

REVIEW ARTICLE

Cervical cancer: screening, diagnosis and staging

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Summary

Purpose: Despite the widespread screening programs, cervical cancer remains the third most common cancer in developing countries. Based on the implementation of cervical screening programs with the referred adoption of improved screening methods in cervical cytology with the knowledge of the important role of the human papilloma virus (HPV) it's incidence is decreased in the developed world. Even if cervical HPV infection is incredibly common, cervical cancer is relatively rare. Depending on the rarity of invasive disease and the improvement of detection of pre-cancerous lesions due to the participation in screening programs, the goal of screening is to detect the cervical lesions early in order to be treated before cancer is developed. In populations

with many preventive screening programs, a decrease in cervical cancer mortality of 50-75% is mentioned over the past 50 years. The preventive examination of vagina and cervix smear, Pap test, and the HPV DNA test are remarkable diagnostic tools according to the American Cancer Association guidelines, in the investigation of asymptomatic women and in the follow up of women after the treatment of pre-invasive cervical cancer. The treatment of cervical cancer is based on the FIGO 2009 cervical cancer staging.

Key words: cervical cancer, diagnosis, FIGO 2009 staging, HPV screening

Introduction

Cervical cancer ranks third in cancer incidence worldwide and is the most frequent gynecological cancer in developing countries [1,2]. The frequency of cervical cancer after treatment for dysplasia is lower than 1% and mortality is less than 0.5% [3]. The increasing trend of the disease in developing countries is attributed to the early beginning of sexual activities, certain sexual behaviors like high number of multiple partners, early age at first intercourse, infrequent use of condoms, multiple pregnancies with Chlamydia association, and immunosuppression with HIV, which is related to higher risk of HPV infection [4]. HIV-infected women have a higher risk and persistence of multiple HPV infections which are associated with increased risk of progression to precancerous cervi-

cal lesions compared to HIV-noninfected [5]. It is estimated that 10-15% of women have oncogenic HPV types (HPV high risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82 and HPV low risk: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81) [6]. In the USA, 16 and 18 types are detected in 70% of high grade squamous intraepithelial lesions (HGSIL) as well as in invasive cervical cancer cases [7]. The use of oral contraceptives is asserted to increase the risk of the disease (administration for >5 year-double risk, >10 year-quadruple risk), although some other risk factors like sexual activity, frequency of gynecological examinations and medication-free interval time should be estimated [7,8]. Smoking is thought to have unclear relation to the disease mainly because of the presence of non special car-

cinogen substances in the smoke [9].

Screening and diagnosis

Currently there are two types of diagnostic tests for cervical cancer screening: Papanicolaou test and HPV test. The first one detects early the precancerous and cancerous cell lesions in order to be effectively treated and the second one infections by HPV types that could lead to cancer. Most of the HPV infections are self-curable and do not cause precancerous cell changes; only chronic infection by specific HPV types could lead to cervical cell abnormalities. If these abnormalities (precancerous or high grade lesions) are not treated, they may evolve into cervical cancer after many years.

Molecular detection of HPV DNA or RNA is currently the gold standard for identification of HPV. Three categories of molecular assays are available for detection of HPV infection in tissue and exfoliated cell samples, all of which are based on the detection of HPV DNA and include non-amplified hybridization assays, southern transfer hybridization (STH), dot blot hybridization (DB) and *in situ* hybridization (ISH), signal amplified hybridization assays such as hybrid capture assays, target amplification assays such as polymerase chain reaction (PCR) and *in situ* PCR. PCR based on detection of HPV is both extremely sensitive and specific [10]. Furthermore, detection of HPV E6/E7 mRNA and the presence of oncogenic activity in cervical specimens can be performed by reverse transcriptase (RT) PCR or by nucleic acid sequence based amplification (NASBA). In NASBA assays, single-stranded nucleic acids or RNA equivalents (e.g. viral genomic RNA, mRNA or rRNA) are amplified in a background of double-stranded DNA [10].

Nowadays, three DNA based and one RNA based assays have been approved by the US Food and Drug Administration (FDA) for routine cervical cancer screening. Among these are the Digene Hybrid Capture 2 High-Risk HPV DNA test (HC2; Qiagen, Hilden, Germany), the Cervista HPV HR test (CER; Hologic, Madison, WI), the Cobas® HPV test (Roche, Pleasanton, USA) and the RNA-based Aptima® HPV assay (Hologic, San Diego, CA). The HC2 test, for the collective detection of at least 13 carcinogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), is a nucleic acid hybridization assay with signal amplification using microplate chemiluminescence for semi-quantitative detection of HPV DNA in cervical specimens [11]. In addition to the 13 carcinogenic HPV types

detected by HC2, the Cervista HPV HR assay also detects putative HR HPV type 66 [12]. The Cobas 4800HPV PCR master mix employs primers that amplify a region of approximately 200 base pairs within the L1 polymorphic region of the HPV genome. The fluorescent signal from 12 HR types of HPV (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) is detected using the same fluorescent label, while the HPV 16, 18, and beta-globin signals are detected with three separate spectrally unique fluorescent labels respectively. The distinct individual wavelengths characterizing each label allow for simultaneous genotyping of HPV 16 and 18 amplicon separately from the other 12 HR types [13].

According to the latest guidelines of the American Cancer Society, screening should begin at the age of 21 [14]. Younger women should not be screened neither with Pap test nor with HPV test. Women between 21-29 years should be screened with Pap test every 3 years. In women between 21-29 years, who have had two or more consecutive negative cytology results, data are not adequate to assert larger interval time between screening (>3 years). The HPV test should be used in these ages only after Pap test abnormal findings. Women between 30-65 years should be screened with both Pap test and HPV test (co-testing) every 5 years. This type of screening is preferable, but the continuing of Pap test screening every 3 years is also acceptable. Data is inadequate to support longer interval time between tests in this age group after a number of negative tests [15].

As for vaccination, three vaccines (Gardasil, Gardasil 9 and Cervarix) are available to prevent infection with multiple types of HPV known to cause cervical cancer. Gardasil 9 contributes to preventing infection with 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58), Gardasil helps preventing infection with 4 HPV types (6, 11, 16 and 18) and Cervarix helps preventing infection with HPV types 16 and 18. Gardasil and Gardasil 9 are given by injection in 3 doses (0,2 and 6 months) and recently it was approved to be given with only 2 injections at 0 and 6 months in young girls less than 15 years old. Cervarix is also administered by injection and requires 3 doses (0,1 and 6 months) [16]. These commercially available vaccines consisting of the L1 capsid protein assembled as virus like particles (VLPs) induce neutralizing antibodies that deny access of the virus to cervical epithelial cells. While greater than 90% efficacy has been demonstrated at the completion of large phase III trials in young women, vaccines developers are now addressing broader issues such as efficacy in boys, longevity of the protection and

inducing cross reactive antibody for oncogenic non-vaccine HPV strains. In the United States, HPV vaccination with any vaccine is recommended for all girls and women who are between ages 9 and 26 years old. HPV vaccination is recommended for boys and men who are between ages 9 and 21 years and can be given up to 26 years of age [16].

Pap test should not be offered every year because sometimes precancerous lesions are mentioned without really existing. These false positive results may lead to treatments that are not needed. The latest guidelines for mass population screening maintain the benefits of diagnostic tests but they reduce the risk of unnecessary treatment [17,18]. Women who have undergone total hysterectomy (including cervix) for benign diseases and do not have cervical cancer or severe precancerous lesions history, should not be screened. Last but not least, women who have been vaccinated against the HPV virus should continue the screening according to the guidelines for their age group.

Increasing the diagnostic precision of Pap test

The Pap smear collection should not be done during menses, shower, sexual intercourse. Use of tampon or local contraception or other vaginal products should be avoided 48 hrs before Pap test.

Women with positive HPV test and negative cytology

According to the American Society for Colposcopy and Cervical Pathology (ASCCP) screening guidelines, women with positive HPV test and negative cytology should either repeat co-test in 12 months or be offered immediate HPV genotype specific testing for HPV 16 alone or HPV 16 and 18. If co-test is repeated in 12 months, women with either positive repeat test should be offered colposcopy. Whereas women with both tests negative should be co-tested in 12 months, they should not be referred to immediate colposcopy (in case of positive HPV and negative cytology) and should not have HPV genotyping for HPV types other than HPV 16 and 18. If immediate HPV genotyping is positive for HPV 16 or HPV 16/18 is positive women should be referred for colposcopy. The use of HPV genotype specific testing for HPV 16 alone or both HPV 16 and 18 is recommended only for the management of women with HPV positive test and negative cytology.

Up to date, there is no adequate data supporting the use of other biomarkers except HPV [17,18].

Women with ASCUS cytology and negative HPV test results

Women with ASCUS cytology and negative HPV test results should continue screening according to the age-specific guidelines.

Women over 65 years old

Women over 65 years with negative prior screening, without CIN 2 history during the last 20 years, should not be screened for cervical cancer in any way. After screening is stopped, it should not be resumed for any reason, even if a woman reports having a new sexual partner. The adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 consecutive negative cytologies and negative HPV testing results within the last 10 years before screening stopping, with the most recent screening within the last 5 years.

Women over 65 years with CIN2, CIN 3 or adenocarcinoma in situ history

After spontaneous resolution or appropriate treatment of CIN 2 and CIN 3 lesions or adenocarcinoma in situ (AIS), women should return to routine screening for at least 20 years (even if screening is extended to past age 65).

In cases of uterine cervix conoid amputation, tumor free distance (TFD), which is defined as the distance from the outermost layer of cervix to the deeper cervical stromal invasion, is an important treatment criterion. TFD is reported to have a prognostic value in patients with cervical cancer who were treated surgically and is a prognostic factor of the pelvic lymph nodes and lymphovascular involvement. The higher the TFD, the longer the disease free survival. A TFD cut off value of 2.5 mm was determined in order to have an effective balance of sensitivity concerning the prediction of disease relapse [19].

According to the updated 2012 guidelines of the American Society of Cervical Cancer and Pathology (ASCCP), women with HGSIL should be managed as CIN 2,3. For women with a histologic diagnosis of CIN 2, CIN 3, or CIN 2,3 and adequate colposcopy, both excision and ablation are acceptable treatment modalities, except in pregnant and young women. For women with a histologic diagnosis of CIN 2, CIN 3 or CIN 2,3 and inadequate

Table 1. FIGO staging of cervical cancer (2009)

Stage I	<i>Carcinoma is strictly confined to the cervix</i>
Stage IA	<i>Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.</i>
Stage IA ₁	<i>Measured stromal invasion <3 mm in depth and <7 mm in extension</i>
Stage IA ₂	<i>Measured stromal invasion >3mm depth and not >5 mm and extension <7 mm</i>
Stage IB	<i>Clinically visible lesions limited to the cervix or pre-clinical cancers >stage IA</i>
Stage IB ₁	<i>Clinically visible tumour <4 cm in greatest dimension</i>
Stage IB ₂	<i>Clinically visible tumour >4 cm in greatest dimension, parametrial involvement, but not into pelvic sidewall</i>
Stage II	<i>Cancer extends beyond cervix though not to the pelvic sidewall or lower third of the vagina</i>
Stage IIA	<i>Involves upper 2/3^d of vagina without parametrial invasion</i>
Stage IIA ₁	<i>clinically visible tumour <4 cm in greatest dimension. Involvement of up to the upper two thirds of the vagina</i>
Stage IIA ₂	<i>clinically visible tumour >4 cm in greatest dimension, but not into pelvic sidewall</i>
Stage IIB	<i>with parametrial invasion, but not into the pelvic sidewall</i>
Stage III	<i>Cancer has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina All cases with hydronephrosis or a non-functioning kidney are Stage III cancers.</i>
Stage IIIa	<i>Tumour involves the lower third of the vagina with no extension to pelvic sidewall .</i>
stage IIIb	<i>Extension to pelvic side wall or causing obstructive uropathy, MR imaging findings that are suggestive of pelvic sidewall involvement include tumour within 3 mm of or abutment of the internal obturator, levator ani, and pyriform muscles and the iliac vessel</i>
Stage IV	<i>Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum extension beyond pelvis or biopsy proven to involve the mucosa of the bladder or the rectum</i>
Stage IVa	<i>Spread of the tumour into adjacent pelvic organs ,extension beyond pelvis or rectal/bladder invasion</i>
Stage IVb	<i>Distant organ spread</i>

colposcopy or endocervical sampling by endocervical curettage showing CIN 2, CIN 3, CIN 2,3 or CIN not graded, ablation is unacceptable and a diagnostic excisional procedure is recommended. Hysterectomy is unacceptable as primary therapy for CIN 2, CIN 3 or CIN 2,3 [20]. Conization of the cervix is defined as excision of a cone-shaped or cylindrical wedge from the cervix uteri that includes the transformation zone and all or a portion of the endocervical canal. Conization can be performed with a scalpel (cold-knife conization), laser or electro-surgical loop. The latter is called loop electro-surgical excision procedure (LEEP) or large loop excision of the transformation zone (LLETZ). Combined conization usually refers to a procedure started with a laser and completed with a cold-knife technique. Laser conization can be excisional or destructive (by vaporization). Techniques for diagnostic and therapeutic conization are virtually identical [20].

For the diagnosis of invasive cervical cancer there are available imaging methods (colposcopy), biophysical methods (fluorescence spectroscopy, polar probe), molecular diagnostic methods (HPV DNA test), morphometric-cytometric methods (nuclear aneuploidy detection, DNA ploidy), new methods of cervical smear preparation (Thin

prep, CytoRich) and methods of automated cervical smear examination (Papnet, Cytoc, Autocyte and Autopap 300) [21].

In locally advanced disease, pelvic MRI and PET-CT should be performed for diagnosis. CT can determine the extent of the original disease, with total accuracy for staging between 75-96% [15]. However, MRI has been proved to offer better analysis of soft tissue imaging than CT and to identify better the extent of tumor, involvement of parametrium and infiltration of adjacent organs. In a series of patients who underwent surgery after staging with the use of MRI, its diagnostic precision in staging was 81% [22]. On the other hand, PET-CT is the best imaging method in localizing lymph nodes, having sensitivity and specificity of 99% for metastatic lymph nodes sized 5mm [22]. Kidd et al. showed that staging of the lymph nodes with the use of PET-CT had high prognostic value for disease free survival, no matter the FIGO stage.

Staging of cervical cancer

According to the International Federation of Gynecology and Obstetrics – FIGO 2009 staging of cervical cancer, stage IA includes the preclin-

ical cancer that is diagnosed only by microscopic findings (Table 1) [23,24]. This stage is divided into IA1 (microinvasive cancer), where the invasion does not exceed 3 mm in depth and 7 mm in width, and in stage IA2 (microcarcinoma), where the stromal invasion depth is between 3 and 5 mm and the width is less than 7 mm. Even though, in the latest FIGO staging, the importance of damaged volume is identified for the first time, other investigators report that the evaluation of the damaged volume by the use of three dimensions is a complicated procedure and not enough practical to be applied routinely [25,26].

The diagnosis of microinvasive carcinoma can only be done after a careful histological examination of the specimen, when all damage is included and the incision has been done in healthy tissue. There are three histologic signs of microinvasion: a) the infiltrative lesion cells are differentiated better than the cells of the intraepithelial neoplasia from which they originate; b) interruption of the basic membrane is seen in the point of invasion; c) in case of microinvasion an obvious stromal reaction including lymphocytes and plasma cells around the lesions can be seen [27]. In microinvasive cervical cancer, the risk of lymph node metastasis and progression into invasive disease after total damage excision is <1% [28]. According to Copeland et al., the risk of progression of microinvasive cancer (invasion depth <3 mm) is 4.4 times higher in case of vascular invasion [29].

The proposed surgical treatment for stages IA2IB1 of cervical cancer is total radical hysterectomy and bilateral pelvic lymphadenectomy (Piver type III/Wertheim's radical hysterectomy). The customized decision making depends on the tumor volume, topic spreading and the patient's desire.

Even though the number of women with invasive cervical cancer is decreased, the number of patients diagnosed with early stages of cervical cancer during pregnancy is increased. In cases of pregnancy, abdominal radical trachelectomy or vaginal radical trachelectomy and cerclage of the remaining cervix with wide permanent suture are proposed [30]. The uterus is separated from the vagina and remains attached to the adnexa and uteroovarian vessels. The incision is planned at or just below the internal os, ideally preserving 5 mm or so of upper endocervix [31-33]. A cerclage using Mersilene band is tied around the "neo-cervix" and the bladder peritoneum is sutured over the cerclage. The stitch is not placed into the cervical stroma but is tied around the cervix with the knot placed anteriorly [31-33]. In a standard radical abdominal trachelectomy, an access to the lateral parametria is opened by dissection of the uterine artery. It is not clear whether limited vascular supply can negatively affect future fertility, although it can be hypothesized that the ovarian vessels may sufficiently adapt [34,35]. There are three different techniques described that allow for successful preservation of the uterine artery.

The final radiotherapy consists of the most accepted treatment method for patients in early stages, unfit for surgical treatment combined with chemotherapy in cases of positive lymph nodes or topically spread tumors >4 cm (stages B2 or >A2 FIGO). It is a combination of radiotherapy and brachytherapy that improves total survival [36]. Maneo et al. recommend in tumors sized up to 3 cm a combination of cisplatin, paclitaxel and ifosfamide (TIP) in spinocellular carcinomas and cisplatin, paclitaxel with doxorubicin (TEP) in adenocarcinomas every 3 weeks followed by cold knife conization and lymphadenectomy [37].

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