The incidence of pathological findings in contralateral reduction mammoplasty specimens in patients with breast cancer

Dr Alexander Diakakis
FC Plast Surg (SA)
0700945T

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of **Master of Medicine in Plastic Surgery**

Supervisors:

Dr C Sofianos FC Plast Surg (SA), MMed (Wits), FRCS Plast

Dr NH Mabe FCS (SA), BSc (MEDUNSA)

Dr C Nel FC Path (Anat Path), MMed (UP)

Dr S Phiri FC Plast Surg (SA)

6 November 2023
Johannesburg, South Africa

Declaration

I, Dr Alexander Diakakis, declare that this Research Report is my own work. It is being submitted for the Degree of MMed in Plastic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Sign: 

Date: 12/09/2023.

Dedication

This project is dedicated to the patients attending the Surgical Breast Unit at the Charlotte Maxeke Johannesburg Academic Hospital.

Acknowledgements

I would like to acknowledge the following people:

1. **Dr Chrysis Sofianos**, for his dedicated supervision and guidance on this project.

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3. **Dr Carolina Nel,** for her supervision and anatomical pathological insight.

4. **Dr Sibusiso Phiri**, for his supervision.

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List of Abbreviations

CMJAH	-	Charlotte Maxeke Johannesburg Academic Hospital
DCIS	-	Ductal carcinoma in situ
ER	-	Oestrogen Receptor
HER2	-	Human Epidermal Growth Factor Receptor 2
HREC	-	Humal Research Ethics Committee
IQR	-	Interquartile ranges
LCIS	-	Lobular carcinoma in situ
MRI	-	Magnetic resonance imaging
NHLS	-	National Health Services Laboratory
PR	-	Progesterone Receptor
SD	-	Standard deviation

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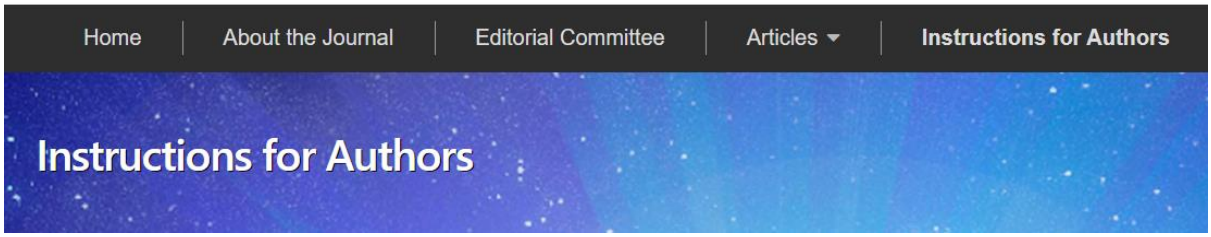
Submission Guidelines

Intended Journal for submission: Journal of Plastic and Reconstructive Surgery (JPRS)

JPRS Journal of Plastic and Reconstructive Surgery



Aims and Scope

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Book chapter
2. Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; 2006. Chapter 24, Regression and correlation methods; p. 447-86.

Entire book
3. Eyre HJ, Lange DP, Morris LB. Informed decisions: the complete book of cancer diagnosis, treatment, and recovery. 2nd ed. Atlanta: American Cancer Society; 2002. 768 p.

Software
4. Nelson KN. Comprehensive body composition software [disk]. Release 1.0 for DOS. Champaign (IL): Human Kinetics, 1997. 1 computer disk: color, 3 1/2 in.

Online journals
5. Terauchi Y, Takamoto I, Kubota N, et al. Glucokinase and IRS-2 are required for compensatory beta cell hyperplasia in response to high-fat diet-induced insulin resistance. J Clin Invest [Internet]. 2007 Jan 2 [cited 2007 Jan 5];117(1):246-57. Available from: http://www.jci.org/cgi/content/full/117/1/246

Database
6. MeSH Database [Internet]. Bethesda (MD): National Library of Medicine (US). 2003 Apr - [cited 2011 Jul 8]. Available from: http://www.ncbi.nlm.nih.gov/mesh

Journal article in a language other than English

7-1. *in a roman alphabet*
Berrino F, Gatta G, Crosignani P. [Case-control evaluation of screening efficacy]. Epidemiol Prev. 2004 Nov-Dec;28(6):354-9. Italian.

7-2. *in a non-roman alphabet*
Zhao L, Li H, Han D. [Effects of intestinal endotoxemia on the development of cirrhosis in rats]. ZhonghuaGanZang Bing ZaZhi. 2001 Jul;9 Suppl:21-3. Chinese.

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Abstract

Objectives

Occult invasive contralateral breast carcinoma negatively affects survival in breast cancer patients. The objective of this study is to measure the incidence of abnormal pathological specimens in reduction mammoplasty specimens in patients known to have contralateral breast cancer in a specialist breast unit in South Africa and to interpret the pathological findings and stratify them according to cancer stage and immunohistochemistry.

Methods

A retrospective record review of the pathological findings in the contralateral breast of patients known with breast cancer who underwent either oncoplastic bilateral breast reduction or unilateral mastectomy and contralateral reduction between January 2017 and December 2022. Data was obtained from the breast cancer database used at our institution (OncoDB) and histology reports were obtained from the National Health Laboratory Services. The association between cancer stage, axillary findings and immunohistochemistry when compared to contralateral histology findings was done using the Chi-squared test.

Results

A total of 112 patients were included with a mean (SD) age of 50.6 (10.8). Within the cohort of patients, 69 underwent mastectomy and contralateral reduction and 43 patients had bilateral oncoplastic breast reductions performed. 91 (81.3%) were

found to have no pathology, 12 (10.7%) had benign lesions, 8 (7.1%) were found to have proliferative lesions and 1 patient (0.8%) had a lobular carcinoma in situ (LCIS).

Conclusion

There was an increased prevalence of contralateral breast pathology in ER positive patients and as cancer stage increased, however these findings were not statistically significant. Findings were similar with regards to PR, HER2 and nodal status.

Word count: 249

Key words: Breast cancer, reduction mammoplasty, occult malignancy, pathology

Research Report

Introduction

Breast cancer is the most commonly diagnosed malignancy in the world, and the leading cause of cancer death among women worldwide. (1) Women who are diagnosed with breast cancer are at increased risk of developing breast cancer in the contralateral breast, with those patients with more than two children and a positive family history of breast cancer, being particularly high risk. (2,3) The majority of contralateral neoplasms are synchronous in nature and are diagnosed in approximately 1-2.6% of patients, and these have been shown to negatively affect survival when compared to those patients who develop metachronous lesions, with a 10% decrease in five-year survival rates.(3)(4)(5)(6) Of note however, in the study by Quan et al, the synchronous cancer group's mean cancer stage at index presentation was higher than that of the metachronous cancer group and this may have had an effect on 10 year survival outcomes.(6) The risk of metachronous contralateral breast cancer is 0.5-1.5% per year for the remainder of the patient's life. (4) Although rarely diagnosed during the treatment of breast cancer, autopsy and contralateral mastectomy studies in the past have shown much higher rates of synchronous contralateral neoplasms than those quoted above. (5)

The work-up for a patient either presenting with or suspected of having breast cancer most commonly consists of clinical assessment, mammography, and tissue biopsy. Mammography is used either as part of the work-up for patients who present with a breast mass, or as a screening tool to detect breast cancer before it becomes clinically apparent. Screening mammography has resulted in a 40% reduction in breast cancer associated mortality since its introduction in the United States of

America and is used all around the world as the standard screening tool in breast cancer management. (7) Screening mammography is considered extremely accurate, with a 90-92% sensitivity. However, overdiagnosis of breast cancer is an important concept to consider. (8) Although difficult to quantify, the Malmo trial suggested a 10% overdiagnosis rate, leading to women undergoing complex and often multimodal treatments that may have been unnecessary. (9) Not only is mammography used to diagnose or identify breast cancer, but it can also be used to guide surgical management, or may indicate a need for further imaging. Most centres therefore rely heavily on mammography for the identification of breast cancer in both the diseased and contralateral breast in order to rule out synchronous breast pathology.

In a study focusing on synchronous breast cancer by Hungness, the method of detection of the contralateral cancer was found to be mammography in 54% and palpation in 24% of patients. Of note, occult synchronous breast cancer was diagnosed in 16% of these patients during prophylactic mastectomy, mirror image biopsies and reduction mammoplasty for symmetry. (5)

Reduction mammoplasty is typically performed in the treatment of symptomatic macromastia or during the treatment of breast cancer. (10) Contralateral reduction mammoplasty is a procedure performed by plastic surgeons in patients with macromastia, to reduce asymmetry in patients who undergo unilateral mastectomy, as part of oncoplastic bilateral breast reduction or to improve the symmetry and overall aesthetic results of either immediate or delayed total breast reconstructions. These bilateral breast procedures in patients with bilateral breast cancers have

advantages other than just aesthetic symmetry. It has been shown that oncoplastic reduction versus wide local excision in patients with large breasts improves radiation dose homogeneity in the affected breast and reduces potential side effects including radiation fibrosis, chronic pain and poor cosmesis. (11,12) There is also evidence to show that oncoplastic breast reductions are associated with lower recurrence rates due to the fact that larger amounts of tissue may be excised safely without jeopardising the cosmetic outcome which may occur in lumpectomies alone. (13) In patients with large breasts, unilateral mastectomy can lead to significant and uncomfortable asymmetry and this asymmetry can lead to long term spinal deformity.(12,14)

Due to improved screening programs and treatment protocols, life expectancy has increased significantly and therefore quality of life is becoming more important in the breast cancer survivor. (15) Therefore, performing a contralateral reduction in patients with macromastia who are undergoing unilateral mastectomy can improve quality of life by preventing these sequelae and improve cosmetic outcomes as was shown by Hernanz et al. (16) It is also important to note that immediate breast reconstruction is 62% cheaper than delayed, two-stage approaches. (15)

The identification of occult neoplasms in the reduction specimen of the unaffected breast has important implications for these patients as it often necessitates completion mastectomy, a possible delay to or adjustment of adjuvant therapies or differing surveillance protocols. (17) Importantly, re-resection or completion mastectomy rates in patients in whom occult invasive cancer is identified should be

close to 100%, as treatment of this newly identified neoplasm is essential to avoid any negative impact it may have on survival.

The rate of incidental abnormal findings in reduction mammoplasty specimens vary greatly in the literature. This heterogeneity can be explained by what authors categorise as pathological in different centres, as well as different sectioning protocols and sampling methods. Looking only at precancerous findings, Clark et al found 52.7% of patients undergoing reduction mammoplasty had benign pathological findings, 4.4% had hyperplasia and 1.8% had carcinoma in situ. (2) It is important to note that the findings of benign pathology on breast specimens is not inconsequential. The American College of Pathologists divide benign pathology into risk categories, namely, no increased risk, slightly increased risk, moderately increased risk, and markedly increased risk lesions. These categories correlate with zero increased risk, 1.5-2 times the risk, 4-5 times the risk and 8-10 times the risk of developing cancer. (18) With this in mind, Clark's study can be interpreted as indicating that 13% of patients have twice the normal risk, 6.2% of patients have five times the risk and 1.8% of patients had a ten times increased risk of developing breast cancer in the contralateral breast based on benign pathological findings alone. (2)

In the largest study to date evaluating pathological findings in elective reduction mammoplasty, Pitanguy et al found that 80.8% of patients had fibrocystic and fibrofatty changes, 3.7% had benign tumours and 0.5% had invasive malignancies found at pathological section. Interestingly, as screening methodologies became more sophisticated during the study period, the identification of occult malignancy

post operatively did not decrease. (19) Sofianos et al performed a similar study in the South African population. All patients were screened via clinical examination and imaging and were deemed cancer-free. In their study, 49% of patients had benign pathology and 2% were found to have occult malignancies. (20) Similarly, Colwell et al found an incidence of occult invasive malignancy in 0.8% of cases, however, they found a significantly higher rate of occult malignancy in those patients undergoing unilateral reduction during the treatment of breast cancer. They also stated that macromastia is an independent risk factor for breast cancer due to an increased volume of breast parenchyma. (21) It has also been shown that the detection of breast cancer can be more challenging in large breasts, and that breast cancer may be seen at younger ages in patients with macromastia. (17)(22)

Colwell's findings are supported by further studies with occult invasive carcinoma being identified in 1.5%-4.6% of patients' contralateral breast reduction during their cancer treatment. (23)(24) These findings were confirmed by a meta-analysis and systematic review by Fitzpatrick et al who found that occult breast cancer was detected in 3.4% of breast reduction specimens in patients with breast cancer, as compared to 0.6% in the normal population. (17)

The literature therefore suggests that the incidence of occult pathology in the reduction specimen of patients undergoing reduction mammoplasty during the treatment of breast cancer is higher than in patients undergoing elective breast reduction. The identification of this pathology may indicate increased risk of, or the presence of, invasive malignancy which has significant impact on the treatment of these patients, and their overall survival. These findings indicate that protocols may

need to be revised with regards to screening methods, counselling and histopathological assessment guidelines when dealing with this specific population group. Although studies have been performed to assess the incidence and outcomes of this entity, no such study has been performed in a South African context. This study will aim to show the incidence of such pathology in our patient group and may help to improve unit protocols and therefore influence treatment outcome.

Methods

A retrospective record review of the pathological findings in the contralateral breast of patients known with breast cancer who underwent either oncoplastic bilateral breast reduction or unilateral mastectomy and contralateral reduction.

This was a single centre study undertaken in the Surgical Breast unit at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a quaternary university hospital in Gauteng, South Africa.

Permission to conduct this research was obtained from University of the Witwatersrand Human Research Ethics committee (HREC) with certificate number M220940 and permission was granted by the CMJAH hospital executive and National Health Services Laboratory (NHLS) to use their records. This was performed according to the declaration of Helsinki.

All patients who underwent contralateral reduction mammoplasty during the treatment of their breast cancer in the six-year period between January 2017 and

December 2022 were included. Patients were identified using theatre records and those patients with previously diagnosed bilateral disease, incomplete records or whose initial surgeries were performed at other hospitals were excluded. Pathological assessments were performed by NHLS pathologists according to standard sectioning protocols.

Data was obtained from the breast cancer database used at our institution (OncoDB) and included age, race, stage of contralateral cancer, procedure performed on the cancerous breast, cancer characteristics and what preoperative imaging had been performed. Histology reports were accessed via the NHLS-Labtrak website (https://trakcarelabwebview.nhls.ac.za/) and pathological findings in the reduction mammoplasty specimens were recorded.

Data was captured using Microsoft Excel spreadsheets (Microsoft Excel, Microsoft 365, Microsoft Corporation, Redmond). The association between cancer stage, axillary findings and immunohistochemistry when compared to histology findings was done using the Chi-squared test. Fisher's exact test was used where the data did not meet the assumptions of the Chi-squared test. Data analysis was carried out using SAS version 9.4 for Windows (SAS institute Incorporated, Cary, North Carolina). A 5% significance level was used.

Results

A total of 124 patients underwent contralateral reduction mammoplasty during the treatment of their breast cancer during the study period. 12 patients were excluded, largely due to incomplete records, leaving 112 patients to be assessed. All 112 patients were female with a mean (SD) age of 50.6 (10.8). All patients had undergone preoperative screening of the contralateral breast via either mammogram (98%) or magnetic resonance imaging (MRI) (2%) and were deemed to be cancer-free in the contralateral breast. Within the cohort of patients, 69 underwent mastectomy and contralateral reduction and 43 patients had bilateral oncoplastic breast reductions performed. Neoadjuvant chemotherapy was given to 60 (54%) of the patients, and the percentage of patients who received neoadjuvant chemotherapy was similar when comparing those patients with contralateral breast pathology and those without.

Characteristics of cancers in the known cancer breast with regards to type of cancer, cancer stage, receptor status and axillary findings can be found in in Table 1. The majority of patients had ductal carcinoma (92.2%) and had stage II (39%) or stage III disease (43%) according to the American Joint Committee on Cancer staging system. We noted a higher-than-normal proportion of metaplastic carcinoma (5.4%) in our study group, however prevalence of mucinous and micropapillary types were in keeping with expected values. (25) On immunohistochemical testing, 70% of patients were Oestrogen receptor (ER) positive, 50% were Progesterone receptor (PR) positive and only 20% were Human Epidermal Growth Factor Receptor 2 (HER2) positive. According to molecular subtypes, 29% were Luminal A, 44% were luminal B, 6.3% were HER2 enriched and 24% of cancers were triple negative.

Table 1 – Characteristics of cancer findings amongst patients undergoing contralateral reduction mammoplasty during the treatment of their breast cancer.

		Number	Percentage
Cancer Stage	**I**	17	15,2
	II	44	39,3
	III	48	42,9
	IV	1	0,9
	In situ	2	1,8
Cancer type	**Ductal carcinoma in situ**	2	1,8
	Ductal	101	90.2
	Mucinous	3	2.6
	Metaplastic	5	4.5
	Micropapillary	1	0.9
Oestrogen receptor status	**Negative**	34	30.4
	Positive	76	67.9
	N/A	2	1.8
Progesterone receptor status	**Negative**	54	48.2
	Positive	56	50
	N/A	2	1.8
Human epidermal growth factor receptor 2 status	**Negative**	88	78.6
	Positive	22	19.6
	N/A	2	1.8
Molecular subtypes	**Luminal A**	33	29.5
	Luminal B	44	39.3
	HER 2 enriched	7	6.3
	Triple negative	27	24.1
	N/A	2	1.8
Axillary lymph node status	**Negative**	44	39.2
	Positive	66	58.9
	N/A	2	1.8

Pathological findings in the contralateral specimens were then recorded and these were categorized into four groups: no pathology, benign lesions, proliferative lesions, and malignant lesions. A total of 91 (81.3%) patients were found to have no pathology, 12 patients (10.7%) had benign lesions, 8 patients (7.1%) were found to have proliferative lesions and 1 patient (0.8%) had a lobular carcinoma in situ (LCIS). The patient with LCIS was 57 years old with stage I ductal carcinoma of the left breast who underwent an oncoplastic breast reduction. She was ER and PR positive, HER2 negative and had positive axillary lymph adenopathy. She is currently being followed up closely in the unit with no current evidence of recurrence.

The correlation between these pathological findings and cancer stage, receptor status and axillary findings can be found in Table 2. A Chi-squared test was performed to assess any correlation between pathological findings in the contralateral breast and these cancer characteristics however no statistically significant findings were found, likely due to the small sample size. Of note, the two patients with no receptor status or axillary lymph node status results both had ductal carcinoma in situ (DCIS) in the cancerous breast, and both of these patients had no pathological findings in their contralateral reduction specimens.

Table 2 – Correlation between pathological findings and cancer stage, immunohistochemistry, and axillary lymph node status.

			No Pathology		Benign		Proliferative		Pre-Malignant		P value
		Number	No	%	No	%	No	%	No	%	
Cancer Stage	**I**	17	15	16.7	1	8.3	1	16.7	1	100	0.92
	II	44	35	38.9	6	50.0	2	33.3	0	0	
	III	48	40	44.4	5	41.7	3	50.0	0	0	
	IV	1	0	0	0	0	0	0	0	0	
	In situ	2	0	0	0	0	0	0	0	0	
Oestrogen receptor status	**N**	34	29	32.8	2	16.7	2	33.3	0	0	0.58
	P	76	60	66.2	10	83.3	4	66.7	1	100	
	N/A	2	2	1.6							
Progesterone receptor status	**N**	54	45	49.7	5	41.7	3	50,0	0	0	0.92
	P	56	44	48.7	7	58.3	3	50.0	1	100	
	N/A	2	2	1.6							
HER2 status	**N**	88	73	80.5	9	75.0	4	66.7	1	100	0.49
	P	22	16	17.9	3	25.0	2	33.3	0	0	
	N/A	2	2	1.6							
Axillary lymph node status	**N**	44	36	40.3	4	33.3	3	42.8	1	100	0.80
	P	66	52	58.1	8	66.7	4	57.2	0	0	
	N/A	2	2	1.6							

Discussion

Contralateral reduction mammoplasty performed in combination with either unilateral mastectomy or as part of an oncoplastic breast reduction serves to improve cosmetic outcome, quality of life and reduce musculoskeletal sequalae of unilateral

mastectomy in patients with macromastia. All patients with breast cancer have screening performed on both breasts to rule out synchronous contralateral breast cancer, however the presence of occult malignancy in the contralateral breast despite routine screening methodologies is a well-documented occurrence. These occult malignancies can affect treatment plans, require further surgery, alter follow-up planning, and can potentially lead to decreased overall survival.

In this study, we examined the pathological findings within contralateral breast reduction specimens in patients known with unilateral breast cancer. Of these patients, 62% underwent bilateral oncoplastic breast reductions and the remaining 38% underwent a unilateral mastectomy and contralateral reduction. Although there is scant literature available on the topic, unilateral mastectomy and contralateral reduction has become commonplace in our unit for a few reasons. Firstly, the CMJAH Breast unit services approximately 4000 patients per year and only has access to two theatre lists a week. With this in mind, there is insufficient time to perform immediate bilateral breast reconstructions routinely and therefore the contralateral reduction can be performed simultaneously during the mastectomy without having a significant impact on theatre time. Secondly, macromastia is prevalent in the South African population, and chronic back pain and spinal deformity are well described sequalae of unilateral mastectomy, especially in patients with macromastia. (14) In performing the contralateral reduction, not only do we reduce the weight discrepancy of the chest wall thereby decreasing musculoskeletal sequalae, but we make it easier for patients to match an external prosthesis to the now smaller remaining breast.

Of the 112 patients' specimens examined, 81.3% had no pathology identified on sectioning. 10.7% of patients were identified as having benign lesions, the majority of these being fibrocystic change. Proliferative lesions such as fibroadenoma, sclerosing adenosis and radial scar were identified in 7.1% of patients and one patient (0.9%) was identified as having a LCIS. No patients in the study group were found to have occult invasive malignancies in the contralateral breast reduction specimens.

In keeping with the American College of Pathologists risk stratification, our findings can be interpreted as: 7.1% of our patients had twice the risk of developing breast cancer in the contralateral breast, and the patient with LCIS had a 10 times increased risk of developing breast cancer as compared to the normal population. (18) Importantly, patients with LCIS are also 2.6 times more likely to develop contralateral breast cancer than those patients with DCIS, which may have played a role in this patient's development of breast cancer on the known diseased breast. (26)

Our study revealed lower rates of occult pathology in contralateral breast specimens in patients known with breast cancer than in the current literature. Occult invasive malignancies are expected to be found in between 1.5-4.6% of contralateral specimens in known breast cancer patients, versus between 0.6-2% in the general population. (17,23,24) Possible reasons for this include that there have been significant technological improvements in mammography equipment and techniques as well an increased utilisation of MRI in high risk or complex cases with improved

sensitivity in recent years. Secondly, processing of pathology specimens varies between laboratories, and this could affect the yield of pathological findings.

Another potential reason for the lower-than-expected yield in our sample was that 54% of the patients received neoadjuvant chemotherapy. Neoadjuvant chemotherapy is an important part of modern breast cancer management. It may be used to reduce tumour size and therefore allow for breast conserving surgery when initial tumour size necessitated mastectomy. It is also used to downstage locally aggressive tumours from inoperable to potentially operable. The advantage of neoadjuvant chemotherapy is that it may lead to improved survival in higher stage patients with subclinical systemic disease, and it allows for assessment of cancer susceptibility when given preoperatively as objective measurement of tumour response is possible. This is not possible during post-operative administration, as the tumour burden is theoretically removed and therefore the effect on any subclinical metastatic disease is almost impossible to quantify. (27) The systemic nature of the medication delivery means that both breasts receive equal dosages of these medications and therefore the potential to reduce the size or eradicate precursor or malignant lesions in the contralateral breast exists.

Additionally, literature regarding occult pathological findings in contralateral breast tissue include both reduction mammoplasty and mastectomy specimens, with mastectomy specimens having a far higher chance of identifying pathology due to sheer volume of tissue versus reduction specimens.

Some trends regarding the cancer characteristics of the known cancer breast and contralateral pathological findings were identified during our statistical analysis. With regards to cancer stage, as the stage increased so did the prevalence of contralateral pathological findings. Patients with stage II and stage III cancer were found to have 18% and 16% positive findings respectively versus 11% of patients with stage I cancer having positive contralateral findings. However, the patient with LCIS, which was the most significant finding in the study, had stage I cancer on the contralateral side.

Interestingly, there was a trend towards increased prevalence of positive pathological findings in patients whose cancer was ER positive, with 25% of ER positive patients having positive pathological findings vs 13% in patients who were ER negative. The Surveillance, Epidemiology, and End Results based analysis from 2021 by Giannakeas et al which included 812 000 patients found that ER positive patients were at less risk of developing contralateral breast cancer than their negative counterparts however our study findings suggest that ER positive patients may be at higher risk in the future.(28) PR status had little effect with similar results in both the positive and negative pathological findings groups. HER2 status behaved in a similar manner to PR status with 23% of HER2 positive patients having pathological findings vs 16% of HER2 negative patients with positive findings. These findings are in keeping with a study including 420 000 patients over 24 years in the United States of America which found no difference in contralateral breast cancer risk with regards to HER2 status. (29)

In a Swedish study by Vichapat et al, the risk of developing contralateral breast cancer was found to be at least two times higher in patients with more than ten positive lymph nodes. (30) In our study, 18% of lymph node negative patients had positive pathological findings and 20% of lymph node positive patients had positive findings and therefore we did not find a correlation between lymph node positivity and contralateral disease.

Despite the lack of identification of occult invasive malignancy in this cohort of patients, we believe it is still critical to submit all breast tissue removed from the contralateral breast for pathological assessment as it enables us to identify those patients that are at higher risk of developing contralateral breast cancer in the future. This recommendation is in keeping with a previous risk stratification guideline published by Ishag et al in which any patient with a personal history of breast cancer should have all resected tissues assessed for occult invasive malignancy. (31)

Conclusion

This is the first study of its kind in South Africa. It shows that the current screening, diagnostic, and treatment protocols in our unit are safe, with no findings of occult malignancy in the contralateral breast specimens over a six-year period. Although there was no statistical significance, there was an increased prevalence of contralateral breast pathology as cancer stage increased, and a higher risk of contralateral breast pathology in patients who were ER positive. While not well described in the literature, performing contralateral reductions in patients undergoing unilateral mastectomy for breast cancer has been shown not to affect their

oncological management and can be performed safely as part of the cancer management.

Limitations

Limitations of this study are that it was a single centre, retrospective review. Although the study included patients over a six-year period, a smaller number of patients than expected were included in the study due to the effects of the Covid-19 pandemic and logistical issues at CMJAH during the year of 2021 which saw the theatre complex closed for six months. The small sample size led to an inability to attain statistically significant results despite obvious trends in our data set and therefore suggest further research with a larger sample size to definitively prove associations between cancer characteristics and identification of occult pathology in the contralateral breast.

Declaration

The primary author, nor any of the supervisors have any conflicts of interest or declarations with regards to the above study.

Word Count: 3930

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List of Appendices

Appendix A
Protocol

Title

The incidence of pathological findings in contralateral reduction mammoplasty specimens in patients with breast cancer.

Name: Alexander Nikolas-John Diakakis

Degree: MMed (Wits)

Supervisors: 1) Dr C Sofianos, FC Plast Surg (SA), MMed (Wits), FRCS Plast

Consultant Plastic Surgeon

Division of Plastic and Reconstructive Surgery

Department of Surgery

University of Witwatersrand

Charlotte Maxeke Jhb Academic Hospital

Jubilee Street, Parktown, Johannesburg, South Africa

2) Dr NH Mabe, BSc (MEDUNSA), MBChB (University of Limpopo), FCS (SA)

Consultant General Surgeon, Surgical Breast Unit

Department of Surgery

University of the Witwatersrand

Charlotte Maxeke Jhb Academic Hospital

Jubilee Street, Parktown, Johannesburg, South Africa

3) Dr S Phiri, FC Plast Surg (SA)

Consultant Plastic Surgeon

Division of Plastic and Reconstructive Surgery

Department of Surgery

University of Witwatersrand

Charlotte Maxeke Jhb Academic Hospital

Jubilee Street, Parktown, Johannesburg, South Africa

4) Dr Carolina Nel

Consultant Histopathologist

Department of Anatomical Pathology

National Health Laboratory Service/University of the Witwatersrand

Charlotte Maxeke Jhb Academic Hospital

Jubilee Street, Parktown, Johannesburg, South Africa

Introduction and Literature Review

Breast cancer is the most commonly diagnosed malignancy in the world, and the leading cause of cancer death among women worldwide.(1) Women who are diagnosed with breast cancer are at increased risk of developing breast cancer in the contralateral breast. (2) The majority of these contralateral neoplasms are metachronous in nature, with a risk of 0.5-1.5% per year for the remainder of the patient's life. (4) Synchronous contralateral breast cancer is diagnosed in approximately 1-2.6% of patients and has been shown to negatively affect survival when compared to those patients who develop metachronous lesions, with 10% decreased five year survival rates. (4) (5)(6)Although rarely diagnosed during the treatment of breast cancer, autopsy and contralateral mastectomy studies in the past have shown much higher rates of synchronous contralateral neoplasms than those quoted above. (5)

The work up for a patient either presenting with, or suspected of having, breast cancer most commonly consists of clinical assessment, mammography and tissue biopsy. Mammography is used either as part of the work up for patients who present with a breast mass or as a screening tool to detect breast cancer before it becomes clinically apparent. Screening mammography has resulted in a 40% reduction in breast cancer associated mortality since its introduction in the US as is used all around the world as the standard screening tool in breast cancer management.(7) Screening mammography is considered extremely accurate, with a 90-92% sensitivity however, overdiagnosis of breast cancer is an important concept to consider.(8) Although difficult to quantify, the Malmo trial suggested a 10% overdiagnosis rate, leading to woman undergoing complex and often multimodal

treatments that may have been unnecessary. (9) Not only is mammography used to diagnose or identify breast cancer, it also guides management with regards to surgical approach or further imaging. These findings therefore show that although mammography is a critical tool in the management of breast cancer, the findings can be misleading.

In a study focusing on synchronous breast cancer by Hungness, the method of detection of the contralateral cancer was found to be mammography in 54% and palpation in 24% of patients. Of note, occult synchronous breast cancer was diagnosed in 16% of these patients during prophylactic mastectomy, mirror image biopsies and reduction mammoplasty for symmetry. (5)

Reduction mammoplasty is typically performed for three indications: symptomatic macromastia, congenital asymmetry or during the treatment of breast cancer. Unilateral reduction mammoplasty is a procedure performed by plastic surgeons in patients with macromastia, to reduce asymmetry in patients who undergo unilateral mastectomy, and to improve the symmetry and overall aesthetic results of either immediate or delayed contralateral total breast reconstructions. The identification of occult neoplasms in the reduction specimen has important implications for these patients as it often necessitates completion mastectomy, a possible delay to or adjustment of adjuvant therapies or differing surveillance protocols. (17) Importantly, re-resection or completion mastectomy rates in patients in whom occult pathology is identified should be close to 100%, as treatment of this newly identified neoplasm is essential to avoid any negative impact it may have on survival.

The rate of incidental abnormal findings in reduction mammoplasty specimens vary greatly in the literature. This heterogeneity can be explained by what authors categorise as pathological in different centres, as well as different sectioning protocols and sampling methods. Looking only at precancerous findings, Clark et al found 52.7% of patients undergoing reduction mammoplasty had benign pathological findings, 4.4% had hyperplasia and 1.8% had carcinoma in situ. (2)
It is important to note that the findings of benign pathology on breast specimens is not inconsequential. The American College of Pathologists divide benign pathology into risk categories, namely, no increased risk, slightly increased risk, moderately increased risk, and markedly increased risk lesions. These categories correlate with 0 increased risk, 1.5-2 times the risk, 4-5 times the risk and 8-10 times the risk of developing cancer. With this in mind, Clark's study can be interpreted as indicating that 13% of patients have twice the normal risk, 6.2% of patients have five times the risk and 1.8% of patients had a ten times increased risk of developing breast cancer in the contralateral breast based on benign pathological findings alone. (2)

In the largest study to date evaluating pathological findings in elective reduction mammoplasty, Pitanguy et al found that 80.8% of the patients had fibrocystic and fibrofatty changes, 3.7% had benign tumours and 0.5% had invasive malignancies found at pathological section. Interestingly, as screening methodologies became more sophisticated during the study period, the identification of occult malignancy post operatively did not decrease. (19)

Sofianos et al performed a similar study in the South African population. All patients were screened via clinical examination and imaging and were deemed cancer free.

In their study, 49% of patients had benign pathology and 2% were found to have occult malignancies. (20) Similarly, Colwell et al found an incidence of occult invasive malignancy in 0.8% of cases, however, they found a significantly higher rate of occult malignancy in those patients undergoing unilateral reduction during the treatment of breast cancer. They also stated that macromastia is an independent risk factor for breast cancer due to an increased volume of breast parenchyma. (21) It has also been shown that the detection of breast cancer can be more challenging in large breasts, and that breast cancer may be seen at younger ages in patients with macromastia. (17)(22)

In a study looking at occult cancer rates in contralateral reduction mammoplasty in breast cancer patients, Petit et al found 3% of patients had carcinoma in situ, and 1,5% had occult invasive malignancies. (23) In a similar study reviewing pathological findings in elective contralateral prophylactic mastectomies, Yi et al found the incidence of occult malignancy to be 4.6%, and a further 15% of patients in this series were found to have high risk lesions. (24)

A meta-analysis and systematic review by Fitzpatrick et al found that occult breast cancer was detected in 3.4% of breast reduction specimens in patients with breast cancer, as compared to 0.6% in the normal population. (17) The risk of developing contralateral breast cancer has also been shown to be increased in patients with higher stage disease. In a Swedish study by Vichapat et al, the risk of developing contralateral breast cancer was found to be at least two times higher in patients with more than ten positive lymph nodes as well as in patients with primary tumours involving either the skin or chest wall.(30)

The literature therefore suggests that the incidence of occult pathology in the reduction specimen of patients undergoing reduction mammoplasty during the treatment of breast cancer is higher than that of the general population. The identification of this pathology may indicate increased risk of, or the presence of, invasive malignancy which has significant impact on the treatment of these patients, and their overall survival. These findings indicate that protocols may need to be revised with regards to screening methods, counselling and histopathological assessment guidelines when dealing with this specific population group. Although studies have been performed to assess the incidence and outcomes of this entity, no such study has been performed in a South African context. This study will aim to show the incidence of such pathology in our patient group and may help to improve unit protocols and therefore influence treatment outcome.

Aim

To assess the incidence and spectrum of pathological findings in reduction mammoplasty specimens in patients who undergo contralateral reduction mammoplasty during the surgical management of their breast cancer in the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Surgical Breast unit.

Study Objectives

- To measure the incidence of abnormal pathological specimens in reduction mammoplasty specimens in patients known to have contralateral breast cancer in a specialist breast unit in Johannesburg, South Africa

- To study and interpret the findings of the pathological diagnosis and stratify it according to the stage of the cancer in the contralateral breast
- To determine the re-excision rate following the identification of pathology

Methods

Site

Surgical Breast Unit (Department of General Surgery and Division of Plastic and Reconstructive Surgery) at CMJAH.

Study design

A retrospective, descriptive study.

Study population

All patients diagnosed with breast cancer who underwent unilateral reduction mammoplasty of the contralateral breast at the CMJAH surgical breast unit during the period of January 2017 until and December 2021.

Data Collection

Patients who are eligible will be identified using the theatre records. The electronic breast cancer database (Onco-DB) will be used to obtain demographic data, diagnosis, breast cancer stage and medical history. Their histopathological reports will be sought from the National Health Laboratory Services (NHLS) system. It will be determined if all patients in the study underwent adequate screening by way of clinical examination, and mammography as is the unit policy. This information will then be collected on the data sheet

Choice of material for study

Pathological examination of surgical specimens is the most accurate way to assess the presence of occult pathology in reduction specimens. These reports will therefore be used to assess the presence or absence of occult pathology.

Pathological assessment

Findings of the pathological reports will be categorized into four groups, no pathology, benign lesions, proliferative lesions, DCIS and invasive tumours. The same anatomical pathology department will have sectioned and examined all of the reduction specimens as per their protocols.

Inclusion criteria

- All women undergoing unilateral reduction mammoplasty during the treatment of breast cancer

Exclusion criteria

- Incomplete records
- Initial operation done at other centres
- Diagnosed bilateral breast pathology

Patient Groups

- Ductal carcinoma in situ
- Invasive Ductal Carcinoma
    - Stage I and II
    - Stage III
- Other Invasive neoplasms

Sample Size

The aim is to identify approximately 100 patients. This figure should correlate with a five year period as 20-30 patients undergo this type of surgery per annum in the unit.

This number of patients should adequately provide a representative sample of patients treated for breast cancer at the CMJAH. All patient records fitting the above inclusion criteria will be included in this study. This should include patient records from January 2017 to December 2021. The number of patients treated during this time may be less than previous years due to the COVID-19 pandemic and the fire at CMJAH in April 2021.

Data analysis

The data collection sheet will be used to capture data (See Appendix A). A study number will be assigned to each participant ensuring anonymity. Raw data will be then captured in an Excel spreadsheet (Microsoft Excel, Microsoft 365, Microsoft Corporation, Redmond) and imported into STATA version 16 (StataCorp LLC, Texas) for statistical analysis. The Shapiro-Wilks test will be applied to determine the normality of continuous data, such as age. Statistical tests will include standard descriptive statistics and means and standard deviations (SD) or medians and interquartile ranges (IQR) will be reported, as appropriate, for continuous variables. Categorical variables will be described using frequencies and proportions. Associations between presence of malignancy and continuous variables will be tested using the T-test or Mann-Whitney U test, as appropriate, whereas associations with categorical variables will be determined by the Chi-squared test and/or Fisher's exact test. A p-value of ≤0.05 will be considered statistically significant.

Study Implications

This study may help to inform and guide screening, pathological assessment, and follow up guidelines used in these patients to improve their breast cancer management, and therefore improve long term survival.

Study Limitations

This study will be retrospective and will rely on the accurate data capture in the Onco-DB system to determine the outcomes. This may decrease the number of patients included in the study

Ethics

Approvals for the study will be obtained from Charlotte Maxeke Johannesburg Academic Hospital and the National Health Laboratory Service . Ethics approval will be obtained through the Human Research Ethics Committee of the University of the Witwatersrand. No identifiable information will be collected in this study and therefore anonymity will be maintained throughout. Only the investigator and supervisors will have access to this information. All data will be stored electronically on a password protected drive. The study and data capturing will only be performed once ethics approval has been granted.

Funding

This study will not incur any significant costs. Expenses will be covered by the primary researcher. Projected expenses include stationery costs and transport costs amounting to an estimated R1000.00.

Timeline

	2022									
	Mar	April	May	June	July	Aug	Sept	Oct	Nov	Dec
Literature review										
Preparing protocol										
Protocol assessment										
Ethics application										
Data collection										
Data analysis										
Writing up thesis										
Writing up paper										

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Appendix B
Data Collection Sheet

Study Number:

Age:		Race:	A / W / C / I / O		
Breast Cancer side:	R / L	Stage:	T:	N:	M:
Cancer type:	DC / LC / DCIS / O	Receptor status:	ER: P / N PR: P/N	Her 2:	Ki67%:
Imaging:	US / MMG / MRI		Imaging findings:	L	R
Clinical examination:	L	R			
Procedure - Cancer:	Mastectomy	/ WLE	Axilla:	ALND / SLNB	
Histology Findings:	No pathology /	Benign /	Proliferative /	DCIS /	Cancer

Histology Details:

Management:

Appendix C

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

06 January 2023
Person No: 0700945T
PAG

Dr ANJ Diakakis
P O Box 664
Riverclub
Sandton
2146
South Africa

Dear Dr Alexander Diakakis

Master of Medicine in Plastic and Reconstructive Surgery: Approval of Title

We have pleasure in advising that your proposal entitled *The incidence of pathological findings in contralateral reduction mammoplasty specimens in patients with breast cancer* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix D

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr ANJ Diakakis

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220940

NAME: (Principal Investigator)	Dr ANJ Diakakis
DEPARTMENT:	School of Clinical Medicine Department of Surgery Medical School University
PROJECT TITLE:	*The incidence of pathological findings in contralateral reduction mammoplasty specimens in patients with breast cancer*
DATE CONSIDERED:	2022/09/30
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs C Sofianos, NH Mabe, C Nel and S Phiri
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/02/02

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **September** and therefore reports and re-certification will be due in the month of **September** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 3/2/23

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2023/03/28

Dr ANJ Diakakis
School of Clinical Medicine
Department of Surgery
Medical School
University

Sent by e-mail to: a.n.diakakis@gmail.com

Dear Dr Diakakis

Re: **Protocol Ref No:** M220940
Protocol Title: *The incidence of pathological findings in contralateral reduction mammoplasty specimens in patients with breast cancer*
Principal Investigators: Dr ANJ Diakakis

Thank you for your e-mail of 2023/03/20.

We have noted and approve of your proposal to extend your data collection window to include all patient records up to and including 2022/12/31.

Thank you for keeping us informed.

Yours Sincerely

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

.....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix E

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
OFFICE OF THE CLINICAL DIRECTOR

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 06 May 2023

GP_202208_100

DEAR DR ALEXANDER DIAKAKIS

RE: FINAL APPROVAL OF STUDY

TITLE: THE INCIDENCE OF PATHOLOGICAL FINDINGS IN CONTRALATERAL REDUCTION MAMMOPLASTY SPECIMENS IN PATIENTS WITH BREAST CANCER.

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~Not Supported~~

Signed by:Jayshina Punwasi
Signed at:2023-05-06 17:38:50 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director

Approved / ~~Not Approved~~

Signed by:Gladys Magugudi Bogoshi
Signed at:2023-05-09 15:06:03 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms G. Bogoshi
Chief Executive Officer: CMJAH

Appendix F

Final Research Report - no ref.docx

ORIGINALITY REPORT

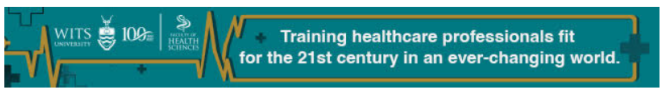
7%	6%	5%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Li, Zaibo, Oluwole Fadare, Omar Hameed, Chengquan Zhao, and Mohamed Mokhtar Desouki. "Incidental atypical proliferative lesions in reduction mammoplasty specimens in patients with a history of breast cancer", Human Pathology, 2013. Publication	1%
2	www.ncbi.nlm.nih.gov Internet Source	1%
3	www.operationpinkbag.org Internet Source	1%
4	www.coxhealth.com Internet Source	1%
5	Lara Goldstein, Mike Wells, Craig Vincent-Lambert. "A Randomized Controlled Trial to Assess the Impact of Upfront Point-of-Care Testing on Emergency Department Treatment Time", American Journal of Clinical Pathology, 2018 Publication	1%

Ekene Nweke
to me

7:16 AM (3 hours ago)



Dear Dr Diakakis,

Herewith your MMed plagiarism report is attached. Your overall similarity index is 7% with a maximum single match of 1% mostly from generic terms. All other matches are ≤ 1%. Therefore, your similarity index is **ACCEPTABLE** within our Department.

For PG submissions - Please only submit the attached page in the attached report, as well as this email stating that your plagiarism report is **ACCEPTABLE** within the Department of Surgery.

Well done!!!!

Dr Ekene Emmanuel Nweke, (Pri Sci Nat), BSc (Hons), MSC, PhD
Researcher | Department of Surgery

E: ekene.nweke@wits.ac.za
T: +27 11 717 2801
W: www.wits.ac.za/clinicalmed/

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WITS SCHOOL OF CLINICAL MEDICINE