# TREATMENT OUTCOMES OF PATIENTS WITH PRECANCEROUS CERVICAL LESIONS MANAGED BY CRYOTHERAPY AND LOOP ELECTROSURGICAL PROCEDURE DONE AT OCEAN ROAD CANCER INSTITUTE

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**Muhimbili University of Health and Allied Sciences**
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**By**

**Edwin Gathendu Miro**

**A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine in Clinical Oncology of Muhimbili University of Health and Allied Sciences**

**October, 2024**

## CERTIFICATION

The undersigned certify that they have read and thus recommend for acceptance by the Muhimbili University of Health and Allied Sciences this research project treatment outcomes of patients with precancerous cervical lesions managed by cryotherapy and loop electrosurgical procedure done at ocean road cancer institute. This is for the partial fulfillment of the requirements for the degree of Master of Medicine in Clinical Oncology of the Muhimbili University of Health and Allied Sciences.

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## DECLARATION AND COPYRIGHT

I Dr Gathendu Edwin hereby declare that this research project is my original work and thus has not been presented and will not be presented to any university for the same or any other degree award.

Signature ..... Date .....

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Overall, to the Almighty God for being gracious, kind and a constant source of strength in the darkest of times *Jeremiah 29:11 For I know the plans I have for you," declares the Lord, "plans to prosper you and not to harm you, plans to give you hope and a future*

## DEDICATION

I dedicate this work to the memory of my late brother Patrick Githiora Kimangu, *wish you were here bro.*

## ABSTRACT

**Background:** Globally the burden of cancer is increasing and noted to be a leading cause of morbidity and mortality contributed by non-communicable diseases. Cervical cancer as of the Global Cancer Observatory (GLOBOCAN) 2022 is the fourth most frequent cancer in women globally accounting for 662,301 new cancer cases and 348,874 cancer deaths. As per this report the region-specific incidence and mortality for East Africa, cervical cancer is the leading cancer with 40.1/100,000 and 28.6/100,000 respectively. In countries like Denmark and Norway cervical cancer was reduced by 50% between 1960s and 1970s(1). The main drivers being a high prevalence of high-risk human papilloma virus (HR HPV), human immunodeficiency virus (HIV) coupled with the lack of effective sustained programs for cervical cancer screening which is in low- and middle-income countries (LMIC). This has led to the introduction of more cost effective and accessible screening services to these countries. There is lack of data looking into the effectiveness of these cost-effective screening services especially those coupled with treatment of precancerous cervical lesions.

**Objective:** This study aimed to estimate the prevalence of precancerous cervical lesions, their treatment outcomes and investigate predictors within the sociodemographic and clinicopathologic factors of clients screened for cervical cancer at Ocean Road Cancer Institute (ORCI).

**Materials and methods:** This study was a retrospective cohort study conducted at the ORCI located in Dar es salaam, Tanzania. It included all clients who visited the institute for cervical cancer screening from January 2020 to December 2022 as the study population. The end point was 1 year follow-up results on re-screening after treatment for a precancerous cervical lesion. The computing tool used for statistical analysis and data visualization was statistics and data software (Stata version 17.0). Quantitative data was summarized using mean and standard deviation while categorical data was summarized using proportions. The Chi test was used to compare proportions and univariate and multivariate analysis used to evaluate factors that are outcome predictive.

**Results:** Clients who were found to have precancerous cervical lesions on visual inspection with acetic acid/ visual inspection with Lugol's iodine (VIA/VILLI) corresponded to 4.8% of all 5074 clients screened, characterized with majority being within the age of 35-45,

interestingly associated with nulliparity and 4 times more prevalent in clients who were HIV positive (adjusted odds ratio (aOR)) = 4.47, 95% CI: 3.28-6.09, p<0.001).

The 1-year follow-up results on re-screening after treatment of precancerous lesions corresponded to 78.2% cure rate of the 78 clients who turned up for follow. Results also reveal that women living with HIV were 3.72 times more likely to turn positive after one year of follow-up (aOR=3.72, 95% CI: 1.03-13.47, p-value = 0.045).

**Conclusions:** In the screening and post treatment screening of clients for cervical cancer, HIV was found to be a significant predictor of both prevalence and treatment failure of precancerous lesions detected using VIA/VILLI. Future research should be directed towards this cohort of clients on customized screen and treat protocols to halt their potential progression to cervical cancer.

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## ABREVIATIONS

ASCCP: American Society for Colposcopy and Cervical Pathology

CCPPZ: Cervical Cancer Prevention Program in Zambia

CIN: Cervical Intraepithelial Neoplasia

HIV: Human Immunodeficiency Virus

HIC: High Income Countries

HPV: Human Papilloma Virus

HSIL: High grade Squamous Intraepithelial Lesion

LMIC: Low- and Middle-Income Countries

ORCI: Ocean Road Cancer Institute

SSA: Sub-Saharan Africa

VIA: Visual Inspection with Acetic acid

VILI: Visual Inspection with Lugol's Iodine

WHO: World Health Organization

# CHAPTER ONE

## 1.0 INTRODUCTION

### 1.1 Background

A precancerous cervical lesion synonymously known as cervical intraepithelial neoplasia (CIN) is a known precursor stage for the development of cervical cancer. It is defined by the changes in the epithelial cells lining the uterine cervix that can be detected cytologically, histologically, and recently by visual inspection with/without magnification. Persistent infection with high-risk human papilloma virus (HR HPV) has been identified as the main driver of these changes which if left untreated result in invasive disease(2). Severity of the lesion is derived from the amount of the cervical epithelial lining showing dysplastic changes, CIN 1 only a third of the epithelial thickness, CIN 2 half to two thirds and CIN 3 almost full thickness involvement. The latter two are known to be high grade lesions and thus taken to be the true precursors to invasive disease.

Cervical cancer as of the Global Cancer Observatory 2020 is the fourth most frequent cancer in women globally accounting for 604,000 new cancer cases and 342,000 cancer deaths(3). As per this report the region-specific incidence and mortality for East Africa is leading with 40.1/100,000 and 28.6/100,000 respectively(3). In Tanzania cervical cancer is the leading cancer among women aged 15-44 years with an incidence and mortality of 62.5/100,000 and 42.7/100,000 respectively(4).

There is a disproportional distribution of cervical cancer globally with the main drivers being a high prevalence of high-risk human papilloma virus (HR HPV), human immunodeficiency virus (HIV) coupled with the lack of effective sustained programs for cervical cancer screening(5) which are predominantly seen in low- and middle-income countries (LMIC). Social factors like multiparity, higher prevalence of sexually transmitted infections (STI) due to unprotected and multiple sexual contacts as well as lack of formal education in the populace also have been found to be drivers towards cervical of cancer in LMIC(6–9). This has led to concerted efforts to bridge this gap in access to cervical cancer preventive services by introducing more cost effective and accessible screening services to these countries(10).

HPV infection which has an established causal relationship with precancerous cervical lesions and cervical cancer as a necessary risk factor(2) is currently considered globally as

the most prevalent sexually transmitted infection in sexually active women(11). Majority of HPV infections in immunocompetent individuals clear spontaneously (12), persistence and progression are mainly seen with high-risk strains like HPV 16 which has a higher tendency to persist(12) or in individuals with an immunosuppressive background like HIV infection(13). The prevalence of cervical cancer in women living with HIV (WLWHIV) in a meta-analysis across four continents revealed a disparity with most HIV attributable cervical cancer in southern and eastern Africa adding to the existing burden of cervical cancer in these regions(14).

Cervical cancer prevention has been deemed possible due to extensive knowledge and research into the necessary risk factor HPV(2,12,15) infection and its natural progression to precancerous cervical lesions and then finally invasive disease(16,17) thus giving a window of opportunity for preventive measures. Currently for primary prevention WHO recommends vaccination against HPV be integrated into national vaccination programs with an ambitious target of 90% coverage before 2030(18,19) and for secondary prevention by prompt detection through screening with HPV DNA testing, cytology, visual inspection with acetic acid (VIA), or visual inspection with Lugol's iodine (VILI) coupled to effective excision or ablative treatment(20). The screening strategy adopted is dependent on its cost effectiveness and practicality, though the most recommended with a large body of evidence to its effectiveness is cytology-based screening. Due to the multiple visits involved and the financial implications of cytology-based screening most LMIC opt for more practical strategies that are more acceptable to their populace and cost effective(21).

These preventive measures have evidenced health and economic impact shown by a study done involving 50 LMIC with reductions in 5 million cervical cancer cases, over 3 million deaths and a reduction of spending of about 22 million dollars on disability. These are the estimates from a ten year roll out of a preventive programme involving primary and secondary prevention at an approximate cost of 3.2 billion dollars(22).

## 1.2 Statement of Problem

The detection and prompt management of precancerous cervical lesions is the cornerstone strategy of secondary prevention of cervical cancer. In Tanzania the incidence and burden posed by precancerous cervical lesions is estimated to be high and this is driven by limited access to essential health care services and social cultural factors that increase infection rates of HPV a necessary risk factor.

Global efforts have been made to tackle these precancerous lesions with the use of highly organized screening programs using effective screening methods such as cervical cytology and HPV testing followed by visualization of lesions either macro or microscopically and prompt management. The incidence of cervical cancer was reduced by almost 50% in some countries such as Denmark, Norway, and Sweden when they introduced sustained population-based screening programs as early as the 1960s and 1970s.

The standard of care for many LMIC due to its cost effectiveness and quick linkage to immediate treatment is VIA which is usually available free of charge in different levels of government and faith-based hospitals. But despite its convenience, VIA has a lower sensitivity and specificity compared to more established tests like Papanicolaou (PAP) smear and HPV testing. Despite these limitations acknowledgments have been made to the fact that even a single round of VIA screening has been associated with a 25–35% reduction in cervical cancer incidence and the frequency of cervical intraepithelial neoplasia grade 2 or worse lesions in randomized-controlled trials(23).

In Tanzania the standard screening procedure for the national cervical cancer screening program utilizes VIA and same visit treatment with either cryotherapy or loop electrosurgical excision procedure (LEEP) for positive cases. The global standard of care that has yielded profound results involves cytologic, histologic or molecular based screening coupled to prompt treatment and stringent follow up post treatment. The challenges posed by cost, opportunistic rather than population-based screening and lack of follow up database has made it difficult to adopt the global standard. Thus, there is a critical need to evaluate the effectiveness of screening and efficacy of the treatment options available to patients attended to at ORCI.

### 1.3 Conceptual Framework

These parameters have influence over the treatment outcome of clients managed for cervical precancerous lesions.

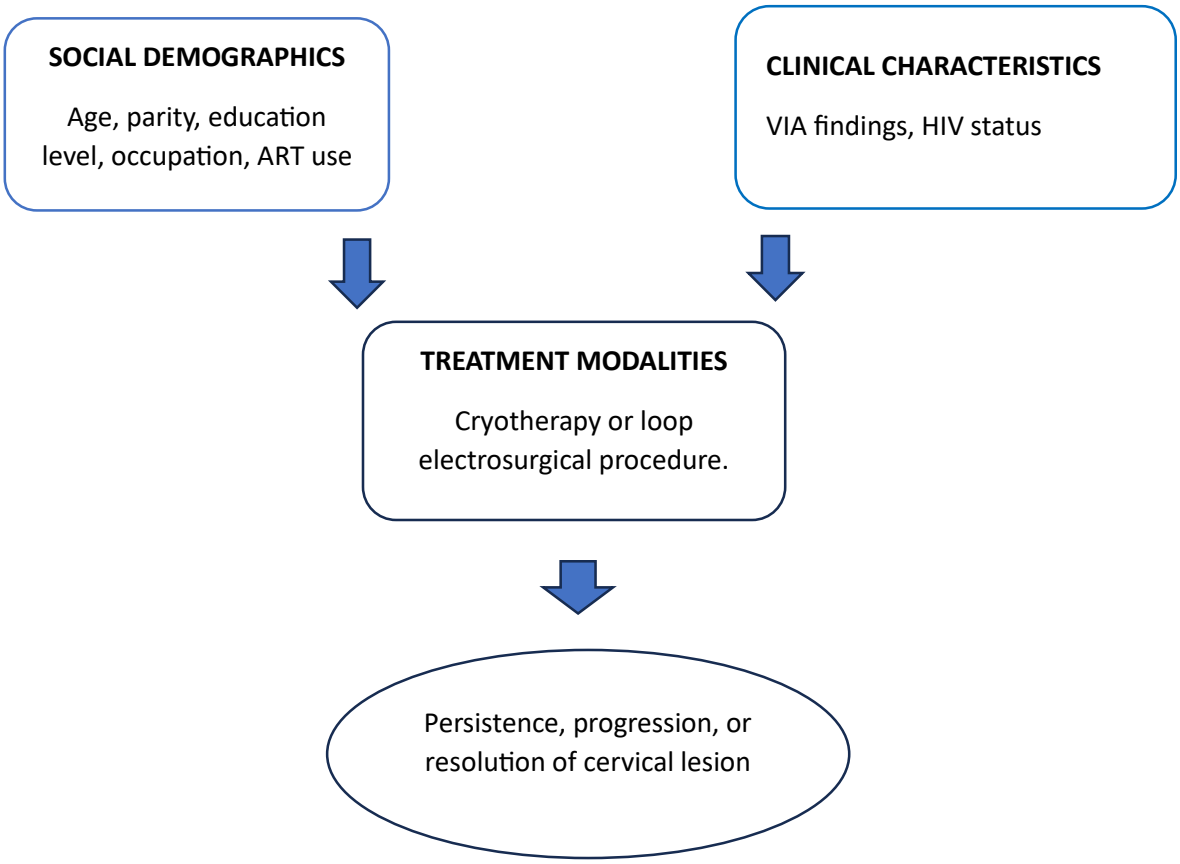



**Figure 1:** conceptual framework describes the link between client social demographics, client clinical characteristics and treatment modality to treatment outcome.

## 1.4 Rationale

Cervical cancer in SSA Tanzania included is a major public health concern due to its high incidence and mortality rates in the region. Currently robust measures are being taken to scale up primary and secondary prevention. The global gold standard for screening, treatment and post treatment follow up is difficult to adopt in Tanzania due to cost and implementation logistics. This study assesses the sociodemographic, clinicopathologic characteristics of screened clients, prevalence of precancerous cervical lesions their predictors as well as treatment outcomes and their predictors. Thus, evaluating the status of the current cervical cancer secondary prevention program adopted. Understanding the predictors of prevalence and treatment outcomes and the preventive potential of the current screening and treatment program adopted in the country will allow for potential policy changes to improve it. Since ORCI follows the government provided guidelines this study can contribute to the improvement of management and ultimately reduce the disease burden imposed by cervical cancer in the country.

## 1.5 Research Questions

### 1.5.1 General research question

What is the one-year treatment outcome of patients managed for precancerous cervical lesions at ocean road cancer institute by cryotherapy or loop electrosurgical procedure from January 2020 to December 2022?

### 1.5.2 Specific research questions

1. What is the prevalence of precancerous cervical lesions among clients attending cervical cancer screening at ORCI?
2. What are the socio-demographic and clinical characteristics of clients screened for precancerous cervical lesions confirmed at screening at ORCI?
3. What is the treatment outcome of patients managed for precancerous cervical lesions at ORCI?
4. What are the predictors of treatment outcome among patients managed for precancerous cervical lesions at ORCI?

### 1.6 Broad objective

To determine one year treatment outcome of clients managed for precancerous cervical lesions managed at ORCI from 2020 January to 2022 December.

### 1.7 Specific objectives

1. To determine the prevalence of precancerous cervical lesions among clients attending cervical cancer screening at ORCI from January 2020 to December 2022.
2. To determine the social-demographic and clinical characteristics of clients screened for precancerous cervical lesions managed at ORCI from 2020 January to 2022 December.
3. To determine treatment outcome of patients managed for precancerous cervical lesions at ORCI between January 2020 to December 2022.
4. To determine the predictors of treatment outcome among patients managed for precancerous cervical lesions at ORCI between January 2020 to December 2022.

### 1.8 Literature Review

The variations in the population affected by precancerous cervical lesions are influenced by social demographic characteristics such as age, marital status, educational status and economic status, reproductive health characteristics such as parity and contraceptive use as well as lifestyle and sexual characteristics. The main drivers of these variations are exposure to the risk factors for precancerous lesion, HPV an established necessary risk factor(24) and factors that assist HPV pathogenesis like HIV infection(25,26), environmental factors such as smoking(27,28), co infection with other sexually transmitted infections(29) and oral contraceptive use(30).

#### 1.8.1 Social demographic characteristics

##### 1.8.1.1 Age

In developed high-income countries (HIC) like North America where the standard screening is cervical cytological or HPV co tested with cytology the peak incidence age for CIN 1 is between the ages of 20 – 24 years while CIN 2/3(high grade intraepithelial lesions) peaks between the ages of 25-35 years(31). In LMIC of which most African countries are, the use of the main established screening technique which is cervical histology or HPV testing

another high performing test cannot be supported by current health systems of the region mainly due to financial implications(10). Thus, adoption of more cost effective and sustainable screening methods is recommended (23).

In a study done in India age above 60 was found to significantly correlate with VIA positivity with a two times likelihood (32), another study done in Ethiopia showed that women aged 40-44 years were four times more likely to be VIA positive upon screening as compared to those aged 30-34 years (33). In Tanzania a study done in 2012 showed almost twice the odds of VIA positivity among women aged 45-59 years as compared to women between 25-34 years (6). In Tanzania there is no recent age distribution of VIA positivity.

#### 1.8.1.2 Marital status

Regional studies have shown that single participants are at an increased risk of developing precancerous lesions, these include a study in Cameroon that showed two times odds of precancerous cervical lesions among single participants as compared to divorced or married with (7). In Tanzania a study to identify the determinants of VIA positivity found 1.5 increased odds of developing precancerous cervical lesions in widowed or separated women which was higher than in married or single clients(6). There is no current data on this association in Tanzania.

#### 1.8.1.3 Educational status

There are studies that support educational status as a factor determining VIA positivity, like a study done in Zambia following the Cervical Cancer Prevention Program in Zambia (CCPPZ) initiative shows education beyond high school almost halves the likelihood of VIA positivity (34). Another study done in Tanzania also supports this with the finding that those with no formal education have a fourfold odds of VIA positivity (6). But there are studies that show education status as a demographic factor that doesn't have an association with detectable precancerous lesions using VIA, like a study in Tanzania (35) conducted between 2008 and 2009 looking into the factors associated with precancerous cervical lesions tested by VIA or cytology.

#### 1.8.1.4 Economic status

Regional studies show low social economic status attributes to detectable precancerous cervical lesions in screening using visual inspection, like a study in Zambia where an income of more than 500,000 Zambian Kwacha was associated with reduced odds of VIA

positivity(34). Another study in Ethiopia shows that women who live in households that earned less that 66 dollars per month have a three times likelihood of having detectable precancerous cervical lesions using VIA during screening(8). The influence of economic status on VIA positivity has not been recently studied in Tanzania.

### 1.8.2 Reproductive characteristics

#### 1.8.2.1 Parity

In a study done in America on the cofactors of HPV infection that aid the progression to cervical cancer showed that women were two times more likely to develop CIN 3 if they were para 3+(30). In a study done in Ethiopia on the associated factors of VIA positivity showed that participants with multiple deliveries were more likely to be VIA positive especially those with more than 5 deliveries who were two times more likely (33). In a similar study done earlier in the year 2012 in Tanzania showed that increased parity is associated with VIA positivity with those who had 5 children or more 3 times more likely (6), though there is no recent data on association between parity and VIA positivity.

#### 1.8.2.2 Contraceptive use

A study done in America that was aimed to establish HPV co-factors that promote transition from infection to precancerous cervical lesions shows that prolonged use of oral contraceptives(10+years) is positively associated with CIN3 with an OR of 2.42(30). Regional studies with visual inspection as the primary screening for precancerous cervical lesions show no association between contraceptive use and detectable lesions.

### 1.8.3 Sexual and lifestyle characteristics

HPV is a necessary risk factor in the pathogenesis of precancerous cervical lesions and their progression to invasive disease (2,24). Since its transmission is primarily sexual (11) means that sexual behavior of participants under study is vital.

#### 1.8.3.1 Age of sexual debut

Delaying the age of sexual debut to above 18 years has been shown to associate with a decreased risk of CIN3 with an OR of 0.44 in a study done in America on co-factors of the pathogenesis of HPV (30). Regionally a case control study done in Ethiopia established that sexual debut below the age 18 years was associated with a four times risk of detectable precancerous cervical lesions using VIA(33)compared to those who debuted above 18 years. Another study done in Zambia to evaluate their screen and treat utilization for the prevention

of cervical cancer shows reporting of a lower age of sexual debut is an independent factor associated with detectable precancerous cervical lesions using VIA (34). Locally age at sexual debut association with VIA positivity is recently yet to be established.

#### 1.8.3.2 Lifetime sexual partners

A study done in America shows that the number of lifetime sexual partners is associated with higher risk of CIN3 and cervical cancer (30). Regionally in a study done in Zambia to evaluate their screen and treat cervical cancer prevention program shows that an increase in number of lifetime sexual partners is an independent factor associated with detectable precancerous cervical lesions using VIA with those with more than 5 partners having close to one and a half likelihood to have detectable precancerous lesions (34). In case control study done in Ethiopia Addis Ababa also confirms that women with two or more lifetime sexual partners, or whose husbands have two or more lifetime sexual partners have a two to three times odds of having detectable precancerous cervical lesions using VIA(9).

Locally a study done in Tanzania to determine the factors associated with detectable precancerous cervical lesions also correlates widowed or separated women with a higher risk of VIA positivity due to their predisposition to having multiple lifetime sexual partners(6). A recent study in Tanzania to determine factors associated with high grade cervical lesions or VIA positivity has established that there is no correlation between the number of lifetime sexual partners and high-grade cervical lesions (35) thus it would be ideal to investigate this association.

#### 1.8.3.3 History of sexually transmitted diseases (STDs)

In a prospective population-based cohort study done in Sweden to determine association between HPV persistence and chlamydia trachomatis established that certain STDs have the potential to be co-factors in the development of precancerous cervical lesions (29). Regionally a case control study done in Ethiopia Addis Ababa to determine the factors associated with VIA detectable precancerous cervical lesions established that women with VIA positive have three times higher odds of having a history of STDs as compared to the control group(9). Other supporting studies include another case control study done in a town in Ethiopia which also established VIA positivity is associated with a history of STDs(33). In Tanzania studies are yet to establish association between history of STDs and VIA detectable precancerous cervical lesions in women who attend cervical cancer screening.

#### 1.8.3.4 Smoking

A case control study done in New South Wales Australia to establish the relationship between smoking and contraceptive use as risk factors to CIN2/3 established significant association between current smoking's especially of 5 or more cigarettes a day with increased risk of high-grade intraepithelial lesions (36). Regionally and locally the association between VIA detectable precancerous cervical lesions and smoking has yet to be fully established.

### 1.8.4 Clinical characteristics

#### 1.8.4.1 HIV infection

In a prospective study done between 1991 and 1996 in America to establish the incidence of pathologically evident cervical precancerous lesions in HIV infected women versus uninfected revealed a five times likelihood of incidence in the HIV infected group(25). Regionally, where detection is mainly using visual inspection multiple studies have supported the above. This includes a study done in Zambia to analyze one of the largest cervical cancer screening programs in sub–Saharan Africa CCPPZ that established a more than two times likelihood of detectable precancerous cervical lesions by VIAC in HIV positive women as compared to those who are negative(34). Other studies like a case control study done in Ethiopia Addis Ababa shows the odds of a history of STDs of which HIV status was included is higher among cases as compared to the controls (9).

In Tanzania a study done to establish the factors associated with precancerous cervical lesions detectable by cytology or visual inspection reveals HIV infection as a risk factor for VIA positivity (35).

### 1.8.5 Prevalence of precancerous cervical lesions

The prevalence of VIA detectable precancerous cervical lesions (VIA positivity rate) varies regionally between countries and within country. This is evidenced by several regional studies done in sub-Saharan Africa where there are ongoing pilot studies. This includes a study done to evaluate one of the largest cervical cancer screening programs in the region, CCPPZ in Zambia which reveals a VIA positivity rate starting from 47% initially to 17%(34).

Other studies include a study done to evaluate screen and treat pilot programs in Benin, cote d'Ivoire and Senegal that reveals great variability within each of the countries and between them with a VIA positivity ranging from 17.6% to 0.7%(37). Locally in a study to investigate

the risk factors of VIA positivity among women in Dar es salaam done at ORCI between 2002 and 2008 reveals a positivity rate of 7%(6). In a more recent cross-sectional study done between 2008 and 2009 in urban and rural Tanzania looking into factors that associate with VIA positivity or high-grade cervical lesions on cytology reveals a VIA positivity rate of 4.3%(35). Investigating a more recent positivity rate of VIA is of epidemiologic importance.

### 1.8.6 Screening, treatment modalities and their outcomes

It is important to acknowledge that there are three main modalities to cervical cancer screening, these are either cytologically based (PAP SMEAR), molecularly based (HPV DNA) or visually based (VIA/VILLI). The most traditionally used of these and with the greatest impact is cytologically based screening and treatment programmes that has been evidenced to significantly reduce mortality from cervical cancer in some developed countries by up to 5 times in period of 50 years(38).

**Table 1:** modalities of cervical cancer screening

| Molecular | Cytologic | Visual inspection |
|---|---|---|
| Nucleic acid amplification tests (NAAT)[a]<br>» high-risk HPV DNA/ NAAT<br>» mRNA<br><br>DNA methylation[b]<br><br>Protein biomarkers[b]<br>» HPV antibodies<br>» oncoproteins | Conventional Pap smear[a]<br><br>Liquid-based cytology (LBC)[a]<br><br>Dual staining to identify p16 and Ki-67[a] | Visual inspection with acetic acid or with Lugol's iodine (VIA/VILI)[a]<br>» naked eye<br>» magnified by colposcope or camera<br><br>Automated visual evaluation of digital images[b] |

In the past 15 years there has been the introduction of molecular based screening major of which is high risk HPV DNA testing with more recent additions of HPV genotyping and HPV mRNA testing. Visual inspection with acetic acid has also been introduced and has been found to bridge the cost gap especially in LMIC where cytology or molecular tests-based screening programmes are not cost effective (23).

Treatment of diagnosed precancerous lesions on screening can be done in a screen and treat approach where the choice to treat is derived from only a positive primary test or a screen,

triage and treat approach where choice to treat is derived from a positive primary test with an additional triage test.

**Table 2:** Approaches to the treatment of diagnosed cervical precancerous lesions.

| | |
|---|---|
| **Screen-and-treat approaches:** | |
| 1 | VIA as the primary screening test, followed by treatment |
| 2 | HPV DNA detection (self- or clinician-collected) as the primary screening test, followed by treatment |
| **Screen, triage and treat approaches:** | |
| 3 | Cytology as the primary screening test, followed by colposcopy triage, followed by treatment |
| 4 | HPV DNA detection as the primary screening test, followed by HPV16/18 triage (when already part of the HPV test), followed by treatment, and using VIA triage for those who screen negative for HPV16/18 |
| 5 | HPV DNA detection as the primary screening test, followed by VIA triage, followed by treatment |
| 6 | HPV DNA detection as the primary screening test, followed by colposcopy triage, followed by treatment |
| 7 | HPV DNA detection as the primary screening test, followed by cytology triage, followed by colposcopy and treatment |

The treatment of precancerous cervical lesions should achieve complete eradication of the transformation zone (TZ) not only the lesion, and this is done by either excision or destructive techniques. Regardless of the technique used, an ablation depth of at least 7mm provides enough safety since intraepithelial neoplasia extends to 4mm depth of cervical gland crypts(39,40). The TZ shows variation in its size and location on the cervix with occasions when it is fully ectocervical and others where it is partially or fully endocervical, this is important since it is a leading factor in determining the treatment technique.

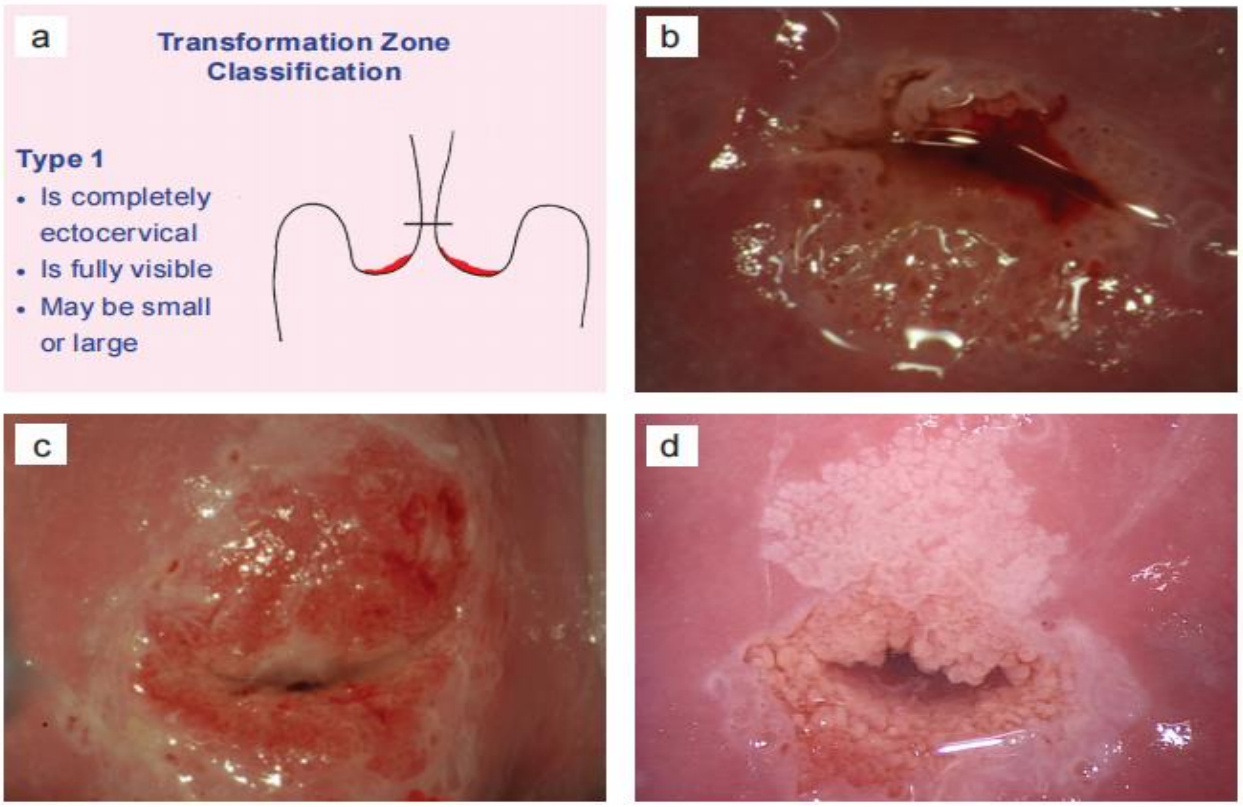



**Figure 2:** shows type 1 transformation zone (TZ) junction

(a) Illustration. (b–d) Examples of type 1 TZs. In each, the entire TZ is visible on the ectocervix.

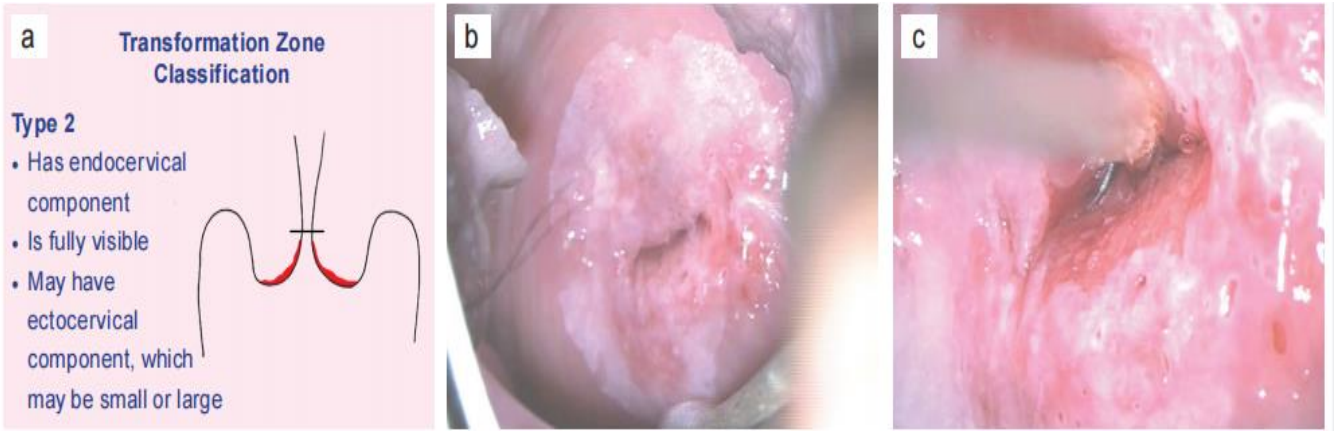



**Figure 3***:* type 2 transformation zone junction

(a) Illustration; the upper limit of the TZ is endocervical but is visible below the upper limit of visibility, (horizontal line). (b, c) A large type 2 TZ; two images of the same cervix. The upper limit of the TZ easily seen on the posterior lip but is visible in the canal only with the aid of a cotton swab.




**Figure 4:** type 3 transformation zone junction

(a) Illustration; the upper limit of the TZ extends beyond the upper limit of visibility, (horizontal line). (b, c) Examples of type 3 TZs. In each, the upper limit of the TZ cannot be seen, as it extends into the canal above the field of view.

**Table 3:** treatment options for different types of transformation zones

| Severity and nature of lesion | Treatment options | | |
|---|---|---|---|
| | Type 1 TZ | Type 2 TZ | Type 3 TZ |
| No visible lesion[a] | Ablation | LLETZ<br>Ablation when the TZ does not extend beyond 2 mm inside the endocervical canal | Type 3 excision by LLETZ |
| Low-grade or high-grade squamous lesions[b] | Ablation (preferred in a screen-and-treat setting or for low-grade lesions)<br>LLETZ | LLETZ<br>Ablation when the TZ does not extend beyond 2 mm inside the endocervical canal | Type 3 excision by LLETZ using a sufficiently long loop, or top-hat excision, SWETZ, or NETZ; CKC (only if the electrosurgical techniques are not feasible) |
| Glandular lesions[c] | Type 3 excision with CKC, SWETZ or NETZ, followed by endocervical curetting<br>LLETZ with a sufficiently long loop, if the other techniques are not feasible | | |
| Microinvasive cancer[d] | Type 3 excision with CKC, SWETZ, or NETZ, followed by endocervical curetting | | |

CKC, cold-knife conization; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LLETZ, large loop excision of the transformation zone; NETZ, needle excision of the transformation zone; SWETZ, straight wire excision of the transformation zone; TZ, transformation zone; VIA, visual inspection with acetic acid.

[a] HPV-positive women in a screen-and-treat setting; cytology suspecting HSIL or glandular abnormalities.

[b] Abnormal VIA in a screen-and-treat setting, colposcopically suspected or histopathologically proved.

[c] Cytology suspecting glandular lesion, suspicion of glandular abnormalities on colposcopy, or adenocarcinoma in situ confirmed on histopathology.

[d] Early invasive cancer suspected on colposcopy although histopathology shows less severe abnormality; microinvasive cancer confirmed on histopathology.

#### 1.8.6.1 Treatment modalities

The main treatment modalities for cervical precancerous lesions are either excisional or ablative.

##### 1.8.6.1.1 Excisional treatment

This treatment technique is also known as cervical conization or cone biopsy which uses one of three procedures laser conization, cold knife conization or large loop excision of the transformation zone (LLETZ) which is also known as loop electrosurgical excision procedure (LEEP) to excise the entire transformation.

##### 1.8.6.1.2 Ablative treatment

This treatment technique uses either cryotherapy (also cryosurgery or cryocautery) or thermal ablation (also thermal coagulation) to destroy the transformation zone and thus unlike excisional treatment no specimen is available for histopathological investigations.

There is preference for excisional rather than ablative treatment techniques in developed countries and this is also the world health organization (WHO) and American Society for Colposcopy and Cervical Pathology (ASCCP) recommendations(41,42) primarily due to the preservation of specimens for histopathological studies. This is of importance in situations where glandular lesions are involved, lesions extending into the endocervix and thus not fully visible (type 2+ TZ), cytology reveals CIN2+ and lesions larger than the reach of the cryotherapy tip. This is despite the fact that a few metanalysis done have not yielded a clear efficacy advantage between ablative and excisional treatment techniques, with some suggesting more odds of treatment failure with ablative techniques(43) while others suggest no clear advantage between the two(44).

#### 1.8.6.2 Follow up after treatment.

The follow up of women who undergo treatment for precancerous cervical lesions is critical since it is evidenced that these women have a greater risk (2-5 times) of developing cervical cancer and more so if lost to follow up (45–47). The first 2 years post treatment should have comprehensive follow up testing since it is within the first 2 years that residual disease will be identified (48). A standard follow-up entails 2 or more cytology studies coupled with 2 or more colposcopy visualizations within the first 2 years post treatment for test of cure then

regular cytologic investigations for 10 or more years (49). Studies done recently have increased support for HPV based post treatment testing rather than standalone cytologic based in identifying persistent or recurrent precancerous cervical lesions (50,51). Furthermore, in LMIC where cytologic studies and colposcopy are expensive and thus cannot be used consistently makes high-risk HPV self-testing a more feasible and even superior option(52).

#### 1.8.6.3 Treatment outcomes

The evidence shows success rates of using ablative or excisional techniques to be quite similar in several publications. One is a meta-analysis of 29 randomized control trials (RCTs) that shows none of the surgical techniques used to treat cervical precancerous lesions surpassing the other except for cryotherapy in the management of CIN 3 with evidenced lower rates of success (44). Thus, suggesting a conclusion that differences in success rate are more user related than technique related (49).

Other outcomes include the post treatment adverse effects which include major bleeding or infection, procedure associated increased secretions or pain and those that affect fertility like, cervical stenosis, infertility, spontaneous abortion, perinatal death, or premature rupture of membranes. Excisional techniques due to the very nature of cutting into a part of the reproductive system are linked to possible reproductive complications especially when extensive excision is done(53) unlike ablative techniques where mostly light bleeding, discomfort and discharge are the common adverse effects unless in cases of post procedure infection.

#### 1.8.6.4 Determinants of treatment outcome

The success or failure of excisional or ablative treatment of precancerous cervical lesions has been linked with evidence to several factors. Surgically margin status where available is a predictor of outcome, where negative margins are achieved precancerous cervical lesions have a high cure rate. A study following up patients treated with cold knife conization for CIN 3 where clear margins are achieved shows that more than 99% of clients after mean follow up of 18 years remained free of high grade intraepithelial squamous lesion (HISL) (CIN 2+)(54). In a meta-analysis looking into post treatment risk of CIN of any grade after

excisional treatment reveals a 5 times risk in those who have positive margins compared to those who have negative or uncertain margins(55).

HPV status post treatment is strongly associated with treatment outcome leading to policies making HPV the follow up test of choice as a test of cure(56–58) and not only high-risk HPV testing but also HPV genotyping since some high-risk strains carry an even higher chance of leading to treatment failure like HPV 16(59). Other factors include cervical glandular involvement which has shown independent of margins can be used as a predictor of recurrent or residual disease after conization for CIN 3(60).

In a comparative study to assess efficacy between cryotherapy, laser ablation and LEEP in management of precancerous cervical lesions followed up to a mean of 16 months shows no significant differences in complications, residual, or recurrent disease. Though it did identify certain clinical and demographic characteristics as risks for persistence and recurrence, these are large lesion size and women aged 30 years and above respectively (61).

Immunosuppression especially attributed to HIV infection is evidently linked to higher failure rate of precancerous cervical lesion treatment. A metanalysis done to investigate prevalence and odds of treatment failure in HIV infected vs HIV uninfected revealed a significant risk of treatment failure among the former (62).

# CHAPTER TWO

## 2.0 METHODOLOGY

### 2.1 Study Design

This study was a retrospective cohort study conducted on the outcomes of the treatment of precancerous cervical lesions.

### 2.2 Study Settings

The study was conducted at ORCI cancer screening department where clients come for routine screening and as referrals from other facilities for further evaluation and treatment of abnormal cervical findings. ORCI is a National Cancer Hospital in Tanzania equipped with necessary human resource, supplies and equipment to cater from primary to tertiary cancer care. There are approximately more than 1500 clients screened for precancerous cervical lesions and cervical cancer at ORCI annually and those that are found to have precancerous cervical lesion testing VIA positive are managed in the same visit by either cryotherapy or LEEP. But those that have features suggestive of cervical cancer biopsies are taken for confirmatory histologic investigations after which they are reviewed for definitive cervical cancer management dependent on the stage of disease.

### 2.3 Target Population

All women who were eligible for cervical cancer screening as per screening guidelines in Tanzania

### 2.4 Accessible Population

All women who were seeking as first visit, follow up or referral for screening services at ORCI between 2020 January to December 2022

### 2.5 Study Population

All women who were screened for precancerous cervical lesions at ORCI between 2020 January and December 2022

## 2.6 Selection Criteria

### 2.6.1 Inclusion criteria

All clients who were screened for precancerous cervical lesions by VIA at ORCI between 2020 January and December 2022 with documented results

### 2.6.2 Exclusion criteria

All clients who had missing information

## 2.7 Sample Size Estimation

Sample size estimation was based on a pilot RCT done in Zambia to evaluate the effectiveness of the countries and regions (SSA) well established screen and treat program that reported a 40% treatment failure rate with cryotherapy(63). The sample size for this study was estimated with the use of a population prevalence formula:

$$\frac{Z^2(P)(1-P)}{c^2}$$

With an assumption that the population proportions (p) is 40%, Z score for confidence interval of 95% being 1.96, with margin of error (C) estimated to be 5%.

$$\frac{1.96^2(40)(100-40)}{5^2}$$

Therefore, the projected sample size was 369

Data retrieval was sorted on clients who were screened for precancerous cervical lesions and cervical cancer between January 2020 and December 2022 and all clients who meet the inclusion criteria were included in this study.

## 2.8 Variables

### 2.8.1 Independent variables

Socio-demographic, reproductive, sexual and lifestyle characteristics which included variables like age, parity, occupation, marital status and residence.

Clinical characteristics which include presence of active known sexually transmitted diseases like HIV.

### 2.8.2 Dependent variable

Treatment outcomes, success or failure of interventions done to the study participants.

### 2.9 Data Collection

A data sheet was used to collect data from the screening registers and hospitals electronic records which were entered into Microsoft excel. Information pertaining to clients' demographic and clinical characteristics were entered as well as treatment and its outcomes. Where necessary when information was needed but not available on electronic or non-electronic sources or was unclear, the client was called and that information sort but strictly after acquiring voluntary verbal consent.

### 2.10 Data Analysis

Data was entered into Excel and analyzed using STATA version 17.0, this is after data collected from extraction forms was double-checked, corrected, and then entered. Continuous data was summarized using mean/standard deviation whereas categorical data was summarized using frequency/percentage. The summarized data was presented in tables, figures, and text. Chi-square test was used to check for association between dependent variable and independent variables. Multiple logistic regression was done to assess the degree, direction and statistical significance of associations between the dependent and independent variables, value of less than 0.05 was considered statistically significant.

**Table 4** : Data analysis plan

| **Specific objective** | **Analysis plan** |
|---|---|
| 1. To describe the socio-demographic and clinicopathologic details of clients screened for precancerous cervical lesions | Frequency, percentages, mean, and standard deviation was used to analyze the social - demographic and clinicopathologic data |
| 2. To determine the prevalence of precancerous cervical lesions in patients screened at ORCI from 2020 January to 2022 December. | Percentages were used for analysis and chi square and logistic regression for sub analysis to establish association between VIA results and sociodemographic/clinicopathologic factors |

| | |
|---|---|
| 3. To determine treatment outcome of patients managed for precancerous cervical lesions at ORCI from 2020 January to 2022 December. | Percentages used for analysis |
| 4. To determine predictors of treatment outcome in patients with precancerous cervical lesions managed at ORCI from 2020 January to 2022 December. | Chi square and logistic regression for analysis |

### 2.11 Ethical Clearance

In keeping with ethical obligations clearance to conduct this study was sort from the relevant institutional review board (IRB) of Muhimbili University of Health and Allied sciences (MUHAS). Verbal consent was also sorted from clients in the study thus allowing for study data not available in the electronic or non-electronic sources to be voluntarily given by the client. Finally, consent was sort from Ocean Road Cancer Institute (ORCI) which allowed for access of patient/client records. Confidentiality of all data collected was maintained by entering and storing it in a password protected personal computer and patient names omitted to further maintain confidentiality.

### 2.12 Dissemination Plan

The findings of this study will be presented in a dissertation that will be submitted to MUHAS for partial fulfillment of master's in clinical Oncology and made public for possible future presentation in National and international conferences.

# CHAPTER THREE

## 3.0 RESULTS

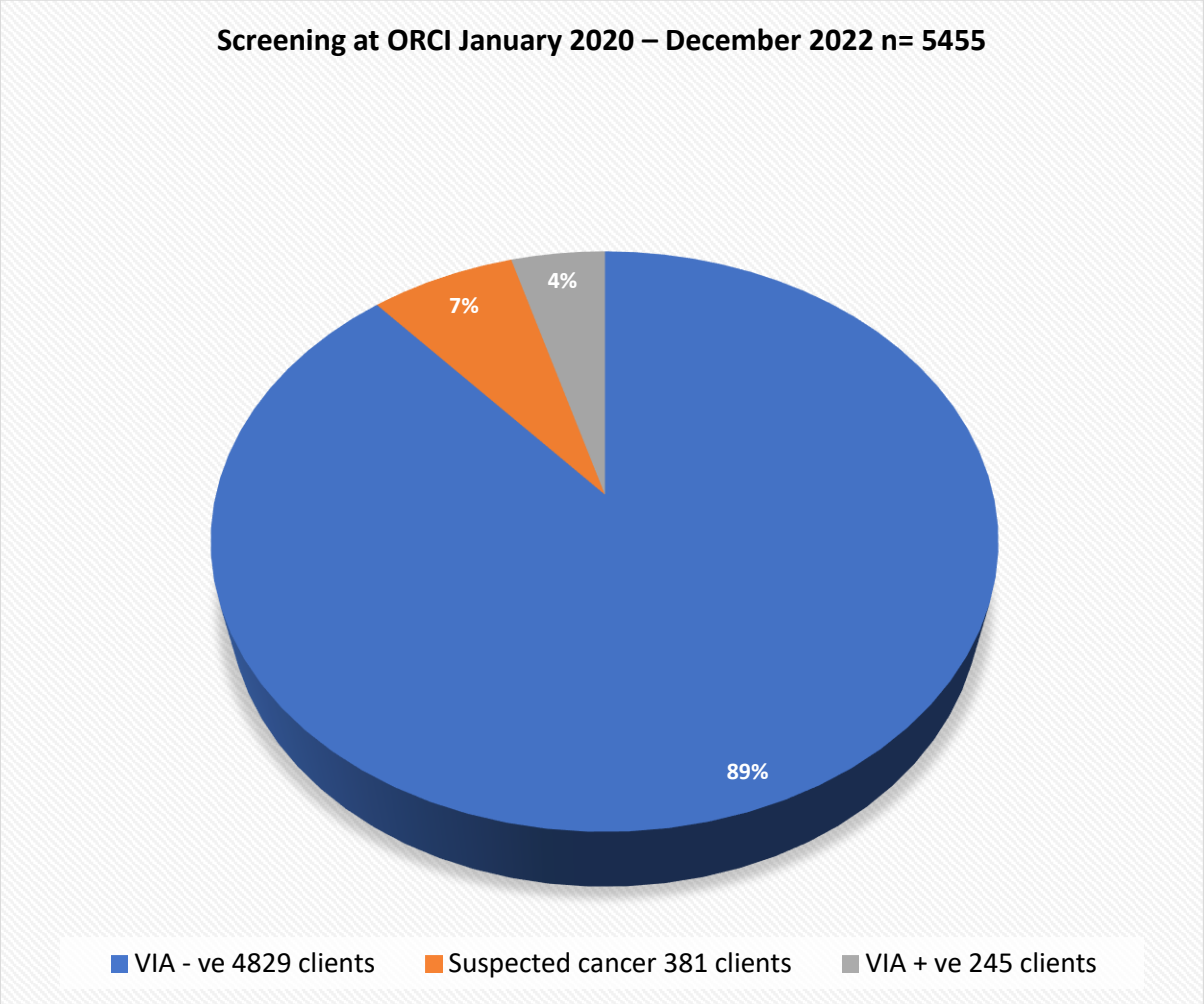



**Figure 5:** Pie chart illustrating the accessible population.

Figure 1. summarizes the entirety of clients who attended cervical screening services between January 2020 and December 2022 and their results. The total number of women screened during the period were 5,455 of whom majority 4829 (89%) tested negative on VIA followed by 381 (7%) who were found to have lesions suspected to be cancerous and finally 245 (4%) who tested positive on VIA.

This study focused on the 5074 women who were screened thus excluding the 381 clients who were already suspected to have cancerous lesions who were directed to have biopsies done for confirmation.

The first part of our study was looking into the documented social demographic and clinical characteristics of the women who were screened, the prevalence of precancerous lesions as defined by VIA positivity and how the client characteristics mentioned above were associated with VIA positivity. We found the mean age of women screened during our study period was 38.9 with a SD of 8.3 and that 46% were between the ages of 35-45 years. The majority had a parity of between 2 and 4 (57%) while a minority 4% were nulliparous. The HIV prevalence in the women screened during our study period was at 10% (table 1) and that Dar es salaam and its environs was the documented residence to 78% of the clients screened while the rest resided in different locations of the country as shown (figure 2).

The prevalence of precancerous cervical lesions as defined by VIA positivity was at 4.8% as shown (table 2). On Chi-square test we found that there was an association between all the independent variables and the VIA status (dependent variable). Logistical regression was then used to determine the magnitude, direction and statistical significance of this association.

After univariate and multivariate logistical regression, we found that clients who were aged 46 years and above were 39% less likely to be VIA positive on screening (aOR =0.62, 95% CI: 0.42-0.89, p= 0.013) compared to those aged 35 to 45 years. Similarly, as parity increased from zero there was an associated decreased risk of VIA positivity on screening. Significantly those who were HIV positive were four times more likely to have a VIA positive result on screening (aOR = 4.47, 95% CI: 3.28-6.09, p<0.001) compared to those who were HIV negative. Finally, those living outside Dar es Salaam were less likely to have a positive VIA result compared to those living in Dar es Salaam (aOR =0.68, 95% CI: 0.47-0.97, p= 0.035) (Table 3).

**Table 5:** The sociodemographic and clinical characteristics of clients who were screened for precancerous cervical lesions at ORCI from January 2020 to December 2022

| Variable | Frequency | Percentage |
|---|---|---|
| **Age groups** | | |
| 18-34 | 1540 | 30.4 |
| 35-45 | 2317 | 45.7 |
| Above 45 | 1211 | 23.9 |
| **Mean & SD 38.9 8.3** | | |
| **Parity** | | |
| 0 | 219 | 4.3 |
| 1 | 866 | 17.1 |
| 2-4 | 2873 | 56.6 |
| Para 5 & above | 620 | 12.2 |
| Missing | 496 | 9.8 |
| **Residence** | | |
| Dar es Salaam | 3970 | 78.2 |
| Outside DSM | 1104 | 21.8 |
| **HIV status** | | |
| Negative | 4491 | 88.5 |
| Positive | 512 | 10.1 |
| Undocumented | 71 | 1.4 |

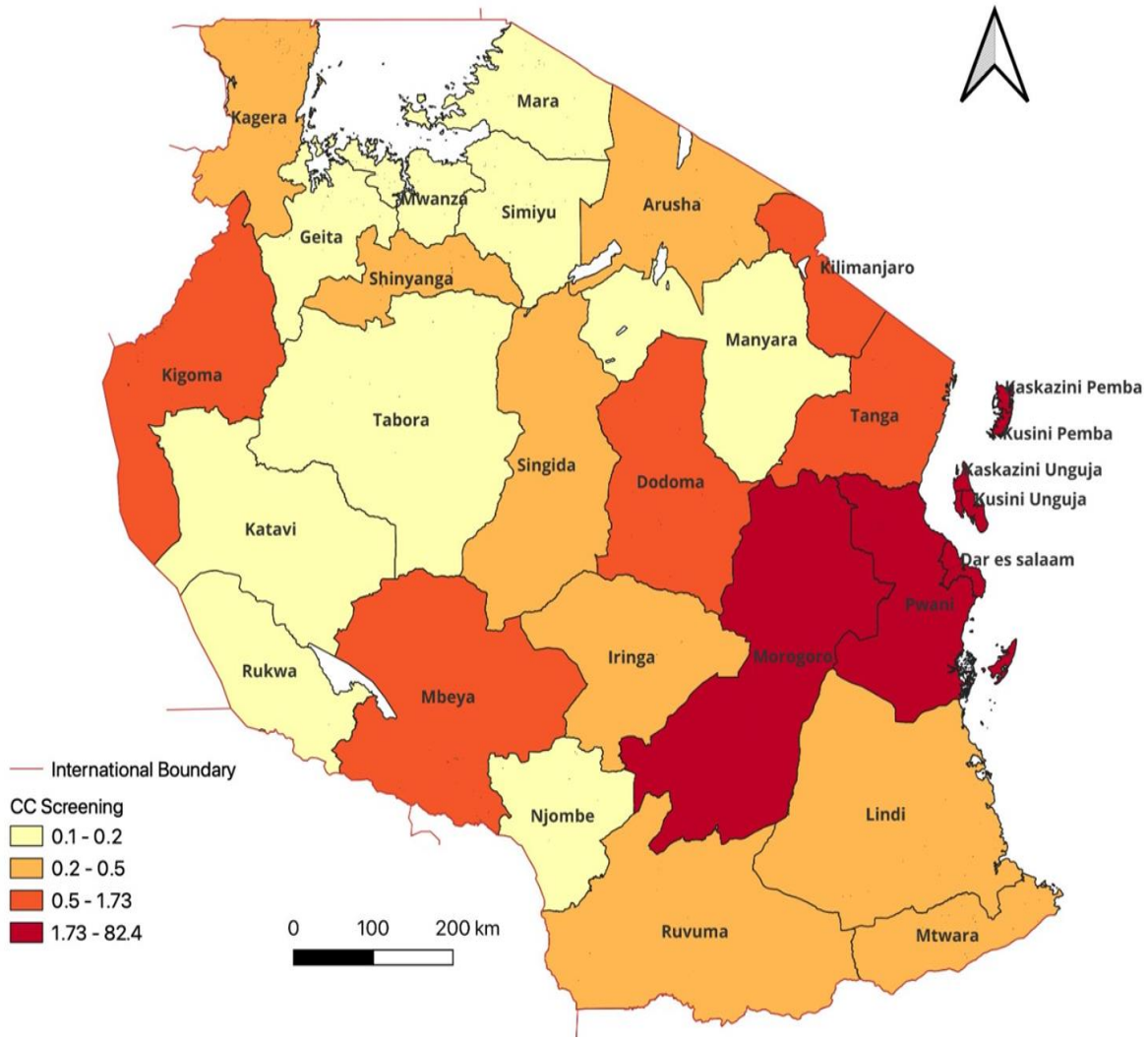



**Figure 6:** Geographical distribution of screening attendees at ORCI n = 5074 from January 2020 to December 2022

**Table 6:** prevalence of precancerous cervical lesions among clients who attended cervical cancer screening at ORCI from January 2020 to December 2022 n= 5074

| Variable | VIA negative n(%) | VIA positive n(%) | Chi-square p-value |
|---|---|---|---|
| ***Total*** | 4829(95.2) | 245(4.8) | |
| ***Age groups*** | | | 0.017 |
| *18-34* | 1457(94.6) | 83(5.4) | |
| *35-45* | 2195(94.7) | 122(5.3) | |
| *Above 45* | 1171(96.7) | 40(3.3) | |
| ***Parity*** | | | <0.001 |
| *0* | 178(81.3) | 41(18.7) | |
| *1* | 820(94.7) | 46(5.3) | |
| *2-4* | 2735(95.2) | 138(4.8) | |
| *Para 5 & above* | 600(96.8) | 20(3.2) | |
| ***HIV status*** | | | <0.001 |
| *Negative* | 4320(96.2) | 171(3.8) | |
| *Positive* | 438(85.5) | 74(14.5) | |
| ***Location*** | | | 0.010 |
| *Dar es Salaam* | 3762(94.8) | 208(5.2) | |
| *Outside DSM* | 1067(96.6) | 37(3.4) | |

**Table 7:** univariate and multivariate logistical regression results of the factors associated with VIA positivity in clients who were screened for precancerous cervical lesions

| Variable | cOR(95% CI) | p-value | aOR(95% CI) | p-value |
|---|---|---|---|---|
| ***Age groups*** | | | | |
| *18-34* | 1.02(0.77-1.37) | 0.866 | 1.11(0.82-1.51) | 0.502 |
| *35-45* | Ref | | Ref | |
| *Above 45* | 0.61(0.43-0.88) | 0.009 | 0.62(0.43-0.9) | 0.013 |
| ***Parity*** | | | | |
| *0* | Ref | | Ref | |
| *1* | 0.24(0.15-0.38) | <0.001 | 0.22(0.13-0.35) | <0.001 |
| *2-4* | 0.22(0.15-0.32) | <0.001 | 0.22(0.15-0.33) | <0.001 |
| *Para 5 & above* | 0.14(0.08-0.25) | <0.001 | 0.18(0.10-0.33) | <0.001 |
| ***HIV status*** | | | | |
| *Negative* | Ref | | Ref | |
| *Positive* | 4.27(3.19-5.7) | <0.001 | 4.47(3.28-6.09) | <0.001 |
| ***Place of residence*** | | | | |
| *Dar es Salaam* | Ref | | Ref | |
| *Outside DSM* | 0.63(0.44-0.9) | 0.010 | 0.68(0.47-0.97) | 0.035 |

The second part of our study was looking into the interventions, treatment outcomes and its predictors of those clients who were VIA positive on screening. Of the 245 clients who were

VIA positive upon screening 73% and 6% had treatment procedures done on the same day with cryotherapy and LEEP respectively. Procedure postponement was at 13% majorly was due to hesitancy to have the procedure done on the same day or active infection that required

antibiotics then rescreening was done after the infection evidently cleared. Procedure booking (4%) was done especially for LEEP due to specialist availability on the day of screening. Some clients (2%) due to the deficiencies of VIA especially for perimenopausal women had to have a confirmatory pap smear done. Finally, about 2% of clients who were VIA positive unfortunately had no documented procedure, booking or documented postponement for any procedure (figure 3)

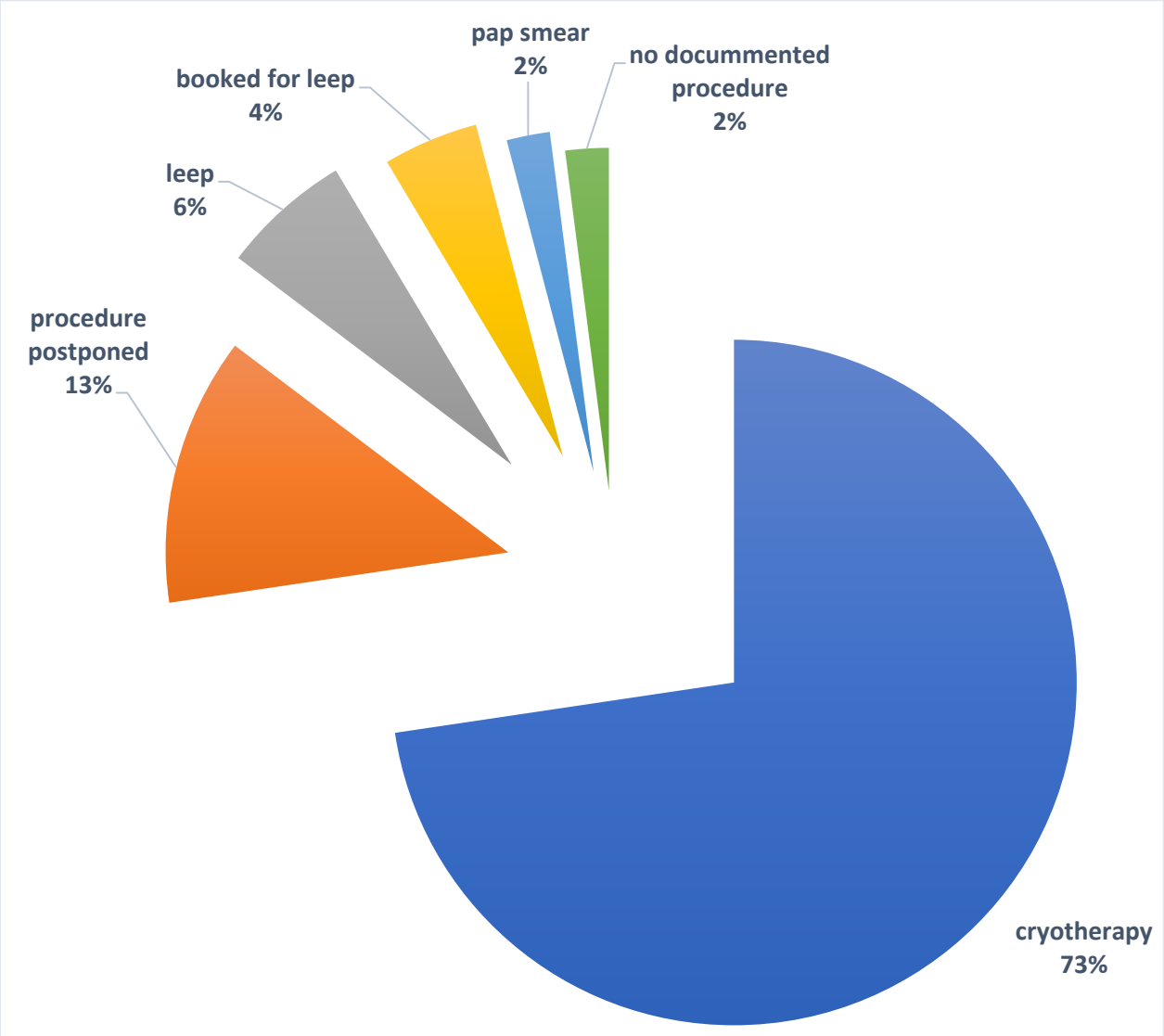



**Figure 7:** Treatment Procedures Performed to the 245 VIA Positive Clients at First Screening Visit at ORCI between January 2020 and December 2022.

The choice of treatment between cryotherapy and LEEP was based on an eligibility criterion that if a client falls within then cryotherapy was done, if not excisional techniques like LEEP were used (41).

Clients who had procedures done were scheduled to come after 1 year for scheduled follow up where rescreening was done to assess treatment outcome. The clients who had documented procedures done (n=193), cryotherapy or LEEP, 40% came for follow up (figure 4) and those who did (n=78) more than three quarters were found to be VIA negative (figure 5).

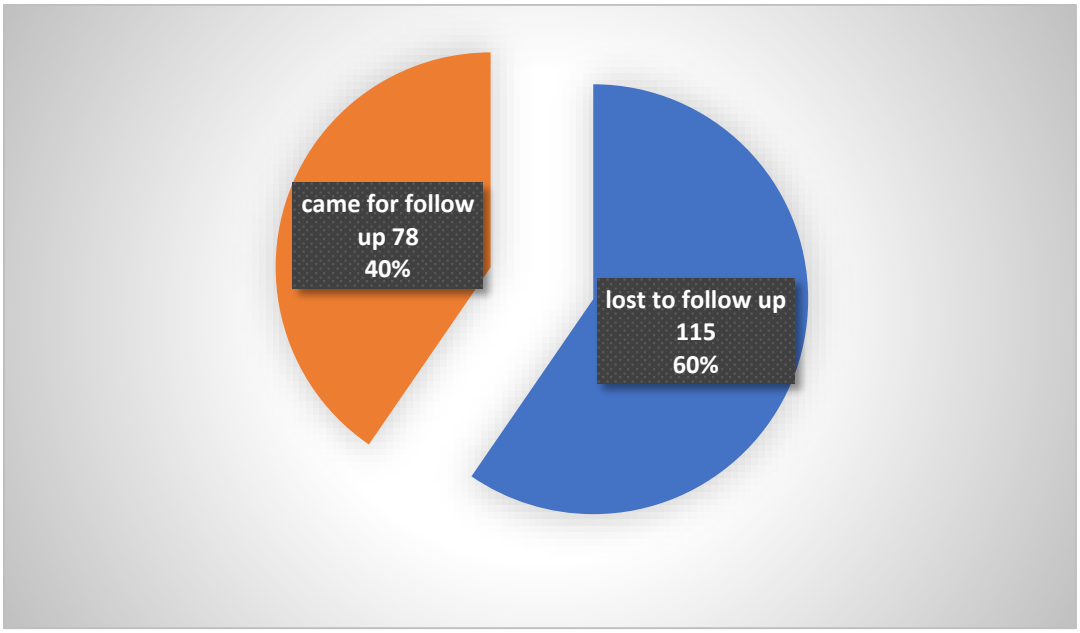



**Figure 8:** One Year Follow up Post Treatment Procedures (LEEP, & Cryotherapy, n=193)

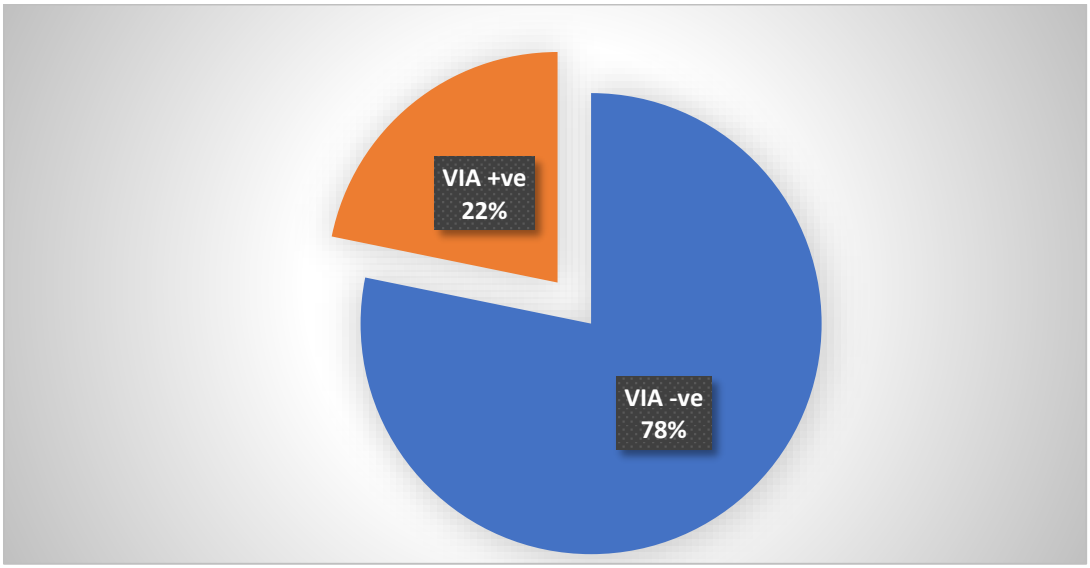



**Figure 9:** Outcome of Repeat VIA One Year Post Treatment **(n=78)**

To determine the predictors of treatment outcome the demographics of clients who came back for follow up were tested for their association with VIA status on rescreening (table 4).

Chi square test showed an association between the independent variables' marital status and HIV status with VIA status (dependent variable). Logistical regression was again used to determine the magnitude, direction and statistical significance of this association.

After univariate and multivariate logistical regression, we found that women living with HIV were 3.72 times more likely to be VIA positive at one year follow-up (aOR=3.72, 95% CI: 1.03-13.47, p-value = 0.045) compared to those with HIV negative status. Additionally, those who were in para 5 and above were 95% less likely to be VIA positive at one year follow-up. Other variables such age, occupation, place of residence, and level of education didn't show significant association with the VIA outcome (table 5).

**Table 8:** Treatment outcome stratified by demographic and clinical characteristics **(n=78)**

| **Variable** | **VIA results after one year** | | **p-value** |
|---|---|---|---|
| | Negative | Positive | |
| ***Total*** | 61(78.2) | 17(21.8) | |
| ***Age groups*** | | | 0.374 |
| *18-34* | 16(80.0) | 4(20.0) | |
| *35-45* | 36(81.8) | 8(18.2) | |
| *Above 45* | 9(64.3) | 5(35.7) | |
| ***Occupation*** | | | 0.079 |
| *Employed* | 14(100.0) | 0(0.0) | |
| *Self employed* | 16(69.6) | 7(30.4) | |
| *Unemployed* | 31(75.6) | 10(24.4) | |
| ***Place of residence*** | | | 0.902 |
| *Dar es Salaam* | 51(78.5) | 14(21.5) | |
| *Outside DSM* | 10(76.9) | 3(23.1) | |
| ***Marital status*** | | | 0.013 |
| *Married* | 49(86.0) | 8(14.0) | |
| *Separated/Divorced* | 3(42.9) | 4(57.1) | |
| *Single* | 9(64.3) | 5(35.7) | |
| ***Parity*** | | | 0.513 |
| *0* | 5(62.5) | 3(37.5) | |
| *1* | 12(85.7) | 2(14.3) | |
| *2-4* | 36(76.6) | 11(23.4) | |
| *Para 5 & above* | 8(88.9) | 1(11.1) | |
| ***Level of education*** | | | 0.788 |
| *Primary* | 36(76.6) | 11(23.4) | |
| *Secondary* | 18(78.3) | 5(21.7) | |
| *Tertiary* | 7(87.5) | 1(12.5) | |
| ***HIV status*** | | | 0.004 |
| *Negative* | 50(86.2) | 8(13.8) | |
| *Positive* | 11(55.0) | 9(21.8) | |

**Table 9:** Univariate and multivariate logistic regression for predictors of treatment outcome

| Variable | cOR (95% CI) | p-value | aOR (95% CI) | p-value |
|---|---|---|---|---|
| ***Age groups*** | | | | |
| *18-34* | 1.13(0.3-4.28) | 0.863 | 0.97(0.21-4.47) | 0.972 |
| *35-45* | Ref | | Ref | |
| *Above 45* | 2.5(0.66-9.5) | 0.179 | 1.36(0.22-8.25) | 0.741 |
| ***Occupation*** | | | | |
| *Employed* | Ref | | Ref | |
| *Unemployed* | 1.38(0.47-4.11) | 0.560 | 1.16(0.32-4.19) | 0.824 |
| ***Place of residence*** | | | | |
| *Dar es Salaam* | Ref | | Ref | |
| *Outside DSM* | 1.09(0.26-4.52) | 0.902 | 1.05(0.16-6.88) | 0.960 |
| ***Marital status*** | | | | |
| *Married* | Ref | | Ref | |
| *Separated/Divorced* | 8.17(1.53-43.52) | 0.014 | 3.79(0.72-19.82) | 0.115 |
| *Single* | 3.4(0.91-12.79) | 0.070 | 3.35(0.49-23.06) | 0.220 |
| ***Parity*** | | | | |
| *0* | Ref | | Ref | |
| *1* | 0.28(0.04-2.2) | 0.225 | 0.09(0.01-1.42) | 0.088 |
| *2-4* | 0.51(0.1-2.48) | 0.403 | 0.20(0.02-2.57) | 0.219 |
| *Para 5 & above* | 0.21(0.02-2.6) | 0.223 | 0.05(0.00-0.87) | 0.040 |
| ***Level of education*** | | | | |
| *Primary* | Ref | | Ref | |
| *Secondary* | 0.91(0.27-3.02) | 0.876 | 0.53(0.07-4.22) | 0.550 |
| *Tertiary* | 0.47(0.05-4.23) | 0.498 | 0.12(0.01-1.71) | 0.118 |
| ***HIV status*** | | | | |
| *Negative* | Ref | | Ref | |
| *Positive* | 5.11(1.61-16.22) | 0.006 | 3.72(1.03-13.47) | 0.045 |

# CHAPTER FOUR

## 4.0 DISCUSSION

Pre-cancerous cervical lesions have been found to pose a significant disease burden and more so in low- and middle-income countries of which Tanzania is one. This is supported by global cancer statistics that have established that 80% of cases of cervical cancer globally are found in resource limited countries (64) with incidences and mortality leading in these regions one of which is SSA.

The management of these precancerous cervical lesions is the core of secondary prevention of cervical cancer incidence evident in developed countries with robust though costly population-based screening. Despite this gap there are effective screening techniques that are available for resource limited countries and when well utilized can be equally effective(23).

However, little is known about the outcomes of the current screening services offered in Tanzania since auditing of the current screen and treat programme practiced in the country has little to no information. This study conducted at ORCI in Dar es salaam was meant to fill this knowledge gap. The findings of this study will offer a glimpse into the effectiveness of the current screen and treat programme and socio demographic or clinical factors that influence its effectiveness.

Demographically according to a previous study done at ORCI in 2012 by Kahesa et al looking into the determinants of acceptance of cervical cancer screening in Dar es salaam. Women aged 35-45 yrs and those older than 45yrs had an increased acceptance with ORs of 1.53 (95% CI: 1.19-2.01) and 2.14 (95% CI: 2.90-1.56) respectively, for participating in a screening program when compared to those aged 25–34 (6,65). This is similar to our study where we found that 70% of women screened were above the age of 35 years. The same study also found that women who were HIV positive were more likely to attend screening services which is reflected in our study where the HIV prevalence of our cohort of 5074 clients was at 10%. This is above HIV prevalence rate of 5% among women aged 15–49 years as reported by a Tanzania HIV impact survey done in 2022/2023(66). This can be explained by the current integration of cervical cancer screening into the care of women living with HIV (WLHIV). In our study more than 75% of clients screened were residents

of Dar es salaam, this might speak to the fact that efforts of decentralizing screening services country wide are improving as access to screening services was identified as one of the barriers of lack of attendance(65).

Out of 5,074 clients screened 245 (4.8%) were found to be VIA positive, 2 prior studies done at ORCI 2010 and 2012 (Twalib et al and Kahesa et al) revealed VIA positivity of 3.8% (n = 10,374) and 7% (n = 14,107) respectively(6,67). This variability corresponds to literature as one of the limitations of VIA as the most feasible screening method in LMIC. Despite this limitation acknowledgments have been made to the fact that even a single round of VIA screening has been associated with a 25–35% reduction in cervical cancer incidence and the frequency of cervical intraepithelial neoplasia grade 2 or worse lesions in randomized-controlled trials(23). This might just facilitate the eventual introduction of superior HPV screening methods with less variability and subjectivity when simple, rapid and affordable HPV tests suitable for use in LMIC become widely available (23).

In our study the influence of age on VIA positivity showed perimenopausal women had a reduced likelihood of having a VIA positive result screening (aOR =0.62, 95% CI: 0.42-0.89, p= 0.013) compared to those aged 35 to 45 years. Though not in keeping with prior studies that found higher odds aOR =1.78,95%CI: 1.51-2.41) of VIA positivity in women older than 45(6) could be due to known limitations of VIA in screening perimenopausal women due to location of the squamocolumnar junction. This cohort predominantly have type 3 TZ junction which was found to limit accuracy when using visual inspection screening techniques rather than cytologic based in this group of clients (68).

Interestingly our study showed increasing parity was associated with lower VIA positivity which did not correspond to many prior studies both locally and regionally. Where one done locally revealing women who had 1–2 children, 3–4 children and 5 or more children had increased ORs of 2.38, 2.43 and 3.19, respectively, for VIA positivity in comparison with nulliparous women (6,33). This finding could be suggestive of possible increase in other risk factors like the use of contraceptives, smoking, multiple sexual partners or increased prevalence of sexually transmitted infections (STI) all of which could tip the scale and are known risk factors to development of precancerous lesions(33,36).

A significant association was found between HIV and VIA positivity with a 4 times likelihood of a VIA positive result in HIV positive clients. This again is seen in the second part of our study where the most significant predictor of a positive VIA result on rescreening was a positive HIV status with 3 times more likelihood. Immunosuppression especially attributed to HIV infection is evidently linked to higher failure rate of precancerous cervical lesion treatment(62). This correlates to many studies done locally, regionally and internationally with one done locally and published in 2019 revealing HIV as the studies strongest risk factor for VIA positivity with 3 times likelihood (OR = 3.48; 95% CI:2.34–5.17) (5,34,35). In terms of HIV being a predictor of treatment failure is evidenced in a pilot randomized control trial (RCT) done in Zambia with a short treatment follow up of 6 months post treatment that revealed despite the procedure HIV-positive participants had lower treatment success compared to those who were HIV negative, irrespective of the treatment method(63). This is explained by the immunosuppression brought about by HIV that decreases the ability to clear HPV infections, increases susceptibility to different strains and potentially activates dormant strains.

Finally, the correlation between VIA positivity and residence could be explained by the easy accessibility of screening services at ORCI to women who live within Dar es Salaam as compared to those who live further away. This is consistent with the study by Kahesa et al that showed that lack of access was one of the barriers to attendance of screening services and thus encouraged decentralization (65). The presence of barriers like access also speaks to a need for outreach services with the use of facilitators like community health workers who will help clients navigate as well as educate them on how to access screening and treatment services thus improving on uptake. Studies have identified that uptake is also influenced by social cultural factors like stigmatization, religion and cultural norms(69) that further cement the need for community health educators and navigators to upscale cervical cancer screening and treatment services

The second part of our study that investigated treatment, follow up, treatment outcomes and its predictors revealed a treatment acceptance of almost 80%. This approximates with audits done in South India and Ethiopia of screen and treat screening programmes that recorded an acceptance of 74% and 90% respectively(70,71). This speaks to the acceptability of treatment linkage to screening that has been supported by policy in a push to avoid loss to

follow up when treatment is scheduled on subsequent visits. Zambia's CCPPZ is the regions first real-world execution-based evidence that screen and treat that was initially targeting at risk HIV positive clients can be escalated to the public with sustained efforts (34).

Post treatment assessment which for most screen and treat programmes is rescreening at 1 year has been marred with loss to follow up regionally and internationally. Screening audits done in Ethiopia and India show a loss to follow up of 50% and 27% respectively though the study in India was a prospective study (70,71). Our study approximates these studies with a loss to follow up of 60%, more so with the retrospective audit done in Ethiopia. This can be explained by the lack of an established client reminder system as suggested by the Ethiopian audit.

Cure rates as defined by negative VIA on rescreening at 1 year in our study was at 78%, again this approximates regional findings like the study in Ethiopia with the same cure definition had a cure rate of 83%(71). This suggests a recurrence rate of more than 10% which WHO estimates for the public(72). The higher recurrence rates can be attributed to the fact that the WHO standard was based on data from developed countries where experienced doctors provided the treatment, lesions were smaller and loss to follow up was less than 20%.

# CHAPTER FIVE

## 5.0 LIMITATIONS, CONCLUSIONS, AND RECOMMENDATIONS

### 5.1 Limitations

1. Conflicting clinical and demographic information due to double registration by entry in screening logbooks and electronic data base, this was mitigated by contacting clients and seeking clarification on their information.
2. Multiple client registration numbers which were also mitigated by seeking clarification from clients.
3. Loss to follow up

### 5.2 Conclusions

1. Our study revealed a VIA positivity of 4.8%, a variation from the rates seen in earlier studies done at ORCI and that HIV infection is a strong predictor of prevalence of precancerous cervical lesions adding to the body of evidence to the link between HIV and cervical cancer incidence.
2. Our study also found that cervical cancer screening using the single visit approach of VIA coupled to treatment is well established at ORCI and well accepted with almost 80% of clients with positive test accepting same day treatment.
3. Despite a loss to follow up of 60% cure was established in 78% of clients defined by repeat negative VIA at 1 yr. follow up, this is comparable to a similar Ethiopian study with loss to follow up of 50% and a cure rate of 83%.
4. We also found HIV was a predictor of treatment failure of precancerous lesions detected using visual inspection with acetic acid.

### 5.3 Recommendations

1. There is a strong justification to move to HR HPV test as the initial screening test with VIA/VILLI for triage. This is due to the inherent weakness of subjectivity evidenced by high variability in VIA positivity like the one evidenced in our study when compared to other studies done at ORCI.
2. There should be continued emphasis on secondary prevention of cervical cancer, especially population awareness on its benefits as evidenced by potential cure after screening.
3. There should be continued auditing of cervical cancer screening services that will make apparent issues like predictors of outcome, reasons of loss to follow up and possible ways to mitigate them. Which may include an earlier time to follow up, phone call reminders or further decentralization of services to allow easy accessibility that would improve compliance with follow up visits.
4. Clients LWHIV should have stringent follow up protocols to reduce their heightened potential risk to development of cervical cancer.

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# APPENDICES

## Appendix I. Study Tool

| | |
|---|---|
| File number | Date of data collection |
| Year procedure was done | Which procedure was done:<br>1. Cryotherapy ☐<br>2. LEEP ☐ |
| Age<br>Age at coitarche<br>Number of previous sexual partners<br>Parity | ☐ |
| Residence | 1. Urban ☐<br>2. Rural |
| Occupation | 1. Employed ☐<br>2. Unemployed<br>3. Self-employed<br>4. Housewife<br>5. Student |
| Marital status | 1. Married ☐<br>2. Separated<br>3. Single<br>4. Widowed |
| Education level | 1. Primary ☐<br>2. Secondary<br>3. Post secondary.<br>4. None |

| | |
|---|---|
| HIV status in the last 3 months | 1. Positive<br>2. Positive on HAART<br>3. Negative<br>4. Unknown |
| Smoking | 1. Yes<br>2. No<br>3. Quit |
| Alcohol | 1. Yes<br>2. No<br>3. Quit |
| Duration to follow up VIA | 1. 12months<br>2. 12-24months<br>3. More than 24 Months |
| Follow up VIA after cryotherapy or LEEP | 1. VIA positive<br>2. VIA negative |
| LEEP histology | 1. LGSIL<br>2. HGSIL |
| Facility where follow up VIA was done | 1. ORCI<br>2. Other facility |

**Appendix II. Verbal consent English**

My name is Dr. Gathendu Edwin, and I attend Muhimbili University of Health and Allied Sciences (MUHAS) to pursue a master's degree in medicine with a focus on clinical oncology (MMED Clinical Oncology). I'm doing research to fulfill a portion of my degree requirements.

**Aim**

The aim of my study is to look at the treatment outcomes of patients treated for precancerous cervical lesions at ORCI.I would like to use a questionnaire to get information from your medical records with your consent. There will be NO consequences if you decide not to engage in the study; participation is entirely voluntary. We will solely utilize the data you submit on this questionnaire for study. After the study is finished, the data will be preserved so that, in accordance with current data sharing norms, it can be shared with other researchers. The responses will be coded and not be utilized in a way that makes it possible to identify each participant.

**Benefits**

Having been managed for precancerous lesions where follow up is very important, contact with health professionals will give you the opportunity to discuss your follow up and possible ways to prevent recurrencies.

**Risks**

Questions asked will be of a private nature thus might be uncomfortable, but you will be in no way at risk of forgoing your legal rights by consenting.

Do you agree to participate, yes no

I agree that I have received a thorough explanation of this consent form in a language I can understand, as well as the chance to ask any questions that I have not found satisfactory answers to. I freely consent to taking part in this study and am aware that I can stop at any moment without incurring any fees.

Contact date …….

Dr Gathendu Edwin Miro
MUHAS
Dar es salaam
0765877311

**Kiswahili**

Jina langu ni Dk. Gathendu Edwin, na ninahudhuria Chuo Kikuu cha Afya na Sayansi Shirikishi Muhimbili (MUHAS) kusomea shahada ya uzamili ya utabibu kwa kuzingatia oncology ya kimatibabu (MMED Clinical Oncology). Ninafanya utafiti ili kutimiza sehemu ya mahitaji yangu ya digrii.

**Lengo**

Madhumuni ya utafiti wangu ni kuangalia matokeo ya matibabu ya wagonjwa waliotibiwa vidonda vya mlango wa kizazi vya kabla ya kansa katika ORCI.Ningependa kutumia dodoso kupata taarifa kutoka kwa rekodi zako za matibabu kwa kibali chako. HAKUTAKUWA na matokeo ikiwa utaamua kutojihusisha na utafiti; ushiriki ni wa hiari kabisa. Tutatumia data utakayowasilisha kwenye dodoso hili kwa ajili ya utafiti pekee. Baada ya utafiti kukamilika, data itahifadhiwa ili, kwa mujibu wa kanuni za sasa za kushiriki data, inaweza kushirikiwa na watafiti wengine. Majibu yatawekewa msimbo na hayatatumika kwa njia ambayo itawezesha kutambua kila mshiriki.

**Faida**

Kwa kuwa umetibiwa vidonda vya mlango wa kizazi vya kabla ya kansa ambapo ufuatiliaji ni muhimu sana, kuwasiliana na wataalamu wa afya kutakupa fursa ya kujadili ufuatiliaji wako na njia zinazowezekana za kuzuia kurejea kwa vidonda hivi na kansa.

**Madhara**

Maswali yatakayoulizwa yatakuwa ya kibinafsi kwa hivyo yanaweza kukukosesha raha, lakini hautakuwa katika hatari yoyote ya kuacha haki zako za kisheria kwa kukubali.

Je, unakubali kushiriki? Ndio Hapana

Ninakubali kwamba nimepokea maelezo ya kina kuhusu fomu hii ya idhini katika lugha ninayoweza kuelewa, pamoja na nafasi ya kuuliza maswali yoyote ambayo sijapata majibu

ya kuridhisha kwayo. Ninakubali kwa uhuru kushiriki katika utafiti huu na ninajua kwamba ninaweza kuacha wakati wowote bila kutozwa ada yoyote.

Tarehe ya simu

Dr Gathendu Edwin Miro

MUHAS

Dar es salaam

0765877311

## Appendix III: Ethical clearance letter

**UNITED REPUBLIC OF TANZANIA**

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATIONS

Ref. No.DA.282/298/01.C/ Date: 09/04/2024

MUHAS-REC-04-2024-2145
edwin gathendu miro
College of Medicine
MUHAS

**RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: TREATMENT OUTCOMES OF PATIENTS WITH PRECANCEROUS CERVICAL LESIONS MANAGED BY CRYOTHERAPY AND LOOPELECTROSURGICAL PROCEDURE DONE AT OCEAN ROAD CANCER INSTITUTE**

Reference is made to the above heading.

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 09/04/2024
EXPIRATION DATE OF APPROVAL: 09/04/2025

**STUDY DESCRIPTION:**
**Purpose:**
the purpose of this retrospective observational cohort study is to determine treatment outcome of patients managed for precancerous cervical lesions at ocean road cancer institute by cryotherapy or loop electrosurgical procedure.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2015201.pdf and in the MUHAS archives.

**The PI is required to:**

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain Data Transfer Agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain Material Transfer Agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country.
8. Apply for and obtain permission to publish the results from National Institute for Medical Research. The application should be before submitting to a publisher and not concurrently through the email publications@nimr.or.tz.
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Dr. Nahya Salim Masoud,
**Chairperson, MUHAS Research and Ethics Committee**