

Prognosis of Cervical Neoplasia Among Women Treated for Precancerous and Cancerous Lesions in Bahir Dar, Northwest Ethiopia: A Longitudinal Cohort Study

Abstract

Introduction: Cervical cancer is a major global health concern, substantially impacting women's morbidity and mortality. Cervical intraepithelial lesions can be detected and treated before they progress to cancer. This study aimed to assess the prognosis of cervical neoplasia after treatment for precancerous and cancerous lesions.

Methods: A longitudinal prospective cohort was conducted among patients attending the gynecology unit of Felege Hiwot Comprehensive Specialized Hospital (FHCSH) in Bahir Dar, northwest Ethiopia. Statistical analyses were performed using SPSS version 26.0. Variables with a p-value of less than 0.05 were considered statistically significant.

Results: A total of 95 women were followed. The regression rate of the lesions after 12-month follow-up was 88.46% (46/52) while the progression rate was 3.85% (2/52). However, four out of 52 (7.69%) had persistent lesions. Women treated with thermocoagulation had good treatment outcomes with a regression rate of 93.75% (15/16) followed by those treated with Loop Electrosurgical Excision Procedure (LEEP) and cryotherapy with regression rates of 85.71% (12/14) and 83.33% (15/18), respectively.

Conclusion: The results of our study, the first in its kind indicated a prognosis of cervical precancer among treated study participants. Cryotherapy, thermocoagulation or LEEP could be used as a treatment method for cervical precancerous lesions in Amhara Regional State and elsewhere in Ethiopia.

Keywords

HPV • Cervical cancer • Prognosis • Regression • Bahir Dar

Research Article

Alemayehu Mengestu*, Endalkachew Nibret and Abaineh Munshea

¹*Department of Biotechnology, Institute of Biotechnology, Bahir Dar University, Bahir Dar P.O. Box 79, Ethiopia*

²*Amhara Public Health Institute, PO Box 477, Bahir Dar, Ethiopia*

³*Department of Biology, College of Science, Bahir Dar University, Bahir Dar PO Box 79, Ethiopia*

***Correspondence:** Alemayehu Mengestu, Department of Health Biotechnology, Institute of Biotechnology, Bahir Dar University, Bahir Dar P.O. Box 79, Ethiopia, E-mail: alexu2love@gmail.com

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Introduction

Human Papilloma Virus (HPV) is one of the primary etiological agents for cervical precancers and cervical cancer [1]. Low-grade dysplasia (CIN (cervical intraepithelial neoplasia)1/LSIL)) is caused by both low-risk and high-risk HPV strains, whereas disease progression is exclusively caused by high-risk HPV strains [2]. Cervical cancer is a significant worldwide health concern for morbidity and mortality of women. Nevertheless, there is an opportunity for intervention due to the natural course of cervical cancer development [3]. Although women in African countries are primarily affected by high morbidity and mortality from cervical cancer, still there is a concern even with the implementation of a comprehensive strategy

for prevention and control of the disease at global scale [4].

In Ethiopia, cervical cancer is the most frequent malignancy among women between the ages of 15 and 44; it is a public health problem [5]. According to estimates from 2022, 5,338 women lose their lives to cervical cancer each year, while 7,445 new cases are identified with the disease annually [6]. The degree and size of the CIN lesion determine the likelihood of progression to invasive carcinoma; invasive cervical cancer eventually develops in about one-third of women with untreated CIN3 [7]. A potentially fatal malignancy can be avoided by identifying and treating CIN lesions at an early stage in the disease's development. Cervical cancer incidence and death have been dramatically lowered in many parts of the world by implementing efficient screening programs and prompt interventions [8].

Numerous cervical screening techniques, including visual inspection with acetic acid (VIA), colposcopy, HPV testing and traditional cytology (Pap smear), have been successfully applied in low- and middle-income countries (LMICs) [9]. Treatment options for cervical pre-cancer lesions have included ablative (destroying abnormal tissue by heating it with thermal coagulation or freezing it with cryotherapy) and excisional (surgically removing abnormal tissue with LEEP (loop electrosurgical excision procedure) or cold-knife conization (CKC) [10,11].

A greater variety of mid-level healthcare professionals, including nurses, are qualified to administer ablative treatment, which is typically seen as safer than excision. Ablative treatment is comparatively effective in treating ectocervical cancer [12]. Treatment options for advanced cervical cancer are costly and are frequently unavailable in Ethiopia [13]. Patients with advanced cervical cancer are primarily managed according to their International Federation of Gynecology and Obstetrics (FIGO) stage [14]. Surgery and/or radiation therapy have a high cure rate when used to treat patients with early-stage disease (stage I–IIIA). However, patients diagnosed with locally advanced cervical cancer (IB3-IVA) have a poorer prognosis and are only candidates for concurrent chemoradiation [15].

Even though there are many studies conducted in Ethiopia on cervical cancer, none of them provide data about

treatment efficacy and prognosis of cervical cancer. The Ethiopian Federal Ministry of Health adopted the Guideline for Cervical Cancer Prevention and Control in 2015, which has been in routine clinical use since then (Federal Democratic Republic of Ethiopia Ministry of Health, 2015). However, there is a lack of research on the prognosis of cervical (pre)cancerous lesions among Ethiopian women and tumor progression to cancer. This study aimed to assess the prognosis of cervical neoplasia after treatment for precancerous and cancerous lesion.

Methods

Study setting and population

A prospective cohort study was conducted among patients attending the gynecology unit of FHCSH in Bahir Dar, northwest Ethiopia, between January and December 2023. A total of 297 women were enrolled in the study. All study participants were screened VIA and cervical cytology examination with pap test. Study participants with positive results from screening tests were examined with colposcopy and biopsy was taken for histopathology. Two follow-up visits were scheduled 6 and 12 months after the baseline visit. All women who visit FHCSH gynecological unit, above 30 years old and willing to participate in the study were included. Although the age of HIV-positive women was less than 30, they were included in the study. All women who took any kind of treatment for cervical cancer or any vaginal medication, vaginal contraceptives or douches 48 hours before the test, those who had sexual intercourse 24 hours before the test; women who are in menstruation and pregnant women were excluded from the study.

Sample size determination

Study one: A single population proportion sample size determination formula (study population size less than 10,000 [16] was used with the assumption of 19% proportion of any screen positive, 5% margin of error and 95% desired level of the confidence interval and considering a 10% non-response rate, the sample size was 255.

Study two: Sample size was determined from the formulation of sensitivity and specificity test using Power Analysis and Sample Size (PASS) software based

on desired type I error, power and effect size [17]. The minimum sample size was determined by taking the prevalence of disease 19%, by assuming the sensitivity of the kit is comparable with the gold standard and the specificity of the kit is greater than 70%, the power is set to be at least 80% and the p-value is set to be less than 0.05. The sample size for sensitivity and specificity of the Onco E6 performance study was 49 positives for histopathology, 196 negative samples with the gold standard histopathology examination and 49 negative controls. By taking 10% contingency, the sample size was 324. The final sample size was the highest sample size of the upper studies, 324 sample size was determined for this study.

Sampling technique and procedure

The sampling technique was systematic random sampling. Every third study participant was selected after a random starting study participant who was selected by lottery method.

Follow up visits

All study participants were screened with a Visual acetic acid test (VIA), genotyping of the HPV DNA test and cervical cytology examination with PAP test in the baseline assessment. Study participants with positive results from screening tests were examined with colposcopy and biopsy was taken for histopathology. Participants with positive results of the screening or diagnostic tests were followed. Two follow-up visits were scheduled 6 and 12 months after the baseline visit.

Specimen collection

In this study, HPV DNA or VIA or PAP positive or CIN II+ women (113/297) from the baseline assessment were included in the follow up study, of which 18/113 women (15.93%) were lost during follow up. The major reason to follow up was change of contact details which made the patients to be unreachable, referred to an oncology center for advanced treatment and death. A total of 95 women were followed. Data were collected from 95 women at three-time points during the study: baseline, 6-month follow-up and 12-month follow-up. At the baseline visit, upon arrival at the cervical cancer unit, trained gynecologists currently working on the cervical cancer unit provide a

physical and gynecological examination, screen with VIA and collect smears for cytologic specimens. Tissue biopsy was collected for all positive study participants from the screening tests when there were positive results of colposcopic impression. The study procedures were explained to each study participant and written informed consent was obtained from those who agreed to participate. Treatment was given for women with positive for VIA and eligible for treatment or grade squamous intraepithelial lesion and above high-grade squamous intraepithelial lesion (HSIL+) for PAP or CIN II+ for histopathology.

Cytology and histopathology examinations

PAP smears and biopsies were independently examined by two experienced pathologists. When the diagnosis differed between the two pathologists, the sample was reviewed by a third pathologist and consensus was obtained. Pap test results were reported as negative for dysplasia/malignancy, *low-grade squamous intraepithelial lesion (LSIL)*, *High-grade squamous intraepithelial lesion (HSIL)* and *carcinoma* [18]. The histopathological diagnosis had confirmed test results as Negative for Dysplasia/malignancy, CIN I, CIN II, CIN III and cervical cancer cases.

Statistical analysis

All the data were coded and entered into Epi-info and transported to SPSS version 26.0 software package for analysis. For controlling errors 10% of the data were double entered, also frequency checks were done. For follow up subjects, baseline results were compared individually and pairwise with 6 months visit and 1-year follow-up diagnosis to assess the prognosis of cervical lesions. The results were presented in the form of tables, figures and text using frequencies and summary statistics such as percentages to describe the study population about relevant variables. Proportion difference at six and twelve months from baseline proportion was analyzed for regression, persistent and progression of precancerous and cancerous lesions. We defined regression as the partial or complete disappearance of the lesion during the 6 and 12-month examinations. We defined persistence as the lesion remaining unchanged. A rise in the size and stage of the lesion was referred to as progression. We defined recurrence as the lesion coming back after a brief period of absence.

Results

Sociodemographic, sexual and reproductive characteristics of study participants

A total of 95 women were followed among women attending gynecology unit of Felege Hiwot Comprehensive Specialized Hospital. About 74.7% (71/95) were within the age range of 30-50 years. 58.9% (56/95) of the participants lived in rural area, majority of study participants (85.3%) were illiterates, more than half of study participants (55.8%) were married and 55.8% (53/95) of them had 4 to 6 children. Forty-four (46.3%) of study participants had their first sexual debut before the age of 18 years.

Seventy-nine (83.2%) of them reported having two or more lifetime sexual partners and 75.8% (72/95) of study participants reported having two or more current sexual partners. Fifty-five (57.9%) of the women reported never using a condom during sexual intercourse, while 32.6% (31/95) reported using hormone contraceptives for more than five years. Most women 71.6% (68/95) never heard about human papillomavirus, cervical cancer and its transmission. Furthermore, 75.8% (72/95) of study participants were not screened for HPV infection and precancerous lesion. History of sexually transmitted infections (STI) was reported by 58.9% (56/95). The socio-demographic, sexual and reproductive characteristics of study participants are summarized in (Table 1).

Variables	Categories	Follow up (n=95)	Percentage
Age (year)	<30	10	10.5
	30-50	71	74.7
	>50	14	14.7
Educational status	Illiterate	81	85.3
	Read and write	2	2.1
	Elementary	5	5.3
	High school and above	7	7.4
Monthly income (Ethiopian Birr)	<2000	25	26.3
	2001-5000	33	34.7
	>5000	37	38.9
Marital status	Single	15	15.8
	Married	53	55.8
	Divorced	10	10.5
	Widowed	17	17.9
Parity	<3	21	22.1
	4-6	53	55.8
	>6	21	22.1
Occupation	Employed	32	33.7
	Others	63	66.3
Residence	Rural	56	58.9
	Urban	39	41.1
Age at first marriage	<18	40	42.1
	18-20	28	29.5
	>20	27	28.4

Age at first sexual debut	<18	44	46.3
	18-20	35	36.8
	>20	16	16.8
Number of lifetime sexual partners	1	16	16.8
	≥2	79	83.2
Number of current sexual partners	1	23	24.2
	≥2	72	75.8
Condom during sexual intercourse.	Yes	40	42.1
	No	55	57.9
Hormonal contraceptive use >5 years	Yes	31	32.6
	No	64	67.4
Personal hygiene	Yes	24	25.3
	No	71	74.7
Have you heard about cervical cancer	Yes	27	28.4
	No	68	71.6
Have you been screened before	Yes	23	24.2
	No	72	75.8
Co-existing medical condition	Yes	43	45.3
	No	52	54.7
Family history of cervical cancer	Yes	9	9.5
	No	86	90.5
History of STI infection	Yes	56	58.9
	No	39	41.1
CD4 count (cells/mm ³)	<500	14	14.7
	501-999	65	68.4
	≥1000	16	16.8

Table 1. Socio-demographic, sexual and reproductive characteristics of study participants included in the follow up study.

Prognosis of precancerous and cancerous lesion among women included in the follow up study

From 95 women included in the follow up study, 43/95 were not treated due to only HPV positive, LSIL for PAP and VIA positive but not eligible for treatment. However, the rest 52/95 women were treated. The regression rate of the lesion after six-month was 88.46% (46/52) while the progression rate was 3.85% (2/52) whereas 7.69% (4/52) had persistent lesions. Women treated with thermocoagulation had good treatment outcomes with a regression rate of 93.75% (15/16), followed by those treated with LEEP and cryotherapy with regression rates

of 85.71% (12/14) and 83.33% (15/18), respectively. The progression rate of precancerous lesions among women who were not treated was 18.60% (8/43), the regression rate of precancerous lesions among women who were not treated was 22/43(55.81%) and 11/43(25.58%) had persistent precancerous lesion. The details are presented in (Table 2). A total of 14 study participants were treated at six months, of which 6/14 were from progression and persistent lesion outcomes which were treated at baseline and 8/14 were new VIA positive and eligible for treatment which had VIA positive results but not eligible for treatment at baseline. The regression rate of the lesion was 92.86% (13/14) and 7.14% (1/14) had persistent lesion (Table 3).

Rate of recurrence at 12 months of follow-up period

A total of 4 lesions (8.69%; 4/46) from 46 already regressed lesions re-occurred at 12-month follow up. Women treated with cryotherapy had 13.33% (2/15) recurrence rate, while those treated with thermocoagulation and LEEP had 6.67% (1/15) and 8.33% (1/12) recurrence rates, respectively, at 12 months. The details are presented in (Table 4).

Discussion

The findings of our study, the first of its kind indicated that the prognosis of cervical lesions was good based on the specific type of treatment given to studied women

as evidenced by 88.46% regression rate of the lesion at 12-month follow up. Cervical precancerous and cancerous lesions were diagnosed with VIA, conventional cytology (PAP) and histopathology with colposcopy and treated with thermocoagulation or cryotherapy or LEEP or hysterectomy based on the severity of the lesion. Those whose transformation zone is not fully visible or the squamocolumnar junction was out of reach did not qualify for ablative methods such as thermocoagulation or cryotherapy.

In our study, thermocoagulation had good treatment outcome with 93.75% (15/16) rate of regression. This finding is in line with a study conducted in Brazil that found

Baseline	6-month follow up			
	Frequency	Progression	Regression	Persistent
Total Treated	52	2(3.85%)	46(88.46%)	4(7.69%)
Cryotherapy	18	1(5.56%)	15(83.33%)	2(11.11%)
Thermocoagulation	16	1(6.25%)	15(93.75%)	0(0%)
LEEP	14	0(0%)	12(85.71%)	2(14.29%)
Hysterectomy	4	0(0%)	4(100%)	0(0%)
No treatment	43	8(18.60%)	24(55.81%)	11(25.58%)

Table 2. Progression, regression and persistent lesion after treatment at the six-month follow up period.

Baseline	6-month follow-up			
	Frequency	Progression	Regression	Persistent
Total Treated	14	0(0%)	13(92.86%)	1(7.14%)
Cryotherapy	4	0(0%)	4(100%)	0(0%)
Thermocoagulation	6	0(0%)	6(100%)	0(0%)
LEEP	3	0(0%)	2(66.67%)	1(33.33%)
Hysterectomy	1	0(0%)	1(100%)	0(0%)

Table 3. Progression, regression and persistent lesion after treatment at 12-month follow up period.

Treatment at baseline	Regression at six-month follow-up	Recurrence at 12 months
Total Treated	46(88.46%)	4/46(8.69%)
Cryotherapy	15(83.33%)	2/15(13.33%)
Thermocoagulation	15(93.75%)	1/15(6.67%)
LEEP	12(85.71%)	1/12(8.33%)
Hysterectomy	4(100%)	0(0%)
No treatment	24(55.81%)	0(0%)

Table 4. Recurrence of lesion at 12- month follow-up period after regression at six-month follow-up period.

thermocoagulation to be 90.8% effective in CIN 2 and 94.9% effective in CIN 3 cases; similar findings were found in a study conducted in Honduras that found 98 (83.1%) of the participants had no signs of infection or CIN2-3 at one year [19]. In the present study, the regression rate for women treated by LEEP was 85.71% (12/14). This finding was found to be lower than the study done in China, which showed that the cure rate at the 3- to 6-month follow-up was 94.35% [20]. The findings of our study indicated cryotherapy treatment also had a good rate of regression 83.33%(15/18). This result is in comparison with a study done in China which indicated among the cryotherapy treatment, 84 (79.2%) had no evidence of disease after 3–6 months, of which 69 (80.2%) were with low grade squamous intraepithelial lesions (LSIL) lesion and 15 (75.0%) were with high grade squamous intraepithelial lesion (HSIL) lesion respectively [20].

The results of our study indicated a significant prognosis of cervical precancer among treated study participants and a comparable outcome from all treatment modalities, which is supported by a randomized controlled trial in Zambia comparing thermal ablation, cryotherapy and large loop excision of the transformation zone, which reported similar treatment outcomes at 6 months [21]. Our result is also in agreement with a Nigerian study that reported cryotherapy and thermo-coagulation have similar efficacy in the treatment of cervical precancers. The cure rate for cryotherapy of 85.5% was not significantly different from that for thermo-coagulation of 89.2% [22]. This finding is also similar to a prospective randomized controlled study conducted in India that reported the efficacy of thermocoagulation was 93.54% and that of cryotherapy was 90.32% [23] and another study conducted in India that indicated the efficacy of thermal ablation was 97.6% and that for cryotherapy was 92% [24].

In the current study, the overall recurrence of lesions was 8.69% (4/46). Cryotherapy had 13.33% (2/15) rate of recurrence and thermocoagulation had 6.67% (1/15) rate of recurrence of lesion at 12 months. This result is comparable with a report from a study done in Côte d'Ivoire which indicated the overall prevalence of recurrences was

8.96% [25]. The result of our study is higher than a study conducted in India that reported after one-year thermal ablative treatment follow-up, 98% had normal Pap smears and 2% of patients had recurrent low-grade CIN lesions [26] and a study in Kenya stated that treatment failure after cryotherapy rates between women living with HIV and women without HIV (15.12% vs 5.62%, $p = 0.039$) respectively [27].

In our study, the recurrence rate of LEEP was 8.33%, which is consistent with a study in China which indicated recurrent CIN2+ was found in 268 patients after LEEP (268/4369, recurrence rate, 6.1% [28] and with a study conducted in Norway that reported 42(5.6%) women were diagnosed with residual disease [29]. Our study was also comparable with a study conducted in Italy that indicated the average recurrence rate of lesions after LEEP was 9.1% [30].

In our study, the rate of regression among women who were not treated was 53.65% (22/43). This finding was comparable with a study conducted in France that reported the lesion spontaneously regressed or disappeared in 76 (59%) patients during a median follow-up of 25 months [31] and another study done in France indicated the lesion spontaneously regressed or disappeared in 36 of 60 patients (60%) with confirmed CIN2 during a median follow-up of 20 months [32]. Our finding was also comparable with a study done in Thailand that indicated one hundred and two patients had spontaneous cytologic regression, showing a regression rate of 66.2% [33-35].

Conclusion

The results of our study indicated a significant prognosis of cervical precancer among treated study participants and a comparable outcome from all treatment modalities. This study identified 88.46% (46/52) regression rate of the lesion. The regression rate of precancerous lesion among treated women was higher than lesion among not-treated women. Cryotherapy, thermocoagulation or LEEP could be used as treatment method for cervical precancerous lesions in Amhara Regional State and elsewhere in Ethiopia.

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