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An evaluation of cervical cancer cases diagnosed at a South African colposcopy clinic

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AN EVALUATION OF CERVICAL CANCER CASES DIAGNOSED AT A SOUTH AFRICAN COLPOSCOPY CLINIC

By

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A research report submitted to The Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine (Obstetrics & Gynaecology)

Signed in Johannesburg, 2019

Declaration

I, Dr Rumbidzai Esinath Mashayamombe declare that this research is my own work. It is submitted in partial fulfilment of the requirements of a degree in Masters of Medicine in the branch of Obstetrics and Gynaecology from the University of the Witwatersrand. This research has not been submitted before.

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Signed …… day of……. 2019.

Abstract

Introduction

The public health impact of a screening programme introduced in SA in 2000 has not shown a reduction in the incidence of or deaths from cervical cancer. An important risk for death is the late stage at presentation. It may be that the women who present with cervical cancer within a screening programme present with early stages.

This study aims to describe women with cervical cancer that were diagnosed within a screened population, who were referred to colposcopy from April 2003 to April 2016.

Methods

The CHBAH colposcopy clinic is a 'see and treat clinic' in a tertiary hospital in Soweto. Women are referred with abnormal cytology reports. A LLETZ is performed immediately when the colposcopic impression is greater than CIN1, if the colposcopy is inadequate, or if cytology and colposcopy are incongruent.

This was a cross sectional study using data from a database and patient files. The following data was extracted: age, parity, contraception, HIV status, cytology, colposcopy, histology and staging.

Results

There were 174 women with cervical cancer.

The median age was 45 years (IQR 38-55), the median parity was 3 (IQR 2-4) and 64 women (36.8%) were post-menopausal. Twenty eight (17.5%) women with a known contraceptive history were on hormonal contraception.

Ninety four women (54.0%) were HIV positive. The median CD4 count was 329 cells/mm^3 (IQR 177-502).

The most frequent cytology results that women were referred with were “HSIL” (88 women, 50.6%), “malignant cells/suspected invasion” (30 women, 17.2%) and, “at least HSIL, cannot exclude invasion” (29 women, 16.7%).

The colposcopic impressions were frank invasion (56 women, 32.2%), CIN3 (38 women, 21.8%), and microinvasion (33 women, 19.0%), CIN2 (21 women, 12.1%) and CIN1 (2 women, 1.2%). In 24 women (13.8%), the colposcopic findings were unknown or not recorded.

The histological subtypes were squamous cell carcinoma (148 women, 85.1%), adenosquamous (9 women, 5.2%), adenocarcinoma (8 women, 4.6%), adenoid-basal (5 women, 2.9%), unspecified (2 women, 1.1%), and small cell neuroendocrine (1 woman, 0.6%). 1 women (0.6%) had a synchronous tumour.

The presenting FIGO stage was known in 161 women. Stage 1A was diagnosed in 63 women (39.1%), 1B in 52 (32.3%), 2A in 5 (3.1%), 2B in 25 (15.5%), 3A in 0 women, 3B in 14 (8.7%), 4A in 1 woman (0.6%) and 4B in 1 woman (0.6%).

Conclusion

Roughly 75% of women in this study presented with FIGO stage 1a to 2a disease, which is associated with a 5 year survival of at least 68.8%. This contrasts to the late presentation which occurs in developing countries. There may be benefit, in that women diagnosed through a screening programme have earlier stage disease.

Dedication

I would like to dedicate this work to my parents, Dr LL Mashayamombe and Mrs TA Mashayamombe, who have supported and encouraged me, and prayed for my success throughout this process. Without you both, this could not have happened.

I would also like to dedicate this work to my daughter, Makaita Madamombe, who missed me, and whom I also missed, whilst I was working on this project. I have persisted in this for you, because I love you and want to give you the future you deserve.

Acknowledgements

I would like to thank and acknowledge Prof. Y Adam, my supervisor, for all of the hours that she put in to help me complete this task. Thank you for being patient with, and kind to me. Thank you for all of the guidance, encouragement, and advice that you gave me during this long and arduous task.

I would also like to thank Dr W Edridge. You have offered a sounding board to my ideas, and offered a fresh perspective and new ideas when my creativity was lacking. Thank you for taking an interest, and caring. Thank you for reassuring and encouraging me when I was low, and celebrating my joy with me when things were going well.

I'd also like to acknowledge and thank Asanda Oyiya, Tshepiso Lenkwe, Sr. Fikile Msimango, Abednego Maphoto, Lindy Bambata and Susara Ferreira, for helping me to find CHBAH files, DXT numbers and CMJAH files. It was a nightmare finding those files, but you were all there and always willing to take time out of your busy schedules to help me. Without your help, this task would have been impossible. Thank you.

Publications and Presentations

Preliminary data from this study was presented as a poster presentation at the South African Society of Gynaecological Oncology (SASGO) conference in Stellenbosch in September 2018.

An abstract for the research was published in the South African Journal of Gynaecological Oncology in 2018. The details are: SASGO 2018 Conference Abstracts. South Afr J Gynaecol Oncol. 2018; 10 (2): supplement 1.

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List of Definitions

Atrophy[1]	A pale, brittle, lack-lustre squamous epithelium. There may be sub-epithelial petechiae caused by trauma to sub-epithelial capillaries during insertion of the speculum. The new squamocolumnar junction is often not visible. Atrophy is a consequence of oestrogen deficiency, usually found in the post-menopausal woman.
Condylomata[1]	Multiple exophytic lesions that present as soft pink or white vascular growths. They have multiple fine, finger-like projections on the surface. Condylomata are caused by infection with HPV.
Deciduosis[1, 2]	Small, reddish, elevated, vascular nodules or sessile polyps appearing on the ectocervix, surrounding the external os. A more pronounced form of cervical ectopy, occurring during pregnancy. The change is progesterone-mediated.
Erosion[1]	Also known as ectopy or ectropion. A large, reddish area on the ectocervix, surrounding the external os. A physiological condition in which the endocervical columnar epithelium everts through the external os, and onto the vaginal portion of the cervix.
Inflammation[1]	*Cervicovaginitis* refers to inflammation of the squamous epithelium of the vagina and cervix. *Cervicitis* refers to inflammation of the columnar epithelium of the cervix. The inflammatory reaction is characterized by damage to surface cells. There is desquamation and ulceration leading to a loss in epithelial thickness. The surface epithelium is covered by cellular debris and mucopurulent secretions. Deeper tissues are swollen and congested.

	Inflammation is most often caused by infection with various organisms. Other causes include foreign bodies, trauma and chemical irritants.
Keratosis[1]	A white, well-demarcated area on the cervix that may be apparent to the naked eye, before the application of acetic acid. The white colour is due to the presence of keratin. Keratosis is usually idiopathic, but may also be caused by chronic foreign body irritation, HPV infection or squamous neoplasia.
Polyp[1]	A benign overgrowth of epithelium from the endocervical canal or from the ectocervix. May be asymptomatic, found incidentally when examining the cervix, or may present with abnormal bleeding.
Early Stage Disease	FIGO stage Ia-IIa cervical cancer
Late Stage Disease	FIGO stage IIb-IVb cervical cancer

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List of Abbreviations

A	
AC	adenocarcinoma
AGC	atypical glandular cells
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ASC	atypical squamous cells
ASC-H	atypical squamous cells, cannot exclude high grade
ASC-US	atypical squamous cells, unknown significance
ASIR	age standardised incidence rate
ASMR	age standardised mortality rate
C	
CDC	Centre for Disease Control
CHBAH	Chris Hani Baragwanath Academic Hospital
CIN	cervical intraepithelial neoplasia
CIS	carcinoma in situ
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
D	
DNA	deoxyribonucleic acid
F	
FIGO	International Federation of Obstetricians and Gynaecologists
G	
GLOBOCAN	Global Cancer Research
H	
HAART	highly active antiretroviral therapy
HCT	HIV Counselling and Testing

	HIV	human immunodeficiency virus
	HPV	human papillomavirus
	HSIL	high grade squamous intraepithelial lesion
I		
	IARC	International Agency for Research on Cancer
L		
	LBC	liquid-based cytology
	LLETZ	large loop excision of the transformation zone
	LSIL	low grade squamous intraepithelial lesion
N		
	NCCP	National Cancer Control Program
	NCR	National Cancer Registry
	NHLS	National Health Laboratory Services
	NOS	not otherwise specified
P		
	Pap	Papanicolaou smear
	PPV	positive predictive value
R		
	RCI	Reid's colposcopic index
S		
	SA	South Africa
	SCC	squamous cell carcinoma
	SCJ	squamocolumnar junction
	Stats SA	Statistics South Africa
T		
	TZ	transformation zone
U		

	UN	United Nations
	UTT	Universal Test and Treat
V		
	VIA	visual inspection with acetic acid
	VILI	visual inspection with Lugol's iodine
W		
	WHO	World Health Organisation
	Wits	University of the Witwatersrand

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7. University of the Witwatersrand Human Ethics Research Committee (HERC) approval to conduct study.
8. Turn-it-in Report (Anti-plagiarism software)

Chapter 1: Introduction

In this chapter, I will give a background to the problem addressed in this study, followed by a literature review of the topic. Thereafter, I will give my problem statement and study justification, followed by the aims and objectives of this study.

1.1 Background

Cervical cancer is a major, preventable public health issue. Data from GLOBOCAN 2018 ranked cervical cancer as the 4th most common cancer in women, and the 4th most common cause of cancer mortality in women worldwide.[1]

GLOBOCAN 2018 estimated that 569 847 new cases of cervical cancer would be diagnosed worldwide in 2018, and that there would be 311 365 deaths from cervical cancer in the same year.[1] The World Health Organization (WHO) reported that more than 85% of cervical cancer deaths occurred in low- and middle-income countries in 2018.[2]

It has been shown in several countries that cervical cancer mortality can be reduced by the implementation of nationwide organised cervical screening programmes.[3, 4] High coverage of a cervical screening programme is an important factor in substantially decreasing mortality.[3, 5]

In addition to reducing cervical cancer mortality, well-established organised screening programmes and regular screening have also been shown to reduce the stage at which cervical cancer presents.[4, 6, 7] Five-year survival rates of cervical cancer diminish with advancing stage at diagnosis.[8]

In South Africa (SA), the National Guidelines for a Cervical Cancer Screening Program were released in 2000, after the adoption of the National Cancer Control Program (NCCP) in 1999.[9] The cervical screening programme is cytology-

based. Asymptomatic women from age 30-50 years are offered three free cervical smears at 10 year intervals.[5, 9] Women with abnormal cytology are then referred for colposcopic evaluation and treatment, based on local referral criteria. With 70% coverage, this programme should have resulted in a 66% reduction in the incidence of cervical cancer.[5]

Whilst good in theory, the national screening programme in SA has not significantly impacted the national cervical cancer incidence or mortality.[5] In fact, the incidence of and mortality from cervical cancer in SA has remained high, and is recently increasing.[10-12]

Data from the SA National Cancer Registry (NCR) showed that the age-standardized incidence rate (ASIR) of cervical cancer fluctuated between 20.3-25.5/ 100 000 from 2000-2011.[10] GLOBOCAN 2012 estimated the ASIR of cervical cancer in SA to be 31.7/ 100 000.[11] In the GLOBOCAN 2018 report, the estimated ASIR in SA had increased to 43.5/ 100 000.[12] The corresponding age-standardized mortality rates (ASMR) for cervical cancer in SA were 18.0/ 100 000 in 2012[11], and 19.2/ 100 000 in 2018.[12] Whilst the actual figures from the NCR and GLOBOCAN may differ, both sources agree that the ASIR is high, and GLOBOCAN additionally shows an increase in both ASIR and ASMR from 2012 to 2018.

There are multiple reasons for the failure of the SA national cervical screening programme to reduce the incidence and mortality of cervical cancer. A major reason is poor coverage. [5, 9] Other factors that may play a role are discussed in the literature review.

The goal of the SA National Cancer Control Program (NCCP) was to screen at least 70% of asymtomatic women in the target population within 10 years, which was calculated to be 686 622 smears in asymptomatic women annually.[9] Although there was a steady increase in cervical smears taken from 2005 to 2016, the number of total annual smears only became more than 600 000 in 2011-2012.[9] Of these, smears taken in asymtomatic women only accounted for a

maximum of 40% of total smears annually.[9] Up until 2016, the calculated target number of cervical smears taken in asymptomatic women had still not been met.[9]

1.2 Literature Review

1.2.1 Natural History of Cervical Cancer

Cervical cancer is caused by sexually-transmitted infection with human papilloma viruses (HPV).[13] There are over 100 types of HPV.[2] The different types may be classified as high risk or low risk in terms of their capacity to cause oncogenic change. The International Agency for Research on Cancer (IARC) has identified HPV types 16, 18, 31, 33, 35, 45, 52 and 58 as being most frequently found in cervical cancer.[14] Infection with HPV types 16 and 18 confers the highest risk of developing cervical cancer.[2, 13-14] These two HPV types are responsible for 70% of pre-invasive lesions and invasive cervical cancers worldwide.[2]

Initial infection of the transformation zone of the cervix with HPV leads to latent infection.[15] Most women are able to clear their infection over 1-2 years.[13, 16] In some women with HPV infection, a phase of productive viral infection is entered into.[15] During this phase, latent HPV begins to replicate independently of the host cell cycle.[15] Large numbers of complete viral particles are produced.[15] During this phase, low grade cervical lesions may be diagnosed, but there is no neoplastic change in the infected epithelium.[15]

Low grade cervical lesions may progress to high grade lesions in some women with persistent HPV infection.[15] The circular viral DNA undergoes changes and is able to incorporate itself into the linear host DNA.[15] The virus can then "hijack" the host cell's protein production apparatus, leading to the production of large copy numbers of virions, and causing neoplastic change within host cell.[15] Persistent infection with high risk types of HPV may lead to progressive grades of cervical intraepithelial neoplasia (CIN), and eventually cervical cancer.[16, 17]

Infection with high-risk HPV is a necessary cause of cervical cancer, but not sufficient cause.[1] There are other important co-factors that increase the risk of developing cervical cancer.[1] These include HIV infection (and other causes of immunosuppression), smoking, high parity and oral contraceptive use.[1]

1.2.2 HIV and Cervical Cancer

According to the World Health Organisation's Global Health Observatory, 36.9 million people were living with HIV/AIDS worldwide in 2017.[18] Nearly two thirds of people living with HIV/AIDS worldwide lived in Africa in 2017.[18]

UNAIDS described South Africa as having "the largest HIV epidemic in the world".[19] Data from UNAIDS estimated that 4.2 million females aged 15 and older were living with HIV in South Africa in 2016,[19] and that the prevalence of HIV in women aged 15-49 was 23.7%. [19] A very similar figure was calculated by Statistics South Africa (Stats SA) in 2018.[20]

Infection with Human Papillomavirus (HPV) remains a necessary cause of the development of pre-invasive and invasive cervical lesions, even in women infected with HIV.[21] However, HIV positive women are at increased risk of acquiring HPV, and are at increased risk of having persistent HPV infection.[22, 23]

Lui et al showed that women infected with HIV were at increased risk of HPV infection (RR 2.64), and increased risk of infection with high-risk types of HPV (RR 2.35) compared to HIV negative women.[22] Denny et al found a 68% prevalence of high-risk HPV infection in HIV positive women.[23] The incidence of new HPV infections during follow-up in these women was 22%.[23]

Women with HIV are also at increased risk of prevalent and incident cytological abnormalities on cervical smears compared to HIV negative women.[22, 23] Lui et al found that the risk of incident LSIL or ASCUS was 3.73 times higher in HIV positive women, whilst the risk of incident HSIL was 1.32 times higher.[22]

The risk of histologically-confirmed CIN in HIV positive women is also increased.[24] A large prospective study by Ellerbrock et al found that the incidence of CIN was significantly higher in HIV-positive women, at 8.3 cases/ 100 person-years vs. 1.8 cases per 100 person-years in HIV negative women.[24] In 2009, a USA population-based study found that immunocompromised women with HIV were 8.9 times more likely to have cervical carcinoma in-situ (which correlates with CIN3/ HSIL) compared to the general population.[25]

Women with HIV are also at an increased risk of developing cervical cancer,[22] tend to present with cancer at a younger age,[26] and tend to present with late-stage disease.[27]

In their 2018 systematic review and meta-analysis, Lui et al found that HIV positive women were 4.1 times more likely to develop cervical cancer than HIV negative women.[22] A large literature review and meta-analysis on population-based risk factors for late-presentation of cervical cancer in Sub-Saharan Africa identified HIV infection as one of the risk factors for late presentation.[27]

Cervical cancer was recognised as an AIDS-defining illness in HIV-positive women by the Centre for Disease Control (CDC) in 1992.[28] In South Africa, Lomalisa found that immunocompromised women were significantly more likely to have advanced stage disease at presentation compared to HIV negative women.[26]

Antiretroviral therapy (ART) improves risk of HPV infection, CIN and cervical cancer in HIV positive women.[29] A 2018 systematic review and meta-analysis found that women on ART had a 17% lower prevalence of high-risk HPV infection, and a 35% lower risk of HSIL/ CIN2 or worse compared to HIV-infected women not on ART.[29] They also found that the incidence of cervical cancer was 60% lower in women on ART compared to HIV-positive women not on treatment.[29]

1.2.3 Burden of Cervical Cancer in Developing Countries

GLOBOCAN defines a high risk region for cervical cancer as one in which the age standardized incidence rate (ASIR) is more than 30/ 100 000.[11] Developing countries bear a higher disease burden of cervical cancer than developed countries. [1, 5, 11, 30]

Regional data from GLOBOCAN 2018 shows that Africa has the highest incidence of cervical cancer in the world.[1] The ASIR is highest in Southern Africa with a regional ASIR of 43.1/ 100 000, followed by Eastern Africa with an ASIR of 40.1/ 100 000.[1] In contrast, Western Europe has an ASIR of 6.8/100 000 and Northern America has an ASIR of 6.4/ 100 000.[1]

Developing countries are also disproportionally burdened with mortality from cervical cancer, with more than 85% of deaths worldwide occurring in these areas in 2012.[2] GLOBOCAN 2018 reported that Africa had the highest mortality rates from cervical cancer in the world.[1] The region with the highest mortality was Eastern Africa (ASMR 30.0/ 100 000), followed by Western Africa and Middle Africa.[1] Southern Africa ranked as the 4th highest region in the world for cervical cancer mortality, with an ASMR of 23.0/ 100 000.[1] In contrast, the ASMR of cervical cancer in 2018 was 2.1/ 100 000 in Western Europe and 1.9/ 100 000 in Northern America.[1]

In regions where the incidence and mortality of cervical cancer are low, the decline over time has been attributed to effective organised screening programmes and improved socio-economic circumstances.[1]

Denny et al reported that some of the causes for the increased burden of cervical cancer in developing countries were as a consequence of the constraints to the health care systems available in these countries.[30] These services are burdened by competing health needs, poorly developed health care services, urban/rural bias in terms of access to health care, and limited financial and human resources available to implement effective screening programmes.[30]

Other reasons were a reflection of social circumstances, such as poorly educated and disempowered women, war and civil strife disrupting healthcare services and access, and widespread poverty.[30]

1.2.4 The South African Context

The GLOBOCAN 2018 report estimated the ASIR of cervical cancer in the Republic of South Africa of 43.5/ 100 000.[12] The corresponding ASMR was 19.2/ 100 000.[12] These data firmly place SA in the category of a "high-risk" country for cervical cancer incidence and mortality.[11]

The main cervical screening programme in SA is the NCCP.[9] As previously described, this offers 3 free ten-yearly Pap smears to asymptomatic women aged 30-50 years. The HCT and UTT programmes encourage immediate cervical screening of newly diagnosed HIV positive women as part of their package of care.[9] In addition, they recommend shorter cervical screening intervals in HIV positive women.[9] The inclusion of cervical screening as part of the package of care for HIV positive women is an important addition, given the high burden of HIV infection in South Africa,[19] and the increased risk of CIN[24] and cervical cancer[22] in these women. Despite these various policies, a reduction in cervical cancer incidence and mortality in SA has not yet been realized[5, 10-12], mainly due to poor uptake of screening.[9]

The first problem in SA is one of resource availability.[9] The public health sector in SA battles with financial constraints, and a chronic shortage of staff, essential medicines and medical equiptment.[9] Only 27% of general practitioners and 45.1% of nurse practitioners work in the public sector.[9] Despite the staff shortages, it is mainly doctors in the public health sector who treat patients with pre-invasive and invasive cervical lesions.[9]

Secondly, the prevention and management of cervical cancer and its precursors in SA occurs in a tiered fashion, in terms of both level of care and geographic

location.[31] Whilst cervical smears are conducted locally at a primary healthcare level, the management of abnormal smears is centralized to fewer centres, mainly in urban areas.[31] Furthermore, for women who are diagnosed with cancer, treatment is offered at tertiary and quaternary centres.[31] This creates a rural/urban bias in access to healthcare.[31] Additionally, there is a high rate of poverty in SA[32]. Financial constraints may impair a woman's ability to comply with follow-up visits that occur at greater and greater distances from her home.[32]

Yet another problem is that there is no formal call-and-recall system for cervical screening in SA.[33] As such, our screening efforts rely on public awareness and opportunistic screening.[9, 33] This results in low recruitment, and high loss to follow-up. [33, 34] The United Kingdom (UK) faced a similar problem prior to the introduction of a computerized population-based call-and-recall system in 1988.[34] They managed to increase their coverage from 40% in the 1980's to 80% after the introduction of their "call-and-recall" system.[34]

1.2.5 Prevention of Cervical Cancer

1.2.5.1. Primary Prevention

Primary prevention of cervical cancer is aimed at preventing initial infection with HPV.[5] This can be achieved by behaviour modification and/or by vaccination against HPV.[5, 9]

Historically, primary prevention has been based on behavioural modification, such as abstinence, mutual monogamy of virgins, and the use of male condoms.[5] In many countries, especially in the developing world, this remains the only primary prevention strategy that can be employed.

Prophylactic HPV vaccines present an effective means of primary prevention of cervical cancer.[5, 35] Randomized placebo-controlled trials have shown that these

vaccines are highly efficacious in the prevention of HPV infection, the prevention of persistent HPV infection, and the prevention of HPV-induced genital tract lesions for the HPV subtypes against which they act.[35]

In South Africa, HPV vaccines have been available since 2008, but uptake was mainly in the private health sector.[36] In March 2014, a public school-based HPV vaccination programme was rolled out nationwide, targeting grade 4 girls (9 years old). [36] The bivalent vaccine was offered free of charge, and in a dose schedule of 2 doses, 6 months apart.[36]

A study was commissioned by the South African National Department of Health to evaluate the roll-out campaign for the 1st dose in March 2014.[36] The uptake of the 1st dose was 86.6% of the 408 273 grade 9 girls who were eligible for vaccination.[36] The uptake of the roll-out was not uniform, and there were 2 sub-districts with low coverage of 40% and 43% respectively.[36]

1.2.5.2. Secondary Prevention

Secondary prevention remains the mainstay method of reducing cervical cancer incidence and mortality in developing countries, including South Africa. Secondary prevention is centred on screening asymptomatic women to detect precancerous lesions of the cervix, followed by treatment of such lesions and surveillance to detect and treat recurrences.[5] There is some overlap with tertiary prevention, in that invasive disease may also be diagnosed by screening strategies.

a) Cervical Screening

Well-established cervical screening programmes in the developed world have been shown to reduce the incidence of, and mortality from cervical cancer.[3, 4] Regular screening has also been shown to reduce the stage at which cervical cancer presents.[4, 7]

Landy et al demonstrated that regular screening reduced the incidence of stage 1a cervical cancer by 67%, and stage 3 and 4 by 95%.[4]

A study by Laara et al in 1987 looked at trends in mortality from cervical cancer in the Nordic countries before and after the introduction of organised screening programmes.[3] All the countries studied showed a decrease in cumulative cervical cancer mortality after the introduction of organised screening.[3] Iceland was the most successful, with an 80% decrease in cumulative cervical cancer mortality.[3] Three decades later, Landy et al estimated that in England, cervical screening prevented 70% of cancer deaths.[4]

A Swedish study on cervical cancer cases diagnosed over 90 years found that cancer was diagnosed at an earlier stage over time.[7] The trend towards early stage at diagnosis was dramatically increased after the introduction of organized screening in the 1960's.[7]

In the UK, Landy et al found that 72.6% of women diagnosed with cervical cancer presented with FIGO stage 1 disease.[4] Coverage of the UK cervical screening programme has been greater than 80% since the 1990's.[34] In contrast, a study conducted in the USA on women without health insurance (and thus limited access to healthcare), found that local disease was diagnosed in only 36% of women.[6] This figure was well below the national average of women diagnosed with local disease (comprising of both insured and uninsured women).[6] Both the UK and USA studies concluded that regular screening reduces the stage at which cervical cancer presents.[4, 6]

The World Health Organization (WHO) recommends that a national cervical cancer screening programme should prioritize women aged 30-49 years old and have a screening interval of not less than 5 years (and not less than 10 years if using HPV DNA testing).[37] It should prioritize maximal coverage and ensure complete follow-up of women with abnormal test results.[37] Also, the programme should offer HIV testing and counselling to women with abnormal test results in high HIV prevalence countries.[37]

It should be noted that the current South African national screening guidelines do not meet the WHO criteria in terms of screening interval.[9, 37] The screening interval for this cytology-based programme is 10-yearly instead of 5-yearly. Also, we are not meeting the performance targets set by the WHO. Coverage of the programme is low,[9] and follow-up of abnormal smears is often incomplete.[38] A study conducted in the Eastern Cape showed that only 54% of the 928 women referred to a colposcopy clinic due to abnormal cytology actually attended their colposcopy clinic appointment.[38]

However, the WHO gives the proviso that women aged 30-49 should be screened at least once in their lifetime.[37] Also, the South African screening programmes for HIV positive women (HCT and UTT) have shorter screening intervals which do meet the WHO criteria.[9, 37]

Different screening tools and screening protocols will be discussed in subsequent sections of the literature review.

b) Treatment and Follow-up of CIN

As mentioned previously, the second part of secondary prevention involves the appropriate management and follow-up of women with cervical cancer precursors. Women who have abnormal screening test results should be referred for further evaluation in order to determine if they truly have CIN, and offered treatment if required.

The majority of CIN1 lesions regress spontaneously, [39, 40] and therefore CIN1 may be managed with surveillance or treated, depending on clinical circumstances.[40] Due to the fact that CIN 2 and CIN 3 have a higher risk of progression to cervical cancer,[39] these lesions should always be treated.[40]

Treatment methods for CIN may be ablative or excisional.[41] In low- and middle income countries, cryotherapy, large loop excision of the transformation zone (LLETZ) and cold knife conisation (CKC) are the 3 principle treatment modalities available for the treatment of CIN.[41] Cryotherapy is an ablative technique, whilst

LLETZ and CKC are excisional techniques. Cryotherapy may only be used when strict patient selection criteria are met.[42] When these criteria are not met, an excisional technique must be used.[42]

Both excisional and ablative techniques are effective for the prevention of cervical cancer compared to no treatment.[41] Both ablative and excisional techniques are associated with a risk of complications, including bleeding, infection, scarring, adverse outcomes in subsequent pregnancies and disease recurrence.[40] A 2013 Cochrane review comparing the different treatment techniques found that there was no superior technique in terms of treatment failure (efficacy) or morbidity.[42]

Excisional techniques have the benefit of providing a histological specimen of the lesion, as well as providing information on the completeness of the excision.[42] Occult invasive cancer is less likely to go undetected when a histological specimen is provided.[42] Incomplete excision is a risk factor for disease recurrence and subsequent development of cancer,[42] and this information is therefore useful. Of the excisional techniques, the Cochrane review found that LLETZ provides the most reliable histology specimen with the least morbidity.[42]

Women treated for CIN remain at an increased risk for the development of cervical cancer compared to the general population.[43-45] Because of this, women previously treated for CIN require more intensive follow-up in the first 2-3 years after treatment.[33] Thereafter, if follow-up screening results remain normal, they may return to routine screening.[33] According to the HPV Advisory Board in South Africa, “routine screening”, where cytology is used as the screening tool, is annually in HIV positive women, and 3-yearly in HIV negative women.[33] This is at odds with the 10-yearly “routine screening” offered by the SA National Department of Health.[9]

1.2.5.3 Tertiary Prevention

Tertiary prevention involves limiting morbidity and mortality in those women who present with cervical cancer.[37] This is dependent upon early diagnosis of cervical cancer, and the provision of appropriate treatment when cervical cancer is diagnosed.[37]

The early diagnosis of cervical cancer is important, as mortality increases with advancing stage at presentation.[8] There are various staging systems for cervical cancer. In South Africa we use the International Federation of Gynecology and Obstetrics (FIGO) classification system of cervical cancer,[46] which was updated in 2018. FIGO stage 1A has a 5-year survival rate in excess of 95%, whereas FIGO stage 4 has a 5-year survival rate of less than 20%.[8] Women in developing countries tend to present with late-stage disease (FIGO stage IIb-IVb).[47]

Whilst traditional cervical screening programmes are appropriate in the setting of asymptomatic women, it is important to be cautious of the symptomatic women, such as those with abnormal discharge, abnormal bleeding, urinary symptoms, backache or pelvic pain, as these may be symptoms of invasive cancer.[48]

The symptoms of cervical cancer are non-specific, and are common in other gynaecological conditions, such as genital infections and side effects of hormonal contraception.[49] Symptomatic young women in the reproductive ages are more likely to have other diagnoses than to have cervical cancer.[49] However, the diagnosis of cervical cancer is often delayed in symptomatic young women in the reproductive ages, with symptoms being attributed to other causes.[49] This highlights the importance of a full pelvic examination, including speculum examination in all symptomatic women, particularly those who are young.[48, 49]

Appropriate investigation for symptomatic women depends on the macroscopic appearance of the cervix.[8, 9] Those with a normal-looking cervix should receive a cervical “screening” test, whilst those with an abnormal cervix should be

biopsied on presentation.[8, 9] This in order to prevent delays in the diagnosis of cervical cancer.

Treatment of cervical cancer is by surgery or radiation.[8, 37, 46-47] Concurrent chemotherapy significantly improves survival in those women undergoing radiation therapy.[8, 30, 46-47] Surgery mainly consists of simple, modified radical, or radical hysterectomy, and is indicated for early-stage disease (FIGO stage I-IIa). [46] Concurrent chemoradiation therapy (CCRT) is the standard of care for advanced disease.[46]

Some African countries have no, or limited trained staff and facilities to provide anti-cancer therapy, particularly radiation therapy.[47] Where radiation therapy is available, the additional cost of concurrent chemotherapy may be prohibitive to the provision of such protocols.[47] In South Africa, facilities and expertise for the treatment of cervical cancer is limited, and based in urban areas.[37, 47]

The WHO recognises that compliance to treatment is a challenge, especially in the case of radiation therapy.[37] Non-compliance may be caused by geographical, financial and social barriers, particularly where long-term treatment is required.[37]

1.2.6 Screening Methods

There are numerous primary screening methods available for the detection of cervical cancer precursors. These include cervical cytology- Papanicolaou smear (Pap smear) using glass slide, cervical cytology- liquid based cytology (LBC), visual inspection with acetic acid (VIA) with or without magnification, visual inspection with Lugol's iodine (VILI), and human papillomavirus DNA testing (HPV testing).[50]

The oldest and most widely used primary screening method for the detection of precancerous cervical lesions is the Papanicolaou smear (Pap smear). This is the basis of the South African national cervical screening programme.[5, 9] Currently,

HPV DNA testing and cervical cytology are the only screening tools recommended by the HPV Advisory Board in South Africa.[33] The WHO recommends HPV DNA testing, cervical cytology and VIA as primary screening tools.[51]

A 2012 meta-analysis by Chen et al looked at the performance of various primary screening tests with regards to detecting CIN2+.[50] With regards to cervical cytology, the sensitivity of Pap smear and liquid-based cytology (LBC) was 59% and 88% respectively, whilst the specificity was 94% and 88% respectively.[50]

An umbrella systematic review and meta-analysis by Mustafa et al was published in 2016.[52] The pooled sensitivity of HPV DNA testing was 94% (95% CI 89-97%), and the pooled specificity was 88% (95% CI 84-92%).[52]

Chen et al found that for VIA with and without magnification, the sensitivity to detect CIN2+ was 64% and 77% respectively.[50] The corresponding specificities were 86%, and 87%.[50]

1.2.7 Colposcopy

Colposcopy refers to the practice of examining the epithelium of the lower genital tract with a colposcope.[53] A colposcope is a low-power microscope with a light source, which allows more careful examination of the appropriate area under magnification.[53] The most common indication for colposcopy in modern practice is to investigate women with an abnormal cervical screening test.[53, 54]

The features of the epithelium are examined whilst sequentially applying normal saline, 3-5% acetic acid, and Lugol's iodine solution to the area of interest.[53] The modified Reid colposcopic index (RCI) is a recommended standardized method of recording and scoring the colposcopic changes observed.[55] It also allows a prediction of the underlying histological diagnosis (colposcopic impression).[55]

An important requirement for performing meaningful colposcopy is a "satisfactory" examination. A "satisfactory" colposcopic examination is one in which the entire transformation zone of the cervix is visible.[54] In a review by Hopman et al, the unsatisfactory examination rate was found to be much higher for microinvasive and invasive disease compared to premalignant disease (61% and 71% respectively, compared to 14% in premalignant disease).[54]

The interpretation of colposcopic images is subjective by nature, because it involves the interpretation of epithelial patterns.[56] Also, the modified RCI does not make provision for the diagnosis of microinvasive or invasive cervical cancer.[55] The IARC colposcopy manual does however give a description of the colposcopic findings associated with microinvasion[57] and frank invasion.[48]

The interpretation of colposcopic findings is therefore dependant on the skill of the colposcopist,[56] and is subject to much intra- and inter- observer variability. [56] In a study by Hopman et al, 56% of microinvasive disease and 30% of invasive lesions were missed by colposcopic impression.[54] A Mexican study found that the correlation between colposcopic impression and histology was 57% in women with cervical cancer.[58]

1.2.8 Screening Protocols

Screening for and treatment of precancerous lesions may be done in a number of ways, from a logistical point of view. Traditionally, cervical screening has been done sequentially in three steps.[5, 37] A primary test is used to identify women with abnormalities.[5, 37] The second step involves colposcopy for those women with abnormalities, and histological confirmation of the lesion with colposcopically-directed punch biopsy.[5] Once there is histological confirmation of the lesion, treatment in the form of excision or ablation is given at a third visit, if required.[5, 37] If treatment is by an excisional method, a fourth visit is required to collect final histology results.

Screen-and-treat protocols have been tested in low-resource settings.[5, 30] This involves employment of a primary screening test that gives a rapid result, e.g. visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI) or point-of-care HPV DNA testing.[5, 30, 37] This is followed by immediate treatment e.g. with cryotherapy if the test is positive. The entire process is thus compressed into one visit.[5, 30, 37]

Such protocols are safe and effective, and also more feasible in low-resource settings.[5, 30] A trial by Sankaranarayanan et al in India showed that VIA followed by immediate cryotherapy if test-positive, reduced cervical cancer incidence by 25%, and mortality by 35%.[59]

A study conducted in rural Thailand involved almost 6 000 women in a screen-and-treat protocol.[60] It showed that uptake of such protocols is excellent.[60] Women were offered VIA, followed by immediate cryotherapy if test-positive. 13.3% of women were VIA test positive.[60] Of these women, 98.5% agreed to immediate treatment with cryotherapy.[60] Additionally, 83.2% of women treated with cryotherapy returned for their follow-up visit.[60]

The benefits of screen-and-treat protocols are that loss to follow-up, costs to the patients and costs of the programme are all reduced, as the number of visits are reduced.[37]

The disadvantage is that there is a risk of overtreatment resulting from a lack of histological confirmation of the lesion before treatment.[37] As previously discussed, there is a risk of morbidity and subsequent adverse pregnancy outcomes with all treatment modalities for CIN.[40] Also, if using ablative techniques for treatment, there is no histological confirmation that invasive disease was not missed, or that the treatment removed the entire lesion.[42]

Sequential protocols are a modification of the screen-and-treat protocols.[37] Women with a positive primary screening test are triaged with a second test that also gives an immediate result.[37] Treatment is given if both tests are positive.[37]

Thus, the number of visits from screening to treatment is 1 or 2, depending on the nature of the primary and triage tests.[37]

The advantage of sequential protocols is that the inclusion of a triage test reduces over-treatment. The disadvantage is that loss-to-follow-up is increased if more than one visit is required. Also, expenses increase, since an additional test is employed.

An example of a sequential protocol is the protocol used at the "see and treat" Chris Hani Baragwanath (CHBAH) colposcopy clinic in Johannesburg, South Africa. The primary screening test used is cervical cytology, and the triage test used is colposcopy. Instead of taking a colposcopy-directed punch-biopsy for women referred with abnormal cytology, treatment is given immediately on the basis of an abnormal colposcopic impression of more than a CIN1, if cytology and colposcopy are incongruent, or if colposcopy is inadequate. Treatment is LLETZ, which will also provide histological confirmation of the lesion, as well as information on the completeness of the excision.

A 2008 study by Adam et al at the CHBAH colposcopy clinic found that the exact correlation between colposcopic impression and histology was 80.2%.[61] The over-treatment rate was 6.7%[61] and the complication rate from treatment was 2.7%.[61]

1.3 Problem Statement

Opportunistic screening has been available to all South African women since the 1970's, [9, 10] and the National Cancer Control Program (NCCP) was adopted in 1999.[9, 10]

It must be remembered that the goal of cervical cancer screening is to detect and treat pre-invasive disease in order to reduce the incidence of invasive disease, with its associated morbidity and mortality. Despite the various government

interventions, coverage of screening programmes remains low,[9] and the incidence of, and mortality from cervical cancer in South Africa is high, and recently increasing.[10-12]

Additionally, women in developing countries continue to present with advanced disease.[47] Studies in Nigeria, Cape Town, Johannesburg and Tanzania all found that the vast majority of women with cervical cancer in their studies presented with advanced disease.[62-65] Late stage disease was diagnosed in 98.9%%, 89.0%, 87.5% and 81.3% respectively. [62-65]

The percentage of screen-detected cervical cancers in South Africa is also very low. Data from the National Health Laboratory Service (NHLS) shows that less than 0.6% of cervical cancers in 2005-2006 were screen-detected.[9] This number had fallen to about 0.2% in 2015-2016.[9] Macroscopically obvious disease should be biopsied rather than smeared,[9] but the percentage of screen-detected cancer is extremely low, even when considering that the majority of women in South Africa present with advanced disease.[47]

The South African cervical screening programme is not reducing incidence,[10-12] stage,[63, 64] or mortality from cervical cancer,[10-12] and only a tiny proportion of cancers are screen-detected.[9] This begs the question: are we wasting our time and resources on cervical screening in South Africa? Is there any benefit at all to cervical screening in South Africa or should we be redirecting our efforts elsewhere?

1.4 Study Justification

There is a paucity of South African literature, and indeed literature from other low-to-middle income countries, that describe the findings of women diagnosed with cervical cancer through a screening programme.

Although we know that the organized cervical screening programme in South Africa is not currently improving national outcomes,[9-12, 47] there is still much value to be obtained from describing women diagnosed with cervical cancer through such a programme. It would add to the sparse body of knowledge about these women, and possibly highlight areas that require more research, or highlight flaws in our current screening programme.

Knowledge of the FIGO stage at which these screened women present is particularly important. If women in our study present with early-stage disease, it shows that organised screening may still be beneficial to the women who do make use of the programme, as we know that 5-year survival diminishes with advancing stage at diagnosis.[8] This encourages us to strengthen our efforts to recruit more women into the programme.

If these "screened" women present with advanced disease despite being diagnosed through a screening programme, this may point to a need for outreach and retraining of staff members at the local clinics from which we receive referrals. Protocols in South Africa dictate that women with macroscopically-obvious cervical cancer should be urgently biopsied, and not referred for colposcopy, where waiting periods can be as long as 18 months.[9] The majority of cervical smears in South Africa are performed by nurse practitioners in primary healthcare facilities,[9] and there is a reliance on these practitioners to be able to recognise macroscopically obvious cancer and follow correct procedures and referral pathways.

1.5 Aim

To describe and evaluate women diagnosed with cervical cancer at the Chris Hani Baragwanath Academic Hospital colposcopy clinic from April 2003 until April 2016.

1.6 Objectives

A) To describe the demographic details and clinical factors of these women.

B) To describe the cervical cytology results in these women.

C) To describe the colposcopic findings.

D) To describe the histological findings.

E) To describe the FIGO stages of cervical cancer.

Chapter 2: Methods

2.1 Study Design

A cross-sectional study involving a retrospective review of data obtained from the Chris Hani Baragwanath Academic Hospital (CHBAH) colposcopy clinic electronic database, hospital files and the National Health Laboratory Services (NHLS) database.

2.2 Study Setting

The CHBAH is a tertiary level public hospital located in Soweto, Johannesburg. Soweto is a high-density urban township. Its population is diverse, including economic migrants from other parts of South Africa, Africa and Asia. In the National Census 2011, the township of Soweto was found to have a population of almost 1.3 million people, of which 50.38% were women.[66]

The CHBAH colposcopy clinic is a direct referral centre for 56 local clinics, 7 community health centres and 1 district hospital. A small number of private patients are also referred to the clinic. The colposcopy clinic is staffed by doctors solely practicing obstetrics and gynaecology, including specialist consultants, senior (post-registrar) medical officers and registrars, all operating under the supervision of an expert colposcopist.

2.3 Study Population

All women referred to the CHBAH colposcopy clinic, from April 2003 to April 2016, diagnosed with invasive cervical cancer on histology. Referral criteria to the CHBAH colposcopy clinic are attached. Appendix 1

2.4 Clinical Procedures

Women were referred to the CHBAH colposcopy clinic with abnormal cervical cytology or histology reports. The histology reports were of non-colposcopically-directed cervical punch biopsies showing CIN. The predominant method by which cytology was obtained was conventional Pap smears performed by nurse practitioners or doctors. A small proportion were liquid-based cytology (<5%).

Referring cervical cytology and histology from all public health facilities was processed and reported on by the NHLS pathology department, and less than five percent of specimens were processed by private laboratories. The NHLS is an accredited laboratory with stringent internal and external quality control mechanisms in place. The cytology was reported on using the Bethesda classification system.[67] Histology was reported on using the CIN classification system.[68]

A clinical history was taken by the colposcopist, and the data was entered into CHBAH OPD cards, and the CHBAH colposcopy clinic electronic database. After 2006, those women whose HIV status was negative or unknown were offered an HIV test. Those women who were HIV positive had a CD4 count done if no recent result was available.

The colposcope used was a Leisegang Optik Model 1 (CooperSurgical, Inc. 95 Corporate Drive. Trumbull, CT 06611, USA). Colposcopic examination of the cervix was done at the baseline visit, using the 'saline technique'. The cervix was examined using the sequential application of normal saline, 3-5% acetic acid, and Lugol's iodine.

Colposcopy was deemed adequate when the entire transformation zone was visible. Colposcopic diagnosis was made using the Modified Reid's Colposcopic Index.[55, Appendix 2.] It must be noted that the modified Reid's colposcopic index makes no provision for the colposcopic diagnosis of cervical cancer. However, the CHBAH colposcopy clinic electronic database does allow the colposcopist to

enter a colposcopic impression of microinvasion or invasion. Colposcopic features of microinvasion and frank invasion have been described in the IARC Colposcopy Manual.[48, 57, Appendix 3.] Other abnormal findings, such as condylomata, keratosis, atrophy, inflammation, deciduosis or polyps were also documented if present. The definitions for these findings are provided in the section on definitions.

Histology was obtained by large loop excision of the transformation zone (LLETZ), cervical punch biopsy, cone biopsy or diagnostic hysterectomy. Endocervical currettage and endometrial sampling were done if clinically indicated.

The CHBAH colposcopy clinic is a "see and treat" clinic. A LLETZ was performed immediately if the colposcopic diagnosis was worse than CIN 1, if colposcopy was inadequate, or if referring cytology/histology report showed HSIL. Punch biopsies were performed where there was a macroscopically obvious cancer, or where the colposcopic impression was CIN1, and referring cytology/histology were congruent with a colposcopic impression of CIN1. Women were referred for cone biopsy or diagnostic hysterectomy at the discretion of the colposcopist, based on previous treatment history for CIN, ability to perform LLETZ safely in an out-patient setting, co-morbid disease or medication, and patient wishes.

The electrocautery device used for LLETZ was a Finesse 2+ (Utah Medical Products Inc. 7043 Cottonwood St, Midvale, UT 84047, USA). Various sizes of standard and contour electrosurgical loops were available (UtahLoop or C-LETZ, Utah Medical Products Inc.). The procedure was performed under cervical block, with 4-6 ml 1% lignocaine hydrochloride injected directly into the cervix with a dental needle and syringe.

Punch biopsy was done using either Tischler or Kevorkian biopsy forceps. Endocervical curettage was done using a Kevorkian curette, if clinically indicated. Endometrial biopsy was only done if clinically indicated. Currently we use the Preferred SureFlex Curette (Bioteque America Inc. 2051 Junction Ave, San Jose, CA 95131, USA). Diagnostic cone biopsies and hysterectomies were done in

theatre. Histology specimens were packaged in plastic specimen bottles or bags, submerged in 10% formalin.

Histology was reported on by the NHLS, using the WHO classification system.[69] In LLETZ, cone biopsy and hysterectomy specimens, the presence or absence of dysplasia or tumour at the margins was documented. The histological sub-type, tumour size and presence or absence of lymphovascular space involvement were also reported on.

At the follow-up visit, women were given their diagnosis of cancer, and counselled by the colposcopist. Staging investigations were done, and the women were clinically staged by two gynaecologists. The cases were then presented at a multi-disciplinary team (MDT) meeting attended by gynaecologic oncologists, radiation oncologists, and medical oncologists. Subsequent management was decided at this meeting. These MDT meetings are conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Women deemed operable had simple or radical hysterectomies at the CHBAH, according to stage. The histology specimens were processed by the NHLS. Women who were inoperable underwent radiotherapy, concurrent chemoradiation, or palliative care. Radiotherapy and concurrent chemoradiation were conducted at the CMJAH.

2.5 Inclusion Criteria

A) Any woman referred to the colposcopy clinic who was subsequently found to have invasive cervical cancer, confirmed on histology.

2.6 Exclusion Criteria

A) Women referred with abnormal vault smears

B) Women who were diagnosed with recurrence after previous treatment for cervical cancer.

2.7 Data Management

2.7.1 Data Collection

As a result of the above system of assessment, diagnosis, referral and management, women had multiple records, including the CHBAH electronic database, the NHLS electronic database, CHBAH out-patient files, CHBAH in-patient files and CMJAH Radiation Oncology files.

The CHBAH colposcopy clinic electronic database was used to identify women diagnosed with cervical cancer, and collect relevant data. The list of women with cervical cancer was extracted from the CHBAH colposcopy clinic electronic database using the keywords “cancer”, “cannot exclude invasion”, “malignant cells” , “microinvasion”, and “invasion”. This was done because the database is clinical, and the colposcopist may not have filled in all fields. Using these keywords, we were able to ensure that no women with cervical cancer were missed.

Each women flagged by the database as having cancer was then cross-referenced with the NHLS electronic database. Only women in whom a histology report confirming invasive cancer was found were included and the rest were excluded. This was to ensure that only confirmed cases of invasive cervical cancer were used in the study.

The other sources were used to supplement and verify data from the colposcopy clinic electronic database. When conflicting data were found, data from the NHLS, and CMJAH radiation oncology files (where details of the case presentation to the MDT meetings, and outcomes of these meetings were recorded) were used as the gold standard.

The following data was collected: Age, parity, smoking, snuff use, HIV-related data, contraceptive history, results of referring cytology and histology, presenting symptoms, colposcopic findings and procedures performed at the clinic. Data on cancer included histology results (sub-types [69] and margin status) and FIGO staging.[70]

2.7.2 Data Analysis

The data was extracted from the CHBAH colposcopy clinic electronic database on 5 April 2017. Hospital files were accessed and the NHLS database was searched for HIV-related data, cytology reports and histology reports. All data were initially recorded on datasheets. [Appendix 4] The datasheets were then used to compile a Microsoft Excel spreadsheet, which was exported to Stata Version 14 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845, USA) for analysis.

Categorical variables were reported as frequencies and/or percentages. Comparisons of categorical variables were analysed using Chi^2 test or Fischer's Exact test. Continuous variables were reported as means with standard deviations, or medians with inter-quartile ranges. Comparisons of continuous variables were analysed using the Student t test or Kruskall-Wallis test.

A comparison was made between women with early-stage disease (Ia-IIa) vs. late stage disease (IIb- IVb). With regards to differences in symptomatology, we compared the presence of any symptom. Individual cases were reported where the clinical stage was found to be more advanced at hysterectomy and where the cancer was diagnosed after the patient had previously been treated for dysplasia.

2.8 Sample Size

No formal sample size was calculated, as the study was descriptive in nature. However, there were approximately 9000 women on the CHBAH colposcopy clinic electronic database by the end of April 2016. Previous studies conducted

using the CHBAH colposcopy clinic electronic database have shown that 1.8-5.0% of women were diagnosed with cervical cancer in their particular study populations.[71, 72] Based on this information 162-450 women were expected.

2.9 Ethics

There was already pre-existing consent for the establishment of the CHBAH colposcopy clinic electronic database and its use for research purposes. Appendix 5 (M080603/M040609)

All women attending the CHBAH colposcopy clinic were counselled by a member of staff, and signed informed consent on the day of attendance. The consent gave permission for the colposcopy and diagnostic procedures to be performed, as well as for their data to be collected for clinical and research purposes. Appendices 6 Informed consent for procedures conducted in theatre was obtained as per standard clinical practice.

Permission to perform this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Wits HREC) (M161036). Appendix 7

Permission to use this data was also obtained from:

1. Chief Executive Officer CMJAH (Access CMJAH files)
2. Medical Advisory Board CHBAH (Access CHBAH files)
3. Head of Departments of the NHLS (Use NHLS electronic database)
4. Head of Department of Radiation Oncology (Access CMJAH radiation oncology files)
5. Head of Department CHBAH Obstetrics & Gynaecology (Access CHBAH gynaecology files)
6. Head of Department CHBAH Colposcopy Clinic (Use CHBAH colposcopy clinic electronic database)

These permission letters were submitted to the Wits HREC.

2.10 Funding

The research was conducted at the researcher's personal expense. No external funding was provided.

Chapter 3: Results

In this chapter I will explain how women were included and excluded, describe the women, and then compare women with early stage disease vs. late stage disease. Women who presented with cancer after having been treated previously for a cervical cancer precursor lesion will then be described. Finally women in whom the surgery was abandoned because of unexpected advanced disease will be described.

There were 186 women identified as having a malignancy in the CHBAH colposcopy clinic electronic database. Figure 3.1 explains the exclusions. A total of 174 women were ultimately included in the study.

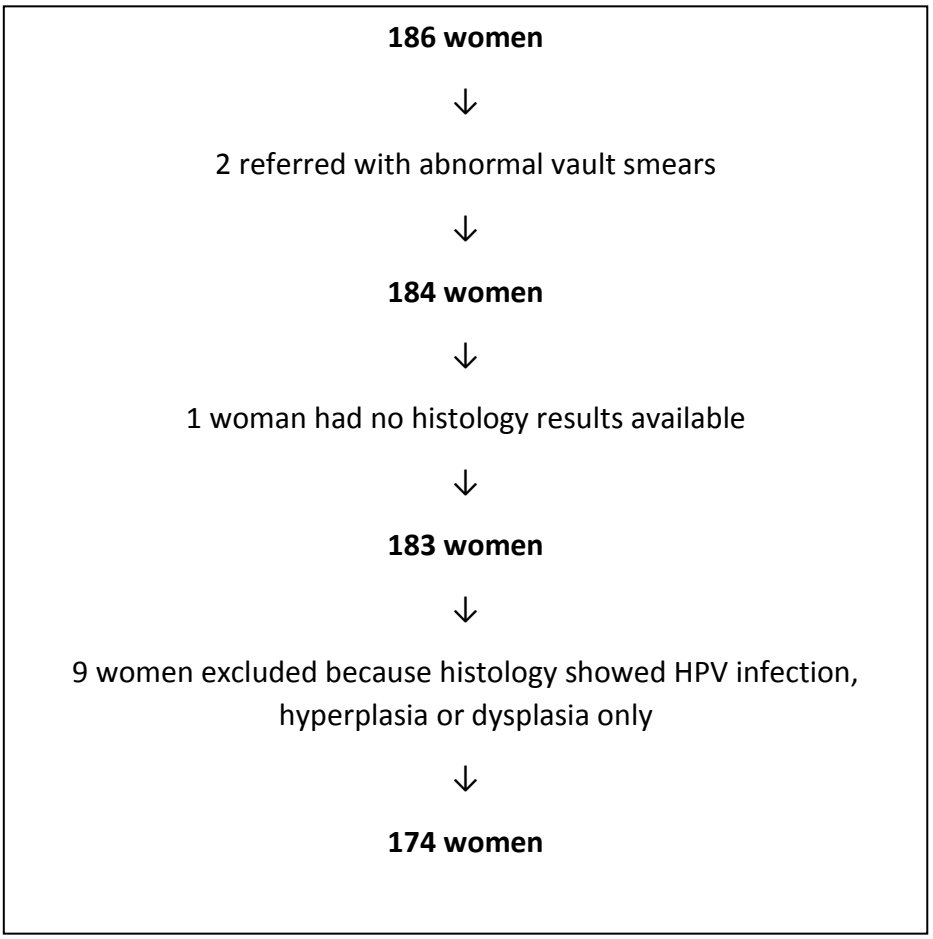


Figure 3.1: The reasons for exclusion in women originally flagged as having cervical cancer on the CHBAH colposcopy clinic electronic database.

The median age of the women was 45 years (IQR 38-55; range 28- 84). There were 110 pre-menopausal women (62.2%), and 64 women (36.8%) were post-menopausal. The median parity was 3 (IQR 2-4; Range 0-10).

The variables concerning smoking and snuff use were only added to the database in 2010. Smoking information was therefore only known in 40 women, 5 (12.5%) of whom were smokers. We obtained data regarding snuff use in only 23 women, and 3 (13.0%) of them used snuff.

The contraceptive use of the women in this study is depicted in the table 3.1 below. The contraceptive history of 160 women (92.0%) was known. Of these women, 28 were on hormonal contraception (17.5%), and 31 women (17.8%) made use of condoms.

Table 3.1: The contraceptive use in women diagnosed with cervical cancer at the CHBAH colposcopy clinic.

Contraception	**Frequency (n)**	**Percent (%)**
Injectable progestogen only	20	11.5
Combined oral contraceptive	4	2.3
Progestogen only pill	1	0.6
Condoms only	28	16.1
Dual Contraception*	3	1.7
Sterilization	12	6.9
Abstention	9	5.2
None	83	47.7
Unknown	14	8.0
Total	174	100

* Condoms and an injectable progestogen

The HIV status was positive in 94 women (54.0%), negative in 55 women (31.6%), and unknown in 25 women (14.4%).

The CD4 count was known in 80 of the HIV positive women (85.1%). The median CD4 count was 329 cells/mm^3 (IQR 177-502; range 19- 1095). Twenty five

women (31.2%) had a CD4 count less than 200 cells/mm^3, 17 women (21.3%) had a CD4 count between 200-349 cells/mm^3, 18 women (22.5%) had a CD4 count between 350-499 cells/mm^3, and 20 women (25.0%) had a CD4 count of 500 cells/mm^3 or more.

The use of antiretroviral therapy (ART) was known in 77 of the HIV positive women (81.9%) and 42 of these women (54.5%) were on treatment.

The reason for referral was recorded in 173 women (99.4%). Of these, 152 women (87.9%) were referred with abnormal Pap smears only, 13 women (7.5%) were referred with both an abnormal Pap smear and a punch biopsy, and 6 women (3.5%) were referred with a punch biopsy alone. One woman (0.6%) was referred with an abnormal Pap smear and z-sample, and 1 woman (0.6%) was referred with an abnormal z-sample alone.

The cytology reports that the women were referred with are illustrated in Figure 3.2 below.

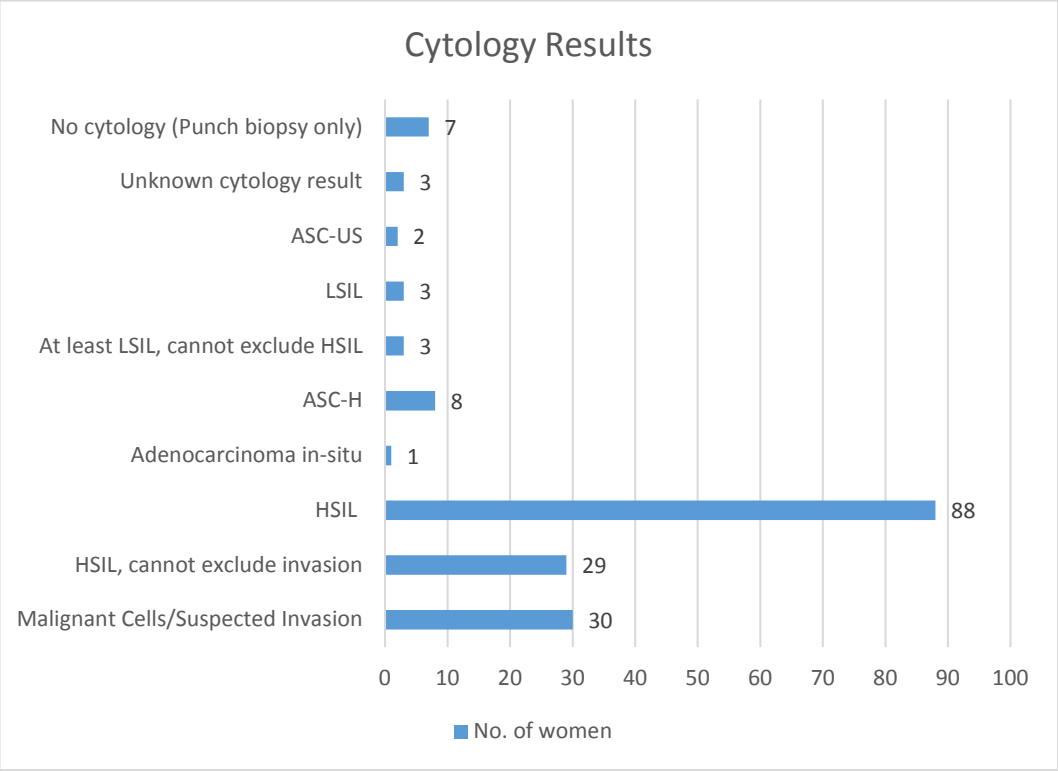


Figure 3.2. The referring cytology results in women diagnosed with cervical cancer at the CHBAH colposcopy clinic.

Of the 164 women (94.3%) with known cytology results, concurrent infections were reported in 29 women (17.7%). Bacterial vaginosis was found in 21 women (12.8%). Candidiasis was found in 3 women (1.8%), and trichomoniasis in 1 woman (0.6%). Three women had both bacterial vaginosis and trichomonas (1.8%), and 1 woman had actinomyces (0.6%).

Nineteen women were referred with punch biopsies (with or without accompanying Pap smears). The results of these punch biopsies is illustrated in figure 3.3 below.

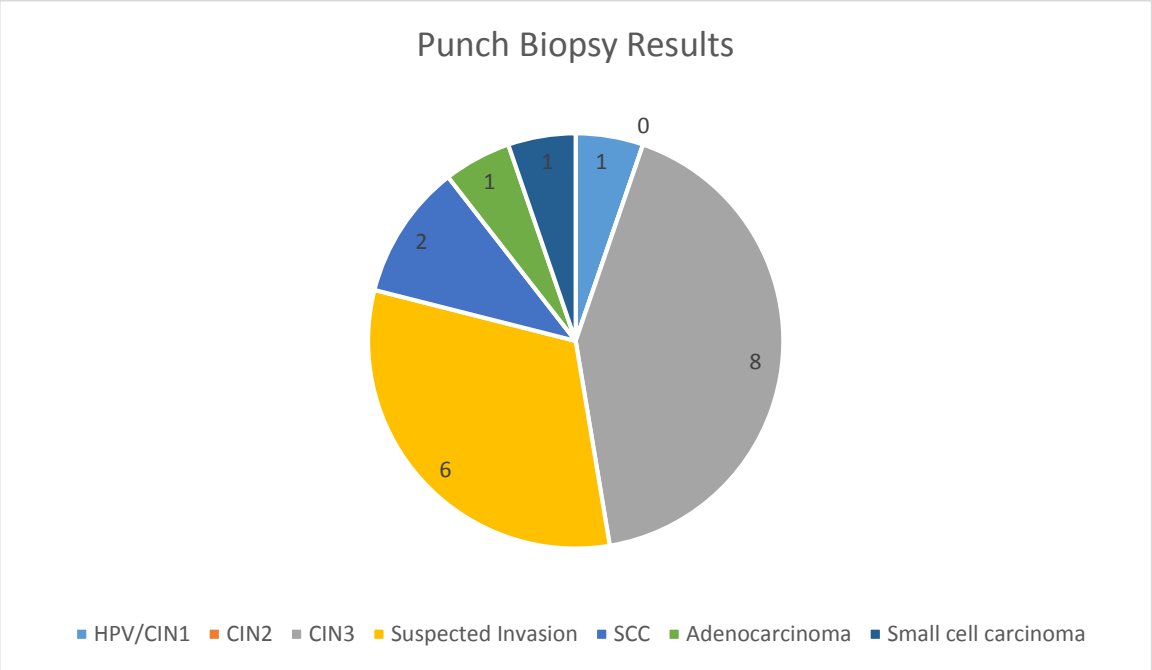


Figure 3.3. The results of referring cervical punch biopsies in women diagnosed with cervical cancer at the CHBAH colposcopy clinic

Four women already had punch biopsies confirming invasive cervical cancer before they attended the CHBAH colposcopy clinic. It is presumed that these results were not seen prior to the colposcopy clinic appointment, as all of these women had subsequent colposcopy and diagnostic procedures performed.

The adequacy of colposcopy was recorded in 147 women (84.5%). Of these, colposcopy was inadequate in 97 women (66.0%) and adequate in 50 women (34.0%).

Colposcopic impression was CIN 1 in 2 women (1.2%), CIN 2 in 21 women (12.1%) and CIN3 in 38 women (21.8%). The colposcopic impression was microinvasion in 33 women (19.0%) and frank invasion in 56 women (32.2%). Colposcopic impression was either unknown or not recorded in 24 women (13.8%).

Other colposcopic findings were found in 10 women (5.7%). Three women had both condylomata and keratosis, 3 women had condylomata alone, 3 women had erosion, and 1 woman had a cervical polyp.

Diagnostic procedures were performed on all 174 women. LLETZ was performed on 142 women (81.6%). Of the women who had a LLETZ, 11 women also had simultaneous endocervical curettage, and 3 had endometrial sampling. Punch biopsy was performed on 24 women (13.8%), 1 of whom had simultaneous endometrial sampling. Three women (1.7%) had diagnostic cone biopsies, and 5 women (2.9%) had diagnostic hysterectomies.

The histological subtypes of cervical cancer diagnosed are presented in table 3.2 below.

Table 3.2: The histological subtypes of cervical cancer diagnosed at the CHBAH colposcopy clinic.

Histological Subtype	**Frequency (n)**	**Percentage (%)**
Squamous Cell Carcinoma	148	85.0
Adenosquamous Carcinoma	9	5.2
Adenoid-Basal Carcinoma	5	2.9
Endometroid Adenocarcinoma	2	1.1
Unspecified Adenocarcinoma	5	2.9
Mucinous Adenocarcinoma	1	0.6
Small Cell Neuroendocrine	1	0.6
Unspecified Subtype	2	1.1
Other Histological sub-type*	1	0.6
Total	174	100

*One woman was classified as having “other” histological subtypes. She had synchronous squamous cell carcinoma and adenoid-basal carcinoma.

Figure 3.4 below illustrates the FIGO stages diagnosed. The FIGO stage was known in 161 women (92.5%). One hundred and fifteen women, (71.4%) presented with FIGO Stage 1 disease. Early stage disease (FIGO stage I-IIa) was found in 120 women (74.5%) and 41 women (25.5%) presented with late stage disease (FIGO stage IIb-IVb).

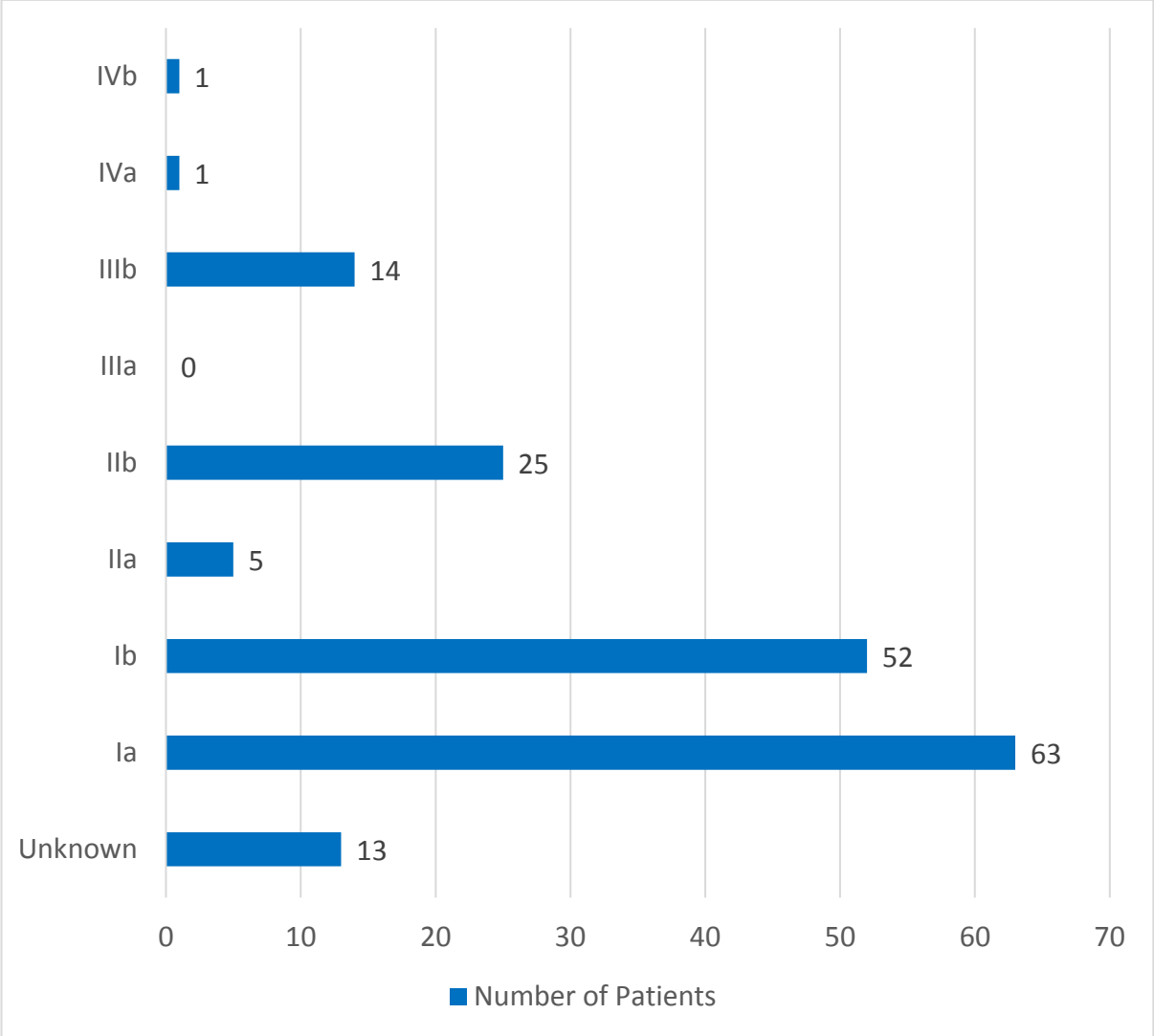


Figure 3.4: The FIGO stages of cervical cancer at presentation to the CHBAH colposcopy clinic.

Presenting complaints were known in 68 women (39.1%). Of these women, 10 (14.7%) were asymptomatic and 58 (85.3%) were symptomatic. Seventeen (25.0%) of the symptomatic women had more than one presenting complaint.

The commonest complaint was abnormal bleeding (49 women, 72.1%), followed by pelvic pain (14 women, 20.6%). Abnormal discharge was present in 9 women (13.2%). Three women (4.4%) had other symptoms, namely backache in 1 woman, weight loss in 1 woman, and a pus-draining inguinal lymph node in 1 woman.

Table 3.3 below compares women presenting with early stage disease to women presenting with late stage disease. There were no differences between the two groups in terms of demographics, risk factors, HIV status and related data, or the presence of any symptom.

The reason for referral was known in 40 of the 41 women presenting with late stage disease. Of these women, 18 (45%) were referred with histology, with or without accompanying cytology.

Cytology reports in the 41 women presenting with late stage disease showed HSIL cannot exclude invasion in 3 women (7.3%) and suspected invasion/malignant cells in 12 women (29.3%). The remaining women had HSIL (13 women, 31.7%), ASC-H (1 woman 2.4%), LSIL (2 women 4.9%), at least LSIL, cannot exclude HSIL in 3 women (7.3%) and AIS (1 woman, 2.4%). Four women (9.8%) had no cytology, but rather histology, and the cytology results are unknown in 2 women (4.9%).

Table 3.3. A comparison between women presenting with early stage disease and late stage disease at the CHBAH colposcopy clinic.

	Early Stage	Late stage	Significance Test (p value)
Median age (IQR)	45 (37-54)	46 (41-55)	0.32*
Age categories (n=161)			
<40	40 (33.3%)	8 (19.5%)	0.11#
>39	80 (66.7%)	33 (80.5%)	
Median Parity (IQR)	3 (2-4)	2 (2-4)	0.70*
Smoking (n=40)			
Non-smoker	26 (88.7%)	9 (90.0%)	1.00#
Smoker	4 (13.3%)	1 (10.0%)	
Snuff (n= 23)			
Snuff User	19 (90.5%)	1 (50%)	0.25#
Non-User	2 (9.5%)	1 (50%)	
HIV Status (n=138)			
HIV Negative	32 (32.7%)	16 (40.0 %)	0.42@
HIV Positive	66 (67.3%)	24 (60.0%)	
Median CD4 count (IQR)	355 (172-498)	286 (191-580)	0.99*
CD4 Count categories (n=78)			
CD4 <200	18 (32.7%)	7 (30.4%)	1.00#
CD4 >199	37 (67.3%)	16 (69.6%)	
Antiretroviral therapy (n=75)			
On ART	32 (58.2%)	10 (50.0%)	0.53@
Not on ART	23 (41.5%)	10 (50.0%)	
Hormonal contraception (n=148)			
No	91 (81.3%)	31 (86.1%)	0.51@
Yes	21 (18.7%)	5 (13.9%)	
Menopause (n=161)			
No	77 (64.2%)	26 (63.4%)	0.93@
Yes	43 (35.8%)	15 (36.6%)	
Condom Use (n=147)			
No	89 (76.7%)	23 (74.2%)	0.09@
Yes	27 (23.3%)	8 (25.8%)	
Symptoms (n=67)			
No	6 (19.4%)	4 (11.4%)	0.50#
Yes	25 (80.6%)	31 (88.6%)	

*Kruskall Wallis, #Fishers Exact, @chi²

Nine women in the study (5.2%) had treatment failure. They were initially treated with LLETZ for cervical dysplasia, but presented at a later stage with invasive cervical cancer. All of the women had initial LLETZ results showing CIN3 and positive margins, and there was crypt involvement in 7 of the women (77.8%). Their information is illustrated in table 3.4 below.

Table 3.4. A description of women diagnosed with cervical cancer after previous treatment for CIN.

Patient No.	1	2	3	4	5	6	7	8	9
Age	55	46	35	41	41	41	29	35	40
Parity	2	2	3	2	2	2	1	2	3
Menopause	yes	no	no	no	no	no	no	no	no
Hormonal Contraception	n/a*	no	no	no	no	no	no	no	yes
HIV Status	neg	pos	pos	pos	pos	pos	pos	pos	pos
CD4 count (cells/mm^3)	n/a	233	161	108	39	229	255	506	593
ART	n/a	yes	yes	yes	yes	yes	no	yes	no
Positive margins	both	Endo$^{\$}$	both	both	Ecto$^{\&}$	Endo$^{\$}$	Endo$^{\$}$	both	both
Crypt Involvement	yes	no	yes	yes	no	yes	yes	yes	yes
Time from LLETZ to cancer diagnosis (months)	47	43	12	41	7	12	14	8	12
Post LLETZ cytology	No result	$^{\times}$MC	HSIL, $^{@}$SI	MC	HSIL	HSIL	HSIL	HSIL	HSIL
FIGO Stage	Ib1	IIb	Ib1	IIb	Ib1	IIb	Ia1	Ib1	Ia1

* Not applicable, $^{\#}$ unknown, $^{\times}$ malignant cells, $^{@}$suspected invasion, $^{\$}$endocervical, $^{\&}$ectocervical

Five women (2.9%) in this study were initially assessed as having FIGO stages amenable to surgery, only to have the surgery abandoned intra-op. One woman was originally staged as 1A, and the others as 1B. Only one LLETZ report discusses lymphovascular space and peri-neural invasion, of which there was no evidence of it being present. Data on time interval between LLETZ and surgery was not routinely collected. It was incidentally collected in the two women for whom histology (of suspicious lymph nodes) was submitted. The time interval between LLETZ and surgery in these two women was 37 days and 43 days respectively. The data of these women is presented in table 3.5 below.

All of the 5 women in whom surgery was abandoned subsequently had primary radiation therapy with or without chemotherapy. There were no documented recurrences at the completion of data collection.

In another 5 women (2.9%), more advanced disease was discovered intra-operatively, but the surgery was completed. Two women (40%) had adjuvant radiation therapy. Two women (40%) did not have adjuvant radiation therapy (one of these women defaulted planned adjuvant therapy). In the last woman (20%), we have no information as to whether adjuvant therapy was planned/received or not. Three of these women in whom surgery was completed (60%) had recurrences of cancer.

Table 3.5. A description of women who were found to have more advanced disease at the time of surgery for cervical cancer and surgery was abandoned.

	1	2	3	4	5
Age	55	43	43	64	41
Parity	6	1	2	2	2
Menopause	yes	no	no	yes	no
Hormonal Contraception	n/a*	no	uk#	n/a	no
Smoking	yes	no	uk#	uk#	no
HIV Status	neg	pos	pos	neg	pos
CD4	n/a	96	169	n/a	1004
ART	n/a	no	no	n/a	yes
Time from LLETZ to surgery (days)	uk#	uk#	37	uk#	43
Intra-op Findings	Parametrial involvement	Parametrial involvement	Lymph node involvement	Parametrial involvement	Lymph node involvement
Histology	no	no	Reactive lymph node	no	Squamous cell carcinoma in lymph node
Initial FIGO Stage	Ib1	Ia2	Ib	Ib1	Ib1

*not applicable, #unknown

Chapter 4: Discussion

In this chapter, I will start off by summarising the main and secondary findings of the study. I will then proceed to discuss each finding within the context of the literature.

4.1 Summary of Findings

The main findings of this study were that: 74.5% of women presented with early stage disease (FIGO I-IIa). There were no differences found between women presenting with early stage disease and late stage disease. Squamous cell carcinoma was the most frequent histological subtype of cervical cancer diagnosed, occurring in 85.1% of women. The majority of women (52.7%) were referred with cytology showing HSIL, which does not trigger an urgent referral for colposcopy at the CHBAH colposcopy clinic. Only 35.3% of women were referred with cytology results that would have warranted urgent referral for colposcopy in our setting.

The secondary findings of this study were that: the prevalence of HIV infection in this study was 54.0%. The accuracy of colposcopic diagnosis was 59.3%. Cervical cancer was diagnosed after previous treatment for CIN in 5.2% of women. In this study, 5.7% of women were initially deemed as having early-stage disease amenable to surgery, but more advanced disease was found intra-operatively and the surgery was abandoned in half of these women.

4.2 Early Stage Disease (FIGO Stage Ia –IIa)

Early stage disease was diagnosed in 74.5% of the women in this study. The majority (71.4%) actually had FIGO stage 1 disease.

In contrast, a previous study conducted at the CHBAH, on all women diagnosed with cervical cancer in 2013, found that only 12.5% of women presented with early stage disease.[64] The proportion of women with a Pap smear in the study was 52.9%.[64] In that study, they did not state the indication for the Pap smears

(i.e. diagnostic vs. screening), when the Pap smears had been performed, or whether these women had attended colposcopy for their abnormality.

Studies in Nigeria, Cape Town and Tanzania had 5/267 (1.1%), 100/912 (11%) and 28/150 (18.7%) of women presenting with early stage disease.[62-63, 65] The percentage of women who had cervical screening prior to diagnosis in the Cape Town and Nigerian studies were 37.8% and 0.0% respectively.[63, 62] In the Tanzanian study, this information is not provided.[65] The Cape Town study was conducted in HIV positive women.[63]

A study on data acquired via the National Breast and Cervical Cancer Early Detection Programme (NBCCEDP) in the USA found that 583 cases of cervical cancer were diagnosed via the programme from 2009-2011.[6] Thirty six percent of women had local disease, and 53% had regional or distant disease.[6] The stage was unknown in the remaining 11%.[6]

The NBCCEDP is targeted at women with a low-income, and without health insurance for breast and cervical cancer screening.[6] The percentage of women with cervical cancer presenting with local disease (early-stage disease) was well below the national statistics for women with cervical cancer presenting with local disease.[6] Sixty four per cent of women were referred purely for screening. The remainder were enrolled for diagnostic purposes i.e. clinical suspicion or symptoms.[6]

The picture with highly-screened populations differs dramatically. In a population-based study from England that included 11 619 women with cervical cancer diagnosed from 2008-2012, 72.6% of women presented with FIGO stage 1 disease.[4] Similarly, an audit of 6508 cervical cancer cases diagnosed in the UK from 2009-2012 found that 81% of women between ages 25-49 years old were diagnosed with FIGO stage 1 disease.[73] The 5-year screening coverage in England has been around 80% since 1993. [34, 73]

We speculate that the high proportion of women diagnosed with early-stage disease in our study, compared to studies where screening was poor,[5, 62-65] and

its similarity to the UK studies,[4, 73] is due to the fact that this study was conducted in a "screened" population. In our study, 152 women (87.9%) were referred to the colposcopy clinic for abnormal cytology alone. Unfortunately, we were unable to collect any direct data as to the reasons for these Pap smears being performed.

It must be re-iterated however, that in South Africa, we do not have a "call and recall" screening system.[33] Our screening services are reliant on public awareness and opportunistic screening.[9, 33] Opportunistic screening, by nature, implies that many women will get a Pap smear when presenting to the local clinic with an unrelated complaint. Also, other women will have smears performed due to the presence of gynaecological symptoms, which may or may not be related to cervical cancer.[49] We were only able to collect data on gynaecological symptoms in 39.1% of the women in our study. Of these women, 85.3% were symptomatic.

The NBCCEDP study from the USA[6] may help to mitigate this worry somewhat. Thirty six per cent of women in that study had cytology performed for diagnostic purposes (i.e. the presence of symptoms) as opposed to screening purposes. Only 36% presented with local disease,[6] compared with the >70% of women in our study.

4.3. Late Stage Disease (FIGO IIb-IVb)

Cervical screening, particularly when done regularly, reduces the FIGO stage at which cervical cancer presents.[4, 6, 7] In England, where there is high coverage of the national cervical screening programme, 19-27% of women still present with late stage disease.[4, 73] In our study, late-stage disease was diagnosed in 25.5% of women, which is congruent with the findings in England.

Poor uptake of screening services amongst certain populations may partially explain why some women presented with late-stage disease in England. We know that high coverage of screening services is one of the most important

factors in a successful programme,[3, 5] and that regular screening reduces the stage at which cervical cancer presents.[4, 6, 7]

Whilst average coverage of cervical screening in England was 78% from 2007-2012, there were variations across different local areas,[74] with coverage as low as 65-67% in some areas.[74] Areas in which the women had poor socioeconomic circumstances were associated with poor uptake of cervical screening.[74]

A 2012 population-based report from England demonstrated significantly higher incidence and mortality rates of cervical cancer, and lower 1 year survival in women from the most deprived communities compared to women in the most affluent communities.[75] Although they did not directly investigate the causes, they attributed their findings to "factors associated with deprivation", which they listed as poor uptake of screening, presentation with more advanced disease, and also smoking, earlier coitarche, HIV-infection, and being an immigrant worker.[75]

Although our finding that 25.5% of women in our study presented with late-stage disease is congruent with the English data, it is still a cause for concern, given our study setting in a colposcopy clinic. If our local referral criteria are strictly adhered to, such cases should not be found at the CHBAH colposcopy clinic, but referred urgently to the Gynaecology emergency out-patient department for clinical examination and punch biopsy, as the disease would be macroscopically-obvious. Appendix 1

Of the women who presented with late-stage disease in this study, 22 women (55%) were referred with cytology alone (as opposed to histology from a punch biopsy). Unfortunately, we were unable to collect data on the appearance of the cervix at the time of smear, given that these procedures were performed prior to arrival at the colposcopy clinic. It may be possible that these women had advanced disease at the time of cytology, and that the diagnosis was missed.

It may also be possible that the disease was not macroscopically visible at the time of cervical smear, and progressed during the waiting period. We did not

collect data on time from cervical smear to colposcopy in this study, but we do have data on waiting intervals from two previous studies conducted at the CHBAH colposcopy clinic. Saayman found a mean waiting interval of 199.29 days, with a range of 1-1702 days.[71] Of the women in his study, 53.58% arrived within 180 days, whilst 46.42% were seen after 180 days.[71] Manamela found that the median interval from cytology to colposcopy was 210 days (IQR 132-313 days) in HIV positive women referred with LSIL.[72]

It is not possible to predict the progression of cancer in an individual. There is a case report of a woman who refused all recommended medical intervention, and chose alternative medicine instead. She was diagnosed with dysplasia at 29 years old, progressed to FIGO stage 1b2 in 10 years, then died from FIGO stage 4b cancer 3 years later.[76]

4.4. Early Stage vs. Late Stage Disease

In this study we found no statistically significant difference in women presenting with early-stage disease vs. late-stage disease with regards to age, menopausal status, parity, use of hormonal contraceptives, condom use, smoking habits, snuff use, HIV status, CD4 count, and use of ART or presence of symptoms. We looked at these factors because they are either generally known to be risk factors for the development of cervical cancer, or have been highlighted as risk factors for advanced stage disease at presentation in previous studies.

A UK population-based audit stated that high parity, HIV infection, oral contraceptive use, and smoking were risk factors for the development of cervical cancer.[73] Similarly, a South African population-based study found that HIV infection, current smoking, snuff use, prolonged use of hormonal contraceptives and a parity >6 were risk factors for the development of cervical cancer.[77]

A study on population risk factors for late presentation of cervical cancer in sub-Saharan Africa found HIV infection, no condom use, high parity and no formal

education to be statistically significant risk factors for late presentation.[78] A Ugandan study found secondary and tertiary education to be protective against presenting with advanced stage cervical cancer, whist parity of 5-9 and pre-referral cancer diagnosis were risk factors for advanced presentation.[79] The same study also found a trend towards more advanced disease being diagnosed with increasing age.[79]

Our study was set in a colposcopy clinic, and the study setting and size may explain why we failed to show a difference between women presenting with early stage disease vs. late stage disease.

Additionally, because of the retrospective study design and reliance on the CHBAH electronic database and history documented in patient files, the data we were able to collect on certain traditional risk factors, was limited.

With regards to contraceptive use, we looked at current use and not lifetime use, which may partially explain why we failed to show a difference. We looked at current use because this is was the only data available. The current contraceptive use in the study overall was low. Almost half of women in this study were on no contraception at all. Only 17.5% of women were on hormonal contraception and only 17.8% of women made use of condoms. Women who were not sexually active, or were post-menopausal would have likely not been using contraception, and also contributed to the low uptake of contraception in this study.

The rate of HIV infection in our study was very high, with 54.0% of women being HIV-infected. The government cervical screening policies in effect during the course of our study were the NCCPP[9] (for all women) and the HCT[9] (for HIV infected women) programmes. Whilst the NCCPP still relies on opportunistic screening and patient awareness, the HCT programme actively included cervical screening as part of the package of care, and also prescribed shorter screening intervals for HIV positive women. This bias towards aggressive and active cervical screening of HIV positive women, as opposed to opportunistic screening for HIV

negative women, could have masked the difference between women presenting with early-stage vs. late-stage disease.

4.5 Histology Results

Squamous cell carcinoma (SCC) was the most common histological subtype of cervical cancer diagnosed in this study (85.1%), followed by adenosquamous carcinoma (5.2%) and adenocarcinoma (AC) (4.6%).

Other studies conducted in countries with poorly-established screening programmes have made similar findings, with SCC more than 85%, AC less than 10%, and adenosquamous carcinoma less than 5%.[62-65, 80]

Where cervical screening programmes are well-established, and have high coverage, the relative proportion of SCC vs. AC shifts. Studies from the UK and the USA found that SCC accounted for roughly 70%, and AC accounted for 20-25% of cases.[73, 81]

The high prevalence of SCC and relatively low prevalence of AC in this study compared to the UK audit[73] and USA study,[81] and its similarity to the African and Polish studies[62-65, 80] are in keeping with the fact that the study was conducted in a country where the cervical screening programme is “poorly-established”.

Whilst SCC remains the most common histological subtype of cervical cancer worldwide,[82-83] it has been found that in countries with well-established cytology-based screening programmes, the relative proportion of AC diagnosed, compared to SCC, increases over time. This fact is illustrated in studies from Sweden, the USA and Denmark, and Sweden[6, 84-85] and documented in studies regarding worldwide data.[86]

Conversely, data from a population-based study in South Africa, where screening is poorly established, found the ASIR of SCC to have increased by 1.4% annually

from 2000 to 2009 (ASIR 17.0-19.0/100 000).[77] The ASIR of AC during the same time period remained stable and low (ASIR 2.0-2.6/100 000).[77]

Some studies have attributed the increase in AC to be an age-cohort effect. They argue that there was an increase in sexual freedom in the 60's, leading to increased HPV infection in younger age cohorts.[6, 86]

In our view, the explanation of increased sexual freedom does not adequately explain why only AC is increasing, whist SCC is decreasing, because both of these subtypes are caused by sexually-transmitted HPV.

Another widely agreed upon explanation for this phenomenon is that the relative increase in the diagnosis of AC over time is because cervical cytology is more effective at diagnosing precursors of SCC than precursors of AC.[87] This leads to a fall in the prevalence of SCC, and a relative increase in the prevalence of AC, where screening programmes are well-established.

The biological basis for this theory is the fact that cytology is obtained from exfoliated cervical cells. SCC arises from the ectocervix, which is easily accessible by spatulas,[86-87] and exfoliates more easily. AC arises from the endocervix, which is less accessible by the same tools and exfoliates less easily.[86-87]

Whatever the explanation, it is agreed that well-developed cytology-based screening programmes reduce the incidence of squamous cell carcinoma to a greater extent than adenocarcinoma, leading to a higher proportion of adenocarcinoma being diagnosed over time.[84-85, 87-88]

4.6 Cytology Results

The most frequent cytology result was HSIL (88 women, 52.7%), followed by suspected invasion/ malignant cells (30 women, 18.0%) and "at least HSIL, cannot exclude invasion" (29 women, 17.3%).

Table 4.1 below compares the cytology results of women in this study to the cytology results of other women diagnosed with cervical cancer in studies from Mexico,[58] China[89] and the USA.[81]

Table 4.1: Cytology results of women diagnosed with cervical cancer at the CHBAH colposcopy clinic, Mexico, China and the USA.

Cytology Results	CHBAH Colposcopy Clinic, South Africa n (%)	Mexico n (%)	China (cytology alone arm) n (%)	USA n (%)
NILM	0	0	21 (12.4%)	0
ASC-US	2 (1.2%)	4 (5.4%)	13 (7.6%)	*(2%)
ASC-H	8 (4.8%)	0	27 (15.9%)	*(4%)
LSIL	3 (1.8%)	9 (12.2%)	1 (0.6%)	*(3%)
At least LSIL, cannot exclude HSIL	3 (1.8%)	0	0	0
HSIL	88 (52.3%)	15 (20.3%)	66 (38.9%)	87 (21.1%)
At least HSIL, cannot exclude invasion	29 (17.4%)	0	0	0
Malignant cells/suspected invasion	30 (18.0%)	46 (62.2%)	30 (17.6%)	0
AGS	0	0	8 (4.7%)	46 (11%)
AIS	1 (0.6%)	0	0	0
Total	167	74	170	419

*n not provided

A comparison of the cytology results shows that HSIL and malignant cells appear to be the most common referring cytology results where the majority of cytology results are known. That being said, there is a wide variation of cytology results in women with cervical cancer, as illustrated in table 4.1 above. This variation cannot be fully explained. It may be due to differences in national cervical screening protocols, indications for cervical cytology being performed (i.e. symptomatic vs. asymptomatic women) or even differences in internal and external quality control mechanisms at the cytopathology laboratories. Unfortunately, there is simply not enough information to explain this variation.

Additionally, the Mexican study found that concordance between cytology and histology results was poor (65%) in women with cervical cancer.[58]

The Chinese study found that the sensitivity of cytology alone (any abnormality) was 85.3% in women with cervical cancer.[89] Given that the vast majority of

women with any cytological abnormality will not have invasive cancer,[90] this finding perhaps has limited clinical utility.

Landy found that the positive predictive value (PPV) of cytology to detect cervical cancer was 5.4% when using a cut-off of "severe dyskaryosis" (HSIL: CIN3) or worse.[90] Specifically, the PPV was 33.50% for "invasive squamous cell carcinoma", and 12.40% for "AGC-favours neoplasia", "AIS", and "adenocarcinoma"combined.[90] These loosely correlate to our cytological diagnoses of "suspected invasion/malignant cells", "AIS" and possibly "at least HSIL, cannot exclude invasion". The positive predictive values for HSIL alone were less impressive, at 3.62% for "severe dyskaryosis" (HSIL: CIN3), and only 0.66% for "moderate dyskaryosis" (HSIL: CIN2).[90]

Rather than discussing the relative frequencies of the different cytology results in women with cervical cancer, perhaps a more pertinent issue is the proportion of results that would trigger an urgent referral to colposcopy. This is particularly important in our study setting, where median cytology to colposcopy intervals in previous studies have been found to be 199 days[71] and 210 days.[72]

According to CHBAH referral criteria [Appendix 1], cytology results of "malignant cells", "suspected invasion" or "at least HSIL, cannot exclude invasion" would trigger an urgent referral to the colposcopy clinic in the absence of a visible lesion that should rather be biopsied immediately. Co-incidentally, these are the same cytology results found to have a high positive predictive value for cervical cancer in the Landy study.[90] In the UK, such cytology results would trigger a colposcopy appointment within 2 weeks.[90]

Disappointingly, only 59 women (35.3%) in our study had cytology results that would trigger an urgent referral to colposcopy, compared to 78% of women with cervical cancer in the Landy study.[90] Whilst we cannot fully explain the difference, it must be borne in mind that the Landy study was much larger (3 372 women were diagnosed with cervical cancer), and was conducted in a country

with a well-established screening programme with a high uptake of screening services i.e. the study population was much different.

In another study, Landy et al demonstrated that co-factors such as age and screening history increase the PPV of cytology results in the detection cervical cancer.[91] They found that the PPV of cytology using a cut-off of moderate dyskaryosis (HSIL: CIN2) or worse was 21.3% in women aged 40-69 who had no previous cervical screening prior to the referring cytology, and 18.1% in women > 70 years old, regardless of screening history.[91] These PPVs for HSIL are much higher than those demonstrated in the previous Landy study.[90]

In our study, the median age was 45 years (IQR 38-55). The majority of women with cervical cancer (88 women, 52.7%) were referred with HSIL (i.e. moderate dyskaryosis/CIN2 and severe dyskaryosis/CIN3). Altogether, 148 women (85.0%) had a cytology report showing HSIL or worse.

Theoretically, adjusting our threshold for urgent referral to colposcopy according to cytology of HSIL and worse, and age >40 years may have increased the number of women with cervical cancer who were referred for urgent colposcopy.

The effect of such a change in urgent referrals on the workload and waiting intervals at the CHBAH colposcopy clinic remains unknown though. Whilst we may detect cervical cancer more quickly, it must be remembered that the majority of women with HSIL will not have cervical cancer.[71, 90-91] The study by Saayman at the CHBAH colposcopy clinic included 2960 women referred to the colposcopy clinic.[71] Sixty five per cent of these women had HSIL, but only 1.2% of women in the entire study actually had cervical cancer.[71] Additionally, Saayman found that a prolonged waiting interval for colposcopy (>180 days), did not upstage the cervical lesion.[71]

4.7 HIV Data

The prevalence of HIV infection amongst women in our study was 54.0%. This is much higher than the 23.7% prevalence of HIV infection in South African women aged 15-49 in 2016,[19] and the 30.8% prevalence of HIV infection in women seeking antenatal care in South Africa in 2015.[92]

Cervical cancer is an AIDS-defining condition[28] and HIV-infection is a risk factor for the development of cervical cancer.[22] As such, a high prevalence of HIV infection may be anticipated in this study.

Whilst incongruent with data from national statistics, our findings do correlate with the findings of other studies performed at the CHBAH colposcopy clinic. Manamela[72] and Saayman[71] found the prevalence of HIV infection at the CHBAH colposcopy clinic to be 63% and 69% respectively.

Their findings are logical because HIV positive women have a higher risk of HPV infection and cytological abnormalities than HIV negative women,[22-23] and thus have indications for colposcopy more frequently. Also, the referral criteria to the CHBAH colposcopy clinic are less stringent for HIV positive women compared to HIV negative women. Appendix 1

Because of all these reasons, it makes sense that there is a high prevalence of HIV infection in women referred to the CHBAH colposcopy clinic, and in women diagnosed with cervical cancer at this site.

4.8 Colposcopy Findings and Diagnostic Procedures

Colposcopy was inadequate in 66.0% of women. These findings are in keeping with the study by Hopman et al, where the rate of inadequate colposcopy was found to be 61% in women with microinvasive disease, and 71% in women with invasive disease.[54]

The accuracy of colposcopic impression in this study was 59.3%, with 89 of the 150 women with a known colposcopic impression being diagnosed with either

microinvasive or invasive cancer based on colposcopic findings. In the Mexican study, the concordance between colposcopy and biopsy in women diagnosed with cervical cancer was 57%,[58] which is in keeping with our findings.

LLETZ was performed 81.6% of women in this study and a punch biopsy was performed in 13.8%. The high proportion of LLETZ is in keeping with the fact that this study was conducted in a "see-and-treat" clinic, where LLETZ is performed if the colposcopic impression is CIN2 or worse. CIN2 or worse was the colposcopic impression in 85.1% of women in this study.

4.9 Treatment Failures

Nine women in this study (5.2%) presented with cervical cancer after previous treatment for cervical dysplasia. Soutter et al estimated that 16% of the 2400 women diagnosed with invasive cervical cancer in England annually were previously treated for CIN.[43]

It is known that women previously treated for CIN remain at an increased risk of developing cervical cancer for compared to the general population.[43-45] Soutter et al found the risk to be 2.8 times higher,[43] whilst Melnikow et al found the risk to be 6 times higher.[44]

The risk of developing invasive cancer remains increased for many years after initial treatment.[43-45] Melnikow[44], Souter[43] and Strander[45] found that women previously treated for CIN remained at increased risk of developing invasive cancer for 6, 10-20, and 25 years respectively. In our study, the time from initial LLETZ for CIN to cancer diagnosis ranged from 7 to 47 months.

A more recently published study by Lili et al contradicted these findings however.[93] They found no cases of invasive cancer developing in a cohort of women treated for high grade CIN after 22 years of follow-up.[93]

The difference between the studies by Souter[43], Strander[45] and Melnikow[44] vs. Lili[93] may be explained by the fact that Lili et al used excisional techniques for treatment of initial CIN, whereas both ablative and excisional techniques were used in the other studies. The use of ablative techniques for the treatment of CIN is not associated with a higher risk of treatment failure,[42] but occult invasive disease is more likely to go undiagnosed where no excisional technique is used.[42] Also, there was strict adherence to annual follow-up in the Lili study,[93] whereas Soutter et al highlighted a lack of adherence to follow-up as one of the possible causes for their findings.[43]

Of the 9 women in our study who developed cervical cancer after previous LLETZ for CIN, 6 women (66.7%) were 40 years or older. All of the women (100%) had initial LLETZ results showing CIN3, and all of the women (100%) had positive margins.

Increased age at initial treatment is a risk factor for the subsequent development of invasive cancer after previous treatment for CIN.[44, 94] Strander et al found that the relative risk of developing invasive cervical or vault cancer after treatment for CIN 3 increased after 40 years old, and increased dramatically after 60 years old.[94]

The grade of CIN is also an important risk factor.[43-44] Soutter et al found that cohorts containing a higher proportion of women initially treated for CIN 3 had higher rates of invasive recurrence.[43] Melnikow et al found that the adjusted OR of developing cancer was 4.1 (95% CI 2.70-6.22) in women initially treated for CIN 3 vs. women treated for CIN 1 or 2.[44]

Positive margins after treatment using excisional techniques is also a risk factor for the development of cervical cancer. Reich et al published 2 studies looking at long-term outcomes after cold-knife conisation for CIN3.[95-96] In the first study, they looked at the outcomes of 4 417 women with clear margins. No cases of cervical cancer were subsequently detected after 30 years of follow-up.[95] In the second study, they looked at the outcomes of 390 women with positive margins.

They detected 5 women (1.3%) with microinvasive disease and 1 women (0.3%) with stage 1b cervical cancer during follow-up.[96]

The review by Soutter et al noted that whilst the rate of invasive recurrence in women previously treated for CIN remained elevated and stable over many years, the rate of subsequent CIN detected in these same women dropped over time.[43] They attributed this discrepancy to a reduction in compliance to follow-up over time.[43]

Our current SA HPV Advisory Board guidelines recommend follow-up screening annually after treatment for CIN until a normal follow-up test result is obtained.[33] Thereafter, the women return to routine screening forever.[33] Routine screening (according to Botha et al), with cytology would be 1-5 yearly, depending on age, HIV status and the available resources.[33] According to the NCCP, routine screening would be 10-yearly.[9]

Soutter et al recommend annual screening for 10 years in order to detect recurrences at a "treatable stage".[43] In the study by Lili et al, where there were no cases of invasive cancer were detected after initial treatment, the women had annual screening until the end of the follow-up period (after a 1 year period of more intense follow-up post-procedure).[93]

Whilst the proportion of women diagnosed with cervical cancer after previous LLETZ is small in our study (5.2%), the disease was potentially more preventable in these women than the other women in our study. They were known to be at a high risk of developing cervical cancer because of their previous diagnosis of CIN 3, the presence of positive margins on histology, and the fact that the majority of the women were older than 40 years.

Our findings highlight the importance of adequate training to ensure clear margins are achieved at LLETZ, particularly where high-grade disease is suspected. Achieving clear margins in these women is particularly important where the women are older, their families are complete and there are no longer concerns about future obstetric outcomes related to tissue loss. It is also

important to ensure strict adherence to follow-up protocols. Lastly, there may be a benefit in adjusting our follow-up protocols to ensure that all women treated for high-grade CIN have annual follow-up for life.

4.10 Advanced Disease Discovered Intra-operatively in Women Clinically- Staged with Early Disease

In this study, we identified 10 women (5.7%) who were initially deemed to have early-stage disease amenable to surgery, but who were found to have more advanced disease intraoperatively. In 5 women, the surgery was abandoned. Unexpectedly finding advanced disease at the time of surgery presents a clinical dilemma, in terms of how to proceed with management. This occurs in less than 10% of cases.[97-98]

In a study by Gray et al, surgery was abandoned because of positive pelvic lymph nodes in 84%, positive para-aortic nodes in 16% and/or peritoneal spread in 16%.[97] There was overlap in terms of the indications for abandoning surgery in some patients.[97] This differs from our findings, where only 40% of surgeries were abandoned due to suspected lymph node involvement, and 60% due to suspected parametrial involvement. The difference is likely because our numbers were very small, with surgery only being abandoned in 5 women.

Ideally, one would hope to identify early-stage women at risk of being diagnosed with advanced disease intra-operatively during the pre-operative assessment. Unfortunately, the study by Gray et al found that there were no pre-operative clinical characteristics that could clearly identify women with early stage disease who were at risk of abandoned surgery.[97]

The management options intra-operatively include proceeding with surgery or abandoning the surgery. In either event, the woman will require concurrent chemoradiation, either adjuvantly or as primary therapy. The women in whom surgery was completed will likely require adjuvant therapy due to pathological

risk factors for recurrence, such as lymph node involvement, parametrial involvement or positive margins.[70]

Gray et al[97] and Derks et al [99] compared morbidity in the abandoned surgery group vs. the completed surgery group. Both arms in both studies underwent (chemo) radiation therapy after surgery. Gray et al found that the rate of major morbidity was 26% in the abandoned surgery group and 34% in the completed surgery group, but the difference was not statistically significant.[97] Derks et al found that chemotherapy-related toxicity was significantly higher in abandoned surgery group vs. completed surgery group (59% vs. 30%).[99] It must be noted however, that only 78% of women in the completed surgery group had concurrent chemoradiation whereas 100% of the women in the abandoned surgery group had concurrent chemoradiation.[99]

Lapuz et al[100] looked at women with stage IB cancer and positive lymph nodes, who either had surgery followed by radiation therapy, or primary radiation therapy. They did not look at abandoned surgery vs. completed surgery per se, but the study is still relevant because 40% of the abandoned surgeries in our study were abandoned due to suspected lymph node involvement.

Lapuz et al found that 32.0% of women in their cohort had relapse, but 97.0% of the recurrences occurred outside of the pelvis.[100] They therefore concluded that there were excellent pelvic control rates regardless of treatment modality,[100] and that a more aggressive approach (i.e. surgery plus adjuvant radiation therapy) was not helpful in preventing recurrence, given that surgery and radiation were both targeted towards pelvic control.[100]

There seems to be no conclusion as to whether or not there is a difference in recurrence rate in women who had surgery abandoned vs. those who had surgery completed in the studies that we looked at. Gray et al found the recurrence rate to be 37% vs. 18%, but the difference was not statistically significant.[97] In contrast, Derks et al found that the pelvic recurrence rate was

significantly lower in completed surgery group vs. abandoned surgery group (2% vs. 16%).[99]

In our study, none of the women in the abandoned surgery group had recurrence at completion of data collection, whilst 60% of the women in the completed surgery group did. All of the women in the abandoned surgery group had "adjuvant" therapy, compared to only 40% of the women in the completed surgery group. Because of the small numbers (5 women in each group), no conclusions can be drawn from our findings.

In the literature, overall survival in women who have surgery abandoned and vs. those who have surgery completed seems to be similar, with no statistically significant difference between the two groups (provided that they undergo post-op radiation therapy).[97-99]

There seems to be no conclusion in the literature as to the correct course of action to undertake in women who are diagnosed with advanced disease during planned surgery for clinically-staged early disease.

Chapter 5: Strengths and Limitations

This study was the first to evaluate women diagnosed with cervical cancer at the CHBAH colposcopy clinic, which represents a “screened” population. It provides valuable information to our institution in terms of describing these women, confirming the successes of our screening programme, and highlighting areas where more training is required.

The study also adds to the body of knowledge with regards to describing women diagnosed with cervical cancer through an organised screening programme in a developing country. There is a paucity of such data in the literature.

Although the study was retrospective in nature, the study made use of electronic databases and hospital files. The information was documented at the time that the women presented.

The use of multiple sources of data helped to achieve a dataset that was as complete and accurate as possible. Also, a hierarchical system of data capture was used, in order to ensure that the best possible quality of data was captured. For example, data involving laboratory results (such as HIV status, CD4 count, cytology and histopathology results) were obtained directly from the National Health Laboratory Services (NHLS) electronic database where possible, and used preferentially.

Also, the data available is reliable, because it was all collected and captured by the researcher herself, and verified by the supervisor.

The limitations of this study were mainly due to the fact that the study was retrospective in nature, and thus relied on information that had already been documented. In order to mitigate this limitation, we made use of multiple records, including electronic databases and patient files from 2 different hospitals.

Data regarding symptoms and screening history prior to the incident Pap smear was not collected on the database. History regarding symptoms was found in hospital files only.

Because Pap smears were most often conducted at the local clinic, we had no information on the appearance of the cervix at the time of Pap smear. Additionally, we did not collect information on cytology-to-colposcopy interval.

Also, no formal sample size calculations were made, because the study was descriptive in nature, and not designed to analyse differences between groups.

Chapter 6: Conclusions

The very high proportion of squamous cell carcinoma, and relatively low proportion of adenocarcinoma diagnosed in this study is reflective of the fact that the study was conducted in a country with a poorly-established cervical screening programme.

Whilst the cervical screening programme in South Africa has not reduced the national incidence or mortality of cervical cancer, the programme is still of benefit to the individual women participating in the programme. We have shown that the majority of women diagnosed in our colposcopy clinic presented with early-stage disease. This is in contrast to other studies at our own institution, and in other settings with poorly-established screening programmes, where the majority of women present with advanced disease. Earlier diagnosis is associated with an improved prognosis.

Whilst the majority of women diagnosed with cervical cancer through our screening programme present with early stage disease, a quarter presented with advanced disease. In roughly half of these women, it is possible that the diagnosis of cancer was missed on initial presentation, or that the disease up-staged during the long waiting time for a colposcopy appointment. Whilst little can be done to minimize waiting intervals, better training (out-reach programmes) may help to reduce missed diagnoses and subsequent late referrals at a primary healthcare level.

Chapter 7: Recommendations

A training programme is required at primary healthcare facilities and also amongst doctors at the CHBAH gynaecology department. This programme would focus on the recognition of the macroscopic appearance of cervical cancer (both early-stage and late-stage disease), and emphasize the correct referral pathways and clinical procedures to be conducted where there is clinical suspicion of cancer.

The indications for urgent referral to the CHBAH colposcopy clinic should possibly be re-visited. We currently regard clinical suspicion of cancer (where histology shows CIN only), and cytology reports showing suspected invasion or malignant cells as the only indications for urgent referrals. We should consider adding age above 40, a lack of previous cervical cytology before the incident report, and the presence of symptoms as further indications for urgent colposcopy. This is because they have been shown to increase the PPV of HSIL on cytology in the diagnosis of women with cervical cancer.

A study looking at the prevalence of these risk factors in all women referred to the CHBAH colposcopy clinic, compared to their prevalence in women ultimately diagnosed with cervical cancer would be required before changing referral protocols. This study would be required in order to gauge the clinical significance of these risk factors in our population. It would also give an idea as to the extent of the increase in "urgent" referrals, which could possibly affect the waiting times for colposcopic assessment in non-urgent cases.

The follow-up of women with positive margins and CIN 3 should be rigorous. All of the women presenting with cervical cancer after previous LLETZ in this study had positive margins. Of all of the risk factors for the development of cervical cancer after LLETZ, positive margins at LLETZ is the only identified modifiable risk factor.

We need to seriously consider implementing a basic electronic database that would allow us to track the follow-up of women with abnormal cervical cytology.

Chapter 8: References

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Chapter 9 Appendices

Appendix 1: Referral criteria for Chris Hani Baragwanath Academic Hospital Colposcopy Clinic

Indications for referral to CHBAH Gynaecology Out-patient Department

Such patients will be seen by a doctor from the gynaecology department and triaged either for immediate cervical biopsy or urgent referral to colposcopy clinic, depending on clinical assessment.

- Cervix clinically suspicious for cancer, with normal or abnormal Pap smear
- Pap smear report:
    - Cannot exclude invasion
    - Malignant cells
    - Endometrial cells in woman older than 35

Indications for non-urgent referral to the CHBAH Colposcopy Clinic

- Recurrent LSIL
- HSIL
- AGUS
- Recurrent ASCUS
- ASC-H
- Immunocompromise and any abnormal Pap smear result, including ASCUS and LSIL

Appendix 2: Modified Reid's Colposcopic Index

Colposcopic Signs	Zero Point	One Point	Two Points
Colour (Aceto-white reaction)	Low-intensity; Indistinct; Beyond the margin of the transformation zone; Pure snow-white colour with intense surface shine	Intermediate shade: grey/white colour and shiny surface	Dull, opaque, oyster white; Grey
Lesion margin and surface configuration	Microcondylomatous or micropapillary contour; Flat lesions with indistinct margins; Feathered or finely scalloped margins; Angular, jagged lesions; Satellite lesions beyond the margin of the transformation zone	Regular-shaped, symmetrical lesions with smooth, straight outlines	Rolled, peeling edges; Internal demarcations between areas of differing colposcopic appearance: a central area of high-grade change and a peripheral area of low-grade change
Vessels	Fine/uniform-calibre vessel- closely and uniformly placed; Poorly-formed patterns of fine punctuation and/or mosaic; Vessels beyond the margin of the transformation zone; Fine vessels within microcondylomatous or micropapillary lesions	Absent vessels	Well-defined coarse punctation or mosaic, sharply-demarcated- and randomly and widely placed
Iodine Staining	Positive iodine uptake giving mahogany-brown colour; Negative uptake of insignificant lesion, i.e. yellow-staining by a lesion scoring 3 or less points on the 1st 3 criteria; Areas beyond the margin of the transformation zone, conspicuous on colposcopy; evident as iodine-negative areas	Partial iodine uptake, variegated speckled appearance	Negative iodine uptake of significant lesion, i.e. yellow staining by a lesion already scoring 4 points or more on the 1st 3 criteria

Colposcopic prediction of histological diagnosis using the Reid Colposcopic Index

RCI (overall score)	Histology
0-2	Likely to be CIN 1
3-4	Overlapping lesion: likely to be CIN 1 or CIN 2
5-8	Likely to be CIN 2-3

Reference:

International Agency for Research on Cancer. Appendix 5: the modified Reid colposcopic index (RCI). In: Sellors JW, Sankaranarayanan R, editors. Colposcopy and treatment of cervical neoplasia: a beginner's manual. Online Version [Internet]. Lyon: IARC/WHO; 2003. [Cited 2016 Jan 1] Available from http://screening.iarc.fr/doc/colpochapterappendix.pdf

Appendix 3: Colposcopic Features of Microinvasive and Invasive Cervical Cancer

Features of Microinvasion

1. Warning signs to examine thoroughly for early invasive cancer[1]:
    a. Large high-grade lesions involving more than 3 quadrants
    b. Wide abnormal transformation zone > 40mm^2
    c. Complex acetowhite lesions involving both lips of the cervix
    d. Lesions obliterating the cervical os
    e. Lesions with irregular, exophytic surface contour
    f. Thick, chalky-white lesions with raised, rolled-out margins
    g. Strikingly excessive atypical vessels
    h. Bleeding on touch
    i. Presence of symptoms such as vaginal bleeding

2. Colposcopic Findings[1]:
    a. Lesion rapidly turns dense chalky-white, grey-white or yellow-white after application of 3-5% acetic acid
    b. Acetowhiteness persists for several minutes
    c. Raised, rolled-out margins in exophytic lesions
    d. Irregular surface contour with mountains and valleys
    e. hard, nodular white areas, sometimes with central necrosis if infiltrating lesions
    f. Irregular longitudinal vessels with bizarre patterns*
    g. Contact bleeding and capillary oozing
    h. turns mustard-yellow or saffron-yellow after application of Lugol's iodine



*Irregular vasculature in microinvasive cervical lesions on colposcopy. Taken from reference 1, Figure 8.5

Features of Frank Invasion

1. Women are often symptomatic, and present with[2]:
    a. Abnormal bleeding,
    b. Excessive seropurulent discharge
    c. Foul smelling discharge
    d. Recurrent cystitis
    e. Urinary frequency and urgency
    f. Backache and lower abdominal pain

2. Features usually apparent after digital examination and vaginal speculum examination, and do not require colposcopy[2]:
    a. Rough, reddish granular area with contact bleeding
    b. Exophytic, endophytic or combined lesions
    c. Exophytic lesions grow into vaginal lumen as a cauliflower-like growth
    d. Endophytic lesions infiltrate the stroma extensively, resulting in an enlarged, irregular, barrel-shaped cervix with a rough surface
    e. Combined lesions are usually ulcerated, with deep infiltration of underlying stroma
    f. Contact bleeding, necrosis and offensive discharge are common features in all types
    g. There may be direct extension to the vagina, parametrium, pelvic side-wall, rectum and bladder, depending on stage.

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Appendix 4: Datasheet

Study Number:

Demographic Data *(from colpo clinic electronic database or hospital files)*

Age:	(continuous)
Parity:	(continuous)
Cigarette smoker: yes/no (only available from 2012)	(categorical)
Snuff user: yes/no	(categorical)
Reason for referral: abnormal Pap smear, abnormal vault smear, clinical suspicion, other	(categorical)

HIV Data *(from NHLS electronic database preferably)*

HIV status: positive/negative/unknown	(categorical)
If positive:	
CD4 count: number	(continuous)
CD4 < 200: yes/no/unknown	(categorical)
Treatment: yes/no	(categorical)
Duration of treatment: months	(continuous)
Duration of diagnosis	(continuous)
Virally supressed: yes/no	(categorical)

Contraception *(from colpo clinic electronic database)*

Nuristerate: yes/no	(categorical)
Depo Provera: yes/no	(categorical)
Combined oral contraceptive: yes/no	(categorical)
Intrauterine contraceptive device: yes/no	(categorical)
Condoms: yes/no	(categorical)

Progesterone only pill: yes/no (categorical)

Sterilization: yes/no (categorical)

None: yes/no (categorical)

Other: yes/no (categorical)

If other, specify (categorical)

Cytology Information *(from NHLS electronic database preferably)*

Cytology result: Normal/LSIL/HSIL/ASC-US/ASC-H/AG-US/AGS/

suspected invasion/ definite invasion (categorical)

If LSIL, specify: CIN1/ HPV/ CIN1 and HPV (categorical)

If HSIL, specify: CIN2/ CIN3 (categorical)

Infection: none/ bacterial vaginosis/ candidiasis/trichomonas/

other (categorical)

If other, specify (categorical)

Colposcopy Information *(from colpo clinic electronic database)*

Adequate: yes/no (categorical)

Colposcopic Diagnosis: normal/ CIN1/CIN2/CIN3/ invasion/ microinvasion/don't know/ other (categorical)

Other:

Specify: condylomata/ keratosis/ Erosion/ Inflammation/ Atrophy/ Deciduosis/ Polyps (categorical)

Histology Information *(from NHLS electronic database)*

Procedure done:

none/ LLETZ/ punch biopsy/ endocervical curettage/ referral (categorical)

Histology Result:

squamous cell carcinoma/ endometrioid adenocarcinoma/ clear cell adenocarcinoma/ adenosquamous carcinoma/ adenoid-cystic carcinoma/ small cell carcinoma/ undifferentiated carcinoma/adenoid-basal carcinoma/ neuroendocrine carcinoma (categorical)

Margins Involved:

both/ endocervical/ ectocervical/ margins clear (categorical)

FIGO Stage *(Hospital files or from NHLS electronic database reports on surgical specimens)*

FIGO Stage: 1A1/ 1A2/ 1B1/ 1B2/ 2A/ 2B/ 3A/ 3B/ 4A/ 4B (categorical)

Symptoms *(hospital files)*

Symptoms: yes/no (categorical)

Abnormal bleeding: yes/no (categorical)

Abnormal discharge: yes/no (categorical)

Pelvic pain: yes/no (categorical)

Notes

Is this a case of treatment failure? If so, details on initial LLETZ are required:

- Date
- Diagnosis
- Margins
- Lymphovascular space invasion
- Perineural Invasion
- Interval from initial LLETZ to cancer diagnosis in months

Is this a case where more advanced disease was diagnosed intra-operatively? If so:

- What made them suspect more advanced disease?
- Was surgery completed or abandoned?
- Did histology confirm more advanced disease?
- Did they receive subsequent therapy?
- Did cancer recur after treatment?

Was there anything else of interest about this case?

Appendix 5: Consent for the establishment of the CHBAH colposcopy clinic electronic database and collection of this data for research purposes

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)
Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

22 November 2013

Dr Yasmin Adam
Head
Dept of Obstetrics & Gynaecology
CH Baragwanath Academic Hospital
University

Sent by email to: yasminadam@gmail.com

Dear Dr Adam

RE: Protocol M080603/M040609
Request for Ethics Approval to Continue the Coloscopy Database at Chris Hani Baragwanath Academic Hospital

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (medical) has reviewed and approved the following amendments on the abovementioned protocols as detailed in your letter dated 05 November 2013:

- Using an International Scoring System 'Modified Reid Score"
- Collecting Gynaecological Information
- Adding a section on Sexual History and Condom Use

Thank you for keeping us informed and updated.

Yours sincerely,

Anisa Keshav
Administrator
Human Research Ethics Committee (Medical)

Appendix 6: Patient Consent Form for Colposcopy and Treatment, and for Their Data to be Used for Research Purposes

Colposcopy Clinic

Ward 58

011 933 9766

Introduction

You have been referred to this clinic because of an abnormal Pap smear.

The abnormal cells found on you Pap smear may one day become a cancer if left untreated.

A biopsy is needed to make a diagnosis. The service we offer at this clinic is to do a LLETZ biopsy. The LLETZ biopsy can be done as an out-patient, under local anaesthetic, or as an in-patient under general anaesthetic. When the abnormal area is too large, or if you choose to have general anaesthetic, this will be arranged.

You will have to come back to the clinic to check the results of the biopsy. When the entire lesion is removed, and when the abnormality is not worse than what it is on the Pap smear, you just need to be checked again in 6 months.

The procedure under local anaesthesia

The mouth of the womb (cervix) will be examined with a colposcope (type of microscope). A local anaesthetic will be given around the cervix, and a wire-loop will be used to remove the abnormal areas.

Complications of LLETZ biopsy under local anaesthesia

1. PAIN. Some women (2 in 100) will feel some pain at the time of the procedure when done under local anaesthetic. Pain after the procedure is uncommon. Most women do not feel any pain.
2. Bleeding. The bleeding is usually stopped by the treatment, or by inserting a tampon. You should expect some bleeding and discharge for up to 4 weeks. BLEEDING THAT IS MORE THAN A PERIOD is too much, and you should come back to the hospital. The bleeding can be so severe that a patient may have to be admitted for further treatment.

3. INFECTION. Pain and an offensive discharge may indicate infection. This procedure may normally be associated with a discharge, but if you suspect an infection, please return to the Gynaecology Out-patient Department to be checked. An antibiotic will be given after the procedure to prevent infection.
4. INFERTILITY. This procedure may result in infertility in a very small number of cases.
5. PREMATURE DELIVERY/ MISCARRIAGE: There is a very small chance of having a miscarriage or premature delivery during a pregnancy after this procedure.

Informed Consent

I have been informed and have read about the abnormality on my Pap smear. I understand the nature of the procedures and the treatment.

I hereby give my consent to have the procedure conducted on me.

Signature…… Date……..

Reason for Referral

Cervix clinically suspicious for cancer, with normal or abnormal Pap smear	Refer to GOPD ASAP
Cannot exclude invasion	
Malignant cells on Pap smear	
Older than 35- endometrial cells on Pap	Refer to GOPD
Immunocompromise and any abnormal Pap, ASCUS, LGSIL	Phone 011 9339766 to make an appointment at colpo clinic
Recurrent LGSIL	
HGSIL	
AGUS	
Repeat ASCUS	
ASC-H	

Name and Surname:

ID Number:

Cell phone:

Age:

Parity:

HIV result if known/ suggest VCT:

Date of HIV test:

Last CD4 count:

MCTC:

Date of ARV Use:

Contraception:

Please enclose Pap result:

Information about the collection of data for study and research purposes

Introduction:

Good morning. I am Dr _____

We would like to ask your permission to use the information about your condition, personal information like your age, number of children, etc. and results of treatment for the purposes of study.

Before you agree to participate, it is important for you to read and understand the following explanation of the purpose of the study.

If you have any questions, please do not hesitate to ask me.

If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

Purpose of the Study:

You have been found to have abnormal cells on your Pap smear, and will be assessed and treated at this clinic.

The procedures that will be used in the treatment are based on proven methods.

The study will be to assess whether patients of all age groups fair equally well, to assess complications, and long-term outcomes

Untreated, these abnormalities may go on to become cancer. We need to assess whether treatment will reduce the number of cancers seen.

We need to assess the nature and number of abnormalities that we treat in the hospital, and to assess the results of treatment, for publication in a medical journal.

Procedures:

These will not be different from non-study participants.

Alternative Treatment:

This is not different from non-study participants.

Rights as participants in this study:

Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating a reason. Your withdrawal will not affect your access to other medical care.

Financial Arrangements:

There will be no payment for participating. You will still be a hospital patient, and will still be required to pay your usual hospital fees.

Ethical Approval:

Confidentiality:

All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

The information might also be inspected by the University of the Witwatersrand Human Research Ethics Committee.

The records will be used by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered, regarding your test results or state of health, as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued

participation in this study, but this information will not be disclosed to any 3rd party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases, where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorized state agency.

Informed Consent:

I hereby confirm that I have been informed by the doctor about the collection of data pertaining to my diagnosis, treatment and follow-up.

I have read, received and understood the above written information regarding the study.

I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.

In view of the requirements of research, I agree that the data collection during the study can be processed in a computer system.

I may, at any stage, withdraw my consent and participation in the study.

I have had sufficient opportunity to ask questions, and (of my own free will) declare myself prepared to participate in the study.

Signature_____ Date:_____

Appendix 7: University of the Witwatersrand Human Research Ethics Approval Committee: Consent to conduct this study

R14/49 Dr Rumbidzai Mashayamombe

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161036

NAME: (Principal Investigator)	Dr Rumbidzai Mashayamombe
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An Evaluation of Cervical Cancer Cases Diagnosed at a South African Colposcopy Clinic
DATE CONSIDERED:	28/10/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Yasmin Adam
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 8: Turn-it-in Anti-plagiarism Report

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ORIGINALITY REPORT

2%	3%	2%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	monographs.iarc.fr Internet Source	1%
2	Submitted to Nelson Mandela Metropolitan University Student Paper	1%

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