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A Comparative Analysis of Hypofractionated and Conventional Radiotherapy for Breast Cancer Patients: A Retrospective Cohort Study

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ABSTRACT

Breast cancer presents a substantial health challenge in Africa and marked by a continuous rise in its incidence and prevalence. The complexities of managing breast cancer on the continent are exacerbated by limited access to healthcare resources and high rates of late-stage disease at initial diagnosis. Recent studies comparing hypofractionated radiotherapy (HFRT), considered cost-effective and non-inferior to conventional fractionated radiotherapy (CFRT), have shown no significant differences in outcomes. This underscores the potential significance of HFRT in breast cancer treatment. Despite encouraging findings from researchers in developing countries, there is a noticeable lack of data on HFRT outcomes, particularly in Sub-Saharan Africa. This retrospective study analyzed individuals diagnosed with early, locally advanced or oligometastatic cancer, and who underwent treatment between January 2010 and December 2020 at Inkosi Albert Luthuli Central Hospital in the KwaZulu Natal Province of South Africa. Relevant clinical treatment details and follow-up information were retrieved from the patients' medical electronic records. This retrospective study included 645 breast cancer patients, categorized into early (37.7%), locally advanced (59.9%), and oligometastatic (2.4%) stages. Treatment modalities included surgery (100%), chemotherapy (77.8%), endocrine therapy (38.8%), and targeted therapy (4.8%). All patients received radiotherapy, with a predominant utilization of HFRT (83.7%) over CFRT (16.3%). Notably, there was no statistically significant difference (p=0.91) observed in survival probability between patients who received HFRT and CFRT. The findings of this study suggest that, in a low-income setting, HFRT does not exhibit a significant variance in survival outcomes compared to CFRT for breast cancer patients. However, to validate this conclusion, additional large-scale randomized clinical trials are imperative.

Key words: Breast cancer; conventional radiotherapy; hypofractionation; survival outcome, Sub-Saharan Africa

Introduction

Breast cancer is a significant public health concern in sub-Saharan Africa (SSA), with the region experiencing a disproportionately high burden compared to the global average.[1] It is the most prevalent malignancy globally, with the highest incidence rates observed in high-income countries (HICs) and a notable surge in low- and middle-income countries (LMICs) within SSA.[2,3] In 2020, it is estimated that sub-Saharan Africa accounted for 206,710 new breast cancer cases and 104,285 deaths, representing approximately 18% of the worldwide breast cancer incidence and 22% of the global breast cancer mortality.[4] This alarming trend underscores the urgent need to improve cancer care and access to essential treatment modalities in the region.[3]

The high prevalence of breast cancer in SSA is driven by a combination of risk factors, which also contribute to many women presenting with late-stage disease. Key risk factors include; genetic mutations, such as BRCA1 and BRCA2, are more common in certain African populations and are associated with earlier onset and more aggressive breast cancers.[5] Reproductive factors like early menarche, late menopause, nulliparity, and late age at first birth are also established risk factors that are prevalent in the region.[6] Hormonal exposures, including use of oral contraceptives and postmenopausal hormone therapy, are additional contributor.[7] Lifestyle factors common in sub-Saharan Africa, such as obesity and physical inactivity, further increase breast cancer risk.[8]

These risk factors, combined with limited access to screening and early detection services, result in many women in sub-Saharan Africa being diagnosed at advanced stages when the cancer is more difficult to treat.[9,10] Studies in Africa have consistently shown that women often present with late-stage breast cancer. A systematic review and meta-analysis of 83 studies from 17 sub-Saharan African countries found that 77% of breast cancer patients were diagnosed at stages III/IV, significantly higher than in high-income countries.[2] A country-level study in South Africa also revealed high rates of late-stage diagnoses, with 75% and 51% of patients presenting with advanced disease, respectively.[11,12] These findings highlight the multifaceted nature of this disparity, encompassing limited awareness about breast cancer symptoms, limited access to or utilization of screening services due to cultural barriers or resource limitations, and delays in accessing healthcare due to financial constraints or geographical limitations.[13] This creates a vicious cycle – a lack of awareness and education about early detection methods results in delayed presentation, ultimately leading to poorer patient outcomes.[12]

Addressing the significant treatment gap in SSA requires a multi-modality approach.[14] Radiotherapy is a recognized, cost-effective, and crucial component of comprehensive cancer treatment, playing a vital role in disease control.[15] However, access to radiotherapy services in SSA remains unacceptably low. This challenge stems from several factors, including a limited number of radiotherapy machines, a scarcity of trained radiation oncology personnel, and the significant travel distances patients must endure to reach treatment centers.[3] The majority of SSA countries have less than 1 radiotherapy machine per 1 million people, which starkly contrasts with high-income countries, where there are 5 or more machines per 1 million people, posing a significant obstacle to effective cancer management.[16,17] This inadequate infrastructure poses a significant obstacle to effective cancer management in the region[3]. Therefore, concerted efforts to enhance the integration of radiotherapy into the broader spectrum of cancer treatment options available in SSA are imperative to mitigate the growing impact of cancer.[5]

The National Comprehensive Cancer Network (NCCN) currently recommends the use of conventional fractionated radiotherapy (CFRT) schedules in breast cancer treatment.[18] This entails administering a total dose (TD) of 50.4 Gy in 25 fractions over a period exceeding 5 weeks, targeting both the chest wall with or without regional lymph nodes as indicated.[19]

While demonstrably effective, advancements in radiotherapy technology have spurred investigations into methods that can reduce treatment-related toxicity, shorten the overall treatment duration, and potentially decrease associated costs.[20]

A promising approach is hypofractionated radiotherapy (HFRT). HFRT involves delivering larger daily doses over a shorter treatment period, offering a significant avenue for improving accessibility and reducing treatment costs without compromising efficacy.[21,22] Moderately HFRT emerges as a safe and effective strategy for breast cancer, as evidenced by findings from European, North American, and Chinese randomized trials.[23-33] In comparison to CFRT, moderate hypofractionation utilizing 15 or 16 fractions demonstrates comparable survival outcomes while potentially minimizing side effects. Notably, the START A and B trials demonstrated that hypofractionated radiotherapy regimens are effectives to the standard longer course of treatment for early-stage disease following breast cancer.[34-36] Ongoing trials are actively evaluating this regimen for node-positive disease. In the palliative setting, hypofractionation has been employed to achieve effective symptom control while preserving patients' quality of life.[37,38] Economic analyses conducted in diverse settings have also underscored the cost-effectiveness of these abbreviated fractionation schedules.[23,27,29,31,39].

While HFRT holds potential benefits, there is limited understanding of its adoption in breast cancer treatment across diverse resource settings, including Sub-Saharan Africa (SSA). This research aims to assess the outcomes of HFRT compared to CFRT for breast cancer patients in a resource-limited setup.

Materials and Methods

STUDY DESIGN

The retrieval of data from the medical records of Inkosi Albert Luthuli Central Hospital (IALCH) was undertaken with approval and a waiver of the requirement for specific informed consent for this retrospective study from the institutional review board. This study was centered on patients diagnosed with breast cancer through histopathological and staging examination, specifically those classified as early, locally advanced, and oligometastatic, who underwent curative intent treatment at IALCH between January 2010 and December 2020.

INCLUSION AND EXCLUSION CRITERIA

To uphold data integrity, individuals with incomplete records, those lost to follow-up, or individuals who received palliative treatment and those that has any of the oncological treatment from other centers were systematically excluded from the study.

DATA COLLECTION

Clinical data encompassing demographics, stages at presentation, and treatment specifics such as surgical interventions, chemotherapy regimens, and radiation therapy were systematically retrieved from patient records. Histopathological reports, detailing tumor characteristics including type, size, grade, nodal involvement, presence of lymphovascular emboli, and perinodal extension, were also obtained. Follow-up data, including patient outcomes, were sourced from hospital records and through electronic medical record. The median follow-up duration amounted to 82 months. Review of case sheets focusing on variables such as age, gender, diagnosis, cancer site, and various aspects of investigations and treatments was done

TREATMENT APPROACH

All patients underwent surgery followed by adjuvant radiotherapy to either chest wall or whole breast with or without regional nodes. Patients eligible for systemic therapy were identified based on staging, grading, margin status, receptor status, and age, and were accordingly recommended for neo-adjuvant and or adjuvant systemic treatment. The specific regimen for chemotherapy, hormonal therapy, and the utilization of targeted therapy (trastuzumab) were determined at the discretion of the Multi-disciplinary Team (MDT) for each case. Patient staging was conducted utilizing the 2010 TNM classification system (AJCC 7),[40] in accordance with institutional practice standards aligning with National

Institutes of Health guidelines established in 1990[40] and subsequent National Comprehensive Cancer Network (NCCN) guidelines published in 1996.[41] Consistent with the sixth edition of the American Joint Committee on Cancer (AJCC) TNM system,[42] surgery, radiotherapy and systemic therapies were administered to all patients as indicated stages and high risk features breast cancer during MDT. Patients not receiving systemic therapies, surgery and radiotherapy either declined treatment, had medical contraindications to radiotherapy, experienced postoperative complications precluding treatment, or were deemed medically unfit to tolerate irradiation and chemotherapy. Neo-adjuvant or adjuvant chemotherapy, typically comprising three to four cycles of an anthracycline-based follow by three to four cycles of docetaxel and regimen, was recommended to all patients following full staging and MDT discussion.

STATISTICAL ANALYSIS

The statistical analysis was performed using R version 4.1.3.[43] Two-sided $\chi 2$ tests (or Fisher's Exact tests) were employed for discrete variables. Patients were censored at the date of the last correspondence or follow-up. A significance level of $p < 0.05$ was applied to all comparisons.

Results

SOCIODEMOGRAPHIC CHARACTERISTICS

From January 2010 to December 2020, 5560 patients were registered, among whom 652 met the inclusion criteria and underwent curative treatments including chemotherapy, surgery, endocrine therapy, and radiation therapy. Of these patients, 647 were female and 5 were male, with a median age at diagnosis of 62 years (range: 20-83 years). Detailed demographic and tumor characteristics are presented in Table 1. Notably, the largest proportion of patients (25.6% and 24.2%) fell within the age ranges of 60-69 and 50-59 years, respectively, while those below 40 years comprised the smallest percentage (9.2%).

The patient cohort predominantly comprised individuals of African (54.0%) and Asian (32.8%) descent, with most presenting with locally advanced tumors (59.8%) and a performance status (PS) of 1 (82.5%). No statistically significant differences were observed in terms of tumor race, clinical stage, performance status, and treatment type.

Table 1: Presents the demographic and clinical characteristics of patients diagnosed with breast cancer at Inkosi Albert Luthuli Central Hospital from January 2010 to December 2020 in Durban, South Africa.

Survival status	Alive (N=645)	Died (N=7)	p-value	Overall (N=652)
Age			Chisq., p = 0.026	
<40yrs	57 (8.8%)	3 (42.9%)	all pwc p.adj ns	60 (9.2%)
40-49yrs	92 (14.3%)	0 (0.0%)	reduced Type I	92 (14.1%)
50-59yrs	157 (24.3%)	1 (14.2%)		158 (24.2%)
60-69yrs	164 (25.4%)	3 (42.9%)		167 (25.6%)
70-79yrs	98 (15.2%)	0 (0.0%)		98 (15.0%)
80+yrs	77 (11.9%)	0 (0.0%)		77 (11.8%)
Gender			Chisq., p = 0.815	
Female	640 (99.2%)	7 (100.0%)		647 (99.2%)
Male	5 (0.8%)	0 (0.0%)		5 (0.8%)
Race			Chisq., p = 0.305	

Survival status	Alive (N=645)	Died (N=7)	p-value	Overall (N=652)
African	349 (54.1%)	3 (42.9%)		352 (54.0%)
Coloured	16 (2.5%)	1 (14.2%)		17 (2.6%)
Indian/Asian	211 (32.7%)	3 (42.9%)		214 (32.8%)
Other	5 (0.8%)	0 (0.0%)		5 (0.8%)
White	64 (9.9%)	0 (0.0%)		64 (9.8%)
Staging			Chisq., p = 0.109	
Early	243 (37.7%)	3 (42.9%)		246 (37.7%)
Locally advanced	387 (60.0%)	3 (42.9%)		390 (59.8%)
Oligometastasis	15 (2.3%)	1 (14.2%)		16 (2.4%)
Performance status			Chisq., p = 0.220	
1	529 (82.3%)	7 (100.0%)		536 (82.5%)
2	114 (17.7%)	0 (0.0%)		114 (17.5%)
Chemotherapy			Chisq., p = 0.611	
NO	144 (22.3%)	1 (14.3%)		145 (22.2%)
YES	501 (77.7%)	6 (85.7%)		507 (77.8%)
Surgery			Chisq., p = 0.739	652(69.3%)
Radical Mastectomy	288 (44.7%)	3 (42.9%)		291 (44.6%)
Simple Mastectomy with SLNB	157 (24.3%)	1 (14.2%)		158 (24.2%)
Wide Local Excision with SLNB	200 (31.0%)	3 (42.9%)		203 (31.1%)
Endocrine therapy			Chisq., p = 0.197	
No	366 (56.7%)	2 (28.6%)		368 (56.4%)
Trastuzumab	31 (4.8%)	0 (0.0%)		31 (4.8%)
Yes	248 (38.4%)	5 (71.4%)		253 (38.8%)
Radiotherapy dose given			Chisq., p = 0.375	652(100%)
50.00Gy/25#	104 (16.1%)	2 (28.6%)		106 (16.3%)
40.05Gy/15#	541 (83.9%)	5 (71.4%)		546 (83.7%)

% and p-values based on non-missing cases | * parametric p-value

Treatment Patterns

SURGERY

The entire cohort of 652 patients underwent surgery, as outlined in Table 1. Within the surgical interventions, 44.6% (n = 291) underwent radical mastectomy, 24.2% (n = 158) underwent wide local excision with sentinel lymph node biopsy (SNLB), and 31.1% (n = 203) underwent simple mastectomy with SLNB. When comparing patients who succumbed in different treatment groups, the majority (42.9%) were those who received radical mastectomy or wide local

excision with SLNB, while 14.3% of patients who received simple mastectomy with SLNB died.

CHEMOTHERAPY

The majority of patients (77.8%) underwent chemotherapy, while a minority (22.2%) did not receive this treatment. Among the deceased patients, 85.7% had received chemotherapy, and 14.3% had not undergone this treatment.

Chemotherapy in breast cancer provides significant benefits in tumor control, surgical outcomes and long-term survival.

ENDOCRINE THERAPY

The majority of patients (56.4%) did not receive endocrine therapy, while a minority (38.8%) did undergo such treatment. A least percentage (4.8%) received targeted therapy (trastuzumab) in cases of HER2-positive breast cancer. Importantly, no significant differences were observed in the proportions of patients receiving targeted, endocrine, or no chemotherapy.

RADIOTHERAPY

There was no statistically significant difference ($p < 0.375$) observed between the majority of patients who received hypofractionated radiotherapy (HFRT) with 40.05 Gy in 15 fractions (83.7%) and those who received conventionally fractionated radiotherapy (CFRT) with 50.00 Gy in 25 fractions (16.3%). While a larger proportion of patients undergoing CFRT (n=5, 71.4%) experienced mortality during treatment compared to the HFRT group (n=2, 21.6%), this disparity did not achieve statistical significance. In the study, 31.1% of patients in the hypofractionated radiotherapy (HFRT) group received whole breast irradiation (WBI) following breast-conserving surgery, while 68.9% received post-mastectomy radiotherapy. The treatment duration was 3 weeks for the HFRT group and 5 weeks for the conventional fractionated radiotherapy (CFRT) group.

Of the 652 patients, 498(76.4%) were treated with chest wall and whole breast irradiation with regional lymph nodes irradiation, while 154(23.6%) received 2-field radiotherapy to the whole breast and chest wall. All patients who underwent whole breast irradiation received a boost of 10 Gy in 5 fractions, with 98.3% of the boosts delivered using photons and 1.7% planned using electrons.

All radiotherapy was delivered either VMAT technique or 3DCRT for both hypofractionated radiotherapy and conventional radiotherapy with electronic portal images (EPID) were acquired from day 1 to 3

CASE PRESENTATIONS AND IMAGING ANALYSIS:

This section presents case studies of three female patients who underwent treatment with different modalities as per their specific cases (Figures 1, 2, and 3). The patients' ages were 42, 39, and 62 years old, respectively.

Figure 1 depicts a case of a 42-year-old female presenting with cT4 N2 M1 breast cancer with PS<2, treated with curative intent. After receiving neoadjuvant chemotherapy consisting of four cycles of anthracycline-based treatment followed by four cycles of taxane, the patient exhibited a clinical complete response with complete resolution of the oligometastasis. Whereas, a case of 39-year-old female patient undergoing wide local excision and sentinel lymph node dissection (SLND) for pT3 pN0 Mx left-side breast cancer was represented in Figure 2. She received external beam radiotherapy, which involved 3-dimensional conformal radiotherapy (3DCRT) with a prescribed dose of 40.05Gy delivered over 15 fractions using both 6 MV and 18 MV photons. The treatment plan focused on ensuring coverage of the planning target volume (PTV) while minimizing the radiation dose to critical organs, adhering to the tolerance limits established by QUANTEC guidelines. Similarly, a case of a 62-year-old female patient who underwent chemotherapy for cT4 N1 M0 locally advanced breast cancer was depicted in Figure 3. She achieved a complete clinical response, followed by surgery and adjuvant external beam radiotherapy. The radiotherapy was administered using the Monaco Volumetric Modulated Arc Therapy (VMAT) technique. The treatment plan targeted the

right whole breast and regional lymph nodes with a dosage of 40.05 Gy over 15 fractions using 6 MV photons, ensuring adequate coverage and adherence to organ-at-risk (OAR) tolerance limits as per QUANTEC guidelines.

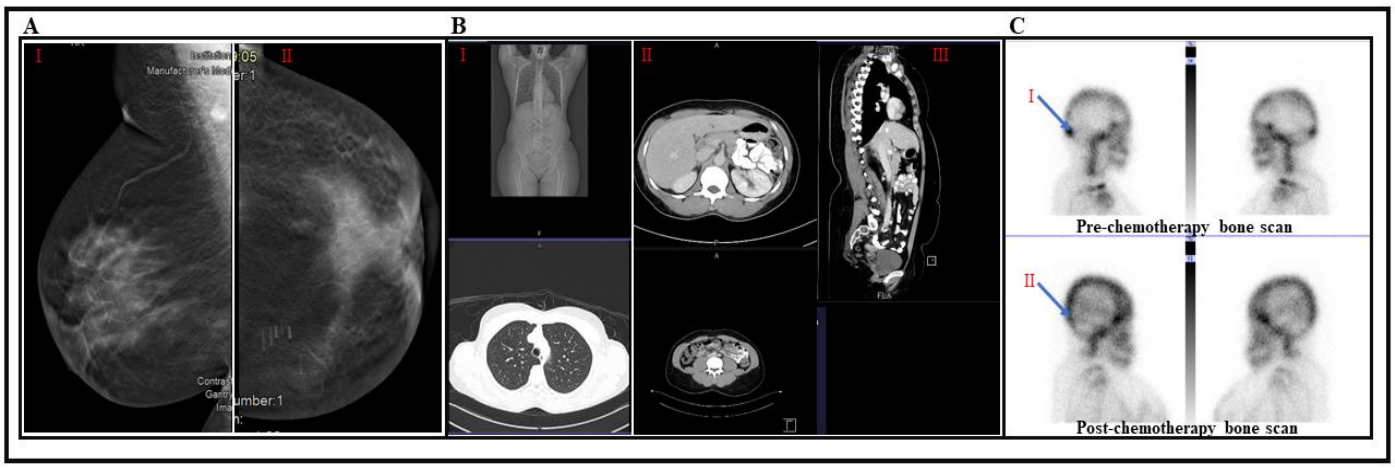

Figure 1: A) Mammography (MMG) shows BIRAD 2 (I) in the right breast and BIRAD 6 (II) in the left breast. B) CT scans of the chest, abdomen, and pelvis indicate no pulmonary or hepatic metastasis. C) A bone scan reveals scintigraphic evidence of osteoblastic skeletal metastases in the occipital bone (B.I). Complete resolution of the oligometastasis (B.II).

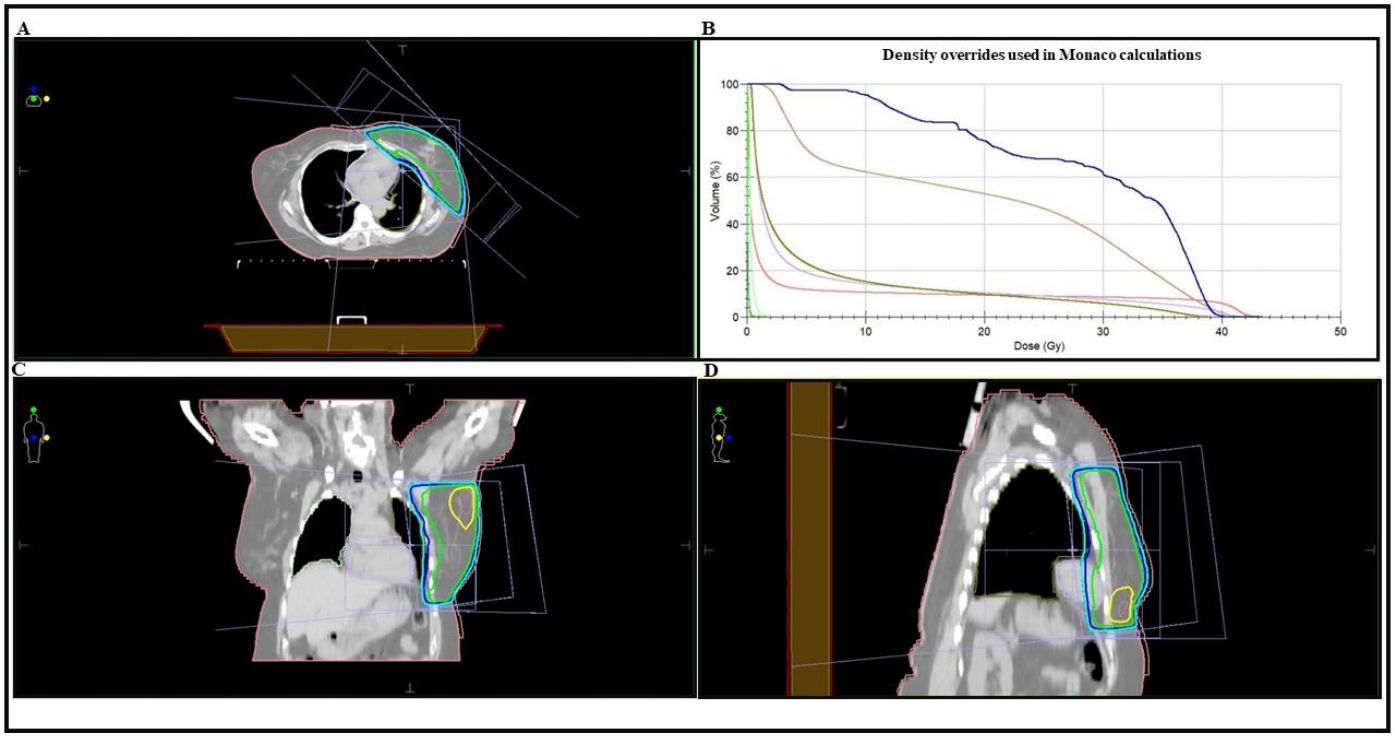

Figure 2: 3DCRT conformational images of a 39 year old female showing: (A) the axial view of the planning scan, (B) the dose-volume histogram (DVH), (C) the coronal view, and (D) the sagittal view of the planning scan.

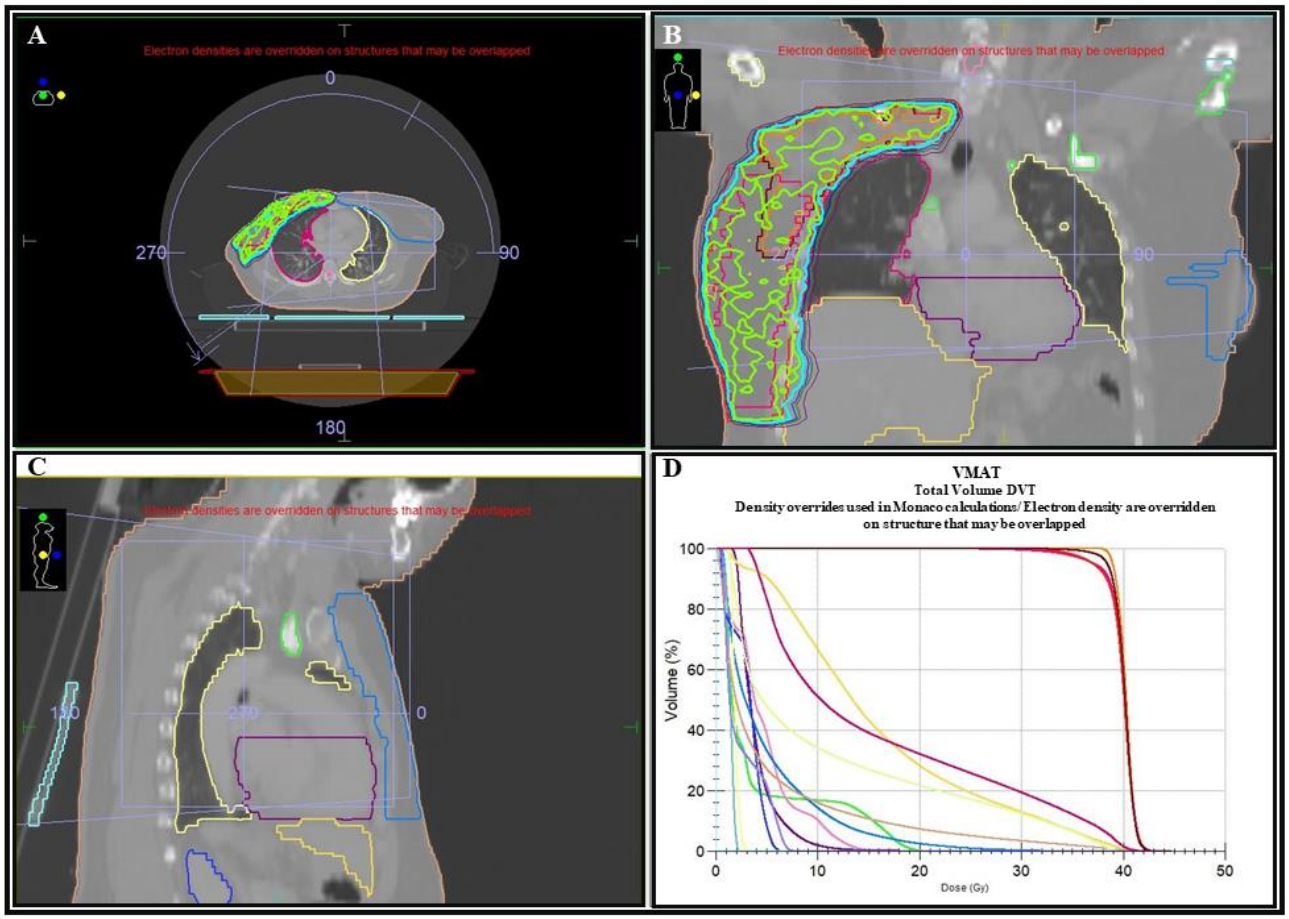

Figure 3: A 62-year-old female in treatment for advanced cancer with radiotherapy administered by Monaco Volumetric Modulated Arc Therapy (VMAT) technique The figure includes: (A) the axial view of the planning scan, (B) the coronal view, (C) the sagittal view of the planning scan, and (D) the dose-volume histogram (DVH).

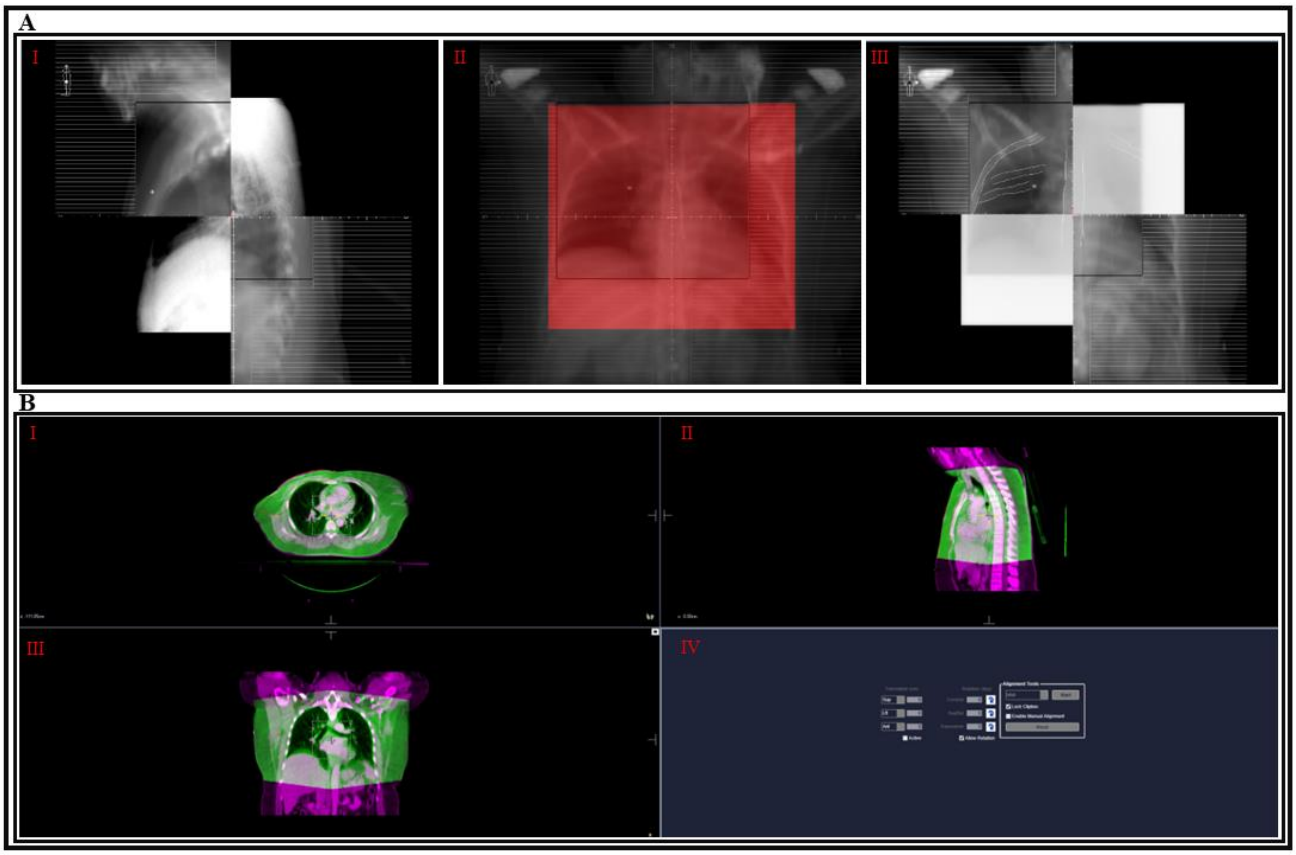

Figure 4: A showcase of (A) electronic portal images (EPID) taken daily from days 1 to 3, and (B) cone-beam computed tomography (CBCT) performed on a weekly basis.

SURVIVAL

By the end of the study period, 7 (1.1%) patients had died. Notably, both male and female patients exhibited a high likelihood of survival during the initial two years of the treatment period, with a slight decrease observed in the subsequent two years, followed by a stable survival rate for the remaining study duration. The survival probabilities for patients undergoing chemotherapy and those not receiving chemotherapy were comparable in the initial three years but exhibited a slight decrease, subsequently stabilizing over the following 9.5 years. A similar trend was observed for patients with early and locally advanced cancers, while the survival rate for oligometastatic patients was comparatively lower (90%). In terms of radiotherapy regimens, both CFRT and HFRT patients demonstrated a comparable survival rate during the first year following treatment, with a slight reduction to a stable rate thereafter (Figure 5).

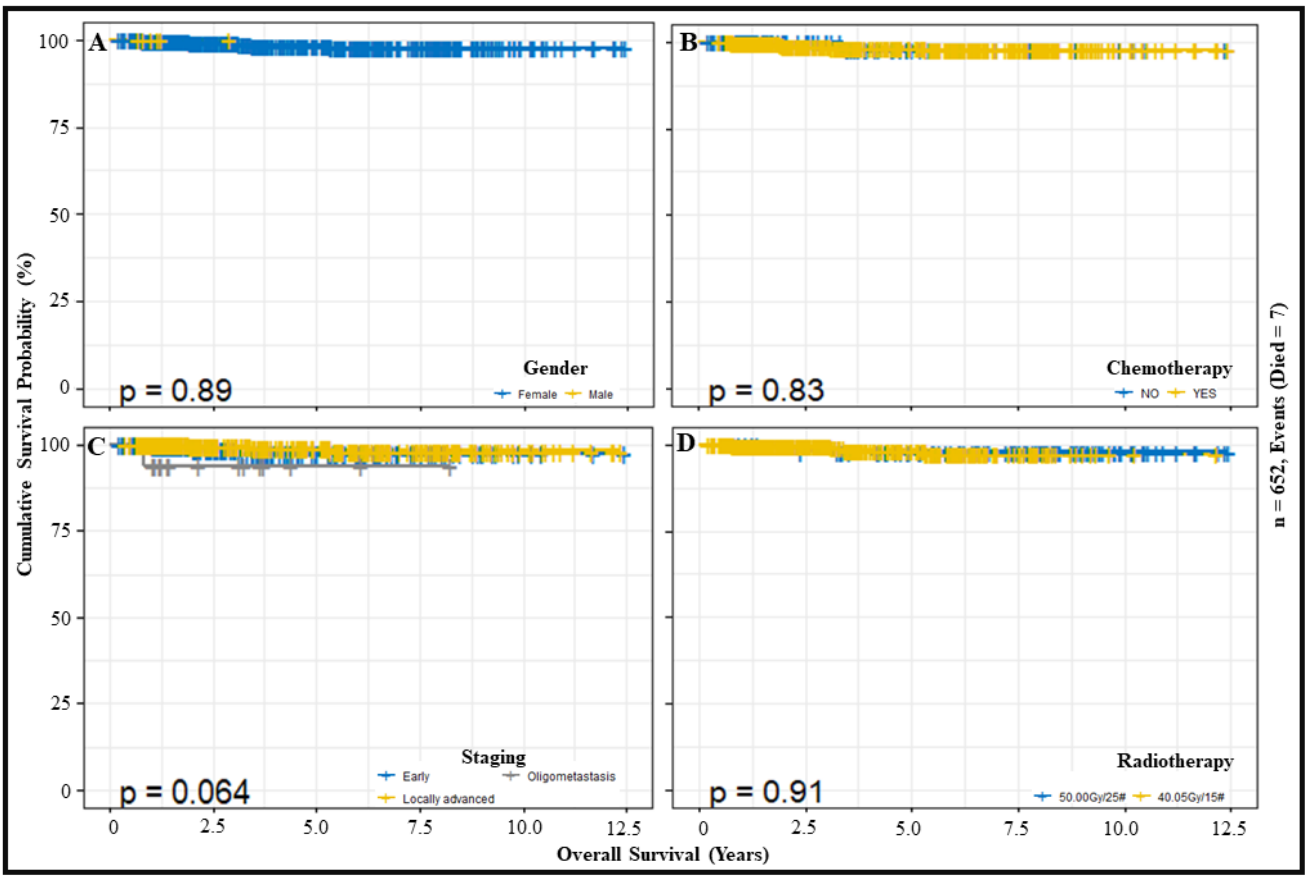

Figure 5: An illustration of Kaplan-Meier survival probability curves for breast cancer patients treated based on A) gender (female and male), B) chemotherapy regimen (received and did not receive), C) cancer staging (early, locally advanced, and oligometastatic), and D) radiotherapy regimens (CFRT and HFRT) at IALCH in Durban, South Africa.

Discussion

Low- and middle-income countries, particularly in SSA, bear a significant global cancer burden, with limited access to essential breast cancer treatments such as radiotherapy[44]. Disparities in access have prompted the exploration of HFRT, delivering larger daily doses over shorter periods, as a cost-effective means to improve accessibility without compromising outcomes.[45] Studies indicate that HFRT is frequently utilized, especially in early-stage breast cancer following breast-conserving surgery. Despite this, a substantial portion of respondents from high-income countries and even more from upper-middle- and lower-middle-income countries still prefer CFRT.[46] Despite these disparities, numerous trials confirm that HFRT outcomes are as effective as conventional fractionated radiotherapy (CFRT) across all stages of disease and types of breast surgery. Rastogi et al.,[47] found similar results in toxicity, tolerability, and locoregional control for both HFRT and CFRT groups.

A multicenter trial in China, involving 734 patients (HFRT: n = 368 and CFRT: n = 366), revealed comparable 5-year cumulative incidence of locoregional recurrence (LR) between HFRT and CFRT groups, with fewer acute skin toxicities (less grade ≤2) in the HFRT group. Overall, CFRT and HFRT with a tumor-bed boost exhibited similar low LR rates and toxicity[32].

In an Egyptian study involving 100 breast cancer patients, the cohort was divided into two groups, each comprising 50 patients. The patient groups underwent prospective treatment with either HFRT at 40 Gy in 15 fractions or CFRT at 50 Gy in 25 fractions. At the 2-year mark, there were no statistically significant differences observed in overall survival (p = 0.7), disease-free survival (p = 0.9), or local disease-free survival (p = 0.9) between the two treatment modalities. The study reported incidences of acute skin reaction grade I-II in the HFRT (44%) and CFRT (50%) groups, along with lower rates of radiation pneumonitis exclusively in the CFRT (4%) group. The conclusion emphasized that post-mastectomy HFRT achieves comparable survival and toxicity to CFRT, with the added benefits of reduced treatment time, burden, and cost.[20]

In line with the findings of this investigation, which encompassed 652 breast cancer patients subjected to either HFRT (n = 546; 40 Gy in 15 fractions; deceased = 2) or CFRT (n = 106; 50 Gy in 25 fractions; deceased = 5). There were no statistically significant differences (p = 0.9) observed in survival rates during the 12.5 years of follow-up. These collective results affirm the efficacy and benefits of HFRT in the context of breast cancer treatment, particularly in settings with limited resources.

While the featured cancer center effectively utilized both CFRT and HFRT for breast cancer treatment (Figures 1-4), delivering HFRT requires advanced technology not readily available throughout Sub-Saharan Africa (SSA). HFRT relies on sophisticated equipment like linear accelerators (linacs) to deliver higher, precise radiation doses per fraction. These advanced machines, along with EPIDs and Cone-Beam CT CBCT used for monitoring, are crucial for successful HFRT implementation.[5,35,48] Unfortunately, access to radiotherapy services in SSA remains critically low. Most countries have a severe shortage of radiotherapy machines, with less than 1 per million people compared to 5 or more in high-income countries.[49-51] This forces patients to endure long and expensive journeys for standard CFRT, the current primary radiotherapy approach in SSA.[20] These logistical and financial burdens often lead to poor treatment adherence and non-compliance, as patients struggle with travel costs, accommodation, and lost wages. Missed or delayed appointments due to these challenges ultimately compromise treatment outcomes.[5] HFRT's potential lies in significantly reducing treatment duration and therefore travel and associated costs, offering a promising solution to improve treatment compliance and access for breast cancer patients in resource-limited settings.[3] In conjunction with radiotherapy, whether utilizing HFRT or CFRT, the broader context of curative management of breast cancer entails a multimodal treatment approach. This approach, recommended for stage I to III disease, encompasses breast surgery(BCS, Mastectomy) and neo-adjuvant/adjuvant systemic interventions, such as cytotoxic chemotherapy, endocrine treatment, and targeted therapy.[52] It is noteworthy that our study aligns with this comprehensive treatment paradigm.

While surgery remains the cornerstone in managing resectable breast cancer, its integration with other therapies is crucial for controlling locally advanced disease. However, limited resources in certain regions of Africa may restrict access to complementary adjuvant therapies, rendering surgery the sole treatment option.[53] Surgical rates across Africa vary, as evidenced by studies in Sudan and Mozambique. In Sudan, among 183 women undergoing breast surgery, modified radical mastectomy and breast-conserving surgery were performed in 61.7% and 38.3% of cases, respectively, with 25.1% receiving surgery post-neoadjuvant chemotherapy.[54] Conversely, in Mozambique, over 80% of patients underwent surgery, predominantly mastectomies,

since only 5% had access to radiotherapy.[55] Langenhoven et al.,[53] reported that surgical rates across Africa generally ranged from 48% to 75%, contrasting with over 90% in European countries. According to Vanderpuye et al.,[56] disparities in surgical rates may stem from a higher incidence of African women presenting with unresectable breast cancer. The indication for breast-conserving surgery is confined to early resectable disease, contingent upon the availability of radiation therapy to sterilize residual breast tissue.[56] Consistent with this trend, our study revealed that a majority (44.6%) of breast cancer patients underwent radical mastectomy, while 31.1% underwent wide local excision with sentinel lymph node biopsy (SLNB), and 24.8% underwent simple mastectomy with SLNB. This distribution may be attributed to over half of the patients presenting with locally advanced disease (59.8 %), underscoring the clinical context influencing the choice of surgical interventions.

In other centers in South Africa, two parallel studies reported patients who presented with advanced stage breast cancer, with incidences of 50% and 55%, respectively.[53,57] Similarly, in Kenya (89.6%) and Nigeria (72.8%,) majority of breast cancer patients presented with advanced stage disease.[58,59] Conversely, Morocco reported a lower incidence, with 33% of cases classified as Stage III and IV breast cancers.[60] In Togo, a study involving 62 breast cancer patients revealed that 69.4% were diagnosed with Stage III disease, while 19 were classified as Stage IV.[61] Notably, these rates of advanced stage breast cancer are markedly higher than those observed in high-income countries.[57]

The success of cancer treatment is significantly improved by early detection.[3] Unfortunately, in low-income countries, a considerable number of cancer cases go unreported, resulting in late-stage diagnoses marked by aggressive disease or metastasis.[62] For these patients, the benefits of chemotherapy may be uncertain.[63] Therefore, general prognostic markers such as performance status (PS) and patient comorbidities are typically used to determine eligibility for this treatment modality.[64-66] Patients with a PS <2 are deemed suitable candidates, while those with a PS >2 receive supportive care. Chemotherapy is considered for patients exhibiting good overall health status, indicated by a World Health Organization's performance status (WHO PS) of 0 or 1.[63,67-69]. This is reflected in our study where a 42-year-old patient with a PS <2 exhibited a clinical complete response with complete resolution of oligometastasis after receiving neoadjuvant chemotherapy consisting of four cycles of anthracycline-based treatment. Furthermore, most of our patients had a PS status of either 1 (82.5%) or 2 (17.5%), of whom the majority received chemotherapy (77.8%).

In hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer, neoadjuvant endocrine therapy (NET) demonstrates comparable clinical response rates to chemotherapy, rendering it a viable and reasonable treatment option.[70] Historically, neoadjuvant endocrine therapy (NET) was primarily reserved for patients deemed frail with significant comorbidities, or those unable to tolerate chemotherapy, or unsuitable for surgery.[71,72] However, NET is increasingly being considered as an alternative to neoadjuvant chemotherapy (NACT) for a broader spectrum of patients with HR-positive and HER2-negative disease.[70,73,74]. In this study, endocrine therapy was administered to a minority (38.8%) of HR-positive cancer patients. Among the subset of patients identified as HER2-positive (4.8%), trastuzumab, a recognized crucial component in anti-HER2 regimens, was administered. Previous studies have shown that trastuzumab plus chemotherapy demonstrates superior efficacy and a more favourable toxicity profile compared to standard chemotherapy alone.[75-77]

Notably, men were diagnosed with breast cancer in this study constituted approximately 1%. This aligns with findings from other studies that highlight the rarity of breast cancer in men, constituting less than 1% of all male malignancies and less than 1% of breast cancer cases.[78]

Conclusion

Overall, this study suggests the non-inferiority of HFRT compared to CFRT and establishes the viability of HFRT as a beneficial treatment modality in resource-constrained settings in Africa. It offers the potential to substantially decrease treatment duration and addresses challenges related to healthcare facility accessibility. This approach may enhance treatment access for patients residing in remote areas and mitigate the burden of extensive travel. Furthermore, the cost-effectiveness of HFRT, attributed to the reduction in treatment sessions, may contribute to increased patient compliance. The multifaceted advantages of HFRT underscore its potential significance in optimizing radiotherapy outcomes within the unique healthcare landscape of Africa. Additionally, efforts to expand access to radiotherapy services through increased availability of treatment centers and machines across Sub-Saharan Africa (SSA) should be a continued priority.

Conflict of Interest:

None

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References:

1. Moodley J, Constant D, Mwaka A, Scott S, Walter F. Mapping awareness of breast and cervical cancer risk factors, symptoms and lay beliefs in Uganda and South Africa. *PloS one.* 2020;15(10): e0240788. Doi.org/10.1371/journal.pone.0240788.

2. Jedy-Agba E, McCormack V, Adebamowo C, dos-Santos-Silva I. Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *The Lancet Global Health.* 2016 ;4(12):e923-e935. DOI: 10.1016/S2214-109X(16)30259-5.

3. Ngwa W, Addai BW, Adewole I, et al. Cancer in sub-Saharan Africa: a lancet oncology commission. *The Lancet Oncology.* 2022;23(6): e251-e312. DOI: 10.1016/S1470-2045(21)00720-8.

4. Singh D, Vignat J, Lorenzoni V, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. *The lancet global health.* 2023;11(2):e197-e206. Doi: 10.1016/S1470-2045(21)00720-8.

5. Patel S, Olatunji E, Mallum A, et al. Expanding radiotherapy access in Sub-Saharan Africa: an analysis of travel burdens and patient-related benefits of hypofractionation. *Frontiers in Oncology.* 2023;13:1136357. Doi.org/10.3389/fonc.2023.1136357.

6. Anderson KN, Schwab RB, Martinez ME. Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast cancer research and treatment.* 2014;144:1-10. DOI: 10.1007/s10549-014-2852-7.

7. Kanadys W, Barańska A, Malm M, Błaszczuk A, Polz-Dacewicz M, Janiszewska M, Jędrych M. Use of oral contraceptives as a potential risk factor for breast cancer: A systematic review and meta-analysis of case-control studies up to 2010. *International journal of environmental research and public health.* 2021;18(9):4638. Doi: 10.3390/ijerph18094638.

8. Beltrán Ponce SE, Abunike SA, Bikomeye JC, et al. Access to radiation therapy and related clinical outcomes in patients with cervical and breast cancer across sub-saharan africa: A systematic review. *JCO Global Oncology.* 2023;9:e2200218. Doi: 10.1200/GO.22.00218.

9. Sanft T, Day A, Peterson L, et al. NCCN Guidelines® insights: survivorship, version 1.2022: featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network.* 2022;20(10):1080-1090. Doi: 10.6004/jnccn.2022.0052.

10. Gradishar WJ, Anderson BO, Abraham J, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network.* 2020; 18(4):452-478. Doi: 10.6004/jnccn.2020.0016.

11. Bhuiyan M, Maele M, Mavhungu R, Ooko F. Breast cancer: Factors influencing late-stage presentation at the Mankweng Hospital breast cancer clinic, Polokwane, Limpopo Province, South Africa. *South African Medical Journal.* 2022;112 (11):906-910. Doi.org/10.7196/SAMJ.2022.v112i11b.16834.

12. Joffe M, Ayeni O, Norris SA, et al. Barriers to early presentation of breast cancer among women in Soweto, South Africa. *PloS one.* 2018; 13(2):e0192071. Doi.org/10.1371/journal.pone.0192071.

13. Agodirin O, Aremu I, Rahman G, Olatoke S, Olaogun J, Akande H, Romanoff A. Determinants of delayed presentation and advanced-stage diagnosis of breast cancer in Africa: a systematic review and meta-analysis. *Asian Pacific journal of cancer prevention: APJCP.* 2021;22(4):1007. Doi: 10.31557/APJCP.2021.22.4.1007.

14. Kraus RD, Weil CR, Abdel-Wahab M. Benefits of adopting hypofractionated radiotherapy as a standard of care in low-and middle-income countries. *JCO global oncology.* 2022;8. DOI: 10.1200/GO.22.00215.

15. Elmore SN, Polo A, Bourque J-M, et al. Radiotherapy resources in Africa: an International Atomic Energy Agency update and analysis of projected needs. *The Lancet Oncology*. 2021;22 (9):e391-e399.
Doi: 10.1016/S1470-2045(21)00351-X.

16. Ndlovu N. Radiotherapy treatment in cancer control and its important role in Africa. *Ecancermedicalscience*. 2019;13.
Doi: 10.3332/ecancer.2019.942.

17. IAEA. Directory of radiotherapy centers. 2022. Https://dirac.iaea.org/Query/Countries.

18. Gradishar WJ, Moran MS, Abraham J, et al. Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*. 2022; 20(6):691-722. Doi: 10.6004/jnccn.2022.0030.

19. Liu L, Yang Y, Guo Q, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. *Radiation Oncology*. 2020;15:1-15. (2020) 15:17.
Doi.org/10.1186/s13014-020-1463-1.

20. Akl FM, Khater A. Hypofractionated versus conventionally fractionated radiotherapy in post-mastectomy breast cancer patients. *Journal of Cancer Therapy*. 2018;9(11):941-954.
DOI: 10.4236/jct.2018.911078.

21. Irabor OC, Swanson W, Shaukat F, et al. Can the adoption of hypofractionation guidelines expand global radiotherapy access? An analysis for breast and prostate radiotherapy. *JCO global oncology*. 2020;6:667-678.
Doi: 10.1200/JGO.19.00261.

22. Swanson W, Kamwa F, Samba R, et al. Hypofractionated radiotherapy in African cancer centers. *Frontiers in Oncology*. 2021;10:618641.
Doi.org/10.3389/fonc.2020.618641.

23. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *Journal of the National Cancer Institute*. 2002;94(15):1143-1150. DOI: 10.1093/jnci/94.15.1143.

24. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiotherapy and oncology*. 2005;75(1):9-17.
Doi: 10.1016/j.radonc.2005.01.005.

25. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *The lancet oncology*. 2006;7(6):467-471.
Doi: 10.1016/S1470-2045(06)70699-4.

26. Yarnold J, Bentzen SM, Coles C, Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. *International journal of radiation oncology, biology, physics*. 2011;79(1):1-9.
DOI: 10.1016/j.ijrobp.2010.08.035.

27. Group ST. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *The Lancet*. 2008;371 (9618):1098-1107.
Doi: 10.1016/S0140-6736(08)60348-7.

28. Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *New England Journal of Medicine*. 2010;362(6):513-520.
DOI: 10.1056/NEJMoa0906260.

29. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *The lancet oncology*. 2013;14(11):1086-1094.
Doi: 10.1016/S1470-2045(08)70077-9.

30. Wang S-L, Fang H, Song Y-W, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority,

open-label, phase 3 trial. *The Lancet Oncology*. 2019;20(3):352-360. Doi: 10.1016/S1470-2045(18)30813-1.

31. Offersen B, Alsner J, Nielsen H, Jakobsen E, Nielsen M, Krause M. Danish Breast cancer Group radiation Therapy committee. hypofractionated Versus standard Fractionated radiotherapy in patients With early Breast cancer or Ductal carcinoma In situ in a randomized phase III Trial: The DBcG hYpO Trial. *J clin Oncol*. 2020;38(31). Doi: 10.1200/JCO.20.01363.

32. Wang S-L, Fang H, Hu C, et al. Hypofractionated versus conventional fractionated radiotherapy after breast-conserving surgery in the modern treatment era: a multicenter, randomized controlled trial from China. *Journal of Clinical Oncology*. 2020;38(31):3604-3614. Doi: 10.1200/JCO.20.01024.

33. Jd C. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31: 1341-1346. Doi: 10.1016/0360-3016(95)00060-C.

34. Brunt AM, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *The Lancet*. 2020;395(10237):1613-1626. Doi:https://doi.org/10.1016/S0140-6736(20)30932-6.

35. Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *Journal of Clinical Oncology*. 2020;38(28):3261. Doi: 10.1200/JCO.19.02750.

36. Group FT. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiotherapy and Oncology*. 2011;100(1):93-100. Doi:10.1200/JCO.19.02750.

37. Veluthattil AC, Sudha SP, Kandasamy S, Chakkalakkoombil SV. Effect of hypofractionated, palliative radiotherapy on quality of life in late-stage oral cavity cancer: a prospective clinical trial. *Indian Journal of Palliative Care*. 2019;25(3):383. Doi: 10.4103/IJPC.IJPC_115_18.

38. Zingeta GT, Worku YT, Awol M, et al. Outcome of Hypofractionated Palliative Radiotherapy Regimens for Patients With Advanced Head and Neck Cancer in Tikur Anbessa Hospital, Ethiopia: A Prospective Cohort Study. *JCO Global Oncology*. 2024;10:e2300253. Doi: 10.1200/GO.23.00253.

39. Shaitelman SF, Lei X, Thompson A, et al. Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: results of a randomized, noninferiority clinical trial. *Journal of Clinical Oncology*. 2018;36(35):3495. Doi: 10.1200/JCO.18.00`317.

40. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology*. 2010;17(6):1471-1474. Doi: 10.1245/s10434-010-0985-4.

41. Engstrom P, Benson 3rd A, Cohen A, et al. NCCN Colorectal Cancer Practice Guidelines. The National Comprehensive Cancer Network. *Oncology (Williston Park, NY)*. 1996;10(11 Suppl):140-175. PMID: 8953601.

42. Green F, Page D, Fleming I, Fritz A, Balch C, Haller D, Morrow M. AJCC cancer staging manual. In: New York: Springer; 2002. https://www.facs.org/media/tauiudl3/ajcc_6thed_cancer_staging_manual_part1.pdf.

43. Team RDC. R: A language and environment for statistical computing. *(No Title)*. 2010. https://www.scirp.org/reference/referencespapers?referenceid=493779.

44. Mushonga M, Weiss J, Liu ZA, et al. Hypofractionation in breast cancer radiotherapy across World Bank income groups: Results of an international survey. *JCO global oncology*. 2023;9:e2200127. Doi.org/10.1200/GO.22.00127.

45. Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. *The*

lancet oncology. 2015;16(10):1153-1186. Doi: 10.1016/S1470-2045(15)00222-3.

46. Monten C, Lievens Y. Adjuvant breast radiotherapy: how to trade-off cost and effectiveness? *Radiotherapy and Oncology*. 2018;126(1):132-138. Doi: 10.1016/j.radonc.2017.11.005.

47. Rastogi K, Jain S, Bhatnagar AR, Bhaskar S, Gupta S, Sharma N. A comparative study of hypofractionated and conventional radiotherapy in postmastectomy breast cancer patients. *Asia-Pacific Journal of Oncology Nursing*. 2018;5(1): 107-113. Doi: 10.4103/apjon.apjon_46_17.

48. Grosche S, Bogdanova NV, Ramachandran D, et al. Effectiveness of hypofractionated and normofractionated radiotherapy in a triple-negative breast cancer model. *Frontiers in oncology*. 2022;12:852694. Doi.org/10.3389/fonc.2022.852694.

49. Korreman S, Rasch C, McNair H, et al. The European Society of Therapeutic Radiology and Oncology–European Institute of Radiotherapy (ESTRO–EIR) report on 3D CT-based in-room image guidance systems: a practical and technical review and guide. *Radiotherapy and Oncology*. 2010;94(2):129-144. Doi: 10.1016/j.radonc.2010.01.004.

50. Datta NR, Samiei M, Bodis S. Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020. *International Journal of Radiation Oncology* Biology* Physics*. 2014;89 (3):448-457. Doi: 10.1016/j.ijrobp.2014.03.002.

51. Abdel-Wahab M, Bourque J-M, Pynda Y, Iżewska J, Van der Merwe D, Zubizarreta E, Rosenblatt E. Status of radiotherapy resources in Africa: an International Atomic Energy Agency analysis. *The lancet oncology*. 2013;14(4):e168-e175. Doi: 10.1016/S1470-2045(12)70532-6.

52. Mutebi M, Anderson BO, Duggan C, et al. Breast cancer treatment: A phased approach to implementation. *Cancer*. 2020;126:2365-2378. Doi: 10.1002/cncr.32910.

53. Langenhoven L, Barnardt P, Neugut AI, Jacobson JS. Phenotype and treatment of breast cancer in HIV-positive and-negative women in Cape Town, South Africa. *Journal of global oncology*. 2016;2(5):284-291. Doi.org/10.1200/JGO.2015.002451.

54. Muddather HF, Elhassan MM, Faggad A. Survival outcomes of breast cancer in sudanese women: a hospital-based study. *JCO Global Oncology*. 2021;7(1):324-332. Doi.org/10.1200/GO.20.00538.

55. Brandão M, Guisseve A, Bata G, et al. Breast cancer subtypes: implications for the \treatment and survival of patients in Africa—a prospective cohort study from Mozambique. *ESMO open*. 2020;5(5):e000829. Doi: 10.1136/esmoopen-2020-000829.

56. Vanderpuye V, Grover S, Hammad N, PoojaPrabhakar n, Simonds H, Olopade F, Stefan D. An update on the management of breast cancer in Africa. *Infectious agents and cancer*. 2017;12:1-12. Doi: 10.1186/s13027-017-0124-y.

57. Cubasch H, Joffe M, Hanisch R, et al. Breast cancer characteristics and HIV among 1,092 women in Soweto, South Africa. *Breast cancer research and treatment*. 2013;140:177-186. Doi: 10.1007/s10549-013-2606-y.

58. Othieno-Abinya N, Nyabola L, Abwao H, Ndege P. Post-surgical management of patients with breast cancer at Kenyatta National Hospital. *East African medical journal*. 2002;79(3):156-162. Doi: 10.4314/eamj.v79i3.8897.

59. Adebamowo C, Adekunle O. Case-controlled study of the epidemiological risk factors for breast cancer in Nigeria. *British Journal of Surgery*. 1999;86(5):665-668. Doi: 10.1046/j.1365-2168.1999.01117.x.

60. Rais G, Raissouni S, Aitelhaj M, et al. Triple negative breast cancer in Moroccan women: clinicopathological and therapeutic study at the National Institute of Oncology. *BMC Women's Health*. 2012;12(1):1-9. Doi: 10.1186/1472-6874-12-35.

61. Darré T, Tchandikou L, Simgban P, et al. Factors associated with late diagnosis of breast cancer in women in Togo, Sub-Saharan Africa. *BMC Women's Health*. 2023;23(1):1-8.

62. Omotoso O, Teibo JO, Atiba FA, et al. Addressing cancer care inequities in sub-Saharan Africa: current challenges and proposed solutions. *International Journal for Equity in Health*. 2023; 22(1):189. Doi.org/10.1186/s12905-023-02257-8.

63. Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy use, performance status, and quality of life at the end of life. *JAMA oncology*. 2015;1(6): 778-784. Doi: 10.1001/jamaoncol.2015.2378.

64. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Annals of Oncology*. 2016;27(8):1386-1422. Doi: 10.1093/annonc/mdw235.

65. Roeland E, LeBlanc T. Palliative chemotherapy: oxymoron or misunderstanding? *BMC palliative care*. 2016;15(1):1-3. Doi: 10.1186/s12904-016-0109-4.

66. Fiorin de Vasconcellos V, RCC Bonadio R, Avanço G, Negrão MV, Pimenta Riechelmann R. Inpatient palliative chemotherapy is associated with high mortality and aggressive end-of-life care in patients with advanced solid tumors and poor performance status. *BMC Palliative Care*. 2019;18 (1):1-8. Doi: 10.1186/s12904-019-0427-4.

67. Bugat R, Bataillard A, Lesimple T, et al. Summary of the standards, options and recommendations for the management of patients with carcinoma of unknown primary site (2002). *British journal of cancer*. 2003;89(1):S59-S66. Doi: 10.1038/sj.bjc.6601085.

68. Seve P, Sawyer M, Hanson J, Broussolle C, Dumontet C, Mackey JR. The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site: a population-based study. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2006;106(9):2058-2066. Doi: 10.1002/cncr.21833.

69. Ettinger DS, Abbruzzese J, Gams R, et al. NCCN practice guidelines for occult primary tumors. *Oncology*. 1998;12(11 A):226-309. Doi: 10.6004/jnccn.2011.0117.

70. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. *Journal of Clinical Oncology*. 2021;39 (13):1485. Doi.org/10.1200/JCO.20.03399.

71. ACSCA N. COVID-19 pandemic ongoing impact on cancer. *Patients and Survivors Survey Findings Summary*. 2020;2020. https://www.fightcancer.org/policy-resources/covid-19-pandemic-ongoing-impact-cancer-community-may-2020.

72. Madigan LI, Dinh P, Graham JD. Neoadjuvant endocrine therapy in locally advanced estrogen or progesterone receptor-positive breast cancer: determining the optimal endocrine agent and treatment duration in postmenopausal women—a literature review and proposed guidelines. *Breast Cancer Research*. 2020;22(1):1-13. Doi: 10.1186/s13058-020-01314-6.

73. Coates AS, Colleoni M, Goldhirsch A. Is adjuvant chemotherapy useful for women with luminal a breast cancer. *J Clin Oncol*. 2012;30 (12):1260-1263. Doi: 10.1200/JCO.2011.37.7879.

74. Hayes DF. Targeting adjuvant chemotherapy: a good idea that needs to be proven! *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2012;30(12):1264-1267. Doi: 10.1200/JCO.2011.38.4529.

75. Alba E, Albanell J, de la Haba J, et al. Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. *British journal of cancer*. 2014;110(5):1139-1147. Doi: 10.1038/bjc.2013.831.

76. Tapia M, Hernando C, Martínez MT, et al. Clinical Impact of New Treatment Strategies for HER2-Positive Metastatic Breast Cancer Patients with Resistance to Classical Anti-HER Therapies. *Cancers.* 2023;15(18):4522. Doi: 10.3390/cancers15184522.

77. Choong GM, Cullen GD, O'Sullivan CC. Evolving standards of care and new challenges in the management of HER2-positive breast cancer. *CA: a cancer journal for clinicians.* 2020;70(5):355-374. Doi: 10.3322/caac.21634.

78. Yalaza M, İnan A, Bozer M. Male breast cancer. *The journal of breast health.* 2016;12(1):1. Doi: 10.5152/tjbh.2015.2711.