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GUIDELINE

Guidelines for cervical cancer screening in South Africa

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on behalf of the SA HPV Advisory Board

Development of the guideline document

- The South African HPV Advisory Board (the Board) is a multi-disciplinary group of experts including professionals from the disciplines of public health, virology, gynaecological oncology, anatomical pathology, and cytology.
- The activities and opinions of the Board are independent of pharmaceutical and diagnostic industries.
- This guidance was drafted after careful updated literature review (not included) and discussion; it is a consensus document.
- This is the third guideline produced by the group and it will be reviewed from time to time as technology develops and knowledge changes.[1,2]
- All users and readers are encouraged to enter the debate on ideal screening strategies for South Africa.

Summary

Cervical cancer, caused by persistent cervical infection by high-risk HPV and made worse by the HIV epidemic, remains an important cause of morbidity and mortality in South Africa. The SA HPV Advisory Board previously recommended HPV-based primary screening, and now international support for this approach is also mounting in view of higher sensitivity. The main advantages for South Africa are the ability to safely increase screening interval and to test cervico-vaginal self-sampled specimens.

Non-discriminatory HPV tests give a "negative" or "positive" answer for the presence of any high-risk HPV. Discriminatory tests differentiate between the highest risk types and "other" high-risk types and results are more specific. Triage or secondary tests are important for patients with a medium risk for a current or future lesion, while those with a higher risk can be treated without triage.

In view of differences in health care systems, several options for screening, triage and treatment are provided. These options still include cytology screening, which the Board recommends should be phased out. Affordability to the health care system, cervical cancer risk and therefore HIV status influences screening entry and exit ages which is generally recommended from 25 to 65 years.

The management of positive screening tests and treatment of women with lesions or risk is an essential part of prevention. Two algorithms are provided to simplify triage, treatment and follow-up decisions, namely for cytology- and HPV-based screening.

Introduction

Cervical cancer is an important cause of morbidity and mortality in South Africa. The incidence of invasive cervical cancer remains unacceptably high, cases are often diagnosed late, and many patients have poor response to treatment.[3] This cancer is caused by persistent cervical infection by a high-risk strain of HPV. The high prevalence of immunodeficient people in the community and poor pre-cancer treatment programmes probably contributed to exceptionally high HPV prevalence in certain test groups especially among poorly serviced communities.[4]

At present the national cervical cancer prevention programme offers three cervical cytology smears per lifetime at public health facilities, starting from the age of 30, at ten-yearly intervals. Guidelines for patients with HIV infection include more frequent cytology tests. Call and recall systems are not in place and the number women lost to follow-up before treatment is high.

In the private sector, cytology based opportunistic screening is well accepted but also not uniformly implemented. Some women present yearly for screening and are therefore over-serviced; many others do not present at all. Disease prevalence is lower, but tolerance for incorrect tests is also lower.

HPV tests are now widely available and offer improved sensitivity for existing and future cervical pre-cancer lesions over a single round of cytology. It is expected that primary HPV-screening will

replace traditional cervical cytology soon in many countries. The possibility of patient-collected specimens (self-sampling) can cater for large numbers of women who may not have access to healthcare facilities.

The development of this new technology and the changing paradigm in cervical cancer screening has caused much uncertainty. The public, primary health care practitioners and specialists are often uncertain of the true advantages as well as the management of positive tests. This document mainly aims to clarify these questions by providing a simplified guideline with treatment algorithms. However, in view of large differences in existing health care systems, a uniform screening program for all health care settings may not be the best way forward for South Africa. Therefore, several options are provided for individual health districts and providers to choose an appropriate screening solution.

International support for HPV-based primary screening

World Health Organisation (WHO)

A Guideline Development Group (GDG) that included experts, clinicians, researchers in cervical cancer prevention and treatment, health programme directors and methodologists, was established by the WHO to consider screening and treatment for cervical pre-cancer. The resulting 2013 guideline document provides different strategies for a national screen-and-treat programme from which health planners could choose.[5] The following important recommendations for the choice of primary screening test and management of positive tests were based on an extensive study of available evidence:

- Use a strategy of screen with an HPV test and treat, over a strategy of screen with VIA and treat.
- Use a strategy of screen with an HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat.
- Use either a strategy of screen with an HPV test followed by VIA and treat, or a strategy of screen with an HPV test and treat.

United States of America

According to new interim guidance from multiple USA societies, primary screening for human papilloma virus (HPV) using a DNA test can be considered an alternative to previous cytology-based cervical cancer screening strategies.[6]

In 2011, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology updated their screening guidelines. At that time, these groups recommended cytology alone and in combination with high-risk HPV testing (co-testing) as primary screening strategies, but not the use of high-risk HPV testing alone.[7]

However, more recently, representatives from the Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology, convened to provide guidance for primary hrHPV screening. Guidance was based on literature review and review of data from an FDA registration study, supplemented by expert opinion. They concluded that "primary hrHPV screening is an important scientific and clinical advance in cervical cancer screening since it offers better reassurance of low cancer risk compared to cytology-only screening"[6] conducted at the same interval. Primary hrHPV screening can therefore be considered an alternative to cytology-based cervical cancer screening approaches, including cytology alone and co-testing.

United Kingdom

In a large randomised longitudinal study performed over three screening rounds (six years), HPV testing as an initial screen was compared to the current practice in the UK, which was cytology. Primary HPV screening was found to be significantly more protective than cytology and it was concluded that HPV screening could allow a safe lengthening of the screening interval. In addition, modelled analysis predicted that primary HPV screening would be both more effective and cost saving compared to cervical cytology. This study and the economic evaluation lend support for the UK to convert from cytology to HPV-based screening.[8]

Australia

In April 2014, the Medical Services Advisory Committee (MSAC) recommended that Australia move to a five-yearly screening program using an HPV test with partial genotyping for HPV16/18 as the primary screening test.[9] Following a comprehensive review of the current evidence for cervical screening, MSAC has made the following recommendations for both HPV vaccinated and unvaccinated women:

- An HPV test every five years
- Commence screening at 25 years of age
- Exit test between 70 and 74 years of age
- Women with symptoms (including pain or bleeding) can have a cervical test at any age.

The committee also concluded that an HPV test every five years is "more effective at protecting against cervical cancer and is just as safe as screening with a Pap test every two years" and "an HPV test every five years can save more lives"[9] and women would need fewer tests than in the current two-yearly Pap test program. HPV vaccinated women will still require cervical screening as the HPV vaccine does not protect against all the types of HPV that cause cervical cancer.

Acceptable technology for HPV-based primary screening

Arbyn et al.[10] published a review on the HPV assays that fulfil the criteria for use in primary screening. More than 125 HPV assays (and over 80 variants of the original assays) have been developed, but evidence of their clinical utility has been

demonstrated for relatively few. A group of experts suggested criteria for test requirements in 2009.[11] At present only seven HPV DNA tests fully meet the requirements and one mRNA test may also meet the criteria when longer follow-up data become available.[10]

Due to the oncogenic importance of type 16 and to a lesser extent other types including 18, 31, 45 and 52 (sometimes referred to as "highest risk HPV"), there is interest in (partial) genotyping as it may add specificity to the result. Individuals who test positive for these highest risk HPV-types are at a bigger risk of disease and an HPV-16 positive result has an even higher likelihood of association with (or prediction of) a pre-malignant or malignant lesion than other types. More specific screening tests need less triage before treatment.

Non-discriminatory tests are those which include the whole array of high-risk HPV viruses and gives a "negative" or "positive" answer. Patients with a positive result can have a high or a medium risk for a current or future lesion and therefore a triage test is important.

Discriminatory tests are usually tests with partial genotyping and give a result of "negative", "positive for the highest risk viral types" (usually 16, 18, sometimes also 45) or "positive for other high-risk HPV types". Patients in the highest risk category can have treatment without triage (similar to HSIL cytology), while the "other high-risk HPV" category should have a triage test to decide on treatment or follow-up.

General considerations for South Africa

Guidelines developed for other countries may not be suitable for the unique conditions in South Africa. Unusual circumstances include the high prevalence of both HIV and HPV infections, parallel systems of public and privately funded health care, well-developed health laboratories services and very good tertiary health care.

Cytology based screening services are well established in the private sector and in certain health districts in the public sector. The change to HPV primary screening will take time and this document will consider ways to improve on cytology where it is still used rather than immediate replacement.

HPV based primary screening is more sensitive in detecting pre-cancer and cancer, and has a better negative predictive value (NPV) than cytology which allows longer screening intervals. It is therefore the opinion of the Board that funders and providers must migrate to HPV primary screening as soon as is practical.

Huge variation exists regarding the degree of sophistication of health systems in different geographical areas of South Africa, therefore the same solutions will not be applicable in all settings. It is recommended by the authors that the best screening algorithm for each district should be determined by a health systems assessment.

Treatment of pre-cancer lesions or cancer risk is an essential part of prevention by screening. There is a clear lack of treatment facilities for pre-cancer and cancer nationally; such facilities must be developed at the same time as improving screening programmes.

Liquid based samples have the advantage that they may be used for primary HPV test and triage tests. The development whereby more laboratories are converting their service facilities is welcomed, but the change should preferably be cost-neutral to the consumer.

Patient self-sampling for molecular tests (such as an HPV DNA or RNA test) may be an attractive option for many districts. Importantly, self-sampling is very well suited for HPV testing but not suited for cytology.

Guidelines

Primary screening tests

The aims and target population of screening

Screening aims to detect women with an unsuspected cancer risk by testing asymptomatic women. It is recommended that all South African women should initiate cervical screening at the age of 25 years (earliest) or at the time of diagnosis of HIV-seropositivity. Women should exit screening only after a negative test and if known or assumed to be HIV negative.

Table 1: Primary screening tests

SETTING	LOW RESOURCE		HIGH RESOURCE	
HIV status	**HIV unknown or negative**	**HIV positive**	**HIV unknown or negative**	**HIV positive**
Initiate screening	Age 25	At diagnosis of HIV	Age 25	At diagnosis of HIV
Exit screening (only after negative test)	Age 55 or hysterectomy	Never end	Age 65 or hysterectomy	Never end
Interval if HPV screening	10-yearly	5-yearly	5-yearly	3-yearly
Interval if cytology screening	5-yearly	3-yearly	3-yearly	1-yearly
Timing	3-yearly: 25,28,30,33,35,38,40,43,45,48,50,53,55,58,60, etc. 5-yearly: 25,30,35,40,45,50,55,60,65, etc. 10-yearly: 25,35,45,55, etc.			
Follow-up	HIV negative or < 35 years: 5-yearly until normal	HIV positive or > 35 years: yearly until normal	HIV negative or < 35 years: yearly until normal	HIV positive or > 35 years: yearly until normal
	Back to screen when normal. Retreat after second abnormal test.			

Table 2: Triage or secondary screening tests

TRIAGE TEST	INDICATIONS	RESULTS	MANAGEMENT
VILI or VIA visual inspection using Lugol's iodine or acetic acid	Low resource settings Medium risk result on cytology or HPV test	Possible invasive lesion	Biopsy
		No lesion	Do not treat
		Small lesion	Cryotreatment or LLETZ
		Large lesion	LLETZ
CYTOLOGY conventional or liquid based cytology	Low or high resource settings Medium risk result on HPV test	Normal	Do not treat
		Positive = ASCUS or worse	Cryotreatment or LLETZ
CYTO-STAIN or similar biomarker	High resource settings Medium risk result on cytology or HPV test	Normal	Do not treat
		Positive	Colposcopy and biopsy
HPV TEST with or without partial genotyping	High resource settings Medium risk result on cytology	Normal	Do not treat
		Positive	Colposcopy and biopsy

Appropriate screening tests

Cervical cytology and HPV testing are both considered suitable for screening in South Africa and screening practitioners or facilities should choose the most appropriate test for their setting.

Screening interval and timing

The screening interval can be longer when HPV testing is chosen and in resource poor environments. It may be helpful to follow birthdays as an alternative to a call system.

Follow-up after treatment

Visits should be at shorter intervals than screening visits until all tests are normal. All these proposals are summarized in Table 1.

Secondary / triage tests

The aim of triage

Triage or secondary testing aims to avoid overtreatment of women with abnormal screening test which may not confer a high risk for severe dysplasia and is therefore a way to manage "intermediate risk" results. A negative triage test means 'follow-up'; a positive triage test means 'treat'.

Appropriate triage or secondary tests

For South Africa these include cytology, HPV test, immuno-cytochemistry, or simple visual inspection with colourant. Triage is usually performed with a different test to the initial screening test and treatment facilities should choose the most appropriate for their setting. Repeat cytology is appropriate triage after medium risk cytology. The tests range from inexpensive to pricey and are summarized in Table 2.

Management of non-squamous cytological abnormalities

Atypical glandular cells on cytology needs adequate investigation of the endocervical canal and endometrium. In young women (less than 30 years of age) a single AGC result may be treated with antibiotics and the cytology repeated. In all women with AGC over the age of 30 or where a repeat cytology remains abnormal, an endocervical or LLETZ sample and endometrial sample must be obtained for cytology and/or histology.

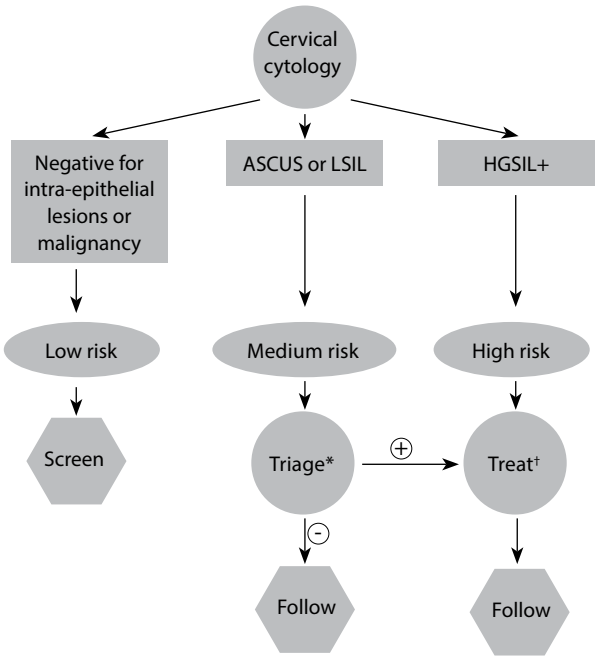
Management of abnormal tests

The management of different cytology and HPV-test results are demonstrated in two treatment algorithms (Figures 1 and 2).

Treatment

Excisional treatment with a loop procedure is the preferred treatment option for an abnormal screening test. The cervical surface must be stained with iodine before the procedure to identify and include all abnormal epithelium. Histology of the excised specimen is preferred. In selected cases where an infiltrating cancer has been excluded, the transformation zone

Figure 1: Guidelines for primary cytology# screening in South Africa

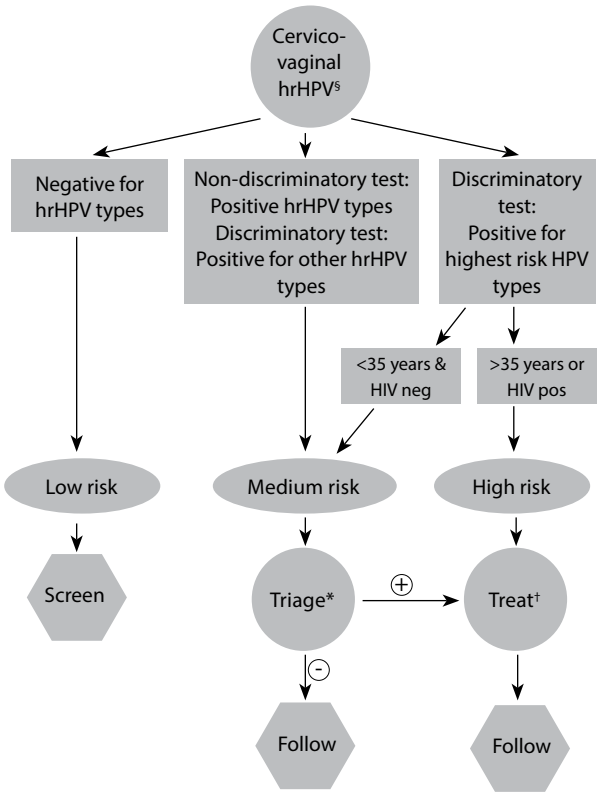


To be phased out over time

* High resource setting: cyto-staining; HPV test, repeat cytology
* Low resource setting: VILI / VIA, repeat cytology

† Treatment in high resource settings is usually done after colposcopy ± biopsy confirmation
† In low resource settings treat all patients at first recall visit

Figure 2: Guidelines for primary HPV screening in South Africa



§Tests for high risk HPV types; DNA or RNA

* High resource setting: cyto-staining; HPV test, repeat cytology
* Low resource setting: VILI / VIA, repeat cytology

† Treatment in high resource settings is usually done after colposcopy ± biopsy confirmation
† In low resource settings treat all patients at first recall visit

is visible and resources for histology is limited, ablative therapy with cryo-treatment or cauterisation is acceptable.

Conclusion

HPV-based screening is preferred to cytology because the higher sensitivity allows a longer safe interval, but both tests remain valid options. Triage or secondary testing is needed after medium risk screening results, while high risk results should lead to treatment.

Tabulated screening and triage guidelines are provided as well as algorithms which simplify the management of test results for all practitioners involved in the prevention of cervical cancer.

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