a critical step in staging breast cancer. It predicts prognosis and guides treatment. Physical examination alone is notoriously inaccurate and suspected axillary involvement should be confirmed by FNA in cN1 disease or with a SLNB in cN0 axillae. FNA's are not routinely done in our resource constrained environment and all patients with CN1 disease on ultrasound and physical examination, undergo ALND. Due to the fact that ALND causes significant morbidity, the need for ALND has been questioned in patients with unproven axillary disease as well as patients with a complete pathological response after neoadjuvant chemotherapy.

A retrospective cohort study will be conducted at CMJAH and CHBAH breast units. Patient records, theatre records and histology results of all female patients that received axillary surgery during the period March 2013 to March 2015, will be reviewed and data collected in a datasheet.

Introduction/Background

The Axilla in Breast Cancer

The axilla receives most of the lymphatic drainage of the breast. Axillary lymph node involvement in breast cancer correlates with tumor size and location, lympho vascular invasion, histological grade, as well as patient age and method of detection (1-4).

Axillary lymph node involvement remains central to the staging of breast cancer and is considered the single most important prognostic factor in patients with invasive breast cancer (5,6). Beside the prognostic implications, it guides local, regional and systemic treatment (7).

Staging of the Axilla

Axillary lymph nodes may appear enlarged clinically and radiologically, which may be due to causes other than breast cancer. Other malignant causes of axillary lymphadenopathy include lymphoma, malignant melanoma and lung, gastric and ovarian carcinomas. Non-malignant causes include various bacterial and viral infections. Among these, HIV is probably the most important factor in our setting. Patients with HIV commonly have palpable lymph nodes and often have bilateral axillary lymphadenopathy on axillary imaging (8).

Several methods are available to evaluate and stage the axilla. These include non-invasive methods such as physical examination and imaging techniques including axillary ultrasound, Mammography, PET-CT and MRI. Clinical evaluation of the axilla by palpation is unfortunately highly inaccurate with an overall error rate of 41% and a false-positive rate (FPR) of 53%. Axillary ultrasound combined with needle biopsy has a sensitivity of 79.6 % and a specificity of 98.3%, PET-CT sensitivity and specificity 56% and 96%, respectively. MRI has a sensitivity of 88% and specificity 97.3% (9).

The gold standard of definitive evaluation therefore remains pathology. Historically, this was performed through an axillary lymph node dissection (ALND) for all breast cancer patients, regardless of their clinical nodal status

(10). Nowadays, the sentinel lymph node biopsy (SLNB) has been adopted as standard of care for clinically node-negative (cN0) patients and ALND in this patient group has become difficult to justify (11). In a contemporary approach, a preoperative ultrasound-guided fine needle aspiration (FNA) of a suspicious lymph node can secure staging in a clinically node-positive (cN1) patient and identify patients who may proceed directly to ALND rather than SLNB (12). In cases in which the cytopathology is negative or nondiagnostic, or in clinically node-negative (cN0) patients, SLNB should be performed for accurate assessment (5,9).

Axillary Lymph Node Dissection

The surgical management of the axilla in breast cancer patients has significantly changed since William Halsted performed the first radical mastectomy in the 19th century (13). ALND served to maximize survival, achieve regional control and establish the most accurate staging of the axilla (14). A contemporary standard ALND consists of removal of level I and II nodal tissue unless level III lymph nodes appear grossly involved (6,15).

ALND is, however, a potentially debilitating procedure with lymphoedema being the most common serious complication. Norman et al investigated factors associated with lymphoedema and found that 24.7% of all women diagnosed with breast cancer experienced mild lymphoedema with 13% reporting severe debilitating lymphoedema. ALND and anthracycline-based chemotherapy regimens were the two most important risk factors (16), others include the presence of positive nodes, the extent of dissection and radiation therapy (17). Further complications include seroma formation, chronic pain, injury or thrombosis of axillary vein, nerve injury and shoulder dysfunction (18).

The NSABP B-04 examined women with cN0 invasive breast cancer who were randomized to radical mastectomy (with ALND), simple mastectomy plus local nodal irradiation, or simple mastectomy with ALND delayed until positive lymph nodes developed; the trial found no difference in disease-free or overall survival rates (19), even on 25-year follow-up (20).

ALND remains the standard of care for node-positive patients but is nowadays

regarded as obsolete in the node-negative patient (11).

Sentinel Lymph Node Biopsy

SLNB was developed as an accurate method of staging in node-negative patients to minimize the anatomic disruption and morbidity of ALND. The concept is based on the orderly pattern of lymphatic drainage from the primary tumor of the breast to the regional lymph nodes. The sentinel lymph node (SLN) is identified as the first lymph node to which the breast and breast cancer will drain (21).

Multiple studies have validated the use of SLNB as a reliable tool in cN0 patients to obviate more extensive surgery (22). The NSABP B-32 evaluated whether SLNB can be compared with ALND in terms of survival and regional control with fewer side effects. They randomly assigned women with invasive breast cancer to SLNB and ALND or SLNB alone only followed by ALND if the SLNB was positive. There was no statistical difference between the two groups in terms of overall survival, disease-free survival and regional control. It was concluded that SLN surgery alone is safe and adequate in cN0 patients if the SLN is found to be negative (14).

Although major prospective studies attained false-negative rates (FNR) of 7% to 10% for SLNB, axillary recurrence occurs in less than 1% of patients with no metastases in the sentinel node (23,24). This questions the clinical relevance of low-volume residual disease in the axilla.

SLNB is accepted as standard of care for cN0 early breast cancer and the indication has been extended to larger (non-inflammatory) tumors, multicentric tumors, prior breast or axillary surgery and patients with ductal carcinoma in situ (DCIS) planned for mastectomy (11).

Broadening Application of SLNB to Avoid ALND

Traditionally, breast cancer patients with a positive SLNB were offered completion ALND (9). A positive SLNB with tumor size >2cm, more than one positive SLN, lymph node metastasis of ≥2mm, lymph vascular invasion, extra

capsular extension and the ratio of involved SLN to uninvolved lymph nodes predicts the presence of non-sentinel lymph node metastasis (25,26). However, in over 50% of patients the SLN is the only involved node (27,28).

Two recent trials, including the ACOSOG Z0011 trail, questioned the need for ALND in patients with a positive SLNB and randomized patients to SLNB alone and SLNB with completion ALND. Follow up revealed no difference in local or regional recurrence between the two groups in patients with micro metastases or less than three involved sentinel nodes. It was concluded that SLNB alone in selected patients with early breast cancer undergoing breast conserving therapy with radiation might be an appropriate method of treatment (29,30). Carette-Weyer et al evaluated the impact of the ACOSOG Z0011 trial results on clinical practice. They found that widespread implementation of the trial could spare 38% of patients an ALND (31).

Another evolving area is the use of SLNB following neoadjuvant chemotherapy. Patients who are cN1 at initial presentation may be downstaged to cN0 in 20-40% (32,33). Chemotherapy may influence the accuracy of the procedure and limited data is available. The ACOSOG Z1071 trail found a FNR of 12.6% in patients who had neoadjuvant chemotherapy followed by SLNB and a completion ALND dissection (34). In the SENTINA trial, the FNR was 14.2% for patients who were initially cN1 and converted to a cN0 status after chemotherapy, but was less than 10% when 3 or more nodes were removed (7). Both trials indicated that double tracer technique and removing at least three lymph nodes decreased the FNR. Although not standard of care, the trials suggest a possibility for SLNB as axilla-conserving surgery in this subgroup of patients.

Summary And Why Do The Study?

Axillary surgery has evolved from a radical approach to increasingly axilla-conserving surgery with expanding application of SLNB. ALND carries high morbidity and is considered obsolete in clinically node-negative patients.

cN1 disease should be proven by FNA. Due to resource constraints this has not been implemented in our units to date and patients deemed node-positive on physical examination and axillary ultrasound all undergo ALND.
Furthermore, the effect of neoadjuvant chemotherapy with potentially complete clinical and pathological response in the axillary nodes may offer an opportunity for axilla-sparing surgery. This has also not been evaluated and initially node-positive patients all undergo an ALND in our setting.

2. Study Objectives

Primary objective is to evaluate the prevalence of node-negative ALND in our units. Secondary objective is to evaluate the likelihood of node-negative dissection both after the administration of neoadjuvant chemotherapy and where the axilla is found to have clinically node-positive disease without histological confirmation.
Results may influence future clinical approaches and research projects.

3. Methods

3.1 Study Design

Retrospective cohort study

3.2 Site of study

CMJAH breast unit and CHBAH breast unit

3.3 Study population

All female primary invasive breast cancer patients that underwent axillary surgery at CMJAH or CHBAH breast units

3.4 Sampling

Subjects will be recruited via theatre records at CMJAH and via the existing database at CHBAH.
Time period of review will be March 2013-March 2015 (2 years). Estimated sample size is N= 500.

Inclusion criteria:

Women above the age of 18

Histologically proven invasive breast cancer

Breast cancer as primary presentation

Axillary surgery performed

Exclusion criteria:

Recurrent disease

3.5 Study groups and

Patients undergoing ALND will be differentiated in the following groups

- Patients undergoing ALND as part of primary surgery
- Patients undergoing ALND after neoadjuvant chemotherapy
- Patients undergoing ALND with histological or cytological confirmation of axillary lymphnode metastasis prior to surgery
- Patients undergoing ALND without histological or cytological confirmation of axillary lymphnode metastasis prior to surgery

3.6 Measuring tool

Histology records and patient records of eligible patients will be reviewed. Patient records will be accessed via the electronic database at CHBAH and via breast clinic files at CMJAH.

3.7 Data collection

2 Data sheets will be used to collect data. Data sheet 1 (Appendix A), will contain identifiable data coded with a study number. This will be kept confidential. Data sheets will be used to record data for each study number in Excel. Extracted data is attached in appendix B. All data collected will be used for demographics.

3.8 Sources of bias:

Incomplete outcome data may be a source of bias. This will be avoided by thorough review of patient records and accessing further sources of records

beyond the breast database and breast clinic files such as the oncology files or hospital admission records or mammography records.

4. Data Analysis

Data analysis will be performed with Statistica.

Prevalence of node-negative ALND in overall ALND will be calculated.

Clinical assessment without histological confirmation of node-positive disease and neoadjuvant chemotherapy will be assessed as risk factors for node-negative ALND. Risk will be assessed by calculation of odds ratios (OR) for node-negative dissection in the presence of these two risk factors. Confidence interval (CI) for the odds ratios will be 95%. Significance will be tested by Fisher's exact test and chi-squared test.

5. Benefit

Results of the study will indicate how commonly we perform inappropriate ALND for node-negative disease and the relevance of risk factors. This may change future clinical approach in our units and guide future research opportunities.

6. Ethics

Clearance to proceed with the retrospective study will be obtained from the ethics committee of the University of the Witwatersrand.

7. Time line

	Jan	Feb	Mar	April	May	June	Jul	Aug	Sept	Oct	Nov	Dec
Literature review	x	x										
Preparing protocol			x	x								

Protocol assessment					x							
Ethics application					x							
Collecting data						x	x	x				
Data analysis									x	x		
Writing up - thesis											x	x
Writing up - paper											x	x

8. Cost

No major expenses are anticipated. The candidate will cover minor expenses such as photocopying and travel.

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Appendix A

Identifiable Data sheet 1:

Study nr	Patient name	Hospital number
1		
2		
3		
4		
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14		

Appendix B

Data collection sheet 2:

- Site
    - CMJAH
    - CHBAH
- Patient information
    - Study nr
    - Age
- Stage at primary presentation
    - T
    - N
    - M
- Histology preoperative
    - Histological type
        - Ductal
        - Lobular
        - Other
    - Immunohistochemistry
        - ER
        - PR
        - HER2
        - Ki67
- Preoperative histological confirmation of axillary metastases
    - None

    - FNA/Core biopsy
    - SLNB
- Type of axillary surgery
    - SLNB
    - ALND
    - Completion ALND after SLNB
- Timing of Surgery
    - Primary Surgery
    - Post neoadjuvant chemotherapy
- Histology postoperative
    - SLNB
        - Nr of SLN removed
        - Nr of positive SLN
    - ALND
        - Nr of LN removed
        - Nr of LN involved
    - Completion ALND
        - Nr of LN removed
        - Nr of LN involved

APPENDIX B – Protocol assessment form

Faculty of Health Sciences, Postgraduate Office
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Cnr York & Princess of Wales Terrace, Parktown 2193
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ASSESSOR GROUP COMMENT FORM

Student Full name(s) &Surname	**Carolette GROENEWALD**		
Student Number	1032909		
Degree	MMed Surgery	Department	Department of Surgery
Title *Axillary lymphnode dissection in Invasive Breast Cancer patients at CMJAH and CHBAH*			

Date of Assessor Group Meeting: 10th June 2015 School / Department / Division: SURGERY

Yes ✓ | No | Is the research question clearly identified and described?

Comments:

Yes | No | Not entirely ✓

Is the design of the study and methods used appropriate for the research question being asked?

Comments:

*The diagnosis must be specified into ultrasound and clinical examination
*Describe clearly the study groups to be investigated
*The study design must be reported as a retrospective cohort instead of case-control

Is the study feasible within: _____

i. the applicant's resources? [Yes ✓] [No]

ii. the departments resources? [Yes ✓] [No]

iii. the time frame? [Yes ✓] [No]

Do you recommend:

i. shortening / lengthening of the protocol? Please specify and explain.

_____

_____

_____

[Yes] [No ✓]

ii. the appointment of a co-supervisor?

Nominee/s : _____

_____

Overall recommendation regarding the protocol :

i. revision of the protocol to the Supervisor (if HOD approval is also required, please specify): [Yes ✓] [No]
(**Candidates**: One copy, list of corrections with page numbers, supervisor approval letter – submit to PG Office)

ii. revision of the protocol to the satisfaction of the Assessor Group: [Yes] [No ✓]
(**Candidates**: One copy, list of corrections with page number, supervisor approval letter – submit to PG Office)
(PG Office to forward to the Assessor Group Chair)

iii. revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: [Yes] [No ✓]
(**Candidates**: six copies, list of corrections with page numbers, supervisor approval Letter - submit one copy to PG Office / 5 to school assessor group administrator/ for PhD all six copies to be submitted to the PG Office)

iv. candidate goes ahead: [Yes ✓] [No]

Student: Carolette **GROENEWALD**

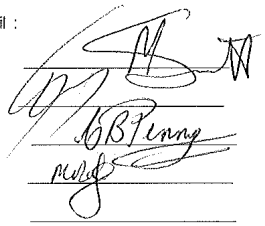
Assessor Names, and Signatures Email :

_PROF M SMITH_____

_DR D SURRIDGE_____

_DR C PENNY_____

_DR M NEL_____





Assessor Group Chair

10th June 2015

Date

Student: Carolette **GROENEWALD**

Appendix C - Ethics approval

R14/49 Dr. Carolette Groenewald

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150549

NAME: (Principal Investigator)	Dr. Carolette Groenewald
DEPARTMENT:	Surgery Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Axillary Lymphnode Dissection in Invasive Breast Cancer Patients at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	29/05/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr. Sarah Nietz
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/10/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D – Supervisor Declaration

28 March 2017

Attention: Faculty of Health Sciences, University of Witwatersrand

Re: Axillary lymph node dissection in invasive breast cancer patients at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital

This letter serves to certify that Carolette Groenewald is the primary author of the above-entitled research. It has been submitted to the South African Journal of Science.

It is sufficient for consideration as a published paper towards the research component of his Mmed degree at the University of Witwatersrand.

Her contribution to the research was as follows:

- Protocol write-up, submission and presentation at the Faculty of Health Sciences
- Ethics application
- Collection of data, entry into relevant processing programs and data analysis
- Research write-up
- Formatting for submission to the journal
- Communication with the journal editor and refining review points

As supervisors of the research project, we reviewed the research at regular intervals, made changes to improve the write-up and verified the data analysis.

We agree that the research was the work of Carolette Groenewald, assisted and refined by us.

……
SL Nietz
sarah.nietz@gmx.de

……
H Cubasch
hcubasch@worldonline.co.za

……
A Mannell
mannell@mweb.co.za

APPENDIX E - Identifiable data sheet 1

Identifiable Data sheet 1:

Study nr	Patient name	Hospital number
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		

APPENDIX F – Data collection sheet 2

Data collection sheet 2:

- Site
    - CMJAH
    - CHBAH
- Patient information
    - Study nr
    - Age
- Stage at primary presentation
    - T
    - N
    - M
- Histology preoperative
    - Histological type
        - Ductal
        - Lobular
        - Other
    - Immunohistochemistry
        - ER
        - PR
        - HER2
        - Ki67
- Preoperative histological confirmation of axillary metastases
    - None
    - FNA/Core biopsy

    - SLNB
- Type of axillary surgery
    - SLNB
    - ALND
    - Completion ALND after SLNB
- Timing of Surgery
    - Primary Surgery
    - Post neoadjuvant chemotherapy
- Histology postoperative
    - SLNB
        - Nr of SLN removed
        - Nr of positive SLN
    - ALND
        - Nr of LN removed
        - Nr of LN involved
    - Completion ALND
        - Nr of LN removed
        - Nr of LN involved

APPENDIX G – SAJS GUIDELINES TO AUTHORS

South African Journal of Surgery Author Guidelines

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to:
(i) conception, design, analysis and interpretation of data;
(ii) drafting or critical revision for important intellectual content; and
(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to surgery. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Obituaries should be about 400 words and may be accompanied by a photograph.
MANUSCRIPT PREPARATION Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.
Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.
Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.
Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...
Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).
ILLUSTRATIONS AND TABLES If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.
Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.
REFERENCES Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the

text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**.
Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]
Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.
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2 The submission has not been previously published, nor is it before

another journal for consideration.
3 The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4 The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5 Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
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8 An abstract has been included where applicable.
9 The research was approved by a Research Ethics Committee (if applicable)
10 Any conflict of interest (or competing interests) is indicated by the author(s).

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