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Cervical Cancer Visual Screening Experience in the Republic of Tajikistan

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ABSTRACT

OBJECTIVES: To study the results of the first pilot study of organized visual cervical cancer (CC) screening for the detection of precancerous pathology of the cervix in two pilot districts of the Republic of Tajikistan.

STUDY DESIGN: In this cross-sectional study, the target group included healthy women of reproductive age (30-49 years) from Kushoniyon and B. Gafurov Districts who underwent visual screening. The total study population was 72,574 out of which 68,391 (94.3%) visited primary healthcare facilities for visual inspection with Lugol's Iodine (VILI). A total of 2958 women with suspicious tests for cervical intraepithelial neoplasia (CIN) were identified (4.3%) and sent to the reproductive health care centers for further diagnostics. Post-screening diagnostic tests were performed to specify cervical lesions, which included colposcopy with acetic acid (VIA) visual inspection, cytology, and biopsy with histological examination. HPV testing wasn't included in the diagnostic protocol due to its high cost.

RESULTS: A total of 164 histologically confirmed cases of CIN were identified (0.25% of number of women screened). The detection rate of precancerous pathology was 26.9 per 100,000 female population, which is 8.2 times higher than the detection rate of CC. All patients regardless of CIN degree underwent loop electrosurgical excision (LEEP)/conization. In the follow-up period (6-48 months), complete recovery after 136 LEEP, 21 conizations, and 7 hysterectomies were observed in 97% (5 recurrences of non-invasive disease).

CONCLUSION: The visual screening showed high efficiency in detecting CIN. The positive experience suggests the implementation of this program nationwide.

Keywords: Cervical cancer, Cervical intraepithelial neoplasia, Loop electrosurgical excision/conization, Organized visual screening

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Introduction

Cervical cancer (CC) is primarily caused by exposure and infection by the oncogenic types of human papillomavirus (HPV) and affects mostly women of reproductive age (1). Most HPV infections resolve spontaneously. However, a fraction of the infections proceed to the more advanced cervical pre-cancer stage, and if not treated properly, will progress into cancer (1).

Despite being a largely preventable disease and the modern achievements in the management of HPV infection, CC continues to be among the leading causes of disability and mortality of women from cancer around the world, and there is a large disparity in CC incidence and mortality rates between countries of various socioeconomic status (1,2). If preventive measures are not taken in developing countries, then annual registration of primary cases in the world between 2018 and 2030 will increase from 570,000 to 700,000, and mortality from 311,000 to 400,000 per year (5). By 2050, CC

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is expected to increase by 50% (5). The highest incidence of CC is observed in women in developing countries, accounting for 78% of cases (6). In 2012, the incidence rate for CC was approximately 528,000 worldwide, with 85% of diagnoses occurring in low- and middle-income countries, and the death rate was approximately 266,000 worldwide, with 231,000 from low- and middle-income countries (1).

Despite easy access to visual examination, cases of CC are detected in advanced form, significantly impacting the management and treatment outcomes (7). In this regard, the implementation of optimized prevention strategies, including HPV vaccination, active screening, and early treatment of precancerous lesions of the cervix are recommended (2,8-12).

There are different opinions regarding the optimal screening strategy and treatment protocols for precancerous lesions of the cervix among different countries, dependent upon the availability of economic resources, national features, and the preparedness of the health system for capital expenditures (1,13-15). In developed countries, cytology screening has been replaced in large part by HPV testing, which demonstrates its high efficiency. However, due to higher costs for healthcare systems and providers, nationwide implementation of HPV testing is unfeasible in developing countries.

The issues of CC screening programs in Eastern countries and Central Asia are the subject of further studies.

According to official statistics, CC is the leading malignant neoplasm in Tajikistan, ranking second in cancer mortality after breast cancer. Each year, there are about 400 registered cases of cervical cancer, resulting in 130 deaths. Moreover, more than half of the newly registered cases are diagnosed at late stages of the disease (stages II-III); 20% of all women with CC die within a year after diagnosis (10,12). In the Republic of Tajikistan, from 2010 to 2020, CC had a steady growth trend with annual incidence fluctuating in the range of 4.7-8.7 per 100 thousand female population and a peak age-specific incidence in the age group of 45-54 years (13). Therefore, the introduction of a vaccine against human papillomavirus infection significantly affects the epidemiological situation of the development of cervical cancer in women of reproductive age (12).

To identify precancerous pathology and cervical cancer in different countries' healthcare systems, various screening methods are practiced, depending on the economic situation. The World Health Organization (WHO) has approved three main screening methods as the most acceptable: virological, cytological, or visual (10,16). For resource-limited countries, WHO recommends visual screening as part of a detection-to-treat strategy. An assessment of the situation regarding the prevention of cervical cancer in Tajikistan has shown that organized visual screening is optimal for the country (16,17). Further economic analysis of various screening methods has indicated that the country has sufficient potential to organize post-screening diagnostics (3,4).

Material and Method

This cross-sectional study was carried out by the State Institution “Republican Cancer Research Center” (RCRC) of the Ministry of Health and Social Protection of Population of the Republic of Tajikistan (MOHSPP). The concept of this study is based on an integrated approach to study the epidemiological situation of CC prevalence in various country regions for the period 2010-2020 and to evaluate in detail the organization and the results of CC screening programs in two pilot districts of the country. This activity in the country was conducted in the country for the first time.

The “screening-diagnostics-treatment” strategy was developed, accepted, and implemented in two densely populated rural districts of the country where high rates of CC were registered: Kushoniyon and B. Gafurov. A special algorithm of pilot-organized visual CC screening was applied to implement the mentioned strategy.

The study was carried out among the healthy female population in the two districts. The target group in the pilot districts consisted of 72,574 women aged 30-49 years. Inclusion criteria for the study were: 1) healthy women aged 30-49 years; 2) written informed consent. The rationale for choosing the age group of 30-49 years as the target was the increase in the age-specific incidence of women with CC in the country, consistent with WHO recommendations.

The practice of visual screening was implemented in 150 primary healthcare facilities (54 rural health centers and 96 health houses for nursing care) in both pilot districts. To conduct visual screening for CC, 570 health professionals were recruited, including 80 family physicians (Kushoniyon District: 8 doctors; B. Gafurov District: 72 doctors) as well as 490 family nurses (Kushoniyon District: 21 nurses; B. Gafurov District: 469 nurses). It should be noted that a family nurse, who works in a health house under structural subordination and supervision of a family doctor located in a health center, can be considered the doctor’s assistant.

The visual test allows the detection of early epithelial tissue changes in the cervix. The visual test technique involves the visual examination of the vagina and cervix using specula, along with staining using a freshly prepared 3% solution of acetic acid (visual inspection with acetic acid - VIA) or 3% Lugol’s solution (visual inspection with Lugol’s Iodine - VILI). Positive or suspicious cases of cervical dysplasia and CC were referred for further post-screening diagnostics to the district reproductive healthcare centers. VIA was usually used during colposcopy, while VILI was used in primary healthcare facilities by primary physicians and nurses trained to perform the tests with high quality, ensuring adequate documentation, tracking of suspicious and pathological test results, and timely referral of women with confirmed lesions to the next diagnostic level and treatment.

Post-screening diagnostics included colposcopy with VIA, cytology, and biopsy of the suspected cervical lesion with morphological examination. All examinations, except for histology, were conducted in district reproductive centers, whereas histology was performed in the regional oncology centers. The District Reproductive Center is situated in the Department for Gynecology and Obstetrics of the central district/city health center, which controls the functioning of all health centers and health houses of the district/city. The Regional (oblast) Oncology Center is the regional section of the Republican Cancer Research Center that serves the population of all districts and cities located in the region.

In accordance with the screening algorithm in our study, a biopsy was indicated following positive/suspicious results from at least one of the following tests: visual VILI test, colposcopy with VIA, or cytology. Following histological examination, women with precancerous cervical lesions were registered for further treatment and monitoring. Patients with invasive CC were referred for hospitalization to oncological regional or national hospitals.

The referral system for initially diagnosed patients with precancerous lesions and CC from primary healthcare centers to specialized care played a key role in establishing a quality control system for primary care workers to improve their skills in performing VILI tests.

Statistical data were carried out using the STATISTICA 12.0 software package (Stat Soft Inc., USA). Variation statistics included the calculation of relative values and representation as fractions (%). Comparative analysis of the fractions was performed using the Chi-square test (χ^2). The null hypothesis was rejected at $p<0.05$.

The pilot project was implemented by MOHSPP with the support of the Government of Tajikistan and generous donations of the common co-investments of the United Nations Population Fund, Hellosmile (Tokyo Family Medicine = Tokyo FM) and United Nations Development Program (UNFPA).

The National Institutional Review Boards of the Republic of Tajikistan reviewed the screening and survey protocol and process and approved the protocol for implementation. (Ethics Committee at the Republican Scientific Center of Oncology. Ethics approval reference number: 18; date September 12, 2023). As part of this study, written consent was obtained from legal representatives of the target groups for participation, the use of data, and the publication of medical data. All procedures were performed according to the Declaration of Helsinki.

Results

According to the results of the study, 41,700 residents of the B. Gafurovsky district and 26,691 women from the target group of the Kushoniyonsky district directly participated in CS screening (Table I). Screening coverage of the target groups reached 95% in the B. Gafurovsky district, 93% in the Kushoniyonsky district, and 94.2% in total for both districts.

All positive and suspicious tests for cervical dysplasia were sent to the upper level for post-screening diagnostics (Table II) in accordance with the algorithm approved by the Ministry of Health and Social Protection of Population (MOHSPP). From the results of visual CC screening, 1450 patients (49%) were referred for cytology examination.

Table I: *Number of women in the study groups*

District	Total female population per district	Number of women of reproductive age (15-49 years old) (% of the total population)	Number of women aged 30-49 years old (% of women of reproductive age)
Kushoniyon	237,700	62,192 (26.2%)	28,700 (46.1%)
B. Gafurov	371,000	100,139 (27.0%)	43,874 (43.8%)
p		<0.001 (χ^2 =50.74)	<0.001 (χ^2 =84.57)
Both districts	**608,700**	**162,331 (26.7%)**	**72,574 (44.7%)**

Note: Official statistics of 2019 (15); p-statistical significance of the difference in the rates between districts in the main group (by Chi-square test).

Table II: *Post-screening diagnostics*

	Main group		p	Both districts
	Kushoniyon	B. Gafurov		
Colposcopy indicated by positive visual screening	635	2323		2958
Cytology performed	478(75.3%)	972(41.8%)	<0.001(χ^2=223.05)	1450(49%)
Histology performed	59(9.3%)	270(11.6%)	>0.05(χ^2=2.74)	329(11.1%)
Precancer (CIN I-III, CIS) per woman screened	35/26,691(0.13%)	129/41,700(0.31%)	<0.001(χ^2=21.61)	164/68391(0.24%)
Identification ratio: CIN/colposcopy	5.5%	5.5%		5.5%
invasive CC per woman screened	5/26,691(0.02%)	15/41,700(0.04%)	>0.05 (χ^2=2.74)*	20/68391(0.03%)

*Note: p – statistical significance of the difference in the rates between districts in the main group (by Chi-square test; * - by Yates corrected Chi-square). CIN= Cervical intraepithelial neoplasia; CIS= Carcinoma in situ; CC= Cervical cancer*

As shown in Table II, the identification level of CIN and CC in both districts was 5.5% of the total number of positive or suspicious cases.

A summary of the results of cytological examination according to the Bethesda scale is presented in Table III. Normal values (negative for intraepithelial lesion or malignancy= NILM) were obtained in 962 cases (66.34%), atypical squamous cells of unknown significance (ASC-US) were identified in 313 cases (21.6%), low-grade squamous intraepithelial lesion (L-SIL) in 114 cases (7.86%), high-grade squamous intraepithelial lesion (H-SIL) in 42 cases (2.89%), and cytological picture of carcinoma in 20 cases (1.3%).

Patients who had at least two positive/suspicious results from visual tests, colposcopy, or cytology were indicated for a biopsy with subsequent histological examination. Out of the 329 cases referred, CIN was histologically confirmed in 164 cases (49.8%). The remaining 165 cases were referred back to Reproductive Health Care Centers for observation near the patients' residencies after receiving negative biopsy results. All patients with a second negative test were excluded from further follow-up visits and were recommended to visit their family health centers every 6 months for follow-up.

Table IV presents the distribution of CINI-III, carcinoma in situ (CIS), and CC among subgroups. CIN I was identified in 99 cases (0.14%) (Kushoniyon subgroup: 29 cases, B. Gafurov subgroup: 70 cases), while CIN II/CIN III/CIS was found in 65 cases (0.095%) (Kushoniyon subgroup: 6 cases, B. Gafurov subgroup: 59 cases), and CC was found in 20 cases (0.03%) (Kushoniyon subgroup: 5 cases, B. Gafurov subgroup: 15 cases).

The ratio CIN to CC in Kushoniyon was 7.0 times and in B. Gafurov 8.6 times higher, which indicates a high prognostic value in the identification of precancerous diseases.

Age distribution showed that CIN incidence reached peak values in the age groups 40-44, with a decrease in incidence in higher age groups (data not shown). Regarding the frequency of CC, there is a shift of the maximum toward the age group 45-49.

Women with CIN underwent the surgical procedure of loop electrosurgical excision (LEEP) regardless of the severity of CIN. All procedures were performed using a high-frequency electrical coagulator (FOTEK E81M) of Russian production.

Treatment was provided to 157 women having CIN from both study districts. The remaining 7 patients with CIN associated with multiple myomas were treated with hysterectomy. All 99 women with CIN I underwent LEEP. Out of 58 cases of CIN II, CIN III, and CIS, 37 women received LEEP, while the remaining 21 women underwent electrosurgical conization.

Table III: *Cytology tests results in the study and control groups*

Results	Study group		Main group	Control group	p
	Kushoniyon (n=478)	B. Gafurov (n=972)	Both districts (n=1450)	Penjikent (n=80)	
NILM	316 (66.1%)	646 (66.5%)	962 (66.3%)	60 (75.0%)	>0.05 (χ^2=2.56)
ASC-US	107 (22.4%)	206 (21.2%)	313 (21.6%)	11 (13.8%)	>0.05 (χ^2=2.79)
L-SIL	38 (7.9%)	76 (7.8%)	114 (7.86%)	7 (8.8%)	>0.05 (χ^2=0.01)*
H-SIL	12 (2.5%)	30 (3.1%)	42 (2.9%)	2 (2.5%)	>0.05 (χ^2=0.02)*
Carcinoma	5 (1.0%)	15 (1.5%)	20 (1.3%)	0	

*Note: A comparison of the shares by districts revealed no statistically significant differences between them; p - statistical significance of the difference in the rates between groups (by Chi-square test; * - by Yates corrected Chi-square test). NILM= Negative for intraepithelial lesion or malignancy; ASC-US= Atypical squamous cells of unknown significance; L-SIL= Low-grade squamous intraepithelial lesion; H-SIL= High-grade squamous intraepithelial lesion*

Table IV: *Distribution of CIN among study groups*

Lesion	Study group		p	Both groups
	Kushoniyon (n =26,691)	B. Gafurov (n =41,700)		
CIN I	29 (0.11%)	70 (0.17%)	=0.047 (χ^2=3.95)	99 (0.14%)
CIN II	6 (0.02%)	18 (0.04%)	>0.05 (χ^2=1.44)*	24 (0.035%)
CIN III, CIS	0	41 (0.10%)		41 (0.06%)
CIN I, II, III, and CIS	35 (0.13%)	129 (0.31%)	<0.001 (χ^2=21.61)	164 (0.24%)
CC	5 (0.02%)	15 (0.035%)	>0.05 (χ^2=2.74)*	20 (0.03%)
The ratio CIN/CC	7.0	8.6		8.2

*Notice: p – statistical significance of the difference in the rates between districts in the main group (by Chi-square test; * - by Yates corrected Chi-square test). CIN= Cervical intraepithelial neoplasia; CIS= Carcinoma in situ; CC= Cervical cancer*

Regular follow-up for 6-48 months (median Me [25Q; 75Q]) revealed 5 cases of relapse. The success rate was 152 out of 164 cases (92.7%). The relapses occurred in patients with CIN I (1 case), with CIN II (3 cases), and with CIN III (1 case). All women with relapse underwent repeated LEEP.

Organized visual CC screening revealed several non-malignant and inflammatory diseases.

Among other pathologies, polyps, inflammatory diseases of the cervix, and uterine fibroids were more common in the Kushoniyon district, whereas there was no high frequency of leucoplakia or condylomas in either district (0.2-0.9%).

Women diagnosed with these pathologies were referred to district reproductive healthcare centers for further outpatient treatment or hospitalization in the gynecological departments of central district hospitals. Further events and long-term outcomes were not within the scope of this study.

One of the advantages of organized visual CC screening was the detection of CC cases among the target groups. In the B. Gafurov subgroup, 15 cases of CC (0.04%) were found. Among these cases, 9 were in stage I-II, 5 cases were in a localized advanced stage, and the remaining 1 case was in a late stage. In Kushoniyon district, 1 case was in an early stage, 3 cases were in stage III, and 1 case was in a late stage.

All women with invasive cervical cancer were referred to regional and national oncologic hospitals for further treatment.

Discussion

The reason for the lower rate of positive tests in the Kushoniyon district (2.4%), which is two times less frequent compared to the B. Gafurov district (5.4%), was the lack of medical personnel in Kushoniyon. Therefore, fewer patients were referred for colposcopy examinations in the Kushoniyon district. However, the final identification ratio (CIN/colposcopy) was the same for both districts (5.5%) (Table II).

Within the target group of the two districts (72,574 women), only 68,391 (94.2%) women underwent the screening tests. Among the remaining 4,183 women (5.8%), 3,305 (4.6%) did not participate in the screening due to internal or external migration, and 878 (1.2%) refused to participate in the screening program.

The low percentage of cytology testing is due to both the lack of access of the rural population to cytology diagnostics and financial barriers to visiting the reproductive health center at the district level, where sampling and testing were performed.

Tajikistan is referred to as a country with limited resources and remains without nationwide CC screening. Organized visual CC screening was implemented for the first time in the country as a pilot project in two selected districts. Piloted visual CC screening among the target group of women identified 164 cases of CIN out of 68,391 women who underwent screening, which is 0.24% with a general coverage of 94.2% of the target women population. The incidence of CC in our study was 20 cases (0.03%).

Chatzistamatiou K. et al, 2021 described different triage strategies and proposed that the best accuracy can be achieved by referring all HPV16-positive women directly to colposcopy, and women positive for HPV18 or other high-risk HPVs only after an ASCUS or worse cytology report (18). Terasawa T et al, 2022 showed, based on a network meta-analysis of 27 prospective studies (185,269 patients) using standalone cytology or primary HPV testing for the detection of H-SIL, that accuracy was higher when a combination of tests was provided (19). WHO recommends applying a second test after receiving a positive result from one of three widely used testing methods: HPV, cytology, or visual tests (1).

We support the approach for developing countries to treat L-SIL and H-SIL by LEEP to avoid losing patients from observation and to reduce the number of visits. Applicable to Tajikistan's healthcare system, we treat in accordance with the "screen-and-treat" strategy. Despite this, many countries with enough resources choose not to treat CIN I immediately and prefer to postpone further diagnostic measures, especially in young women. For women after menopause with H-SIL, many authors prefer to perform conization, and we observed that in cases associated with uterine problems, 7 of the patients underwent hysterectomy.

This article describes that LEEP applied for CIN I has a lower probability of relapse compared to H-SIL. Considering all cases with CIN, we could document a cure rate of 97% (5 relapses out of 164 precancerous cases).

Contrary to the approaches mentioned above, the present study proposes a more practical approach to the problem through organized visual screening among the population using a visual test. Our research has shown that this technique can significantly improve access to the population. The data obtained showed that identifying the asymptomatic course of the disease along with treatment by LEEP and conization exhibited high efficiency and curability. This was achieved by using a set of post-screening tests for triage, including extended colposcopy, cytology, on-site treatment, and sending the resulting material for histological confirmation.

The clinical and organizational experience, along with the achievements obtained through piloting cervical screening in two districts of Tajikistan, open up new avenues for further development of cervical screening in the country. This includes scaling up visual screening to the national level, enhancing cytological capacity and histological evaluation, and

introducing virologic testing within the tested algorithm, among other possibilities.

Additionally, based on the results of this research, an action plan for the introduction of visual screening at the national level in three stages until 2030 is planned: 2021-2024, 2025-2027, and 2027-2030.

Currently, this screening method is utilized in 16 primary care institutions. Dushanbe, Bokhtar, and Khujand regional institutions have already implemented it, and personnel from the network of KATS institutions in other cities and districts of the republic are undergoing training for its further implementation.

The main goal of this plan is the mandatory use of the screening method in the activity of every employee of the health care system, and all women of reproductive age and over 50 years of age should be included in the screening examination in a plan and free of charge.

For the implementation of this algorithm, 32,391 employees of the KATS structure and 2017 limited specialists are involved.

Conclusion

For the first time, organized visual CC screening in Tajikistan demonstrated high efficacy in detecting precancerous lesions of the cervix. The use of the visual screening method, piloted in two districts, showed the following advantages for the healthcare system in Tajikistan:

1. CC morbidity and mortality rates in Tajikistan tend to increase with the age of the patient, peaking in the age group of 45-54 years. In 20% of the cases, the patient's initial diagnoses are made in late stages and patients die within a year.

2. Organized visual CC screening is an optimal instrument adapted to the local conditions of Tajikistan, as it is simple, economically feasible, and at the same time provides better access to the rural population.

3. The first pilot project of visual screening demonstrated a high coverage of 94.2% among the target population aged 30-49 years, effectively detecting precancerous lesions of the cervix at a rate of 0.24%, with an incidence rate of 55.6 per 100,000 population.

4. The incidence rate of CIN is 8.2 times higher than that of CC itself, showing high potential for successful treatment of patients in the early stages.

5. The strategy of "screening-diagnostics-treatment" applies to Tajikistan.

Thus, the Ministry of Health and Social Protection of Population approved plans for the further expansion of organized visual CC screening to the national level.

Declarations

Ethics approval and consent to participate

All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of the Ethics Committee at the Republican Scientific Center of Oncology (Ethics approval reference number: 18; date September 12, 2023). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials

The data supporting this study is available through the corresponding author upon reasonable request.

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Author Contributions Statement:

Nilufar A. Muhsinzoda conceived the idea presented, contributed to the manuscript, and analyzed the data. Alex Bingjie Yuan, Edward Wight, and Rustam A. Tursunov contributed to the writing of the manuscript and its statistical analysis. All authors discussed the results and contributed to the final version of the manuscript.

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