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Treatment outcomes of young patients with invasive breast cancer treated radically at Groote Schuur Hospital from 2013 to 2017: A single centre study

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Table of Contents

Publication- Ready Manuscript

Part A: Abstract

ABSTRACT

Treatment outcomes of young patients with invasive breast cancer treated radically at Groote Schuur Hospital from 2013 to 2017: A single centre study

Background: Breast cancer is the leading cause of cancer- related deaths globally, and the commonest cancer in women under 40 years. There is currently a lack of data relating to treatment outcomes of young women with breast cancer particularly in low-and middle-income countries.

Aim: This study aims to evaluate the treatment outcomes of young patients (under 40 years) treated radically for invasive breast cancer in a low-and middle-income setting.

Settings: Groote Schuur Hospital, Cape Town, South Africa

Methods: A retrospective review of 101 women under 40 years, with invasive breast cancer treated radically, between 2013 and 2017 was conducted. Patient characteristics, tumour characteristics, disease stage, treatment, and follow-up were recorded. Primary objectives included evaluating overall and disease free survival, and analysing recurrence patterns and clinicopathological features.

Results: The five-year overall and disease free survival for the entire cohort was 77% and 51%, respectively. Five-year overall survival by molecular subtype showed that Luminal A had the best survival, while triple negative breast cancer had the worst overall survival.

Conclusion: Young women with breast cancer have poor survival outcomes despite early presentation. There is limited data regarding breast cancer treatment outcomes in patients under forty years.

Keywords: breast cancer young women, breast cancer Africa, breast cancer South Africa, breast cancer survival, breast cancer under 40 years, breast cancer treatment outcomes, low-and middle-income countries

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PART B: Publication-ready Manuscript

Introduction

Breast cancer has been reported to be the most frequently diagnosed invasive cancer in women worldwide.[1, 2]Breast cancer is also the leading cause of cancer related deaths in women and the most prevalent cancer globally.[34] According to Ademuyiwa et al. 2016, breast cancer at a young age is rare; yet it is the most frequently diagnosed cancer in women under 40 years.[5] Numerous studies have shown young women with breast cancer to have a poorer prognosis when compared to older women.[6] Literature has also reported that younger women with breast cancer tend to present with advanced stage disease; and even in the context of modern-day adjuvant therapies, women under 40 years have poorer survival outcomes.[7] Furthermore, multiple studies have suggested that breast cancer in young patients is usually more biologically aggressive.[8] Breast cancer in patients under 40 years may represent a unique entity as it has different tumour biology, risk factors and clinical outcomes.[9] Although breast cancer in younger patients is comparatively rare, it is important as the diagnosis impacts severely on the lives and futures of these patients.[8]

The World Health Organisation reported that in 2020 there were 2.3 million women newly diagnosed with breast cancer, 685 thousand deaths and 7.8 million women living with breast cancer globally.[4] Approximately 6.6% of all breast cancer cases are diagnosed in women aged less than forty, 2.4% in women less than thirty-five and 0.65% in women less than thirty years.[10] Sharma 2020, reported that the burden of breast cancer in Africa is increasing and breast cancer is the leading cancer site in African females.[11] In low- and middle-income countries(LMICs), similar to South Africa, the incidence of breast cancer is rising rapidly adding to the increasing burden of non-communicable diseases.[12]

Data regarding breast cancer survival in Sub Saharan Africa is scarce as there are a limited number of studies with comprehensive patient management records. Mortality rates are higher and survival rates lower in LMICs than in high-income countries due various factors including oncology resource constraints for the preventing, diagnosing, and managing breast cancer.[11] Other reasons for poor outcomes include an advanced stage at diagnosis, aggressive tumour biology, age under 30 years at diagnosis, HIV positive status and sub-standard treatment.[13]

The primary aim of this study was to evaluate the treatment outcomes of young patients (under 40 years) treated radically for invasive breast cancer in a LMIC setting. In addition, the study sought to detail the clinicopathological profile and patterns of recurrence in this population of young patients at our institution.

Methods

Study Design

A retrospective study, involving a cohort of radically treated invasive breast cancer patients under the age of 40 years, was conducted.

The primary objective of the study was to evaluate the 5-year disease free survival, and overall survival of young breast cancer patients treated radically at Groote Schuur Hospital in Cape Town, South Africa. The secondary objectives were to describe the clinical and pathological features of the tumours experienced by these patients and, to establish the patterns of recurrence and treatment completion in this group of patients.

Participants

All patients younger than forty years of age, with a primary diagnosis of invasive breast cancer, who were treated radically in the Groote Schuur Hospital Oncology breast clinic from January 2013 to 31 December 2017 were included. The study only included clinical stage 1 to 3 breast cancer patients as per the 7th Edition of the American Joint Committee on Cancer (AJCC 7) staging system for breast cancer, which was in use at the time of diagnosis and treatment.

Data Collection

Institutional approval to access and collect patient data was sought from the Groote Schuur Hospital management after ethics approval was granted by the University of Cape Town Human Research Ethics Committee. Patient records were reviewed, and anonymized clinical data was recorded onto the data collection tool on Red Cap data management software.

Clinical data collected from patient records included date of diagnosis, demographic details, history of breast cancer, family history of breast cancer, smoking history, parity, body mass index, co-morbidities, clinical stage at presentation, histopathology, hormone receptor status, molecular subtype, treatment details, completion of treatment, evidence of recurrence, site of recurrence, vital status, genetic counselling and genetic testing.

Treatment

Radical treatment for breast cancer in our institution was administered according to the departmental protocol, which closely followed international guidelines, within the means of available resources. Management decisions were all made in a multidisciplinary team clinic involving clinical oncologists, breast surgeons, plastic surgeons, pathologists , radiologists and with support of genetic counsellors , a social worker and a breast health nurse.

Surgical options included modified radical mastectomy or breast conserving surgery, coupled with level I and II axially lymph node clearance, or sentinel lymph node biopsy where indicated.

Radiotherapy involved hypofractionated regimens of 40.05Gy/15 fractions with boost of 10.68Gy/4 fractions for remaining breast tissue, as the standard of care, after breast conserving surgery. High tangential fields are also used to ensure coverage of the axilla to the same dose. Post mastectomy radiation involved a total dose of 40.05Gy/15 fractions to the chest wall or 50Gy/25 fractions if the patient had breast implants.

In the earlier part of the study, from 2013 to 2016, recommended chemotherapy regimens for both adjuvant and neoadjuvant treatment, consisted mainly of 5-flourouricil, epirubicin, cyclophosphamide (FEC). Later, anthracyclines combined with taxol were introduced in line with the current standard of care regimens. There has never been access to trastuzumab in our setting to date.

Tamoxifen was used as a first line hormonal therapy for these patients; however, some women were switched to an aromatase inhibitor with ovarian suppression if side effects were intolerable.

Ethics

Ethics approval was granted from the Human Research Ethics Committee of the University of Cape Town (HREC 551/2020) prior to commencing the study. Anonymized data was collected onto a secure password-protected database . Individual informed consent was not sought as the study relied on retrospective data that was collected as part of routine patient care.

Statistical Analysis

Descriptive statistics were used to describe patient, tumour and treatment characteristics. Kaplan- Meier curves were used to estimate survival time. Survival curves by molecular

subtype were also generated and compared using log rank testing. Pairwise log rank comparisons were conducted to determine where significant differences in the survival distributions were and a Bonferroni correction was applied to avoid type 1 error.

Overall survival was determined from the time of initial diagnostic biopsy to the last follow-up encounter or death. Disease free survival was determined from the length of time from completion of primary treatment (surgery), to presenting with evidence of local or metastatic disease, or date of last follow up if no date of relapse. Treatment completion was defined as completing the initially prescribed treatment plan without any treatment interruption or default.

The data was analysed using SPSS version 27 for all descriptive and inferential statistics.

Results

A total of 202 records of invasive breast cancer patients under the age of forty diagnosed between 1 January 2013 and 31 December 2017, were identified using the electronic patient registry in the department of Radiation Oncology at Groote Schuur Hospital. Of these records, 101 of the patients met the inclusion criteria for the study and were analysed. The inclusion criteria comprised of female patients, age less than forty years, managed with radical intent between 01/01/2013 and 31/12/2017.

101 patients were excluded from the study due to exclusion criteria which included metastatic breast cancer patients, non-invasive breast cancer patients, age 40 years and older, male gender, and patients treated with palliative intent.

The mean age of diagnosis for patients was 34.2 years with a range of 23 to 39 years. Fourteen (13.9%) patients had co-morbidities of which the most common was hypertension (n=9, 64.3%). The majority of patients (n= 87, 86.1%) were HIV negative. The mean BMI for this group of patients was 29, with a range of 16.02 to 49.45. Ninety five (94.1%) patients had children while 6 (5.9%) were nulliparous. None of the patients had a previous history of breast cancer. Eighteen (18%) patients reported a positive family history of breast cancer. Most of the patients (n= 64, 63%) had never smoked cigarettes. The patient characteristics are presented in Table 1.

Table 1 patient characteristics

Patient characteristics	N (number) or mean	% /range
Age(years)	34.7	23 - 39
Body Mass Index	29.08	minimum 14.02, maximum 49.45
Co-Morbidities:		
Yes	14	13.9
No	87	86.1
Multiparous	95	94.1
Nulliparous	6	5.9
Past History of breast Ca:	0	0
Family history of breast Ca:		
Yes	18	18
No	82	82
HIV status		
Negative	87	86.1
Positive	14	13.9
Smoking		
Current smoker	31	30.7
Ex- smoker	4	4.0
Never smoked	64	63.4
Unknown	2	2.0

Forty-eight (47.5%) patients were referred for genetic counselling and of these 37.5% (n=18) had a positive family history while 43.8% (n=21) could afford to have genetic testing. Four patients (19%) were BRCA positive, 16 (76%) were BRCA negative, and 1 (4.8%) patient had a p53 mutation.

The most commonly occurring histopathological subtype was infiltrating ductal carcinoma (n=87, 86.1%), followed by lobular carcinoma (n=7, 6.9%). Forty-seven (46.5%) patients had clinical stage T2 tumours. Clinical stage N0 was the most common axillary stage (n=58, 54.7%). Most patients had pathological T stage of pT2 (n=48, 47.5%). Fifty-seven (58.2%) patients had pathological nodal involvement on histopathological analysis of the specimen. Forty (39.6%) patients had pathological N0 axillary staging. Many of the tumours (n =44, 43.6%) had lymphovascular invasion, with most tumours being high grade (n=45, 44.6%). The majority of tumours (n=83, 91.2%) were resected with clear margins. Seventy-three (72.3%) patients were ER positive; 35 (34.7%) patients were HER 2 positive, and 28 (27.7%) patients were HER 2 equivocal.

The most common molecular subtype in the cohort was Luminal B (n= 44, 43.6%), followed by Luminal A (n=14,13.9%), then HER 2 enriched (n=9, 8.9%), and lastly triple negative (n= 15, 14.9%). Nineteen patients (18.8%) who were HER 2 equivocal were unable to be classified into the molecular subgroups as Ki67 and FISH studies were not routinely available to all patients during the study period due to resource limitations. The most common clinical group stage at presentation for these patients was stage 2A (n=36 35.6%). Twenty-four (23.8%) patients presented with stage 2B, 12 (11.9%) with stage 3A, 15 (14.9%) with 3B, 1 (1%) with

stage 3C, and 13 (12.9%) with stage 1A. There were no patients with stage 1B disease in this cohort. [Table 2]

Table 2 Tumor characteristics

Tumour Characteristics	N (number)	%
Affected side		
Left	49	48.5
Right	52	51.5
Histological Subtype		
IDC	87	86.1
Lobular	7	6.9
Mixed IDC/lobular	2	2.0
Other	5	5.0
Grade		
I	12	11.2
II	34	33.7
III	45	44.6
Lymphovascular invasion		
Yes	44	43.6
No	43	42.6
Margin status		
Positive	8	8.7
Negative	83	91.20
Immunohistochemistry		
ER positive	73	72.3
HER 2 positive	35	34.7
HER 2 EQUIVOCAL	28	27.7
Molecular subtype		
Luminal A	14	13.9
Luminal B	44	43.6
HER 2 enriched	9	8.9
Tripple Negative	15	14.9
Unable to classify	19	18.8
Clinical T stage		
T1	17	16.8
T2	47	46.5
T3	19	18.8
T4a	1	1
T4b	16	15.8
T4c	1	1
Clinical N stage		
N0	58	57.4
N1	35	34.7
N2	7	6.9
N3	1	1
Clinical Group Stage		
1A	13	12.9
2A	36	35.6
2B	24	23.8
3A	12	11.9
3B	15	14.9
3C	1	1.0
Pathological T stage		
T1	21	20.8
T2	48	47.5
T3	30	19.8
T4	2	2
pCr	10	9.9
Pathological N stage		
N0	40	39.6
N1	34	33.7
N2	15	14.9
N3	8	7.9

All patients in this cohort were treated with at least some form of surgery. Eighty patients (79.2%) had mastectomy and axillary node clearance, 11 (10.9%) had mastectomy and sentinel lymph node biopsy, 7(6.9%) had wide local excision with sentinel lymph node biopsy while 3(3%) patients had wide local excision and axillary node clearance.

Approximately one third of the patients (n=39, 38%) were scheduled to have neoadjuvant therapy. Only thirty four (87.2%%) patients completed neoadjuvant chemotherapy as planned. Of the 5(12.8%)patients that did not complete neoadjuvant chemotherapy as planned, 1 (2.6%) patient had toxicity, 3(7.9%) patients had disease progression on the chemotherapy and 1 (2.6%) patient refused treatment. The most common neoadjuvant chemotherapy regimens were 5 fluorouracil Epirubicin Cyclophosphamide (FEC) and Adriamycin Cyclophosphamide Paclitaxel (ACP). Ten (29.4%) patients had FEC, and 10 (29.4%) had ACP. Of those that completed NACT, 10 (29%) patients achieved pCR. The rate of pCR in patients who had NACT is therefore 29%.

More than half of the patients (n=53, 52.5%), were scheduled for adjuvant chemotherapy of which 46 (86.8%) completed the adjuvant chemotherapy. Seven (13.2%) patients did not receive adjuvant chemotherapy as planned due to treatment toxicity (n=1,1.9%), loss to follow-up (n=4, 7.54%) and refusal (n=2, 3.8%). The most common adjuvant chemotherapy regimen was FEC.

The majority of patients (n= 82, 81.2%) were scheduled to receive adjuvant radiotherapy of which 67 (81.7%) completed adjuvant radiotherapy as planned. Fifteen(18.3%) patients did not receive adjuvant radiotherapy as prescribed due to disease recurrence (n=7, 8.5%), loss to follow up (n=3, 3.7%) and patient refusal (n=4,4.9%).

Most patients (n= 71, 70.3%) were planned to receive adjuvant hormonal therapy. Only 16(15.8%) patients completed the hormonal therapy as prescribed. Most patients (n=55, 54.5%) did not receive the full course of hormonal therapy during the course of the study period due to ongoing treatment (n=12, 16.9%), disease progression (n =17, 23.9%), patient refusal (n=3, 4.2%) , and loss to follow-up (n=23, 32.4%). Thirty-one (30.7%) patients completed their entire prescribed course of treatment, and the treatment completion rate was 30%.

Forty-four (43%) patients had evidence of recurrence. Thirty-nine (88%) patients out of those who recurred had distant metastasis, while 2(4.5%) and 3(6.8%) patients presented with regional and local recurrence respectively. Fifty-seven (56.4%) patients had gone through

treatment during the study period without any recurrence. Luminal B cancers were the most commonly recurring cancers (n=15, 34%), followed by triple negative (n=14, 31.8%).

The overall survival for the entire cohort was 83% at three years and 77% at five years. [figure 1] The overall survival by molecular subtype showed that Luminal A had the best survival at three and five years of 100%. The luminal B molecular subgroup had an overall survival of 89% and 81% at three and five years respectively. The overall survival for HER 2 enriched was 71% at three and five years. Triple negative molecular subtype had the worst survival of 46% at three years and 0% at five years.[figure 2] The difference in overall survival between the molecular subtypes was statistically significant ($p < 0.001$, log rank test). The significant differences in overall survival were between triple negative vs Luminal A($p < 0.001$, log rank test), and triple negative vs luminal B ($p < 0.001$, log rank test). In contrast there was no significant difference between HER2 enriched and triple negative subtypes($p = 0.25$, log rank test).

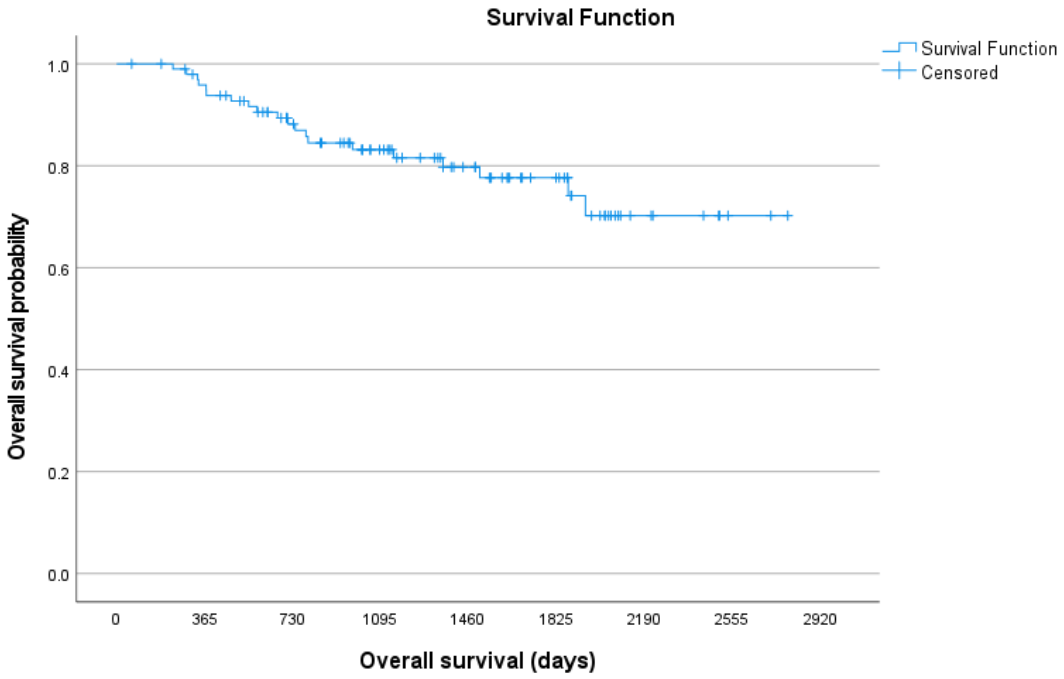

Figure 1 Overall survival for the entire cohort of patients under 40 years treated radically for invasive breast cancer.

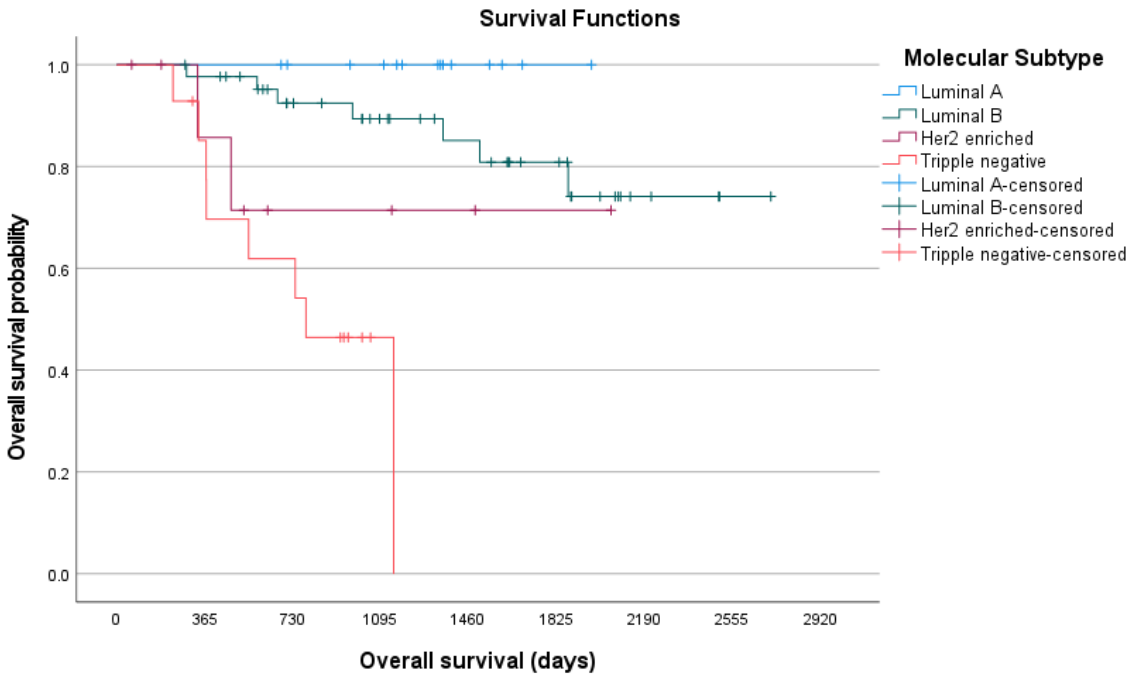

Figure 2 Overall survival split by molecular subtype, for patients under 40 years treated radically for invasive breast cancer.

The disease free survival for the entire cohort was 60% at three years and 51% at five years. [figure 3] The disease free survival by molecular subtype showed that patients with Luminal A subtype had the best disease free survival of 83% at 3 and 5 years, followed by Luminal B with 66% and 59% at three and five years. [figure 4] Her 2 enriched had a disease free survival of 43% at three and five years whilst all patients with triple negative molecular subtype had a disease recurrence at three years. The disease free survival distributions for the different molecular subtypes were statistically significantly different ($p = < 0.001$, log rank test). The significant differences in disease free survival followed the same pattern as overall survival.

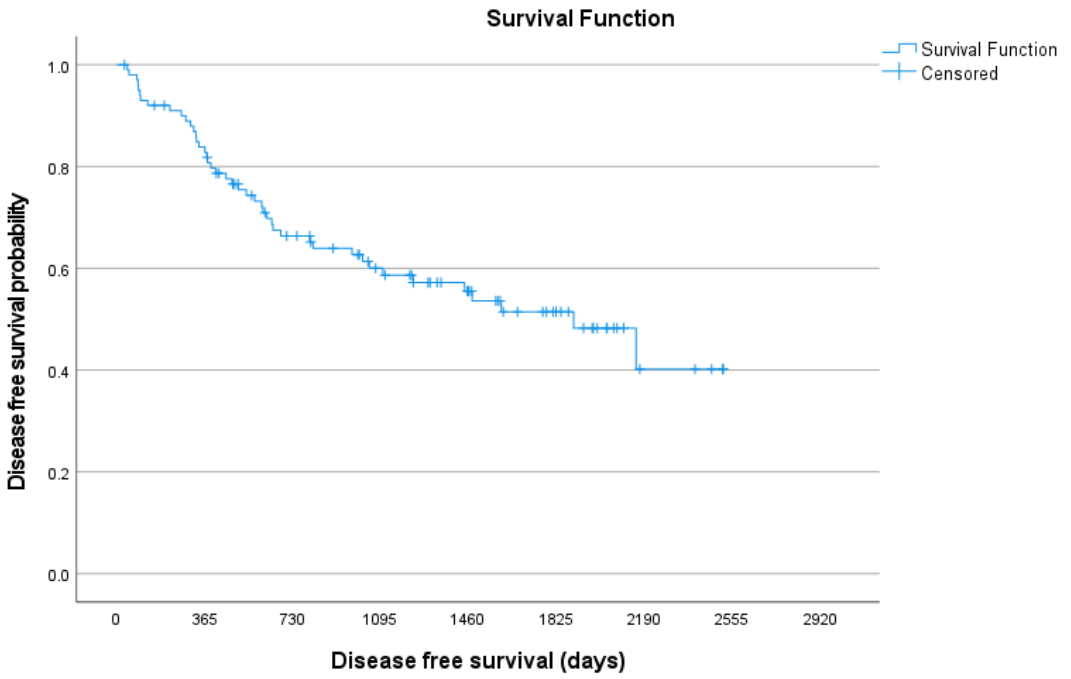

Figure 3 Disease free survival of the entire cohort of patients under 40 years treated radically for invasive breast cancer.

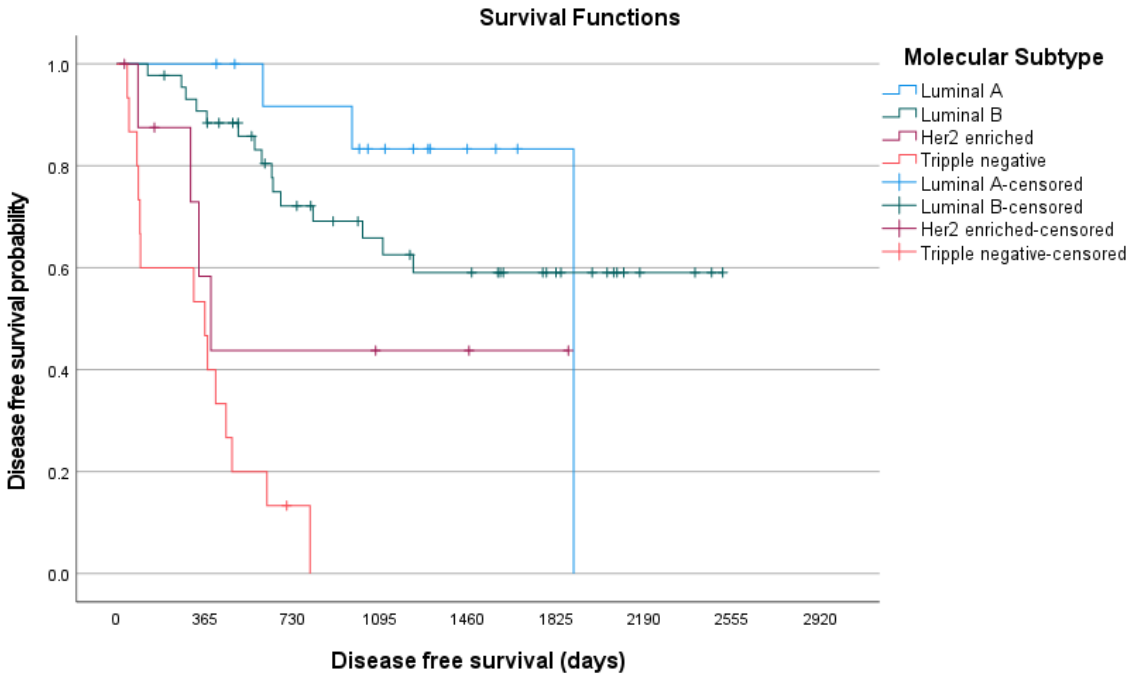

Figure 4 Disease free survival split by molecular subtype, for patients under 40 years treated radically for invasive breast cancer.

Discussion and Conclusion

This study, evaluating treatment outcomes of young patients treated radically for invasive breast cancer at our institution, showed that patients with HER 2 enriched and triple negative breast cancer had poor survival outcomes. The most common pattern of diseases recurrence was distant metastases, and there was a low rate of treatment completion due to the high rate of non-adherence to adjuvant hormonal therapy.

Our study, which included women under the age of 40 years (range 23-39), showed that the overall five-year survival for the entire cohort was 77%. Similarly, large prospective study in the UK that investigated a cohort of patients diagnosed under the age of 40 years, reported a five-year overall survival of 81.9% relative to 90.4% for older women aged 40 to 69 years.[16]

When survival was analysed by molecular subtype, only those patients in whom the molecular subtype was known with certainty were included. The triple negative patients had the worst overall survival outcome with more than half (OS=46%) having died at three years, and all of them having succumbed at five years. One study conducted in Sweden that assessed outcomes of women under 40 years reported a 5-year breast cancer specific survival of 72% for triple negative patients. [7] Our outcome is considerably poorer, suggesting that the tumour biology of triple negative breast cancer in our population may be different or more aggressive. Further research needs to be carried out to ascertain the contributory factors for this difference.

The 5-year disease free survival for the entire cohort was 51%. When compared by luminal subtype for three and five years, triple negative was the worst (0%), followed by HER 2 enriched (43%). Luminal A subtype had the longest disease free survival (83%) at three and five years whilst luminal B had disease free survival of 66% and 59% at three and five years respectively. A statistically significant difference was established between the luminal subtypes and triple negative disease (p =<0.001). The HER 2 enriched subtype trended towards a longer disease free survival compared to triple negative cancers. However, this difference was not statistically significant (p=0.108). This outcome was not surprising in our setting where anti-HER2 therapy is not available.

Histopathological analysis showed that invasive intraductal carcinoma accounted for most (86.1%) of the tumours, with invasive lobular carcinoma (6.9%), mixed ductal/lobular (2.0%), and other less common subtypes accounting for the rest. This spread of histological subtypes is similar to that reported in the UK POSH study that showed 86.5% of patients under the age

of 40 having intraductal carcinoma, followed by lobular (4.5%) and mixed ductal/lobular (2.6%). [16] Eric et al. 2018 reported 70.9% of the tumour's as intraductal carcinoma in their cohort of young women.[3] To the best of our knowledge, there are no published data in the African continent on the histological subtypes in this particular age group. However, one study done in Ethiopia for all age groups reported that the most common histological subtype was invasive ductal carcinoma (n=822, 79.2%).[17]

The most common clinical stage at presentation for our cohort was stage 2A. However, 58.2% had lymph node positive disease on the pathological specimen. The majority of patients in our study also had lymphovascular invasion and high grade (grade 3) tumours. This demonstrates aggressive tumour biology despite early stage breast cancer diagnosis. This early stage at presentation is in contrast to other studies in LMICS which state that most patients present with advanced stage and aggressive biological features.[8] This finding is similar to the conclusions of a study done in a single Pakistani Institution, that reported that the most common clinical stage at diagnosis was stage 2 in patients younger than 40 years.[18] They also reported biologically worse disease with patients more likely to present with more lymph node positive disease and high grade tumours. [18]

The pattern of recurrence that was most common was that of distant metastases. Most of the recurrences noted were in patients with Luminal B cancers(n=15, 34%) followed by triple negative (n=14, 31.8%) cancers. This result is similar to a Swedish study that reported that younger women had a higher risk of distant and locoregionally recurrent disease even with early detection. This was more prominent in the Luminal B subtype. [7] Similarly, in our cohort the most common pattern of recurrence was distant metastasis(n= 39, 88.6%) followed by locoregional recurrence. Literature reports that women with Luminal B cancers benefit less from endocrine therapy than Luminal A cancers, and less benefit from anthracycline and taxane containing neoadjuvant chemotherapy than triple negative or HER 2 enriched breast cancer.[16]

Only thirty-one (30.7%) patients completed the entire prescribed course of treatment. This may largely be attributable to the high nonadherence to adjuvant hormonal therapy that was observed in our cohort, as well as in other studies. A significant number of the patients who did not complete treatment in our cohort were Luminal(n=23, 41.8%) patients who did not adhere to hormonal therapy as prescribed. Published data have reported that women under 40 years of age had the highest risk of discontinuation of hormone therapy, and they reported a noncompliance rate of 32%. [19,20] Hershman et al. 2009, documented that 40-60% of patients

with breast cancer do not complete their prescribed course of hormonal therapy despite data proving that recurrence rates are higher with treatment durations of less than five years. [19] The level of adherence in our cohort was deduced by analysing patient script refill. It is possible that the non-adherence rate was even higher than that reported in our study and thus the treatment completion rate may be less than that reported. This high rate of non-adherence requires further investigation in future studies which may contribute to development of strategies to improve treatment completion rates and outcomes.

Family history of breast cancer has been shown to increase the risk for developing breast cancer, and this risk has been proven to be higher when the affected family member was diagnosed at a young age.[14] In this study, 18% of the patients had a positive family history of breast cancer. Similarly, McAree et al (2010) found that 10.5% of the patients under 40 years of age had a first degree relative with breast cancer in their single centre study. [15] It has been reported that between 15% and 30% of young patients with breast cancer have a germline BRCA1 or BRCA 2 mutation.[15] The extent of the contribution of BRCA1 and BRCA2 germline mutations to the cancer burden in African populations is unclear.[8] Nineteen per cent of the patients in our cohort who could afford genetic testing were found to have BRCA mutation. However, this result does not represent the whole cohort because genetic testing was performed following referral for genetic counselling in a different department, and some patients would not attend. Furthermore, genetic testing was only available to those patients who could afford to pay for the test privately, as this expense was not covered by the hospital, thus contributing to poor uptake of genetic testing. While our data did not demonstrate a strong presence of family history and genetic germline mutation, clinicians should legitimately be suspicious of breast cancer in patients under the age of 40 years presenting with breast symptoms even in the absence of family history or proven genetic evidence.

The retrospective nature of this research was the main limitation. Another limitation is that the study involved data from one centre resulting in a small sample size and data that may not align with other treatment sites in the region.

Conclusion

In conclusion, this study has highlighted that, young women in our setting have poor survival outcomes despite early presentation, which is in line with other published results. The outlook is particularly dismal for those that have HER 2 enriched and triple negative breast cancer. This demonstrates the need for more comprehensive screening, diagnostic, and treatment modalities that are used internationally as standard of care, in order to improve the outlook for these young

patients. The survival data for young age breast cancer is lacking, therefore this data will act as a baseline for comparison for future studies in our region.

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Competing Interests

The authors declare no competing interests. No fees or financial incentives were received by the authors in preparation of this manuscript.

Authors Contribution

Dr Gomolemo Tangane conducted the literature review, data collection, data interpretation and analysis, write up and editing of the article. Dr Tselane Thebe was the primary supervisor and the breast radiation oncology specialist. Dr Thebe also assisted with project initiation, guidance on interpretation of statistics, reviewing and editing. Dr Alistair Hunter was the co -supervisor, and also assisted with statistical guidance and review of the article.

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Data Availability

No restrictions on data availability. No unique identifiers of patients. Raw data available on request from the corresponding author.

Disclaimer

The views and opinions expressed in this research article are those of the authors and do not reflect the official policy or position of any affiliated agency of the authors.

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Abbreviations

Table 1: List of Abbreviations

Abbreviation	Meaning
LMICs	Low and middle income countries
BMI	Body mass index
AJCC 7	American Joint Committee on Cancer 7th Edition
RedCap	Research Electronic Data Capture
FEC	5-flourouricil, epirubicin, cyclophosphamide
ACP	Adriamycin, Cyclophosphamide, Paclitaxel
BRCA	Breast Cancer associated gene

APPENDICES

Data Collection Tool

Confidential

Breast Cancer Outcomes

Hospital folder number	_____
GSH Folder Number	_____
Date of Registration at LE33	_____
Date of Diagnosis	_____
Date of birth	_____
Age at Diagnosis	_____
CO-MORBIDITIES	○ YES ○ NO
Commorbidities	☐ Hypertension ☐ Diabetes mellitus ☐ Renal dysfunction ☐ Cardiac disease ☐ Other
Nulli Parity	☐ Yes ☐ No ☐ Unknown
History of Breast Cancer	☐ Yes ☐ No ☐ Unknown
Family history	☐ Yes ☐ No ☐ Unknown
Smoking	☐ current smoker ☐ ex smoker ☐ never smoked ☐ unknown
HIV status	○ negative ○ positive ○ unknown
Laterality	○ Left ○ Right ○ Both

Clinical T Stage	○ Tx ○ Tis ⊗ T1 ○ T2 ○ T3 ○ T4a ○ T4b ○ T4c ○ T4d
Clinical N Stage	○ Nx ○ N0 ⊗ N1 ○ N2 ○ N3
Group Stage	☐ Stage IA ☐ Stage 1B ☐ Stage 2A ☐ Stage 2B ☐ Stage 3A ☐ Stage 3B ☐ Stage 3C ☐ Stage 4
Resectable Upfront	○ Yes ○ No
Histopathology sub type	☐ idc ☐ lobular ☐ mixed idc lobular ☐ other
Pathological T stage	☐ pT1 ☐ pT2 ☐ p3 ☐ pT4 ☐ pCR ☐ T0 ☐ PTX
Grade	○ I ⊗ II ○ III
Pathological N stage	☐ pN0 ☐ pN1 ☐ pN2 ☐ pN3 ☐ PN1mi ☐ pNX
Lymphovascular invasion	⊗ Yes ○ No
Margin Status	○ positive ○ negative

ER status	○ positive ○ negative ○ unknown
PR status	○ positive ○ negative ○ unknown
HER2 status	○ positive ○ negative ○ equivocal ○ unknown
ki67	○ high ○ low ○ unknown
Molecular Subtype	○ Luminal A ○ Luminal B ○ Her2 enriched ○ Tripple Negative ○ unable to classify
Weight	_____
Height	_____
Genetic Counselling	○ Yes ○ No
Genetic Testing done	○ Yes ○ No
Genetics Test Results	○ BRCA Pos ○ BRCA Neg ○ P53 ○ other ○ Unknown
TREATMENT	☐ NEO ADJUVENT CHEMO ☐ ADJUVENT CHEMO ☐ RT ☐ SURGERY ☐ HORMONAL THERAPY
Neo Adjuvant Chemo	○ Yes ○ No
Neo Adjuvant Chemo Regimens	○ FEC ○ ACP ○ ECP ○ TC ○ Carbo/pacli ○ EC ○ AC ○ P ○ FEC + P

If no what is the reason;	○ Toxicity ○ Progression ○ Lost to follow-up ○ Refusal ○ Other
Adjuvant Chemo	○ Yes ○ No
Adjuvant Chemo Regimens	○ FEC ○ ACP ○ ECP ○ TC ○ Carbo/pacli ○ EC ○ AC ○ P ○ FEC + P
If no what is the reason;	○ Toxicity ○ Progression ○ Lost to follow-up ○ Refusal ○ Other
Radiotherapy	○ Yes ○ No
Radiotherapy regimens	○ Chest wall supraclava ○ BCT ○ BCT and Boost ○ CW
If no what is the reason;	○ Toxicity ○ Progression ○ Lost to follow-up ○ Refusal ○ Other
Surgery	○ Yes ○ No
Surgery type	○ Mastectomy ANC ○ ANC ○ Mastectomy and SLNB ○ WLE and SLNB ○ WLE and ANC
If no what is the reason;	○ Toxicity ○ Progression ○ Lost to follow-up ○ Refusal ○ Other
Hormonal Therapy	○ Yes ○ No

Hormonal Therapy Types	○ Tamoxifen ○ Aromatase inhibitor ○ BOTH (SWITCHED)
Duration	○ 5 Years ○ > 5 Years ○ < 5 Years
If no what is the reason;	○ Toxicity ○ Progression ○ Lost to follow-up ○ Refusal ○ Other ○ ongoing
TREATMENT COMPLETION	○ YES ○ NO
Active treatment end date	_____
Vital status	○ Alive ○ Deceased ○ Could not confirm
Date last seen	_____
Date of Death	_____
EVIDENCE OF RECURRENCE	○ YES ○ NO
SITE OF RECURRENCE	○ LOCAL ○ REGIONAL ○ DISTANT
Date of Diagnosis of Reccurence	_____
Treatment Outcome	☐ Remission ☐ Recurrence ☐ Death ☐ lost to follow up ☐ Progression

Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

15 September 2020

HREC REF: 551/2020

Dr T Thebe
Division of Radiation Oncology
J-Block GSH
Email: tselane.thebe@uct.ac.za
Student: tnggom001@myuct.ac.za

Dear Dr Thebe

PROJECT TITLE: TREATMENT OUTCOMES OF YOUNG PATIENTS WITH INVASIVE BREAST CANCER TREATED RADICALLY AT GROOTE SCHUUR HOSPITAL FROM 2013 TO 2017: A SINGLE CENTRE STUDY-MASTERS CANDIDATE-DR GOMOLEMO TANGANE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 September 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Gomolemo Tangane will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/09/22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	29/7/24

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	28/09/2021		
HREC REF Number	551/2020	Current Ethics Approval was granted until	30 September 2021
Protocol title	Treatment outcomes of young patients with primitive brain cancer treated radically at Groote Schuur Hospital from 2015 to 2019: A Single Cancer C		
Principal Investigator	Dr Tselane Thebe		
Department / Office Internal Mail Address	Groote Schuur Hospital. Department of Radiation Oncology - L Block 1 floor.		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☑	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/register/repository

n/A

HUMAN RESEARCH ETHICS COMMITTEE
29 SEP 2021
HEALTH SCIENCES FACULTY UCT

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		60
Total number of records or specimens collected, reviewed or stored since last progress report		60 no 60 n
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI		Date	28/09/2021

Departmental Approval

Radiation Oncology

Professor Jeannette Parkes
Head of Division

Groote Schuur Hospital, Observatory, 7925, South Africa

Tel: +27 (0) 21 404 4263/5, +27 (0) 21 406 6805 Fax: +27 (0) 21 404 5259
E-mail: Jeannette.parkes@uct.ac.za

5 February 2021

Dear Dr Tangane

Permission is hereby granted for the following study to be conducted in the department of radiation Oncology:

HREC REF: 551/2020

Project: Treatment outcomes of young patients with invasive breast cancer radically at Groote Schuur Hospital from 2013 to 2017: A single centre study

Please note that permission is also required from Dr Eick through Lionel Naidoo's institutional research committee, and from Ethics committee before the trial may commence.

Kind regards

Prof Jeannette Parkes
Radiation Oncology Department

Institutional Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHResearch.Request@westerncape.gov.za

Dr Tselane Thebe
RADIATION MEDICINE – RADIATION ONCOLOGY

E-mail: tselane.thebe@uct.ac.za / tnggom001@myuct.ac.za

Dear Dr Thebe,

RESEARCH PROJECT: Treatment Outcomes of Yong Patients With Invasive Breast Cancer Treated Radically At Groote Schuur Hospital From 2013 to 2017: A Single Centre Study (Masters Dr Gomolemo Tangane)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 September 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges.
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
o) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 10 March 2021

C.C. Mr. L. Naidoo / Dr H. Aziz / Professor J. Parkes

G46 Management Suite, Old Main Building,
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South African Journal of Oncology Authors Instructions

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title:

- Full title: Specific, descriptive, concise, and comprehensible to readers outside the field. Max 95 characters (including spaces).
- Tweet for the journal Twitter profile: This sentence/statement will be used on the journal Twitter profile to promote your published article. Max 101 characters (including spaces). If you have a Twitter profile, please provide us your Twitter @ name. We will tag you to the Tweet.

Abstract: The Abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. The Abstract should not exceed 250 words. Please minimize the use of abbreviations and do not cite references in the abstract. Refer to the relevant article type's guideline you are submitting for the abstract sections.

Introduction: The Introduction should put the focus of the manuscript into a broader context and explain its social and scientific value. Address this to readers who are not experts in this field and include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned. Conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods: The Methods section should provide clarity about how and why a study was done in a particular way. It should provide enough detail for reproduction of the findings. Protocols for new methods should be included, but well-established methodological procedures may simply be referenced. A full description of the methods should be included in the manuscript itself rather than in a supplemental file. Only information that was available at the time the plan or protocol for the study was being written must be included; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.
The methods section should include:

- The selection and description of participants or description of materials.
- The aim, design and setting of the study.
- The description of the processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses.
- The type of statistical analysis used, including a power calculation if appropriate.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Results: Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample." Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Conclusion: It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses, when warranted and label them clearly.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

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