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Quality Indicators of Breast Cancer Surgery in South Africa



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Student Number: 378514

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy

Supervisors:

Prof Paul Ruff

Prof Shane Norris

Johannesburg, 2025

DECLARATION

I, Sarah Lena Nietz, declare that this thesis is my own original, unaided work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at any other university or institution.



Sarah Lena Nietz

03.07.2025

DEDICATION

This thesis is dedicated to my mother, Liz.

“The gull sees farthest who flies highest.”

(Johnathan Livingstone Seagull by Richard Bach)

ACKNOWLEDGEMENTS

I am profoundly grateful to my supervisors, Professor Paul Ruff and Professor Shane Norris, for the invaluable opportunity to pursue my PhD under their guidance. I value the extensive knowledge, skills, direction, and insights they provided during my PhD journey.

In addition to my supervisors' contributions, I will be forever thankful for the support I received from numerous experts who assisted with my PhD, from the conceptualisation of the study to data analysis and interpretation, as well as the drafting and revision of the various manuscripts that culminated in this thesis: Dr Ines Buccimazza, Dr Wenlong Carl Chen, Professor Herbert Cubasch, Professor Jenny Edge, and Dr Maureen Joffe. I would also like to express my thanks to Professor Thifhelimbilo Luvhengo, Professor Martin Smith, and Dr Sue Tager for their support and encouragement during the early stages of my PhD.

I thank the Miller Foundation for awarding me the Senior Miller Fellowship to travel and visit three German breast units and for the invaluable insights and connections this provided.

This research would not have been possible without the research team led by Professor Paul Ruff, Professor Herbert Cubasch, and Dr Maureen Joffe, who enabled the SABCHO study, which formed the backbone of this subsequent research. I extend my gratitude to all the experts contributing to the two consensus papers included in this thesis, who are duly acknowledged in the respective manuscripts.

I sincerely respect and appreciate the SABCHO study participants and hope this research will contribute to the improved quality of care and outcomes they deserve.

I am deeply grateful to my mother for everything, always.

Lastly, a heartfelt thank you to my husband and sons, who supported me and allowed me the time to complete this thesis.

THESIS CONTRIBUTIONS AND MATERIALS

Together with my supervisors, I was responsible for the overall study design and the conceptualisation of each sub-study, the development of the study protocol, and the development of the Delphi rating questionnaires. I led the systematic review and cofacilitated both consensus meetings. I was the site principal investigator at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) for the South African Breast Cancer and HIV Outcomes (SABCHO) study, where I contributed to data collection and led clinical patient care. I also contributed to project management, quality control, data cleaning, and the statistical analysis of the results presented.

FUNDING AND AWARDS

The SABCHO project was enabled by grants from the NIH of USA National Cancer Institute (Grant numbers: R01-CA192627, R01-CA250012 and P30-CA13696): Drs Jacobson, Joffe, Neugut, Cubasch and Ruff; as well as University of Witwatersrand/South African Medical Research Council Common Epithelial Cancer Research Centre Grant (CECRC): Prof Ruff, and these are hereby acknowledged.
The PhD study received no funding.

In 2018, I received the Senior Miller Travel Fellowship, which enabled me to travel to Germany to visit three breast centres and learn about the implementation of breast centre requirements and quality improvements. Furthermore, I received staff bursaries for PhD fees through the University of the Witwatersrand in 2018 and 2019.

I was awarded first prize for the oral presentation at the Bert Myburgh Research Forum in November 2019 (Nietz S, Ruff P, Chen WC, O'Neil DS, Norris SA. *Quality indicators for the diagnosis and surgical management of breast cancer in South Africa)* and third prize for the oral presentation at the Bert Myburgh Research Forum in November 2020 (Nietz S, O'Neil DS, Ayeni O, Chen WC, Joffe M, Jacobson JS, et al. *A comparison of complete pathologic response rates following neoadjuvant chemotherapy among South African breast cancer patients with and without concurrent HIV infection).*

PUBLICATIONS AND PRESENTATIONS

The research findings from this PhD study were written up as four separate manuscripts. Three manuscripts have been submitted to peer-reviewed scientific

journals: two have been accepted and published, while one is awaiting review. The last manuscript was written in dissertation style and is currently being edited for planned submission. The signed co-author agreement for the use of each publication within this thesis is located in Appendix A. Results from this study were also presented in the form of oral and poster presentations at various academic and scientific conferences.

Peer-Reviewed Publications:

Paper 1 (Chapter 3)

Nietz S, Ruff P, Chen WC, O'Neil DS, Norris SA. Quality indicators for the diagnosis and surgical management of breast cancer in South Africa. *The Breast*, 2020 Dec;54:187–96. DOI: http://dx.doi.org/10.1016/j.breast.2020.09.012 (Appendix E)

Paper 2 (Chapter 4)

Nietz S, Cubasch H, Buccimazza I, Čačala S, Phakathi B, Joffe M, et al. An initial benchmark of the quality of the diagnosis and surgical treatment of breast cancer in South Africa. *S Afr Med J*. 2025 Feb115(1):e2292 https://doi.org/10.7196/SAMJ.2025.v115i1.2292 (Appendix E)

Paper 3 (Chapter 5)

Nietz S, Edge J, Buccimazza I, Demetriou G, Tunmer M, Smilg J, et al. Establishing Requirements for Breast Centers in Low- and Middle-Income Countries: A South African Perspective. JCO Global Oncology. 2025 Jun;(11). Available from: http://dx.doi.org/10.1200/go-25-00168

Related Peer-Reviewed Publications:

Nietz S, O'Neil DS, Ayeni O, Chen WC, Joffe M, Jacobson JS, et al. A comparison of complete pathologic response rates following neoadjuvant chemotherapy among South African breast cancer patients with and without concurrent HIV infection. *Breast Cancer Research and Treatment.* 2020 Sep 1;184(3):861–72. DOI: http://dx.doi.org/10.1007/s10549-020-05889-8 **(Appendix F)**

Toma A, O'Neil D, Joffe M, Ayeni O, Nel C, van den Berg E, Nayler S, Cubasch H, Phakathi B, Buccimazza I, Čačala S, Ruff P, Norris N and **Nietz, S.** Quality of Histopathological Reporting in Breast Cancer: Results From Four South African Breast

Units. *JCO Global Oncology*, 2021 Dec;(7):72–80. DOI: http://dx.doi.org/10.1200/go.20.00402 **(Senior author and MMed Supervisor, Appendix F)**

O'Neil DS, Chen WC, Ayeni O, **Nietz S**, Buccimazza I, Singh U, et al. Breast Cancer Care Quality in South Africa's Public Health System: An Evaluation Using American Society of Clinical Oncology/National Quality Forum Measures. *JCO Global Oncology.* 2019 Dec;(5):1–16. Available from: http://dx.doi.org/10.1200/jgo.19.00171

Pothas C, **Nietz S**, Oluwa T, Witness M, Cubasch H, Joffe M. Time to first health care contact, referral pathways and stage at presentation – the experience from four South African breast units. *European Journal of Cancer*, 2020 Oct;138:S69. DOI: http://dx.doi.org/10.1016/s0959-8049(20)30710-3 **(MMed Supervisor)**

Groenewald C, Cubasch H, Mannell A, Ayeni O, **Nietz S**. Axillary lymph node dissection for patients with invasive breast cancer at Charlotte Maxeke and Chris Hani Baragwanath Academic Hospitals. *South African Journal of Surgery*. 2019;57(4):18–24. **(Senior author and MMed Supervisor**

Presentations and Posters:

Nietz S, Ruff P, Chen WC, O'Neil DS, Norris SA. *Quality indicators for the diagnosis and surgical management of breast cancer in South Africa,* Oral presentation at the Bert Myburgh Research Forum, November 2019,

Nietz S, Ruff P, Chen WC, O'Neil DS, Norris SA. *Quality indicators for the diagnosis and surgical management of breast cancer in South Africa,* Poster presentation at the Breast Interest Group of South Africa Conference, September 2020,

Nietz S, Cubasch H, Buccimazza I, Čačala S, Phakathi B, Joffe M, et al. *The effect non-adherence to quality indicators on overall survival among South African women with breast cancer,* Oral presentation at the Bert Myburgh Research Forum, November 2024

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NOMENCLATURE

ABC-DO	African Breast Cancar- Disparities in Outcome
AJCC	American Joint Committee on Cancer
AHRQ	Agency for Healthcare Research and Quality
ALND	Axillary lymph node dissection
ANOVA	Analysis of variance
ASBrS	American Society of Breast Surgeons
ASCO/NCCN	American Society of Clinical Oncology/National Comprehensive Cancer Network
BCS	Breast conserving surgery BCT
	Breast conserving therapy
BIGOSA	Breast Interest Group of Southern Africa
BIRADS	Breast imaging reporting and data system
BRICS	Brazil, Russia, India, China, South Africa
CECRC	Common Epithelial Cancer Research Centre
CHBAH	Chris Hani Bragawanath Academic Hospital
CI	Confidence Interval
CMSA	College of Medicine of South Africa
CoC/ACS	Commission on Cancer of the American College of Surgeons
COVID-19	Coronavirus disease 2019
CV	Coefficient variation
DCIS	Ductal carcinoma in situ
DKG	Deutsche Krebs Gesellschaft
ER	Oestrogen receptor
EPR	Electronic patient record

EUSOMA	European Society of Breast Cancer Specialists
GDP	Gross Domestic Product
GH	Grey’s Hospital
GLOBOCAN	Global Burden of Cancer (IARC)
HDI	Human development index
HER-2	Human epidermal growth factor 2
HIC	High-income country
HIV	Human immunodeficiency virus
HPCSA	Health Professions Council of South Africa
HR	Hazard ratio
HREC	Human Research Ethics Committee
IALCH	Inkosi Albert Luthuli Central Hospital
IHC	Immunohistochemistry
KZN	KwaZulu-Natal
LABC	Locally advanced breast cancer
LoE	Level of evidence
LMIC	Low-to-middle-income country
LRR	Local recurrence rate
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
NABON	National Breast Cancer Organisation Netherlands
NACT	Neoadjuvant chemotherapy
NAPBC	National Accreditation Program for Breast Centers
NCD	Non-communicable diseases
NCR	National Cancer Registry
NGT	Nominal Group Technique

NHI	National Health Insurance
NICE	National Institute for Health and Care Excellence (UK)
NIH	National Institutes of Health (USA)
NQF	National Quality Forum
OR	Odds ratio
PR	Progesterone receptor
PREM	Patient-reported experience measures
PROM	Patient-reported outcome measures
QI	Quality Indicator
REDCap	Research Electronic Data Capture
RT	Radiotherapy
SABCHO	South African Breast Cancer and HIV Outcomes
SLNB	Sentinel lymph node biopsy
SA	South Africa
SD	Standard deviation
SSA	Sub-Saharan Africa
TNBC	Triple-negative breast cancer
UHC	Universal health coverage
UMIC	Upper-middle-income country
USA	United States of America
WHO	World Health Organization

ABSTRACT

Introduction

Quality indicators (QIs) have contributed to improved patient outcomes in high-income countries (HICs), yet they have not been established for lower-resourced healthcare settings. Quality improvements are particularly crucial in low- to middle-income countries (LMICs), where patient outcomes, such as survival rates, are disproportionately poor. It is probable that quality indicators, along with structural requirements, are not readily transferable but need to be tailored for successful application in LMICs. The quality of surgical breast cancer care has never been assessed in South Africa and will likely reveal significant gaps in care. Furthermore, identifying key indicators with a demonstrable impact on survival would provide actionable interventions to enhance patient outcomes.

Objectives

The thesis had four distinct objectives.

1) To review the literature on quality indicators within the global and LMIC context and develop a contextual local South African set of diagnostic and surgical QIs.
2) To measure the adherence rates to these QIs amongst women with breast cancer in South Africa.
3) To establish the requirements of breast centres in South Africa.
4) To assess the effect of individual and composite QI adherence on overall survival in women with breast cancer in South Africa and to compare treatment pathways across sites.

Methods

1) The literature on quality indicators (QIs) for the diagnosis and surgical management of breast cancer was systematically reviewed and a local set of QIs was defined with a modified Delphi process.
2) QI adherence levels were measured in 3545 patients from the South African Breast Cancer and HIV Outcomes (SABCHO) cohort, cross-site variances were identified with descriptive statistics, and comparisons were made against international standards.
3) Breast centre requirements were examined by compiling tables of existing international standards alongside proposed South African standards. This was

followed by a facilitated discussion to reach expert consensus on centre requirements and a stepwise implementation process for Southern Africa.

4) A survival model was sequentially developed using 2716 patients to evaluate the impact of individual and composite model QI non-adherence on survival. It employed both univariate and multivariate logistic regressions and Cox's proportional hazard regressions. Kaplan–Meier survival curves were stratified by QIs, and survival comparisons were determined by a log-rank test. Patient treatment pathways from the different study sites were compared and plotted onto Sankey diagrams and network plots.

Results

1) We defined a South African set of ten mandatory QIs.
2) Adherence to QIs was overall lower than in HICs, with emergent gaps identified in the delivery of radiation after breast-conserving surgery (66.7% adherence) and underutilisation of sentinel lymph node biopsy (39.6%). Multidisciplinary team (MDT) discussion (72.2%), histopathology reporting (62.0%) and the rate of breast-conserving surgery (19.4%) need to be improved.
3) We defined a set of breast centre requirements tailored to LMICs in subSaharan Africa with a step-by-step implementation plan. Both the QI set and the centre requirements were endorsed by the Breast Interest Group of Southern Africa (BIGOSA).
4) The overall 5-year survival was 43%. The different SABCHO sites showed significant variances in treatment pathways, which were adjusted to local resource availability, particularly to the delay to radiotherapy. Survival was affected by various individual QIs, including MDT discussion, receipt of radiotherapy and BCS, as well the composite QI model.

Conclusion

1) A South African set of QIs for the diagnosis and surgical treatment of breast cancer was developed.
2) This was applied to establish the first benchmark of care in South Africa. Overall, adherence levels were lower compared to international standards, highlighting poor radiation delivery, among other gaps in care.

3) The centre requirements and the QI set offer implementable approaches to measure and improve care and a tool for step-wise implementation.
4) Overall survival rates were alarmingly low, necessitating urgent interventions. Both individual and composite QI adherence levels are associated with improved survival outcomes. Mandatory MDT discussions can significantly enhance breast cancer survival in South Africa.

PREFACE

My path to becoming a doctor began when my mother suffered a severe stroke, and I became her primary carer at the age of six. As my mother gradually regained some functions over the following decade, it taught me patience, empathy, resilience, and perseverance, attributes that have been invaluable in my clinical work as well as in my pursuit of this PhD.

When I started my medical studies, I was firmly convinced I would pursue a career as a translational researcher, not a clinician. Time proved me wrong, and during my internship, I fell in love with surgery, drawn by its pragmatism, technical challenges, and instantaneous results. After my specialisation, I chose to become a breast surgeon, fascinated by their leading role in oncological paradigm shifts, evidencebased practices, and the rapidly advancing research and surgical approaches. I found myself in charge of breast services at a central university hospital very early in my career, where I taught myself and worked hard to establish a well-rounded breast service for the community it served. I was struck by the plight of my patients, mostly women with poor access to health care and late-stage presentations, breadwinners and mothers. Caring for women seemed both intuitive to me and my intended path.

Overwhelmed by clinical work and training, I first seriously considered pursuing a PhD when the SABCHO cohort commenced, and I was given the opportunity to participate as a site principal investigator. As a clinician and researcher, I sought to enhance my academic capabilities and engage in research that would significantly impact the service we provide to our patients. Given the poor quality of service I observed and the remarkable differences I managed to implement in a short period, I opted to concentrate on the quality of breast cancer care and the ways to measure and enhance it.

As is commonly observed in pursuing a PhD, various life circumstances lead to intermittent interruptions from its progress. This includes the COVID-19 pandemic, the birth and upbringing of my two sons, a move from the public sector to private practice, and caring for my mother, who, as decided by fate, was diagnosed with metastatic breast cancer and passed away.

My passion for my clinical work and the privilege I feel in treating women remain. As I approach the end of my PhD journey, I take immense pride in these results and hope that this work will lay the groundwork for improved outcomes for many women in South Africa, extending beyond my own practice.

This PhD thesis is presented in an integrated format, comprising four manuscripts. Two of the manuscripts have been published, while one has been submitted for publication. The fourth manuscript is presented in dissertation style to facilitate a comprehensive demonstration of methodologies and results and is currently undergoing editing for submission.

The thesis is divided into three sections that are further divided into seven chapters:

- **Section 1: Introduction**

This section describes the literature around the topic, the aims and objectives of the study, the study context and the approach taken to conduct the research.

○ Chapter 1: Background and Literature Review ○

Chapter 2: Methodology

- **Section 2: Empirical Papers**

This section consists of four empirical manuscripts that report on the findings of the PhD study.

- Chapter 3: Quality indicators for the diagnosis and surgical management of breast cancer in South Africa
- Chapter 4: An initial benchmark of the quality of the diagnosis and surgical treatment of breast cancer in South Africa
- Chapter 5: The role and minimum requirements for breast centres in lowto-middle-income countries: a South African perspective
- Chapter 6: The effect non-adherence to quality indicators on overall survival among South African women with breast cancer
- **Section 3: Integrated Discussion**

This section consists of an integrated discussion that consolidates the findings of the four manuscripts and ends with an overall conclusion.

○ Chapter 7: Discussion and Conclusion

PART 1: INTRODUCTION

“We choose our next world through what we learn in this one. Learn nothing, and the next world is the same as this one, all the same limitations and lead weights to overcome.”

(Johnathan Livingstone Seagull by Richard Bach)

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.1 Breast Cancer Incidence Rates

Breast cancer is the most common cancer among women worldwide and is the second most common overall cancer, following lung cancer. In 2022, an estimated 2.3 million new cases and 666,000 deaths were reported(1). Incidence rates are illustrated in Figure 1 and vary across countries, with higher rates in high-income countries (HICs) compared to low- and middle-income countries (LMICs), and is highest in Australia, the United States of America (USA) and Western Europe, where one in eight to ten women will develop breast cancer during their lifetime(1,2).

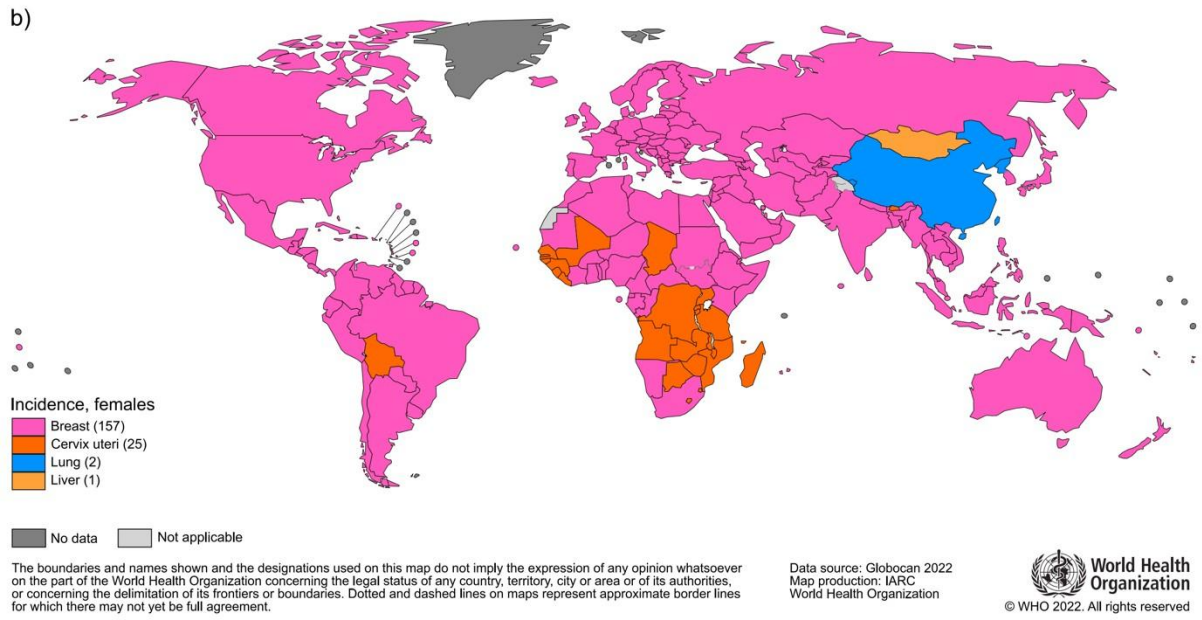


Figure 1: Global breast cancer incidence

Global map presenting the most common type of cancer incidence in 2022 in each country among women. The numbers of countries represented in each ranking group are included in the legend. Source: GLOBOCAN 2022, CA Cancer J Clin, 2024.(1)

It is important to note that these incidence rates have stabilised in HICs, whereas in LMICs with their societies in transition, they are steadily increasing with better diagnosis and reporting, greater life expectancy, population growth and adoption of urban lifestyles with less physical activity and high-fat, low-fibre, convenient food diets(3). The Global Burden of Cancer Study (GLOBOCAN) 2012 data predicted a doubling of cancer incidence, including breast cancer, in sub-Saharan Africa (SSA) by 2050(4).

According to the pathology-based South African National Cancer Registry (NCR), breast cancer is the most common malignancy, having surpassed cervical cancer as the most common malignancy among females in South Africa (SA). Over 11,200 new breast cancer diagnoses were reported to the NCR in 2022(5). Although differences in incidence among population groups remain apparent, the overall incidence is still considerably lower than in HIC(5,6).

1.2 Breast Cancer Mortality Rates

All-stage 5-year breast cancer survival in HICs is approximately 85-90%(7). Breast cancer survival has been inconsistently described in SSA and, when addressed, is often conducted selectively within a restricted number of countries or centres. Two meta-analyses show a pooled 5-year survival of 52% in Africa, including North African countries(8), and 40% in SSA(9). More recent results from the South African Breast Cancer and HIV Outcomes study (SABCHO) as well as the African Breast Cancer - Disparities in Outcomes study (ABC-DO) show considerably poor outcomes with a 3year survival of 60.4-63%, which is mainly determined by late-stage presentation, as well as suboptimal therapies(10,11). Although South African breast cancer survival is considerably lower than in HICs, it remains higher than in many other African countries, and survival appears to reflect the human development index (HDI) of countries as well as government healthcare expenditure (Figure 2)(8,12).

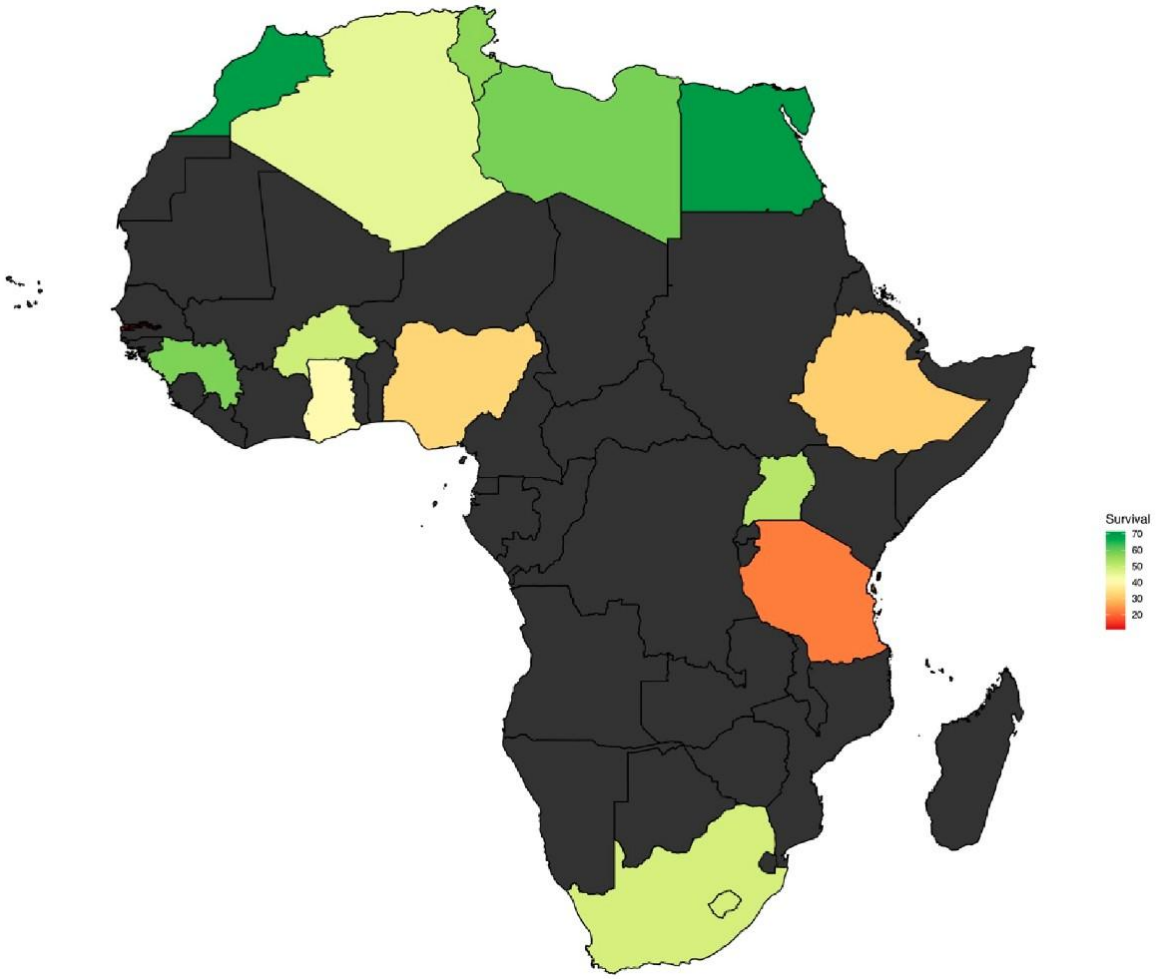


Figure 2: Survival rates in Africa

Survival rate (%) of breast cancer shaded by the country from which the papers used in the metaanalysis were published. No data in black shade. Source: Ssetongo et al, PloS One, 2019(8).

1.3 Socioeconomic Impact of Breast Cancer

The impact of breast cancer on families and societies extends far beyond mere survival. Breast cancer not only has the highest incidence rate among women globally, but it is also the most prevalent resulting in a high rate of disability-adjusted life years; it disrupts family life and causes loss to national economies, perpetuating the cycle of poverty(13,14). As the centre of a family, the premature death of a mother of young children is particularly devastating. In the year 2020, a total of 4.4 million women succumbed to cancer globally, resulting in 1.04 million children being maternally orphaned; of these children, 25% lost their mother due to breast cancer(15). This is particularly relevant in South Africa, where the majority of children (42%) live solely

with their mother, and 21% do not reside with either parent, but typically with their guardian grandmothers(16).

Treatment for breast cancer is particularly costly and has a significant impact on governmental healthcare expenditure but also significant financial toxicity to the patients and their families(17,18). In several HICs and the private sector in SA, direct treatment costs require an escalating contribution of out-of-pocket patient funds(19). Although the extant literature has mostly focused on the direct costs of treatment for funders and societies, there is growing attention on the costs indirectly incurred by patients and their families(20). In the SA public sector, although diagnostics and treatment costs are covered by the Public Health System, patients face significant outof-pocket costs such as transport, loss of income, supporting medication and a change in dietary requirements(21). This, in addition to some persisting cultural beliefs, can cause alienation within the family, the workplace and communities(22,23).

Treatments also have significant long-term toxicity and impacts on the patients' health, body image, psychosocial functioning and general well-being(24).

Nevertheless, socioeconomically disadvantaged cancer patients in South Africa are better off than those from low-income countries in sub-Saharan Africa, where universal access to diagnostics and treatments is not covered by health systems, and the majority of patients cannot afford the costs of cancer diagnostics and treatment.

1.4 Global Disparity of Breast Cancer Care and Outcomes

Each year, 2.3 million women globally receive a breast cancer diagnosis(1). However, the timeliness of their healthcare access and the quality of the affordable diagnostic and treatment options they receive largely depend on their geographical location and socioeconomic status, especially when they are impoverished or socially marginalised(13,25). Disparities in treatment quality and survival rates have been observed both across Europe and within countries in both LMIC and HIC regions and are influenced by race, income, education, and various sociodemographic factors(25–27).

With the predicted rise in incidence in LMICs, the greatest share of the global breast cancer burden will fall on LMICs. These countries generally have weaker healthcare structures, struggling to cope with the rise in cancer rates while diseases of poverty and infection still persist, and provide a lower quality of breast cancer care to patients,

resulting in disproportionately higher mortality rates(13). It is estimated that at least a third of the predicted 416,000 breast cancer deaths that will occur in the SSA region over the next decade could be prevented with earlier access and better treatment quality(10). The provision of care, such as access to optimal therapies or waiting times, accounts for about one-third of survival differences; however, lack of guidelines, quality control, and regulatory framework may also account for up to a quarter of survival differences(28). At present, the survival rates reported by the ABC-DO study reflect survival rates seen in HICs almost a century ago, and this disparity is unacceptable(29).

Urgent, effective interventions are required to close the global survival gap and improve outcomes for patients in LMICs. In recent years, the magnitude of this challenge has become a strong focus of the global oncology community, with various projects, such as the Breast Health Global Initiative and Lancet Commission on Breast Cancer, working on potential solutions(29,30).

1.5 Overview of the Treatment of Breast Cancer

A detailed description of the complex and nuanced treatment options is beyond the scope of this dissertation, and the following sections aim to provide a simplified overview. Treatment decisions are generally based on tumour biology, anatomical stage and patient factors.

1.5.1 Tumour Biology

After the groundbreaking work of Perou et al, it is now understood that there are at least four major molecular subtypes of breast cancer(31). However, conducting molecular testing for all patients is not feasible or affordable in clinical practice, especially in South Africa. Instead, immunohistochemistry (IHC) on the oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), and Ki-67 are used as a surrogate to categorise breast cancer subtypes (Figure 3).

Clinicopathological subtype	*Immunohistochemical surrogates*		
	ER/PR	*HER-2*	*Ki-67*
Luminal A	*+/-*	*-*	*<20%*
Luminal B (HER-2 negative)	*+/-*	*-*	*>20%*
Luminal B (HER-2 positive)	*+/-*	*+*	*>20%*
Basal-like (triple-negative)	*-*	*-*	*Generally high*
HER-2 - enriched (non luminal)	*-*	*+*	*Generally high*

Figure 3: Clinicopathological subtypes and immunohistochemical surrogates

The Ki-67, a proliferative marker, is used as the cut-off between the luminal types, but there is substantial uncertainty as to what value should be used, compounded by significant interobserver variability. The initial cut-off proposed as the St Gallen Consensus was 14% but was increased to 20% in 2013(32,33). The higher cut-off is supported by more recent literature, including the work of Dix-Peek et al. on a South African cohort(34). Luminal tumours, particularly luminal A, have a better prognosis and are not responsive to chemotherapy but are well responsive to endocrine therapy alone. Luminal B tumours have more aggressive features, such as higher grade, or Ki-67, and may benefit from chemotherapy followed by endocrine therapy. Molecular testing in terms of multigene signatures is only available in private healthcare settings in South Africa and is typically used to differentiate tumor biology in cases where there are borderline features between luminal A and B subtypes. This information helps

make decisions about whether to use chemotherapy or not (Figure 4). HER-2 positive tumours historically carried a poor prognosis, but HER-2 targeted therapy has substantially changed the outcome of these patients(35)(36). Basal-like or triplenegative breast cancer (TNBC) remains the most difficult to treat, although recent immunotherapy and targeted treatment advances have brought hope to improve these patient outcomes(37). In general, there is a preference to treat more aggressive tumour subtypes with systemic therapy first, whereas luminal lower-risk tumours tend to have surgery as the primary treatment modality (Figure 4).

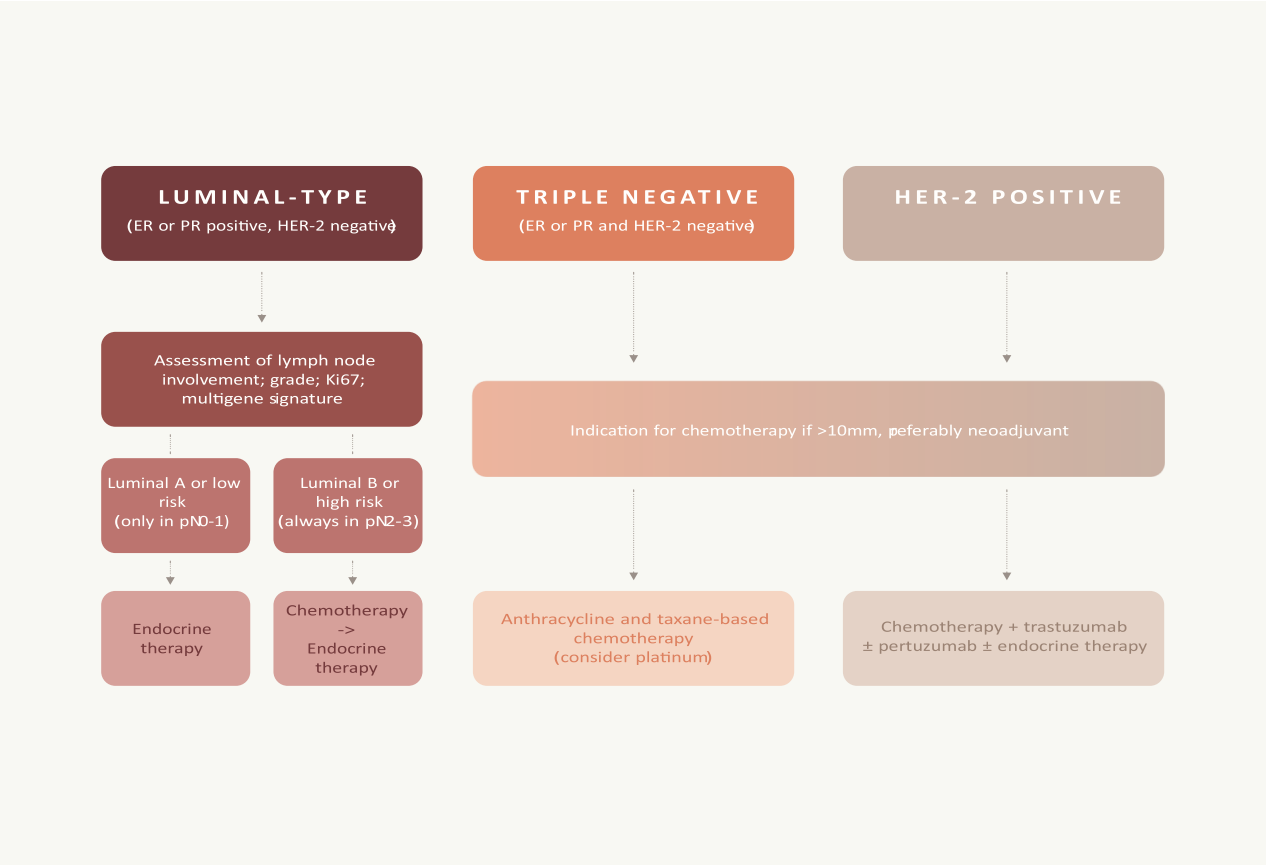


Figure 4: Systemic therapy choices by tumour biology
Informed by Harbeck and Gnant, Lancet 2017(38).

1.5.2 Tumour Staging

Breast cancer is staged using the AJCC (American Joint Committee on Cancer) staging system and remains pivotal in the primary assessment and treatment planning of all patients with breast cancer. Historically, this was a pure anatomic assessment of primary tumour size (T), lymph node involvement (N), and metastasis (M) based on clinical and pathological evaluations. The more recent advances in understanding tumour biology and prognostic markers were integrated in the most recent 8th Edition,

which now combines prognostic markers and disease extent for better prognostication(39).

1.5.3 Patient and Physician Factors

Patient preferences, age, pregnancy, breast size and shape, comorbidities, body mass index (BMI) and socioeconomic factors are just some of the patient-specific factors that are considered and also influence treatment choices. Physician factors also influence choice, especially in surgery, with more breast-conservative surgery offered by female, more experienced and high-volume surgeons(40).

1.6 Treatment Modalities and Sequencing

The main treatment modalities include surgery and radiotherapy, regarded as locoregional therapies, and chemotherapy, targeted therapies such as endocrine therapy and HER-2 targeted treatments, and immunotherapy, regarded as systemic therapies (Figure 5).

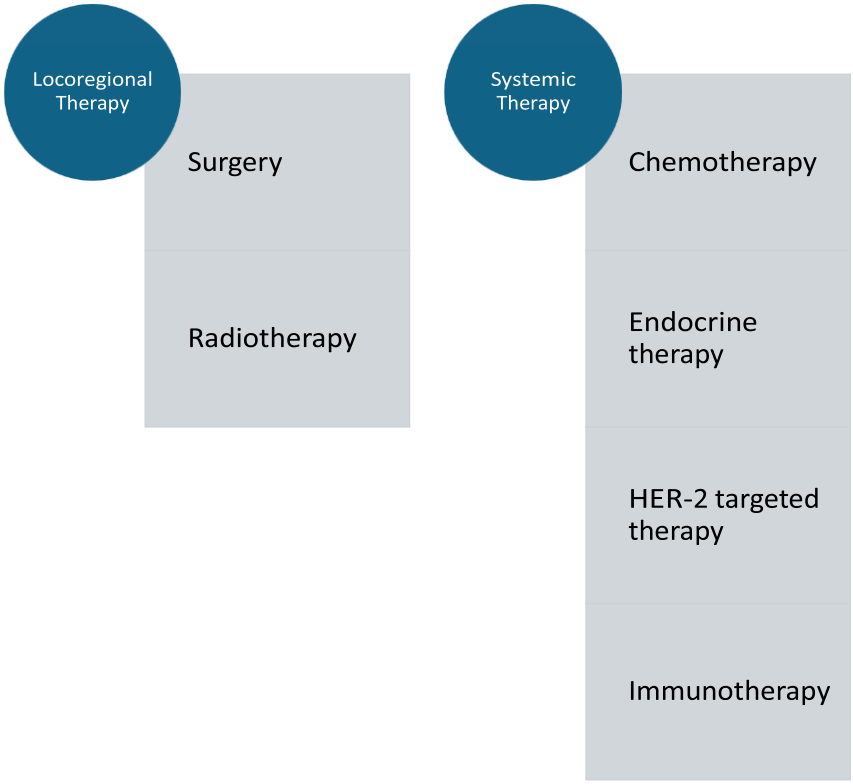


Figure 5: Core treatment modalities

Available resources and local protocols influence treatment options and sequencing. In general, in patients with early disease (Stages 1-2), the treatment is mainly dictated by tumour biology, with a preference for primary surgery in lower-risk tumours, and

neoadjuvant therapy higher risk tumours such as triple-negative or HER-2 positive breast cancers (Figure 6)(41). However, locally advanced breast cancer (stage 3) is usually treated with systemic therapy first to downstage disease before surgery. Stage 4 metastatic breast cancer changes the treatment intent from curative to palliative and consists of systemic therapy and potentially radiation as indicated. Surgery is usually of limited benefit but can be considered for local disease control or oligometastic disease in selected cases(42).

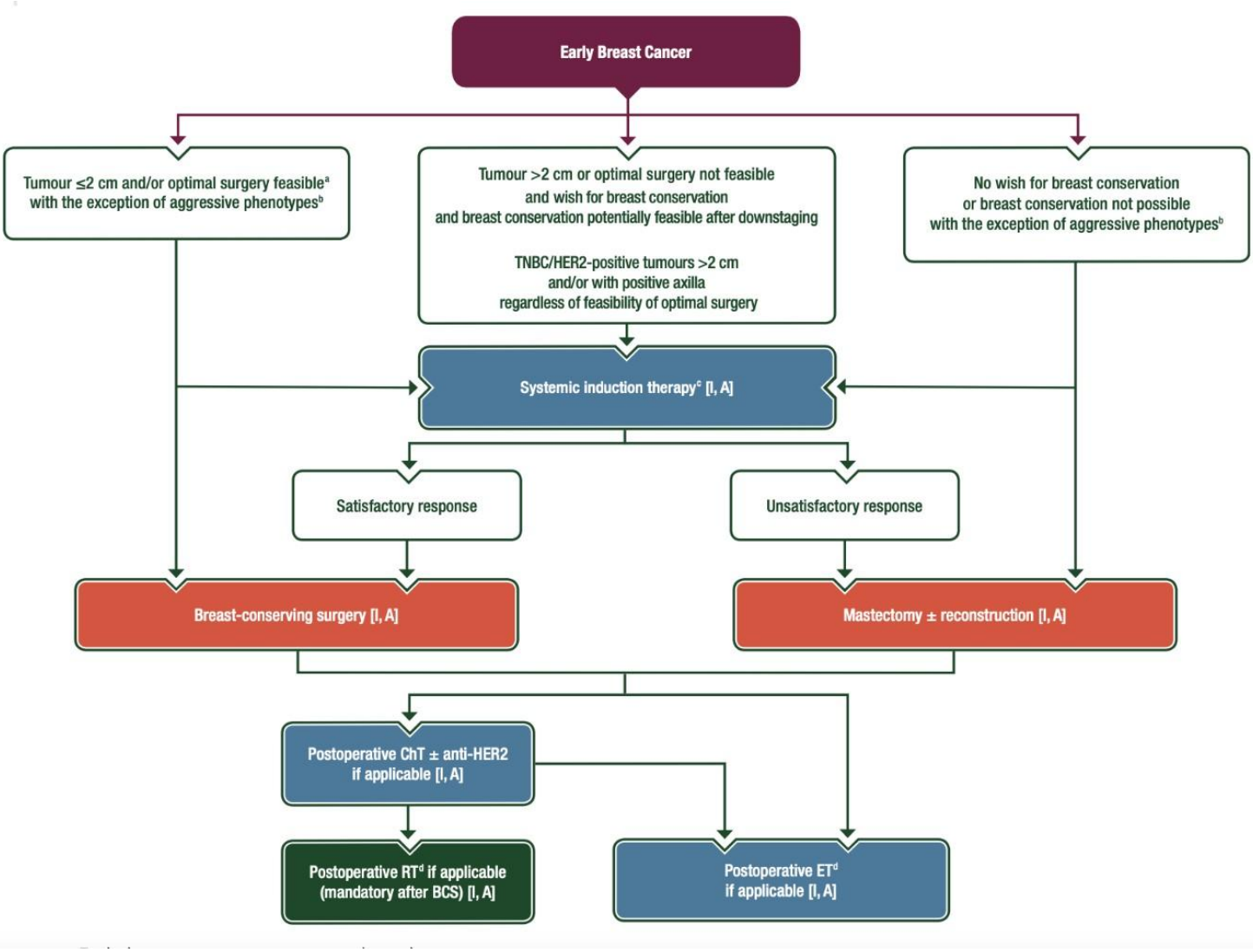


Figure 6: Treatment approach in early-stage breast cancer

a) Biology that requires chemotherapy (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative chemotherapy
b) Aggressive phenotypes: TNBC or HER2-positive breast cancer.
c) If chemotherapy is planned, it should all be given as neoadjuvant.
d) Concomitant postoperative RT, postoperative ET and anti-HER2 therapy.

BCS, breast-conserving surgery; ChT, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; RT, radiotherapy, TNBC, triple-negative breast cancer.
Square brackets indicate level of evidence and strength of recommendation

Source ESMO 2019 guidelines, Ann Oncology, 2019(43)

1.7 Multidisciplinary Team Approach

It is generally accepted that breast cancer is best treated within multidisciplinary teams (MDTs) that include experts from each treatment modality(28). Core specialties include surgery and plastic surgery, radiation oncology, medical oncology, radiology and pathology. Furthermore, the extended team includes breast nurses and navigators, nuclear medicine, oncology rehabilitation, dieticians, fertility preservation, palliative care, psychological support amongst others. Figure 7 illustrates the MDT composition.



Figure 7: The multidisciplinary team

1.8 Treatment Pathways

The treatment pathway of breast cancer patients is complex and involves many healthcare providers. Ideally, integrated breast care should include aspects of the entire patient journey from symptom presentation, diagnosis, work-up, multidisciplinary team discussion to treatments, palliative care, follow-up, and survivorship(44,45). Navigation of the multiple steps and providers can be difficult for both patients and clinicians (Figure 8).

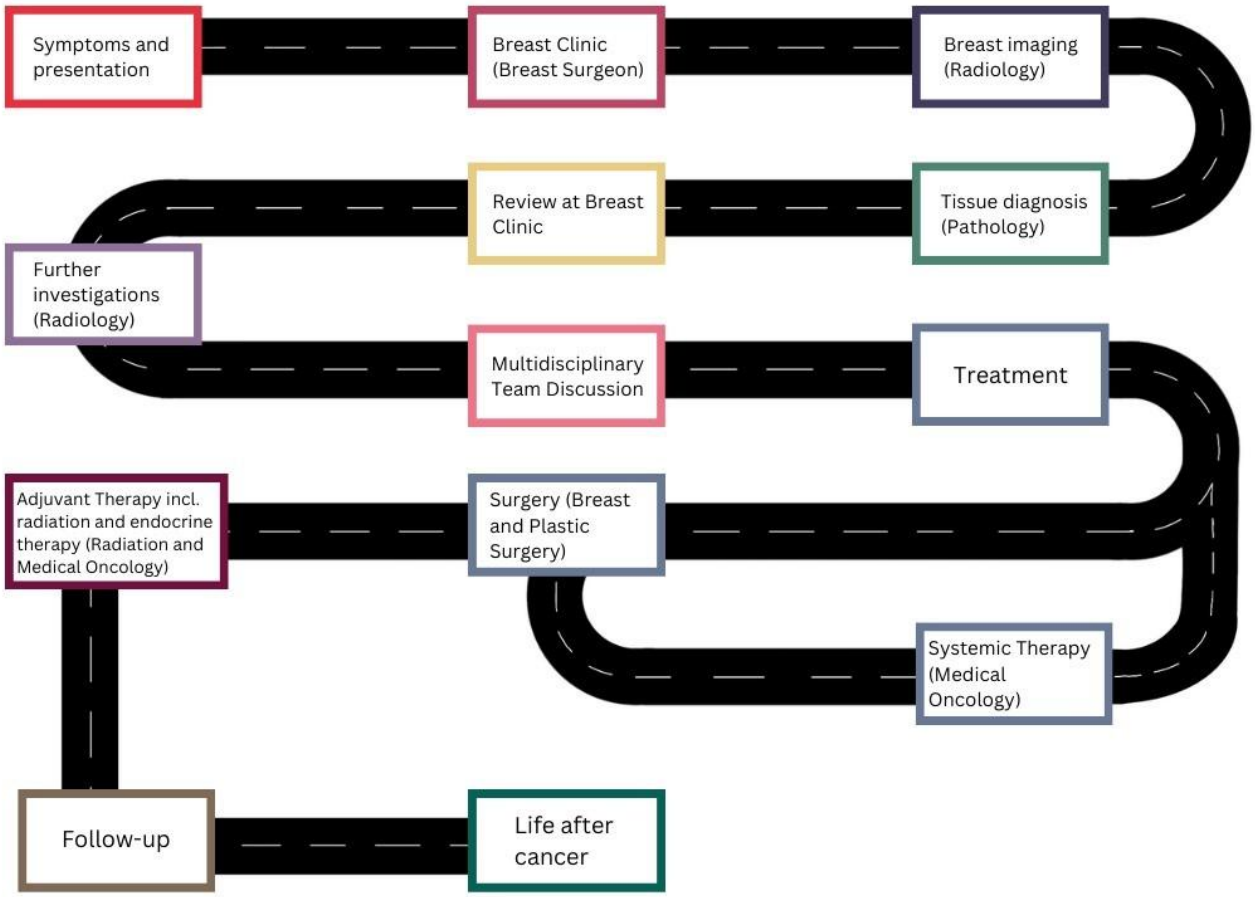


Figure 8: Steps in the classic breast cancer pathway

Clinical pathways are methods for mutual decision-making and care organisation for a well-defined group of patients during a well-defined period. Integrated breast cancer assistance processes, including preventive, diagnostic, therapeutic, follow-up, and care activities, aim for comprehensive management of individuals with breast cancer

and those at increased risk(46,47). To ensure quality processes, quality indicators (QIs) are generally defined along specific sections of the treatment pathway to monitor and ensure good outcomes(48–50).

The surgeon has an important role in the management of breast cancer patients, not only because surgery is a mainstay of treatment, especially in early-stage breast cancer, but also because the vast majority of patients in both the public and private sectors will start their treatment journey with the surgeon, who is responsible for establishing a diagnosis, appropriate workup, discussion in the MDT, communication with the patient, and referral to other specialties.

1.9 South African Healthcare System

South Africa's infrastructure arose from the violent oppression of indigenous people, the appropriation of their land, and their forced minimum wage labour to generate wealth for the white minority(51). Since the post-Apartheid democracy in 1994, the South African healthcare system rapidly expanded access to healthcare to all population groups and has had to face four concurrent epidemics: the growing rate of non-communicable diseases (NCDs), including cancers; diseases of poverty; HIV; and trauma. Although health policies are often excellent on paper, implementation has often been unsuccessful due to failures in leadership, human resource restriction, and wasteful expenditure. Despite the relatively high-income rankings of the country, the health outcomes are often poorer than in other LMICs(51).

According to the World Bank, South Africa is an upper-middle-income country (UMIC). The Gross Domestic Product (GDP) per capita was US$ 6,253.2 in 2023, but a high unemployment rate and gross inequality still mar the country(52). This is reflected by a dual healthcare system in which over 85% of the population relies on the underresourced and overburdened public sector, and under 15% have access to the private sector(53). Health expenditure is similar between the two sectors at 4.2% and 4.4% of the GDP, and over 60% of doctors work in the private sector(19). The uneven allocation of resources results in disparities in health outcomes, reflecting the geographical and socioeconomic divisions rooted in years of discrimination exacerbated by Apartheid.

To address healthcare disparities, the South African government has passed a bill in 2024 on the implementation of a National Health Insurance (NHI) to achieve affordable and

accessible Universal Health Coverage (UHC), which the WHO defines as “all people have access to the full range of quality health services they need, when and where they need them, without financial hardship(54,55).

1.10 Quality of Healthcare

The World Health Organization (WHO) defines quality of care as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes.” Although healthcare quality can be defined in various ways, it is generally acknowledged that it must be effective, safe, people-centred, timely, equitable, integrated and efficient(56). Quality in health care is a complex concept that has evolved, emphasising the importance of meeting standards for delivered care, thereby ensuring patients, funders and clinicians alike that their care quality is optimised through accountability and transparency(57).

1.11 Measuring Quality of Care

Donabedian’s landmark paper “Evaluating the Quality of Medical Care” was first published in 1966 and reprinted in 2005 with over 14,000 collective citations to date(58). In the classic Donabedian model, quality indicators are divided into structure, process and outcome indicators. Structural indicators assess the capacity of the healthcare system to deliver services, including the availability of resources, qualified personnel, and specialised expertise, and are commonly utilised in accreditation processes. Process indicators permit the evaluation of adherence rates to recommended healthcare processes and are the most commonly used indicators to measure quality of care as they are the most sensitive, more accessible to measure and interpret, and allow for immediate directed interventions(59). Process performance measures should however be linked to outcomes to be regarded as relevant(60). Outcome measures such as progression-free and overall survival and quality of life carry the most intrinsic interest and are often regarded as the gold standard in oncology care but are challenging to measure and interpret because of long follow-up requirements and the influence of innumerable patient and clinical factors(61,62). Most QIs are not merely the result of interaction between the provider and the individual patient; they are influenced by many factors, including the structure of the health system, which affects these interactions and must be assessed when defining quality of care(63).

1.12 Conceptual Framework for Quality in Cancer Care

While general concepts of quality of care are frequently used in cancer care, they may inadvertently downplay or ignore elements that are particular to this unique and intricate field of healthcare service. There is no widely accepted framework for the quality of cancer care, but Chiew et al. synthesised 12 cancer-specific aspects of care and integrated them with the classic Donabedian model (Figure 9)(60). In addition to classic structural, process and outcome indicators, the adoption of the concept of value of care introduces a shift to focus on patient-reported outcome measures (PROMs).



Figure 9: Conceptual framework for the quality of cancer care

Source: Chiew et al., European Journal of Cancer Care, 2018(60).

1.13 Quality Indicators for Breast Cancer Care

Quality indicators for breast cancer treatment serve as measurement tools, aiding in identifying deficiencies in the care process and ensuring compliance with clinical guidelines in actual treatment practices. These indicators are subsequently employed to evaluate and monitor the quality of care provided for breast cancer patients.

Several HICs have undertaken significant efforts and developed and applied sets of QIs within Western Europe, North America, Taiwan, and Japan; many also include minimum standards that allow for regular audits and quality control(49,64–66). Despite the numerous quality indicators proposed to standardise and measure breast cancer care processes and outcomes, a consensus across countries, societies and administrations remains elusive and the multiple existing sets of QIs make direct outcome comparisons difficult(67).

Resources and local requirements vary, so QIs created in different settings need adaptation to accommodate diverse patient and professional cultures and clinical practices(68). China was the only LMIC and the only member of BRICS (Brazil, Russia, India, China, South Africa) that had already developed QIs at the beginning of this project(69). South Africa had no quality indicators for breast cancer management, and only very recently was a set of QIs for cancer care in LMICs published. However, this set focuses mostly on medical oncology and is not specifically for breast cancer(70).

Globally, the most prominent set of breast cancer QIs is from EUSOMA (European Society of Breast Cancer Specialists); the first set was published in 2010(71) and updated in 2017(66) and 2024(49). There are various other European documents, including from the Netherlands(72), Germany(73), Belgium(74), England(75), Spain(67), and France(76). The USA has various sets of QIs(65,76,77), but the most prominent is the NAPBC (National Accreditation Program for Breast Centers)(50).

Commonly addressed QIs include preoperative definitive diagnosis, appropriate breast imaging and clinical examination of breast and axilla, complete histopathological evaluation, MDT discussion, breast conservation surgery, receipt of a single operation, receipt of radiotherapy after BCS or post-mastectomy with heavy nodal burden, sentinel node biopsy in clinically node-negative patients, immediate reconstruction rates, use of chemotherapy in ER-negative and HER-targeted therapy

in HER-2 positive patients(49,50,78–80,65,67,69,72–75,77). In response to a global shift towards value-based care, the International Consortium for Health Outcomes Measurement (ICHOM) has integrated various patient-reported experience (PREMS) and PROMS which have been applied in various HICs(81).

Adherence levels to QIs vary across countries and sites and have been reported mainly in HICs. A single unit review from Rwanda was the only publication from an LMIC available at the start of this thesis(82). More recently, additional publications have emerged from China(83), a single unit audit from Nepal(84), and a single unit audit from India.(85). ASCO (American Society of Clinical Oncology) and EUSOMA (European Society of Breast Cancer Specialists) QIs were adapted for the Rwandan publication, EUSOMA QIs were used for the publications from India and Nepal, whereas China applied their own set of QIs. Adherence rates to various QIs from HICs and LMICs are summarised in Tables 1 and 2, respectively.

The implementation of QIs is manageable in various settings and improves the quality of care over time(86,87). Adherence to EUSOMA QIs was assessed in 22 breast centres across Europe from 2006 to 2015. The minimum standard was achieved initially in eight out of 13 QIs but improved to achieve the minimum standards in all QIs by 2015(88).

Numerous studies demonstrated improved quality of care and guideline adherence using QIs and audits(73,74,86–93). Most studies have shown that clinical guidelines adherence can have a positive impact on patient survival outcomes in the field of breast cancer(94–96) but some have had paradox results(97,98). A recent metaanalysis clearly showed improved survival, with 129 more patients surviving with guideline-adherent care for every 1000 patients treated(99). Fewer studies have examined the impact of individual QI adherence on survival. As breast cancer treatment is highly complex and involves many factors, it can be challenging to determine the effects of individual QIs; consequently, most studies examine a survival effect based on a composite indicator or overall adherence to guidelines rather than single QIs alone(83,99–102).

Table 1: Summary of HIC adherence rates for invasive breast cancer

Quality Indicator	**Adherence rates in HICs**								
	Belgium, 2011[72]	Germany (DKG certified), 2014(87) and 2024(103)	Europe (EUSOMA-certified), 2017(88)	Netherlands, 2017[72]	Norway, 2018(104)	France, 2019[76]	France, 2022[79]	Italy, 2023(105)	USA, 2019 (106)
Multidisciplinary discussion									
Multidisciplinary team discussion	61.4% (2003) 80.3% (2006)	-	-	-	-	97.6%	-	-	-
Postoperative MDT discussion	-	99.3% (2009) 100% (2012) 99.4% (2022)	-	91.0% (2011) 99.0% (2014	-	-	-	-	-
Pretreatment MDT discussion	-	37.7% (2010) 58.3% (2012) 79.84% (2022)	-	83.0% (2011) 98.0% (2014)	-	-	-	-	-

Discussion of recurrence or metastases	-	20.0% (2010) 18.0% (2012) 94.35% (2022)	-	-	-	-	-	-	-
Diagnostic workup									
Mammography and ultrasound prior to surgery	84.9% (2001) 86.0% (2006)	-	-	-	-	-	-	-	-
Preoperative definitive diagnosis	50.4% (2001) 71.5% (2006)	97.6% (2009) 97.5% (2012) 98.4% (2022)	80.2% (2006) 91.5% (2015)	-	94.0%	97.6%	94.5%	100%	90.0%
Complete histopathology reporting	-	-	92.1% (2006) 97.5% (2015)	83.0% (2011) 89% (2014)	-	-	-	100%	-
BI-RADS classification used in radiology report	-	-	-	97.0% (2011) 99.0% (2014)	-	-	-	-	-

Breast MRI	-	-	-	In patients undergoing neoadjuvant chemotherapy 28.0% (2012) 31.0% (2014)	-	-	-	46.0%	-
Baseline staging in stage 3 patients	-	-	-	-	-	79.1%	-	-	-

Breast surgery									
Breast conserving surgery (BCS) in T1	-	87.1% (2009) 85.3% (2012) 83.7% (2022)	-	-	-	-	-	-	-
BCS in <3 cm	-	-	73.7% (2006) 84.7% (2015)	-	81.0%	80.8%	-	90.0%	-
BCS in early stage breast cancer	55.3% (2001) 58.4% (2006)	-	-	-	-	-	-	-	-

50% BCS rate in early stage breast cancer	-	-	-	-	-	-	-	-	93%
Mastectomy rate	-	21.6% (2009) 28.6% (2012) 26.5% (2022)	-	-	-	-	-	-	-
Reoperation rate	-	2.2% (2009) 3.1% (2012) 11.8% (2022)	19.8% (2006) 8.8% (2015)	For BCS only 6.0% (2011) 7.0% (2014)	6.0%	12.5%	14.4%	9.0%	-
Specification of resection margins	-	100% (2009) 99.9% (2012)	-	-	-	-	-	-	-

Positive margin rate	-	-	-	5.9% (2011) 4.6% (2014	-	-	-		-
Immediate reconstruction with mastectomy	-	-	-	14.0% (2011) 21.0% (2014)	-	-	-	56.0%	-

Intraoperative specimen radio/ sonography	-	100% (2009) 100% (2012) 100% (2022)	-	-	-	-	-	77.0%	-
Axillary surgery									
Sentinel lymph node biopsy only in pathologically node-negative patients	-	90.7% (2009) 95.2% 2012) 93.3% (2022)	61.5% (2006) 96.7% (2015)	-	98.0%	76.2%	30.7%	95.0%	-
> 5 lymph nodes with sentinel lymph node biopsy	-	-	-	2.3% (2011) 1.7% (2014)	-	-	-	95.0% (≤ 3 nodes)	-
>10 lymph nodes examined in axillary dissection	-	-	89.7% (2006) 86.5% (2015)	-	77.0%	-	-	84.0%	-

Determination of axillary nodal status	-	96.9% (2009) 97.7% (2012) 96.84% (2022)	-	-	-	-	-	-	-

Radiotherapy									
Radiotherapy receipt after breastconserving surgery	82.0% (2001) 89.8% (2006)	98.0% (2010) 97.8% (2012) 97.7% (2022)	95.5% (2006) 95.1% (2015)	-	93.0%	87.8%	94.5%	96.0%	90.0%
Radiotherapy receipt after mastectomy where recommended	-	95.6% (2010) 95.2% (2012)	-	75.0% (2011) 84.0% (2013)	-	95.2%	-	100%	84.0%
Systemic therapy									
Receipt of recommended chemotherapy in ER-negative patients	-	86.2% (2010) 89.5% (2012)	88.9% (2006) 87.3% (2015)	-	-	82.6%, 95.8% in <70 years	-	95.0%	92.0%
Receipt of recommended chemotherapy in ER-positive patients with	-	77.3% (2010) 75.0% (2012) 61.6% (2022)	-	-	-	-	-	-	-

nodal involvement									
Proportion of neoadjuvant chemotherapy in operable t2-3 patients	5.5% (2001) 18.9% (2006)	-	-	-	-	-	-	-	-
Receipt of recommended endocrine therapy in ERpositive patients	-	96.7% (2010) 96.3% (2012) 96.9% (2022)	94.4% (2006) 95.4% (2015)	-	-	93.0%	-	97.0%	90.0%
Receipt of HER-2 targeted therapy in Her2 positive patients	-	83.3% (2010) 93.8% (2012) 95.1% (2022)	-	-	-	98.1%	-	100%	-
Timeliness									
First treatment within 6 weeks post mammogram/ presentation	-	-	-	-	-	-	42.3%	62.0%	-

< 5 weeks between diagnosis and primary surgery	-	-	-	81.0% (2011)	-	-	-	-	-
(without immediate reconstruction)				88.0% (2014)					
< 5 weeks between diagnosis and primary surgery (with immediate reconstruction)	-	-	-	43.0% (2011) 56.0% (2014)	-	-	-	-	-
Receipt of adjuvant radiotherapy within 12 weeks post-surgery	-	-	-	38.0% (2011) 51.0% (2014) (< 5 weeks)	-	-	86.2%	88.0%	-
Receipt of adjuvant chemotherapy within 6 weeks postradiotherapy	-	-	-	65.0% (2011) 64.0% (2013) (< 5 weeks)	-	-	81.9%	-	-

< 5 weeks between diagnosis and start neo-adjuvant chemotherapy	-	-	-	66.0% (2011) 81.0% (2014)	-	-	-	-	-
< 5 weeks between end chemotherapy	-	-	-	77.0% (2011)	-	-	-	-	-

and start radiotherapy				82.0% (2013)					
<5 weeks between end radiotherapy and start of chemotherapy	-	-	-	93.0% (2011) 94.0% (2013)	-	-	-	-	-
Outcomes									
5-year overall survival	Stage 1 93.0% Stage 2 84.0% Stage 3 64.0% Stage 4 26.0%	-	-	-	-	-	-	-	-

Others									
Psychooncologic care	-	66.7% (2009) 69.0% (2012 53.8% (2022)	-	-	-	-	-	-	-
Primary case numbers per centre (median)	-	176.5 (2009) 170.5 (2012) 185.5 (2022)	-	-	-	-	-	-	-
Receipt of first follow-up mammogram	-	-	-	-	-	-	61.5%	-	-
Social service counselling	-	89.5% (2009) 87.9% (2012) 68.3% (2022)	-	-	-	-	-	-	-
Research participation	-	21.5% (2009) 11.3% (2012) 22.6% (2022)	-	-	-	-	-	-	-

Table 2: Summary of LMIC adherence rates for invasive breast cancer

Quality Indicator	Adherence rates in LMICs			
	Rwanda, 2017(82)	Nepal,2022(84)	India, 2024(85)	China, 2024(83)
Multidisciplinary discussion				
Multidisciplinary team discussion	-	0%	88.6%	-
Diagnostic workup				
Mammography, physical examination, and ultrasound of both breast and axilla	-	53.8%	98.2%	-
Image guided axillary staging (by ultrasound and core or fine needle biopsy	-	-	89.3%	-
Preoperative definitive diagnosis	-	97.1%	100%	60.1%

Complete histopathology reporting	Defined as tumour type and hormone receptor status: 98.0%	78.2%	100%	ER and PR assessment before systemic therapy: 85.7% HER-2 assessment before systemic therapy: 83.6% Postop category of primary tumour and regional lymph nodes with histologic grade: 69.8% Postop hormone receptor status: 72.2% Postop tumour size: 98.1%
Breast MRI	-	-	39.5% (excluding patients with neoadjuvant therapy) 25.9% (of patients with neoadjuvant therapy)	-
Baseline staging tests stage 3 patients	-	10.8%	100%	-
Breast surgery				
BCT in T1	-	-	100%	-
BCT in <3 cm	-	36.0%	63.3%	-

BCS in early stage breast cancer	-	-	-	17.4%
Reoperation rate	-	5.2%	0%	-
Immediate reconstruction with mastectomy	-	-	0.9%	-
Axillary surgery				
Sentinel lymph node biopsy only in pathologically nodenegative patients	-	-	98.7%	Among clinically node negative patients with primary <3cm: 31.6%
Proportion of breast cancer patients who underwent breast surgery and SLNB concurrently	-	-	-	21.5%
> 5 lymph nodes with sentinel lymph node biopsy	-	-	26.0%	-
>10 lymph nodes examined in axillary dissection	-	83.2%	-	-
Curable mastectomy patients receiving ALND	87.9%	-	-	-

Radiotherapy				
Radiotherapy receipt after breast-conserving surgery	Radiotherapy not available	94.7%	96.1%	-
Radiotherapy receipt after mastectomy where recommended	Radiotherapy not available	76.9%	77.4% 100% with N2 axilla	-
Systemic therapy				
Receipt of recommended chemotherapy in ER-negative patients	-	95.0%	90.1%	-
Receipt of recommended chemotherapy in ER-positive patients with nodal involvement	In curable patients without documented negative lymph nodes receiving at least four cycles of chemotherapy: 73.6%	-	-	-
Receipt of recommended endocrine therapy in ERpositive patients	Within 1 year of diagnosis: 83.3%	88.7%	100%	66.5%

Receipt of HER-2 targeted therapy in Her-2 positive patients	-	4.8%	85.4%	-
Neoadjuvant chemotherapy for locally advanced or inflammatory breast carcinoma	-	30.6%	93.8%	-
Patients treated by trastuzumab in whom heart function was monitored every three months	-	-	-	48.7%
Timeliness				
First treatment within 6 weeks post mammogram/ presentation	Within 8 of weeks diagnosis: 74.7%	88.4%	100%	-
Curable patients without disease progression receiving all indicated curative therapy within 1 year of first biopsy	Radiation not available, for the others: 57.3%			
Others				
Genetic counselling referral	-	-	11.8%	-

Data on life status and recurrence rate (for at least 5 years)	-	-	76.4%	-
Routine annual mammographic screening and 6/12 months clinical evaluation in the first 5 years after primary surgery	-	-	96.3%	-
Breast nurse availability and counseling	-	-	100%	-
Availability of data manager	-	-	yes	-

1.14 The Concept of Breast Units

It is well-accepted that breast cancer is best treated in multidisciplinary teams with the appropriate expertise and patient volume and the concept of a breast unit formalises and organises the historically fragmented and chaotic treatment pathways. With the condensation of multidisciplinary expertise and resources come various benefits, including improved patient outcomes, such as survival and quality of life, guidelineadherent care, appropriate use of multidisciplinary treatment modalities, increased cost efficiency, and decreased litigation(87,107,108).

In Europe, formal breast centers were established more than twenty-five years ago. This initiative was prompted by the historic Florence consensus statement from 1998, which called for all women to have access to fully equipped multidisciplinary breast clinics, advocating for one center for every 250,000 people to ensure optimal service(108). In America, the first free-standing breast centre, the Van Nuys Breast Center, was created by Silverstein(109).

Although the term breast centres may be readily used and new centres may develop and theoretically provide high-quality service, this is not always guaranteed, and the critical question for patients and referring physicians is how to assess the quality of a breast centre objectively. There are several set requirement and accreditation systems, most prominently EUSOMA in Europe(28), NAPBC the United States of America(50), and Onkozert from the DKG (Deutsche Krebs Gesellschaft) in Germany(110), but none have been adapted for LMICs that reflect our healthcare setting and needs. Formal accreditation processes have been used since 2000 in Europe through EUSOMA(111), 2003 through the DKG (Deutsche Krebs Gesellschaft)(112), and 2006 through the NAPBC in the USA(113). Though international accreditation exists for all three organisations, their standards may not be suitable or financially viable, making them rarely reproducible in LMICs.

1.15 The Current State of South African Surgical Breast Cancer Care

The National Department of Health developed and published the Breast Cancer Control Policy in 2017(114), identifying breast cancer as a national priority. This was followed by the Breast Cancer Management Guideline in 2019(115), which further described specific breast centre requirements and proposed treatment timelines. Both

documents contain good policies, but, unfortunately, they entirely lack implementation(116).

Surgical subspecialties are formally recognised for vascular, trauma, upper and lower GIT, but not for breast or breast and endocrine surgery. Although significant efforts have been made repeatedly over the past decade to have breast surgery (with or without combination with endocrines surgery) recognised as a subspecialty, these efforts have not been supported by the College of Medicine of South Africa (CMSA) and Health Professions Council of South Africa (HPCSA). The surgical treatment of breast cancer is, therefore, still mainly in the hands of generalists, with a few exceptions of surgeons who have focused or entirely limited their practice to the treatment of breast disease.

Access to breast care is difficult for patients in South Africa and the majority present with an advanced stage. Reasons for this include lacking patient education, breast cancer knowledge and awareness, socioeconomic and geographical barriers, as well as significant health system inefficiencies(117,118).

Currently, there are less than ten specialised breast units in the public sector in SA and less than ten in the private sector. This contrasts with the European optimum of one breast unit per 250.000 total population(28). However, their incidence rates are approximately three times higher than in South Africa, and I would therefore estimate the number of units countrywide for optimal service to be around 80, based on one unit per 750.000 total population of 62 million.

The quality of breast cancer care is mainly ungoverned, and patients are likely to receive very different quality of care and outcomes depending on their geographical location and socioeconomic status. Although access to care may be easier in the private sector compared to the public sector, the quality of care is not necessarily better on either side due to a lack of governance, implementation of guidelines, and specialised multidisciplinary care.

1.16 Gaps in the Literature and Motivation for the Study

It is well recognised that breast cancer incidence is rising in South Africa and other LMICs with disproportionately high mortality rates and that urgent and effective interventions are required to improve patient survival.

There is no data on the quality of surgical and diagnostic breast cancer care in South Africa and no quality frameworks such as quality indicators and requirements for breast centres have been developed for our setting. Diagnostic and surgical breast cancer care quality has never been measured, which would inform on the level of care, gaps in care and opportunities for directed interventions. Site adaptations (successful or otherwise) of treatment pathways in response to resource constraints have never been demonstrated, although our group is beginning to characterise such adaptations in the South African Breast Cancer and HIV Outcomes (SABCHO) cohort study(119).

Although QI adherence appears to improve survival in HICs, it is unclear whether there would be any measurable effects of individual QIs for LMICs, where survival is heavily influenced by the stage at presentation and healthcare systems are less consistent in their delivery. Should there be identifiable QIs with a significant impact on survival, this would offer targets for feasible and effective interventions and inform health policy.

1.17 Aims and Objectives of the Study

The overarching aim of this study was to define quality frameworks and investigate the quality of diagnostic and surgical breast cancer care in South Africa.

The specific objectives were:

1. To review breast surgery QIs within the global and LMIC context and develop a set of diagnostic and surgical QIs for South Africa.
2. To measure the adherence rates to QIs amongst women with breast cancer in South Africa.
3. To establish the requirements of breast centres in South Africa.
4. To assess the effect of individual and composite QI adherence on overall survival in women with breast cancer in South Africa and to compare treatment pathways across sites.

1.18 Study Questions and Hypotheses

With reference to the forementioned objectives, the following study questions and hypotheses were formulated:

1. ***Which are the most appropriate quality indicators for the surgical management of breast cancer in South Africa?***

Little data on breast cancer quality indicators exists in LMICs and need to be adjusted to local context.

2. ***What is the rate of adherence to QIs in the SABCHO cohort?***
   Adherence levels are overall lower than in HICs with lower quality of care received in the SABCHO cohort.
3. ***What are the most appropriate requirements for breast centres in LMICs in sub-Saharan Africa?***
   Sparse data on breast cancer centres exists in LMICs and needs to be adjusted to local context.
4. ***Does individual or combined QI non-adherence have a measurable effect on overall survival in our cohort? Did sites adjust treatment pathways in response to resource constraints?***
   Individual QIs will not have measurable effects on survival, but a composite measure may show an effect; sites will have adjusted treatment pathways to specific resource constraints.

CHAPTER 2: METHODOLOGY

This chapter outlines the study setting and designs, data measurement and management techniques, and the ethical considerations associated with this thesis.

The study was conducted in South Africa. The series of studies set out to accomplish four unique objectives and utilised four different but complementary methodologies in a mixed-methods approach. Our focus was on quality indicators of surgical breast cancer care, and included histopathology, as it is essential in surgical decisionmaking, as well as an assessment of radiotherapy following breast conserving surgery (BCS), which may affect surgical choices.

National expert panels were established to make recommendations for the first mixedmethod and third qualitative consensus papers. The SABCHO cohort formed the basis for the second and fourth quantitative papers. Each empirical paper (Section Two) further details specific methodologies and statistical analyses.

2.1 Study setting and SABCHO cohort

Recruitment took place at six sites (Figure 10) and included patients from Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg and Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, both located in the Gauteng province, as well as Inkosi Albert Luthuli Central Hospital (IALCH) and Addington Hospital in Durban, Ngwelezana Hospital in Empangeni and Grey's Hospital (GH) in Pietermaritzburg in Kwa-Zulu Natal. Recruitment commenced in 2015 and concluded in December 2018 at the KZN sites, while the Gauteng sites have continued recruitment up to the present. All women with newly diagnosed invasive breast cancer, at least 18 years of age and residing in South Africa for at least five years were eligible for enrolment. The SABCHO protocol is detailed in Cubasch et al(120) and further described in Chapters 3 and 6.

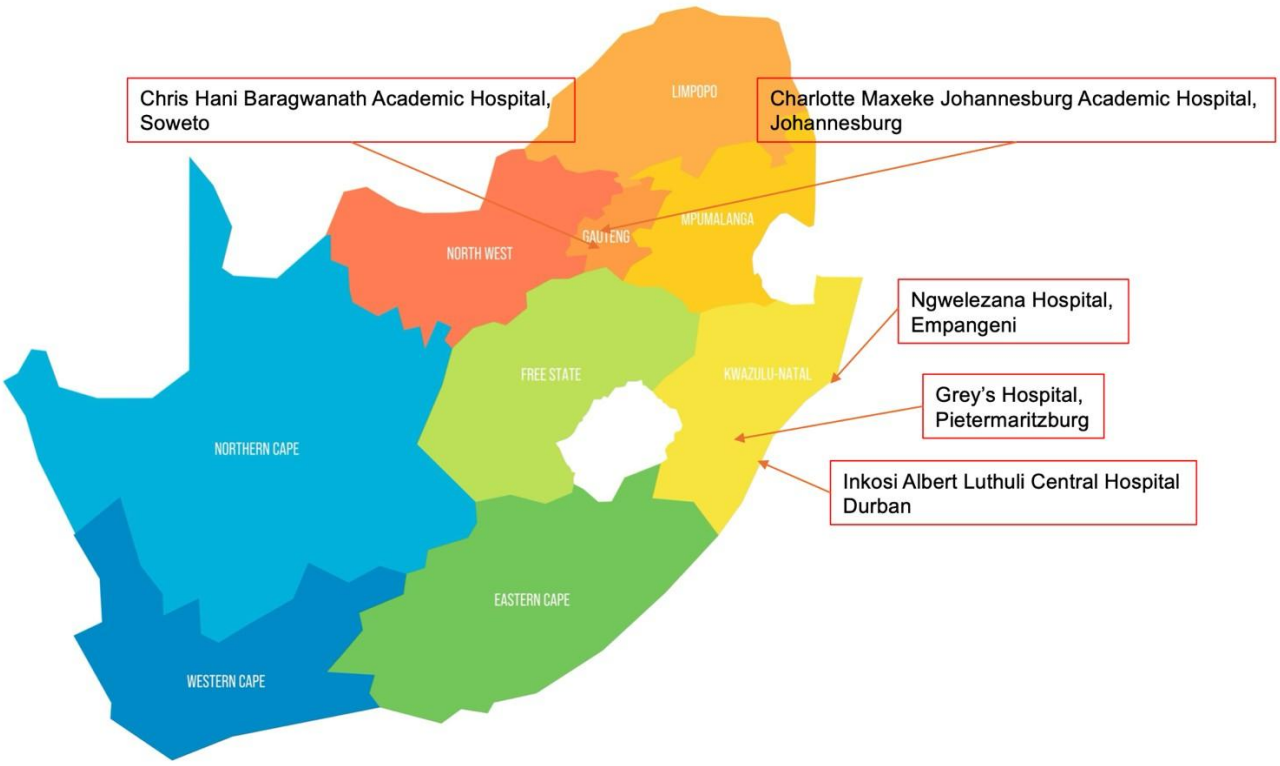


Figure 10: Map of SABCHO study sites

2.2 Provinces

Gauteng is landlocked, the smallest province by land area, but the most populous province in South Africa. It is home to 21.4% of the national population and is almost entirely urban(121,122). Gauteng comprises three metropolitan municipalities: the City of Ekurhuleni, City of Johannesburg, and City of Tshwane. Gauteng translates to “the place of gold” in Sotho. Following the discovery of gold in 1886, a surge of people flooded into the area, making Johannesburg the world's largest gold producer at the time. Johannesburg remains the powerhouse of South Africa and the heart of its commercial and industrial sectors today. It is the largest city in South Africa, covering approximately 1,645 km²(123,124). Soweto, the South Western Township, was established to house black residents who were forced from their homes in Johannesburg due to the implementation of the racial segregation policy called the Group Areas Act of 1950(125). This is South Africa's biggest township, featuring an exceptionally high population density of approximately 6357 people/km, compared to Johannesburg's total density of 2696 people/km(126).

KwaZulu-Natal is located in the east of South Africa, bordering the Indian Ocean, and is the second most populous province in South Africa, with a mixed urban and rural population. Although Pietermaritzburg is KZN's capital, Durban is larger and is the third most populated city in South Africa(127).

2.3 Hospital Sites

Chris Hani Baragwanath Academic Hospital is also fondly referred to as "Bara" and is the largest hospital in South Africa and the African continent, ranked as the seventh largest worldwide with 3200 patient beds and 6760 staff(127). It offers a broad spectrum of tertiary and quaternary services and is a referral centre for much of Gauteng, the North West province, and parts of the Northern Cape, and informally the rest of South Africa, except the Western Cape(127).

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) was formerly known as Johannesburg General Hospital "Joburg Gen" and has 1088 patient beds and over 4000 staff. It is mandated to offer a full spectrum of secondary, tertiary, quaternary and highly specialised services and is a referral centre for Gauteng and other provinces(128).

Inkosi Albert Luthuli Central Hospital (IALCH) is a tertiary care referral hospital with 846 beds(129). Grey's Hospital (GH) is also a tertiary hospital offering specialised services to the western parts of KZN and has 530 commissioned beds(130).

Both CHBAH and CMJAH are academic teaching hospitals for the University of the Witwatersrand, and IALCH and GH are teaching hospitals for the University of KwaZulu-Natal.

The hospitals have varying levels of oncology service capacity and serve different populations, as summarised in Table 3. The central Johannesburg CMJAH unit and the urban KZN units in Durban and Pietermaritzburg offered diagnostic, surgical and endocrine therapy and full access to on-site oncology services such as radiation and chemotherapy. At the time of recruitment, the Soweto CHBAH unit offered diagnostic, surgical and endocrine services but had no on-site oncology access, and patients had to be referred to CMJAH. Since 2021, an Oncology Unit providing medical oncology services has been treating cancer patients at CHBAH.

Table 3: Study site description

	Soweto hospital, Johannesburg[1]	Central Johannesburg hospital[2]	KZN Durban hospitals[3]	KZN Pietermaritzburg hospital[4]	KZN rural hospital[5]
Location	Johannesburg (Gauteng province)	Johannesburg (Gauteng province)	Durban (KwaZulu-Natal Province)	Pietermaritzburg (KwaZulu-Natal Province)	Empageni (KwaZulu-Natal Province)
Main population catchment area (N)	Soweto (3 million)	Johannesburg, East and Central (3.5 million)	Durban metropolitan, (3.5 million)	Western KwaZulu-Natal and distant rural communities (3.5 million),	Uthungulu, Umkhanyakude, Zululand (3 million)
Surgery	Surgery performed at this hospital	Surgery performed at this hospital	Surgery performed at this hospital and in secondary hospitals	Surgery performed at this hospital and in secondary hospitals	Surgery performed at this hospital or at KZN Durban Hospitals
Oncology capacity (Chemotherapy and radiotherapy)	None. Patients referred to CMJAH	Full oncology capacity	Full oncology capacity	Full oncology capacity	None. Patients are referred to KZN Durban hospitals.

[1] Chris Hani Baragwanath Academic Hospital, Soweto Johannesburg
[2] Charlotte Maxeke Johannesburg Academic Hospital
[3] Addington Hospital and Inkosi Albert Luthuli Central Hospital, Durban, KwaZulu-Natal
[4] Grey's Hospital, Pietermaritzburg, KwaZulu-Natal
[5] Ngwelezana Hospital, KwaZulu-Natal

Adapted from Ayeni et al.(131)

The KZN rural hospital offered only diagnostic services, basic surgery and endocrine treatments, and follow-up care for patients after undergoing surgery, chemotherapy, or radiation therapy at Durban hospitals over 200 km away. In Gauteng, all surgeries were performed at the tertiary breast units, whereas these were performed at regional hospitals or the tertiary units in KZN. The patients' education and socioeconomic status also varied widely, with those from rural communities accessing the KZN Pietermaritzburg and Ngwelezana units tending to be less educated and more impoverished than their urban counterparts.

2.4 Methodological Approach

We employed a mixed methods approach, utilising both quantitative and qualitative research methods. We integrated these in a concurrent mixed method design during the Delphi process and a sequential exploratory mixed method design throughout the overall sequence of studies with the early development of the QIs for use in the quantitative papers.

The sequential design was deliberately chosen. First, the literature was reviewed, and a contextually relevant set of QIs) was developed, integrating both qualitative and quantitative components. This set then served as the foundation for the subsequent quantitative paper aimed at evaluating adherence levels and identifying gaps in care, which in turn informed the development of survival models to assess the impact on overall survival. The breast centre requirements were established following the first quantitative paper, with the achieved initial benchmark highlighting the specific relevance of structural quality components.

2.5 Data Management and Analysis

Data collected for Paper 1 was collected on the Research Electronic Data Capture (REDCap) data management platform(132,133), hosted by the University of the Witwatersrand. Data for Papers 2 and 4 was captured on OncoDB, a purposefully designed comprehensive breast database and electronic patient record (EPR) initiated at CHBAH in 2008. Data was entered by clinicians as well as SABCHO research staff. QI were extracted by review of clinical records and histopathology entries.

The data manager and principal investigators (PIs) of SABCHO act as gatekeepers, and requests for access and usage of the data were made in accordance with the

research unit processes. The data were analysed by myself, and findings subsequently discussed and reviewed with my supervisors and co-authors. Data management involved performing quality checks and cleaning data related to all key variables at various time points for each study. Data were evaluated for accuracy, consistency and outliers. Data manipulation included the creation of new variables (e.g. quality indicator adherences) and the recoding of existing variables as well as transforming or converting variables (e.g. continuous variables to categorical variables). All statistical analyses were conducted using Stata (StataCorp, version 14 and 16(134,135). Details regarding the statistical tests employed are provided in each empirical paper.

2.6 Ethical Approval

Ethics clearance for the PhD study was granted by the University of the Witwatersrand‘s Human Research Ethics Committee (HREC) (Medical); ethics clearance certificate M180671: Quality indicators of Breast Cancer Surgery in South Africa. All questionnaires were coded to ensure participant names were not used, maintaining confidentiality. An extension to M180671 was granted in 2024, M240165. In addition, an amendment on M240165 to include a breast centres consensus paper was received. The SABCHO study received separate ethics clearances from the University of the Witwatersrand‘s Human Research Ethics Committee (HREC) (Medical), The University of Kwa-Zulu Natal’s Biological Research Ethics Committee and Columbia University’s Vagelos School of Physicians and Surgeons Institutional Review Board (IRB). Copies of all PhD ethics clearance certificates can be found in Appendix B.

PART 2: EMPIRICAL CHAPTERS

“Don’t believe what your eyes are telling you. All they show is limitation.”

(Johnathan Livingstone Seagull by Richard Bach)

CHAPTER 3: QUALITY INDICATORS FOR THE DIAGNOSIS AND SURGICAL MANAGEMENT OF BREAST CANCER

Nietz S, Ruff P, Chen WC, O'Neil DS, and Norris SA. Quality indicators for the diagnosis and surgical management of breast cancer in South Africa. *The Breast*, 2020 Dec;54:187–96. DOI: http://dx.doi.org/10.1016/j.breast.2020.09.012 (Appendix E)

3.1 Abstract

Introduction

Quality indicators (QIs) for breast cancer care have been developed and applied in high-income countries and contributed to improved quality of care and patient outcomes over time.

Materials and Methods

A modified Delphi process was used to derive expert consensus. Potential QIs were rated by a panel of 17 breast cancer experts from various subspecialties and across South African provinces. Each QI was rated according to importance to measure, scientific acceptability and feasibility. Scoring ranged from 1 (no agreement) to 5 (strong agreement). Inclusion thresholds were set *a priori* at mean ratings ≥4 with a coefficient variation of ≤ 25%. Levels of evidence were determined for each indicator.

Results

The literature review identified 790 potential QIs. After categorisation and removal of duplicates, 52 remained for panel review. There was strong consensus for 47 which were merged to 30 QIs by exclusion of similar indicators and indicator grouping. The final set included eight QIs with level I or II evidence and two QIs with level III evidence which were deemed "mandatory" due to clinical priority and impact on care. The remaining QIs with lower-level evidence were grouped as eight "recommended" QIs (regarded as standard of care) and twelve "optional" QIs (not regarded as standard of care).

Conclusion

A regional set of QIs was developed to facilitate standardised treatment and auditing of surgical care for breast cancer patients in South Africa. Routine monitoring of the

ten mandatory QIs, which were selected to have the most substantial impact on patient outcomes, is proposed.

3.2 Introduction

Breast cancer is the most common malignancy among women in Sub-Saharan Africa(136). Patient outcomes remain poorer in low- to middle-income countries (LMICs) compared to high-income countries (HICs), and reasons include difficult access, late presentation, decreased awareness, and limited treatment resources(137). Robust data on the quality of surgical breast cancer care in South Africa is non-existent to date, but considerable variations depending on the geographical location and socioeconomic status of the patient are likely. A recent report on timely delivery of chemotherapy, radiation, and endocrine treatment showed considerable non-adherence and the need for focused quality improvement in South Africa(138). Although South Africa is regarded as an upper-middle-income country (UMIC) by the World Bank, it has a high index of inequality. Socioeconomic disparities characterise its heterogeneous society which, together with other factors, affect health status and patient outcomes; a divide that is particularly obvious in the dual public and private health care system(51).

Breast cancer is a heterogeneous disease and is best treated by a multidisciplinary specialist team. Case volume and expertise clearly affect outcomes and women treated by specialist surgeons are more likely to receive guideline-adherent therapy with better oncological outcomes(93,139,140). Despite these clear benefits and increasing breast cancer incidence, there are very few dedicated surgical breast units in the South African public sector that offer standardised care, and these are often burdened with high patient volumes and inadequate resource allocation.

Specific breast cancer QIs have been developed and applied in various HICs(65,66,71) with China being the only LMIC to have published dedicated QIs to date(69). Implementation of QIs is feasible in various settings and tends to improve quality over time(86,87). The process of audit facilitates awareness and adherence to guidelines(88). QIs are not always readily transferable and need to be adjusted to each setting to allow for variations in clinical practice and health care systems(68).

Non-communicable diseases including cancer were recently declared a priority by the

South African National Department of Health (NDoH) and National Breast Cancer Policy Guidelines were developed and published. However, they remain to be implemented(114). The onus therefore still remains with clinicians to find solutions to standardise and improve breast cancer care in South Africa. This study aimed to develop a regional set of QIs for the diagnosis and surgery of breast cancer in South Africa, through a clinician-driven process using a modified Delphi method.

3.3 Materials and Methods

Systematic review

The literature was reviewed on databases including PubMed, Springer, and MEDLINE, as well as QIs published by various international institutes and societies including the American Society of Breast Surgeons (ASBrS), American Society of Clinical Oncology/National Comprehensive Cancer Network (ASCO/NCCN), American Society of Clinical Oncology/National Initiative for Cancer Care Quality (ASCO/NICCQ), Commission on Cancer of the American College of Surgeons (CoC/ACS), European Society of Breast Cancer Specialists (EUSOMA), German Cancer Society (DKG), National Breast Cancer Organisation Netherlands (NABON), National Institute for Health and Care Excellence (NICE), National Quality Forum (NQF) and Scottish Cancer Taskforce. Search terms included “quality indicator”, “quality measures”, “quality parameters”, “breast cancer”, “breast surgery” and “breast pathology”. National and international clinical guidelines and breast centre accreditation criteria, such as EUSOMA criteria and National Accreditation Program for Breast Centers (NAPBC) were considered(141,142).

A national expert panel

A panel of experts was selected according to: (i) provincial representativeness, (ii) subspecialties and expertise in breast cancer diagnosis and treatment, (iii) knowledge of the local health care system, and (iv) clinical and academic seniority. The final panel consisted of 17 experts: ten surgeons, two medical oncologists, two radiation oncologists, two pathologists, and one radiologist (Figure 11). Each participant was consented and received a study participant number and an electronic link to each Delphi rating round by email. All ratings were anonymous with controlled feedback following each rating round. In October 2018, a face-to-face meeting at the Breast Interest Group of Southern Africa (BIGOSA) conference in Durban, was attended by

all members of the expert panel. The potential QIs, their definitions, and the process of selecting the QIs were presented, discussed, and accepted as valid and further locally relevant QIs were invited for inclusion.

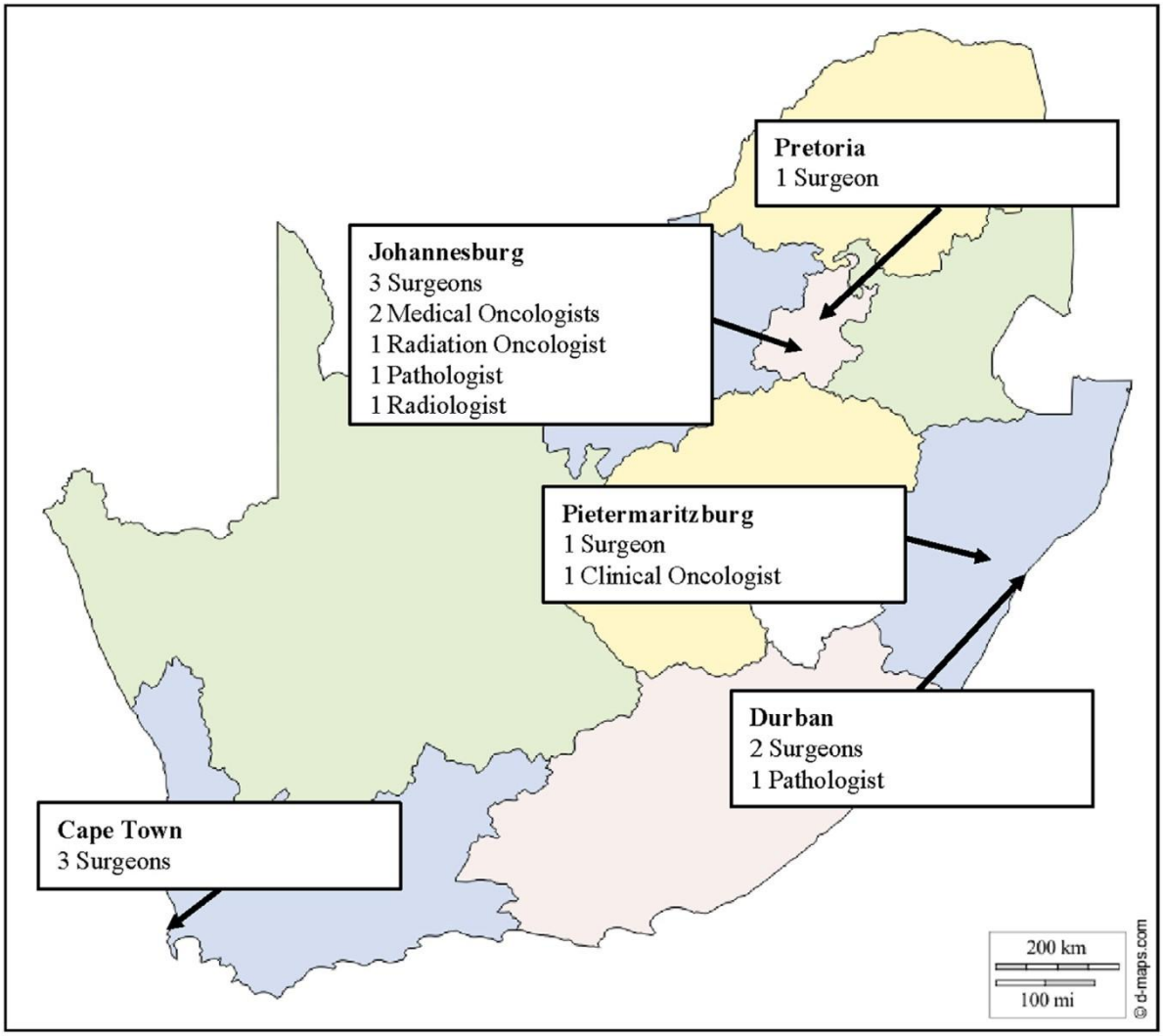


Figure 11: Expert panel composition

Delphi rounds

The Delphi process assumes that group judgements are more valid than individual judgements and is a widely recognised method to reach expert consensus in a structured manner. Key principles include statistical group response and iteration with controlled feedback. The strengths of the Delphi process are the effective use of a committee and the anonymity of equally-weighted responses which reduces the risk of opinion shifts and peer pressure. Limitations of the Delphi process include the lack of clear methodological guidelines and limited reliability and validity(143). The Nominal

Group Technique (NGT) was considered as an alternative which is based on structured meetings with facilitated discussion but the Delphi process was selected for its anonymity of ratings. However, the Delphi process was modified to include a face-to-face meeting, essentially merging one component from the NGT to allow for critical discussion while preserving anonymous rating as the key strength of the Delphi process. The inclusion of a meeting is a commonly used modification in Delphi projects for healthcare quality indicators(144).

Three rounds were planned whereby each QI was rated according to: a) importance to measure (relevance and priority), b) scientific acceptability (reliability and validity), c) appropriateness to our local setting (feasibility). Scoring ranged from 1 (no agreement) to 5 (strong agreement). Inclusion thresholds were set *a priori* at mean ratings $\geq$4 with a coefficient variation of ≤ 25%. The first Delphi rating round took place during the face-to-face meeting by anonymous electronic rating. The subsequent two rating rounds were conducted electronically by emailed invitation following the meeting. Study participant numbers were not identifiable to any of the authors. Study data were collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tool and processed by an independent analyst(133). *Level of evidence*

Lastly, the respective level of evidence (LoE) for each indicator was determined to allow for practical prioritisation of QIs. Levels of evidence were adopted from previously published guidelines or determined through literature review by the authors. For ease of application, the LoE was determined by the United States Agency for Healthcare Research and Quality (AHRQ, www.ahrq.org) classification(145):

- Level 1 – Requires good-quality randomised controlled trials or systematic reviews
- Level 2 – Requires well designed quasi-experimental studies
- Level 3 – Requires well designed descriptive studies
- Level 4 – Expert judgement

3.4 Results

The literature review revealed 920 potential QIs. Those which did not address preoperative diagnosis or surgical management were removed, leaving 129 potential

QIs. Duplicate QIs were also removed, and 52 potential QIs remained for expert panel consideration (Figure 12).

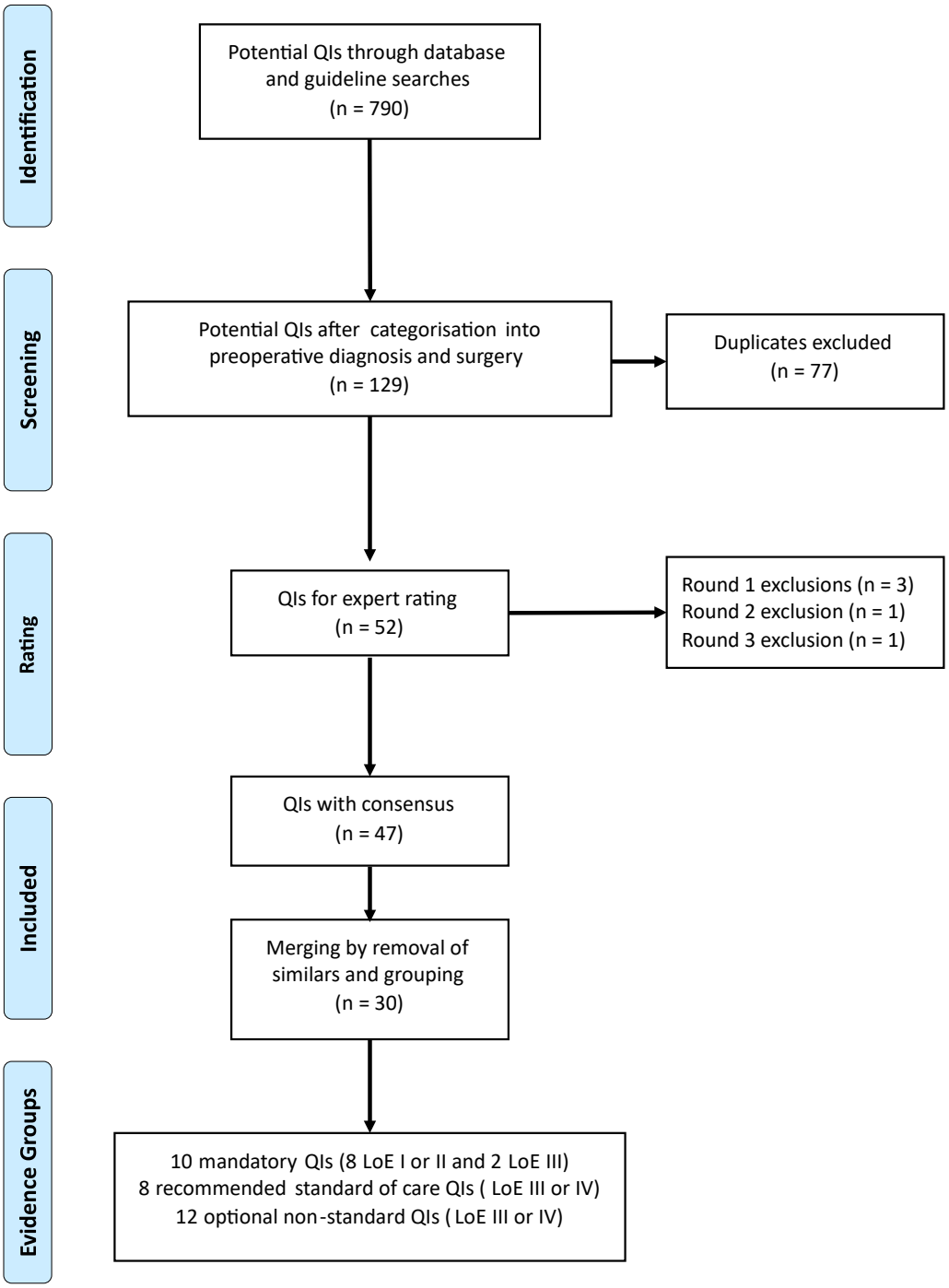


Figure 12: Consort diagram

The first rating round excluded three QIs that failed to achieve a consensus of importance (Supplementary Figure 1, Appendix G). These included “intraoperative use of ultrasound by the surgeon”, “documentation of contralateral breast cancer risk” and “intraoperative pathology assessment of sentinel lymph nodes”. “Use of preoperative magnetic resonance imaging (MRI)” and “appropriate axillary surgery in ductal carcinoma in situ (DCIS)” did not reach consensus in the initial rating round but were rescued after discussion and revote. All 17 experts were present and completed the rating.

The second rating round excluded one indicator on the “use of preoperative MRI” due to a coefficient variation of >25% (Supplementary Figure 2, Appendix G); 13 expert responses were received, of which 12 were complete and used for analysis. One indicator was deemed not feasible in the third rating round with a coefficient variation of >25% (“appropriate clinical assessment of the axilla with sonar and fine needle aspiration”). The third round had 11 complete responses (Supplementary Figure 3, Appendix G). There was no dissension in round two and three and no revote was required.

47 QIs had expert consensus following the Delphi process. Three indicators showed similarity including “single operation rate for invasive breast cancer” and “single operation rate for DCIS” compared to “reoperation rate”, as well as “pathology assessment of lymph nodes” which was included in “complete histopathological characterisation” and the indicators with higher overall panel ratings were retained. A further 22 parameters were merged into eight grouped QIs which resulted in a final set of 30 QIs. Of these, eight QIs had strong LoEs (level 1 or 2). Two additional indicators with lower LoE (unit and surgeon case volumes and multidisciplinary discussion) were regarded as critical for quality improvement and were incorporated into the mandatory set (Table 4 and 5). A further eight QIs were regarded as standard of clinical care but had lower LoE (level 3 or 4). These were deemed recommended (Table 6). A further twelve QIs were not regarded as clinical standard of care with lower LoE and should be regarded as optional non-standard QIs (Table 7).

Table 4: Top ten mandatory quality indicators

#	Top ten critical quality indicators		Definition	Numerator	Denominator
1	Complete histopathological characterisation:	a) invasive breast cancer	Proportion of cases for which the following prognostic/predictive parameters have been recorded: Histological type; Grading; ER; PR; HER-2; Proliferation index (Ki67). In addition to the above parameters, the following parameters must be recorded after surgery: Pathological stage; Size in mm for the invasive component; Lymphovascular invasion; Distance to nearest radial margin.	Invasive breast cancer patients for which all prognostic/predictive parameters have been recorded.	All invasive breast cancer patients.
		b) noninvasive breast cancer	Proportion of cases for which the following prognostic/ predictive parameters have been recorded: Grading; Dominant histological pattern; Size in mm; Distance to nearest radial margin; ER.	Non-invasive breast cancer patients for which all prognostic/predictive parameters have been recorded.	All non-invasive breast cancer patients.
2	Breast conserving surgery (BCS) rate		Proportion of patients undergoing BCS among all patients who receive surgery for the primary breast cancer.	Patients with breast cancer who undergo BCS.	All patients with breast cancer who undergo surgery for the breast primary.
3	Rate of positive margins after breast BCS		Proportion of patients with positive margins after BCS among all patients who underwent BCS.	Patients with positive margins after BCS.	All patients who undergo BCS.

4	Reoperation rate		Proportion of patients with breast cancer who required a reoperation for the breast primary within six months of the initial surgery.	Patients who required a reoperation for the primary tumour within six months of initial surgery.	All patients who underwent surgery for the primary tumour.
5	Appropriate axillary surgery:	a) rate of surgery in invasive breast cancer	Proportion of invasive breast cancer patients who underwent axillary surgery.	Patients with invasive breast cancer who underwent axillary surgery.	All patients with invasive breast cancer.
		b) sentinel node biopsy (SLNB) only in clinically nodenegative disease	Proportion of patients with invasive cancer and clinically negative axilla who underwent SLNB only (excluding patients who received primary systemic therapy).	Patients with invasive cancer and clinically negative axilla who underwent sentinel lymph node biopsy only.	All patients with invasive cancer and clinically negative axilla who underwent axillary surgery
		c) no axillary lymph node dissection (ALND) in patients with ductal carcinoma insitu (DCIS) only	Proportion of patients with DCIS only undergo ALND.	Patients with DCIS only who undergo axillary lymph node dissection.	All patients with DCIS.

6	Number of nodes excised during axillary surgery:	a) ALND ³10 nodes	Proportion of breast cancer patients undergoing ALND who have at least 10 nodes examined (excluding patients who received primary systemic therapy).	Patients undergoing ALND with at least 10 nodes examined.	All patients who underwent ALND.
		b) SLNB £ 5 nodes	Proportion of patients with invasive cancer who underwent SLNB with no more than 5 nodes excised.	Patients with invasive cancer who underwent SLNB with no more than 5 nodes excised.	All patients with invasive cancer who underwent SLNB.
7	Receipt of radiotherapy after BCS		Proportion of invasive breast cancer patients who received radiotherapy after BCS.	Patients who received radiotherapy after BCS.	All patients BCS for invasive breast cancer.
8	Appropriate treatment sequencing in inoperable locally advanced breast cancer (LABC)		Proportion of patients with inflammatory or nonoperable LABC who undergo primary systemic treatment before surgery.	Patients with inflammatory or non-operable LABC who undergo primary systemic treatment before surgery.	All patients undergoing surgical treatment for inflammatory or nonoperable LABC.
9	Case Volume:	a) breast unit ³150 newly diagnosed cases per annum	Each unit needs to see a set minimum number of 150 patients with newly diagnosed breast cancer per annum.	N/A.	N/A.
		b) surgeon volume ³50 breast cancer cases per annum	Each surgeon needs to perform a set minimum number of surgeries on patients with newly diagnosed breast cancer per annum. In units which train surgeons this would include supervised (scrubbed in) surgeries.	N/A.	N/A.

10	Multidisciplinary team discussion	Proportion of patients with breast cancer who are discussed in a MDT meeting (ideally pre- and postoperatively).	Patients with breast cancer who are discussed in the MDT meeting.	All patients with breast cancer.

Table 5: Mandatory quality indicators with evidence levels and results from the Delphi rounds

#	Quality Indicator Title		Level of Evidence	Round 1: Mean Score(SD); CV	Round 2: Mean Score(SD); CV	Round 3: Mean Score(SD); CV	Mean Sum Score (SD)
1	Complete histopathological characterisation:	a) invasive breast cancer	2.0	5.0 (0.0); 0.00	5.0 (0.0); 0.00	5.0 (0.0); 0.00	15.0 (0.0)
		b) non-invasive breast cancer	2.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.5)
2	Breast conserving surgery (BCS) rate		1.0	4.0 (1.0); 0.25	5.0 (0.5); 0.10	4.5 (0.5); 0.11	13.5 (2.0)
3	Rate of positive margins after breast conserving surgery (BCS)		2.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
4	Reoperation rate		2.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (1.0); 0.22	14.0 (2.5)
5	Appropriate axillary surgery:	a) rate of axillary surgery in invasive breast cancer	1.0	5.0 (1.0); 0.20	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (2.0)

		b) sentinel node biopsy only in clinically nodenegative disease	1.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.5)
		c) no ALND in patients with DCIS only	2.0	4.0 (1.5); 0.38	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.0 (2.5)
6	Number of nodes excised during axillary surgery:	a) lymph node dissection ^{3}10 nodes	2.0	5.0 (1.0); 0.20	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (2.0)
		b) sentinel node biopsy £5 nodes	1.0	4.0 (1.0); 0.25	5.0 (0.5); 0.10	4.5 (0.5); 0.11	13.5 (2.0)
7	Receipt of radiotherapy after breast conserving surgery		1.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
8	Appropriate treatment sequencing in inoperable LABC		2.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
9	Case Volume:	a) breast unit ^{3}150 newly diagnosed cases per annum	3.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
		b) surgeon volume ^{3}50 breast cancer cases per annum	3.0	4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (2.0)
10	Multidisciplinary team discussion		3.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.0 (1.0); 0.25	14.0 (2.0)

SD = standard deviation, CV = coefficient variation

Table 6: Recommended standard of care quality indicators with evidence levels and results from the Delphi rounds

#	Quality Indicator Title		Level of Evidence	Round 1: Mean Score(SD); CV	Round 2: Mean Score(SD); CV	Round 3: Mean Score(SD); CV	Mean Sum Score (SD)
1	Definitive diagnosis prior to treatment		3.0	5.0 (0.0); 0.00	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.0)
2	Appropriate clinical assessment and breast imaging		3.0	5.0 (0.0); 0.00	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.0)
3	Use of BIRADS classification in imaging reports		3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (1.5)
4	Specimen orientation		4.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
5	Use of marker clips to aid radiation		3.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
6	Use of imaging marker clip in patients for BCS undergoing primary systemic therapy		3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.0 (1.0); 0.25	13.5 (2.0)
7	Documentation of staging:	a) preoperative (clinical)	4.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.5 (1.5)
		b) postoperative (pathologic) breast cancer staging	4.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.5)
8	Documentation of outcomes:	a) locoregional recurrence rate	N/A	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
		b) progression-free survival	N/A	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.0 (1.0); 0.25	13.5 (2.5)
		c) overall survival	N/A	4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (1.0); 0.22	13.5 (2.5)

SD = standard deviation, CV = coefficient variation

Table 7: Optional non-standard of care quality indicators with evidence levels and results from the Delphi rounds

#	Quality Indicator Title		Level of Evidence	Round 1: Mean Score(SD); CV	Round 2: Mean Score(SD); CV	Round 3: Mean Score(SD); CV	Mean Sum Score (SD)
1	Timeliness of care:	a) first diagnostic examination to initial treatment	4.0	5.0 (1.0); 0.20	5.0 (0.5); 0.10	4.5 (1.0); 0.22	14.5 (2.5)
		b) needle biopsy to pathology report	4.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.5 (1.5)
		c) needle biopsy pathology report to treatment	4.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
		d) surgery to pathology report	4.0	4.0 (1.0); 0.25	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.0 (2.0)
		e) surgery to adjuvant chemotherapy	3.0	5.0 (0.5); 0.10	4.5 (1.0); 0.22	5.0 (0.5); 0.10	14.5 (2.0)
		f) last surgery or chemotherapy to adjuvant radiation	3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.5 (1.5)
2	Postoperative complications:	a) Readmission rate	3.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (1.0); 0.22	14.0 (2.5)
		b) Surgical site infection rate	3.0	4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (2.0)
3	Documentation of eligibility for BCS		4.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (1.5)
4	Oncoplastic procedure rate		4.0	4.5 (0.5); 0.11	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (1.5)
5	Discussion of surgical options		4.0	4.5 (0.5); 0.11	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (1.5)
6	Failure of identification of the sentinel node		3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (1.5)

7	Node positivity rate in SLNB	4.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
8	Tracer use in sentinel lymph node biopsy	4.0	4.0 (1.0); 0.25	4.0 (1.0); 0.25	4.5 (1.0); 0.22	12.5 (3.0)
9	Concurrent SLNB with breast surgery	4.0	4.0 (1.0); 0.25	5.0 (0.5); 0.10	4.5 (0.5); 0.11	13.5 (2.0)
10	Efficient diagnosis (number of visits required to initiation of treatment)	4.0	4.0 (1.0); 0.25	4.5 (0.5); 0.11	4.5 (1.0); 0.22	13.0 (2.5)
11	Lymphoedema rate	4.0	4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (2.0)
12	Quality audit rate	4.0	4.0 (1.0); 0.25	4.5 (0.5); 0.11	4.5 (1.0); 0.22	13.0 (2.5)

SD = standard deviation, CV = coefficient variation

3.5 Discussion

The first set of quality indicators for the diagnosis and surgical management of breast cancer in South Africa was developed.

Consensus was strong amongst the panel, which affirmed the foundation work and preselection of potential QIs. Nevertheless, such a large number of QIs is not practical for clinical application and a three-tiered set is therefore proposed with mandatory, recommended and optional QIs based on LoE and clinical priority.

Evidential Strength and Clinical Priority

Table 4 shows the mandatory QIs and their definitions: eight have high LoE (I or II) and two have lower LoE (III or IV) which we regard as clinically essential for quality improvement. Complete histopathological evaluation of tumours is critical for appropriate treatment planning. An incomplete evaluation can lead to repeated biopsies, unnecessary surgery and other treatments, all of which carry potential morbidity and mortality for the patient(146). The standard evaluation should include the histological type, tumour grading, oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) and Ki-67 proliferation marker on the preoperative biopsy. In addition to these parameters, the surgical specimen requires pathological staging, with the size of the invasive component and nodal assessment, lymphovascular invasion and distance to the nearest margin.

Two trials on breast-conserving surgery (BCS) in conjunction with radiation therapy (RT) were published in the early 80's and demonstrated equivalent survival rates despite increased local recurrence rate (LRR) after BCS and RT(147,148). Twentyyear follow-up of these trials confirmed the equivalent survival and paved the way for BCS as the preferred treatment option for early-stage breast cancer(149,150). Newer data shows lower LRRs and suggests that it has become a rare event with contemporary treatment and is probably rather a reflection of tumour biology than the extent of surgery(151).

Reoperations should generally be kept to a minimum as they increase morbidity and health care expenses. However, they are significantly higher with breast cancer surgery than in other surgical fields. This is due to the increased burden of reoperations for positive margins after BCS and completion axillary lymph node dissection (ALND) after a positive sentinel lymph node biopsy (SLNB), particularly after mastectomy(152–154). One of the confounding factors for increased

reoperations has been the variable definition of a positive margin. An adequate margin for invasive breast cancer has now been defined as “no ink on tumour” for invasive disease(155,156) and 2 mm for non-invasive disease(157) which should reduce reoperation rates in future, especially in specialised centres. The rate of BCS, reoperations, and positive margins are a sound reflection of the quality of surgery and are influenced by multiple factors such as quality of preoperative assessment, tumour localisation, use of neoadjuvant systemic therapy, surgical expertise and oncoplastic skill.

Similarly to the shift towards BCS within the breast, there has also been a major shift towards conservative approaches in the axilla and appropriate use of axillary surgery as well as the number of nodes excised should be measured on a mandatory basis. SLNB allows for accurate assessment of the axilla with lesser morbidity compared to ALND, which is inappropriate in clinically node-negative patients with invasive breast cancer or patients with non-invasive breast cancer(158,159). Morbidity, especially lymphoedema, is related to the number of nodes excised during axillary surgery and should not exceed five for a SLNB; but should also not be less than ten for an ALND in patients undergoing primary surgery(160,161).

Breast cancer treatment is multidisciplinary and the modern surgeon has to understand oncological principles and neoadjuvant and adjuvant therapies. Radiotherapy reduces local recurrence risk and improves progression-free survival following BCS. A postoperative referral is standard of care with the exception of select patient subgroups(162). Equally, inflammatory or other non-operable locally advanced breast cancer (LABC) should always be treated with neoadjuvant systemic therapy(163). Mandatory QIs, therefore, include the rate of RT post BCS and rate of neoadjuvant therapy for non-operable LABC.

Although case volumes and MDT discussions do not have high LoE, these two indicators are deemed important to improve the quality of care in South Africa. Critical case volumes for units and surgeons are well described and a breast unit should treat at least 150 newly diagnosed patients per annum. A surgeon should personally operate on no less than 50 cases per annum(141). Patients treated by specialised surgeons and units are more likely to have BCS, undergo sentinel lymph node biopsy and are more likely to receive appropriate adjuvant therapies resulting in better outcomes in terms of local recurrence and survival. In addition, treatment is more

costeffective and litigation decreases with treatment in specialised centres adhering to benchmarking and quality control(164). This obviously needs to be seen in the context of accessibility which is extremely varied in South Africa. Ideally, further breast units should be established in areas of need with training of subspecialists and support from existing units in a hub and spoke model. Nevertheless, decentralisation with care by general surgeons is critical in very remote areas, to avoid further barriers to care. MDTs lead to improved, evidence-based clinical decision-making, quality of treatment, provide guidance in non-standard treatment decisions and offer the opportunity to establish a complete treatment plan for each patient(165). Ideally, the patient should be discussed at diagnosis before initiation of any therapy, postoperatively and at any point of disease progression.

The second group of recommended QIs are listed in Table 6 and should be regarded as standard of care in any modern practice. Prior to any breast cancer surgery, there should be pathological confirmation of diagnosis, appropriate clinical examination and breast imaging with bilateral mammography and ultrasound. The routine use of breast imaging reporting and data system (BIRADS) should be applied to imaging reports, all breast specimens should be orientated, surgical clips should always be placed after BCS to aid RT and a tissue marker clip should be placed for patients who are planned for BCS after neoadjuvant systemic therapy. Clinical and pathological staging, locoregional recurrence, progression-free survival and overall survival should all be part of standard follow-up documentation.

The third group of QIs are optional and listed in Table 7. The panel deemed them valuable, but they do not have a high LoE and were not regarded as standard of care.

Five QIs were excluded by the panel. “Intraoperative use of ultrasound by the surgeon”, “documentation of contralateral breast cancer risk” and “intraoperative pathology assessment of sentinel lymph nodes” were deemed to have low relevance or clinical priority in our setting. Intraoperative ultrasound, although widely used in European breast centres, is rarely available in South Africa. The intraoperative evaluation of lymph nodes is often inaccurate and controversial, with the current omission of ALND in patients with micrometastases and selected patients with macrometastases undergoing BCS and RT(166). “Use of preoperative MRI” and “appropriate clinical assessment of the axilla with sonar and fine needle aspiration”

are applied in HICs(66) but were excluded due to concerns over reliability and validity, as well as feasibility in our constrained health care system.

Implications and Implementation

This set of QIs has been endorsed by the Breast Interest Group of Southern Africa (BIGOSA). Although implementation within surgical practices will be voluntary, BIGOSA will circulate the mandatory set with a strong recommendation that they should be applied and regularly audited by any practice performing surgery on breast cancer patients (Table 4). Rapid implementation can be expected by established breast units and high-volume surgical practices, but these are still very scarce in South Africa. Many breast surgeries are performed by general surgeons and the greatest improvement of quality is anticipated after application of the QI set in the nonspecialised setting. The QI set will therefore also be published locally as BIGOSA clinical guidelines and audit results of participating units will be presented at general surgical conferences in order to reach a broader surgical community. However, clinical regulation is historically difficult in South Africa with poorly resourced clinical governance, a divided health care system and a very high degree of autonomy given to the individual practitioner. At present, there is no breast surgical clinical regulation, no directed audit and no accreditation processes for units or MDT meetings. This project therefore should be seen as a collective starting point to initiate and direct quality improvements in breast cancer care. It will be the first attempt to measure current regional quality and offer a gauge for practices with more standardised treatment over time.

The critical ten indicators contain core data and their application appears feasible even in lower resourced settings. Even though the indicators with high evidential strength are likely to have the biggest impact, this remains to be proven in South Africa. Evidence-based medicine has limitations and “high level of evidence studies” with randomisation is often not feasible. Therefore, clinical experience and reasoning may have to be applied; two QIs with lower evidence were incorporated into the mandatory group because of their overwhelming clinical priority. Although the quality indicators were described with the classic division into process, structural or outcome markers, it is important to note that many indicators are not solely dependent on the quality of a surgical practice but interlinked with various patient and system factors. In a complex health care scenario such as the multidisciplinary treatment of breast cancer within a

resource-constrained health care system, as in South Africa, shortcomings of other factors such as access to care and screening or the availability of adjuvant therapies will invariably have a more substantial impact than in well-resourced health care systems. This will for instance decrease the achievable rate of BCS which should be regarded as an outcome rather than a pure process metric. It is for this reason, that no benchmarks were allocated to the indicators in this project; benchmarks from HICs are likely unachievable and reasonable benchmarks within a resource-constrained system will need to be determined through future application of the QIs by established local breast centres.

It is likely that this QI set will evolve over time to further accommodate to our local needs. Regional variations may exist, for instance time delays to treatment do not show strong evidence in HICs but decreased overall and disease-specific survival have been described(167,168). In the case of much more extensive delays in constrained health care systems, these effects may be amplified.

There are several pitfalls anticipated in the implementation of this QI set. Firstly, the most obvious is that a set with too many parameters could overwhelm and discourage use. Even though the indicators in the recommended group are standard of care and practice, most should be already routinely applied and measurements are less likely to yield major effects. The mandatory set was therefore condensed to only include essential QIs with the most substantial anticipated impact. Secondly, data may not be immediately available in all practices and will require incremental, prospective data collection. Differences in resources for additional data management are expected between academic and non-academic units, as well as provincial and private practices. Thirdly, any practice change will initially increase workload and evoke resistance with implementation varying according to clinician knowledge and attitude. Nevertheless, successful implementation over time will not only improve quality of care but also streamline processes, close clinical gaps, strengthen health care systems and improve practice workflow.

There are several other ways to improve quality of care besides measuring QIs. Access to rapid, high-quality diagnosis and multidisciplinary high-quality units is needed as well as advocacy, policy change, innovation, as well as strengthening of local research and training of specialists and subspecialists. Health care professionals need to overcome their resistance to change and innovation, whether this is due to

adherence to usual routines, or to protect personal interests. The most systematic approach is the establishment and accreditation of specialised breast centres. Although validated in HICs, some of the established EUSOMA or NAPBC criteria may not be feasible in lower resourced settings. These include routine pathology review of biopsies performed outside of the respective breast centre or breast imaging accreditation criteria that do not exist in South Africa. This initial effort for quality improvement will hopefully form the basis of establishing reasonably adjusted local accreditation criteria in future. Overall, there are promising developments for breast cancer care in South Africa: breast cancer policy and guidelines were issued by the National Department of Health, BIGOSA is gaining traction, and applications for the implementation of a breast and endocrine surgery subspecialty are in process.

Future research

In a future study, the entire QI set will be applied to the surgical breast units participating in the South African Breast Cancer and HIV Outcomes (SABCHO) study(120) to allow for an initial audit, validation and reasonable benchmarking within our resource-constrained health care system. Furthermore, we will attempt to evaluate if individual QI non-adherence results in worse intermediate patient outcomes. These will include potential locally relevant factors with lower evidence, such as timeliness to care.

Limitations

This study has several limitations in keeping with the limitations of a Delphi process. In addition, the modification to include a face-to-face meeting facilitated essential discussion but may have compromised the methodology of a pure Delphi process despite keeping all ratings anonymous. Furthermore, results will always be bound by the quality and knowledge base of the panel. Our study is limited to diagnostics and surgical therapy and does not include all aspects of multidisciplinary care. However, a broad panel including various subspecialties represented the interlinked multidisciplinary approach during every step of a contemporary treatment pathway. In addition, the surgical part of the panel was diverse, representing all but one established breast unit within the South African public sector, as well as surgeons from more remote areas and high-volume surgeons from the private sector. In South Africa, most patients will present with symptomatic disease and will be seen in surgical clinics

and practices first. It is crucial to improve the quality of the first point of contact as well as surgical therapy which remains a critical component in the care of breast cancer.

3.6 Conclusions

A three-tiered set of QIs was developed based on locally obtained consensus to improve the quality of surgical breast cancer care. Application of the ten critical QIs should be mandatory for all practices treating breast cancer patients. The proposed QIs await implementation but are a pragmatic first step towards improved quality of breast cancer care.

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CHAPTER 4: AN INITIAL BENCHMARK OF THE QUALITY OF THE DIAGNOSIS AND SURGICAL TREATMENT OF BREAST CANCER IN SOUTH AFRICA

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4.1 Abstract

Background

Monitoring quality indicators to improve breast cancer care is well-established in highincome countries. This is the first evaluation of diagnostic and surgical quality indicators for initial benchmarking of breast cancer care in South Africa.

Objective

To measure the adherence rates to QIs amongst women with breast cancer in South Africa

Methods

Ten quality indicators were evaluated for 3 545 breast cancer patients across four SA surgical breast units using a shared electronic patient record system. Data quality and adherence rates with differences between units were determined. The effect of HIV status on adherence was assessed by multivariate Poisson regression analyses.

Results

Our electronic patient record reliably measured most quality indicators. Rates of positive margins (5.7%), overall axillary surgery (95.8%) and appropriate treatment sequencing in locally advanced breast cancer patients (98.4%) consistently reached minimum international standards. Rates of multidisciplinary team discussion (72.2%), radiotherapy (66.7%) and sentinel node biopsy (39.6%) showed wide cross-site variance. Histopathology reporting (62.0%), breast-conserving surgery (19.4%) and number of nodes excised with axillary dissection (47.3%) and sentinel node biopsy (82.7%) were consistently below minimum standards. Unit volumes were achieved consistently in Gauteng Province, but only for some years in KwaZulu-Natal Province;

surgeon volumes were achieved across all units. HIV status did not affect adherence levels. Most quality indicators were well measurable, but data quality on reoperations and surgeon volumes were poor.

Conclusion

We evaluated local quality indicators for an initial benchmark, and the most emergent gaps in care are the receipt of radiotherapy and underutilisation of sentinel node biopsy.

4.2 Background

Quality indicators (QI) for breast cancer treatment have been measured in highincome countries (HIC) and used to monitor and improve the quality of patient care over time(49,65). Data on the quality of breast cancer care in low- to middle-income countries (LMIC) is scarce, but it suggests lower and variable quality of care depending on the patient's socioeconomic background and geographical location, along with the associated availability of treatment services(137,138).

Breast cancer is a complex and heterogeneous disease and is best treated in multidisciplinary teams (MDT) with specialist expertise and resources from each treatment modality to achieve the best patient outcomes. Quality of care is defined as the degree to which health services increase the likelihood of desired health outcomes and are consistent with current professional knowledge. QIs have classically been divided into the Donabedian model of structural, process, and outcome measures(58). Structural indicators examine the ability of the health care system to provide a service, such as the provision of resources, staffing or expertise, and have been used extensively in accreditation processes. Process indicators permit the evaluation of adherence rates to recommended healthcare processes and are the most commonly used indicators to measure quality of care. Outcome measures such as disease-free survival and quality of life are often regarded as the gold standard in cancer care but these are difficult to measure because of long follow-up requirements and the potential influence of various patient and clinical factors(61).

In 2019, a critical set of ten QIs for the diagnosis and surgical treatment of breast cancer was established in South Africa through expert consensus(169). This study now evaluates the data quality of these QIs within the existing electronic patient record

(EPR) data and adherence to them in patient cohorts. This is the first investigation of diagnostic and surgical breast cancer QIs in sub-Saharan Africa.

4.3 Methods

The South African Breast Cancer and HIV Outcomes (SABCHO) study has prospectively collected information on access to healthcare as well as numerous components of patient and disease factors to develop evidence-based guidelines on the management of breast cancer in HIV (human immunodeficiency virus) positive and negative women, as well as to improve breast cancer treatment in a resourceconstrained environment(120). An EPR system was implemented in 2015 at all study sites to collect prospective clinical data. We retrospectively reviewed all patients enrolled in the SABCHO study between 01.07.2015 and 31.08.2020. To mitigate any potential impact on the quality metrics, we chose the time of the first COVID-19 wave in South Africa as a cut-off. The sites included Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Greys Hospital (GH), and Durban complex (Inkosi Albert Luthuli Central Hospital, Addington hospital and Ngwelezana hospital). CHBAH and CMJAH are in
Johannesburg, Gauteng province, while Durban complex and GH are in KwaZuluNatal (KZN) province. All are public-sector academic surgical breast units, but they serve different populations and have different staff resources (Table 8).

Data entry was made prospectively on OncoDB, an EPR initiated in 2006 at CHBAH that has since grown into a purposefully designed comprehensive breast database. Both clinicians and SABCHO research staff entered data, although some fields are only used by clinicians and others only by research staff. The extent of OncoDB use differed across sites (Table 8).

Table 8: Study sites

Sites	**CHBAH**	**CMJAH**	**GH**	**Durban**
Residential demographics	Soweto (3 million) **Urban**	Johannesburg East and Central (1.5 million) **Urban**	Western KwaZulu-Natal (3.5 million) **Urban / Rural mix**	Durban Metropolitan (3.5 million) **Urban** Uthungulu, Umkhanyakude, Zululand (3 million) **Rural**

Surgical staff	3 surgeons	2 surgeons	1 surgeon	1 surgeon
Research staff	10	5	2	3
OncoDB use	Main recordkeeping tool Clinical management and research	Main recordkeeping tool Clinical management and research	Only used for study purpose Not all functions used	Only used for study purpose Not all functions used

The selection process, definitions, as well as the nominators and denominators of the ten QIs were previously described(169). For QI 1, histopathology reports were considered complete if they included the following parameters for core biopsy: histological type, tumour grade, oestrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER-2) with a confirmatory in-situ hybridisation test if HER-2 was equivocal, and Ki67 score. In addition to the above parameters, the following were required for QI 2 on surgical specimens: pathological stage, size in millimetres for the invasive component, peritumoural lymphovascular invasion, and distance to the nearest invasive margin; receptors did not require repeating as they are routinely done on core biopsy. We defined a Ki67 cut-off of 20% to define immunohistochemical (IHC) surrogates for molecular subtypes(33). A reoperation (QI 4) was defined as a second surgery on the same side within six months. For QI 6 we only included patients who had primary surgery as neoadjuvant therapy affects the number of nodes excised. For QI 8, inoperable locally advanced breast cancer (LABC) was defined as T4a, c or d or N3 and neoadjuvant systemic therapy had to precede surgery to fulfill appropriate modality sequencing.

The reliability and validity of EPR measures are evaluated by data completeness, data accuracy, timeliness or “currency,” clinical specificity or “granularity,” and data comparability(170). We graded our data quality based on a) data entry personnel, which was either the clinician or research staff driven, with better data completeness, accuracy, currency and comparability when entered by research staff, b) a structured data cleaning process by research staff, and c) the use of structured versus unstructured data with improved completeness, accuracy, currency and granularity with structured data. We then classified reliability and validity as good (3 points), varied (1-2 points), or poor (0 points) to reflect the integrity of our results.

We described the frequency and percentages of adherence to the ten mandatory QIs among the different sites. Site differences were evaluated with a chi-squared test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables, and the effect of HIV status on adherence levels was evaluated with multivariate Poisson regressions, adjusting for age, hospital site, stage of disease, and intrinsic subtype of breast cancer. All participants provided written informed consent for data collection and analysis. The SABCHO study and this project are overseen by the Human Research Ethics Committees of the University of Witwatersrand (Johannesburg) and the University of KwaZulu-Natal (Durban), and separate ethics clearance was obtained for this substudy (M180761).

4.4 Results

A total of 3545 patients with invasive breast cancer were included. Mean age was 55.7 years, 34.4% of patients were early stage (stage 1-2), 47.8% were locally advanced (stage 3) and 17.8% were metastatic (stage 4) at presentation. Of the 3545 patients, 2271 underwent surgery during their treatment process (64.1%). 21.9% were HIVpositive, with higher rates in CHBAH and GH. Table 9 displays the detailed distribution based on immunohistochemical surrogates and patient characteristics, as well as, the significant differences across sites.

Table 10 tabulates data source and entry, structure, reliability, and validity. Most QI data were well measurable, with good validity and reliability. Operative notes to evaluate reoperations were inconsistent across sites, only entered by clinicians, and contained unstructured data, with poor reliability and validity for reoperations and surgeon volume QIs. Clinicians across sites inconsistently entered reoperations measured by pathology reports and MDT discussions, and reliability and validity were varied despite the use of structured fields. Table 11 tabulates the results of QI adherence, and Figure 13 illustrates the highest and lowest adherence levels and their relation to international minimum standads.

Complete histopathological characterisation was achieved in 62.0% of initial core biopsy specimens and 65.6% of surgical specimens. Adherence varied across sites from 91.9% to 5.7% and 82.1% to 22.0%, respectively ($p>0.001$). Breast-conserving surgery (BCS) rate overall was 19.4% and 31.6% for patients with early-stage breast cancer; rates were highest in Durban and lowest at GH ($p>0.001$). The positive margin rate was 5.7% with no significant cross-site variance. The reoperation rate was 2.9%

on evaluating pathology reports and 8.0% on evaluating operation notes. Surgical operation notes were only entered by the Gauteng sites and therefore not measurable across sites; reliability and validity were poor. Of patients who underwent surgery, 95.8% had axillary surgery with little cross-site variation. Sentinel lymph node biopsy (SLNB) only in clinically node-negative patients was recorded in 39.6%, with a wide site variation between 71.9% and 1.9% (p>0.001). HIV-positive patients were less likely to have a SLNB (p=0.008, OR: 0.58 (0.38-0.86).

The percentage of patients with axillary lymph node dissection (ALND) with ^{3}10 nodes was 47.3%, while 82.0% of patients with SLNB had £5 nodes dissected. GH achieved the highest rate (72.6%) while IALCH recorded none (0%). However, only four patients had primary surgery and ALND in this unit, as they mainly treated node-positive patients with neoadjuvant therapy. Radiotherapy receipt after BCS was documented in 66.7% with site variance of 92.7% to 44.7% (p>0.001). HIV-positive patients were less likely to receive adjuvant radiotherapy (p=0.010, OR: 0.52 (0.31-0.85). Neoadjuvant therapy was given to 98.4% of 440 inoperable locally advanced cancer patients prior to surgery. MDT discussion was documented in 72.2% with site variance between 92.2% and 14.3%, data reliability and validity were varied.

Table 9: Clinical characteristics of the cohort

	Overall (n/%)		**CHBAH (n/%)**		**CMJAH (n/%)**		**GH (n/%)**		**DURBAN (n/%)**		**Pvalue**
Enrolled Patients	3545		1455	41.0%	931	26.3%	530	15.0%	629	17.7%	
Age (mean - SD)	55.7	14.2	55.1	14.5	54.5	13.5	57.6	14.4	57.2	14.1	*<0.001*
Stage 1 - 2	1221	34.4%	546	37.5%	309	33.2%	176	33.2%	190	30.2%	
Stage 3	1693	47.8%	724	49.8%	484	52.0%	212	40.0%	273	43.4%	*<0.001*
Stage 4	631	17.8%	185	12.7%	138	14.8%	142	26.8%	166	26.4%	

Received Surgery	2271	64.1%	984	67.6%	547	58.8%	362	68.3%	378	60.1%	*<0.001*
Luminal A [α]	829	23.4%	228	15.7%	240	25.8%	130	24.5%	231	36.7%	
Luminal B [α]	1838	51.8%	885	60.8%	456	49.0%	255	48.1%	242	38.5%	
HER-2 negative	*1241*	*35.0%*	*580*	*39.9%*	*315*	*33.8%*	*194*	*36.6%*	*152*	*24.2%*	
HER-2 positive	*597*	*16.8%*	*305*	*21.0%*	*141*	*15.1%*	*61*	*11.5%*	*90*	*14.3%*	*<0.001*
HER-2 enriched [α]	235	6.6%	83	5.7%	73	7.8%	32	6.0%	47	7.5%	
Triple-negative [α]	548	15.5%	216	14.8%	148	15.9%	95	17.9%	89	14.1%	
Unspecified	95	2.7%	43	3.0%	14	1.5%	18	3.4%	20	3.2%	
HIV +	775	21.9%	359	24.7%	163	17.5%	137	25.8%	116	18.4%	
HIV -	2713	76.5%	1071	73.6%	741	79.6%	393	74.2%	508	80.8%	*<0.001*
HIV unknown	57	1.6%	25	1.7%	27	2.9%	0	0.0%	5	0.8%	

% denotes the column percentage per category.

[α] Luminal A was defined as ER/PR positive, ki67 ≤20%. Luminal B as ER and/or PR positive, Ki67 ≥20%, HER-2 negative or positive. HER-2 enriched as ER/PR negative, HER-2 positive. Triple-negative as ER/PR/HER-2 negative.

Table 10: Quality indicator data quality

#	Quality Indicator Title		Raw Data Source	Data Entry	Data Field Structure	Cleaned	Reliability and Validity
1	**Complete histopathological characterisation of invasive breast cancer:**	**i) on core biopsy**	Pathology report	Research staff	Structured	Yes	Good
		ii) on surgical specimen	Pathology report	Research staff	Structured	Yes	Good
2	**a) Breast-conserving surgery (BCS) rate:**		Pathology report	Research staff	Structured	Yes	Good
	b) Breast-conserving surgery rate among stages 1 and 2:		Pathology report	Research staff	Structured	Yes	Good
3	**Rate of positive margins after breast-conserving surgery:**		Pathology report	Research staff	Structured	Yes	Good
4	**Reoperation rate:**	**i) on pathology reports**	Pathology report	No routine entry	Structured	No	Varied
		ii) on operation notes	Operation note function	Clinicians	Unstructured	No	Poor
5	**Appropriate axillary surgery:**	**i) rate of axillary surgery in invasive breast cancer**	Pathology report	Research staff	Structured	Yes	Good
		ii) sentinel node biopsy only in clinically node-negative disease	Pathology report	Research staff	Structured	Yes	Good
6	**Number of nodes excised during axillary surgery:**	**i) lymph node dissection ≥10 nodes**	Pathology report	Research staff	Structured	Yes	Good
		ii) sentinel node biopsy ≤5 nodes	Pathology report	Research staff	Structured	Yes	Good
7	**Receipt of radiotherapy after breast-conserving surgery:**		Treatment functions	Research staff	Structured	Yes	Good
8	**Appropriate treatment sequencing in inoperable locally advanced breast cancer (LABC)**		Initial diagnostic workup function and treatment functions	Research staff	Structured	Yes	Good
9	**Case volume:**	**i) breast unit ≥150 newly diagnosed cases per annum**	New patient entry	Research staff	Structured	Yes	Good

		ii) surgeon volume ≥50 breast cancer cases per annum	Operation note function or single surgeon units	Clinicians	Unstructured	No	Poor
10	**Multidisciplinary team discussion:**		Follow up function	Clinicians	Structured	No	Varied

Table 11: Quality indicator adherence

#	Quality Indicator Title		International minimum standard (%)	Overall documented adherence (n)	(%)	CHBAH (n)	(%)	CMJAH (n)	(%)	GH (n)	(%)	Durban (n)	(%)	P-value [α]	HIV's effect on overall adherence (Pvalue; RR [95%CI] [β]
1	**Complete histopathological characterisation of invasive breast cancer:**	**i) on core biopsy**	>95%[49]	2199/3545	62.0%	1240/1455	85.2%	856/931	91.9%	30/530	5.7%	73/629	11.6%	***<0.001***	0.832
		ii) on surgical specimen	>95%[49]	1490/2271	65.6%	808/984	82.1%	353/547	64.5%	246/362	68.0%	83/378	22.0%	***<0.001***	0.741
2	**a) Breast-conserving surgery rate:**		-	441/2271	19.4%	161/984	16.4%	126/547	23.0%	41/362	11.3%	113/378	29.9%	***<0.001***	0.051
	b) Breast-conserving surgery rate among stages 1 and 2:		>50%(142)	332/1051	31.6%	121/465	26.0%	92/257	35.8%	31/164	18.9%	88/165	53.3%	***<0.001***	0.071
3	**Rate of positive margins after breast-conserving surgery:**		<20%(146)	26/456	5.7%	13/169	7.7%	10/128	7.8%	1/42	2.4%	2/117	1.7%	0.084	0.664
4	**Reoperation rate:**	**i) on pathology reports**	<20%[49]	66/2271	2.9%	47/984	4.8%	9/547	1.6%	7/362	1.9%	3/378	0.8%	***<0.001***	0.741
		ii) on operation notes	<20%[49]	123/1531	8.0%	78/984	7.9%	45/547	8.2%	-/-	-	-/-	-	0.836	***0.039, 0.57 [0.33-0.97])***
5	**Appropriate axillary surgery:**	**i) rate of axillary surgery in invasive breast cancer**	>90%[49]	2176/2271	95.8%	948/984	96.3%	522/547	95.4%	348/362	96.1%	358/378	94.7%	0.546	0.998
		ii) sentinel node biopsy only in clinically nodenegative disease	>90%[49]	319/806	39.6%	124/361	34.3%	111/226	49.1%	2/105	1.9%	82/114	71.9%	***<0.001***	0.648
6	**Number of nodes excised during axillary surgery:**	**i) lymph node dissection ≥10 nodes**	>80%(146)	245/518	47.3%	86/251	34.3%	24/77	31.2%	135/186	72.6%	0/4	0.0%	***<0.001***	0.858

		ii) sentinel node biopsy ≤5 nodes	>90%[49]	228/278	82.0%	110/133	82.7%	100/117	85.5%	1/2	50.0%	17/26	65.4%	0.064	0.910
7	**Receipt of radiotherapy after breast-conserving surgery:**		>90%[49]	294/441	66.7%	72/161	44.7%	82/126	65.1%	38/41	92.7%	102/113	90.3%	***<0.001***	0.253
8	**Appropriate treatment sequencing in inoperable LABC:**		>90%[49]	440/447	98.4%	126/130	96.9%	136/137	99.3%	100/102	98.0%	78/78	100.0%	0.274	0.820
9	**ᵀCase volume:**	**i) breast unit ≥150 newly diagnosed cases per annum**	>150 cases[49] 100%	78.6%		2016-2019 (100%)		2016-2019 (100%)		2017 (33.3%)		2016-2017 (66.6%)		-	-
		ii) surgeon volume ≥50 breast cancer cases per annum	>50 cases[49] 100%	100%		2016-2019 (100%)		2016-2019 (100%)		2016-2018 (100%)		2016-2018 (100%)		-	-
10	**Multidisciplinary team discussion:**		>90%[49]	2560/3545	72.2%	1198/1455	82.3%	706/931	75.8%	76/530	14.3%	580/629	92.2%	***<0.001***	0.476

CHBAH - Chris Hani Baragwanath Academic Hospital; CMJAH - Charlotte Maxeke Johannesburg Academic Hospital; GH - Greys Hospital; IALCH - Inkosi Albert Luthuli Central Hospital. [α] Pearson's Chi-square test was used to test for differences in adherence between the study sites.

[β] Multivariate Poisson regressions, adjusting for age, hospital site, stage of disease and intrinsic subtype of breast cancer, were used to assess the impact of HIV status on overall adherence. RR – Relative risk; CI – Confidence interval.

[Π] Case volumes calculated for full calendar-year enrolments: 2016 – 2019 for CMJAH and CHBAH; 2016 – 2018 for GH and IALCH.



$ - QI 3, 4i, 4ii are transformed and plotted as 100%-(adherence levels) for presentation consistency.

Figure 13: Radar chart comparing South African adherence levels to international standards

4.5 Discussion

The levels of QI adherence varied across sites and were mostly inferior to minimum standards in HICs (Table 11 and Figure 13). Nevertheless, they represent an inital benchmark in our resource-constrained setting and a starting point from where to identify gaps and improve quality of care over time.

QIs fulfilling international standards across sites:

The rate of positive margins, overall axillary surgery and appropriate treatment sequencing for LABC consistently achieved international minimum standards across sites. Margins in breast cancer excisions have been subject to many debates but the recent recommendation is “no tumour on ink”(157). Historically, re-excision rates have been reported as 25-40%(146,171) and our positive margin rate is comparatively low at 5.7%. This is likely due to the early adoption of the new margin definition and liberal use of advanced oncoplastic techniques in our units, which allows for greater volume resections and lower re-excision rates(172). The axilla was evaluated surgically in 95.8% of cases. Non-resectable LABC was appropriately treated with neoadjuvant therapy before surgery in 98.4% of cases, reflecting safe patient evaluation and treatment.

QIs with site variance to international standards:

It is alarming that only 66.7% of patients received radiotherapy after BCS, with Gauteng sites significantly less likely to deliver than KZN sites. Patients at CHBAH had the lowest adherence level at 44.7%. One of the possible barriers may have been the need to travel to CMJAH as radiotherapy is unavailable on-site. However, CMJAH patients, who shared an exact breast clinic location with radiation oncology within the hospital, only received radiation in 65.1% of cases. This starkly contrasts to KZN where both units achieved the minimum target of 90%. These results point to a specific barrier to radiation care in Gauteng that needs to be addressed urgently.

Critical case volumes for units and surgeons are well described. A breast unit should treat at least 150 newly diagnosed patients annually, while a surgeon should operate on at least 50 cases annually(28). Surgeon volumes were consistently achieved across sites, but unit volumes were achieved only in Gauteng sites for all years of the full assessment, whereas KZN sites fell short in some years. It is important to note that

actual unit volumes were larger than recorded, as foreign patients were not included in SABCHO.

The MDT discussion is a critical process to ensure the review of each patient and to form a complete treatment pathway; they result in better evidence-based clinical decision-making and higher quality of treatment(165). This QI was a clinician-driven data entry and was not reliably entered across sites. Adherence level was 72.2% overall but IALCH was the only unit to consistently document MDT discussion and achieve the >90% standard. GH did not routinely enter the discussions on the EPR (14.3%) but routine MDT meetings were held, and points to differences between documentation and received treatment. Adherence levels are generally higher than measured, a described pitfall in using EPRs to assess quality(173). Improving the documentation of MDT discussions is important, particularly in our healthcare system where patients may need to visit various hospitals to receive different treatments and encounter different healthcare providers during each visit.

QIs below international standards:

The completeness of histopathology was overall low but Gauteng sites were significantly more compliant in assessing core biopsy and surgical specimens. Our recent publication describes these findings in more detail and emphasises the need to improve reporting of tumour grade, HER-2 confirmatory tests, excision margins, pathologic staging, and lymphovascular invasion. Reporting standards differ among laboratories, and it is overdue to establish a South African pathology consensus and introduce the routine use of data sheets and synoptic reports to enhance completeness and clear communication of the results with the clinician(174).

BCS rates were 19.4% overall and 31.6% for patients with early-stage breast cancer; none of the sites were close to international standards of >50%(182). BCS requires higher resources and expertise, especially with impalpable tumours, after neoadjuvant therapy and with advanced oncoplastic techniques. In addition, BCS requires postoperative radiotherapy, a factor that may have influenced the rates in Gauteng. At GH, some patients were not offered the option of BCS due to limited radiotherapy availability, where treatment would fall outside of the recommended treatment time period. This emphasises our opinion that BCS should be seen as an outcome and not

a pure process measure in our setting as it is impacted heavily by factors external to the surgical units(169).

Only 39.6% of clinically node-negative patients received a SLNB only, with significant variance noted among sites. GH had the lowest rate at 1.9% as they did not have resources to trace sentinel nodes. We have previously reported on the low use of SLNB in our Gauteng units and the potential reasons for this such as large tumour size, the intraoperative impression of nodal involvement with conversion to ALND, or non-availability of critical consumables or equipment(175). We also hypothesised that HIV status may influence nodal assessment and surgery; but this was not proven in this cohort (RR 0.91). Given the ever-expanding applications for SLNB, suspicious lymph nodes should ideally be confirmed with fine needle aspiration and resources need to be provided and the use of SLNB expanded across all sites(176). Historically, the number of nodes dissected during ALND has been set at $^{3}10$(177). Our overall rate was low at 47.3%; and although the indicator measures technical surgical success, its clinical utility is questionable due to factors such as the pathologist's variation in specimen review and the current clinical shift towards more preserving surgery.

QIs with poor data reliability and validity:

We attempted to measure reoperations with operative and pathology records. However, operative notes were only entered by clinicians in Gauteng; IALCH and GH entered operative notes on their separate hospital EPR. A common challenge in using EPRs is that data entry is more likely to be of poor quality when entered by busy frontline staff and when it requires duplication of work processes(178). Analysis of Gauteng operative notes shows a reoperation rate of 8%. The data using histopathology is also flawed as specimens would only be sent for re-excision or early recurrence but not for emergent reoperations like sepsis or bleeding. Furthermore, entry of the second pathology report was also less consistent than the first pathology report as it did not form part of the routine data entry protocols for research staff. As expected, the reoperation rate based on pathology reports is lower at 2.9% and is not representative. The database will require an update for reoperations with structured data fields. This underlines our experience that building EPRs for clinical management and research purposes is an iterative rather than a linear process requiring many revisions.

QIs within the context of our resource-constrained health system:

We hypothesised that we would be more prone to interferences, especially in the complex multidisciplinary treatment of breast cancer where indicators are not solely dependent on the quality of a surgical practice but are interlinked with patient and health system factors(169). Our results reflect this expected process when starting the quality control process. The commitment to quality improvement, audit, accreditation, and structured guideline-adherent breast care dates back to the 1990s in Europe. The gradual improvements in quality through investigation and benchmarking and repeated internal and external audits have been well documented; a review of European centres showed compliance in eight out of 13 QIs in 2006 compared to complete compliance in 2015(88). Similarly, radiation after BCS improved from 75.8 to 95.8% after the initiation of an audit process by the National Quality Forum in the United States of America(179). We hope this audit will also trigger a series of gradual improvements in South Africa.

EPR and study strengths and limitations:

Our study shows the unique benefits of EPRs in research, such as access to already collected data, large sample sizes, reduced administrative efforts, costs, and sample selection bias(178). The challenges are that our QI data fields were not predefined and were not all collected specifically for research or quality control purposes. Functions were not uniformly used across sites, especially when this required clinician entry or duplication of workflow. Although structured data is best for research, the clinical nuances of cancer care often require unstructured data fields, the evaluation of which is flawed even with natural language processing methods(173). It is critical to understand clinical workflow so that routine EPRs do not increase workload but aid the clinician. Many routine data points require administrative research staff for reliable data collection in a busy clinic and cannot be entered by frontline staff. Therefore, the success of EPRs and quality control measures depends on the synergy between clinicians, administrators, researchers and informaticians. A further limitation of this study is that it only includes data from the public sector and two provinces, limiting representation. The time of enrolment was set for an initial benchmark and offers no time trends in adherence which will be assessed in a future publication.

4.6 Conclusion

Adherence to QIs varied widely across sites and was mostly inferior to HIC standards. We achieved international standards in the volume criteria for surgeons, and unit volumes in Gauteng, and showed very low positive margin rates, likely due to the generous use of oncoplastic techniques. Our results highlight gaps in breast cancer care; the most urgent are the lack of radiation delivery in Gauteng and the underutilisation of SLNB. BCS rates must be improved, but reliable radiotherapy and sufficient resources are required. MDT discussion requires better documentation to assist patients with complex breast cancer treatment pathways. EPRs are essential in continuous QI monitoring and require adjustment within the EPR to document QI adherence directly. Reliable data collection calls for administrative research staff to avoid overburdening busy frontline workers.

CHAPTER 5: THE ROLE AND MINIMUM REQUIREMENTS OF BREAST CENTRES IN LOW- TO MIDDLE-INCOME COUNTRIES: A SOUTH AFRICAN PERSPECTIVE

Nietz S, Edge J, Buccimazza I, Demetriou G, Tunmer M, Smilg J, et al. The Role and Minimum Requirements for Breast Centres in Low- to Middle-Income Countries: A South African Perspective. JCO Global Oncology. 2025 Jun;(11). Available from: http://dx.doi.org/10.1200/go-25-00168

5.1 Abstract

Breast centres provide comprehensive interdisciplinary care, standardise historically fragmented patient care pathways, and have led to improved outcomes in various high-income countries. Quality improvement initiatives are urgently needed in low-tomiddle-income countries, but the requirements for centres in lower-resource settings have yet to be defined and must be tailored to local environments. In South Africa, breast care lacks governance and standardisation, necessitating urgent improvements in patient care and outcomes. This consensus paper outlines the first set of breast centre requirements tailored for low-to-middle-income countries in sub-Saharan Africa. It emphasises the value and necessity of breast centres in resourceconstrained settings, details centre requirements, and provides a step-by-step plan for initial implementation.

5.2 Introduction

Breast cancer is the most common cancer among women in South Africa, with over 11,200 new cases reported by the National Cancer Registry in 2022(5). Numbers are steadily increasing in low and middle-income countries (LMICs), and while incidence remains lower than in high-income countries (HICs), mortality rates are disproportionately higher, reflecting weaker healthcare infrastructure and late-stage presentation among multifactorial barriers to care(1,118). The provision of care, such as access to optimal therapies or waiting times, accounts for about one-third of survival differences; however, lack of guidelines, quality control, and regulatory framework may also account for up to a quarter of survival differences(28).

The global disparities in breast cancer outcomes are a major challenge, and significant focus has been placed on the strengthening of care in LMICs where implementable quality improvement initiatives are urgently needed(180,181). In South Africa, breast cancer survival is considerably lower than in HICs but better than in many other countries in sub-Saharan Africa, and survival appears to reflect the human development index of countries(10–12).

The available resources and healthcare spending vary widely across LMICs, and are relatively better in South Africa compared to most other sub-Saharan countries(10,182). South Africa has a highly unequal, dual healthcare system in which over 85% of the population relies on the lower-resourced public sector, and under 15% have access to the private sector(53). Access to high-quality breast services is limited in South Africa and depends on the patient's geographical location and socioeconomic situation. At present, we estimate that there are less than ten specialised high-volume multidisciplinary breast care services in the public sector and less than ten in the private sector, serving a population of over 62 million people.

Breast centres condense multidisciplinary expertise and resources with improved patient outcomes including survival, guideline-adherent care with appropriate use of multidisciplinary treatment modalities, and increased cost efficiency(53). They offer the structural capacity to implement complex quality frameworks to increase the quality of care (see Chapter 1, Figure 9). The process of internal and external audits and accreditation processes have been shown to improve the quality of care over time(72,88).

There are several set requirement and accreditation systems, most prominently EUSOMA (European Society of Breast Cancer Specialists) in Europe(28), NAPBC (National Accreditation Program for Breast Centres) in the USA(50), and Onkozert from the DKG (Deutsche Krebs Gesellschaft) in Germany(110). Although accreditation with all three is available internationally, their standards are not uniformly appropriate in the LMIC setting, and the international accreditation process is not affordable and, therefore, not widely reproducible. This has left a gap for providers in LMICs where implementation of quality initiatives are particularly relevant; however, it is essential that the processes are pragmatic and involve systematic, sequential steps for implementation(183).

Although sub-Saharan countries vary, this South African perspective reflects diverse resource levels and offers a consensus for South Africa and a pragmatic implementation approach for a quality improvement initiative applicable to all LMICs. This document intends to provide a consensus on the required structures and processes, describe the role of the centres, and offer a step-by-step plan for initial implementation. These are intended to be achievable with appropriate expertise and effort, widely reproducible and affordable while elevating the overall standard of care, fostering transparency, and protecting the public.

5.3 Methods

The consensus process is illustrated in Figure 14. The literature was reviewed, and international accreditation standards of EUSOMA, NAPBC, and DKG, as well as the 2018 South African Clinical Guidelines for Breast Cancer Control and Management from the South African National Department of Health (NDoH), were structured in a table with recommended South African requirements tailored to our setting. Our primary review team included all authors and the final tables and base documents were circulated to the broader consensus team for review prior to the meeting. The consensus meeting was held virtually in August 2024, and the discussion was moderated by SN and PR. The consensus meeting had 29 participants comprising ten clinical experts from the executive committee of the Breast Interest Group of Southern Africa (BIGOSA), one representative each from the South African Society of Medical Oncology (SASMO), the South African Society of Clinical and Radiation Oncology (SASCRO), and the Association of Surgeons of South Africa (ASSA); five further current heads of academic breast units, seven further clinical experts with particular academic seniority, one representative for advocacy from the Cancer Association of South Africa (CANSA), as well as private sector funder representatives from Discovery Health and Medscheme, two of South Africa's largest private health care administrators. The National Department of Health was invited to participate, but no response was received.

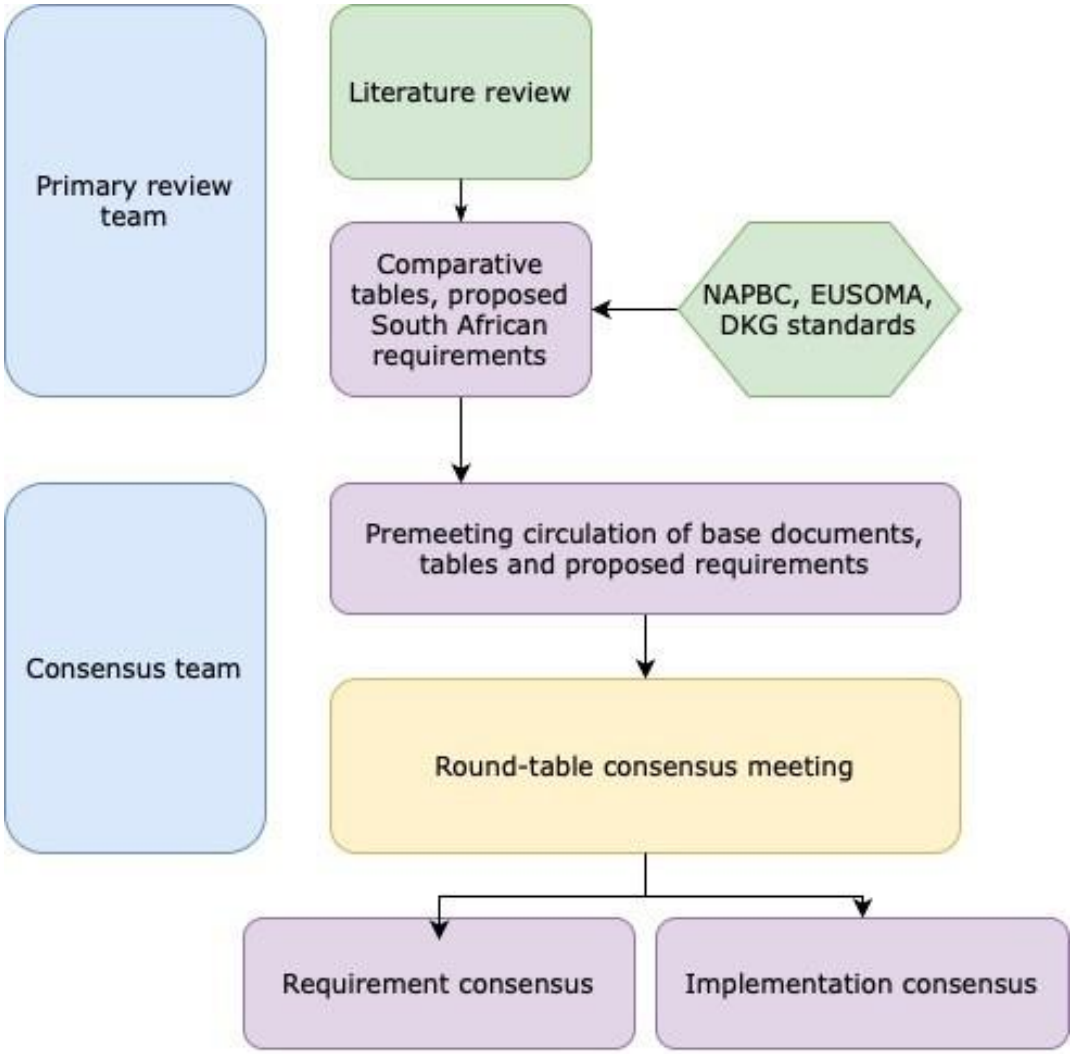


Figure 14: Consensus process

5.4 Results

We categorised requirements into eight broader categories. During discussion in the round table meeting, we achieved unanimous consensus on all requirement components except one abstention in the general specialist and expertise category (consensus 96%), and we were unable to reach a consensus on the patient volume requirements for radiologists, as well as for medical, and clinical/radiation oncologists. Volume requirements for clinical and radiation oncologists were received by SASCRO, and the participating radiologists provided volume requirements which were included. Treating advanced metastatic breast cancer with systemic therapies is complex and

often involves multiple therapy lines, making volume requirements challenging to assess.

The consensus on the implementation was unanimous in supporting BIGOSA as a means to assist in the initial project implementation with South Africa. At the time of writing, this consensus document had received official endorsement by BIGOSA, SASCRO, and CANSA.

5.4.1 Centre Governance and Administration

A breast centre is a structured team of specialists in breast cancer who work as a multidisciplinary team (MDT) with access to all necessary resources and treatments. While single-location centres are preferable, multiple locations can cooperate through agreements and shared treatment protocols.

The centre needs a governance document outlining the organisation, team members, and resource locations, which should be publicly accessible along with treatment protocols. Local guidelines should be followed where applicable. Cooperation agreements between participating practices should be in place and updated annually.

A director should be appointed, who can be a specialist from any speciality on the MDT core team. The steering committee, which should include three specialists from other core specialities, supports the director, and together, they are responsible for MDT participation, data collection, and internal review and audit of the centre's performance.

5.4.2 Specialist Expertise and Resource

The team's mandatory core specialities include radiology, pathology, surgery, plastic surgery, and medical and clinical/radiation oncology. A dedicated breast nurse and clinical navigators improve patient outcomes. Each centre should have at least one breast nurse or trained navigator(184,185).

Ideally, the extended team should include nuclear medicine, human genetics, psychology, palliative care, rehabilitation, dieticians, and fertility preservation. However, these services are often unavailable in LMICs, but are important to highlight, especially the advantages of the availability and early engagement of palliative care.

Ideally, there should be at least two members from each core speciality to enhance treatment options, encourage discussion, and prevent dominance in decision-making.

However, resource constraints may necessitate accepting one member from each speciality.

Participating radiologists should spend a significant portion of their time working in breast imaging. In terms of resources and expertise, the radiology centres should have tomosynthesis digital mammography, high-resolution ultrasound, and must be able to perform ultrasound-guided core biopsies and localisations. Within South Africa, which is relatively well-resourced, breast MRI, and stereotactic biopsy (and localisation) should be available, or there must be an established referral system. Imaging and reports should be stored digitally, and reporting must be standardised and follow the BI-RADS (Breast Imaging Reporting and Data System) classification.

Pathologists are scarce in South Africa and even more so in other sub-Saharan African countries, leading to a lack of specialised breast pathologists(174). However, breast centre pathologists should meet international volume criteria and have specific experience in breast disease. EUSOMA and NAPBC suggest a mandatory internal review of every pathology performed outside of the centre. This is not feasible in LMICs; instead, we recommend that the report must be reviewed in the MDT meeting, and a formal tissue review can be requested if there is clinical concern or discordance.

The breast surgeon must dedicate most of their working time to treating breast disease, meet the volume criteria, and ideally, have completed at least 12 months of post-qualification training or academic experience in breast surgery. There is compelling evidence for improved patient outcomes with specialisation, including a reduction in the relative risk of death at five years of up to 33% compared to lowvolume non-specialised surgeons(186). Given the scarcity of breast surgeons and the lack of formal national training programs, this is a recommended but not a mandatory requirement. Nevertheless, the operative skill set for a specialised centre in South Africa must include the appropriate performance of axillary dissection, sentinel node biopsy and targeted axillary surgery, localisation techniques for impalpable tumours, breast-conserving and oncoplastic procedures and all types of mastectomies (including nipple-sparing and skin-reducing techniques). This skill set is only achievable with specific training, and it is therefore critical that fellowships in breast surgery are recognised and available in LMICs.

Plastic and reconstructive surgeons should fulfill the volume criteria. The centre should be able to offer a wide range of advanced oncoplastic techniques, immediate and delayed implant-based and autologous reconstructions.

Medical oncologists (or clinical oncologists) should have specific experience in treating breast cancer. They must lead the decisions on and oversee all systemic therapies including endocrine therapy, chemotherapy, targeted therapy, and immunotherapy, and provide follow-up information.

The radiation oncologists (or clinical oncologists) should equally have specific experience in the treatment of breast cancer. They should be competent in all breast radiation techniques, including 2D radiotherapy, 3D conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image-guided radiotherapy (IGRT), respiratory-motion-management techniques, stereotactic radiotherapy, and palliative care techniques. They must be skilled in breast cancer contouring and encouraged to complete an online course every five years to stay current. Breast radiotherapy protocols should be regularly updated and include dose planning objectives for target volumes and organ at risk (OAR) constraints for different fractionation schedules. Breast radiotherapy planning and peer review meetings should involve at least two clinical/radiation oncologists, planning radiotherapists, treating radiotherapists, and medical physicists to review cases and assess treatment strategy, fractionation schedule, contours, and dosevolume histograms. Adverse event data should be documented weekly, and follow-up data should be collected after completing treatment. Furthermore, national radiation control regulations and quality assurance must be followed.

5.4.3 Patient Volumes

A critical volume is necessary to build and maintain expertise in some of the core specialities and justify the additional resources and costs for a centre(93,164). The centre must manage a minimum caseload of 100 newly diagnosed or referred patients annually. In addition, each breast surgeon should operate on at least 50 primary breast cancers, and plastic surgeons should perform at least 50 postmastectomy reconstructions or advanced oncoplastic procedures. The systemic treatment of breast cancer is complex and frequently necessitates multiple treatment lines, complicating volume assessment. Clinical/radiation oncologists should aim to create at least 50 new

oncology treatment plans. To ensure adequate breast imaging expertise, radiologists should report at least 300 mammograms annually, perform at least 200 ultrasounds, at least 36 biopsies or localisations, and, for those reporting MRIs, report at least 36 annually.

5.4.4 Multidisciplinary Meetings

Multidisciplinary meetings foster interdisciplinary care and adherence to guidelines, reduce overservicing, overtreatment and futile care, and improve cancer survival(164,187,188). The centre must have at least bimonthly multidisciplinary meetings. Attendance is mandatory and must include all core members. All newly diagnosed, postoperative, and patients with disease recurrence or distant progression must be discussed with clear documentation of team recommendations and treatment pathways. Radiology imaging should be available and viewed at the meeting. Patients who had their imaging elsewhere should have this reviewed by the centre radiologists. Decisions and recommendations must be communicated to the patient. In principle, these recommendations are binding, and if there is a deviation from the clinical treatment plan, the reasons must be discussed and documented.

5.4.5 Patient Care Principles

Figure 15 shows the patient care principles and pathway. Breast care should be standardised and evidence-based with shared decision-making. These choices must be within the constraints of available resources. MDT recommendations must be shared with the patient. Ideally, patients should have written information on treatment options and pathways.

Access to care should be streamlined. A diagnosis and referral to an appropriate centre should take no longer than four weeks from symptoms or a screening-detected abnormality. Treatment should be timely, but patients must not be rushed. Treatment should commence no earlier than a week after diagnosis, but ideally within four weeks of diagnosis(115).

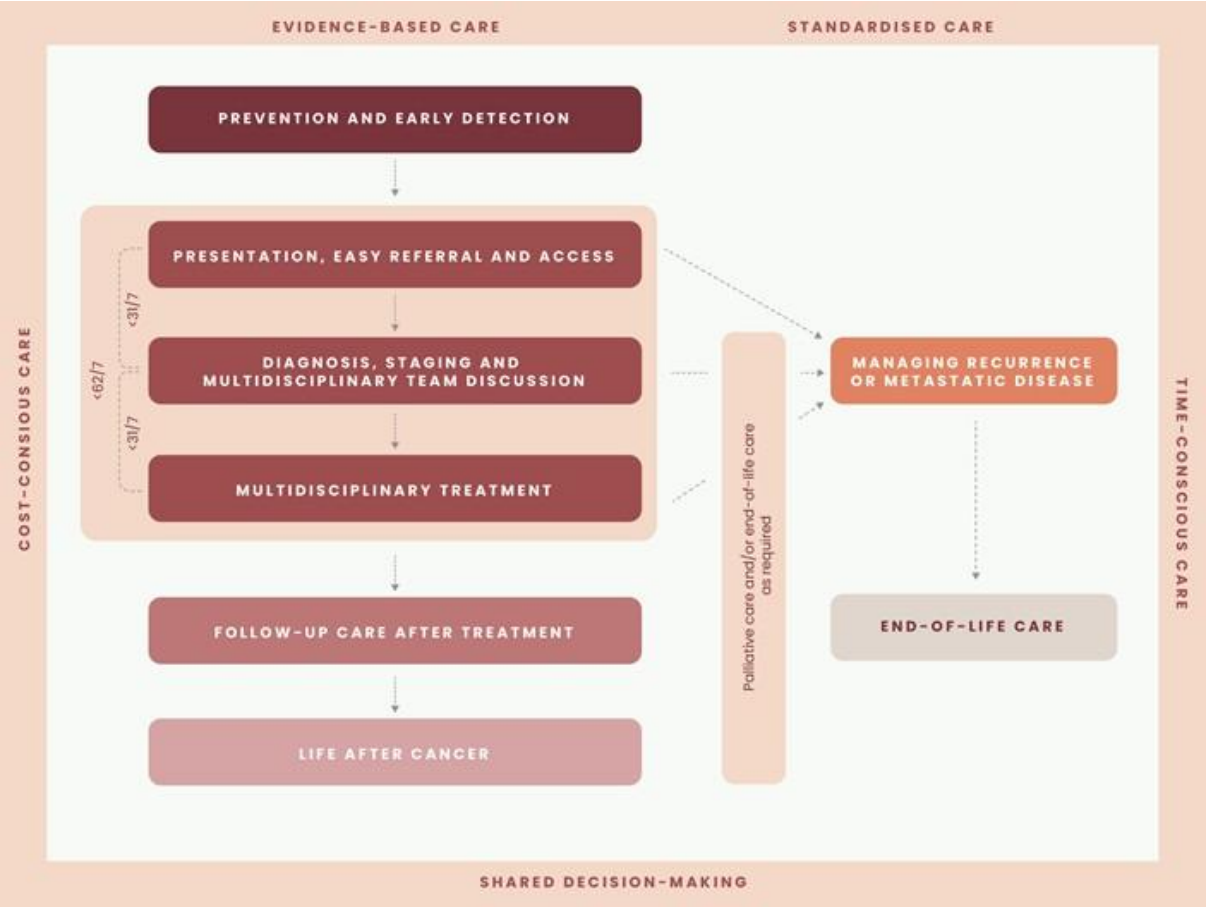


Figure 15: Patient pathway and care principles

Costs are particularly important in LMICs, and emphasis must be placed on both affordability and value of care. High-cost treatments do not necessarily translate to better outcomes and high cost-drivers with little impact are well described(189). Although more complex to implement, in the longer term, breast centres across LMICS should adopt the concept of value-based care(189–191).

5.4.6 Electronic Data Records

A well-functioning electronic record is preferable for a breast centre and forms the basis for research, audit, and quality control. Initial key data should include stage, tumour biology, age, timelines, and treatments received.

Outcome indicators are more laborious to document and would require data or research assistants, resources not commonly available in either healthcare sector in South Africa. Nevertheless, we recommend recording patient-reported outcome measures (PROMs)(81) and conducting survival follow-up for a minimum of five years where possible. The centre

should appoint a data manager to ensure data completeness and extract data for research and audits wherever feasible. The electronic database must ensure data security and confidentiality.

5.4.7 Audit and Quality Control

The breast centre ought to conduct annual audits to identify gaps, followed by a minimum of two interventions as quality improvement initiatives in response. Data sets can be adapted to local resources and are easily expandable; however, we recommend the following initial quality measurements to achieve a broad quality overview:

- Timeliness of care, with documentation of time from presentation to MDT discussion, to treatment modality dates
- Rate of discussion of newly diagnosed patients at MDT
- Rate of breast-conserving surgery
- Rate of sentinel lymph node biopsy in clinically node-negative patients
- Rate of post-mastectomy immediate reconstruction
- Rate of radiation receipt following breast-conserving surgery
- Rate of hypofractionation
- Rate of systemic therapy received for patients with hormone receptor negative tumours
- Rate of HER-2 targeted therapy received in patients with HER-2 positive tumours

5.4.8 Research and Training

Breast centres must engage in research and training to enhance clinical practice, especially in LMICs where training of specialists is critical(180). In South Africa, academic units meet this demand, often in challenging conditions. Private centres should support this effort by participating in research and aiding academic training programs. We advocate for national collaborations between academic and private centres, emphasising private sector support for academic programs.

5.5 Discussion

We propose an implementable step-wise approach to build breast centres in SSA, which should be applicable throughout other LMICs. We recognise that some categories may not be achievable in low-resource settings, but argue that the stepwise

approach, the systematic documentation of resources and gaps in care, and the process of internal or external audit would improve the quality of care over time, transparently and timeously inform on the status of care and build breast care capacity in SSA. At present, minimum targets for quality indicators are unsuitable in LMICs, where participation in quality improvements must be encouraged across all resource levels. The initial data collection should first identify and address existing gaps, but may establish benchmarks over time.

Within South Africa, we urgently need to expand breast cancer capacity with wellsupported breast centres across healthcare sectors that provide standardised and safe care over a broad geographical area. A careful balance should be established between creating high-quality centres and still providing access, potentially with support of peripheral services through a hub-and-spoke system(183). Breast centres were part of the National Department of Health 2017 breast cancer control policy, which flagged breast cancer as a national priority(114). The document described the importance of these centres but implementation is yet to happen. Existing breast academic units remain under-resourced with no new centres established to date.

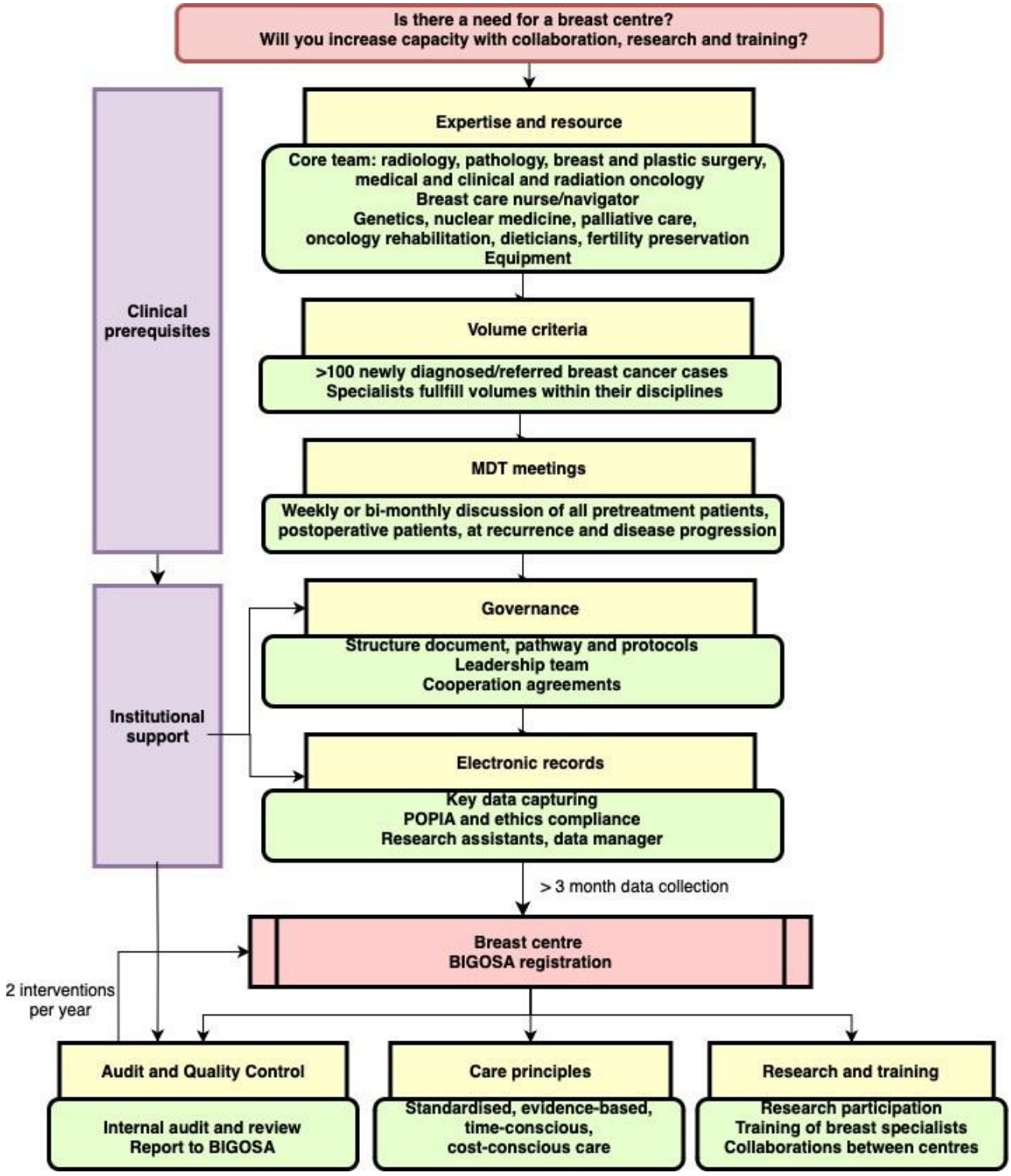
We propose this consensus as a clinician-based initiative to increase capacity by forming public-private partnerships. Establishing collaborative centres would improve integration across healthcare sectors. At present, specialists are primarily trained in academic hospitals; private sector exposure would enhance training for all subspecialties, but it generally produces less research, has poor data collection, and lacks transparency. Affiliating with academic centres would improve documentation and transparency, reduce patient overservicing, and increase research capacity. Besides assisting with training, supportive collaboration could include funding data management, aiding trainee examinations, and financing shared trainee positions.

Initial implementation:

Voluntary participation and self-reporting of audits is a well-described and appropriate step in the implementation phase of breast centres(192). The document offers a stepby-step plan to facilitate this process (Figure 16) and in principle, appropriate multidisciplinary services can implement these steps independently at a low cost. Any

new centre must add value and build capacity; there must be a need for a centre and willingness to collaborate, transparently share audit results, and participate in training and research. The clinicians can then form appropriate teams and resources, with established patient volumes and MDT meetings. Once these clinical prerequisites are met, the next steps should be taken to cover governance and electronic recordkeeping requirements. These will increase administrative workload and commitments and require institutional support. Within southern Africa, new centres could register themselves after three months of clinical data collection with BIGOSA.

Key data and indicators, along with their intervention plans, should be shared collaboratively. Reviews must be anonymous and non-punitive, with compliance status attained through active participation and transparent data sharing.



POPIA = Protection of Personal Information Act

Figure 16: Breast centre implementation steps

Future implementation phases:

The implementation of quality improvement initiatives is complex across healthcare environments, particularly in LMICs(193). BIGOSA is presently not resourced and experienced to collate multi-site audit results, and will require funding and data management support but is intended to serve as a central repository with the opportunity to benchmark quality of care over time. Initial key data and indicators will hopefully be expanded over time. Formal accreditation was intended in the 2018 National Department of Health document and may be a future step after initial benchmarking. There are appropriate third-party accreditors available in South Africa who could fulfil this role, but this would need the involvement and support of statutory bodies and further funding. The BIGOSA executive committee will create a working group to address implementation phases, secure funding, support academic centres and affiliations, address ethics, and gain statutory support.

5.6 Conclusion

We have provided an initial framework and implementation guide for breast centres in SSA. Participation in the registration as a breast centre and audits should be voluntary and non-punitive, and results will be collated and presented annually by BIGOSA. The implementation of the initial steps will assist to standardise care, build capacity and improve overall quality of breast cancer care in SSA.

CHAPTER 6: THE EFFECT OF NON-ADHERENCE TO QUALITY INDICATORS ON OVERALL SURVIVAL AMONG SOUTH AFRICAN WOMEN WITH BREAST CANCER

This chapter is presented in dissertation format and is currently being edited for submission to Lancet Global Health.

6.1 Abstract

Introduction

Quality indicators (QIs) have been applied in high-income countries and contributed to improved outcomes, but there is no data from low-to-middle-income countries on the effect of QI non-adherence on survival. South African breast units function under

resource constraints, and effective interventions are urgently required to improve patient outcomes.

Objectives

The primary objective was to assess the effect of individual QI non-adherence on overall survival; secondary objectives were to evaluate a composite QI adherence model and to analyse site variance in treatment pathways.

Methods

Patients were recruited in a prospective multi-centre cohort study. The clinicopathological factors, treatment pathways, and QI adherence rates were described using Pearson's chi-squared, one-way ANOVA and Kruskal-Wallis tests. Cox's proportional hazard regressions were used for univariate and multivariate analyses to assess the effect of non-adherence to QIs on overall survival.

Results

We included 2716 patients from the NIH-funded SABCHO study with a median followup of 3.5 (1.5-5.0) years. 5-year overall survival was 43.5%. In the adjusted multivariate model, there were significant hazard ratios for breast-conserving surgery (BCS) for the overall cohort (HR 1.622 p=<0.001, 95% CI 1.263-2.083), BCS for stage 1 and 2 (HR 1.491, p=0.025, 95% CI 1.050-2.116), axillary surgery (HR 1.515, p=0.025, 95% CI 1.053-2.181), receipt of radiotherapy after BCS (HR 1.844, p=0.021, 95% CI 1.096-3.103), and multidisciplinary team discussion (HR 1.492, p=<0.001, 95% CI 1.295-1.1.718). The composite adherence model showed worse survival with increasing non-adherence levels (HR 2.4, p=<0.001, 95% CI 1.830-3.147). There was significant site variance in treatment pathways across sites.

Conclusions

Better individual QI and composite adherence levels were associated with improved overall survival. Mandatory MDT discussion will be an effective first intervention to improve breast cancer survival in South Africa. Despite poor radiotherapy delivery, BCS is not unjustified in our selected patients and not associated with worse outcomes. Critically, radiation access must be urgently improved. Breast units showed remarkable resilience and flexibility and adjusted their treatment pathways to local resource availability.

6.2 Introduction

6.2.2 Background

Quality indicators (QIs) are standardised measures used to determine healthcare outcomes. Using the Donabedian framework, they can be subdivided into three types: structure, process, and outcome(58), and can be integrated into a more comprehensive breast cancer quality framework (see Chapter 1, Figure 9). Process measures are the most amenable to measuring quality of care, and we recently demonstrated significant variance of QI adherence among breast units in the South African public sector with geographical differences in the access to essential resources such as equipment for sentinel node biopsy and access to radiotherapy(194).

In high-income countries (HICs), adherence to QIs and consequent guidelineadherent treatment has improved patient outcomes(88,99,195). Although geographical variations exist, these countries typically have stronger healthcare systems, including population-based screening programs for early detection and treatment, robust cancer policies, and relatively ubiquitous and efficient access to specialised breast care. Multiple studies have measured and demonstrated improved QI adherence levels over time(87,88,196). Fewer studies have examined the impact of QI adherence on survival. As breast cancer treatment is highly complex and involves many factors, it can be challenging to determine the effects of individual QIs; consequently, most studies examine a survival effect based on a composite indicator or overall adherence to guidelines rather than single QIs alone(76,83,99–102). Most studies show a survival benefit, although some have also highlighted paradoxical outcomes(97,98).

Data on breast cancer survival in South Africa shows considerably poorer outcomes with 3-year survival of 60.4-63% compared to women living in HICs, and is mainly determined by late-stage presentation, as well as suboptimal therapies(10,11). South Africa, a low-to-middle-income country with high social inequality, still maintains a dual healthcare system, where most resources are in the private sector, accessible to under 20% of the population(197). The public sector caters to most of the population, but there is significant variation in the quality of care, which is often compromised due to weak healthcare infrastructure, limited resources, poor governance, corruption, and disruptions or inefficiencies in service delivery(198,199). As breast cancer is the most common cancer among women in South Africa and incidence is expected to rise further(1,5), it poses a significant challenge in terms of economics and healthcare

policy, with an urgent need for effective and feasible interventions to elevate public health services and patient outcomes.

In the context of low- and middle-income countries (LMICs), only publications from China describe QI adherence rates and a rankability-weighted composite QI score, yet they have not analysed the impact on survival(83,200). It is, therefore, unclear whether there are measurable effects on survival in LMICs or if we could identify key QIs that offer feasible targeted interventions in our setting, where survival is heavily influenced by factors such as late-stage presentation, lack of cancer policy implementation, and inefficiencies or failures in healthcare delivery.

6.2.3 Aim of the Study

To assess the effect of QI non-adherence on overall survival in South African women with breast cancer.

6.2.4 Research Questions

Does individual or combined QI non-adherence have a measurable effect on overall survival in our cohort? Did sites adjust treatment pathways in response to resource constraints?

6.2.5 Hypotheses

Individual QIs will not have measurable effects on survival in our cohort, but a composite measure may show effect. Sites will have adjusted treatment pathways to specific resource constraints.

6.3 Methods

6.3.1 Study Design and Settings

We accessed data collected by the South African Breast Cancer and HIV Outcomes (SABCHO) Study, which is a prospective multi-centre cohort study that includes breast cancer patients from six hospitals in the Gauteng and KwaZulu-Natal (KZN) provinces of South Africa. Chris Hani Baragwanath Academic Hospital (CHBAH), a tertiary hospital in Soweto, and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary hospital in central Johannesburg, are both in the Gauteng province. Inkosi Albert Luthuli Central Hospital Addington Hospital is a tertiary hospital in Durban, and Addington Hospital in Durban and Ngwelezana Hospital in Empangeni in rural northern KZN are regional hospitals. In this analysis, the three sites are

combined as the Durban complex. Grey's Hospital (GH) is a tertiary hospital in Pietermaritzburg and serves a mixed rural and urban population. The various sites differ considerably in terms of the populations they serve and the level of treatment resource availability during the study period (Figure 17). Recruitment started in July 2015 in Gauteng sites and was rolled out to include KZN sites by January 2016. Due to funding and personnel constraints, the KZN sites stopped recruiting by December 2018 , while the Gauteng sites continued enrolment.

For this analysis, we included women who presented to all participating breast units between 1 July 2015 and 31 December 2018. We selected this period to reduce the introduction of site bias and to avoid the potential effects of the Covid-19 pandemic on treatment quality.

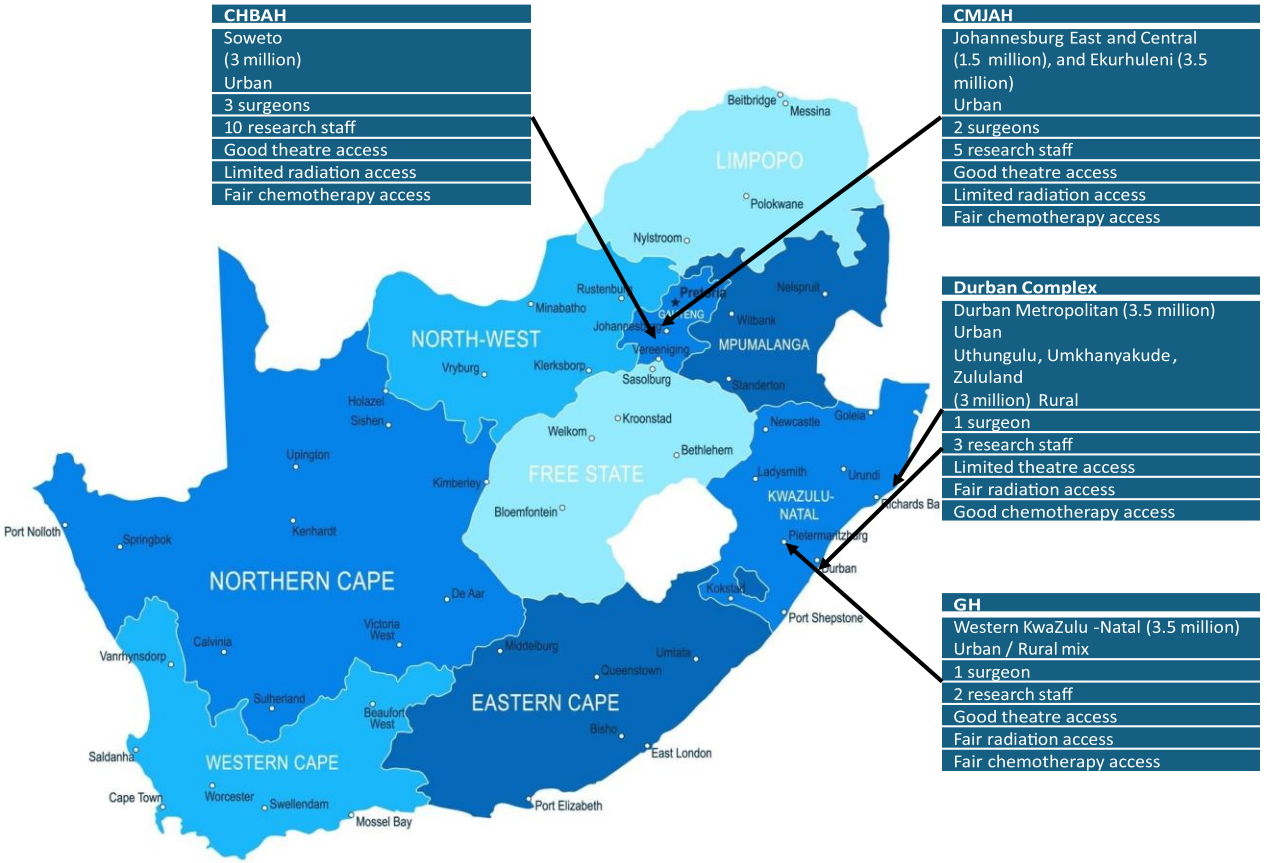

CHBAH
Soweto
(3 million)
Urban
3 surgeons
10 research staff
Good theatre access
Limited radiation access
Fair chemotherapy access
CMJAH
Johannesburg East and Central
(1.5 million), and Ekurhuleni (3.5 million)
Urban
2 surgeons
5 research staff
Good theatre access
Limited radiation access
Fair chemotherapy access
Durban Complex
Durban Metropolitan (3.5 million)
Urban
Uthungulu, Umkhanyakude, Zululand
(3 million) Rural
1 surgeon
3 research staff
Limited theatre access
Fair radiation access
Good chemotherapy access
GH
Western KwaZulu -Natal (3.5 million)
Urban / Rural mix
1 surgeon
2 research staff
Good theatre access
Fair radiation access
Fair chemotherapy access
LIMPOPO
NORTH-WEST
MPUMALANGA
FREE STATE
KWAZULU-NATAL
NORTHERN CAPE
EASTERN CAPE
WESTERN CAPE
Beitbridge
Messina
Polokwane
Nylstroom
Rustenburg
Pretoria
Nelspruit
Minabatho
GAUTENG
Witbank
Johannesburg
Vereeniging
Vryburg
Klerksdorp
Sasolburg
Standerton
Holazel
Sishen
Kroonstad
Welkom
Bethlehem
Newcastle
Golela
Upington
Kimberley
Ladysmith
Urundi
Bloemfontein
Richards Ba
Port Nolloth
Springbok
Kenhardt
Pietermaritzburg
Durban
Koksta
De Aar
Port Shepstone
Victoria West
Calvinia
Middelburg
Umtata
Vanrhynsdorp
Queenstown
Sutherland
Beaufort West
Bisho
East London
Saldanha
Cape Town
Worcester
Swellendam
Port Elizabeth
Mossel Bay

Figure 17: Study site populations and resources

6.3.2 Enrolment Period and Participant Recruitment

The inclusion and exclusion criteria and the detailed SABCHO methods and protocol were published previously(120). All women presenting to the participating units with newly diagnosed invasive breast cancer, who were at least 18 years of age and had resided in South Africa for at least five years, were eligible for enrolment in the SABCHO Study. We excluded women with a previous cancer diagnosis, except noninvasive cervical cancer or nonmelanoma skin cancer, or those who were unable to give informed consent.

6.3.3 Data Collection

Data were collected across study sites with a customised electronic patient record (EPR) system called OncoDB. The collection of QI data was not part of the SABCHO protocol and was extracted retrospectively from the available clinical data, such as histopathology and clinical records on the EPR.

6.3.4 Quality Indicator Selection

The selection of QIs was based on our previous publication, which defined a QI set for the diagnosis and surgical management of breast cancer in South Africa and included ten critical QIs(169). We previously measured our dataset's respective QI data quality and adherence rates and found that the reoperation rate was not reliably measurable; therefore, this QI has been excluded from this analysis(194). Volume QIs were also excluded from survival analyses as surgeon volume was uniformly greater than the international target, and unit volumes may have been underestimated as not all patients treated were also eligible for SABCHO enrolment. However, we added timeliness indicators as these may be of greater importance in LMICs and have also been added to the most recent European Society of Breast Cancer Specialists (EUSOMA) QIs(49). The definitions, numerators, and denominators of QIs are listed in Table 12.

6.3.5 Outcome Data

Our primary outcome was the effect of QI non-adherence on overall survival. Throughout the SABCHO study, patients were contacted telephonically every three months to confirm vital status. If the patient, next of kin, or other close contacts could not be reached with two further follow-up calls, we searched the publicly available

administrative database to ascertain vital status. Our vital status data comes from various sources, does not differentiate the cause of death, and therefore cannot be used to evaluate disease-specific survival. Similarly, we do not have reliable data on local recurrence or distant disease progression and, therefore, cannot evaluate more intermediate outcomes, such as disease-free or progression-free survival.

6.3.6 Statistical Analysis

We utilised sensitivity analyses to examine exclusions and missingness by comparing key demographic and clinicopathologic variables of included patients to those who were enrolled thereafter. The clinicopathological factors, QI adherence rates, and treatment pathways across sites were described using Pearson's chi-squared test, except for age, for which we used one-way Analysis of Variance (ANOVA), and the comparison of the median for timeliness indicators, for which we employed the Kruskal-Wallis test.

QIs were not universally applicable to all patients and were defined as applicable with adherence or non-adherence, or not applicable. We used a stepwise approach to build our QI survival models. Initially, we evaluated the odds ratios (ORs) for each QI nonadherence with logistical regression in a univariate model, followed by a multivariate model adjusting for potential and known predictors of survival, including hospital site, age, stage, HIV status, receptor status, and proliferative rate(201).

We then progressed to Cox's proportional hazard regressions for univariate and multivariate analyses, adjusting for the same factors to assess the hazard ratios (HRs) of non-adherence to individual QIs. The final model was a composite QI adherence model that calculated HRs for patients with over 50% adherence to applicable QIs compared to patients with under 50% and 0% adherence levels. Forest plots were created to visualise results.

Survival analyses were illustrated on a time-since-diagnosis scale with the at-risk period starting on the date of histologically confirmed breast cancer diagnosis and ending on the earliest date of death from any cause, the date on which the participant was last known to be alive, or the administrative censoring date of 31 December 2023. We constructed Kaplan–Meier survival curves (202) stratified by QIs, sites, stage, and human immunodeficiency virus (HIV) status and survival comparisons were determined by log-rank test.

Patient treatment pathways from the different study sites were compared and plotted onto Sankey diagrams and network plots.

All statistical analyses were performed using Stata version 16 (Stata Corp Ltd., College Station, TX)(135).

6.3.7 Ethical Considerations

The SABCHO Study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical), the University of KwaZulu-Natal Biomedical Research Committee, and the Institutional Review Board of Columbia University. This sub-study received approval from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M180761, extension M240165).

Table 12: Quality indicator description

#	Quality Indicators		Definition	Numerator	Denominator
1	Complete histopathological characterisation:	a) on core biopsy	Proportion of cases for which the following prognostic/predictive parameters have been recorded: Histological type; grading; ER; PR; HER-2; proliferation index (Ki-67).	Invasive breast cancer patients for which all prognostic/predictive parameters have been recorded.	All invasive breast cancer patients.
		b) on the operative specimen	In addition to the above parameters, the following parameters must be recorded after surgery: Pathological stage; size in mm for the invasive component; lymphovascular invasion; distance to nearest radial margin.	Invasive breast cancer patients for which all prognostic/predictive parameters have been recorded.	All invasive breast cancer patients who underwent surgery.
2	Breast conserving surgery (BCS) rate	a) across stages	Proportion of patients undergoing BCS among all patients who receive surgery for the primary breast cancer.	Patients with breast cancer who undergo BCS.	All patients with breast cancer who undergo surgery for the breast primary.
		b) stage 1 and 2			
3	Rate of positive margins after breast BCS		Proportion of patients with positive margins after BCS among all patients who underwent BCS.	Patients with positive margins after BCS.	All patients who undergo BCS.
4	Reoperation rate *		Proportion of patients with breast cancer who required a reoperation for the breast primary within six months of the initial surgery.	Patients who required a reoperation for the primary tumour within six months of initial surgery.	All patients who underwent surgery for the primary tumour.

5	Appropriate axillary surgery:	a) rate of surgery in invasive breast cancer	Proportion of invasive breast cancer patients who underwent axillary surgery.	Patients with invasive breast cancer who underwent axillary surgery.	All patients with invasive breast cancer who underwent surgery.
		b) sentinel node biopsy (SLNB) only in clinically node-negative disease	Proportion of patients with invasive cancer and clinically negative axilla who underwent SLNB only (excluding patients who received primary systemic therapy).	Patients with invasive cancer and clinically negative axilla who underwent primary surgery and sentinel lymph node biopsy only.	All patients with invasive cancer and clinically negative axilla who underwent primary surgery
6	Number of nodes excised during axillary surgery:	a) ALND ^{3}10 nodes	Proportion of breast cancer patients undergoing ALND who have at least 10 nodes examined (excluding patients who received primary systemic therapy).	Patients undergoing primary ALND with at least 10 nodes examined.	All patients who underwent primary ALND.
		b) SLNB £ 5 nodes	Proportion of patients with invasive cancer who underwent SLNB with no more than 5 nodes excised.	Patients with invasive cancer who underwent SLNB with no more than 5 nodes excised.	All patients with invasive cancer who underwent SLNB.
7	Receipt of radiotherapy after BCS		Proportion of invasive breast cancer patients who received radiotherapy after BCS.	Patients who received radiotherapy after BCS.	All patients who had BCS for invasive breast cancer.

8	Appropriate treatment sequencing in inoperable locally advanced breast cancer (LABC)	Proportion of patients with inflammatory or non-operable LABC who undergo primary systemic treatment before surgery.	Patients with inflammatory or nonoperable LABC who undergo primary systemic treatment before surgery.	All patients undergoing surgical treatment for inflammatory or nonoperable LABC.
9	Case Volume*: a) breast unit [3]150 newly diagnosed cases per annum	Each unit needs to see a set minimum number of 150 patients with newly diagnosed breast cancer per annum.	N/A.	N/A.
	Case Volume*: b) surgeon volume [3]50 breast cancer cases per annum	Each surgeon needs to perform a set minimum number of surgeries on patients with newly diagnosed breast cancer per annum. In units which train surgeons this would include supervised (scrubbed in) surgeries.	N/A.	N/A.
10	Multidisciplinary team discussion	Proportion of patients with breast cancer who are discussed in a MDT meeting (ideally pre- and postoperatively).	Patients with breast cancer who are discussed in the MDT meeting.	All patients with breast cancer.
11	Timeliness: a) biopsy to first treatment	Proportion of patients with breast cancer who receive their first treatment within 6 weeks from biopsy.	Patients with breast cancer who receive their first treatment within 6 weeks from biopsy.	All patients with breast cancer.

		b) from surgery or last chemoptherapy to radiotherapy	Proportion of patients with breast cancer who underwent surgery or chemotherapy who receive their first radiotherapy treatment within 12 weeks.	Patients with breast cancer who receive their first radiotherapy treatment within 12 week	All patients with breast cancer who receive curative radiotherapy.
				after surgery or last chemotherapy.	
		c) from neoadjuvant chemotherapy to surgery	Proportion of patients with breast cancer who underwent neoadjuvant chemotherapy who receive surgery within 12 weeks.	Patients with breast cancer who receive surgery within 12 week after last chemotherapy.	All patients with breast cancer who receive surgery after neoadjuvant chemotherapy.
		d) from surgery to adjuvant chemotherapy	Proportion of patients with breast cancer who underwent underwent surgery and received adjuvant chemotherapy within 12 weeks.	Patients with breast cancer who commence adjuvant chemotherapy within 12 week after surgery.	All patients with breast cancer who receive adjuvant chemotherapy after surgery.

* Reoperation was excluded from this analysis due to poor data quality(206), case volumes excluded as surgeon volumes uniformly high and unit volumes may be underrepresented as not all treated patients were eligible for SABCHO enrolment.

6.4 Results

6.4.1 Enrolment

We included 2716 patients in this analysis; 211 patients were excluded from the 2927 total SABCHO records as they did not have invasive breast cancer but ductal carcinoma in situ (DCIS) only. The enrolment is illustrated in Figure 18.

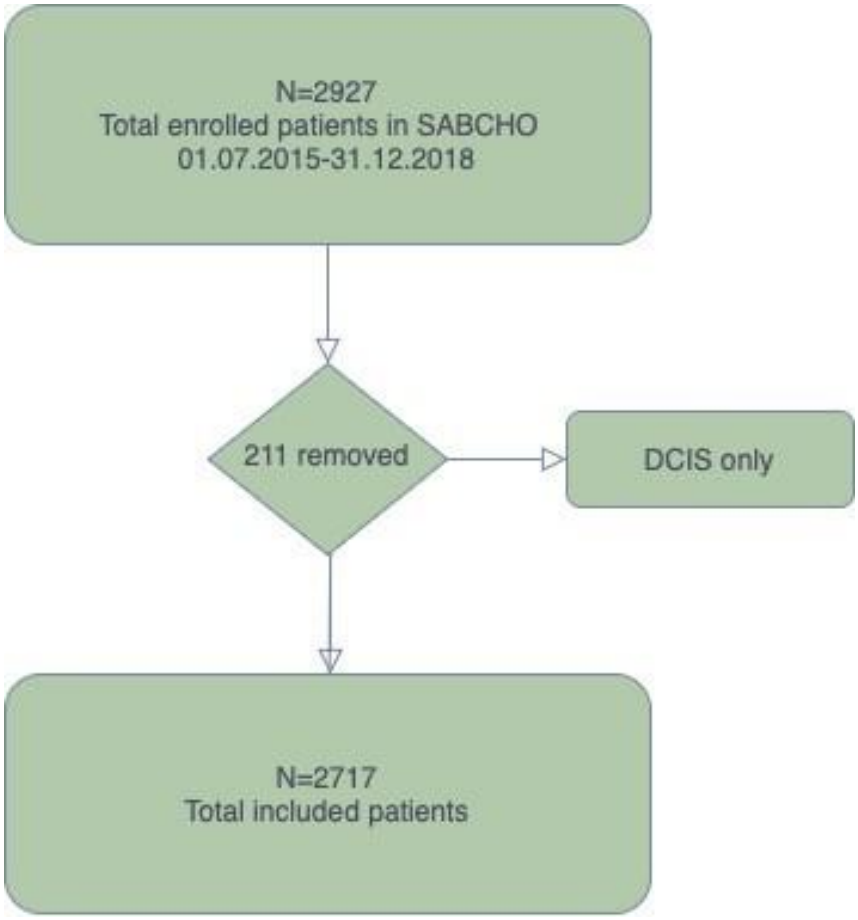


Figure 18: Patient enrolment flowchart

6.4.2 Clinicopathological Risks and QI Adherence Levels

Demographics and clinicopathological features

The patients' mean age was 56 years(SD 14.4), with 585 patients who were human immunodeficiency virus (HIV) positive (21.5%), and 1807 patients who presented with locally advanced or metastatic disease (66.5%). Clinicopathological risk factors and QI adherence rates are described in Table 13 and show wide variance between sites, largely in keeping with previous data(206).

Sensitivity analysis

The sensitivity analysis showed a few differences in the enrolled cohort compared to the later cohort, which included patients during and post COVID-19. Age of patients was younger post-COVID-19 (means of 54.7 and 52.9, p=0.094), with a marginally more single status (p=0.047), higher education status (p=0.000), less pregnancies (p=0.032) and different core biopsy receptor status (p=0.002). These changes are likely driven by the impact of the COVID-19 pandemic.

Timeliness

Regarding timeliness, the median time from date of biopsy to first treatment was 54 days, 32.2% of patients received treatment within six weeks, whereas 79.6% had received their first therapy within 120 days. The median time from surgery or last chemotherapy to radiotherapy (RT) was 154 days, if received, only 13.3% received RT within 12 weeks. The median time from neoadjuvant chemotherapy (NACT) to surgery was 43 days, and 53 days from NACT to surgery.

Table 13: Description of cohort and quality indicator adherence

Exposure domain N (%)	**Total (%)**	**CHBAH**	**CMJAH**	**Durban**	**GH**	**P-values**
Number of women enrolled	2716	943	647	614	512	
CLINICAL RISKS						
HIV status at the time of breast cancer diagnosis						<0.001
Positive	585 (21.5)	233 (24.7)	111 (17.2)	115 (18.7)	126 (24.6)	
Missing	*23 (0.8)*	*16 (1.7)*	*2 (0.3)*	*5 (0.8)*	*0 (0.0)*	
Stage at diagnosis						0.016
Late stage (III + IV)	1807 (66.5)	592 (62.8)	436 (67.4)	431 (70.2)	348 (68.0)	
Missing	*3 (0.1)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	
Cancer proliferation risk						<0.001

High: Ki67 ≥ 20%	1742 (64.1)	735 (77.9)	433 (66.9)	254 (41.4)	320 (62.5)	
Missing	*177 (6.5)*	*26 (2.8)*	*11 (1.7)*	*60 (9.8)*	*80 (15.6)*	
Receptor subtype risk						<0.001
HR+/HER2-	1581 (58.2)	502 (53.2)	387 (59.8)	379 (61.7)	313 (61.1)	
HR+/HER2+	454 (16.7)	209 (22.2)	98 (15.1)	88 (14.3)	59 (11.5)	
HR-/HER2+	180 (6.6)	52 (5.5)	51 (7.9)	45 (7.3)	32 (5.3)	
HR-/HER2-	421 (15.5)	141 (15.0)	103 (15.9)	88 (14.3)	89 (17.4)	
Missing	*80 (2.9)*	*39 (4.1)*	*8 (1.2)*	*14 (2.3)*	*19 (3.7)*	
AGE RISK						
Age at diagnosis						0.514
Mean (SD)	56.0 (14.4)	55.0 (14.7)	54.8 (14.0)	57.3 (14.0)	57.8 (14.4)	
Missing	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	
QUALITY INDICATOR ADHERENCE						
Q1: Complete histopathological characterisation of invasive						
a) On core biopsy						
Applicable	2716 (100)	943 (100)	647 (100)	614 (100)	512 (100)	<0.001
Adherence	1604 (59.1)	883 (93.6)	618 (95.5)	73 (11.9)	30 (5.9)	
Nonadherence	1112 (40.9)	60 (6.4)	29 (4.5)	541 (88.1)	482 (94.1)	
Not applicable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
b) On surgical specimen						
Applicable	1769 (65.1)	659 (69.9)	401 (62)	364 (59.3)	345 (67.4)	<0.001
Adherence	1155 (65.3)	549 (83.3)	293 (73.1)	82 (22.5)	231 (67)	

Nonadherence	614 (34.7)	110 (16.7)	108 (26.9)	282 (77.5)	114 (33)	
Not applicable	947 (34.9)	284 (30.1)	246 (38)	250 (40.7)	167 (32.6)	
Q2:						
a) Breast-conserving surgery rate						
Applicable	1769 (65.1)	659 (69.9)	401 (62)	364 (59.3)	345 (67.4)	<0.001
Adherence	341 (19.3)	97 (14.7)	97 (24.2)	108 (29.7)	39 (11.3)	
Nonadherence	1428 (80.7)	562 (85.3)	304 (75.8)	256 (70.3)	306 (88.7)	
Not applicable	947 (34.9)	284 (30.1)	246 (38)	250 (40.7)	167 (32.6)	
b) Breast-conserving surgery rate among stages 1 and 2						
Applicable	800 (29.5)	302 (32)	188 (29.1)	158 (25.7)	152 (29.7)	<0.001
Adherence	256 (32)	73 (24.2)	70 (37.2)	84 (53.2)	29 (19.1)	
Nonadherence	544 (68)	229 (75.8)	118 (62.8)	74 (46.8)	123 (80.9)	
Not applicable	1916 (70.5)	641 (68)	459 (70.9)	456 (74.3)	360 (70.3)	
QI3: Rate of positive margins after breast-conserving surgery						
Applicable	352 (13)	102 (10.8)	98 (15.1)	112 (18.2)	40 (7.8)	0.130
Adherence	334 (94.9)	95 (93.1)	90 (91.8)	110 (98.2)	39 (97.5)	
Nonadherence	18 (5.1)	7 (6.9)	8 (8.2)	2 (1.8)	1 (2.5)	
Not applicable	2364 (87)	841 (89.2)	549 (84.9)	502 (81.8)	472 (92.2)	
QI4: Reoperation rate						
a) On pathology reports						
Applicable	1769 (65.1)	659 (69.9)	401 (62)	364 (59.3)	345 (67.4)	0.012
Adherence	1723 (97.4)	632 (95.9)	392 (97.8)	361 (99.2)	338 (98)	

Nonadherence	46 (2.6)	27 (4.1)	9 (2.2)	3 (0.8)	7 (2)	
Not applicable	947 (34.9)	284 (30.1)	246 (38)	250 (40.7)	167 (32.6)	
b) on operation notes€						
Applicable	1060 (39)	659 (69.9)	401 (62)	- (-)	- (-)	0.630
Adherence	973 (91.8)	607 (92.1)	366 (91.3)	- (-)	- (-)	
Nonadherence	87 (8.2)	52 (7.9)	35 (8.7)	- (-)	- (-)	
Not applicable	530 (33.3)	284 (30.1)	246 (38)	- (-)	- (-)	
QI5: Appropriate axillary surgery						
a) Rate of axillary surgery in invasive breast cancer						
Applicable	1769 (65.1)	659 (69.9)	401 (62)	364 (59.3)	345 (67.4)	0.124
Adherence	1703 (96.3)	643 (97.6)	384 (95.8)	345 (94.8)	331 (95.9)	
Nonadherence	66 (3.7)	16 (2.4)	17 (4.2)	19 (5.2)	14 (4.1)	
Not applicable	947 (34.9)	284 (30.1)	246 (38)	250 (40.7)	167 (32.6)	
b) Sentinel node biopsy only in clinically node-negative disease						
Applicable	619 (22.8)	239 (25.3)	174 (26.9)	108 (17.6)	98 (19.1)	<0.001
Adherence	271 (43.8)	94 (39.3)	97 (55.7)	78 (72.2)	2 (2)	
Nonadherence	348 (56.2)	145 (60.7)	77 (44.3)	30 (27.8)	96 (98)	
Not applicable	2097 (77.2)	704 (74.7)	473 (73.1)	506 (82.4)	414 (80.9)	
QI6: Number of nodes excised during axillary surgery						
a) Lymph node dissection ≥10 nodes						
Applicable	352 (13)	124 (13.1)	52 (8)	4 (0.7)	172 (33.6)	<0.001

Adherence	185 (52.6)	46 (37.1)	16 (30.8)	0 (0)	123 (71.5)	
Nonadherence	167 (47.4)	78 (62.9)	36 (69.2)	4 (100)	49 (28.5)	
Not applicable	2364 (87)	819 (86.9)	595 (92)	610 (99.3)	340 (66.4)	
b) Sentinel node biopsy ≤5 nodes						
Applicable	224 (8.2)	100 (10.6)	98 (15.1)	24 (3.9)	2 (0.4)	<0.116
Adherence	184 (82.1)	80 (80)	86 (87.8)	17 (70.8)	1 (50)	
Nonadherence	40 (17.9)	20 (20)	12 (12.2)	7 (29.2)	1 (50)	
Not applicable	2492 (91.8)	843 (89.4)	549 (84.9)	590 (96.1)	510 (99.6)	
QI7: Receipt of radiotherapy after breast-conserving surgery						
Applicable	341 (12.6)	97 (10.3)	97 (15)	108 (17.6)	39 (7.6)	<0.001
Adherence	268 (78.6)	62 (63.9)	72 (74.2)	98 (90.7)	36 (92.3)	
Nonadherence	73 (21.4)	35 (36.1)	25 (25.8)	10 (9.3)	3 (7.7)	
Not applicable	2375 (87.4)	846 (89.7)	550 (85)	506 (82.4)	473 (92.4)	
QI8: Appropriate treatment sequencing in inoperable LABC						
Applicable	373 (13.7)	88 (9.3)	105 (16.2)	78 (12.7)	102 (19.9)	<0.148
Adherence	371 (99.5)	88 (100)	105 (100)	78 (100)	100 (98)	
Nonadherence	2 (0.5)	0 (0)	0 (0)	0 (0)	2 (2)	
Not applicable	2343 (86.3)	855 (90.7)	542 (83.8)	536 (87.3)	410 (80.1)	
QI9: Case volume[$]						

a) Breast unit ≥150 newly diagnosed cases per annum		2016-2018 (100)	2016-2018 (100) 2016-2018 (100)	2016-2017 (66.6)	2017 (33.3)	
b) Surgeon volume ≥50 breast cancer cases per annum		2016-2018 (100)		2016-2018 (100)	2016-2018 (100)	
QI10: Multidisciplinary team discussion						
Applicable	2716 (100)	943 (100)	647 (100)	614 (100)	512 (100)	<0.001
Adherence	1907 (70.2)	762 (80.8)	504 (77.9)	566 (92.2)	75 (14.6)	
Nonadherence	809 (29.8)	181 (19.2)	143 (22.1)	48 (7.8)	437 (85.4)	
Not applicable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
QI11: Timeliness						
a) Time from diagnosis (date of biopsy) to first treatment (adherence within 42 days/6 weeks)						
Median time in days (IQR)	54 (35-88)	41 (27-62)	52 (41-76)	93 (61-131)	53 (34-79)	<0.001
Applicable	2507 (92.3)	867 (91.9)	571 (88.3)	579 (94.3)	490 (95.7)	<0.001
Adherence	875 (34.9)	461 (53.2)	170 (29.8)	66 (11.4)	178 (36.3)	
Nonadherence	1632 (65.1)	406 (46.8)	401 (70.2)	513 (88.6)	312 (63.7)	
Not applicable	209 (7.7)	76 (8.1)	76 (11.7)	35 (5.7)	22 (4.3)	
b) Time from surgery or last chemotherapy to RT (adherence within 84 days/12 weeks)						
Median time in days (IQR)	154 (110-225)	158.5 (128-244)	174 (129-243.5)	135 (94-185)	156 (86-269)	<0.001
Applicable	1050 (38.7)	334 (35.4)	212 (32.8)	301 (49)	203 (39.6)	<0.001
Adherence	140 (13.3)	18 (5.4)	7 (3.3)	66 (21.9)	49 (24.1)	
Nonadherence	910 (86.7)	316 (94.6)	205 (96.7)	235 (78.1)	154 (75.9)	

Not applicable	1666 (61.3)	609 (64.6)	435 (67.2)	313 (51)	309 (60.4)	
c) Time from last (neoadjuvant) chemotherapy to surgery (adherence within 84 days/12 weeks)						
Median time in days (IQR)	43 (28-76)	28 (19-44)	41 (32-55)	72 (42-100)	48 (34-76)	<0.001
Applicable	684 (25.2)	215 (22.8)	174 (26.9)	214 (34.9)	81 (15.8)	<0.001
Adherence	545 (20.1)	195 (20.7)	157 (24.3)	129 (21)	64 (12.5)	
Nonadherence	139 (5.1)	20 (2.1)	17 (2.6)	85 (13.8)	17 (3.3)	
Not applicable	2032 (74.8)	728 (77.2)	473 (73.1)	400 (65.1)	431 (84.2)	
d) Time from surgery to (adjuvant) chemotherapy (adherence within 84 days/12 weeks)						
Median time in days (IQR)	52 (40-70)	49.5 (38-69)	56 (45-76)	53 (38-65)	53 (42-71.5)	0.199
Applicable	635 (23.4)	271 (28.7)	110 (17)	86 (14)	168 (32.8)	0.252
Adherence	538 (19.8)	237 (25.1)	88 (13.6)	74 (12.1)	139 (27.1)	
Non-adherence	97 (3.6)	34 (3.6)	22 (3.4)	12 (2)	29 (5.7)	
Not applicable	2081 (76.6)	672 (71.3)	537 (83)	528 (86)	344 (67.2)	
QI Composite Adherence Percentage[#]						<0.001
0% Composite adherence	110 (4.1)	10 (1.1)	2 (0.3)	13 (2.1)	85 (16.6)	
1-50% Composite adherence	873 (32.1)	150 (15.9)	88 (13.6)	343 (55.9)	292 (57)	
>50% Composite adherence	1733 (63.8)	783 (83)	557 (86.1)	258 (42)	135 (26.4)	

[$]Case volumes calculated for full calendar-year enrolments: 2016 – 2018 for Johannesburg, Soweto, Durban and Pietermaritzburg.

[€]Operations only recorded in Soweto and Johannesburg.

[#]Composite adherence percentage is calculated by the number of adherent QIs divided by the number of total applicable QIs for each patient.

Follow-up and overall survival

The median time of follow-up since diagnosis was 3.7 years (1.5-5.0) with 2% lost to follow-up. 5-year crude survival was 43.5% and survival data is detailed in Table 14.

Table 14: Survival of the cohort

	Total (%)	CHBAH	CMJAH	Durban	GH
Number of women enrolled	2716	943	647	614	512
Median time since diagnosis (range), years	3.7 (1.5 5.0)	3.9 (1.6-5.0)	3.4 (1.5-5.0)	4.0 (1.8-5.0)	3.5 (1.3-5.0)
Status at end of follow-up					
Died	1581 (58.2)	522 (55.4)	379 (58.6)	353 (57.5)	327 (63.9)
Administrative censoring at 5 years	1065 (39.2)	385 (40.8)	240 (37.1)	258 (42)	182 (35.5)
Administrative censoring before 5 years	17 (0.6)	9 (1)	4 (0.6)	2 (0.3)	2 (0.4)
Lost to follow-up	53 (2)	27 (2.9)	24 (3.7)	1 (0.2)	1 (0.2)
Number of deaths during the time period since diagnosis, years					
0 to <1	408 (25.8)	131 (25.1)	112 (29.6)	76 (21.5)	89 (27.2)
1 to <2	413 (26.1)	139 (26.6)	87 (23)	96 (27.2)	91 (27.8)
2 to <3	329 (20.8)	123 (23.6)	73 (19.3)	80 (22.7)	53 (16.2)
3 to <4	204 (12.9)	58 (11.1)	54 (14.2)	53 (15)	39 (11.9)
4 to <=5	227 (14.4)	71 (13.6)	53 (14)	48 (13.6)	55 (16.8)

Median age (IQR) of deceased patients during the 5-year follow-up period	56 (45-68)	55 (44-67)	54 (45-66)	57 (47-68)	58 (46-70)
1-year survival					
Crude survival	84.9% (83.5-86.2)	86.0% (83.7-88.1)	82.6% (79.585.3)	87.6% (84.790.0)	82.6% (79.185.6)
Net survival	87.7% (86.2-89.0)	88.7% (86.2-90.8)	85.4% (82.1-88.1)	90.3% (87.3-92.7)	85.5% (81.7-88.5)
Age-standardised net survival	87.7% (86.1-89.0)	88.6% (86.0-90.8)	85.4% (81.9-88.3)	89.8% (86.5-92.3)	85.4% (81.5-88.5)
3-year survival					
Crude survival	57.3% (55.4-59.1)	57.8% (54.5-60.9)	57.3% (53.4-61.1)	58.9% (54.9-62.7)	54.5% (50.0-58.7)
Net survival	62.7% (60.7-64.7)	63.1% (59.5-66.4)	62.6% (58.2-66.6)	64.6% (60.1-68.6)	60.2% (55.3-64.7)
Age-standardised net survival	62.8% (60.6-64.9)	63.1% (59.4-66.6)	63.1% (58.4-67.4)	64.3% (59.7-68.5)	59.6% (54.6-64.3)
5-year survival					
Crude survival	43.5% (41.6-45.4)	45.4% (42.1-48.6)	42.5% (38.6-46.3)	44.3% (40.4-48.2)	40.3% (36.0-44.5)
Net survival	50.5% (48.3-52.7)	52.2% (48.3-56.0)	49.2% (44.6-53.6)	51.9% (47.1-56.4)	47.5% (42.4-52.5)

Age-standardised net survival	50.6% (48.3-52.9)	52.3% (48.2-56.2)	49.7% (44.7-54.6)	51.7% (46.8-56.4)	47.0% (41.8-52.0)

6.4.3 Effect of QI Non-Adherence on Overall Survival

In the univariate model there were significant Odds Ratios (ORs) for QI2a breastconserving surgery (BCS) for the overall cohort (OR 2.967, p=<0.001, 95% CI 2.259-
3.396), QI2b BCS for patients with stage 1 and 2 (OR 1.864, p=<0.001, 95% CI 1.2982.676), QI 5a axillary surgery OR 1.668, p=0.043, 95% CI 1.016-2.737), QI 7 receipt of RT after BCS (OR 1.971 p=0.021, 95% CI 1.107-3.509), and QI 10 multidisciplinary team discussion (OR 1.765, p=<0.001, 95% CI 1.386-2.249).

In the multivariate model, the following QIs remained significant: QI 2a, breastconserving surgery (BCS) for the overall cohort, remained significant (OR 1.757, p=<0.001, 95% CI 1.295-2.384), QI 2b, BCS for patients with stage 1 and 2, (OR 1.556, p=0.031, 95% CI 1.042-2.325), QI 5a, axillary surgery, (OR 1.963, p=0.023, 95% CI 1.097-3.512), and QI 10, multidisciplinary team discussion, (OR 1.911, p= <0.001, 95% CI 1.433-2.548). The QI 7, receipt of RT after BCS missed significance (OR 1.963 p=0.051, 95% CI 0.996-3.868).

Adherence to ≥10 lymph nodes excised on axillary node dissection (ALND) had an inverse effect on survival, although not significant (OR 0.865, p=0.505, 95% CI 0.5651.324). None of the timeliness QIs had significant ORs. The ORs are shown in Table
15.

Table 15: Odds ratios of quality indicators on overall survival

	Unadjusted Models			**Adjusted Models ##**		
Exposure domain N (%)	Odds Ratio	P-value	95% CI	Odds Ratio	P-value	95% CI:
QUALITY INDICATOR ADHERENCE						

Model 1						
Q1: Complete histopathological characterisation of invasive						
On core biopsy						
Adherence	1.000			1.000		
Non-adherence	1.063	0.442	0.909 - 1.244	0.937	0.759	0.618 - 1.420
Model 2						
On surgical specimen						
Adherence	1.000			1.000		
Non-adherence	1.019	0.852	0.835 - 1.243	0.905	0.456	0.696 - 1.177
Model 3						
Q2:						
Breast-conserving surgery rate						
Adherence	1.000			1.000		
Non-adherence	2.967	<0.001	2.259 - 3.896	1.760	<0.001	1.291 - 2.399
Model 4						
Breast-conserving surgery rate among stages 1 and 2						

Adherence	1.000			1.000		
Non-adherence	1.864	0.001	1.298 - 2.676	1.603	0.024	1.065 - 2.414
Model 5						
QI3: Rate of positive margins after breast-conserving surgery						
Adherence	1.000			1.000		
Non-adherence	0.972	0.961	0.305 - 3.097	0.822	0.761	0.232 - 2.908
Model 6						
QI5: Appropriate axillary surgery						
Rate of axillary surgery in invasive breast cancer						
Adherence	1.000			1.000		
Non-adherence	1.668	0.043	1.016 - 2.737	1.873	0.035	1.046 - 3.356
Model 7						
Sentinel node biopsy only in clinically node-negative disease						
Adherence	1.000			1.000		
Non-adherence	1.407	0.059	0.988 - 2.005	0.970	0.891	0.627 - 1.500
Model 8						
QI6: Number of nodes excised during axillary surgery						
Lymph node dissection ≥10 nodes						
Adherence	1.000			1.000		
Non-adherence	0.865	0.505	0.565 - 1.324	1.071	0.821	0.593 - 1.932
Model 9						
Sentinel node biopsy ≤5 nodes						
Adherence	1.000			1.000		
Non-adherence	1.453	0.336	0.679 - 3.109	1.243	0.639	0.502 - 3.076
Model 10						
QI7: Receipt of radiotherapy after breast-conserving surgery						

Adherence	1.000			1.000		
Non-adherence	1.971	0.021	1.107 - 3.509	2.004	0.046	1.013 - 3.966
Model 11						

QI8: Appropriate treatment sequencing in inoperable LABC						
Adherence	1.000			1.000		
Non-adherence	0.129	0.151	0.008 - 2.105	0.108	0.143	0.006 - 2.118
Model 12						
QI10: Multidisciplinary team discussion (GH included)						
Adherence	1.000			1.000		
Non-adherence	1.492	<0.001	1.255 - 1.773	1.694	<0.001	1.303 - 2.201
QI10: Multidisciplinary team discussion (GH excluded)						
Adherence	1.000					
Non-adherence	1.771	<0.001	1.392 - 2.252	1.916	<0.001	1.436 - 2.555
Model 13						
QI11: Timeliness						
Time from diagnosis (date of biopsy) to first treatment						
Time in days	1.000	0.604	0.999 - 1.001	1.001	0.368	0.999 - 1.002
Model 14						

Time from surgery or last chemotherapy to RT						
Time in days	1.000	0.327	1.000 - 1.001	1.000	0.960	0.999 - 1.001
Model 15						
Time from last (neoadjuvant) chemotherapy to surgery						
Time in days	1.000	0.768	0.998 - 1.002	1.001	0.546	0.998 - 1.003
Model 16						
Time from surgery to (adjuvant) chemotherapy						
Time in days	1.001	0.085	1.000 - 1.002	1.001	0.136	1.000 - 1.003
Model 17						
QI Composite Adherence Percentage ###						
0% Composite adherence	4.832	<0.001	2.780 - 8.399	3.892	<0.001	1.940 - 7.808
1-50% Composite adherence	1.338	0.001	1.132 - 1.582	1.541	<0.001	1.217 - 1.950
>50% Composite adherence	1.000			1.000		

In the hazard regression analyses, the univariate model showed significant hazard ratios (HRs) for QI 2a breast-conserving surgery (BCS) for the overall cohort (HR 2.452, p=<0.001, 95% CI 1.945-3.092), QI 2b BCS for patients with stage 1 and 2 (HR 1.727, p=<0.001, 95% CI 1.255-2.375), QI 5a axillary surgery (HR 1.465, p=0.024, 95% CI 1.053-2.039), QI 7 receipt of RT after BCS (HR 1.813, p=0.015, 95% CI 1.1125-

2.929), and QI 10 multidisciplinary team discussion (OR 1.340, p=<0.001, 95% CI 1.207-1.488).

In the adjusted multivariate model, there were significant hazard ratios (HRs) for QI 2a breast-conserving surgery (BCS) for the overall cohort (HR 1.622 p=<0.001, 95% CI 1.263-2.083), QI 2b BCS for patients with stage 1 and 2 (HR 1.491, p=0.025, 95% CI 1.050-2.116), QI 5a axillary surgery (HR 1.515, p=0.025, 95% CI 1.053-2.181), QI 7 receipt of RT after BCS (HR 1.844, p=0.021, 95% CI 1.096-3.103), and QI 10 multidisciplinary team discussion (HR 1.488, p=<0.001, 95% CI 1.295-1.1.718). The HRs are shown in Table 16 and as a forest plot in Figure 19.

In the composite QI model, 4.1% of patients had 0% adherence for all applicable QIs, 32.1% had <50%, and 63.8% had >50% adherence levels with significant site difference and lowest adherence levels in GH (26.4% with >50% adherence) and highest in CMJAH (86.1% >50% adherence). HR for <50% adherence was 1.380 (p=0.001, CI 95% 1.202-1583) and 2.400 for 0% adherence (p=0.001, CI 95% 1.830-3.147). The forest plot for the composite model is shown in Figure 20.

Table 16: Cox regression analysis assessing the effects of quality indicator adherence on overall survival

	Unadjusted Models			**Adjusted Models ##**		
Exposure domain N (%)	Hazard Ratio	P-value	95% CI	Hazard Ratio	P-value	95% CI:
QUALITY INDICATOR ADHERENCE						
Model 1						

Q1: Complete histopathological characterisation of invasive						
On core biopsy						
Adherence	1.000			1.000		
Non-adherence	1.048	0.358	0.948 – 1.158	0.990	0.930	0.788 – 1.244
Model 2						
On surgical specimen						
Adherence	1.000			1.000		
Non-adherence	1.023	0.764	0.882 – 1.187	0.918	0.361	0.765 – 1.103
Model 3						
Q2:						
Breast-conserving surgery rate						
Adherence	1.000			1.000		
Non-adherence	2.452	<0.001	1.945 – 3.092	1.622	<0.001	1.263 – 2.083
Model 4						
Breast-conserving surgery rate among stages 1 and 2						
Adherence	1.000			1.000		
Non-adherence	1.727	0.001	1.255 – 2.375	1.491	0.025	1.050 – 2.116

Model 5						
QI3: Rate of positive margins after breast-conserving surgery						
Adherence	1.000			1.000		
Non-adherence	1.000	0.999	0.366 – 2.731	0.818	0.701	0.293 – 2.282

Model 6						
QI5: Appropriate axillary surgery						
Rate of axillary surgery in invasive breast cancer						
Adherence	1.000			1.000		
Non-adherence	1.465	0.024	1.053 – 2.039	1.515	0.025	1.053 – 2.181
Model 7						
Sentinel node biopsy only in clinically node-negative disease						
Adherence	1.000			1.000		
Non-adherence	1.341	0.054	0.996 – 1.807	1.030	0.865	0.733 – 1.446
Model 8						
QI6: Number of nodes excised during axillary surgery						
Lymph node dissection ≥10 nodes						
Adherence	1.000			1.000		
Non-adherence	0.890	0.475	0.648 – 1.224	0.919	0.682	0.614 – 1.375
Model 9						
Sentinel node biopsy ≤5 nodes						
Adherence	1.000			1.000		
Non-adherence	1.370	0.337	0.720 – 2.608	1.163	0.700	0.539 – 2.513
Model 10						
QI7: Receipt of radiotherapy after breast-conserving surgery						
Adherence	1.000			1.000		

Non-adherence	1.815	0.015	1.125 – 2.929	1.844	0.021	1.096 – 3.103
Model 11						
QI8: Appropriate treatment sequencing in inoperable LABC						
Adherence	1.000			1.000		
Non-adherence	0.375	0.328	0.053 – 2.672	0.311	0.253	0.042 – 2.304
Model 12						
QI10: Multidisciplinary team discussion (GH included)						
Adherence	1.000			1.000		
Non-adherence	1.340	<0.001	1.207– 1.488	1.492	<0.001	1.295 – 1.718
QI10: Multidisciplinary team discussion (GH excluded)						
Adherence	1.000					
Non-adherence	1.483	<0.001	1.291 – 1.704	1.549	<0.001	1.332 – 1.800
Model 13						
QI11: Timeliness						
Time from diagnosis (date of biopsy) to first treatment						
Time in days	1.000	0.876	0.999 – 1.001	1.000	0.701	0.999 – 1.001
Model 14						
Time from surgery or last chemotherapy to RT						
Time in days	1.000	0.772	1.000 – 1.001	1.000	0.312	0.999 – 1.000
Model 15						
Time from last (neoadjuvant) chemotherapy to surgery						
Time in days	0.999	0.399	0.998 – 1.001	1.000	0.842	0.998 – 1.001
Model 16						
Time from surgery to (adjuvant) chemotherapy						
Time in days	1.001	0.184	1.000 – 1.001	1.000	0.619	0.999 – 1.001
Model 17						
QI Composite Adherence Percentage ###						

0% adherence	Composite	2.733	<0.001	2.212 – 3.377	2.400	<0.001	1.830 – 3.147
1-50% adherence	Composite	1.256	<0.001	1.130 – 1.395	1.380	<0.001	1.202 – 1.583
>50% adherence	Composite	1.000			1.000		

Models adjusted for enrolment site, HIV status at time of breast cancer diagnosis, receptor subtype, cancer proliferation risk, and stage of diagnosis.

Composite adherence indicator was calculated by the number of adherence indicators divided by the total number of applicable indicators (excluding clinic case volume).

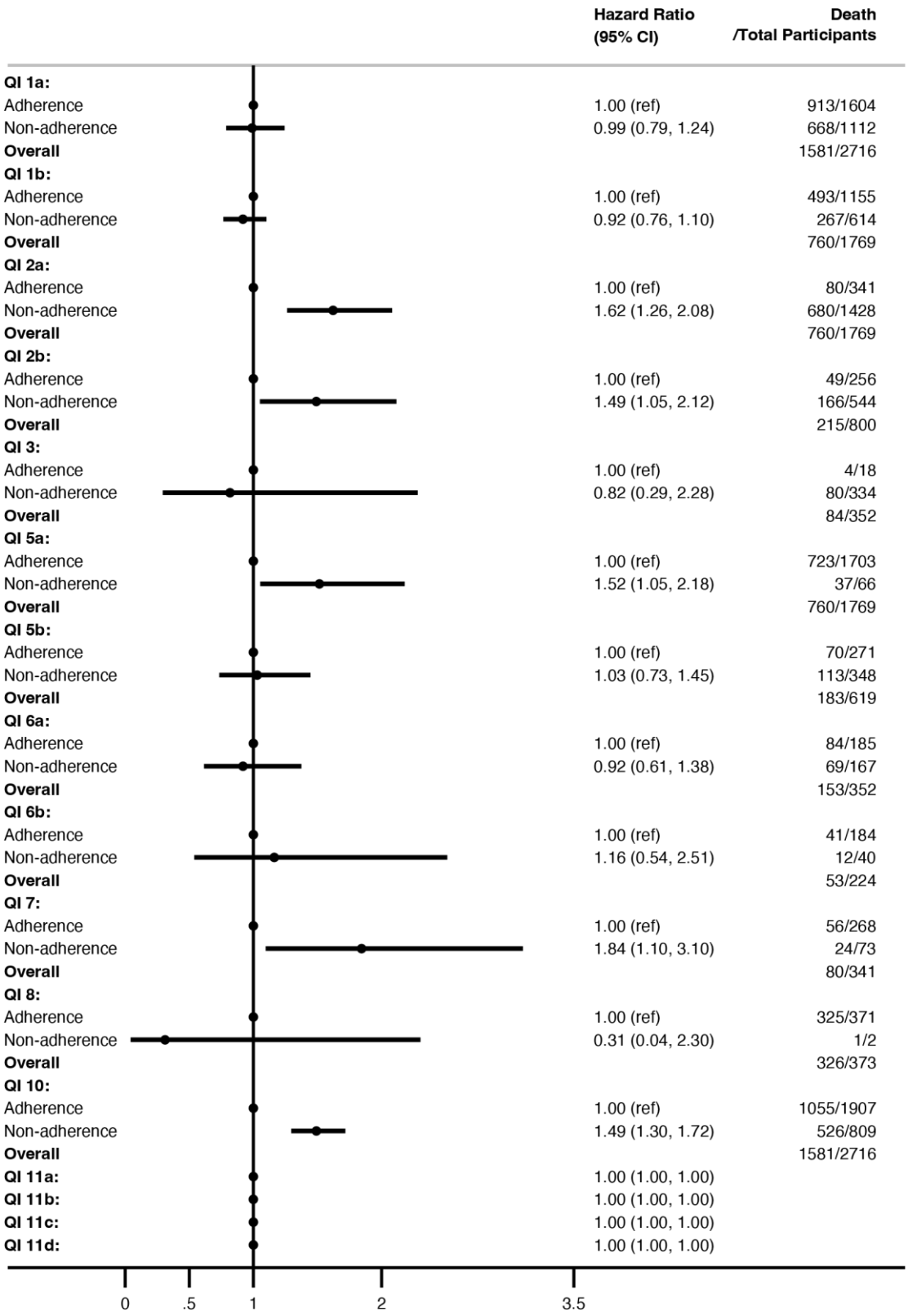
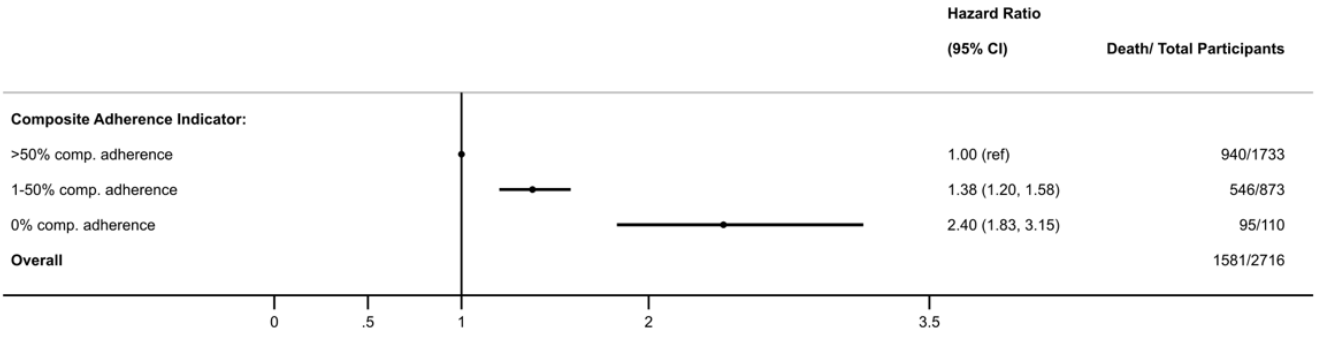


Figure 19: Forest plot showing the HRs of QI non-adherence

Figure 20: Forest plot showing the HRs of the composite QI model



Kaplan-Meier survival estimates

Late-stage vs early-stage cancer was associated with an HR of 3.59 for the risk of death; HIV-positive patients had an HR of 1.48, and sites showed little difference. Figures 21-27 show significant QIs and Figure 28 the QI composite model..

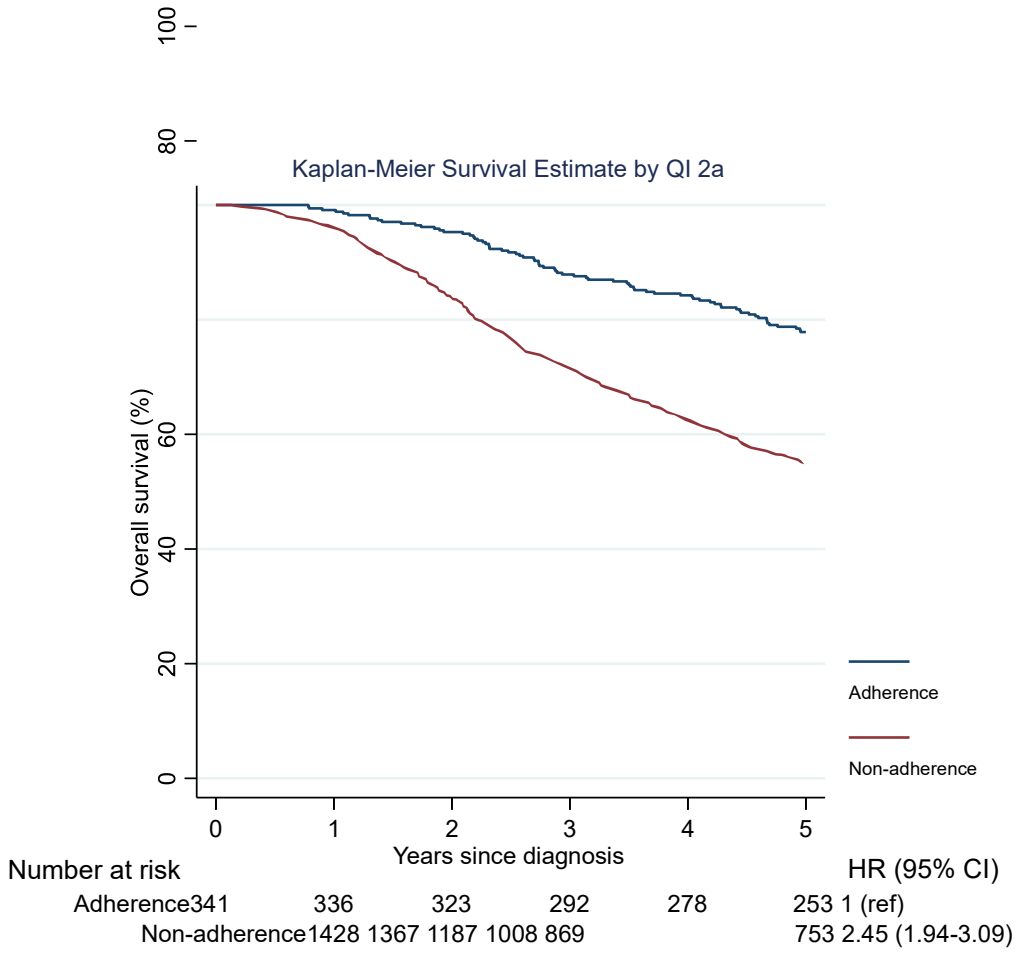


Figure 21: Kaplan-Meier curves for QI 2a breast-conserving surgery across stages

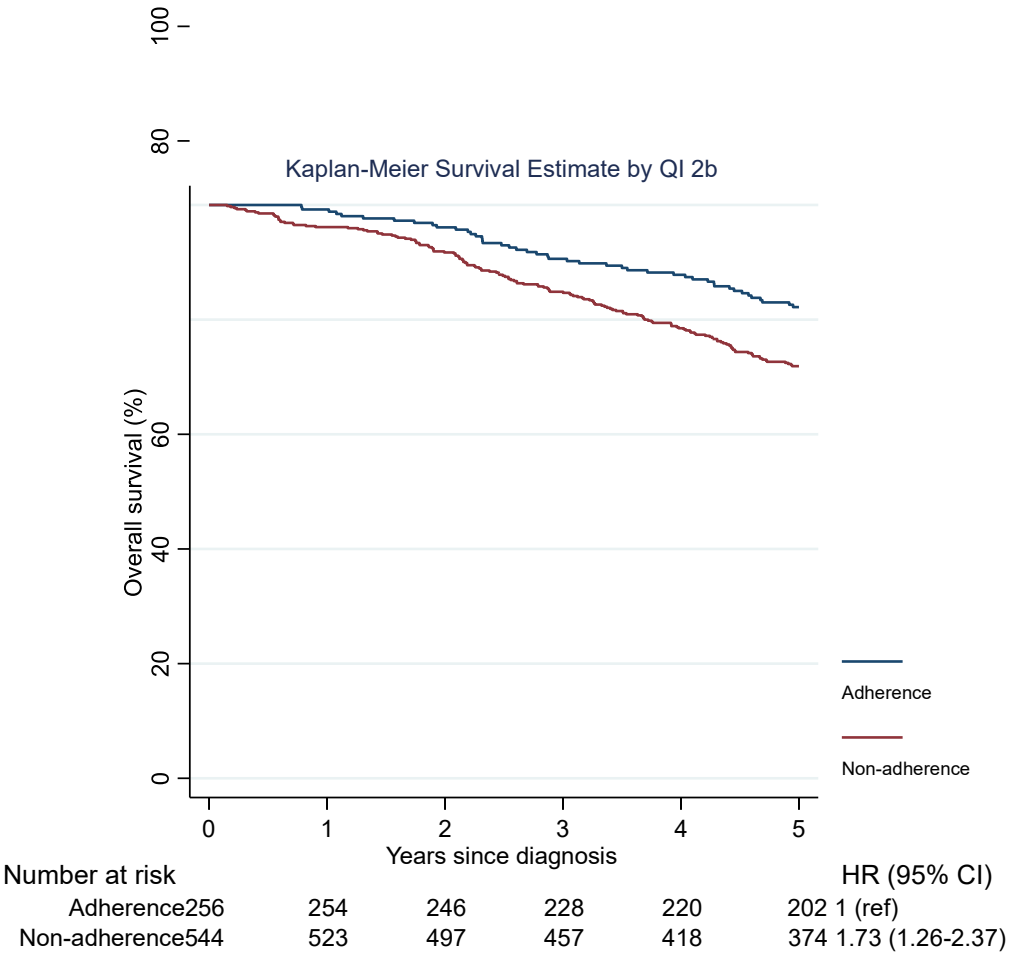
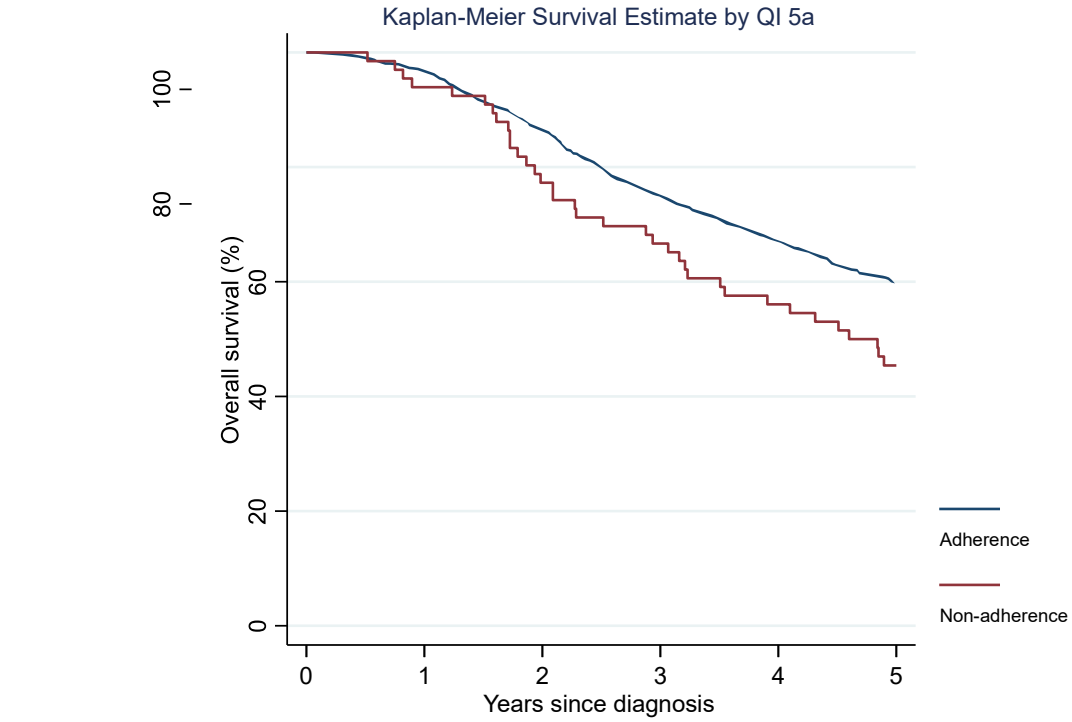
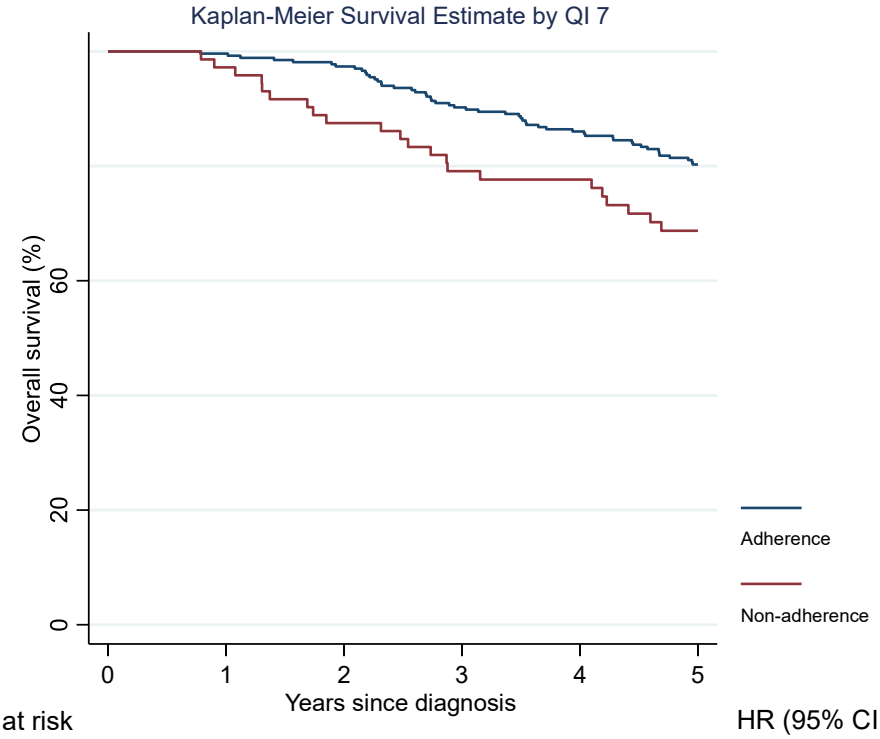


Figure 22: Kaplan-Meier curves for QI2b breast-conserving surgery in stage 1-2



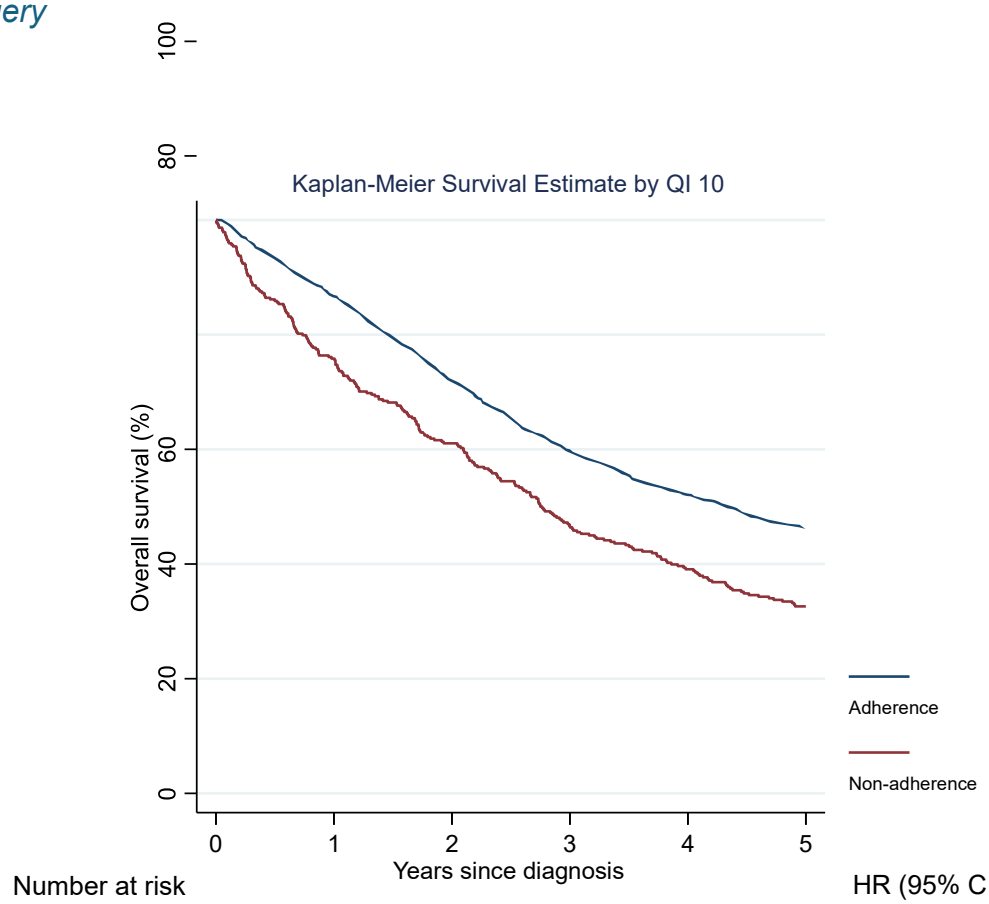
Number at risk							HR (95% CI)
Adherence	1703	1641	1459	1256	1110	977	1 (ref)
Non-adherence	66	62	51	44	37	29	1.46 (1.05-2.04)

Figure 23: Kaplan-Meier curves for QI 5a receipt of axillary surgery



Number at risk							HR (95% CI)
Adherence	268	266	260	237	225	208	1 (ref)
Non-adherence	73	70	63	55	53	45	1.82 (1.13-2.93)

Figure 24: Kaplan-Meier curves for QI 7 receipt of radiation after breast conserving surgery



Number at risk HR (95% CI)

Adherence1832 1577 1300 1071 921 806 1 (ref) Non-adherence371 278 222 166 139 113 1.48 (1.29-1.70)

Figure 25: Kaplan-Meier curves for QI 10 multidisciplinary discussion

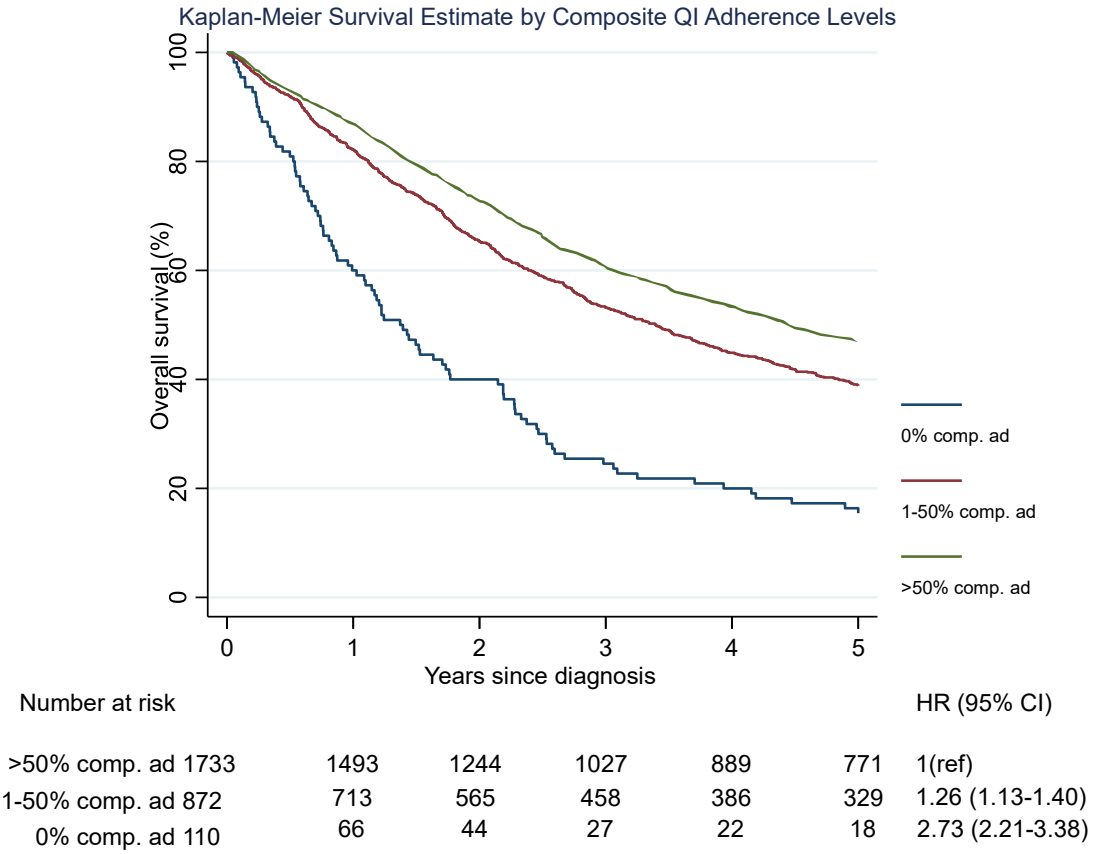


Figure 26: Kaplan-Meier curves for composite QI adherence model

6.4.4 Variance in Treatment Pathways Across Sites

Preferential treatment pathways varied significantly across sites and are summarised in Table 17. Their complexity is illustrated with a Sankey diagram and network plot (Figures 27-28). The primary treatment modality at CHBAH was surgery (41.9%), chemotherapy at CMJAH (45.9%), chemotherapy in Durban (49.2%) and surgery at GH (39.1%).

Table 17: Order of treatment modalities

	Total (%)	**CHBAH**	**CMJAH**	**Durban**	**GH**	**P-value**
Number of women enrolled	2716	943	647	614	512	
First treatment						<0.001
Endocrine	446 (16.4)	107 (11.3)	36 (5.6)	213 (34.7)	90 (17.6)	
Surgery	853 (31.4)	395 (41.9)	202 (31.2)	56 (9.1)	200 (39.1)	
Chemotherapy	1103 (40.6)	340 (36.1)	297 (45.9)	302 (49.2)	164 (32)	

Radiation	39 (1.4)	17 (1.8)	9 (1.4)	3 (0.5)	10 (2)	
No Treatment	275 (10.1)	84 (8.9)	103 (15.9)	40 (6.5)	48 (9.4)	
Second treatment						<0.001
Endocrine	537 (22)	176 (20.5)	123 (22.6)	129 (22.5)	109 (23.5)	
Surgery	746 (30.6)	232 (27)	173 (31.8)	219 (38.2)	122 (26.3)	
Chemotherapy	568 (23.3)	259 (30.2)	107 (19.7)	61 (10.6)	141 (30.4)	
Radiation	112 (4.6)	33 (3.8)	16 (2.9)	44 (7.7)	19 (4.1)	
No Treatment	478 (19.6)	159 (18.5)	125 (23)	121 (21.1)	73 (15.7)	
Third treatment						<0.001
Endocrine	656 (33.4)	288 (41.1)	152 (36.3)	90 (19.9)	126 (32.2)	
Surgery	167 (8.5)	32 (4.6)	25 (6)	87 (19.2)	23 (5.9)	
Chemotherapy	106 (5.4)	30 (4.3)	7 (1.7)	44 (9.7)	25 (6.4)	
Radiation	434 (22.1)	146 (20.9)	95 (22.7)	116 (25.6)	77 (19.7)	
No Treatment	600 (30.6)	204 (29.1)	140 (33.4)	116 (25.6)	140 (35.8)	
Fourth treatment						0.002
Endocrine	141 (10.3)	61 (12.3)	30 (10.8)	27 (8)	23 (9.2)	
Surgery	2 (0.1)	0 (0)	1 (0.4)	1 (0.3)	0 (0)	
Chemotherapy	1 (0.1)	1 (0.2)	0 (0)	0 (0)	0 (0)	
Radiation	550 (40.4)	179 (36.1)	101 (36.2)	166 (49.3)	104 (41.4)	
No Treatment	669 (49.1)	255 (51.4)	147 (52.7)	143 (42.4)	124 (49.4)	

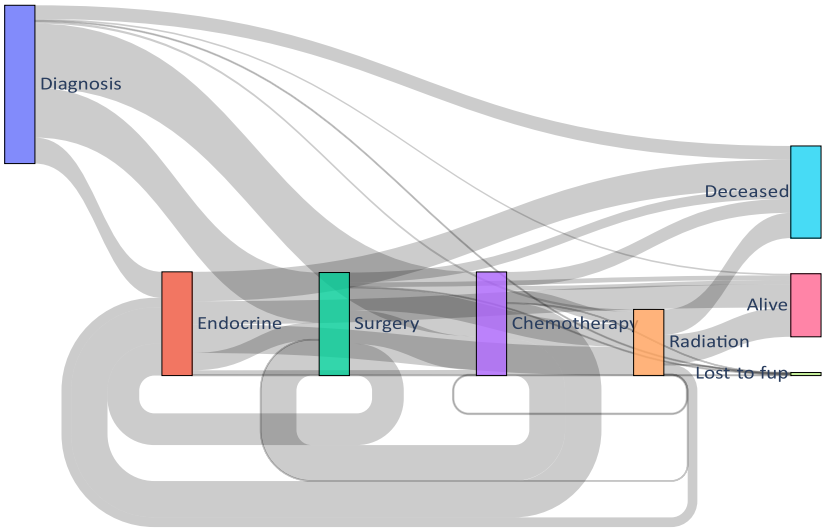


Figure 27: Treatment pathways total cohort

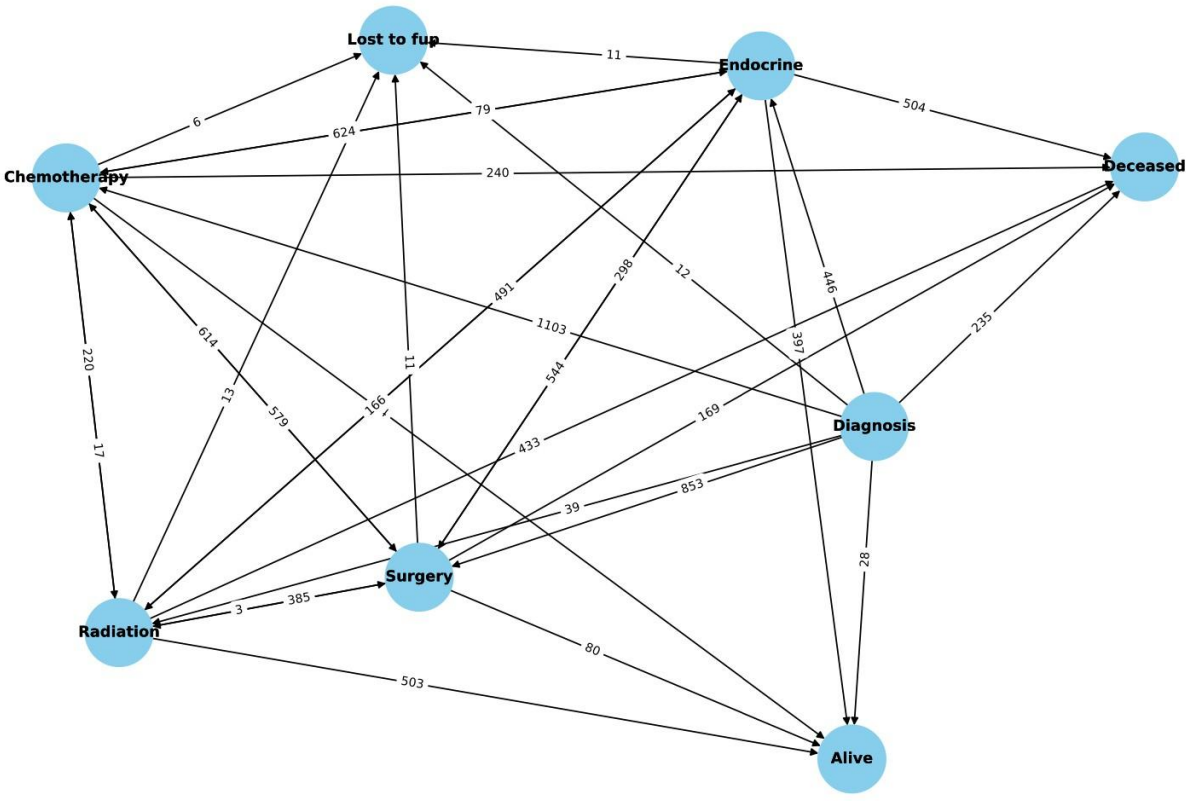


Figure 28: Treatment network plot total cohort

6.5 Discussion

Our findings provide substantial insights into improving breast cancer care in LMICs, especially in sub-Saharan Africa. They incorporate local survival data with critical quality indicators (QIs) that exert an independent effect on overall survival and examine

how breast cancer units adapted their treatment pathways to align with available local resources.

6.5.1 Survival

Our cohort's five-year crude survival rate of 43.5% is notably lower when contrasted with recent survival data from high-income countries, which approximates 85-90% across all disease stages(7). This is the first analysis of 5-year survival data from the SABCHO data, as we previously reported only on 3- or 4-year survival (11,201,203). Survival data from LMICs appear to mirror the countries' Human Development Index (HDI), and survival differences are driven mainly by late-stage presentation and poorer treatment delivery. In this cohort, 66.5% of women were locally advanced or metastatic at presentation. We know that survival differences depend not only on stage and tumour biology but are multifactorial and highly complex. Differences in treatment quality and survival have been noted across European countries(25) but also within countries in both LMICs and HICs, depending on race, education and other sociodemographic factors(26,27). Within sub-Saharan Africa, it is estimated that with downstaging and directed improvement in the quality of care, approximately a third of the predicted 416,000 breast cancer deaths could be prevented over the next decade(26). Feasible and effective interventions that improve treatment are, therefore, crucial to narrowing the breast cancer survival gap.

6.5.2 Survival Effects of QI Non-Adherence

Several QIs independently affected overall survival in our cohort. We did not expect to find such marked effects of individual QIs, which have not been consistently reported in HICs, but due to our relatively high rate of QI non-adherence and low survival rates, effects may be more measurable in our setting.

6.5.3 Breast-Conserving Surgery

BCS is recognised as the preferred surgical treatment option, particularly for earlystage breast cancer. Evidence indicates comparable survival rates to mastectomy; however, a recent publication even suggests better survival among women who underwent BCS in comparison to mastectomy (204). Our BCS rate of 19.3% is in keeping with our previous publications and remains very low compared to HICs, where BCS rates in smaller tumours target >85%(49,205). Although we see a high proportion of advanced disease, which may preclude some patients, we offer safe BCS to selected patients

with a high utilisation of oncoplastic techniques and relatively low involved margin rates of 5.1%(194,206). We routinely re-excise positive margins or perform completion mastectomies across all units, and therefore, positive margins did not affect survival (HR 0.82). In light of the suboptimal access to radiotherapy within our Gauteng public sector units, we have frequently faced inquiries regarding the ethical implications of providing BCS. Numerous colleagues in the field of general surgery have recommended limiting the treatment options to mastectomy only. Despite criticism, our units maintained BCS as an available standard of care, as it may improve patients' quality of life, and these techniques are essential for training of our surgical trainees.

In our adjusted models, patients who did not receive BCS had worse survival, with an HR of 1.62 across stages and 1.49 for early-stage patients. We advise caution in interpreting these results due to the limited patient numbers for BCS. Although we adjusted for stage, age, and tumour biology, we did not account for multimorbidity, body mass index (BMI), or socioeconomic factors. These, among other potentially unconsidered variables, likely bias our selection for BCS and a comprehensive future study investigating factors in BCS selection and survival is warranted. Nevertheless, our results confirm that BCS is justified in our limited-resource setting and should be offered wherever possible and safe. Efforts to downstage patients at presentation and optimal resource delivery of radiation and theatre time will be essential to expand our BCS rates further.

6.5.4 Axillary Surgery

The majority of our cohort who underwent surgery for the breast primary had some form of axillary surgery (96.3%). Only 3.7% had no record of axillary node surgery, and these patients had a 51% increased risk of death, emphasising the importance of addressing the axilla surgically in some way. The sentinel lymph node biopsy (SLNB) rate was overall low (43.8%) and was not generally available at GH (2%); as expected, this did not affect overall survival, but it is likely to have affected quality of life. Interestingly, over ten nodes dissected in an ALND only had 52.6% adherence and had an inverse effect on survival, although this was not statistically significant. This contrasts with a previous publication, although they specifically looked at pN2-3 patients(102). In our cohort, we did not subdivide according to pathological lymph node stage, and our numbers were low as we excluded all patients who underwent primary

systemic therapy. Given the rapidly changing approaches to the axilla and non-uniform treatment approaches in clinical practice(207), we would hypothesise that surgeons intraoperatively adjusted the extent of dissection to the disease burden.

6.5.5 Receipt of Radiotherapy After BCS

Radiotherapy is an essential adjunct to breast-conserving surgery and halves the locoregional recurrence risk, along with a reduction of breast cancer-specific mortality by about a sixth(208). Although there are now selected low-risk patient groups in whom radiotherapy may safely be omitted, this hardly reflects any patients in our unscreened patient cohort(209). Our patients generally present with symptomatic disease, and those who did not receive radiation after BCS had an 84% increased risk of death. Gauteng patients were significantly less likely to receive radiation than KZN patients. Overall, waiting times were long, and radiation was seldom delivered within the recommended 12 weeks from the last chemotherapy or surgery (13.3%). Of the patients who underwent BCS, 21.4% never received radiation at all.

6.5.6 Multidisciplinary Team Discussion

MDT discussions constitute the clinical foundation for organised multidisciplinary care. Their primary purpose is to discuss the overall care of patients and to develop a comprehensive treatment plan. Discussing breast cancer patients has demonstrated various enhancements in care quality and outcomes in HICs. These include an increase in breast-conserving procedures, avoidance of unnecessary surgeries or futile care, improved adherence to treatment guidelines, and a higher quality of life along with improved survival rates(187,188,210). MDT meetings also have several downsides: they demand significant time and preparation and require the willingness and availability of all team members, organisation, and documentation of the treatment plan and feedback mechanism. In HICs, MDTs are often mandatory as part of certification processes(28,50), and meeting coordinators are employed to lighten the clinicians' workload. However, in South Africa, MDTs are entirely clinician-driven and self-funded. There are currently no support structures offered in the public sector units, and there is little facilitation and no remuneration of MDT meetings in the private sector. However, investing in and strengthening MDTs would be an excellent intervention in LMICs as patients who had no documentation of MDT discussion had a 49% higher risk of death in our cohort. When we excluded GH patients who only documented MDT

discussions in 14.6% but indicated they often had MDTs, yet they did not use the EPR to record it, the risk of death by non-discussion increased to 55%.

6.5.7 Site Differences and Treatment Pathways

Our sites showed significant variance in stage and tumour biology as in previous publications(174). CHBAH had the lowest rate of late-stage presentation with 62.8%, a unit that had previously reported on downstaging over time(211), compared to 70.2% in the Durban complex. Regarding QI adherence, there were significant differences in the BCS rate, SLNB rate, receipt of radiation after BCS, and MDT discussion rate that were previously reported(194). It is noteworthy, though, that in this analysis, the receipt of radiotherapy after BCS is higher in the Gauteng units, 63.9% and 74.2% vs the previously reported 44.7% and 65.1%, but this change is likely due to the longer followup time reflecting the inappropriately long median time to radiotherapy of 154 days (IQR 110-225) with significantly longer waiting time in Gauteng units. Internationally, the recommended waiting time for radiotherapy after BCS is 6-12 weeks after surgery, and there is a lack of evidence for its efficacy beyond 12 weeks(212–214). It would appear that some patients did receive their radiation late but approximately a third still do not receive radiation following BCS at all in Gauteng. Overall, radiation is the most common fourth treatment (Table 17). This is against standard practice where radiation should follow surgery in cases that do not benefit from chemotherapy, or it should follow surgery after neoadjuvant therapy or after primary surgery and adjuvant chemotherapy. Either way, it generally is the second or third treatment modality but our units had to use endocrine therapy wherever possible to bridge the waiting time to radiation.

Each site had different resource availabilities, and the treatment pathways were adjusted accordingly. The starkest example is Durban, where they had very limited theatre time and only one breast surgeon at the time of this analysis. In addition, 70.2% of patients were stage 3 or 4 at presentation. They had the longest time to treatment initiation of a median of 93 days, reflecting limited access to their clinic and required investigations. Most patients started on primary systemic therapy, chemotherapy in

49.2% and endocrine therapy in 34.7%, which were readily available. Only 9.1% proceeded to primary surgery, although 29.8% were early stage and 61.7% were HRpositive and HER-2 negative. Patients were preferentially referred for systemic

therapy or were provided neo-endocrine therapy, as the availability of surgical theatre time was extremely constrained. Even when writing this paper, the Durban team reports a current waiting period for theatre extending to five months.

In contrast, CHBAH's primary surgery rate was 41.9%. They had excellent availability of surgery and routinely booked patients for the following week after completion of workup. Access to chemotherapy was more limited with triaged access and waiting times according to stage and other factors.

Despite all differences in resources and clinicopathological presentations, the units adjusted pathways to readily available treatments, and there is little difference in the primary outcome of overall survival across site (Table 17).

The Sankey diagrams and treatment plots picture the variances and the extreme fragmentation and complexity of breast cancer care pathways. They tell a tale of flexibility and resilience of four academic specialised breast units that function under varying pressures and constraints. In South Africa, there is an urgent need for oversight, accountability, and patient navigation, ideally in the form of appropriately supported and resourced specialised breast units(215).

6.5.8 Strengths and Limitations

Our strengths encompass prospectively collected data, the sample size, and the duration of follow-up; additionally, there is substantial relevance with unique data from an LMIC. The study also has several limitations. Firstly, the QIs were not predefined at the onset of SABCHO but extrapolated from histopathology and clinical data. This has compromised the reliability and currency of some QIs and led to the exclusion of reoperation rates. Secondly, we only have reliable data on overall survival and lack data on quality of life, disease-specific survival or more intermediate outcomes such as disease-free or progression-free survival. Fourthly, we adjusted for age, stage, tumour biology and site but did not include more subtle factors such as socioeconomic factors, BMI and comorbidities, which may have further affected survival. Fifthly, we focused on the quality of diagnostic and surgical care and did not include indicators of systemic therapy, which are an integral part of the breast cancer care continuum.

Lastly, we only have data from two South African provinces and only from units in the public sector, limiting the representation of all population groups.

6.6 Conclusion

Overall survival of women with breast cancer in South Africa is poor and urgently calls for effective interventions. Mandatory discussion of breast cancer patients in MDTs will be a highly effective and feasible first intervention to improve patient outcomes in LMICs. In addition, the non-delivery of radiation after BCS was associated with an 84% increased risk of death, and the radiation delivery crisis in Gauteng must be urgently addressed.

Meaningful change and improvement of quality of breast care and, with that, improvement of patient survival in South Africa will require dedicated allocation of resources, spanning across the entire treatment pathway in a multidisciplinary team.

PART 3: INTEGRATED DISCUSSION AND CONCLUSION

“Look with your understanding, find out what you already know, and you’ll see the way to fly.”

(Johnathan Livingstone Seagull by Richard Bach)

7 INTEGRATED DISCUSSION AND CONCLUSION

This chapter summarises the key findings from the empirical papers presented in Chapters 3 to 6. It also identifies and discusses the main emerging themes and empirical contributions to the body of knowledge on the quality of surgical breast cancer care, and revisits the conceptual framework for cancer care quality, integrating the contributions and gaps of this thesis. Recommendations are made in the context of South African breast cancer care, and the strengths and limitations of the PhD study are reflected upon. Lastly, this chapter explores potential future research and concludes with an overall conclusion that outlines the key take-home message.

7.1 Consolidated Findings

This PhD study aimed to explore the quality of South African surgical breast cancer care by employing four different objectives: firstly, to contextualise the quality of breast cancer care landscape in South Africa and LMICs and establish a local set of quality indicators; secondly, to provide an initial benchmark of the current quality of care received, thirdly, to establish the requirements of breast centres in South Africa; and lastly, to explore the effects of non-adherence to quality indicators on overall survival. The overall aim of this thesis was to enhance understanding of the quality of breast cancer care and identify measures to improve that quality within the South African context.

Each objective was achieved through an empirical study presented as an individual chapter within this thesis, and Table 18 summarises each chapter's key findings.

Objective	Chapter	Main Findings	Conclusion
Objective 1: To review breast surgery QIs within the global and LMIC context and develop a set of diagnostic and surgical QIs for South Africa.	3	• Little data exists on breast cancer QIs from LMICs with only one article from China at the time of publication. • QIs need adaptation to local context, resources and culture. • 920 potential QIs were identified in the systematic review. • 47 QIs achieved consensus and were graded according to a level of evidence. • A set of 10 mandatory critical QIs was established. • The QIs have been endorsed by the Breast Interest Group of Southern Africa (BIGOSA).	• A contextually relevant set of South African QIs for the diagnosis and surgical treatment of breast cancer was developed.
Objective 2: To measure QI adherence levels in the SABCHO cohort.	4	• Our electronic patient record measured most QIs reliably. • Adherence levels overall were lower than in HICs. • The most emergent gaps in care were the lack of receipt of radiotherapy and underutilisation of SLNB. • MDT discussion, histopathology reporting, and breast conservation rates need to be improved. • Data entries made or cleaned by research staff had better data quality. • HIV status did not affect adherence levels.	• Adherence levels are overall lower compared to HICs and an initial benchmark was established which highlighted several emergent gaps in care.
Objective 3: To establish requirements for breast centres in South Africa.	5	• Eight main components with minimum requirements were defined. • A step-by-step plan is provided for individual unit implementation. • Implementation will have to rely on self-reporting of units initially as there is no effective governing body to drive implementation. • Varied societal support, likely due to concerns over institutional power and members' financial disincentives to change. • Value-based care is a discussed goal, once basics of quality improvement achieved.	• A contextually relevant set of breast centre requirements for LMICs in sub-Saharan Africa was developed and a step-by-step implementation guide provided.
Objective 4: To assess the effect of individual and composite QI adherence on overall	6	• 5-year overall survival was poor compared to HIC outcomes. • Several individual QIs and composite adherence levels were associated with better overall survival. • Radiation therapy access must urgently be improved.	• Overall survival is low compared to HIC and QI-adherent care is associated with improved survival.

survival in women with breast cancer in South Africa and to compare treatment pathways across sites.		• Despite poor radiotherapy delivery, BCS is not associated with worse outcomes and needs to be expanded. • MDT discussion was identified as a key indicator with a clear effect on overall survival and an effective first intervention to improve patient outcomes in South Africa and other LMICs. • Units adjusted treatment pathways according to available resources. • Despite variances in treatment pathways and resource, overall survival similarly poor across sites.	MDT discussion is a key indicator to improve patient outcomes in LMICs.

7.2 Hypotheses Revisited

Below are the study‘s hypotheses, along with an explanation of whether the findings support or reject them.

H1) Little data on breast cancer quality indicators exists in LMICs and need to be adjusted to local context; this hypothesis is accepted as supported by the systematic review, and a local set of QIs was developed.

H2) Adherence levels are overall lower than in HICs with lower quality of care received in the SABCHO cohort; this hypothesis is accepted as most QI adherence levels were significantly lower than HIC minimum targets.

***H3)* Sparse data on breast cancer centres exists in LMICs and requirements needs to be adjusted to local context;** this hypothesis is accepted as no breast centre criteria from LMICs were found in the existing literature, and the expert panel modified the criteria from HICs.

***H4a)* Individual QIs will not have measurable effects on survival, but a composite measure may show an effect;** this hypothesis is rejected as both individual QIs and the composite model demonstrated effects on overall survival.

H4b) Sites will have adjusted treatment pathways to specific resource constraints; this hypothesis is accepted as units exhibited significant variance in treatment pathways.

7.3 Emerging Themes

This section examines overarching themes arising from the conducted research and is structured into two main sections. The initial section addresses methodological themes, while the subsequent section reflects upon the empirical themes that emerged.

7.3.1 Methodological Themes

During the design phase of the studies included in this PhD, various methodologies were evaluated to best define QIs and breast centre requirements for our local context, benchmark the current level of care, and explore the correlation between the quality of care and patient outcomes. We selected a mixed-methods approach incorporating several methodologies, and each step, from the systematic review of QIs, the

consensus meeting and Delphi rounds, the review of evidence levels for each QI, the round table discussion on breast centres, the benchmarking of care, to the quantitative analyses, was carefully considered and intentional, although it undoubtedly presented its unique challenges. The strengths and challenges of each approach are summarised in Table 19.

7.3.1.1 Mixed Methods Approach

Mixed methods research connects diverse paradigms by integrating research methods that were traditionally considered incompatible and is referred to as the third research movement(216,217). Historically, attempts to combine qualitative and quantitative methods in research have frequently relied on weak methodological bases. Additionally, these approaches tend to be combined without a solid rationale for their integration selection. However, when applied correctly, with a clear rationale for the choices made, it can provide a deeper understanding of complex problems, expand the breadth of knowledge, and can be used to tackle a wider range of research questions.

The selection of methodologies was guided pragmatically, meaning more by the research questions posed than by traditional methodological and philosophical frameworks. Our reasons for the use of mixed methods were to employ complementarity and triangulation, which aims to use different approaches that offset inherent weaknesses and biases, confirm findings, and increase the validity of the findings. In addition, we sought development and initiation for the exploratory sequential approach towards the quantitative sections. Figure 29 shows the triangulation of methodologies, the evidence collected, and the emerging empirical themes.

The deliberate integration of qualitative and quantitative strands is crucial in mixed method research and took place at various levels in this thesis(218). For instance, at the design level, we integrated both a concurrent mixed method design in the Delphi process and a sequential exploratory mixed method design in the overall sequence of studies with the early development of the QIs for use in the quantitative papers.

Overall, the mixed method approach allowed for expansion in this thesis and a more rounded and in-depth engagement with the broad and complex topic of the quality indicators for surgical breast cancer care.

Table 19: Strengths and challenges of methodologies

	Strengths	Challenges
Systematic Review & Modified Delphi Process (Concurrent Mixed-Method)	**Systematic review** • Provided a summary of the extant literature on quality indicators in HICs and LMICs. • Provided a broad understanding of the complexity of quality of care measurements in cancer care and research foundation. • Provided an extensive list of quality indicators. • Identified gaps in knowledge. • Facilitated the QI selection for the of the quantitative components that were to follow.	**Systematic review** • Extremely time consuming task. • Literature changes constantly and requires updates. • Potentially introduces bias.
	Modified Delphi Process • Provided a unique South African QI set. • Most reliable consensus method. • Decisions based on experts are likely to be valid and contextually applicable. • Because ratings are anonymous, it avoided conflicts, bias and encouraged equal participation.	**Modified Delphi Process** • Long and laborious process. • Criteria can be subjective and influenced.
Qualitative Section – Round Table Consensus	• The qualitative parts allowed for an inclusive approach with integration of various specialities	• Vulnerable to single person dominating and subjectivity if not well facilitated.

	reflecting the interdisciplinary nature of breast centres. • The discussions allowed to explore the South African context with invaluable contributions made from panel experts	
Quantitative Sections – Papers 2 and 4	• The studies provided a range of actionable recommendations and highlights emergent gaps of care. • Key indicators with clear effect on overall survival were identified. • Clear methodology and analyses.	• Large data sets, some QIs needed recoding of data fields. • The QI data was not predefined in the SABCHO data collection protocol but was extrapolated from clinical records and histopathology records; this could have compromised the accuracy of adherence rates.

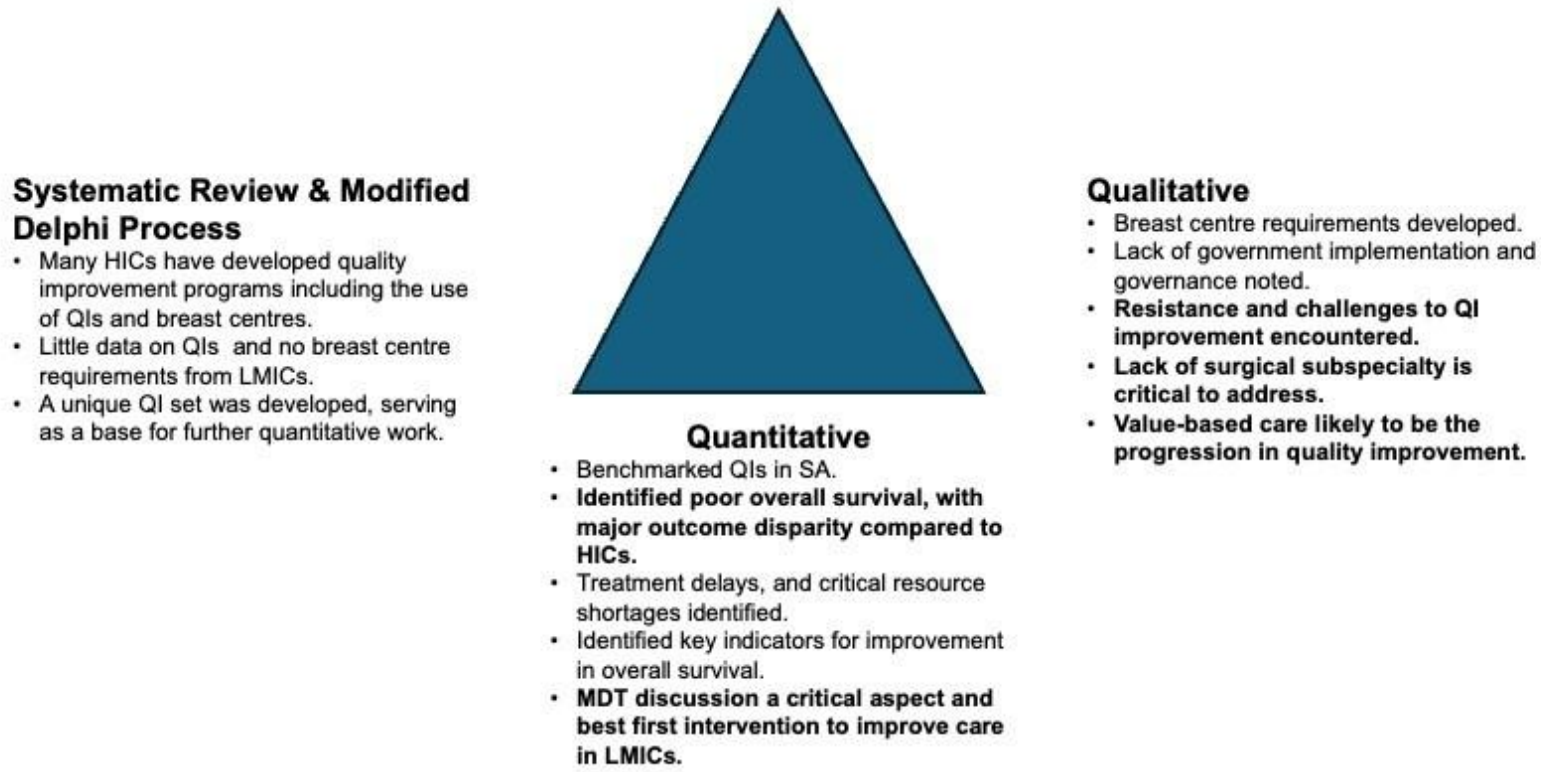


Figure 29: Triangulation of methodologies and emerging empiric themes

7.3.2 Empirical Themes

The specific results of the four empirical studies have been thoroughly discussed and compared to findings from related studies in the relevant chapters. Four key thematic areas have emerged by consolidating the findings and reflecting on the broader experiences throughout the PhD. Firstly, closing the gap in outcome disparities; secondly, key interventions to improve breast cancer care; thirdly, barriers to implementation of quality improvement initiatives; and fourthly, the shift towards valuebased care. These are discussed below.

7.3.2.1 Closing the Gap in Outcome Disparities

Paper 4 has elucidated the concerningly low overall survival rate among patients with breast cancer within the SABCHO cohort. The units included are four of the few existing public sector specialised breast units, with a total estimate of less than ten units nationwide. The patients in the SABCHO cohort probably received far better care than the average breast cancer patient in South Africa without access to one of the very few functioning breast centres, and we can assume that overall care and outcomes for breast cancer are even worse in the rest of the public healthcare sector in South Africa. Several priority areas for health systems strengthening have been identified as essential for achieving more equitable cancer care. These areas include national cancer control policies, adequate healthcare funding and resources, affordable and accessible care, public awareness, advocacy, cancer prevention, sufficient and appropriately trained staff, adherence to evidence-based guidelines, and availability of health information technologies, amongst others(30,137,181)

Within the private sector, data is also sparse. Discovery Health, South Africa's largest private health insurance administrator, published 5-year overall survival of 84.1% among patients with breast cancer(219). This data demonstrates significantly better outcomes compared to patients in the public sector; however, it includes patients with non-invasive disease and lacks stage-stratified results, as well as any details on the quality of care received. In my experience, the quality of care in the private sector is highly variable, lacking governance, transparency, and quality control, and is highly susceptible to overtreatment. I would hypothesise that improved outcomes are mainly due to the stage at presentation, earlier access to care, and the insured population’s

better educational and socioeconomic status. Nevertheless, private-sector patients seem to perform better with access to more resources and timely care delivery.

Universal health coverage has been proposed as a solution to improve outcomes in LMICs. The South African government advocates for the NHI, which aims to provide a single healthcare system for all South Africans. Given the government's poor track record in governance and implementation, many clinicians and societies remain opposed, even while recognising that the principle of universal health access is desirable. Therefore, implementation of the NHI is likely to be delayed. In the meantime, both the public and private sectors require significant improvement in the quality of cancer care, as access alone will not change patient outcomes.

Access to care is a critical issue, as many patients present late due to individual and health system-level factors, leading to delays in care, multiple hospital visits, and a complex, chaotic, and dysfunctional referral system(118). It is essential to establish more appropriate breast units with the capacity to accept patients easily and directly. This must be complemented by demonstrably high quality of care; the Lancet Global Health Commission on High-Quality Health Systems has shown that inadequate quality of care contributes to preventable mortality as significantly as having no access to healthcare at all(220), emphasising the need for quality frameworks alongside increased access to improve cancer outcomes meaningfully.

7.3.2.2 Key Interventions to Improve Breast Cancer Care

Two essential components have emerged to drive change, both highly actionable: firstly, the enhancement of surgical capacity and the need for breast surgery subspecialisation, and secondly, the requirement for mandatory MDT discussions. These are discussed below.

The Role of the Surgeon in the Breast Cancer Care and the Need for Specialisation in South Africa

The surgeon's role in the breast cancer pathway extends well beyond the execution of the operation. In most countries, including South Africa, surgeons are the patient's first contact as patients generally present with symptoms to the surgeon first, or, as may be the case in the private sector, they will be referred with screening-detected lesions to the surgeon(113,221,222). It is the surgeon's role to evaluate, stage, and counsel these patients at their first diagnosis, present them at the MDT meeting, and

communicate their treatment plan to the patient and their families(222). Moreover, appropriate surgical management is fundamentally important for improving overall survival rates, with clearly improved outcomes with specialised surgeons(223). The combination of the key intervention of MDT discussion, which frequently depends on the surgeon to enrol the patient, along with the documented patient outcome benefits of treatment by a specialised breast surgeon, makes strengthening of surgical capacity in South Africa a top priority.

Surgery is also the most examined phase of cancer care for quality variation, partly due to its clinical relevance and outcomes linked to surgeon and hospital factors(221). In South Africa, surgeons have recorded the necessary interdisciplinary data detailing the receipt of various breast cancer treatment modalities and patient outcomes. Internationally, surgeons have demonstrated leadership in cancer care for over a century and have been at the forefront of various quality improvement programmes(221). In addition, most national and international breast centres are led by surgeons(224), which seems well-suited, and an increase in breast centres is critical in both the South African public and private sectors.

Breast surgery fellowships and certification processes are available in various countries but do not formally exist in South Africa, where only the surgical subspecialties of critical care, gastrointestinal surgery, vascular surgery, and trauma surgery have been established(225). For the past decade, several attempts to have a breast surgery subspecialty recognised, both independently and in combination with endocrine surgery, failed. A motivation to the Colleges of Medicine of South Africa (CMSA), first authored by myself in 2018, is attached in Appendix G. Subspecialty training would increase the number of competent breast surgeons, increase training and research capacity, increase the number of breast centres and functioning MDTs, to drive the overall quality improvement of breast cancer care.

Mandatory MDT Discussion

The surgeon may hold a central role as the patient's first contact, but breast cancer is also a systemic disease, and the MDT discussion allows for the integration of all appropriate treatment modalities. The patients in our cohort who had any documented MDT discussion had a 48% less likely chance of death at five years. We only examined the effect on overall survival, but the process of MDT discussion is known to

consolidate the patient's individual findings, organise care pathways and ensure that patients receive the correct treatment modalities in the correct sequence, and it improves other outcomes such as the receipt of BCS(226,227).

Although MDTs are part of the outlined requirements for breast centres and their establishment is crucial for enhancing breast cancer care in South Africa, creating effective MDTs and ensuring the mandatory discussion of all breast cancer patients may be a more achievable first step in quality improvement.

At present, there are no South African clinical guidelines on MDTs, so optimal structure and processes are not defined. They require appropriate technological equipment and platforms, which are often not provided in the public sector. MDTs are very timeconsuming in preparing, and attending, as is communicating results to the patient and their families. They are entirely honorary in the private sector, which may pose a significant barrier to expansion. Furthermore, private MDTs generally must cover the costs of the technological platforms and equipment, which is financially disincentivising.

Technologies supporting MDTs are rapidly evolving and need to be improved to include assistance in the preparation and hosting of MDTs, incorporate machine learning tools with evidence-based clinical decision support and prognostication, ensure proper documentation of MDT decisions with a correlation to actual delivered care, and longer-term patient outcomes(228).. These technologies are often not accessible and affordable in either of the healthcare sectors of South Africa.

With a limited skilled workforce and few established robust MDTs and specialised units, there is a pressing need to expand these services, potentially allowing nonspecialised clinicians to present their patients from peripheral sites, as well as the training of subspecialists and the establishment of new MDTs and centres within a hub-and-spoke model(180).

7.3.2.4 Barriers to Implementation of Quality Improvement Initiatives

Measurement of QIs and quality improvement programs are highly relevant to delivering high-quality care, especially in the complex and interdisciplinary field of cancer care. Like all clinical practice changes, implementing these programs faces several barriers, which are amplified in LMICs(229).

This PhD process and its empirical results highlight several barriers to change, including inadequate resources dedicated to QIs, clinicians, institutional, technological, and political barriers.

Although both the QIs and the breast centre requirements were endorsed by BIGOSA, they have no regulatory role, and implementation will remain in the hands of the clinicians. Clinicians in South Africa face an extraordinarily heavy clinical workload in both the public and private sectors, and neither have readily available administrative or research assistants. This high clinical workload has been described in the literature, highlighting disproportionately higher workloads in LMICs and a particular shortage across all oncology staff, including surgery, pathology, medical and radiation oncology. There is also a high rate of burnout and a brain drain of oncological skills moving from LMICs to HICs(230–235). Quality improvement programs will require dedicated resources and administrative personnel as clinicians in both private and public sectors are working at maximum capacity. During the breast centre process, there were also concerns that the introduction of quality improvement programmes could be used punitively, with publicly shared results or poor performers excluded from funding in the private sector. Another isolated opinion raised was that a formal South African approach to breast centre structures was unnecessary; these routine components were already being performed without a systematic approach. As noted in the existing literature, the increased workload, the absence of compensation for quality measurements and improvements, and possible financial disincentives will present substantial obstacles in our setting(236–240).

Notably, during the development of breast centre criteria, we garnered significant support from clinicians on the panel, patient advocacy, health funders, and some speciality societies but encountered resistance from a few other specialty and subspecialty societies. Some of these societies declined to engage, citing that all members of their specialty should be able to offer specialised services and were not supportive of any minimum requirements. The institutional resistance to change is probably due to their perceived loss of institutional power and financial disincentives for their members.

Quality improvement requires reliable and accurate data collection, which remains scarce in South Africa. Ideally, the data collected should be comparable across units and must completely anonymise data for statistical purposes. Without a robust

electronic database and sufficient administrative or research staff like those in the SABCHO study, data collection will be challenging for tracking quality indicators. Several panel experts were concerned about the ability to collect the required data due to the non-availability of internet access and computers in the public sector and the non-availability of affordable and appropriate programs in the private sector. The OncoDB system has already been successfully implemented at various public surgical breast units and is offered free of charge to any public sector unit, and affordable electronic platforms are available in the private sector.

Governmental oversight and support for cancer care in general and quality improvements have been lacking in South Africa. Although guidelines have been developed by the National Department of Health, they have not been implemented. It is likely that the government will also not readily implement QI improvement programmes, although they would align with the stated national priorities. It must be acknowledged that the political environment in which we operate imposes significant limitations on governance, as well as on the resources and staff dedicated to quality improvement activities(241,242). Our results highlight several critical staff and resource limitations, including access to radiotherapy or SLNB, that need adequate funding and effective governance to resolve. Given the multitude of pressing issues, constraints of scarce skills, limited resources and equipment, QI work may not appear to be the top priority. However, without QIs, deficiencies in care will not be identified timeously, leading to missed opportunities to rectify or at least report these issues promptly.

7.3.2.5 Shift to Value-Based Care

The importance of value-based care emerged as a discussion point at the breast centre discussions. As oncology treatment costs rise worldwide, there is a distinct shift towards value-based care(243). Because value depends on results rather than inputs, value in healthcare is assessed by the outcomes achieved, not the quantity of services provided. Therefore, shifting focus from volume to value, specifically value from a patient's perspective, presents a future challenge(244). Value-based care holds significant relevance for all health systems; however, it is of utmost importance to LMICs due to constrained health budgets, weak health infrastructure, and the heightened burden of disease(245). From the perspective of individual patients, many

face significant out-of-pocket expenses in both the South African private and public sectors, which can be financially devastating for patients and their families.

Quality improvements remain in their early stages in South Africa compared to HICs, and the basics still need to be implemented and established. Nevertheless, it is important to note that value-based approach to healthcare is likely to be part of the progression in quality improvement and signifies a shift from mainly process-based metrics to goals that patients value and includes measurement of PROMs and patientreported experience measures (PREMs), which should be integrated as early as possible in quality improvement initiatives(81,191).

7.3.3 Conceptual Frameworks

This section revisits the quality of cancer care framework introduced in Chapter 1 and reflects on the contributions of the thesis, as well as identified gaps. The local structural elements were enhanced through the development of quality indicators and breast centre requirements in Papers 1 and 3. Both Papers 2 and 4 provided local insights into the process and structural elements of current breast cancer care in South Africa. The conceptual model, along with the main contributions and gaps from the thesis, is illustrated in Figure 30. The thesis does not address value, PROMs, and patient-reported experience measures (PREMs), which are significant gaps to consider in the future. A standard set has been proposed by the International Consortium for Health Outcomes Measurement (ICHOM) Initiative(81).

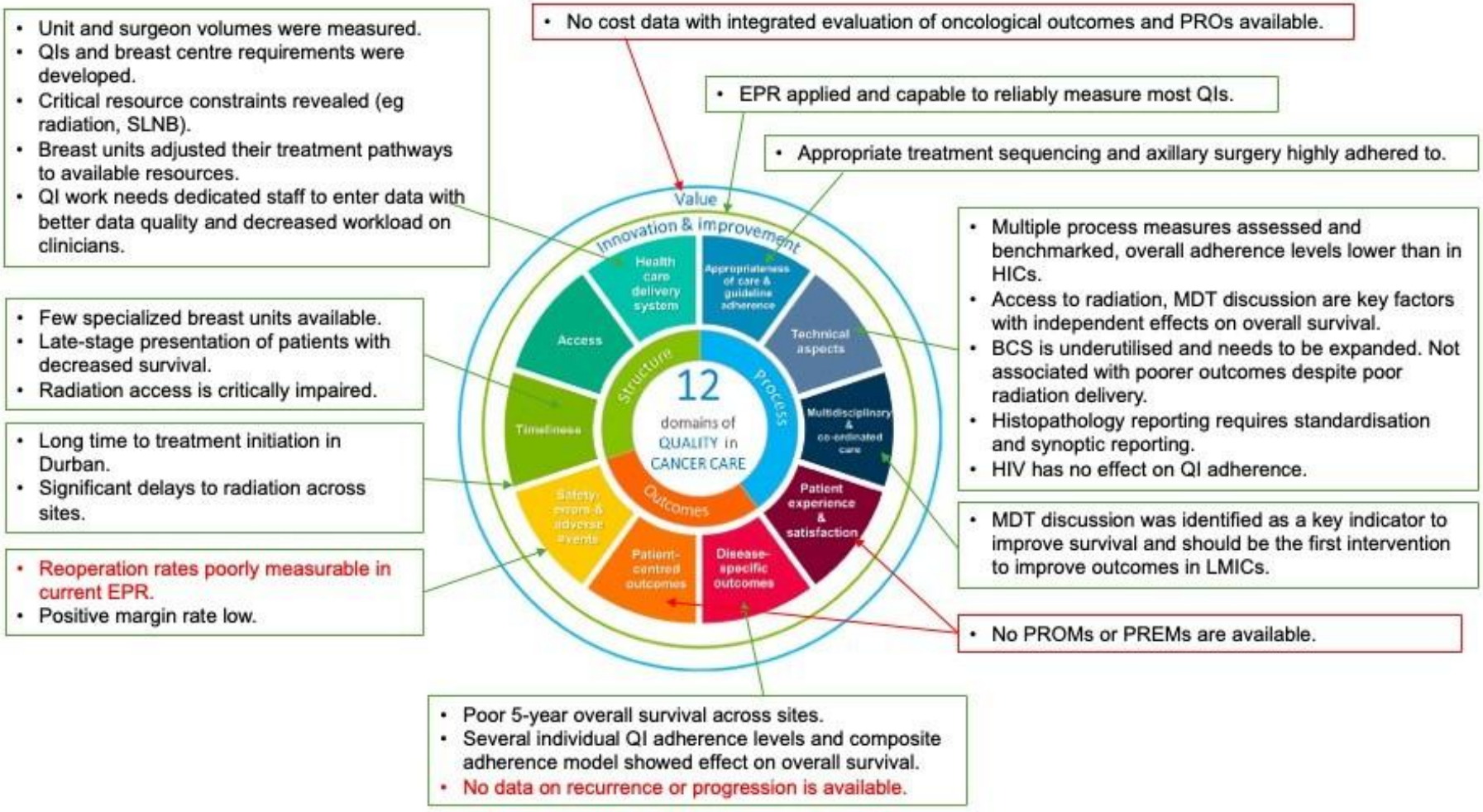

• Unit and surgeon volumes were measured.
• QIs and breast centre requirements were developed.
• Critical resource constraints revealed (eg radiation, SLNB).
• Breast units adjusted their treatment pathways to available resources.
• QI work needs dedicated staff to enter data with better data quality and decreased workload on clinicians.
• No cost data with integrated evaluation of oncological outcomes and PROs available.
• EPR applied and capable to reliably measure most QIs.
• Appropriate treatment sequencing and axillary surgery highly adhered to.
• Multiple process measures assessed and benchmarked, overall adherence levels lower than in HICs.
• Access to radiation, MDT discussion are key factors with independent effects on overall survival.
• BCS is underutilised and needs to be expanded. Not associated with poorer outcomes despite poor radiation delivery.
• Histopathology reporting requires standardisation and synoptic reporting.
• HIV has no effect on QI adherence.
• Few specialized breast units available.
• Late-stage presentation of patients with decreased survival.
• Radiation access is critically impaired.
• Long time to treatment initiation in Durban.
• Significant delays to radiation across sites.
• Reoperation rates poorly measurable in current EPR.
• Positive margin rate low.
• MDT discussion was identified as a key indicator to improve survival and should be the first intervention to improve outcomes in LMICs.
• No PROMs or PREMs are available.
• Poor 5-year overall survival across sites.
• Several individual QI adherence levels and composite adherence model showed effect on overall survival.
• No data on recurrence or progression is available.
Value
Innovation & improvement
Health care delivery system
Appropriateness of care & guideline adherence
Technical aspects
Multidisciplinary & co-ordinated care
Patient experience & satisfaction
Disease-specific outcomes
Patient-centred outcomes
Safety, errors & adverse events
Timeliness
Access
Structure
Process
Outcomes
12
domains of
QUALITY in
CANCER CARE

Figure 30: Revisited conceptual framework for the quality of breast cancer care

Adapted from Chiew et al. European Journal of Cancer Care, 2018(60)

7.3.4 Implications and Recommendations

The findings of this series of studies are the first of its kind in the South African context, employing a triangulation of various forms of evidence to assess the quality of breast cancer care. The contextual implications and recommendations are listed and categorised below under methodology, patient, clinician, and policy.

Methodology

- The mixed method is intuitive to clinicians who typically combine qualitative and quantitative measurements in their daily clinical practice. It provides a pragmatic approach to complex clinical research topics and offers a more rounded and in-depth perspective.
- EPRs are essential to any outcome measurement and quality improvement initiative and need to be implemented widely.
- Administrative or research staff is required to enter data. Data quality is better, and workload is taken from the clinicians.
- PROMs and PREMs should be integrated as outcome and process measures.
- Technologies to support MDT implementation and documentation need to be expanded and accessible to LMICs.

Patient-Related

- The quality of breast cancer care that patients receive is often below international standard, with outcomes being poor.
- Patient advocacy organisations need to address the poor outcomes, limited resources, MDT availability and breast surgical subspecialisation to urge the government, institutions and funders for significant change. There is particular urgency in addressing the radiation delivery crisis.
- Enhancing public awareness, potentially through mass media campaigns, can reduce the stage at which patients present. However, sufficient resources and high-quality access points need to be established before this.

Clinician-Related

- Quality improvement demands a cultural shift, and clinicians must acknowledge that the status quo is unacceptable and use foresight and transparency to implement new care paradigms.

- QI measurements are essential to identify emerging gaps in care promptly.
- It is important to enhance the application of SLNB rather than ALND.
- The use of BCT can be safely broadened.
- The radiation constraints need to be considered in treatment sequencing.
- MDT discussions should be mandatory for all breast cancer patients.
- There is an urgent need to train and expand the oncology workforce, in particular breast surgeons.
- Clinicians can follow the step-by-step plan to establish breast centres.
- The concept of value-based care must be embraced in the longer term.

Policy-related

- Government must increase meaningful engagement with key stakeholders from the public and academic sectors to refine strategies to improve breast cancer care quality.
- Access to all treatment modalities is critical and appropriate resources and specialist staffing must be provided to public sector units.
- Breast surgeons play a critical role in quality improvements through multidisciplinary teams (MDTs) and breast centres.
- Breast surgery must be recognised as a subspecialty and appropriate training must be offered as fellowships.
- MDTs need to be strengthened in the public sector with appropriate technologies and dedicated time allocations.
- MDTs in the private sector must be funded and participants should be fairly compensated.
- The organisation of breast care in breast centres is key to providing high-quality care and there is an urgent need to expand access in South Africa.
- BIGOSA is not equipped and will require dedicated funding and personnel to oversee the implementation of breast centres and data collection and interpretation.
- Breast cancer QI programs will need administrative staff to support this and take the workload off the physicians.

- Health funders should offer financial incentives to private sector clinicians and units who participate in QI measurements and improvement programs, with additional incentives to those who perform well.
- Partnerships between public and private sectors are essential for enhancing care quality across both sectors.
- Private funders, hospital groups, universities, and national and provincial government should collaborate constructively with clinicians and avoid using quality assessments punitively.
- Histopathology reporting with appropriate biomarkers requires a national consensus with key data definitions and synoptic reporting.

7.4 Strengths and Limitations

Like all studies, this PhD research has its strengths and limitations. The primary strength of this study is that it addresses a significant gap in breast cancer care in South Africa. Another strength lies in its mixed methods approach and purposeful sequential design. Furthermore, there is its novelty; it is the first study ever conducted in Africa to develop breast quality indicators, the first to benchmark surgical breast care in sub-Saharan Africa, and the first study in LMICs to observe the effects of adherence and non-adherence to QIs on patient outcomes. It also offers clinically meaningful results for LMICs with actionable recommendations.

The limitations of each study have been discussed in the various chapters, but the following is added. We have no data on disease progression or locoregional recurrence and could, therefore, not evaluate these. Similarly, reoperation rates and surgical complications were not measurable. In the future, OncoDB should be adjusted to include unambiguous data fields for these. Despite efforts to minimise subjectivity and bias, there remains a risk with the largely qualitative approach chosen for developing breast centre requirements. Nevertheless, it allowed open input from various stakeholders on an extremely complex and interdisciplinary topic and provided significant internal political insight and reflections on emerging themes. Our focus was on quality indicators of surgical breast cancer care, which included histopathology and an assessment of radiotherapy following BCS. However, this does not integrate all aspects of the clinical breast cancer pathway, specifically systemic therapies and more

detailed information on radiotherapy. These factors all affect patient outcomes, and quality initiatives should expand to be inclusive of all modalities in the future.

7.5 Future Studies

This study has identified several areas of research that warrant further exploration. Such subsequent studies will assist researchers and clinicians in attaining a more comprehensive understanding of the quality of breast cancer care and how to improve it within the South African context. A selection of potential future studies is provided below:

Development of National MDT Guidelines and Quality Improvement of MDT Discussions

MDT discussion is a key process indicator with a clear clinical impact on patient outcomes. There are currently no guidelines for MDTs in South Africa, and this would be a good step prior to a quality improvement initiative. I would use a concurrent mixed-methods design with a modified Delphi process:

1) Systematic review of MDT structure, requirements and documentation.
2) Modified Delphi process integrating discussion and quantitative questionnaires.

For the subsequent quality improvement initiative, I would use the classic Plan-DoStudy-Act methodology, again a mixed-methods approach, for implementation.

1) Participant observation technique to conceptualise the MDT and create a process map. Root cause analysis through Fishbone and Pareto diagrams to understand the key barriers to MDT discussion.
2) Addressing identified barriers with intervention.
3) Measurement of MDT discussion rates post-intervention.
4) Upscale intervention or introduce other interventions with cyclical remeasurements

Integration of Value-Based Care

Value is a complex but crucial concept in quality improvement and must be applied in LMICs. It is essential to identify vital elements of value-based care, including patientfocused strategies, coordinated care through various treatment methods, outcomes assessment, and innovative payment structures, followed by

implementation to achieve better outcomes while containing costs. I would adopt a stepwise approach using an exploratory sequential mixed-methods approach:

1) Exploration of the concept of value and health needs specific to LMICs by systematic review, patient interviews and provider and funder discussion in focus groups.
2) Measurement of appropriately selected, existing PROMs and PREMS tools.
3) Estimation of avoidable health costs, such as the utilisation patterns of recognised low-value surgical interventions.
4) Measurement of oncological outcomes and patient outcomes with correlation to surgical cost estimates.

Barriers to BCS and Survival Determinants in Patients Receiving BCS

The results of this thesis highlight a low BCS rate, even among patients with earlystage presentation. Patients who received BCS did not have worse outcomes despite the poor delivery of radiotherapy, which is concerning and puzzling. I would employ a concurrent mixed-methods design to unpack this complex topic:

1) Qualitative interviews to explore patient and provider barriers to BCS.
2) Quantitative analysis of potential factors in multivariate logistical regressions, including socioeconomic and comorbidity factors.
3) Comparison of survival determinants between patients who received and did not receive radiotherapy.

Radiation Delivery in South Africa

The findings of this thesis illustrate a treatment modality in crisis in Gauteng, and under strain in KZN. Although radiotherapy falls outside of my specialty, it deserves attention. The data only examined patients who had BCS but did not include the large number of post-mastectomy patients with locally advanced tumours in our cohort. The full extent of non-delivery and its effects is therefore not clear:

1) Qualitative interviews with patients and providers and root cause analysis.
2) Quantitative analysis with inclusion of all patients with radiotherapy indication and comparisons of timelines as well receipt of care.
3) Multivariate regressions to establish the effect on survival.
4) Rate of hypofractionation and ultra-fractionation as well as cost and time analysis if applied throughout the cohort

7.6 Conclusion

In conclusion, this study has developed contextually relevant QIs that have been applied to a large cohort and demonstrate that South African women experience varying levels and generally lower quality of breast cancer care and consequently poor overall survival. Mandatory MDT discussion improves patients' outcomes especially overall survival and serves as a key process indicator for enhancing patient outcomes, whereas breast surgery subspecialisation and the establishment of breast centres are key structural components for quality improvement in South Africa.

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LIST OF APPENDICES

APPENDICES

Appendix A: Author's Agreement

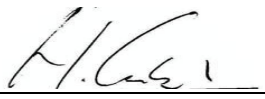
Author's Agreement

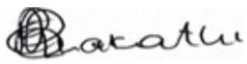
By signing this declaration, the co-authors listed below agree to the use of the specified article by the student, Sarah Nietz, as part of her thesis.

1 Nietz S, Ruff P, Chen WC, O'Neil DS, Norris SA. Quality indicators for the diagnosis and surgical Management of breast cancer in South Africa. The Breast, 2020 Dec;54:187–96. DOI: http://dx.doi.org/10.1016/j.breast.2020.09.012

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Daniel S. O'Neil		13.02.2025
Shane A Norris		19.01.2025

2 Nietz S, Cubasch H, Buccimazza I, Čačala S, Phakathi B, Joffe M, et al. An initial benchmark of the quality of the diagnosis and surgical treatment of breast cancer in South Africa. S Afr Med J. 2025 Feb115(1):e2292 https://doi.org/10.7196/SAMJ.2025.v115i1.2292

Co-author name	Signature	Date
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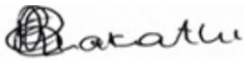
Ines Buzzimazza		29.01.2025
Sharon Čačala		11.02.2025
Boitumelo Phakathi		11.02.2025
Maureen Joffe		19.01.2025
Wenlong Carl Chen		11.02.2025
Shane A Norris		19.01.2025
Paul Ruff		19.01.2025

3 Nietz S, Edge J, Buccimazza I, Demetriou G, Tunmer M, Smilg J, et al. The role and minimum requirements for breast centres in low-to-middle-income countries: a South African perspective. Submitted to JCO Global Oncology

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Duvern Ramiah		31.01.2025

Peter Schoub		10.02.2025
Shane A Norris		19.01.2025
Paul Ruff		19.01.2025

4 Nietz, S, Chen C, Cubasch H, Phakathi B, Čačala S, Buccimazza I, Joffe M, Ruff P, Norris S. The effect of non-adherence to quality indicators on overall survival among South African women with breast cancer. Under editing for submission to Lancet Global Health.

Co-author name	**Signature**	**Date**
Wenlong Carl Chen		11.02.2025
Herbert Cubasch		19.01.2025
Boitumelo Phakathi		12.02.2025
Sharon Čačala		12.02.2025
Ines Buccimazza		29.01.2025
Maureen Joffe		19.01.2025
Paul Ruff		19.01.2025
Shane A Norris		19.01.2025

Appendix B: Ethics Clearance Certificates

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Sarah Nietz et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180671

NAME: (Principal Investigator)	Dr Sarah Nietz et al
DEPARTMENT:	Surgery Charlotte Maxeke Johannesburg Academic Hospital Breast Unit
PROJECT TITLE:	Quality indicators of Breast Cancer Surgery in South Africa
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Paul Ruff and Prof Shane Norris
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/06/2018

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 Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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

2 July 2024

Dr S Nietz, et al
School of Clinical Medicine
Department of General Surgery
Medical School
University

Sent by e-mail to: Sarah.Nietz@wits.ac.za

Dear Dr Nietz

Protocol Ref No: M240165
Protocol Title: *Quality indicators of breast cancer surgery in South Africa*
Principal Investigator: Dr S Nietz, et al

Thank you for your letter of 20 June 2024.

We have noted and approve of your plan to assemble a group of experts for an online discussion on breast centres in South Africa.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

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

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

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr S Nietz, et al
School of Clinical Medicine
Department of General Surgery
Medical School
University

E-mail: Sarah.Nietz@wits.ac.za

CC: Supervisor: Professors P Ruff and SA Norris
PRuff@iafrica.com
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 27 February 2024

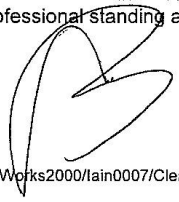
REF: R14/49

PROTOCOL NO: **M240165** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Quality indicators of breast cancer surgery in South Africa*

Approved unconditionally

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.



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Appendix C: Participant Information Sheets

Information sheet for the study entitled "**Development of South African Quality Indicators for Breast Cancer Diagnosis and Surgery"**

Dear Colleague,

My name is Dr Sarah Nietz from the Breast Unit at Charlotte Maxeke Johannesburg Academic Hospital and the Department of Surgery of the University of the Witwatersrand, Faculty of Health Sciences. I cordially invite you among other key clinicians to take part in this study which is a part of my Doctor of Philosophy project "Quality of Breast Cancer Surgery in South Africa".

Our identification of you as a stakeholder expert is based on 1) your expertise and in-depth knowledge of our South African public health system; 2) depth of breast cancer experience and 3) academic seniority.

Rationale for requesting your participation in our study is to develop a standard set of quality indicators of breast cancer diagnosis and surgery in South Africa.

Data on the performance of cancer services in low-to middle income countries is scarce and evaluation of key quality indicators in breast cancer care is required to improve services and assist in policy. Quality indicators have been developed and applied in high-income countries. China is the only low-to middle income country and only member of BRICS (Brazil, Russia, India, China, South Africa) to develop quality indicators to date. Resources and local requirements differ and indicators developed in other settings require modification to allow for variation in professional culture and clinical practice. South Africa has no recognized quality indicators for breast cancer management to date.

We need your help to develop a unique set for our setting with particular reference to preoperative and operative management by the breast surgeon. This will set standard measurements with the aim to improve national quality in surgical breast cancer care.

This study is completely voluntary and confidential. It will require approximately 30 minutes of your time to complete an online survey. There are no risks and no direct benefits to participation, however your input will enable the development of a South African set of quality indicators. You have the right to withdraw from the survey at any time without any fear of any consequence.

To ensure anonymity, a de-identified study ID number has been allocated to you. You will need to use this number when answering the survey. You can find this number on the email invitation communication. Only the research team will have access to the identifiable information that will be securely stored at the research site.

Our research approach is by modified Delphi process and is two-fold:

Firstly, we have already performed a comprehensive literature review, added local novel indicators and have listed 52 potential quality indicators. These require your rating as the exert panel. Rating is according to importance to measure (relevance and priority), scientific acceptability (reliability and validity) and appropriateness to our local setting (feasibility). Scoring will range from 1 to 5. Inclusion thresholds will be set at mean ratings >4 with a coefficient variation of <25%. If weak consensus is achieved on indicators, the process may need to be repeated until strong consensus is reached on stakeholder responses.

Once this survey has been completed our research team will analyse responses on all potential indicators and send results to all participating stakeholders. We anticipate a 3-week period between the survey and analysis result to receive and analyse stakeholder responses.

Secondly, you will be invited to a subsequent consolidation-seeking workshop to discuss the results, set definitions and achieve a common set of indicators for future adherence evaluation.

Only de-identified survey information and indicators agreed to by the collective group will be released for presentations and publications.

Ethics clearance has been applied for from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Please include your unique study ID provided in the email in the space provided on the electronic survey.

To confirm your consent to participate in the study and to access the first survey, please click on the link provided in the email. If this is not successful, please copy and paste the link into your browser.

Thank you for reading this information sheet. We greatly appreciate your time. If you have any queries related to the research, please contact Prof Paul Ruff on 011 488 3901 or email paul.ruff@wits.ac.za

Regards

Dr. Sarah Nietz

Department of Surgery, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand

073 313 1366

04 June 2018

Information sheet for the study entitled "**The Role and Minimum Requirements for Breast Centres in South Africa"**

Dear Colleague,

My name is Dr Sarah Nietz from the Department of Surgery of the University of the Witwatersrand, Faculty of Health Sciences. I cordially invite you among other key clinicians to take part in this study which is a part of my Doctor of Philosophy project “Quality Indicators of Breast Cancer Surgery in South Africa”.

Our identification of you as a stakeholder expert is based on 1) your expertise and in-depth knowledge of our South African health system; 2) depth of breast cancer experience and 3) academic seniority.

The rationale for requesting your participation in our study is to reach a round-table consensus on the role and requirement for breast centres in South Africa.

Breast centers condense multidisciplinary expertise and resources. The literature amply demonstrates their value, with improved patient survival, guideline-adherent care, and appropriate use of multidisciplinary treatment modalities. Internal and external accreditation processes and audits improve the quality of care over time. There are a number of set requirements and accreditation systems, most prominently EUSOMA (European Society of Breast Cancer Specialists) in Europe, NAPBC (National Accreditation Program for Breast Centers) in the Unites States of America and Onkozert from the DKG (Deutsche Krebs Gesellschaft) in Germany, but none have been adapted for transitioning countries that reflect our healthcare setting and needs.

We need your help to define the role and requirements for breast centres in our setting with the aim to build capacity and improve the quality of breast cancer care over time.

Participation in this study is completely voluntary. The virtual discussion round will require approximately 90 minutes of your time. There are no risks or direct benefits to participation; however, your input will enable the development of a consensus paper on the role and requirements for breast cancer centres in South Africa. You have the right to withdraw from this study at any time without fear of any consequence.

We have already performed a comprehensive literature review, and compared the three most prominent accreditation systems. The base documents and comparative tables will be circulated to you seven days before the agreed meeting date.

The different requirements, the centre's role within our healthcare system, and the first planned implementation steps will be discussed in the round-table discussion. After the meeting, the consensus document will be drafted and circulated to all participants for approval.

Ethics clearance has been applied for from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (“Committee”). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact Iain Burns from the Committee, who may be contacted on telephone number 011 717 1252, or by e-mail on Iain.Burns@wits.ac.za.

To confirm your consent to participate in the study you will click on the circulated meeting link.

Thank you for reading this information sheet. We greatly appreciate your time. If you have any queries related to the research, please contact Prof Paul Ruff on 082 880 4546 or email pruff@iafrica.com

Regards

Dr. Sarah Nietz

Department of Surgery, University of the Witwatersrand

073 313 1366

20 June 2024

Appendix D: Delphi Questionnaire

Delphi Questionnaire – Quality Indicators of Breast Cancer Diagnosis and Surgery

Dear Colleague,

Thank you for participating in this study.

Please score the following candidate quality indicators according to

1. Importance to measure (relevance and priority)
    - Do you think we should measure this indicator?
2. Scientific acceptability (reliability and validity)
    - Do you think measurement of this indicator will offer us reproducible and credible results?
3. Appropriateness to our local setting (feasibility)
    - Do you think this indicator can be measured without undue strain?

<u>Candidate Quality Indicators of Breast Surgery</u>

1) Diagnosis

1.1) Title: Definitive diagnosis prior to treatment

Definition: Proportion of patients with breast cancer (invasive or in situ) who had a preoperative histologically or cytologically confirmed malignant diagnosis **Numerator:** Breast cancer patients who had a preoperative histologically or cytologically confirmed malignant diagnosis

Denominator: All breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)

Importance to measure					
Scientific acceptability					
Appropriateness					

1.2) Title: Histopathological characterization for invasive breast cancer

Definition: Proportion of invasive cancer cases for which the following prognostic/predictive parameters have been recorded:

- Histological type
- Grading
- ER
- PR
- HER-2
- Proliferation index (Ki67)

In addition to the above parameters, the following parameters must be recorded after surgery:

- Pathological stage (pT and pN, or ypT and ypN in case of primary systemic therapy)
- Size in mm for the invasive component
- Lymphovascular invasion
- Distance to nearest radial margin

Numerator: Invasive breast cancer patients for which the above prognostic/predictive parameters have been recorded

Denominator: All invasive breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

1.3) Title: Histopathological characterization for non-invasive breast cancer

Definition: Proportion of non-invasive cancer cases for which the following prognostic/ predictive parameters have been recorded:

- Grading
- Dominant histological pattern
- Size in mm
- Distance to nearest radial margin
- ER

Numerator: Non-invasive breast cancer patients for which the above prognostic/predictive parameters have been recorded

Denominator: All non-invasive breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)

Importance to measure					
Scientific acceptability					
Appropriateness					

1.4) Title: Appropriate clinical assessment and breast imaging

Definition: Proportion of patients with breast cancer who preoperatively underwent mammography, physical examination and ultrasound of both breasts and axillae

Numerator: Breast cancer patients who preoperatively underwent mammography, physical examination and ultrasound of both breasts and axillae

Denominator: All breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

1.5) Title: Use of BIRADS classification in imaging reports

Definition: Proportion of breast cancer patients in whom the diagnostic imaging report uses the BIRADS classification

Numerator: Breast cancer patients in whom the diagnostic imaging report uses the BIRADS classification

Denominator: All breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

1.6) Title: Appropriate clinical assessment of the axilla

Definition: Proportion of patients with invasive cancer who underwent image-guided axillary staging (by US followed by FNA/CNB for suspicious nodes)

Numerator: Breast cancer patients who underwent image-guided axillary staging (by US followed by FNA/CNB for suspicious nodes)

Denominator: All invasive breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					

Appropriateness					

1.7) Title: Use of MRI

Definition: Proportion of cancer cases examined preoperatively by MRI

Numerator: Breast cancer patients who had a preoperative MRI

Denominator: All breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

1.8) Title: Use of imaging marker clip in patients for BCS undergoing primary systemic therapy

Definition: Proportion of patients undergoing primary systemic therapy before planned BCS who have an imaging marker clip placed in breast primary

Numerator: Patients undergoing primary systemic therapy before planned BCS who have an imaging marker clip placed in breast primary

Denominator: All patients undergoing primary systemic therapy before planned BCS

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

2) Multidisciplinary Management

2.1) Title: Multidisciplinary team discussion

Definition: Proportion of patients with breast cancer who are discussed in a MDT meeting. Ideally this should take place pre- and postoperatively.

Numerator: Patients with breast cancer who are discussed in the MDT meeting **Denominator:** All patients with breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

2.2) Title: Documentation of preoperative (clinical) breast cancer staging **Definition:** Proportion of breast cancer patients with documentation of preoperative

(pre-treatment) breast cancer staging (AJCC)

Numerator: Breast cancer patients with documentation of preoperative (pretreatment) breast cancer staging (AJCC)

Denominator: All breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

2.3 Title: Documentation of postoperative (pathologic) breast cancer staging

Definition: Proportion of breast cancer patients with documentation of postoperative (pathologic) breast cancer staging (AJCC)

Numerator: Breast cancer patients with documentation of postoperative (pathologic) breast cancer staging (AJCC)

Denominator: All breast cancer patients who underwent surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					

Scientific acceptability					
Appropriateness					

2.4 Title: Appropriate treatment sequencing in LABC

Definition: Proportion of patients with inflammatory or locally advanced non-operable breast cancer who undergo primary systemic treatment before surgery

Numerator: Patients with inflammatory or locally advanced non-operable breast cancer who undergo primary systemic treatment before surgery

Denominator: All patients undergoing surgical treatment for inflammatory or locally advanced non-operable breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

2.5 Title: Receipt of radiotherapy after breast conserving surgery

Definition: Proportion of invasive breast cancer patients who received radiotherapy after BCS

Numerator: Patients who received radiotherapy after BCS

Denominator: All patients BCS for invasive breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3) Breast Surgery

3.1) Title: Breast conserving surgery (BCS) rate

Definition: Proportion of patients undergoing BCS among all patients who receive surgery for the primary breast cancer

Numerator: Patients with breast cancer who undergo BCS

Denominator: All patients with breast cancer who undergo surgery for the breast primary

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.2) Title: Documentation of eligibility for BCS

Definition: Proportion of patients with documentation of eligibility for BCS

Numerator: Patients with documentation of eligibility for BCS

Denominator: All patients undergoing surgical treatment for breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.3) Title: Rate of positive or close (<1mm) margins after breast conserving surgery (BCS)

Definition: Number of patients with positive or close (<1mm) margins after BCS among all patients who underwent BCS

Numerator: Patients with positive or close (<1mm) margins after BCS

Denominator: All patients who undergo BCS

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					

Scientific acceptability					
Appropriateness					

3.4) Title: Oncoplastic procedure rate

Definition: Number of patients who received an oncoplastic procedure for breast conserving surgery among all patients who underwent breast conserving surgery

Numerator: Patients who received an oncoplastic procedure for breast conserving surgery

Denominator: All patients who underwent breast conserving surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.5) Title: Readmission rate

Definition: Proportion of patients requiring readmission within 30 days after breast cancer surgery

Numerator: Patients requiring readmission within 30 days after breast cancer surgery

Denominator: All patients undergoing breast cancer surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.6) Title: Reoperation rate

Definition: Proportion of patients with breast cancer who required a reoperation for the breast primary within six months of the initial surgery

Numerator: Patients who required a reoperation for the primary tumour within six months of initial surgery

Denominator: All patients who underwent surgery for the primary tumour

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.7) Title: Single operation rate for invasive cancer

Definition: Proportion of patients with invasive cancer who received a single breast operation for the primary tumour (excluding reconstruction)

Numerator: Patients who received a single breast operation for the primary tumour (excluding reconstruction)

Denominator: All patients with invasive cancer who underwent surgery for the primary tumour

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.8) Title: Single operation rate for DCIS

Definition: Proportion of patients with DCIS only who received a single breast operation for the primary tumour (excluding reconstruction)

Numerator: Patients with DCIS only who received a single breast operation for the primary tumour (excluding reconstruction)

Denominator: All patients with DCIS only who underwent surgery for the primary tumour

Score	1 (no agreement)	2	3	4	5 (strong agreement)

Importance to measure					
Scientific acceptability					
Appropriateness					

3.9) Title: Use of marker clips to aid radiation

Definition: Proportion of patients with placement of marker clips to aid radiation after breast conserving surgery

Numerator: Patients with placement of marker clips after breast conserving surgery

Denominator: All patients undergoing breast conserving surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.10) Title: Surgeon use of intraoperative ultrasound

Definition: Number of patients undergoing breast conserving surgery with surgeon use of intraoperative ultrasound among all patients who underwent breast conserving surgery

Numerator: Patients who underwent breast conserving surgery with surgeon use of intraoperative ultrasound

Denominator: All patients who underwent breast conserving surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.11) Title: Specimen orientation

Definition: Proportion of primary breast cancer specimens with intraoperative orientation labeling by the surgeon

Numerator: Specimens with intraoperative orientation labeling by the surgeon
Denominator: All primary breast cancer specimens

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.12) Title: Rate of surgical site infections

Definition: Proportion of patients with surgical site infection after surgery for breast cancer

Numerator: Patients with surgical site infection

Denominator: All patients undergoing surgery for breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

3.13) Title: Discussion of surgical options

Definition: Proportion of patients with breast cancer with recorded evidence of discussion of surgical options

Numerator: Patients with recorded evidence of discussion of surgical options

Denominator: All patients who underwent surgery for the primary tumour

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					

Scientific acceptability					
Appropriateness					

3.14) Title: Documentation of contralateral breast cancer risk

Definition: Proportion of patients with preoperative documentation of contralateral breast cancer risk

Numerator: Patients with documentation of contralateral breast cancer risk
Denominator: All patients undergoing surgery for breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4) Management of the Axilla

4.1) Title: Axillary surgery rate in invasive breast cancer

Definition: Proportion of invasive breast cancer patients who underwent axillary surgery

Numerator: Patients with invasive breast cancer who underwent axillary surgery

Denominator: All patients with invasive breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.2) Title: Appropriate use of sentinel node biopsy

Definition: Proportion of patients with invasive cancer and clinically negative axilla who underwent sentinel lymph node biopsy only (excluding patients who received primary systemic therapy)

Numerator: Patients with invasive cancer and clinically negative axilla who underwent sentinel lymph node biopsy only

Denominator: All patients with invasive cancer and clinically negative axilla who underwent axillary surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.3) Title: Number of nodes excised in sentinel node biopsy

Definition: Proportion of patients with invasive cancer who underwent sentinel lymph node biopsy with no more than 5 nodes excised

Numerator: Patients with invasive cancer who underwent sentinel lymph node biopsy with no more than 5 nodes excised

Denominator: All patients with invasive cancer who underwent sentinel lymph node biopsy

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.4) Title: Appropriate axillary surgery in DCIS

Definition: Proportion of patients with DCIS only who do not undergo axillary lymph node dissection

Numerator: Patients with DCIS only who do not undergo axillary lymph node dissection

Denominator: All patients with DCIS

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.5) Title: Intraoperative pathology assessment for sentinel nodes

Definition: Proportion of patients undergoing sentinel lymph node biopsy (SLNB) who have intraoperative pathology assessment of the sentinel node(s)

Numerator: Patients with intraoperative pathology assessment of the sentinel node(s)
Denominator: All patients who underwent SLNB

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.6) Title: Number of nodes excised during axillary lymph node dissection

Definition: Proportion of breast cancer patients undergoing axillary lymph node

dissection (ALND) who have at least 10 nodes examined (excluding patients who received primary systemic therapy)

Numerator: Patients undergoing ALND with at least 10 nodes examined

Denominator: All patients who underwent ALND

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.7) Title: Pathology reporting of lymph nodes

Definition: Proportion of breast cancer patients after axillary surgery with a pathology report stating the number of examined and positive lymph nodes

Numerator: Breast cancer patients who underwent axillary surgery with a pathology report stating the number of examined and positive lymph nodes **Denominator:** All breast cancer who underwent axillary surgery

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					

Appropriateness					

4.8) Title: Tracer use in sentinel lymph node biopsy

Definition: Proportion of patients undergoing SLNB in whom both blue dye and radiocolloid was used

Numerator: Patients undergoing SLNB in whom both blue dye and radiocolloid was used

Denominator: All patients undergoing SLNB

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.9) Title: Failure of identification of the sentinel node

Definition: Proportion of patients undergoing SLNB in whom the sentinel node could not be identified and went on to have an immediate ALND

Numerator: Patients undergoing SLNB in whom the sentinel node could not be identified and went on to have an immediate ALND

Denominator: All patients undergoing SLNB

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.10) Title: Node positivity rate in SLNB

Definition: Proportion of patients undergoing SLNB in whom the sentinel node is positive

Numerator: Patients undergoing SLNB in whom the sentinel node is positive
Denominator: All patients undergoing SLNB

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

4.11) Title: Concurrent SLNB with breast surgery

Definition: Proportion of patients with invasive breast cancer undergoing SLNB during the same operation as the breast surgery

Numerator: Patients undergoing SLNB combined with breast surgery

Denominator: All patients undergoing SLNB

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

5) Timeliness of Care

5.1) Title: Timeliness of initial treatment

Definition: Proportion of breast cancer patients with an interval of no more than 6 weeks, from the date of first diagnostic examination within the breast centre to the date of surgery or start of other treatment.

Numerator: Proportion of patients with an interval of no more than 6 weeks to initial treatment

Denominator: All presenting breast cancer patients

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					

Scientific acceptability					
Appropriateness					

5.2) Title: Time from needle biopsy to pathology report

Definition: Time in days from date of needle biopsy to date of pathology report

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

5.3) Title: Time from needle biopsy pathology report to treatment

Definition: Time in days from date of needle biopsy pathology report to date of surgery or initiation of other therapy

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

5.4) Title: Time from cancer surgery to pathology report

Definition: Time in days from date of cancer surgery to date of pathology report

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

5.5) Title: Timeliness of adjuvant chemotherapy

Definition: Time (in days) between receipt of last surgery and first chemotherapy where applicable

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

5.6) Title: Timeliness of adjuvant radiation

Definition: Time (in days) between receipt of last surgery or adjuvant chemotherapy and first radiotherapy dose where applicable

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					

Appropriateness					

5.7) Title: Efficient diagnosis

Definition: Number of visits required until treatment is initiated

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

6) Structure and Outcome

6.1) Title: Surgeon volume

Definition: Each surgeon needs to perform a set minimum number of surgeries on patients with newly diagnosed breast cancer per annum. In units which train surgeons this would include supervised (scrubbed in) surgeries.

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

6.2) Title: Breast unit volume

Definition: Each unit needs to see a set minimum number of patients with newly diagnosed breast cancer per annum.

Numerator: N/A

Denominator: N/A

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

6.3) Title: Locoregional recurrence rate

Definition: Proportion of patients with locoregional recurrence among all patients with surgically treated breast cancer

Numerator: Patients with locoregional recurrence

Denominator: All patients with surgically treated breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

6.4) Title: Progression-free survival

Definition: Proportion of patients without progression of disease at a predefined time point among all patients with breast cancer

Numerator: Patients without progression of disease

Denominator: All patients who presented with breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					

Appropriateness					

6.5) Title: Overall survival

Definition: Proportion of patients alive at a predefined time point among all patients with breast cancer

Numerator: Alive patients

Denominator: All patients who presented with breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

6.6) Title: Lymphoedema rate

Definition: Proportion of patients with lymphoedema of the arm after axillary surgery for breast cancer

Numerator: Patients with lymphoedema of the arm after axillary surgery for breast cancer

Denominator: All patients undergoing axillary surgery for breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

6.7) Title: Quality audit rate

Definition: Proportion of patients entered into a quality audit (any type: institutional, personal case log, regional, national) among all patients with breast cancer

Numerator: Patients entered into a quality audit

Denominator: All patients with breast cancer

Score	1 (no agreement)	2	3	4	5 (strong agreement)
Importance to measure					
Scientific acceptability					
Appropriateness					

Appendix E: Published Papers

The Breast 54 (2020) 187–196

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Quality indicators for the diagnosis and surgical management of breast cancer in South Africa

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article info

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Keywords: Breast cancer surgery
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abstract

Introduction: Quality indicators (QIs) for breast cancer care have been developed and applied in high income countries and contributed to improved quality of care and patient outcomes over time.

Materials and methods: A modified Delphi process was used to derive expert consensus. Potential QIs were rated by a panel of 17 breast cancer experts from various subspecialties and across South African provinces. Each QI was rated according to importance to measure, scientific acceptability and feasibility. Scoring ranged from 1 (no agreement) to 5 (strong agreement). Inclusion thresholds were set a priori at mean ratingsResults:!The literature review identi4 with a coefficient variation offied 790 potential QIs. After categorisation and removal of duplicates,!25%. Levels of evidence were determined for each indicator.

52 remained for panel review. There was strong consensus for 47 which were merged to 30 QIs by exclusion of similar indicators and indicator grouping. The final set included eight QIs with level I or II evidence and two QIs with level III evidence which were deemed "mandatory" due to clinical priority and impact on care. The remaining QIs with lower-level evidence were grouped as eight "recommended" QIs (regarded as standard of care) and twelve "optional" QIs (not regarded as standard of care).

Conclusion: A regional set of QIs was developed to facilitate standardised treatment and auditing of surgical care for breast cancer patients in South Africa. Routine monitoring of the ten mandatory QIs, which were selected to have the most substantial impact on patient outcome, is proposed.

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1. Introduction

Breast cancer is the most common malignancy among women in Sub-Saharan Africa [1]. Patient outcomes remain poorer in low-to middle-income countries (LMICs) compared to high-income countries (HICs), and reasons include difficult access, late presentation, decreased awareness, and limited treatment resources [2]. Robust data on the quality of surgical breast cancer care in South Africa is non-existent to date, but considerable variations depending on the geographical location and socioeconomic status of the patient are likely. A recent report on timely delivery of chemotherapy, radiation, and endocrine treatment showed marked non-adherence and the need for focused quality improvement in South Africa [3]. Although South Africa is regarded as an uppermiddle-income country (UMIC) by the World Bank, it has a high index of inequality. Socioeconomic disparities characterise its heterogeneous society which, together with other factors, affect health status and patient outcomes; a divide that is particularly obvious in the dual public and private health care system [4].

Breast cancer is a heterogeneous disease and is best treated by a multidisciplinary specialist team. Case volume and expertise clearly affect outcomes and women treated by specialist surgeons are

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more likely to receive guideline-adherent therapy with better oncological outcomes [5e7]. Despite these clear benefits and increasing breast cancer incidence, there are very few dedicated surgical breast units in the South African public sector that offer standardised care, and these are often burdened with high patient volumes and inadequate resource allocation.

Specific breast cancer QIs have been developed and applied in various HICs [8e10] with China being the only LMIC to have published dedicated QIs to date [11]. Implementation of QIs is feasible in various settings and tends to improve quality over time [12,13]. The process of audit facilitates awareness and adherence to guidelines [14]. QIs are not always readily transferable and need to be adjusted to each setting to allow for variations in clinical practice and health care systems [15].

Non-communicable diseases including cancer were recently declared a priority by the South African National Department of Health and National Breast Cancer Policy Guidelines were developed and published. However, they remain to be implemented [16]. The onus therefore still remains with clinicians to find solutions to standardise and improve breast cancer care in South Africa. This study aimed to develop a regional set of QIs for the diagnosis and surgery of breast cancer in South Africa, through a clinician-driven process using a modified Delphi method.

2. Materials and Methods

2.1. Systematic review

The literature was reviewed on databases including PubMed, Springer, and MEDLINE, as well as QIs published by various international institutes and societies including the American Society of Breast Surgeons (ASBrS), American Society of Clinical Oncology/ National Comprehensive Cancer Network (ASCO/NCCN), American Society of Clinical Oncology/National Initiative for Cancer Care Quality (ASCO/NICCQ), Commission on Cancer of the American College of Surgeons (CoC/ACS), European Society of Breast Cancer Specialists (EUSOMA), German Cancer Society (DKG), National Breast Cancer Organisation Netherlands (NABON), National Institute for Health and Care Excellence (NICE), National Quality Forum (NQF) and Scottish Cancer Taskforce. Search terms included “quality indicator”, “quality measures”, “quality parameters”, “breast cancer”, “breast surgery” and “breast pathology”. National and international clinical guidelines and breast centre accreditation criteria, such as EUSOMA criteria and National Accreditation Program for Breast Centres (NAPBC) were considered [17,18].

2.2. A national expert panel

A panel of experts was selected according to: (i) provincial representativeness, (ii) subspecialties and expertise in breast cancer diagnosis and treatment, (iii) knowledge of the local health care system, and (iv) clinical and academic seniority. The final panel consisted of 17 experts: ten surgeons, two medical oncologists, two radiation oncologists, two pathologists, and one radiologist (Fig. 1). Each participant was consented and received a study participant number and an electronic link to each Delphi rating round by email. All ratings were anonymous with controlled feedback following each rating round. In October 2018, a face-to-face meeting at the Breast Interest Group of Southern Africa (BIGOSA) conference in Durban, was attended by all members of the expert panel. The potential QIs, their definitions, and the process of selecting the QIs were presented, discussed, and accepted as valid and further locally relevant QIs were invited for inclusion.

2.3. Delphi rounds

The Delphi process assumes that group judgements are more valid than individual judgements and is a widely recognized method to reach expert consensus in a structured manner. Key principles include statistical group response and iteration with controlled feedback. The strengths of the Delphi process are the effective use of a committee and the anonymity of equallyweighted responses which reduces the risk of opinion shifts and peer pressure. Limitations of the Delphi process include the lack of clear methodological guidelines and limited reliability and validity [19]. The Nominal Group Technique (NGT) was considered as an alternative which is based on structured meetings with facilitated discussion but the Delphi process was selected for its anonymity of ratings. However, the Delphi process was modified to include a face-to-face meeting, essentially merging one component from the NGT to allow for critical discussion while preserving anonymous rating as the key strength of the Delphi process. The inclusion of a meeting is a commonly used modification in Delphi projects for healthcare quality indicators [20].

Three rounds took place whereby each QI was rated according to: a) importance to measure (relevance and priority), b) scientific acceptability (reliability and validity), c) appropriateness to our local setting (feasibility). Scoring ranged from 1 (no agreement) to 5 (strong agreement). Inclusion thresholds were set a priori at mean ratings ¦4 with a coefficient variation of ¦25%. The first Delphi rating round took place during the face-to-face meeting by anonymous electronic rating. The subsequent two rating rounds were conducted electronically by emailed invitation following the meeting. Study participant numbers were not identifiable to any of the authors. Study data were collected and managed using the REDCap electronic data capture tool and processed by an independent analyst [16].

2.4. Level of evidence

Lastly, the respective level of evidence (LoE) for each indicator was determined to allow for practical prioritisation of QIs. Levels of evidence were adopted from previously published guidelines or determined by literature review. For ease of application, the LoE was determined by the United States Agency for Healthcare Research and Quality (AHRQ, www.ahrq.org) classification [21].

" Level 1systematic reviewse Requires good-quality randomised controlled trials or

""" Level 4Level 3Level 2 eee Expert judgementRequires well designed descriptive studiesRequires well designed quasi-experimental studies

3. Results

The literature review revealed 920 potential QIs. Those which did not address preoperative diagnosis or surgical management were removed,leaving 129 potentialQIs. Duplicate QIswere also removed, and 52 potential QIs remained forexpert panel consideration (Fig. 2).

The first rating round excluded three QIs that failed to achieve a consensus of importance (supplementary figure 1). These included “intraoperative use of ultrasound by the surgeon”, “documentation of contralateral breast cancer risk” and “intraoperative pathology assessment of sentinel lymph nodes”. “Use of preoperative magnetic resonance imaging (MRI)” and “appropriate axillary surgery in ductal carcinoma in situ (DCIS)” did not reach consensus in the initial rating round but were rescued after discussion and revote. All 17 experts were present and completed the rating.

The second rating round excluded one indicator on the “use of preoperative MRI” due to a coefficient variation of >25%

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(supplementary figure 2); 13 expert responses were received, of which 12 in the third rating round with a coefficient variation of >25% (“appropriate clinical were complete and used for analysis. One indicator was deemed not feasible assessment of the axilla with sonar and fine needle aspiration”). The third round

had 11 complete responses (supplementary figure 3). There was no dissension in round two and three and no revote was required.

47 QIs had expert consensus following the Delphi process. Three indicators showed similarity including "single operation rate for invasive breast cancer" and "single operation rate for DCIS" compared to "reoperation rate", as well as "pathology assessment of lymph nodes" which was included in "complete histopathological characterisation" and the indicators with higher overall panel ratings were retained. A further 22 parameters were merged into eight grouped QIs which resulted in a final set of 30 QIs. Of these, eight QIs had strong LoEs (level 1 or 2). Two additional indicators with lower LoE (unit and surgeon case volumes and multidisciplinary discussion) were regarded as critical for quality improvement and were incorporated into the mandatory set (Tables 1 and 2). A further eight QIs were regarded as standard of clinical care but had lower LoE (level 3 or 4). These were deemed recommended (Table 3). A further twelve QIs were not regarded as clinical standard of care with lower LoE and should be regarded as optional non-standard QIs (Table 4). 4. Discussion

The first set of quality indicators for the diagnosis and surgical management of breast cancer in South Africa was developed.

Consensus was strong amongst the panel, which affirmed the foundation work and preselection of potential QIs. Nevertheless, such a large number of QIs is not practical for clinical application and a three-tiered set is therefore proposed with mandatory, recommended and optional QIs based on LoE and clinical priority.

4.1. Evidential strength and clinical priority

Table 1 shows the mandatory QIs and their definitions: eight have high LoE (I or II) and two have lower LoE (III or IV) which we regard as clinically essential for quality improvement. Complete histopathological evaluation of tumours is critical for appropriate treatment planning. An incomplete evaluation can lead to repeated biopsies, unnecessary surgery and other treatments, all of which carry potential morbidity and mortality for the patient [22]. The standard evaluation should include the histological type, tumour grading, oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) and Ki-67 proliferation marker on the preoperative biopsy. In addition to these parameters, the surgical specimen requires pathological staging, with the size of the invasive component and nodal assessment, lymphovascular invasion and distance to the nearest margin.

Two trials on breast-conserving surgery (BCS) in conjunction with radiation therapy (RT) were published in the early 80's and demonstrated equivalent survival rates despite increased local recurrence rate (LRR) after BCS and RT [23,24]. 20-year follow-up of these trials confirmed the equivalent survival and paved the way for BCS as the preferred treatment option for early-stage breast cancer [25,26]. Newer data shows lower LRRs and suggests that it has become a rare event with contemporary treatment and is probably rather a reflection of tumour biology than the extent of surgery [27]. Reoperations should generally be kept to a minimum as they increase morbidity and health care expenses. However, they are significantly higher with breast cancer surgery than in other surgical fields. This is due to the increased burden of reoperations for positive margins after BCS and completion axillary lymph node dissection (ALND) after a positive sentinel lymph node biopsy (SLNB), particularly after mastectomy [28e30]. One of the confounding factors for increased reoperations has been the variable definition of a positive margin. An adequate margin for invasive breast cancer has now been defined as "no ink on tumour" for invasive disease [31,32] and 2 mm for non-invasive disease [33] which should reduce reoperation rates in future, especially in specialised centres. The rate of BCS, reoperations, and positive margins are a sound reflection of the quality of surgery and are influenced by multiple factors such as quality of preoperative assessment, tumour localisation, use of neoadjuvant systemic therapy, surgical expertise and oncoplastic skill.

Similarly to the shift towards BCS within the breast, there has also been a major shift towards conservative approaches in the axilla and appropriate use of axillary surgery as well as the number of nodes excised should be measured on a mandatory basis. SLNB allows for accurate assessment of the axilla with lesser morbidity compared to ALND, which is inappropriate in clinically node-negative patients with invasive breast cancer or patients with non-invasive breast cancer [34,35]. Morbidity, especially lymphoedema, is related to the number of nodes excised during axillary surgery and should not exceed five for a SLNB; but should also not be less than ten for an ALND in patients undergoing primary surgery [36,37].

Breast cancer treatment is multidisciplinary and the modern surgeon has to understand oncological principles and neoadjuvant and adjuvant therapies. Radiotherapy (RT) reduces local recurrence risk and improves progression-free survival following BCS. A postoperative referral is standard of care with the exception of select patient subgroups [38]. Equally, inflammatory or other nonoperable locally advanced breast cancer (LABC) should always be treated with neoadjuvant systemic therapy [39]. Mandatory QIs, therefore, include the rate of RT post BCS and rate of neoadjuvant therapy for non-operable LABC.

Although case volumes and MDT discussions do not have high LoE, these two indicators are deemed important to improve the quality of care in South Africa. Critical case volumes for units and surgeons are well described and a breast unit should treat at least 150 newly diagnosed patients per annum. A surgeon should personally operate on no less than 50 cases per annum [40]. Patients treated by specialised surgeons and units are more likely to have BCS, undergo sentinel lymph node biopsy and are more likely to receive appropriate adjuvant therapies resulting in better outcomes in terms of local recurrence and survival. In addition, treatment is more cost-effective and litigation decreases with treatment in specialised centres adhering to benchmarking and quality control [41e49]. This obviously needs to be seen in the context of accessibility which is extremely varied in South Africa. Ideally, further breast units should be established in areas of need with training of subspecialists and support from existing units in a hub and spoke model. Nevertheless, decentralisation with care by general surgeons is critical in very remote areas, to avoid further barriers to care. MDTs lead to improved, evidence-based clinical decision-making, quality of treatment, provide guidance in nonstandard treatment decisions and offer the opportunity to establish a complete treatment plan for each patient [50]. Ideally, the patient should be discussed at diagnosis before initiation of any therapy, postoperatively and at any point of disease progression.

The second group of recommended QIs are listed in table 3 and should be regarded as standard of care in any modern practice. Prior to any breast cancer surgery, there should be pathological confirmation of diagnosis, appropriate clinical examination and breast imaging with bilateral mammography and ultrasound. The routine use of breast imaging reporting and data system (BIRADS) should be applied to imaging reports, all breast specimens should be orientated, surgical clips should always be placed after BCS to aid RT and a tissue marker clip should be placed for patients who are planned for BCS after neoadjuvant systemic therapy. Clinical and pathological staging, locoregional recurrence, progression-free survival and overall survival should all be part of standard followup documentation.

The third group of QIs are optional and listed in table 4. The panel deemed them valuable, but they do not have a high LoE and were not regarded as standard of care.

Five QIs were excluded by the panel. "Intraoperative use of ultrasound by the surgeon", "documentation of contralateral breast cancer risk" and "intraoperative pathology assessment of sentinel lymph nodes" were deemed to have low relevance or clinical priority in our setting. Intraoperative ultrasound,

although widely used in European breast centres, is rarely available in South Africa. The intraoperative evaluation of lymph nodes is often inaccurate and controversial, with the current omission of ALND in patients with micrometastases and selected patients with macrometastases undergoing BCS and RT [51]. "Use of preoperative MRI" and "appropriate clinical assessment of the axilla with sonar and fine needle aspiration" are applied in HICs [9] but were excluded due to concerns over reliability and validity, as well as feasibility in our constrained health care system.

4.2. Implications and implementation

This set of QIs has been endorsed by the Breast Interest Group of Southern Africa (BIGOSA). Although implementation within surgical practices will be voluntary, BIGOSA will circulate the mandatory set with a strong recommendation that they should be applied and regularly audited by any practice performing surgery on breast cancer patients (Table 1). Rapid implementation can be expected by established breast units and high-volume surgical practices, but these are still very scarce in South Africa. Many breast surgeries are performed by general surgeons and the greatest improvement of quality is anticipated after application of the QI set in the nonspecialised setting. The QI set will therefore also be published locally as BIGOSA clinical guidelines and audit results of participating units will be presented at general surgical conferences in order to reach a broader surgical community. However, clinical regulation is historically difficult in South Africa with poorly resourced clinical governance, a divided health care system and a very high degree of autonomy given to the individual practitioner. At present, there is no breast surgical clinical regulation, no directed audit and no accreditation processes for units or MDT meetings. This project therefore should be seen as a collective starting point to initiate and direct quality improvements in breast cancer care. It will be the first attempt to measure current regional quality and offer a gauge for practices with more standardised treatment over time.

The critical ten indicators contain core data and their application appears feasible even in lower resourced settings. Even though the indicators with high evidential strength are likely to have the biggest impact, this remains to be proven in South Africa. Evidencebased medicine has limitations and "high level of evidence studies" with randomisation is often not feasible. Therefore, clinical experience and reasoning may have to be applied; two QIs with lower evidence were incorporated into the mandatory group because of their overwhelming clinical priority. Although the quality indicators were described with the classic division into process, structural or outcome markers, it is important to note that many indicators are not solely dependent on the quality of a surgical practice but interlinked with various patient and system factors. In a complex health care scenario such as the multidisciplinary treatment of breast cancer within a resource-constrained health care system, as in South Africa, shortcomings of other factors such as access to care andscreeningor the availabilityofadjuvanttherapies will invariably have a more substantial impact than in well-resourced health care systems. This will for instance decrease the achievable rate of BCS which should be regarded as an outcome rather than a pure process metric. It is for this reason, that no benchmarks were allocated tothe indicators in this project; benchmarks from HICs are likely unachievable and reasonable benchmarks within a resourceconstrained system will need to be determined through future application of the QIs by established local breast centres.

It is likely that this QI set will evolve over time to further accommodate to our local needs. Regional variations may exist, for instance time delays to treatment do not show strong evidence in HICs but decreased overall and disease-specific survival have been described [52,53]. In the case of much more extensive delays in constrained health care systems, these effects may be amplified.

There are several pitfalls anticipated in the implementation of this QIset.Firstly, the mostobviousis that a set with too many parameters could overwhelm and discourage use. Even though the indicators in the recommended group are standard of care and practice, most should be already routinely applied and measurements are less likely to yield major effects. The mandatory set was therefore condensed to only include essential QIs with the most substantial anticipated impact. Secondly, data may not be immediately available in all practices and will require incremental, prospective data collection. Differences in resources for additional data management are expected between academic and non-academic units, as well as provincial and private practices. Thirdly, any practice change will initially increase workload and evoke resistance with implementation varying according to clinician knowledge and attitude. Nevertheless, successful implementation over time will not only improve quality of care but also streamline processes, close clinical gaps, strengthen health care systems and improve practice workflow.

There are several other ways to improve quality of care besides measuring QIs. Access to rapid, high-quality diagnosis and multidisciplinary high-quality units is needed as well as advocacy, policy change, innovation, as well as strengthening of local research and training of specialists and subspecialists. Health care professionals need to overcome their resistance to change and innovation, whether this is due to adherence to usual routines, or to protect personal interests. The most systematic approach is the establishment and accreditation of specialised breast centres. Although validated in HICs, some of the established EUSOMA or NAPBC criteria may not be feasible in lower resourced settings. These include routine pathology review of biopsies performed outside of the respective breast centre or breast imaging accreditation criteria that do not exist in South Africa. This initial effort for quality improvement will hopefully form the basis of establishing reasonably adjusted local accreditation criteria in future. Overall, there are promising developments for breast cancer care in South Africa: breast cancer policy and guidelines were issued by the National Department of Health, BIGOSA is gaining traction, and applications for the implementation of a breast and endocrine surgery subspecialty are in process.

4.3. Future research

In a future study, the entire QI set will be applied to the surgical breast units participating in the South African Breast Cancer and HIV Outcomes (SABCHO) study [54] to allow for an initial audit, validation and reasonable benchmarking within our resourceconstrained health care system. Furthermore, we will attempt to evaluate if individual QI non-adherence results in worse intermediate patient outcomes. These will include potential locally relevant factors with lower evidence, such as timeliness to care.

4.4. Limitations

This study has several limitations in keeping with the limitations of a Delphi process. In addition, the modification to include a faceto-face meeting facilitated essential discussion but may have compromised the methodology of a pure Delphi process despite keeping all ratings anonymous. Furthermore, results will always be bound by the quality and knowledge base of the panel. Our study is limited to diagnostics and surgical therapy and does not include all aspects of multidisciplinary care. However, a broad panel including various subspecialties represented the interlinked multidisciplinary approach during every step of a contemporary treatment pathway. In addition, the surgical part of the panel was diverse, representing all but one established breast unit within the South African public sector, as well as surgeons frommore remote areas and high-volume surgeons from the private sector. In South Africa, most patients will presentwithsymptomaticdiseaseandwill beseen insurgical clinics and practices first.It is crucialtoimprove the qualityof the first point of contact as well as surgical therapy which remains a critical component in the care of breast cancer.

5. Conclusions

A three-tiered set of QIs was developed based on locally obtained consensus to improve the quality of surgical breast cancer care. Application of the ten critical QIs should be mandatory for all practices treating breast cancer patients. The proposed QIs await implementation but are a pragmatic first step towards improved quality of breast cancer care.

Declaration of competing interest

None.

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Appendix

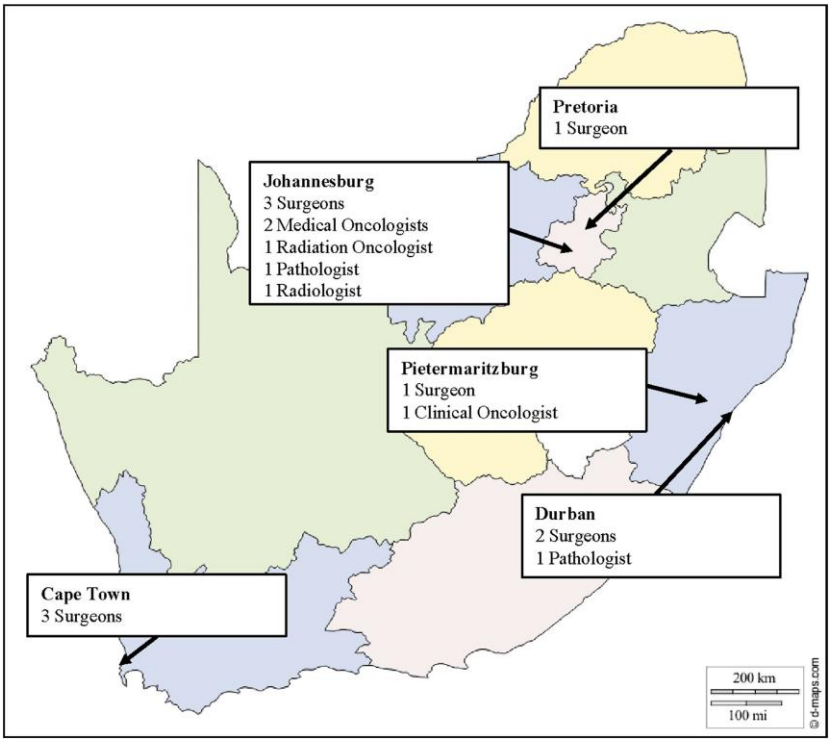


Fig. 1. Expert panel composition.

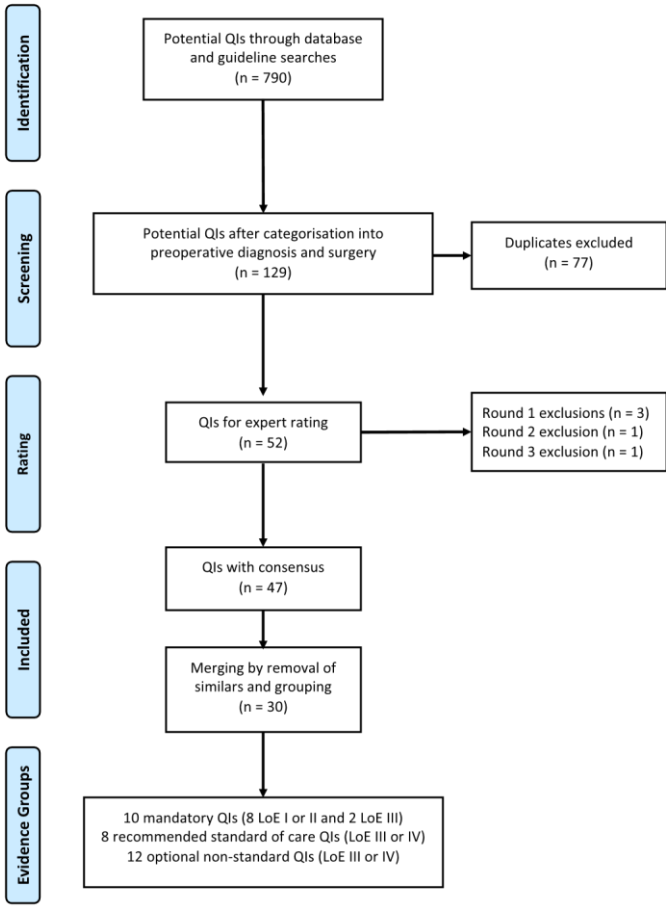


Fig. 2. Consort figure.

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Top ten mandatory quality indicators.

#	Top ten critical quality indicators		Definition	Numerator	Denominator
1	Complete	a) invasive breast cancer	Proportion of cases for which the following	Invasive breast cancer patients	All invasive breast cancer

	histopathological characterisation:	prognostic/predictive parameters have been recorded: Histological type; Grading; ER; PR; HER-2; Proliferation index (Ki67). In addition to the above parameters, the following parameters must be recorded after surgery: Pathological stage; Size in mm for the invasive component; Lymphovascular invasion; Distance to nearest radial margin.	for which all prognostic/ predictive parameters have been recorded.	patients.
	b) non-invasive cancer breast	Proportion of cases for which the following parameters have been recorded: Grading; Dominant histological pattern; Size in mm; Distance to nearest radial margin; ER.	Non-invasive breast cancer patients for which all prognostic/ predictive parameters have been recorded.	All non-invasive breast cancer patients.
2	Breast conserving surgery (BCS) rate	Proportion of patients undergoing BCS among all patients who receive surgery for the primary breast cancer.	Patients with breast cancer who undergo BCS.	All patients with breast cancer who undergo surgery for the breast primary.
3	Rate of positive margins after breast BCS	Proportion of patients with positive margins after BCS among all patients who underwent BCS.	Patients with positive margins after BCS.	All patients who undergo BCS.
4	Reoperation rate	Proportion of patients with breast cancer who required a reoperation for the breast primary within six months of initial surgery.	Patients who required a reoperation for the primary tumour.	All patients who underwent surgery for the primary tumour.
5	Appropriate axillary surgery:	a) rate of surgery in invasive breast cancer	Proportion of invasive breast cancer patients who underwent axillary surgery.	Patients with invasive breast cancer who underwent axillary surgery.	All patients with invasive breast cancer.
		b) sentinel node biopsy in clinically node-negative disease	Proportion of patients with invasive cancer and clinically negative axilla who underwent SLNB only (excluding patients who received primary systemic therapy).	Patients with invasive cancer and clinically negative axilla who underwent sentinel lymph node biopsy only.	All patients with invasive (SLNB) only in whocancer and clinically negative axilla who underwent axillary surgery
		c) no axillary lymph node dissection (ALND) in DCIS.	Proportion of patients with DCIS only undergo ALND.	Patients with DCIS only who undergo axillary lymph node dissection.	All patients with ductal carcinoma in-situ (DCIS) only
6	Number of nodes axillary surgery:	a) ALND !10 nodes	Proportion of breast cancer patients undergoing ALND who have at least 10 nodes examined (excluding patients who received primary systemic therapy).	Patients undergoing ALND with at least 10 nodes examined.	All patients who underwent excised during ALND.
		b) SLNB "5 nodes	Proportion of patients with invasive cancer who SLNB with no more than 5 nodes excised.	Patients with invasive cancer who underwent SLNB with no more than 5 nodes SLNB.	All patients with invasive cancer who underwent excised.
7	Receipt of radiotherapy after BCS	Proportion of invasive breast cancer patients who radiotherapy after BCS.	Patients who received radiotherapy after BCS.	All patients BCS for invasive breast cancer.	received
8	Appropriate treatment sequencing in inoperable (LABC)	Proportion of patients with inflammatory or non-operable LABC who undergo primary systemic treatment before surgery.	Patients with inflammatory or non-operable LABC who undergo surgical treatment for primary systemic treatment operable LABC.	All patients undergoing locally advanced breast cancer inflammatory or nonbefore surgery.	
9	Case Volume:	a) breast unit !150 diagnosed cases per annum.	newly Each unit needs to see a set minimum number of 150 patients with newly diagnosed breast cancer per annum	N/A.	N/A.
		b) surgeon volume !50 surgeries on patients with newly diagnosed breast cancer per annum.	Each surgeon needs to perform a set minimum number of In units which train surgeons this would include supervised (scrubbed in) surgeries.	N/A.	N/A. breast cancer cases per
10	Multidisciplinary team discussion	Proportion of patients with breast cancer who are discussed in the MDT meeting (ideally pre- and	Patients with breast cancer who are	All patients with breast cancer. postoperatively).	discussed in a MDT meeting.

Table 2

Mandatory quality indicators with evidence levels and results from the Delphi rounds, SD ¼ standard deviation, CV ¼ coefficient variation.

#	Quality Indicator Title	Level of Evidence	Round 1: Mean Score(SD); CV	Round 2: Mean Score(SD); CV	Round 3: Mean Score(SD); CV	Mean Sum Score (SD)
1	Complete histopathological a) invasive breast cancer characterisation:	2.0	5.0 (0.0); 0.00	5.0 (0.0); 0.00	5.0 (0.0); 0.00	15.0 (0.0)
	b) non-invasive breast cancer	2.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.5)
2	Breast conserving surgery (BCS) rate	1.0	4.0 (1.0); 0.25	5.0 (0.5); 0.10	4.5 (0.5); 0.11	13.5 (2.0)
3	Rate of positive margins after breast conserving surgery (BCS)	2.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
4	Reoperation rate	2.0	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (1.0); 0.22	14.0 (2.5)
5	Appropriate axillary surgery: a) rate of axillary surgery in invasive breast cancer	1.0	5.0 (1.0); 0.20	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (2.0)
	b) sentinel node biopsy only in clinically node-negative disease	1.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.5)
	c) no ALND in patients with DCIS only	2.0	4.0 (1.5); 0.38	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.0 (2.5)
6	Number of nodes excised during a) lymph node dissection "10 nodes	2.0	5.0 (1.0); 0.20	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (2.0)
	axillary surgery: b) sentinel node biopsy #5 nodes	1.0 7	Receipt of radiotherapy	4.0 (1.0); 0.25	5.0 (0.5); 0.10	4.5 (0.5); 0.11	13.5 (2.0)
	after breast conserving surgery	1.0		5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
8	Appropriate treatment sequencing in inoperable LABC	2.0		5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
9	Case Volume: a) breast unit "150 newly diagnosed	3.0	cases per annum	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
	b) surgeon volume "50 breast cancer	3.0	cases per annum	4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (2.0)
10	Multidisciplinary team discussion	3.0		5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.0 (1.0); 0.25	14.0 (2.0)

Table 3
Recommended standard of care quality indicators with evidence levels and results from the Delphi rounds.

#	Quality Indicator Title	Level of Evidence	Round 1: Mean Score(SD); CV	Round 2: Mean Score(SD); CV	Round 3: Mean Score(SD); CV	Mean Sum Score (SD)
1	Definitive diagnosis prior to treatment	3.0	5.0 (0.0); 0.00	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.0)
2	Appropriate clinical assessment and breast imaging	3.0	5.0 (0.0); 0.00	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.0)
3	Use of BIRADS classification in imaging reports	3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (1.5)
4	Specimen orientation	4.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
5	Use of marker clips to aid radiation	3.0	5.0 (0.5); 0.10	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.5 (1.5)
6	Use of imaging marker clip in patients for BCS undergoing primary systemic therapy	3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.0 (1.0); 0.25	13.5 (2.0)
7	Documentation of a) preoperative (clinical)	4.0	staging: b) postoperative (pathologic) breast	4.5 (0.5); 0.11	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.5 (1.5)
		4.0	cancer staging	5.0 (0.5); 0.10	5.0 (0.5); 0.10	5.0 (0.5); 0.10	15.0 (1.5)
8	Documentation of a) locoregional recurrence rate	N/A	outcomes: b) progression-free survival	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
		N/A		4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.0 (1.0); 0.25	13.5 (2.5)
	c) overall survival	N/A		4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (1.0); 0.22	13.5 (2.5)

SD ¼ standard deviation, CV ¼ coefficient variation.

Table 4
Optional non-standard of care quality indicators with evidence levels and results from the Delphi r

#	Quality Indicator Title	Level of Evidence	Round 1: Mean Score(SD); CV	Round 2: Mean Score(SD); CV	Round 3: Mean Score(SD); CV	Mean Sum Score (SD)
1	Timeliness of care: a) first diagnostic examination to initial 4.0 treatment		5.0 (1.0); 0.20	5.0 (0.5); 0.10	4.5 (1.0); 0.22	14.5 (2.5)
	b) needle biopsy to pathology report	4.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.5 (1.5)
	c) needle biopsy pathology report to 4.0 treatment		4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
	d) surgery to pathology report	4.0	4.0 (1.0); 0.25	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.0 (2.0)
	e) surgery to adjuvant chemotherapy	3.0	5.0 (0.5); 0.10	4.5 (1.0); 0.22	5.0 (0.5); 0.10	14.5 (2.0)
	f) last surgery or chemotherapy to adjuvant radiation	3.0	4.5 (0.5); 0.11	5.0 (0.5); 0.10	5.0 (0.5); 0.10	14.5 (1.5)
2	Postoperative a) Readmission rate	3.0	complications: b) Surgical site infection rate	4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (1.0); 0.22	14.0 (2.5)
		3.0		4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (2.0)
3	Documentation of eligibility for BCS	4.0		4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (1.5)
4	Oncoplastic procedure rate	4.0		4.5 (0.5); 0.11	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (1.5)
5	Discussion of surgical options	4.0		4.5 (0.5); 0.11	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (1.5)
6	Failure of identification of the sentinel node	3.0		4.5 (0.5); 0.11	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (1.5)
7	Node positivity rate in SLNB	4.0		4.5 (1.0); 0.22	5.0 (0.5); 0.10	4.5 (0.5); 0.11	14.0 (2.0)
8	Tracer use in sentinel lymph node biopsy	4.0		4.0 (1.0); 0.25	4.0 (1.0); 0.25	4.5 (1.0); 0.22	12.5 (3.0)
9	Concurrent SLNB with breast surgery	4.0		4.0 (1.0); 0.25	5.0 (0.5); 0.10	4.5 (0.5); 0.11	13.5 (2.0)
10	Efficient diagnosis (number of visits required to initiation of	4.0	treatment)	4.0 (1.0); 0.25	4.5 (0.5); 0.11	4.5 (1.0); 0.22	13.0 (2.5)
11	Lymphoedema rate	4.0		4.5 (1.0); 0.22	4.5 (0.5); 0.11	4.5 (0.5); 0.11	13.5 (2.0)
12	Quality audit rate	4.0		4.0 (1.0); 0.25	4.5 (0.5); 0.11	4.5 (1.0); 0.22	13.0 (2.5)

SD ¼ standard deviation, CV ¼ coefficient variation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.09.012.

Ethical approval

This study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (No. M180671).

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Table 1
Top ten mandatory quality indicators.

#	Top ten critical quality indicators	Definition	Numerator	Denominator
1	Complete histopathological characterisation:	a) invasive breast cancer	Proportion of cases for which the following prognostic/predictive parameters have been recorded: Histological type; Grading; ER; PR; HER2; Proliferation index (Ki67). In addition to the above parameters, the following parameters must be recorded after surgery: Pathological stage; Size in mm for the invasive component; Lymphovascular invasion; Distance to nearest radial margin.	Invasive breast cancer patients	All invasive breast cancer patients for which all prognostic/ predictive parameters have been recorded.
		b) non-invasive cancer breast	Proportion of cases for which the following prognostic/predictive parameters have been recorded: Grading; Dominant histological pattern; Size in mm; Distance to nearest radial margin; ER.	Non-invasive breast cancer patients	All non-invasive breast cancer for which all prognostic/
2	Breast conserving surgery (BCS) rate		Proportion of patients undergoing BCS among all patients who receive surgery for the primary breast cancer.		
3	Rate of positive margins after breast BCS		Proportion of patients with positive margins after BCS among all patients who underwent BCS.		
4	Reoperation rate		Proportion of patients with breast cancer who required a reoperation for the breast primary within six months of the initial surgery.		
5	Appropriate rate of surgery in invasive breast cancer:	a) Proportion of invasive breast cancer patients who axillary surgery: underwent axillary surgery.			
		b) sentinel node biopsy only in clinically negative disease	Proportion of patients with invasive cancer and clinically negative axilla who underwent SLNB only (excluding patients who received primary systemic therapy).		
		c) no axillary lymph node dissection (ALND) in patients with ductal carcinoma in-situ (DCIS) only	Proportion of patients with DCIS only undergo ALND.		
6	Number of nodes axillary surgery:	a) ALND !10 nodes	Proportion of breast cancer patients undergoing excised during ALND who have at least 10 nodes examined (excluding patients who received primary systemic therapy).		
		b) SLNB "5 nodes	Proportion of patients with invasive cancer who underwent SLNB with no more than 5 nodes excised.		
7	Receipt of radiotherapy after BCS		Proportion of invasive breast cancer patients who received radiotherapy after BCS.		
8	Appropriate treatment sequencing in inoperable cancer (LABC)	Proportion of patients with inflammatory or nonlocally advanced breast operable LABC who undergo primary systemic treatment before surgery.			
9	Case Volume:	a) breast unit !150 newly diagnosed cases per annum.	Each unit needs to see a set minimum number of 150 patients with newly diagnosed breast cancer per annum		
		b) surgeon volume !50 per annum	Each surgeon needs to perform a set minimum breast cancer cases number of surgeries on patients with newly diagnosed breast cancer per annum. In units which train surgeons this would include supervised (scrubbed in) surgeries.		
10	Multidisciplinary team discussion		Proportion of patients with breast cancer who are discussed in a MDT meeting (ideally pre- and postoperatively).		

predictive parameters have been recorded.

Patients with breast cancer who undergo BCS.	All patients with breast cancer who undergo surgery for the breast primary.	Patients with invasive cancer and clinically negative axilla who underwent sentinel lymph node biopsy only. Patients with DCIS only who undergo axillary lymph node dissection.	Patients with breast cancer who are discussed in the MDT meeting.
Patients with positive margins after BCS.	All patients who undergo BCS.		All patients with invasive cancer and clinically negative axilla who underwent axillary surgery All patients with DCIS.
Patients who required a reoperation for the primary tumour within six months of initial surgery.	All patients who underwent surgery for the primary tumour.		
Patients with invasive breast cancer who underwent axillary surgery.	All patients with invasive breast cancer.		All patients who underwent ALND.
ALND with at least 10 nodes examined.		Patients undergoing	All patients with invasive cancer who underwent SLNB. All patients BCS for invasive breast cancer. All patients undergoing surgical treatment for inflammatory or nonoperable LABC. N/A.
Patients with invasive cancer who underwent SLNB with no more than 5 nodes excised. Patients who received radiotherapy after BCS. Patients with inflammatory or non-operable LABC who undergo primary systemic treatment before surgery. N/A.			N/A.
N/A.			All patients with breast cancer.

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SAMJ RESEARCH

An initial benchmark of the quality of the diagnosis and surgical treatment of breast cancer in South Africa

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Background. Monitoring quality indicators to improve breast cancer care is well established in high-income countries. This is the first evaluation of diagnostic and surgical quality indicators for initial benchmarking of breast cancer care in South Africa (SA).
Objective. To measure the adherence rates to quality indicators among women with breast cancer in SA.
Methods. Ten quality indicators were evaluated for 3 545 breast cancer patients across four SA surgical breast units using a shared electronic patient record system. Data quality and adherence rates with differences between units were determined. The effect of HIV status on adherence was assessed by multivariate Poisson regression analyses.
Results. Our electronic patient record reliably measured most quality indicators. Rates of positive margins (5.7%), overall axillary surgery (95.8%) and appropriate treatment sequencing in locally advanced breast cancer patients (98.4%) consistently reached minimum international standards. Rates of multidisciplinary team discussion (72.2%), radiotherapy (66.7%) and sentinel node biopsy (39.6%) showed wide cross-site variance. Histopathology reporting (62.0%), breast-conserving surgery (19.4%) and number of nodes excised with axillary dissection (47.3%) and sentinel node biopsy (82.7%) were consistently below minimum standards. Unit volumes were achieved consistently in Gauteng Province, but only for some years in KwaZulu-Natal Province; surgeon volumes were achieved across all units. HIV status did not affect adherence levels. Most quality indicators were well measurable, but data quality on reoperations and surgeon volumes was poor. **Conclusion**. We evaluated local quality indicators for an initial benchmark, and the most emergent gaps in care are the receipt of radiotherapy and underutilisation of sentinel node biopsy.

Keywords: breast cancer, quality indicators, low- to middle-income countries, electronic patient records

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Quality indicators (QIs) for breast cancer treatment have been measured in high-income countries (HICs), and used to monitor and improve the quality of patient care over time.[1,2] Data on the quality of breast cancer care in low- to middle-income countries (LMICs) are scarce, but suggest lower and variable quality of care depending on the patient's socioeconomic background and geographical location, along with the associated availability of treatment services.[3,4]

Breast cancer is a complex and heterogeneous disease, and is best treated in multidisciplinary teams (MDTs) with specialist expertise and resources from each treatment modality to achieve the best patient outcomes. Quality of care is defined as the degree to which health services increase the likelihood of desired health outcomes and are consistent with current professional knowledge. QIs have classically been divided into the Donabedian model of structural, process and outcome measures.[5] Structural indicators examine the ability of the healthcare system to provide a service, such as the provision of resources, staffing, or expertise, and have been used extensively in accreditation processes. Process indicators permit the evaluation of adherence rates to recommended healthcare processes and are the most commonly used indicators to measure quality of care. Outcome measures such as disease-free survival and quality of life are often regarded as the gold standard in cancer care, but these are difficult to measure because of long follow-up requirements and the potential influence of various patient and clinical factors.[6]

In 2019, a critical set of 10 QIs for the diagnosis and surgical treatment of breast cancer was established in South Africa (SA) through expert consensus.[7] The present study now evaluates the data quality of these QIs within the existing electronic patient record (EPR) data, and adherence to them in patient cohorts. This is the first investigation of diagnostic and surgical breast cancer QIs in subSaharan Africa.

Methods

The SA Breast Cancer and HIV Outcomes (SABCHO) study has prospectively collected information on access to healthcare, as well as numerous components of patient and disease factors to develop evidence-based guidelines on the management of breast cancer in HIV-positive and negative women, as well as to improve breast cancer treatment in a resource-constrained environment.[8] An EPR system was implemented in 2015 at all study sites to collect prospective clinical data. We retrospectively reviewed all patients enrolled in the SABCHO study between 1 July 2015 and 31 August 2020.[8] To mitigate any potential impact on the quality metrics, we chose the time of the first COVID-19 wave in SA as a cut-off. The sites included Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Grey's Hospital (GH) and Durban complex (Inkosi Albert Luthuli Central Hospital, Addington Hospital and Ngwelezana Hospital (IALCH)). CHBAH and CMJAH are in

Johannesburg, Gauteng Province, while Durban complex and GH are in KwaZulu-Natal (KZN) Province. All are public sector academic surgical breast units, but they serve different populations and have different staff resources (Table 1).

Data entry was made prospectively on OncoDB, an EPR initiated in 2008 at CHBAH that has since grown into a purposefully designed comprehensive breast database. Both clinicians and SABCHO research staff entered data, although some fields are only used by clinicians and others only by research staff. The extent of OncoDB use differed across sites (Table 1).

The selection process, definitions as well as the nominators and denominators of the 10 QIs were previously described.[7] For QI 1, histopathology reports were considered complete if they included the following parameters for core biopsy: histological type; tumour grade; oestrogen receptor (ER) status; progesterone receptor (PR) status; human epidermal growth factor receptor-2 (HER-2) with a confirmatory *in situ* hybridisation test if HER-2 was equivocal; and proliferative Ki67 score. In addition to the above parameters, the following were required for QI 2 on surgical specimens: pathological stage; size in millimetres for the invasive component; peritumoural lymphovascular invasion; and distance to the nearest invasive margin. Receptors did not require repeating as they are routinely done on core biopsy. We defined a Ki67 cut-off of 20% to define immunohistochemical surrogates for molecular subtypes.[9] A reoperation (QI 4) was defined as a second surgery on the same side within 6 months. For QI 6 we only included patients who had primary surgery, as neoadjuvant therapy affects the number of nodes excised. For QI 8, inoperable locally advanced breast cancer (LABC) was defined as T4a, c or d or N3, and neoadjuvant systemic therapy had to precede surgery to fulfil appropriate modality sequencing.

The reliability and validity of EPR measures are evaluated by data completeness, data accuracy, timeliness or 'currency,' clinical specificity or 'granularity,' and data comparability.[10] We graded our data quality based on *a*) data entry personnel, which was either the clinician or research staff driven, with better data completeness, accuracy, currency and comparability when entered by research staff; *b*) a structured data cleaning process by research staff; and *c*) the use of structured v. unstructured data with improved completeness, accuracy, currency and granularity with structured data. We then classified reliability and validity as good (3 points), varied (1 - 2 points), or poor (0 points) to reflect the integrity of our results.

We described the frequency and percentages of adherence to the 10 mandatory QIs among the different sites. Site differences were evaluated with a χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables, and the effect of HIV status on adherence levels was evaluated with multivariate Poisson regressions, adjusting for age, hospital site, stage of disease and intrinsic subtype of breast cancer. All participants provided written informed consent for data collection and analysis. The SABCHO study and this project are overseen by the Human Research Ethics Committees of the University of the Witwatersrand (Johannesburg) and the University of KwaZulu-Natal (Durban), and separate ethical clearance was obtained for this substudy (ref. no. M180761).

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Results

A total of 3 545 patients with invasive breast cancer were included. The mean age was 55.7 years, 34.4% of patients were in early stages (stage 1 - 2), 47.8% were locally advanced (stage 3) and 17.8% were metastatic (stage 4) at presentation. Of the 3 545 patients, 2 271 underwent surgery during their treatment process (64.1%). A total of 21.9% were HIV positive, with higher rates in CHBAH and GH. Table 2 displays the detailed distribution based on immunohistochemical surrogates and patient characteristics, as well as the significant differences across sites.

Table 3 tabulates data source and entry, structure, reliability and validity. Most QI data were well measurable, with good validity and reliability. Operative notes to evaluate reoperations were inconsistent across sites, only entered by clinicians, and contained unstructured data, with poor reliability and validity for reoperation and surgeon volume QIs. Clinicians across sites inconsistently entered reoperations measured by pathology reports and MDT discussions, and reliability and validity were varied despite the use of structured fields. Table 4 tabulates the results of QI adherence, and Fig. 1 illustrates the highest and lowest adherence levels and their relation to international minimum standards.

Complete histopathological characterisation was achieved in 62.0% of initial core biopsy specimens, and 65.6% of surgical specimens. Adherence varied across sites from 91.9% to 5.7% and 82.1% to 22.0%, respectively (p>0.001). Breast-conserving surgery (BCS) rate overall was 19.4%, and 31.6% for patients with earlystage breast cancer; rates were highest in Durban and lowest at GH (p>0.001). The positive margin rate was 5.7%, with no significant cross-site variance. The reoperation rate was 2.9% on evaluating pathology reports, and 8.0% on evaluating operation notes. Surgical operation notes were only entered by the Gauteng sites, and therefore not measurable across sites; reliability and validity were poor. Of patients who underwent surgery, 95.8% had axillary surgery, with little cross-site variation. Sentinel lymph node biopsy (SLNB) only in clinically node-negative patients was recorded in 39.6%, with a wide site variation between 71.9% and 1.9% (p>0.001). HIV-positive patients were less likely to have a SLNB (p=0.008, odds ratio (OR) 0.58 (0.38 - 0.86)).

The percentage of patients with axillary lymph node dissection (ALND) with ≥10 nodes was 47.3%, while 82.0% of patients with SLNB had ≤5 nodes dissected. GH achieved the highest rate (72.6%), while IALCH recorded none (0%). However, only four patients had primary surgery and ALND in this unit, as they mainly treated node-positive patients with neoadjuvant therapy. Radiotherapy receipt after BCS was documented in 66.7%, with site variance of 92.7% - 44.7% (p>0.001). HIV-positive patients were less likely to receive adjuvant radiotherapy (p=0.010, OR 0.52 (0.31 - 0.85)). Neoadjuvant therapy was given to 98.4% of 440 inoperable locally advanced cancer patients prior to surgery. MDT discussion was documented in 72.2%, with site variance between 92.2% and 14.3%. Data reliability and validity were varied.

Discussion

The levels of QI adherence varied across sites, and were mostly inferior to minimum standards in HICs (Table 4 and Fig. 1). Nevertheless, they represent an inital benchmark in our resourceconstrained setting, and a starting point from which to identify gaps and improve quality of care over time. **QIs fulfilling international standards across sites** The rate of positive margins, overall axillary surgery and appropriate treatment sequencing for LABC consistently achieved international minimum standards across sites. Margins in breast cancer

Table 2. Clinical characteristics of cohort, *N*=3 545

Characteristic	Overall, *n* (%)*	CHBAH, *n* (%)*	CMJAH, *n* (%)*	GH, *n* (%)*	Durban complex, *n* (%)*	*p*-value
Enrolled patients	3 545 (100)	1 455 (41.0)	931 (26.3)	530 (15.0)	629 (17.7)	
Age, mean (SD), years	55.7 (14.2)	55.1 (14.5)	54.5 (13.5)	57.6 (14.4)	57.2 (14.1)	<0.001
Stage 1 - 2	1 221 (34.4)	546 (37.5)	309 (33.2)	176 (33.2)	190 (30.2)	<0.001
Stage 3	1 693 (47.8)	724 (49.8)	484 (52.0)	212 (40.0)	273 (43.4)	
Stage 4	631 (17.8)	185 (12.7)	138 (14.8)	142 (26.8)	166 (26.4)	
Received surgery	2 271 (64.1)	984 (67.6)	547 (58.8)	362 (68.3)	378 (60.1)	<0.001
Luminal A†	829 (23.4)	228 (15.7)	240 (25.8)	130 (24.5)	231 (36.7)	<0.001
Luminal B†	1838 (51.8)	885 (60.8)	456 (49.0)	255 (48.1)	242 (38.5)	
HER-2 negative	1 241 (35.0)	580 (39.9)	315 (33.8)	194 (36.6)	152 (24.2)	
HER-2 positive	597 (16.8)	305 (21.0)	141 (15.1)	61 (11.5)	90 (14.3)	
HER-2 enriched†	235 (6.6)	83 (5.7)	73 (7.8)	32 (6.0)	47 (7.5)	
Triple-negative†	548 (15.5)	216 (14.8)	148 (15.9)	95 (17.9)	89 (14.1)	
Unspecified	95 (2.7)	43 (3.0)	14 (1.5)	18 (3.4)	20 (3.2)	
HIV positive	775 (21.9)	359 (24.7)	163 (17.5)	137 (25.8)	116 (18.4)	<0.001
HIV negative	2 713 (76.5)	1 071 (73.6)	741 (79.6)	393 (74.2)	508 (80.8)	
HIV unknown	57 (1.6)	25 (1.7)	27 (2.9)	5 (0.8)	0 (0.0)	

CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital; GH = Grey's Hospital; Durban complex = Inkosi Albert Luthuli Central Hospital, Addington Hospital and Ngwelezana Hospital; SD = standard deviation. *Unless otherwise indicated.
†Luminal A was defined as oestrogen receptor (ER)/progesterone (PR) positive, ki67 ≤20%. Luminal B as ER and/or PR positive, Ki67 ≥20%, human epidermal growth factor receptor-2 (HER-2) negative or positive. HER-2 enriched as ER/PR negative, HER-2 positive. Triple-negative as ER/PR/HER-2 negative.

Table 1. Study site characteristics

Site		Surgical staff, *n*	Research staff, *n*			Residential demographics OncoDB use
CHBAH	Soweto (3 million), urban	3	10	Main record-keeping tool; clinical management and research		
CMJAH	Johannesburg East and Central (1.5 million), urban	2	5	Main record-keeping tool; clinical management and research		
GH	Western KwaZulu-Natal (3.5 million),	1	2	Only used for study purpose; not all functions used urban/rural mix		
Durban complex	Durban Metropolitan (3.5 million), Umkhanyakude, Zululand (3 million), rural	1	3	Only used for study purpose; not all functions used urban; Uthungulu,		

CHBAH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital; GH = Grey's Hospital; Durban complex = Inkosi Albert Luthuli Central Hospital, Addington hospital and Ngwelezana Hospital.

excisions have been subject to many debates, but the most recent recommendation is 'no tumour on ink'.[13] Historically, re-excision rates have been reported as 25% - 40%,[14] and our positive margin rate is comparatively low at 5.7%. This is likely due to the early adoption of the new margin definition and liberal use of advanced oncoplastic techniques in our units, which allows for greater volume resections and lower re-excision rates.[15] The axilla was evaluated surgically in 95.8% of cases. Non-resectable LABC was appropriately treated with neoadjuvant therapy before surgery in 98.4% of cases, reflecting safe patient evaluation and treatment. **QIs with site variance to international standards** It is alarming that only 66.7% of patients received radiotherapy after BCS, with Gauteng sites significantly less likely to deliver than KZN sites. Patients at CHBAH had the lowest adherence level, at 44.7%. One of the possible barriers may have been the need to travel to CMJAH, as radiotherapy is unavailable onsite. However, CMJAH patients, who shared an exact breast clinic location with radiation oncology within the hospital, only received radiation in 65.1% of cases. This starkly contrasts with KZN, where both units achieved the minimum target of 90%. These results point

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to a specific barrier to radiation care in Gauteng that needs to be addressed urgently.

Critical case volumes for units and surgeons are well described. A breast unit should treat at least 150 newly diagnosed patients annually, while a surgeon should operate on at least 50 cases annually.[17] Surgeon volumes were consistently achieved across sites, but unit volumes were achieved only in Gauteng sites for all years of the full assessment, whereas KZN sites fell short in some years. It is important to note that actual unit volumes were larger than recorded, as foreign patients were not included in SABCHO.

The MDT discussion is a critical process to ensure the review of each patient and to form a complete treatment pathway; it results in better evidence-based clinical decision-making and higher quality of treatment.[17] This QI was a clinician-driven data entry, and was not reliably entered across sites. Adherence level was 72.2% overall, but IALCH was the only unit to consistently document MDT discussion and achieve the >90% standard. GH did not routinely enter the discussions on the EPR (14.3%), but routine MDT meetings were held, which points to differences between documentation and received treatment. Adherence levels are generally higher than measured, a described pitfall in using EPRs to assess quality.[18]

Table 3. Quality indicator data quality

QI number	QI title	Raw data source	Data entry	Data field structure	Cleaned	Reliability and validity
1	Complete histopathological characterisation of invasive breast cancer					
	1i. On core biopsy	Pathology Good report	Research staff	Structured	Yes	
	1ii. On surgical specimen	Pathology Good report	Research staff	Structured	Yes	
2	BCS					
	BCS rate	Pathology Good report	Research staff	Structured	Yes	
	BCS rate among stages 1 and 2	Pathology report	Research staff	Structured	Yes	Good
3	Rate of positive margins	Pathology	Research staff	Structured	Yes	Good after BCS
4	Reoperation rate					
	4i. On pathology reports	Pathology Varied report	No routine entry	Structured	No	
	4ii. On operation notes	Operation Poor note function	Clinicians	Unstructured	No	
5	Appropriate axillary surgery					
	5i. Rate of axillary surgery report	Pathology	Research staff	Structured	Yes	Good in invasive breast cancer
	5ii. Sentinel node biopsy Good only in clinically node-	Pathology report negative disease	Research staff	Structured	Yes	
6	Number of nodes excised during axillary surgery					
	6i. Lymph node dissection ≥10 nodes	Pathology report	Research staff	Structured	Yes	Good
	6ii. Sentinel node biopsy ≤5 nodes	Pathology report	Research staff	Structured	Yes	Good
7	Receipt of radiotherapy	Treatment	Research staff	Structured	Yes	Good after BCS functions
8	Appropriate treatment workup	Initial	Research staff	Structured	Yes	Good sequencing in diagnostic function and treatment functions	inoperable LABC
9	Case volume					
	9i. Breast unit ≥150 newly Good diagnosed cases per	New patient entry annum	Research staff	Structured	Yes	
	9ii. Surgeon volume ≥50 annum	Operation or single surgeon units	Clinicians	Unstructured	No	Poor breast cancer cases per note function
10	Multidisciplinary team	Follow-up	Clinicians	Structured	No	Varied discussion function

QI = quality indicator; BCS = breast-conserving surgery; LABC = locally advanced breast cancer.

Improving the documentation of MDT discussions is important, particularly in our healthcare system where patients may need to visit various hospitals to receive different treatments, and encounter different healthcare providers during each visit.

QIs below international standards

The completeness of histopathology was overall low, but Gauteng sites were significantly more compliant in assessing core biopsy and surgical specimens. Our recent publication[19] describes these findings

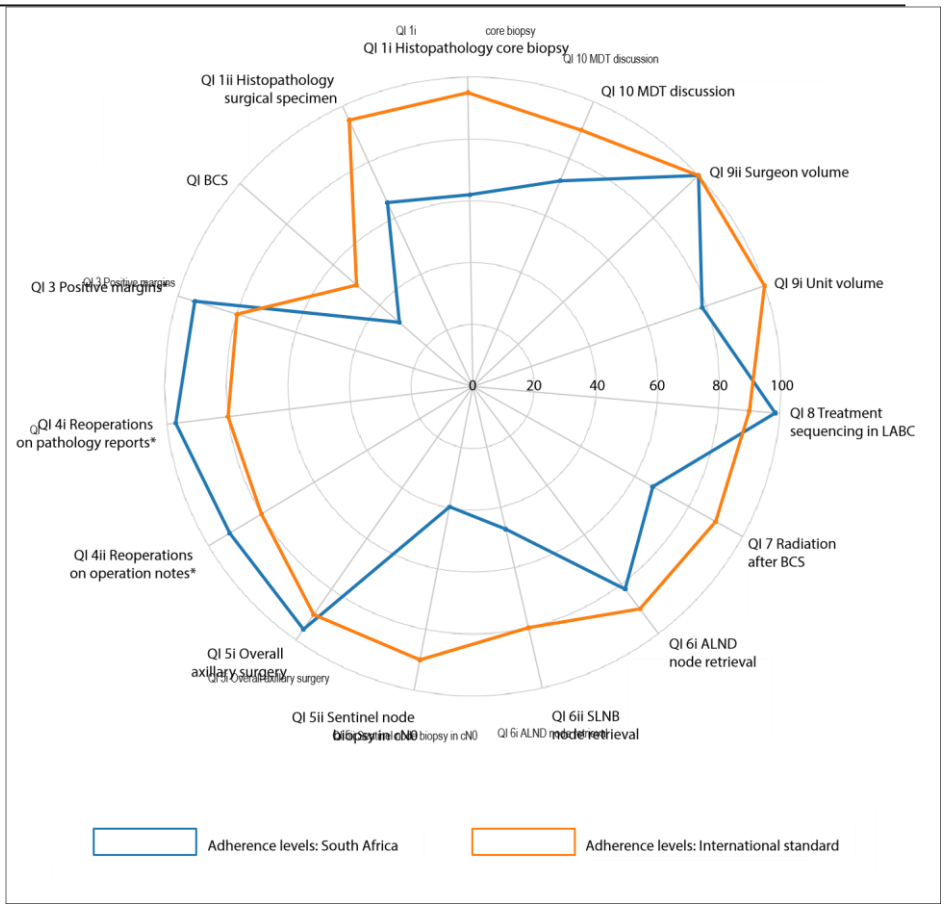


Fig. 1. Radar chart comparing South African adherence levels to international standards. (QI = quality indicator; MDT = multidisciplinary team; LABC = locally advanced breast cancer; BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; cN0 = clinically node-negative.)

**QI 3, 4i, 4ii are transformed and plotted as 100% (adherence levels) for presentation consistency.*

in more detail, and emphasises the need to improve reporting of tumour grade, HER-2 confirmatory tests, excision margins, pathological staging and lymphovascular invasion. Reporting standards differ among laboratories, and it is overdue to establish an SA pathology consensus and introduce the routine use of data sheets and synoptic reports to enhance completeness and clear communication of the results with the clinician.[19]

BCS rates were 19.4% overall, and 31.6% for patients with earlystage breast cancer; none of the sites was close to international standards of >50%.[12] BCS requires greater resources and expertise, especially with impalpable tumours, after neoadjuvant therapy and with advanced oncoplastic techniques. In addition, BCS requires postoperative radiotherapy, a factor that may have influenced the rates in Gauteng. At GH, some patients were not offered the option of BCS owing to limited radiotherapy availability, where treatment

would fall outside of the recommended treatment time period. This strengthens our opinion that BCS should be seen as an outcome and not a pure process measure in our setting, as it is impacted heavily by factors external to the surgical units.[7]

Only 39.6% of clinically node-negative patients received an SLNB only, with significant variance noted among sites. GH had the lowest rate at 1.9%, as they did not have resources to trace sentinel nodes. We have previously reported on the low use of SLNB in our Gauteng units, and the potential reasons for this such as large tumour size, the intraoperative impression of nodal involvement with conversion to ALND, or non-availability of critical consumables or equipment.[20] We also hypothesised that HIV status may influence nodal assessment and surgery, but this was not proven in this cohort (risk ratio 0.91). Given the ever-expanding applications for SLNB, suspicious lymph nodes should ideally be confirmed with fine needle aspiration, and

Table 4. Quality indicator adherence

QI number	QI title		International minimum standard (%)	Overall documented adherence, *n* (%)	CHBAH, *n* (%)	CMJAH, *n* (%)	GH, *n* (%)	Durban, *n* (%)	*p*-value*	HIV effect on overall adherence, *p*-value
1	Complete histopathological characterisation of invasive breast cancer									
		1i. On core biopsy	>95[1]]	2 199/3 545 (62.0)	1 240/1 455 (85.2)	856/931 (91.9)	30/530 (5.7)	73/629 (11.6)	<0.001	0.832
		1ii. On surgical specimen	>95[1]	1 490/2 271 (65.6)	808/984 (82.1)	353/547 (64.5)	246/362 (68.0)	83/378 (22.0)	<0.001	0.741
2	BCS									
		Breast-conserving surgery rate	-	441/2 271 (19.4)	161/984 (16.4)	126/547 (23.0)	41/362 (11.3)	113/378 (29.9)	<0.001	0.051
		Breast-conserving surgery rate among stages 1 and 2	>50[11]	332/1 051 (31.6)	121/465 (26.0)	92/257 (35.8)	31/164 (18.9)	88/165 (53.3)	<0.001	0.071
3	Rate of positive margins after breast-conserving surgery		<20[12]	26/456 (5.7)	13/169 (7.7)	10/128 (7.8)	1/42 (2.4)	2/117 (1.7)	0.084	0.664
4	Reoperation rate									
		4i. On pathology reports	<20[1]	66/2 271 (2.9)	47/984 (4.8)	9/547 (1.6)	7/362 (1.9)	3/378 (0.8)	<0.001	0.741
		4ii. On operation notes	<20[1]	123/1 531 (8.0)	78/984 (7.9)	45/547 (8.2)	-	-	0.836	0.039; 0.57 (0.33 - 0.97)†
5	Appropriate axillary surgery									
		5i. Rate of axillary surgery in invasive breast cancer	>90[1]	2 176/2 271 (95.8)	948/984 (96.3)	522/547 (95.4)	348/362 (96.1)	358/378 (94.7)	0.546	0.998
		5ii. Sentinel node biopsy only in clinically node-negative disease	>90[1]	319/806 (39.6)	124/361 (34.3)	111/226 (49.1)	2/105 (1.9)	82/114 (71.9)	<0.001	0.648
6	Number of nodes excised during axillary surgery									
		6i. Lymph node dissection ≥10 nodes	>80[12]	245/518 (47.3)	86/251 (34.3)	24/77 (31.2)	135/186 (72.6)	0/4 (0.0)	<0.001	0.858
		6ii. Sentinel node biopsy ≤5 nodes	>90[1]	228/278 (82.0)	110/133 (82.7)	100/117 (85.5)	1/2 (50.0)	17/26 (65.4)	0.064	0.910
7	Receipt of radiotherapy after breast-conserving surgery		>90[1]	294/441 (66.7)	72/161 (44.7)	82/126 (65.1)	38/41 (92.7)	102/113 (90.3)	<0.001	0.253

(Continued ...)

Table . (continued) Quality indicator adherence

QI number	QI title	International minimum standard (%)	Overall documented adherence, *n* (%)	CHBAH, *n* (%)	CMJAH, *n* (%)	GH, *n* (%)	Durban, *n* (%)	*p* value*	HIV effect on overall adherence, *p* value
8	Appropriate treatment sequencing in inoperable LABC	>90[1]	440/447 (98.4)	126/130 (96.9)	136/137 (99.3)	100/102 (98.0)	78/78 (100.0)	- 0.274	- 0.820
9	Case volume†	cases [1]							
	i. Breast unit newly diagnosed cases per annum	≥150 cases >150	100 (78.6)	2019 (100)	2019 (100)	2017 (33.3)	2016 - 2017 (66.6%)	-	-
	ii. Surgeon volume breast cancer cases per annum	≥50 cases >50	>50 (100)	2016 - 2019 (100)	2016 - 2019 (100)	2016 - 2018 (100)	2016 - 2018 (100)	-	-
10	Multidisciplinary team discussion	>90[1]	2560/3545 (72.2)	198/1455 (82.3)	706/931 (75.8)	76/530 (14.3)	580/629 (92.2)	<0.001	0.476

QI=quality indicator; CHBAH=Chris Hani Baragwanath Academic Hospital; CMJAH=Charlotte Maxeke Johannesburg Academic Hospital; GH=Grey's Hospital; Durban complex=Inkosi Albert Luthuli Central Hospital, Addington Hospital and Ngwelezana Hospital; RR=relative risk; CI=confidence interval; LABC=locally advanced breast cancer; LABC=locally advanced breast cancer.

*Pearson's χ^2 test was used to test for differences in adherence between the study sites.

†RR: 95% CI. Multivariate Poisson regressions, adjusting for age, hospital site, stage of disease and intrinsic subtype of breast cancer, were used to assess the impact of HIV status on overall adherence.

‡Case volumes calculated for full calendar-year enrolments: 2016 - for CMJAH and CHBAH; 2016 - 2018 - for GH; 2016 - 2019 - for CMJAH; 2018 - 2019 - for CHBAH.

resources need to be provided and the use of SLNB expanded across all sites.[21] Historically, the number of nodes dissected during ALND has been set at ≥10.[22] Our overall rate was low at 47.3%, and although the indicator measures technical surgical success, its clinical utility is questionable owing to factors such as the pathologist's variation in specimen review and the current clinical shift towards more preserving surgery.

QIs with poor data reliability and validity We attempted to measure reoperations with operative and pathology records. However, operative notes were only entered by clinicians in Gauteng; IALCH and GH entered operative notes on their separate hospital EPR. A common challenge in using EPRs is that data entry is more likely to be of poor quality when entered by busy frontline staff, and when it requires duplication of work processes.[23] Analysis of Gauteng operative notes show a reoperation rate of 8%. The data using histopathology are also flawed, as specimens would only be sent for re-excision or early recurrence, but not for emergent reoperations such as sepsis or bleeding. Furthermore, entry of the second pathology report was also less consistent than the first pathology report, as it did not form part of the routine data entry protocols for research staff. As expected, the reoperation rate based on pathology reports is lower, at 2.9%, and is not representative. The database will require an update for reoperations with structured data fields. This underlines our experience that building EPRs for clinical management and research purposes is an iterative rather than a linear process, requiring many revisions.

QIs within the context of our resource-constrained health system

We hypothesised that we would be more prone to interference, especially in the complex multidisciplinary treatment of breast cancer, where indicators are not solely dependent on the quality of a surgical practice but are interlinked with patient and health system factors.[7] Our results reflect this expected process when starting the quality control process. The commitment to quality improvement, audit, accreditation and structured guideline-adherent breast care dates back to the 1990s in Europe. The gradual improvements in quality through investigation and benchmarking and repeated internal and external audits have been well documented; a review of European centres showed compliance in 8 out of 13 QIs in 2006, compared with complete compliance in 2015.[24] Similarly, radiation after BCS improved from 75.8% to 95.8% after the initiation of an audit process by the National Quality Forum in the USA.[25] We hope this audit will also trigger a series of gradual improvements in SA. **EPR and study strengths and limitations** Our study shows the unique benefits of EPRs in research, such as access to already collected data, large sample sizes, reduced administrative efforts, reduced costs and sample selection bias.[23] The challenges are that our QI data fields were not predefined, and were not all collected specifically for research or quality control purposes. Functions were not uniformly used across sites, especially when this required clinician entry or duplication of workflow. Although structured data are best for research, the clinical nuances of cancer care often require unstructured data fields, the evaluation of which is flawed even with natural language processing methods.[17] It is critical to understand clinical workflow so that routine EPRs do not increase workload, but instead aid the clinician. Many routine data points require administrative research staff for reliable data collection in a busy clinic, and cannot be entered by frontline staff. Therefore, the success of EPRs and quality control measures depends on the synergy

between clinicians, administrators, researchers and informaticians. A further limitation of this study is that it only includes data from the public sector and two provinces, limiting representation. The time of enrolment was set for an initial benchmark, and offers no time trends in adherence, which will be assessed in a future publication.

Conclusion

Adherence to QIs varied widely across sites, and was mostly inferior to HIC standards. We achieved international standards in the volume criteria for surgeons, and unit volumes in Gauteng, and showed very low positive margin rates, likely due to the generous use of oncoplastic techniques. Our results highlight gaps in breast cancer care; the most urgent are the lack of radiation delivery in Gauteng and the underutilisation of SLNB. BCS rates must be improved, but reliable radiotherapy and sufficient resources are required. MDT discussion requires better documentation to assist patients with complex breast cancer treatment pathways. EPRs are essential in continuous QI monitoring and require adjustment within the EPR to document QI adherence directly. Reliable data collection calls for administrative research staff to avoid overburdening busy frontline workers.

Data availability. Study data are available from the first author on request. **Declaration.** This study forms part of SN's PhD (Surgery) degree at the University of the Witwatersrand.

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Conflicts of interest. None.

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Original Reports | Breast Cancer

Establishing Requirements for Breast Centers in Low- and Middle-Income Countries: A South African Perspective

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ABSTRACT

PURPOSE

In South Africa, breast care lacks governance and standardization, necessitating urgent improvements in patient outcomes. Quality improvement initiatives are urgently needed in low- and middle-income countries (LMICs), but requirements for breast centers in lower resource settings remain undefined and must be tailored to local environments. This consensus document outlines the role and requirements of breast centers in LMICs and presents a step-by-step implementation plan.

METHODS The literature was systematically reviewed, and the primary review team tabulated international accreditation standards alongside the 2018 South African Clinical Guidelines for Breast Cancer Control and Management from the South African National Department of Health, along with proposed South African standards. The broader consensus panel consisted of 29 clinical experts and representatives from societies, advocacy, and funders.

RESULTS We categorized requirements into eight broader categories and achieved unanimous consensus on all requirement components, except for 1 abstention in the general specialist and expertise category. We were unable to reach consensus on the patient volume requirements for radiologists as well as for medical and clinical/radiation oncologists. Volume requirements for clinical and radiation oncologists were later provided by the South African Society of Clinical and Radiation Oncology (SASCRO), along with the volume requirements submitted by the participating radiologists. We also achieved unanimous consensus for the Breast Interest Group of Southern Africa (BIGOSA) to house the initial project implementation. This consensus document is endorsed by BIGOSA, SASCRO, and the Cancer Association of South Africa.

CONCLUSION We emphasize the importance and necessity of breast centers in resourceconstrained environments, outline the first set of requirements for breast centers tailored to LMICs in sub-Saharan Africa, and present a feasible and detailed plan for initial implementation.

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INTRODUCTION

Breast cancer is the most common cancer among women in South Africa and most countries worldwide.[1,2] Numbers are steadily increasing in low- and middle-income countries (LMICs), and mortality rates are disproportionately higher, reflecting weaker health care infrastructure and late-stage presentation among multifactorial barriers to care.[2,3] The provision of care, such as access to optimal therapies or waiting times, accounts for approximately one third of survival differences; however, lack of guidelines, quality control, and regulatory framework may also account for up to a quarter of survival differences.[4]

The global disparities in breast cancer outcomes are a major challenge, and significant focus has been placed on the strengthening of care in LMICs where implementable quality improvement initiatives are urgently needed.[5,6] In South Africa, breast cancer survival is considerably lower than in high-income countries but better than in many other countries in sub-Saharan Africa, and survival seems to reflect the Human Development Index of countries.[7-9]

The available resources and health care spending vary widely across LMICs and are relatively better in South Africa
compared with other sub-Saharan countries.[7,10] South Africa has a highly unequal, dual health care system in which over

CONTEXT

Key Objective
What are the requirements for breast centers in low- and middle-income countries (LMICs), and how can they be effectively implemented?

Knowledge Generated
This consensus document describes the tailored requirements for breast centers in LMICs and their relevance in resourceconstrained settings and provides a step-by-step implementation plan.

Relevance
Breast centers have been widely adopted in some high-income countries; however, their standards are not universally applicable, and accreditation remains unaffordable, hindering widespread adoption in LMICs. The tailored center requirements present a feasible intervention that will strengthen health care systems and enhance clinical capacity.

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80% of the population relies on the lower resourced public sector and less than 20% have access to the private sector.[11] Access to high-quality breast services is limited in South Africa and depends on the patient's geographical location and socioeconomic situation. At present, we estimate that there are <10 specialized high-volume multidisciplinary breast care services in the public sector and less than 10 inthe private sector, serving a population of over 62 million.

Breast centers condense multidisciplinary expertise and resources with improved patient outcomes including survival, guideline-adherent care with appropriate use of multidisciplinary treatment modalities, and increased cost efficiency.[12] The process of internal and external audits and accreditation processes have been shown to improve the quality of care over time.[13,14]

There are several set requirement and accreditation systems, most prominently European Society of Breast Cancer Specialists (EUSOMA) in Europe,[4] National Accreditation Program for Breast Centers (NAPBC) in the United States,[15] and Onkozert from Deutsche Krebs Gesellschaft (DKG) in Germany.[16] Although accreditation with all three is available internationally, their standards are not uniformly appropriate in the LMIC setting, and the international accreditation process is not affordable and, therefore, not widely reproducible. This has left a gap for providers in LMICs where implementation of quality initiatives is particularly relevant; however, it is essential that the processes are pragmatic and involve systematic, sequential steps for implementation.[17]

Although sub-Saharan countries vary, this South African perspective reflects diverse resource levels and offers a consensus for South Africa and a pragmatic implementation approach for a quality improvement initiative applicable to all LMICs. This document intends to provide a consensus on the required structures and processes, describes the role of the centers, and offers a step-by-step plan for initial implementation. These are intended to be achievable with

appropriate expertise and effort, widely reproducible and affordable while elevating the overall standard of care, fostering transparency, and protecting the public.

METHODS

The consensus process is illustrated in Figure 1. The literature was reviewed, and international accreditation standards of EUSOMA, NAPBC, and DKG, as well as the 2018 South African Clinical Guidelines for Breast Cancer Control and Management from the South African National Department of Health (NDoH), were compiled in a table with recommended South African requirements tailored to our setting. Our primary review team included all authors, and the final tables and base

documents were circulated to the broader consensus team for review before the meeting. The consensus meeting was held virtually in August 2024, and the discussion was moderated by S.N. and P.R. The consensus meeting had 29 participants comprising 10 clinical experts from the executive committee of the Breast Interest Group of Southern Africa (BIGOSA); 1 representative each from the
South African Society of Medical Oncology (SASMO), the South African Society of Clinical and Radiation Oncology
(SASCRO), and the Association of Surgeons of South Africa (ASSA); five further current heads of academic breast units; seven further clinical experts with particular academic seniority; 1 representative for advocacy from the Cancer Association of South Africa (CANSA), as well as private sector funder representatives from Discovery Health and Medscheme, two of South Africa's largest private health care administrators. The NDoH was invited to participate, but no response was received.

RESULTS

We categorized the requirements into eight broader categories. During discussion in the roundtable meeting, we achieved unanimous consensus on all requirement components, except 1 abstention in the general specialist and expertise category (consensus 96%), and we were unable to reach a consensus on the volume requirements for radiologists, as well as medical and clinical and radiation oncologists. Volume requirements for clinical and radiation oncologists were received by SASCRO, and the participating radiologists provided volume requirements, which were included. Treating advanced metastatic breast cancer with systemic therapies is complex and often involves multiple therapy lines, making volume requirements challenging to assess in medical oncology.

The consensus on the implementation was unanimous in supporting BIGOSA as a means to assist in the initial project implementation with South Africa. At the time of writing, this consensus document had received official endorsement by BIGOSA, SASCRO, and CANSA.

Center Governance and Administration

A breast center is a structured team of specialists in breast cancer who work as a multidisciplinary team (MDT) with access to all necessary resources and treatments. Although single-location centers are preferable, multiple locations can cooperate through agreements and shared treatment protocols.

The center needs a governance document outlining the organization, team members, and resource locations, which should be publicly accessible along with treatment protocols.

Local guidelines should be followed where applicable. Cooperation agreements between participating practices should be in place and updated annually.

A director should be appointed, who can be a specialist from any specialty on the MDT core team. The steering committee, which should include three specialists from other core specialties, supports the director, and together, they are responsible for MDT participation, data collection, and internal review and audit of the center's performance.

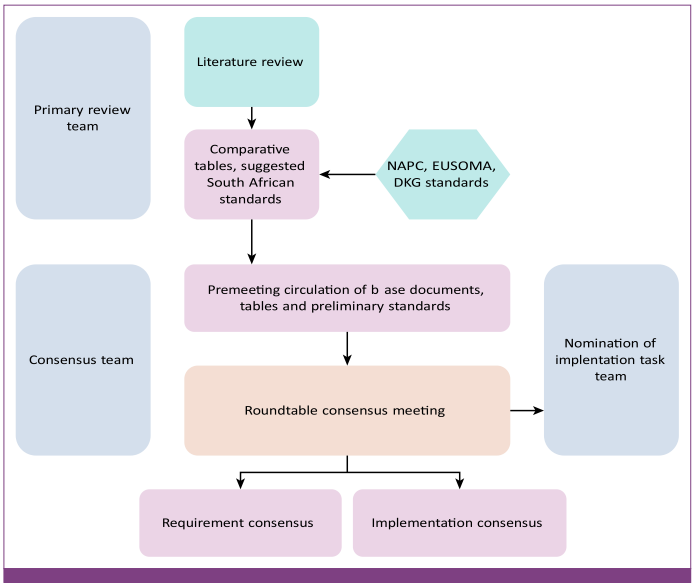


FIG 1. Consensus process.

Specialist Expertise and Resource

The team's mandatory core specialties include radiology, pathology, breast surgery, plastic surgery, and medical and clinical and radiation oncology. A dedicated breast nurse and clinical navigators improve

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patient outcomes, and the center should have at least 1 breast nurse or trained navigator.[18,19]

Ideally, the extended team should include nuclear medicine, human genetics, psychologic support, palliative care, rehabilitation, dieticians, and fertility preservation. However, these services are often unavailable in LMICs, but are important to highlight, especially the advantages of the availability and early engagement of palliative care.

Ideally, there should be at least two members from each core specialty to enhance treatment options, encourage discussion, and prevent dominance in decision making. However, resource constraints may necessitate accepting 1 member from each specialty.

For breast radiology, the participating radiologists should spend a significant portion of their time working in breast imaging. In terms of resources and expertise, the radiology center should have tomosynthesis digital mammography, high-resolution ultrasound and must be able to perform ultrasound-guided core biopsies and localizations. Within South Africa, which is relatively well resourced, breast magnetic resonance imaging (MRI) and stereotactic biopsy (and localization) should be available, or there must be an established referral system. Imaging and reports should be stored digitally, and reporting must be standardized and follow the Breast Imaging Reporting and Data System classification.

Pathologists are scarce in South Africa and even more so in other sub-Saharan African countries, leading to a lack of specialized breast pathologists.[20] However, breast center pathologists should meet international volume criteria and have specific experience in breast disease. EUSOMA and NAPBC suggest a mandatory internal review of every pathology performed outside of the center. This is not feasible in LMICs; instead, we recommend that the report must be reviewed in the MDT meeting, and a formal tissue review can be requested if there is clinical concern or discordance.

The breast surgeon must dedicate most of their working time to treating breast disease, meet the volume criteria, and ideally, have completed at least 12 months of postqualification training or academic experience in breast surgery. There is compelling evidence for improved patient outcomes with specialization, including a reduction in the relative risk of death at 5 years of up to 33% compared with low-volume nonspecialized surgeons.[21] Given the scarcity of breast surgeons and lack of formal national training programs, this is a recommended but not a mandatory requirement. Nevertheless, the operative skill set for a specialized center in South Africa must include the appropriate performance of axillary dissection, sentinel node biopsy and targeted axillary surgery, localization techniques for impalpable tumors, breast-conserving and oncoplastic procedures, and all types of mastectomies (including nipplesparing and skin-reducing techniques). This skill set is only achievable with specific training, and it is therefore critical that fellowships in breast surgery are recognized and offered in LMICs.

Plastic and reconstructive surgeons should fulfill the volume criteria. The center should be able to offer a wide range of advanced oncoplastic techniques, immediate and delayed implant-based and autologous reconstructions.

Medical oncologists (or clinical oncologists) should have specific experience in treating breast cancer. They must lead the decisions on and oversee all systemic therapies including

endocrine therapy, chemotherapy, targeted therapy, and immunotherapy and provide follow-up information.

The radiation oncologists (or clinical oncologists) should equally have specific experience in the treatment of breast cancer. They should be competent in all breast radiation techniques, including 2D radiotherapy, 3D conformal radiotherapy, intensity-modulated radiotherapy, volumetric modulated arc therapy, image-guided

radiotherapy, respiratory motion management techniques, stereotactic radiotherapy, and palliative care techniques. They must be skilled in breast cancer contouring and encouraged to complete an online course every 5 years to stay current. Breast radiotherapy protocols should be regularly updated and include dose-planning objectives for target volumes and organ-atrisk constraints for different fractionation schedules. Breast radiotherapy planning and peer-review meetings should involve at least two clinical and radiation oncologists, planning radiotherapists, treating radiotherapists, and medical physicists to review cases and assess treatment strategy, fractionation schedule, contours, and dose-volume histograms. Adverse event data should be documented weekly, and follow-up data should be collected once patients have completed treatment. Furthermore, national radiation control regulations and their quality assurance must be followed.

Patient Volumes

A critical volume is necessary to build and maintain expertise in some of the core specialties and justify the additional resources and costs for a center.[22,23] The center must manage a minimum caseload of 100 newly diagnosed or referred patients annually. In addition, each breast surgeon should operate on at least 50 primary breast cancers, and plastic surgeons should perform at least 50 postmastectomy reconstructions or advanced oncoplastic procedures. The systemic treatment of breast cancer is complex and frequently necessitates multiple treatment lines, complicating volume assessment. Clinical and radiation oncologists should aim to create at least 50 new oncology treatment plans. To ensure adequate breast imaging expertise, participating radiologists should report at least 300 mammograms per year, perform at least 200 breast ultrasounds per year, perform at least 36 biopsies or localizations a year, and, for those reporting breast MRI, they should report at least 36 per year.

Multidisciplinary Meetings

Multidisciplinary meetings foster interdisciplinary care and adherence to guidelines; reduce overservicing, overtreatment, and futile care; and improve breast cancer survival.[24-26] The center must have at least bimonthly multidisciplinary meetings. Attendance is mandatory and must include the core team members. All newly diagnosed patients, postoperative patients, and patients with disease recurrence or distant disease progression must be discussed with clear documentation of team recommendations and treatment pathways. Radiology imaging

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should be available and viewed at the meeting. Patients who had their imaging outside of the breast center should have this reviewed by the center radiologists. Decisions and recommendations from the team must be communicated to the patient. In principle, these recommendations are binding, and if there is a deviation from the clinical treatment plan, the reasons must be discussed and documented.

Patient Care Principles

Figure 2 shows the patient care principles and pathway. Breast care should be standardized and evidence based with shared decision making. These choices must be within the detected abnormality was found. Treatment should be timely, but patients must not be rushed. They should commence treatment no earlier than a week after diagnosis, but ideally within 4 weeks of diagnosis.[27] Patientsmust beallowed to seek a second opinion without fear of disadvantage.

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constraints of available resources. MDT recommendations must be shared with the patient. Ideally, patients should have written information on treatment options and the treatment pathway.

A well-functioning and fit-for-purpose electronic record i preferable for a breast center and forms the basis for resear audit, and quality control. Initial key data should inclu stage, tumor biology, age, timelines, and treatments received

Access to care should be streamlined. A diagnosis and referral to an appropriate center should take no longer than 4 weeks from when the patient noticed symptoms or a screening-

Outcome indicators are more laborious to document and woul require data or research assistants, resources not commonly available in either health care sector in South Africa.

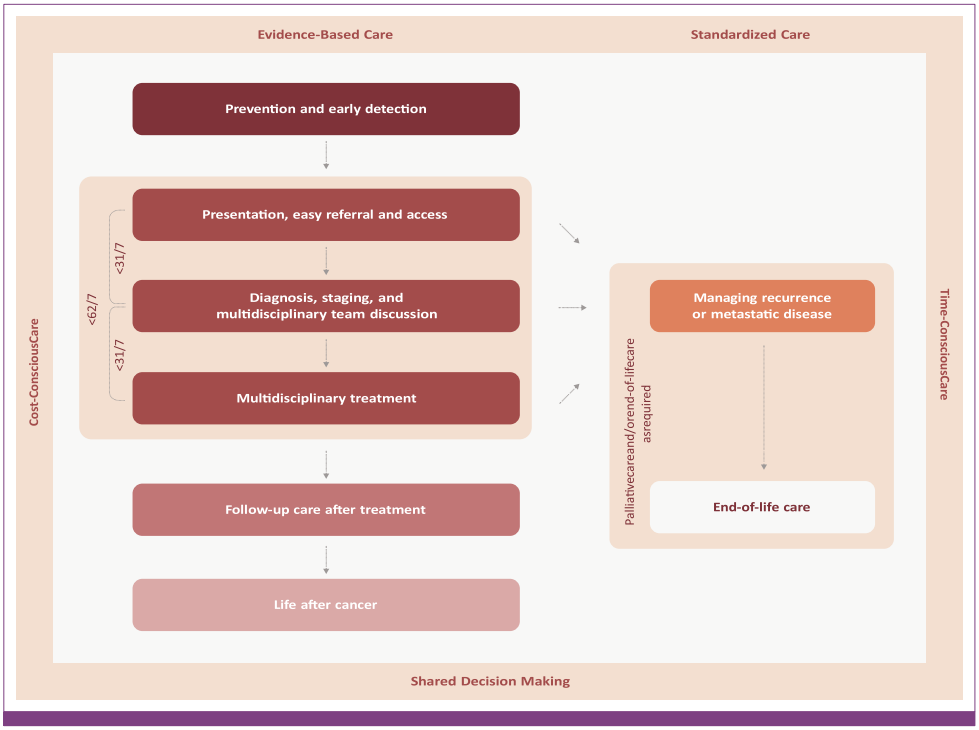


FIG 2. Patient pathway and care principles.

Treatment costs are particularly important in LMICs, and emphasis must be placed on both cost and value of care. High-cost treatment do not necessarily translate to better outcomes and high-cost drivers with little impact on value are well described.[28] Although more complex to implement, in the longer term, breast centers across LMICs should adopt the concept of value-based care.[28,29] Electronic Data Records

Table 1. Initial Quality Indicators

Quality Indicators
Timeliness of care, with documentation of time from presentation to MDT discussion, to treatment modality dates
Rate of discussion of newly diagnosed patients at MDT
Rate of breast-conserving surgery
Rate of sentinel lymph node biopsy in clinically node-negative patients
Rate of postmastectomy immediate reconstruction
Rate of radiation receipt after breast-conserving surgery
Rate of hypofractionation
Rate of systemic therapy received for patients with ER-negative tumors
Rate of HER2 targeted therapy received in patients with HER2-positive tumors

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MDT, multidisciplinary team.

Nevertheless, we recommend recording patient-reported outcome measures[17] and conducting survival follow-up for a minimum of 5 years wherepossible. The center should appoint a data manager to ensure data completeness and extract data for research and audits wherever feasible. The electronic database must ensure data security and confidentiality. Audit and Quality Control

The breast center ought to conduct annual audits to identify gaps, followed by a minimum of two interventions as quality improvement initiatives. Data sets can be adapted to local resources and are easily expandable; however, we recommend the following initial quality measurements to achieve a broad quality overview (Table 1).

Research and Training

Breast centers must engage in research and training to enhance clinical practice, especially in LMICs where training of specialists is critical. In South Africa, academic units meet this demand, often in challenging conditions. Private centers should support this effort by participating in research and aiding academic training programs. We advocate for national collaborations between academic and private centers, emphasizing private sector support for academic programs.

DISCUSSION

We propose an implementable stepwise approach to build breast centers in Southern Africa, which may be applicable throughout other LMICs. We recognize that some categories may not be achievable in low-resource settings, but argue that the stepwise approach, the systematic documentation of resources and gaps in care, and the process of internal or external audit would improve the quality of care over time, transparently and timeously inform on the status of care and build breast care capacity in Southern Africa. At present, minimum targets for quality indicators are unsuitable in LMICs, where participation in quality improvements must be encouraged across all resource levels. The initial data collection should first identify and address existing gaps, but may establish benchmarks over time.

Within South Africa, we urgently need to expand breast cancer capacity with well-supported breast centers across health care sectors that provide standardized and safe care over a broad geographical area. A careful balance should be established between creating high-quality centers and still providing broad access, potentially with support of peripheral services through a hub-and-spoke system.[17] In a region with relatively scarce oncology services, the focus is not on a single site but on improving multiple sites with the goal of increasing capacity over time. No overall cancer control policy is in place in South Africa but three documents were published by the NDoH for breast, cervical, and lung cancers. Breast centers were part of the NDoH 2017 breast cancer control policy, which flagged breast cancer as a national priority.[30] The document described the importance of these centers but implementation is yet to happen and existing breast academic units remain largely underresourced with no new centers established to date. In view of this, we propose this consensus as a clinician-based initiative to increase capacity by forming public-private partnerships for implementation. Establishing collaborative centers would improve integration across health care sectors. At present, specialists are primarily trained in academic hospitals; private sector exposure would enhance training for all subspecialties, but it generally produces less research, has poor data collection, and lacks transparency. Affiliating with academic centers would improve documentation and transparency, may reduce patient overservicing, and increase research capacity. Besides assisting with training, supportive collaboration could include funding data management, aiding trainee examinations, and financing shared trainee positions.

Voluntary participation and self-reporting of audits is a well-described and appropriate step in the first implementation phase of breast centers.[31] The document offers a step-by-step plan to facilitate the implementation process (Fig 3), and in principle, appropriate multidisciplinary services can implement these steps independently at a low cost. Any new center must add value and build capacity; there must be a need for a center and willingness to collaborate, transparently share audit results, and participate in training and research. The clinicians can then form the appropriate teams and resources, with established patient volumes and MDT meetings. Once these clinical prerequisites are met, the next implementation steps should be taken to cover governance and electronic record-keeping requirements. These will create additional administrative workload and commitments and require institutional support. Within Southern Africa, new centers could register themselves after 3 months of clinical data collection with BIGOSA.

Key data and indicators, along with their intervention plans, shouldbe sharedcollaboratively.Reviewsmustbe anonymous

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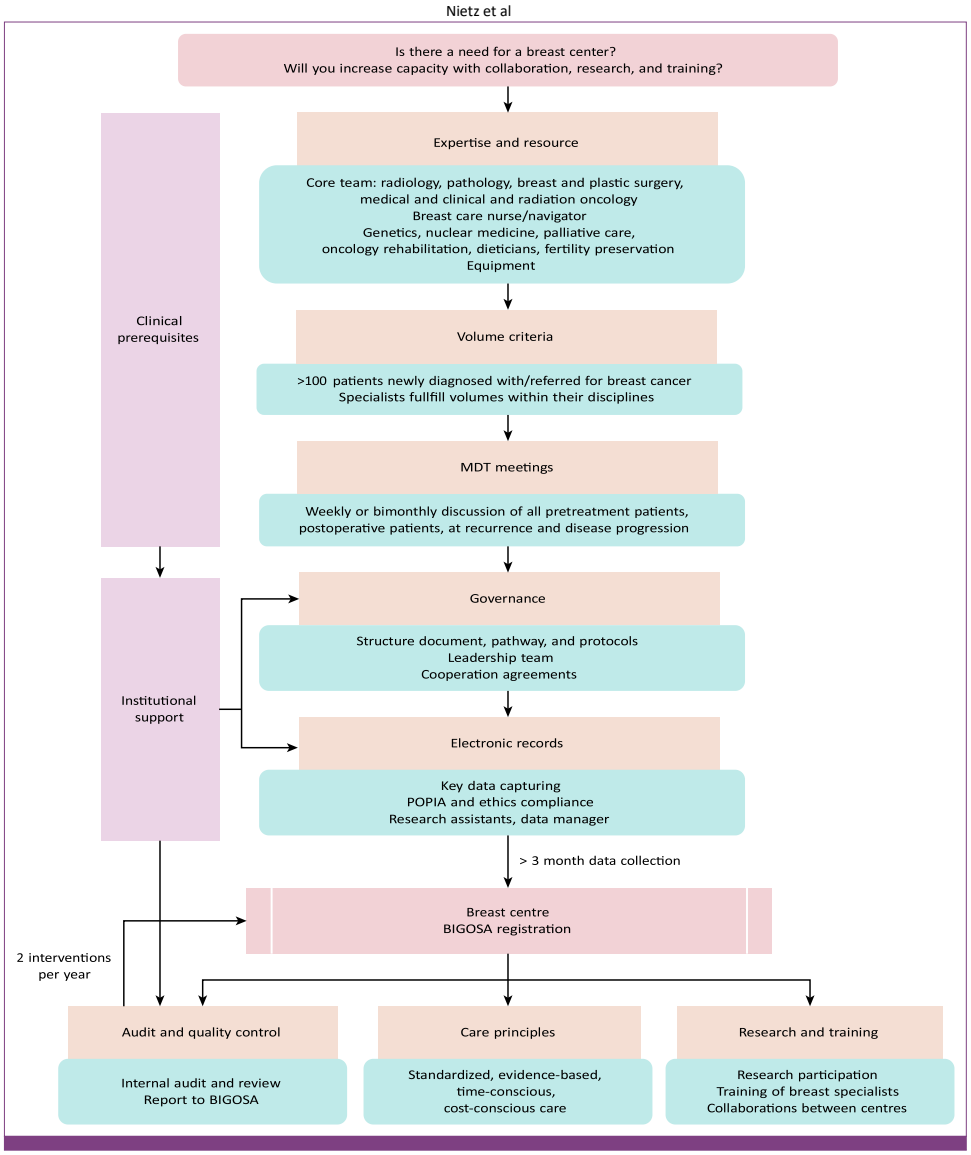


FIG 3. Breast center implementation steps. BIGOSA, Breast Interest Group of Southern Africa; MDT, multidisciplinary team; POPIA, Protection of Personal Information Act.

and nonpunitive, with compliance status attained through LMICs.[32] BIGOSA is presently not equipped and experienced active participation and transparent data sharing. to collate multisite audit results, and this will require funding and data management support. Initial key data and The implementation of quality improvement initiatives is indicators will hopefully be expanded over time. Formal complex across health care environments, particularly in accreditation was intended in the 2018 NDoH document and

may be a possible future step after initial benchmarking. There are appropriate third-party accreditors available in South Africa who could fulfill this role, but this would need the involvement and support of statutory bodies and further funding. The BIGOSA executive committee will create a working group to address implementation phases, secure funding, support academic centers and affiliations, address ethics, and gain statutory support.

In conclusion, we have provided an initial framework and implementation guide for breast centers in Southern Africa. Participation in the registration as a breast center and audits should be voluntary and nonpunitive, and results will be collated and presented annually by BIGOSA. The implementation of the initial steps will assist to standardize care, build capacity, and improve overall quality of breast cancer care in Southern Africa.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix F: Related First or Senior Authored Papers

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BREASTCANCER

original reports abstract

Quality of Histopathological Reporting in Breast Cancer: Results From Four South African Breast Units

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PURPOSE High-quality histopathology reporting forms the basis for treatment decisions. The quality indicator for pathology reports from the European Society of Breast Cancer Specialists was applied to a cohort from four South African breast units.

METHODS The study included 1,850 patients with invasive breast cancer and evaluated 1,850 core biopsies and 1,158 surgical specimen reports with cross-center comparisons. A core biopsy report required histologic type; tumor grade; and estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status, with a confirmatory test for equivocal HER2 results. Ki-67 was regarded as optional. Pathologic stage, tumor size, lymphovascular invasion, and distance to nearest invasive margin were mandatory for surgical specimens. Specimen turnaround time (TAT) was added as a locally relevant indicator.

RESULTS Seventy-five percent of core biopsy and 74.3% of surgical specimen reports were complete but showed large variability across study sites. The most common reason for an incomplete core biopsy report was missing tumor grade (17.9%). Half of the equivocal HER2 results lacked confirmatory testing (50.6%). Ki-67 was reported in 89.3%. For surgical specimens, the closest surgical margin was reported in 78.1% and lymphovascular invasion in 84.8% of patients. Mean TAT was 11.9 days (standard deviation [SD], 10.8 days) for core biopsies and 16.1 days (SD, 11.3) for surgical specimens.

CONCLUSION Histopathology reporting is at a high level but can be improved, especially for tumor grade, HER2, and Ki-67, as is reporting of margins and lymphovascular invasion. A South African pathology consensus will reduce variability among laboratories. Routine use of standardized data sheets with synoptic reports and ongoing audits will improve completeness of reports over time.

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INTRODUCTION

Breast cancer incidence has significantly increased, and has become the most common malignancy in women from low- and middle-income countries (LMICs) having higher mortality rates than women in high-income countries (HICs).[2,3]

High-quality histopathology reporting with clear communication of predictive and prognostic markers is critical for clinical decision making. South Africa is an upper- and middle-income country with more advanced breast pathology resources than most subSaharan African countries.[4] Not all diagnostic tests are feasible in lower-resourced areas, and the Breast Cancer Initiative 2.5 (BCI 2.5) stratifies diagnostic services according to available resources into basic, limited, enhanced, and maximum levels. In South Africa, there is a dual health care system that fulfills criteria of an enhanced level in the public sector and among women in South Africa.[1] Delayed presentation and poorer overall quality of care has resulted in maximum level in the private sector.[5] Although many HICs have adopted multigene assays to determine recurrence risk and guide therapies, these are not available in the public sector in South Africa, and breast units rely on grade, receptor status, lymphovascular invasion (LVI), and Ki-67 for treatment decisions.

For many years, efforts have been made to standardize high-quality breast cancer care in HICs, and various guidelines have been established to improve the quality of breast cancer pathology reporting.[6-10] To date, there is a paucity of data from South Africa and other LMICs on the adequacy of breast histopathology reporting, and there are no national guidelines for breast histopathology reporting.

ASSOCIATED CONTENT Appendix and support information (if applicable) appear at the end of this article.

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CONTEXT Key

Objective

To evaluate the quality of breast cancer histopathology reporting among four South African academic breast units Knowledge Generated

The quality of reporting is not uniform across academic units and needs to be improved. A national pathology consensus and routine use of reporting templates and synoptic reports will increase report completeness and quality over time.

Relevance

Efforts must be made to improve quality of breast cancer care in low- and middle-income countries. Complete and reliable reporting of breast cancer histopathology is a key component for clinical decision making and patient treatment. Highquality reporting of routine parameters, such as tumor grade and Ki-67, are particularly important in resource-constrained settings where multigene arrays are not available.

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One of the widely applied sets of quality indicators (QIs) was published by the European Society of Breast Cancer Specialists (EUSOMA).[10] This study aimed to apply the EUSOMA histopathology QIs to a South African cohort to evaluate local breast cancer histopathology reports and compare reporting quality across participating centers.

METHODS

Patients and Data Collection

This is a retrospective review of patients enrolled in the South African Breast Cancer and HIV Outcomes (SABCHO) study, which evaluates the impact of HIV on the care and outcomes of women with breast cancer.[11] The period of review was July 2015 to September 2017 and included 1,850 consecutive patients from Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Inkosi Albert Luthuli Central Hospital (IALCH), and Grey's Hospital (GH). CHBAH and CMJAH are both located in Johannesburg in the Gauteng province, and IALCH and GH are both in the KwaZulu-Natal (KZN) province. All four are public sector academic breast cancer units and serve socioeconomically disadvantaged patients.

The pathology reports of 3,008 specimens, including 1,850 core biopsies and 1,158 surgical specimens, were evaluated. Reports for specimens from Gauteng sites were generated by the hospital's respective pathology departments from the National Health Laboratory Services (NHLS), which serves the public health sector in South Africa. The majority of samples from KZN units had been outsourced to private laboratories.

This study was approved by the human research ethics committee of the University of the Witwatersrand. All patients signed written informed consent at the time of enrollment into the SABCHO study.

QIs

Reports were considered complete if they included the following parameters for core biopsy[10]: histologic type, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status with a confirmatory in situ hybridization test for equivocal results (usually fluorescence in situ hybridization [FISH] in our setting). During the study period, HER2 2+ (equivocal) status was generally defined as circumferential membrane staining that is weak to moderate in . 10% of cells or complete and circumferential membrane staining that is intense within , 10% of tumor cells. HER2 3+ status was considered positive and did not require confirmatory testing. A Ki-67 score is recommended but not required in the EUSOMA guidelines. Because Ki-67 is routinely considered for clinical decisions in our units, it was added as an optional parameter with a cutoff of 20% to define immunohistochemical (IHC) surrogates for molecular subtypes.[12] In addition to these parameters, the following were required for surgical specimens[10]: pathologic stage, size in millimeters for the invasive component, peritumoral LVI, and distance to nearest invasive margin; receptors did not require repeat because we expected them routinely on core biopsy. The EUSOMA guidelines set a minimum standard of ≥ 95% complete reports with an ideal target of ≥ 98%. Report turnaround time (TAT) was measured as a locally relevant parameter, defined as the number of days between the laboratory receiving the specimen to final report release, and included IHC where performed.

Statistical Analysis

The proportion of complete reports in each center was recorded as frequency with percentage and compared among centers by Pearson's χ^2 test or Fisher's exact test for sparse data. Analysis was carried out using Stata 14 statistical software (StataCorp, College Station, TX).

RESULTS

Demographic characteristics of the cohort, tumor grade, and IHC subtype distributions are listed in Table 1. Unknown IHC receptor subtyping was 8.4% overall, ranging from 5.2%, 5.4%, and 5.7% at the CMJAH, IALCH, and

TABLE 1 Demographics and Tumor Characteristics on Core Biopsy Report

Characteristic	Total	Institution, No. (%)				P
		CHBAH	CMJAH	IALCH	GH	
No. of patients	1,850	643	442	409	356	
Mean age 6 SD	56.0 6 14.4	54.8 6 14.3	55.3 6 14.1	57.5 6 14.3	57.4 6 14.9	.004
Ethnicity						
Black	1,417 (76.6)	590 (91.8)	322 (72.9)	225 (55)	280 (78.7)	
Colored	91 (4.9)	38 (5.9)	25 (5.7)	12 (2.9)	16 (4.5)	
Indian	203 (11.0)	5 (0.8)	15 (3.4)	136 (33.3)	47 (13.2)	, .001
White	139 (7.5)	10 (1.6)	80 (18.1)	36 (8.8)	13 (3.7)	
Tumor grade						
Missing	332 (17.9)	27 (4.2)	23 (5.2)	222 (54.3)	60 (16.9)	
No. reported	1,518	616	419	187	296	, .001
1	114 (7.5)	41 (6.7)	24 (5.7)	10 (5.3)	39 (13.2)	
2	817 (53.8)	323 (52.4)	189 (45.1)	135 (72.2)	170 (57.4)	
3	587 (38.7)	252 (40.9)	206 (49.2)	42 (22.5)	87 (29.4)	
IHC-based subtype						
Missing	156 (8.4)	37 (5.7)	23 (5.2)	22 (5.4)	74 (20.8)	
No. reported	1,694	606	419	387	282	, .001
Luminal A	356 (21.0)	79 (13.0)	96 (22.9)	139 (35.9)	42 (14.9)	
Luminal B (HER2 negative)	649 (38.3)	257 (42.4)	101 (38.7)	101 (26.1)	129 (45.7)	
Luminal B (HER2 positive)	285 (16.8)	144 (23.8)	62 (14.8)	47 (12.1)	32 (11.4)	
HER2 enriched	136 (8.0)	34 (5.6)	34 (8.1)	41 (10.6)	27 (9.6)	
Triple negative	268 (15.8)	92 (15.2)	65 (15.5)	59 (15.2)	52 (18.4)	

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey's Hospital; HER2 human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry; SD,

standard deviation.

CHBAH sites, respectively, to 20.8% at the GH site. The majority of patients had hormone receptor–positive disease (76.1%), and 16.8% had luminal B HER2-positive disease; only 8.0% were HER2 enriched, and 15.8% had triplenegative breast cancer. Luminal B HER2 negative was the most common subtype for the cohort (38.3%), except at IALCH where luminal A was more common at 35.9%.

The proportion of complete core biopsy reports, when not considering Ki-67, was 75% overall, with rates of 90.2%, 91.6%, 43.0%, and 63.5% at CHBAH, CMJAH, IALCH, and GH, respectively (Table 2). With inclusion of Ki-67, this dropped to 69.7% overall, with rates of 89.0%, 90.5%, 34.5%, and 49.4% at CHBAH, CMJAH, IALCH, and GH, respectively. Completeness of IHC reporting was high overall throughout all sites (ER, 98%; PR, 97.9%; HER2, 97.8%). The most common reasons for incomplete core biopsy reports were missing tumor grade; no FISH testing for equivocal HER2 results; and, when included, missing Ki-67 (Table 2). Ki-67 was reported in absolute percentage values at all sites except for IALCH, where it was reported as ≤ 14% or . 14%. Significant cross-center differences were found for overall report completeness, grade, confirmatory HER2 testing, and Ki-67 (all P≤ .001).

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The completeness of surgical specimen reporting was 74.3% overall (CHBAH, 89.66%; CMJAH, 86.78%; IALCH, 37.96%; GH, 70.76%; Table 3). Failure to report on closest invasive margin, LVI, and tumor grade were the most commonly missing parameters. Closest invasive margin reporting was 78.1% overall, ranging from 88.5%, 86.0%, and 81.8% at CHBAH, CMJAH, and GH, respectively, to 48.2% at IALCH (P≤ .001). LVI was included in 84.8% of cases overall, with 92.4%, 89.7%, 72.2%, and 78.8% reporting at CHBAH, CMJAH, IALCH, and GH, respectively (P ≤ .001). Tumor grade was reported in 92.1%, ranging from 97.5% at CHBAH to 90.7% at GH
(P≤ .001). Histopathological type and pathologic staging were reported in 98.8% and 94.7%, respectively, but still showed significant cross-center differences (P ≤ .001). Average overall TAT was 11.9 6 10.8 days for core biopsies and 16.1 6 11.3 days for surgical specimens, again with significant cross-center differences (Table 4).

DISCUSSION

None of the sites fulfilled the EUSOMA minimum requirement of 95% complete histopathology reports. Among the overall cohort, there was complete reporting for

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TABLE 2 Core Biopsy Reporting

Reporting Parameter	Institution, No. (%)					P
	Total	CHBAH	CMJAH	IALCH	GH	
No. of patients	1,850	643	442	409	356	
Complete core biopsy (excluding Ki-67)						, .001
Complete	1,387 (75.0)	580 (90.2)	405 (91.6)	176 (43.0)	226 (63.5)	
Incomplete	463 (25.0)	63 (9.8)	37 (8.4)	233 (57.0)	130 (36.5)	
Complete core biopsy (including Ki-67)						, .001
Complete	1,289 (69.7)	572 (89.0))	400 (90.5)	141 (34.5)	176 (49.4)	
Incomplete	561 (30.3)	71 (11.0)	42 (9.5)	268 (65.5)	180 (50.6)	
Histologic type						.005*
Reported	1,830 (98.9)	639 (99.4)	432 (97.7)	409 (100)	350 (98.3)	
Missing	20 (1.1)	4 (0.6)	10 (2.3)	0 (0.0)	6 (1.7)	
Tumor grade						, .001
Reported	1,518 (82.1)	616 (95.8)	419 (94.8)	187 (45.7)	296 (83.1)	
Missing	332 (17.9)	27 (4.2)	23 (5.2)	222 (54.3)	60 (16.9)	
ER						.094*
Reported	1,813 (98.0)	626 (97.4)	432 (97.7)	407 (99.5)	348 (97.8)	
Missing	37 (2.0)	17 (2.6)	10 (2.3)	2 (0.5)	8 (2.2)	
PR						.082*
Reported	1,811 (97.9)	626 (97.4)	431 (97.5)	407 (99.5)	347 (97.5)	
Missing	39 (2.1)	17 (2.6)	11 (2.5)	2 (0.5)	9 (2.5)	
HER2 IHC						.523
Reported	1,810 (97.8)	628 (97.7)	431 (97.5)	404 (98.8)	347 (97.5)	
Missing	40 (2.2)	15 (2.3)	11 (2.5)	5 (1.2)	9 (2.5)	
HER2 2+ status requiring FISH						, .001
No.	235	90	38	30	77	
Reported	116 (49.4)	22 (24.4)	12 (31.6)	17 (56.7)	65 (84.4)	
Missing	119 (50.6)	68 (75.6)	26 (68.4)	13 (43.3)	12 (15.6))	
Ki-67						, .001
Reported	1,652 (89.3)	619 (96.3)	422 (95.5)	349 (85.3)	262 (73.6)	
Missing	198 (10.7)	24 (3.7)	20 (4.5)	60 (14.7)	94 (26.4)	

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; ER, estrogen receptor; FISH, fluorescence in situ hybridization; GH, Grey's Hospital; HER2, human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry; Ki-67, protein encoded by the MKI67 gene; PR, progesterone receptor.

*By Fisher's exact test.

75.0% of core biopsies and 74.3% of definitive surgical specimens. There were striking differences among the study sites, with significantly higher completeness rates for both core and surgical specimens among Gauteng sites compared with KZN sites.

The audit of core biopsy specimens showed serious under-reporting of grade and HER2 equivocal FISH reporting. For surgical specimen reporting, the Gauteng sites approached EUSOMA reporting standards, whereas the KZN sites were deficient in reporting of LVI and closest invasive margin, which compromises the assessment of adequacy of surgery as well as the need for reoperations or adjuvant therapies.

Tumor grade is an established prognostic marker, and reliability in core specimens is relatively high. The propensity toward grade 2 reporting at IALCH is particularly noteworthy: At 72.2%, this is much higher than reported in the literature.[13] While grading may not be possible in very few cases on core biopsy, IALCH did not report grade in 54.3% of core biopsies and 17.6% of surgical specimens, and the overall reliability of grade reporting therefore seems questionable. The extremely high number of missing grade was the main contributor to the overall very low complete core biopsy reporting of 43% at IALCH.

HER2-targeted treatment was not accessible in the public sector during most of the study period but has now become

TABLE 3 Surgical Specimen Reporting

Reporting Parameter	Institution, No. (%)					P
	Total	CHBAH	CMJAH	IALCH	GH	
No. of specimens	1,158	435	242	245	2236	
Complete surgical specimen						, .001
Complete	860 (74.3)	390 (89.7)	210 (86.8)	93 (37.9)	167 (70.8)	
Incomplete	298 (25.7)	45 (10.3)	32 (13.2)	152 (62.1)	69 (29.2)	
Total	1,158 (100.0)	435 (100.0)	242 (100.0)	245 (100.0)	236 (100.0)	
Histologic type						, .001
Reported	1,144 (98.8)	434 (99.8)	242 (100.0)	241 (98.4)	227 (96.2)	
Missing	14 (1.2)	1 (0.2)	0 (0.0)	4 (1.6)	9 (3.8)	
Tumor grade						, .001
Reported	1,067 (92.1)	424 (97.5)	227 (93.8)	202 (82.4)	214 (90.7)	
Missing	91 (7.9)	11 (2.5)	5 (6.2)	43 (17.6)	22 (9.3)	
LVI						, .001
Reported	982 (84.8)	402 (92.4)	217 (89.7)	177 (72.2)	186 (78.8)	
Missing	176 (15.2)	33 (7.6)	25 (10.3)	68 (27.8)	50 (21.2)	
Closest invasive margin						, .001

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Reported	904 (78.1)	385 (88.5)	208 (86.0)	118 (48.2)	193 (81.8)	
Missing	254 (21.9)	50 (11.5)	34 (14.0)	127 (51.8)	43 (18.2)	
Pathologic staging						, .001
Reported	1,097 (94.7)	418 (96.1)	237 (97.9)	215 (87.8)	227 (96.2)	
Missing	61 (5.3)	17 (3.9)	2.1 (5)	30 (2.2)	9 (3.8)	
Tumor size						.974
	1,079 (93.2)	406 (93.3)	225 (93.0)	227 (92.7)	221 (93.6)	
Reported	79 (6.8)	29 (6.7)	17 (7.0)	18 (7.3)	15 (6.4)	
Missing						

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey's Hospital; IALCH, Inkosi Albert Luthuli Central Hospital; LVI, lymphovascular invasion.

available for selected patients. Nevertheless, even in the absence of targeted treatment, HER2 should always be tested because it is a predictive marker for the utility of chemotherapy. The BCI 2.5 classification suggests HER2 status as the process metric for quality control for settings of an enhanced level, such as the South African public sector.[5] HER2 IHC was tested in the majority of biopsy specimens across all study sites (97.8%). Two hundred thirty-five specimens were HER2 2+ and regarded as equivocal. However, 50.6% of these equivocal HER2 results lacked further FISH testing (75.6%, 68.4%, 43.3%, and 15.6% at CHBAH, CMJAH, IALCH, and GH, respectively). Differences in complex laboratory processes and outsourcing of FISH testing may explain site differences, and silver in situ hybridization testing within the laboratories may assist to overcome logistical hurdles.

EUSOMA does not classify Ki-67 reporting as mandatory but has recommended its routine use.[12] In South African public sector units, where multigene assays are not affordable, Ki-67 status is routinely used for decisions about chemotherapy, especially in hormone receptor–positive breast cancers. Routine reporting of Ki-67 at the Gauteng NHLS laboratories was 96.3% and 95.5% at CHBAH and CMJAH. In contrast, only 85.3% of core biopsies reported Ki-67 at IALCH and 74.6% at GH. The inclusion of Ki-67 decreased overall complete reports from 75% to 69.7%,

TABLE 4 Specimen TATs

	TAT, Mean Days 6 SD					
Report	Total	CHBAH	CMJAH	IALCH	GH	P
Core biopsy specimen	11.9 6 10.8	8.0 6 6.2	12.0 6 8.3	18.6 6 15.8	10.9 6 15.8	, .001
Surgical specimen	16.1 6 11.3	15.4 6 9.9	20.3 6 11.2	12.9 6 9.2	15.5 6 13.8	.010

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey's Hospital; IALCH, Inkosi Albert Luthuli Central Hospital; SD, standard deviation; TAT, turnaround time.

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a drop that was almost exclusively noted within KZN units. Although Ki-67 has caused many controversies with interobserver, interlaboratory, and intraobserver variations, most of these have been addressed by international working groups, and there are clear guidelines for preanalytical, analytical, and data handling.[14] Ki-67 is used in various predictive models, some of which estimate Oncotype DX (Genomic Health, Redwood City, CA) recurrence scores, which adds clinical utility, especially in settings where multigene assays are unavailable.[15,16] Ki-67 interpretation can be significantly improved through application of digital image analysis technology, removing a subjective component to interpretation.[17] Strict quality control, national standardization, and laboratory accreditation will further result in more consistent and robust Ki-67 results.

The significant differences in tumor grade and IHC subtype distribution among the sites need additional investigation. The majority of patients had luminal B tumors across all sites, with the exception of IALCH that had more luminal A tumors. Exploratory analyses,

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including only Black patients to remove confounding around ethnicity and adjusting the Ki-67 cutoff to ≤ 14%, made no difference (Appendix Tables A1 and A2). It is probable that these differences are due to interlaboratory variations in Ki-67 scoring and not due to true differences in tumor biology. This illustrates, however, that allocations to subtypes are flawed: Grading and Ki-67 evaluation do not seem to be uniformly reproducible among our sites. In the absence of multigene assays, it is important that these results are improved to assist clinicians with treatment decisions.

The mean TATs for core biopsies and surgical specimens were 11.9 and 16.1 days, respectively, and need to be improved. In comparison, TATs for breast biopsies in Botswana were reported at 8 days and 57 days for surgical specimens, which the authors hypothesized to be due to pre-analytical delays with a reported goal TAT of , 7 days for all specimens in the future.[18] In HICs, reported mean TATs for surgical pathology specimens and mastectomies are 2.7 and 3.8 days, respectively.[19,20] There is no international recommendation on TATs for histopathology reports and certainly no national consensus. CHBAH aims to process uncomplicated surgical specimens within 5 working days, but excision breast specimens are often complex and may require a second review of the macroscopic specimen for additional sections to be taken and additional analyses. Furthermore, TATs for teaching units in the public sector cannot be expected to equal those of private laboratories because trainees need supervision at each stage of the work-up before reports are authorized. This may delay TATs but is critical for teaching and to increase local pathology capacity over the longer term.

The EUSOMA QIs were selected because they are most reflective of local practice, and all mandatory parameters are included as essential pathology parameters in the Breast Cancer Control Policy published by the South African National Department of Health in 2017.[21] It needs to be acknowledged that histopathologists are scarce and often overburdened in South Africa, a situation that has already led to the outsourcing of government patient specimens to the private sector in some provinces. Although South Africa has the second highest number of pathologists in sub-Saharan Africa, with one pathologist/ 224.897 population, this is still in stark contrast to one pathologist/15-20.000 population estimated for HICs.[4] Most pathology departments lack specialists in breast pathology, and while we do have pathologists with special interests, the limited number of pathologists in South Africa, particularly in the public sector, means that it is probably not feasible to have pathologists who are purely breast pathologists.

Although EUSOMA standards were not met in this cohort, the results must be seen in context with other audits in the literature. They are far superior compared with other countries in sub-Saharan Africa. A study from Ethiopia showed that only 61% of specimens included basic-level reporting of T and N staging, tumor grading, and histologic type and only 1% included ER status, margins, and LVI.[22] Two studies from West Africa reported grading in only 12% of patients, and only 26% had hormone receptors tested.[23,24] Compared with first audits in HICs, only 64.7% had complete reports according to the College of American Pathologists guidelines in an audit from 2010,[25] and only 28% fulfilled all recommendations in an audit from Australia in 1995.[26] Report completeness improves over time, and with ongoing audits, more recent European studies have shown . 94% complete reports according to EUSOMA standards.[27,28]

In this audit, the variation in report quality among sites is more worrisome than the overall results and point toward differences in provincial health care administration and resources and interlaboratory differences between academic NHLS laboratories and the private laboratories that process the outsourced state patient specimens. Although Gauteng units did not meet EUSOMA standards, they consistently reported on most parameters, including grade and Ki-67. Both units had almost all their specimens reported by the respective NHLS laboratories, whereas the majority of reports in KZN were from private, nonacademic laboratories. One of the most pertinent differences is the use of standardized synoptic reports at both CMJAH and CHBAH NHLS laboratories, whereas the reporting in KZN was predominantly free text at the time of the study. Templates and synoptic reporting increase report completeness, they ensure a clearer communication of core data to the treating multidisciplinary team, they increase satisfaction among all team members, and they may also increase awareness of QIs among pathologists.[29,30] In our study, the most disadvantageous effect of free text reporting was observed at IALCH, where clear documentation of tumor grade, a critical oncology parameter for clinical decision making, was missing in an extremely high number of cases.

There are three interventions that have consistently led to higher quality of reporting in the literature. First, pathology departments that have reporting templates with checklists and synoptic reports have shown higher report completeness.[25,26,29-31] Second, the process of audits has facilitated increasing completeness after each audit process, and third, the implementation of national recommendations or a guideline often improves report adequacy.[31-34]

There are several limitations to this study. First, this is a retrospective review. However, data were collected in a prospective manner for the SABCHO study, and missing data were minimal. All reports with missing parameters were rechecked in the clinical database and with laboratories. This data set only includes two provinces and is therefore not fully representative of all South African provinces. In addition, the audit was of a

clinical cohort, and the results may not be entirely reflective of the laboratories' overall standards. Although the majority of specimens in KZN were reported by private laboratories, there are no specific data on private versus public laboratory sites to enable precise comparisons. Nevertheless, there are also

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clear strengths to this study, such as the large sample size and multicenter design. To our knowledge, this is the largest breast histopathology audit from an LMIC to date.

In conclusion, the quality of histopathology reporting of breast cancer specimens in South Africa is not uniform among academic breast units and can be improved. Special efforts should be made to improve reporting of tumor grade and HER2 confirmatory tests as well as excision margins, pathologic staging, and LVI. From a clinical point of view, we also recommend routine testing and guideline-adherent reporting of Ki-67 for more accurate risk assessment in the absence of multigene arrays. Reporting standards vary across laboratories, and a South African pathology consensus is required, including a national target for TATs. All pathology services should use data sheets and synoptic reports to improve completeness and communication to the clinician. Increasing pathology resources and ongoing quality audits or accreditation processes within pathology services should be encouraged to continually improve standards countrywide. In the absence of a consensus and standardized reporting, the responsibility will remain with the treating clinician to request clinically adequate reports and ensure patient safety.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1 Subanalysis of IHC-Based Subtype in Black Patients Only

Reporting Element	Institution, No. (%)					
	Total	CHBAH	CMJAH	IALCH	GH	P
No. of patients	1,417	590	322	225	280	
IHC-based subtype						, .001
Luminal A	227 (17.6)	68 (12.2)	61 (20.1)	68 (31.9)	30 (13.8)	
Luminal B + HER2 negative	508 (39.3)	237 (42.5)	113 (37.2)	58 (27.2)	100 (46.1)	
Luminal B + HER2 positive	239 (18.5)	131 (23.5)	55 (18.1)	28 (13.1)	25 (11.5)	
HER2 enriched	110 (8.5)	33 (5.9)	27 (8.9)	26 (12.2)	24 (11.1)	
Triple negative	207 (16.0)	88 (15.8)	48 (15.8)	33 (15.5)	38 (17.5)	
Unknown	126	33	18	12	63	

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey's Hospital; HER2, human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry.

TABLE A2 IHC-Based Subtype With Ki-67 Cutoff ≤ 14%

Institution, No. (%)

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Variable	Total	CHBAH	CMJAH	IALCH	GH	P
No. of patients	1,850	643	442	409	356	
IHC-based subtype for core biopsy						, .001
Luminal A	302 (17.8)	57 (9.4)	80 (19.1)	132 (34.1)	33 (11.7)	
Luminal B + HER2 negative	703 (41.5)	279 (46.0)	178 (42.5)	108 (27.9)	138 (48.9)	
Luminal B + HER2 positive	285 (16.8)	144 (23.8)	62 (14.8)	47 (12.1)	32 (11.3)	
HER2 enriched	136 (8.0)	35 (5.6)	34 (8.1)	41 (10.6)	27 (9.6)	
Triple negative	268 (15.8)	92 (15.2)	65 (15.5)	59 (15.2)	52 (18.4)	
No. unknown	156	37	23	22	74	

Abbreviations: CHBAH, Chris Hani Baragwanath Academic Hospital; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; GH, Grey's Hospital; HER2, human epidermal growth factor receptor 2; IALCH, Inkosi Albert Luthuli Central Hospital; IHC, immunohistochemistry; Ki-67, protein encoded by the MKI67 gene.

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EPIDEMIOLOGY

A comparison of complete pathologic response rates following neoadjuvant chemotherapy among South African breast cancer patients with and without concurrent HIV infection

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Abstract

Purpose Among patients diagnosed with breast cancer (BC), women also living with HIV (WLWH) have worse survival than women without HIV. Chronic HIV infection may interfere with the effectiveness of BC treatment, contributing to this disparity. We attempted to determine the impact of HIV infection on response to neoadjuvant chemotherapy (NACT) among South African women with BC.

Methods We evaluated women from the South African Breast Cancer and HIV Outcomes cohort study who had stage I–III disease, initiated NACT, underwent definitive breast surgery, and had available surgical pathology reports. We compared pathologic complete response (pCR) rates among women with and without HIV infection, using multivariable logistic regression to control for differences in tumor characteristics. We also evaluated the impact of HIV infection on pCR within subgroups based on patient and tumor factors.

Results Of 715 women, the 173 (24.2%) WLWH were less likely to achieve pCR than women without HIV (8.7% vs 16.4%, [odds ratio (OR) 0.48, 95% confidence interval (95% CI) 0.27–0.86]). WLWH continued to have lower likelihood of

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achieving pCR on multivariable analysis (OR 0.52, 95% CI 0.28–0.98). A similar pattern was seen within subgroups, although HIV infection appeared to affect pCR more in ER/PR-positive BC (OR 0.24, 95% CI 0.08–0.71) than in ER/PR-negative BC (OR 0.94, 95% CI 0.39–2.29).

Conclusion WLWH were less like to achieve pCR following NACT for BC than women without HIV. This reduced response to systemic therapy may contribute to the poorer BC outcomes seen in WLWH.

Keywords HIV · Neoadjuvant chemotherapy response · Global oncology · South Africa

Introduction

Among people living with HIV (PLWH) around the world, widespread access to antiretroviral therapies (ART) has steadily slowed progression to AIDS and improved life expectancy [1–3]. HIV remains strongly associated with the development of the AIDS-defining cancers (ADCs): Kaposi's sarcoma, non-Hodgkin lymphomas and cervical cancer, but their incidence has declined [4]. Concurrently, the incidence of non-AIDS-defining cancers (NADCs) among PLWH has increased [5]. Among PLWH in the United States (US), the proportion over 65 years old is projected to increase from 9 to 21% between 2010 and 2030, and NADCs, many of which are age-related, are expected to become eightfold more common than ADCs [6]. SubSaharan Africa (SSA) is home to 20.6 million of the world's 37.9 million PLWH, and approximately 75% of women living with both HIV and breast cancer (BC) currently reside in SSA [7, 8]. The number of BC cases diagnosed annually in SSA is projected to nearly double by 2040, and the number of women living with HIV (WLWH) and BC in SSA can also be expected to grow [9].

Sarah Nietz and Daniel S. O'Neil have contributed equally to the preparation of this manuscript.

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Even though HIV does not increase the risk of developing BC, it does appear to affect clinical outcomes [10–12]. Cancer and HIV registry data from the US demonstrate worse cancer-specific mortality [hazard ratios (HRs) range 1.85–2.64] and overall mortality (HR 1.85) among BC patients living with HIV than among uninfected women [13–15]. SSA lacks comparable registry data, but in small retrospective cohorts from Uganda and South Africa, WLWH and BC have been found to have non-significantly higher mortality than those with BC alone (HR range 1.4–2.0) [16, 17]. Although external factors, such as differences in socioeconomic status and treatment utilization patterns, may explain some of these survival disparities, differences in tumor biology and drug interactions may also contribute [15, 18, 19]. Even virally suppressed WLWH show immunologic deficiencies that might diminish inherent anti-tumor immune surveillance or response to systemic BC therapies [20]. Beyond the theoretical, responses to BC treatment among WLWH have seldom been studied.

In South Africa, most non-metastatic breast cancer patients present with locally advanced disease and have an indication for chemotherapy [21]. Among these women, 60% receive their chemotherapy before surgery [22]. In the United States, where women present with earlier stage disease, approximately a third of chemotherapy for non-metastatic disease is neoadjuvant, with the proportion increasing over time [23]. Pathologic complete response (pCR) following neoadjuvant chemotherapy (NACT) is associated with reduced BC recurrence and improved overall survival, and a comparison of pCR rates among women with and without HIV may provide insight into one possible way that HIV might impact BC outcomes [24, 25]. Expected pCR rates vary by molecular subtype. Recent neoadjuvant clinical trial data show complete response rates of 17% with estrogen or progesterone receptor (ER/PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative BC, 40–68% with HER2-positive BC, and 42% with triple-negative BC [26]. Rates seen in SSA may be lower, particularly for HER2positive disease, given the absence of targeted therapies.

This study aimed to compare South African BC patients' responses to NACT by HIV status and to explore tumor and HIV-related factors that might influence those responses.

Methods

We conducted a retrospective cohort study among a subgroup of women enrolled in the South African Breast Cancer and HIV Outcomes (SABCHO) study, comparing pCR rates following NACT between women with and without HIV infection.

Context and setting

South Africa is an upper middle-income country with a high degree of income inequality and co-existing private and public healthcare systems that produce significantly different BC outcomes [27–29]. State-funded cancer care available at public tertiary and quaternary hospitals includes surgery, chemotherapy, endocrine therapy, and radiation therapy, although timely access to these modalities is highly variable [30]. The most commonly used BC chemotherapy regimens are anthracycline and cyclophosphamide, with or without 5-fluorouracil, and usually followed by a taxane. Adjuvant trastuzumab was added to the National Essential Medicines List in 2019, but HER2targeted agents were not available during our study period. National HIV prevalence is 14.0% overall and 20.6% among black women [31]. National guidelines during the study period recommended ART initiation for all PLWH whose CD4 counts were < 350 cells/mL. All PLWH with a new cancer diagnosis are also initiated on ART regardless of CD4 count. In 2018, the guidelines were changed to recommend ART for all PLWH. The standard first-line regimen during the study period was fixed-dose combination tenofovir, emtricitabine, and efavirenz. The most common second-line ART was combination abacavir and lamivudine with ritonavir-boosted lopinavir.

Since July 2015, the SABCHO study has been prospectively enrolling women newly diagnosed with BC and presenting to the oncology clinics at five public South African hospitals [32]. The study's primary aim is to characterize the impact of HIV on BC biology and its clinical course. Participating hospitals are in the provinces of Gauteng and KwaZulu Natal, serving both rural and urban populations. Women eligible for SABCHO enrollment were over 18 years of age, newly diagnosed with histologically proven BC, had no history of other invasive cancers, received their BC care at a study hospital, and provided signed informed consent.

Participants

We analyzed data from women who had been enrolled between July 1, 2015, and December 31, 2018, had known HIV status, had American Joint Committee on Cancer 7th edition stage I-III disease, and had received at least 2 cycles of NACT. For our primary analysis of pathologic response, we included only those women who underwent curative-intent surgery and had available reports of their surgical specimen pathology.

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Data collection, variables, and outcomes

All study data had been prospectively collected as part of SABCHO study procedures. We extracted information on participant age, height, weight, ethnicity, highest educational level, employment status, clinical tumor size and nodal status, clinical stage, tumor grade, ER/PR status, HER2 expression, Ki-67 index, NACT combinations used, and number of cycles received. HIV status at the time of BC diagnosis was determined by screening serology testing or self-report in known WLWH. Among WLWH, CD4 count and viral load levels were captured at the time of BC diagnosis. Sociodemographic data were gathered through patient questionnaires. A household wealth variable was created by conducting principal component analysis of data from a patient survey of household possessions and facilities and ranking individuals into quintiles using the first principal component value. Laboratory and pathology data were generated by either the National Health Laboratory Service of South Africa or private laboratories accredited by the South African National Accreditation System. We extracted other clinical data from a study database that also served as an electronic medical record system for participating study sites. Trained study staff also reviewed clinic paper medical records for any data missing from the electronic study database.

Our primary outcome was pathologic complete response (pCR) rate, defined as absence of invasive BC in the breast and sampled regional lymph nodes. According to this definition, patients with only residual carcinoma in situ still qualified as having had a pCR.

Statistical considerations

Study participants were categorized by HIV infection status at the time of BC diagnosis. Descriptive statistics and chi-squared tests were used to compare sociodemographic and clinical characteristics of women with and without HIV. We then compared the groups' pCR rates, reporting a crude odds ratio and *p*-value from chi-squared testing. We followed with multivariable logistic regression to account for possible confounding by demographic and clinical factors. The model included clinical variables selected a priori for their known impact on NACT response: age (< 40 vs 40–49 vs 50–59 vs ≥ 60 years), clinical T-stage (0–2 vs 3–4), clinical N-stage (0 vs 1–3), ER/PR status, and HER2 status. We selected additional model covariates by analyzing all other collected variables for a significant association with pCR, using univariable logistic regression analysis (Wald testing $p \leq 0.1$). Only body mass index (BMI) at the time of diagnosis (< 25 vs 25–29.9 vs ≥ 30.0 kg/m^2) met this threshold; it was also added to the multivariable model. We reported odds ratios

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(OR) for age-adjusted crude association of each covariate with pCR and for the full multivariable model.

To evaluate for effect modifiers, we repeated the multivariable analysis using the same covariates within subgroups based on age (< 40, 40–49, 50–59, ≥ 60 years), ethnicity (Black African, Others), province of treating hospital (Gauteng, KwaZulu Natal), household wealth quintile, BMI (< 25, 25–29.9, ≥ 30 kg/m^2), clinical T-stage (0–2 vs 3–4), clinical N-stage (0 vs 1–3), tumor grade (Bloom-Richardson Grade 1–2, Grade 3), ER/PR status, and HER2 status. We reported the OR of pCR in WLWH versus women without HIV within each subgroup. We also individually added an interaction term between HIV status and each of the above characteristics to the full multivariable model and report the *p*-value of Wald testing for each interaction term.

As an exploratory analysis, among only WLWH, we compared pCR rates within subgroups based on current ART use, viral load (≤ 100 vs > 100 copies/mL), and CD4 count (≤ 200 vs > 200 cells/μL) at time of BC diagnosis, while also adjusting for the covariates used in the previously described multivariable model.

For our primary analysis, evaluating only patients with surgical pathology meant excluding those that progressed on NACT and never underwent surgery. We conducted a sensitivity analysis to check for an association between HIV infection and failure to undergo surgery after NACT initiation.

Analyses were performed using SAS v9.4 (Cary, North Carolina) and Fig. 2 was created using RStudio v1.2 (Boston, Massachusetts).

Ethics

All participants provided written informed consent for data collection and analysis. The SABCHO study and this project are overseen by the Human Research Ethics Committees of the University of Witwatersrand (Johannesburg), the University of KwaZulu Natal (Durban), and the Institutional Review Board of Columbia University Irving Medical Center (New York City).

Results

During the study period, 2898 women were enrolled in the SABCHO study (Fig. 1). Of these, 2365 had stage I–III disease, 956 initiated NACT, and 728 subsequently

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received definitive surgery. Surgical pathology reports were available for 715 of these women, all of whom were included in our primary analysis (Fig. 1).

Of the 715 women, 173 (24.2%) were WLWH at the time of BC diagnosis and 542 (75.8%) were HIV-negative (Table 1). The WLWH were younger than those without HIV

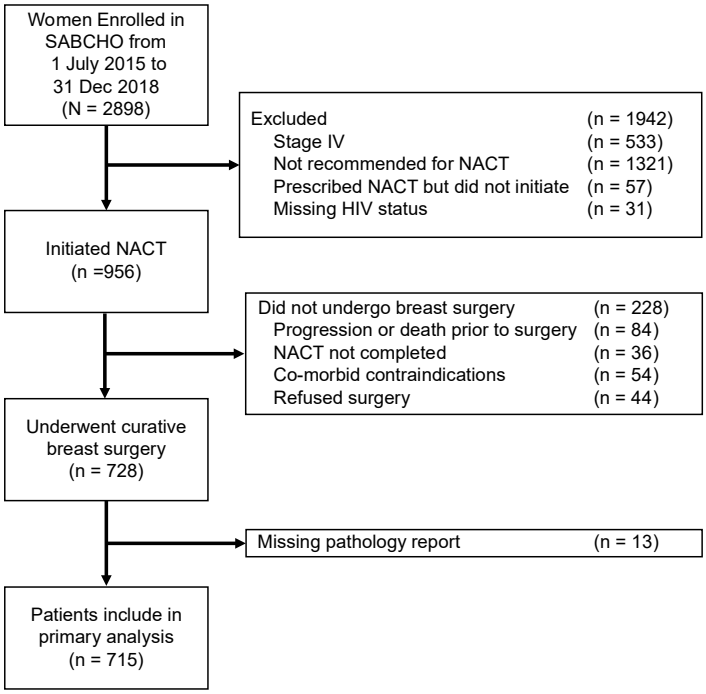


Fig. 1 Patients included in the primary analysis. *NACT* neoadjuvant chemotherapy, *SABCHO* South African Breast Cancer and HIV Outcomes study

(30.1% vs 14.9% < 40 years old; 7.5% vs 33.2% ≥ 60 years old). Larger proportions were black Africans (98.8% vs 71.0%), employed (44.5% vs 30.8%), and in the lowest quintile of the household wealth index (31.8% vs 14.0%). A larger proportion had body mass index < 25 kg/m^2 (26.0% v 12.0%), but a smaller proportion had grade 3 tumors (37.0% vs 50.1%). HIV status was not associated with clinical T-stage, clinical N-stage, ER/PR status, HER2 status, anthracycline use, or taxane use.

In the full cohort, 15 (8.7%) WLWH and 89 (16.4%) women without HIV had a pCR (OR 0.48, 95% confidence interval (95% CI) 0.27–0.86, p = 0.01). In multivariable analysis, WLWH remained less likely to achieve pCR than women without HIV (OR 0.52, 95% CI 0.28–0.98), and covariates age, clinical T-stage, clinical N-stage, and HER2 status were not associated with pCR. The only covariates significantly associated with likelihood of pCR were ER/PR status and BMI (≥ 30 compared with < 25 kg/m^2) (Table 2).

Within nearly all clinical subgroups evaluated, smaller proportions of WLWH than of women without HIV had a pCR (Fig. 2). The impact of HIV on pCR appeared greatest in women with ER/PR-positive BC (OR 0.24, 95% CI 0.08–0.71) and no impact was appreciable in women with ER/PR-negative

disease (OR 0.94, 95% CI 0.39–2.29). A significant interaction was also seen between ER/PR status and HIV status on likelihood of pCR (p = 0.03). HIV infection also seemed to have a diminishing association with pCR as BMI increased, but the interaction between BMI and HIV status was non-significant (p = 0.23) (Fig. 2).

In our exploratory analysis of the 173 WLWH, neither current ART use, nor viral load, nor CD4 count at BC diagnosis was associated with pCR (Table 3). However, of the 173 WLWH, just 36 (20.8%) were not using ART and just 12 (6.9%) had CD4 counts ≤ 200 cells/mL at time of BC diagnosis, limiting our power to detect a difference in pCR rates.

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Among the 228 women who did not receive surgery after NACT, 94 progressed or died on NACT, 36 defaulted treatment, 44 refused surgery, and 54 were deemed ineligible for surgery due to comorbidities. The proportions of WLWH and women without HIV who did not undergo surgery after initiating NACT were similar (27.2% vs 22.3%, $p = 0.12$).

Characteristic	HIV Positive *N* = 173 *n* (%)	HIV Negative *N* = 542	Total *N* = 715	*p*-value[a]
Age (years) < 40	52 (30.1)	81 (14.9)	133 (18.6)	< 0.001
40–49	78 (45.1)	135 (24.9)	213 (29.8)	
50–59	30 (17.3)	146 (26.9)	176 (24.6)	
≥ 60	13 (7.5)	180 (33.2)	193 (27.0)	
Ethnicity Black African	171 (98.8)	385 (71.0)	556 (77.8)	< 0.001
Others	2 (1.2)	157 (29.0)	159 (22.2)	
Hospital Province				
Gauteng	96 (55.5)	304 (56.1)	400 (55.9)	0.89
KwaZulu Natal	77 (44.5)	238 (43.9)	315 (44.1)	
Highest level of education				
No education/primary school only	29 (16.9)	118 (21.9)	147 (20.6)	0.16
Secondary education and above	143 (83.1)	422 (78.1)	565 (79.4)	
Missing	1	2	3	
Employment status				
Employed	77 (44.5)	167 (30.8)	244 (34.1)	0.001
Unemployed	96 (55.5)	375 (69.2)	471 (65.9)	
Household wealth index				
< 20th percentile (least wealthy)	55 (31.8)	76 (14.0)	131 (18.3)	< 0.001
20th–39th percentile	45 (26.0)	107 (19.7)	152 (21.3)	
40th–59th percentile	32 (18.5)	105 (19.4)	137 (19.2)	
60th–79th percentile	22 (12.7)	126 (23.3)	148 (20.7)	
≥ 80th percentile (most wealthy)	19 (11.0)	128 (23.6)	147 (20.6)	
Body mass index (kg/m^2) < 25	44 (26.0)	63 (12.0)	107 (15.4)	< 0.001

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5 **Table 1** Sociodemographic and clinical characteristics of SABCHO cohort members who received neoadjuvant chemotherapy, by HIV status

	25–29.9	45 (26.6)	135 (25.7)	180 (25.9)	
	≥ 30.0	80 (47.3)	327 (62.3)	407 (58.7)	
	Missing	4	17	21	
Clinical T-stage 1–2					
		44 (25.4)	148 (27.3)	192 (26.9)	0.89
	3	46 (26.6)	142 (26.2)	188 (26.3)	
	4	83 (48.0)	252 (46.5)	335 (46.9)	
Clinical N-stage 0					
		22 (12.7)	89 (16.4)	111 (15.5)	0.52
	1	87 (50.3)	243 (44.8)	330 (46.2)	
	2	51 (29.5)	172 (31.7)	223 (31.2)	
	3	13 (7.5)	38 (7.0)	51 (7.1)	
Grade 1–2					
		87 (63.0)	209 (49.9)	296 (53.1)	0.007
	3	51 (37.0)	210 (50.1)	261 (46.9)	
	Missing	35	123	158	
ER/PR status Positive					
		128 (74.0)	373 (68.8)	501 (70.1)	0.20
	Negative	45 (26.0)	169 (31.2)	214 (29.9)	

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Table 1 (continued)

Table 2 Odds ratios for pathologic complete response (pCR) to neoadjuvant chemotherapy, adjusted for various clinical factors
(*N* = 690)

1 3						
≥ 60	26/188 (13.8)	1.04 (0.54–2.00)	0.76	0.65 (0.32–1.33)	0.12	
Clinical T-stage 1–2						
Characteristic	HIV Positive *N* = 173 *n* (%)	HIV Negative *N* = 542	Total *N* = 715	*p*-value[a]		
3–4	36/186 (19.4)	65/504 (12.9)	1 (Ref) 0.61 (0.39–0.96)	0.03	1 (Ref) 0.73 (0.45–1.19)	0.21
HER2 status Positive						
Clinical N-stage 0						
	56 (32.7)	148 (27.5)	204 (28.7)	0.13		
Negative	107 (62.6)	377 (69.9)	484 (68.2)			
1–3	22/166 (20.8)	79/584 (13.5)	1 (Ref) 0.60 (0.36–1.02)	0.06	1 (Ref) 0.71 (0.41–1.26)	0.24
Equivocal	8 (4.7)	14 (2.6)	22 (3.1)			
ER/PR Status Positive						
		46/481 (9.6)	0.29 (0.19–0.45)	< 0.001	0.31 (0.20–0.48)	< 0.001
Missing	2	3	5			
Negative		55/209 (26.3)	1 (Ref)		1 (Ref)	
Ki-67						
HER2 Status Positive						
< 15%	37 (23.1)	120 (23.9)	157 (23.7)	0.85		
Negative						
≥ 15%	123 (76.9)	383 (76.1)	506 (76.3)			
		32/189 (16.1)	1.17 (0.71–1.84)	0.50	1.20 (0.75–1.93)	0.45
		69/491 (14.1)	1 (Ref)		1 (Ref)	
Missing	15	39	52			
BMI (kg/m^2)						
< 25		7/105 (6.7)	1 (Ref)		1 (Ref)	
25–29.9		27/180 (15.0)	2.51 (1.05–5.99)	0.17	1.97 (0.81–4.80)	0.45
≥ 30		67/405 (16.5)	2.79 (1.24–6.29)	0.03	2.45 (1.06–5.63)	0.04
Anthracycline-containing NACT Yes	169 (97.7)	510 (94.1)	679 (95.0)	0.07		
No	4 (2.3)	32 (5.9)	36 (5.0)			
Taxane-containing NACT Yes						
	160 (92.5)	500 (92.3)	660 (92.3)	0.92		
No	13 (7.5)	42 (7.7)	55 (7.7)			

BMI body mass index, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *PR* progesterone receptor

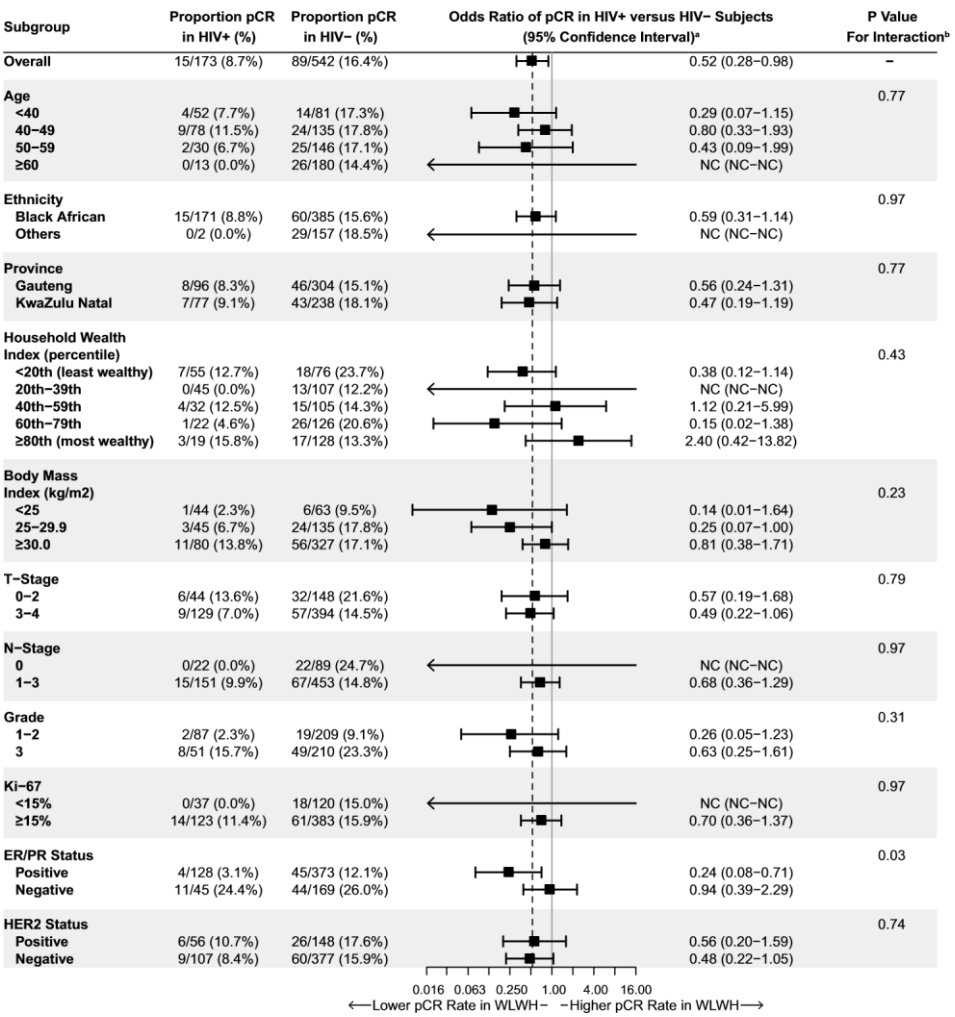
ER estrogen receptor, *HER2* human epidermal growth factor receptor 2, *NACT* neoadjuvant chemotherapy, *PR* progesterone receptor, *SABCHO* South African Breast Cancer and HIV Outcomes study [a] Chi-squared testing

Covariate	pCR/total (%)	Age-adjusted crude analysis		Full multivariable model analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
HIV status Positive					
	15/167 (9.0)	0.47 (0.26–0.85)	0.01	0.52 (0.28–0.98)	0.04
Negative	86/523 (16.4)	1 (Ref)		1 (Ref)	
Age (years) < 40					
	17/127 (13.4)	1 (Ref)		1 (Ref)	
40–50	32/209 (15.3)	1.17 (0.62–2.21)	0.72	1.05 (0.54–2.04)	0.37
50–60	26/166 (15.7)	1.20 (0.62–2.33)	0.63	0.93 (0.46–1.88)	0.84

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Fig. 2 Relative risk of stage, ER/PR status, HER2 status, and BMI values as defined for the logistic regression model presented in

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complete pathologic response following neoadjuvant chemotherapy according to HIV status. **a** Adjusted for age, clinical T-stage, clinical N-stage, ER/PR status, HER2 status, and BMI values as defined for the logistic regression model presented in Table 2. **b** Wald testing of the interaction between the listed characteristic and HIV status within the logistic regression model presented in Table 2. *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *NC* non-calculable, *pCR* complete pathologic response, *PR* progesterone receptor, *WLWH* women living with HIV

Discussion

1 3

We found that a smaller proportion of WLWH than of women without HIV achieved a pCR following NACT (OR 0.52, 95% CI 0.28–0.98). We performed various subgroup analyses, classifying patients by a variety of demographic and clinical characteristics. The differences in pCR rates between women with and without HIV were similar in

presented in Table 2

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Table 3 HIV-related factors and complete pathologic response to neoadjuvant chemotherapy among women living with HIV at time of breast cancer diagnosis

Characteristic	Complete response *N* = 15 *n* (%)	Residual cancer *N* = 158	Total *N* = 173	OR (95% CI)[a]	*p*-value[a]
ART use Yes	11 (8.0)	126 (92.0)	137 (100.0)	1 (Ref)	0.92
No	4 (11.1)	32 (88.9)	36 (100.0)	1.13 (0.11–11.75)	
HIV viral load (copies/mL) ≤ 100	8 (7.3)	101 (92.7)	109 (100.0)	1 (Ref)	0.73
> 100	7 (10.9)	57 (89.1)	64 (100.0)	0.71 (0.10–4.91)	
CD4 count (cells/mL) > 200	13 (8.1)	148 (91.9)	161 (100.0)	1 (Ref)	0.18
≤ 200	2 (16.7)	10 (83.3)	12 (100.0)	5.87 (0.44–78.98)	

ART antiretroviral therapy

[a] Adjusted for age, clinical T-stage, clinical N-stage, ER/PR status, HER2 status, and BMI values as defined for the logistic regression model

magnitude in most categories across these groups, although in the smaller subgroups they were not statistically significant. The greatest discrepancy in subgroups was between women with ER/PR-positive cancers (among whom HIV reduced the prospect of pCR by more than 70%) and those with ER/PR-negative cancers (among whom HIV made no difference). Within the BMI subgroup, HIV seemed to have more impact on NACT response in normal and underweight women, but a significant interaction was not appreciated. Among WLWH, ART use, viral suppression, and CD4 count did not appear to affect the response to NACT, though the power of that analysis was limited by the relatively few women with poorly controlled HIV, a tribute to the success of the ART rollout in South Africa over the past decade.

Our findings have several possible explanations. WLWH and women without HIV differed in several patient and tumor characteristics, some of which we were not able to control through regression analysis. Women with high histologic grade BCs are more likely than those with lower grade tumors to achieve pCR, and the WLWH in our cohort had fewer high grade tumors (37% vs 50%) [33–35]. We excluded grade from our multivariable analyses because 158 women (22.1%) were missing data and because the local clinician authors questioned the reliability of the grade data that were available. WLWH were also more likely to be of African ancestry, but black race does not appear to impact pCR rates in studies that account for tumor and treatment heterogeneity [36–39]. Race was also not associated with response on univariable analysis of this group of women. Because WLWH in our cohort were poorer and more likely to be employed than women without HIV, they could theoretically have been less adherent to NACT. However, because neither of those factors was associated with

likelihood of pCR on univariable testing, their influence is also likely to have been too small to explain our findings.

The association we observed between obesity and pCR was unexpected. Higher BMI is generally associated with worse BC outcomes and lower pCR rates [39–43]. Recent work suggests that the balance and distribution of adipose tissue and skeletal muscle play a role in chemotherapy sensitivity and survival [44, 45]. We did not have detailed anthropometric measurements of our study participants or data on sarcopenia. Lower body weight among WLWH may have correlated with more HIV-related comorbidities, which could decrease chemotherapy tolerance. If lower weight WLWH required more frequent reductions in chemotherapy dose, their chance for pCR would also be diminished.

Chronic HIV infection may itself impair the response to chemotherapy. The immune system's contribution to BC control is well documented: both tumor-infiltrating lymphocyte (TIL) density and programmed death-ligand 1 (PDL1) expression are predictive of NACT response and overall prognosis [46–51]. Even with effective viral suppression, PLWH have continued immune dysregulation, including fewer circulating CD4 + and CD8 + naïve T-cells and fewer mucosal CD4 + T-cells [52]. The tumor microenvironment of BC in WLWH has not been

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described. In anal cancer, cutaneous squamous cell cancer, and B-cell lymphomas, TIL density and PD-L1 expression differ between patients with and without HIV infection, suggesting differences in antitumor immune response [53–56]. However, triple-negative and HER2-positive BC are more immunogenic than ERpositive BC [57]. If HIV-associated immune dysregulation were the primary driver of lower sensitivity to NACT, a stronger association would have been expected in the ERnegative subgroup.

Chronic HIV infection is also accompanied by a persistent proinflammatory state, detectable through elevated circulating inflammatory markers (e.g., CRP, IL-6, fibrinogen, D-dimer) and associated with increased coronary artery disease, dementia, and other diseases of aging [58]. The proinflammatory environment generated by white adipose tissue is thought to mediate the poor prognosis and reduced chemotherapy sensitivity of obese women with BC [59]. HIV-related inflammation may similarly impair chemotherapy response.

HIV infection may also indirectly decrease chemotherapy responsiveness through drug-drug interactions between ART and chemotherapeutic agents, which have been described [60]. Efavirenz (a non-nucleoside reverse transcriptase inhibitor) is a potent CYP3A4 inducer. Thankfully, pharmacokinetic studies have not yet shown meaningful changes in exposure to anthracyclines, alkylating agents, or taxanes from concurrent use of CYP34Ainducing ART medications [61]. On the other hand, CYP34A inhibitors, such as ritonavir (a protease inhibitor), may increase toxicity from taxanes and make it difficult to deliver full dose treatment on schedule [61, 62].

Widespread efavirenz use in our cohort may also contribute to the larger observed impact of HIV infection on chemotherapy responsiveness in ER/PR-positive disease. Efavirenz causes gynecomastia in 6–8% of exposed African men [63–65]. In vitro studies have demonstrated efavirenz's direct effects on the estrogen receptor, including an ability to induce growth in ER-positive BC cell lines [66]. Further research on pCR and survival patterns in WLWH and using efavirenz is needed before making specific recommendations about modifying ART regimens for breast cancer patients.

This study has several limitations. We did not have data on chemotherapy relative dose intensity. As in much of the world, WLWH in South Africa have overlapping socioeconomic factors that might impact reliable and complete treatment adherence. The lower body weights seen among WLWH may also suggest a higher comorbidity burden that could impact chemotherapy tolerance. However, we do not know if a systematic difference in total chemotherapy exposure could explain our findings. We plan to address that question in future work. Of note, our earlier work found that South African WLWH from an overlapping cohort did not received lower quality BC care, as measured using 3 standard process metrics [30]. The pCR rate seen in our entire cohort was lower than those observed in high-income countries (HICs), probably due in part to the late presentations, large primary tumors, and extensive nodal disease seen in South Africa [33, 34, 67]. The lack of HER2-targeted treatments certainly decreased response in HER2 + women. These differences mean our results may be less generalizable to HICs. Nonetheless,

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they are relevant to the lower-resourced settings where the large majority WLWH and BC are diagnosed and treated.

Given that three-quarters of the world's WLWH and BC live in SSA, the study of HIV's impact on BC must include African women. Our study may be the largest describing WLWH who have received NACT for BC to date. We found compelling evidence that WLWH had a poorer response to NACT and were less likely to achieve pCR than women without HIV. That pattern seemed to be present across various subgroups and persisted after accounting for any differences in age, BMI, tumor stage, and BC subtype. PCR following NACT predicts improved diseasefree and overall survival, and the differences in chemotherapy responsiveness that we observed may contribute to the disparities in survival seen between BC patients with and without concurrent HIV infection [14, 17, 25]. Further work is needed to clarify the extent to which our findings are explained by the differences in chemotherapy exposure, HIV-associated immune dysregulation, chronic inflammation, or pharmacologic interactions.

Author contributions All authors contributed to the initial design of this study and interpretation of the data. SN, MJ, PR, IB, US, SČ, LS, and HC all participated in patient recruitment and contributed data. SN, DSO, OA, and WCC conducted the primary data analysis. DSO and SN wrote the initial manuscript and prepared the included tables and figures. AIN, PR, and HC provided supervision. All authors contributed revisions to the manuscript and approved of the final manuscript prior to submission.

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Data Availability The datasets generated during and analyzed during the current study are not publicly available due to local national policy but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest Dr. Neugut has received consulting fees from Otsuka, UBC, Hospira and EHE International. Dr. Ruff has received honoraria from Sanofi, Amgen, and Roche and research funding from Amgen, Sanofi,

Merck, Novartis. All other authors declare they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of Columbia University in New York City and the human research ethics committees of the University of Witwatersrand in Johannesburg and the University of KwaZulu Natal in Durban and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human and animal participants This article does not contain any studies with animals performed by any of the authors.

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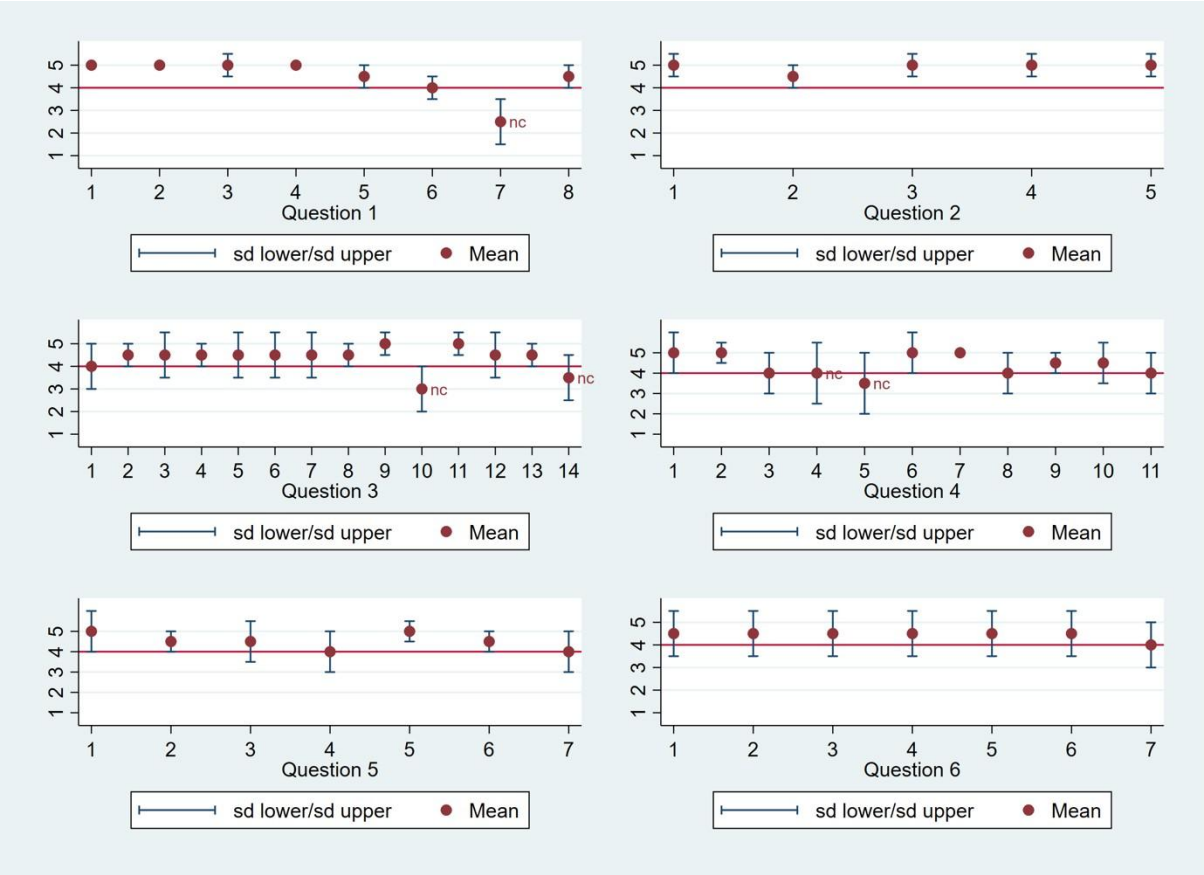
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Appendix G: Supplemental Tables

Chapter 3

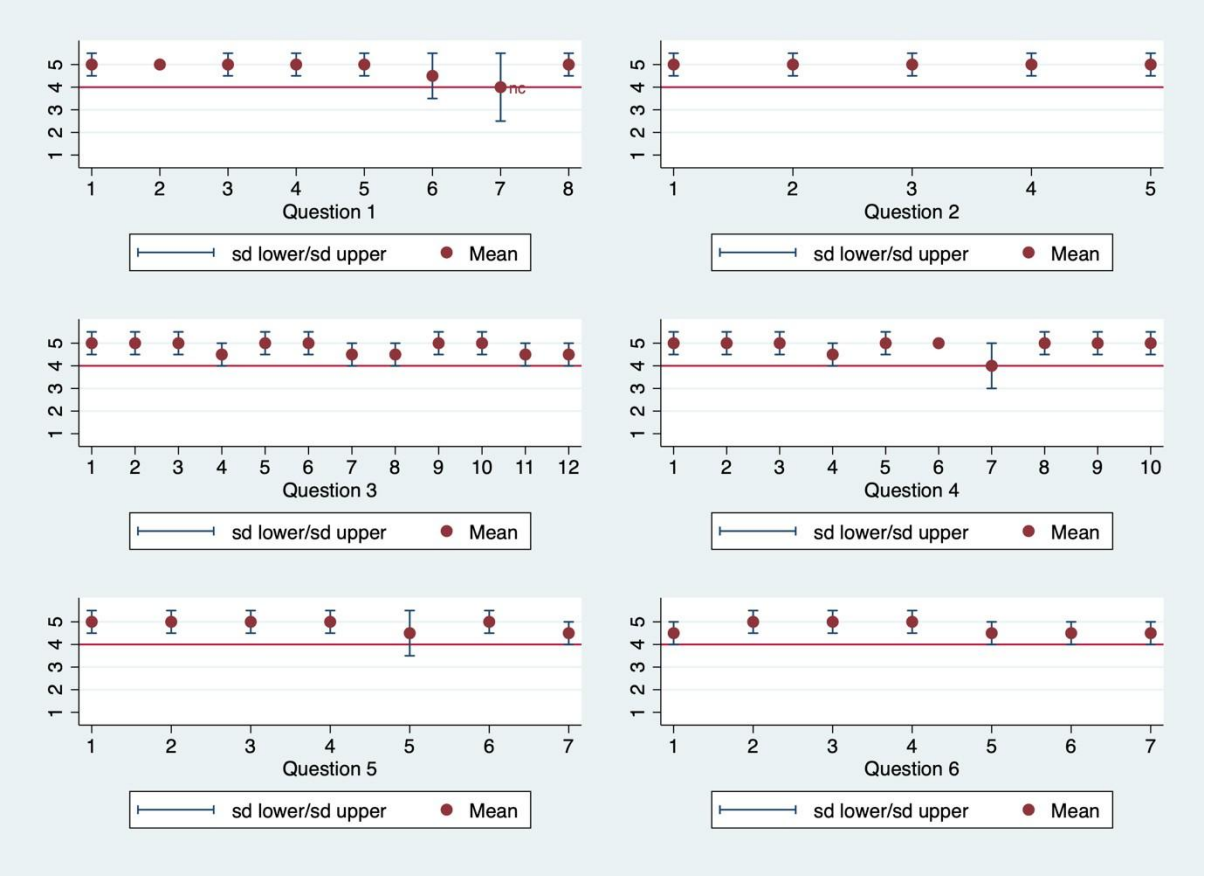
Supplementary Figure 1: Round 1 rating on importance to measure (relevance and priority)



nc = no consensus

Question complexes include indicators on 1) diagnosis, 2) multidisciplinary management, 3) breast surgery, 4) management of the axilla, 5) timeliness of care, 6) structure and outcome

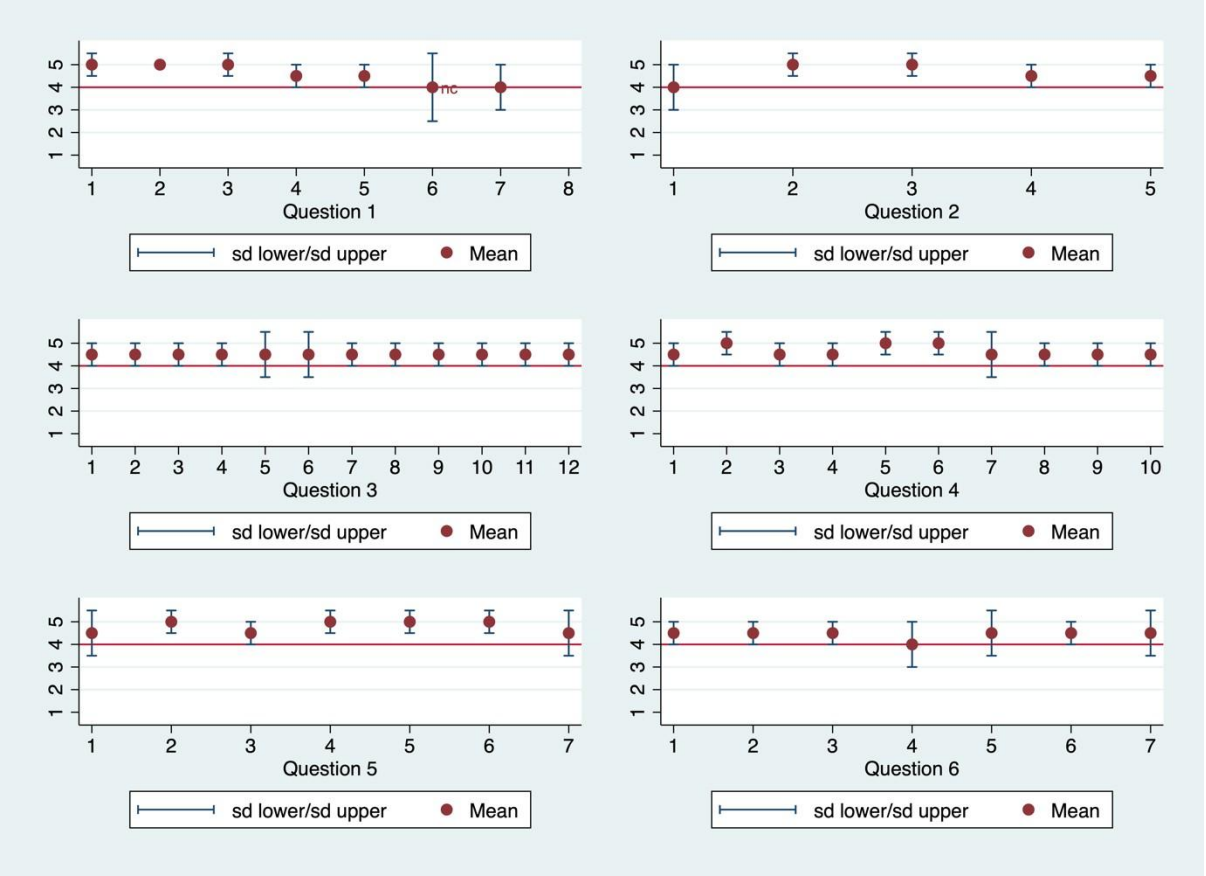
Supplementary Figure 2: Round 2 rating on scientific acceptability (reliability and validity)



nc = no consensus

Question complexes include indicators on 1) diagnosis, 2) multidisciplinary management, 3) breast surgery, 4) management of the axilla, 5) timeliness of care, 6) structure and outcome

Supplementary Figure 3: Round 3 rating on appropriateness to our local setting (feasibility)



nc = no consensus

Question complexes include indicators on 1) diagnosis, 2) multidisciplinary management, 3) breast surgery, 4) management of the axilla, 5) timeliness of care, 6) structure and outcome

Chapter 5

Appendix H: Motivation of Breast Surgery Speciality

Preliminary Application – Breast Surgery Subspecialty

March 2018

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Relevance to the health system

Breast cancer has been regarded as a disease affecting mostly high-income countries (HIC). However incidences in low-to middle income countries (LMIC) have increased due to a combination of factors including better diagnosis and reporting, greater life expectancy, population growth and adoption of western urban lifestyles with less physical activity[1].

GLOBOCAN data predicts a doubling of cancer including breast cancer burden in subSaharan Africa by 2030[2]. According to the pathology-based National Cancer Registry, breast cancer has surpassed cervical cancer as the most common malignancy among females in South Africa (SA)[34]. The increased incidence in SA is partly due to the treatment of HIV with an increasing life expectancy; cancer and other noncommunicable diseases are likely to pose the next major challenge to our health system.

The National Department of Health has recognized cancer and specifically breast cancer as a priority. A National Breast Cancer Policy has been recently developed and efforts are currently underway to establish national clinical guidelines[5].

Outcomes of breast cancer patients in LMICs appear decreased in comparison to those in HICs[678]. Delayed clinical presentation, limited healthcare access and resources are major reasons for disparities in mortality rates between HICs and LMICs[9]. An initiative to train surgical specialists with a specific focus on the management of breast cancer, is thus an important consideration when planning the future health resources of South Africa.

Societal need and gains in health outcomes

SA is regarded as an upper middle income country by the World Bank but also has a high index of inequality[10]. This lack of equality is apparent in the dual health care system with private and public health care. Socioeconomic disparities in our heterogeneous society remain and together with other factors, affect health status[11].

To date, there are few centers in SA that offer specialized multidisciplinary high-quality breast care. According to a European position paper there should be one breast center for every 250.000 total population[12] and the requirements of a specialized breast unit have been well described[13]. In view of this position paper, there appears to be a major lack of breast centers in South Africa. The projected increase in cancer burden further

emphasizes the urgency to develop more cancer centers and to train future breast specialists[1].

Women form a particularly vulnerable population group in SA which experience greater barriers to care. Specialized surgery and treatment centers with guidelineconform treatment will offer and improve structural, process and outcome quality measures. Data on the performance of cancer services in LMICs is scarce and evaluation of key quality indicators (QI) in breast cancer care is required to improve services and assist in policy[14].

Benchmarking and quality indicators (QI) have been developed and applied in HICs and minimum standards were defined which include regular audit and quality control.[151617]. China is the only LMIC and only member of BRICS (Brazil, Russia, India, China, South Africa) to develop QIs to date[18]. Implementation of QIs and benchmarking are manageable in various settings and improve quality of care over time[1920]. Adherence to EUSOMA (European Society of Breast Cancer Specialists) QIs were assessed in 22 breast centres across Europe from 2006 to 2015. The minimum standard was achieved initially in eight out of 13 main QIs but improved to achieve minimum standard in all QIs by 2015[21]. Local quality audits and research are needed to improve quality of healthcare in LMICs and provide insight and answers particular to our setting which will guide future policy[9].

Specialized breast surgeons are required to promote high standard of breast health services which constitute approximately 25% of surgical work load. Adequately trained surgeons will assist the national priority of efficient and cost-effective breast cancer treatment by

- Advocating for centres of excellence with equitable and timeous access to appropriate care
- Promoting guideline-conform treatment
- Training surgeons
- Leading local breast research

Definition of the subspecialty and clinical acceptability

The subspecialty of breast surgery has been long recognized and practiced in various other countries.

A breast surgeon has the expertise to manage the entire scope of breast disease both operatively and non-operatively. This includes benign breast disease, management of high-risk lesions, genetic susceptibility, prevention, diagnosis as well as the management of breast cancer.

Breast cancer is heterogeneous and the management is complex with many steps along the process chain including diagnosis, surgical treatment, facilitation of a multidisciplinary approach and adjuvant therapies, allied health services, navigation and follow-up.

In addition, a breast surgeon should participate in clinical and/or translational research, regular audit and quality control.

Outcomes are improved with greater surgeon volume (proposed minimum of 50 cases per annum operated by a single surgeon) and center volume (more than 150 newly diagnosed cases per annum)[1322]. Patients treated by specialized surgeons and centers are more likely to have breast conserving surgery (BCS), undergo sentinel node biopsy (SLNB), have a lower false-negative rate of SLNB, are more likely to receive appropriate adjuvant therapies and have better outcomes in terms of local recurrence and survival[232425262728–36]. In addition, treatment is more cost-effective and litigation decreases with treatment in specialized centers adhering to benchmarking and quality control[3738].

The treatment of breast cancer is one of the most rapidly advancing fields in medicine with a vast body of knowledge and research and has moved from a “maximum tolerable” to “minimum effective” approach[39].

From a surgical perspective alone, the development of the SLNB is one of the most prominent examples for this transition to less invasive procedures with minimized

riskbenefit ratio[4041]. The application of SLNB has since further expanded. Most notably a positive SLNB does not necessarily require a completion axillary node dissection in select patient groups[424344] and patients who were initially node-positive but converted to clinically node-negative after primary systemic therapy may require a SLNB only[4546].

Overall, there is a clear trend towards axilla-preserving approaches to minimize morbidity including lymphedema whilst maintaining oncological safety. Expertise is required to make these individualized decisions.

Breast conserving surgery is another field requiring specialized surgical skill. Two trials on BCS in conjunction with radiation therapy (RT) were published in the early 80's and demonstrated equivalent survival rates despite increased local recurrence rate (LRR) after BCS and RT[47,48]. 20-year follow-up of these trials confirmed the equivalent survival and paved the way for BCS as the preferred treatment option for early-stage breast cancer[4950]. Newer data shows much lower LRRs of 1.1% over five years and suggests that this has become a rare event with contemporary treatment and is probably rather a reflection of tumour biology than the extent of surgery[51]. In addition, there is new evidence that even suggests an improved survival of breast conserving therapy compared to mastectomy[52]. The contraindications for BCS have decreased over time and many patients who were deemed unsuitable can nowadays be offered BCS following primary systemic therapy and utilizing oncoplastic procedures, which combine a plastic surgery technique with an oncological resection to allow for larger volume excisions without compromising cosmesis[5354]. Breast conservation rates have varied over time and in geographical location with greater adoption among European centers and less in centers from the USA[55]. Data on the rate of BCS in South Africa is limited, 20% BCS was reported in a local cohort from 2009-2011 with higher rates of mastectomy for both LABC and early-stage breast cancer[56].

Support by base specialty

Although general surgeons are often adequately trained to perform a standard mastectomy and ALND they will not have the expertise to safely perform SLNBs and advanced breast conserving procedures.

In addition, general surgeons face a similar increase in surgical volume and it is unlikely that they will be able to service the increase in breast oncology as well[57]. This will lead to further difficulties in access and treatment delays[23].

There are general surgeons in SA who already provide specialized surgical breast care and who have the experience to train future breast surgeons. General surgeons will have the base training and skill required to be trained as breast surgeons.

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FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Sarah Lena Nietz (Student number: 378514) am a student registered for the degree of Doctor of Philosophy (Surgery) in the academic year 2025.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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