Impact of no residual versus residual disease after hysterectomy for stage 1 cervical cancer on recurrence

A minor dissertation in fulfilment for the requirements of the degree Master of Medicine (MMED) in Obstetrics and Gynaecology

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DISSERTATION SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

Signature: Signed by candidate

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Plagiarism Declaration and Supervisor Authentication

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Finally, we are grateful to the late Professor Denny, she came up with this fascinating research topic.

Appendices

1. Data collection sheet

Impact of residual disease following hysterectomy for stage 1 cervical cancer on recurrence

Identifier	
Age	
hiv 0=neg 1=pos	
cd4count	
cd4category 1=< 350 2=≥350 3=unknown	
comorbid1 0=nil 1=hpt 2=dm 3=resp 4=autoimmune 5=prevabdosurg 6=other 7=unknown	
comorbid2 0=nil 1=hpt 2=dm 3=resp 4=autoimmune 5=prevabdosurg 6=other 7=unknown	
LEEP or CKCmethod 1=leep 2=ckc	
marginspostLEEP or CKC 1=positive for cancer 2=negative for cancer 3=close margins 4=undetermined	
marginspostLEEP or CKC 1=positive for CIN2+ 2=negative for CIN2+ 3=close margins 4=undetermined	

surgerytype 1=simple hysterectomy 2=simple hyst + lymphad 3=radical hysterectomy	
hystspecimen 1=residual cancer 2=noresidualcancer	
stromalinvasion 1=≤ 3mm 2=3mm-5mm 3=> 5 mm =3 4=unknown	
lvsi 1=yes 2=no 3=unknown	
histology 1=squamous 2=adenocarcinoma 3=adenosquamous 4=other	
positivenodes 1=yes 2=no 3=unknown	
adjuvant 1=yes 2=no	
recurrence in 60 months 0=no 1=yes 3=unknown	
cancerrecurrence in (months)	
siterecurrence 0=none 1=pelvis 2=distant 3=unkown	
causeofdeath 0=alive 1=cancer related 2=not cancer related 3=loss to follow up	
alive60months 1=yes 2=no 3=unknown	
followuptime in months	

2. Ethics approval letter (see attached)
3. List of tables and Figures

Table I: Summarises demographic and clinical data

Age (years): - **Mean 47** - **Range (27 – 76)**		
HIV Status **Negative** **Positive** **CD 4 count > 350** **CD 4 count < 350** **Unknown**	Residual disease 74 (89.2%) 9 (10.8%) 6 (66.7%) 3 (33.3%) 0	No residual disease 39 (60.9%) 25 (39.1%) 8 (32%) 16 (64%) 1 (4.0%)
Comorbidities: **No comorbidities** **Hypertension** **Respiratory disease** **Autoimmune** **Previous abdominal surgery** **Other**	 79 (53.7%) 44 (29.9%) 3 (2.0%) 2 (1.4%) 5 (3.4%) 11 (7.5%)	

Table II: Summarises the associated impact of histological risk factors on presence of residual disease on hysterectomy specimen

	Residual disease	No residual disease	P value
Patients	83 (56.5)	64 (43.5)	
Stage IA_1 IA_2 IB_1 IB_2	 15 (18.1) 7 (8.43) 60 (72.3) 1 (1.2)	 40 (62.5) 4 (6.3) 20 (31.3) 0	< 0.0001
Histology Squamous Adenocarcinoma Adenosquamous Undetermined	 63 (52.5) 11 (68,8) 5 (83) 4 (80)	 57 (47.5) 5 (31.3) 1 (16.7) 1 (20)	0.2
LVSI	27 (65.9)	14 (34.2)	0.23
Lymph node involvement	13 (92.9)	1 (7.1)	0.004
Stromal invasion < 3mm 3 – 5 mm > 5mm Unknown	 21(25.3) 19 (22.9) 41 (49.4) 2 (2.1)	 36 (56.3) 14 (21.9) 7 (10.9) 6 (9.38)	< 0.0001
Margins post LEEP or CKC: Positive for cancer Negative for cancer Close margins Undetermined	 43 (51.8) 18 (21.7) 1 (1.2) 21 (25.3)	 18 (28.1) 31 (48.4) 9 (14.1) 6 (9.38)	< 0.0001

Table III: Comparing recurrence rate in patients with residual cancer vs no residual cancer

	Recurrence in 60 months			
	No	Yes	Unknown	total
Residual disease	69 (83.1%)	13 (15.7%)	1 (1.2%)	83 (100%)
No residual disease	62 (96.9 %)	1 (1.6%)	1 (1.6%)	64 (100 %)
Total	131 (89.1%)	14 (9.5%)	2 (1.4%)	147 (100%)

Pearson $Chi^2 = 8.34$, p value = 0.015

Table IV: Demonstrating distribution of surgical type performed for each stage of the disease

Cancer stage	**Simple Hysterectomy**	**Simple hysterectomy + lymphad**	**Radical hysterectomy**	**No of participants**
1A1	40 (73%)	11 (20%)	4 (7%)	55
1A2	2 (18%)	6 (55%)	3 (27%)	11
1B1	2 (3%)	1 (1%)	77 (96%)	80
1B2	0	0	1 (100%)	1
Total	**44**	**18**	**85**	**147**

Table V: Demonstrating recurrence rate after adjuvant therapy in patients who had residual disease

	Recurrence in 60 months in patients who had residual disease			
Adjuvant	**No**	**Yes**	**Unknown**	**No of participants**
Yes	**22 (76%)**	**6 (21%)**	**1 (3%)**	**29**
No	**47 (87%)**	**7 (13%)**	**0**	**54**
Total	**69**	**13**	**1**	**83**

Figures

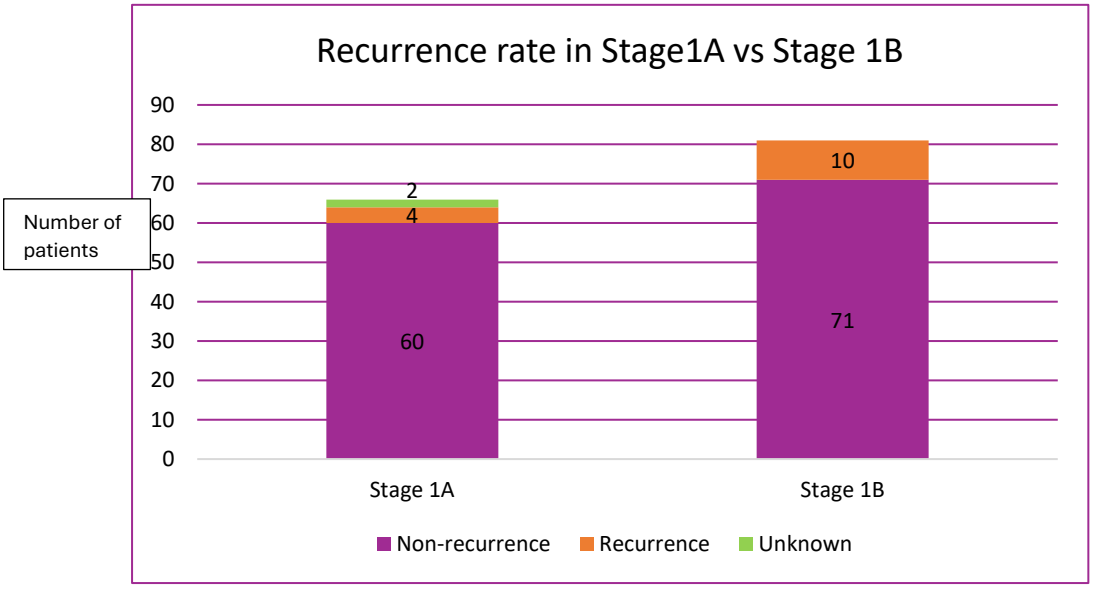

Figure 1: Demonstrating recurrence rate between stage 1A and stage 1B in numbers

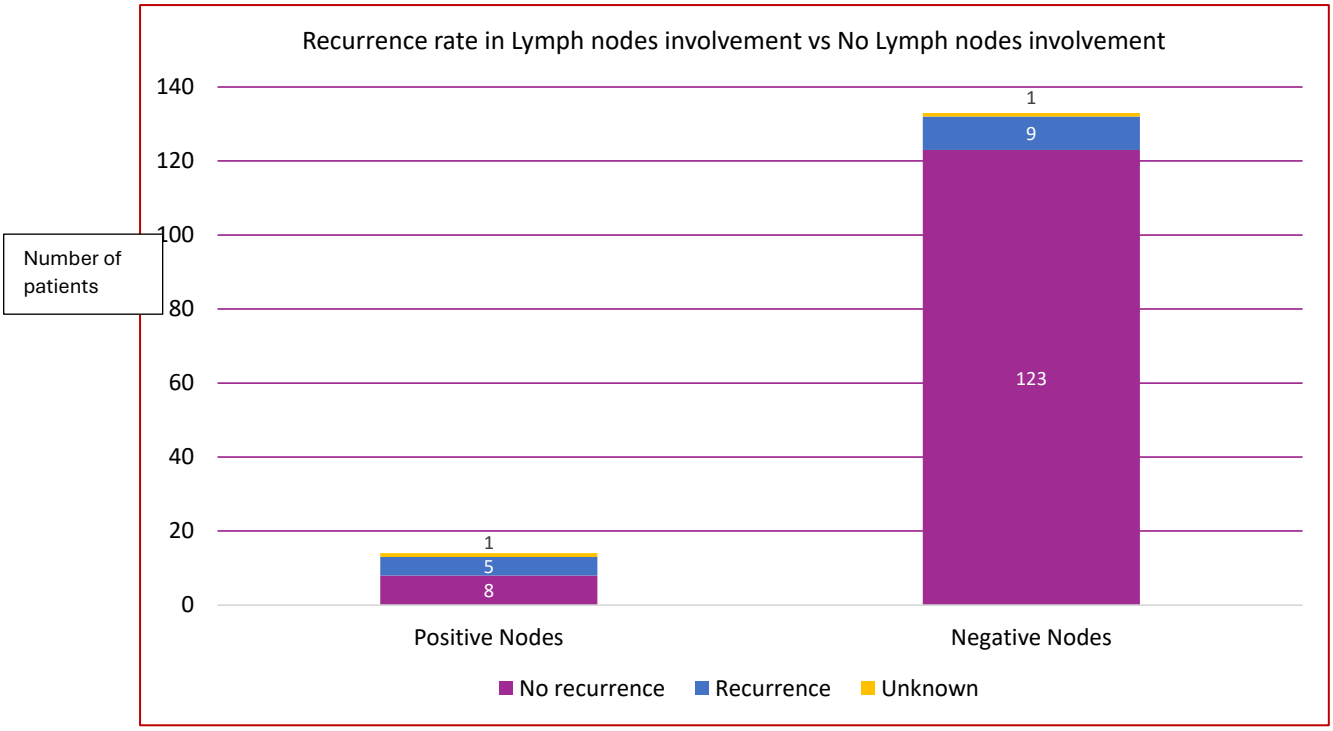

Figure 2: recurrence rate in patients with lymph node involvement vs those with no lymph node involvement in numbers

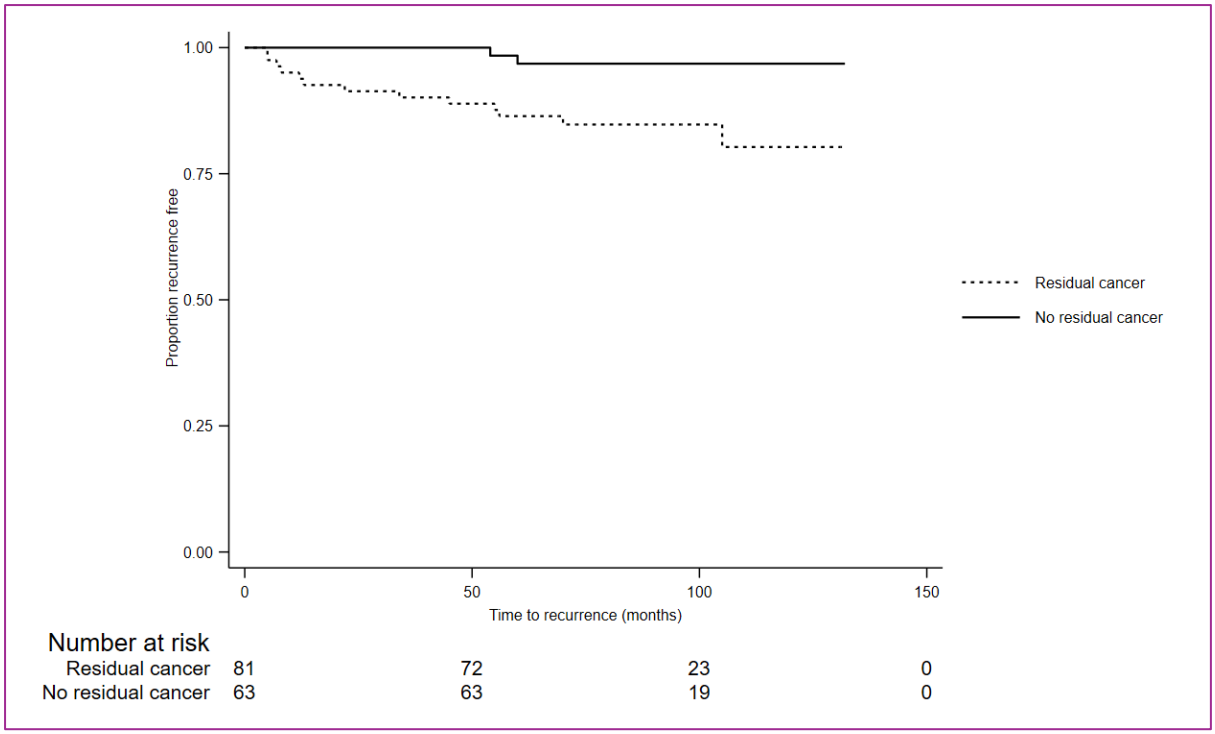

Figure 3: Kaplan-Meir curve demonstrating disease free interval in patients with residual disease vs those with no residual disease

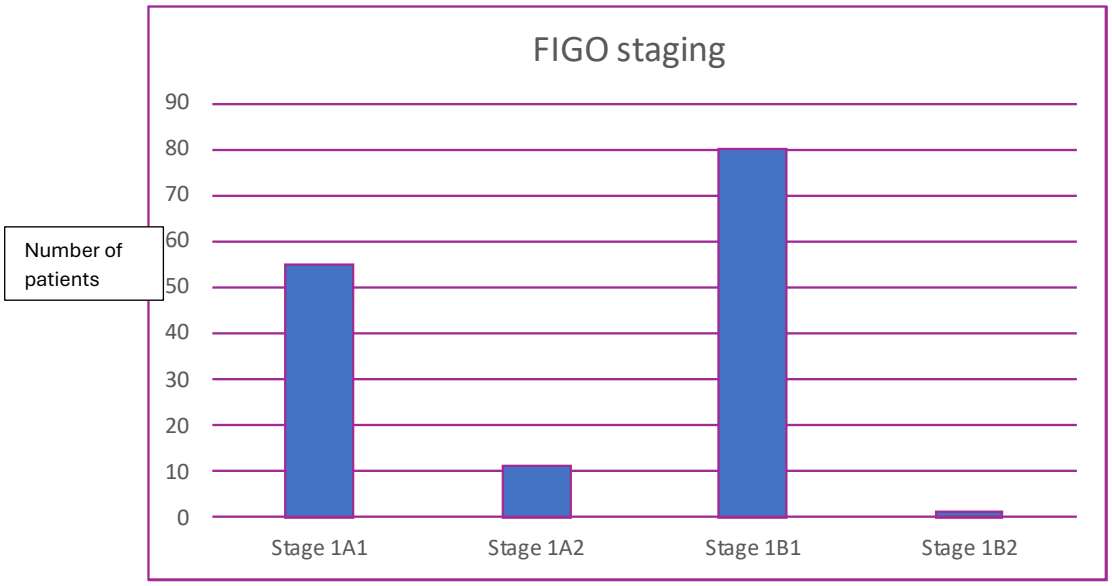

Figure 4: illustrates Percentage representation of each FIGO 2018 stage I sub-stage

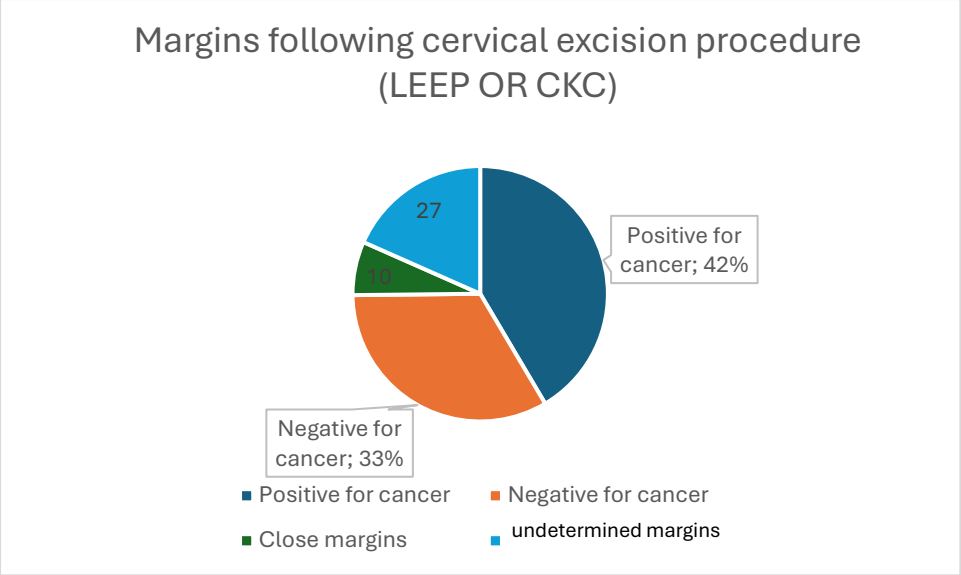

Figure 5 : demonstrating margin status post LEEP OR CKC

4. Abstract

Background: Histopathological risk factors for recurrence of cervical cancer following hysterectomy for stage I disease are well established. The impact of residual disease after LEEP in patients undergoing hysterectomy for stage 1 cervical cancer on recurrence has not been extensively studied.

Design and Methods: Records of all patients who underwent hysterectomy for stage I cervical cancer from 2008 to 2017 were reviewed. The follow-up period was at least 60 months or until death. Data collected included demographic information, histopathological risk factors, residual disease status on hysterectomy specimen, treatment modalities and recurrence rates.

Results: We analysed 147 patients: 55 stage $1A_1$, 11 stage $1A_2$, 80 stage $1B_1$ and 1 with stage $1B_2$. Median age was 47 (27 – 76) years. All patients had either a LEEP or CKC for histological diagnosis, followed by simple hysterectomy (29.6%), simple hysterectomy with lymphadenectomy (12.3%) or radical hysterectomy (58.2%). The prevalence of residual disease on hysterectomy specimen was 56.5%, versus no residual disease (43.5%). The overall recurrence rate was 9.5%. Thirty patients received adjuvant radiotherapy, of these, 29 had residual disease, with 6.2% of them developing disease recurrence. The overall survival (OS) and disease-free interval (DFI) were 96.6% and 91.6% respectively.

Conclusion: This study found a correlation between lymphovascular space invasion (LVSI), depth of stromal invasion, size of the lesion with the presence of residual disease. All patients that had recurrence had residual disease. When excluding those with lymph node metastasis, there were no recurrences in the group with no residual disease.

Key words: cervical cancer, residual disease, histopathological risk factors, cervical excision procedure, cervical cancer recurrence

5. **Chapter 1: Literature Review**

1. Purpose of the Study

This study aims to assess whether there is any correlation between residual disease found on hysterectomy specimens for stage 1 cervical cancer and the recurrence of cervical cancer, where the diagnosis of cancer was made using a cervical excision procedure (LEEP OR CKC). If the presence of residual disease is a risk factor for recurrence, it may have an impact not only on the treatment offered, but also on patient counselling.

Primary outcomes

1. To evaluate the recurrence rate and survival related to residual disease in patients with stage 1 cervical cancer who underwent hysterectomy.

Secondary measures

1. Demographic data
2. Review of tumour histological types: Squamous cell carcinoma vs Adenosquamous vs adenocarcinomas
3. To determine the proportion of women with positive margins on the LEEP OR CKC specimen who had residual disease during hysterectomy. These would be categorized as negative margins (no cancer) and malignant margins.
4. Predict/assess the factors associated with residual disease during hysterectomy.
5. To assess the treatment methods employed, such as surgery alone (simple vs. Radical Hysterectomy), whether adjuvant therapy was offered to each group.
6. Analysis of survival data: Cancer-associated and Overall survival.

2. Literature review

Definitions

Residual disease will be defined as invasive disease on a hysterectomy specimen in this study.

Disease-free survival (DFS) is the time it takes after primary cancer treatment for the patient to survive without any signs or symptoms of cancer before recurrence. This will be defined as five years from hysterectomy to recurrence.

Overall Survival (OS) is the length of time from the start of treatment (hysterectomy) for a disease (cancer); patients diagnosed with the disease are still alive. For this study, the number of patients who were still alive at least 5 years after surgery will be recorded.

Cervical Excision Procedure(LEEP OR CKC) for diagnosis of cervical cancer: refers to Loop Electrosurgical Excision Procedure LEEP), Cold Knife Conization (CKC), biopsy of an abnormal lesion at colposcopy examination of the cervix

Negative margin: (ecto- and endocervical) is considered negative if there is no malignant or pre-malignant (CIN II–III) lesion on histology specimen after LEEP OR CKC in this study.

Close margins: are defined as margins with malignant disease < 5mm on histology specimen after LEEP OR CKC in this study.

2.1. Background

Introduction

Cervical cancer is caused by the Human Papilloma Virus (HPV), a virus that is mostly transmitted sexually. Risk factors include persistent infection, multiple sexual partners (or a partner with multiple sexual partners), smoking, immune compromise, and commonly HIV and AIDS, among other risk factors that are all preventable behavioral or lifestyle issues. Primary prevention through HPV vaccination is in progress worldwide, with some countries, including South Africa, finding less success than others in terms of reaching the targeted

population. Cervical screening, in the form of a Pap Smear, visual inspection techniques, or HPV-DNA testing are secondary preventative measures. The screening findings inform the decision to continue surveillance according to the guidelines or refer the patient for a colposcopy exam or treatment. Patients with microscopic or stage 1 cervical cancer are usually diagnosed using LEEP OR CKC. Following the diagnosis; the crucial histopathological information required to guide treatment options include the following:

a. Depth of stromal invasion
b. Presence of lymphovascular space involvement (LVSI)
c. Surgical margin status: whether margins are involved with CIN, Cancer, or clear.

The extent or radicality of definitive surgery is determined by the above findings. Few studies have assessed the impact of residual disease on disease recurrence.

The magnitude of the problem

Cervical cancer is a leading cause of mortality among women(1).In 2020, an estimated 604 000 women were diagnosed with cervical cancer worldwide and about 342 000 women died from the disease(1). For South Africa, the WHO's International Agency for Research in Cancer (IARC) estimated an age-standardised cervical cancer incidence of 43.5 per 100 000 women in 2018(2). This is more than three times the global average of 13.1 per 100 000, but similar to estimates for Southern Africa (43.1) and Eastern Africa (40.1)(2).

This reflects how socioeconomic factors play a role in the incidence of cervical cancer. In developed countries, the incidence of cervical cancer is lower, with some countries reporting less than 4 per 100 000 in 2018(2). The socio-economic impact of cervical cancer has been studied and found to have negative consequences on treatment compliance(3). Furthermore, a qualitative study conducted in South Africa concluded that patients were burdened with physical changes (due to chronic disease) that aggravated their already difficult financial situation and had to live with unattended healthcare needs(4).

Treatment strategies

The WHO 2030 Cervical Cancer elimination strategy

WHO proposes a strategy to eliminate cervical cancer as a public health concern by 2030. This strategy proposes a threshold of 4 per 100 000 women years for elimination as a public health problem. The targets to be met are 90-70-90, that is,

- 90% of girls to be fully vaccinated by the age of 15 years.
- 70% of women are to be screened by high-performance test by the age of 35 years and again by the age of 45 years.
- 90% of women to be identified to have cervical disease are treated.

These treatment modalities are classified as primary, secondary, and tertiary prevention. For this study, the focus will be on tertiary prevention.

Primary interventions

General principles such as health education, especially reproductive health, use of condoms to protect against HIV and HPV infection, and improvement in socioeconomic status fall under this category. Most importantly, HPV vaccines are used in adolescents. The HPV vaccine was initiated in South Africa in 2014 through an integrated school health program. The uptake of the HPV vaccine was reported to be 85% for the first dose, but there was a decline to 21.4% for the second dose, and in 2016, a reported uptake of only 26%(5). Reasons for poor uptake may include the cost and availability of the vaccines, vaccine storage, chain issues, and lack of prioritization of adolescents' health, amongst other things. Only 14.3% of women aged 16-24 years had heard of the HPV vaccine before, in a study conducted in Durban South Africa, which assessed vaccine acLEEP or CKCtability(6). Until such issues are addressed, secondary and tertiary interventions remain well-established in South Africa.

Secondary interventions

Cytology: this can either be in the form of a pap smear or liquid-based cytology. The current South African policy is that each HIV-negative woman, starting from the age of 30 years gets

at least (depending on the results) 3 free pap smears and that HIV-positive women get a pap smear at diagnosis and then 3 yearly (depending on the results).

HPV DNA: screens for the presence of high-risk HPV, such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58. The sensitivity ranges from 74.8 – 77.7%, depending on the kit used, and the second specificity ranges from 93.4 – 94.2%(7). The cost versus benefits might be justifiable in resource-poor areas with the use of HPV – gene expert results become available on the same day.

Colposcopy: The cervix can be evaluated more thoroughly, and a biopsy may be performed under colposcopic guidance. This is critical for diagnosing malignant diseases and planning for further management.

Management options for stage 1 cervical cancer

The National Comprehensive Cancer Network (NCCN) guidelines 2020 Clinical Practice Guidelines in Oncology, cervical cancer (8), are generally followed for treatment options.: For stage $1A_1$ (measured stromal invasion ≤ 3mm) with no LVSI, a cone biopsy or an extra-fascial hysterectomy is advised. Stage $1A_1$ LVSI-modified radical hysterectomy with pelvic node dissection is recommended. The prognostic significance of LVSI in stage 1A disease (depth less than 5 mm) is doubtful. Margolis et. al, in a review of patients with stage $1A_1$ and $1A_2$ cervical cancer, found 7.8% and 14.6% positive node rates with LVSI, respectively(9). In the same study, patients in the group without LVSI, 1% with stage $1A_1$, and 1.7% with stage $1A_2$ had positive lymph nodes(9). This high rate of lymph node positivity justifies pelvic lymph node dissection, in addition to either trachelectomy or hysterectomy in patients with stage 1A with LVSI. Interestingly Park et. al concluded that occult stage $1A_1$ cervical cancer found after a simple hysterectomy can be followed up safely without adjuvant therapy, regardless of LVSI status(10). This was a small study with 48 patients with stage $1A_1$ disease, of which only 12 % (6 patients) had LVSI(10). Therefore, it is difficult to generalize these findings.

In stage $1A_2$ (3–5 mm deep), a modified radical hysterectomy with PLND/sentinel lymph node is advised. For FIGO (2018) stages $1B_1$, $1B_2$, and 2A, radical hysterectomy with PLND ± para-aortic lymph node dissection is recommended.

For stage, $1A_2$ -1B and selected cases of stage IIA, radical hysterectomy is considered curative in most cases. Adjuvant therapy is considered in certain patients according to risk stratification. Radiotherapy alone or a combination of chemotherapy and radiotherapy is often considered in situations where the risks of the procedure outweigh the benefits, or in situations where skilled personnel are not available. Importantly, chemotherapy alone is not beneficial. Radiotherapy alone or chemotherapy combined with radiotherapy has been found to have comparable outcomes, with disease-free survival (DFS) and overall survival (OS) of 93% and 94%, respectively, over 10 years (10,11). This is in contrast to older studies that showed poorer outcomes despite adjuvant therapy(12). Ideally, radical hysterectomy should be performed by specialists and gynecological oncologists trained in this procedure because of technical challenges and morbidity associated with the procedure. In the above-mentioned studies, surgery was performed in specialized units; therefore, one would argue that radiotherapy is a reasonable alternative in cases where specialists are unavailable. Furthermore, even in patients who have undergone surgery, radiation therapy may still be beneficial when known criteria are used to decide on further therapy. In a randomized control trial by Sedlis et al., who used criteria (>1/3 depth of stromal invasion, LVSI, tumor diameter) as a means of risk stratification in patients with stage 1 B disease, radiotherapy was found to be of benefit when compared to no further treatment(13). Another benefit of surgery, especially in younger patients, is the preservation of ovarian and sexual function. With more women diagnosed with cervical cancer at a young age (14), determining the predictive value of residual disease on recurrence may benefit these patients if the risk of recurrence is low.

Currently, the absence or presence of residual disease (cancer) on hysterectomy specimens does not determine adjuvant treatment options. This study aims to establish whether the residual disease has an impact on the recurrence rate. This would then influence decision making regarding adjuvant therapy and follow-up plans. We aim to determine the predictive value of residual disease on recurrence post-hysterectomy for stage 1 cervical cancer.

2.2 Known Risk factors for recurrence after definitive therapy for stage 1 cervical cancer.

To our knowledge, few studies have assessed the impact of residual disease as an independent predictor of disease recurrence. This study will evaluate the predictive value of residual disease as an independent risk factor for recurrence. This can be achieved by comparing the rate of recurrence of cervical cancer in patients who underwent hysterectomy for stage 1 cervical cancer. Patients with known risk factors will be included in the study. A sub-analysis of patients without known risk factors will be performed, and the recurrence rate will be compared between groups (those with known risk factors vs. those without known risk factors).

This study will assess whether the presence or absence of residual disease in the hysterectomy specimen after LEEP OR CKC adds any value to the known risk factors. This can be achieved by assessing its value as a single risk factor and in combination with known risk factors.

Known risk factors or predictors of recurrent disease following successful surgery include the stage, histological type, grade, depth of stromal invasion, and lymphovascular space invasion (LVSI). Several studies (2–6) have evaluated the risk factors for recurrent disease following surgery for early disease. The definitive treatment required following LLETZ, or cold knife cone (CKC) is determined by the size, presence of LVSI, and the margin involvement on the specimen.

Patients who are considered at high or intermediate risk for tumor recurrence upon pathological examination of surgical specimens are offered adjuvant RT or chemo-radiation therapy(15). The risk stratification is as follows:

- High-risk features: any one of three factors (positive surgical margins, lymph node involvement, parametrial spread)
- Intermediate features: any two of three factors (tumor size > 4 cm, lymphovascular space invasion, and greater than one-third stromal invasion).

Delgado et. al(16) performed a prospective study in 645 patients with cervical cancer stage IB, assessing the disease-free interval (DFI) in patients with the above-mentioned risk factors. They concluded that clinical tumor size, depth of invasion, and LVSI were independent prognostic factors. The degree of tumor invasion was inversely proportional to the disease-free interval(16).

Depth of Invasion (DOI) and Lymphovascular Space Invasion (LVSI)

The depth of invasion refers to the breach of the stroma by abnormal cells. Once abnormal epithelial cells invade the stroma, the disease becomes invasive. Both stage 1A and 1B diseases are subcategorized according to the depth of stromal invasion, with 1B further categorized according to the measured greatest dimension of the tumor. Delgado et al, did a prospective study of histologically confirmed stage 1 cervical cancer with stromal invasion > 3mm, assessing a 3-year disease-free interval (DFI)(16). The depth of stromal invasion is one of the histopathological factors that have been studied. They found that DFI correlated strongly with depth of stromal invasion, with DFI over 3 years of 94.6 %, for ≤ 5 mm, 86.0 % for 6-10mm, 75.2 % for 11-15mm, 71.5 % for 16-20mm, and 59.5% ≥ 21mm(16). In the same study, The DFI was 77.0% for patients with positive capillary lymphatic spaces(CLS) and 88.9% for those with negative CLS(16). In a more recent study, there were similar findings, where the depth of stromal invasion was not only found to be an independent predictor of DFI but also to have a strong correlation with other histopathological risk factors, such as LVSI and tumor diameter, among other risk factors(17).

Histological Type

Adenocarcinomas have a 2.5 times chance of recurrences, compared to squamous carcinoma, regardless of negative pelvic lymph node status(18). It is important to note that the patients in this study included patients with stage IIB disease, which may have influenced the recurrence rate. In our study, we shall be only looking at those who had stage I disease. In another study, there was no correlation between the histological type and recurrence rate(19).

Margin Status

Margin status refers to the presence of residual cervical intraepithelial neoplasia (CIN) or invasive malignancy after excision of the transformation zone. Positive margins are those involved with the disease, and negative margins are those with no disease involvement. Different reasons could result in positive margins after the excision procedures. These include attempts to preserve the length of the cervix during LEEP/ Cone biopsy to minimize the risk of preterm labor in women of reproductive age with fertility desire(20,21) and technical issues, especially in inexperienced providers. A prospective study by Alder et al(22) assessed the long-term risk of residual/persistent high-grade cervical intraepithelial neoplasia among women previously treated for cervical intraepithelial neoplasia 2/3, and how this varies according to margin status. In their study, 111 patients with CIN 2/3 were followed-up over a period of 16 years. They found that the risk of residual or persistent CIN2+ was significantly greater with involved margins in excisional treatment. However, it is important to note that this study was performed in patients with premalignant lesions. Studies about residual malignant diseases are lacking; therefore, our study will be asking a similar question, but only focusing on malignant disease as a residual disease on a hysterectomy specimen. In a study that examined the association between positive margins in patients with malignant disease, there was no significant correlation between positive margins and lymph node involvement or patient prognosis when compared to negative margins for cervical cancer(23).

What is already known about the impact of no residual disease on recurrence?

Casarin et al (24) concluded that the size of the tumor and residual disease on the hysterectomy specimen correlated with the recurrence of the disease, with patients who had the residual disease at the time of surgery, having a five- to six-fold chance of relapse compared to those who did not have a tumor in the cervix. This study included patients who underwent laparoscopic hysterectomy and excluded those with stage $1B_2$.

Wright et. al did a prospective study to evaluate the outcome of stage 1 cervical cancer with no residual tumor (T0) in hysterectomy specimens; 594 patients were included in the study, of which 29% had no residual cancer. They found T0 to have favorable outcomes; none of

the T0 patients were found to have lymph node or parametrial disease. Adjuvant therapy was not administered to any T0 patient. There were no recurrences or cancer-related deaths, and they demonstrated improved disease-free and overall survival in T0 subjects compared to subjects with residual tumors (25). The limitations of this study were as follows: patients were not risk stratified according to histological factors, such as LVSI, depth of invasion, and whether margins were clear at conization. This information was not included because conization was carried out outside the institution where the study was conducted. The follow-up period was 38 weeks. Another study by Biliatis et al(26) assessed patients with FIGO stage 1B1 cervical cancer who underwent LEEP or hysterectomy with pelvic lymph node dissection. The authors found that the absence of residual tumor (assessed by performing a second LLETZ) was associated with a lower risk of recurrence and good prognosis(26). In their study, 79% of the cases were squamous cell carcinoma, 17.7% had adenocarcinoma, and 3.3 % had adenosquamous carcinoma. The authors assessed whether the tumor was completely excised on the first LLETZ, in which case these patients were managed conservatively if the family was still desired and pelvic lymph nodes were negative. Those with completely excised tumors after the second LLETZ were also grouped as having no residual disease and were managed conservatively if fertility was desired. For patients with incompletely excised tumors after the second LLETZ, radical hysterectomy/trachelectomy was performed. Chemoradiation was performed for all patients with positive lymph nodes. There were no cases of recurrence in patients without residual disease after 56 months of follow-up. This study only reported on patients who had no residual disease, and there were no reports of patients in the group with residual disease. That is, their study's main aim was to assess conservative management in patients with no residual disease, rather than to compare outcomes of residual disease and no residual disease.

Studies designed specifically to evaluate the correlation between residual disease on hysterectomy specimens for stage 1 cervical cancer and recurrence are lacking in the literature. Some of the studies that investigated the topic concluded that residual disease was associated with poorer outcomes than no residual disease(11,12). Unfortunately, these were studies in which patients underwent simple hysterectomies for benign conditions. Therefore, their findings in terms of recurrence will be different from those of patients who

were scheduled for surgery, applicable to their stage of the disease with known histological risk factors. Other studies have only focused on the impact of no residual disease and did not report the impact of residual disease.

The Impact of HIV infection on cervical cancer

The HIV burden has seen an increase in morbidity and mortality due to cervical cancer, especially in developing countries, where HIV incidence and prevalence are high(27). In most clinical situations, more especially of acute onset, HIV seropositive women with low viral load and high CD4 count have similar treatment outcomes. The impact of HIV on progression and outcome of pre-malignant cervical lesions is well documented(28–31). There is very little in the literature regarding the treatment outcomes on patients who are HIV seropositive, who had hysterectomy for stage 1 cancer. In one study there were no recurrences of cervical cancer after hysterectomy for stage 1 cervical cancer, 3 years after surgery(27). However, the sample size for this group of patients was very small. A sub-analysis will be done where HIV positive women will be compared to HIV negative women. This will be carried out to assess whether HIV seropositivity contributes to recurrence and therefore interpret the result to our main question with this background knowledge.

3. Problem statement and rationale

This research seeks to investigate the importance and significance of residual disease on the recurrence of stage 1 cervical cancer. If the study finds residual disease to be of value in assessing the risk of recurrence, then a sub-analysis of residual disease as an independent determining factor in disease recurrence will be performed.

4. Research question

Does the presence of cancer on a hysterectomy specimen for stage 1 cervical cancer where the cancer was diagnosed using a LEEP OR CKC procedure have an impact on survival? If so, what is the predictive value?

Is there a correlation between the histological risk factors, such as LVSI, margin status after LEEP OR CKC and histological subtype (adenocarcinoma, adenosquamous and squamous cell carcinoma) and residual disease?

5. Hypothesis and alternative hypothesis

Null Hypothesis (H_0): recurrence rate in patients who had a hysterectomy for stage 1 cervical cancer with no residual disease on hysterectomy specimen is the same as in patients with residual disease on hysterectomy specimen.

Hypothesis (H_1): recurrence rate is different in patients with residual disease on hysterectomy specimens compared to those with no residual disease.

6. Methodology

6.1. Study design

Data will be collected from the records of all patients diagnosed with stage 1 cervical cancer on LEEP OR CKC and who underwent any form of hysterectomy after diagnosis. All LEEP OR CKC and post-hysterectomy surgical specimens will have been reviewed by a dedicated gynaecological pathologist from the National Health Laboratory Services (NHLS). Patients will be divided into two groups: those who were found to have residual cancer and those who did not have residual cancer on hysterectomy specimens. In each group, the following information will be assessed: time at disease recurrence following hysterectomy, histological factors such as histological type, tumour size, LVSI, Lymph node involvement, involvement of the endo- and ecto-margins, and depth of invasion. In doing so, the researchers will assess the correlation between the histological risk factors and residual cancer as a first step, and then the correlation between residual cancer and recurrence. The focus will be on those diagnosed between 1st January 2008 and 31st December 2017 to assess 5-year survival. This will be expressed as a disease-free period in percentage form over 5-years as well as overall survival (and specify the cause of death in those who died). FIGO 2009 staging will be used. Patients who had lymphadenectomy and histologically proven lymph node involvement (stage 3C-according to FIGO 2018) will be excluded.

6.2. Study setting/site

Data will be collected from the gynae oncology registry (LE 33) at Groote Schuur Hospital, database title: Radiation Oncology electronic patient registry – EPR HREC No. R016/2013 and correlated with histopathology reports from the NHLS. These will include all patients in the

Groote Schuur Hospital drainage area (Metro West and West Coast) who were diagnosed with stage 1 cervical cancer on LEEP OR CKC and underwent hysterectomy within the defined period.

6.3. Study population

6.3.1. Sample characteristics

Women who underwent hysterectomy for stage 1 cervical cancer. The study will include HIV-negative and HIV-positive women. The CD 4 count of those who are positive will be analysed. Assessment of HIV status of patients in the study aims to analyse whether there is a direct link between the HIV status and recurrence, as there is not a lot of data on the subject. This will also help identify and mitigate (by doing sub-analysis of HIV status) any potential biasness in assessing recurrence of cervical cancer in patients with residual cancer on hysterectomy specimen.

6.3.2. Inclusion criteria

- Patients who underwent hysterectomy for FIGO stage 1 cervical cancer, had been worked up and staged according to FIGO 2009. Patients must have been diagnosed via a cervical excisional procedure.
- Patients were followed up until discharge or death (whichever occurred first) and for at least five years in those who were still alive.
- Histological type: squamous cell, adenosquamous, and adenocarcinoma confirmed and available for review.

6.3.3. Exclusion criteria

- Rare histological subtypes of cervical malignancy
- Patients lost to follow-up after hysterectomy.
- Where the cancer diagnosis was made using punch biopsy of macroscopic disease
- Patients co-managed elsewhere, where clinical data and consent are not obtained.
- Patients who had lymph node involvement.

6.3.4. Sample size calculation and Recruitment Strategy

The records of all the patients who were diagnosed with early invasive cervical cancer, stage IA to IB by LEEP OR CKC, and underwent subsequent simple hysterectomy or radical hysterectomy at the Gynae-oncology Unit, Groote Schuur Hospital, and its associated hospitals in the Metro-West and West Coast. This will include only those managed between 1st January2008 and 31st December 2017. The data will be retrieved from the electronic patient record system. Therefore, the sample size will be determined by the number of patients who fulfil the above criteria over the specified period.

6.4. Data collection

6.4.1. Procedure

Once the ethics approval has been granted, data will be collected from gynae oncology records at Groote Schuur Hospital LE 33 and NHLS. Patients will be recorded by unique identifying numbers only; no names or folder numbers will be used. The records of patients who were diagnosed with early invasive cervical cancer stage IA to IB by LEEP OR CKC and underwent any form of hysterectomy at Groote Schuur Hospital and surrounding centres (that refer to Groote Schuur) between 2008 and 2017 will be retrieved from the cancer registry. Disease staging will follow the FIGO 2009 classification. Pathologic data to be retrieved include histologic subtype, depth of tumour invasion, LVSI, pelvic node status and status of the margins of excision, disease recurrence, and the site of recurrence. Excision margins on the hysterectomy specimen will be categorized as negative margins, pre-cancerous margins, and malignant margins. The disease-free period will range from the date of surgery to five years post-surgery.

Patients with no evidence of invasive cancer on the hysterectomy specimens will be classified as having no residual tumour. Histological characteristics will be obtained through a review of LEEP OR CKC specimens. The depth of tumour invasion for patients with residual tumours in their uterine specimens will be assessed. Lymph node involvement at the time of surgery will be analysed. Data on the type of additional therapy post-hysterectomy, if any, will be collected. The demographic data will include age, HIV status and CD 4 count.

6.4.2. Measures

Data that will be collected include the stage of the disease, the workup performed, and any form of post-hysterectomy anti-cancer treatment. The primary outcome of interest/measure will be whether there was a recurrence of cancer in the follow-up period. Disease-free survival and overall survival over five years will be assessed.

6.5. Data safety and monitoring plan

Data will be stored on Google Drive in password-guarded storage and under UCT account.

6.6. Data analysis plan

The association between residual disease and recurrence of cervical cancer will be assessed using the Chi-squared test, and the final data will be summarized using the observed frequencies table as shown below:

Patients who had a hysterectomy for stage 1 cervical cancer at GSH: 2008-2017			
	Residual disease	No residual disease	Total
Recurrence	a	b	a + b
No recurrence	c	d	c + d
Total	$n_1 = a + c$	$n_2 = b + d$	n = a + b + c + d
Proportion with recurrence	$p_1 = a/n_1$	$p_2 = b/n_2$	p = a + b/n

The unpaired t-test will be used where necessary to compare the mean between two variables from two unrelated groups, or the Wilcoxon rank sum test as necessary, where the P-value will be interpreted. The association between demographic and clinicopathological features and disease recurrence will also be evaluated. Survival curves will be addressed by the Kaplan-Meir curves. A P-value of less than 0.05 will be considered statistically significant. This is based on previous studies that investigated a similar question. Histological variables such as LVSI, depth of invasion, and margin status after LEEP will also be analyzed, and

correlations between these variables and recurrence and residual disease should be assessed. Data will be entered in Excel. Statistical analysis will be performed using a statistical package for the social sciences (SPSS) for Windows and a statistician will be consulted for input and expertise on the above-mentioned methods and possibly other methods. A sub-analysis in patients with residual cancer will be done, assessing the impact of additional therapy versus no additional therapy as shown below:

Patients with residual cancer on hysterectomy specimen (a sub-analysis from the above group)			
	Additional therapy	No additional therapy	Total
Recurrence			
No recurrence			
Total			
Proportion with recurrence			

The treatment outcomes with regards to HIV status and rate of cancer recurrence will be assessed as follow:

All patients who had hysterectomy for cervical cancer stage 1 diagnosed after LEEP OR CKC			Total
	Recurrence	No recurrence	
HIV positive CD4 >350 CD4 <350			
HIV Negative			
Total			
Proportion with recurrence			

To further assess the correlation between the HIV status and recurrence, patients who HIV positive will be assessed further, regarding the additional therapy received. This is to minimise biasness from a possible protective effect (from recurrence) that additional therapy may provide.

HIV Positive patients who had hysterectomy for stage 1 cervical cancer diagnosed after LEEP OR CKC			
	Additional therapy	No additional therapy	Total
Recurrence			
No recurrence			
Total			
Proportion with recurrence			

In assessing the correlation between histological risk factors and residual disease, a similar approach will be followed.

Histological Findings on specimen after LEEP OR CKC		Findings on uterine specimen after hysterectomy		Total
		Residual cancer	No residual cancer	
Margins positive with CIN 2+				
Margins positive with cancer				
Histological subtype: Squamous Adenosquamous Adenocarcinoma				
Total				
Proportion with residual cancer				

7. Ethical and regulatory compliance

7.1. Approval by regulatory authorities

Ethical approval will be obtained from the University of Cape Town HREC. Study approval will also be obtained from the NHLS and Groote Schuur Department of Gynaecology.

The study will be conducted in accordance with the Declaration of Helsinki and Department of Health guidelines for good clinical practice. Patients will be identified using only numbers/identifiers, and no names or folder numbers will be entered into the datasheet.

7.2. Informed consent

The study will use an HREC approved data base: Radiation Oncology electronic patient registry – EPR HREC No. R016/2013. Approval will need to be obtained from Groote Schuur Hospital since hospital records will be analysed.

7.3. Risks and benefits to participants

There is no risk to the participants as all the information is retrospective and will be kept confidential. Benefits may not be direct to the participants but may improve knowledge. The information might assist with future management of cervical cancer.

7.4. Social value

The results from this study will be used to assess whether the presence of residual disease in a hysterectomy specimen can be used as an additional form of risk stratification for the recurrence of cervical cancer after hysterectomy. This information may then further advise on follow-up strategies for these patients and whether adjuvant therapy is required, as determined by the presence of residual disease in the hysterectomy specimens. The researchers aim to highlight or give an idea of what case fatality ratio might be in low-middle income countries and to give a South African perspective.

8. Study limitations and assumptions

The sample may be small due to time constraints, however, should that be the case a bigger study in the future may be carried out. Another limiting factor may be that patients usually present late with advanced disease and, therefore, cannot be included in this study, which may result in an even smaller sample size. The fact that the study is retrospective may introduce recall bias, especially if some of the information is missing from the folders. Furthermore, patients in Groote Schuur may have other co-morbidities, which would then harm the generalisability of the study findings.

9. Conflict of interest

None to declare.

10.Study budget

We will apply for funding from the departmental research fund, to assist with data collection, analysis, and publishing.

Item/Activity	Estimated price
Statistician	R2400
Stationery and Printing	R1000
Possible publication	R8000

11.Dissemination of results

Results will be shared with the Department of Gynae Oncology at Groote Schuur and may be presented in relevant congresses with other medical practitioners if there are significant findings.

12. References

1. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. Second edition. Geneva: World Health Organization; 2021.

2. Schalkwyk C, Moodley J, Welte A, Johnson LF. Modelling the impact of prevention strategies on cervical cancer incidence in South Africa. Int J Cancer. 2021 Oct 15;149(8):1564–75.

3. Arrossi S, Matos E, Zengarini N, Roth B, Sankaranayananan R, Parkin M. The socio-economic impact of cervical cancer on patients and their families in Argentina, and its influence on radiotherapy compliance. Results from a cross-sectional study. Gynecol Oncol. 2007 May;105(2):335–40.

4. Ntinga S, Maree J. Living with the late effects of cervical cancer treatment: a descriptive qualitative study at an academic hospital in Gauteng. South Afr J Gynaecol Oncol. 2015 Jan 2;7(1):21–6.

5. Ngcobo NJ, Burnett RJ, Cooper S, Wiysonge CS. Human papillomavirus vaccination acLEEP or CKCtance and hesitancy in South Africa: Research and policy agenda. S Afr Med J. 2018 Dec 13;109(1):13.

6. Russell VL, Ogilvie G, Beksinska M, Nyrenda M, Mitchell-Foster S, Lavoie J, et al. Human papillomavirus and cervical cancer risk perLEEP or CKCtion and vaccine acLEEP or CKCtability among adolescent girls and young women in Durban, South Africa. S Afr Med J. 2020 Aug 31;110(9):887.

7. HPV DNA Testing in Cervical Cancer Screening: Results From Women in a High-Risk Province of Costa Rica.

8. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Jan;17(1):64–84.

9. Margolis B, Cagle-Colon K, Chen L, Tergas AI, Boyd L, Wright JD. Prognostic significance of lymphovascular space invasion for stage IA1 and IA2 cervical cancer. Int J Gynecol Cancer. 2020 Jun;30(6):735–43.

10. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Management of occult invasive cervical cancer found after simple hysterectomy. Ann Oncol. 2009 Oct 25;21(5):994–1000.

11. Crane CH, Schneider BF. OCCULT CARCINOMA DISCOVERED AFTER SIMPLE HYSTERECTOMY TREATED WITH POSTOPERATIVE RADIOTHERAPY. 1999.

12. Andras EJ, Fletcher GH, Rutledge F. Radiotherapy of carcinoma of the cervix following simple hysterectomy. Am J Obstet Gynecol. 1973 Mar 1;115(5):647–55.

13. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A Randomized Trial of Pelvic Radiation Therapy versus No Further Therapy in Selected Patients with Stage IB Carcinoma of the Cervix after Radical Hysterectomy and Pelvic Lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol. 1999 May;73(2):177–83.

14. Human Papillomavirus and Related Diseases Report SOUTH AFRICA [Internet]. Available from: www.hpvcentre.net

15. WHO Framework for strengthening and scaling-up services for the management of invasive cervical cancer [Internet]. 2020. Available from: http://apps.who.int/bookorders.

16. Delgado G, Bundy B, Zaino R, Sewn B uwe, Creasman WT, Major F. Prospective Surgical-Pathological Study of Disease-Free Interval in Patients with Stage I6 Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. Vol. 38, GYNECOLOGIC ONCOLOGY. 1990 p. 352–7.

17. Zhu J, Cao L, Wen H, Bi R, Wu X, Ke G. The clinical and prognostic implication of deep stromal invasion in cervical cancer patients undergoing radical hysterectomy. J Cancer. 2020;11(24):7368–77.

18. Samlal RA &#xfffd;K., Velden J van der, Kate FJ &#xfffd;W. T, Schilthuis MS, Hart AA &#xfffd;M., Lammes FB. Surgical pathologic factors that predict recurrence in stage IB and IIA cervical carcinoma patients with negative pelvic lymph nodes. Cancer. 1997 Oct 1;80(7):1234–40.

19. Tinga DJ, Bouma J, Aalders JG. Patients with squamous cell versus adeno(squamous) carcinoma of the cervix, what factors determine the prognosis? Int J Gynecol Cancer. 1992 Mar;2(2):83–91.

20. Sopracordevole F, Carpini GD, Del Fabro A, Serri M, Alessandrini L, Buttignol M, et al. Role of Close Endocervical Margin in Treatment Failure After Cervical Excision for Cervical Intraepithelial Neoplasia: A Retrospective Study. Arch Pathol Lab Med. 2019 Aug 1;143(8):1006–11.

21. Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol. 2017 Dec;18(12):1665–79.

22. Alder S, Megyessi D, Sundström K, Östensson E, Mints M, Belkić K, et al. Incomplete excision of cervical intraepithelial neoplasia as a predictor of the risk of recurrent disease—a 16-year follow-up study. Am J Obstet Gynecol. 2020 Feb 1;222(2):172.e1-172.e12.

23. Nagao Y, Yokoi A, Yoshida K, Sumi M, Yoshihara M, Tamauchi S, et al. Clinical effects of cervical conization with positive margins in cervical cancer. Sci Rep. 2021 Dec 2;11(1):23288.

24. Casarin J, Buda A, Bogani G, Fanfani F, Papadia A, Ceccaroni M, et al. Predictors of recurrence following laparoscopic radical hysterectomy for early-stage cervical cancer: A multi-institutional study. Gynecol Oncol. 2020 Oct 1;159(1):164–70.

25. Wright JD, Grigsby PW, Rader JS, Mutch DG, Powell MA, Gao F, et al. Effect of a T0 radical hysterectomy specimen on survival for early stage cervical cancer. Gynecol Oncol. 2007 Nov;107(2):280–4.

26. Biliatis I, Kucukmetin A, Patel A, Ratnavelu N, Cross P, Chattopadhyay S, et al. Small volume stage 1B1 cervical cancer. Gynecol Oncol. 2012 Jul;126(1):73–7.

27. Mapanga W, Singh E, Feresu SA, Girdler-Brown B. Treatment of pre- and confirmed cervical cancer in HIV-seropositive women from developing countries: a systematic review. Syst Rev. 2020 Dec;9(1):79.

28. Lodi CT, Michelin MA, Lima MI, Teixeira NC, Adad SJ, Murta EF, et al. Factors associated with recurrence of cervical intraepithelial neoplasia after conization in HIV-infected and noninfected women. Arch Gynecol Obstet. 2011 Jul;284(1):191–7.

29. Reimers LL, Sotardi S, Daniel D, Chiu LG, Arsdale AV, Wieland DL, et al. Outcomes after an excisional procedure for cervical intraepithelial neoplasia in HIV-infected women. Gynecol Oncol. 2010 Oct;119(1):92–7.

30. Nappi L, Carriero C, Bettocchi S, Herrero J, Vimercati A, Putignano G. Cervical squamous intraepithelial lesions of low-grade in HIV-infected women: recurrence, persistence, and progression, in treated and untreated women. Eur J Obstet Gynecol Reprod Biol. 2005 Aug;121(2):226–32.

31. Rahatgaonkar V, Deshpande A, Oka G. Screening for cervical cancer in HIV-infected women: A review of literature. Indian J Cancer. 2021;0(0):0.

6. Chapter 2 Publication-ready Manuscript

TITLE:

Impact of no residual versus residual disease after hysterectomy for stage 1 cervical cancer on recurrence

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Supervisor: A/Professor N. Mbatani

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Co-supervisor: Dr. N. Fakie

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Statistics : A/Professor G. Petro

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Conflict of interest

The authors have no conflict of interest to declare

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Impact of no residual versus residual disease after hysterectomy for stage 1 cervical cancer on recurrence

S. Ntunja, N. Fakie and N. Mbatani

Abstract

Background: Histopathological risk factors for recurrence of cervical cancer following hysterectomy for stage I disease are well established. The impact of residual disease after LEEP in patients undergoing hysterectomy for stage 1 cervical cancer on recurrence has not been extensively studied.

Design and Methods: Records of all patients who underwent hysterectomy for stage I cervical cancer from 1st January 2008 to 31st December 2017 were reviewed. The follow-up period was at least 60 months or until death. Data collected included demographic information, histopathological risk factors, residual disease status on hysterectomy specimen, treatment modalities and recurrence rates.

Results: We analysed 147 patients: 55 stage $1A_1$, 11 stage $1A_2$, 80 stage $1B_1$ and 1 with stage $1B_2$. Median age was 47 (27 – 76) years. All patients had a cervical excision procedure (LEEP OR CKC) for histological diagnosis, followed by simple hysterectomy (29.6%), simple hysterectomy with lymphadenectomy (12.3%) or radical hysterectomy (58.2%). The prevalence of residual disease on hysterectomy specimen was 56.5%, versus no residual disease (43.5%). The overall recurrence rate was 9.5%. Thirty patients received adjuvant radiotherapy, of these, 29 had residual disease, with 6.2% of them developing disease recurrence. The overall survival (OS) and disease-free interval (DFI) were 96.6% and 91.6% respectively.

Conclusion: This study found a correlation between presence of residual disease and known histological risk factors, that is size of the lesion and depth of stromal invasion. However, there was no strong correlation between residual disease and lymphovascular space invasion in this study. All patients that had recurrence had residual disease. When excluding those with lymph node metastasis, there were no recurrences in the group with no residual disease.

Key words: cervical cancer, residual disease, histopathological risk factors, cervical excision procedure, cervical cancer recurrence

Introduction

In 2020, an estimated 604 127 women were diagnosed with cervical cancer worldwide and about 342 000 women died from the disease[1]. Cervical cancer was ranked second commonest cancer in women aged 15 to 44 years by International Agency for Research in Cancer (IARC), with a 19 per 100 000 mortality rate in South Africa[2].

The risk factors that determine adjuvant treatment of stage I cervical cancer have been well documented in the literature and they include positive margins, LVSI, depth of stromal invasion, size of the lesion, parametrial involvement and lymph node involvement[3-6]. The presence of residual disease has been shown to be a poor prognostic factor in previous studies, and the absence of residual disease to be a good prognostic factor.

However, several confounding factors were identified, including the inclusion of patients who underwent laparoscopic hysterectomy, the absence of risk stratification based on known histological risk factors, and a shorter follow-up period[9].

This study aimed to assess whether there is any correlation between residual disease found on hysterectomy specimens for stage I cervical cancer and the recurrence of cervical cancer, where the diagnosis of cancer was made using a cervical excision procedure (LEEP OR CKC). This study differs from previous research in two key aspects. First, it assesses recurrence in both patients with and without residual disease. Second, it considers established determinants of disease recurrence when drawing conclusions. While Wright et al.[9] conducted a similar study, their follow up period was limited to 38 weeks.

Objectives

To evaluate the recurrence rate and survival related to residual disease in patients with stage 1 cervical cancer who underwent hysterectomy. The secondary objectives include determining the proportion of patients with positive margins after LEEP OR CKC, assessing the known histological risk factors and correlation of these to residual disease in the hysterectomy specimen and cancer recurrence.

Study design and methodology

This was a retrospective cohort study of all women diagnosed with stage 1 cervical cancer on LEEP OR CKC and underwent hysterectomy at Groote Schuur Hospital (GSH) between 2008 and 2017. Ethics approval was granted from the University of Cape Town, Health Science

faculty Research Committee, approval number: HREC REF 737/2023. Data was collected from the gynaecologic oncology registry at GSH, database title: Radiation Oncology electronic patient registry – EPR HREC No. R016/2013.

For each patient that fulfilled the criteria, the presence or absence of residual disease, lymphovascular space involvement (LVSI), histological type of cancer, depth of invasion, margin status after LEEP OR CKC were all reported by pathologist on National Health Laboratory Services (NHLS) reports. Demographic and any additional information such as HIV status and CD 4 count at diagnosis, medical/surgical co-morbidities, treatment modality, recurrence of the disease was acquired from the patients' folders

Inclusion criteria:

- Patients who underwent hysterectomy for FIGO stage 1 cervical cancer, confirmed on clinical examination/pathology (LEEP OR CKC) or histology, were evaluated and staged according to the FIGO 2009 guidelines.
- Patients were followed up for at least 5 years, or death (whichever occurred first).

Exclusion criteria was as follows:

- Loss to follow up.
- Rare histological subtypes.
- Disease beyond the cervix.

Treatment details

Staging

Staging was according to FIGO 2009, whereby in stage 1 the cervical carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).

The FIGO 2009 staging system did not classify lymph node metastasis as advanced-stage cervical cancer. Patients that had lymph node metastasis in our study were included as stage I, however, these were analysed separately as they no longer form part of stage I disease in FIGO 2018. Clinically visible lesions (stage 1B1: <4cm and stage 1B2 >4cm) are big lesions and they are known to be associated with low disease-free interval, as demonstrated by Delgado[10]. These patients were analysed separately. Metastatic work-up included: Ultrasound scan of the pelvis and abdomen to look for hydronephrosis and metastasis to the liver. Chest X-rays were done as part of staging and preparing the patients for anaesthesia.

Hysterectomy

All hysterectomies were either performed or supervised by a gynaecologic oncologist. Patients that had laparoscopic hysterectomy were not included in the study, as the laparoscopic route has been previously shown to be associated with lower rates of disease free survival and overall survival than laparotomy[11]. We used a tailored surgical approach which was based on tumor size, presence of LVSI, and margin status, to ensure comprehensive treatment while minimizing overtreatment. Patients with Stage 1A without LVSI had simple hysterectomy. Patients with stage 1A2 or with LVSI had simple hysterectomy with lymph node dissection if margins were clear after LEEP or had radical hysterectomy if margins were positive after the LEEP. All patients with stage 1B had radical hysterectomy.

Adjuvant radiotherapy

Multi-disciplinary team discussions included gynaecologic oncologists, pathologists, oncologists to assess a need for adjuvant therapy. The assessment was based on Sedlis criteria, which include greater than one-third stromal invasion ≥ 10mm, LVSI or cervical tumor diameter more than 4 cm[12,]

Follow up and diagnosis of recurrence

1. **Follow-Up Schedule**:
    - **First 3 Years**: Patients were followed up every 3 months.
    - **Years 4–5**: Follow-up every 6 months.
    - **After 5 Years**: Discharged to level 2 hospitals for annual lifelong follow-ups.
2. **Assessment During Follow-Up**:
    - **Routine Evaluation**:
        - History taking and clinical examination at every visit.
        - Annual vault smear for cervical cancer recurrence or inspection and examination of the vault area for those patients who had received any form of pelvic / vault radiotherapy.
    - **Imaging**:
        - Not performed routinely.
        - Imaging was done only if there was clinical suspicion of a recurrence based on history or examination findings.

Statistical analysis

Statistical analysis was performed using a statistical software package, STATA. We summarised continuous variables using mean and categorical variables using percent. We tested the association between categorical variables using Chi-squared test or Fisher's exact test. The cumulative probabilities of recurrence free survival and probabilities of dying for patients with and without residual cancer were estimated using Kaplan-Meier estimation method and compared using log-rank test. We reported hazard ratio (HR) as measures of association with corresponding 95% confidence interval. The association between the clinicopathological features, such as LVSI, size and depth of the lesion, histological type, was assessed. Statistical significance was set at $p < 0.05$. Data was extracted from the Gyne Oncology database [UCT HREC Ref number. R016/2013]

Results

Demographic and clinical data

A total of 147 patients were included. Patients included in the study were patients who had a hysterectomy for stage 1 cervical cancer between 2008 and 2017, who fulfilled the inclusion criteria. Eighteen patients were excluded. All 18 patients had surgery outside Groote Schuur Hospital and their folders were missing.

The mean age of the patients was 47 years, range (27 – 76). Twenty three percent of the patients were HIV positive, of which 32.3 % had CD 4 count less than 350. There was no correlation between the HIV status and residual disease (Table I). The majority (53.7%) of the patients had no co-morbidities.

Table I: Summarises demographic and clinical data

Age (years): - **Mean 47** - **Range (27 – 76)**		
HIV Status	Residual disease	No residual disease
Negative	74 (89.2%)	39 (60.9%)
Positive	9 (10.8%)	25 (39.1%)
CD 4 count > 350	6 (66.7%)	8 (32%)
CD 4 count < 350	3 (33.3%)	16 (64%)
Unknown	0	1 (4.0%)
Comorbidities:		
No comorbidities	79 (53.7%)	
Hypertension	44 (29.9%)	
Respiratory disease	3 (2.0%)	
Autoimmune	2 (1.4%)	
Previous abdominal surgery	5 (3.4%)	
Other	11 (7.5%)	

Histological data

The majority, 54.4 % had stage $1B_1$ (≤ 4cm) followed by stage $1A_1$ with 37.4%. One patient had a tumour which was more than 4cm (Stage $1B_2$) (**figure 4)**. For patients with residual disease in the hysterectomy specimens, the depth of invasion from the LEEP specimen was added to the depth of invasion (DOI) from the hysterectomy specimen. A total of 64 patients had stage 1A disease, of the 64 patients, four patients had recurrence, making recurrence rate of 6.3%, when stage 1B was excluded (**figure 1**). The patient with stage $1B_2$ (> 4 cm) that was included in the study had residual disease and LVSI, but no recurrence after 60 months.

Loop electrosurgical procedures were commonly performed, 70.8%, compared to cold knife conization (CKC) (29.2%). Thirty of the patients with stage $1A_1$ had a LEEP, while 25 had

cold knife cone. This was influenced by the high number of patients requiring repeat excision procedures under general anaesthesia due to a shortened cervical length. In stage $1A_2$, 10 patients had a LEEP and 1 had a CKC. Residual disease was observed in more than 50% of patients who had positive margins following a cervical excision procedure, highlighting the strong association between margin status and persistent cervical pathology. Negative margins post LEEP OR CKC were protective of developing a residual disease, with 48% of patients that had negative margins for cancer in the group with no residual disease and 51.8% of patients with positive margins for cancer in the group with residual disease, with p value < 0.0001 for margin status post LEEP OR CKC **(table II)**. Undetermined margin status (charred margins-electrocautery artefacts) after LEEP was shown to be associated with residual disease.

The most common cell type was squamous cell carcinoma, (81.6 %), followed by adenocarcinoma (10.9%) while 4.1% had adeno-squamous. There was no correlation between residual disease and histological cell type, p value 0.2.

The depth of stromal invasion was associated with residual disease, with 49.4% of patients in the residual disease group having an invasion depth >5 mm, compared to 10.9% in the no residual disease group. A shallower depth of stromal invasion on the LEEP specimen appeared to strongly correlate with the absence of residual disease, suggesting a potential protective effect (**table II)**.

In our study, 27.8% of the patients had LVSI, with 65.9% of these patients in the group with residual disease, versus 34.2% in the group with no residual disease. In addition, 20 (41.7%) patients in the group with depth of invasion > 5mm, had LVSI. However, there was no statistics significance found, with p value 0.23 (**Table II**).

Lymph nodes were positive for malignancy in 13 patients. Of the 13 patients, 10 were stage $1B_1$ and three were $1A_2$. All these patients were offered adjuvant radiotherapy. The recurrence rate in patients with lymph node involvement was noted to be high. In the 132 patients with no lymph node involvement, 9 patients had recurrence, and 1 patient's lymph node status was not documented. This reduced the recurrence rate from 9.5% (when patients with lymph node involvement were included) to 7.3% (when patients with lymph node involvement were excluded) (**Figure 2**). A further sub analysis demonstrated an association between lymph node metastasis and residual disease, with 92.9% of the patients with lymph

node involvement in the group with residual disease, and a statistically significant p value 0. 004 (**Table II**).

Table II: Summarises the associated impact of histological risk factors on presence of residual disease.

	Residual disease	**No residual disease**	**P value**
Patients	83 (56.5)	64 (43.5)	
Stage			< 0.0001
IA_1	15 (18.1)	40 (62.5)	
IA_2	7 (8.43)	4 (6.3)	
IB_1	60 (72.3)	20 (31.3)	
IB_2	1 (1.2)	0	
Histology			0.2
Squamous	63 (52.5)	57 (47.5)	
Adenocarcinoma	11 (68,8)	5 (31.3)	
Adenosquamous	5 (83)	1 (16.7)	
Other	4 (80)	1 (20)	
LVSI	27 (65.9)	14 (34.2)	0.23
Lymph node involvement	13 (92.9)	1 (7.1)	0.004
Stromal invasion			< 0.0001
< 3mm	21(25.3)	36 (56.3)	
3 – 5 mm	19 (22.9)	14 (21.9)	
> 5mm	41 (49.4)	7 (10.9)	
Unknown	2 (2.1)	6 (9.38)	
Margins post LEEP OR CKC:	43 (51.8)	18 (28.1)	< 0.0001
Positive for cancer	18 (21.7)	31 (48.4)	
Negative for cancer	1 (1.2)	9 (14.1)	
Close margins	21 (25.3)	6 (9.38)	
Undetermined			

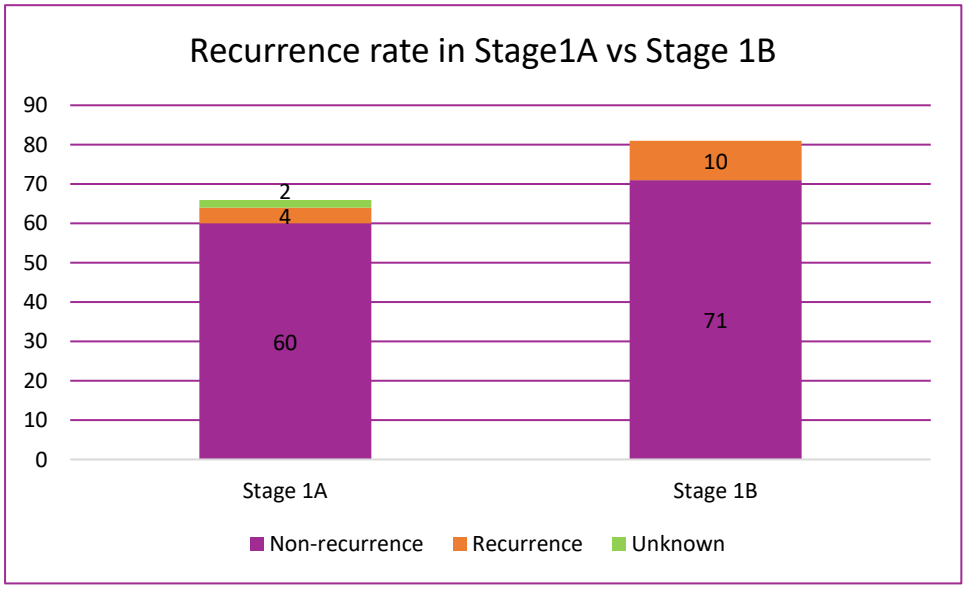

Figure 1: Demonstrating recurrence rate between stage 1A and stage 1B

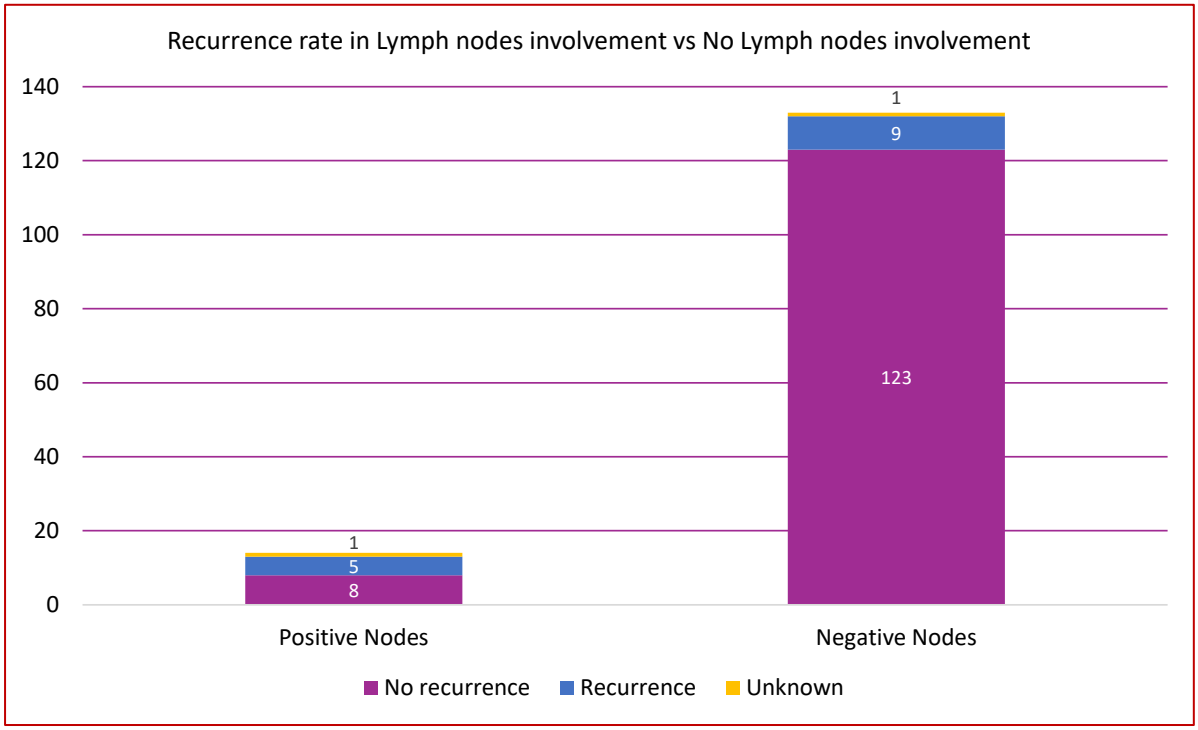

Figure 2: recurrence rate in patients without lymph node involvement vs those with lymph node involvement

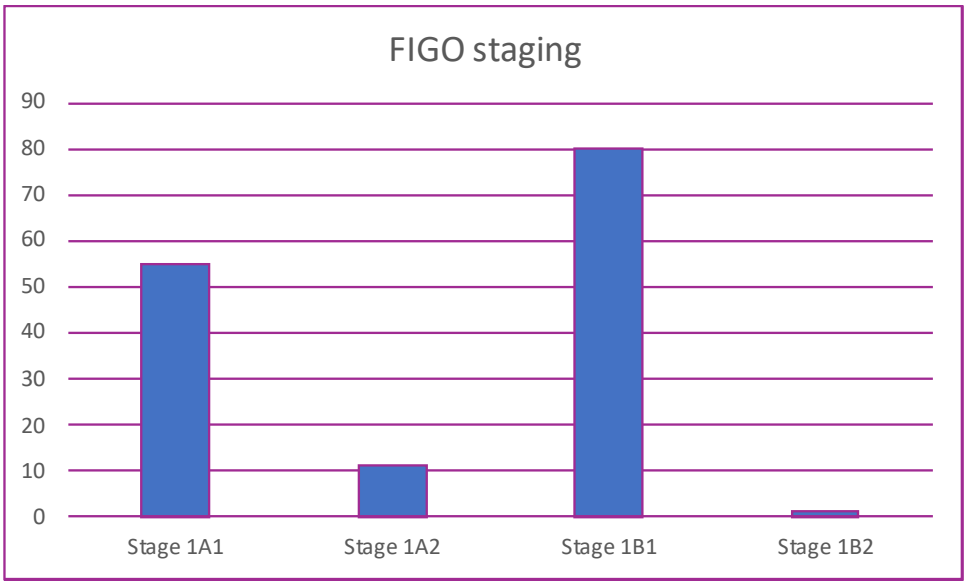

Figure 3: illustrates Percentage representation of each FIGO 2018 stage I sub-stage

Treatment data

All 147 patients included in the study had a hysterectomy. Most patients, 58.2 % had radical hysterectomy, 29.6% had a simple hysterectomy, while 12.3 % had a hysterectomy and lymphadenectomy. Simple hysterectomy was mostly performed in early disease, with 73% of this surgery done in stage $1A_1$ patients. Radical hysterectomy was mostly performed (96%) in stage $1B_1$ (**Table IV**).

Twenty-nine of the 30 patients who received adjuvant therapy were in the group with residual disease, 6.2% of them developed recurrence despite adjuvant radiotherapy (**Table V**).

Outcomes

A high percentage (42%) of patients had positive margins for cancer post LEEP OR CKC (**See figure 2**). There was a correlation between positive margins for cancer and residual disease, with 70% of patients with positive margins in the group with residual disease. Twenty-seven patients had undetermined margin status, 77% had residual disease. There was no association between close margins and residual cancer (**Table II**).

There was a marginal difference in prevalence of residual disease (56.5%), versus no residual disease (43.5%). The rate of cancer recurrence in a 5-year period was 9.5% in our study. Of the patients that had recurrence, 92.9% had residual disease and only 7.1% had no residual

disease (**Table III**). The odds ratio of recurrence was 8.3 in patients with residual disease, with a statistically significant p-value of 0.015.

This study demonstrated a reduction in DFI in patients with residual disease when compared to patients with no residual, as shown in Kaplan-Meir survival curve (Figure 3). The time at risk of recurrence in patients with residual disease was 12 months. The Hazard ratio for recurrence was 10.65, 95% CI 1.39-81.44, with a significant p-value 0.0016.

Table III: Comparing recurrence rate in patients with residual cancer vs no residual cancer

Recurrence in 60 months				
	No	Yes	Unknown	total
Residual disease	69 (83.1%)	13 (15.7%)	1 (1.2%)	83 (100%)
No residual disease	62 (96.9 %)	1 (1.6%)	1 (1.6%)	64 (100 %)
Total	131 (89.1%)	14 (9.5%)	2 (1.4%)	147 (100%)

Pearson $Chi^2 = 8.34$, p value = 0.015

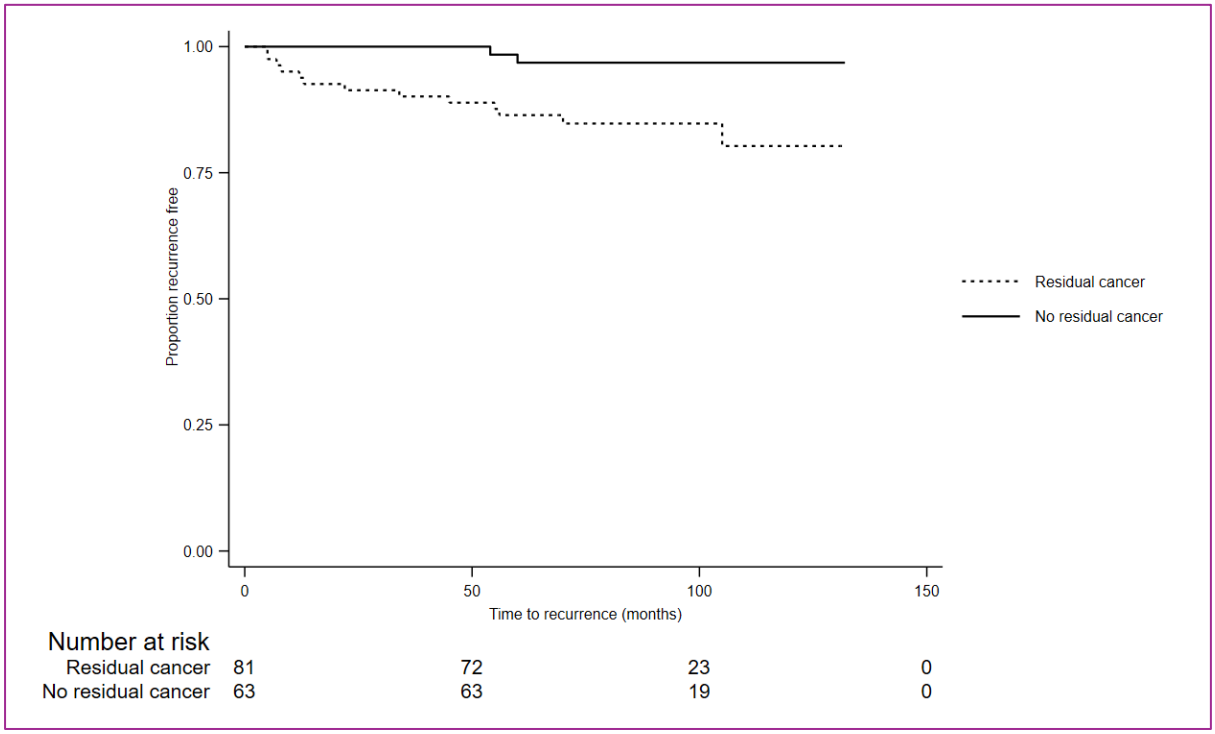

Figure 3: Kaplan-Meir curve demonstrating disease free interval in patients with residual disease vs those with no residual disease

Discussion

This retrospective cohort study found recurrence of cervical cancer after hysterectomy for stage 1 disease to be 9.5% when patients were staged using FIGO 2009. The recurrence was 6.3 % and 6.5% when patients with stage 1B and lymph node metastasis, respectively, were excluded. These findings are in keeping with findings by Taarnhøj et. al[13], in their study, the recurrence rate was 6.5%. The sub-analysis of patients with no lymph node involvement was to accommodate the FIGO 2018 staging, while the sub-analysis excluding stage 1B was to assess recurrence rate in smaller lesions after cervical excision procedure had been performed. These were efforts to limit both lymph node metastasis and bigger cervical lesions as confounding factors in results analysis of the impact of residual versus no residual disease on recurrence.

We found an association between the presence of residual disease and recurrence after hysterectomy for stage 1 cancer with odds ratio of 8.3 and a statistically significant p-value of 0.015. It was not possible to isolate the presence of residual disease factor as a sole determinant of disease recurrence in our study. However, there was a strong correlation between the above-mentioned histological risk factors and the presence of residual disease (Table II). In stage 1A, 60.1% of the patients within this stage of the disease had a LEEP and 39.3% had a CKC. All five patients that had undetermined margins were patients that had a LEEP, with no patient with undetermined margins in the CKC group. This is in keeping with findings from previous studies, that demonstrated that LEEP to be associated with tissue fragmentation and uninterpretable result, when compared with CKC[14-15]. The difficulty with interpreting margins was found to be associated with residual disease in our study. Regarding positive margins post cervical excision procedure, 4 out of 26 patients with stage 1A who had CKC had margins positive for cancer, versus 10 who had positive margins of 30, post LEEP, making the positive margins 15.4 % versus 25 % respectively. This sub-analysis aims to highlight the different outcomes post cervical excision procedure in early-stage disease.

A study by Crane, et al concluded that patients with residual disease perform poorly post hysterectomy and with radiotherapy, but radiotherapy alone maybe less morbid, compared to re-operation[8]. In a meta-analysis by Rogers, et al, two randomised controlled trials concluded that there was no significant difference in survival at 5 years between women who received radiation and those who received no further treatment[16]. However, radiation therapy was found to be associated with lower risk of disease progression in their meta-analysis. In our

study, we analysed the recurrence rate in patients who had radiotherapy, in the group with residual disease and found no difference in disease recurrence, in keeping with the above-mentioned studies.

Overall survival and disease-free interval at 60 months were 96.6% and 91.6% respectively. The DFI and OS in our study was significantly higher than previous study by Mehta et al, where the OS and DFI were 85.0 % and 81.8% respectively[17]. This is likely because in their study, stage IIA disease was included. Thirteen patients in the group with residual disease developed recurrence, while 1 patient in the no residual group developed recurrence in our study. The hazard ratio was 10.65, 95%CI 1.39-81.44, p=0.0016. The one patient who developed recurrence (with no residual disease) had lymph node involvement and lymphovascular space invasion. This means that, when patients with lymph node involvement were excluded, there was no recurrence in the group with no residual disease.

To our knowledge, there are no studies that have been designed to assess risk of recurrence in patients diagnosed on LEEP OR CKC with stage 1 disease, with and without residual disease on hysterectomy specimen. We have found the rate of residual disease to be high in patients who had recurrent disease post hysterectomy for stage 1 cervical cancer. The likelihood of recurrence higher in the first 12 months after hysterectomy in those that developed recurrence.

Limitations of our study include a retrospective nature of the study, with 18 records of the patients missing and had to be excluded from the study.

The strength of our study is that a sub analysis of patients with stage 1A disease was performed, to assess the recurrence of smaller lesions post hysterectomy in patients who had cervical excision procedures. Not only did we assess the impact of no residual disease (as in previous studies), but we assessed the impact of residual disease as well. We were able to analyse the association between known histological risk factors for recurrence and residual disease. This could be an additional important strategy in risk assessment for recurrence and therefore patient counselling, follow up and treatment strategies.

We recommend a similar study that assesses only patients with residual disease and analyse how this performs as a predictor of recurrence when compared with other known risk factors for disease recurrence.

Conclusion

Patients who had hysterectomy for stage 1 cervical cancer had a recurrence rate of 9.5% when those with lymph node involvement were included and the recurrence dropped to 7.3% when patients with lymph node involvement were excluded. This is in keeping with findings from the international studies. All patients that had recurrence had residual disease on hysterectomy specimen. Absence of residual disease was found to be protective of recurrence. The was a strong correlation between known histological risk factors, depth of stromal invasion, size of the lesion with residual disease. This study demonstrated a correlation between residual disease and recurrence of cervical cancer after hysterectomy for stage 1 disease. We recommend that residual disease be considered, in addition to other risk factors, as a predictor for disease recurrence after hysterectomy for stage 1 cervical cancer.

Conflict of interest

The authors declare no conflict of interest

Funding source

No funding source to be declared

Research committee approval

This retrospective data review was approved by University of Cape Town, Health Sciences Human Research Ethics Committee. Approval number: HREC REF 737/2023

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Bibliography

1. World Health Organization, Special Programme of Research, Development, and Research Training in Human Reproduction (World Health Organization). WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. Second edition. Geneva: World Health Organization; 2021. https://iris.who.int/bitstream/handle/10665/350652/9789240040434-eng.pdf. Accessed 30 December 2024.

2. Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 10 March 2023. https://hpvcentre.net/statistics/reports/XWX.pdf. Accessed 30 December 2024.

3. Margolis B, Cagle-Colon K, Chen L, Tergas AI, Boyd L, Wright JD. Prognostic significance of lymphovascular space invasion for stage IA1 and IA2 cervical cancer. Int J Gynecol Cancer. 2020 Jun;30(6):735–43. http://dx.doi.org/10.1136/ijgc-2019-000849

4. Zhu J, Cao L, Wen H, Bi R, Wu X, Ke G. The clinical and prognostic implication of deep stromal invasion in cervical cancer patients undergoing radical hysterectomy. J Cancer. 2020;11(24):7368–77. http://dx.doi.org/10.7150/jca.50752

5. Tinga DJ, Bouma J, Aalders JG. Patients with squamous cell versus adeno(squamous) carcinoma of the cervix, what factors determine the prognosis? Int J Gynecol Cancer. 1992 Mar;2(2):83–91. http://dx.doi.org/10.1046/j.1525-1438.1992.02020083.x

6. Wenzel HHB, Van Kol KGG, Nijman HW, Lemmens VEPP, Van Der Aa MA, Ebisch RMF, et al. Cervical cancer with ≤5 mm depth of invasion and >7 mm horizontal spread — Is lymph node assessment only required in patients with LVSI? Gynecologic Oncology. 2020 Aug;158(2):282–6. http://dx.doi.org/10.1016/j.ygyno.2020.04.705

7. Casarin J, Buda A, Bogani G, Fanfani F, Papadia A, Ceccaroni M, et al. Predictors of recurrence following laparoscopic radical hysterectomy for early-stage cervical cancer: A multi-institutional study. Gynecologic Oncology. 2020 Oct;159(1):164–70. http://dx.doi.org/10.1016/j.ygyno.2020.06.508

8. Crane CH, Schneider BF. Occult carcinoma discovered after simple hysterectomy treated with postoperative radiotherapy. International Journal of Radiation

Oncology*Biology*Physics. 1999 Mar;43(5):1049–53. http://dx.doi.org/10.1016/S0360-3016(98)00523-9

9. Wright J, Grigsby P, Rader J, Mutch D, Powell M, Gao F, et al. Effect of a T0 radical hysterectomy specimen on survival for early-stage cervical cancer. Gynecologic Oncology. 2007 Nov;107(2):280–4. http://dx.doi.org/10.1016/j.ygyno.2007.06.013

10. Delgado G, Bundy B, Zaino R, Sewn B, Creasman W, and Major F. Prospective Surgical-Pathological Study of Disease-Free Interval in Patients with Stage IB Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. GYNECOLOGIC ONCOLOGY 1990; 38: 352-357. http://dx.doi.org/10.1016/0090-8258(90)90072-S

11. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018 Nov 15;379(20):1895–904. http://dx.doi.org/10.1056/NEJMoa1806395

12. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A Randomized Trial of Pelvic Radiation Therapy versus No Further Therapy in Selected Patients with Stage IB Carcinoma of the Cervix after Radical Hysterectomy and Pelvic Lymphadenectomy: A Gynecologic Oncology Group Study. Gynecologic Oncology. 1999 May;73(2):177–83. http://dx.doi.org/10.1097/00006254-199909000-00017

13. Taarnhøj GA, Christensen IJ, Lajer H, Fuglsang K, Jeppesen MM, Kahr HS, et al. Risk of recurrence, prognosis, and follow-up for Danish women with cervical cancer in 2005-2013: A national cohort study. Cancer. 2018 Mar;124(5):943–51. http://dx.doi.org/10.1002/cncr.31165

14. Mathevet P, Dargent D, Roy M and Beau G. A Randomised Prospective Study Comparing Three Techniques of Conization: Cold Knife, Laser and LEEP: Gynaecologic Oncology. 1994 August; 54(2):175-9. https://doi.org/10.1006/gyno.1994.1189

15. Wang XI, Huang F, Zhang S. Loop Electrosurgical Excision Procedure vs. Cold Knife Cone in Treatment of Cervical Intraepithelial Neoplasia: Review of 447 Cases. 2017;47(6). http://www.annclinlabsci.org/

16. Rogers L, Siu SSN, Luesley D, Bryant A, Dickinson HO. Radiotherapy and chemoradiation after surgery for early cervical cancer. Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, editor. Cochrane Database of Systematic Reviews

[Internet]. 2012 May 16 [cited 2024 Dec 16];2014(2). http://dx.doi.org/10.1002/14651858.CD007583.pub3

17. Mehta N, Desai S, Dhakad V, Patel D, Saldanha E. Treatment and outcomes of early and operable recurrent cervical cancer: A prospective study. Niger J Surg. 2021;27(1):28. http://dx.doi.org/10.4103/njs.NJS_14_20

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Authors' Guidelines

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Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med. 1998;289(1):350-355. https://doi.org/10.1000/hgjr.182.

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002. Accessed 16 January 2010.

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