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Review Article

Evaluation of Different Guidelines for Cervical Cancer Screening and Management of Abnormal Cervical Cytology

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Abstract

This is a comparison review article of the various guidelines that currently exist for cervical cancer screening. The guidelines used for comparison include the American College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), American College of Physicians (ACP), American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP), Centers for Disease Control and Prevention (CDC), American Society for Colposcopy and Cervical Pathology, National Institute for Health and Care Excellence (NICE) guidelines, Singapore guidelines, National Health Service (NHS) Guidelines, The Canadian Task Force on Preventive Health Care, Society Of Obstetricians And Gynecologists Of Canada, World Health Organization (WHO), and The European Guidelines For Quality Assurance In Cervical Cancer Screening. As there is no universal screening guideline that is currently agreed upon, this article serves to highlight the key differences and resemblances between those guidelines with regards to the age of screening initiation and cessation, the screening intervals and management of abnormal screening results. Comparisons are made in the discussion, presented as individual tables, and comparison tables with regards to cytology and histology.

Tables summarizing the different guidelines available regarding screening for cervical cancer.

Abbreviations

ACOG: American College of Obstetricians and Gynecologists; USPSTF: United States Preventive Services Task Force; ACS: American Cancer Society; ASCCP: American Society for Colposcopy and Cervical Pathology; ASCP: American Society for Clinical Pathology; CDC: Centers for Disease Control and Prevention; ACP: American College of Physicians; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; VIA: Visual Inspection with Acetic Acid; HPV: Human Papillomavirus; ASCUS: Atypical Squamous Cells of Undetermined Significance; LSIL: Low Grade Squamous Intraepithelial Lesion; HSIL: High Grade Squamous Intraepithelial Lesion; ASC-H: Atypical Squamous Cells in which HSIL cannot be excluded; AGC: Atypical Glandular Cells; AIS: Adenocarcinoma in Situ; CIN: Cervical Intraepithelial Neoplasia; SCC: Squamous Cell Carcinoma; LEEP/LLETZ: Large Loop Excision of The Transformation Zone; CKC: Cold Knife Conization

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NHS/NICE classification equivalency to Bethesda classification.	
Atypical squamous cells of undetermined significance	ASCUS
Atypical squamous cells, cannot exclude HSIL	ASC-H
Low-grade dyskaryosis (mild)	LSIL
High-grade dyskaryosis (moderate-severe)	HSIL

Introduction

The introduction of cervical cancer screening programs has accounted for a significant reduction in the incidence and mortality of cervical cancer [1]. In countries where cervical cancer screening is not available, cervical cancer remains the second most common cause of cancer as well as the second most common cause of cancer deaths among women [2]. Therefore, it is widely established that cervical cancer screening is undoubtedly essential as it permits early discovery of the disease and hence, early treatment and better prognosis. It also allows the detection of pre-malignant states, thus prevent the progression into invasive cancer [3]. Globally, various guidelines exist for cervical cancer screening as different countries and societies have developed different algorithms for screening. Those algorithms may agree about or vary in the age at which screening should be initiated and ceased, the intervals of screening as well as the steps involved in management of any abnormal screening result. Yet, there is no universe screening guideline that all countries, worldwide, may follow.

This article will discuss different cervical cancer screening programs that exist. It will highlight the key differences and resemblances between those guidelines with regards to the age of screening initiation and cessation, the screening intervals and management of abnormal screening results.

Discussion

Cervical Cancer Screening Guidelines: A Comparison Between Various Available Cervical Cancer Screening Guidelines

Age of screening initiation

The age to begin routine screening for cervical cancer is controversial. The American guidelines, including the guidelines of the American College of Obstetricians and Gynecologists (ACOG), the United States Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Society for Clinical Pathology (ASCP), the American College of Physicians (ACP) and the American Society for Colposcopy and Cervical Pathology, agree to start routine screening for cervical cancer at the age of 21years [4]. However, the guidelines of Singapore and Canada, as well as the NICE and NHS guidelines, recommend starting screening at the age of 25years [5-8]. The World Health Organization (WHO), on the other hand, recommends beginning screening at age 30 for HIV-negative women [9]. Nevertheless, those guidelines give similar rationales behind their recommendations; cervical cancer is uncommon among younger women and to offer screening for that age group may lead to over-treatment and ultimately, more harm than good.

Age of screening cessation

The American guidelines for cervical screening, recommend that screening shall be ceased once a woman is above 65years of age and has no history of CIN2 or higher. However, this would be applicable only if either of the following is true; having 3 previous consecutive negative cytology results, or; having 2 previous consecutive negative co-test results, in the previous 10years with the most recent test being within 5years. Furthermore, screening shall also be discontinued for women who have had total hysterectomy with removal of the cervix and no history of CIN 2 or higher 4. The guidelines of Singapore are similar, as they recommend no further screening for women aged above 65 if there was a previous negative smear in the last 3years [6]. As per the NICE guidelines and the NHS, women above the age of 65 shall only undergo cervical screening if there has been no screening done up to the age of 50years or if there is a recent abnormal cytology result. Otherwise, no screening should be offered in older women due to the infrequency of cervical cancer in this age group [7].

The Canadian guidelines, on the other hand, suggest stopping screening at the age of 70 for women who have had satisfactory screening, for instance 3 consecutively negative Pap test results in the previous 10years, as there is limited evidence of benefit to continue screening in this age group. Nevertheless, for women at 70years of age or older who have not yielded 3 negative test results, the recommendation is to continue adequate screening until these results have been obtained [5].

Screening intervals

The American guidelines recommend screening via cytology (Pap smear or liquid-based cytology) every 3years. However, if the woman wishes to lengthen the screening interval, a combination of cytology and HPV testing can be done every 5years instead. However, it is not recommended to do HPV testing for average-risk women in the age group between 20 and 31. Moreover, there is insufficient evidence to support longer screening intervals for women between the age of 21 and 30 with 2 or more consecutive negative cytology results 4. The screening intervals recommended by the NICE guidelines and the NHS are as follows: 3-yearly for women between the ages of 25-49years and 5-yearly for women between the ages of 50-65years [7]. (Please see Table 1, which summarizes the NHS guideline and Table 2, which summarizes the NHS guidelines). The Canadian guidelines recommend a 3-yearly screening interval for women between the ages 25-69years. This recommendation is based on 13 case-control and 2 cohort studies, which established that a screening interval of 5years or less provides a significant protection against cervical cancer [5], (Please see table 3, which summarizes The Canadian Task Force on Preventive Health Care screening for cervical cancer guidelines). The guidelines of Singapore recommend a 3-yearly screening interval as well for women between the ages 25-65years, however, more frequent screening if high-risk [6].

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Table 1: National Institute for Health and Care Excellence (NICE) guidelines on screening for cervical cancer.

Classification		NICE guidelines			
Overview		<25year old	25-49years old	50-65years old	>65years old
		No screening	Initiate screening at the age of 35years Screen every 3years	Screen every 5years	Screen only if no screening was done from 50years or if a recent abnormal cervical cytology was present
	Borderline changes	- If HPV positive: Do colposcopy within 8weeks - If HPV negative: Return to normal routine screening			
	Low-grade dyskaryosis (mild)				
	High-grade dyskaryosis (moderate-severe)	Do colposcopy within 4weeks			
	AIS	If 3 consecutive inadequate samples: Repeat cytology in 3months			
	High-grade dyskaryosis? invasive squamous cell carcinoma	Do colposcopy within 2weeks			
	Invasive glandular neoplasia of endocervical type				
	Invasive glandular neoplasia non-cervical				
Histology	CIN 1	- Do a cytological smear with or without colposcopy at 12months - Generally based on the patient's preference; either provide treatment or keep patient under observation and treat if no regression occurred after 24months			
	CIN 2	Treat either by ablation or large loop excision of the transformation zone			
	CIN 3				
	Invasive carcinoma	Refer for surgical or non-surgical management			

Table 2: National Health Service (NHS) Guidelines on screening for cervical cancer.

Classification		NHS Guidelines			
Overview		24.5	25-49	50-64	≥ 65
		First invitation (to ensure that women can be screened for the first time by their 25th birthday No screening for age <24.4	Screen every 3years by LBC	Screen every 5years by LBC	Invitation as required for women who have had recent abnormal tests or women who have not had adequate screening tests reported since age 50
Cytology	Borderline changes		Do colposcopy within 6weeks if HPV positive		
	Low-grade dyskaryosis (mild)				
	High-grade dyskaryosis (moderate-severe)		Do colposcopy within 2weeks		
	High-grade dyskaryosis ?invasive SCC				
	Invasive glandular neoplasia of endocervical type				
	Invasive glandular neoplasia non-cervical		Give an appointment with gynecologist within 2weeks		

Table 3: The Canadian Task Force on Preventive Health Care on screening for cervical cancer.

Classification	The Canadian Task Force on Preventive Health Care				
Overview	<20	20-24	25-29	30-69	≥70
	Routine screening not recommended (strong recommendation/high-quality evidence)a	Routine screening not recommended (weak recommendation/ moderate-quality evidence)	Routine screening is recommended every 3years (weak recommendation/ moderate-quality evidence)	Routine screening is recommended every 3years (strong recommendation/ high-quality evidence)	Women aged 70years and older who have undergone adequate screening (i.e., 3 successive negative Pap test results in the previous 10years), we recommend that routine screening may end. For women aged 70years and older who have not undergone adequate screening, we recommend continued screening until 3 negative test results have been obtained. (Weak recommendation; low-quality evidence.)
			HPV co-testing: current recommendations do not recommend so. But decision will be revisited once more data available		

Management of abnormal screening tests

The American guidelines (American College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP), Centre of Disease Control and Prevention (CDC), American College of Physicians (ACP)): Whenever HPV co-testing is positive, it is recommended to do an immediate HPV genotype-specific testing for HPV 16 or HPV 16/18. On the one hand, if the genotype-specific testing is positive, the patient should be referred to colposcopy. On the other hand, if the latter is negative, HPV co-testing should be repeated in 12months time [4,8]. If screening via

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cytology revealed atypical squamous cells of undetermined significance (ASCUS) and HPV co-testing was negative, it is recommended to preform routine age-based screening only. This is simply explained by the low risk of pre-cancerous or invasive lesions seen in HPV-negative women with ASCUS, as studies have shown [8]. However, if the result of the cytology were as either; atypical squamous cells–cannot exclude HSIL (ASC-H), Low Grade Squamous Intraepithelial Lesion (LSIL), high Grade Squamous Intraepithelial Lesion (HSIL) or Atypical Glandular Cells (AGC), it is recommended to do HPV co-testing after 12months with referral for colposcopy [4,8]. In addition, for women with history of CIN 2 or higher, the ACOG recommends to screen via cytology every 3years for a period of 20years after the initial post-treatment surveillance period. This would also be applicable if the woman underwent a total or supra-cervical hysterectomy [4,8]. The American Society for Colposcopy and Cervical Pathology: The main 2 categories of population regarding this guideline is based on age group, that is, people younger than 21years old and people older than 21years old. Initiation of screening is recommended 3years after first sexual intercourse or at the age of 21, whichever comes first in the less than 21years old population. Screening is advised every 3years in the older group. For any age group, if HPV test is positive and cytology is negative, a conservative approach should be considered, that is repeating both test in 12months' time. However, if both HPV test and cytology are positive, referral to colposcopy is recommended. In the <21year old patients, a cytology revealing ASCUS or LSIL needs to be repeated in 12months and if the change still persists for more than 24months, then referral to colposcopy is indicated. If the lesion shows HSIL, colposcopy is recommended. In the event of a cytology showing AGC initially and on repeated cytology in 24months, referral for colposcopy is advised. Patients having CIN 1 lesions on colposcopy will need repeat cytology in 12months and if the changes still persist for 24months, colposcopy will be required. In the >21year old population, in case cytology shows ASCUS, 3 options are available, HPV test, cytology in 6 or 12months and colposcopy. In case colposcopy is chosen and revealed negative, repeat cytology in 6 or 12months or HPV test in 12months. If HPV test done is positive or repeated cytology done in 6 or 12months shows ASCUS or HPV test done in 12months is positive, colposcopy is advisable. Any LSIL changes noted on cytology should be referred to colposcopy. If colposcopy is found to be positive for any changes except for CIN 2 and CIN 3, cytobrush and endocervical curette is recommended; otherwise HPV test is recommended in 12months or cytology in 6 and 12months. If HSIL is found on cytology, the initial test recommended are diagnostic procedures (immediate loop electrosurgical excision) or colposcopy with endocervical assessment. If no CIN 2 or 3 was found on colposcopy and endometrial sampling is negative, diagnostic procedures or cytology or colposcopy every 6months can be considered. However, if HSIL persists at 6 or 12months, referral for excision should be considered. In cytology showing AGC, colposcopy with endocervical sampling and HPV test are recommended, especially in the suspicion of high risk of endometrial cancer. In the event of a cytology showing AIS, diagnostic excisional procedure is recommended. For CIN 1 persisting for 2years, observe the changes but if it was preceded by HSIL or AGC-NOS, then diagnostic excision or cytology and colposcopy in 6 and 12months are recommended. If there is any unsatisfactory colposcopy or positive sampling or previous treatment, refer for excision. Please see summary tables 4-9, which covers each of the six discussed guidelines.

In addition, please see Table 10, which compares cervical cancer screening guidelines based on cytology and Table 11, which compares cervical cancer screening guidelines based on histology.

NICE guidelines

If cytology reveals ASCUS or LSIL, the following action depends on the HPV co-testing result. If HPV is positive, colposcopy should be done within 8weeks. However, if HPV

Table 4: American College of Obstetricians and Gynecologists (ACOG) guidelines on screening for cervical cancer.

Classification		American College of Obstetricians and Gynecologists (ACOG)			
		<21year old	21-30year old	31-65year old	>65year old
Overview		No screening is done for women under the age of 21years with the exception of HIV-positive or immune-compromised women	A 3-yearly screen via cervical cytology only	A 5-yearly screening via cervical cytology and high-risk HPV DNA testing OR a 3-yearly screen via cervical cytology only	Screening is ceased in women above the age of 65years with no history of ≥ CIN 2 with either 3 consecutive negative cytology results or 2 consecutive negative co-test results over the past 10years, with the most recent test being done within the last 5years Screening is also stopped for women who have undergone total hysterectomy and have no history of ≥ CIN 2
Cytology	HPV test positive			Colposcopy	
	ASCUS	Return back to routine screening if a HPV co-test was done and indicated a negative result			
	ASC-H			Refer to colposcopy and do a co-test with HPV after 12months	
	LSIL				
	HSIL				
Histology	CIN 1				
	CIN 2	Treatment will be given and later, the patient will return back to routine age-based screening for a period of 20years from the initial post-treatment surveillance (past age 65years if necessary) For women with total hysterectomy and history of either CIN 2 or higher in previous 20years or cervical cancer ever, screen with cervical cytology alone every 3years for 20years after initial post-treatment surveillance period For women with a supracervical hysterectomy and history of CIN 2 or higher perform routine screening every 3years for 20years after initial post treatment surveillance period			
	CIN 3				
	AIS				

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Table 5: United States Preventive Services Task Force (USPSTF) guidelines on screening for cervical cancer.

Classification	United States Preventive Services Task Force (USPSTF)			
Overview	<21year old	21-30year old	31-65year old	>65year old
	No screening is recommended	Screen via cytology (Pap smear or liquid-based cytology) every 3years If a longer screening interval is desired, screening with a combination of cytology and HPV co-testing may be done every 5years		No screening is recommended if there were adequate normal previous screening tests and the women is no other-wise at high risk for cervical cancer Adequate previous screening may be defined as 3 consecutive negative cytology results or 2 consecutive negative co-test results over the past 10years, with the most recent test being done within the last 5years Screening is also stopped for women who have undergone total hysterectomy with removal of the cervix and have no history of ≥ CIN 2

Table 6: American College of Physicians (ACP) on screening for cervical cancer.

Classification	American College of Physicians (ACP)			
Overview	<21year old	21-30year old	31-65year old	>65year old
	No screening is done	Start screening asymptomatic average-risk women at the age of 21years Do a 3-yearly screen with cytology Do not screen more frequently than once every 3years Do not perform HPV testing in average-risk women < 30years old	Do a 3-yearly screen with cytology A combination of Pap smear and HPV testing once every 5years may be used in women who prefer screening less frequently than once every 3years	Screening is ceased in women above the age of 65years with no history of ≥ CIN 2 with either 3 consecutive negative cytology results or 2 consecutive negative co-test results over the past 10years, with the most recent test being done within the last 5years

Table 7: American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP) on screening for cervical cancer.

Classification		American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP)			
Overview		<21year old	21 - 30year old	31 - 65year old	>65year old
		Do not screen women aged <21years old regardless of risk factors including the age at which sexual activity was initiated	Begin cervical cancer screening at the age of 21years Screen with cytology alone every 3years There is insufficient evidence to support longer screening intervals for women in this age group with ≥ 2 consecutive negative cytology results	Co-testing with cytology and HPV testing every 5years or cytology alone every 5years	Screening is ceased in women above the age of 65years with no history of ≥ CIN 2 with either 3 consecutive negative cytology results or 2 consecutive negative co-test results over the past 10years, with the most recent test being done within the last 5years Screening is also stopped for women who have undergone total hysterectomy and have no history of ≥ CIN 2.
		Screening practice is not altered based on HPV vaccination status			
Cytology	HPV test positive	Do a HPV-genotype specific-testing for HPV 16 or HPV 16/18 immediately: - If HPV 16 or HPV 16/18 positive: Refer to colposcopy - If HPV 16 or HPV 16/18 negative: Repeat co-testing in 12months			
	ASCUS		Resume routine screening		
	ASC-H		Do HPV co-testing after 12months with referral for colposcopy		
	LSIL				
	HSIL				
Histology	CIN 1				
	CIN 2	Continue to screen women following spontaneous regression or appropriate management of CIN 2, CIN 3, or Adenocarcinoma in situ for at least 20years			
	CIN 3				

Table 8: Centers for Disease Control and Prevention (CDC) on screening for cervical cancer.

Classification	Centers for Disease Control and Prevention (CDC)			
Overview	<21year old	21 - 30year old	31 - 65year old	>65year old
	Same guidelines as (ACS/ASCCP/ASCP) are followed			

is negative, routine screening schedule should be resumed. Conversely, if the cytology reveals HSIL, the patient should be referred to colposcopy within 4weeks, regardless of the HPV test result. Further, colposcopy referral should be within 2weeks if the cytology showed high-grade dyskaryosis, query invasive squamous cell carcinoma, invasive glandular neoplasia of endocervical type or invasive glandular non-cervical neoplasia [7]. If histology examination was done and a CIN grade 1 was seen, a cytological smear should be done with or without colposcopy at 12months. Depending on the patient's desire, treatment can be initiated for CIN 1 or the patient may opt to watch and wait and treat only if no regression occur within 24months. However, if the histology reveals CIN grade 2 or grade 3; the lesion will be treated with either ablation or large loop excision of the transformation zone [7]. Please see Table 7 at the end of this review article, which summarizes the discussed guideline.

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Table 9: American Society for Colposcopy and Cervical Pathology on screening for cervical cancer.

Classification		American Society for Colposcopy and Cervical Pathology			
Overview		<21year old	21-30year old	31-65year old	>65year old
		Initiate screening with cytology 3years after sexual intercourse OR at the age of 21 (whichever comes first)	Screen is recommended every 3years		
Cytology	HPV test positive	- If HPV test is positive and cytology is negative: conservative follow-up is advised with repeat co-testing at 12months - If HPV test is positive and cytology is positive: referral to colposcopy is recommended			
	ASCUS	Repeat cytology in 12months, if the change persists for more than 24months then refer to colposcopy	1) HPV test is preferred for triage and colposcopy is advisable for positive HPV test 2) Repeat cytology in 6months or 12months 3) o an immediate colposcopy - If colposcopy done was negative: repeat cytology in 6months and 12months OR HPV test in 12months - if repeated cytology in the following 6 or 12months still shows ASCUS, then refer again to colposcopy - if HPV test done in the following 12months is still positive, then refer to colposcopy		
	ASC-H		Refer to colposcopy		
	LSIL	Repeat cytology in 12months, if the change persists for more than 24months then refer to colposcopy	=> Colposcopy • if colposcopy is positive for any changes, cytobrush or Endocervical curette is recommended • if colposcopy is positive (NOT CIN 2 OR CIN 3), HPV test is recommended in 12months OR cytology in 6 months and 12months respectively		
	HSIL	Refer to colposcopy	1) Initial tests recommended are: - diagnostic procedure (High risk and done with childbearing) - colposcopy with Endocervical assessment 2) diagnostic OR cytology and colposcopy every 6months till the tests are negative 3) if HSIL persists at 6 OR 12months, refer for excision		
	AGC	If the change persists for more than 24months then refer to colposcopy	Colposcopy with Endocervical sampling and HPV test are recommended (especially high risk of endometrial Cancer) - if AGC unremarkable and HPV is positive, then refer to cytology and HPV in 6months - if HPV is negative, refer to cytology and HPV in 12months		
	AIS		Diagnostic excisional procedure		
Histology	CIN 1	Repeat cytology in 12months, if the change persists for more than 24months then refer to colposcopy	1) If persistent for 2years, observe the changes - if preceded by HSIL OR AGC-NOS, then diagnostic excision is recommended OR cytology and colposcopy in 6months and 12months 2) If unsatisfactory colposcopy OR positive sampling OR previous treatment, refer for excision		
	CIN 2	1) Observation 2) colposcopy and cytology every 6months till 2years 3) Treatment with excision or ablation 4) if CIN 2 => observation preferred 5) CIN 3 => treatment	1) + satisfactory colposcopy => ablation OR diagnostic excision 2) monitor post treatment - HPV - cytology alone or with HPV also		
	CIN 3				
	AIS		HPV, colposcopy, endocervical sampling in 6months - AGC-favoring neoplasia or AIS by cytology and no invasion => Excisional procedure - AIS by histology => hysterectomy		

The Society of obstetricians and gynecologists of canada guidelines

If a cytology result showed borderline changes, i.e. ASCUS, colposcopy should be done within 12weeks. If a lesion is found on colposcopy, a biopsy will be obtained. However, if no lesion was found, a biopsy of the transformation zone will be obtained. Nevertheless, if such result was found in a woman less than 21years of age, cytology should be repeated. If a cytology result revealed atypical squamous cells in which HSIL (ASC-H) cannot be excluded, colposcopy should be done within 6weeks. If the cytology shows mild dyskaryosis (i.e. LSIL), a similar guideline as above will be followed, i.e.; colposcopy within 12weeks, biopsy of any found lesion or biopsy of the transformation zone if no lesion was found. And similarly, if the age group was below 21years, only cytology will be repeated. Moreover, any moderate or severe dyskaryosis (i.e. HSIL) will necessitate a colposcopy within 4weeks. If no lesion was found on colposcopy, endocervical curettage or directed biopsy will be done. However, if a lesion was to be found and the transformation zone could not be seen and the endocervical curettage and/or biopsy were negative; a diagnostic excisional procedure will be required. Whenever atypical glandular cells or adenocarcinoma in-situ were to be found on cytology, colposcopy and endocervical curettage are to be done within 6weeks. Besides, if the age is above 35years and per-vaginal bleeding is evident, endometrial sampling will be required. If the colposcopy shows no lesion, a diagnostic excisional procedure will be done. Furthermore, if histology then shows CIN1, the patient will be kept under observation and either cytology at 12months or colposcopy at 12months will be done. On the other hand, a CIN2 or 3 in an age group more than 25years will necessitate treatment via excision. If a positive margin was found, colposcopy and directed Bx and/or endocervical curettage will be required. In case of any recurrence or persistent lesions, excision will be required as well. Please see Table 12, which summarizes the discussed guideline.

Singapore guidelines

Firstly, based on the cytology result, if atypical squamous cells of undetermined significance were found (ASCUS), PAP

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Table 10: Comparison of Cervical Cancer Screening Guidelines based on Cytology.

Cytology							
Guidelines	**Age Group**	**ASCUS**	**LSIL**	**ASC-H**	**HSIL**	**AGC**	**AIS**
The American Guidelines	21-65	Resume routine screening	Refer to colposcopy and do a co-test with HPV after 12months				
American Society for Colposcopy and Cervical Pathology	<21	Repeat cytology in 12months, if persists for more than 24months refer to colposcopy			Refer to colposcopy	If persists for more than 24months refer to colposcopy	
	21-65	1) Triage: HPV test and colposcopy 2) Repeat cytology in 6months or 12months OR do an immediate colposcopy 3) If colposcopy was negative: repeat cytology in 6months or 12months - repeat cytology in 6 or 12months -> ASCUS => colposcopy - HPV test in 12months -> positive => colposcopy	1) Colposcopy • negative => cytobrush or Endocervical curette • positive (NOT CIN 2/3) => HPV test in 12months OR cytology in 6months and 12months	Refer to colposcopy	1) Initial - diagnostic procedure (High risk and done with childbearing) - colposcopy with Endocervical assessment 2) diagnostic/cytology and colposcopy every 6months till above negative 3) if HSIL persists at 6/12months => excision	Colposcopy with Endocervical sampling and HPV test (especially high risk of endometrial Cancer) - if AGC unremarkable and HPV positive => cytology and HPV in 6months and HPV negative => cytology and HPV in 12months	Diagnostic excisional procedure
NICE	25-65	- If HPV positive: do colposcopy within 8weeks - If HPV negative: return to normal routine screening			Do colposcopy within 4weeks		If 3 consecutive inadequate samples: repeat cytology in 3months
Singapore	25-65	Repeat smear in 6months: if positive refer to colposcopy / if negative repeat again in 6months, then if still negative return to routine screening	1. If mild dyskaryosis or not otherwise specified: Colposcopy 2. If HPV effect: Repeat in 6months: a. If negative: Repeat in 1 year > if still negative resume routine screening b. If still HPV effect or more severe abnormality: colposcopy	Refer to colposcopy	1. If moderate or severe dyskaryosis: colposcopy 2. If severe dyskaryosis and cannot rule out invasive Cancer: Urgent colposcopy	Refer to colposcopy	Endocervical adenocarcinoma in-situ: colposcopy
NHS	25-65	Do colposcopy within 6weeks if HPV positive			Do colposcopy within 2weeks		
Society Of Obstetricians And Gynecologists Of Canada	< 21	Repeat cytology			Colposcopy within 4weeks		
	21-65	Do colposcopy within 12week: if a lesion was found: do a biopsy, if no lesion was found: do a biopsy of the transformation zone		Colposcopy within 6weeks	Do colposcopy within 4weeks, if no lesion found: do endocervical curettage/directed biopsy. If lesion was found and transformation zone was not seen and endocervical curettage and/or biopsy were negative: do a diagnostic excisional procedure	Do colposcopy and endocervical curettage within 6weeks (plus endometrial sampling if bleeding and age more than 35years). If no lesion was found on colposcopy: do a diagnostic excisional procedure	
WHO	30-49	Any positive cytology (≥ASCUS): do colposcopy: - If colposcopy was negative: repeat screening in 3year time - If colposcopy was positive and no biopsy was done: Treat with cryotherapy if eligible or with LEEP if not. Later, do a follow-up screen in a 1 year time - If colposcopy was positive and biopsy was done: for ≥CIN2 treat with cryotherapy or LEEP and then do a follow-up screen in a 1-year time. However, if biopsy shows a ≤CIN1 repeat screening in 3-year time. - If cancer was suspected: refer the patient for appropriate diagnosis and treatment					
The European Guidelines For Quality Assurance In Cervical Cancer Screening	30-65	Re-test in 6-12months or refer to colposcopy		Refer to colposcopy		Re-test in 6-12months or refer to colposcopy	Refer to colposcopy

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Table 11: Comparison of Cervical Cancer Screening Guidelines based on Histology.

		Histology			
Guidelines	**Age Group**	**CIN1**	**CIN 2, CIN 3**	**Invasive carcinoma**	**AIS**
The American Guidelines	21-65		Continue to screen women following spontaneous regression or appropriate management of CIN 2, CIN 3, or Adenocarcinoma in situ for at least 20years		
American Society for Colposcopy and Cervical Pathology	<21	Repeat cytology in 12months, if persists for more than 24month refer to colposcopy	1) Observation 2) colposcopy and cytology every 6months till 2years 3) Treatment with excision or ablation 4) if CIN 2 => observation preferred 5) CIN 3 => treatment		
	21-65	1) If persistent for 2years => observation - if preceded HSIL/AGC-NOS => diagnostic excision OR cytology and colposcopy in 6 months and 12months 2) unsatisfactory colposcopy/positive sampling/ previous Treatment => Excision	1) + satisfactory colposcopy => ablation OR diagnostic excision 2) monitor post-treatment - HPV - cytology alone or with HPV also		HPV, colposcopy, endocervical sampling in 6months - AGC-favoring neoplasia or AIS by cytology and no invasion => Excisional procedure - AIS by histology => hysterectomy
NICE	25-65	- Do a cytological smear with or without colposcopy at 12months - Generally based on the patient's preference; either provide treatment or keep patient under observation and treat if no regression occurred after 24months	Treat either by ablation or large loop excision of the transformation zone	Refer for surgical or non-surgical management	
Singapore	25-65	Controversial: 2 options available: 1. Treat with ablation or excision then follow-up with PAP smear at 3-6months, PAP smear and colposcopy at 12months > yearly PAP smear x4 > return to routine screening 2. Observe and repeat PAP smear and colposcopy +/- biopsy in 6months	After treatment screen with PAP smear at 3-6months > PAP smear and colposcopy at 12months > PAP smear 6monthly for 2nd year > yearly PAP smear		
Society Of Obstetricians And Gynecologists Of Canada	21-65	Observation and repeat cytology or do colposcopy at 12months	Excisional procedure If positive margin: colposcopy and directed Biopsy and/or endocervical curettage If recurrent or persistent lesions: Excision	Do colposcopy within 2weeks with biopsy	Diagnostic excisional procedure OR type 3 transformation zone excision If positive margin: do a second excisional procedure After treatment: If woman completed her family: consider hysterectomy. If family still no completed and negative margin: further excisional procedure unnecessary

smear will be repeated in 6months. If the repeated smear was positive, patient will be referred to colposcopy, however, if negative, it will be repeated again in 6months, then if a persistent negative smear was found, the patient will be referred back to routine screening. Moreover, if atypical squamous cells in which HSIL (ASC-H) cannot be excluded, the patient will be referred immediately to colposcopy 6.

For Low Grade Squamous Intraepithelial Lesion (LSIL)

- If mild dyskaryosis was found or not otherwise specified, the patient will be referred to colposcopy.
- If a HPV effect was found, cytology will be repeated in 6months. If the repeated cytology was negative, it will be repeated again in 1year after which if persistent negative smear was found, routine screening schedule will be resumed. However, if the initial repeated cytology showed a HPV effect or more significant abnormality, colposcopy will be done.

For High Grade Squamous Intraepithelial Lesion (HSIL)

Moderate or severe dyskaryosis: referral to colposcopy will be done and an urgent referral if severe dyskaryosis in which invasive carcinoma cannot be ruled out 6. If atypical glandular cells or endocervical adenocarcinoma in-situ was found, the patient will be referred to colposcopy.

Any inflammatory smear will require the following actions

- Treatment of any infection or atrophy then repetition of smear in 4-6months.

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- If 2nd smear has similar changes, the same action as per 1st smear will be done.
- If 3rd smear has again similar changes, the patient will be referred to a gynecologist.
- If changes resolve after 1st or 2nd smears, routine screening will be resumed.

Regarding the recommended approaches towards histological findings, the management of a grade 1 cervical intraepithelial lesion is controversial. One possible approach is to treat the lesion via ablation or excision then follow it up with PAP smear at 3-6months then PAP smear and colposcopy at 12months then a yearly PAP smear (four smears) and then finally return to routine screening. The other option is to observe the lesion and repeat PAP smear and colposcopy +/- biopsy in 6months [6].

Grade 2 and 3 cervical intraepithelial lesions will require treatment. Following treatment, screening via PAP smear will be done at 3-6months then PAP smear and colposcopy at 12months then PAP smear 6monthly for the 2nd year and finally a yearly PAP smear [6].

Please see table 13, which summarizes the discussed guideline.

The WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention:

The new WHO guidelines recommend a screen-and treat approach for cervical neoplasms. As the name suggests, this strategy involves screening followed by initiation of appropriate treatment once screening is positive [9]. Screening is initiated at the age of 30. There are no recommendations to preform screening for women aged less than 30years of age [9]. The guidelines suggest that screening via HPV testing is superior to screening with cytology (PAP smear). However, the guidelines provide algorithms for both screening methods (9).

First, if screening with HPV was done, the following steps are taken

- If HPV negative: repeat screening every 5years minimum.
- If HPV positive> do VIA to assess eligibility for treatment with cyotherpay and to exclude a cervical cancer.
- If VIA negative: repeat screening in 1-year time and then 3-5yearly .
- If VIA positive: Treat with cryotherpay if eligible or with LEEP if not. Later, do a follow-up screen in a 1year time.
- If cancer was suspected: refer the patient for appropriate diagnosis and treatment.

Alternatively, if HPV test was positive, colposcopy can be done instead of VIA

- **If colposcopy was negative**: Repeat screening in 3years' time.
- **If colposcopy was positive and no biopsy was done**: Treat with cryotherapy if eligible or with LEEP if not. Later, do a follow-up screen in a 1year time.

Table 12: Society Of Obstetricians And Gynecologists Of Canada Guidelines on screening for cervical cancer.

Classification		Society Of Obstetricians And Gynecologists Of Canada			
Overview		<21year old	21 - 30year old	31 - 65year old	>65year old
		No cytological screening recommended			
	ASCUS	Repeat cytology	Do colposcopy within 12week: if a lesion was found: do a biopsy, if no lesion was found: do a biopsy of the transformation zone		
	ASC-H		Colposcopy within 6weeks		
	LSIL	Repeat cytology	Do colposcopy within 12week: if a lesion was found: do a biopsy, if no lesion was found: do a biopsy of the transformation zone		
	HSIL	Colposcopy within 4weeks	Do colposcopy within 4weeks, if no lesion found: do endocervical curettage/directed biopsy. If lesion was found and transformation zone was not seen and endocervical curettage and/or biopsy were negative: do a diagnostic excisional procedure		
	AGC		Do colposcopy and endocervical curettage within 6weeks (plus endometrial sampling if bleeding and age more than 35years). If no lesion was found on colposcopy: do a diagnostic excisional procedure		
	AIS				
Histology	HPV on biopsy		1) no HPV test as screening 2) HPV positive and cytology negative => provincial routine	Positive HPV and cytology negative => HPV and cytology at 12months	
	CIN 1		Observation and repeat cytology or do colposcopy at 12months		
	CIN 2		Excisional procedure If positive margin: colposcopy and directed Biopsy and/or endocervical curettage If recurrent or persistent lesions: Excision		
	CIN 3				
	AIS		Diagnostic excisional procedure OR type 3 transformation zone excision If positive margin: do a second excisional procedure After treatment: If woman completed her family: consider hysterectomy. If family still no completed and negative margin: further excisional procedure unnecessary		
	SCC or Adenocarcinoma		Do colposcopy within 2weeks with biopsy		

Citation: Ismail MS, Hsu S, Alkhalifa MA, Ali MF, Codabux MF, Al-Sindi K, et al. (2020) Evaluation of Different Guidelines for Cervical Cancer Screening and Management of Abnormal Cervical Cytology. Ann Cytol Pathol 5(1): 001-012. DOI: https://dx.doi.org/10.17352/acp.000011

Table 13: Singapore guidelines on screening for cervical cancer.

Classification		Singapore guidelines	
Overview		25-65	> 65
		PAP smear once every 3years (more frequently if high risk) Women who have never had sexual intercourse: no need for PAP smear unless symptomatic	No need for further screening if PAP smear at age 65 was negative and previous negative smear in last 3years
	ASCUS	Repeat smear in 6months: if positive refer to colposcopy / if negative repeat again in 6months, then if still negative return to routine screening	
	ASC-H	Refer to colposcopy	
	LSIL	1. If mild dyskaryosis or not otherwise specified: colposcopy 2. If HPV effect: repeat in 6months: a. If negative: repeat in 1year > if still negative resume routine screening b. If still HPV effect or more severe abnormality: colposcopy	
	HSIL	1. If moderate or severe dyskaryosis: colposcopy 2. If severe dyskaryosis and cannot rule out invasive Cancer: urgent colposcopy	
	AGC	Refer to colposcopy	
	AIS	Endocervical adenocarcinoma in-situ: colposcopy	
	Inflammatory smear	1. Treat any infection or atrophy then repeat in 4-6months: 2. 2nd smear has similar changes: Treat any infection or atrophy then repeat in 4-6months 3. 3rd smear has similar changes: refer to gynecologist Note: once changes resolve after 1st or 2nd smear: resume routine screening	
Histology	HPV on biopsy	1. Treat if any CIN or condylomas present 2. HPV but no CIN: yearly PAP smear x2 > if negative > return to routine screening	
	CIN 1	Controversial: 2 options available: 1. Treat with ablation or excision then follow-up with PAP smear at 3-6months, PAP smear and colposcopy at 12months > yearly PAP smear x4 > return to routine screening 2. Observe and repeat PAP smear and colposcopy +/- biopsy in 6months	
	CIN 2	After treatment screen with PAP smear at 3-6months > PAP smear and colposcopy at 12months > PAP smear 6monthly for 2nd year > yearly PAP smear	
	CIN 3		

- **If colposcopy was positive and biopsy was done**: For ≥CIN2 treat with cryotherapy or LEEP and then do a follow-up screen in a 1-year time. However, if biopsy shows a ≤CIN1 repeat screening in 3-year time.
- **If cancer was suspected**: Refer the patient for appropriate diagnosis and treatment [9].
- Second, if screening was done via cytology (PAP smear), the following algorithm is used:
- **If cytology negative**: Repeat screening 3-5yearly.

If cytology positive (≥ASCUS): Do colposcopy

- **If colposcopy was negative**: Repeat screening in 3years' time.
- **If colposcopy was positive and no biopsy was done**: Treat with cryotherapy if eligible or with LEEP if not. Later, do a follow-up screen in a 1 year time.

If colposcopy was positive and biopsy was done

For ≥ CIN2 treat with cryotherapy or LEEP and then do a follow-up screen in a 1-year time. However, if biopsy shows a ≤CIN1 repeat screening in 3-year time.

If cancer was suspected: Refer the patient for appropriate diagnosis and treatment [9].

For those recommendations, cryotherapy is the superior treatment method. However, the WHO specifies eligibility criteria for cryotherapy that requires the entire lesion and the squamocolumnar junction to be visible and the lesion should not cover more than 75% of the ectocervix. If this criteria was not met, LEEP would be the alternative option [9].

Please see table 14 which summarizes the discussed guideline.

The European guidelines for quality assurance in cervical cancer screening

The recent guidelines published in 2015 indicate that the use of HPV alone as a screening test for cervical cancer is more beneficial than cytology. They also show that co-testing is not superior to HPV testing alone as it may lead to an increase in costs and unnecessary referrals to colposcopy. However, this is only applicable for the ages between 30-65, as beyond this range, cytology remains the primary screening tool [10]. If a HPV test was negative, re-screening should be done at least 5-yearly. Moreover, not all HPV-positive tests will be referred to colposcopy. Cytology will be done on the same sample collected. If cytology was negative, the test will be repeated in 6-12months' time. If cytology indicated ASC-H, HSIL or AIS, the patient will be referred immediately to colposcopy. If cytology indicated ASCUS, AGC or LSIL, either the test will be repeated in 6-12months' time or the patient will be referred

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Table 14: World Health Organization (WHO) Guidelines on screening for cervical cancer.

Classification	WHO Guidelines
The new WHO guidelines recommend a **screen-and-treat approach** for cervical neoplasms. This strategy compromise of screening for cervical cancer via one of the following methods; HPV test, VIA or cytology (Pap smear). Once a screening test has been done and showed a positive result, treatment will be initiated via one of the following methods; cryotherapy, LEEP/LLETZ or CKC.	
Overview	<30year old: Screening not recommended 30-49year old: 30years is the age recommended to initiate screening for cervical cancer
Screening with HPV test, followed by VIA or colposcopy	- If HPV negative: repeat screening every 5years minimum - If HPV positive > do VIA to assess eligibility for treatment with cryotherapy and to exclude a cervical cancer - If VIA negative: repeat screening in 1-year time and then 3-5yearly - If VIA positive: Treat with cryotherapy if eligible or with LEEP if not. Later, do a follow-up screen in a 1year time - If cancer was suspected: refer the patient for appropriate diagnosis and treatment - Alternatively, if HPV test was positive, colposcopy can be done instead of VIA: - If colposcopy was negative: repeat screening in 3year time - If colposcopy was positive and no biopsy was done: Treat with cryotherapy if eligible or with LEEP if not. Later, do a follow-up screen in a 1year time - If colposcopy was positive and biopsy was done: for ≥CIN2 treat with cryotherapy or LEEP and then do a follow-up screen in a 1-year time. However, if biopsy shows a ≤CIN1 repeat screening in 3-year time. - If cancer was suspected: refer the patient for appropriate diagnosis and treatment
Screening with cytology (PAP smear) followed by colposcopy	- If cytology negative: repeat screening 3-5yearly - If cytology positive (≥ASCUS): do colposcopy: - If colposcopy was negative: repeat screening in 3year time - If colposcopy was positive and no biopsy was done: Treat with cryotherapy if eligible or with LEEP if not. Later, do a follow-up screen in a 1year time - If colposcopy was positive and biopsy was done: for ≥CIN2 treat with cryotherapy or LEEP and then do a follow-up screen in a 1-year time. However, if biopsy shows a ≤CIN1 repeat screening in 3-year time. - If cancer was suspected: refer the patient for appropriate diagnosis and treatment

to colposcopy [10]. Please see table 15, which summarizes the discussed guideline.

Human Papilloma Virus

Screening and Vaccination

- Human Papilloma Virus (HPV) is a double-stranded DNA virus with a well-established connection with cervical cancer. Almost all cases of cervical cancer are linked to HPV (99%). In particular, HPV 16 and 18 are attributed to 50% and 20% of cervical cancer cases, respectively [11].
- High-risk HPV viruses include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66.
- Not only is HPV linked to cervical cancer, but also to vaginal, vulvular, oropharyngeal and anal cancers. Anogenital wart is also another complication [12].
- HPV vaccines include bivalent and quadrivalent vaccines that contain HPV 16, 18 and HPV 6, 11, 16 and 18, respectively.
- In 2014, the Food and Drug Administration (FDA) approved a 9-valent HPV vaccine which includes 4 genotypes of HPV vaccine; 6, 11, 16 and 18 [13].
- The timing for vaccination relies on the age. The best time to start vaccination is prior to sexual intercourse. The target age group for HPV vaccination is young girls between the ages 9years and 14years.

Table 15: The European Guidelines For Quality Assurance In Cervical Cancer Screening.

Classification		The European Guidelines For Quality Assurance In Cervical Cancer Screening		
Overview		<30year old: Cytology may be used as the primary screening tool	30-65year old: Screen via HPV alone	>65year old: Cytology may be used as the primary screening tool
HPV test negative			Re-screen at least 5-yearly	
HPV test positive			Do cytology	
Cytology	Cytology negative		Re-test in 6-12months	
	ASC-H, HSIL or AIS		Refer to colposcopy	
	ASCUS, AGC or LSIL		Re-test in 6-12months or refer to colposcopy	

- The vaccine regimen depends on the age at which the vaccine is to be given. For example, if the female was less than 15years of age, the vaccine is given as 2 doses 6-months apart. However, if the female was more than 15years of age, a 3-doses regimen is recommended [14].
- Regardless of the vaccination status, women will still have to be screened as per the routine screening guidelines. This is explained by the fact that 10%-30% of the cervical cancer cases are caused by other types of HPV that are not included in the vaccines. Also, there is a possibility that the vaccinated woman was already

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infected with the virus before the vaccine was delivered [10-15].

- The efficacy of vaccination depends on whether the individual was previously infected or not. The best protection lies in those who were never infected. Vaccination is more effective in younger women than older ones though older women would still benefit from vaccination. The immunoprotection of HPV vaccine lasts approximately 84months. Antibodies developed against HPV after vaccination is found to last about 10years.

- HPV vaccination is not recommended in pregnancy due to few data concerning its safety. However, no increased risk of adverse pregnancy outcomes was noted in patients who have been vaccinated.

- HPV vaccination is recommended in immunocompromised patients. 3 doses should be administered for all patients through 26years old.

- The risks associated with vaccination are minimal. Parents might think that vaccination might lead to sexual disinhibition but surveys performed suggest that there was no increase in risky sexual behavior. Hence, HPV vaccination should be promoted and administered to both men and women.

Cervical cancer screening and HPV in Bahrain

In Bahrain, a recent report was published with local statistics of cervical cancer and HPV. It indicated an annual incidence of 22 for cervical cancer in Bahrain. It also demonstrated the prevalence of HPV infection among the following: normal cytology (2.2), low-grade cervical lesions (24), high-grade cervical lesions (52.3) and cervical cancer (72.4) [16].

Bahrain is one of the countries with an established screening program for cervical cancer. The guidelines state to screen all women between the ages 30 and 65years once every 5years. However, currently, there is no established HPV vaccination program in Bahrain [16].

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